POLARIZATION EVOKED POTENTIALS assess the nervous system from peripheral nerve to cortex. Clinical use emphasizes discrete lesions of the nervous system, brachial plexus,1 brainstem,2 spinal cord3 and hemisphere.4-5 Somatosensory evoked potential (SEP) is altered by systemic insults such as oligemia,6-7 anemia,8 intracranial hypertension,9 and hypoxia.10 The changes in superficially recorded waves during systemic oxygen deprivation6-8-10 are similar to those recorded when the cortical region (somatosensory cortex) is directly involved1 and therefore may be as useful in quantitating the degree of insult in generalized insult as in localized insult.

SUMMARY The effects of hypoxic hypoxia on cerebral hemodynamics and somatosensory evoked potential (SEP) were studied in 10 pentobarbital anesthetized dogs. Cerebral blood flow (CBF) was measured using the venous outflow technique and cerebral oxygen consumption (CMRO2) was calculated from the arterio-cerebro-venous oxygen difference times CBF. SEP was evaluated by percutaneous stimulation of an upper extremity nerve and was recorded over the contralateral somatosensory cortex. The latencies of the initial negative wave (N1), second positive wave (P2) and the amplitude of the primary complex (P1N1) were measured. Animals were breathed sequentially with oxygen concentrations of 21, 10, 6, 5, and 4.5% for five minutes each. Animals were returned to room air breathing when the amplitude of the SEP decreased to < 20% of control and were observed for 30 minutes following reoxygenation. Severe hypoxia (4.5% O2) increased CBF to 200% of control, decreased CMRO2 to 45% of control, decreased amplitude and increased latency of SEP. Following reoxygenation, as CMRO2 increased toward control, latency of SEP decreased and amplitude increased and CBF returned to baseline within 30 min. During hypoxia and reoxygenation, the latencies of N1 and P2 and the amplitude of P1N1 were correlated with CMRO2 in individual animals. We conclude that changes in SEP amplitude and latency reflect changes in CMRO2 despite high CBF during rapidly progressive hypoxic hypoxia and following reoxygenation.

Relationship of Somatosensory Evoked Potentials and Cerebral Oxygen Consumption During Hypoxic Hypoxia in Dogs

ROBERT W. MCPHERSON, M.D.,* SCOTT ZEGER, PH.D.,† AND RICHARD J. TRAYSTMAN, PH.D.*

From the Department of Anesthesiology and Critical Care Medicine,* and Department of Biostatistics,† Johns Hopkins Medical Institutions, Baltimore, Maryland.

This work was supported in part by USPHS, National Institutes of Health — Grant NS20020.

Address correspondence to: Robert W. McPherson, M.D., Johns Hopkins Hospital, Department of Anesthesiology and Critical Care Medicine, Meyer 8-138, 600 N. Wolfe Street, Baltimore, Maryland 21205.

Received February 6, 1985; revision #1 accepted July 17, 1985.

Previous studies have not explored the relationship between oxygen delivery and changes in brain electrical activity. Verification of the relationship of cerebral oxygen delivery and brain electrical activity allows assessment of adequacy of oxygen availability and utilization when cerebral blood flow (CBF) and other important factors such as blood oxygen carrying capacity cannot be measured. Studies of non-oligemic insults on SEP have failed to include information on CBF or cerebral oxygen consumption (CMRO2).8-10 It is therefore unclear if a consistent relationship of changes in CMRO2 and SEP exists.

We studied the relationship of CMRO2 and SEP in a model in which CBF increases in response to cerebral oxygen deprivation to test the hypothesis that somatosensory evoked potentials reflect oxygen availability to the brain regardless of CBF.

Methods

Ten adult mongrel dogs (20-25 kg) of either sex were utilized in this study. Anesthesia consisted of sodium pentobarbital (30 mg/kg, i.v.) supplemented with increments of pentobarbital (60 mg, i.v.) as nec-
cessary during the surgical preparation in response to pedal and ocular reflexes. Pancuronium bromide (3–4 mg, i.v.) was administered to minimize muscle contractions related to the electrocautery. Heparin (500 µg/kg, i.v.) was used as the anticoagulant.

