Spreading and Synchronous Depressions of Cortical Activity in Acutely Injured Human Brain

Anthony J. Strong, DM; Martin Fabricius, DMSc; Martyn G. Boutelle, PhD; Stuart J. Hibbins, MSc; Sarah E. Hopwood, PhD; Robina Jones, MRCS; Mark C. Parkin, BSc; Martin Lauritzen, DMSc

Background and Purpose—Cortical spreading depression (CSD) has been much studied experimentally but never demonstrated unequivocally in human neocortex by direct electrophysiological recording. A similar phenomenon, peri-infarct depolarization, occurs in experimental models of stroke and causes the infarct to enlarge. Our current understanding of the mechanisms of deterioration in the days after major traumatic or ischemic brain injury in humans has not yielded any effective, novel drug treatment. This study sought clear evidence for the occurrence and propagation of CSD in the injured human brain.

Methods—In 14 patients undergoing neurosurgery after head injury or intracranial hemorrhage, we placed electrocorticographic (ECoG) electrodes near foci of damaged cortical tissue.

Results—Transient episodes of depressed ECoG activity that propagated across the cortex at rates in the range of 0.6 to 5.0 mm/min were observed in 5 patients; this rate of propagation is characteristic of CSD. We also observed, in 8 of the 14 patients, transient depressions of ECoG amplitude that appeared essentially simultaneous in all recording channels, without clear evidence of spread.

Conclusions—These results indicate that CSD or similar events occur in the injured human brain and are more frequent than previously suggested. On the basis of these observations, we suggest that the related phenomenon, peri-infarct depolarization, is indeed likely to occur in boundary zones in the ischemic human cerebral cortex. (Stroke. 2002;33: 2738-2743.)

Key Words: brain injuries ■ electroencephalography ■ head injury ■ hemorrhage ■ penumbra ■ spreading cortical depression ■ trauma
cortical recordings (n=2), we placed an ECoG recording strip on cortex accessible from the craniotomy. After surgery, patients were transferred to the intensive care unit, where core variables were monitored continuously (arterial and intracranial pressures [n=10] and arterial oxygen saturation [S_o2, pulse oximetry]). The intracranial pressure transducer (Codman) was located on the same side as the craniotomy and usually in the cortical parenchyma near the ECoG strip (hematoma cases). In the final 7 patients, these core variables were logged continuously into the same data set as the ECoG data. All patients were ventilated but were paralyzed only exceptionally, and sedation was largely with fentanyl and midazolam. Propofol was used primarily only in preparation for withdrawal of sedation (because it was largely with fentanyl and midazolam. Propofol was used tomata cases). In the final 7 patients, these core variables were logged transducer (Codman) was located on the same side as the craniotomy and usually in the cortical parenchyma near the ECoG strip (hematoma cases). In the final 7 patients, these core variables were logged transducer (Codman) was located on the same side as the craniotomy and usually in the cortical parenchyma near the ECoG strip (hematoma cases). In the final 7 patients, these core variables were logged

Location of Cortical Recordings
In each patient we placed a single ECoG strip so that it would lie partly on mildly contused cortex (thought nevertheless to be viable) and partly on cortex of entirely healthy appearance, adjacent to a site of contusion, intracerebral hematoma, or surgical corticotomy. In many cases part of the electrode strip lay outside the area of cortex exposed by the craniotomy so that placement of the entire strip on a single gyrus, although usually attempted, could not be verified. We used the single linear strip of electrodes to facilitate removal at the bedside and to minimize infection risk.

Electrocorticography
Four active data channels were acquired from 6-electrode (linear array) subdural strips (Wyler; platinum, 5-mm diameter, 10-mm interval between electrode centers; Ad-Tech Medical) continuously for periods of up to 63 hours. Five electrodes were connected to 4 CED 1902 (Cambridge Electronic Designs) preamplifiers in sequential bipolar fashion, with the sixth electrode used as ground. Thus, the recordings were from a strip of cortex of approximately 3 to 4 cm in length. The CED 1902 filter settings were as follows: pass range 0.5 to 70 Hz, alternating current filtered, 50-Hz notch filter in operation. Data were digitized (128 Hz per channel) with a CED 1401 analog/digital converter and recorder (and later reviewed) with the use of Spike2 software (CED).

