Evoked Potentials in Cerebral Ischemia

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THREE PAPERS in this issue of Stroke highlight the use of short latency somatosensory evoked potentials (SEPs) to quantify neuronal dysfunction in models of cerebral ischemia. These investigators, and others, have taken advantage of two special properties of SEPs, and "early" EPs in general: a relative resistance to general anesthesia, and an approximate localization of cortical SEP generators to the somatosensory cortex, (or the ectosylvian gyrus in animals), allowing correlation of electrical activity with local CBF. Unfortunately, this literature is arduous reading, even for the initiated. Because SEPs are likely to be used more often to validate models of ischemia and to study stroke patients, it is important to understand the technical difficulties, to appreciate the care required for a dependable result, and to recognize the limitations on interpretation, especially in ischemia.

Technical Matters

Comparing data from different experimental models is difficult because of widely varying methods; in addition there are significant problems inherent in measuring electrical phenomena in ischemic tissue. Animal species and stimulus sites differ, but the models reported in this issue have been used previously by others. In cats, the first major negativity thought to be generated from the cortex after median nerve stimulation has had an absolute latency of 10.8 msec,1 11.4 msec,2 12 msec,3 12.5 msec (Coyer et al in this issue), or 13.2 msec.4 Presumably, these are all the same potential but the latency differences demonstrate how technical aspects of stimulation and recording influence results. Interpretation of published material therefore requires information on at least: Stimulus site, intensity, and frequency; Number of repetitions; Amplifier bandpass; Filters; Polarity; Recording derivations; and waveform reproducibility (replication). Untouched SEP tracings with wave peaks labelled and calibration markers are also essential in judging the quality and comparability of the work. Research using middle (30–75 msec) or long latency (>75 msec) EPs (as opposed to the short latency studies) must be interpreted cautiously because later waves are less reproducible and subject to greater variation with minor changes in technique and physiologic state.

The technical aspects of the three papers in this issue compare favorably to much of the existing literature. McPherson's description of SEP technique is exemplary; the others omit some data such as stimulus frequency, intensity, and reproducibility during the pre-ischemic period, but the material is generally interpretable. The amplitudes of the cortical SEP reported in publications using similar techniques in the same animal vary so widely that authors have resorted to using percentage change from control amplitude and pooling data in order to quantify amplitude changes during ischemia. The comparability of results in the literature is further limited because some report SEP latency, others amplitude, and a few, both. The timing of SEP recording with respect to the onset of ischemia is particularly important if latency is considered.

There are potential problems arising from the conducting properties of ischemic tissue and difficulties with recording SEPs during brief and rapidly changing periods of ischemia. The surface recorded SEP is the sum of local electrical activity and volume conducted potentials from adjacent regions. Ischemic tissue has increased impedance, in part accounting for a diminished SEP amplitude. (There are theoretical reasons why this cannot be the whole explanation). Branston has observed that stimulation of the somatosensory pathways at high rates itself increases cortical blood flow slightly, probably by placing increased metabolic demands on the active neurons.5 Compounding these problems is the inability to record more than one brief trial of SEPs because CBF measurements must be almost simultaneous in order to make correlations. The polarographic hydrogen clearance technique tends to be less accurate at the low levels of CBF required to alter the SEP, further reducing the certainty of CBF results. Producing a meaningful SEP during ischemia is difficult, demands technical expertise, and great care in interpretation. CBF thresholds related to SEP changes may have only limited precision.

Nomenclature

Waves generated by subcortical structures are more resistant to ischemia than those from the cortex.2,6 Enough experimental work has been done in animals for most workers to agree tentatively that the first major wave recorded from the scalp is generated by cortical neurons. Animal and human electrophysiology have not always been identical; the negativity in man is thought by some to be generated in the thalamus. Cortical waves in some animals have positive polarity but are equivalent to the N19-P22 (N20) of the median nerve SEP in humans. In cats, however, the important cortical potential for median nerve stimulation has been called P2-MN1 or Wave V3.4 used by Coyer et al. It would be helpful if investigators labelled waves by polarity and time of appearance in milliseconds, and displayed an upward deflection for negativity at the active electrode.

