Electrical Correlates of Brain Injury Resulting from Severe Hypotension and Hemodilution in Monkeys

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The effects of hypotension, hemodilution, and their combination on the relationship between concurrent brain electrical activity and resulting brain injury were studied in anesthetized monkeys. The authors compared changes in the electrocerephalogram and somatosensory and auditory evoked potentials with eventual neurologic outcome. Our goals were: 1) to define the margin of safety for the monkey brain during hemodilution and hypotension under several simulated clinical conditions, and 2) to determine whether noninvasive measurements of brain electrical activity can predict ischemic brain cell damage. Forty-one monkeys were anesthetized with halothane (0.8 vol % inspired) and ventilated mechanically. Arterial hypotension was induced with trimethaphan (25 ± 8 mmHg mean arterial blood pressure [MABP] for 30 min). Hemodilution was induced by replacing blood with lactated Ringer's solution (14 ± 2% hematocrit for 1 h). Combined hemodilution and hypotension consisted of 30 min of hemodilution alone followed by superimposing hypotension for 30 min (16 ± 3% hematocrit and 29 ± 5 mmHg MABP). Ten monkeys died following severe hypotension alone or combined hemodilution and hypotension as a consequence of cardiac arrest or undetermined (possibly neurologic) causes. No histologic evidence of ischemic brain cell injury was found in surviving monkeys subjected to hemodilution or hypotension alone. Neuropathologic alterations in the cerebral cortex, cerebellum, hippocampus and globus pallidus as well as neurologic and behavioral deficits were found in seven of 16 surviving monkeys subjected to both hemodilution and hypotension. These findings resulted from combinations of hematocrit less than 20% and MABP below 40 mmHg. Only the degree of amplitude reduction in cortical components of the somatosensory evoked potentials during the stress period indicated a high probability of neurologic outcome. (Key words: Anesthetics, volatile: halothane. Blood pressure: hypotension; trimethaphan. Blood volume: hematocrit; isovolumic hemodilution. Brain: electroencephalogram; evoked potentials; neuropathology.)

CONTROLLED HYPOTENSION, isovolumic hemodilution and, occasionally, the combination of the two are used to reduce bleeding during surgery in order to enhance visibility and minimize the need for blood transfusion.1,2 These techniques, singly, and especially in combination, may decrease oxygen delivery to the brain and other vital organs, which could result in hypoxic tissue damage.3,4 While vast clinical experience with controlled hypotension has established a clinically accepted minimum level of blood pressure,5,6 we were concerned that adding hemodilution to hypotension might decrease tolerance to hypotension.

Our goal was to define the safe limits of hemodilution and hypotension for the monkey brain under several simulated clinical conditions that included stable halothane anesthesia and the maintenance of normal arterial blood oxygenation and acid–base status. To determine whether noninvasive measurements of brain electrical activity could predict ischemic brain cell damage, we correlated changes in the electrocerephalogram and somatosensory and auditory evoked potentials to the eventual neurologic outcome.

Methods

PREPARATION AND PROTOCOL

Forty-one adult male monkeys (Macaca fascicularis), weighing 2.1–6.4 kg (mean 3.9 ± 1.0 kg), were fasted overnight and examined for neurobehavioral status. Anesthesia was induced with halothane in O2 by mask, the trachea was intubated, and mechanical ventilation was initiated with 50% O2, balance N2 at a tidal volume of 15 ml/kg body weight. Anesthesia was maintained throughout each experiment with 0.83% ± 0.15 (SD) inspired halothane, as confirmed by gas chromatography. Ventilatory frequency was adjusted to achieve an endtidal pCO2 of 35–40 mmHg measured by infrared analysis.

Surgical procedures were carried out using aseptic technique. A catheter was placed in a femoral artery for anaerobic sampling, measurement of blood pressure with a strain gauge transducer, and removal of arterial blood during hemodilution. A catheter was placed in the ipsilateral femoral vein for administration of drugs, lactated Ringer's solution, or blood. Urine output was monitored with a transurethral bladder catheter. Body temperature, measured with an esophageal thermometer, was maintained at 37.5°C ± 0.4 (SD) with a circulating water blanket. The electroencephalogram (EEG) and evoked potentials were recorded with electrodes of multistrand stainless steel wires placed through small holes in the skull onto the dural surface; the holes were sealed over with dental

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resin. A bilateral parasagittal array of these EEG electrodes was located 1.7–2.0 cm lateral to midline over the frontal, parietal, and occipital regions. One of the parietal electrodes was used for recording somatosensory evoked potentials (SEP), and an additional epidural wire electrode was placed at the vertex for recording auditory evoked potentials (AEP).

