Profound Arterial Hypotension in Dogs: Brain Electrical Activity and Organ Integrity


To determine whether non-invasive measurement of brain electrical activity can predict ischemic brain damage, we recorded the electroencephalogram (EEG) and somatosensory- (SEP) and auditory- (AEP) evoked potentials before, during, and after trimethaphan-induced profound arterial hypotension in dogs. The authors set out to compare the change in electrical activity with the degree of brain damage, as determined by microscopic examination. Dogs were anesthetized with halothane (1.4 vol % inspired), maintained horizontal (head at the level of the heart), and ventilated mechanically (FIO2 0.50); deviations from normal acid-base status were corrected. Twenty animals received a 1.5-mg/kg intravenous bolus of trimethaphan. Three animals were resistant to the drug. The remaining animals had profound hypotension [mean arterial blood pressure (MABP) at some steady level between 12 and 25 mmHg] for 1 h. Eight of these animals died during or soon after the hypotensive period as a consequence of cardiac arrest (three), intestinal bleeding (three) or unknown cause (two). In all survivors, EEG intensity and the amplitude of the SEP decreased during hypotension; both variables recovered with restoration of MABP. All nine animals surviving hypotension had no apparent neurologic or behavioral deficit nor any histologic evidence of ischemic brain cell injury. We were thus unable to find a MABP threshold for brain injury or to determine what degree of electrical change correlated with minimal brain injury. Our findings suggest, under the conditions of our experiments, a great margin of tolerance for profound hypotension by the brain in this species. Other organ systems—the heart, gastrointestinal tract, and liver—proved to be more susceptible to ischemic damage. Eight of the nine surviving animals had elevations in serum alanine transaminase (SGPT), aspartate transaminase (SGOT), and alkaline phosphatase. Animals with the greatest increase in these enzymes showed centrilobular hepatocyte degeneration. (Key words: Blood pressure; hypotension; trimethaphan; Brain: electroencephalogram; evoked potential. Gastrointestinal tract. Heart. Liver.)

CONTROLLED HYPOTENSION is used to decrease blood loss and transfusion requirement during surgery. The safety of drug-induced hypotension has been debated1

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as the reported incidence of complications has varied from 0 to 9%.2–7 Since many of these complications are neurologic, Lindop1 has emphasized the need for a monitor of brain function that is a reliable indicator of impending ischemic brain damage.

The margin of safety for the brain during clinical drug-induced hypotension has not been defined carefully. The current rationale for the safe lower limit of mean arterial blood pressure (MABP) of 50–55 mmHg in normothermic patients is based on the observed lower limit of autoregulation of cerebrovascular flow.8,9 Studies by Brierley et al. and Selkoe and Myers11 in non-human primates have set the actual threshold for hypertensive brain cell damage at a MABP of 25 mmHg for at least 15 min. These investigators attempted to correlate brain function during hypotension with eventual neuropathologic outcome by measuring spontaneous11,12 and evoked12 brain electrical activity. However, conditions in these studies were in some ways different from those encountered in clinical practice: barbiturates were used for anesthesia, phlebotomy was used in place of or in addition to trimethaphan to obtain the desired degree of hypotension, animals were allowed to breathe spontaneously, and progressive deterioration of acid-base status was not prevented.

We set out to determine whether non-invasive measurement of brain electrical activity can predict regional ischemic brain cell damage. We recorded the electroencephalogram (EEG) and somatosensory- (SEP) and auditory- (AEP) evoked potentials before, during, and after profound arterial hypotension. We have used a dog model in which bolus administration of trimethaphan alone maintained MABP at some steady level between 12 and 25 mmHg for 1 h. Simulated clinical conditions included stable halothane anesthesia and the maintenance of arterial blood oxygenation and normal acid-base status. Evidence of post-surgical brain damage was sought by neurologic assessment and by microscopic examination of brain tissue fixed 72 h after the hypotensive episode. The latter approach is thought by Brierley and associates13–15 to be the most sensitive means of detecting minimal brain damage in animals.

Surprisingly, no animal that survived the hypotensive episode incurred detectable brain damage. Although brain electrical activity varied with the degree of hypotensive insult, the EEG and SEP were variable between animals that they may prove to be insufficiently
TABLE 1. Neurologic and Behavioral Evaluation of the Dog

<table>
<thead>
<tr>
<th>General cerebral functions</th>
<th>Motor functions</th>
<th>Autonomic functions</th>
<th>Sensory functions</th>
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Adapted from McGrath\textsuperscript{16} and Hoerlein.\textsuperscript{17}

precise to be used as critical monitors of permanent injury. Our most striking result was that, under the conditions of our study, the heart, gastrointestinal tract, and liver were more susceptible to injury in profound hypotension than the brain.

