

ORIGINAL RESEARCH

Effects of Sodium Nitroprusside Administered Via a Subdural Intracranial Catheter on the Microcirculation, Oxygenation, and Electrocortical Activity of the Cerebral Cortex in a Pig Cardiac Arrest Model

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BACKGROUND: Postischemic cerebral hypoperfusion has been indicated as an important contributing factor to secondary cerebral injury after cardiac arrest. We evaluated the effects of sodium nitroprusside administered via a subdural intracranial catheter on the microcirculation, oxygenation, and electrocortical activity of the cerebral cortex in the early postresuscitation period using a pig model of cardiac arrest.

METHODS AND RESULTS: Twenty-nine pigs were resuscitated with closed cardiopulmonary resuscitation after 14 minutes of untreated ventricular fibrillation. Thirty minutes after restoration of spontaneous circulation, 24 pigs randomly received either 4 mg of sodium nitroprusside (IT-SNP group) or saline placebo (IT-saline group) via subdural intracranial catheters and were observed for 5 hours. The same dose of sodium nitroprusside was administered intravenously in another 5 pigs. Compared with the IT-saline group, the IT-SNP group had larger areas under the curve for tissue oxygen tension and percent changes of arteriole diameter and number of perfused microvessels from baseline (all $P < 0.05$) monitored on the cerebral cortex during the 5-hour period, without severe hemodynamic instability. This group also showed faster recovery of electrocortical activity measured using amplitude-integrated electroencephalography. Repeated-measures analysis of variance revealed significant group–time interactions for these parameters. Intravenously administered sodium nitroprusside caused profound hypotension but did not appear to increase the cerebral parameters.

CONCLUSIONS: Sodium nitroprusside administered via a subdural intracranial catheter increased post–restoration of spontaneous circulation cerebral cortical microcirculation and oxygenation and hastened electrocortical activity recovery in a pig model of cardiac arrest. Further studies are required to determine its impact on the long-term neurologic outcomes.

Key Words: heart arrest ■ hypoxia ■ ischemia ■ vasodilator agents

Brain injury is a major cause of mortality and disability following cardiac arrest.¹ Most patients resuscitated from cardiac arrest fail to achieve

long-term survival with favorable neurologic outcomes because of brain injury.^{2,3} Targeted temperature management may improve neurological outcomes after

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CLINICAL PERSPECTIVE

What Is New?

- Sodium nitroprusside administered via a subdural intracranial catheter increased the cerebral cortical microcirculation and oxygenation after resuscitation from cardiac arrest.
- Sodium nitroprusside administered via a subdural intracranial catheter significantly reduced the duration of exposure to cerebral cortical hypoxia and led to faster recovery of electrocortical activity.
- Sodium nitroprusside administered intravenously did not appear to increase the cerebral cortical microcirculation and oxygenation after resuscitation from cardiac arrest.

What Are the Clinical Implications?

- Our findings suggest the potential of intrathecal sodium nitroprusside administration as a treatment for postresuscitation cerebral cortical hypoperfusion and tissue hypoxia.
- Our study suggests the possible therapeutic potential of intrathecal vasodilator administration in hastening the recovery of electrocortical activity after cardiac arrest.

Nonstandard Abbreviations and Acronyms

aEEG	amplitude-integrated electroencephalography
IT-saline	intrathecal saline placebo
IT-SNP	intrathecal sodium nitroprusside
IV-SNP	IV sodium nitroprusside
MFI	microvascular flow index
PctO₂	cortical tissue oxygen tension
ROSC	restoration of spontaneous circulation
SNP	sodium nitroprusside

cardiac arrest and is the standard treatment for patients who are comatose following cardiac arrest.⁴⁻⁶ However, despite implementation of this therapy, the number of patients who fail to achieve meaningful neurologic recovery remains overwhelmingly greater than that of patients who survive with favorable neurologic outcomes. There is thus a critical need for novel effective therapies to reduce brain injury after cardiac arrest.

Cerebral blood flow is a major determinant of cerebral oxygenation.^{7,8} Several studies have reported derangement of cerebral perfusion after resuscitation

from cardiac arrest, characterized by transient cerebral hyperemia and subsequent hypoperfusion.^{9,10} Cerebral hypoperfusion appears within the 1st hour after restoration of spontaneous circulation (ROSC), despite maintaining adequate cerebral perfusion pressure, and persists for several hours or even days¹¹⁻¹⁴; this may contribute to secondary cerebral injury after ROSC by causing cerebral tissue hypoxia.^{15,16} Vasospasm is considered a mechanism responsible for this phenomenon.¹⁷ IV vasodilator drug administration has been evaluated as a measure to treat post-ROSC cerebral hypoperfusion.¹⁸⁻²² However, experimental studies have yielded conflicting results,¹⁸⁻²¹ and clinical studies in patients after cardiac arrest have failed to show benefits of IV vasodilator administration in terms of neurologic recovery.^{22,23} The lack of a clear neurologic benefit of this treatment might be attributed to impaired delivery of systemically administered vasodilator drugs to vascular smooth muscles of vasoconstricted cerebral vessels. Decreased blood flow to a hypoperfused cerebral region could markedly compromise drug delivery to vascular smooth muscles in the hypoperfused cerebral region. Multiple studies have suggested that post-ROSC cerebral hypoperfusion is more pronounced in the cerebral cortex than in other brain regions.^{24,25} Intrathecal administration via a subdural intracranial catheter may effectively deliver a vasodilator drug to the hypoperfused cerebral cortex. Indeed, intrathecal vasodilator drug administration has been successfully used to treat cerebral vasospasm after subarachnoid hemorrhage.²⁶ However, the effectiveness of intrathecally administered vasodilators as a treatment for post-ROSC cerebral cortical hypoperfusion remains undetermined.

Here, as a first step to assessing intrathecal vasodilator administration as a treatment for post-ROSC cerebral cortical hypoperfusion, we evaluated the effects of sodium nitroprusside (SNP) administered via a subdural intracranial catheter on the microcirculation, oxygenation, and electrocortical activity of the cerebral cortex in the early post-ROSC period using a pig cardiac arrest model. We hypothesized that intrathecally administered SNP would ameliorate the post-ROSC cerebral cortical hypoperfusion and thereby improve tissue oxygenation and electrocortical activity recovery.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request. Thirty-one Yorkshire/Landrace cross pigs weighing 24.8±1.2 kg were used for this study. Twenty-six animals were used to compare the effects of SNP administered via a subdural intracranial catheter with those of saline placebo administered the same

way. The effects of the same dose of intravenously administered SNP were investigated in another 5 animals. This study was approved by the Animal Care and Use Committee of Chonnam National University Hospital (CNUH IACUC-21014) and was performed in accordance with the Animal Care and Use Committee guidelines.

Preparation

After arriving at the experimentation facility, the animals were allowed to acclimate for 1 week in a temperature- and light-controlled room (21 °C; 12-hour light/dark cycle) with free access to feed and tap water. The anesthesia, preparation, and data collection procedures have been previously described.^{27–30} Briefly, following initial sedation with intramuscular administration of ketamine (20 mg/kg) and xylazine (2.2 mg/kg), the animals were tracheostomized and mechanically ventilated with a 70/30 mixture of N₂O/O₂ and sevoflurane (titrated to maintain adequate anesthesia). An end-tidal carbon dioxide sampling line was placed between the ventilator circuit and tracheal tube. A 6.0-F introducer sheath was placed in the right external jugular vein for pacing-catheter insertion and right atrial pressure monitoring. A 9.3-F intravascular heat exchange catheter (Cool Line catheter; ZOLL Medical Corporation, Chelmsford, MA) was placed in the right femoral vein for temperature management. A 7.0-F catheter was placed in the left femoral artery for arterial-blood sampling and pressure monitoring. Following the placement of intravascular catheters, the animals were turned to the prone position. After subcutaneous infiltration of 2% lidocaine solution, a longitudinal midline skin incision was made to expose the L2 spinous process, followed by removal of the spinous process. Laminectomy was performed to expose the dura, and a 5-F catheter was introduced into the intrathecal space and advanced to the midthoracic level for cerebrospinal fluid (CSF)-pressure monitoring. After exposure of the right and left parietal regions of the skull, four 10-mm diameter burr holes were made over the right and left parietal cortices (Figure 1). The 2 burr holes located 10-mm posterior to the coronal suture were used to assess cerebral cortical microcirculation and oxygenation. The dura mater underneath 1 burr hole was cut and removed to expose the cerebral cortex. A cover glass was then placed over the burr hole and secured with dental cement to produce a closed cranial window for observation of cerebral cortical microcirculation. After perforation of the dura mater underneath the other burr hole, an optical oxygen sensor (PM-PSt7; PreSens-Precision Sensing GmbH, Regensburg, Germany) was placed in contact with the cerebral cortex to measure cortical tissue oxygen tension (PctO₂). Through the 2 burr holes located 30-mm posterior to the coronal

suture, a 20-G catheter (Perifix ONE Pediatric Epidural Anesthesia Catheter; B. Braun, Bethlehem, PA) was inserted into the subdural space per each burr hole for intrathecal SNP administration. The burr holes for insertion of the optical oxygen sensor and subdural intracranial catheters were then sealed with dental cement to prevent CSF leakage. The animals were turned to the supine position with maximal neck flexion, and, to obtain the amplitude-integrated electroencephalography (aEEG) signal, a pair of needle electrodes were placed on the right and left parietal regions of the animal's head, corresponding to the P3 and P4 positions of the international 10 to 20 system, with a frontal reference electrode. Rectal temperature was monitored and maintained at 37.5±0.5 °C throughout the experiment using an intravascular temperature management system (CoolGard 3000®; ZOLL Medical Corporation). Saline was infused to maintain a right atrium pressure of 6 to 12 mm Hg during the preparation period.