Following surgery, animals were placed in the prone position, paralyzed with gallamine triethiodide (1.0–1.5 mg/kg iv), and allowed to stabilize their condition for at least 30 min. Gallamine triethiodide was given to prevent reflexive movements and muscle-related artifacts resulting from nerve stimulation during electrophysiologic recording. Arterial blood and inspired and expired gases were then sampled for gas chromatographic determination of halothane concentration.

Studies were performed on four groups designated control (C), hypotension (HT), hemodilution (HD), and hemodilution and hypotension (HD/HT). Electrophysiologic (EEG, SEP, and AEP) and blood gas data were collected during a 30-min control period followed by a stress period (60 min HD, 30 min HT) superimposed on 30 min of HD following 30 min HD alone—HD/HT—and a 30-min recovery period. At 10-min intervals throughout each period, arterial blood samples were drawn for measurement of hematocrit (Hct) and plasma pH, Pco2, and P02 with appropriate electrodes. Blood gas values were corrected from 37° C to the animal’s temperature. Acid–base status was maintained within normal limits by adjusting minute ventilation and with intravenous infusion of 1 mM NaHCO3 solution as required.

Hemodilution was induced by slowly withdrawing over 20 min a predetermined volume of blood, which was simultaneously replaced with three times that volume of lactated Ringer’s solution containing 2 mM/L MgSO4. The electrolyte solution-to-blood ratio of 3:1 was found in previous empirical observations to maintain normovolemic and normotensive conditions. The volume of blood removed over 20 min was determined using an empirically derived expression: EBV · (Hctb – Hct0) · 3.

We relied on an estimated blood volume (EBV) of 75 ml/kg and used the terms Hctb as the Hct at baseline and Hct0 as the desired Hct (<20%). The simultaneous replacement of lactated Ringer’s solution for blood over 20 min permitted a progressive decrease from baseline Hct, a final plateau near the desired Hct stable for 1 h, and possibly little or no change in blood volume as confirmed in several animals with central venous pressure (CVP) measurements. Blood was stored in a bag containing citrate-phosphate-dextrose solution as the anticoagulant. Prior to the recovery period, the blood was reinfused and furosemide (2 mg/kg iv) was given to induce diuresis. Hypotension was induced and maintained for 30 min with a bolus of trimethaphan camsylate (1.2–10 mg/kg iv). Mean arterial blood pressure (MABP), measured relative to the external auditory meatus (approximately at the same level as the heart), decreased over 1–2 min to a level between 17 and 36 mmHg and remained at that level for 30 min until reversed with an intravenous infusion of 0.01% phenylephrine hydrochloride. Monkeys were weaned from pressor support within 1 h. Some monkeys also received atropine sulfate (0.02 mg/kg iv) and neostigmine methylsulfate (0.06 mg/kg iv) to reverse neuromuscular blockade.

Surviving animals underwent repeat daily neurobehavioral evaluation. We assessed general cerebral functions by rating social behavior (relation to humans and to the environment), food intake, and motor behavior (climbing ability, response to tactile stimulation). Sensory functions such as vision (pupillary response) and olfaction (sniffing food) were also examined and scored. Neurologically impaired animals fell into two categories: 1) minor injury that allowed the animals to move around and feed themselves adequately—these animals required no special care; and 2) severe injury in animals that never awoke and died while remaining on ventilatory support. On the third postsurgical day the surviving monkeys were again anesthetized with halothane, brain electrical measurements were repeated, and with anesthesia maintained, brain and spinal cord were fixed by perfusion and removed for neuropathologic examination.

**Electrophysiologic Measurements**

During periods of data collection (i.e., control, stress, recovery, three days postsurgery) the EEG, SEP, and AEP were recorded serially every 15 min: 2 min of EEG, followed by an averaged SEP (5 min), followed by an averaged AEP (2 min), completed by a second 2-min period of EEG recording. The EEG was recorded from six pairs of bilateral skull electrodes (frontal–occipital, frontal–parietal, and parietal–occipital) with a polygraph and stored on magnetic tape. Impedance across electrode pairs was less than 10 KΩ. The AC preamplifiers had a bandpass of 0.3–75 Hz. The real-time EEG signal was digitized at 128 Hz and analyzed by computer (Digital Equipment Corporation, Maynard, MA, PDP 15/40) to obtain the simultaneous power spectrum of all six EEG channels.

