ANESTHESIOLOGY

Post–cardiac arrest Sedation Promotes Electroencephalographic Slow-wave Activity and Improves Survival in a Mouse Model of Cardiac Arrest

Takamitsu Ikeda, M.D., Ph.D., Edilberto Amorim, M.D., Yusuke Miyazaki, M.D., Ph.D., Risako Kato, Ph.D., Eizo Marutani, M.D., Michael G. Silverman, M.D., M.P.H., Rajeev Malhotra, M.D., M.S., Ken Solt, M.D., Fumito Ichinose, M.D., Ph.D.

ANESTHESIOLOGY 2022; 137:716–32

EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- In animal studies of brain ischemia, barbiturate or propofol sedation is neuroprotective
- Sedation may act by reducing reperfusion cerebral hyperemia
- The optimal timing and dose of sedation for patients after cardiac arrest is unclear, but the ability for the brain to generate slow waves in response to a propofol infusion has been associated with improved long-term neurologic outcomes

What This Article Tells Us That Is New

- Sedation with propofol or dexmedetomidine, started at the time of return of spontaneous circulation, results in better survival and neurologic outcomes than no sedation, in an animal model of cardiac arrest
- Sedation was associated with increased slow-wave electroencephalogram power and normalization of electroencephalogram patterns, which were positively correlated with neurologic outcome
- These beneficial effects are not seen if the sedation is commenced an hour after recovery of spontaneous circulation

ABSTRACT

Background: Patients resuscitated from cardiac arrest are routinely sedated during targeted temperature management, while the effects of sedation on cerebral physiology and outcomes after cardiac arrest remain to be determined. The authors hypothesized that sedation would improve survival and neurologic outcomes in mice after cardiac arrest.

Methods: Adult C57BL/6J mice of both sexes were subjected to potassium chloride–induced cardiac arrest and cardiopulmonary resuscitation. Starting at the return of spontaneous circulation or at 60 min after return of spontaneous circulation, mice received intravenous infusion of propofol at 40 mg · kg^{-1} · h^{-1}, dexmedetomidine at 1 μg · kg^{-1} · h^{-1}, or normal saline for 2 h. Body temperature was lowered and maintained at 33°C during sedation. Cerebral blood flow was measured for 4 h postresuscitation. Telemetric electroencephalogram (EEG) was recorded in freely moving mice from 3 days before up to 7 days after cardiac arrest.

Results: Sedation with propofol or dexmedetomidine starting at return of spontaneous circulation improved survival in hypothermia-treated mice (propofol [13 of 16, 81%] *vs.* no sedation [4 of 16, 25%], $P = 0.008$; dexmedetomidine [14 of 16, 88%] *vs.* no sedation [4 of 16, 25%], $P = 0.002$). Mice receiving no sedation exhibited cerebral hyperemia immediately after resuscitation and EEG power remained less than 30% of the baseline in the first 6 h postresuscitation. Administration of propofol or dexmedetomidine starting at return of spontaneous circulation attenuated cerebral hyperemia and increased EEG slow oscillation power during and early after sedation (40 to 80% of the baseline). In contrast, delayed sedation failed to improve outcomes, without attenuating cerebral hyperemia and inducing slow-wave activity.

Conclusions: Early administration of sedation with propofol or dexmedetomidine improved survival and neurologic outcomes in mice resuscitated from cardiac arrest and treated with hypothermia. The beneficial effects of sedation were accompanied by attenuation of the cerebral hyperemic response and enhancement of electroencephalographic slow-wave activity.

(ANESTHESIOLOGY 2022; 137:716–32)

Cardiac arrest is a major public health challenge worldwide.[1] Despite advances in resuscitation methods, cardiac arrest is still associated with high mortality and morbidity.[2] As part of postresuscitation care, targeted temperature management has been used in patients who achieved return of spontaneous circulation with the aim of minimizing hypoxic–ischemic brain damage after cardiac arrest.[3] Nevertheless, the burden of postanoxic brain injury remains unacceptably high, with the majority of cardiac

This article is featured in "This Month in Anesthesiology," page A1. Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are available in both the HTML and PDF versions of this article. Links to the digital files are provided in the HTML text of this article on the Journal's Web site (www.anesthesiology.org). This article has a video abstract. This article has a visual abstract available in the online version. Part of the work presented in this article has been presented at the American Society of Anesthesiologists, October 3, 2020, Virtual (The Best of Abstracts: Basic Science session) and the Resuscitation Science Symposium, American Heart Association, November 14 to 16, 2020, Virtual.

Submitted for publication December 12, 2021. Accepted for publication September 15, 2022. Published online first on September 28, 2022.

Takamitsu Ikeda, M.D., Ph.D.: Anesthesia Center for Critical Care Research, Department of Anesthesia, Critical Care and Pain Medicine, Massachusetts General Hospital, Boston, Massachusetts.

arrest survivors presenting in coma or with an altered level of consciousness.[2]

Patients undergoing targeted temperature management are routinely sedated with drugs that promote cardiorespiratory stabilization, facilitate mechanical ventilation, and control agitation, pain, anxiety, delirium, and shivering.[4–6] Preclinical studies suggest that sedatives exert neuroprotective effects in animals subjected to focal or global brain ischemia and reperfusion.[7,8] In cardiac arrest survivors with impaired cerebral autoregulation, sedation may protect the brain against secondary brain injury by modulating cerebral blood flow and cerebral metabolic rate of oxygen.[6,9,10] On the other hand, randomized clinical trials conducted in the general intensive care unit showed that minimizing or avoiding sedation provides better outcomes, including shorter duration of mechanical ventilation and hospital length of stay.[11,12] Based on these observations, the benefits of using sedation in unresponsive cardiac arrest patients have been questioned.[13] However, patients with severe acute brain injury (*e.g.*, comatose patients after cardiac arrest, ischemic or traumatic brain injury) have been excluded from previous studies.[11,12] The role of pharmacologic sedation in comatose cardiac arrest patients remains to be determined.

The electroencephalogram (EEG) reflects oscillatory extracellular electrical currents and potentials arising from neuronal activity in the cortical and subcortical brain structures. In healthy individuals, sedative–hypnotic agents give rise to low-frequency, high-amplitude activity that becomes slower with deepening levels of sedation/anesthesia,[14] while altering EEG power within a specific frequency range (*e.g.*, propofol-induced α oscillations and dexmedetomidine-induced spindle oscillations).[15] Although there has been a growing interest in the use of EEG analysis for outcome prediction after cardiac arrest, knowledge about sedation-induced EEG changes in the post–cardiac arrest population is limited.[16,17] Because sedation during targeted temperature management affects consciousness and potentially interferes with interpretation of EEG, optimal sedation is recommended in postresuscitation care to allow early awakening and limit confounding in accurate prognostication.[9,18] On the other hand, the ability to generate slow waves in response to propofol infusion at $4\,mg \cdot kg^{-1} \cdot h^{-1}$ has been proposed as an early predictor of neurologic recovery in comatose cardiac arrest patients.[19,20] The slow-wave activity is recognized as a neurophysiologic signature of normal brain function observed during sleep and deep sedation/anesthesia,[14,21] which is hypothesized to provide rest for individual neurons and prevent long-term neuronal damage.[22] Nevertheless, little is known about the significance of sedation-induced EEG changes in neurologic recovery after cardiac arrest.

The objective of the current study was to elucidate the impact of pharmacologic sedation on neurologic outcomes in mice resuscitated from cardiac arrest managed with therapeutic hypothermia. We hypothesized that sedation would improve survival and neurologic outcomes after cardiac arrest in hypothermia-treated mice. To test this hypothesis, we sought to characterize the effects of two commonly used sedatives: propofol (2,6-di-isopropylphenol), a γ-aminobutyric receptor agonist, and dexmedetomidine, a highly selective α_2-adrenoceptor agonist, in mice resuscitated from experimental cardiac arrest with continuous EEG monitoring and cerebral blood flow measurement.

Materials and Methods

Animal Preparation

Laboratory animal housing, handling, and procedures were performed in compliance with the protocols approved by the Institutional Animal Care and Use Committee at Massachusetts General Hospital (Boston, Massachusetts). We studied adult male (10 to 12 weeks old, 25 to 30 g) and female (15 to 20 weeks old, 21 to 26 g) C57BL/6J wild-type mice. In response to peer review, additional data from female mice were obtained. All mice were housed in a 24-h light/dark cycle (lights on at 7:00 AM and off at 7:00 PM), temperature-controlled room (20° to 23°C) with free access to food and water. All mice were within a healthy body weight range at baseline. The individual animal was considered the experimental unit. The number of mice used for each experiment (survival study, brain histology, cerebral blood flow measurement, and EEG recording) is summarized in Supplement Digital Content 1 table 1 (n refers to the number of animals; http://links.lww.com/ALN/C948).

Mouse Model of Cardiac Arrest

Before cardiac arrest and cardiopulmonary resuscitation (CPR), mice were anesthetized with 5% isoflurane in 100% oxygen and intubated with a 20-gauge catheter

Edilberto Amorim, M.D.: Department of Neurology, University of California San Francisco, San Francisco, California; Neurology Service, Zuckerberg San Francisco Hospital, San Francisco, California.

Yusuke Miyazaki, M.D., Ph.D.: Anesthesia Center for Critical Care Research, Department of Anesthesia, Critical Care and Pain Medicine, Massachusetts General Hospital, Boston, Massachusetts.

Risako Kato, Ph.D.: Department of Anesthesia, Critical Care and Pain Medicine, Massachusetts General Hospital, Boston, Massachusetts; Department of Physiology and Oral Physiology, Graduate School of Biomedical and Health Sciences, Hiroshima University, Hiroshima, Japan.

Eizo Marutani, M.D.: Anesthesia Center for Critical Care Research, Department of Anesthesia, Critical Care and Pain Medicine, Massachusetts General Hospital, Boston, Massachusetts.

Michael G. Silverman, M.D., M.P.H.: Cardiology Division, Massachusetts General Hospital, Boston, Massachusetts.

Rajeev Malhotra, M.D., M.S.: Cardiology Division, Massachusetts General Hospital, Boston, Massachusetts.

Ken Solt, M.D.: Department of Anesthesia, Critical Care and Pain Medicine, Massachusetts General Hospital, Boston, Massachusetts.

Fumito Ichinose, M.D., Ph.D.: Anesthesia Center for Critical Care Research, Department of Anesthesia, Critical Care and Pain Medicine, Massachusetts General Hospital, Boston, Massachusetts.

(Angiocath; Becton Dickinson, USA). Mice were then mechanically ventilated with a respiratory rate of 110 breaths/min and a tidal volume of 10 μl/g (mini-vent; Harvard Apparatus, USA). During isoflurane anesthesia at 1.5%, mice were instrumented with microcatheters (PE-10; Becton Dickinson) that were placed in the femoral artery for monitoring mean arterial pressure and in the femoral vein for administrating drugs. The experimental procedures were conducted during the light phase in the previously described manner with some modifications.[23] In brief, male mice were subjected to potassium chloride–induced cardiac arrest for 8 min followed by chest compression in combination with resumption of mechanical ventilation with 100% oxygen and intravenous epinephrine administration. Female mice were subjected to cardiac arrest for 8.5 min because they are less sensitive to brain ischemia than male mice.[24] Isoflurane anesthesia was discontinued when cardiac arrest was induced in all mice. Core body temperature was measured throughout the procedure using an esophageal temperature probe. Bupivacaine (2 mg/kg) was injected in the surgical wounds preoperatively in conjunction with administration of buprenorphine (0.1 mg/kg) for postoperative analgesia. All animals were treated in the same manner before, during, and after cardiac arrest and CPR in terms of pre–cardiac arrest anesthesia, mechanical ventilation, temperature control, monitoring, and postoperative care, including analgesia, whether or not they received post–cardiac arrest sedation.

