Early Component Changes in Corticomotor Evoked Potentials Following Experimental Stroke

Richard K. Simpson Jr., MD, PhD, and David S. Baskin, MD

Corticomotor evoked potentials have recently been used in experimental animals and patients as a measure of neurologic function after stroke. However, little is known about the fundamental electrophysiologic properties contributing to the formation of these potentials. To define some of these properties, corticomotor evoked potentials were recorded from the contralateral hindlimb in response to transcortical stimulation in cats anesthetized with halothane. These potentials were obtained hourly for 6 hours after middle cerebral artery occlusion. Four major identifiable components were recorded in control responses. Immediately after infarction, all component amplitudes were significantly attenuated. However, after approximately 5 hours, the early latency components exceeded control values; late latency components were also increased. Corresponding somatosensory evoked potentials were abolished and did not return throughout the recording session. Based on classic neurophysiologic studies, the amplitude increment can be explained as combined activation of low-threshold brainstem facilitatory centers and/or direct activation of subcortical axonal pathways. With further study, corticomotor evoked potentials may be a valuable adjunct to current electrophysiologic monitoring techniques, particularly with regard to defining the extent and location of an infarct, as well as to assessing functional recovery. (Stroke 1987;18:1141-1147)

Somatosensory evoked potentials (SSEPs) have been used to assess neurologic function for decades. Both normal and pathologic conditions of the central nervous system have been studied by SSEP analysis in humans and in many animal models. Such investigations have historically included SSEP evaluation in cerebral ischemia. Several attempts have been made to correlate cerebral blood flow, infarct size, or neurologic deficit to changes in SSEP waveforms. SSEPs, however, primarily reflect the integrity of the sensory system. Extrapolation of motor function from altered features in SSEP characteristics has been criticized. Residual motor function following a cerebral ischemic event is of considerable therapeutic and prognostic importance. Therefore, a noninvasive, quantitative, and objective tool for assessing postinfarct motor function is desirable.

Recently, a transcranial method for noninvasive stimulation of the motor cortex has been developed. By this method, motor evoked potentials produced by the spinal cord, peripheral nerves, or muscles can be recorded in response to transcranial stimulation. Very few studies have employed corticomotor evoked potentials (CMEPs) as a technique for evaluating stroke. Although CMEPs should prove to be a valuable adjunct to methods of patient assessment, relatively few principles of normal waveform formation or component alterations secondary to injury have been clearly defined. The present study was undertaken in an attempt to clarify the effect of acute stroke in CMEP configuration.

Materials and Methods

Fifteen mongrel male cats weighing 3–5 kg were initially tranquilized with 15 mg/kg i.m. ketamine hydrochloride. The cats were then given 3% halothane anesthesia in 100% O2 for approximately 2 minutes by facemask and intubated. The cats were maintained on 1–2% halothane in 100% O2. Throughout the procedure, the cats' blood pressure, body temperature, and minute volume were kept stable. A detailed description of this method has been previously reported.

Cats were then placed into a stereotaxis apparatus (Figure 1, left). Percutaneous needle stimulating electrodes were then placed into the upper extremity along the course of the radial nerve (cathode proximal). Needle electrodes for recording SSEP were placed into the scalp overlying the cortical receiving area for the contralateral forelimb (anode reference). Needle electrodes were also placed into the scalp overlying the primary motor cortex for the forelimb (anode) and into the hard palate (cathode) for transcranial stimulation. Needle recording electrodes were then placed percutaneously into the muscle mass of the contralateral distal forelimb, and bilateral control CMEPs and SSEPs were obtained. A right transorbital middle cerebral artery (MCA) occlusion was then performed using a modification of the technique described by O'Brien and Waltz.

From the Section of Neurosurgery, Veterans Administration Hospital and Department of Neurosurgery, Baylor College of Medicine, Houston, Tex.

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Address for correspondence: Richard K. Simpson Jr., MD, PhD, Department of Neurosurgery, Baylor College of Medicine, 1 Baylor Plaza, Houston TX 77030.