The AEP was recorded from the vertex electrode referred to a subcutaneous needle electrode at the mastoid process. Impedance between the active and reference electrodes was less than 10 KΩ. A click stimulus, 50 μs in duration and 55.5 dB above human hearing threshold in amplitude, was applied biaurally through headphones at a rate of 5 Hz. The SEP was recorded from the parietal electrode referred to a subcutaneous needle electrode at the nose (3–8 KΩ impedance). A bipolar square-wave
electrical stimulus, 0.1 ms in duration and 40–50 V in amplitude, was applied at 2 Hz via needle electrodes placed percutaneously into the region of the superficial radial nerve contralateral to the recording electrode. Evoked potentials were led into high input impedance AC preamplifiers (Grass, Quincy, MA, P511<sup>a</sup>) with a bandpass of 35 Hz to 2 KHz (3 dB down points, 6 dB/octave slope) and stored on magnetic tape (Ampex, Redwood City, CA, FR-1300). Averaged evoked potentials were obtained off-line by summing 512 trials with a digital signal averager (Nicolet, Madison, WI, 1070). Each averaged potential contained 1,024 data points (20, 25, or 80 μs/point sampling rate).

**HISTOLOGIC ANALYSIS**

Following electrophysiologic recordings on the third postsurgical 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% formaldehyde 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 formaldehyde solution for at least 2 weeks. Coronal sections of the cerebrum and horizontal sections of the cerebellum and brain stem 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. The examining neuropathologist (C.-M.S.) looked specifically for ischemic–hypoxic cell change in the brain and spinal cord, but was unaware of the treatment to which an animal had been subjected.

**DATA ANALYSIS**

Significance of changes from control in physiologic variables measured was determined using Student’s <i>t</i> test for paired variables, each animal serving as its own control. A change was considered significant if <i>P</i> was less than 0.05.

**Results**

**SEVERITY OF HYPOXIC STRESS AND NEUROPATHOLOGIC OUTCOME**

Monkeys in each experimental group were maintained close to normal arterial blood oxygenation and acid–base status during the control, stress, and recovery periods. MABP in the HT and HD/HT groups and mean Hct in the HD and HD/HT groups were decreased significantly during the stress period compared with the control period (table 1).

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C = control; HT = hypotension; HD = hemodilution.
Numbers of animals in each group are given as n. Values are arithmetic means (±SD) of serial measurements made every 10 min during control, stress, and recovery periods.
* Significant (<i>P</i> < 0.05) decrease from control.

The relationship of average MABP and Hct during the stress period to survival and brain injury is illustrated in figure 1. Ten of 41 monkeys died following HT or HD/HT: five of these deaths were due to cardiac arrest during the stress or recovery period; the other five deaths in animals requiring mechanical ventilation resulted from undetermined (possibly neurologic) causes and occurred within 48 h following the stress. One control monkey also died from cardiac–respiratory depression during anesthesia induction with halothane. Seven of the 30 surviving monkeys exhibited brain damage, and these were found exclusively in the 16 monkeys subjected to HD/HT. No brain damage was seen in surviving monkeys subjected to either HD or HT alone. No brain injury was observed with Hct greater than 20% even when accompanied by MABP as low as 17 mmHg. With Hct less than 20% a MABP below 40 mmHg was required to produce brain injury.

In the seven monkeys that exhibited neuropathologic alterations, hypoxic–ischemic changes were located in the central nervous system at single or multiple sites that in-
cluded the cerebral cortex, cerebellum, hippocampus, and globus pallidus. Macroscopic examination of surface as well as coronal and horizontal standard slices of brain revealed marked diffuse cerebral and cerebellar edema, cerebellar tonsillar herniation and focal hemorrhagic and ischemic necrosis in the cerebellar hemispheres and frontoparietal cortex. Light microscopic examination provided substantial evidence of hypoxic–ischemic changes. Multifocal ischemic and hemorrhagic infarcts in cerebral cortex were found predominantly in the middle and inferior frontal gyri and the deep laminar layers of the parietal and occipital gyri. The cortical distribution of lesions was highly suggestive of lesions within arterial boundary zones, but could also be the result of severe cerebral edema compressing sulcal arteries. These lesions were characterized by well-demarcated pallor, decreased numbers of neurons, loss of myelin, rarefaction of neuropil, capillary proliferation, increase in microglial cells, and acute ischemic changes of surviving neurons (fig. 2A). Cerebellar infarcts, also suggestive of “watershed” lesions, were found generally in the anterior and posterolateral cerebellum, and more specifically in the lateral hemispheres, anterior vermis, and posterior paramedian hemispheres. The cerebellar lesions were characterized by ischemic changes of Purkinje cells and sponginess of the Purkinje cell and granular cell layer (fig. 2B). Less frequently observed were

