Epinephrine Versus Placebo During Resuscitation After Neonatal Hypoxic Cardiac Arrest: The Effect on ROSC and Markers of CNS Outcome Investigated in a Piglet Model

Hannah Brogaard Andersen (hannah.brogaard@clin.au.dk)
Aarhus University Hospital: Aarhus Universitetshospital https://orcid.org/0000-0003-3322-0790
Mads Andersen
Aarhus University Hospital: Aarhus Universitetshospital
Ted Carl Andelius
Aarhus University Hospital: Aarhus Universitetshospital
Mette Vestergård Pedersen
Aarhus University Hospital: Aarhus Universitetshospital
Bo Løfgren
Aarhus University Hospital: Aarhus Universitetshospital
Michael Pedersen
Aarhus University Hospital: Aarhus Universitetshospital
Steffen Ringgaard
Aarhus University Hospital: Aarhus Universitetshospital
Kasper Jacobsen Kyng
Aarhus University Hospital: Aarhus Universitetshospital
Tine Brink Henriksen
Aarhus University Hospital: Aarhus Universitetshospital

Research

Keywords: Cardiac arrest, hypoxia, cardiopulmonary resuscitation, newborn, epinephrine, CNS outcome, magnetic resonance spectroscopy, magnetic resonance imaging.

Posted Date: June 29th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-638347/v1

Abstract

Background: Epinephrine is an integral component of neonatal resuscitation guidelines, despite sparse evidence. The association between advanced cardiopulmonary resuscitation (CPR) and poor neurodevelopment is well known, and epinephrine may improve short-term survival but at the cost of poor neurologic outcome. Our objectives were to investigate the effect of epinephrine vs placebo in a piglet model of neonatal hypoxic cardiac arrest (CA) by: 1) return of spontaneous circulation (ROSC), 2) time-to-ROSC, 3) markers of CNS outcome by magnetic resonance spectroscopy and imaging (MRS/MRI), and 4) composite endpoint of death or severe CNS outcome.

Methods: Twenty-five newborn piglets under 12 hours of age underwent hypoxia. Hypoxia was induced by clamping the endotracheal tube until CA (mean arterial blood pressure <20 mmHg and heart rate <60 bpm). CPR was commenced five minutes after CA. The animals were randomized to either CPR + intravenous epinephrine or CPR + placebo (saline). MRS/MRI was performed six hours after resuscitation.

Results: ROSC was more frequent in animals subjected to epinephrine than placebo; RR = 2.31 (95 % CI: 1.09 to 5.77). We found no difference between groups in time-to-ROSC. Among survivors, we found no difference between groups in brain lactate/N-acetyl-aspartate ratios (Lac/NAA), N-acetyl-aspartate/creatine ratios (NAA/Cr), diffusion-weighted-signal, or oxygenation-dependent-signal. We found a tendency towards reduced risk of the composite endpoint of death or severe CNS outcome in animals resuscitated with epinephrine compared to placebo, RR = 0.7 (95 % CI: 0.37 to 1.19).

Conclusions: Resuscitation with epinephrine compared to placebo improved ROSC frequency after neonatal hypoxic CA. Surviving animals after resuscitation with epinephrine compared to placebo showed no difference in MRS/MRI markers of brain damage. These results support that epinephrine improves short-term survival without increasing brain injury measured by early imaging biomarkers.

Introduction

Epinephrine is an integral component of neonatal resuscitation guidelines [1–5]. However, despite decades of research and clinical use, the effect and safety of epinephrine remains controversial. In animal studies, epinephrine-mediated peripheral vasoconstriction increases coronary perfusion pressure and ultimately the chance of achieving return of spontaneous circulation (ROSC) [6–8]. However, animal studies have suggested adverse effects of epinephrine on cerebral microvascular blood flow and myocardial function [9, 10] and similar concerns exist in adult cardiac arrest (CA) [11]. The association between advanced CPR (including epinephrine) and poor neurodevelopmental outcome is well known [12–14], and one may speculate that epinephrine improves short-term survival but at the cost of poorer long-term outcomes [11].

Magnetic resonance spectroscopy and imaging (MRS/MRI) are used as prognostic tools to predict neurological impairment in newborns suffering from encephalopathy after a hypoxic-ischemic insult [15].

Lactate/N-acetyl-aspartate ratio (Lac/NAA) measured in the thalamus by MRS is considered the most accurate early biomarker for prediction of neurologic outcome [15, 16].

The aim of this randomized controlled study was to evaluate the effect of epinephrine in a piglet model of neonatal hypoxic cardiac arrest (CA). Our primary outcome was ROSC, and the secondary outcomes were time-to-ROSC, markers of CNS outcome by MRS/MRI and composite endpoint of death or severe CNS outcome.

Materials And Methods

Ethics

The study was approved by The Danish Animal Experiments Inspectorate (license no: 2018-15-0201-01555). Reporting complies with the ARRIVE 2.0 guidelines [17].

Study design

The study was a randomized placebo-controlled study. Two animals from the same litter and of same sex were included at a time. One animal was randomized to either epinephrine (0.01 mg/kg, equating a volume of 0.1 ml/kg) or placebo (0.1 ml/kg 0.9% saline), the other animal received the treatment different from the randomized littermate. Randomization was completed prior to CA induction and all investigators were blinded to the allocated treatment during the entire study.

