Study of the Effects of Epinephrine on Cerebral Oxygenation and Metabolism During Cardiac Arrest and Resuscitation by Hyperspectral Near-Infrared Spectroscopy

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Objectives: Epinephrine is routinely administered to sudden cardiac arrest patients during resuscitation, but the neurologic effects on patients treated with epinephrine are not well understood. This study aims to assess the cerebral oxygenation and metabolism during ventricular fibrillation cardiac arrest, cardiopulmonary resuscitation, and epinephrine administration.

Design: To investigate the effects of equal dosages of IV epinephrine administrated following sudden cardiac arrest as a continuous infusion or successive boluses during cardiopulmonary resuscitation, we monitored cerebral oxygenation and metabolism using hyperspectral near-infrared spectroscopy.

Settings: A randomized laboratory animal study.

Subjects: Nine healthy pigs.

Interventions: None.

Measurements and Main Results: Our study showed that although continuous epinephrine administration had no significant impact on overall cerebral hemodynamics, epinephrine boluses transiently improved cerebral oxygenation (oxygenated hemoglobin) and metabolism (cytochrome c oxidase) by 15% ± 6.7% and 49% ± 18%, respectively ($p < 0.05$) compared with the baseline (untreated) ventricular fibrillation. Our results suggest that the effects of epinephrine diminish with successive boluses as the impact of the third bolus on brain oxygen metabolism was 24.6% ± 3.8% less than that of the first two boluses.

Conclusions: Epinephrine administration by bolus resulted in transient improvements in cerebral oxygenation and metabolism, whereas continuous epinephrine infusion did not, compared with placebo. Future studies are needed to evaluate and optimize the use of epinephrine in cardiac arrest resuscitation, particularly the dose, timing, and mode of administration. (*Crit Care Med* 2019; 47:e349–e357)

Key Words: cardiac arrest; cerebral metabolism; epinephrine; near-infrared spectroscopy

Sudden cardiac arrest (SCA) is a major public health issue worldwide. Despite advances in medical treatment, overall survival rates remain low (1). In the past decade, treatment advances targeted improvements in short-term cardiac outcomes, such as return of spontaneous circulation (ROSC), but this has not resulted in significant improvements in neurologic outcomes (2). Postcardiac arrest brain injury is a common cause of significant morbidity and mortality. It is thought that the brain is uniquely vulnerable in cardiac arrest due to its limited tolerance to the initial ischemic insult. Over two thirds of SCA patients die during their hospital admissions secondary to irreversible neurologic injuries, which are likely

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due to prolonged ischemia and subsequent reperfusion (3, 4). Furthermore, approximately one third of SCA survivors who are discharged from hospital have irreversible cognitive disabilities (5, 6).

Epinephrine has been used to treat SCA during resuscitation for decades. Animal studies have shown that epinephrine increases myocardial and cerebral blood flow during resuscitation but had no significant impact on blood oxygen saturation (7–9). Observational human studies suggest that epinephrine can significantly improve rates of ROSC and admission to hospital after SCA; however, there are concerns that it can also decrease brain perfusion and oxygenation and result in a reduction of long-term survival and of neurologic outcomes compared with patients not treated with epinephrine (10–13). Therefore, there is a need to better understand the effects of epinephrine on brain perfusion, oxygenation, and metabolism during cardiac arrest resuscitations.

Cytochrome c oxidase (Cyt-ox) is the final enzyme in the mitochondrial electron transport chain responsible for 95% of cellular oxygen consumption and energy synthesis (14, 15) which is an intracellular marker of oxygen utilization and metabolism. The total in vivo concentration of Cyt-ox is relatively constant (over short periods of time) and significantly lower (~10%) than that of hemoglobin. Cyt-ox rapidly changes between reduced and oxidized states and thus is reported as changes in the difference between the oxidized and reduced states (redox changes or Δ[Cyt-ox]) rather than the changes in absolute concentration of Cyt-ox (16, 17). In recent years, a significant progress has been made in the methodology of noninvasive measurement of Δ[Cyt-ox] in animals and humans by using hyperspectral near-infrared spectroscopy (hNIRS) (16).

In this study, we employed a novel hNIRS signal processing algorithm (18) to measure regional temporal changes in the concentrations of oxygenated hemoglobin (Hbo_2) and deoxygenated hemoglobin (HHb) and the Δ[Cyt-ox] in a porcine model of SCA. This is the first study directly investigating the effects of epinephrine on cerebral tissue oxygenation and metabolism during SCA resuscitation.