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Peripheral nerves were stimulated using 3–5 mA for 100 μsec. Motor cortex stimulation required 20–25 mA for 1 msec. Cadwell constant-current monopolar square-wave stimulators were used; all signals were amplified, digitized, and filtered (10–500 Hz) by a Cadwell 7400 Evoked Potential System (Kennewick, Wash.). Twenty-five individual 50-msec signals were averaged for each record. The averages were then stored on disks by the evoked potential system and displayed on paper by a dot matrix printer.

In preliminary experiments on 6 cats, control records were obtained for 6 hours to detect changes in CMEP configuration due to anesthesia. Likewise, spinal cord transection and neuromuscular blocking studies were done to determine if electrical artifacts were present in the signal. Cervical cord transections were performed in 3 cats using a surgical microscope while the animals were anesthetized and ventilated. CMEPs were obtained before and after the cord lesion. In 3 separate cats, 2 mg/kg i.m. succinyl choline was given, and CMEPs and SSEPs were obtained before and after recovery from the drug. In the remaining 9 cats, bilateral CMEPs and SSEPs were obtained immediately and every hour thereafter for 6 hours following the stroke.

At the conclusion of the 6-hour postinfarct recording session, the cats were killed and the brains were quickly removed. The brains were sectioned at the level of the optic chiasm and mamillary bodies and were incubated in 2,3,5-triphenyltetrazolium chloride (TTC) for 25 minutes, a technique recently reported to be useful to define cerebral infarct size. Control and postinfarction potentials were compared, with each cat serving as its own control. Differences in waveform characteristics (amplitude and latency) were subjected to paired t test analysis and determined to be significant if p < 0.05.

Results

Various cortical stimulation and compound muscle action potential recording parameters were tested, based on an earlier report, to produce a CMEP with the greatest component complexity, highest amplitude, and shortest initial waveform latency. The parameters described above reflect the optimum experimental protocol. A graphic illustration of these waveforms is shown in Figure 1, right. Four major identifiable components were consistently produced. These included an early (< 15 msec) latency group, P1 and N1, and a late (> 15 msec) latency group, N2 and P2. For comparison, a graphic illustration of the 3 major identifiable SSEP components (P1, N1, and P2) is also provided.

To detect the presence of stimulus or muscle artifacts from scalp, facial, neck, or paraspinal muscles, the cervical spinal cord was transected. No CMEP components could be recorded after complete interruption of all conducting pathways (Figure 2, left). Peripheral muscle origin of these potentials was verified using a neuromuscular blocking agent. During the blockade, no CMEP waveforms were demonstrable (Figure 2, right). After the effect of the drug had terminated, all waveforms returned to control configura-
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BEFORE TRANSECTION  AFTER TRANSECTION

![Corticomotor evoked potentials (CMEPs) recorded before and after complete interruption of cervical spinal cord. No recognizable activity could be recorded. Right: CMEPs and somatosensory evoked potentials (SSEPs) recorded before (control), during (paralysis), and after (recovery) administration of neuromuscular blocker. CMEP was temporarily abolished while SSEP remained unchanged.](image)

Control records obtained over 6 hours (Figure 3) revealed some variation in component configuration with time, particularly in the late-latency waveforms. However, no consistent alterations could be detected.

Control and postinfarction component amplitudes and latencies from contralaterally and ipsilaterally produced CMEPs and SSEPs were then compared (Figure 4). Immediately after right MCA occlusion, while stimulating the right motor cortex, P1 and N1 component amplitudes decreased significantly (Figure 5, top left and top right) by 10.7 ± 4.6 (mean ± SD) and 5.6 ± 2.4 μV, respectively. N2 and P2 component amplitudes were also reduced by 5.8 ± 1.7 and 4.1 ± 2.2 μV, respectively (Figure 5, bottom left and bottom right). No significant changes in latency were measured. For the next 4 hours, the CMEP component amplitudes gradually returned to control levels. However, at 5 hours after infarction, early latency waveform amplitudes significantly exceeded control levels. P1 and N1 amplitudes were increased by 12.4 ± 5.6 and 9.8 ± 5.1 μV, respectively. A similar increase in amplitude (13.7 ± 7.4 and 13.3 ± 5.3 μV, respectively) was seen at 6 hours after infarction. Again, no significant changes in latency were detected. Both N2 and P2 component amplitudes were also increased at 6 hours after infarction; however, the increment was not significantly higher than control voltages. No recognizable SSEP could be recorded from the infarcted cortex throughout the recording session. SSEPs recorded from the noninfarcted cortex demonstrated no consistent change in waveform amplitude or latency throughout the recording session. Although variability