Methods

**Preparation and Protocol**

Twenty healthy male mongrel dogs, averaging 20.1 kg body weight (range 16.0–23.6 kg), were fasted overnight and examined for neurobehavioral status (table 1).\textsuperscript{16,17} After anesthesia was induced with halothane (Halocarbon Laboratories) in O\textsubscript{2} by mask, a cuffed endotracheal tube was placed and mechanical ventilation initiated with 50% O\textsubscript{2} and N\textsubscript{2} at a tidal volume of 15 ml/kg body weight. Anesthesia was maintained with 1.34 ± 0.22 (SD) vol % inspired halothane, as confirmed by gas chromatography. Ventilatory frequency was adjusted to achieve an end-tidal P\textsubscript{CO\textsubscript{2}} of 35–40 mmHg, as determined by on-line infrared analysis (Beckman Instruments, LB-1).

All surgical procedures were carried out using aseptic techniques. A catheter was placed in a femoral artery for anaerobic sampling of arterial blood and for measurement of arterial blood pressure with a strain gauge transducer (Statham, P23AA). Catheters were placed in the ipsilateral femoral vein for administration of drugs and lactated Ringer’s solution, in a cephalic vein for administration of 5% dextrose in water, and in the bladder for monitoring urine output. Body temperature, measured with an esophageal thermistor (Yellow Springs Instruments), was maintained at 37.3° C ± 1.2 (SD, n = 20) with a heated circulating water blanket. The EEG and evoked potentials were recorded from electrodes of multistrand stainless steel wire secured onto the skull surface with self-tapping screws sealed over with a layer of dental acrylic. A bilateral parasagittal array of these electrodes over the frontal, parietal, and occipital cranial regions (1.5 cm lateral to midline) was used for recording the EEG, one of the frontal electrodes was used for SEP, and a seventh skull electrode was placed at the vertex for AEP.

Following surgery, animals were placed in the prone position, paralyzed with gallamine triethiodide (Flaxedil\textsuperscript{16}, American Cyanimid; 0.5 mg/kg), and not disturbed for at least 30 min. Arterial blood and inspired and expired gases were then sampled for gas chromatographic determination of halothane concentration. An arterial blood sample also was taken for serum chemistry (ions, glucose, creatinine, BUN, bilirubin, albumin, total protein) and enzyme determinations [alanine transaminase (SGPT), aspartate transaminase (SGOT), alkaline phosphatase (AP), lactate dehydrogenase].

Electrical (EEG, SEP, and AEP) and blood-gas data were collected during a subsequent 30-min control period, a 60-min hypotension period, and a 30-min recovery period. At 15-min intervals throughout each period, arterial blood samples were drawn for measurement of hematocrit and of plasma pCO\textsubscript{2}, pO\textsubscript{2}, and P\textsubscript{O\textsubscript{2}} with appropriate electrodes (Radiometer Copenhagen, BMS5 MK2) at 37° C. Blood gas values were corrected to the animal’s temperature.\textsuperscript{18} Any base deficit was corrected by intravenous infusion of 1 m NaHCO\textsubscript{3} solution. Hypotension was induced with an intravenous bolus of trimethaphan camsylate (Arfonad\textsuperscript{16}, Roche; 1.5 mg/kg). Mean arterial blood pressure (measured relative to the external auditory meatus, approximately at the same level as the heart) decreased over the following 1–2 min to a level between 15 and 25 mmHg and remained at that level for 60 min until reversed with an intravenous infusion of 0.01% phenylephrine hydrochloride (Neo-Synephrine\textsuperscript{16}, Winthrop). Animals were weaned from pressor support within 20–60 min.

Animals surviving profound hypotension underwent neurologic evaluation (table 1) each day subsequent to the experimental procedure. On the third post-surgical day they were again anesthetized with halothane, samples of blood and CSF were taken for chemical assays, the electrical measurements were repeated, and the brain and spinal cord were fixed and removed for neuropathologic examination.

**Electrical Measurements**

During a period of data collection (control, hypotension, recovery) the EEG, SEP, and AEP were recorded serially in 15-min cycles: 2 min of EEG, followed by an
averaged SEP, followed by an averaged AEP, completed by a second 2-min period of EEG recording.

