A Comparison of Cerebral Ischemic Flow Thresholds during Halothane/N\textsubscript{2}O and Isoflurane/N\textsubscript{2}O Anesthesia in Rats

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Isoflurane/N\textsubscript{2}O anesthesia has been reported to reduce the cerebral blood flow (CBF) threshold at which electroencephalographic changes occur in humans during carotid occlusion (when compared to halothane/N\textsubscript{2}O). To further evaluate this observation, normocapnic, normothermic rats were anesthetized with 0.75 MAC isoflurane or halothane in combination with 60% N\textsubscript{2}O. The electrocorticogram (ECoG) and the cortical DC potential were recorded using glass microelectrodes. Both carotid arteries were occluded, and mean arterial pressure (MAP) was reduced over 3–5 min (by phlebotomy) to predetermined values between 30 and 75 mm Hg. This MAP was maintained for 10 min, and CBF was then measured in cortical gray matter using [\textsuperscript{3}H]-nicotine. Flows were then correlated with ECoG changes and with the presence or absence of cortical depolarization (which reflects the loss of transmembrane ion homeostasis). In other rats, the cortical cerebral metabolic rate for glucose (CMR\textsubscript{glc}) was determined autoradiographically using [\textsuperscript{14}C]-deoxyglucose. Finally, the time to depolarization was determined in rats killed with KCl and in rats subjected to hypotension (MAP = 30–55 mm Hg) followed by abrupt bilateral carotid occlusion. The distributions of CBF values in the anesthetic groups were essentially identical. The incidence of either major ECoG changes or ischemic change did not differ between anesthetics. The CBF associated with major ECoG changes (excluding isoelectricity) were 35 ± 12 and 39 ± 18 ml·100 g\textsuperscript{-1}·min\textsuperscript{-1} in the halothane/N\textsubscript{2}O and isoflurane/N\textsubscript{2}O groups respectively (mean ± SD, difference not significant [NS]). Isoelectricity was seen at 7 ± 4 ml·100 g\textsuperscript{-1}·min\textsuperscript{-1} (median = 6.5) with halothane/N\textsubscript{2}O and 17 ± 19 ml·100 g\textsuperscript{-1}·min\textsuperscript{-1} (median = 11) with isoflurane/N\textsubscript{2}O (again, NS). The incidence of sustained depolarization did not differ between anesthetics (9 of 25 for halothane/N\textsubscript{2}O, 8 of 24 with isoflurane/N\textsubscript{2}O). CBF associated with sustained depolarization was 13 ± 12 ml·100 g\textsuperscript{-1}·min\textsuperscript{-1} (median = 10) with halothane/N\textsubscript{2}O, compared with 9 ± 6 ml·100 g\textsuperscript{-1}·min\textsuperscript{-1} (median = 9) for isoflurane/N\textsubscript{2}O (NS). In rats subjected to cardiac arrest, the time to depolarization was longer with isoflurane/N\textsubscript{2}O (102 ± 19 s vs. 77 ± 7 s). In rats subjected to carotid occlusion at a MAP = 30–35 mm Hg, the time to depolarization was again longer with isoflurane/N\textsubscript{2}O (210 ± 78 s vs. 122 ± 44 s). Cortical CMR\textsubscript{glc} was lower with isoflurane/N\textsubscript{2}O (25 ± 5 μmol·100 g\textsuperscript{-1}·min\textsuperscript{-1}) than with halothane (43 ± 13 μmol·100 g\textsuperscript{-1}·min\textsuperscript{-1}, P = 0.03). The results indicate that isoflurane/N\textsubscript{2}O anesthesia delays the onset of ischemic cell depolarization. However, when ischemia was prolonged for 10 min, we found no differences in either the incidence of sustained depolarization or the CBF values associated with depolarization. (Key words: Anesthetics, gases: nitrous oxide. Anesthetics, volatile: halothane; isoflurane. Brain, blood flow: cerebral ischemia. Monitoring, electroencephalogram: anoxic depolarization; DC potentials.)

In 1987, Messick et al. and Michenfelder et al. reported that the cerebral blood flow (CBF) at which ischemic EEG changes appeared during carotid cross-clamping ("critical CBF") was less in patients anesthetized with isoflurane/N\textsubscript{2}O than in a comparison group of patients receiving halothane/N\textsubscript{2}O.1,2 Michenfelder et al. also reviewed data that had been collected over a 14-yr period on 2,223 patients undergoing a carotid endarterectomy and found that electroencephalographic (EEG) changes were less frequent (≈18%) in patients anesthetized with isoflurane/N\textsubscript{2}O than in patients given halothane/N\textsubscript{2}O (≈25%).3 Based on these and other findings, some authors have concluded that isoflurane, compared to halothane, may provide protection against the effects of cerebral ischemia.2–4

It may, however, be inappropriate to conclude that anesthetic-related differences in either EEG-based critical CBF or in the incidence of EEG change represents "protection." In particular, drug-induced differences in "critical CBF" as defined by EEG slowing may have only limited relevance to tissue injury. Jones et al. have shown that the onset of clinical deficits occurs in awake primates at a CBF = 18–20 ml·100 g\textsuperscript{-1}·min\textsuperscript{-1}.5 In primates anesthetized with chloralose, somatosensory evoked responses do not change until CBF decreases to ≈15 ml·100 g\textsuperscript{-1}·min\textsuperscript{-1}, while cellular ion homeostasis is not lost until CBF reaches 6–10 ml·100 g\textsuperscript{-1}·min\textsuperscript{-1}.5,6–8 In view of these facts, it is appropriate to define several different levels of "critical CBF," each dependent on a different endpoint, such as EEG changes, evoked response changes, or the loss of ion homeostasis. Many other critical flows might be defined, but this last threshold (the loss of ion homeostasis) may be a better indicator of potential tissue injury since cell death does not occur unless flows of 10–12 ml·100 g\textsuperscript{-1}·min\textsuperscript{-1} are maintained for 2–3 h.5,9 Lower flows result in more rapid cell death.

There is no a priori reason to believe that just because a drug reduces one critical CBF value, it will reduce others in parallel. For example, isoflurane might reduce "critical CBF" as defined by EEG changes and yet have no effect on the flow at which cell depolarization occurs. If cell
death occurs only when the lowest flow values are reached, differences in EEG-defined critical flow might not be an appropriate indicator of "protection." It is also possible that time plays an important role. In other words, a decrease in critical CBF determined during an acute CBF change (such as occurs immediately after carotid occlusion) does not imply an improvement in tolerance to a prolonged period of such low flows.