![Corticomotor evoked potential (CMEPs) and somatosensory evoked potentials (SSEPs) recorded over 6 hours in control cats subjected to the entire experimental procedure except middle cerebral artery occlusion. No consistent variation in late-latency components was observed.](image)
in amplitude occurred, CMEPs obtained by stimulation of the noninfarcted cortex showed no consistent waveform alteration or changes significantly different from control amplitudes.

The photomicrograph shown in Figure 6 illustrates the perimeter of infarcted tissue (unstained area). Histologic evaluation of all cats revealed consistent MCA infarction with minimal variation in infarct size.

**Discussion**

CMEPs have been reported recently to be useful in determining the size of an infarct in laboratory ani-

**Figure 4.** Top: Corticomotor evoked potentials (CMEPs) recorded before and after right middle cerebral artery stroke. CMEPs produced by stimulating right hemisphere showed initial amplitude loss in all components. Over approximately 3 hours after infarct, all components returned to control amplitudes. Early components surpassed control amplitudes at 5 hours after infarct (note change in calibration). No consistent changes were observed in CMEPs produced by stimulation of left hemisphere. Bottom: Somatosensory evoked potentials (SSEPs) recorded before and after right middle cerebral artery stroke. SSEPs recorded from infarcted hemisphere were abolished and did not return. SSEPs recorded from noninfarcted hemisphere remained unchanged.
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PI COMPONENT CHANGES

N1 COMPONENT CHANGES

N2 COMPONENT CHANGES

P2 COMPONENT CHANGES

FIGURE 5. Column graphs demonstrating mean change in component amplitudes from control amplitudes over 6-hour recording session. Top left: P1 component changes. Top right: N1 component changes. Bottom left: N2 component changes. Bottom right: P2 component changes.

In cats, Oro and Levy have shown that the perimeter of functioning nervous tissue can be precisely outlined by observing cortically evoked activity at the spinal cord or peripheral nerves. Konrad et al, using a dog model, have reported that motor evoked activity is exquisitely sensitive to global cerebral ischemia. Levy et al have recently demonstrated the potential clinical applicability of CMEPs in humans suffering a stroke. Further understanding of the basic neurophysiologic mechanisms contributing to waveform formation in the normal or injured state will certainly enhance both laboratory and clinical utility of CMEPs.

Our investigation attempts to partly describe the changing electrophysiologic events that occur soon after cerebral infarction. CMEPs recorded from peripheral muscles were analyzed because the entire descending neuraxis can be evaluated in this manner. Based on cord transection and neuromuscular blockade studies, the responses obtained do not simply reflect stimulus artifacts or volume-conducted neural or muscular potentials. The responses obtained are generated distal to the myoneural junction and are summed, compound muscle action potentials that represent activity in the final common pathway.

Amplitude changes seen in the CMEPs produced by stimulation of infarcted brain suggest that a biphasic electrophysiologic response to injury occurs, particularly with regard to the early components. The temporal sequence of events appears to be an initial period of inhibition of CMEP formation, followed by a gradual recovery of waveform formation, followed approximately 5 hours later by a period of facilitation whereby CMEP amplitudes are significantly larger than control responses. CMEPs produced by stimulation of the noninfarcted cortex showed some degree of alteration; however, this was not consistent nor significant. SSEPs, however, are abolished immediately after infarction and do not return. SSEPs recorded from the noninfarcted cortex did not significantly change throughout the recording session, suggesting that later-alization and not a diffuse subcortical, electrophysiologic process occurs in response to stroke.

