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Experimental paper

The cerebral and cardiac effects of Norepinephrine in an experimental cardiac arrest model

Deborah Jaeger[a,b], *Marinos Kosmopoulos*[a], *Christopher Gaisendrees*[a,c], *Rajat Kalra*[a], *Alexandra Marquez*[a], *Tahar Chouihed*[b,d], *Kevin Duarte*[d], *Demetris Yannopoulos*[a,*]

Abstract

Introduction: Epinephrine has been the main drug recommended for decades during cardiopulmonary resuscitation (CPR). But epinephrine's ß-adrenergic effects might increase myocardial oxygen consumption and may cause arrythmias after ROSC. Norepinephrine has a weaker ß-adrenergic effect and could be useful during CPR. Studies on norepinephrine's effect on hemodynamic parameters and cerebral perfusion are scarce. This study aimed to assess norepinephrine's hemodynamic impact in an experimental model of cardiac arrest.

Methods: After an initial dose study to determine the optimal dose, we conducted a prospective randomized study with 19 pigs. After 3 minutes of untreated ventricular fibrillation, animals received boluses of 0.5 mg Epinephrine (EPI) or 1 mg Norepinephrine (NE) every 5 minutes during CPR. Coronary perfusion pressure (CPP), carotid blood flow (CBF) and cerebral perfusion pressure (CePP) were evaluated.

Results: At baseline, hemodynamic parameters did not differ between the two groups. During CPR, CPP and CBF were similar: 17.3 (12.8; 31.8) in the EPI group vs 16.0 (11.1; 37.7) in the NE group, $p = 0.9$ and 28.4 (22.0; 54.8) vs 30.8 (12.2; 56.3) respectively, $p = 0.9$. CePP was not significantly lower during resuscitation in the NE group compared to the EPI group: 12.2 (−8.2; 42.2) vs 7.8 (−2.0; 32.0) $p = 0.4$. Survival rate was low with only one animal in the EPI group and 2 in the NE group.

Conclusion: Cerebral perfusion pressure, coronary perfusion pressure and carotid blood flow during CPR did not significantly differ between the norepinephrine group and the epinephrine group. Further investigations should evaluate different options such as a continuous NE infusion.

Keywords: Cardiac arrest, Norepinephrine, Resuscitation, Vasopressor

Introduction

Norepinephrine (NE) is widely used for its blood pressure-stabilizing abilities in the treatment of cardiogenic and septic shock.[1–4] It has a potent α-adrenergic effect and a very weak ß-adrenergic effect in physiological settings. On the other hand, epinephrine, the only vasoactive drug recommended in cardiac arrest (CA) since 1974, stimulates α- and ß-adrenergic receptors.[5] Its use during CA is based on its vasoconstrictive properties, which increases coronary perfusion pressure (CPP) during cardiopulmonary resuscitation (CPR) and thus increasing the chances of return of spontaneous circulation (ROSC).[6,7] Nevertheless, epinephrine's beneficial α-adrenergic effects have been questioned recently as it may also contribute to diminished cerebral microcirculation and thus potentially increase cerebral injuries.[8] In addition, epinephrine's ß-adrenergic effects have also been suggested to be deleterious. Its positive chronotropic and inotropic effects increase myocardial oxygen consumption and may cause arrythmias after ROSC.[9–11] It might even lead to a decreased post-resuscitation myocardial function.[10] The use of beta-blockers in association with epinephrine has shown to improve post-resuscitation myocardial function and reduce arrhythmia recurrences.[12] Another approach would be to use a catecholamine such as NE with a weaker ß-adrenergic effect during CPR.