Fig. 1. Relationship of mean arterial blood pressure (MABP) and hematocrit (Hct) during the stress period to neuropathologic outcome. Closed (intact) and open (brain injured) circles represent monkeys that survived. Monkeys that died during the stress period, recovery period, or within 48 h after the stress period are represented as open triangles.

Fig. 2. A. Coronal slice of the cerebral hemispheres shows a focal ischemic infarct in the cortex along the superior and inferior frontal sulci on the right side. Monkey 17M. Luxol fast blue/periodic acid-Schiff/hematoxylin stain. B. Horizontal slice of the cerebellum and medulla shows bilateral symmetrical ischemic infarcts involving the middle portion of the cerebellar hemispheres. Monkey 17M. Luxol fast blue/periodic acid-Schiff/hematoxylin stain. C. Coronal slice of the ventral portion of the cerebral hemispheres shows ischemic infarcts in the Rose H1 area of hippocampus bilaterally. Monkey 23M. Luxol fast blue/periodic acid-Schiff/hematoxylin stain.
ischemic infarcts in the hippocampus and globus pallidus. Hypoxic lesions in the hippocampus had extensive necrosis, homogenizing cell changes, and spongy degeneration of neuropil (fig. 2C). In summary, the neuropathologic changes were located in regions of the brain that are known to be susceptible to damage by a hypoxic–ischemic sequela.9

All monkeys that had neuropathologic alterations also had abnormal behavior. These monkeys were lethargic and minimally responsive to investigator handling and physical restraint (i.e., avoidance/escape behavior) and to presentation of food. They sat up, but did not climb, and had poor coordination in locomotion and grasping of objects. Some brain-damaged monkeys had difficulty with eye–head orientation to light and sound stimuli. The pupils were equal in size but slowly reactive to light. One monkey with extensive hypoxic lesions and edema in the cerebral cortex, cerebellum, hippocampus, and basal ganglia displayed spontaneous and episodic head–body rotations in one direction. No change in behavior was observed in histologically intact animals.

**EFFECTS ON EEG**

EEG activity changed in all monkeys subjected to HD, HT, or HD/HT. During the stress period, all EEG activity except in the 0–4 Hz frequency band (delta) was significantly reduced or abolished. Prolonged isoelectric EEG or suppression-burst activity was never observed in surviving animals. Attenuation of power in the 4–8 Hz (theta), 8–15 Hz (alpha), and 15–30 Hz (beta) bands of the EEG was seen in all but the control group. The total relative power of the EEG within each frequency band and across all frequency bands was not significantly different between the brain injured and intact animals (see fig. 3). Therefore, changes in the power spectrum of the EEG were not predictive of neuropathologic outcome. Some monkeys with ischemic brain damage following HD/HT had greater power in the 4–8 Hz band during the stress period than did monkeys subjected to the same degree of HD/HT without resulting injury.

While no significant differences in EEG spectral power during the stress period between monkeys that survived with and without brain injury were noted, significant differences in the EEG during the recovery period were found between brain-damaged and intact monkeys that were subjected to HD/HT. As seen in figure 3, differences in EEG power during recovery were significant in the 4–8, 8–15, and 15–25 Hz bands. No significant difference in EEG power between brain-injured and intact monkeys was seen in any frequency band at 3 days following the HD/HT stress period.

The EEG power spectra were significantly different between surviving and nonsurviving monkeys subjected to HT or HD/HT. Those that died had either an isoelectric EEG during both stress and recovery periods or an isoelectric EEG during the stress period and a partial recovery of power in the 0–4 and 4–8 Hz bands.

**EFFECTS ON SOMATOSENSORY EVOKED POTENTIALS**

Somatosensory evoked cortical potentials were attenuated by the hypoxic stress of HT, HD, and HD/HT. Examples of SEP are shown in figure 4. In the control period (top trace), the positive and negative components are designated by alphanumeric symbols beginning with the initial positive wave (P1). Wave components P1, N1, P2, N2, P3, and N3 had mean peak latencies of 5.9 ± 0.3 (SD), 7.9 ± 0.5, 11.0 ± 1.4, 19.7 ± 1.8, 35.6 ± 7.7, and 51.3 ± 11.2 ms, respectively. Reduction of wave amplitude during the stress period was not accompanied by significant changes in peak latency. In comparison with stress by HT or by HD alone, the combination of HD/HT caused a greater decrease in the amplitude of all components except P1. In figure 4 (middle trace), all components except P1 were abolished during HD/HT. The
amplitude of component P1 was unaffected by HD, HT, or HD/HT.