The following laboratory study was undertaken to compare the effects of typical "clinical" doses of halothane/N₂O and isoflurane/N₂O anesthesia on the relationships between CBF and two electrophysiologic endpoints of central nervous system dysfunction: EEG (or, more accurately, electrocorticographic [ECOg]) change and the loss of ion homeostasis as indicated by cortical depolarization. In addition, we determined the delay between the onset of ischemia and depolarization in both "low-flow" and "zero-flow" conditions. These observations were related to measured differences in cortical cerebral metabolic rates for glucose (CMRglu) with the two anesthetics.

Material and Methods

All aspects of this study were approved by the University of Iowa Animal Care and Use Committee. Male Sprague-Dawley rats, weighing 359 ± 23 g (mean ± SD), were fasted overnight with free access to water. Anesthesia was induced with 4% halothane or isoflurane in oxygen. After tissue infiltration with 1% lidocaine, a tracheotomy was performed and mechanical ventilation was started (tidal volume ≈ 3.5 ml, frequency 45–55 breaths/min). During surgical preparation, anesthesia was maintained with 0.75–1.25 MAC of inhalation anesthetic in oxygen/N₂O (FlO₂ ≈ 0.4). (Halothane MAC for the rat was taken as 1.1%, and MAC for isoflurane was assumed to be 1.4%.) 10 Muscle relaxation was obtained with 0.9 mg d-tubocurarine chloride given subcutaneously. A rectal thermistor was placed, and temperature was maintained at 37.5–38.5 °C with a warming blanket and an overhead lamp. The right and left common carotid arteries were then isolated and encircled with silk thread. Both ends of the silk loops were threaded through pieces of plastic tubing, creating a snare that could later be used for carotid occlusion.

Three arteries and two veins were cannulated, again after tissue infiltration with 1% lidocaine. These included 1) the tail artery, which was used for continuous blood pressure monitoring and arterial blood sampling; 2) the left femoral artery, which was used for the infusion or withdrawal of blood during the later induction of hemorrhagic hypotension; 3) the right femoral artery, used for withdrawal of the reference sample during CBF determination; 4) the left femoral vein, which was used for isotope infusion during CBF measurements; and 5) the right femoral vein, which was used for drug and fluid administration. Throughout the surgical period, mean arterial pressure (MAP) was maintained > 80 mmHg, with 6% hetastarch given as necessary. Hematocrit, glucose, pH, PaCO₂, and PaO₂ were determined intermittently, and ventilation was adjusted if necessary to maintain PaO₂ > 100 mmHg and PaCO₂ between 36 and 42 mmHg.

When the above surgery was completed, the animal was turned prone and the head fixed in a stereotactic frame (David Kopf Instruments, Tujunga, CA). The scalp was infiltrated with 1% lidocaine and reflected laterally to expose the calvarium. A right frontoparietal craniectomy (approximately 4 × 12 mm) was performed with a high-speed electric drill, under a surgical microscope. The drilling site was irrigated with cool saline to avoid thermal trauma, and care was taken to leave the dura intact. When the craniectomy was complete, the inspired concentration of volatile agent was reduced to 0.75 MAC (0.8% halothane or 1.1% isoflurane, as verified with a Datex Anesthetic Agent Monitor 222), combined with 60% N₂O. A needle thermistor was then placed into the pericranial tissues adjacent to the craniectomy, and cranial temperature was thereafter kept at 37.5–38.5 °C with an overhead heating lamp.

DC Potential and Electrocorticographic Recordings

Through a small slit in the dura, two saline-filled glass microelectrodes with tip diameters of 1–5 μm were inserted 0.2 mm into the cortical surface, using micromanipulators, with care taken to avoid damage to cortical vessels. A Ag/AgCl wire in the barrel of each served as the electrical contact. The microelectrodes were placed with their tips as close to each other as possible (<1 mm apart). One electrode, which was referenced to bilateral platinum needles placed at the base of both ears, was used to record ECoG activity using a Grass 7P155 amplifier equipped with a Grass H1P5 high-impedance input probe. Filter settings were 1 and 30-Hz, with a 60-Hz notch filter. The signal was recorded on paper using a Grass model 79 polygraph and simultaneously passed to an IBM/AT computer for on-line Fourier processing and spectral analysis, which was stored on disk for later review. The second microelectrode, referenced to a single Ag/AgCl disk electrode attached to shaved skin of the animal's back (Red Dot, 3M), was used to record the DC potential of the cortical surface via a Grass 7P122 amplifier (also with a high-impedance input). When the electrodes were in place, the craniectomy was filled with light mineral oil, and a copper-screen Faraday cage was closed around the animal to minimize electrical noise. Fifty units of heparin were administered intravenously.
PROTOCOL AND CEREBRAL BLOOD FLOW MEASUREMENTS

Total preparation time was approximately 2 h and 15 min (from induction of anesthesia to the start of ECoG and DC potential monitoring). Immediately after electrode insertion was complete, the left common carotid artery was occluded using the previously placed snare. After a 5-min wait, the right carotid artery was also occluded. No other intervention took place for the next 20 min. If depolarization occurred during this time, the experiment was terminated. At the end of this interval (and after the inspired volatile agent concentration had been constant for \( \approx 40 \) min), blood gases and glucose concentrations were measured, and the left femoral arterial catheter was opened to a saline-filled reservoir suspended at a predetermined height above the animal. As blood spontaneously flowed into the reservoir, mean arterial pressure decreased (over approximately 3–5 min) to 70–75, 60–65, 50–55, or 30–35 mmHg, with pressure defined by the height of the reservoir. The selected pressure was then maintained for 10 min while ECoG and cortical DC voltage were continuously monitored.

At the end of the hypotensive interval, the stopcock connecting the animal with the blood pressure control reservoir was closed, and CBF was determined using \(^{3}H\)-nicotine according to the indicator-fractionation method. \(^{11-19}\) \(^{3}H\) nicotine (25–30 \( \mu \)Ci) in 0.6 ml saline was intravenously infused over 40 s. Simultaneously, a reference sample was withdrawn from the right femoral arterial catheter into a preweighed syringe. Both the infusion and withdrawal pumps were set at a rate of 0.75 ml/min. At the end of the isotope infusion period, the animal was killed by the injection of 1 ml saturated KCl. Arterial pressure was monitored during isotope infusion.