Studies using NE as a vasopressor in cardiac arrest are scarce and go back to the early 1990s. The data is rather controversial. Results in animal models range from improved myocardial oxygen extraction rate, higher myocardial blood flow and increased survival rate to higher oxygen consumption and lower survival.[13–16] When looking at cerebral perfusion, NE seemed to improve cerebral blood flow compared to saline and was, at least, as effective as high doses

* Corresponding author at: Center for Resuscitation, Medicine, University of Minnesota Medical School, Minneapolis, MN 55401, USA.
E-mail address: yanno001@umn.edu (D. Yannopoulos).

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of epinephrine.[17,18] At that time, NE was primarily administered as boluses and in high doses. To the best of our knowledge, different NE dosages have not been tested and effects of lower doses of NE on myocardial and cerebral perfusion have not been evaluated.

In this study, we used a swine model of VF CA to: 1) compare 2 different doses of NE on coronary perfusion pressure and then 2) compare the hemodynamic effects and cerebral perfusion between norepinephrine and epinephrine.

Material and methods

Ethical statement

This study was approved by the University of Minnesota Institutional Animal Care and Use Committee (Protocol n°: 2208-40313A). A certified and licensed veterinarian assured the protocol performance was in compliance with these guidelines.

Animal preparation

Female Yorkshire farm-raised swine were acclimated in the animal care facility for at least 3 days. They were fasted overnight with free access to water. An intramuscular injection of Ketamine and Xylazine was used to anaesthetized the pigs (20–30 mg/kg and 1–3 mg/kg respectively). Animals were moved to the surgical suite. An IV line was placed in an ear vein to administer propofol (1–2 mg/kg). They were then intubated. Isoflurane was administered during the whole preparation to maintain anesthesia at a dose of 1 to 4 %. Tidal volume was set at 10 ml/kg using room air and respiratory rate at 10–16/min to maintain oxygen saturation above 95 % and end tidal carbon dioxide ($EtCO_2$) between 36–40 mmHg on a volume-controlled ventilator (Narkomed, Draeger Medical, Telford, Pennsylvania). Animal received normal saline intravenously during preparation (5–10 ml/kg/h and Carprofen (2–3 mg/kg subcutaneously) with Buprenorphine (0.1–0.3 mg/kg IV) for pain management normal after intubation. Temperature was monitored with an esophageal probe, and maintained between 36.5 and 38.5 °C.

After placing the animal in a prone position, a 4 mm burr hole was drilled through the frontal bone and a micromanometer-tipped catheter (Mikro-Tip® Transducer, Millar Instruments, Inc. Houston, TX) was inserted into the parietal lobe to measure intracranial pressure (ICP). A modified Seldinger percutaneous technique was used to cannulate the femoral artery and the right external jugular vein. A micromanometer-tipped catheter (Mikro- Tip Transducer, Millar Instruments, Houston, TX) was placed through the right femoral artery into the descending aorta to measure central aortic blood pressure (AP). Similarly, a catheter was placed in the right external jugular vein through the right atrium to measure right atrial (RA) pressure. Placement of catheters was confirmed by fluoroscopy if necessary. A cut down to the left common carotid was done to place an ultrasonic flow probe (Transonic, Ithaca, New York) around the artery and measure carotid blood flow (CBF) (Fig. 1).

All animals received 5000 UI of heparin after surgical preparation.

Arterial blood gases (ABG) were drawn through the femoral artery catheter and analyzed.

Study protocol

Isoflurane was weaned off 3 minutes before the start of the experiment. VF was induced using a pacing wire inserted through the right jugular catheter. Once VF was initiated, ventilation was discontinued, and 3 minutes of no-flow were observed.

Cardiopulmonary resuscitation (CPR) was started with active compression and decompression performed by a pneumatically driven automatic piston device at a rate of 100 compressions/min, with a 50 % duty cycle. During CPR, ventilation was provided as recommended, with 100 % oxygen at 10 respirations/min and 10 mL/kg of tidal volume.

Dose study

For the study dose we arbitrarily decided to compare boluses of 1 and 3 mg. Four pigs received 4 boluses of NE every 5 minutes. Doses of NE were randomized in order for each animal to receive 2 boluses of 1 mg and 2 boluses of 3 mg in a different order. Animals were terminated 5 minutes after the last drug injection. This was a pilot study without a sample size calculation.