MATERIALS AND METHODS

Cardiac Arrest and CPR Setup

Nine healthy pigs (Yorkshire, either sex, 6–9 wk old, 33–39.3 kg) were fasted overnight and sedated with ketamine (20 mg/kg intramuscular ["Ketalean" Bimeda-MTC Animal Health, Cambridge, ON]). Anesthesia was induced with thiopental sodium (8 mg/kg IV [Hospira Healthcare, Saint-Laurent, QC]) and maintained with isoflurane (1–4% via inhalation [Pharmaceutical Partners of Canada, Richmond Hill, ON]) for the duration of the surgical procedure. Once anesthetized, pigs were endotracheally intubated and maintained by continuous administration of isoflurane (1–3% mixed with 100% oxygen). Mechanical ventilation was provided by an Ohmeda ventilator (Ohio Medical Products, Madison, WI), with a tidal volume and rate set to maintain the arterial pH, Pco_2, and Po_2 in the physiologic range (pH 7.35–7.45, Pco_2 35–45 mm Hg, Po_2 > 100 mm Hg) measured via arterial blood samples.

Core temperature was maintained between 36.5°C and 38.5°C using a heating blanket (Micro-Temp Pump, Charlottesville, VA). A peripheral ear vein was cannulated, and normal saline (NS) was infused at a rate of 2–4 mL/kg/hr to prevent hypovolemia. Three limb leads were placed for electrocardiogram recording. Defibrillation patch electrodes (EDGE Quik-Combo; Physio-Control, Redmond, WA) for defibrillation and cardiac monitoring were adhered to the left and right chest. A monophasic action potential catheter (EP Technologies, Sunnyvale, CA) was positioned at the apex of the right ventricle via the right femoral vein to allow for pacing and inducing ventricular fibrillation (VF). Two micromanometer-tipped catheters (Mikro-Tip Transducer; Millar Instruments, Houston, TX) were placed in the aortic arch via the right femoral artery to allow for the recording of aortic pressure and in the right atrium via the left femoral vein for the recording of the right atrial pressure (RAP). A catheter sheath attached to a pressure transducer (Cobe CDX3, Lakewood, CA) was inserted in the left femoral artery for arterial pressure monitoring and for drawing arterial blood gas (Pco_2 and Po_2) samples during the experiment. The left carotid artery was exposed to allow placement of a perivascular flow probe to monitor carotid flow (TS420 Perivascular Flowmeter Module, Transonic T403; Transonic Systems, Ithaca, NY). Once all introducing sheaths were in place, 2500 IU of heparin (Sandoz, Boucherville, QC) were administered to fully anticoagulate the animal. The mean aortic pressure (mAoP) (average of systolic and diastolic pressures) and mean carotid flow (mCaF) were calculated for further analyses.

Resuscitation Protocol

Prior to the induction of VF, all animals were weaned off all anesthetic gases for at least 15 minutes, and sedation was achieved using IV fentanyl. VF was induced and left untreated for 6 minutes before starting continuous cardiopulmonary resuscitation (CPR) using closed chest compressions delivered continuously with a pneumatically driven automatic piston device (LUCAS; Physio-Control Inc/Jolife AB, Lund, Sweden). The compression rate was 100/min with an 8 cm circular compression pad positioned over the sternum; compression depth was 4–6 cm (approximately 25% of the anterior-posterior diameter of the chest wall). After each compression, the chest wall was allowed to recoil completely without residual lean from the compression device. Manual ventilation was administered using AMBU bag (Ambu, Glen Burnie, MD) with 100% oxygen at 10 breaths/min. All boluses and infusions of study agents were in identical, unlabeled syringes and were blindly administered through a peripheral ear vein using a three-way stopcock by a research team member blinded to their contents. After 2 minutes of CPR, nine animals from were randomized to one of three groups:

1) Epinephrine infusion with placebo bolus—An IV infusion of epinephrine, at a concentration of 0.04 mg/mL in 0.9% NS was infused over 12 minutes total, starting after 2 minutes of CPR. In addition, boluses of NS (placebo) of equivalent volume to an epinephrine bolus, followed by 10 mL of

NS flush, were administered starting after 2 minutes of CPR and every 4 minutes after for a total of three doses.

2) Placebo infusion with epinephrine bolus—An IV bolus dose of 0.015 mg/kg of epinephrine in NS at a concentration of 0.1 mg/mL followed by 10 mL NS flush was given after 2 minutes of CPR and administered every 4 minutes for three doses total. As well, an IV infusion of an equivalent volume of NS (as calculated above in the epinephrine infusion group) was started after 2 minutes of CPR and administered for 12 minutes total.
3) Placebo infusion with placebo bolus—Equivalent volumes of an IV NS infusion and NS bolus doses and timing as the epinephrine infusion and bolus groups.

The dose of epinephrine is equivalent to the current cardiac arrest dose of 1 mg in an average 70 kg adult. Twenty minutes after induction of VF (14 min after onset of CPR), defibrillation was attempted with a Medtronic-Physio Control Lifepak 12TM (Medtronic Inc, Redmond, WA) using up to four shocks at 360 J. ROSC was defined as the resumption of sustained perfusing cardiac activity with systolic aortic pressure greater than 40 mm Hg for greater than or equal to 60 seconds.

