Central Conduction Time in Primate Brain Ischemia — A Study in Baboons

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SUMMARY The relationship between central conduction time (CCT) and levels of regional blood flow were studied in 9 primates. Flows were recorded in both hemispheres using the method of hydrogen (2 min) clearance. The somatosensory evoked potentials were recorded over the contralateral cortex and the dorsal columns, following median nerve stimulation. The CCT, a measure of the brain's electrical conduction, was determined by the difference in latencies between N10, (the arrival of the afferent volley at the sensory cortex) and N7 (its arrival at the dorsal column). Ischemia was produced by transorbital occlusion of the right middle cerebral artery.

In the acute ischemic phase within 5 minutes of occlusion, there was a significant correlation between the change in CCT and the decrease in flow. In the later occlusive phase, the CCT was unaltered with flows above 15 ml/100g/min. Below that level smaller decreases in flow resulted in progressively larger changes in CCT until a flow was reached where the N10 disappeared or the entire cortex was electrically silent.

Focal ischemia had no effect on the first positive deflection recorded from the cortex (P8) or the first negative peak response from the cervical region (N7). However, the latency of P8 was increased or it was absent with the introduction of hypotension, while N8 was unaltered.

From our measurements, it appears that prolongation of CCT can be related to developing ischemia, and that the thresholds for change are not dissimilar to those already recorded for somatosensory evoked responses on the basis of amplitude alterations in the cortex. Below these levels, prolongation of CCT appears to bear a parametric relationship to alteration in blood flow. While the measurement displays only one of the many alterations which are induced by ischemia in the brain, its attraction lies in its simplicity and in the fact that it may be applied with relative ease in the clinical situation. Under these circumstances, it appears to be an adequately sensitive monitor of developing brain ischemia, and deserves further study.

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Changes in the brain's electrical activity are related to cerebral blood flows below 20 ml/100g/min in man and the primate. The somatosensory evoked potential has been shown to be similar in man and primates following median nerve stimulation. Although still controversial, it is generally agreed that the major negative peak recorded over C2 represents arrival of the afferent stimulus at a (N14) fixed generator site, probably the dorsal column nuclei (DCN). The first major negative peak recorded from the somatosensory cortex (N20) represents the arrival of the afferent volley at the cortex. Hume and Cant, in 1978, introduced the concept of central conduction time (CCT) N20-N14, to measure the electrical conduction in the central nervous system independent of peripheral involvement. Dorfman's estimate (1977) of conduction time in the central pathway was the same as the N20-N14 latency difference of Hume and Cant. His values were derived by measuring F-wave latency, sensory and motor and the onset latency of N20.

Methods

Nine baboons (Papio cynocephalus) weighing 6-10.5 kg were used in this study. The animals were sedated with phencyclidine (IM) and intubated under IV thiopentone. Alphachloralose (60 mgm/kg) was given IV prior to the start of surgery to maintain anesthesia. The stimulating electrodes were placed over the median nerve at the wrist and the voltage adjusted to produce an adequate thumb twitch. Gallamine triethiodide (1 mgm/kg IV) was given as often as necessary to maintain the animal in a paralyzed state.

Ventilation was maintained by a Starling pump at a volume adjusted to maintain the arterial Pco2 constant throughout. End-tidal CO2, mean systemic arterial pressure, Pao2, Paco2, pH and temperature (37°) were monitored. The H-clearance technique was used to determine regional blood flows.

In 6 of the baboons, a partial laminectomy was performed with the removal of the spinous process of C3 and the posterior portion of the lamina of C2. A silver ball electrode was placed midline over the dorsal columns at C2, secured to the adjacent bone with dental acrylic, and the wound closed.

Following removal of the scalp and temporalis muscle, the SSEP was localized for both hemispheres. A burr hole was made, and the dura opened to allow placement of a silver ball electrode and H-electrodes. H-electrodes were also placed in area A and C of the right hemisphere as described in a previous paper. A screw reference electrode for the EP was placed in the bone of the frontal sinus and a silver/silver-chloride reference electrode for the hydrogen clearance system placed subcutaneously in the animal's chest wall. A transorbital approach exposed the right middle
cerebral artery for its subsequent occlusion with a Scoville clip.*

Recording

In the control period, cerebral blood flow (CBF) was measured with the animal in a steady state. The evoked potential (EP) was recorded from both hemispheres and C2 following appropriate median nerve stimulation. In the first 3 baboons, the cortical evoked potential (CEP) and the neck responses were recorded separately but within 2-4 minutes of each other. In this group of animals a spinal needle was placed in the muscle in the region of C1-C2 and the EP recorded.