Animal preparation

We included Danish Landrace piglets of either sex, under 12 h of age, and weight between 1500 g and 2000 g. Anesthesia was induced by inhalation of 2–4% sevoflurane. Peripheral venous access was obtained and a bolus of propofol (10 mg/kg), fentanyl (30 µg/kg) and rocuronium (1 mg/kg) was administered. Animals were intubated and mechanically ventilated, adjusted to maintain an end-tidal CO_2 of 4.5 to 5.5 kPa. Anesthesia was maintained by continuous infusion of propofol (4–12 mg/kg/h) and fentanyl (5–10 µg/kg/h). Anesthesia was paused during CA and resuscitation and continued after ROSC at the lowest relevant dose. A 3.5 Fr catheter was inserted in an umbilical artery and in the umbilical vein for blood sampling, continuous measurement of mean arterial blood pressure (MABP) and fluid and drug administration. Intravenous gentamicin 5 mg/kg and ampicillin 30 mg/kg were administered once. Normal values of blood glucose and normohydration were maintained by continuous intravenous infusion of 5–10 ml/kg/h NeoKNaG (Na^+ 15 mmol/L, K^+ 10 mmol/L, Cl^- 25 mmol/L, glucose 505 mmol/L). Core temperature was measured by a rectal probe and maintained at 38.5 to 39 °C (normothermia for piglets) by a heated inflatable air mattress. Percutaneous oxygen saturation, electrocardiography (ECG), MABP, and heart rate (HR) were measured continuously. Arterial blood samples were analyzed (ABL Radiometer Medical, Denmark) to monitor blood electrolytes, CO_2, O_2, glucose, pH, and lactate.

CA and resuscitation protocol

Baseline data were obtained 30 minutes prior to CA induction. CA was induced by clamping the endotracheal tube (ETT). CA was defined as MABP < 20 mmHg and heart rate < 60 bpm (assessed by auscultation or arterial pressure curve). CPR was initiated after 5 minutes of CA and performed according to ILCOR 2015 guidelines [1]. ROSC was evaluated every 30 seconds throughout the resuscitation process. ROSC was defined as MABP > 40 mmHg or HR > 100 bpm sustained for five minutes. Time-to-ROSC was registered at the beginning of the five minutes. Resuscitation was commenced by restoring ventilation (FiO_2 = 21%, rate = 40/min, positive end expiratory pressure (PEEP) = 5 cm H_2O and peak inspiratory pressure (P_{insp}) = 10 cm H_2O). If CA persisted after 30 seconds of uninterrupted ventilation, manual chest compressions were initiated and delivered asynchronous to ventilations at a rate of 3:1 (90 compressions and 30 ventilations per minute), a depth of 1/3 of the thoracic anteroposterior diameter, using the two-thumb encircling technique. Simultaneously, FiO_2 was adjusted to 100%. If ROSC was not achieved after 30 seconds of chest compression, epinephrine (0.01 mg/kg equivalent to a volume of 0.1 ml/kg) or placebo (0.1 ml/kg 0.9% saline) was administered through the umbilical venous catheter. If CA persisted, administration was repeated every four minutes for a maximum of six doses. Resuscitative efforts were discontinued if ROSC was not achieved within 30 minutes after CA.

If successfully resuscitated, the animals were treated with therapeutic hypothermia (TH). Target core temperature was between 33 and 34 °C. Whole-body cooling was initiated by placing 5 °C water bags directly on the piglet. Anesthetic and hemodynamic support was titrated according to protocol (Supplementary S1). The duration of post-resuscitation observation and monitoring was six hours. Euthanasia occurred under general anesthesia via injection of a lethal dose of pentobarbital (80 mg/kg).

Magnetic resonance spectroscopy and imaging

At six hours post ROSC, MRS/MRI was performed using a 3.0 T system (Skyra model; Siemens, Germany). Images were obtained according to a standard protocol, previously established by our group [18] (Supplementary S2). Briefly, proton MRS (repetition-time/echo-time: 2000/135 ms) was obtained from 8×8×8 mm^3 voxels. Lactate/N-acetyl-aspartate ratio (Lac/NAA) and N-acetyl-aspartate/creatine ratio (NAA/Cr) were assessed in frontal cortex (fCTX), occipital cortex (oCTX), thalamus (Thal) and white matter (WM). Diffusion-weighted images (DWI) were attained, and the apparent diffusion coefficient value (ADC) was calculated. Blood-oxygenation level-dependent (BOLD) imaging was employed using a multi-echo gradient-echo sequence, and the apparent relaxation constant T2* was calculated. All MRS/MRI data analyses were blinded to treatment allocation.

Composite endpoint analysis of death or severe CNS outcome

Severe CNS outcome was defined as values within the upper quartile of thalamic Lac/NAA ratio [15].

Statistics

The limited amount of previously published data did not allow for estimation of a standard deviation and effect size for power calculation. Accounting for the potential number of animals achieving ROSC before

treatment intervention, mortality, and animal ethics, we estimated that 14 animals per group were sufficient for analysis.

Statistical analyses were performed using GraphPad PRISM version 8.00 (GraphPad Software, San Diego, California USA). Dichotomous data (ROSC, death post ROSC, and vasopressor treatment) were analyzed by Fisher's exact test, and reported as relative risk (RR) with 95 % confidence interval (CI). Continuous variables (time-to-CA, time-to-ROSC, Lac/NAA ratio, NAA/Cr ratio, ADC, BOLD and hemodynamic- and metabolic variables) were compared by either Student's t-test (if normally distributed) and presented as mean values with standard deviation (± SD) or by Mann-Whitney rank sum test (if non-normally distributed) and presented as median values with interquartile range (IQR). The composite endpoint of death or severe CNS outcome was reported as RR with 95 % CI. A sensitivity analysis including animals with missing CNS outcome was conducted. Hemodynamic and metabolic variables were shown graphically and depicted based on parameters from mixed effects analyses, with assumed sphericity, missing values at random and corrected for multiple comparison by Bonferroni's test. A two-sided p-value < 0.05 was considered statistically significant.

Results

One of 28 animals was not randomized due to unsuccessful arterial access. ROSC occurred before treatment intervention in two of the remaining 27 animals (one from each group); these animals were euthanized right after ROSC. All 27 animals were included in an *intension to treat* analysis (Supplementary S3). The two animals that achieved ROSC before treatment intervention were excluded from the final analysis [19]. The following results are based on *per protocol* analysis of 25 animals: epinephrine (n = 13) vs placebo (n = 12). We found no difference in results analyzed according to *intension to treat vs per protocol*. A flow chart is presented in Supplementary S4.