Cerebral hNIRS Setup and Measurements

hNIRS allows for the measurement of the absolute concentrations of tissue [Hbo_2], [HHb], and Δ[Cyt-ox]. A custom-made hNIRS system (18, 19) was used to measure brain variables by placing optodes on the dura mater at an interoptode distance of 10 mm (after removing the skin and skull at the region of measurement). Based on the differential path length factor of 5 and interoptode distance of 10 mm, the mean optical path length was calculated to be ~50 mm with an approximate penetration depth of 16 mm (20–22). This optical path length minimizes interference from the dura, which was assumed to be 1 mm thick. hNIRS data acquisition was performed using a portable spectrometer (QE65000 Ocean Optics, Dunedin, FL) (23). Specific details of our hNIRS system setup and methods have been previously reported (18, 24).

Temporal changes in the concentrations of chromophores were resolved using a multistep data-fitting algorithm based on the analytical solution to diffusion equation for semi-infinite medium with the extrapolated boundary condition (18, 25, 26). The algorithm produced values of the concentrations of tissue [Hbo_2], [HHb], and Δ[Cyt-ox] (18, 24). The total hemoglobin and tissue oxygen saturation (tSo_2) were calculated as follows:

$$Total[Hb] = [HbO_2] + [HHb] \qquad tSO_2 = \frac{[HbO_2]}{[HbO_2] + [HHb]}$$

Analysis Methods

All the experiments were carried out and reported in accordance with the Animal Research: Reporting of In Vivo Experiments guidelines (27). All protocols were approved by the Animal Care Committee of St. Michael's Hospital (Toronto, ON, Canada) and conformed to the guide for the care and use of laboratory animals, U.S. National Institutes of Health (NIH Publication number. 85–23, revised 1996).

Data processing was performed using MATLAB_R2015b (Mathworks, Natick, MA). The baseline variables were calculated as the average over 30 seconds prior to induction of VF, and the VF-induced changes were assessed as the average over the last 30 seconds of VF before starting the CPR. Hemodynamic variables were averaged over the last 30 seconds of CPR before receiving any infusion or bolus. The effect of infusion was assessed 180 seconds after the start of the infusion and was averaged over the following 60 seconds. The impact of each epinephrine/placebo bolus was assessed by averaging a 40-second period 60 seconds after receiving the bolus. hNIRS measurements of cerebral hemodynamics during different parts of the experiment were measured as following: before VF (30 s average baseline), during VF (the average over last 30 s of untreated VF), during CPR (averaged over 30 s of chest compressions), and after epinephrine/placebo administration (averaged over 30 s).

Area under the curves (AUC) were calculated for cerebral variables for each time epoch (8–12, 12–16, and 16–20 min) corresponding to each IV bolus of epinephrine or placebo. AUCs were measured over 4-minute intervals immediately after administration of each bolus. The data point before the first bolus (after the first 2 min of CPR) was used as the reference (zero) point for AUC calculations. The AUCs were used to compare the effect of placebo and epinephrine blouses on hemodynamics and cerebral metabolism.

All statistical analysis was performed in SPSS software (IBM SPSS statistics 24, Armonk, NY). The normality of the datasets was investigated using Shapiro-Wilk test. The overall effectiveness of CPR on cerebral variables was assessed through paired sample *t* test. To assess the significance of the observed changes during different steps of resuscitation, one-way repeated measures analysis of variance was performed between "during VF", "during CPR", and "After each epinephrine/placebo infusion or bolus", followed by pair-wise comparison (post hoc test).

RESULTS

Hemodynamics

The standard prearrest demographics and hemodynamics including sex, weight, mAoP, mean RAP, arterial blood gas concentrations (Pco_2 and Po_2), and pH are presented in **Supplemental Table 1** (Supplemental Digital Content 1, http://links.lww.com/CCM/E293). No significant difference was found between different study groups ($p > 0.05$).

Figure 1 and **Table 1** represent the average changes in mAoP and mCaF during the experiments for each resuscitation protocol. Epinephrine boluses increased mAoP more than the infusion or placebo groups (increase of 23.3 vs –1.5 and 2.8 mm Hg, respectively); however, mCaF did not significantly change. The transient increases in mAoP in the epinephrine bolus group are shown in Figure 1*A*, and the cerebral oxygenation and metabolism changes in **Supplemental Figure 1*a–d*** (Supplemental Digital Content 2, http://links.lww.com/CCM/E294). In the