Unlike reduced EEG power, decreased amplitudes of the N1–P2 components of the SEP during the stress period were predictive of neuropathologic outcome in the HD/HT group. Mean SEP amplitudes before, during, and after HD/HT are shown in figure 5. A significant difference in the peak-to-peak amplitude of N1–P2 between seven brain damaged and nine intact monkeys was found at 15 min of HD/HT. The amplitude of N1–P2 was reduced to 30 ± 18% of control amplitude in monkeys surviving with subsequent brain injury, whereas, the amplitude was reduced only to 61 ± 33% of control value in intact monkeys. No surviving monkey maintaining a N1–P2 amplitude greater than 60% of control amplitude at 15 min after onset of HD/HT incurred brain damage; seven out of 11 HD/HT survivors whose N1–P2 amplitude decreased below this level sustained brain injury. Only two of 11 monkeys from the HT and HD groups had an N1–P2 amplitude less than 60% of control amplitude. The N1–P2 amplitude in all surviving monkeys returned to control level by 3 days after HD/HT and showed no correlation with existing ischemic cell injury at that time.

Short-latency (<6.0 ms), brain stem (far-field) components of the auditory evoked potentials were unaffected by HD, HT, or HD/HT in surviving monkeys. This observation was consistent with the lack of amplitude and peak latency changes associated with the short-latency, P1 far-field component of the SEP. Long-latency (>6.0 ms), cortical (near-field) components of the AEP were recorded, but are not reported in this study because of wide variations in waveform, amplitude, and latency between anesthetized monkeys.
The N1–P2 amplitudes were significantly lower in monkeys that did not survive HT or HD/HT than in those that did survive. In all nonsurviving monkeys, the N1–P2 wave components were abolished after a progressive amplitude reduction during the stress and recovery periods. The initial positive wave (P1) of the SEP and brain stem components of the AEP in these monkeys were significantly reduced in amplitude or abolished. These data suggest that extensive brain stem damage could have contributed to deaths in the HD and HD/HT groups.

**Discussion**

**Hypotension or Hemodilution**

We found no histologic evidence of ischemic brain cell injury in monkeys that survived arterial hypotension (range of MABP 17–36 mmHg) for 30 min or isovolemic hemodilution (range of Hct 11–15%) for 1 h without hypoxemia, hypercapnia, and acidosis. In all cases, the spontaneous (EEG) and evoked (SEP) brain electrical activity during HT or HD were reduced but recovered after restoration of control MABP or Hct.

The electrophysiologic and histologic findings in monkeys made hypotensive are in agreement with those of Gamache and Myers in barbiturate-anesthetized rhesus monkeys subjected to an MABP of 25 mmHg for 15–30 min and of Dong et al. in halothane-anesthetized dogs subjected to an MABP of approximately 20 mmHg for 1 h. While these levels of MABP were not associated with brain injury in the animals that survived the immediate stress, they are by no means safe; three out of ten monkeys in this study as well as a number of animals in previous studies failed to survive the immediate hypotensive stress. Studies by Brierley et al. and Selkoe and Myers in monkeys have set the actual threshold for hypotensive brain cell damage at an MABP of 25 mmHg for at least 15 min. Correlations were found between the severity of brain damage and the duration of isoelectric EEG or time course of changes in SEP amplitude during hypotension. Conditions in those studies differed from those in our study and 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, deterioration of acid–base status was not prevented. The administration of trimethaphan as a bolus in our study did not simulate clinical conditions and was based on previous studies in order to achieve a rapid decrease in MABP and a low, stable MABP.

Our findings, which show reduction of SEP during isovolemic hemodilution and SEP recovery after Hct restoration, are in agreement with those of Nagao et al. in phencyclidine-anesthetized monkeys subjected to Hct below 10%. Studies in dogs have shown that lowering the Hct to 5% was compatible with long-term survival and well maintained cardiovascular function. The lack of adverse neurologic, behavioral, and neuropathologic findings in our study suggests that the brain has a wide margin of tolerance for isovolemic, normotensive hemodilution.