Baseline and CA-characteristics

Baseline characteristics are shown in Table 1 and characteristics at time of CA in Table 2. Hemodynamic and metabolic parameters from baseline to end of experiment are shown in Fig. 1. Blood glucose at baseline was higher in the epinephrine group compared to the placebo group. This difference was not observed at CA or after ROSC. In all animals, the primary arrest rhythms were asystole or pulseless electrical activity (PEA). Conversion from the primary non-shockable rhythm to ventricular fibrillation (VF) was observed in 7/13 (54%) animals in the epinephrine group and 4/12 (33%) in the placebo group, RR = 1.6 (95 % CI: 0.7 to 4.3).

Table 1
Physiologic and metabolic characteristics at baseline in animals randomized to epinephrine versus placebo.

	Epinephrine (n = 13)	**Placebo (n = 12)**
Weight (g)	1815 (208)	1850 (278)
Male/female	8/5	7/5
HR (bpm)	143 (22)	151 (11)
MABP (mm Hg)	52 (7.1)	52 (6.6)
Rectal temperature (°C)	38.9 (0.5)	39.1 (0.4)
pH	7.52 (0.05)	7.54 (0.06)
BE (mmol/L)	8.2 (3.1)	8.8 (3.4)
Lactate (mmol/l)	1.4 (1.3-2.0)	1.4 (1.2–1.7)
pCO_2 (kPa)	5.0 (0.7)	5.0 (0.6)
Glucose (mmol/l)	7.5 (6.7-9.0)	6.4 (5.6–7.3)*

Values are presented as means (± SD) or medians (IQR). * $p < 0.05$ epinephrine vs placebo. HR; heart rate, MABP; mean arterial blood pressure, BE; base excess, SD; standard deviation, IQR; interquartile range.

Table 2
Physiologic and metabolic characteristics at cardiac arrest in animals randomized to epinephrine versus placebo.

	Epinephrine (n = 13)	Placebo (n = 12)
Time to CA (min)	17 (15–22)	22 (18–26)
HR (bpm)	0 (0)	0 (0)
MABP (mmHg)	0 (0)	0 (0)
Rectal temperature (°C)	38.4 (0.4)	38.4 (0.3)
pH	< 6.75	< 6.75[a]
Lactate (mmol/l)	18.5 (3.6)	18.3 (3.3)
pCO_2 (kPa)	> 14.7	> 14.7[b]
Glucose (mmol/l)	9.4 (5.4)	6.9 (4.1)
Epinephrine doses (n)	1 (1–2)	

Values are presented as means (± SD) or medians (IQR). [a] Lower detection limit for pH = 6.75.

[b] Upper detection limit of pCO_2 = 14.7. CA; cardiac arrest, HR; heart rate, MABP; mean arterial blood pressure, SD; standard deviation, IQR; interquartile range.

ROSC and six hour survival

Animals that received epinephrine had significantly higher rate of ROSC (RR 2.31; 95 % CI: 1.09 to 5.77). We found no difference between the groups in time-to-ROSC (median (IQR) time-to-ROSC; epinephrine: 120 (113–211) sec vs placebo 153 (116–503) sec, $p = 0.66$).

Due to refractory hypotension, four of the 14 animals in which ROSC was achieved, died before the six-hours MRS/MRI examination (epinephrine: 3/10 vs. placebo: 1/4, RR = 0.9 (95 % CI: 0.5 to 2.5)). One additional animal was euthanized prior to MRS/MRI due to technical issues. Thus, nine animals completed the MRS/MRI acquisition (epinephrine: n = 6 vs. placebo: n = 3) (Supplementary S4).

Magnetic resonance spectroscopy

There was no difference between animals that received epinephrine and placebo with regards to Lac/NAA ratio measured in fCTX, oCTX and thalamus (Fig. 2). In white matter, we were unable to detect lactate-peaks in 3/6 animals resuscitated with epinephrine and 3/3 animals resuscitated with placebo. We found no difference between groups in NAA/creatine ratio measured in fCTX, oCTX, thalamus, or WM (Fig. 2).

Magnetic resonance imaging

The degree of cerebral edema quantified by DWI was similar in animals resuscitated with epinephrine versus placebo (Fig. 3). MRI BOLD analysis revealed no difference in cerebral oxygenation between the two groups (Fig. 3).

Composite endpoint of death or severe CNS outcome

A reduced but not statistically significant risk of the composite endpoint of death or severe CNS outcome was found in animals resuscitated with epinephrine compared to placebo, RR = 0.7 (95 % CI: 0.37 to 1.19). When including the animal with missing CNS outcome in a sensitivity analysis assigning the piglet to a good or severe CNS outcome the RR was 0.65 (95 % CI: 0.34 to 1.12) and 0.74 (95 % CI: 0.41 to 1.23), respectively.

Discussion

In our neonatal piglet model of hypoxic cardiac arrest, the use of epinephrine compared to placebo during resuscitation resulted in more than twice as many piglets with ROSC, and we found no difference in early biomarkers of brain damage between the groups six hours after resuscitation.

Our findings related to ROSC are consistent with some, but not all, previous experimental animal studies. Sobotka et al. [20] reported that chest compressions alone were insufficient to achieve ROSC and that epinephrine administration was critical to increase heart rate, carotid arterial pressure, and cerebral blood flow. Mendler et al. [21] and Solevåg et al. [22] also found that at least one dose of epinephrine was required for successful resuscitation. In contrast, Wagner et al. [23], Linner et al. [24], and McNamara et al. [25] concluded that epinephrine failed to increase the rate of ROSC. These conflicting results are likely explained by essential differences in the study protocols. The most striking difference between the three former studies and the three later studies is the chosen CA-criteria. In the study by Wagner et al. [23], CA was defined as HR < 25 % of baseline, and in the study by Linner et al. [24], CA was defined as HR < 50 bpm and MABP < 25 mmHg, however; if the criteria were not reached within 12 minutes of apnea, resuscitation was commenced. This indicates that the hypoxic insult was less severe in these studies. In the study by McNamara et al. [25], the CA criteria were similar to ours, yet the no-flow period was only 4 minutes compared to 5 minutes in our study. Furthermore, epinephrine was administered three minutes after resuscitation onset, compared to one minute in our study. Studies of pediatric CA have shown that the chance of achieving ROSC is decreased by every minute epinephrine administration is delayed [26, 27]. Additionally, only one dose of epinephrine was administered (two animals in our study required more than one dose epinephrine to achieve ROSC), and resuscitative efforts were discontinued if ROSC was not achieved within six minutes after chest compression onset (one animal in our study achieved ROSC beyond six minutes after chest compression onset).