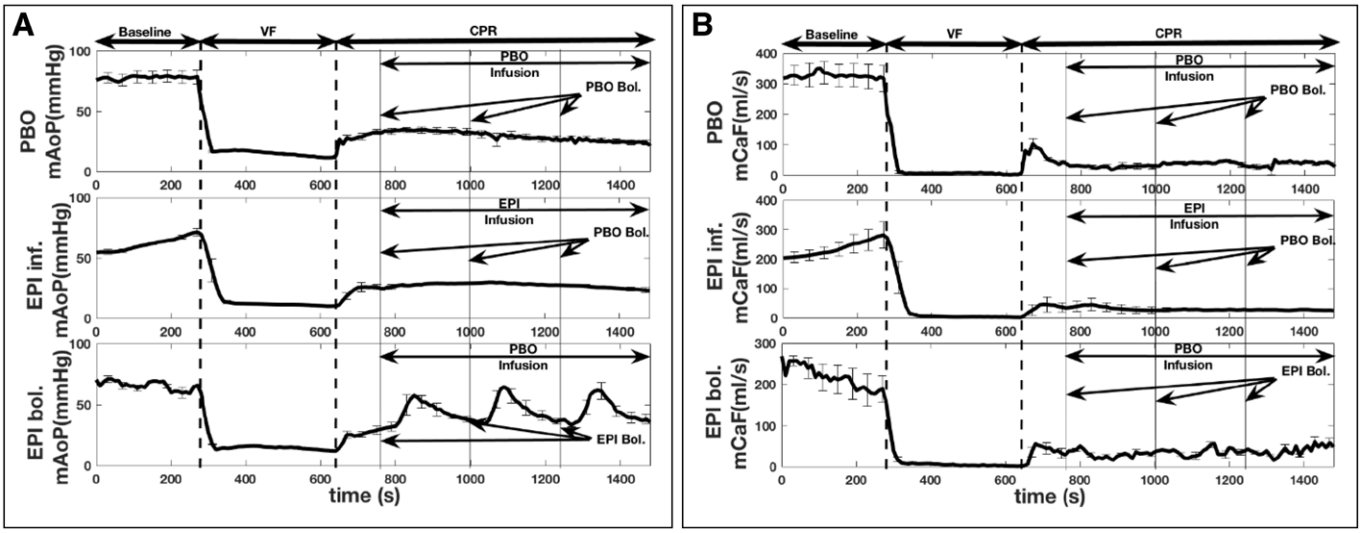

Figure 1. The average changes of mean aortic pressure (mAoP) (**A**) and mean carotid flow (mCaF) (**B**), during the experiment for three groups of treatments. The "EPI/PBO Bol." *arrows* indicate the time at which the epinephrine (EPI) and/or placebo (PBO) boluses (Bol.) were injected. The shown "EPI/PBO infusion" interval represent the period during which the EPI/PBO was continuously injected. The error bars represent the SE which was calculated as SD divided by the square root of number of samples. CPR = cardiopulmonary resuscitation, Inf. = infusion, VF = ventricular fibrillation.

TABLE 1. The Average Mean Aortic Pressure and Mean Carotid Flow Measured Using Electrode Catheters During the Experiments in Each Study Group That Received Placebo and/or Epinephrine as IV Continuous Infusion or Boluses

Groups	Catheter-Measured Variables	Before VF	During VF	During Cardiopulmonary Resuscitation	After Epinephrine Infusion	After First Epinephrine/ Placebo Bolus	After Second Epinephrine/ Placebo Bolus	After Third Epinephrine/ Placebo Bolus
Placebo infusion + placebo bolus	mAoP (mm Hg) ± SD	**77.64** ± 13.6	**11.76** ± 2.19	**30.04** ± 7.02	Not applicable	**32.88** ± 6.49	**30.27** ± 7.33	**25.97** ± 4.53
	p				0.06			
	mCaF (mL/min) ± SD	**319** ± 99	**3.44** ± 2.95	**37.73** ± 4.92	Not applicable	**26.85** ± 17.02	**40.19** ± 9.46	**44.99** ± 9.58
	p				0.05			
Epinephrine infusion + placebo bolus	mAoP (mm Hg) ± SD	**72.26** ± 5.68	**11.24** ± 1.98	**26.79** ± 2.47	**29.93** ± 1.58	**28.43** ± 3.12	**30.15** ± 1.09	**28.34** ± 2.71
	p				**0.02**[a]			
	mCaF (mL/min) ± SD	**269.1** ± 82.9	**1.79** ± 1.99	**53.89** ± 38.45	**57.58** ± 40.77	**56.67** ± 40.36	**46.70** ± 36.46	**50.26** ± 30.95
	p				0.22			
Placebo infusion + epinephrine bolus	mAoP (mm Hg) ± SD	**63.14** ± 4.26	**12.37** ± 1.72	**28.50** ± 6.68	Not applicable	**51.80** ± 11.01	**54.53** ± 12.52	**52.48** ± 14.35
	p				**0.007**[b]			
	mCaF (mL/min) ± SD	**180.7** ± 91.5	**1.16** ± 1.29	**35.07** ± 25.39	Not applicable	**27.71** ± 9.85	**25.92** ± 6.30	**28.64** ± 11.71
	p				0.25			

mAoP = mean aortic pressure, mCaF = mean carotid flow , VF = ventricular fibrillation.

[a]Post hoc: cardiopulmonary resuscitation (CPR), second and third placebo boluses significantly increased mAoP compared with during VF ($p < 0.05$).