Post–cardiac arrest Sedation Starting at Return of Spontaneous Circulation

Starting at return of spontaneous circulation, 30 male and 18 female mice were randomly assigned to receive continuous intravenous infusion of propofol at a rate of 40 mg · kg^{-1} · h^{-1} or dexmedetomidine at a rate of 1 μg · kg^{-1} · h^{-1} or normal saline (vehicle) for 2 h (10 male mice and 6 female mice per group; Supplemental Digital Content 1 table 1, http://links.lww.com/ALN/C948). The infusion rate of the drugs was determined based on our pilot experiments (Supplemental Digital Content 2 fig. 1, http://links.lww.com/ALN/C938). In addition, a group of male mice undergoing EEG recording received administration of propofol at 10 mg · kg^{-1} · h^{-1} starting at return of spontaneous circulation (Supplemental Digital Content 1 table 1, http://links.lww.com/ALN/C948) to investigate the dose-dependent effects of propofol. All mice were weaned from mechanical ventilation at 20 min after return of spontaneous circulation when the spontaneous respiratory rate exceeded 100 breaths/min, and oxygen was administered continuously through a T-piece circuit up to 40 min after return of spontaneous circulation. Mean arterial pressure, heart rate, and respiratory rate were recorded up to 120 min after return of spontaneous circulation. Body temperature was maintained at 37°C until 20 min after return of spontaneous circulation and was subsequently lowered and maintained at 33°C until administration of propofol or dexmedetomidine or vehicle was discontinued. After removal of the catheters, all mice were returned to their cages where they are allowed to equilibrate at the ambient temperature. The detailed experimental timeline is shown in Supplemental Digital Content 3 fig. 2A (http://links.lww.com/ALN/C939). Mice were followed up for 10 days after cardiac arrest, and survival rates were assessed by an investigator blinded to the experimental groups. The animals were euthanized with an overdose of isoflurane at the end of the study follow-up period.

Post–cardiac arrest Sedation Starting at 60 Min after Return of Spontaneous Circulation

Starting at 60 min after return of spontaneous circulation, 30 male mice in another group were randomly assigned to receive administration of propofol at 40 mg · kg^{-1} · h^{-1} or dexmedetomidine at 1 μg · kg^{-1} · h^{-1} or normal saline (vehicle) for 2 h (10 male mice per group; Supplemental Digital Content 1 table 1, http://links.lww.com/ALN/C948). In these experiments, body temperature was maintained at 33°C up to 180 min after return of spontaneous circulation (Supplemental Digital Content 3 fig. 2B, http://links.lww.com/ALN/C939). Mice were followed up for 10 days after cardiac arrest, and survival rates were assessed by an investigator blinded to the experimental groups. The animals were euthanized with an overdose of isoflurane at the end of the study follow-up period.

Neurologic Outcome Assessment

Neurologic function was assessed at 24, 48, 72, 96, and 120 h after cardiac arrest by an investigator blinded to the experimental groups. Animals in the different experimental groups were assessed in sequential order. The previously reported neurologic function scoring system was used with minor modifications (scale 1).[23] For mice that underwent continuous EEG recording, we used an alternative scoring system (scale 2) to avoid applying a stimulus that could affect EEG recording, which was based partly on a scale evaluating postischemic neurologic function in a different murine model of global cerebral ischemia.[25] In both scales, higher scores indicate better neurologic outcomes. Dead mice were scored at 0 points and were included in the statistical analysis. Details about scale 1 and 2 are shown in Supplemental Digital Content 4 table 2 (http://links.lww.com/ALN/C949).

Histologic Assessment

Histologic examination was performed in a separate group of male mice (n = 12) that were randomly assigned to receive no sedation (vehicle administration) or sedation with propofol at 40 mg · kg^{-1} · h^{-1} or dexmedetomidine at 1 μg · kg^{-1} · h^{-1} starting at return of spontaneous circulation, or no sedation (Supplemental Digital Content 1 table 1, http://links.lww.com/ALN/C948). Brains were harvested from

mice euthanized at 24 h after cardiac arrest in the previously described manner with minor modifications.[26,27] In brief, Fluoro-Jade B was used to stain dying neurons in combination with counterstaining with 4′,6-diamidino-2-phenylindole that allows nuclear staining. To assess the degree of neuronal degeneration in the cerebral cortex, three images were randomly selected from two different brain sections per mouse. Fluoro-Jade B– and 4′,6-diamidino-2-phenylindole–positive neurons were counted by an investigator blinded to the identity of samples, using ImageJ 1.53g (National Institutes of Health, Bethesda, Maryland), and the percentage of Fluoro-Jade B–positive neurons to 4′,6-diamidino-2-phenylindole–positive neurons was reported.

Cerebral Blood Flow Monitoring

In a separate group of male mice (n = 33) that were randomly assigned to receive sedation with propofol at 40 mg · kg^{-1} · h^{-1} or dexmedetomidine at 1 μg · kg^{-1} · h^{-1} starting at return of spontaneous circulation or at 60 min after return of spontaneous circulation, or no sedation (vehicle administration starting at return of spontaneous circulation or at 60 min after return of spontaneous circulation; Supplemental Digital Content 1 table 1, http://links.lww.com/ALN/C948), we measured cerebral blood flow using a laser Doppler flowmeter (moorVMD-LDF1; Moor Instruments Inc., USA) affixed to the skull over the middle cerebral artery region. Before induction of cardiac arrest, baseline cerebral blood flow was measured for 2 min with isoflurane anesthesia. The laser Doppler flowmeter was calibrated to set the baseline value as 100% in each mouse. Cerebral blood flow was recorded for 4 h after return of spontaneous circulation, and the relative value of cerebral blood flow was calculated as percent of the baseline value.

Electroencephalogram Transmitter Implantation

A telemetric EEG transmitter (ETA-F10; Data Sciences International, USA) was used in the current study. During isoflurane anesthesia, the EEG transmitter was implanted subcutaneously so that the biopotential leads were positioned parallel to the long axis of the body. Two electrodes were placed at the following coordinates: the negative lead at 1.0 mm anterior and 1.0 mm lateral to Bregma, and the positive lead at 3.0 mm posterior and 3.0 mm lateral to Bregma on the contralateral side.[28] After electrical contact with the dura membrane was established, dental acrylic was applied to the lead entry holes to ensure that the electrodes remained affixed to the skull. Bupivacaine (2 mg/kg) was injected in the surgical wounds preoperatively in conjunction with administration of buprenorphine (0.1 mg/kg) for postoperative analgesia. Ten to 14 days after EEG transmitter implantation, mice were subjected to cardiac arrest and CPR, and thereafter randomly assigned to receive administration of propofol or dexmedetomidine or normal saline (vehicle) to examine the effects of sedation on EEG.

Electroencephalogram Acquisition and Processing

EEG was continuously recorded in 30 male and 5 female mice from 3 days before and up to 7 days after cardiac arrest (Supplemental Digital Content 1 table 1, http://links.lww.com/ALN/C948). Telemetric data from the implantable EEG transmitters were digitally collected from freely moving mice at a sampling rate of 500 Hz in the Dataquest Advanced Research Technology system (Data Sciences Internationa) and analyzed with the use of NeuroScore 3.3.1 (Data Sciences International). The derived EEG signals were band-pass filtered in the frequency ranges as follows: delta (0.5 to 4 Hz), theta (4 to 8 Hz), alpha (8 to 12 Hz), sigma (12 to 16 Hz), beta (16 to 24 Hz), and gamma (30 to 90 Hz) oscillations. For each frequency band, total EEG power during the light phase of the day before cardiac arrest (12 h) was calculated as the pre–cardiac arrest baseline where both sleep and awake states were included. To describe time-dependent EEG changes after resuscitation, post–cardiac arrest EEG power was calculated for each frequency band at consecutive 1-h time blocks up to 48 h after return of spontaneous circulation, or at consecutive 10-min time blocks up to 6 h after return of spontaneous circulation. The post–cardiac arrest EEG power at each time block was expressed as percent of the pre–cardiac arrest baseline EEG power that was adjusted to match the length of the post–cardiac arrest time block (*i.e.*, 1 h or 10 min). For example, to calculate the percent post–cardiac arrest EEG power of a 1-h time block, the post–cardiac arrest EEG power of the 1-h time block was divided by the 1-h pre–cardiac arrest baseline EEG power, which was obtained by dividing the total EEG power during the 12-h light phase before cardiac arrest by 12.

MATLAB R2020a (MathWorks, USA) was used for spectral analysis. The spectrogram and power spectrum were computed using the multitaper method implemented in Chronux,[29] an open-source software package including a MATLAB toolbox for signal processing of neurobiologic time series data. The multitaper approach was used to create EEG spectrograms for the purpose of providing clear and accurate high-resolution spectral estimates. Time-frequency spectrograms before cardiac arrest and in the first 24 h after return of spontaneous circulation were generated using the Chronux function "mtspectrumc" with a time-bandwidth product TW = 3, number of tapers K = 5, and window length T = 3 s. Power spectral density plots were generated for 60-s windows at 6 time points during and after sedation (30, 60, 90, 120, 240, and 360 min after return of spontaneous circulation) to quantify the difference in the frequency distribution of EEG power between mice without sedation and those sedated with propofol or dexmedetomidine. The median power values were plotted by frequency with 95% CI derived from 1,000-fold bootstrapping (calculated using the MATLAB bootstrap function "bootci").[30]

Statistical Analysis

Variables were tested for normality with the Shapiro-Wilk test and Q-Q plots. Data were presented as means and standard deviations for normally distributed variables, and median and interquartile ranges otherwise. For comparisons between mice without sedation and those sedated with propofol or dexmedetomidine, parametric data were analyzed using a one-way analysis of variance (ANOVA) followed by Sidak's multiple comparisons test. The Kruskal-Wallis test followed by Dunn's multiple comparisons test was used when data were not normally distributed. The Dunnett's multiple comparisons test was performed as the *post hoc* test following a two-way repeated-measures ANOVA to determine the propofol- or dexmedetomidine-induced effects on mean arterial pressure, heart rate, respiratory rate, cerebral blood flow, and quantitative EEG. Survival data were visualized using a Kaplan-Meier survival plot, and the log-rank test was used for comparing survival curves. The number of animals required for the survival study was estimated by a power analysis as 10 per group based on the assumption that the median survival times in the control and experimental treatment groups are 2 days and 9 days, respectively, during a follow-up period of 10 days ($\alpha = 0.05$, $\beta = 0.2$, [Power = 80%], two-sided; PS: Power and Sample Size Calculation version 3.1.6). *A priori* sample size calculation was not performed in mice undergoing cerebral blood flow measurement and EEG recording because the effects of sedation on cerebral blood flow and quantitative EEG changes were unknown. The Spearman correlation coefficient was used to measure the degree of association between the relative EEG power early after resuscitation and neurologic function at 24 h after cardiac arrest. Mortality, neurologic function, and physiologic variables were examined with the individual animal as the unit of analysis. All statistical tests were two-tailed with significance set at $P < 0.05$. GraphPad Prism 9.2.0 (GraphPad Software Inc., USA) was used for statistical analyses.