The early temporal sequence of tissue changes fol-
lowing infarction has received little attention. Although astrocytic changes can be seen within 2 hours after stroke, neuronal alteration cannot be detected by light microscopy until 6–12 hours after infarction. If postinfarction brains are sectioned at different times after stroke, neuropathologic studies indicate that deep cortical nuclei undergo degenerative changes earlier than the cortex. This difference is thought to be secondary to overall cell size, greater metabolic demand, and cerebral cortex. The increased electrical susceptibility to ischemia was, in turn, more resistant than the thalamus, which was, in turn, more resistant than the cerebralstem. Lower segments of the neuraxis, i.e., brainstem, were most resistant to ischemic insults. The thalamus was, in turn, more resistant than the cerebral cortex. The increased electrical susceptibility to ischemia followed a pattern of increasing encephalization. It was suggested that more complex synaptic structures from multiple sources might manifest partial failure in neurotransmission more easily, hence the diminished recorded electrical activity. This hypothesis has been recently supported by Sato et al. While recording evoked potentials and blood flow from the spinal cord and cerebral cortex, neural structure sensitivity to ischemia correlated with the degree of synaptic complexity. This could explain the rapid loss of SSEP activity and electroencephalographic activity observed in this study and by other investigators. Initial loss of cortically evoked motor activity could also be explained by this mechanism. The recovery and facilitation of CMEP waveforms, however, requires a quite different explanation.

Classic neurophysiologic studies by Magoun have demonstrated the presence of a facilitatory center in the brainstem that is responsible for increased motor tone and the response to the stretch reflex following decerebration. These centers, found to be as high as the diencephalon in cats, can facilitate cortically evoked muscle responses. In decorticate animals, simultaneous stimulation of the pyramidal tracts and the brainstem also causes considerable augmentation of motor responses and the response to the stretch reflex measured by electromyography (EMG). By occluding the MCA and infarcting the brain, which includes the cortex and basal ganglia, a partial anemic decerebration has been performed. Abatement of inhibitory influences normally exerted by the cortex and/or basal ganglia, or disinhibition, may be manifest as a heightened response in the artificially produced evoked motor activity.

As the facilitatory centers in the brainstem are low-threshold structures, the descending motor pathways, including both pyramidal and extrapyramidal systems, may be stimulated directly by the applied transcranial current. Electrophysiologic studies have shown that the tissue impedance only doubles, several hours after infarction. This would not be a sufficient barrier to prevent current density from activating low-threshold axonal structures and brainstem centers. The early-latency waveforms of the CMEP have been shown by us and others to reflect activity conducted in axonal structures. A combination of direct axonal stimulation coupled with a disinhibition of descending motor activity secondary to the loss of activity from a higher inhibitory center may be responsible for the amplitude changes in the CMEP seen following stroke. Konrad et al. and Oro and Levy reported that a brief facilitation in spinal motor evoked potential amplitude occurred following cerebral ischemia in animals. A similar observation was made by Chan et al. in patients with completed strokes. EMG activity generated by the stretch reflex revealed a heightened initial response from the hemiplegic limb but not from the normal side. Enlarged late EMG responses evoked by ankle joint displacement have been reported by Diener et al. in patients suffering from central lesions.

Important phenomena have been observed in serially obtained CMEPs after stroke. An initial inhibitory influence soon followed by a facilitatory influence on component amplitudes has been measured. Results from the present investigation have clearly shown that cortical responses to ischemia can be evaluated using CMEPs. Future experimental applications include correlating the functional extent of infarction with anatomic and electrical data and long-term monitoring of neuronal recovery using both surface and depth electrodes. As recording techniques that involve only percutaneous EMG electrodes and cortical stimulation can now be safely and comfortably performed in humans using noninvasive magnetic stimulators, CMEPs may prove to be both a useful and a clinically
practical tool in assessing functional damage and recovery from cerebral infarction in humans.

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R K Simpson, Jr and D S Baskin

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