In the following 6 animals, a laminectomy was performed for more accurate placement of the recording electrodes over the DCN as described above. In the last 6 baboons simultaneous EP recordings were made from cortex, H-electrodes and C2, using a 4-channel analyzer.

After obtaining control values for regional cerebral blood flow (rCBF) and EP (cortical and cervical response) a Scoville clip was placed on the right MCA. During the immediate post-occlusion period, flows were again obtained. The EP from the right cortex, H-electrodes in area B (right) and the contralateral C2 (DCN) were recorded at the time the clip was placed, averaging 64 sweeps.

Systemic hypotension was induced in 4 animals by stepwise exsanguination as previously described.10

Analysis of SSEP and C2-DCN response

The following peaks, comprising the short latency responses, were evaluated:

SSEP (cortex)
P, first positive deflection
N, first major negative peak
C2(DCN)
N, first major negative peak

CCT represents DCN to sensory cortex or the difference in latencies of N, (cortex) minus N, (C2).

For analysis of part of the data, the animals were divided into 2 groups because of the difference in size (6-7 kg — group I, and 9-10.5 kg — group II) and the difference in techniques used to obtain and record the C2 response. Unless otherwise specified, the animals are analyzed as a group with each animal acting as its own control. All EP recordings from the cortex were performed at least 3 hours after alpha-chloralose was given, since preliminary studies indicate that immediately following alpha-chloralose IV the CCT was increased over pre-chloralose values but returned to normal by 3 hours.

Results

Figure 1 demonstrates evoked potential recorded from C2 and sensory cortex in man and the baboon. The latencies are presented in table 1 for the group II baboons and humans.11

Further analysis using the paired t-test showed no significant difference (t = 0.04, 6 animals) in the baboons for conduction time to right vs left hemisphere. This observation also holds true for humans.12 Therefore, in cases of lateralized lesions, i.e. unilateral MCA occlusion, the unaffected hemisphere, as well as the control values for the affected hemisphere, can be used to determine significant variations in CCT.

The average flows in area B are recorded in table 2 for the right and left cortex. There was no significant difference between the control flows for the 2 hemispheres or following the occlusion of the right MCA in the left cortex. However, there was a significant difference (p < 0.003) in the right cortex following occlusion.

The immediate occlusive phase, within the first 5

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**Table 1. Comparison of Cortical and Cervical Evoked Responses Recorded from Human and Primate**

<table>
<thead>
<tr>
<th></th>
<th>C-2 EP peak latency (msec) mean ± S.D.</th>
<th>CEP peak latency (msec) mean ± S.D.</th>
<th>CCT (msec) mean ± S.D.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Humans*</td>
<td>13.8 ± 0.3</td>
<td>16.6 ± 0.4</td>
<td>19.4 ± 0.7</td>
</tr>
<tr>
<td>(Symon et al.)</td>
<td></td>
<td></td>
<td>5.6 ± 0.6</td>
</tr>
<tr>
<td>Primate (group II)</td>
<td>7.1 ± 0.4</td>
<td>7.9 ± 0.3</td>
<td>10.5 ± 0.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3.3 ± 0.1</td>
</tr>
</tbody>
</table>

CEP (P16) = P16.
CEP (N16) = N16.
minutes of placement of the clip on the MCA and the later phase in which the individual H-electrode SEP was related to the flow obtained in the region of recording, have been examined. When flow and SEP are related in this manner, it must be remembered that the SEP represents not only the electrical cortical activity in the area of recording, but also volume conducted potentials from the surrounding tissue, while the H-clearance method gives flow only in the immediate region of the recording.

The animals were not in a steady state at the time the EPs were obtained during the first flows. The relationship between the change in flow and the change in CCT in the acute ischemic phase (first 5 minutes) is significant (p = 0.03), (fig. 2) for the 9 baboons. Recordings were not made from the left cortex at this time because the protocol called for continuous monitoring of the right cortex during the occlusion period. However, the CCT for the left cortex, during a period when the right cortex was either electrically silent or CCT prolonged, was not significantly different from control values.

In the later post-occlusion phase (after 5 minutes), EPs recorded from the individual H-electrodes were related to the flow obtained by the individual H-electrode. The SEP recorded from the silver ball electrode on the cortex was related to the average flows obtained from all H-electrodes in area B. Twenty-seven observations were analyzed. No change in CCT was found with rCBF above 15 ml/100g/min. The change in CCT over control values as related to absolute rCBF is shown in table 3. Only values where a change in CCT could be related to flow were used. Observations were not used where the CCT could not be obtained because of loss of major negative peak. Graphically, figure 3 shows the change in CCT related to absolute rCBF during the later post-occlusion period. (If a hyperbola is fitted to the data, as shown, the correlation co-efficient (r = −0.91) is statistically significant (p < 0.001)). When the flow falls below 15 ml/100g/min, small changes in rCBF cause increasingly larger changes in the CCT until a level is reached where the cortex is electrically silent.

