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## Clinical paper

### Effects of epinephrine on cerebral oxygenation during cardiopulmonary resuscitation: A prospective cohort study<sup>☆</sup>

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#### ABSTRACT

**Background:** Epinephrine has been presumed to improve cerebral oxygen delivery during cardiopulmonary resuscitation (CPR), but animal and registry studies suggest that epinephrine-induced capillary vasoconstriction may decrease cerebral capillary blood flow and worsen neurological outcome. The effect of epinephrine on cerebral oxygenation ( $rSO_2$ ) during CPR has not been documented in the clinical setting. **Methods:**  $rSO_2$  was measured continuously using cerebral oximetry in patients with in-hospital cardiac arrest. During CPR, time event markers recorded the administration of 1 mg epinephrine.  $rSO_2$  values were analysed for a period beginning 5 min before and ending 5 min after the first epinephrine administration. **Results:** A total of 56 epinephrine doses were analysed in 36 patients during CPR. The average  $rSO_2$  value in the 5-min following epinephrine administration was 1.40% higher (95% CI = 0.41–2.40%;  $P = 0.0059$ ) than in the 5-min period before epinephrine administration. However, there was no difference in the overall rate of change of  $rSO_2$  when comparing the 5-min period before, with the 5-min period immediately after a single bolus dose of epinephrine (0.88%/min vs 1.07%/min respectively;  $P = 0.583$ ). There was also no difference in the changes in  $rSO_2$  at individual 1, 2, 3, or 4-min time windows before and after a bolus dose of epinephrine ( $P = 0.5827, 0.2371, 0.2082$ , and  $0.6707$  respectively). **Conclusions:** A bolus of 1 mg epinephrine IV during CPR produced a small but clinically insignificant increase in  $rSO_2$  in the five minutes after administration. This is the first clinical data to demonstrate the effects of epinephrine on cerebral  $rSO_2$  during CPR.

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## Introduction

The aim of cardiopulmonary resuscitation (CPR) is to deliver sufficient oxygen to vital organs, in particular the heart and the brain, in order to maintain tissue viability until return of spontaneous circulation (ROSC). Of these two organs, cerebral function appears to be the more vulnerable to hypoxemia, with more patients initially resuscitated from cardiac arrest (CA) subsequently succumbing to

irreversible cerebral ischemia rather than the effects of myocardial ischemia.<sup>1,2</sup> Although the brain weighs 2% of total body mass, in a healthy state, it accounts for 15% of total cardiac output and 20% of overall oxygen consumption. This disproportionate need continues during resuscitation.

In healthy states, cerebral blood flow is controlled by cerebral pressure autoregulation, neurogenic regulation, and flow-metabolism coupling (metabolic) autoregulation to ensure that cerebral perfusion pressure (CPP) remains constant in the range of 60–160 mmHg. At the lower limit of autoregulation, cerebral vasodilation is maximal, but as mean arterial pressure (MAP) decreases below this threshold, capillaries collapse and cerebral blood flow (CBF) decreases passively.<sup>3–5</sup> Following cardiac arrest, transient sympathetically-mediated vasoconstriction gives way to a fall in vascular resistance as the brainstem becomes more ischaemic and sympathetic outflow is reduced.<sup>6</sup> Locally mediated mechanisms involving adenosine<sup>7</sup> and nitric oxide<sup>5</sup> are thought to

**Abbreviations:** CA, cardiac arrest; CBF, cerebral blood flow; CPP, cerebral perfusion pressure; CPR, cardiopulmonary resuscitation;  $DO_2$ , oxygen delivery; IHCA, in-hospital cardiac arrest; IV, intravenous; OHCA, out-of-hospital cardiac arrest;  $PaO_2$ , arterial oxygen saturation; MAP, mean arterial pressure; ROSC, return of spontaneous circulation;  $rSO_2$ , cerebral oxygen saturation;  $VO_2$ , oxygen consumption.

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further contribute to a decrease in vascular tone and this progressive vasodilation, coupled with a failure in autoregulation, results in a rapid decline in microvascular blood flow that ceases after 3 min of cardiac arrest.<sup>8</sup>

Administration of epinephrine during cardiac arrest aims to increase CPP through alpha-adrenergic mediated vasoconstriction to increase both systolic and diastolic blood pressure, optimising the limited intravascular pressure generated through external cardiac massage. However, although epinephrine increases aortic blood pressure during CPR,<sup>9,10</sup> excessive vasoconstriction of vascular beds may paradoxically limit cerebral blood flow and subsequent oxygen delivery. In animal studies of cardiac arrest, epinephrine decreases cerebral capillary blood flow<sup>8,11,12</sup> and decreases cerebral cortical oxygen tension.<sup>12</sup> Subsequently, some clinical studies have raised concerns that epinephrine may fail to improve overall survival and specifically, neurologically-intact survival from cardiac arrest.<sup>13,14</sup>