Experimental Protocol

The experimental timeline is shown in Figure 2. Immediately after baseline measurements were obtained, ventricular fibrillation cardiac arrest was induced by delivering an electrical current (alternating current, 60 Hz, 30 mA) through the pacing catheter positioned in the right ventricle. Cardiac arrest was left untreated for 14 minutes without anesthesia, ventilation, or saline infusion. After 14 minutes of untreated cardiac arrest, cardiopulmonary resuscitation (CPR) was started using a mechanical chest compression device (Life-Stat, Michigan Instruments, Grand Rapids, MI), which was set to deliver chest compressions at a rate of 100/min with a depth of ≈20% of the anteroposterior chest diameter. During CPR, ventilation with high flow oxygen (15 L/min) was provided at a rate of 10 L/min. The animals received 0.4 U/kg of vasopressin intravenously at the start of CPR. Defibrillation using a single biphasic 200-J electric shock was attempted every 2 minutes during CPR. If ROSC was not achieved, 0.02 mg/kg of epinephrine was administered 3 minutes after the start of CPR and thereafter every 3 minutes during CPR. CPR was discontinued if ROSC was not achieved within 12 minutes.

Where ROSC was achieved, mechanical ventilation was resumed with 100% oxygen, with the other ventilator settings at the pre-arrest baseline. Fifteen minutes after ROSC, the fraction of inspired oxygen and ventilation rate were adjusted to maintain oxygen saturation of 94% to 99% and end-tidal carbon dioxide of 35 to 40 mm Hg, respectively, and sevoflurane anesthesia was resumed. During the post-ROSC period, mean arterial pressure (MAP) was maintained at >65 mm Hg with norepinephrine infusion on an as-needed basis. For the study to compare the effects of

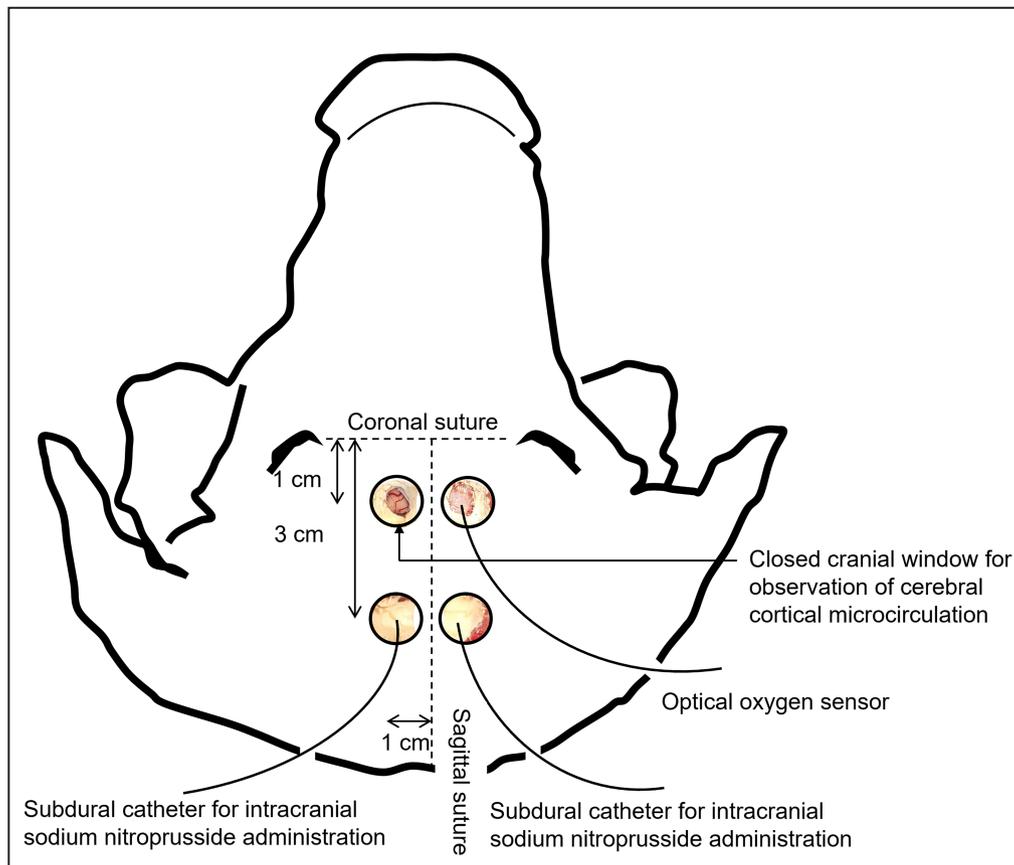


Figure 1. Locations of cranial burr holes for assessment of cerebral cortical microcirculation and oxygenation and for insertion of subdural intracranial catheters.

Cerebral cortical microcirculation and oxygenation were assessed through 2 burr holes located 10-mm posterior to the coronal suture. The assessment side (left or right) was randomized and counterbalanced. The subdural intracranial catheters were inserted through 2 burr holes located 30-mm posterior to the coronal suture.

SNP administered via a subdural intracranial catheter with those of saline placebo, an investigator assigned the animals to the intrathecal saline placebo group (IT-saline group) or the intrathecal SNP group (IT-SNP group) according to the information in a sealed envelope immediately after ROSC and prepared either a saline placebo or SNP solution (4 mg) in equal volumes (1 mL). The concentration of SNP solution was selected based on a previous study involving 21 patients with subarachnoid hemorrhage,²⁶ where 1 to 2 mL of 4 mg/mL SNP solution was intrathecally administered 3 times a day for the prevention of cerebral vasospasm. In our study, we chose to administer 4 mg SNP only once to observe the drug's effect over time. All other investigators were blinded to group assignment. Thirty minutes after ROSC, either the SNP solution or saline placebo was administered via the right and left subdural intracranial catheters (0.5 mL via each catheter). For the study to investigate the effects of intravenously administered SNP, 4 mg of SNP was administered into the right atrium 30 minutes after ROSC (IV-SNP group). The animals were monitored for 5 hours after

the assigned treatment and were then humanely euthanized using an infusion of potassium chloride under deep sevoflurane anesthesia (5%). Autopsy was performed for all animals to inspect for internal-organ injuries or catheter dislocation.

Measurements

Arterial and CSF pressures were continuously monitored and sampled at the pre-arrest baseline, 1-minute intervals for 15 minutes after the assigned treatment, 30 minutes, and 1, 2, 3, 4, and 5 hours after the assigned treatment. Coronary perfusion pressure during CPR was calculated as the difference between the arterial and right atrium pressures, measured at end-diastole. Arterial blood gases (GEM Premier 3000; Instrumentation Laboratory Company, Lexington, MA) were measured at the pre-arrest baseline, immediately before the assigned treatment, at 15, 30, and 60 minutes after the assigned treatment, and thereafter every 60 minutes. Background aEEG activity was monitored using an electroencephalography machine (EEG-1250;

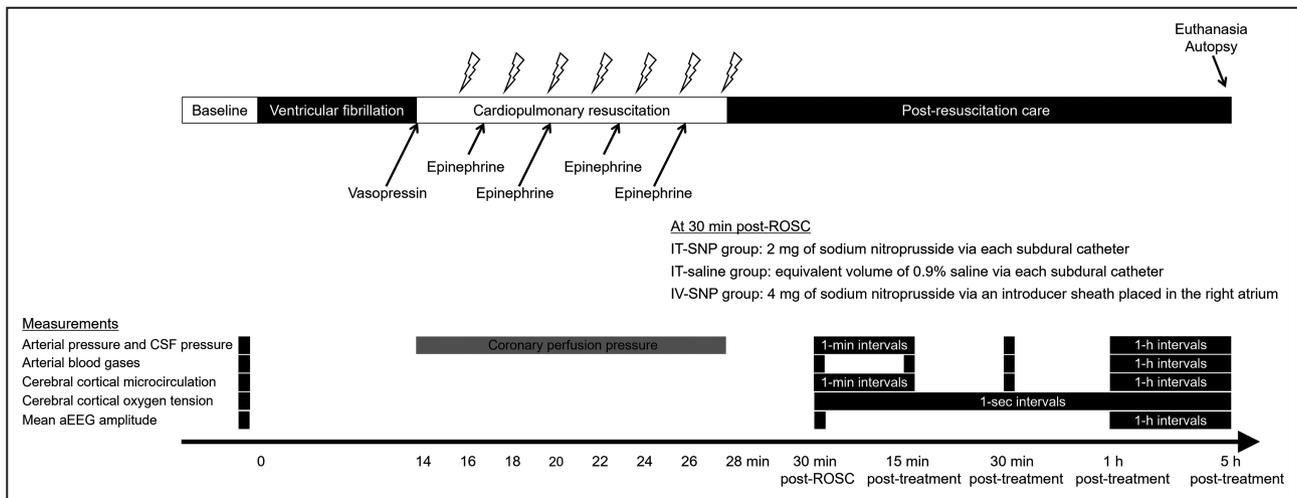


Figure 2. Experimental timeline.