[b]Post Hoc: CPR, first and second epinephrine boluses significantly increased mAoP compared with during VF ($p < 0.05$).

p values were calculated using one-way repeated measures analysis of variance.

epinephrine bolus group, the mAoP started to increase ~40 seconds and peaked ~90s after each bolus. The observed effect of epinephrine boluses in cerebral metabolism (Δ[Cyt-ox]) decreased after successive doses compared with mAoP. The mCaF did not follow the same pattern as mAoP, Hbo_2, or Δ[Cyt-ox] (Fig. 1*B*). Only one animal in the epinephrine bolus group regained ROSC.

NIRS-Measured Cerebral Hemodynamics

The average near-infrared spectroscopy (NIRS)–measured cerebral hemodynamics are shown in **Table 2** and Supplemental Figure 1 *a–c* (Supplemental Digital Content 2, http://links.lww.com/CCM/E294).

There were no significant changes in tSo_2 in all three groups during CPR (at any of the epochs during 14 min resuscitation) compared with "during VF" ($p > 0.05$).

In epinephrine bolus group, Hbo_2 concentration significantly increased after each bolus of epinephrine compared with "during CPR" by an average of 5.5 ± 0.2 μM (corresponding to 11.2% ± 2%) and compared with during untreated VF by an average of 6.4 ± 2.7 μM (corresponding to 15% ± 6.7%) (average $p = 0.03$). In the epinephrine bolus group, Hbo_2 started to increase ~50 seconds and peaked ~110s after each bolus. After 14 minutes of resuscitation, Hbo_2 increased by an average of 5.1 ± 1.1 μM (11.6% ± 2%) compared with untreated VF ($p = 0.007$). There were no significant changes in HHb during CPR and epinephrine/placebo administration in any of the intervention groups (average $p = 0.41$).

Cerebral Metabolism

The first 2 minutes of CPR increased Δ[Cyt-ox] in all three intervention groups by an average of 0.4 ± 0.5 μM compared with "during VF" ($p = 0.03$) (Table 2; and Supplemental Fig. 1 *d*, Supplemental Digital Content 2, http://links.lww.com/CCM/E294).

Δ[Cyt-ox] did not significantly change in the epinephrine infusion and placebo groups during resuscitation compared with the untreated VF and CPR only epochs (average $p = 0.22$). In the epinephrine bolus group, each epinephrine bolus transiently increased Δ[Cyt-ox] shortly after injection by an average of 1.3 ± 0.3 μM compared with "during VF" (average $p = 0.02$), which corresponds to a 49.6% ± 18.2% increase with respect to the nadir of Δ[Cyt-ox] during untreated VF. The bolus-induced changes in Δ[Cyt-ox] are considered physiologically significant (> 1 μM) (17). In the epinephrine bolus group, Cyt-ox started to increase ~60 seconds and peaked ~115s after each bolus.

By the end of the resuscitation, Δ[Cyt-ox] increased by 1 ± 0.4 μM (37.5% ± 12.1%) in the epinephrine bolus group ($p = 0.03$) and by 0.3 ± 0.3 μM (9.5% ± 5.4%) in the placebo group ($p = 0.10$) when compared with during the untreated VF period, respectively. In the epinephrine infusion group, there was a significant decrease in Δ[Cyt-ox] by 0.3 ± 0.1 μM (15.7% ± 171.6%) compared with during untreated VF ($p = 0.04$).

Analysis of the AUC

Figure 2 shows the measured AUCs of Hbo_2, tSo_2, Δ[Cyt-ox], and mAoP over 4 minute epochs in each intervention group. The AUCs of Δ[Cyt-ox], tSo_2, and mAoP were significantly larger in epinephrine bolus group compared with the placebo and infusion groups ($p = 0.013$, $p = 0.007$ and $p = 0.02$ respectively). In the epinephrine infusion group, the AUC for HHb was significantly larger compared with the epinephrine bolus and placebo groups ($p = 0.02$).

There were no significant differences in the AUCs of Hbo_2, Δ[Cyt-ox], and mAoP between the first and subsequent epinephrine boluses. The AUCs of Hbo_2, Δ[Cyt-ox], and mAoP after the third epinephrine bolus was an average of 24.6% ± 3.8% smaller compared with the first two boluses although this was not statistically significant ($p = 0.09$). The AUC of HHb after the third epinephrine bolus was significantly larger than that of the first two boluses ($p = 0.048$).

DISCUSSION

Epinephrine administered as IV boluses increased cerebral oxygenation (Hbo_2) and oxygen metabolism (Δ[Cyt-ox]) during cardiac arrest resuscitation. In contrast, a continuous infusion of epinephrine did not have any significant effect on cerebral oxygenation or metabolism over placebo.