The EEG was recorded from six pairs of skull electrodes (frontal-occipital, frontal-parietal, parietal-occipital; right and left sides) with an 8-channel polygraph (Grass, 7PS) and stored on magnetic tape (Vetter, Model A). The AC preamplifiers were set for a bandpass of 0.3 to 75 Hz. The real-time EEG signal was digitized at 128 Hz and analyzed by computer (Digital Equipment Corporation, PDP 15/40) to obtain the simultaneous power spectrum†† of all six EEG channels.

The AEP was recorded from the vertex skull electrode referenced to a subcutaneous needle electrode at the mastoid process. A click stimulus, 50 μs in duration and 55.5 dB above human hearing threshold in amplitude, was applied to one ear at a rate of 12 Hz. The SEPs were recorded from a frontal skull electrode referenced to a subcutaneous needle electrode at the nose. A bipolar square-wave electrical stimulus, 0.1 ms in duration and 40–50 V in amplitude, was applied at 3 Hz via needle electrodes placed percutaneously into the region of the superficial radial nerve contralateral to the recording electrode. Evoked potentials were measured with high input impedance AC preamplifiers (Grass, P511) with a bandpass of 35 Hz to 2 kHz and stored on magnetic tape (Ampex, FR-1300). Averaged evoked potentials were obtained off-line by summing 1024 trials with a digital signal averager (Tracor-Northern, NS-570A).

Tissue Preparation and Examination

Following electrical recording on the third post-surgical day, the brain and upper spinal cord were fixed by retrograde perfusion through the descending aorta of heparinized normal saline followed by phosphate-buffered 10% formalin solution at a pressure of 120 mmHg. Following 24 h of cold storage, the brain was removed from the cranium and immersed in 10% buffered formalin solution for at least 2 weeks. Coronal sections of the cerebrum and horizontal sections of the cerebellum and brainstem were made after fixation. Sections, 3–5 mm thick, were embedded in paraffin, sectioned 5–10 μm thick, and alternate slides were stained with hematoxylin and eosin or Luxol fast blue/periodic acid-Schiff/hematoxylin stains for light microscopic examination. Sample blocks of liver were prepared similarly, sectioned, and stained with hematoxylin and eosin. The examining pathologist looked specifically for ischemic tissue changes, in the brain for characteristic hypoxic cell change,15 but was unaware of the treatment to which an animal had been subjected.


Figure 1. Time course of arterial pH, P<sub>CO<sub>2</sub></sub>, P<sub>O<sub>2</sub></sub>, mean arterial blood pressure, and hematocrit. Mean values and standard deviations were determined from the nine surviving dogs. Abscissa indicates sampling periods and number of consecutive samples obtained approximately 15 min apart during hypotension and recovery.

Statistical Analysis

Significance of changes from control in variables measured was determined using Student's t test for paired variables, each animal serving as its own control.
A change was considered statistically significant if \( P \) was less than 0.05.

**Results**

Three of 20 animals that received trimethaphan were either resistant to several bolus infusions of the drug or spontaneously regained a near-control MABP within 1 h. Of the 17 animals made profoundly hypotensive by a single bolus infusion, only nine survived 72 h. Three died of cardiac arrest during the hypotensive period when MABP fell below 15 mmHg, three died of intestinal bleeding with sloughing of the intestinal mucosa, and two died of undetermined causes within 12 h after MABP had returned to control levels. The animals that died following the hypotensive episode had, on average, a control MABP [82 ± 6 mmHg (SD)] and hypotensive MABP (19 ± 6 mmHg) that was not different from the nine survivors.

For the nine surviving dogs, mean values of arterial blood gases and MABP measured before, during and after profound hypotension are summarized in figure 1; also shown is hematocrit, which increased presumably due to splenic contraction. MABP decreased from 84 ± 17 (SD) to 20 ± 6 mmHg for 1 h. Return of MABP to control value was attained in all cases by infusion of phenylephrine.

During severe arterial hypotension, the EEG was characterized by low frequency, low amplitude activity, and, only infrequently, by brief electrical silence. In figure 2, the effects of hypotension of the EEG in one animal are illustrated. During the control period (fig.
FIG. 3. Time course of changes in EEG intensity in several frequency bands. EEG was derived from the right frontal and occipital leads in the nine surviving dogs. The abscissa shows sampling periods and number of consecutive samples. The ordinate indicates the mean percent change in EEG intensity for different frequency bands and across all bands.