After induction of anesthesia, animals were intubated and ventillated utilizing a positive pressure respirator (Harvard respiration pump 607). Tidal volume and respiratory rate were adjusted to give an alveolar (end-expiratory) carbon dioxide of 4% as monitored by a CO₂ analyzer (Beckman LB2). The CO₂ analyzer was calibrated regularly with mixtures of CO₂ in air analyzed to a precision of 0.1%. Electrocautery was used to expose one femoral artery and both femoral veins. The femoral artery was cannulated for continuous monitoring of mean arterial blood pressure (MABP). One femoral vein was cannulated and was utilized to return cerebral venous outflow while the other femoral vein was cannulated and used for infusion of fluids and drugs. Rectal temperature was maintained at 38° ± 1 centigrade using heating lamps. All pressures were measured with Statham P-23 transducers, and all data were recorded on a Gould-Brush recorder.

Measurement of Cerebral Blood Flow

The technique used to measure cerebral venous outflow has been described by Rapela and Green. The confluence of the cerebral sinuses was cannulated and the lateral sinuses and occipital emissary veins were occluded with bone wax to minimize communication between intracranial and extracranial venous circulations. From the confluence of the sinuses blood then passed through a previously calibrated electromagnetic flow probe, before returning to the dog via the femoral vein. With this technique approximately 50–70% of the mass of the brain is drained at the confluence of the sagittal and straight sinuses. Cerebral venous outflow pressure was measured upstream from the flow probe. This pressure measures the resistance to the flow of blood induced by the flow transducer because the outflow cannula was set at the level of the right atrium and all pressures were referred to this common zero reference plane. Brain perfusion pressure was estimated as systemic arterial pressure minus cerebral venous outflow pressure. Intracranial vascular resistance was calculated by dividing brain perfusion pressure by cerebral venous outflow.

The verification of the measurement of CBF utilizing this venous outflow technique has been described in detail elsewhere. In addition, the viability and responsivity of the cerebral vasculature to hypercapnia, hypoxia, and ability to autoregulate using this technique has been previously demonstrated.

Measurement of Somatosensory Evoked Potential (SEP)

Stimulating needle electrodes were placed percutaneously in the volar surface of a foreleg in a location which caused a distinct digital twitch and the stimulus intensity just sufficient for a motor response (motor threshold) was determined. The needles were secured and a large surface ground pad was attached to the extremity proximal to the stimulating electrodes. Silver ball electrodes with shielded cables were placed in depressions drilled in the skull over the contralateral somatosensory cortex. A needle electrode with shielded cable was placed in the snout and acted as reference. The junction of the lambdoidal and sagittal suture is an easily indentifiable landmark in the dog and was chosen as an anatomical reference point. Two parallel rows of electrode locations were examined in each animal. One row consisted of electrode locations 2 cm from the midline, with electrode locations 4, 6, and 7.5 cm anterior to the lambdoidal suture. A second row was located 4 cm from the midline posteriorly and 3.5 cm from the midline anterior. Electrodes were placed at 4, 6, and 7.5 cm anterior to the lambdoidal suture. In each animal, the electrode location with maximum amplitude was considered to be nearest the somatosensory cortex and was analyzed for this study.

The SEP was developed using a 4 channel signal averager (Nicolet Med 80, Nicolet Biomedical, Madison, Wisc). A stimulus intensity twice motor threshold and a stimulus duration of 150 usec was used. One hundred twenty eight stimuli were delivered at a rate of 5.9/sec and averaged. Upper and lower band pass filters were 5 and 1500 Hz respectively. Waveforms were stored on magnetic disk for later analysis. In the control period, replicate waves were generated to ensure stability of the waveform. High amplitude electrical artifact was automatically rejected by the computer. The peripheral nerve was stimulated only during study periods (approximately 45 sec each).

This active electrode and reference system yields a consistent wave-form in the dog. The waveform consists of a small positive wave (P1) and 15 ms after stimulus, a large negative wave (N1) and about 20–25 ms after stimulus and a large positive wave (P2) occurring 35–45 ms after stimulation. The amplitude and latency of the waveform were evaluated using the cursor mode of the computer. The latencies of the first negative (N1) and second positive (P2) waves were determined. The latency was measured at the midpoint of the wave. The amplitude of the initial complex (P1N1) was measured from the maximum positive deflection of the initial positive wave (P1) to the maximum negative deflection at N1. A representative wave is provided (fig. 1).