Our study results are consistent with previous studies that used other methods of measuring cerebral oxygenation, such as microcirculation phospherence (28), optical sensors (29, 30), or cerebral arteriovenous oxygen content difference (31). However, Ristagno et al (29) suggested that epinephrine injection during VF worsens cerebral ischemia due to a reduction in cerebral blood flow, whereas other studies suggested that epinephrine increases myocardial and brain perfusion by enhancing peripheral vascular resistance (selective vasoconstriction) and cerebral oxygen uptake (7, 32, 33). These mixed results may be due to the different doses and timing of epinephrine (7, 32, 33). Our study also had a relatively longer phase of untreated VF (6 min), which may have resulted in more severe cardiovascular collapse thus reducing brain perfusion that was improved with epinephrine boluses but not by a continuous epinephrine. Clinical studies have shown that early administration of epinephrine (< 10 min after onset of cardiac arrest) may improve clinical outcomes including neurologically intact survival (34–36).

The effects of epinephrine on vascular smooth muscles are through α-adrenergic receptors causing vasoconstriction and β-adrenergic receptors resulting in vasodilation (37). Our study results highlight important pharmacodynamics of epinephrine; when epinephrine was administered as an infusion, a lower concentration of epinephrine may have preferentially stimulated β receptors more than α receptors leading to decreased vasoconstriction (38). In contrast, when epinephrine was given as a large bolus, the α effects may have predominated leading to increased vasoconstriction and cerebral perfusion (4).

Our results also suggest that epinephrine increases total hemoglobin, oxygen delivery (Hbo_2), oxygen consumption, and metabolism (Δ[Cyt-ox]). It may be possible that epinephrine directly stimulates cerebral metabolism (39). Previous studies have shown that prolonged (> 5 min) untreated VF leads to

TABLE 2. The Average Near-Infrared Spectroscopy–Measured Cerebral Hemodynamics and Metabolism in Each Study Group That Received Placebo and/or Epinephrine as IV Continuous Infusion or Boluses

Groups	Near-Infrared Spectroscopy–Measured Variables, Mean ± SD	Before VF (Baseline)	During VF (Untreated)	During Cardiopulmonary Resuscitation	After Epinephrine Infusion	After First Epinephrine/Placebo Bolus	After Second Epinephrine/Placebo Bolus	After Third Epinephrine/Placebo Bolus
Placebo infusion + placebo bolus	Hbo_2 (μM)	50.73 ± 1.51	42.33 ± 9.51	42.89 ± 9.92	Not applicable	43.26 ± 10.99	43.7 ± 11.81	44.03 ± 12.36
	p				0.77			
	HHb (μM)	20.81 ± 1.17	27.43 ± 4.90	26.92 ± 4.78	Not applicable	26.93 ± 4.98	27.01 ± 5.34	27.27 ± 5.37
	p				0.66			
	Total hemoglobin (μM)	71.57 ± 0.34	69.9 ± 4.88	71.2 ± 5.67	Not applicable	71.41 ± 6.02	71.52 ± 6.54	71.12 ± 6.28
	p				0.22			
	tSo_2 (%)	70.7 ± 1.99	59.93 ± 9.74	60.77 ± 10.3	Not applicable	60.75 ± 11.13	61.18 ± 11.6	60.63 ± 11.56
	p				0.72			
	Δ[Cyt-ox] (μM)	−0.12 ± 0.30	−2.83 ± 0.92	−2.69 ± 0.82	Not applicable	−2.72 ± 0.78	−2.51 ± 0.55	−2.46 ± 0.53
	p				0.37			
Epinephrine infusion + placebo bolus	Hbo_2 (μM)	50.72 ± 2.64	38.66 ± 2.73	40.98 ± 5.14	42.85 ± 5.01	41.11 ± 5.25	43.81 ± 4.78	43.90 ± 4.43
	p				0.13			
	HHb (μM)	19.92 ± 0.20	27.98 ± 2.16	28.17 ± 0.80	28.65 ± 1.38	28.22 ± 1.58	28.68 ± 1.54	29.10 ± 1.67
	p				0.4			
	Total hemoglobin (μM)	70.71 ± 2.79	66.64 ± 1.03	69.33 ± 4.56	71.33 ± 4.44	71.65 ± 3.77	72.3 ± 3.69	73 ± 2.93
	p				0.12			
	tSo_2 (%)	71.9 ± 0.6	58.1 ± 3.5	59.5 ± 3.8	59.9 ± 4.1	59.5 ± 4.00	60 ± 4.3	60 ± 4.01
	p				0.27			
	Δ[Cyt-ox] (μM)	−0.08 ± 0.07	−2.33 ± 0.62	−2.17 ± 0.50	−2.31 ± 0.65	−2.30 ± 0.72	−2.35 ± 0.70	−2.48 ± 0.60
	p				0.08			
Placebo infusion + epinephrine bolus	Hbo_2 (μM)	51.31 ± 1.86	43.48 ± 1.96	44.90 ± 0.81	Not applicable	48.87 ± 2.18	50.57 ± 2.39	50.24 ± 2.69
	p				0.034[a]			
	HHb (μ M)	20.14 ± 0.56	29.45 ± 0.64	28.54 ± 0.69	Not applicable	26.25 ± 1.34	26.60 ± 2.41	27.95 ± 2.56
	p				0.16			
	Total hemoglobin (μM)	71.47 ± 2.40	73.12 ± 1.82	73.31 ± 1.18	Not applicable	76.86 ± 3.95	78.28 ± 4.61	78.52 ± 4.66
	p				0.042[b]			
	tSo_2 (%)	71.9 ± 0.10	59.7 ± 1.72	61.2 ± 0.70	Not applicable	63.8 ± 1.33	65.5 ± 2.64	64 ± 1.31
	p				0.18			
	Δ[Cyt-ox] (μM)	0.35 ± 0.16	−2.80 ± 1.22	−1.99 ± 1.62	Not applicable	−1.54 ± 1.23	−1.46 ± 0.94	−1.64 ± 0.81
	p				0.008[c]			