2A), high amplitude, bilaterally symmetrical activity was seen in all frequency bands, characteristic of light anesthesia. At 2 min of hypotension (fig. 2B), EEG intensity decreased in the 4–8 Hz (theta) and 8–15 Hz (alpha) bands. In this animal there was also an atypical increase in intensity in the 15–30 Hz (beta) band at this time. At 15 min (fig. 2C) and 45 min (fig. 2D) of hypotension, activity remained only in the 0–4 Hz (delta) band. We never observed prolonged isoelectric EEG or suppression burst activity. Results for the nine animals that survived for 3 days following hypotension are summarized in figure 3. Average EEG intensity in the 4–8, 8–15, and 15–25 Hz bands was reduced significantly during and immediately following the hypotensive episode. Average intensity had returned to control level when measured 3 days later.

Brainstem (far-field) components of the SEP and AEP are short-latency waves designated I–III and I–VII, respectively (fig. 4). Wave I of both the SEP and AEP was not observed in all animals; variability in amplitude precluded accurate measurement. The cortical (near-field) SEP components are of longer latency and are labeled P1, N1, P2, N2, and P3. Cortical AEP were not considered in this study because of wide variations in waveform, amplitude, and latency between anesthetized animals. Effects of hypotension on cortical and brainstem SEP and brainstem AEP are shown in figure 5. The decrease in EEG intensity during hypotension was accompanied by significant reductions in the average amplitude of cortical (N1, N2, P3) and brainstem (II, III) components of the SEP (fig. 5, lower and middle panels, respectively). Recovery of average SEP amplitudes (fig. 5), unlike recovery of EEG intensity in the higher frequency bands (8–32 Hz, fig. 3), occurred immediately after MABP returned to the control value. Brainstem AEP amplitudes were not affected by hypotension (fig. 5, upper panel). Changes in peak latency of SEP and AEP components were small and not statistically significant (fig. 6).

Neurobehavioral testing of the nine survivors on each post-surgical day revealed no abnormal signs. Gross examination of surface and standard slices of brain and spinal cord did not disclose any swelling or lesions. Moreover, light microscopic examination of the same tissue did not reveal abnormalities such as ischemic neuronal alterations (i.e., dark cell or homogenizing cell changes), cell loss, or gliovascular reaction.

Thus, the post-hypotension electrophysiologic, neurologic, behavioral, and neuropathologic findings suggest integrity of central neural structure and function. However, results from our enzyme screen indicate hepatocellular damage. Serum concentrations of SGPT, SGOT, and AP were increased significantly 3 days after the hypotensive episode (table 2). SGPT increased from 4–8 times over the pre-hypotension value, SGOT increased from 1.2–14 times, and AP increased 5–13 times. Examination of liver tissue showed that animals with the greatest increases in SGPT, SGOT, and AP had pericentral lobular hepatocyte degeneration and, in the worst case, pericentral lobular necrosis. In Figure 7 are light micrographs comparing normal (A) with mildly (B) and moderately (C) damaged livers. We found no correlation between the degree of hypotension and the severity of liver injury.

We infer that the kidneys did not suffer severe damage as the blood urea nitrogen and creatinine contents did not increase above the normal range following hypotension (table 2).
Fig. 4. Control auditory- (AEP) and somatosensory- (SEP) evoked potentials. Duplicate auditory brainstem (far-field, upper panel), somatosensory brainstem (far-field, middle panel), and somatosensory cortical (near-field, lower panel) evoked potentials are shown in 20-, 40-, and 300-ms sweep durations, respectively. The dotted vertical line in each panel corresponds to stimulus onset and is preceded by 5 ms of baseline activity. Each evoked potential represents an average of 1,024 trials. Amplitude (μV) calibration is at the right in each panel. Brainstem and cortical potentials, respectively, are designated by roman numerals and alphanumerics.

Discussion
Dogs subjected to profound arterial hypotension without hypoxemia, hypercapnia, and acidosis either died during or soon after the event, or survived without evidence of brain injury. Survivors had reduced, but discernible, spontaneous (EEG) and evoked (SEP) brain
activity during hypotension. After restoration of MABP, the AEP and SEP recovered immediately; EEG recovery was slower. These results are consistent with those of Gamache and Myers\textsuperscript{29} in barbiturate-anesthetized rhesus monkeys subjected to a MABP of about 25 mmHg for 15–30 min.