The primary endpoint was coronary perfusion pressure. The dose of NE with the highest CPP was chosen for the following Epinephrine vs Norepinephrine study.

Epinephrine vs. Norepinephrine study

Nineteen animals were randomized to receive either 5 doses of 1 mg of norepinephrine in the Norepinephrine group (NE) or in the control (EPI) group, 5 doses of 0.5 mg of epinephrine every 5 minutes. A randomization table was used to randomize animals before the start of the experiment. Drugs were administered without blinding. We assessed that to be clinically relevant, the increase in carotid blood flow should reach 15 %. Given this, and with a type I error of 0.05 and a power of 80 %, this study would have to include 20 subjects, 9 in each group. One animal in the Epinephrine group had a massive hemorrhage during CPR and was excluded of the study.

Five minutes after the last drug injection, the animal was defibrillated up to 3 times (Fig. 2). If ROSC was obtained, sedation was resumed. Hemodynamic parameters were stabilized using NE if needed to maintain a mean arterial pressure (MAP) over 60 mmHg and amiodarone if required. All parameters were recorded for 1 hour before the animal was euthanized.

The primary endpoint was to compare cerebral perfusion pressure between the NE and the EPI groups. Secondary endpoints were mean arterial pressure, carotid blood flow and coronary perfusion pressure.

Data analysis

Data, including aortic pressure, RA pressure, ICP pressure and CBF were continuously recorded in LabVIEW (LabVIEW 2015, National Instruments, Austin, Texas).

CPP was calculated as the difference between diastolic aortic blood pressure measured in the descending thoracic aorta and diastolic RA pressure in spontaneous circulation and the difference between decompression phase aortic pressure and RA pressure during CPR.

Cerebral perfusion pressure was calculated as the difference between mean aortic pressure and mean intracranial pressure.

Statistical analysis

Continuous variables were described as medians (min; max) and categorical variables as counts (%). Missing data have been excluded. Continuous variables were compared using the Wilcoxon exact test and categorical variables were compared with the Fisher's exact test. All analyses were performed using the R software (the R Foundation for Statistical Computing). A two-tailed significance level was set at $p < 0.05$.