Results

Sedation with Propofol or Dexmedetomidine Starting at Return of Spontaneous Circulation Improved Survival and Neurologic Outcomes after Cardiac Arrest

Continuous intravenous infusion of propofol at 40 mg · kg^{-1} · h^{-1} modestly decreased mean arterial pressure (~10%) compared to no sedation in the first 2 h after return of spontaneous circulation (Supplemental Digital Content 5 fig. 3A, http://links.lww.com/ALN/C940). Sedation with propofol or dexmedetomidine was associated with lower heart rate (≈15%) than no sedation between 80 to 120 min after return of spontaneous circulation (Supplemental Digital Content 5 fig. 3B, http://links.lww.com/ALN/C940). Compared to mice that received no sedation, those sedated with propofol or dexmedetomidine exhibited improved survival at 10 days after cardiac arrest (fig. 1A; log-rank, propofol [13 of 16, 81%] *vs.* no sedation [4 of 16, 25%], $P = 0.008$; dexmedetomidine [14 of 16, 88%] *vs.* no sedation [4 of 16, 25%], $P = 0.002$; Supplemental Digital Content 6 fig. 4, http://links.lww.com/ALN/C941). The neurologic function score was significantly higher in propofol- or dexmedetomidine-treated mice than in those without sedation at 5 days after cardiac arrest (fig. 1B; Kruskal-Wallis test, propofol 11.5 [9.0 to 12.0] *vs.* no sedation 1.5 [0.0 to 7.0], $P = 0.0005$; dexmedetomidine 10.0 [9.3 to 11.8] *vs.* no sedation 1.5 [0.0 to 7.0], $P = 0.002$). The range of times required for CPR is reported in Supplemental Digital Content 7 table 3 (http://links.lww.com/ALN/C950). Mice sedated with propofol or dexmedetomidine exhibited reduced neuronal death after cardiac arrest on histology, compared to those receiving no sedation (fig. 1C and 1D). These results suggest that administration of propofol at 40 mg · kg^{-1} · h^{-1} or dexmedetomidine at 1 μg · kg^{-1} · h^{-1} starting at return of spontaneous circulation prevented brain injury after cardiac arrest in hypothermia-treated mice.

Sedation with Propofol or Dexmedetomidine Attenuated the Cerebral Hyperemic Response after Return of Spontaneous Circulation

To determine the effects of sedation on cerebral perfusion in mice after cardiac arrest, we continuously measured cerebral blood flow for 240 min after return of spontaneous circulation. In mice that received no sedation after return of spontaneous circulation, cerebral blood flow surged to approximately 160% of the baseline at 20 min after return of spontaneous circulation, returned to baseline levels temporarily, and then increased again to approximately 150% of the baseline around 120 min after return of spontaneous circulation (fig. 1E). In contrast, sedation with propofol or dexmedetomidine markedly attenuated cerebral hyperemia immediately after return of spontaneous circulation. Even after reaching its nadir, cerebral blood flow remained lower in sedated mice than in those without sedation up to 240 min after return of spontaneous circulation (fig. 1E). These observations suggest that the effects of sedation with propofol or dexmedetomidine starting at return of spontaneous circulation were characterized by attenuation of the cerebral hyperemic response immediately after resuscitation.

Delayed Sedation with Propofol or Dexmedetomidine Starting at 60 Min after Return of Spontaneous Circulation Did Not Improve Outcomes after Cardiac Arrest

To further characterize the relationship between early cerebral hyperemia and beneficial effects of sedation in post–cardiac arrest mice, we delayed the start of sedation until 60 min after return of spontaneous circulation so that the initial peak increase of cerebral blood flow after return of spontaneous circulation would not be affected by administration of propofol or dexmedetomidine. In comparison with vehicle administration starting at 60 min after

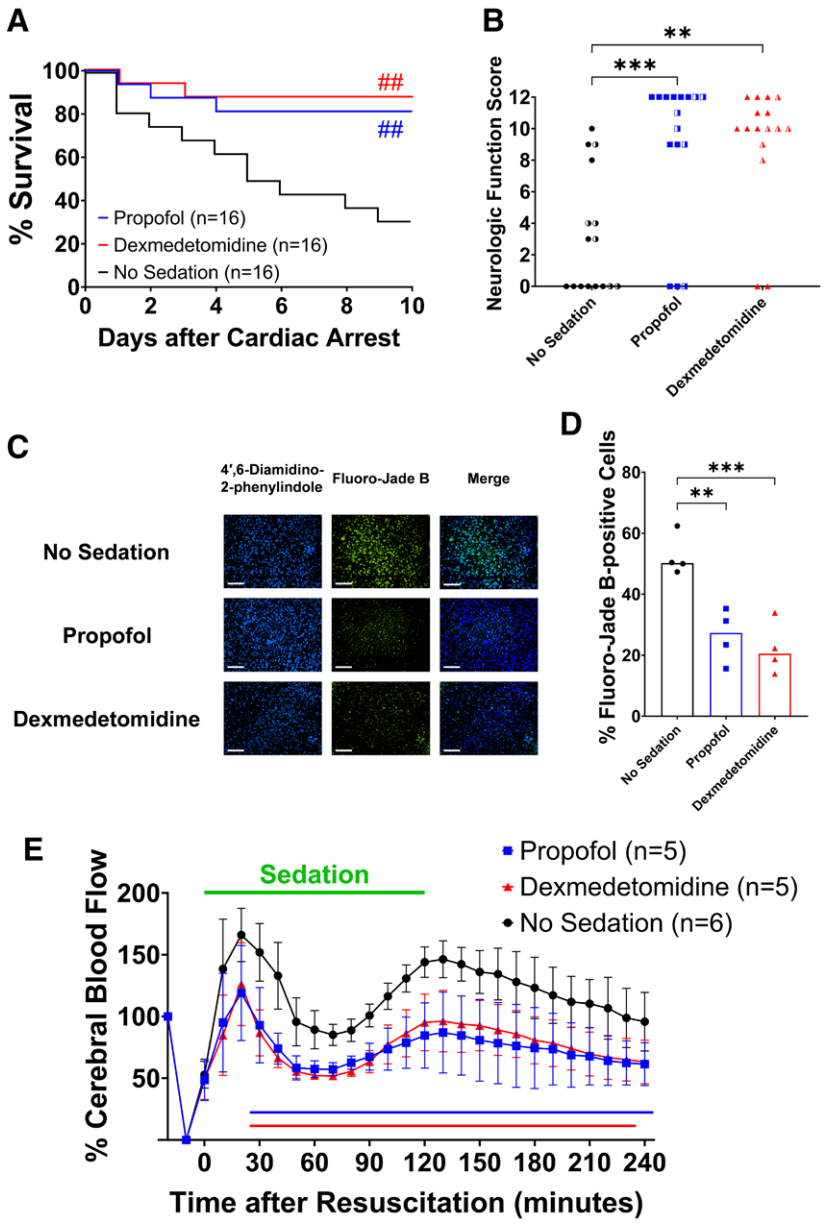


Fig. 1. Effects of sedation with propofol or dexmedetomidine starting at return of spontaneous circulation. (*A*) Percent survival in the first 10 days after cardiac arrest. Ten male mice and 6 female mice per group. $^{\#\#}P < 0.01$; *blue*: propofol *versus* no sedation, *red*: dexmedetomidine *versus* no sedation. (*B*) Neurologic function scores at 5 days after cardiac arrest that were assessed using scale 1. Ten male mice and 6 female mice per group. The *half-colored* symbols represent female animals. Note that dead mice (scored at 0 points) were included in the statistical analysis. $^{**}P < 0.01$, $^{***}P < 0.001$; *versus* no sedation. (*C*) Representative images of the cerebral cortex at 24 h post–cardiac arrest from male mice without sedation and those sedated with propofol or dexmedetomidine. Neuronal degeneration was visualized by double staining with Fluoro-Jade B and 4′,6-diamidino-2-phenylindole. *Scale bar* = 100 μm. (*D*) The percentage of Fluoro-Jade B–positive cells to 4′,6-diamidino-2-phenylindole–positive cells in the cerebral cortex was significantly lower in male mice sedated with propofol or dexmedetomidine starting at return of spontaneous circulation (one-way analysis of variance [ANOVA], propofol 26.3 ± 8.7 *versus* no sedation 52.5 ± 6.7, $P = 0.002$; dexmedetomidine 22.2 ± 8.5 *versus* no sedation 52.5 ± 6.7, $P = 0.0009$). $^{**}P < 0.01$, $^{***}P < 0.001$; *versus* no sedation. (*E*) Changes in the relative cerebral blood flow in the first 240 min after return of spontaneous circulation in male mice without sedation and those sedated with propofol or dexmedetomidine starting at return of spontaneous circulation. Data are presented as mean ± SD. A two-way repeated-measures ANOVA with the *post hoc* Dunnett's test was used (two-way repeated-measures ANOVA, propofol *versus* no sedation, interaction effect [group × time]: $P < 0.0001$; dexmedetomidine *versus* no sedation, interaction effect [group × time]: $P < 0.0001$). The *colored lines* below indicate statistically significant differences from the no sedation group at specific time points after return of spontaneous circulation ($P < 0.05$; *blue*: propofol *vs.* no sedation, *red*: dexmedetomidine *vs.* no sedation; Dunnett's test).

return of spontaneous circulation, administration of propofol starting at 60 min after return of spontaneous circulation decreased mean arterial pressure (approximately 20%; Supplemental Digital Content 5 fig. 3D, http://links.lww.com/ALN/C940). In contrast to sedation starting immediately after resuscitation, delayed sedation with propofol or dexmedetomidine failed to improve survival at 10 days after cardiac arrest (fig. 2A; log-rank, propofol [3 of 10, 33%] *vs.* no sedation [3 of 10, 33%], $P = 0.872$; dexmedetomidine [3 of 10, 33%] *vs.* no sedation [3 of 10, 33%], $P = 0.705$). No difference was found in the neurologic function score among groups at 5 days after cardiac arrest (fig. 2B; Kruskal-Wallis test, propofol 0.0 [0.0 to 9.3] *vs.* no sedation 0.0 [0.0 to 8.0], $P > 0.999$; dexmedetomidine 0.0 [0.0 to 10.3] *vs.* no sedation 0.0 [0.0 to 8.0], $P = 0.953$). The cerebral blood flow changed similarly in the first 60 min after return of spontaneous circulation in mice that received vehicle administration and those sedated with propofol or dexmedetomidine starting at 60 min after return of spontaneous circulation. Delayed administration of propofol or dexmedetomidine did not decrease cerebral blood flow from 60 until 180 min after return of spontaneous circulation except that there was a significant reduction in cerebral blood flow at 90 and 100 min after return of spontaneous circulation during sedation with dexmedetomidine (fig. 2C). These results suggest that sedation