The lightning marks indicate the onset of a 10-second pause in chest compression for rhythm analysis and a biphasic 200-J electric shock, if indicated. aEEG indicates amplitude-integrated electroencephalography; CSF, cerebrospinal fluid; IT-saline, intrathecal saline placebo; IT-SNP, intrathecal sodium nitroprusside; IV-SNP, IV sodium nitroprusside; and ROSC, restoration of spontaneous circulation.

Nihon Kohden, Tokyo, Japan), and the mean aEEG amplitude, calculated by averaging the voltage levels of the upper and lower margins of the aEEG band, was determined at the pre-arrest baseline, immediately before the assigned treatment, and at 1-hour intervals after the assigned treatment. To assess cerebral cortical microcirculation, an experienced investigator obtained cerebral cortical microcirculation videos using a hand-held microscope (G-Scope G5; Genie Tech, Seoul, Korea) placed over the closed cranial window at the pre-arrest baseline, 1-minute intervals for 15 minutes after the assigned treatment, 30 minutes, and 1, 2, 3, 4, and 5 hours after the assigned treatment. The microscope showed an area of interest of $1800 \times 1000 \mu\text{m}^2$ at $\times 250$ magnification. Two investigators blinded to group assignment counted the number of perfused microvessels ($< 20 \mu\text{m}$ in diameter) using the method described by Serné et al³¹ and measured the microvascular flow index (MFI) for the microvessels (absent flow=0, intermittent flow=1, sluggish flow=2, and normal flow=3) by consensus.^{32–34} In addition, a pial arteriole of 30- to 70- μm diameter at the pre-arrest baseline was selected, and the diameter of the arteriole at predetermined time points during the post-ROSC period was measured using ImageJ (Softonic; National Institute of Mental Health, Bethesda, MD). The number of perfused microvessels and the diameter of the arteriole were expressed as a percent of the value relative to that at the pre-arrest baseline (%number of perfused microvessels and %arteriole diameter, respectively) to account for interanimal variations. The PctO_2 was continuously monitored with an oxygen meter (OXY-1 ST; PreSens-Precision Sensing GmbH) and sampled at the pre-arrest baseline and 1-second intervals for

5 hours after the assigned treatment. Cerebral cortical hypoxia was defined as $\text{PctO}_2 < 20 \text{ mm Hg}$,³⁵ and the duration of exposure to cerebral cortical hypoxia after the assigned treatment was determined.

Statistical Analysis

The primary outcomes of this study were PctO_2 and cerebral cortical microcirculation parameters including MFI, number of perfused microvessels, and arteriole diameter. The sample size for the study to compare the IT-saline and IT-SNP groups was calculated based on the PctO_2 data from a pilot study, where the area under the curve (AUC) of PctO_2 during the 5-hour period after the assigned treatment was $386\ 809 \pm 123\ 178$ and $646\ 881 \pm 197\ 860 \text{ mm Hg}\cdot\text{s}$ in the IT-saline and IT-SNP groups, respectively. We calculated that a sample size of $N=10$ per group would be needed to reach $\alpha=0.05$ and power=90% and decided to include 13 animals per group to minimize any effect of data loss. Continuous variables were expressed as means \pm SD or medians with interquartile ranges, whereas categorical variables were expressed as numbers of cases with percentages. For continuous variables serially obtained after the assigned treatment, we calculated the AUC for each animal to measure the overall level of each variable during the 5-hour period after the assigned treatment. AUCs were calculated using the trapezoidal rule and expressed as means \pm SE or medians with interquartile ranges. Comparisons between the groups were conducted using the 2-sample *t* test or Mann-Whitney *U* test for continuous variables and Fisher exact test for categorical variables. Continuous variables, serially obtained after the assigned treatment, were also compared using repeated-measures ANOVA, except for the MFI.

Repeated-measures ANOVA could not be applied to the MFI because the numerous identical numbers at each time point caused an analysis error. The PctO₂ sampling at 1-second intervals for 5 hours after the assigned treatment resulted in 18 000 sampling time points. Inclusion of all data of the 18 000 time points in the repeated-measures ANOVA caused an analysis error because of the numerous time points. Thus, for inclusion in the repeated-measures ANOVA, PctO₂ was resampled at 30-minute intervals for the 5-hour period. If a significant group–time interaction was observed, post-hoc comparisons between the 2 groups at each time point were conducted with Bonferroni corrections. Given the numerous time points for PctO₂, the post-hoc comparisons for PctO₂ were conducted for every 1 minute. Because the experiments for the IV-SNP group were performed after completion of the study to compare the IT-saline and IT-SNP groups, data of the IV-SNP group were not compared with those of the other groups. A 2-tailed $P < 0.05$ was considered significant. Statistical analyses were performed using R version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria) and T&F program version 4.0 (YooJin BioSoft, Goyang, Korea).

RESULTS

Of the 26 animals used in the study to compare the IT-saline and IT-SNP groups, 2 animals failed to achieve

ROSC and were excluded from further analyses. The remaining 24 animals were successfully randomized and survived the 5-hour period after the assigned treatment. All 5 animals in the IV-SNP group survived the 5-hour observation period. Pre-arrest baseline measurements in these animals were within normal limits and did not differ between the IT-saline and IT-SNP groups (Table 1). The repeated-measures ANOVA of the coronary perfusion pressure during CPR revealed no group effect or group–time interaction. Duration of CPR, number of epinephrine doses, and measurements immediately before the assigned treatment were also comparable between the groups (Table 2).

Effects of Intrathecal SNP Administration on Hemodynamic and Blood Gas Parameters

Figure 3 shows the hemodynamic and blood gas data after the assigned treatment. Unlike IV SNP administration, which caused profound hypotension, intrathecal SNP administration caused only a small transient drop of the MAP within 5 minutes. The repeated-measures ANOVA of the MAP revealed a significant group–time interaction ($P = 0.010$), but no significant difference was found between the IT-saline and IT-SNP groups at any time point in the post-hoc analysis. The AUC for MAP also did not differ between the groups. The

Table 1. Pre-Arrest Baseline Measurements

Variable	IT-saline group (N=12)	IT-SNP group (N=12)	P value*	IV-SNP group (N=5)
Weight, kg	24.6±1.5	24.8±1.0	0.816	25.1 (24.8–25.7)
Systolic arterial pressure, mm Hg	116±12	122±7	0.153	127 (110–128)
Diastolic arterial pressure, mm Hg	80±13	84±5	0.342	75 (64–86)
Mean arterial pressure, mm Hg	95±11	98±7	0.479	90 (77–107)
Systolic right atrial pressure, mm Hg	9±2	9±2	0.690	9 (9–10)
Diastolic right atrial pressure, mm Hg	5 (5–5)	5 (4–5)	0.927	4 (4–5)
Mean right atrial pressure, mm Hg	7±2	7±1	0.718	6 (6–7)
Heart rate, beats/min	94±6	91±9	0.377	87 (86–91)
Rectal temperature, °C	37.1±0.7	37.2±0.5	0.661	37.0 (36.9–37.1)
Arterial pH	7.514±0.038	7.536±0.029	0.132	7.490 (7.480–7.490)
Paco ₂ , mm Hg	39.8±3.1	38.1±3.0	0.174	44.0 (43.0–45.0)
PaO ₂ , mm Hg	135.0±14.3	141.7±15.5	0.285	136.0 (126.0–150.0)
Arterial lactate, mmol/L	1.32±0.35	1.38±0.58	0.736	1.10 (1.10–1.30)
PctO ₂ , mm Hg	35.7±5.9	36.1±7.9	0.896	40.5 (38.5–43.7)
CSF pressure, mm Hg	8±1	8±2	0.892	6 (5–7)
Mean aEEG amplitude, µV	52.2±12.5	55.6±20.5	0.627	44.0 (41.0–48.0)
Microvascular flow index	3.0 (3.0–3.0)	3.0 (3.0–3.0)	0.266	3.0 (3.0–3.0)
Number of perfused microvessels, N	15±3	15±2	0.699	18 (17–19)

Data are presented as mean±SD or medians with interquartile ranges. aEEG indicates amplitude-integrated electroencephalography; CSF, cerebrospinal fluid; IT-saline, intrathecal saline placebo; IT-SNP, intrathecal sodium nitroprusside; IV-SNP, IV sodium nitroprusside; Paco₂, partial pressure of arterial carbon dioxide; PaO₂, partial pressure of arterial oxygen; and PctO₂, cortical tissue oxygen tension.

*P values were computed using the 2-sample *t* test or Mann–Whitney *U* test for differences between the IT-saline and IT-SNP groups.