Note: assignment of animals to the four blood pressure groups was not random. The goal was to achieve CBF values that spanned the range from near zero to well above any anticipated ischemic thresholds. We also hoped to have a large number of animals with flows in the range between 0 and 30 ml \( \cdot \) 100 g \(^{-1} \cdot \) min \(^{-1} \), since we expected that the thresholds for both ECoG change and depolarization would lie in this range. Initially, eight animals (four with each anesthetic) were assigned to each of three pressure ranges (70–75, 50–55, and 30–35 mmHg). After inspection of the resultant flows, it was decided to 1) add eight rats (four with each anesthetic) to a 60–65-mmHg pressure group and 2) enter all additional animals into the 50–55-mmHg group, since this was believed to result in the widest scatter of flows with the range of interest.

To verify appropriate functioning of the electrodes and the recording system, a maximum of 2 min was allowed to pass after KCl administration to verify the occurrence of terminal anoxic depolarization and the appearance of ECoG isoelectricity (if these had not already occurred). The microelectrodes were then removed, and the brain at the craniectomy site was frozen in situ by pouring liquid \( N_2 \) over the skull. A cortical brain sample approximately 2 mm \( \times \) 10 mm \( \times \) was then removed via the craniectomy. All underlying white matter was carefully removed. The gray matter sample was placed on a glass coverslip, weighed, and placed in a 20-ml scintillation vial (approximate sample weight \( = 58 \pm 6 \) mg). One milliliter of tissue solubilizer (TS-1, Research Products International Corp., Mt. Prospect, IL) was added, and the vial was capped and heated overnight in an oven at 50°C. The samples were neutralized with 34 \( \mu \)l glacial acetic acid, and 18 ml 3a70 scintillation cocktail (Research Products International Corp.) was added.

After adding 500 units (0.5 ml) of heparin to the syringe, the arterial reference sample was weighed. Five 50-\( \mu \)l aliquots were pipetted into scintillation vials, and 0.6 ml TS-1 was added to each. The samples were incubated at 50°C for 20 min, decolorized with 200 \( \mu \)l benzoyl peroxide, and again heated at 50°C for 30 min. After adding 15 \( \mu \)l glacial acetic acid and 18 ml 3a70, the vials were closed and were kept overnight at 50°C.

All samples were protected from light for 4 days before counting in a Tracor Mark III 6880 Liquid Scintillation System (TM Analytic, Middleton, WI). After determination of the isotope content (\(^{3}H\) disintegrations per minute) in the reference sample and in the brain sample, CBF was calculated using the following equation:\(^{11}\):

\[
\text{CBF} = \left( \frac{\text{Reference syringe flow} \times \text{brain tissue} \left( ^{3}H\right) \text{dpm}}{\text{Reference syringe} \left( ^{3}H\right) \text{dpm}} \right) / \text{brain tissue weight}
\]

ELECTROCORTICOGRAHAM ANALYSIS

All ECoGs were examined by one of the investigators (MMT) who was blinded as to anesthetic group, blood pressure, and the presence/absence of depolarization. Initially, the raw tracings were surveyed, and the patterns present at the time of CBF measurement were compared with those seen prior to carotid occlusion. To simplify our analysis, the changes were categorized according to a five-level scale: unchanged; minor change (loss of amplitude or minimal slowing but with persistent high-frequency [\( > 8–12 \) Hz] activity); moderate change (persistent high-amplitude-low-frequency [\( < 8–12 \) Hz] activity); major change but with some persistent activity (defined as a tracing with large reductions in amplitude and frequency, but not isoelectric); and isoelectric. Second, plots of total electrical power and spectral edge frequency versus time were generated from the stored spectral data and were examined without knowledge of group, pressure, etc. The
information from this survey was used to “check” the initial categories. For example, a reduction in total power without a change in spectral edge frequency corresponded with a “minor change,” and a large reduction in spectral edge frequency associated with either no power change or an increase in power corresponded to a “moderate change.” The distinction between “major/persistent” and “isoelectric” could be made only by inspection of the raw tracings.

ADDITIONAL STUDIES

Latency to Isoelectricity and Depolarization

Twelve rats were randomly anesthetized with either halothane/N₂O (n = 6) or isoflurane/N₂O (n = 6) and prepared as described above, except that only one femoral artery and vein were cannulated. Anesthesia was also maintained as above, i.e., 0.75 MAC with 60% N₂O. After a stabilization period of 30 min, the animals were killed with 1 ml saturated KCl given intravenously. The subsequent time (in seconds) to the development of isoelectric EEG and to terminal anoxic depolarization were recorded (fig. 1).

After completion of our initial data analysis and examination of the CBF values obtained in the various hemorrhagic hypotension groups, a second series of animals was used to determine the time to terminal depolarization under circumstances of low (but not zero) CBF. Twelve rats were prepared as described above, with 6 in each of the two anesthetic groups. When preparation was complete, arterial pressure was reduced to 30–35 mmHg. When MAP was stable, both carotid arteries were occluded as quickly as possible, and the times to EEG isoelectricity and terminal depolarization were recorded.

Cerebral Metabolic Rate

Ten rats were randomly anesthetized with halothane/N₂O or isoflurane/N₂O (n = 5 each). Two arterial catheters and a single venous catheter were placed in each. The carotid arteries were isolated but were not occluded. A right parietal craniectomy was performed, but micro-electrodes were not placed. Cranial temperature was controlled. Anesthesia was maintained as above (0.75 MAC volatile agent with 60% N₂O). When surgery was complete, a stabilization period of 1 h was allowed. At the end of this period (≈2 h after induction of anesthesia), 100 µg/kg [¹⁴C]-2-deoxyglucose was infused intravenously at a constant rate of 45 s. Arterial blood samples of ≈100 µl were taken at 0.5, 1, 2, 3, 5, 7, 10, 15, 20, and 45 min after the infusion, while MAP was kept > 80 mmHg by infusion of rat donor blood if necessary.

At the end of the 45-min sampling period, the animals were decapitated, and the brains removed and immediately frozen in 2-methylbutane. The blood samples were centrifuged, and glucose concentrations were measured in duplicate in ≈20 µl of separated plasma. A 20-µl sample of the remaining plasma was placed in a scintillation vial, mixed with scintillation fluid, and counted. Twenty-micrometer-thick frozen coronal sections were cut from the region of brain underlying the craniectomy site. These sections were dried for 5 min on a hot plate and exposed to autoradiographic film along with standards. The autoradiographs were digitized and processed as described previously to create a pseudocolor image of the distribution of radioactivity. The cortical gray matter mantle was then outlined, and radioactivity was determined by reference to autoradiographic [¹⁴C] standards. Using this cortical radioactivity, the time course of radioactivity in plasma, and the plasma glucose values, CMRGlu was calculated using the equations developed by Sokoloff et al. A lumped constant of 0.483 was used.