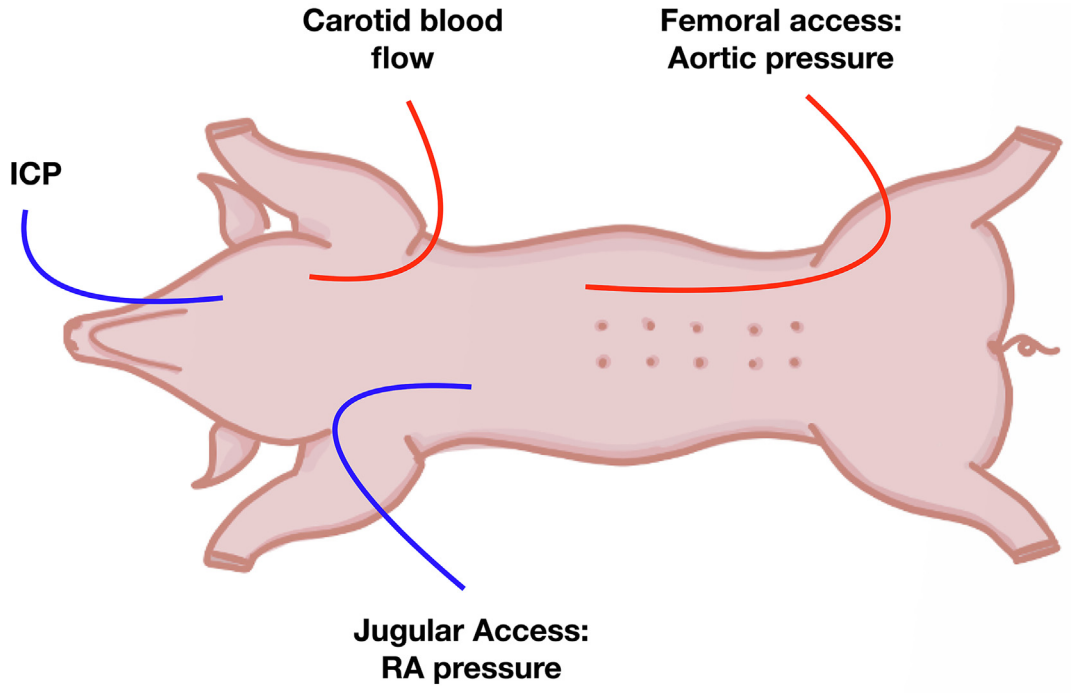

Fig. 1 – Schematic representation of vascular and cerebral accesses. ICP: Intracranial pressure, RA: right atrial.

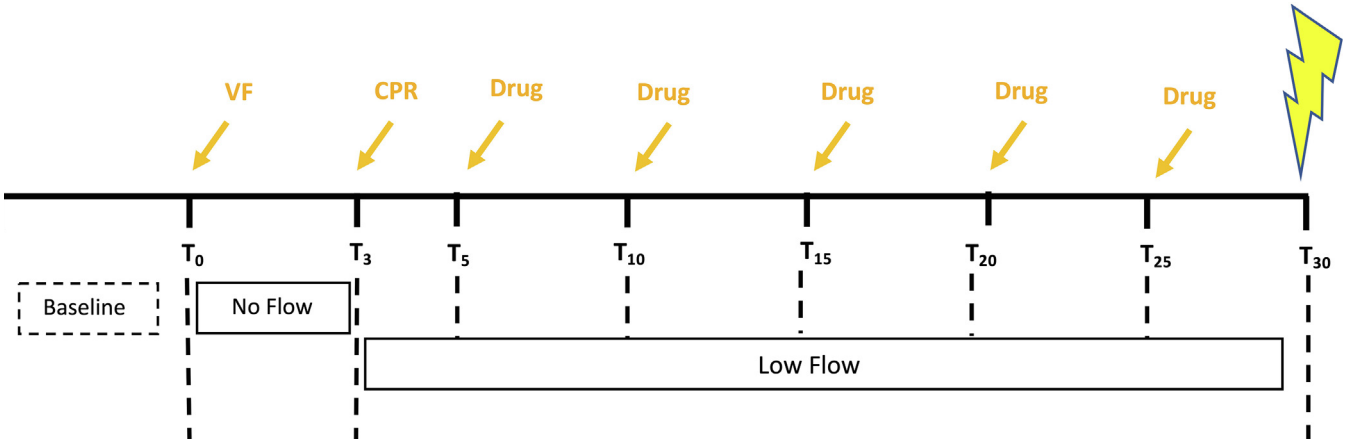

Fig. 2 – Epinephrine vs. Norepinephrine study protocol.

Results

Dose study

Mean CPP was 99 (67; 104.2) mmHg during baseline. This dropped to 14.1 (1.4; 40) mmHg during CPR with 1 mg bolus of NE and to 9.3 (0.1; 34.9) mmHg with 3 mg bolus of NE. Mean CBF was at 183.3 mL/min during baseline recordings and was nearly identical during CPR after 1 mg or 3 mg of NE with 14.1 (−5.7; 76.4) mL/min and 19.7 (−5.7; 69.5) mL/min (Table1).