Hbo_2 = oxygenated hemoglobin, HHb = deoxygenated hemoglobin, tSo_2 = tissue oxygen saturation.

[a]Post hoc: "All three epinephrine boluses" significantly increased Hbo_2 compared with "during cardiopulmonary resuscitation" and "during VF" ($p < 0.05$).

[b]Post hoc: After the "third epinephrine bolus" the total hemoglobin was significantly greater than "during VF" and "before VF" ($p < 0.05$).

[c]Post hoc: All epinephrine boluses significantly increased cytochrome c oxidase compared with "during VF" ($p < 0.05$).

The Δ[Cyt-ox] is the difference between the reduced and oxidized states (redox changes) of the cytochrome C oxidase. The *p* values were calculated using the repeated measures one-way analysis of variance.

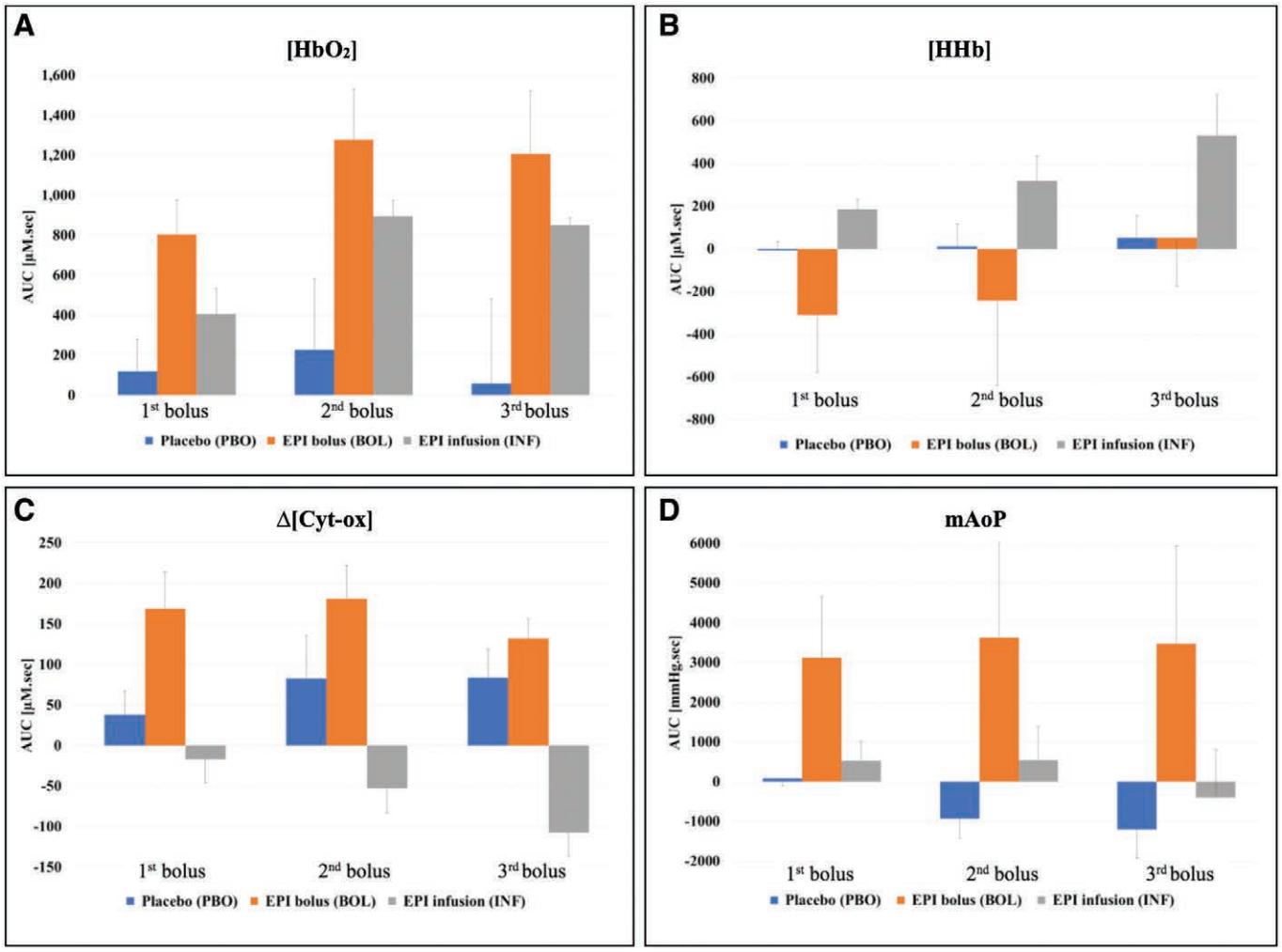

Figure 2. The area under the curves (AUC) calculated over 4-min intervals following administration of each epinephrine (EPI) or placebo (PBO) boluses (i.e., Epoch 1 time 8–12 min, Epoch 2 time 12–16 min, Epoch 3 16–20 min for oxygenated hemoglobin [Hbo_2] (**A**), deoxygenated hemoglobin [HHb] (**B**), Δ[Cyt-ox] (**C**), and mean aortic pressure [mAoP]) (**D**). In AUC calculations, the moment before administration of the first bolus was considered as the baseline (reference). The Δ[Cyt-ox] is the difference between the reduced and oxidized states (redox changes) of the cytochrome C oxidase. BOL = bolus, INF = infusion.

blood-brain barrier (BBB) disruption, and epinephrine further increases the BBB permeability and directly stimulates neuronal metabolism, potentially leading to a mismatch between cerebral oxygenation and metabolism as observed in our study (39–42). There was a net increase in cerebral oxygenation with epinephrine boluses, and the increase in Hbo_2 was at least partially offset by the increase in oxygen consumption. Interestingly, the effects of epinephrine were transient with peaks in aortic pressure and cerebral total hemoglobin, Hbo_2, and Δ[Cyt-ox] (Figs. 1*A* and 2). These short-lived effects of epinephrine boluses on cerebral perfusion are consistent with a previously published study (43) suggesting that the effects of epinephrine diminish with successive boluses, which may represent tachyphylaxis, a known phenomenon with vasopressors (44).

We observed that carotid flow did not correspond with cerebral oxygenation and metabolism as measured by hNIRS suggesting that that total brain blood flow does not necessarily represent flow to the cerebral cortex, which has also been observed in previous animal and human studies (28–31, 43, 45–48). Voelckel et al (49) have also reported that no significant improvement in cerebral blood flow (after prolonged VF) in response to epinephrine