STATISTICS

Because of the different tests used, statistical methods will be described in conjunction with the results. All tests were performed using commercial statistical programs (StatView II and SuperANOVA, Abacus Concepts, Berkeley, CA).

RESULTS

Sixty-two animals were successfully prepared for study. Nine animals showed cortical depolarization with initial

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**Fig. 1.** Representative polygraph tracing from an animal subjected to a cardiac arrest during electrocorticogram (EEG) and DC potential recordings. In this example, the latency to isoelectricity is 7 s, and the time to depolarization (bottom tracing, labeled “DC voltage”) is 83 s.
TABLE 1. Distribution of Animals According to Anesthetic and Hypotensive Groups

<table>
<thead>
<tr>
<th>MAP Group</th>
<th>Halothane/N₂O</th>
<th>Isoflurane/N₂O</th>
</tr>
</thead>
<tbody>
<tr>
<td>30–35</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>50–55</td>
<td>14</td>
<td>15</td>
</tr>
<tr>
<td>60–65</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>70–75</td>
<td>9</td>
<td>4</td>
</tr>
<tr>
<td>Totals</td>
<td>25</td>
<td>24</td>
</tr>
</tbody>
</table>

MAP = mean arterial pressure during hypotension (mmHg).

carotid occlusion (i.e., prior to any MAP manipulation) and were discarded. This left a total of 26 rats that were anesthetized with halothane/N₂O and 27 that received isoflurane/N₂O. One animal in the isoflurane/N₂O group developed severe hypotension during isoflurane infusion, and one halothane/N₂O animal died suddenly during CBF measurements. Two isoflurane/N₂O-anesthetized animals showed cortical depolarization during isoflurane infusion and also were discarded. This left 25 halothane/N₂O animals and 24 isoflurane/N₂O animals available for final data analysis. The distribution of animals among the four assigned blood pressures ranges is shown in table 1.

Baseline (prior to blood pressure manipulation) MAP, temperature, hematocrit, and blood gases did not differ between anesthetic groups (as assessed by an unpaired t test). Plasma glucose was significantly greater in the isoflurane/N₂O animals (table 2). 16

DISTRIBUTION OF CEREBRAL BLOOD FLOW VALUES

The distribution of CBF values within the two anesthetic groups is shown in figure 2. There were no differences between the groups as assessed by a Kolmogorov-Smirnov test, indicating that equivalent distributions of flow had been achieved in the two groups. Two-way analysis of variance (ANOVA) demonstrated a significant effect of blood pressure on CBF, but there were no differences between the two anesthetics. These data are also included in figure 2.

CEREBRAL BLOOD FLOW AND ELECTROCORTICOGRAPHIC CHANGES

Initial examination of the relationships between CBF and ECoG changes indicated significantly different CBFs for the various categories except for the "moderate" and "major/persistent" change subgroups. When data for the two anesthetics were combined, these two subgroups had CBF values of 41 ± 11 and 55 ± 15 ml·100 g⁻¹·min⁻¹, respectively. Therefore, for subsequent analysis, these

FIG. 2. Cumulative frequencies of cerebral blood flow (CBF) in the two anesthetic groups. Flows (on the x-axis) are grouped by units of 10 ml·100 g⁻¹·min⁻¹. For example, a point above the 10 ml·100 g⁻¹·min⁻¹ mark represents animals with flows between > 0 and 10 ml·100 g⁻¹·min⁻¹ (inclusive), and the point above the 50 ml·100 g⁻¹·min⁻¹ mark represents the percentage of animals with flows between > 0 and 50 ml·100 g⁻¹·min⁻¹. There were no differences in the distribution of flows. The included table shows mean ± SD CBF for the various MAP groups. The numbers of animals in each cell can be found in table 1. There were no differences between the two anesthetics. MAP = mean arterial pressure during hypotension.

TABLE 2. Baseline Physiologic Parameters

<table>
<thead>
<tr>
<th></th>
<th>Halothane/N₂O (n = 25)</th>
<th>Isoflurane/N₂O (n = 24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (g)</td>
<td>357 ± 18</td>
<td>361 ± 97</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>123 ± 18</td>
<td>132 ± 25</td>
</tr>
<tr>
<td>Rectal temperature (°C)</td>
<td>37.6 ± 0.4</td>
<td>37.8 ± 0.4</td>
</tr>
<tr>
<td>Cranial temperature (°C)</td>
<td>37.1 ± 0.3</td>
<td>37.1 ± 0.5</td>
</tr>
<tr>
<td>Hematocrit (vol%)</td>
<td>43 ± 2</td>
<td>44 ± 2</td>
</tr>
<tr>
<td>pH (units)</td>
<td>7.40 ± 0.03</td>
<td>7.38 ± 0.02</td>
</tr>
<tr>
<td>Pao₂ (mmHg)</td>
<td>38 ± 2</td>
<td>39 ± 2</td>
</tr>
<tr>
<td>PaO₂ (mmHg)</td>
<td>118 ± 17</td>
<td>113 ± 29</td>
</tr>
<tr>
<td>Glucose (mg/dl)</td>
<td>138 ± 17</td>
<td>183 ± 34*</td>
</tr>
</tbody>
</table>

Values obtained immediately after carotid occlusion but before the onset of hypotension. All values are mean ± SD. Statistical comparison was performed using a Student’s t test.

* P = 0.0001, halothane/N₂O versus isoflurane/N₂O.

MAP = mean arterial pressure.
Table 3. Electroencephalogram Categories and CBF

<table>
<thead>
<tr>
<th>ECoG Change</th>
<th>Anesthetic Group</th>
<th>n</th>
<th>Isoflurane/N₂O</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>No change</td>
<td>Halothane/N₂O</td>
<td>133 ± 38</td>
<td>2</td>
<td>84 ± 37</td>
</tr>
<tr>
<td>Minor change</td>
<td>Halothane/N₂O</td>
<td>74</td>
<td>1</td>
<td>42 ± 11</td>
</tr>
<tr>
<td>Major change</td>
<td>Halothane/N₂O</td>
<td>55 ± 12 [34]</td>
<td>16</td>
<td>39 ± 18 [55]</td>
</tr>
</tbody>
</table>

All values are milliliters per 100 g per minute, mean ± SD. The values in brackets are medians. There were no anesthetic-related statistical differences between either the incidence of different electroencephalogram (ECoG) changes (as assessed by contingency analysis) or between cerebral blood flow (CBF) values associated with the different patterns. CBF in each successive ECoG category was significantly different than in all others (both anesthetics combined). The interaction between anesthetic, ECoG change, and CBF was evaluated by two-way ANOVA. There were no differences after removal of animals in the “no change” and “minor change” groups from the analysis (which was done because of the number of data points). Contrast analysis for the “major change” and “isolectric” groups also failed to demonstrate any effect of the anesthetics.

were combined in a single group labeled “major change.”