Other studies addressing the same question have provided quite different results. Using trimethaphan-augmented oligemic hypotension, Selkoe and Myers\textsuperscript{11} found a threshold of 22 mmHg for isoelectric EEG in barbiturate-anesthetized rhesus monkeys. They found that duration of EEG silence and the fraction of the hypotensive period with EEG silence both correlated with the severity of brain injury. Brierley \textit{et al.}\textsuperscript{10} and Meldrum \textit{et al.}\textsuperscript{12} found brain injury in barbiturate-anesthetized monkeys whose cerebral perfusion pressure de-
creased quickly to below 25 mmHg and remained below this level for at least 15 min. In these animals, the EEG changed markedly, becoming flat for various durations. In studies using barbiturate-anesthetized dogs and continuous trimethaphan infusion, EEG suppression burst activity, slowing, and high voltages were seen at MABPs of 40–47 mmHg, and an isoelectric EEG was seen at 35–47 mmHg. Although microscopic examination of the brain was not performed in these studies, the EEG changes were presumed to be symptomatic of impending morbidity. Michenfelder and Theye observed clear neurologic deficits in two of five dogs anesthetized with nitrous oxide (and 0.1% halothane) and subjected to trimethaphan-induced hypotension with a MABP of 40 mmHg for 1 h.

Several factors may influence the EEG during hypotension and the neuropathologic outcome, perhaps accounting for differences between present and earlier findings. Thus, comparison of results is made difficult by species differences (dog vs. monkey), anesthesia (halothane vs. barbiturates or nitrous oxide), acid-base management during hypotension (controlled vs. uncontrolled), and means of inducing hypotension (trimethaphan only vs. trimethaphan and bleeding and/or head-up tilt or PEEP, or bleeding only). We do not yet know fully.

**Fig. 6.** Effects of hypotension on latencies of AEP and SEP component waves. The abscissa indicates the sample period and number of consecutive samples. The ordinate shows the mean change in peak latency (ms) for each component of the AEP and SEP recorded in the nine surviving dogs.

**Fig. 7.** Light micrographs showing sections of liver stained with hematoxylin-eosin from three dogs. A: normal; B: mild pericentral hepatocyte degeneration; and C: pericentral necrosis.
to what extent each of these variables is responsible for the outcome of our study. Studies just completed in our laboratory show the same tolerance by the brain in monkeys (range of MABP 17–36 mmHg; unpublished results).

The EEG, SEP, and AEP of non-surviving and surviving dogs in the present study were indistinguishable during hypotension and immediately following restoration of MABP. Similarly, Gamache and Myers found a period of full EEG recovery in both their surviving and non-surviving monkeys. Gamache et al. did observe that the EEG of their non-surviving monkeys deteriorated 2.5 h after restoration of MABP, but such EEG changes were associated with cardiorespiratory failure, increased cisterna magna CSF pressure, increased blood and CSF glucose concentrations, or brain swelling. From these data we would conclude that brain activity measured during or shortly following the hypotensive episode is not reliably predictive of eventual neuropathologic outcome. On the other hand, Selkoe and Myers found a correlation between the degree of brain damage and the period of EEG silence. Therefore, it is still not clear whether monitoring brain electrical activity during hypotension will prove to be a reliable means of detecting imminent brain injury.

Under the conditions of our study, other organs appeared to be at greater risk than the brain. Three dogs died of cardiac arrest during hypotension and three more died of intestinal ischemia after recovery of MABP. Among the 3-day survivors, liver damage was found in animals with the highest elevations of SGPT, SGOT, and AP. Since these serum enzymes are elevated maximally 72 h after liver injury, the hepatocellular degeneration was probably the direct result of the profound arterial hypotension. Moreover, the nature of the liver injury is consistent with that found following hypoperfusion. Halothane also might have contributed to the liver injury by virtue of its property as a hepatotoxin under certain conditions. Why does liver damage occur before brain damage? In other studies with brain injury at MABPs of 20–30 mmHg, head-up tilt was used, perhaps favoring abdominal organ perfusion over that of brain. Trimeprathapen also is known to decrease mesenteric blood flow and increase mesenteric vascular resistance, possibly contributing directly to liver and gut ischemia. Subsequent further reduction of gastrointestinal and hepatic blood flow by phenylephrine also might have placed these organs at risk of injury.

In summary, our goal to relate the threshold of brain injury to the degree of change in brain electrical activity during profound hypotension was not attained, as none of the dogs incurred brain cell injury. By no means is a MABP of 20 mmHg safe, however, as half of our animals subjected to that degree of hypotension died. In the animals that did survive, the liver seemed to be at greater risk of injury than the brain.

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