Conversion from PEA or asystoli to VF was observed in 44% of the animals during the resuscitation period. Conversion from a non-shockable rhythm to a shockable rhythm (treated) is a good prognostic sign in pediatric CA [28]. As per the current standard for human neonatal resuscitation, defibrillation was

not part of our procedure, and we observed no difference in the rate of ROSC between animals with and without VF in either experimental group (Supplementary S5). Swine are known to be more arrhythmogenic than humans [29]. High frequencies of VF were also observed by McNamara et al. [25]. These high frequencies emphasize the necessity of studies of arrest rhythms in human neonates.

In this study, very importantly, resuscitation with epinephrine did not result in worse markers of CNS outcome at six hours after ROSC. We found no difference in Lac/NAA ratio or NAA/Cr ratio between animals resuscitated with epinephrine compared to placebo. The Lac/NAA ratio is known to increase during the secondary phase of energy failure between 6 and 24 hours after cerebral hypoxia-ischemia [30]. Thus, it is possible that we failed to capture the differences, i.e., both beneficial and adverse effects of epinephrine, due to the relatively short interval between CA and MRS. However, Zheng et al. [31] showed that brain lactate levels peaked between 2 to 6 hours following hypoxia-ischemia, and during our pilot studies we performed both 6- and 12-hours MRS/MRI examinations with no additional information gained. Still, studies on long-term outcomes are warranted.

MRI-based DWI is a marker of cerebral edema [32]. In newborns with hypoxic ischemic encephalopathy (HIE) and in adults post CA, low ADC values have been associated with unfavorable neurologic outcome [33, 34]. The ADC values were low in animals with and without exposure to epinephrine (compared to healthy control piglets (n = 4) included in a previous study by our group; mean (SD) ADC = 974 (145) 10^{-6} mm^2/sec, unpublished data), indicating severe edema in both experimental groups. However, acute brain edema does not always persist; therefore, ADC measured six hours post ROSC, may not be a reliable predictor of irreversible tissue damage and later brain injury [35].

BOLD MRI measures regional differences in concentrations of oxy- and deoxyhemoglobin in response to neural activity via calculations of T2* values [36]. We found no difference between animals resuscitated with epinephrine compared to placebo in T2* measured in thalamus. The T2* values were low in both groups, (compared to healthy control piglets (n = 4), included in a previous study by our group; mean (SD) T2* = 63.3 (5.0) ms, unpublished data) possibly due to a compensatory increased oxygen extraction in the early hours after the hypoxic-ischemic insult. Furthermore, hypoperfusion may add to this finding. Early hypoperfusion (20 min to 12 hours after ROSC) has been demonstrated in animal models of adult/pediatric CA [37, 38] and has also been observed in neonates with HIE [39]. There is concern that epinephrine may impair cerebral perfusion and oxygenation [10]. However, in our BOLD measurements, epinephrine and placebo resulted in similar cerebral hemodynamics six hours post ROSC.

Our ROSC data and MRS/MRI data support that epinephrine increases short term survival without increasing brain injury. Our composite endpoint analysis of death or severe CNS outcome further supports this finding. However, our results were no longer significant due to a 25–30 % post-ROSC mortality in both experimental groups, and small absolute numbers of animals.

This study has a number of limitations; 1) we used anaesthetized and intubated animals. Anesthetics and drugs for pain relieve are necessary for ethical reasons, but may influence ROSC [40]. We did,

however, pause all drugs during CA and resuscitation. 2) Newborns exhibit transitional cardiac- and lung physiology, while our study represents post-transitional neonatal hypoxic CA, and although the majority of CA in newborns are hypoxic in origin, co-morbidities such as infection or hypovolemia exist [41, 42]. 3) Although the anatomy of the newborn pig is very similar to that of the newborn human, it is possible that the beneficial effect of epinephrine on ROSC may be species specific. Interspecies differences in vascular sensitivity to catecholamines likely exist, and caution must be exercised when translating to human neonates. 4) All animals received TH, which might postpone the processes involved in the developing brain injury beyond the range of our observation period. This effect was, however, not evident in the study by Tang et al. [43] who investigated the effect of TH vs normothermia on brain injury by MRS/MRI at 6, 12, 24 and 72 hours post ROSC. 5) We used an MRS echo time of 135 ms for easy identification of lactate-peak due to peak inversion, and a small voxel to certify high spatial resolution. However, a small voxel decreases signal-to-noise ratio, which could challenge the detection of lactate peaks. A larger voxel and an echo time of 288 ms may help resolve this issue in future studies.

Conclusion

We found that resuscitation with epinephrine compared to placebo improved the rate of ROSC after neonatal hypoxic CA. We found no difference in time-to-ROSC. Animals who survived resuscitation with epinephrine compared to placebo were similar with respect to MRS/MRI markers of brain damage.

Abbreviations

ROSC
Return of spontaneous circulation
CPR
Cardio pulmonary resuscitation
CA
Cardiac arrest
MRS
Magnetic resonance spectroscopy
MRI
Magnetic resonance imaging
Lac/NAA
Lactate/N-acetyl-aspartate ratio
NAA/Cr
N-acetyl-aspartate/creatine ratio
MABP
Mean arterial blood pressure
HR
Heart rate

PEEP
Positive end expiratory pressure
P_{insp}
Peak inspiratory pressure
TH
Therapeutic hypothermia
fCTX
Frontal cortex
oCTX
Occipital cortex
Thal
Thalamus
WM
White matter
DWI
Diffusion-weighted imaging
ADC
Apparent diffusion coefficient
BOLD
Blood-oxygenation level-dependent imaging
PEA
Pulseless electrical activity
VF
Ventricular fibrillation

Declarations

Acknowledgement

We wish to thank the staff at the animal research facilities at Institute of Clinical Medicine, Aarhus University.