Table 2. Resuscitation Variables and Measurements Before the Assigned Treatment

Variable	IT-saline group (N=12)	IT-SNP group (N=12)	P value*	IV-SNP group (N=5)
Resuscitation variables				
Number of electrical countershocks, N	2 (2–5)	4 (2–5)	0.422	3 (2–5)
Number of epinephrine doses, N [†]	1	1	NA	1
Duration of CPR, min	4 (4–4)	4 (4–4)	0.166	4 (4–4)
Measurements immediately before the assigned treatment				
Systolic arterial pressure, mm Hg	115±28	111±18	0.699	112 (112–126)
Diastolic arterial pressure, mm Hg	83±22	79±14	0.636	82 (78–95)
Mean arterial pressure, mm Hg	96±24	91±14	0.532	93 (93–109)
Systolic right atrial pressure, mm Hg	14±3	14±3	0.470	17 (13–18)
Diastolic right atrial pressure, mm Hg	8±3	9±2	0.101	9 (7–9)
Mean right atrial pressure, mm Hg	10±3	11±2	0.212	11 (9–13)
Heart rate, beats/min	173±28	161±20	0.223	162 (152–175)
Rectal temperature, °C	36.9±0.5	36.8±0.6	0.806	36.6 (36.3–37.0)
Arterial pH	7.194±0.064	7.213±0.056	0.404	7.170 (7.160–7.170)
Paco ₂ , mm Hg	51.6±6.9	48.0±4.8	0.156	57.0 (54.0–59.0)
PaO ₂ , mm Hg	109.4±16.9	113.5±18.3	0.576	93.0 (90.0–103.0)
Arterial lactate, mmol/L	7.78±0.57	7.95±1.00	0.604	8.10 (7.70–8.70)
PctO ₂ , mm Hg	34.6±15.7	36.1±13.2	0.796	37.2 (25.0–37.3)
CSF pressure, mm Hg	10±2	11±2	0.508	9 (7–12)
Mean aEEG amplitude, µV	9.0±2.3	9.5±4.1	0.735	7.0 (7.0–8.5)
Microvascular flow index	2.9 (2.8–3.0)	3.0 (2.8–3.0)	0.447	3.0 (3.0–3.0)
%Number of perfused microvessels, %	105±12	103±12	0.602	105 (104–106)
%Arteriole diameter (%)	99 (89–115)	99 (93–111)	0.977	96 (87–118)

Data are presented as mean±SD or medians with interquartile ranges except for the AUC of CPP, which is presented as mean±SE. aEEG indicates amplitude-integrated electroencephalography; AUC, area under the curve; CPP, coronary perfusion pressure; CPR, cardiopulmonary resuscitation; CSF, cerebrospinal fluid; IT-saline, intrathecal saline placebo; IT-SNP, intrathecal sodium nitroprusside; IV-SNP, IV sodium nitroprusside; NA, not available; Paco₂, partial pressure of arterial carbon dioxide; PaO₂, partial pressure of arterial oxygen; and PctO₂, cortical tissue oxygen tension.

*P values were computed using the 2-sample *t* test or Mann-Whitney *U* test for differences between the IT-saline and IT-SNP groups.

[†]The number of epinephrine doses was 1 in all animals.

total dose of norepinephrine administered after the assigned treatment was similar between the IT-saline and IT-SNP groups (0.04 [0.01–0.13] mg and 0.03 [0–0.09] mg in the IT-saline and IT-SNP groups, respectively; *P*=0.597). In the IV-SNP group, a relatively high dose of norepinephrine (0.27 [0.11–0.32] mg) was administered after the assigned treatment. The CSF pressure gradually increased over time in both groups, with no significant difference in the AUC of CSF pressure between the groups. Neither the AUC of PaO₂ nor that of Paco₂ differed between the groups. The repeated-measures ANOVA of the CSF pressure, PaO₂, and Paco₂ also revealed no group effects or group–time interactions.

Effects of Intrathecal SNP Administration on the Microcirculation, Oxygenation, and Electrocardiac Activity of the Cerebral Cortex

Figure 4 shows the cerebral cortical microcirculation, PctO₂, and mean aEEG amplitude data after the

assigned treatment. In the IT-saline group, the arteriole diameter and number of perfused microvessels decreased to ≈87% and 91% of the baseline values, respectively, at 15 minutes after the assigned treatment (45 minutes after ROSC), and thereafter increased gradually. In this group, the MFI decreased to ≈84% of the baseline values at 5 minutes after the assigned treatment and remained decreased for 2 hours. Intrathecal SNP administration immediately increased the arteriole diameter and number of perfused microvessels (Video S1). The arteriole diameter and number of perfused microvessels increased to 170.8% and 151.2% of the baseline values, respectively, at 3 minutes after the intrathecal SNP administration and remained increased throughout the 5-hour observation period. In the IT-SNP group, MFI remained close to 3 throughout the 5-hour observation period. The AUCs of %arteriole diameter (*P*<0.001), %number of perfused microvessels (*P*=0.004), and MFI (*P*=0.022) were significantly higher in the IT-SNP group than in the IT-saline group. The PctO₂ rapidly increased after

intrathecal SNP administration; it gradually decreased after 5 minutes but remained at higher levels than in the IT-saline group throughout the observation period. The AUC for PctO₂ was significantly higher in the IT-SNP group than in the IT-saline group ($P=0.014$). The repeated-measures ANOVA of the %arteriole diameter, %number of perfused microvessels, and PctO₂ revealed significant group effects ($P<0.001$ for %arteriole diameter and %number of perfused microvessels; $P=0.034$ for PctO₂) and group–time interactions ($P=0.042$ for %arteriole diameter; $P<0.001$ for %number of perfused microvessels and PctO₂). In the post-hoc analyses, %number of perfused microvessels and %arteriole diameter of the IT-SNP group increased significantly compared with the IT-saline group for 1 and 2 hours after the assigned treatment, respectively. The PctO₂ of the IT-SNP group increased significantly compared with the IT-saline group for 25 minutes after the assigned treatment. Eight animals (66.7%) in the IT-saline group and 3 animals (25.0%) in the IT-SNP group developed cerebral cortical hypoxia after the assigned treatment ($P=0.100$). The duration of exposure to cerebral cortical hypoxia was significantly shorter in the IT-SNP group (0 [0–0.1] minute) than in the IT-saline group (3.8 [0–41.5] minute, $P=0.028$). IV SNP administration did not produce remarkable changes as shown after intrathecal SNP administration with regard to the arteriole diameter, number of perfused microvessels, MFI, and PctO₂. In the IV-SNP group, the arteriole diameter and number of perfused vessels increased only to $\approx 132.2\%$ and 117.0% of the baseline values, respectively, at 2 minutes after the IV SNP administration, and these effects lasted for <10 minutes. Immediately after inducing cardiac arrest, the mean aEEG amplitude was severely depressed in all animals. Although the AUC of the mean aEEG amplitude did not differ between the IT-saline and IT-SNP groups, the recovery of mean aEEG amplitude was faster in the IT-SNP group than in the IT-saline group. At the end of the 5-hour observation period, the mean aEEG amplitude recovered to $43.6\pm 15.0\%$ of the baseline values in the IT-SNP group and to $31.9\pm 8.3\%$ of the baseline values in the IT-saline group ($P=0.030$). The repeated-measures ANOVA of the mean aEEG amplitude revealed a significant group–time interaction ($P=0.008$). The recovery rate of the mean EEG amplitude in the IV-SNP group was similar to that in the IT-saline group.

DISCUSSION

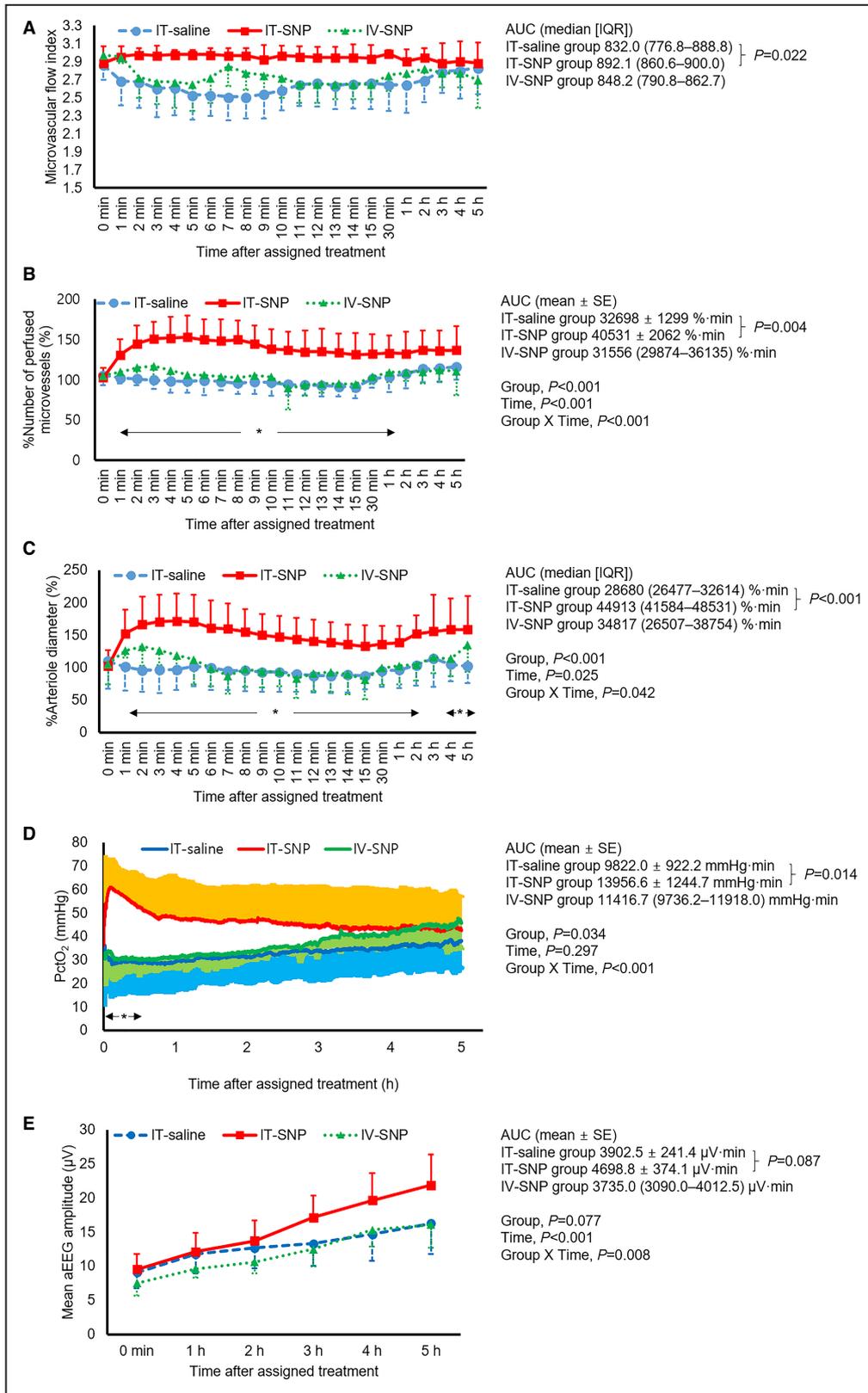
To our knowledge, this was the first study to evaluate the effectiveness of intrathecal vasodilator administration as a treatment for post-ROSC cerebral hypoperfusion. Here, SNP administered via a subdural intracranial catheter markedly increased arteriole diameter, number of perfused microvessels, MFI, and tissue oxygen