In 4 of the group II baboons, stepwise exsanguination was carried out to lower the mean systemic arterial pressure (MSAP) to hypotensive levels (SAP < 60 torr) in order to determine the effect of ischemia plus systemic hypotension on the CCT. In 3 baboons, the mean systemic arterial pressure was reduced to 49 ± 4 torr. However, in the fourth baboon, following removal of 100 cc of blood, the MSAP had only dropped from 105 torr to 92 torr. Two of the animals lost the major negative peak.  

<table>
<thead>
<tr>
<th>TABLE 2. Control and Immediate Post Occlusion rCBFs for the Right and Left Cortex.</th>
<th>TABLE 3. Change in CCT Related to Levels of Regional Cerebral Blood Flow.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control—rCBF</td>
<td>Immediate post-occlusion phase rCBF</td>
</tr>
<tr>
<td>(ml/100g/min)</td>
<td>(ml/100g/min)</td>
</tr>
<tr>
<td>p</td>
<td>p</td>
</tr>
<tr>
<td>Right</td>
<td>0.000</td>
</tr>
<tr>
<td>cortex</td>
<td>43.9</td>
</tr>
<tr>
<td>(area B)</td>
<td></td>
</tr>
<tr>
<td>NSD</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td></td>
</tr>
<tr>
<td>cortex</td>
<td></td>
</tr>
<tr>
<td>(area B)</td>
<td>61.9</td>
</tr>
<tr>
<td></td>
<td>38.8</td>
</tr>
<tr>
<td></td>
<td>53.6</td>
</tr>
</tbody>
</table>

N = Nine animals.  NSD = No significant difference.  p < < 0.003 (paired t-test).

FIGURE 2. The relationship between the change in regional cerebral blood flow and the change in CCT in the acute ischemic phase (within 5 min). A linear interpretation, under the present experimental conditions, is considered the best fit for the data.
within 2 minutes of the start of the exsanguination period. The third animal demonstrated further prolongation ($p < 0.001$) at 2 minutes and an unobtainable CCT by 13 minutes.

The fourth animal showed variations in CCT which could easily be related to failure to lower the MSAP which remained (> 92 torr) and increase of the rCBF from 26 ml/100g/min to 51 ± 7 ml/100g/min during bleeding.

Figure 4 shows relationship between the SSEP, CCT and rCBF in the control, post-occlusion and during systemic hypotension. The change during the acute ischemic phase is marked by an increase in the latency of the N10, following a decrease in flow to 21% of control and an increase in CCT. At the time prior to exsanguination, the CCT was 3.5, which, although significantly higher than control, was an improvement over the acute ischemic phase. This may represent influence of the collateral circulation on the area in question or the influence of volume conduction from adjacent areas. Following removal of 10 cc of blood the N10 was no longer present but the positive after potential, although reduced in amplitude, remains. At the termination of the experiment, following removal of 50 cc of blood, the MSAP = 35 torr, rCBF = 3 ml/100g/min, and the tracing was flat except for the survival of P8. The SSEP recorded from the left cortex at the same period (rCBF = 22 ml/100g/min and MSAP = 33 torr) shows no increase in latency and no significant change in CCT.

The effect of focal hemispheric ischemia on N7 (DCN) and P8 (CEP) is presented in table 4. The group II animals individually or as a group (average mean) showed no significant difference in latencies between control and post-occlusion values. Exsanguination had no significant effect on N7 either compared to control or post-occlusion values. P8 however, was affected by hypotension. As long as the MSAP was ≥ 50 torr there was no significant change in the latency. When the MSAP was decreased to 42 ± 6 torr the latencies significantly increased ($p < 0.003$) or P8 disappeared. Focal ischemia seems to have no effect on either N7 (CEP) or P8 (SSEP). Systemic hypotension only effects P8 when MSAP = 42 ± 6 torr but at that level of hypotension the N7 was unaltered.

**Discussion**

The central conduction time has previously been shown to be a sensitive indicator to impending
ischemia in patients following SAH \cite{11} and as a predictor of outcome following head injury. \cite{3} Our study was designed to further investigate the effect of ischemia and systemic hypotension on the CCT, using the baboon stroke model.

We have examined the acute ischemic phase (within 5 minutes of the clip) and a later phase when other factors may be important. In the acute ischemic phase, changes in CCT are correlated with decreases in \textit{rCBF}. Branston et al. \cite{14} observed that following occlusions of the MCA, there was a rapid change in the amplitude of the trigeminal evoked response with flows below 16 ml/100g/min and complete loss of the amplitude below 12 ml/100g/min.