Authors' contributions

HBA, TCA, BL, KJK, and TBH contributed to the conception and design of the study. HBA, MA, TCA, and MVP undertook the experiments. HBA, SR, MP, and TCA, contributed to the analysis and/or interpretation of data. HBA drafted the manuscript. All authors contributed to revising the manuscript critically for important intellectual content. All authors have approved the final version of the manuscript for publication.

Funding

The study was funded by the Elsass Foundation (Grant nr: 17-3-1448) and Aarhus University.

Ethics approval and consent to participate

The study was approved by The Danish Animal Experiments Inspectorate (license no: 2018-15-0201-01555). Experiments were performed in accordance with national guidelines on animal welfare. Reporting complies with the ARRIVE 2.0 guidelines.

Consent for application

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

References

1. Perlman JM, Wyllie J, Kattwinkel J, Wyckoff MH, Aziz K, Guinsburg R, et al. Part 7: Neonatal resuscitation 2015 international consensus on cardiopulmonary resuscitation and emergency cardiovascular care science with treatment recommendations (reprint). Pediatrics. American Academy of Pediatrics; 2015;136:S120–66.
2. Atkins DL, Berg MD, Berg RA, Bhutta AT, Biarent D, Bingham R, et al. 2005 American Heart Association (AHA) guidelines for cardiopulmonary resuscitation (CPR) and emergency cardiovascular care (ECC) of pediatric and neonatal patients: Pediatric advanced life support. Pediatrics. 2006;117.
3. Wyckoff MH, Aziz K, Escobedo MB, Kapadia VS, Kattwinkel J, Perlman JM, et al. Part 13: Neonatal resuscitation: 2015 American Heart Association guidelines update for cardiopulmonary resuscitation and emergency cardiovascular care. Circulation. 2015;132:543–60.
4. Kattwinkel J, Perlman JM, Aziz K, Colby C, Fairchild K, Gallagher J, et al. Special Report - Neonatal resuscitation: 2010 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. Pediatrics. 2010;126.
5. Madar J, Roehr CC, Ainsworth S, Ersdal H, Morley C, Rüdiger M, et al. European Resuscitation Council Guidelines 2021: Newborn resuscitation and support of transition of infants at birth. Resuscitation Ireland. 2021;161:291–326.
6. Schleien CL, Dean JM, Koehler RC, Michael JR, Chantarojanasiri T, Traystman R, et al. Effect of epinephrine on cerebral and myocardial perfusion in an infant animal preparation of cardiopulmonary resuscitation. Circulation United States. 1986;73:809–17.

7. Mavroudis CD, Ko TS, Morgan RW, Volk LE, Landis WP, Smood B, et al. Epinephrine's effects on cerebrovascular and systemic hemodynamics during cardiopulmonary resuscitation. Crit Care Critical Care. 2020;24:1–13.
8. Kapadia VS, Wyckoff MH. Epinephrine use during newborn resuscitation. Front Pediatr. 2017;5:1–8.
9. Sun S, Tang W, Song F, Yu T, Ristagno G, Shan Y, et al. The effects of epinephrine on outcomes of normothermic and therapeutic hypothermic cardiopulmonary resuscitation. Crit Care Med. 2010;38:2175–80.
10. Ristagno G, Tang W, Huang L, Fymat A, Chang Y, Te, Sun S, et al. Epinephrine reduces cerebral perfusion during cardiopulmonary resuscitation. Crit Care Med. 2009;37:1408–15.
11. Perkins GD, Ji C, Deakin CD, Quinn T, Nolan JP, Scomparin C, et al. A randomized trial of epinephrine in out-of-hospital cardiac arrest. N Engl J Med Massachussetts Medical Society. 2018;379:711–21.
12. Laptook AR, Shankaran S, Ambalavanan N, Carlo WA, McDonald SA, Higgins RD, et al. Outcome of term infants using Apgar scores at 10 minutes following hypoxic-ischemic encephalopathy. Pediatrics United States. 2009;124:1619–26.
13. Harrington DJ, Redman CW, Moulden M, Greenwood CE. The long-term outcome in surviving infants with Apgar zero at 10 minutes: a systematic review of the literature and hospital-based cohort. Am J Obstet Gynecol. 2007;196:463.e1-463.e5.
14. Wyckoff MH, Salhab WA, Heyne RJ, Kendrick DE, Stoll BJ, Laptook AR. Outcome of extremely low birth weight infants who received delivery room cardiopulmonary resuscitation. J Pediatr United States. 2012;160:239–44.e2.
15. Lally PJ, Montaldo P, Oliveira V, Soe A, Swamy R, Bassett P, et al. Magnetic resonance spectroscopy assessment of brain injury after moderate hypothermia in neonatal encephalopathy: a prospective multicentre cohort study. Lancet Neurol. 2019;18:35–45.
16. Thayyil S, Chandrasekaran M, Taylor A, Bainbridge A, Cady EB, Chong WKK, et al. Cerebral magnetic resonance biomarkers in neonatal encephalopathy: A meta-analysis. Pediatrics. 2010;125.
17. Kilkenny C, Browne W, Cuthill IC, Emerson M, Altman DG. Animal research: Reporting in vivo experiments: The ARRIVE guidelines. Br J Pharmacol. 2010;160:1577–9.
18. Andelius TCK, Pedersen MV, Andersen HB, Andersen M, Hjortdal VE, Pedersen M, et al. No Added Neuroprotective Effect of Remote Ischemic Postconditioning and Therapeutic Hypothermia After Mild Hypoxia-Ischemia in a Piglet Model. Front Pediatr. 2020;8:1–10.
19. Fergusson D, Aaron SD, Guyatt G, Hébert P. Post-randomisation exclusions: The intention to treat principle and excluding patients from analysis. Br Med J. 2002;325:652–4.
20. Sobotka KS, Polglase GR, Schmölzer GM, Davis PG, Klingenberg C, Hooper SB. Effects of chest compressions on cardiovascular and cerebral hemodynamics in asphyxiated near-term lambs. Pediatr Res Nature Publishing Group. 2015;78:395–400.
21. Mendler MR, Weber C, Hassan MA, Huang L, Waitz M, Mayer B, et al. Effect of Different Respiratory Modes on Return of Spontaneous Circulation in a Newborn Piglet Model of Hypoxic Cardiac Arrest. Neonatology Switzerland. 2016;109:22–30.