The distribution of ECoG changes among the various subgroups and the associated CBFs are shown in table 3. The incidences of the various ECoG changes present at the end of the 10-min ischemic period did not differ significantly between anesthetics, as examined by contingency table analysis ($X^2 = 0.61$, table 3). Two-way ANOVA initially indicated a significant difference between the two anesthetic groups for the ECoG X CBF interaction. However, this was due entirely to anesthetic-related differences in CBF between animals with no ECoG changes. When these were removed from the analysis, there were no significant differences between anesthetics for ECoG change versus CBF (also table 3). The only subgroups large enough to carry out further statistical evaluation were “major” and “isolectric.” For these subgroups, contrast analysis showed no significant differences in CBF between isoflurane/N₂O and halothane/N₂O for either the “major” or “isolectric” ECoG subgroups. We also examined the “major” and “isolectric” groups by a nonparametric test (Mann-Whitney) and again found no differences between anesthetics ($P = 0.57$ for “major” ECoG changes; $P = 0.35$ for “isolectric”).

Information for individual animals is shown in figure 3. While there is no apparent difference in the upper limit of flows associated with major ECoG changes, the three lowest flows associated with the maintenance of an essentially unchanged ECoG were in isoflurane/N₂O animals. By contrast, two isoflurane/N₂O animals had isoelectric ECoGs at CBFs of 42 and 55 ml·100 g⁻¹·min⁻¹. It should, however, be noted that both of these animals showed marked burst-suppression on their preischemia ECoG and both also showed transient cortical depolarization early in the ischemic period.

Cerebral Blood Flow and Depolarization

The incidences of transient and sustained depolarization in the various blood pressure groups is presented in table 4. The incidence of sustained depolarization present at the end of 10 min of hypotension was the same for both anesthetics as determined by contingency analysis, i.e., 36% of animals in the halothane/N₂O group (9 of 25) and 33% in the isoflurane/N₂O group (8 of 24). Fewer isoflurane/N₂O-anesthetized rats showed transient de-

![Fig. 3. Individual electroencephalogram (ECoG) changes present at the end of the 10-min hypotensive period versus measured cerebral blood flow (CBF) for the two anesthetic groups. CBF units are milliliters per 100 g per minute. A downward bar represents an animal with either no ECoG changes or “minor” ECoG changes, and an upward bar represents an animal with either “major” changes (solid lines) or isoelectricity (dashed lines noted by arrows). A thick bar indicates two animals with identical flows. For both anesthetics, the upper limit of flow associated with a major ECoG change was 50–60 ml·100 g⁻¹·min⁻¹. In the halothane/N₂O group, the median CBF associated with serious ECoG changes (“major + isoelectric”) was 32 ml·100 g⁻¹·min⁻¹, compared with 51 ml·100 g⁻¹·min⁻¹ for isoflurane/N₂O. For isoelectricity, the respective median flows were 6.5 and 11 ml·100 g⁻¹·min⁻¹. Note, however, that the three lowest flows associated with an unchanged ECoG occurred in isoflurane/N₂O animals (at CBFs of 32, 50, and 57 ml·100 g⁻¹·min⁻¹).](http://anesthesiology.pubs.asahq.org/pdfaccess.ashx?url=/data/journals/jasa/931329/ on 05/07/2018)
TABLE 4. Sustained and Transient Depolarization in the Various Blood Pressure and Anesthetic Groups

<table>
<thead>
<tr>
<th>MAP Group (mmHg)</th>
<th>Halothane/N₂O</th>
<th>Isoflurane/N₂O</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sustained</td>
<td>Transient</td>
</tr>
<tr>
<td></td>
<td>Depolarization</td>
<td>Depolarization</td>
</tr>
<tr>
<td>30–35</td>
<td>4/4</td>
<td>0/4</td>
</tr>
<tr>
<td>50–55</td>
<td>5/14</td>
<td>4/14</td>
</tr>
<tr>
<td>60–65</td>
<td>0/4</td>
<td>3/4</td>
</tr>
<tr>
<td>70–75</td>
<td>0/3</td>
<td>2/3</td>
</tr>
<tr>
<td>Total</td>
<td>9/25 (36%)</td>
<td>9/25 (36%)</td>
</tr>
</tbody>
</table>

Values represent the number of animals with either sustained or transient depolarization out of the total number of animals in any given MAP subgroup i.e., zero of three halothane/N₂O-anesthetized animals in the 70–75-mmHg subgroup demonstrated sustained depolarization (i.e., depolarization present at the time of cerebral blood flow [CBF] measurement), whereas two of these three animals demonstrated some transient depolarization (but had repolarized by the time CBF was measured). Cell sizes made statistical comparisons impossible for individual blood pressure subgroups. Overall, there were no anesthetic-related differences for sustained depolarization. However, fewer isoflurane/N₂O-anesthetized animals showed transient depolarization (13% vs. 36% for halothane/N₂O), although this achieved a P value of only 0.09.

MAP = mean arterial pressure during hypotension.

polarization (with repolarization present at the time of CBF determination), although the P value for this difference was only 0.09.

Mean CBF in those halothane/N₂O-anesthetized animals with sustained cortical depolarization was 13 ± 12 ml·100 g⁻¹·min⁻¹, as compared with 9 ± 6 ml·100 g⁻¹·min⁻¹ in the isoflurane/N₂O group. Two-way ANOVA demonstrated no anesthetic effects (P = 0.6). An unpaired t test for the CBF values in animals with sustained depolarization also indicated no significant difference between anesthetics (P = 0.43). Because the power of this test to detect a difference of 5 ml·100 g⁻¹·min⁻¹ is only approximately 0.2, group sizes in excess of 50 rats each (with cortical depolarization occurring in every animal) would be needed to achieve significance given the variance observed. Also, the median CBFs associated with depolarization in the two groups were 10 and 9 ml·100 g⁻¹·min⁻¹ for halothane/N₂O and isoflurane/N₂O, respectively.

The data for CBF versus sustained depolarization in individual animals is shown in figure 4. In both groups, CBF values > 20 ml·100 g⁻¹·min⁻¹ were essentially never associated with depolarization (except in one animal in the halothane/N₂O group with a CBF of 42 ml·100 g⁻¹·min⁻¹). By contrast, CBF values < 20 ml·100 g⁻¹·min⁻¹ were found in all but one animal with cortical depolarization (the exception was one isoflurane/N₂O-anesthetized rat with a CBF of 12 ml·100 g⁻¹·min⁻¹).