Epinephrine vs norepinephrine study

Baseline characteristics

Baseline characteristics were similar between the 19 swine included in the study. Weight was 56.2 kg in the EPI group and 57.2 kg in the NE group. CPP at baseline was 72.6 (53.5; 129.7) mmHg in the EPI group and 74.6 (63.2; 97.3) mmHg in the NE group ($p = 0.84$). Mean CBF and CePP were similar in both groups: 151.7 (102.0; 283.1) mL/min vs 206.9 (131.4; 253.8) mL/min ($p = 0.11$) and 72.2 (40.4; 116.6) mmHg vs 59.6 (43.2; 99.6) mmHg ($p = 0.55$) respectively (Table 2).

CPR

During CPR, hemodynamic parameters did not differ significantly between the two groups (Table 2).

MAP dropped to 42.9 (31.2; 57.0) mmHg during the two first minutes of CPR in the Epi group and to 38.6 (30.3; 45.4) mmHg in the NE group ($p = 0.09$). After the first bolus MAP rose to 49.9 (48.0; 69.5) mmHg for the next 5 minutes in the EPI group and to 50.8 (46.4; 64.2) mmHg in the NE group ($p = 0.72$). Overall, during CPR MAP was slightly higher in the EPI group: 40.1 (28.4; 64.0)

Table 1 – Dose-study parameters.

Parameters(Median, min; max)	**Baseline (*n* = 4)**	**1 mg NE (*n* = 4)**	**3 mg NE (*n* = 4)**
SBP (mmHg)	127.6 (95; 135.1)	65.9 (14.1; 117.2)	77.5 (23.6; 125.7)
MAP (mmHg)	105.4 (75.1; 111.5)	33 (−13.2; 74.6)	39.6 (12.3; 77.6)
$RAP_{diastolic}$ (mmHg)	7.5 (3.1; 10.1)	8.9 (5; 14.7)	8.7 (2.1; 17.6)
CPP (mmHg)	99 (67; 104.2)	14.1 (1.4; 40)	9.3 (0.1; 34.9)
CBF (mL/min)	183.3 (149; 219.8)	14.1 (−5.7; 76.4)	19.7 (−5.7; 69.5)

SBP: systolic blood pressure, MAP: mean aortic pressure, RAP: right atrial pressure, CPP: coronary perfusion pressure, CBF: carotid blood flow.

Table 2 – Baseline Parameters for the NE/Epi study.

Parameters(Median, min; max)	**Epinephrine (*n* = 9)**	**Norepinephrine (*n* = 10)**	**p-value**
Weight (kg)	56.2 (42–63)	57.2 (52–62)	0.66
SBP (mmHg)	97.8 (79.8; 160.2)	100.1 (87.5; 128.2)	0.97
MAP (mmHg)	78.7 (61.2; 135.9)	82.8 (72.7; 103.6)	0.84
$RAP_{diastolic}$ (mmHg)	4.8 (0.4; 8.8)	4.5 (2.3; 8.8)	0.97
CPP (mmHg)	72.6 (53.5; 129.7)	74.6 (63.2; 97.3)	0.84
CBF (mL/min)	151.7 (102.0; 283.1)	206.9 (131.4; 253.8)	0.11
ICP (mmHg)	19.3 (3.1; 27.8)	20.9 (3.0; 32.6)	0.36
CePP (mmHg)	72.2 (40.4; 116.6)	59.6 (43.2; 99.6)	0.55

SBP: systolic blood pressure, MAP: mean aortic pressure, RAP: right atrial pressure, CPP: coronary perfusion pressure, CBF: carotid blood flow, ICP: intracranial pressure, CePP: cerebral perfusion pressure.

mmHg vs 35.5 (32.9; 56.6) mmHg (p = 0.5). The difference in the variation of MAP between baseline and CPR was non-significant between the two groups, p = 0.66.

CPP after the first bolus of any drug was similar in the two groups: 28.9 (16.1; 35.7) mmHg for EPI and 24.7 (20.2; 48.1) mmHg for NE, p = 0.97. CPP between T3 and T30 was low and similar in both groups, respectively 17.3 (12.8; 31.8) mmHg and 16.0 (11.1; 37.7) mmHg, p = 0.9.