tension of the cerebral cortex, all of which did not appear to increase with IV SNP administration. Intrathecal SNP administration significantly reduced the duration of exposure to cerebral cortical hypoxia and led to faster recovery of the mean aEEG amplitude. These results suggest the potential of intrathecal SNP administration as a treatment for post-ROSC cerebral cortical hypoperfusion.

Sufficient cerebral oxygenation would be critical to prevent secondary hypoxic brain injury after cardiac arrest. Multiple studies in patients with severe traumatic brain injury have suggested that the magnitude and duration of cerebral tissue hypoxia correlate with poor outcomes.^{36–39} A significant number of patients following cardiac arrest may be exposed to cerebral tissue hypoxia during the post-ROSC period despite maintaining adequate cerebral perfusion pressure and arterial oxygenation. Here, 66.7% of the animals in the IT-saline group experienced cerebral cortical hypoxia, although the MAP and Pao₂ clearly remained within the normal range throughout the 5-hour observation period; multiple studies have reported similar findings.^{27,28,40} In a clinical study including 14 patients comatose following cardiac arrest who underwent multimodal neuromonitoring, 7 (50%) experienced PctO₂ <20 mm Hg.⁴⁰ Microcirculation is dissociated from macrovascular circulation during the early post-ROSC period.^{41,42} Cerebral cortical hypoxia in the absence of hypoxemia or hypotension is likely caused by impaired cerebral cortical microcirculation, as reflected by decreases in arteriole diameter, number of perfused microvessels, and MFI in the IT-saline group.

Multiple mechanisms, including increased blood viscosity, intravascular platelet aggregation, perivascular edema, and vasospasm, have been proposed as causative factors of post-ROSC cerebral hypoperfusion.^{43–46} The marked increase in cerebral cortical microcirculation after intrathecal SNP administration seen here supports the possibility of vasospasm as an important factor responsible for post-ROSC cerebral hypoperfusion. Vasospasm during the post-ROSC period may be caused by imbalance between local vasodilators and vasoconstrictors.^{17,47,48} SNP causes relaxation of vascular smooth muscles by releasing nitric oxide to the vascular wall and has long been used to treat vasospasm.⁴⁹ The mechanism by which intrathecally administered SNP increases PctO₂ is likely related to the SNP action on the vascular smooth muscles of pial arterioles on the brain surface, which is a major site for regulation of local cerebral blood flow.⁴⁶ We believe that SNP-induced pial arteriolar dilation increased oxygen delivery to brain tissue by increasing blood flow to the capillaries, the primary site of oxygen and nutrient exchange between blood and brain tissue.

In our study, IV SNP administration increased the arteriole diameter to a similar extent as previously



reported.⁵⁰ In anesthetized rats, IV SNP infusion, at doses that lowered arterial pressure to a similar extent as in our study, increased the pial arteriolar diameter by $\approx 33.1\%$.⁵⁰ However, in our study, this effect

disappeared within 10 minutes following termination of administration, and consequently, cerebral parameter results of the IV-SNP group were overall similar to those of the IT-saline group. The rapid dissipation

Figure 4. Microvascular flow index (A), %number of perfused microvessels (B), %arteriole diameter (C), PctO₂ (D), and mean aEEG amplitude (E) after the assigned treatment.

Error bars represent the SD. * $P < 0.05$ after Bonferroni correction (IT-saline group vs IT-SNP group). P values for difference in AUCs between the IT-saline and IT-SNP groups were computed using the 2-sample t test or Mann–Whitney U test. P values for group effect, time effect, and group–time interaction were computed using repeated-measures analysis of variance. aEEG indicates amplitude-integrated electroencephalography; AUC, area under the curve; IQR, interquartile range; IT-saline, intrathecal saline placebo; IT-SNP, intrathecal sodium nitroprusside; IV-SNP, IV sodium nitroprusside; and PctO₂, cortical tissue oxygen tension.

of the effect of intravenously administered SNP might result from its very short serum half-life. Given this finding, IV SNP administration would likely fail to improve cerebral microcirculation, especially in the presence of typical postischemic cerebral hypoperfusion. In addition, IV SNP administration, not unexpectedly, caused profound hypotension and led to a very high norepinephrine requirement to reach and maintain the target MAP, rendering this treatment unsuitable for clinical use. The high norepinephrine dose in the IV-SNP group could also have limited the ability of intravenously administered SNP to increase cerebral cortical microcirculation.⁵¹

In contrast, intrathecal administration of the same dose of SNP markedly increased cerebral cortical microcirculation. Intrathecally administered drugs might be less diluted compared with the same drugs administered intravenously (because of the smaller volume of the CSF compartment relative to that of the blood compartment), and they bypass systemic circulation, leading to reduced drug metabolism. Given these points, intrathecal administration in our study likely achieved high CSF drug concentration and maintained it for a prolonged time. In addition, drug administration via a subdural intracranial catheter likely provided ready access of the drug to cortical arterioles independent of the blood flow to the arterioles. Importantly, unlike intravenously administered SNP that caused profound hypotension, intrathecally administered SNP did not cause serious hemodynamic side effects.

Sodium nitrite, which causes vasodilation by generating nitric oxide like SNP, has been investigated as a potential agent to improve neurologic outcomes after cardiac arrest but failed to show a consistent benefit in improving neurologic outcomes after cardiac arrest. Sodium nitrite improved neurologic outcome and survival in some murine models of cardiac arrest but not in another cardiac arrest model.^{52–54} In a large randomized clinical trial of sodium nitrite versus saline placebo for adult out-of-hospital cardiac arrest,⁵⁵ sodium nitrite given by paramedics during active resuscitation failed to improve survival or neurologic outcome. The reason why sodium nitrite failed to show consistent neurologic benefit in these studies is not clear. It is possible that nitric oxide delivered to cerebral microvessels did not sufficiently improve post-ROSC cerebral hypoperfusion. Given the marked increases in cerebral cortical microcirculation and oxygenation following intrathecal

SNP administration, intrathecal SNP administration as a potential treatment to improve neurologic outcomes after cardiac arrest warrants further investigation.

It should be pointed out that cerebral cortical hypoperfusion in the IT-saline group was not as pronounced as expected. In ventricular fibrillation cardiac arrest models with untreated cardiac arrest duration similar to that in our study,^{10,25,56,57} cerebral blood flow was reduced to 50% to 60% of the baseline values in the early postresuscitation period. However, in the IT-saline group of our study, only a subtle reduction in cerebral cortical microcirculation was observed during the 5-hour observation period. Although 66.7% of animals in this group developed cerebral cortical hypoxia at some time points after ROSC, the PctO₂ values, which mirrored the changes in cerebral cortical microcirculation,^{8,58} remained close to baseline values during the 5-hour observation period. The reason why cerebral cortical hypoperfusion was not pronounced in the IT-saline group is not clear, but several factors could have contributed to this. In our study, the animals were ventilated with a mixture of N₂O/O₂ and kept anesthetized by sevoflurane during the post-ROSC period. Both N₂O and sevoflurane have been shown to dilate cerebral microvessels and increase cerebral blood flow.^{59–62} Hyperoxemia and hypocapnia, both of which could cause cerebral vasoconstriction,⁶³ were strictly avoided during the post-ROSC period. In fact, although adjustment of ventilation rate to maintain normocapnia was initiated 15 minutes before the assigned treatment, the Paco₂ level was still in the hypercapnic range for 15 minutes after the assigned treatment. Young age might also have contributed to the non-prominent development of cerebral cortical hypoperfusion in our model.⁶⁴ Unlike our model in which cerebral cortical hypoperfusion was not prominent, the effects of intrathecal SNP administration may be small or even insignificant in a model with pronounced cerebral cortical hypoperfusion. Thus, further studies are required to confirm the ability of intrathecal SNP administration to ameliorate cerebral cortical hypoperfusion.