In recent years, the importance of optimizing brain resuscitation during cardiac arrest has led to the identification of cerebral oximetry as a potential marker of effective brain resuscitation. Early studies by this group<sup>15,16</sup> and others,<sup>17,18</sup> have demonstrated the utility of cerebral oxygen saturation, a measure of the balance between cerebral oxygen delivery and uptake, to act as a promising marker of effective resuscitation during CPR. In particular, improvements in outcome appear to be correlated with increasing cerebral oxygenation during resuscitation attempts.<sup>18–21</sup> With the variable effects of epinephrine on cerebral oxygen delivery during resuscitation and concerns about the clinical efficacy of epinephrine administration, there is a need to better understand the pathophysiological effects of epinephrine during CPR, as it is currently recommended as the principle drug during advanced life support. This retrospective cohort study aimed to examine changes in cerebral oximetry values to understand whether epinephrine improves cerebral tissue oxygenation during in-hospital CPR.

## Methods

### *Study population and enrollment*

This study was conducted using a convenience sample of patients recruited during working hours (mostly 0800–1700 weekdays) as part of a prospective study using cerebral oximetry to examine the association between cerebral oxygenation and cardiac arrest outcomes.<sup>22</sup> Participants were enrolled between 08/2011 and 09/2014. Inclusion criteria were witnessed in-hospital cardiac arrest (IHCA) requiring a resuscitation attempt, age  $\geq 18$  years, and the administration of epinephrine during CA. Exclusion criteria were unwitnessed IHCA, IHCA where resuscitation was not attempted, patients receiving vasopressin (or any vasopressor other than epinephrine) at any time during the resuscitation attempt and patients whose initial arrest was an out-of-hospital cardiac arrest (OHCA).

The research protocol was approved by the UK multicenter national research ethics committee (MREC reference 11/EE/0003) and the Stony Brook Hospital institutional review board prior to the start of patient recruitment and data collection. Patients were enrolled with waiver of consent authorization from the ethics committee. Retrospective written informed consent was obtained from all CA survivors.

### *Study definitions and outcome measures*

According to Utstein definitions,<sup>23</sup> cardiac arrest was defined as the cessation of cardiac mechanical activity as confirmed by the absence of signs of circulation. Return of spontaneous circula-

tion (ROSC) was defined as the return of any palpable pulse in the absence of ongoing chest compressions.

### *Patient characteristics*

We recorded or calculated the following: patient gender, age, sex, ethnicity and the chronic disease burden using the Charlson comorbidity index (a scale from 0 to 33, with higher scores indicating greater burden of coexisting conditions).<sup>24</sup> We also collected data related to potential confounders and effect modifiers of cerebral oxygen saturation: hemoglobin and PaO<sub>2</sub> as well as CPR-related factors: initial cardiac rhythm, CPR duration, and hospital site.

### *The use of cerebral oximetry*

All patients received CPR in accordance with the American Heart Association<sup>25</sup> or European Resuscitation Council<sup>26</sup> advanced life support guidelines 2010. These guidelines recommend administering epinephrine every second CPR cycle, which in practice is every 3–5 min. The plasma half-life of epinephrine is about 2–3 min,<sup>27</sup> so in order to evaluate the impact of a specific 1 mg standard dose of epinephrine administration (epinephrine event) on cerebral oxygenation, we excluded any epinephrine event that was preceded by another epinephrine event within a five-minute window in order to minimise (although not completely exclude) the haemodynamic effects of a prior epinephrine dose. As with other studies, the periodicity of epinephrine administration was sometimes greater than 5 min, providing a 5-min window within which epinephrine had not been administered prior to a subsequent dose. Thus, although a patient may have received multiple doses of epinephrine, only doses those that met this time criterion were used in the analysis.

Dedicated research staff at each participating site were provided with a pager that was linked in with the hospital-wide cardiac arrest paging system. Research staff attended all cardiac arrest events announced through the hospital pager and established cerebral oximetry monitoring (Equanox 7600, Nonin Medical, Plymouth, MN, USA). An adhesive sensor with two near-infrared light sources and detectors was placed on the forehead of each patient for cerebral oximetry monitoring. A single sensor on either side of the forehead was considered sufficient to measure rSO<sub>2</sub>, since cerebral perfusion during cardiac arrest is predominantly dependent on the quality of the circulation.<sup>9</sup> Cerebral oximeters were calibrated according to the manufacturer's instructions and recorded values every six seconds.