CBF and the SEP

Meldrum and Brierly in 19697 were the first to suggest exploiting SEPs for ischemia research. In the last decade, the extensive and careful work of Branson and Symon's group,3,6,8,9 has delineated the relationship between CBF and SEP. Most previous work, including theirs, suggests that the amplitude of cortical SEP waves is most closely associated with ischemia; latency changes are more variable. In the first several minutes of ischemia cortical SEP latency has varied with CBF over a wide range of decreased blood flows (15–50 ml/100 gm/min), but then has remained un-
changed until flows are low enough to cause electro-
cerebral inactivity (12–15 ml/100 g/min). SEP ampli-
tude begins decreasing at approximately 18 ml/100 
g/min and progressively declines until the wave can no
longer be recorded at 12 ml/100 g/min. These num-
bers approximate reported results in baboons, dogs, 
and cats. Assuming that SEP and EEG are similarly
affected during carotid endarterectomy, corresponding 
CBF values in humans are probably the same.
SEPs seem to provide an excellent way of docu-
menting and quantifying cerebral ischemia. However,
before accepting them as a major advance in stroke
research, it should be pointed out that the same win-
dow of CBF that alters the SEP causes progressive 
slowing of the EEG, burst suppression, and ultimately, 
loss of EEG activity. EEG changes occur in patients as 
CBF decreases from 30 to 18 ml/100 g/min; severe 
slowing and reduced voltage invariably occur below 18 
ml/100 g/min. Moreover, the EEG changes within 
seconds of ischemia, while EPs take minutes to be 
registered.

Meaning of SEPs in Ischemia

The looming problem in this research is uncertainty 
about the relationship of the ischemic threshold for 
SEPs, approximately 12–18 ml/100 g/min, and cere-
bral infarction. Persistence of SEPs does not assure 
the absence of infarction, though there is a tendency for 
larger infarcts to cause greater reductions in SEP laten-
cy. In addition, a simple ischemic threshold for the 
SEP gives an incomplete idea of the mechanism of 
stroke; the all important element of duration of isch-
emia has not been studied with SEPs.

Why does the SEP disappear as neurons become 
ischemic? In experimental models of ischemia we as-
sume that coupling of CBF and metabolism persists.
McPherson’s paper in this issue makes a nice con-
tribution by demonstrating that the SEP diminishes 
and recovers in parallel with metabolic impairment 
(CMRO2) of brain tissue, regardless of CBF or cere-
bral oxygen availability. Unfortunately, both blood 
flow and CMRO2 were global measurements, so the 
precise effects of hypoxia on SEP pathways remained 
unknown. They did observe SEP amplitude was de-
creased to less than 20% of control when the EEG was 
flat or showed burst suppression.

Another group has found that prolonged latency of 
cortical SEP waves correlated with white matter, not
grey matter, ischemia and the cortical SEP was abol-
ished only when white matter CBF and ATP fell to 
critical levels. Some animals had reduced SEP ampli-
tude with normal cortical CBF. With further reduction 
in flow the cortical wave was lost when white matter 
ATP became totally depleted, while energy levels in 
the cortex remained high. More meaningful indicators 
of irreversible neuronal damage, failure of the Na/K 
pumps and membrane depolarization, occur at even 
lower levels of flow than required to abolish the SEP. 
CBF persistently below 10 ml/100 g/min is necessary 
for potassium efflux from cells and cell death. Therefore, the truly “lethal” flow threshold for stroke is 
below the level that completely suppresses the SEP. 
Maintaining CBF above 12 ml/100 g/min for pro-
longed periods produced no histological changes in 
the cortex in one experimental model, and both energy 
state and ion homeostasis have been restored after pro-
longed ischemia in this range. Astrup et al, in a 1981 
editorial, summarized current concepts of flow thresh-
old for infarction and suggested that loss of electrical 
function at 12–18 ml/100 g/min might be a protective 
sacrifice by neurons. Whatever the precise level and 
duration of ischemia associated with stroke, changes in the SEP do not directly reflect the fundamental path-
ophysiological mechanisms causing cerebral infarction; 
they are only markers of reduced CBF.

The most intriguing feature of SEPs, similar to the 
EEG, may be the contrast between resistance to anes-
thesia, and sensitivity to ischemia. Anesthetics (and 
hypothermia) are unique in producing coma and greatly 
decreased cerebral metabolic rate without structural 
damage. Until recently, anesthetics were thought to 
suppress most neurophysiological activity in parallel, as 
reflected by the EEG. Anesthesia may spare the ability 
of neurons to respond to an electrical volley, or more 
likely, it may specifically suppress the diencephalic 
drivers of EEG activity.

Suggestions

SEPs as research tools have potential drawbacks, 
but when used carefully under controlled cir-
cumstances they promise to teach us much about the 
ischemic brain. Even with their modest limitations, an
improvement in SEP amplitude resulting from therapy 
for ischemia would be convincing evidence of benefit.
When used haphazardly, simply to legitimize an ex-
perimental model, as evidence of infarction, or as re-
reflecting some primary function of the sensory system, 
they only add to the existing confusion. I would make 
a plea for more uniformity in stimulus and recording 
technique, nomenclature, and above all, interpreta-
tion. The ability of SEPs to reflect neuronal function is 
impressive, but conclusions about ischemia based pre-
dominantly on SEPs can be misleading; at the moment 
these experiments tell us as much about SEPs as they 
do about ischemia.

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