This study has several limitations. First, it was performed using young healthy pigs. Human patients who experience cardiac arrest are typically older and frequently have comorbidities such as hypertension. It is thus difficult to directly extrapolate the findings of this study to human patients who experience cardiac arrest. In particular, given the relatively low intracranial

CSF volume in young pigs,⁶⁵ the SNP concentration in CSF and its cerebral effects after administration of the same dose of SNP via a subdural catheter may decrease in adult patients with cardiac arrest. Second, we did not assess the impact of intrathecal SNP administration on neurologic function. We neither assessed biomarkers of brain injury, such as neuron-specific enolase, nor performed a histologic assessment of the cerebral injury. These assessments require support and observation of the animals for a prolonged period of time as biochemical, histologic, and functional neurologic consequences of hypoxic–ischemic brain injury are established over several days.^{66,67} However, because of our limited resources, we could not support and keep the animals for a long period of time. Given that multiple studies have suggested a significant inverse correlation between the background aEEG activity and severity of hypoxic–ischemic brain injury,^{68,69} the faster recovery of the mean aEEG amplitude in the IT-SNP group than in the IT-saline group suggested that IT-SNP administration might facilitate neurologic recovery after cardiac arrest. Further studies, including biochemical, histologic, and functional neurologic assessments of cerebral injury, are required to verify this possibility. Third, the cerebral measurements were limited to the cerebral cortex; thus, we could not evaluate cerebral perfusion in other brain regions including in deep brain structures. A study to address this issue by means of dynamic susceptibility contrast-magnetic resonance imaging is currently under way in our laboratory. Fourth, we chose 14 minutes as the duration of untreated cardiac arrest to obtain marked development of post-ROSC cerebral cortical hypoperfusion to allow monitoring of treatment effects. This prolonged duration of untreated cardiac arrest may not be suitable for evaluation of a therapy aimed at ameliorating post-ROSC cerebral hypoperfusion and the corresponding effects on neurologic outcomes. Previous studies have reported that the severity of neuronal injury increases with increased duration of untreated cardiac arrest, and no animals achieve a good neurologic recovery after untreated cardiac arrest of ≥ 14 minutes.^{70,71} Our model might induce severe histologic brain injury with little or no chance of recovery with a treatment to augment cerebral perfusion, thus making it less relevant when evaluating this type of therapy. Fifth, we could not determine the optimal dose and dosing interval of intrathecal SNP.

CONCLUSIONS

SNP administered via a subdural intracranial catheter augmented post-ROSC cerebral cortical microcirculation and oxygenation in a pig cardiac arrest model. This was accompanied by a reduced duration of exposure

to cerebral cortical hypoxia and hastened the recovery of electrocortical activity. Further studies are required to evaluate the potential of this treatment as a therapy to improve neurologic outcomes following cardiac arrest.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Video S1

REFERENCES

- Lemiale V, Dumas F, Mongardon N, Giovanetti O, Charpentier J, Chiche JD, Carli P, Mira JP, Nolan J, Cariou A. Intensive care unit mortality after cardiac arrest: the relative contribution of shock and brain injury in a large cohort. *Intensive Care Med*. 2013;39:1972–1980. doi: [10.1007/s00134-013-3043-4](https://doi.org/10.1007/s00134-013-3043-4)
- Ong MEH, Shin SD, De Souza NNA, Tanaka H, Nishiuchi T, Song KJ, Ko P-I, Leong B-H, Khunkhlay N, Naroo GY, et al. Outcomes for out-of-hospital cardiac arrests across 7 countries in Asia: the Pan Asian Resuscitation Outcomes Study (PAROS). *Resuscitation*. 2015;96:100–108. doi: [10.1016/j.resuscitation.2015.07.026](https://doi.org/10.1016/j.resuscitation.2015.07.026)
- Kim SH, Park KN, Youn CS, Chae MK, Kim WY, Lee BK, Lee DH, Jang TC, Lee JH, Choi YH, et al. Outcome and status of postcardiac arrest care in Korea: results from the Korean Hypothermia Network prospective registry. *Clin Exp Emerg Med*. 2020;7:250–258. doi: [10.15441/ceem.20.035](https://doi.org/10.15441/ceem.20.035)
- Hypothermia after Cardiac Arrest Study Group. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. *N Engl J Med*. 2002;346:549–556.
- Bernard SA, Gray TW, Buist MD, Jones BM, Silvester W, Gutteridge G, Smith K. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. *N Engl J Med*. 2002;346:557–563. doi: [10.1056/NEJMoa003289](https://doi.org/10.1056/NEJMoa003289)
- Lascarrou J-B, Merdji H, Le Gouge A, Colin G, Grillet G, Girardie P, Coupez E, Dequin P-F, Cariou A, Boulain T, et al. Targeted temperature management for cardiac arrest with nonshockable rhythm. *N Engl J Med*. 2019;381:2327–2337. doi: [10.1056/NEJMoa1906661](https://doi.org/10.1056/NEJMoa1906661)
- Doppenberg EM, Zauner A, Bullock R, Ward JD, Fatouros PP, Young HF. Correlations between brain tissue oxygen tension, carbon dioxide tension, pH, and cerebral blood flow—a better way of monitoring the severely injured brain? *Surg Neurol*. 1998;49:650–654. doi: [10.1016/S0090-3019\(97\)00355-8](https://doi.org/10.1016/S0090-3019(97)00355-8)