A single bipolar EEG channel was monitored ipsilateral to the stimulated extremity. One electrode was placed posteriorly and the anterior electrode was placed in the same coronal plane as the active SEP electrode.

Hypoxia Administration and Blood Gas Analysis

Animals were subjected to hypoxic hypoxia by administration of a mixture of air and nitrogen. The inspired oxygen concentration was measured utilizing an oxygen analyzer (Beckman LB-2). The inspired oxygen concentration was decreased sequentially from 21 to 10, 6, 5, and 4.5% and each level of hypoxia was maintained for approximately 5 minutes or until the SEP was suppressed to < 20% of control. Endtidal
**Results**

**Hypoxia**

Decreasing the inspired O₂ concentration from control (21%) to 10, 6, 5 and 4.5%, decreased PaO₂ from 92 ± 5 to 31 ± 1, 19 ± 1, 17 ± 1 and 14 ± 1 mmHg, respectively (table 1). Fractional O₂ extraction increased markedly from control (.47 ± .02) at a PaO₂ of 92 ± mmHg, to .74 ± .02 at a PaO₂ of 14 ± 1 mmHg. pH and PaCO₂ were unchanged throughout the different O₂ levels. The cerebral hemodynamic changes with hypoxia are shown in figure 2. MABP increased from 127 ± 4 to 150 ± 6 mmHg as PaO₂ increased markedly to 240% of control at 14 ± 1 mmHg. CBF increased markedly to 240% of control at

**Table 1 Blood Gas Changes During Hypoxia and Recovery**

<table>
<thead>
<tr>
<th>Time after return to room air (min)</th>
<th>pH</th>
<th>PaO₂ (mm Hg)</th>
<th>PaCO₂ (mm Hg)</th>
<th>Fractional extraction</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>7.28 ± 0.01*</td>
<td>71 ± 7*</td>
<td>36 ± 2*</td>
<td>0.13 ± 0.02*</td>
</tr>
<tr>
<td>4</td>
<td>7.29 ± 0.01*</td>
<td>86 ± 4</td>
<td>33 ± 2</td>
<td>0.15 ± 0.03*</td>
</tr>
<tr>
<td>6</td>
<td>7.30 ± 0.01*</td>
<td>85 ± 4</td>
<td>33 ± 2</td>
<td>0.20 ± 0.03*</td>
</tr>
<tr>
<td>8</td>
<td>7.31 ± 0.01*</td>
<td>87 ± 5</td>
<td>31 ± 1</td>
<td>0.23 ± 0.04*</td>
</tr>
<tr>
<td>10</td>
<td>7.31 ± 0.01*</td>
<td>88 ± 5</td>
<td>32 ± 1</td>
<td>0.25 ± 0.02*</td>
</tr>
<tr>
<td>15</td>
<td>7.32 ± 0.01*</td>
<td>86 ± 6</td>
<td>31 ± 1</td>
<td>0.35 ± 0.04*</td>
</tr>
<tr>
<td>20</td>
<td>7.33 ± 0.01*</td>
<td>86 ± 5</td>
<td>30 ± 1</td>
<td>0.44 ± 0.04</td>
</tr>
<tr>
<td>30</td>
<td>7.35 ± 0.01</td>
<td>87 ± 5</td>
<td>31 ± 1</td>
<td>0.47 ± 0.04</td>
</tr>
</tbody>
</table>

* = p < 0.05.
Hemodynamic Changes Following Return To Room Air

(n = 10; \( \pm \) SEM)

Mean Arterial Blood Pressure (mmHg)

Cerebral Blood Flow (ml/min)

Cerebral Oxygen Consumption (ml/min)

Time After Return to Room Air (minutes)

FIGURE 2. Hemodynamic and cerebrovascular changes to a progressive decrease in inspired oxygen concentration (21, 10, 6, 5, and 4.5% \( \text{O}_2 \)) is shown (\( n = 10 \), mean \( \pm \) SEM). Animals were returned to room air when the amplitude of SEP decreased to less than 20% of control. Differences from control value (* = \( p < .05 \)) were evaluated using analysis of variance for repeated measures.