22. Solevåg AL, Dannevig I, Nakstad B, Saugstad OD. Resuscitation of severely asphyctic newborn pigs with cardiac arrest by using 21% or 100% oxygen. Neonatology. 2010;98:64–72.
23. Wagner M, Cheung PY, Li ES, Lee TF, Lu M, O'Reilly M, et al. Effects of epinephrine on hemodynamic changes during cardiopulmonary resuscitation in a neonatal piglet model. Pediatr Res Nature Publishing Group. 2018;83:897–903.
24. Linner R, Werner O, Perez-de-Sa V, Cunha-Goncalves D. Early adrenaline administration does not improve circulatory recovery during resuscitation from severe asphyxia in newborn piglets. Resuscitation. 2012;83:1298–303.
25. McNamara PJ, Engelberts D, Finelli M, Adeli K, Kavanagh BP. Vasopressin improves survival compared with epinephrine in a neonatal piglet model of asphyxial cardiac arrest. Pediatr Res Nature Publishing Group. 2014;75:738–48.
26. Andersen LW, Berg KM, Saindon BZ, Massaro JM, Raymond TT, Berg RA, et al. Time to Epinephrine and Survival After Pediatric In-Hospital Cardiac Arrest. JAMA. 2015;314:802–10.
27. Matsuyama T, Komukai S, Izawa J, Gibo K, Okubo M, Kiyohara K, et al. Pre-Hospital Administration of Epinephrine in Pediatric Patients With Out-of-Hospital Cardiac Arrest. J Am Coll Cardiol. 2020;75:194–204.
28. Goto Y, Funada A, Goto Y. Subsequent shockable rhythm during out-of-hospital cardiac arrest in children with initial non-shockable rhythms: A nationwide population-based observational study. J Am Heart Assoc. 2016;5:1–11.
29. Lelovas PP, Kostomitsopoulos NG, Xanthos TT. A comparative anatomic and physiologic overview of the porcine heart. J Am Assoc Lab Anim Sci. 2014;53:432–8.
30. Hassell KJ, Ezzati M, Alonso-Alconada D, Hausenloy DJ, Robertson NJ. New horizons for newborn brain protection: Enhancing endogenous neuroprotection. Arch Dis Child Fetal Neonatal Ed. 2015;100:F541–51.
31. Zheng Y, Wang XM. Expression changes in lactate and glucose metabolism and associated transporters in basal ganglia following hypoxic-ischemic reperfusion injury in piglets. Am J Neuroradiol. 2018;39:569–76.
32. Robertson RL, Glasier CM. Diffusion-weighted imaging of the brain in infants and children. Pediatr Radiol. 2007;37:749–68.
33. Van Laerhoven H, De Haan TR, Offringa M, Post B, Van Der Lee JH. Prognostic tests in term neonates with hypoxic-ischemic encephalopathy: A systematic review. Pediatrics. 2013;131:88–98.
34. Choi SP, Park KN, Park HK, Kim JY, Youn CS, Ahn KJ, et al. Diffusion-weighted magnetic resonance imaging for predicting the clinical outcome of comatose survivors after cardiac arrest: A cohort study. Crit Care. 2010;14:1–11.
35. Fiehler J, Foth M, Kucinski T, Knab R, von Bezold M, Weiller C, et al. Severe ADC decreases do not predict irreversible tissue damage in humans. Stroke United States. 2002;33:79–86.
36. Kroll H, Zaharchuk G, Christen T, Heit JJ, Iv M. Resting-State BOLD MRI for Perfusion and Ischemia. Top Magn Reson Imaging United States. 2017;26:91–6.

37. Manole MD, Foley LM, Hitchens TK, Kochanek PM, Hickey RW, Bayir H, et al. Magnetic resonance imaging assessment of regional cerebral blood flow after asphyxial cardiac arrest in immature rats. J Cereb Blood Flow Metab. 2009;29:197–205.
38. Van Den Brule JMD, Van Der Hoeven JG, Hoedemaekers CWE. Cerebral perfusion and cerebral autoregulation after cardiac arrest. Biomed Res Int. 2018;2018.
39. Hansen a, Gregas MC, Robertson RL, Warfield SK. Brain Perfusion in Asphyxiated Newborns. Ajnr Am J Neuroradiol. 2011;1–7.
40. Kurita T, Morita K, Kazama T, Sato S. Comparison of isoflurane and propofol-fentanyl anaesthesia in a swine model of asphyxia. Br J Anaesth. 2003;91:871–7.
41. Aziz K, Chadwick M, Baker M, Andrews W. Ante- and intra-partum factors that predict increased need for neonatal resuscitation. Resuscitation. 2008;79:444–52.
42. Randis TM, Rice MM, Myatt L, Tita ATN, Leveno KJ, Reddy UM, et al. Incidence of early-onset sepsis in infants born to women with clinical chorioamnionitis. J Perinat Med. 2018;46:926–33.
43. Tang Z-R, Li C-S, Zhao H, Gong P, Zhang M-Y, Su Z-Y, et al. Effects of hypothermia on brain injury assessed by magnetic resonance imaging after cardiopulmonary resuscitation in a porcine model of cardiac arrest. Am J Emerg Med United States. 2013;31:86–93.