LATENCY TO DEPOLARIZATION

There were no significant differences between the two anesthetics in the time from the onset of hypotension to depolarization (334 ± 87 s for halothane/N₂O and 331 ± 160 s for isoflurane/N₂O, unpaired t test). Furthermore, if this latency was examined according to MAP subgroups (via two-way ANOVA), no anesthetic-related differences were seen.

ADDITIONAL STUDIES

Latency to Isoelectricity and Depolarization

Because the onset of ischemic conditions occurred over several minutes in the animals above, and because flows varied widely within the study, the above-noted latencies to depolarization represent data from a very heterogeneous group. Hence, latencies were examined in two added groups of animals in which both the onset of ischemia and the resultant CBFS were better defined. Physiologic variables in these animals (MAP, arterial blood gases, etc.) were similar to those in the study above, with no differences between anesthetics except for plasma glucose. Latency results are shown in table 5.

When CBF was abruptly reduced to zero by a KCl-induced cardiac arrest, the time to terminal depolarization was significantly longer for isoflurane/N₂O (102 ± 19 s) than for halothane/N₂O (77 ± 7 s, P = 0.013 by unpaired t test; table 5). Latency time to ECoG isoelectricity was the same for both anesthetics (halothane/N₂O = 9 ± 2 s and isoflurane/N₂O = 8 ± 2 s).

In the second group of rats, MAP was reduced to 30–35 mmHg, and both carotids were then abruptly occluded. In the earlier studies (see above), CBF associated with these circumstances was 5 ± 4 ml·100 g⁻¹·min⁻¹ (both anesthetics combined, fig. 2), with a range of 1–11 ml·100 g⁻¹·min⁻¹. Again, latency was significantly longer in isoflurane/N₂O-anesthetized animals (P = 0.036, table 5). Note that the times to ECoG isoelectricity appeared to be shorter in animals with a MAP of 30–35 mmHg than in those subjected to cardiac arrest.
However, MAP in these animals was reduced to \( \approx 30 \) mmHg prior to carotid occlusion, and most animals demonstrated some ECoG changes prior to applications of the carotid clamps.

**Cerebral Metabolic Rate**

Cortical CMR\(_{\text{gly}}\) values in the right cortical gray matter mantle were significantly less with isoflurane/N\(_2\)O than with an equipotent concentration of halothane/N\(_2\)O (25 \( \pm \) 5 \( \mu \)mol \( \cdot \) 100 g\(^{-1}\) \( \cdot \) min\(^{-1}\) vs. 43 \( \pm \) 13 \( \mu \)mol \( \cdot \) 100 g\(^{-1}\) \( \cdot \) min\(^{-1}\), \( P = 0.03 \) by unpaired \( t \) test). Similar values were measured in the left parietal cortex (40 \( \pm \) 11 for halothane/N\(_2\)O vs. 28 \( \pm \) 4 for isoflurane/N\(_2\)O and \( P = 0.01 \)), indicating that the creation of the craniectomy did not influence metabolic rates.

**Discussion**

As noted in the introduction to this paper, there is evidence suggesting a lower "critical CBF" (based on EEG changes) in patients anesthetized with isoflurane/N\(_2\)O than in patients given halothane/N\(_2\)O.\(^2\) However, the CBF at which EEG changes initially appear is higher than the CBF at which cellular ion homeostasis is lost or at which histopathologic damage occurs, at least after short periods of time.\(^6\)-\(^{17,19}\) Therefore, the current study was undertaken to examine the relationship between CBF, ECoG, and another index of ischemic dysfunction, cortical depolarization, an event that clearly signals major energy failure and that occurs at flows much closer to those associated with relatively rapid cell death.\(^7\),\(^8\),\(^17\)-\(^{19}\)

We should begin with a discussion of methodology. We used different levels of hypotension combined with bilateral carotid occlusion to obtain a spectrum of CBF values in the two anesthetic groups. We then examined the coincident ECoG changes and noted the presence or absence of ischemic depolarization after a 10-min period of stable conditions. We used carotid occlusion (rather than hypotension alone) because it allowed us to achieve very low CBF values without using near-fatal levels of hypotension. In addition, a similar model has long been used in our laboratory and others for the examination of histopathologic brain injury in rats.\(^20\),\(^21\)

Strictly speaking, we did not determine the "threshold" for either ECoG changes or for terminal depolarization, although this term is commonly used by most laboratories that use similar methods. To determine "thresholds" precisely in individual animals, we would need to reduce CBF gradually in each animal and then measure flow at the instant the desired electrophysiologic change was observed. There are several serious problems with this approach. First, depolarization (unlike ECoG changes) does not occur immediately after the onset of appropriate ischemic conditions. For example, 65–131 s passed before depolarization when CBF was reduced to zero, and even longer latencies occurred with higher flows (i.e., in the 30–35-mmHg subgroup). To determine an acute depolarization threshold in a single animal, CBF would need to be very slowly reduced—a protocol that would be ex-

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**Table 5. Latency to Isoelectricity and to Terminal Depolarization**

<table>
<thead>
<tr>
<th>Group</th>
<th>Halothane/N(_2)O</th>
<th>Isoflurane/N(_2)O</th>
</tr>
</thead>
<tbody>
<tr>
<td>Latency to EEG Isoelectricity (seconds)</td>
<td>9 ( \pm ) 2</td>
<td>8 ( \pm ) 2</td>
</tr>
<tr>
<td>Cardiac arrest</td>
<td>4 ( \pm ) 5</td>
<td>3 ( \pm ) 2</td>
</tr>
<tr>
<td>MAP 30–35 mmHg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Latency to Depolarization (seconds)</td>
<td>77 ( \pm ) 7</td>
<td>102 ( \pm ) 19*</td>
</tr>
<tr>
<td>Cardiac arrest</td>
<td>122 ( \pm ) 44</td>
<td>210 ( \pm ) 78*</td>
</tr>
<tr>
<td>MAP 30–35 mmHg</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

All values are mean \( \pm \) SD. Latencies are from the onset of cardiac arrest or from the moment of carotid occlusion (in the MAP = 30–35 mmHg group). Differences between anesthetics were examined using unpaired \( t \) tests (since the experiments were done separately).

\* \( P < 0.05 \), isoflurane/N\(_2\)O versus halothane/N\(_2\)O.
tremely difficult to implement without dramatically prolonging the hypotensive period and incurring severe acid-base disturbances. Furthermore, there is a possibility that some types of depolarization — such as that which accompanies spreading depression — may result in immediate (although transient) CBF changes.\textsuperscript{25–24} Hence, one ideally should measure CBF immediately prior to depolarization.