PaO\(_2\) of 19 ± 1 mmHg but then decreased to 160% of control as PaO\(_2\) was reduced to 14 ± 1 mm Hg. CMR\(_{\text{O}_2}\) was reduced (75% of control) at PaO\(_2\) of 19 ± 1 mmHg and was 54 and 36% of control at PaO\(_2\) of 17 ± 1 and 14 ± 1 mmHg, respectively. Two minutes following the return of the animal to room air breathing, PaO\(_2\) was increased to 71 ± 7 mmHg and by 4 minutes was at the control value (86 ± 4 mmHg) (table 1). Brain oxygen extraction did not return to normal until 20 minutes after reoxygenation (table 1). Following reoxygenation, CBF was elevated and required 20 min to return to its control value, whereas CMR\(_{\text{O}_2}\) had returned to control by 10 min (figure 3). MABP decreased immediately after reoxygenation and remained unchanged over the 30 minute period.

The relationship between amplitude (P1N1) and latency (N1, P2) of the SEP and CMR\(_{\text{O}_2}\) during hypoxia and recovery is shown in figure 4. Hypoxia (PaO\(_2\) = 14 ± 1 mmHg) decreased P1N1 amplitude to 17% of control, increased N1 latency to 111% of control, and increased P2 latency to 107% of control. As PaO\(_2\) decreased to the lowest level (14 ± 1 mmHg), EEG progressively slowed and showed electrocortical silence or prolonged burst suppression (5–10 sec) occurred when the SEP amplitude was decreased to 17% of control. Two minutes after reoxygenation, P1N1 amplitude had increased to 53% of control while N1 latency was still elevated at 112% of control, and P2 latency was 109% of control (fig. 4). Thirty minutes after reoxygenation, P1N1 amplitude, and N1 and P2 latency had returned to control values.

Table 2 shows the slope of changes in CMR\(_{\text{O}_2}\) and changes in latency of N1 and P2 and amplitude P1N1 in individual animals during both hypoxia and recovery. It can be seen that the slopes of these responses are similar in the group of animals and that a correlation exists in each animal. The values during hypoxia and recovery were pooled in each animal. The average slope of latency N1 versus CMR\(_{\text{O}_2}\) is \(-0.46 \pm 0.19\) (95% confidence interval), P2 versus CMR\(_{\text{O}_2}\) is \(-0.19 \pm 0.13\), and amplitude vs CMR\(_{\text{O}_2}\) N1P2 is \(0.15 \pm 0.06\).

**Discussion**

The model of cerebral oxygen deprivation (hypoxic hypoxia) differs from other models used to assess changes in SEP, oligemia, and increased tissue pressure because increases in CBF may preserve oxygen delivery to the brain despite low oxygen content of blood. Previous studies have related SEP and CBF without assessment of CMR\(_{\text{O}_2}\). In those studies, the insult was delivered over a prolonged period of time and the experimental design excluded cerebral com-
The present experiments evaluated the adequacy of O$_2$ delivery and its effect on SEP in a rapidly changing situation. The stress of O$_2$ deprivation was rapid and reoxygenation was accomplished quickly at a point of exhaustion of cerebral compensatory mechanisms (increased CBF). Lack of equilibration could appear to decrease the relationship of the changes in cerebral O$_2$ uptake and parts of the SEP waveform. However, despite the potential for a non steady state condition, changes in SEP were well correlated with CMRO$_2$. The parameters used to acquire SEP data allowed data acquisition in 30–45 seconds and should minimize the effect of changes of neural function occurring during the data acquisition period. It is unlikely that oxygen deprivation of peripheral structures (peripheral nerve or spinal cord) contributed to the SEP changes noted. The spinal cord components of SEP are less sensitive than cortical components during ischemia$^{21}$ and during hypoxic hypoxia.$^{22}$