Direct current (DC) potential recording would in principle be desirable to confirm that any observed ECoG suppression events indicate depolarization. However, although such recordings are possible in an experimental laboratory, we doubt whether a reliable body of DC potential data could be collected in a clinical intensive care unit. Moreover, the nonpolarizable electrodes required for DC recordings would likely be neurotoxic.12

Data Collection and Analysis
The time series data for the core monitoring variables were digitized (Powerlab 16s, ADInstruments) and collected in the same data matrix as the ECoG data (Chart-4 software, ADInstruments) in the fifth and subsequent patients. Each transient period of ECoG amplitude reduction or loss seen in the data sets was examined according to the following electrophysiological criteria: (1) nonspreading transient depolarizations: a rapidly developing reduction of ECoG amplitude of ≥50% at ≥2 electrodes, without clear evidence of propagation between electrode sites, followed by gradual recovery; (2) definite CSD: sequential onset at 3 or 4 adjacent recording sites of a rapidly developing reduction of ECoG amplitude of ≥50%, followed by gradual recovery; and (3) possible CSD: sequential onset at 2 adjacent recording sites of a rapidly developing reduction of ECoG amplitude of ≥50%, followed by gradual recovery.

On the basis of the close association of spreading ECoG amplitude loss and depolarization (as indicated by a negative DC potential transient) first reported by Leão10 and universally agreed on since then, we interpret those episodes of ECoG suppression that we observed to spread as indicating CSD with depolarization.

Results
Clinical data of the patients are shown in the Table, which also records the transient ECoG events observed, classified according to the aforementioned criteria. Transient, abrupt reductions in ECoG amplitude occurred in 10 patients, and most could be assigned qualitatively to 2 categories: (1) events in which abrupt amplitude loss occurred in several channels within a short space of time that would only allow assignment as synchronous and (2) 29 events in 5 patients in which there was a delay between onset of amplitude loss at different electrodes, in a sequence indicating propagation of the event along the array at a velocity in the range for CSD of −0.43 to 5 mm/min. Six of these events showed spread between 3 or 4 channels. Detailed descriptions and illustrations of propagating and synchronous events in patients 5 and 6 are shown in Figure 1. In Figure 2 we show data from another patient (patient 9), also with a traumatic intracerebral hematoma, in whom recurrent episodes of ECoG loss occurred, with evidence for propagation in both directions along the electrode strip at different times. In patient 11 there were 7 episodes of ECoG suppression propagating between 2 of 3 electrodes available on this occasion. Velocities in 5 consecutive events were in the range of 0.43 to 0.48 mm/s. This demonstrates the occurrence of a stereotyped process, spreading at a constant speed. These 2 electrodes straddled the superior temporal sulcus, which may account for the low speed of propagation calculated for ECoG events at these electrodes (in cats13 [gyrencephalic] PIDs invariably spread around the full depth of a sulcus rather than bridging it, and propagation in sulci is slower than over gyri14).

The frequency distribution of velocities of propagating events (“definite” plus “possible”) among all patients was examined, and after we weighted the data to allow for the uneven numbers of events in different patients, the modal values ranged from 0.43 to 3 mm/min (Figure 3). Since a CSD wave reaching the electrode array from an oblique angle will appear to propagate more rapidly than one propagating along the array, the frequency distribution of velocities to be expected from a set of model CSDs reaching the array from a random distribution of angles between 0 and 89 degrees was calculated, with the result shown in Figure 3. There was good agreement between the observed and modeled frequency distributions.

The duration of the electroencephalographic suppression of the spreading events was in the range of 4.2 to 28 minutes (mean, 13.1 minutes), and the range for the synchronous events was 5 to 20 minutes (mean, 13.0 minutes). These values are compatible with the experimentally observed values for CSD, even if some suppressions were quite long lasting. In some events, the recovery time for ECoG activity was much longer in the vicinity of the lesion compared with more distant electrodes (eg, 20 versus 5 minutes). In 7 studies in which simultaneous pressure and oxygen saturation data were available in the same data file, there were no simultaneous reductions in cerebral perfusion pressure (mean arterial pressure less intracranial pressure) or S_o2 that preceded or accompanied ECoG suppression/depolarization events and thus might have caused them.
In 4 patients there were no episodes that met our criteria for significant events. One patient (patient 3) was observed for a short period of 6.8 hours. In another patient (patient 12; Table) in whom no ECoG suppressions occurred, aneurysm surgery had been uneventful and outcome was good, so that CSD-like events might not be expected. In the last 2 patients (patients 13 and 14, both with head injury), ECoG suppression episodes occurred that probably spread but did not, however, meet another criterion for CSD: abrupt loss of ECoG amplitude of >50%.

Discussion

In his initial article, Leão described a loss of surface ECoG amplitude that propagated across the cortex: we therefore chose ECoG as a marker of depolarization-like events because electroencephalographic recordings from the scalp do not possess the topographical resolution required to demonstrate propagation across the cerebral cortex.