Staff marked the time of each dose of epinephrine administered, using a dedicated event-marking button on the cerebral oximeter. In order to minimize data collection errors, staff were trained and certified in study procedures for collecting cerebral oximetry data, the completion of study case report forms and data entry into REDCap, [<http://project-redcap.org>] a web-based data entry system, prior to study commencement. Study protocols were reinforced during monthly teleconference meetings conducted for the length of data collection. All rSO<sub>2</sub> data were recorded and automatically stored on the equipment without the need for further input from research staff, thus minimizing operator bias errors.

Artifact and noise were identified by values that were more than three standard deviations away from the mean value. Missing or incomplete data, were defined as any missing or incomplete values during each 4-s sampling period. As achieving ROSC (cardiac contractility), is associated with a rapid increase in rSO<sub>2</sub> independent of epinephrine administration, we re-analysed the rSO<sub>2</sub> data after excluding any epinephrine event that was associated with ROSC within the five-minute study period after epinephrine had been administered.

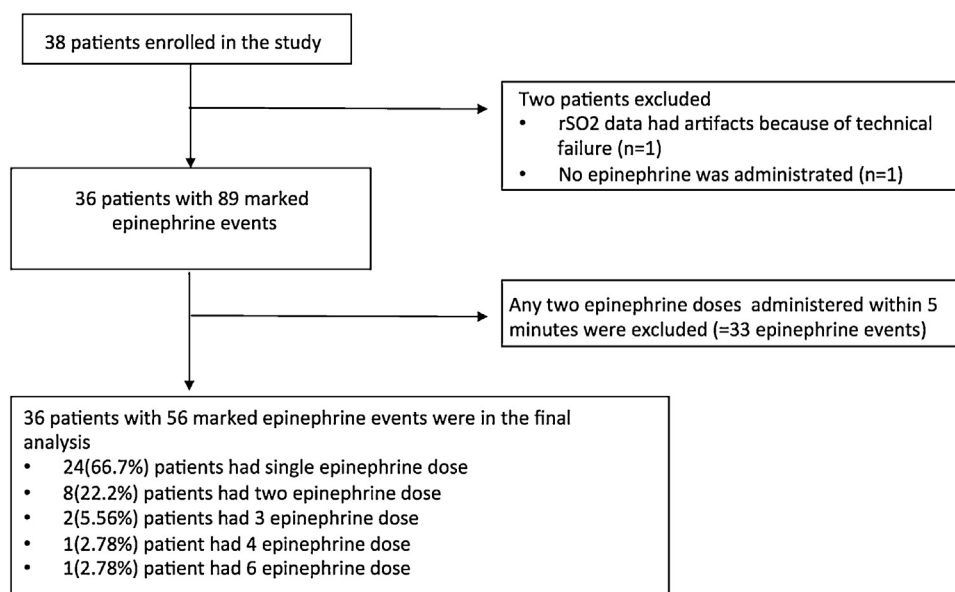


Fig. 1. Flow chart showing patients entered into the study and subsequent data available for analysis.

Data were downloaded to a designated study computer and transmitted to the Data Coordinating Center at Stony Brook University using REDCap. All rSO<sub>2</sub> data were managed at Stony Brook University by a data coordinator. Two dedicated statisticians analysed all rSO<sub>2</sub> data.

#### Statistical analysis

Demographic and clinical characteristics are presented using parametric and non-parametric evaluation as appropriate.

#### Absolute change in rSO<sub>2</sub> before and after epinephrine administration

Patients' average rSO<sub>2</sub> profiles over time were illustrated through Kernel smoothed lines.<sup>28</sup> Continuous rSO<sub>2</sub> data was arranged so that time=0 was the time that the first dose of epinephrine was administered. Time was treated as a continuous variable in the linear mixed models. An autoregressive structure,<sup>28</sup> which implies correlations decline exponentially with time unit, was used to describe the within-subject dependence structure-correlation of the epinephrine events' rSO<sub>2</sub> during different time periods. Normality assumption for linear mixed model was confirmed.

#### Change in rSO<sub>2</sub> slope before and after epinephrine administration

A linear mixed model was used to test if epinephrine affected the linear changing pattern in rSO<sub>2</sub> over time, i.e. the slope before, compared with after, the initial epinephrine administration.

#### Changes in rSO<sub>2</sub> at 1 min intervals before and after epinephrine administration

Additional linear mixed effect models were fitted to investigate the timing of changes in the rSO<sub>2</sub> in relation to each 1, 2, 3, or 4 min time windows following the initial epinephrine injection.

Statistical significance was set at  $P \leq 0.05$  and analyses were performed using SAS 9.3 (SAS Institute, Inc., Cary, NC).