The SEP was evaluated for changes of both amplitude and latency. Latency of waves from peripheral nerve to the cortex is a function of white matter and the amplitude of the cortical waves is primarily a function of gray matter. Amplitude of SEP is easier to evaluate visually than latency, particularly in a situation of rapid change. Early parts of the SEP wave, representing arrival of the afferent volley at the cortex, were chosen for evaluation because of their constancy in this preparation and the resistance of these early wave to anesthetic drugs$^{23,24}$ which make them preferable to later waves for intraoperative or intensive care monitoring. Our studies demonstrate that changes in wave latency correlated well with CMRO$_2$. The delay from peripheral nerve to cortex increased as O$_2$ availability was decreased and then decreased toward normal as O$_2$ became available following reoxygenation. The change in latency N1 from room air to severe hypoxia was 11% and the latency of P2 was changed by 8%. The magnitude of amplitude change was much greater (84% decrease) and changes in amplitude (pN1) appear to be a more reliable indicator than changes in latency (as indicated by a more narrow confidence interval of the slope). For rapid assessment of CMRO$_2$ change, amplitude appeared preferable because of the much larger change.

The recovery phase of this experiment is particularly important. In this circumstance, changes in SEP correlated with decreased CMRO$_2$ due to metabolic impairment, when cerebral O$_2$ delivery was normal. Hence, alteration in CBF and cerebral O$_2$ availability do not alter SEP unless CMRO$_2$ is decreased whether due to limited O$_2$ availability or metabolic impairment. A potential area of usefulness of SEP monitoring is the brain injured patient. Since SEP is related to brain metabolic function, regardless of CBF or cerebral oxygen availability, it may be a useful tool to assess brain function during the period following brain injury in which hyperemia may be followed by oligemia. Hence a measure of function (SEP) might be more useful than
by patient. Although severe hypoxia was necessary to alter the SEP, the SEP was depressed only when cerebral oxygen availability was limited. In addition to lowered PaO₂, decreased oxygen carrying capacity (Anemia), and lowered cerebral blood flow may lower cerebral oxygen delivery. Our study supports the concept that any combination of oxygen carrying and cerebral blood flow which limits cerebral oxygen delivery will be demonstrated by alteration in SEPs and correction of the abnormality will return the SEP toward normal. Indeed, uses of changes of SEP to evaluate therapy appears useful when other currently used methods are inadequate or not feasible. SEP evaluation is possible without movement of the patient to special facilities, and is useful at a stage of disease when other methods are too complicated (PET Scanner), or provide inadequate information concerning CBF, CMRO₂, or cerebral perfusion pressure.

The cerebrovascular, cerebral metabolic and electrical (EEG) responses and recovery to hypoxic hypoxia are similar to those noted previously 25 although we produced a more severe degree of hypoxia. The degree of hypoxic stress in our study was greater than in that study by effects on both CMRO₂ and EEG amplitude. The time course of return of brain high energy compounds to control reported previously 25 are similar to the return of the brain’s ability to use O₂ (fractional oxygen extraction) in the present study. We have shown that the SEP reflects cerebral O₂ deprivation, even in a non-steady state situation.

It is important to note that both return of CBF and the ability of the brain to extract oxygen (fractional extraction) returned slowly toward control. Indeed, correlation of SEP components with CMRO₂ when the brain was metabolically impaired (increase CBF, decrease O₂, extraction) returned slowly toward control. Indeed, correlation of SEP components with CMRO₂, when the brain was metabolically impaired (increase CBF, decrease ability to extract oxygen) substantiates the importance of SEP as a monitor of O₂ adequacy. Studies using oligemic methods stress a pressure threshold of 40 mm Hg above the presumed normal value. Indeed, we and others, 1-15 have used non-normal, that is SEP altered by anesthetics, potential changes in position related brainstem ischemia. Anesthesia and Analgesia 60: 248-252, 1984

The superb technical assistance of Eleonora Alderson and Robert Johnson during this study is gratefully recognized. The efforts of Renee Craig and Candace Berryman in typing this manuscript are also appreciated.

References
3. McPherson RW, North RB, Udvarhelyi GB, Rosenbaum AE: Mi-


Relationship of somatosensory evoked potentials and cerebral oxygen consumption during hypoxic hypoxia in dogs.
R W McPherson, S Zeger and R J Traystman

Stroke. 1986;17:30-36
doi: 10.1161/01.STR.17.1.30

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/17/1/30

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/