CBF decreased drastically between baseline and CPR. However, it dropped even more after administration of either drug, from 70.4 (55.9; 138.0) mL/min at T3-T5 to 48.7 (22.0; 73.6) mL/min at T5-T10 in the EPI group and from 76.8 (39.0; 112.7) mL/min to 42.9 (20.4; 57.4) mL/min in the NE group, p = 1 and p = 0.72 respectively. Median CBF during CPR was 28.4 (22.0; 54.8) mL/min and 30.8 (12.2; 56.3) mL/min respectively, p = 0.9 (Table 3). The difference in the variation of CBF between baseline and CPR was non-significant between the two groups: −82.5 (−85.5; −49.3) mL/min in the EPI group and −86.4 (−94.6; −66.6) mL/min in the NE group, p = 0.13.

Finally, CePP was lower in the NE group at all timepoints during CPR although that difference was not statistically significant. Overall CePP was 12.2 (−8.2; 42.2) mmHg in the EPI group and 7.8 (−2.0; 32.0) mmHg in the NE group, p = 0.4 (Table 3). The diminution of CePP between baseline and CPR was greater in the NE group than in the EPI group: −88.4 (−104; −50.9) mmHg and −78.5 (−111.3; −25) mmHg, p = 0.45 respectively.

Only one animal achieved ROSC in the EPI group and 2 in the NE group.

Discussion

In this first experimental study, the dose-study performed first allowed us to establish that a bolus of 1 mg of NE resulted in higher CPP compared to 3 mg. It almost reached the threshold of 15 mmHg (mean of 14.1 mmHg) defined as the minimum to get ROSC during the entire CPR duration (23minutes).[19] Further, when comparing hemodynamic parameters of 1 mg of NE boluses to epinephrine, we showed that NE and epinephrine both have strong α-adrenergic effects and that CPP, CBF or CePP did not differ significantly during CPR between the two groups.

Although epinephrine has been the drug of choice in CPR for decades, overall survival rates after CA remain low and epinephrine's harmful effects have been greatly questioned. The main and most recent randomized trial comparing the use of epinephrine to placebo has relaunched the debate about epinephrine potentially worsening patient's neurological outcome.[20] Although more patients survived at 30 days, the survival with good neurological outcome was similar between the epinephrine and the placebo groups. Similar results were found when focusing on the initial cardiac rhythm.[21] As a matter of fact, cerebral microcirculation seems to be greatly diminished during CPR but also during the first minutes after ROSC when epinephrine is administered.[8] Previous studies have shown that the use of epinephrine during CPR affects CBF. Although CePP increases with vasopressors, CBF significantly drops and the relationship between those parameters and their effect on neurological outcome remains unclear.[22,23] But, by stimulating ß-adrenergic receptors, epinephrine also increases the myocardial oxygen consumption and thus increases the severity of myocardial infarction.[10,24] After ROSC, ß-adrenergic inotropes are prone to induce arrhythmias and more severe post-arrest myocardial dysfunction.[10,25,26] Pure α-agonist drugs such as phenylephrine or methoxamine have shown in previous studies to be as effective or even led to higher pressures and cerebral blood flow.[27–29]

Following this trend, high doses of NE ranging from 0.045 mg/kg to 0.16 mg/kg had been used during CPR in experimental studies and compared to high doses of epinephrine.[30] Resuscitation

Table 3 – Comparison of hemodynamic parameters between the Epinephrine and Norepinephrine groups.