8. Valadka AB, Hlatky R, Furuya Y, Robertson CS. Brain tissue PO₂: correlation with cerebral blood flow. *Acta Neurochir Suppl.* 2002;81:299–301.
9. Tanahashi N, Fukuchi Y, Tomita M, Kobari M, Takeda H, Yokoyama M. Pentoxifylline ameliorates postischemic delayed hypoperfusion of the cerebral cortex following cardiac arrest in cats. *J Neurol Sci.* 1995;132:105–109. doi: [10.1016/0022-510X\(95\)00153-S](https://doi.org/10.1016/0022-510X(95)00153-S)
10. Sterz F, Safar P, Johnson DW, Oku K, Tisherman SA. Effects of U74006F on multifocal cerebral blood flow and metabolism after cardiac arrest in dogs. *Stroke.* 1991;22:889–895. doi: [10.1161/01.STR.22.7.889](https://doi.org/10.1161/01.STR.22.7.889)
11. Drabek T, Foley LM, Janata A, Stezoski J, Hitchens TK, Manole MD, Kochanek PM. Global and regional differences in cerebral blood flow after asphyxial versus ventricular fibrillation cardiac arrest in rats using ASL-MRI. *Resuscitation.* 2014;85:964–971. doi: [10.1016/j.resuscit.ion.2014.03.314](https://doi.org/10.1016/j.resuscit.ion.2014.03.314)
12. Sterz F, Leonov Y, Safar P, Johnson D, Oku K-I, Tisherman SA, Latchaw R, Obrist W, Stezoski SW, Hecht S, et al. Multifocal cerebral blood flow by Xe-CT and global cerebral metabolism after prolonged cardiac arrest in dogs. Reperfusion with open-chest CPR or cardiopulmonary bypass. *Resuscitation.* 1992;24:27–47. doi: [10.1016/0300-9572\(92\)90171-8](https://doi.org/10.1016/0300-9572(92)90171-8)
13. Manole MD, Foley LM, Hitchens TK, Kochanek PM, Hickey RW, Bayir H, Alexander H, Ho C, Clark RS. 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. doi: [10.1038/jcbfm.2008.112](https://doi.org/10.1038/jcbfm.2008.112)
14. Liachenko S, Tang P, Hamilton RL, Xu Y. Regional dependence of cerebral reperfusion after circulatory arrest in rats. *J Cereb Blood Flow Metab.* 2001;21:1320–1329. doi: [10.1097/00004647-200111000-00008](https://doi.org/10.1097/00004647-200111000-00008)
15. Johansson SE, Larsen SS, Povlsen GK, Edvinsson L. Early MEK1/2 inhibition after global cerebral ischemia in rats reduces brain damage and improves outcome by preventing delayed vasoconstrictor receptor upregulation. *PLoS One.* 2014;9:e92417. doi: [10.1371/journal.pone.0092417](https://doi.org/10.1371/journal.pone.0092417)
16. Roine RO, Launes J, Nikkinen P, Lindroth L, Kaste M. Regional cerebral blood flow after human cardiac arrest. A hexamethylpropyleneamine oxime single photon emission computed tomographic study. *Arch Neurol.* 1991;48:625–629. doi: [10.1001/archneur.1991.00530180081021](https://doi.org/10.1001/archneur.1991.00530180081021)
17. Buunk G, van der Hoeven JG, Frölich M, Meinders AE. Cerebral vasoconstriction in comatose patients resuscitated from a cardiac arrest? *Intensive Care Med.* 1996;22:1191–1196. doi: [10.1007/BF01709335](https://doi.org/10.1007/BF01709335)
18. Vaagenes P, Cantadore R, Safar P, Moosy J, Rao G, Diven W, Alexander H, Stezoski W. Amelioration of brain damage by lidoflazine after prolonged ventricular fibrillation cardiac arrest in dogs. *Crit Care Med.* 1984;12:846–855. doi: [10.1097/00003246-198410000-00002](https://doi.org/10.1097/00003246-198410000-00002)
19. Steen PA, Newberg LA, Milde JH, Michenfelder JD. Nimodipine improves cerebral blood flow and neurologic recovery after complete cerebral ischemia in the dog. *J Cereb Blood Flow Metab.* 1983;3:38–43. doi: [10.1038/jcbfm.1983.4](https://doi.org/10.1038/jcbfm.1983.4)
20. Steen PA, Gisvold SE, Milde JH, Newberg LA, Scheithauer BW, Lanier WL, Michenfelder JD. Nimodipine improves outcome when given after complete cerebral ischemia in primates. *Anesthesiology.* 1985;62:406–414. doi: [10.1097/00000542-198504000-00007](https://doi.org/10.1097/00000542-198504000-00007)
21. Sakabe T, Nagai I, Ishikawa T, Takeshita H, Masuda T, Matsumoto M, Tateishi A. Nicardipine increases cerebral blood flow but does not improve neurologic recovery in a canine model of complete cerebral ischemia. *J Cereb Blood Flow Metab.* 1986;6:684–690. doi: [10.1038/jcbfm.1986.124](https://doi.org/10.1038/jcbfm.1986.124)
22. Forsman M, Aarseth HP, Nordby HK, Skulberg A, Steen PA. Effects of nimodipine on cerebral blood flow and cerebrospinal fluid pressure after cardiac arrest: correlation with neurologic outcome. *Anesth Analg.* 1989;68:436–443. doi: [10.1213/00005539-198904000-00003](https://doi.org/10.1213/00005539-198904000-00003)
23. Brain Resuscitation Clinical Trial II Study Group. A randomized clinical study of a calcium-entry blocker (lidoflazine) in the treatment of comatose survivors of cardiac arrest. *N Engl J Med.* 1991;324:1225–1231.
24. Mörtberg E, Cumming P, Wiklund L, Wall A, Rubertsson S. A PET study of regional cerebral blood flow after experimental cardiopulmonary resuscitation. *Resuscitation.* 2007;75:98–104. doi: [10.1016/j.resuscit.ion.2007.03.020](https://doi.org/10.1016/j.resuscit.ion.2007.03.020)
25. Mörtberg E, Cumming P, Wiklund L, Rubertsson S. Cerebral metabolic rate of oxygen (CMRO₂) in pig brain determined by PET after resuscitation from cardiac arrest. *Resuscitation.* 2009;80:701–706. doi: [10.1016/j.resuscitation.2009.03.005](https://doi.org/10.1016/j.resuscitation.2009.03.005)
26. Thomas JE, Rosenwasser RH, Armonda RA, Harrop J, Mitchell W, Galaria I. Safety of intrathecal sodium nitroprusside for the treatment and prevention of refractory cerebral vasospasm and ischemia in humans. *Stroke.* 1999;30:1409–1416. doi: [10.1161/01.STR.30.7.1409](https://doi.org/10.1161/01.STR.30.7.1409)
27. Lee HY, Shamsiev K, Mamadjonov N, Jung YH, Jeung KW, Kim JW, Heo T, Min YI. Effect of epinephrine administered during cardiopulmonary resuscitation on cerebral oxygenation after restoration of spontaneous circulation in a swine model with a clinically relevant duration of untreated cardiac arrest. *Int J Environ Res Public Health.* 2021;18:5896. doi: [10.3390/ijerph18115896](https://doi.org/10.3390/ijerph18115896)
28. Jung YH, Shamsiev K, Mamadjonov N, Jeung KW, Lee HY, Lee BK, Kang BS, Heo T, Min YI. Relationship of common hemodynamic and respiratory target parameters with brain tissue oxygen tension and the absence of hypoxemia or hypotension after cardiac arrest: a post-hoc analysis of an experimental study using a pig model. *PLoS One.* 2021;16:e0245931. doi: [10.1371/journal.pone.0245931](https://doi.org/10.1371/journal.pone.0245931)
29. Lee HY, Mamadjonov N, Jeung KW, Jung YH, Lee BK, Moon KS, Heo T, Min YI. Pralidoxime-induced potentiation of the pressor effect of adrenaline and hastened successful resuscitation by pralidoxime in a porcine cardiac arrest model. *Cardiovasc Drugs Ther.* 2020;34:619–628. doi: [10.1007/s10557-020-07026-5](https://doi.org/10.1007/s10557-020-07026-5)
30. Jung YH, Ryu DH, Jeung KW, Na JY, Lee DH, Lee BK, Heo T, Min YI. Effect of pralidoxime on coronary perfusion pressure during cardiopulmonary resuscitation in a pig model. *Clin Exp Emerg Med.* 2019;6:204–211. doi: [10.15441/ceem.18.036](https://doi.org/10.15441/ceem.18.036)
31. Serné EH, Gans RO, ter Maaten JC, Tangelder GJ, Donker AJ, Stehouwer CD. Impaired skin capillary recruitment in essential hypertension is caused by both functional and structural capillary rarefaction. *Hypertension.* 2001;38:238–242. doi: [10.1161/01.HYP.38.2.238](https://doi.org/10.1161/01.HYP.38.2.238)
32. De Backer D, Hollenberg S, Boerma C, Goedhart P, Büchele G, Ospina-Tascon G, Dobbe I, Ince C. How to evaluate the microcirculation: report of a round table conference. *Crit Care.* 2007;11:R101. doi: [10.1186/cc6118](https://doi.org/10.1186/cc6118)
33. Spronk PE, Ince C, Gardien MJ, Mathura KR, Oudemans-van Straaten HM, Zandstra DF. Nitroglycerin in septic shock after intravascular volume resuscitation. *Lancet.* 2002;360:1395–1396. doi: [10.1016/S0140-6736\(02\)11393-6](https://doi.org/10.1016/S0140-6736(02)11393-6)
34. Boerma EC, Mathura KR, van der Voort PH, Spronk PE, Ince C. Quantifying bedside-derived imaging of microcirculatory abnormalities in septic patients: a prospective validation study. *Crit Care.* 2005;9:R601–R606.
35. Le Roux P, Menon DK, Citerio G, Vespa P, Bader MK, Brophy GM, Diring MN, Stocchetti N, Videtta W, Armonda R, et al. Consensus summary statement of the International Multidisciplinary Consensus Conference on Multimodality Monitoring in Neurocritical Care : a statement for healthcare professionals from the Neurocritical Care Society and the European Society of Intensive Care Medicine. *Intensive Care Med.* 2014;40:1189–1209. doi: [10.1007/s00134-014-3369-6](https://doi.org/10.1007/s00134-014-3369-6)
36. van den Brink WA, van Santbrink H, Steyerberg EW, Avezaat CJ, Suazo JA, Hogesteeger C, Jansen WJ, Kloos LM, Vermeulen J, Maas AJ. Brain oxygen tension in severe head injury. *Neurosurgery.* 2000;46:868–876.
37. Valadka AB, Gopinath SP, Contant CF, Uzura M, Robertson CS. Relationship of brain tissue PO₂ to outcome after severe head injury. *Crit Care Med.* 1998;26:1576–1581. doi: [10.1097/00003246-199809000-00029](https://doi.org/10.1097/00003246-199809000-00029)
38. Maloney-Wilensky E, Gracias V, Itkin A, Hoffman K, Bloom S, Yang W, Christian S, LeRoux PD. Brain tissue oxygen and outcome after severe traumatic brain injury: a systematic review. *Crit Care Med.* 2009;37:2057–2063. doi: [10.1097/CCM.0b013e3181a009f8](https://doi.org/10.1097/CCM.0b013e3181a009f8)