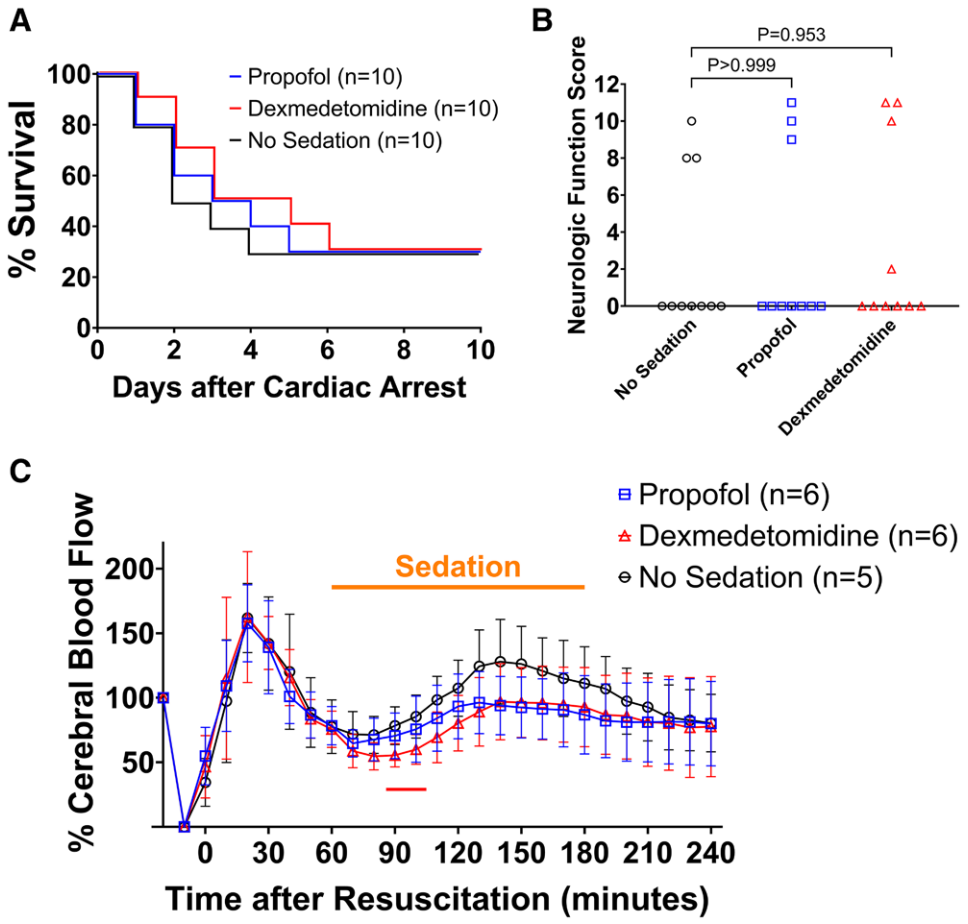


Fig. 2. Effects of delayed sedation with propofol or dexmedetomidine starting at 60 min after return of spontaneous circulation. (*A*) Percent survival in the first 10 days after cardiac arrest. Ten male mice per group. (*B*) Neurologic function scores at 5 days after cardiac arrest that were assessed using scale 1. Ten male mice per group. Note that dead mice (scored at 0 points) were included in the statistical analysis. (*C*) Changes in the relative cerebral blood flow in the first 240 min after return of spontaneous circulation in male mice without sedation and those sedated with propofol or dexmedetomidine starting at 60 min after return of spontaneous circulation. Data are presented as mean ± SD. A two-way repeated measures analysis of variance (ANOVA) with the *post hoc* Dunnett's test was performed during and after the period of sedation (two-way repeated measures ANOVA, propofol *versus* no sedation, interaction effect [group × time]: $P = 0.011$; dexmedetomidine *versus* no sedation, interaction effect [group × time]: $P = 0.074$, main effect: $P = 0.202$). The *colored line* below indicates statistically significant differences from the no sedation group at specific time points after return of spontaneous circulation ($P < 0.05$; *red*: dexmedetomidine *vs.* no sedation; Dunnett's test).

with propofol or dexmedetomidine failed to improve outcomes when initiated at 60 min after return of spontaneous circulation.

Sedation with Propofol or Dexmedetomidine Accelerated EEG Recovery after Cardiac Arrest (0 to 48 h after Return of Spontaneous Circulation)

Because brain electrical activity is tightly coupled with cerebral metabolism that changes in tandem with cerebral blood flow,[31] we hypothesized that attenuation of cerebral hyperemia with pharmacologic sedation is associated with suppression of neuronal activity in the early phase of recovery after hypoxic–ischemic brain injury. To address this hypothesis, EEG was continuously recorded in freely moving mice before and after experimental cardiac arrest. Survival rates in mice that underwent EEG recording are summarized in Supplemental Digital Content 8 fig. 5 (mice that were not resuscitated from cardiac arrest were excluded; http://links.lww.com/ALN/C942).

Representative EEG spectrograms and unprocessed waveforms are displayed in figure 3 from pre–cardiac arrest awake mice (fig. 3A), post–cardiac arrest mice that received no sedation (fig. 3B), sedation with propofol (fig. 3C), and sedation with dexmedetomidine (fig. 3D). Spectrograms for the individual animals are provided in Supplemental Digital Content 9 fig. 6 (http://links.lww.com/ALN/C943). In mice that received no sedation, the EEG was isoelectric early after resuscitation, and EEG

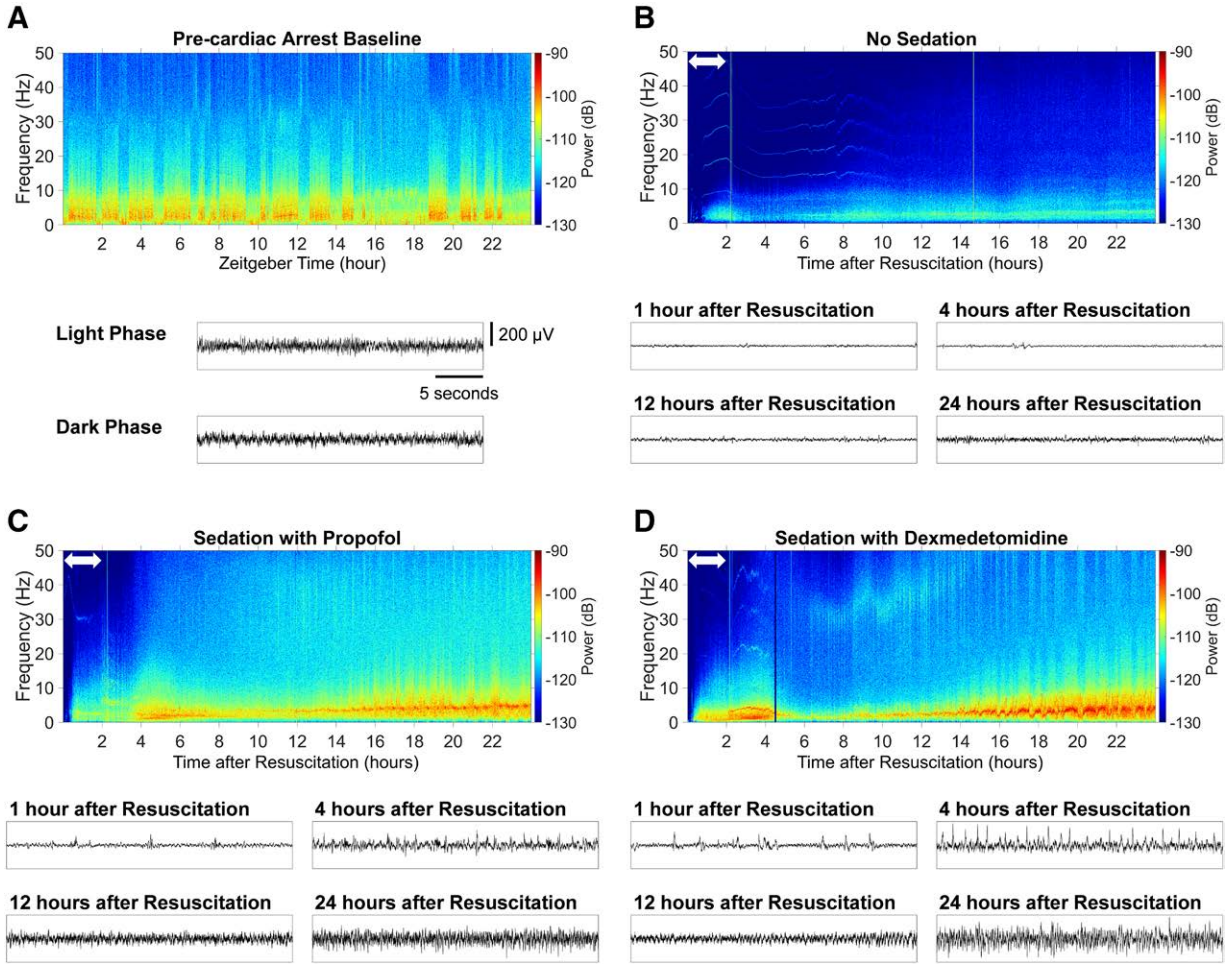


Fig. 3. Representative electroencephalogram (EEG) spectrograms before cardiac arrest and in the first 24 h after return of spontaneous circulation. (*A*) Baseline spectrogram (the day before cardiac arrest). Mice were housed individually, exposed to a 24-h light/dark cycle (light: 7:00 am to 7:00 pm, dark: 7:00 pm to 7:00 am). Normal cycling between sleep and wake states was observed before cardiac arrest. Unprocessed EEG waveforms during the light and dark phase are also provided. Examples of spectrograms in the first 24 h after return of spontaneous circulation from (*B*) male mice that received no sedation, (*C*) those sedated with propofol at 40 mg · kg^{-1} · h^{-1} starting at return of spontaneous circulation, and (*D*) those sedated with dexmedetomidine at 1 μg · kg^{-1} · h^{-1} starting at return of spontaneous circulation. The *white double-headed arrow* in the spectrogram indicates the period of (*B*) vehicle administration, (*C*) sedation with propofol, or (*D*) sedation with dexmedetomidine. Unprocessed EEG waveforms at 1 h, 4 h, 12 h, and 24 h after return of spontaneous circulation are also provided.

power remained lower in the first 24 h after return of spontaneous circulation compared to the pre–cardiac arrest baseline. In contrast, mice sedated with propofol at 40 mg · kg^{-1} · h^{-1} or dexmedetomidine at 1 μg · kg^{-1} · h^{-1} starting at return of spontaneous circulation exhibited pronounced EEG activity within frequencies up to 10 Hz in the first 6 h after return of spontaneous circulation, which was followed by gradually increasing EEG power over 12 to 24 h after resuscitation. Quantitative analysis showed that in contrast to mice without sedation, those sedated with propofol at 40 mg · kg^{-1} · h^{-1} or dexmedetomidine at 1 μg · kg^{-1} · h^{-1} starting at return of spontaneous circulation exhibited electrophysiologic recovery at earlier points in time after resuscitation across all frequency bands (fig. 4A to 4F). Although the body temperature recorded by an EEG transmitter showed a temporary decrease to less than 33°C after the experimental procedure followed by a gradual increase over time, no statistically significant differences were found in body temperature among groups up to 24 h after return of spontaneous circulation, except at 3 points in time (4, 5, and 24 h; Supplemental Digital Content 10 fig. 7, http://links.lww.com/ALN/C944). These results indicate that sedation with propofol at 40 mg · kg^{-1} · h^{-1} or dexmedetomidine at 1 μg · kg^{-1} · h^{-1} starting at return