Parameters (Median, min; max)	**Epinephrine (*n* = 9)**	**Norepinephrine (*n* = 10)**	**p-value**
MAP (mmHg)			
T3-T5	42.9 (31.2; 57.0)	38.6 (30.3; 45.4)	0.09
T5-T10	49.9 (48.0; 69.5)	50.8 (46.4; 64.2)	0.72
T10-T15	43.5 (33.1; 67.0)	45.0 (40.3; 60.6)	0.45
T15-T20	37.7 (27.7; 65.5)	38.9 (34.7; 57.7)	0.60
T20-T25	32.0 (14.3; 61.5)	26.3 (17.9; 58.2)	0.55
T25-T30	29.9 (11.8; 59.6)	17.7 (10.2; 51.8)	0.45
T3-T30	40.1 (28.4; 64.0)	35.5 (32.9; 56.6)v	0.50
Δ BL and T5-10	−37.3 (−53.3; −2.8)	−38.0 (−46.8; −17.3)	0.72
Δ BL and CPR (%)	−68.5 (−85.3; −33.3)	−65.3 (−74.6; −33.9)	0.66
CPP (mmHg)			
T3-T5	22.8 (9.1; 30.5)	15.3 (8.2; 26.1)	0.16
T5-T10	28.9 (16.1; 35.7)	24.7 (20.2; 48.1)	0.97
T10-T15	22.3 (13.7; 31.9)	20.6 (15.7; 39.2)	0.66
T15-T20	15.2 (2.9; 32.4)	15.5 (11.6; 39.2)	0.72
T20-T25	16.1 (7.6; 31.8)	6.9 (2.3; 37.5)	0.24
T25-T30	9.4 (5.1; 30.5)	9.6 (1.7; 35.2)	0.50
T3-T30	17.3 (12.8; 31.8)	16.0 (11.1; 37.7)	0.9
Δ BL and T5-10	−63.9 (−85.3; −35.7)	−67.4 (−74.7; −38.2)	0.78
Δ BL-CPR (%)	−72.9 (−88.2; −48.2)	−79.7 (−83.5; −44.6)	0.97
CBF (mL/min)			
T3-T5	70.4 (55.9; 138.0)	76.8 (39.0; 112.7)	1.00
T5-T10	48.7 (22.0; 73.6)	42.9 (20.4; 57.4)	0.72
T10-T15	28.8 (19.1; 66.0)	32.7 (10.3; 59.5)	0.84
T15-T20	27.9 (16.9; 49.5)	26.9 (6.2; 57.6)	0.78
T20-T25	19.4 (5.5; 44.0)	13.7 (5.4; 55.4)	0.32
T25-T30	14.0 (2.2; 35.5)	8.9 (1.9; 55.9)	0.66
T3-T30	28.4 (22.0; 54.8)	30.8 (12.2; 56.3)	0.90
Δ BL and T5-10	−76.4 (−82.9; −31.9)	−80.3 (−90.9; −65.2)	0.24
Δ BL-CPR (%)	−82.5 (−85.5; −49.3)	−86.4 (−94.6; −66.6)	0.13
CePP (mmHg)			
T3-T5	19.9 (−1.6; 39.2)	6.3 (−1.6; 31.7)	0.11
T5-T10	26.6 (6.4; 50.8)	22.6 (10.6; 50.0)	0.24
T10-T15	19.4 (−6.9; 42.4)	18.4 (5.3; 36.6)	0.72
T15-T20	14.2 (−10.7; 43.0)	13.8 (3.3; 30.1)	0.90
T20-T25	5.2 (−16.4; 41.7)	−3.2 (−14.9; 23.2)	0.40
T25-T30	0.5 (−19.4; 36.0)	−9.5 (−17.4; 20.2)	0.45
T3-T30	12.2 (−8.2; 42.2)	7.8 (−2.0; 32.0)	0.40
Δ BL and T5-10	−64.7 (−91.2; −9.5)	−66.4 (−78.9; −43.5)	0.66
Δ BL-CPR (%)	−78.5 (−111.3; −25.0)	−88.4 (−104.0; −50.9)	0.45
ROSC N(%)	1 (11.1)	2 (20)	-