39. Okonkwo DO, Shutter LA, Moore C, Temkin NR, Puccio AM, Madden CJ, Andaluz N, Chesnut RM, Bullock MR, Grant GA, et al. Brain oxygen optimization in severe traumatic brain injury phase-II: a phase II randomized trial. *Crit Care Med.* 2017;45:1907–1914. doi: [10.1097/CCM.0000000000002619](https://doi.org/10.1097/CCM.0000000000002619)
40. Sekhon MS, Ainslie PN, Menon DK, Thiara SS, Cardim D, Gupta AK, Hoiland RL, Gooderham P, Griesdale DE. Brain hypoxia secondary to diffusion limitation in hypoxic ischemic brain injury postcardiac arrest. *Crit Care Med.* 2020;48:378–384. doi: [10.1097/CCM.0000000000004138](https://doi.org/10.1097/CCM.0000000000004138)
41. van Genderen ME, Lima A, Akkerhuis M, Bakker J, van Bommel J. Persistent peripheral and microcirculatory perfusion alterations after out-of-hospital cardiac arrest are associated with poor survival. *Crit Care Med.* 2012;40:2287–2294. doi: [10.1097/CCM.0b013e31825333b2](https://doi.org/10.1097/CCM.0b013e31825333b2)
42. 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;35:2145–2149. doi: [10.1097/01.CCM.0000280427.76175.D2](https://doi.org/10.1097/01.CCM.0000280427.76175.D2)
43. Hossmann V, Hossmann KA, Takagi S. Effect of intravascular platelet aggregation on blood recirculation following prolonged ischemia of the cat brain. *J Neurol*. 1980;222:159–170. doi: [10.1007/BF00313114](https://doi.org/10.1007/BF00313114)
 44. Safar P, Stezoski W, Nemoto EM. Amelioration of brain damage after 12 minutes' cardiac arrest in dogs. *Arch Neurol*. 1976;33:91–95. doi: [10.1001/archneur.1976.00500020019004](https://doi.org/10.1001/archneur.1976.00500020019004)
 45. Little JR, Kerr FW, Sundt TM Jr. Microcirculatory obstruction in focal cerebral ischemia: an electron microscopic investigation in monkeys. *Stroke*. 1976;7:25–30. doi: [10.1161/01.STR.7.1.25](https://doi.org/10.1161/01.STR.7.1.25)
 46. Hill RA, Tong L, Yuan P, Murikinati S, Gupta S, Grutzendler J. Regional blood flow in the normal and ischemic brain is controlled by arteriolar smooth muscle cell contractility and not by capillary pericytes. *Neuron*. 2015;87:95–110. doi: [10.1016/j.neuron.2015.06.001](https://doi.org/10.1016/j.neuron.2015.06.001)
 47. Shaik JS, Poloyac SM, Kochanek PM, Alexander H, Tudorasu DL, Clark RS, Manole MD. 20-hydroxyeicosatetraenoic acid inhibition by HET0016 offers neuroprotection, decreases edema, and increases cortical cerebral blood flow in a pediatric asphyxial cardiac arrest model in rats. *J Cereb Blood Flow Metab*. 2015;35:1757–1763. doi: [10.1038/jcbfm.2015.117](https://doi.org/10.1038/jcbfm.2015.117)
 48. Troelsen TT, Granfeldt A, Secher N, Tønnesen EK, Simonsen U. Impaired NO-mediated vasodilatation in rat coronary arteries after asphyxial cardiac arrest. *Acta Anaesthesiol Scand*. 2015;59:654–667. doi: [10.1111/aas.12482](https://doi.org/10.1111/aas.12482)
 49. Hirsh LF. Intra-arterial nitroprusside treatment of acute experimental vasospasm. *Stroke*. 1980;11:601–605. doi: [10.1161/01.STR.11.6.601](https://doi.org/10.1161/01.STR.11.6.601)
 50. Lu GP, Kaul DK, Feldman SM, Orkin LR, Baez S. Sodium nitroprusside (SNP) hypotension: intracranial pressure (ICP) and hemodynamics in pial arteriole in the rat. *Microcirc Endothelium Lymphatics*. 1990;6:315–341.
 51. Busija DW, Leffler CW. Exogenous norepinephrine constricts cerebral arterioles via alpha 2-adrenoceptors in newborn pigs. *J Cereb Blood Flow Metab*. 1987;7:184–188.
 52. Dezfulian C, Alekseyenko A, Dave KR, Raval AP, Do R, Kim F, Perez-Pinzon MA. Nitrite therapy is neuroprotective and safe in cardiac arrest survivors. *Nitric Oxide*. 2012;26:241–250. doi: [10.1016/j.niox.2012.03.007](https://doi.org/10.1016/j.niox.2012.03.007)
 53. Dezfulian C, Shiva S, Alekseyenko A, Pendyal A, Beiser DG, Munasinghe JP, Anderson SA, Chesley CF, Vanden Hoek TL, Gladwin MT. Nitrite therapy after cardiac arrest reduces reactive oxygen species generation, improves cardiac and neurological function, and enhances survival via reversible inhibition of mitochondrial complex I. *Circulation*. 2009;120:897–905. doi: [10.1161/CIRCULATIONAHA.109.853267](https://doi.org/10.1161/CIRCULATIONAHA.109.853267)
 54. Uray T, Empey PE, Drabek T, Stezoski JP, Janesko-Feldman K, Jackson T, Garman RH, Kim F, Kochanek PM, Dezfulian C. Nitrite pharmacokinetics, safety and efficacy after experimental ventricular fibrillation cardiac arrest. *Nitric Oxide*. 2019;93:71–77. doi: [10.1016/j.niox.2019.09.003](https://doi.org/10.1016/j.niox.2019.09.003)
 55. Kim F, Maynard C, Dezfulian C, Sayre M, Kudenchuk P, Rea T, Sampson D, Olsufka M, May S, Nichol G. Effect of out-of-hospital sodium nitrite on survival to hospital admission after cardiac arrest: a randomized clinical trial. *JAMA*. 2021;325:138–145. doi: [10.1001/jama.2020.24326](https://doi.org/10.1001/jama.2020.24326)
 56. Oku K, Sterz F, Safar P, Johnson D, Obrist W, Leonov Y, Kuboyama K, Tisherman SA, Stezoski SW. Mild hypothermia after cardiac arrest in dogs does not affect postarrest multifocal cerebral hypoperfusion. *Stroke*. 1993;24:1590–1597. doi: [10.1161/01.STR.24.10.1590](https://doi.org/10.1161/01.STR.24.10.1590)
 57. Leonov Y, Sterz F, Safar P, Johnson DW, Tisherman SA, Oku K. Hypertension with hemodilution prevents multifocal cerebral hypoperfusion after cardiac arrest in dogs. *Stroke*. 1992;23:45–53. doi: [10.1161/01.STR.23.1.45](https://doi.org/10.1161/01.STR.23.1.45)
 58. Manole MD, Kochanek PM, Bayir H, Alexander H, Dezfulian C, Fink EL, Bell MJ, Clark RS. Brain tissue oxygen monitoring identifies cortical hypoxia and thalamic hyperoxia after experimental cardiac arrest in rats. *Pediatr Res*. 2014;75:295–301. doi: [10.1038/pr.2013.220](https://doi.org/10.1038/pr.2013.220)
 59. Iida H, Ohata H, Iida M, Watanabe Y, Dohi S. Isoflurane and sevoflurane induce vasodilation of cerebral vessels via ATP-sensitive K⁺ channel activation. *Anesthesiology*. 1998;89:954–960. doi: [10.1097/0000542-199810000-00020](https://doi.org/10.1097/0000542-199810000-00020)
 60. Oshima T, Karasawa F, Okazaki Y, Wada H, Satoh T. Effects of sevoflurane on cerebral blood flow and cerebral metabolic rate of oxygen in human beings: a comparison with isoflurane. *Eur J Anaesthesiol*. 2003;20:543–547. doi: [10.1097/00003643-200307000-00005](https://doi.org/10.1097/00003643-200307000-00005)
 61. Dashdorj N, Corrie K, Napolitano A, Petersen E, Mahajan RP, Auer DP. Effects of subanesthetic dose of nitrous oxide on cerebral blood flow and metabolism: a multimodal magnetic resonance imaging study in healthy volunteers. *Anesthesiology*. 2013;118:577–586. doi: [10.1097/ALN.0b013e3182800d58](https://doi.org/10.1097/ALN.0b013e3182800d58)
 62. Lam AM, Mayberg TS, Eng CC, Cooper JO, Bachenberg KL, Mathisen TL. Nitrous oxide-isoflurane anesthesia causes more cerebral vasodilation than an equipotent dose of isoflurane in humans. *Anesth Analg*. 1994;78:462–468. doi: [10.1213/00000539-199403000-00007](https://doi.org/10.1213/00000539-199403000-00007)
 63. Floyd TF, Clark JM, Gelfand R, Detre JA, Ratcliffe S, Guvakov D, Lamberts CJ, Eckenhoff RG. Independent cerebral vasoconstrictive effects of hyperoxia and accompanying arterial hypoxemia at 1 ATA. *J Appl Physiol*. 2003;95:2453–2461. doi: [10.1152/japplphysiol.00303.2003](https://doi.org/10.1152/japplphysiol.00303.2003)
 64. Harada J, Takaku A, Endo S, Kuwayama N, Fukuda O. Differences in critical cerebral blood flow with age in swine. *J Neurosurg*. 1991;75:103–107. doi: [10.3171/jns.1991.75.1.0103](https://doi.org/10.3171/jns.1991.75.1.0103)
 65. Fil JE, Joung S, Zimmerman BJ, Sutton BP, Dilger RN. High-resolution magnetic resonance imaging-based atlases for the young and adolescent domesticated pig (*Sus scrofa*). *J Neurosci Methods*. 2021;354:109107. doi: [10.1016/j.jneumeth.2021.109107](https://doi.org/10.1016/j.jneumeth.2021.109107)
 66. Vondrakova D, Kruger A, Janotka M, Malek F, Dudkova V, Neuzil P, Ostadal P. Association of neuron-specific enolase values with outcomes in cardiac arrest survivors is dependent on the time of sample collection. *Crit Care*. 2017;21:172. doi: [10.1186/s13054-017-1766-2](https://doi.org/10.1186/s13054-017-1766-2)
 67. Back T, Schüller OG. The natural course of lesion development in brain ischemia. *Acta Neurochir Suppl*. 2004;89:55–61.
 68. Thoresen M, Haaland K, Løberg EM, Whitelaw A, Apricena F, Hankø E, Steen PA. A piglet survival model of posthypoxic encephalopathy. *Pediatr Res*. 1996;40:738–748. doi: [10.1203/00006450-199611000-00014](https://doi.org/10.1203/00006450-199611000-00014)
 69. Tichauer KM, Elliott JT, Hadway JA, Lee TY, St. Lawrence K. Cerebral metabolic rate of oxygen and amplitude-integrated electroencephalography during early reperfusion after hypoxia-ischemia in piglets. *J Appl Physiol*. 2009;106:1506–1512. doi: [10.1152/japplphysiol.91156.2008](https://doi.org/10.1152/japplphysiol.91156.2008)
 70. Babini G, Grassi L, Russo I, Novelli D, Boccardo A, Luciani A, Fumagalli F, Staszewsky L, Fiordaliso F, De Maglie M, et al. Duration of untreated cardiac arrest and clinical relevance of animal experiments: the relationship between the "no-flow" duration and the severity of post-cardiac arrest syndrome in a porcine model. *Shock*. 2018;49:205–212. doi: [10.1097/SHK.0000000000000914](https://doi.org/10.1097/SHK.0000000000000914)
 71. Högl S, Sterz F, Sipos W, Schratzer A, Weihs W, Holzer M, Janata A, Losert U, Behringer W, Tichy A, et al. Distribution of neuropathological lesions in pig brains after different durations of cardiac arrest. *Resuscitation*. 2010;81:1577–1583. doi: [10.1016/j.resuscitation.2010.07.005](https://doi.org/10.1016/j.resuscitation.2010.07.005)