administration alone. Deakin et al (50) found that a 1 mg epinephrine bolus during in-hospital cardiac arrest resuscitation of patients showed a small but clinically insignificant increase (1.4%) in regional cerebral oxygenation using a commercially available multispectral NIRS systems. This may be due to the limitations of multispectral monitors using a fixed arterial/venous ratio to calculate cerebral oxygenation when there may be significant biologic variation during hypoxia (51). Similarly, we did not observe a significant increase in tSo_2 after each epinephrine bolus in our experimental model.

There were several limitations in this study. This was a substudy of a larger multilaboratory study, and our study was limited due to a small sample size. Due to a small sample size, we were not able to determine associations between measured cerebral variables and outcomes (e.g., ROSC). There may also

have been other differences in measured cerebral variables between the three intervention groups that were not detected in our study. Furthermore, our current hNIRS technology has its limitations. It uses a broad bandwidth of near-infrared light and requires a large high-powered light source, a highly sensitive spectrometer, and a connection between the optical sensor and the detector by the optical fiber bundle (18). The optical fiber bundle is significantly larger than those used by the commercial NIRS devices, which use only a few wavelengths produced by laser optodes. Although its design serves its use in controlled settings (e.g., animal laboratory or operating room), its use in cardiac arrest resuscitations in patients, particularly in the out-of-hospital setting, is challenging. The current hNIRS technology to detect Cyt-ox requires further development to adapt to real-world resuscitations.

This is the first study to describe Cyt-ox redox changes due to epinephrine during cardiac arrest resuscitation. The Cyt-ox redox changes may be a better integrated measure of oxygen availability and extraction by cells over time. Our study suggests that Δ[Cyt-ox] is a valuable marker to measure during cardiac arrest. Further study of Δ[Cyt-ox] measured by hNIRS is required to evaluate outcomes after cardiac arrest, particularly the use of epinephrine during resuscitation.

CONCLUSIONS

Epinephrine administration by bolus showed transient increases in cerebral oxygenation and metabolism, whereas a continuous epinephrine infusion did not, compared with placebo. Future studies are needed to evaluate and optimize the use of epinephrine in cardiac arrest resuscitation, particularly the dose, timing, and mode of administration.

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