MAP: mean aortic pressure, Δ: variation between baseline and CPR epochs, CPP: coronary perfusion pressure, CBF: carotid blood flow, CePP: cerebral perfusion pressure, ROSC: retour of spontaneous circulation

durations were significantly reduced and myocardial oxygen extraction as well as myocardial blood flow were improved.[13,14,16]

In our study we focused on evaluating CePP and CBF with lower doses of NE and standard doses of epinephrine in an experimental model of VF without looking at microcirculation. We did not show any significant difference between the two groups although the negative variation between baseline and CPR CePP were greater at each timepoint for the NE vs EPI group. This might be explained by a limited effect of NE on cerebral vascularization compared to Epinephrine with a lower vasoconstrictive effect driving to higher intracranial pressure and thus lower CePP. A few papers have suggested that NE might not pass freely the blood–brain barrier thus leading to less vasoconstriction on cerebral vessels.[31,32] Also, CePP is calculated as the difference between MAP and ICP. If systemic vasoconstriction leads to increased ICP due to, among other factors, reduced venous drainage, CePP could be reduced despite a higher MAP. This complex interplay between systemic and cerebral circulation and pressures underscores the importance of understanding the physiological responses to vasopressors during CPR.

An interesting further investigation would be to use a continuous infusion of NE instead of boluses to have a potential steadier effect and increase in CPP and CePP. To the best of our knowledge, there has been no publication on the effect of a NE infusion during CPR compared to a standard dose of epinephrine. Also, the effect on arrhythmias and post-resuscitation myocardial function needs to be evaluated.

Our study had several limitations. The dose of 1 mg was chosen after a preliminary study comparing boluses of 1 and 3 mg of NE but these dosages had been chosen arbitrarily. Another NE dosage may have been more effective. Our ROSC rate was unexpectedly low and we could not evaluate the difference in CPP, CePP and CBF in post-resuscitation due to the low number of survivors. We have no expla-

nation to explain this low survival rate except the length of CPR. Also, ICP was higher than expected in both group at baseline. Although we have no specific explanation, animals did not show any sign of hemorrhage and the NE and Epinephrine ICP's were not significantly different at baseline. Moreover, during CA, ICP is always higher than normal in pigs due to the supine position that limits venous return and has the brain compressing the venous sinuses with its weight. The use of a swine model remains the most reliable CA model but a human trial could show different results.

Conclusion

The use of NE during CPR did not improve hemodynamic parameters. Cerebral perfusion pressure, coronary perfusion pressure and carotid blood flow during CPR did not significantly differ when a bolus of 1 mg of norepinephrine was administered compared to standard doses of epinephrine in an experimental cardiac arrest model of VF. Further investigations assessing for example a continuous infusion rate for NE, could be valuable in a CA model.

CRediT authorship contribution statement

Deborah Jaeger: Writing – review & editing, Writing – original draft, Investigation, Formal analysis, Conceptualization. **Marinos Kosmopoulos:** Writing – review & editing, Formal analysis. **Christopher Gaisendrees:** Writing – review & editing, Formal analysis. **Rajat Kalra:** Writing – review & editing, Methodology. **Alexandra Marquez:** Writing – review & editing, Methodology. **Tahar Chouihed:** Writing – review & editing, Validation, Conceptualization. **Kevin Duarte:** Writing – review & editing, Formal analysis, Data curation. **Demetris Yannopoulos:** Writing – review & editing, Validation, Supervision, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Author details

[a]*Department of Medicine-Cardiovascular Division, University of Minnesota, Minneapolis, MN, USA* [b]*INSERM U 1116, University of Lorraine, Vandœuvre-lès-Nancy, France* [c]*Department of Cardiothoracic Surgery, Heart Centre, University of Cologne, Cologne, Germany* [d]*University of Lorraine, Centre d'Investigations Cliniques Plurithématique 1433, INSERM DCAC, CHRU de Nancy, F-CRIN INI-CRCT, Vandoeuvre-lès-Nancy 54500, France*

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