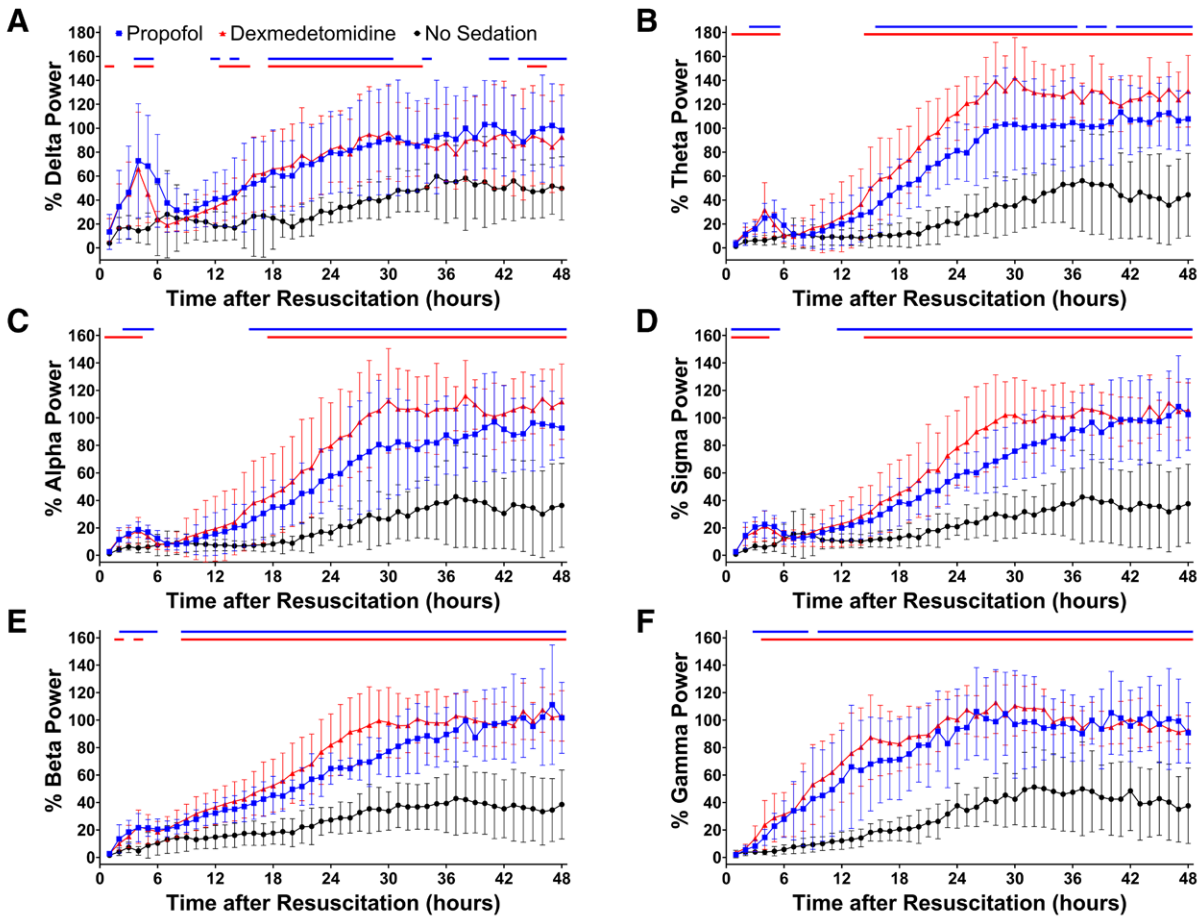


Fig. 4. Quantitative changes in electroencephalogram (EEG) power after cardiac arrest. Changes in (*A*) delta, (*B*) theta, (*C*) alpha, (*D*) sigma, (*E*) beta, and (*F*) gamma power up to 48 h after return of spontaneous circulation are provided in male and female mice sedated with propofol at 40 mg · kg^{-1} · h^{-1} starting at return of spontaneous circulation, those sedated with dexmedetomidine at 1 μg · kg^{-1} · h^{-1} starting at return of spontaneous circulation, and those receiving no sedation. EEG power was calculated for each frequency band at consecutive 1-h time blocks up to 48 h after return of spontaneous circulation, which was expressed as percent of the baseline EEG power before cardiac arrest. Data are presented as mean ± SD. The *P* values for the interaction effect [group × time] are summarized in Supplemental Digital Content 14 table 4 (http://links.lww.com/ALN/C951). The *colored lines* on top indicate statistically significant differences from the no sedation group at specific time points after return of spontaneous circulation ($P < 0.05$; blue: propofol *vs.* no sedation, red: dexmedetomidine *vs.* no sedation; Dunnett's test).

of spontaneous circulation accelerated electrophysiologic recovery in mice after cardiac arrest.

Sedation with Propofol or Dexmedetomidine Induced Slow-wave Activity in Post–cardiac arrest Mice (0 to 2 h after Return of Spontaneous Circulation)

To further analyze propofol- or dexmedetomidine-induced EEG changes over time during sedation in comatose post–cardiac arrest mice, we generated power spectral density plots at 3 time points during sedation. Compared to mice sedated with propofol or those without sedation, mice sedated with dexmedetomidine at 1 μg · kg^{-1} · h^{-1} exhibited greater EEG power at 30 min after return of spontaneous circulation, whereas sedation with propofol at 40 mg · kg^{-1} · h^{-1} was associated with increased EEG power across frequencies less than 25 Hz compared to no sedation (fig. 5A). At 60 and 90 min after return of spontaneous circulation, EEG power was greater across a frequency range up to approximately 35 Hz in mice sedated with propofol or dexmedetomidine than in those receiving no sedation (fig. 5B and 5C).

To visualize quantitative EEG changes, the relative EEG power was calculated for all EEG frequency bands in consecutive 10-min time blocks up to 120 min after return of spontaneous circulation. In mice receiving no sedation, EEG power remained less than about 20% of the baseline across all frequency bands in the first 120 min after return of spontaneous circulation (fig. 5D to 5I, Supplemental Digital Content 11 fig. 8, http://links.lww.com/ALN/C945). As compared with mice without sedation, there was a noticeable increase in delta power early during sedation in mice sedated with propofol or dexmedetomidine (fig. 5D, Supplemental Digital Content 11 fig. 8, http://links.lww.com/ALN/C945). Although less prominent than changes in slow oscillation power, sedation with propofol or dexmedetomidine was associated with increased EEG power in theta, alpha, sigma, and beta frequency ranges (fig. 5E to 5H). Unlike frequencies less than 30 Hz, no increase in gamma power was observed during sedation (fig. 5I).

Sedation with Propofol or Dexmedetomidine Enhanced Recovery of EEG Power in the Early Hours after Sedation (2 to 6 h after Return of Spontaneous Circulation)

To quantify the time-dependent changes in EEG frequency distribution after sedation, we generated power spectral density plots at 3 time points in the first 4 h after sedation was discontinued. EEG power was greater up to approximately 45 Hz at 120 min after return of spontaneous circulation (at the end of sedation) in mice sedated with propofol at 40 mg · kg^{-1} · h^{-1} or dexmedetomidine at 1 μg · kg^{-1} · h^{-1} starting at return of spontaneous circulation than in those receiving no sedation (fig. 6A).

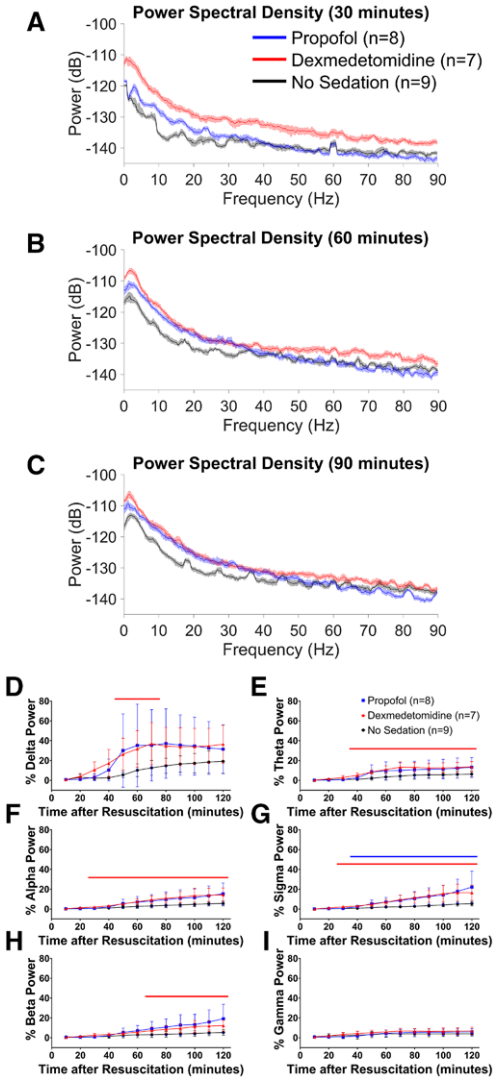


Fig. 5. Propofol or dexmedetomidine-induced electroencephalogram (EEG) changes during post–cardiac arrest sedation (0 to 2 h after return of spontaneous circulation). Power spectral density at (*A*) 30, (*B*) 60, and (*C*) 90 min after return of spontaneous circulation in male and female mice without sedation and those sedated with propofol at 40 mg · kg^{-1} · h^{-1} or dexmedetomidine at 1 μg · kg^{-1} · h^{-1} starting at return of spontaneous circulation. The median and 95% confidence intervals of spectral density are displayed. Changes in (*D*) delta, (*E*) theta, (*F*) alpha, (*G*) sigma, (*H*) beta, and (*I*) gamma power in the first 120 min after return of spontaneous circulation. EEG power was calculated for each frequency band at consecutive 10-min time blocks, which was expressed as percent of the baseline EEG power before cardiac arrest. Data are presented as mean ± SD. The *P* values for the interaction effect [group × time] are summarized in Supplemental Digital Content 14 table 4 (http://links.lww.com/ALN/C951). The *colored lines* in each graph indicate statistically significant differences from the no sedation group at specific time points after return of spontaneous circulation ($P < 0.05$; *blue*: propofol *vs.* no sedation, *red*: dexmedetomidine *versus* no sedation; Dunnett's test).

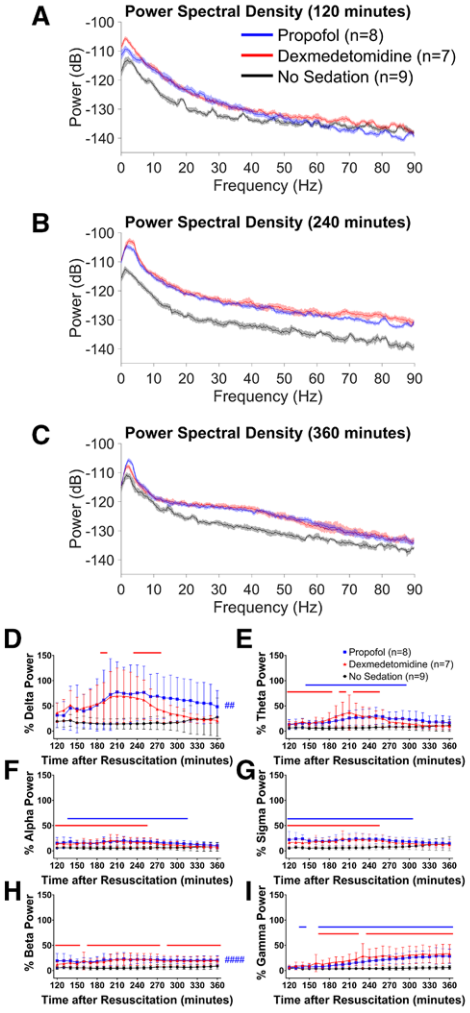


Fig. 6. Propofol or dexmedetomidine-induced electroencephalogram (EEG) changes early after sedation (2 to 6 h after return of spontaneous circulation). Power spectral density at (*A*) 120, (*B*) 240, and (*C*) 360 min after return of spontaneous circulation in male and female mice without sedation and those sedated with propofol at 40 mg · kg^{-1} · h^{-1} or dexmedetomidine at 1 μg · kg^{-1} · h^{-1} starting at return of spontaneous circulation. The median and 95% confidence intervals of spectral density are displayed. Changes in (*D*) delta, (*E*) theta, (*F*) alpha, (*G*) sigma, (*H*) beta, and (*I*) gamma power from 120 min up to 360 min after return of spontaneous circulation. EEG power was calculated for each frequency band at consecutive 10-min time blocks, which was expressed as percent of the baseline EEG power before cardiac arrest. Data are presented as mean ± SD. The *P* values for the interaction effect [group × time] are summarized in Supplemental Digital Content 14 table 4 (http://links.lww.com/ALN/C951). $^{\#\#}P < 0.01$, $^{\#\#\#\#}P < 0.0001$; *blue*: propofol *versus* no sedation (main effect). The *colored lines* in each graph indicate statistically significant differences from the no sedation group at specific time points after return of spontaneous circulation ($P < 0.05$; *blue*: propofol *vs.* no sedation, *red*: dexmedetomidine *vs.* no sedation; Dunnett's test).

Spectral analysis revealed an increase in EEG power across a broad frequency range up to 90 Hz at 240 min after return of spontaneous circulation (2 h after the end of sedation) in mice sedated with propofol or dexmedetomidine (fig. 6B). At 360 min after return of spontaneous circulation (4 h after the end of sedation), mice that received post–cardiac arrest sedation were associated with increased EEG power across frequencies less than 5 Hz and between 10 and 90 Hz (fig. 6C).

Quantitative EEG changes were visualized by calculating the relative EEG power in consecutive 10-min time blocks from 120 min up to 360 min after return of spontaneous circulation. EEG power remained less than about 30% of the baseline levels in mice receiving no sedation, whereas mice sedated with propofol or dexmedetomidine exhibited a notable increase in delta power from 210 to 240 min after return of spontaneous circulation (fig. 6D). These sedated mice also showed increased EEG power within theta, alpha, sigma, and beta frequencies with a time course similar to that of delta power (fig. 6E to 6H). In contrast to the other frequency bands, gamma power was continuously increased after the end of sedation with propofol or dexmedetomidine (fig. 6I).