Of course, this is impossible, unless some method were available to measure flow continuously.\textsuperscript{6} Instead, we used the method used by most investigators; i.e., standard hemodynamic conditions were produced, and these in turn generated a range of flows. We then retrospectively correlated CBF with electrophysiology. This yields a “population estimate” of threshold, rather than a precise animal-by-animal measurement.

The present study was carried out using 0.75 MAC doses of volatile agent in combination with 60% N\textsubscript{2}O. This differs from the more typical laboratory protocol in which isoflurane is given in relatively large doses to produce profound EEG suppression.\textsuperscript{5,21,20,27} This is usually done to achieve maximal metabolic depression with the drug.\textsuperscript{28} We instead chose the lower concentrations for several reasons. First, they represent doses typically used in clinical anesthesia. Despite the interest in “cerebral protection” with isoflurane, relatively few anesthesiologists are willing to administer 1.5–2.0 MAC isoflurane to the typical patient undergoing carotid endarterectomy. Data indicate that the achievement of burst-suppression with isoflurane results in markedly more hemodynamic depression than is seen with an EEG-equivalent dose of barbiturate (see Discussion in ref. 29). In addition, the differences in critical CBF and incidence of EEG changes seen by Messick \textit{et al.} and by Michenfelder \textit{et al.} were found in patients given sub-MAC concentrations of the agents in combination with N\textsubscript{2}O.\textsuperscript{1,12} Finally, marked suppression of EEG activity would make it very difficult to determine the existence of changes during ischemia. In fact, the occurrence of burst-suppression EEG patterns in our isoflurane/N\textsubscript{2}O-anesthetized rats may have caused problems for our ECoG analysis (see below). Fortunately, the doses of volatile agent used resulted in large reductions in CMR\textsubscript{glu} compared with awake values of 60–80 \textmu mol·100 g\textsuperscript{−1}·min\textsuperscript{−1}.\textsuperscript{30} We also observed a large difference in cortical CMR\textsubscript{glu} between the isoflurane/N\textsubscript{2}O-and halothane/N\textsubscript{2}O-anesthetized animals. The size of this difference was similar to that observed in earlier studies with 1 MAC doses of volatile agent alone.\textsuperscript{14}

We examined two indicators of ischemia: ECoG and DC depolarization. To avoid confusion stemming from the different baseline ECoG patterns seen with the different anesthetics (which makes it impossible to apply rigid, absolute frequency/amplitude criteria), ECoG changes were categorized by a single observer who was blinded for anesthetic, MAP, CBF, and DC potential. We limited the number of ECoG categories to simplify analysis, and after completion of the study, decided to combine two different categories (“moderate” change and “major/ persistent” change) into one (“major”) because there were no differences in CBF values between the groups. It is interesting to note, however, that all of the “moderate” ECoG changes were seen in halothane/N\textsubscript{2}O rats, whereas the most common ischemic ECoG patterns noted with isoflurane/N\textsubscript{2}O anesthesia were “major/persistent” and “isoelectric.” We believe that this is a reflection of the difficulties encountered in trying to detect relatively modest ECoG changes in the face of occasional burst-suppression produced by isoflurane, even at the doses used here. In other words, “isoelectricity” (or “major change”) may represent a slightly different event when judged against a prior pattern of marked burst-suppression than when compared with a continuously active EEG. One possible extreme example of this may be the isoelectric ECoGs seen in two isoflurane/N\textsubscript{2}O animals with measured CBFs of 42 and 55 ml·100 g\textsuperscript{−1}·min\textsuperscript{−1}, values much higher than we typically associate with isoelectricity. Because of these difficulties, we also chose cortical DC potential changes (“depolarization”) as a more discrete marker of severe ischemic failure of ion homeostasis. Depolarization clearly does not occur until ischemia is relatively severe\textsuperscript{19} and appears coincidently with an abrupt increase in extracellular [K\textsuperscript{+}] and a decrease in extracellular [Ca\textsuperscript{2+}].\textsuperscript{31} All of these changes are at least in part the result of severe depletion of energy stores and the failure of normal ATP-dependent pumping mechanisms that maintain normal transmembrane ion gradients.\textsuperscript{17,19} We chose to record DC potential rather than extracellular [K\textsuperscript{+}] largely as a matter of convenience: the voltage change is large and easily recognized; the microelectrodes are easy to prepare; and both depolarization and K\textsuperscript{+} release occur simultaneously.\textsuperscript{19}

We looked at ECoG and DC voltage changes in a tiny area of cortex as measured with our microelectrodes. CBF and CMR\textsubscript{glu} were measured in a slightly larger but still small volume of gray matter that corresponded to the tissue region in which electrophysiologic measurements were taken. This approach ensures that all measurements were derived from a relatively homogeneous tissue compartment. This may not be true when recording the EEG from multiple scalp electrodes and attempting to relate it to CBF obtained from a single extracranial detector and CMR calculated from a cortical CBF measurement combined with arterial and jugular venous blood samples (which reflect changes in the whole brain). In addition,
we did not attempt to relate CBF, ECoG, and DC voltage changes until 10 min of ischemia had been present. This differs from the human situation in which CBF and the EEG have been recorded at the moment of carotid occlusion.1,2

We chose this approach largely to ensure relative stability. CBF in humans and animals is quite unstable in the few minutes immediately following carotid occlusion. For example, Halsey et al., using a transcranial Doppler, have shown that flow velocity in the middle cerebral artery decreases precipitously with application of the cross clamp, but rapidly increases to some intermediate plateau in many patients.92 We have observed similar changes with continuous laser-Doppler measurements of cortical CBF in rats (unpublished observations). In such studies, CBF decreases precipitously after carotid occlusion (even when MAP is normal) but quickly rebounds (within about 1 min) and continues to increase over the next 5 min. Hence, we believe that CBF and EEG changes measured in the acute period after carotid clamping reflect a highly unsteady state that may not reflect conditions that will be present several minutes later. Also, since cell injury in the face of incomplete ischemia requires many minutes (unless CBF is zero), measurements made after some stability is achieved are likely to be more relevant to ultimate neurologic dysfunction or histopathologic changes.

Our goal was to determine whether similar ischemic conditions were associated with similar electrophysiologic changes in the presence of two different anesthetics. To accomplish this, it was necessary to ensure that the distribution of CBFs within the two experimental groups was truly similar. Figure 2 indicates that this was achieved; in fact, the distribution of CBF values was essentially identical in the two anesthetic groups.