Figures

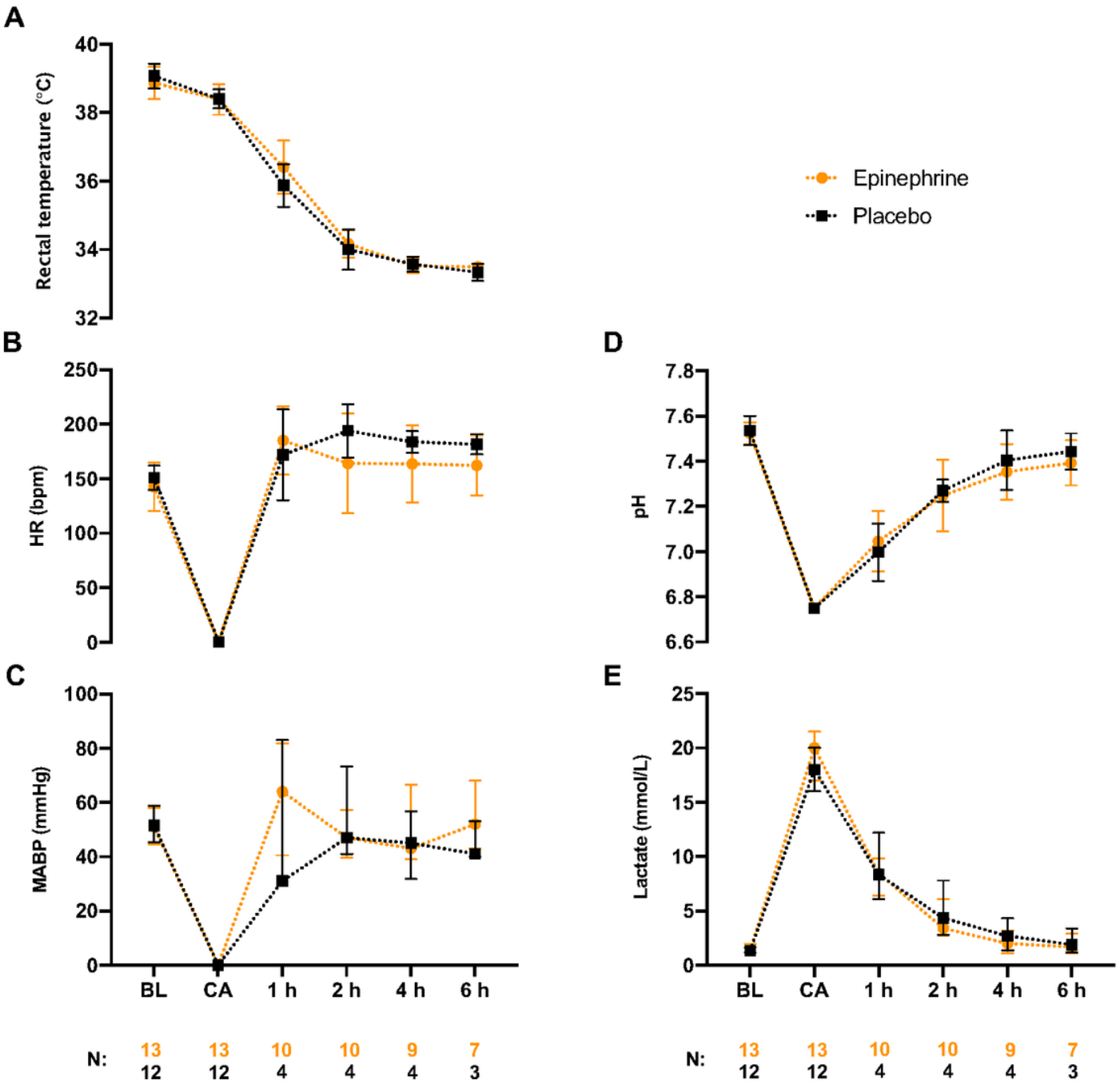

Figure 1

Hemodynamic and metabolic parameters from baseline (BL) to end of experiment in animals randomized to epinephrine versus placebo. A: Rectal temperature, B: heart rate (HR), C: Mean arterial blood pressure (MABP), D: pH and E: lactate. Number of animals alive at each timepoint is denoted below the x-axis, color denotes group. Number of animals per group; epinephrine/placebo: BL (n = 13/12), CA (n = 13/12), 1h (n = 10/4), 2h (n = 10/4), 4h (n = 9/4), 6h (n = 7/3). Rectal temperature, HR and pH are means ± standard deviation. MABP and lactate are medians with interquartile range.