Sedation with Low-dose Propofol and Delayed Sedation with Propofol Starting at 60 Min after Return of Spontaneous Circulation Did Not Accelerate Electrophysiologic Recovery in Hypothermia-treated Mice

Unlike sedation with propofol at 40 mg · kg^{-1} · h^{-1} starting at return of spontaneous circulation, the time-dependent increases in EEG were not observed in mice sedated with propofol at 10 mg · kg^{-1} · h^{-1} starting at return of spontaneous circulation or propofol at 40 mg · kg^{-1} · h^{-1} starting at 60 min after return of spontaneous circulation (Supplemental Digital Content 12 fig. 9, http://links.lww.com/ALN/C946 and Supplemental Digital Content 13 fig. 10, http://links.lww.com/ALN/C947). In fact, EEG power changed over time similarly in mice without sedation and those sedated with propofol starting at 60 min after return of spontaneous circulation. There was no apparent tendency for delta activity to increase during and after sedation with propofol at 40 mg · kg^{-1} · h^{-1} starting at 60 min after return of spontaneous circulation.

Early Recovery of Electrophysiologic Activities Predicted Post–cardiac arrest Outcomes in Hypothermia-treated Mice

To explore whether early recovery of electrophysiologic function would predict outcomes after cardiac arrest, we investigated the association between the relative EEG power in the early postresuscitation phase and neurologic outcomes in a total of 35 mice that underwent EEG recording. There was a positive correlation between the neurologic function score at 24 h after cardiac arrest and the relative

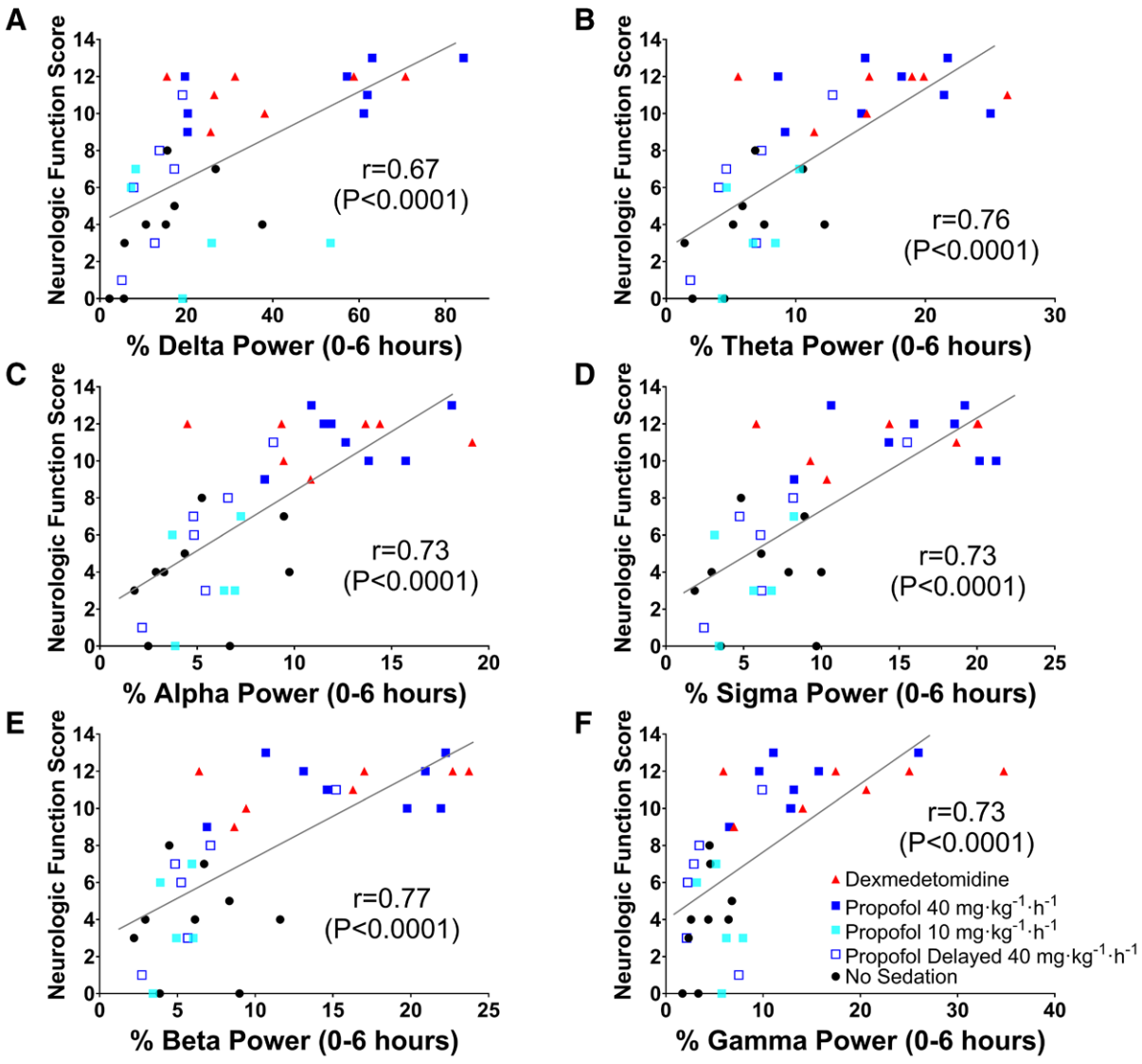


Fig. 7. Relationship between electroencephalogram (EEG) power early after resuscitation and neurologic function at 24 h post–cardiac arrest in male and female mice. The horizontal axis represents the relative EEG power in (*A*) delta, (*B*) theta, (*C*) alpha, (*D*) sigma, (*E*) beta, and (*F*) gamma frequencies in the first 6 h after return of spontaneous circulation, and the vertical axis represents the neurologic function scores at 24 h post–cardiac arrest that were assessed using scale 2. The Spearman correlation coefficient is reported. Note that dead mice were included in the analysis.

EEG power across all frequency bands in the first 6 h after return of spontaneous circulation (fig. 7).

Discussion

Our study uncovered the effects of post–cardiac arrest sedation in comatose hypothermia-treated mice. As compared with no sedation, mice that were sedated with propofol at 40 mg · kg^{-1} · h^{-1} or dexmedetomidine at 1 μg · kg^{-1} · h^{-1} starting at return of spontaneous circulation had improved survival and neurologic outcomes. Early administration of sedation ameliorated histologic brain injury and was accompanied by attenuation of early cerebral hyperemia and enhancement of EEG slow-wave activity during and early after sedation. Our findings suggest a possible neuroprotective effect of post–cardiac arrest sedation, which is associated with modulation of slow-wave activity and prevention of cerebral hyperemia immediately after resuscitation.

In animal models of global brain ischemia, the temporal course of cerebrovascular changes after reperfusion is characterized by early cerebral hyperemia followed by a hypoperfusion phase lasting several hours.[32–34] Preclinical

studies have suggested a possible benefit of blunting post-resuscitation cerebral hyperemia.[35,36] Our findings that sedation with propofol or dexmedetomidine starting at resuscitation, but not at 60 min after resuscitation, improved neurologic outcomes would be consistent with early evidence that barbiturates ameliorated ischemic brain damage when administered early, but not late postischemia.[8] Propofol produces cerebral vasoconstriction indirectly as a result of reduced cerebral metabolism in the healthy human brain.[37] Similarly, dexmedetomidine reduces cerebral blood flow possibly *via* α_2-adrenoreceptor–mediated cerebral vasoconstriction.[38] It is therefore conceivable that these agents altered the cerebral vasculature in post–cardiac arrest mice, thereby attenuating supernormal cerebral perfusion early after resuscitation. Sedatives may also limit cerebral oxygen supply/demand mismatch by exerting a coupled reduction of cerebral blood flow and cerebral metabolic rate of oxygen in conditions of impaired autoregulation.[9] Our observations highlight the potential of pharmacologic sedation as a protective intervention targeted to stabilize cerebrovascular function in the immediate postresuscitation phase.

Because the primary intended effect of sedation is to modulate neuronal activity, we hypothesized that administration of sedative–hypnotic agents to unconscious post–cardiac arrest mice would produce a deeper state of unconsciousness, or at least sustain the comatose state during the period of pharmacologic sedation. To our surprise, early administration of propofol at 40 mg · kg^{-1} · h^{-1} or dexmedetomidine at 1 μg · kg^{-1} · h^{-1} altered quantitative EEG profiles in comatose mice by inducing slow-wave activity. In contrast, the majority of mice without sedation remained in a state of prolonged unconsciousness with slow oscillation power being less than 30% of the baseline up to 24 h after cardiac arrest. These results are in alignment with the recent clinical observation that early recovery of EEG slow-wave activity during propofol sedation is associated with favorable outcomes in comatose cardiac arrest survivors.[20] Slow oscillations have been considered as a shared EEG feature of general anesthesia and sleep in healthy brains.[14,21] Sedative–hypnotic agents cause neocortical neurons to oscillate at approximately 1 Hz between a depolarizing state of intense firing and a hyperpolarizing state of silence.[39,40] The cortically generated rhythmic pattern of the electrical activity synchronizes into traveling waves over the cortical surface and gives rise to spatiotemporal slow (0.5 to 4 Hz) oscillations.[41] Sensory deafferentation during anesthesia or sleep and rhythmic input from intrinsically oscillating thalamocortical neurons also contribute to the full expression of slow oscillations.[42] Because the synchronized interaction of large neuronal populations between the cortical and subcortical areas is responsible for the formation of slow waves, it has been hypothesized that this electrophysiologic phenomenon can be disrupted by severe acute brain injury.[19] In the current study, the failure of delayed sedation with propofol to induce slow-wave activity and improve post–cardiac arrest outcomes may reflect ongoing or severe disruption of the delicate neuronal networks required to generate slow oscillations.

Recent evidence shows that slow oscillations during non–rapid eye movement sleep play an essential role in sleep homeostasis and higher cognitive function.[43,44] There is an emerging concept that views the globally synchronized neuronal off periods as a cellular maintenance process in which minor cellular injury can be ameliorated to prevent progression to irreversible injury.[22] In line with this conceptual framework, it is tempting to speculate that pharmacologic sedation produced states of neuronal silence in the early phase of recovery after hypoxic–ischemic brain injury, thereby allowing damaged neurons to shut down before primary cellular dysfunction is exacerbated to the point of causing permanent damage. Modulation of slow-wave activity induced by post–cardiac arrest sedation with propofol or dexmedetomidine may be an electroencephalographic signature of anesthetic-induced metabolic suppression that enables brain cells to rest and recuperate from deleterious ischemic insults. Whether induction of slow-wave activity early after resuscitation serves, not only as a marker of the electroencephalographic reactivity to anesthetics, but also as a potential strategy of neuroprotection, warrants further investigation.

Although propofol administration starting at return of spontaneous circulation dose-dependently exerted neuroprotective effects, EEG burst suppression was absent during sedation with propofol at 40 or 10 mg · kg^{-1} · h^{-1}. These observations are in agreement with the findings of Warner *et al.*[45] that barbiturates ameliorated brain damage after focal brain ischemia at low doses causing modest depression of electrical activity, with no additional benefit observed at higher doses sufficient to cause EEG burst suppression. Our findings imply that a possible dose–response relationship for the protective effect of propofol may be present at doses less than those required for EEG quiescence. Additional studies are required to examine detailed dose–response effects of post–cardiac arrest sedation.