## Results

### Patients' demographic and clinical characteristics

Thirty-six patients who had received a total of 89 epinephrine doses were initially identified. Thirty-three of the 89 epinephrine events were preceded by another epinephrine event within a five-minute window, and were thus excluded a priori from the analysis, leaving a total of 36 patients receiving a total of 56 epinephrine doses included in the study (Fig. 1). Overall, eleven of 36 (30.6%) patients achieved ROSC; five within the five minute period following epinephrine administration. The study flowchart is shown in Fig. 1. Summary statistics of patients' demographic and clinical characteristics are shown in Table 1.

#### Absolute change in rSO<sub>2</sub> before and after epinephrine administration

Among the 56 epinephrine events, we examined the rSO<sub>2</sub> values during a five-minute interval before injecting epinephrine, followed by a five-minute period after injecting epinephrine, during which time, no further epinephrine was administered (Fig. 2).

The mean rSO<sub>2</sub> value increased by 1.40% in the five minutes after epinephrine administration compared with the five minutes before (95% CI = 0.41–2.40%;  $P = 0.0059$ ).

#### Change in rSO<sub>2</sub> slope before and after epinephrine administration

There was a 0.88%/min increase in rSO<sub>2</sub> prior to epinephrine administration, compared with 1.07%/min after epinephrine administration. This was not statistically different ( $P = 0.583$ ). The regression equation before and after epinephrine ( $N = 56$ ) was as follows:

$$rSO_2 = \begin{cases} 38.8491 + 0.8812 * \text{time} & \text{before adrenaline injections} \\ 38.8491 + 1.07401 * \text{time} & \text{after adrenaline injections} \end{cases}$$

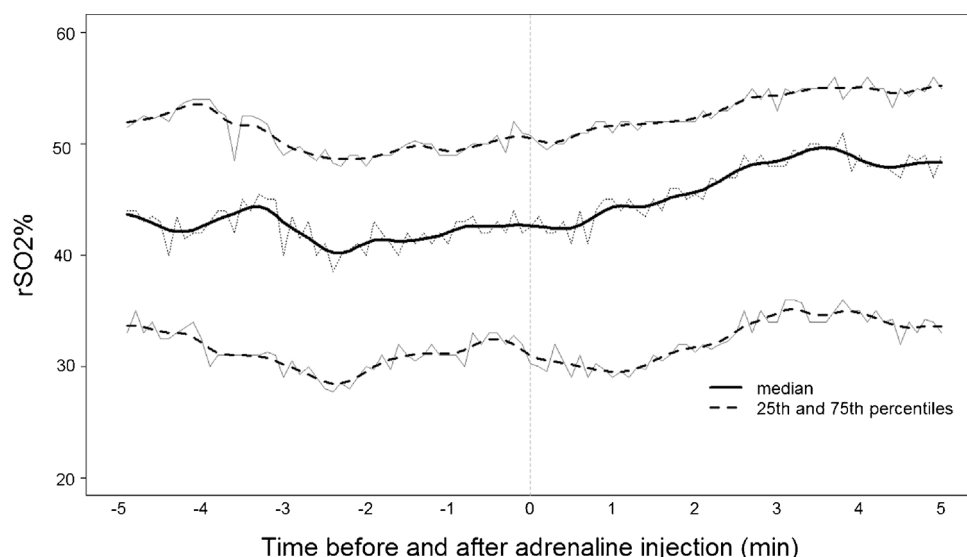
**Table 1**  
Patients' demographic and clinical characteristics (N = 36). (CA = cardiac arrest; ROSC = return of spontaneous circulation; ASYS = asystole; PEA = pulseless electrical activity; VF = ventricular fibrillation; VT = ventricular tachycardia; ACLS = advanced cardiac life support.) Continuous variables are shown as median (IQR Q1, Q3) and categorical variables are shown as count.

Variable		
Age (years)		77.0 (77.5,81.75)
Sex	Male	21
	Female	15
Ethnicity	Caucasian	34
	Hispanic	1
	Asian	1
Initial rhythm	ASYS/PEA	34
	VF/VT	2
Hemoglobin (g/dL) within 24 h of cardiac arrest <sup>a</sup>		11.9 (10.3,12.9)
Age adjusted Charlson Co-Morbidity Index <sup>c</sup>		6 (5,7)
Duration of ACLS (min)		21 (11,29)
Duration of oximetry monitoring during cardiac arrest (min) <sup>c</sup>		15.5 (8.3,22.8)
Time to placement of oximeter sensor (min) <sup>c</sup>		5 (3,7)
PaO <sub>2</sub> mmHg <sup>b</sup>		
Overall (N = 36)	104.7 ± 149.2	P = 0.049
ROSC (N = 11)	180.0 ± 163.7	
No ROSC (N = 25)	79.6 ± 139.9	

<sup>a</sup> Hemoglobin data prior to cardiac arrest were available for 27 patients.