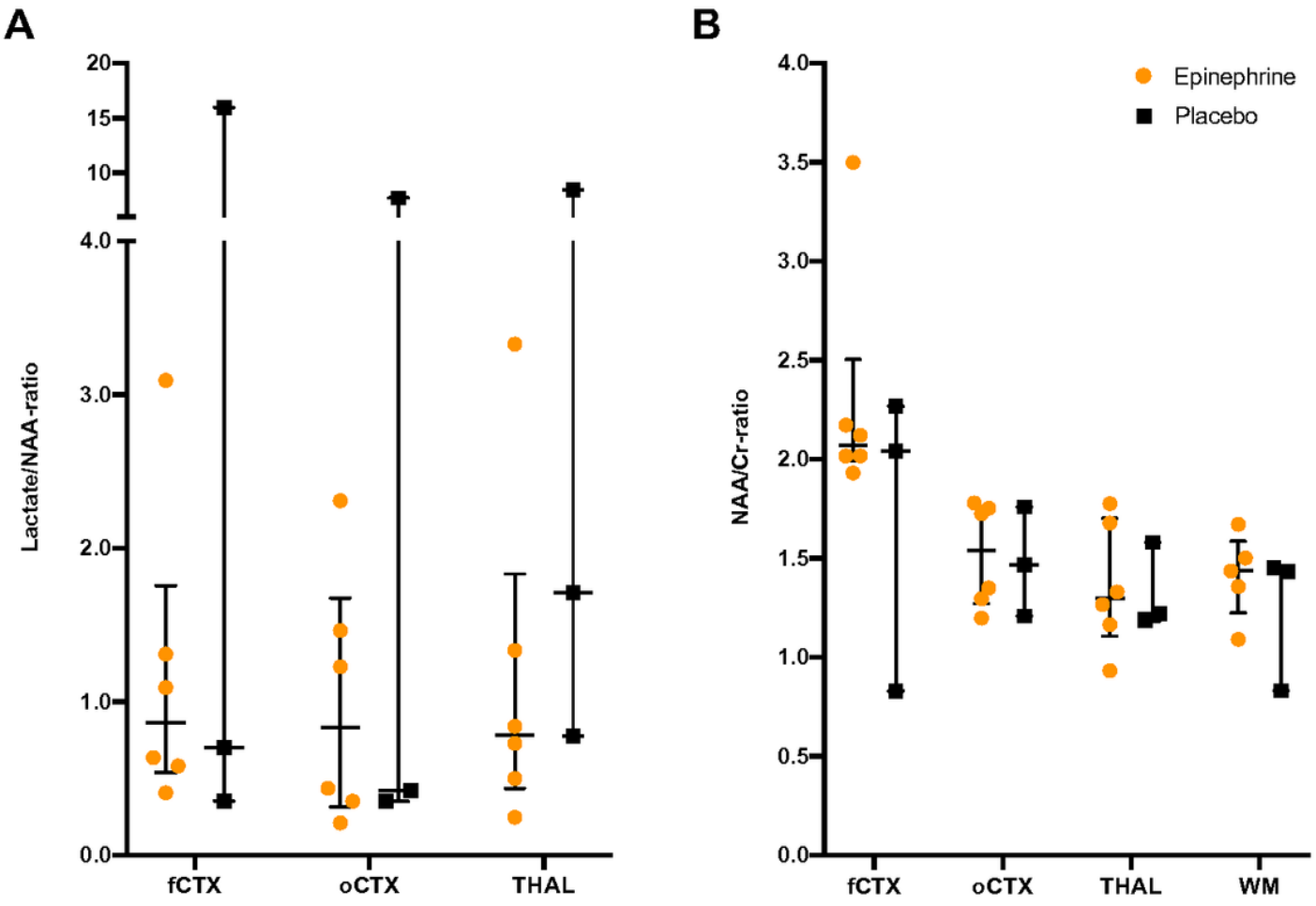

Figure 2

Magnetic resonance spectroscopy of animals randomized to epinephrine versus placebo. A: Lactate/NAA-ratio. B: NAA/Cr-ratio. Scans were performed 6 hours after ROSC. NAA; N-acetyl aspartate, Cr; creatine, fCTX; frontal cortex, oCTX; occipital cortex, THAL; thalamus, WM; white matter. Data are scatter plots with superimposed medians and interquartile range.

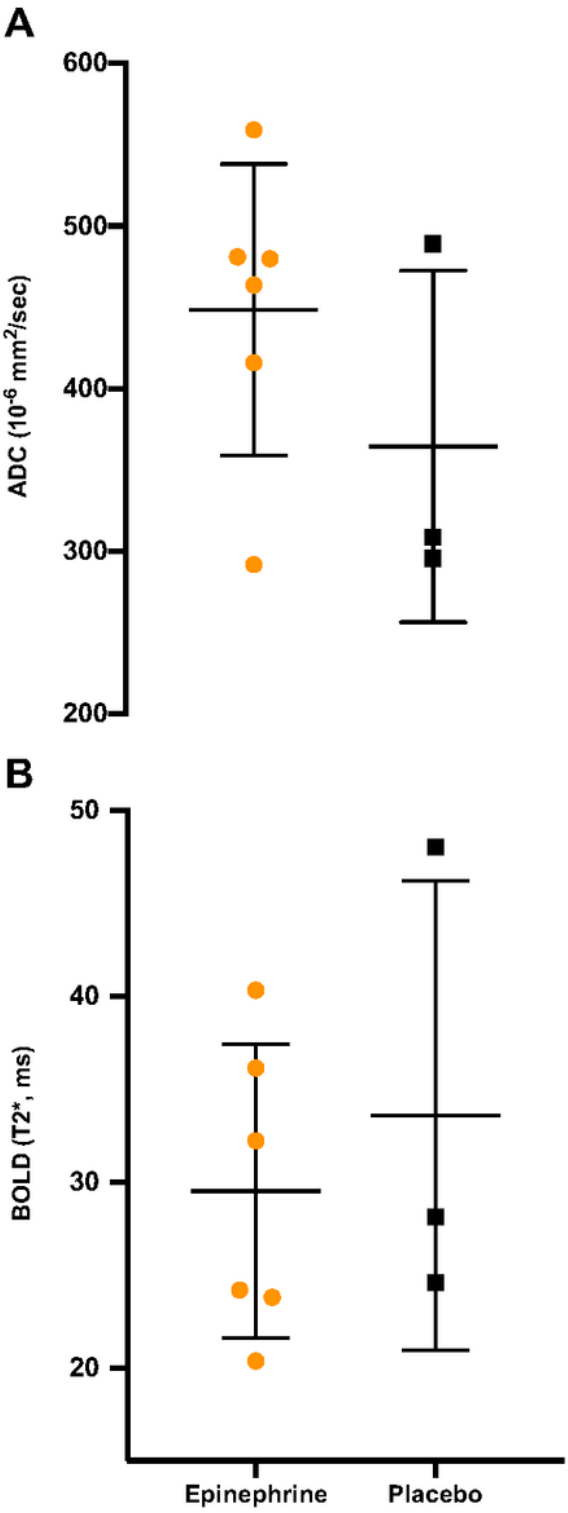

Figure 3

Magnetic resonance imaging of animals randomized to epinephrine versus placebo. A: ADC; apparent diffusion coefficient. B: BOLD; blood oxygen level dependent scan. Scans were performed 6 hours after ROSC. Data are scatter plots with superimposed means ± standard deviation.

Supplementary Files

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