**Combined Hemodilution and Hypotension**

While neither hypotension nor hemodilution alone resulted in survival with brain injury in this study, the combination caused moderate damage in 44% of cases. Hypoxic–ischemic changes did result from combinations of Hct less than 20% and MABP below 40 mmHg. The probability of brain hypoxia was higher for HD/HT because each technique relies on a decrease in cerebral vascular resistance to maintain adequate oxygen delivery. During induced hypotension in humans, CBF remains constant (autoregulation) until a mean arterial pressure of 55–60 mmHg is reached. At this point further cerebral vasodilation no longer keeps pace with decreasing perfusion pressure and a pressure-dependent reduction in flow occurs. Hemodilution also uses the cerebral vasodilator reserve to maintain brain oxygen supply. Our observations suggest that cerebral vasodilator reserves are exhausted at higher perfusion pressures if hemodilution is combined with hypotension. We acknowledge that trimethaphan may decrease cerebral blood flow more than nitroprusside at a given severe degree of hypotension. Thus, the same level of hypotension produced with sodium nitroprusside and combined with hemodilution might have been better tolerated. Nevertheless, the combination of HD and HT, like severe HT alone, is an extremely life-threatening procedure—seven out of 23 monkeys in this study died from cardiovascular collapse and possibly neurologic injury.

Our observations from a limited number of surviving monkeys indicate a 64% probability of brain injury if the SEP amplitude (i.e., components N1 and P2) decreases below 60% of control amplitude at 15 min after onset of HD/HT. Thus, SEP monitoring could indicate circumstances during which monkeys are likely to, but will not necessarily, develop brain pathology. Ischemic neuronal changes were found in the sensorimotor cortices as well as other areas of the central nervous system. However, the degree of SEP amplitude reduction in any given animal was not indicative of the extent and severity of the ischemic brain injury. The SEP components recorded in the present study are identical in form, polarity, and latency to those reported by Arezzo et al. Based on the findings of Arezzo et al., component P1 (6 ms) originates from current generator sources located in the thalamocortical radiation (cell bodies in thalamus), whereas com-
ponents P2 (11 ms)–N2 (20 ms), P3 (36 ms), and N3 (51 ms) originate most likely from the posterior bank of the cortical central sulcus (areas 3a and 3b), the lateral portion of the parietal lobe (area 7b), and the somatotopic areas of postcentral cortex (wide distribution), respectively. The absence of neuronal damage in thalamus was consistent with the lack of change in component P1 during HD/HT. The diminution or loss of SEP has been attributed to a failure of cellular energy supplies or metabolic deficiency in the cortex.13

Our results showed that changes in SEP, when compared with changes in EEG activity during HD/HT, provided a better prediction of subsequent brain tissue damage. Brierley et al.9 also showed in their brain hypoxia model that the SEP predicted adverse outcome better than the EEG. This finding is expected because the SEP is more resistant to cerebral ischemia than is the EEG and change in the SEP is associated with a more profound reduction in cerebral oxygen delivery. Studies in humans22–25 and monkeys13,26–28 indicate that the EEG becomes isoelectric at rates of cerebral blood flow higher than those which produce complete loss of the SEP. Unlike previous studies of oligemic hypoxia,5,12,15,29–31 we did not observe prolonged isoelectric EEG or suppression-burst activity in surviving monkeys that had neuropathologic alterations. These different EEG findings might be attributed to differences in anesthesia, arterial oxygenation, acid–base status, and the degree of stress. Because we were attempting to identify the threshold for brain injury, the hypoxic stress imposed may be less than in previous studies. We did observe in brain-injured monkeys a significantly slower recovery of EEG activity in the 4–25 Hz frequency bands (see also Prior52). In contrast, no significant differences in recovery of SEP amplitude were observed between injured and intact monkeys. These results suggest that hypoxia has differential effects on neuronal mechanisms that generate spontaneous as opposed to evoked brain activity. We have no adequate explanation for the complete recovery of EEG and SEP in brain-injured monkeys by three days after HD/HT. It is possible that the hypoxic–ischemic changes were not sufficiently global and severe to damage permanently the generator sites of the EEG and SEP, or that the electrical phenomena observed were not necessarily direct reflections of the function of cells vulnerable to injury with HD/HT. In any case, corroborative studies using other experimental designs must be performed before the SEP can be considered a practical and reliable intraoperative measure to predict neurologic injury under the dangerous conditions of combined hypotension and hemodilution.

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