<sup>b</sup> Arterial blood gas analysis from the period during the resuscitation attempt.

<sup>c</sup> Data available for 34 patients.



**Fig. 2.** rSO<sub>2</sub>(%) values before and after administration of epinephrine (N = 51 epinephrine events). The time (0) of the first epinephrine injection is shown by the vertical line. The solid line represents median values, while the dotted lines represent 75th and 25th percentiles of corresponding values. Thin lines connect the raw percentiles while bold lines represent the corresponding lines using kernel smoothing.

#### Changes in rSO<sub>2</sub> at 1 min intervals before and after epinephrine administration

There was no significant change in value of rSO<sub>2</sub> after epinephrine was administered at each of the 1, 2, 3, or 4-min time windows, following the initial epinephrine injection (P = 0.583, 0.237, 0.208, and 0.671, respectively).

#### Sensitivity analysis excluding those with ROSC

Although, 18 of the 56 (31.6%) epinephrine events were from the 11 patients who eventually achieved ROSC, ROSC was detected

within the five-minute interval after epinephrine had been administered in just 5 of the 56 events. As ROSC may independently increase rSO<sub>2</sub> values, we repeated the analysis after excluding the rSO<sub>2</sub> data from these five epinephrine events (Fig. 2). In this analysis, carried out among 51 epinephrine events, the mean rSO<sub>2</sub> increase following epinephrine administration was 1.35% (95% CI = 0.27–2.44%) higher than the mean rSO<sub>2</sub> in the five-minute window prior to epinephrine administration (P = 0.0148). There was no change in the rate of rSO<sub>2</sub> rise before and after epinephrine administration (0.92 vs. 1.09 respectively, P = 0.645). The regres-



sion equation before and after epinephrine (N=51) was as follows:

$$rSO_2 = \begin{cases} 37.8904 + 0.9175 * \text{time} & \text{before adrenaline injections} \\ 37.8904 + 1.089 * \text{time} & \text{after adrenaline injections} \end{cases}$$

## Discussion

Cerebral oximetry uses near-infrared spectroscopy (NIRS) to estimate the oxygenation of cerebral cortical tissue; an area of the brain that is particularly susceptible to changes in the demand and supply of oxygen, and which has a limited oxygen reserve. Although previous studies using this modality have demonstrated that cerebral oxygen saturation correlates well with the quality of CPR<sup>16</sup> and return of spontaneous circulation,<sup>19,29</sup> to the best of our knowledge, this is the first published clinical study to demonstrate the effects of intravenous epinephrine boluses administered during CPR on cerebral oxygen saturation. Epinephrine boluses failed to show any clinically significant increase in  $rSO_2$  in the five minutes following administration of each bolus. Even after removing  $rSO_2$  data from patients who achieved ROSC during this time window, the results remained unchanged.

In animal studies, peak plasma concentrations of adrenaline occur at about 90 s after a peripheral injection and the maximum effect on coronary perfusion pressure is achieved around the same time (70 s).<sup>9</sup> We therefore analysed a five-minute window during which only a single dose of epinephrine had been injected in an attempt to isolate the effect of each single epinephrine dose, rather than multiple, accumulating doses. Epinephrine has been thought to improve cerebral blood flow and therefore cerebral oxygen delivery, by vasoconstriction of other vascular beds and preferentially increasing cerebral and myocardial perfusion pressures.<sup>9,30</sup> However, these data suggest that cerebral cortical oxygenation does not change after a 1 mg dose of epinephrine. Failure to deliver more oxygen to cerebral tissues despite an increase cerebral blood flow may be caused by shunting of blood away from vasoconstricted capillary beds whilst overall blood flow through larger vessels is promoted; a similar effect to the epinephrine-induced worsening of ventilation-perfusion mismatch that occurs during CPR.<sup>31</sup>

The measured cerebral oxygen saturation reflects a balance between oxygen delivery and oxygen consumption; an increase indicating oxygen delivery exceeding consumption and vice versa. One possible explanation of an unchanged value is that oxygen consumption has increased in parallel with oxygen delivery, as epinephrine increases tissue oxygen consumption by increasing the basal metabolic rate whilst also facilitating oxygen delivery.<sup>32</sup> Without directly measuring cerebral oxygen extraction, the explanation of this observed failure of epinephrine to increase cerebral oxygen saturation is not certain, but if it is because of a parallel increase in consumption and delivery, then it is clearly a finely balanced effect. In animal studies, epinephrine significantly decreased microcirculatory blood flow and associated cerebral cortical oxygen tension despite increases in arterial pressure<sup>12</sup>; this suggests that the failure to increase cerebral tissue oxygenation in our study is more likely related to limited capillary blood flow rather than increased oxygen extraction.