There are limitations in our study. First, all mice were anesthetized with isoflurane before inducing cardiac arrest. Although isoflurane was discontinued at onset of cardiac arrest, it is possible that some isoflurane that remained in mouse tissues provided some sedative effects after resuscitation. Second, a longer arrest time was used for female mice because they are more resistant to brain ischemia than male mice.[24] Although survival and neurologic outcomes after cardiac arrest appear to be similar between male and female animals, the uneven distribution of female mice allocated to each treatment group could be a potential source of bias. Third, body temperature of mice decreased to less than 33°C after they were returned

to home cages and active warming was stopped. Although the body temperature was similar among groups up to 24 h after return of spontaneous circulation, the possibility was not ruled out that this unintended hypothermia influenced the results. Given the recent results of the Targeted Temperature Management 2 trial and updated clinical guidelines that do not recommend hypothermia in post–cardiac arrest patients, the effects of sedation need to be studied in normothermia in future studies.[46,47] Fourth, the decision to discontinue mechanical ventilation was not based on arterial blood gas analysis. In all mice, weaning from mechanical ventilation and cessation of oxygen administration was uniformly performed at 20 and 40 min, respectively, after return of spontaneous circulation on resumption of spontaneous ventilation (more than 100 breaths/min). Although there was no difference in the respiratory rate with or without sedation, the presence of hypoxemia or hypercapnia was not ascertained. Fifth, the infusion rate of propofol used in this study (40 mg · kg^{-1} · h^{-1}) was selected based on our pilot experiments in mice and is considerably higher than the recommended dose for patients. Finally, a mouse model of potassium chloride–induced cardiac arrest was used in the current study. Therefore, the applicability of the current results to clinical cardiac arrest is unknown. Further clinical studies are needed to elucidate the role of post–cardiac arrest sedation on neurologic outcomes.

In conclusion, post–cardiac arrest sedation with propofol or dexmedetomidine starting immediately after resuscitation improved survival and neurologic outcomes in hypothermia-treated mice. The beneficial effects of pharmacologic sedation early after resuscitation were associated with attenuation of cerebral hyperemia and early recovery of EEG power during and after sedation. In particular, our observations shed light on the ability of sedation to induce EEG slow-wave activity in comatose mice and improve neurologic outcomes after cardiac arrest. These results should stimulate future studies to gain further insight into the effects of sedation on neurologic recovery in cardiac arrest patients.

Research Support

This work was supported by a grant from the ZOLL Foundation (Chelmsford, Massachusetts) to Dr. Ikeda, and funds from the Department of Anesthesia, Critical Care and Pain Medicine, Massachusetts General Hospital (Boston, Massachusetts) to Dr. Ichinose.

Competing Interests

Dr. Amorim was supported during this research by the National Institutes of Health (Bethesda, Maryland; 1K23NS119794), Hellman Fellows Fund, Regents of the University of California (Resource Allocation Program), CURE Epilepsy Foundation (Chicago, Illinois; Taking Flight Award), Weil-Society of Critical Care Medicine (Mount Prospect, Illinois) Research Grant, ZOLL Foundation Grant (Chelmsford, Massachusetts), American Heart Association (Dallas, Texas; 20CDA35310297). Dr. Malhotra was supported by the National Heart, Lung, and Blood Institute (Bethesda, Maryland; R01HL142809), the American Heart Association (18TPA34230025), and the Wild Family Foundation (Miami, Florida). Dr. Malhotra receives research funding from Amgen (Thousand Oaks, California) and serves as a consultant for Myokardia/Bristol Myers Squibb (Brisbane, California), Renovacor (Narberth, Pennsylvania), and Third Pole (Waltham, Massachusetts). Dr. Malhotra is a co-inventor for a patent on pharmacologic bone morphogenetic protein (BMP) inhibitors (along with Mass General Brigham) for which he is entitled to royalties. Dr. Malhotra also receives royalties from UpToDate (Riverwoods, Illinois) for scientific content authorship. Dr. Solt was a consultant to Takeda Pharmaceuticals (Tokyo, Japan). Dr. Ichinose was supported by the National Institutes of Health (R01NS112373 and R21NS116671) and was a consultant to Nihon Kohden Innovation Center (Cambridge, Massachusetts) and received sponsored research agreement from Kyowa Hakko Bio (Tokyo, Japan) and Cyclerion Therapeutics (Boston, Massachusetts). The other authors declare no competing interests.

Correspondence

Address correspondence to Dr. Ichinose, Anesthesia Center for Critical Care Research, Department of Anesthesia, Critical Care and Pain Medicine, Massachusetts General Hospital, Thier 503, 55 Fruit St, Boston, MA 02114. fichinose@mgh.harvard.edu. This article may be accessed for personal use at no charge through the Journal Web site, www.anesthesiology.org.

Supplemental Digital Content

Supplementary Figure 1, http://links.lww.com/ALN/C938
Supplementary Figure 2, http://links.lww.com/ALN/C939
Supplementary Figure 3, http://links.lww.com/ALN/C940
Supplementary Figure 4, http://links.lww.com/ALN/C941
Supplementary Figure 5, http://links.lww.com/ALN/C942
Supplementary Figure 6, http://links.lww.com/ALN/C943
Supplementary Figure 7, http://links.lww.com/ALN/C944
Supplementary Figure 8, http://links.lww.com/ALN/C945
Supplementary Figure 9, http://links.lww.com/ALN/C946
Supplementary Figure 10, http://links.lww.com/ALN/C947
Supplementary Table 1, http://links.lww.com/ALN/C948
Supplementary Table 2, http://links.lww.com/ALN/C949
Supplementary Table 3, http://links.lww.com/ALN/C950
Supplementary Table 4, http://links.lww.com/ALN/C951

References

1. Benjamin EJ, Muntner P, Alonso A, Bittencourt MS, Callaway CW, Carson AP, Chamberlain AM, Chang AR, Cheng S, Das SR, Delling FN, Djousse L, Elkind MSV, Ferguson JF, Fornage M, Jordan LC, Khan SS, Kissela BM, Knutson KL, Kwan TW, Lackland DT, Lewis TT, Lichtman JH, Longenecker CT, Loop MS, Lutsey PL, Martin SS, Matsushita K, Moran AE, Mussolino ME, O'Flaherty M, Pandey A, Perak AM, Rosamond WD, Roth GA, Sampson UKA, Satou GM, Schroeder EB, Shah SH, Spartano NL, Stokes A, Tirschwell DL, Tsao CW, Turakhia MP, VanWagner LB, Wilkins JT, Wong SS, Virani SS; American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee: Heart disease and stroke statistics-2019 update: a report from the American Heart Association. Circulation 2019; 139:e56–e528
2. Geocadin RG, Callaway CW, Fink EL, Golan E, Greer DM, Ko NU, Lang E, Licht DJ, Marino BS, McNair ND, Peberdy MA, Perman SM, Sims DB, Soar J, Sandroni C; American Heart Association Emergency Cardiovascular Care Committee: Standards for studies of neurological prognostication in comatose survivors of cardiac arrest: a scientific statement from the American Heart Association. Circulation 2019; 140:e517–42
3. Madden LK, Hill M, May TL, Human T, Guanci MM, Jacobi J, Moreda MV, Badjatia N: The implementation of targeted temperature management: an evidence-based guideline from the Neurocritical Care Society. Neurocrit Care 2017; 27:468–87
4. Peberdy MA, Callaway CW, Neumar RW, Geocadin RG, Zimmerman JL, Donnino M, Gabrielli A, Silvers SM, Zaritsky AL, Merchant R, Vanden Hoek TL, Kronick SL; American Heart Association: Part 9: post-cardiac arrest care: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation 2010; 122(18 Suppl 3):S768–86
5. Citerio G, Cormio M: Sedation in neurointensive care: advances in understanding and practice. Curr Opin Crit Care 2003; 9:120–6
6. Dell'Anna AM, Taccone FS, Halenarova K, Citerio G: Sedation after cardiac arrest and during therapeutic hypothermia. Minerva Anestesiol 2014; 80:954–62
7. Young Y, Menon DK, Tisavipat N, Matta BF, Jones JG: Propofol neuroprotection in a rat model of ischaemia reperfusion injury. Eur J Anaesthesiol 1997; 14:320–6
8. Bleyaert AL, Nemoto EM, Safar P, Stezoski SM, Mickell JJ, Moossy J, Rao GR: Thiopental amelioration of brain damage after global ischemia in monkeys. Anesthesiology 1978; 49:390–8
9. Oddo M, Crippa IA, Mehta S, Menon D, Payen JF, Taccone FS, Citerio G: Optimizing sedation in patients with acute brain injury. Crit Care 2016; 20:128
10. Keegan MT: Sedation in the neurologic intensive care unit. Curr Treat Options Neurol 2008; 10:111–25
11. Strøm T, Martinussen T, Toft P: A protocol of no sedation for critically ill patients receiving mechanical ventilation: a randomised trial. Lancet 2010; 375:475–80
12. Kress JP, Pohlman AS, O'Connor MF, Hall JB: Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. N Engl J Med 2000; 342:1471–7
13. Kalbhenn J, Knörlein J, Posch MJ: "Do no further harm" - Why shall we sedate unresponsive patients? Intensive Care Med 2021; 47:807–8
14. Brown EN, Lydic R, Schiff ND: General anesthesia, sleep, and coma. N Engl J Med 2010; 363:2638–50
15. Akeju O, Pavone KJ, Westover MB, Vazquez R, Prerau MJ, Harrell PG, Hartnack KE, Rhee J, Sampson AL, Habeeb K, Gao L, Lei G, Pierce ET, Walsh JL, Brown EN, Purdon PL: A comparison of propofol- and dexmedetomidine-induced electroencephalogram dynamics using spectral and coherence analysis. Anesthesiology 2014; 121:978–89
16. Drohan CM, Cardi AI, Rittenberger JC, Popescu A, Callaway CW, Baldwin ME, Elmer J: Effect of sedation on quantitative electroencephalography after cardiac arrest. Resuscitation 2018; 124:132–7
17. Amorim E, Rittenberger JC, Zheng JJ, Westover MB, Baldwin ME, Callaway CW, Popescu A; Post Cardiac Arrest Service: Continuous EEG monitoring enhances multimodal outcome prediction in hypoxic-ischemic brain injury. Resuscitation 2016; 109:121–6
18. Samaniego EA, Mlynash M, Caulfield AF, Eyngorn I, Wijman CA: Sedation confounds outcome prediction in cardiac arrest survivors treated with hypothermia. Neurocrit Care 2011; 15:113–9
19. Kortelainen J, Väyrynen E, Huuskonen U, Laurila J, Koskenkari J, Backman JT, Alahuhta S, Seppänen T, Ala-Kokko T: Pilot study of propofol-induced slow waves as a pharmacologic test for brain dysfunction after brain injury. Anesthesiology 2017; 126:94–103
20. Kortelainen J, Ala-Kokko T, Tiainen M, Strbian D, Rantanen K, Laurila J, Koskenkari J, Kallio M, Toppila J, Väyrynen E, Skrifvars MB, Hästbacka J: Early recovery of frontal EEG slow wave activity during propofol sedation predicts outcome after cardiac arrest. Resuscitation 2021; 165:170–6
21. Purdon PL, Pierce ET, Mukamel EA, Prerau MJ, Walsh JL, Wong KF, Salazar-Gomez AF, Harrell PG, Sampson AL, Cimenser A, Ching S, Kopell NJ, Tavares-Stoeckel C, Habeeb K, Merhar R, Brown EN: Electroencephalogram signatures of loss and recovery of consciousness from propofol. Proc Natl Acad Sci U S A 2013; 110:E1142–51