Our study was concerned with changes in the latency of N10 thereby increasing the CCT rather than amplitude changes in the later components. CCT is a measure of the time (msec) it takes for the afferent stimulus to travel from the DCN to the sensory cortex and reflects the entire pathway's integrity. In the acute ischemic phase, changes in CCT were found only when the regional cerebral blood flow was below 15 ml/100g/min. In the later phase, with flows below 12 ml/100g/min, smaller decreases in flow were correlated with proportionally greater increases in CCT until a point was reached where the first negative (N10 — CEP) could no longer be recorded, and measuring of CCT then became impossible. Hemispheric ischemia had no effect on the cerebral response, which therefore played no part in CCT except as a marker for the start of the electrical activity within the central nervous system.

The range of flow between 20 ml/100g/min and 8 ml/100g/min has been noted in previous work to be critical for the development of a number of changes within the cortex. Branston et al. \cite{14} have already pointed out that, measuring the amplitude of the cortical evoked response, there appears to be a threshold flow value of about 16 ml/100g/min above which the amplitude of the cortical evoked response is fully sustained and below which it falls to near zero. Further work has demonstrated that at rather low flows, around 10 ml/100g/min, there is a considerable disturbance of potassium homeostasis with a massive increase in extracellular potassium activity. \cite{15} Small, self-limiting alterations in extracellular potassium occur in the range between 12-16 ml/100g/min flow. Below the flow bounds of about 20 ml/100g/min, an accumulation of water in ischemic cortex can be noted, both in the primate \cite{16} and the gerbil. \cite{17} At even lower levels of blood flow, between 8 and 10 ml/100g/min, impedance increases are noticed \cite{18} and distortion of clearance from evoked effluxes of potassium into the extracellular space suggests that at very low levels of flow there is a complete loss of clearance of potassium from the extracellular space. \cite{19}

The change in central conduction time can be related possibly to these effects in the following way. Above 15 ml/100g/min we have observed no change in central conduction time. However, in the range 12-15 ml/100g/min, at a time when edema is beginning, and small effluxes of potassium into the extracellular space have been noted, CCT becomes significantly prolonged. At the flow level below 10 ml/100g/min, when there is a massive disturbance in ionic homeostasis in the cortex, and corresponding evidence of considerable increase in extracellular water, progressively smaller decreases in CBF cause proportionately larger changes in CCT.

Systemic hypotension induced by exsanguination, following MCA occlusion in the primate, caused impairment of autoregulation in all 3 zones in the affected hemisphere. \cite{10} In the animals in which the MSAP was reduced to hypotensive levels, the evoked response from the hemisphere subjected to ischemia was abolished in 1-13 minutes. The CCT to the left hemisphere although slightly affected was not significantly different from control values.

Hemispheric ischemia and systemic hypotension had no significant effect on the cervical recorded EP. However, the first positive peak (P8) recorded from the right cortex was significantly affected by systemic hypotension but not hemispheric ischemia. The P8 recorded from the left cortex was unaltered by focal ischemia, but systemic hypotension caused a slight, although not significant increase in latency ($p = 0.08$) during periods of maximum hypotension. When a paired $t$-test was used (control versus maximum hypotension) no significant difference was found.

Controversy continues to exist over the generator site of the first positive wave recorded over the somatosensory cortex. Although there is general agreement that it is a subcortical component. Small and his co-worker \cite{19} feel that the first small positive deflection in the cortical response is synchronous with the cervical response (DCC) and may be due to volume conduction of the latter. However, the findings of Nakanishi et al. \cite{20} suggest that P15 potential is the result of activity of the afferent pathways from the medulla to thalamus, since it is unaltered with thalamic lesions, but is absent or profoundly altered in patients with vascular lesions of the brain stem. Sance et al. \cite{21} after transection of the cervical (C1-2) cord in monkeys found no response recorded rostral to the transection. Following mid-pontine transection, vertex to mastoid and C1-DCN recordings showed a persistence of the early component and disappearance
of EP from cortical recordings, indicating to them the generator site was between Cl-DCN and mid-pons.

Vascular lesions of the brain stem in man often show bilaterally prolonged CCT, without any clinical evidence of hemispheric involvement.12 This can only happen if the delay is caused by slowed conduction through the pathways in the brain stem.

Our present data are in agreement with those authors13-15 who suggest a subcortical generator site for the first positive wave recorded cortically. Since systemic hypotension significantly altered or abolished this component, while it had no effect on the DCN response, our results are more in agreement with Sance et al. and Nakanishi et al.; that the generation site is between Cl-DCN and mid-pontine level rather than a volume conducted response from DCN.

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