A further explanation may be related to the measurements that are collated to provide a single cerebral oxygen saturation value. Oxygenated and deoxygenated hemoglobin, together with dissolved tissue oxygen, are thought to comprise all sources of oxygen in the brain.<sup>33</sup> Each absorbs different light wavelengths and the magnitude of absorption at each given wavelength must be calculated, together with weighted algorithm values for arterial, venous, and capillary oxygen in order to acquire cerebral oxygenation values. The Nonin EQUANOX Model 7600 Regional Oximetry System

assumes cerebral blood to be composed of 70% venous and 30% arterial blood. However, calculated cerebral oximetry values do not take into account changes in the relative proportions of arterial or venous blood in a capillary bed and changes in this ratio, such as may occur with venous congestion during cardiac arrest, are likely to result in a lower calculated cerebral oximetry value, perhaps offsetting any increase resulting from improved oxygenated blood delivery.

Not only therefore is cerebral oxygenation a balance between oxygen delivery and oxygen extraction, but it is also a more complex measure of changing overall oxygen content. The precise explanation for the failure of epinephrine to increase cerebral cortical tissue oxygenation is unclear, but irrespective of the exact mechanism, it would appear that epinephrine does not result in a significant surplus of tissue oxygen content.

A further possibility may be that any harmful effects of adrenaline on neurologic outcome may be more a reflection of the ability of epinephrine to achieve ROSC in patients with non-viable neurological function, rather than through changes in  $rSO_2$ . Epinephrine has been shown to be associated with ROSC (in a dose dependent fashion as suggested by high dose adrenaline studies) due to its effects on cardiac/vascular tissue, despite many of these victims having irreversible hypoxia-induced neurological injury, especially when resuscitation is initiated after a prolonged downtime. Limiting data analysis to witnessed cardiac arrest patients in future studies may enable us to address this possible explanation.

Several recent studies have cast doubt on the ability of epinephrine to improve neurologically-intact survival from cardiac arrest. Although epinephrine may improve rates of short-term myocardial resuscitation, particularly in patients with non-shockable rhythms, there is no evidence that it improves the rates of survival with good neurological outcome.<sup>13,34</sup> Indeed recent low-quality evidence suggests that epinephrine may worsen neurological outcome, particularly when given late in a resuscitation attempt.<sup>35–37</sup> These findings are consistent with a dose-dependent relationship between total epinephrine dose and impairment of  $DO_2$  and  $VO_2$  in the post-resuscitation period,<sup>38</sup> and recent animal studies that have documented a reduced cerebral capillary blood flow following epinephrine administration.<sup>11,12</sup>

Our study was limited by the fact that this was a convenience sample of patients suffering a cardiac arrest, which was a relatively small, non-consecutive population. The study was not blinded to clinicians who were aware that cerebral oximetry measurements were being made, although the clinicians did not have sight of the data during the resuscitation attempt. Reassuringly, the data from patients who did achieve ROSC showed increases in  $rSO_2$ , thus providing some positive control data that the equipment was capable of detecting change under these circumstances.<sup>22</sup> The 5-min epinephrine-free window that was required to provide baseline data prior to recording the effects of a further epinephrine dose was a window in which epinephrine levels from the preceding dose would have been declining. With a 2–3 min half-life,<sup>27</sup> epinephrine levels at 5 min would be approximately one quarter of that present following an epinephrine bolus. The effect that we were observing was therefore the effect of 1 mg epinephrine given on top of the already circulating epinephrine. Other than being able to record a baseline prior to the very first dose of epinephrine administration, it is difficult to see how this effect could be avoided. As discussed, autoregulation is lost following cardiac arrest and cerebral blood flow and therefore cerebral tissue oxygenation is likely to be related to the quality of chest compressions and ventilation. The quality of CPR was not monitored, either as a subjective measure (e.g. depth of compression) or as an objective measure (e.g. invasive blood pressure) and we have assumed that the quality of CPR was the same before and after epinephrine administration. Furthermore, the effects of epinephrine could be different according to both the

mechanism of the cardiac arrest and individual phenotypes<sup>39</sup> so the findings of this study may not be applicable to all cardiac arrests where epinephrine is administered.

The potential use of cerebral oximetry monitoring during cardiac arrest includes the optimization of the delivery of effective resuscitation and also as a prognostic indicator, both of ROSC and perhaps neurologically-intact survival. Whether this can be achieved with a rSO<sub>2</sub> at a specific endpoint such as at the beginning of resuscitation, or the actual changes to rSO<sub>2</sub> during resuscitation are a more sensitive indicator remain to be seen.