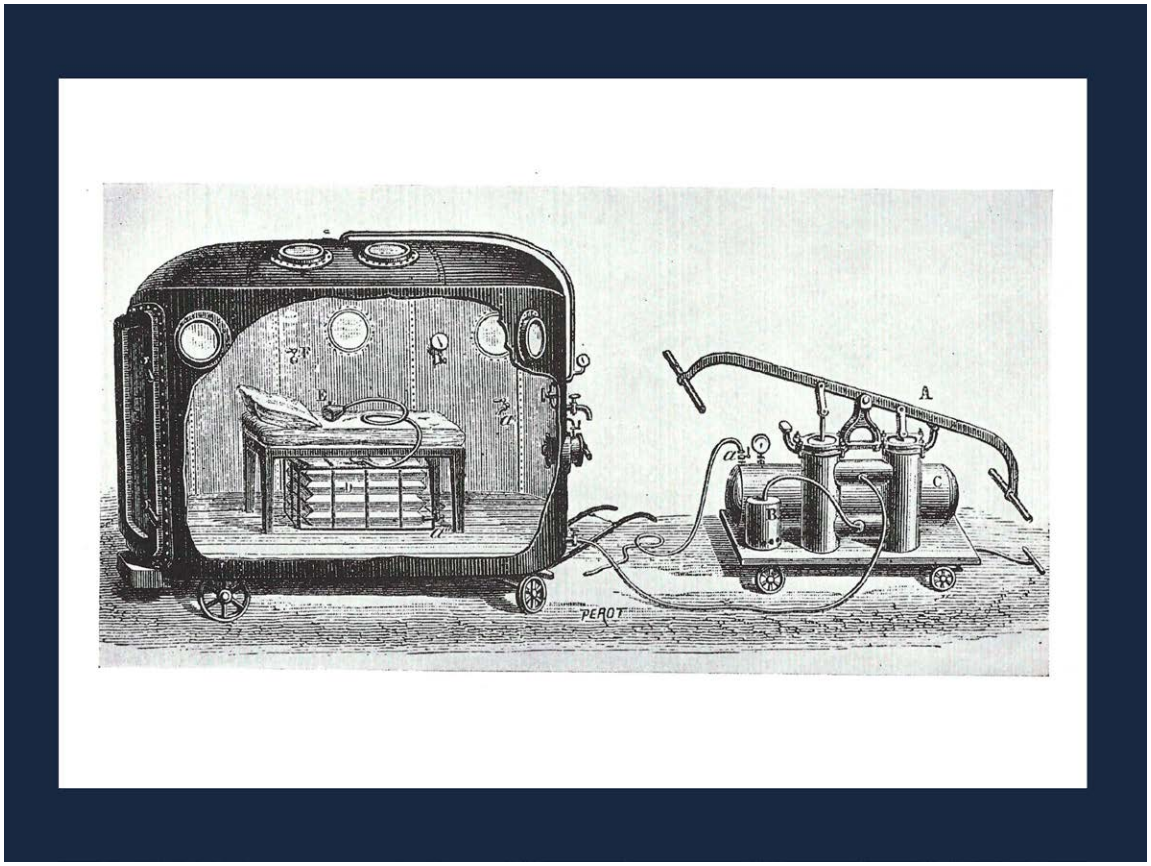
22. Vyazovskiy VV, Harris KD: Sleep and the single neuron: the role of global slow oscillations in individual cell rest. Nat Rev Neurosci 2013; 14:443–51
23. Minamishima S, Bougaki M, Sips PY, Yu JD, Minamishima YA, Elrod JW, Lefer DJ, Bloch KD, Ichinose F: Hydrogen sulfide improves survival after cardiac arrest and cardiopulmonary resuscitation via a nitric oxide synthase 3-dependent mechanism in mice. Circulation 2009; 120:888–96
24. Marutani E, Morita M, Hirai S, Kai S, Grange RMH, Miyazaki Y, Nagashima F, Traeger L, Magliocca A, Ida T, Matsunaga T, Flicker DR, Corman B, Mori N, Yamazaki Y, Batten A, Li R, Tanaka T, Ikeda T, Nakagawa A, Atochin DN, Ihara H, Olenchock BA, Shen X, Nishida M, Hanaoka K, Kevil CG, Xian M, Bloch DB, Akaike T, Hindle AG, Motohashi H, Ichinose F: Sulfide catabolism ameliorates hypoxic brain injury. Nat Commun 2021; 12:3108
25. Thal SC, Thal SE, Plesnila N: Characterization of a 3-vessel occlusion model for the induction of complete global cerebral ischemia in mice. J Neurosci Methods 2010; 192:219–27
26. Hayashida K, Bagchi A, Miyazaki Y, Hirai S, Seth D, Silverman MG, Rezoagli E, Marutani E, Mori N, Magliocca A, Liu X, Berra L, Hindle AG, Donnino MW, Malhotra R, Bradley MO, Stamler JS, Ichinose F: Improvement in outcomes after cardiac arrest and resuscitation by inhibition of s-nitrosoglutathione reductase. Circulation 2019; 139:815–27
27. Miyazaki Y, Marutani E, Ikeda T, Ni X, Hanaoka K, Xian M, Ichinose F: A sulfonyl azide-based sulfide scavenger rescues mice from lethal hydrogen sulfide intoxication. Toxicol Sci 2021; 183:393–403
28. Tang X, Sanford LD: Telemetric recording of sleep and home cage activity in mice. Sleep 2002; 25:691–9
29. Mitra P, Bokil H: Observed Brain Dynamics. Oxford; Oxford University Press, 2008
30. Moody OA, Zhang ER, Arora V, Kato R, Cotten JF, Solt K: D-Amphetamine accelerates recovery of consciousness and respiratory drive after high-dose fentanyl in rats. Front Pharmacol 2020; 11:585356
31. Du F, Zhu XH, Zhang Y, Friedman M, Zhang N, Ugurbil K, Chen W: Tightly coupled brain activity and cerebral ATP metabolic rate. Proc Natl Acad Sci U S A 2008; 105:6409–14
32. Nemoto EM, Snyder JV, Carroll RG, Morita H: Global ischemia in dogs: cerebrovascular CO_2 reactivity and autoregulation. Stroke 1975; 6:425–31
33. Kofke WA, Nemoto EM, Hossmann KA, Taylor F, Kessler PD, Stezoski SW: Brain blood flow and metabolism after global ischemia and post-insult thiopental therapy in monkeys. Stroke 1979; 10:554–60
34. Kågström E, Smith ML, Siesjö BK: Local cerebral blood flow in the recovery period following complete cerebral ischemia in the rat. J Cereb Blood Flow Metab 1983; 3:170–82
35. Manole MD, Kochanek PM, Foley LM, Hitchens TK, Bayır H, Alexander H, Garman R, Ma L, Hsia CJ, Ho C, Clark RS: Polynitroxyl albumin and albumin therapy after pediatric asphyxial cardiac arrest: effects on cerebral blood flow and neurologic outcome. J Cereb Blood Flow Metab 2012; 32:560–9
36. Cerchiari EL, Hoel TM, Safar P, Sclabassi RJ: Protective effects of combined superoxide dismutase and deferoxamine on recovery of cerebral blood flow and function after cardiac arrest in dogs. Stroke 1987; 18:869–78
37. Matta BF, Mayberg TS, Lam AM: Direct cerebrovasodilatory effects of halothane, isoflurane, and desflurane during propofol-induced isoelectric electroencephalogram in humans. Anesthesiology 1995; 83:980–5; discussion 27A
38. Slupe AM, Kirsch JR: Effects of anesthesia on cerebral blood flow, metabolism, and neuroprotection. J Cereb Blood Flow Metab 2018; 38:2192–208
39. Ní Mhuircheartaigh R, Warnaby C, Rogers R, Jbabdi S, Tracey I: Slow-wave activity saturation and thalamocortical isolation during propofol anesthesia in humans. Sci Transl Med 2013; 5:208ra148
40. Lőrincz ML, Gunner D, Bao Y, Connelly WM, Isaac JT, Hughes SW, Crunelli V: A distinct class of slow (~0.2–2 Hz) intrinsically bursting layer 5 pyramidal neurons determines UP/DOWN state dynamics in the neocortex. J Neurosci 2015; 35:5442–58
41. Massimini M, Huber R, Ferrarelli F, Hill S, Tononi G: The sleep slow oscillation as a traveling wave. J Neurosci 2004; 24:6862–70
42. David F, Schmiedt JT, Taylor HL, Orban G, Di Giovanni G, Uebele VN, Renger JJ, Lambert RC, Leresche N, Crunelli V: Essential thalamic contribution to slow waves of natural sleep. J Neurosci 2013; 33:19599–610
43. Tononi G, Cirelli C: Sleep and synaptic homeostasis: a hypothesis. Brain Res Bull 2003; 62:143–50
44. Marshall L, Helgadóttir H, Mölle M, Born J: Boosting slow oscillations during sleep potentiates memory. Nature 2006; 444:610–3
45. Warner DS, Takaoka S, Wu B, Ludwig PS, Pearlstein RD, Brinkhous AD, Dexter F: Electroencephalographic burst suppression is not required to elicit maximal neuroprotection from pentobarbital in a rat model of focal cerebral ischemia. Anesthesiology 1996; 84:1475–84
46. Dankiewicz J, Cronberg T, Lilja G, Jakobsen JC, Levin H, Ullén S, Rylander C, Wise MP, Oddo M, Cariou A, Bělohlávek J, Hovdenes J, Saxena M, Kirkegaard H, Young PJ, Pelosi P, Storm C, Taccone FS, Joannidis M, Callaway C, Eastwood GM, Morgan MPG, Nordberg P, Erlinge D, Nichol AD, Chew MS, Hollenberg J, Thomas M, Bewley J, Sweet K, Grejs AM, Christensen S, Haenggi M, Levis A, Lundin A, Düring J, Schmidbauer S, Keeble TR, Karamasis GV, Schrag C, Faessler E, Smid O, Otáhal M, Maggiorini M, Wendel Garcia PD, Jaubert P, Cole JM, Solar M, Borgquist O,

Leithner C, Abed-Maillard S, Navarra L, Annborn M, Undén J, Brunetti I, Awad A, McGuigan P, Bjørkholt Olsen R, Cassina T, Vignon P, Langeland H, Lange T, Friberg H, Nielsen N; TTM2 Trial Investigators: Hypothermia *versus* normothermia after out-of-hospital cardiac arrest. N Engl J Med 2021; 384:2283–94

47. Sandroni C, Nolan JP, Andersen LW, Böttiger BW, Cariou A, Cronberg T, Friberg H, Genbrugge C, Lilja G, Morley PT, Nikolaou N, Olasveengen TM, Skrifvars MB, Taccone FS, Soar J: ERC-ESICM guidelines on temperature control after cardiac arrest in adults. Intensive Care Med 2022; 48:261–9

ANESTHESIOLOGY REFLECTIONS FROM THE WOOD LIBRARY-MUSEUM

Paul Bert's OR on Wheels: A Hyperbaric Nitrous Oxide Chamber



Paul Bert (1833 to 1886), a French physiologist and politician, embraced the power of ideas to improve lives. A consummate scholar, Bert first studied engineering, then obtained successive doctorates in law, medicine, and the natural sciences. During his final years of schooling, he worked as the great Claude Bernard's laboratory assistant for 16 h a day. Bert eventually succeeded Bernard as Chair of Physiology at the Sorbonne and published his magnum opus, *La pression barométrique*, in 1878. Long called the "Bible of aviation medicine," the book included a glorious exposition of the relationship between atmospheric pressure and oxygen tension within alpinists, balloonists, and divers—people who worked at extreme heights or depths. Bert would soon apply this knowledge to anesthesia. As nitrous oxide (N_2O) could induce unconsciousness at 1 atm, the gas had to be delivered in pure form under normal-pressure conditions. Seeking to prolong N_2O's sedative effect while preventing asphyxia, Bert proposed using a hyperbaric chamber to deliver a N_2O and oxygen (O_2) mixture. Inspired by Bert's ideas, Parisian surgeon Fontaine built a traveling operating room *(image above)* that fit up to 12 people and provided N_2O-O_2 anesthesia for 27 surgeries within 3 months. A large hand pump ("A," *right*) controlled the delivery of the anesthetic mixture from a storage cylinder ("C," *right*), through a hose, and into a face mask within the chamber ("E," *left*). (Copyright © the American Society of Anesthesiologists' Wood Library-Museum of Anesthesiology. www.woodlibrarymuseum.org)

Jane S. Moon, M.D., Assistant Clinical Professor, Department of Anesthesiology and Perioperative Medicine, University of California, Los Angeles, California.