We next examined the incidences of both ECoG changes and depolarization in the two groups. Again, we found no anesthesia-related differences. In the halothane/N2O group, 64% of animals demonstrated major ECoG changes; 24% had an isoelectric ECoG; and 35% showed persistent cortical depolarization at the end of the 10 min ischemic period. In the isoflurane/N2O group, the respective percentages were 42%, 38%, and 33%. Although there appears to be a slightly lower incidence of “major” ECoG changes with isoflurane/N2O, this was offset by a higher incidence of isoelectricity. These differences also did not achieve statistical significance. It is possible that the differences in the incidence of ECoG abnormalities arose from difficulties in distinguishing between “major” and “isoelectric” ECoG patterns in isoflurane/N2O-anesthetized animals, since burst-suppression was commonly seen during ischemia (see above). However, if we combined these two patterns (“major” and “isoelectric”), we found that 88% of our halothane/N2O animals and 84% of our isoflurane/N2O animals developed clearly abnor-

mal ECoG changes. It is possible, of course, that a difference in the incidence of more minor ECoG changes might have been found, but we had an insufficient number of animals with these “minor” changes to allow this determination. Furthermore, we were more interested in more severe ischemic situations.

Finally, we determined the various CBFs associated with the different endpoints. For example, the median CBF found in halothane/N2O-anesthetized animals with persistent cortical depolarization was 10 ml·100 g−1·min−1, compared with 9 ml·100 g−1·min−1 for isoflurane/N2O, even though large differences in cerebral metabolic rate were found between halothane/N2O and isoflurane/N2O. It should be noted that our two “critical CBF” values (for ECoG changes and depolarization) are generally similar to those found by other groups. For example, Harris and Symon noted that extracellular [K+] began to increase at cortical CBFs below 15 ml·100 g−1·min−1,31 and both Mabe et al. and Todd et al. noted the appearance of EEG isoelectricity at flows between 10–15 ml·100 g−1·min−1.33,34 By contrast, initial EEG changes occur in halothane- and isoflurane-anesthetized rats at CBF values of 25–30 ml·100 g−1·min−1,41 again generally similar to the observations made here.

It is tempting at this point to conclude that there were no important distinctions between halothane/N2O and isoflurane/N2O anesthesia. However, we did find certain striking differences. We initially noted that the incidence of transient depolarization was somewhat less with isoflurane/N2O (even though the difference did not quite achieve statistical significance). Because the incidence of sustained depolarization was not different, this suggested that time might be playing some role. We have noted the variable nature of CBF in the immediate postocclusion period. We reasoned that a brief decrease in CBF below the depolarization threshold might explain the transient voltage shifts and further reasoned that the lower CMRGlu in isoflurane/N2O animals might “buy” enough time to prevent depolarization until flow recovered. We therefore directly determined whether the anesthetic influenced the latency to depolarization. This was done both under conditions of zero CBF (cardiac arrest) and low (but not zero) CBF. In both situations, latency to depolarization was longer with isoflurane/N2O. This confirms some role for CMR suppression; a similar relationship between decreasing CMR and increasing latency to depolarization has been observed by Astrup et al.35 It is noteworthy that we found no differences in the latencies to ECoG isoelectricity. However, since isoelectricity appears long before high-energy phosphate compounds disappear, it may not

be related to energy failure and is unlikely to be related to CMR$_{\text{glu}}$. In fact, Raffin et al. have suggested that ECoG suppression after the onset of ischemia is a protective mechanism, since it slows the decrease of tissue P$_{O_2}$.

Although these anesthesia-related differences in the time to energy failure are clear, their importance appears to be minor, since no differences in the incidences of electrophysiologic events or their associated flows were found with longer (10 min) ischemic periods. In other words, isoflurane delayed the onset of depolarization by about 90 s in rats with bilateral carotid occlusion subjected to a MAP of 30–35 mmHg. Isoflurane also seemed to reduce the incidence of transient depolarization events, perhaps caused by transient reductions in CBF below the values at which flow eventually stabilized. However, far longer periods of ischemia are required for histopathologic injury, and it seems unlikely that a 90-s delay in achieving total energy failure is meaningful. This is supported by a recent study by Sano et al. in which halothane- and isoflurane-anesthetized rats were subjected to 10 min of bilateral carotid occlusion and hypotension to 35 mmHg. These authors found no differences in histopathologic outcome.

We do believe that conditions might exist (i.e., when CBF is slightly higher) in the use of isoflurane could indefinitely prolong the time to depolarization. In fact, we did have one isoflurane/N$_2$O animal with a CBF of 12 ml·100 g$^{-1}$·min$^{-1}$ and no depolarization present by the end of 10 min (although transient cortical depolarization did occur earlier). However, the rarity of this situation suggests that the flow window in which isoflurane would “protect” for a long period is very narrow. This is supported by the work of Warner et al., who found no improvement in histopathologic outcome in rats subjected to bilateral carotid occlusion combined with hypotension to 50 mmHg—conditions that should yield some animals with flows in the range where isoflurane might dramatically prolong the time to depolarization. This hypothesis could be directly tested by subjecting large numbers of halothane- and isoflurane-anesthetized animals (i.e., 50–60 animals per group) to a “modest” ischemic insult (e.g., bilateral carotid occlusion and hypotension to 50 mmHg) and determining the number of animals in each group with no histopathologic injury. In such a study, the “minor” protective effects of isoflurane might be manifested not by differences in average histopathologic outcome (which we know are not different) but by a greater number of “normal” animals.

In summary, we have demonstrated that isoflurane/N$_2$O anesthesia leads to lower cortical CMR$_{\text{glu}}$ values than those produced by halothane/N$_2$O. This is associated with a significantly longer delay in the time to ischemic cell depolarization. However, when the ischemic period was prolonged to 10 min, we were unable to identify any differences in either the incidence of major electrophysiologic changes (sustained depolarization, major ECoG changes, or isoelectricity) or in CBF values associated with those events. The only differences may have been a reduction in the incidence of transient depolarization, early in the ischemic period in isoflurane/N$_2$O-anesthetized animals. We conclude that no major anesthetic-related differences exist in the threshold CBF values for either ECoG change or cortical depolarization, at least when the ischemic period is ≥ 10 min in duration. It is important to note that although depolarization occurs at flows similar to those associated with histopathologic injury and has also been associated with the onset of a complex cascade of potentially detrimental biochemical events, we did not determine whether such injury was present (or would develop). It would hence be unwise to draw any conclusions regarding the clinical “protective” utility of either of these anesthetics. However, we also believe it unwise to conclude that differences in “critical CBF” based on EEG changes alone represent “protection” in the absence of evidence for improved clinical or histopathologic outcome.

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