In summary, 1 mg intravenous epinephrine, administered during advanced life support resuscitation, was not associated with a clinically significant change in cerebral tissue oxygenation. This is consistent with several other clinical studies and animal studies. This observation raises questions regarding the ability of epinephrine to increase cerebral oxygen delivery during CPR.

## Conflict of interest statement

CDD, JY, RN, JZ, JPN, DGP and SP declare no conflicts. SJB was supported by the National Institute for Health Research (NIHR) Comprehensive Biomedical Research Centre based at Imperial College Healthcare NHS Trust and Imperial College London. GDP's institution receives support for his roles as a NIHR Senior Investigator and as Director of Research for the Intensive Care Foundation.

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## Data sharing

All authors either had access to all the anonymized data or had the opportunity to review all aggregate data during analysis.

## Ethics statement

This study have been approved by the appropriate ethics committee and has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

## References

- Laver S, Farrow C, Turner D, Nolan J. Mode of death after admission to an intensive care unit following cardiac arrest. *Intensive Care Med* 2004;30:2126–8.
- Lemiale V, Dumas F, Mongardon N, et al. Intensive care unit mortality after cardiac arrest: the relative contribution of shock and brain injury in a large cohort. *Intensive Care Med* 2013;39:1972–80.
- Itoh Y, Suzuki N. Control of brain capillary blood flow. *J Cereb Blood Flow Metab* 2012;32:1167–76.
- Lindner KH, Prengel AW, Pfenninger EG, et al. Vasopressin improves vital organ blood flow during closed-chest cardiopulmonary resuscitation in pigs. *Circulation* 1995;91:215–21.
- Krismer AC, Lindner KH, Wenzel V, Rainer B, Mueller G, Lingnau W. Inhibition of nitric oxide improves coronary perfusion pressure and return of spontaneous circulation in a porcine cardiopulmonary resuscitation model. *Crit Care Med* 2001;29:482–6.
- Paradis N, Halperin H, Kern K, Wenzel V, Chamberlain D, editors. *The Science and Practice of Resuscitation Medicine*. 2nd Edition Cambridge University Press; 2007.
- Phillis JW, Walter GA, Simpson RE. Brain adenosine and transmitter amino acid release from the ischemic rat cerebral cortex: effects of the adenosine deaminase inhibitor deoxycytosine. *J Neurochem* 1991;56:644–50.
- Ristagno G, Tang W, Sun S, Weil MH. Cerebral cortical microvascular flow during and following cardiopulmonary resuscitation after short duration of cardiac arrest. *Resuscitation* 2008;77:229–34.
- Pytte M, Kramer-Johansen J, Eilevstjonn J, et al. Haemodynamic effects of adrenaline (epinephrine) depend on chest compression quality during cardiopulmonary resuscitation in pigs. *Resuscitation* 2006;71:369–78.
- Ristagno G, Gullo A. Rationale of the use of vasopressor agents for cardiopulmonary resuscitation. Is epinephrine the correct first choice? Maybe not. *Am J Emerg Med* 2008;26:368–70, author reply 370.
- Ristagno G, Sun S, Tang W, Castillo C, Weil MH. Effects of epinephrine and vasopressin on cerebral microcirculatory flows during and after cardiopulmonary resuscitation. *Crit Care Med* 2007;35:2145–9.
- Ristagno G, Tang W, Huang L, et al. Epinephrine reduces cerebral perfusion during cardiopulmonary resuscitation. *Crit Care Med* 2009;37:1408–15.
- Atikawedparit P, Rattanasiri S, McEvoy M, Graham CA, Sittichanbuncha Y, Thakintian A. Effects of prehospital adrenaline administration on out-of-hospital cardiac arrest outcomes: a systematic review and meta-analysis. *Crit Care* 2014;18:463.
- Goto Y, Maeda T, Goto Y. Effects of prehospital epinephrine during out-of-hospital cardiac arrest with initial non-shockable rhythm: an observational cohort study. *Crit Care* 2013;17:R188.
- Ahn A, Yang J, Inigo-Santiago L, Parnia S. A feasibility study of cerebral oximetry monitoring during the post-resuscitation period in comatose patients following cardiac arrest. *Resuscitation* 2014;85:522–6.
- Parnia S, Nasir A, Ahn A, et al. A feasibility study of cerebral oximetry during in-hospital mechanical and manual cardiopulmonary resuscitation. *Crit Care Med* 2014;42:930–3.
- Bougle A, Daviaud F, Bougouin W, et al. Determinants and significance of cerebral oximetry after cardiac arrest: a prospective cohort study. *Resuscitation* 2016;99:1–6.
- Genbrugge C, Dens J, Meex I, et al. Regional cerebral oximetry during cardiopulmonary resuscitation: useful or useless? *J Emerg Med* 2016;50:198–207.
- Asim K, Gokhan E, Ozlem B, et al. Near infrared spectrophotometry (cerebral oximetry) in predicting the return of spontaneous circulation in out-of-hospital cardiac arrest. *Am J Emerg Med* 2014;32:14–7.
- Sanfilippo F, Serena G, Corredor C, et al. Cerebral oximetry and return of spontaneous circulation after cardiac arrest: a systematic review and meta-analysis. *Resuscitation* 2015;94:67–72.
- Singer AJ, Ahn A, Inigo-Santiago LA, Thode Jr HC, Henry MC, Parnia S. Cerebral oximetry levels during CPR are associated with return of spontaneous circulation following cardiac arrest: an observational study. *Emerg Med J* 2015;32:353–6.
- Parnia S, Santiago LI, Ahn A, et al. The utility of cerebral oximetry (rSO<sub>2</sub>%) during in-hospital cardiac arrest as a marker for the prediction of return of spontaneous circulation (ROSC). *Circulation* 2013;128:A104.
- Perkins GD, Jacobs IG, Nadkarni VM, et al. Cardiac arrest and cardiopulmonary resuscitation outcome reports: update of the Utstein resuscitation registry templates for out-of-hospital cardiac arrest. *Resuscitation* 2015;96:328–40.
- Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987;40:373–83.
- Neumar RW, Otto CW, Link MS, et al. Part 8: adult advanced cardiovascular life support: 2010 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation* 2010;122:S729–67.
- Deakin CD, Nolan JP, Soar J, et al. European resuscitation council guidelines for resuscitation 2010 section 4: adult advanced life support. *Resuscitation* 2010;81:1305–52.
- Adrenaline (Epinephrine) injection BP 1 in 1000.
- Wand MP, Jones CM. Kernel smoothing. vol. 60. CRC Press; 1995. p. 114–6.
- Singer AJ, Ahn A, Inigo-Santiago LA, Thode Jr HC, Henry MC, Parnia S. Cerebral oximetry levels during CPR are associated with return of spontaneous circulation following cardiac arrest: an observational study. *Emerg Med J* 2015;32:353–6.
- Michael JR, Guerci AD, Koehler RC, et al. Mechanisms by which epinephrine augments cerebral and myocardial perfusion during cardiopulmonary resuscitation in dogs. *Circulation* 1984;69:822–35.
- Tang W, Weil MH, Gazmuri RJ, Sun S, Duggal C, Bisera J. Pulmonary ventilation/perfusion defects induced by epinephrine during cardiopulmonary resuscitation. *Circulation* 1991;84:2101–7.
- Johansson J, Gedeberg R, Rubertsson S. Vasopressin versus continuous adrenaline during experimental cardiopulmonary resuscitation. *Resuscitation* 2004;62:61–9.
- Toet MC, Lemmers PM. Brain monitoring in neonates. *Early Hum Dev* 2009;85:77–84.
- Lin S, Callaway CW, Shah PS, et al. Adrenaline for out-of-hospital cardiac arrest resuscitation: a systematic review and meta-analysis of randomized controlled trials. *Resuscitation* 2014;85:732–40.
- Nakahara S, Tomio J, Nishida M, Morimura N, Ichikawa M, Sakamoto T. Association between timing of epinephrine administration and intact neurologic survival following out-of-hospital cardiac arrest in Japan: a population-based prospective observational study. *Acad Emerg Med* 2012;19:782–92.

36. Koscik C, Pinawin A, McGovern H, et al. Rapid epinephrine administration improves early outcomes in out-of-hospital cardiac arrest. *Resuscitation* 2013;84:915–20.
37. Donnino MW, Saliccioli JD, Howell MD, et al. Time to administration of epinephrine and outcome after in-hospital cardiac arrest with non-shockable rhythms: retrospective analysis of large in-hospital data registry. *BMJ* 2014;348:g3028.
38. Rivers EP, Wortsman J, Rady MY, Blake HC, McGeorge FT, Buderer NM. The effect of the total cumulative epinephrine dose administered during human CPR on hemodynamic, oxygen transport, and utilization variables in the postresuscitation period. *Chest* 1994;106:1499–507.
39. Voelckel WG, Lurie KG, McKnite S, et al. Effects of epinephrine and vasopressin in a piglet model of prolonged ventricular fibrillation and cardiopulmonary resuscitation. *Crit Care Med* 2002;30:957–62.