Spreading Events

We submit that the phased onset of ECoG amplitude loss that we observed in a number of instances and patients, with interelectrode delays indicating a rate of propagation of the event characteristic of CSD, is compelling evidence that CSD is indeed the correct interpretation of this set of observations in our study. To our knowledge these data are the first from multiple ECoG electrodes on the human neocortex that enable this conclusion to be drawn. The essential criterion on which the claim is based is that of (1) apparently spontaneous, transient reduction in ECoG amplitude, with gradual recovery after a period of almost complete silence, coupled with (2) evidence that the event spreads across the cortex at or near the rate that is characteristic of CSD. The pattern of recurrent ECoG suppressions that we saw closely resembles ECoG recordings from moderately ischemic cortex (“penumbra”), which is well illustrated in a recent report of an experimental model of focal cerebral ischemia. (Although the ECoG profiles of CSD and PIDs are similar, their hemodynamic and metabolic features differ; see Introduction and below). Among the 5 patients in whom phased onset of episodes of ECoG suppression indicated definite or probable propagation, we analyzed the frequency distribution of calculated propagation velocities (Figure 3) and found a modal value in the range 1 to 3 mm/min (63% of velocities). Although the modal value is slightly low, this may reflect the fact that we are unable to exclude that electrode strips crossed a sulcus (as was certainly the case in patient 11; see Results). The fact that most values for speed of spread were close to that typical of CSD (as indicated by the close similarity of frequency distributions of observed and modeled propagation speeds) strongly supports our interpretation of propagating ECoG suppressions as representing CSD. Thus, the pattern and time course of propagation in these 5 patients are fully in accord with the original report of Leão.

### Summary of Clinical Electroctographic Data in 14 Patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>M/F</th>
<th>Age</th>
<th>Principal Lesion Site</th>
<th>Number of Episodes of ECoG Suppression</th>
<th>Hours From Injury to First Record</th>
<th>Hours of Observation</th>
<th>ECoG Events per Hour</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Synchronous</td>
<td>Possible Spread</td>
<td>Definite Spread</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>F</td>
<td>68</td>
<td>L frontotemporal ASDH</td>
<td>1</td>
<td></td>
<td></td>
<td>18</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>69</td>
<td>R frontotemporal ASDH</td>
<td>1</td>
<td>2 (3–4)</td>
<td></td>
<td>&gt;72</td>
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<td>3</td>
<td>M</td>
<td>67</td>
<td>L frontotemporal ASDH</td>
<td>0‡</td>
<td></td>
<td></td>
<td>26</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>53</td>
<td>R frontotemporal ASDH</td>
<td>2</td>
<td></td>
<td></td>
<td>21</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>24</td>
<td>L temporal ASDH</td>
<td>9</td>
<td>5</td>
<td>1 (2.2–2.4)</td>
<td>66</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>22</td>
<td>Bifrontal ASDH</td>
<td>2</td>
<td>3</td>
<td>1 (1.0–5.0)</td>
<td>39</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>21</td>
<td>Bifrontal ASDH</td>
<td>1</td>
<td></td>
<td></td>
<td>24</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>65</td>
<td>Middle cerebral artery aneurysm</td>
<td>1</td>
<td></td>
<td></td>
<td>n/a</td>
</tr>
<tr>
<td>9</td>
<td>F</td>
<td>57</td>
<td>Frontotemporal ASDH</td>
<td></td>
<td>6</td>
<td>4 (1.1–3.4)</td>
<td>19.2</td>
</tr>
<tr>
<td>10</td>
<td>M</td>
<td>51</td>
<td>ASDH</td>
<td>2</td>
<td></td>
<td></td>
<td>9</td>
</tr>
<tr>
<td>11</td>
<td>F</td>
<td>57</td>
<td>Hypertensive intracerebral hematoma</td>
<td>7 (0.43–2.1)</td>
<td></td>
<td></td>
<td>25</td>
</tr>
<tr>
<td>12</td>
<td>M</td>
<td>45</td>
<td>Clipping of aneurysm</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>13</td>
<td>F</td>
<td>68</td>
<td>Frontal traumatic intracerebral hematoma</td>
<td>0‡</td>
<td>0</td>
<td>0</td>
<td>24</td>
</tr>
<tr>
<td>14</td>
<td>M</td>
<td>65</td>
<td>Frontotemporal traumatic intracerebral hematoma</td>
<td>0‡</td>
<td>0</td>
<td>0</td>
<td>49</td>
</tr>
</tbody>
</table>

ECoG indicates electrocorticogram; ASDH, acute subdural hematoma and contusion; n/a, not applicable.

*Numbers in parentheses are ranges of propagation velocity (mm/min).
†No value is appropriate for patient 1 in view of the short observation period.
‡In patients 3, 13, and 14, ECoG suppressions occurred that did not meet the criteria initially set for inclusion in the data (please see text).
Simultaneous or Synchronous Events
ECOG events that appeared essentially simultaneous or synchronous in all channels were less common (n=19) than those that clearly or probably spread between electrodes (n=29). It is not entirely clear from our present data whether the distinction is a genuine one. A calculated propagation rate corresponding to classic, experimental CSD can only arise from a depolarization originating on or near the axis of the electrode strip (rather than to 1 side of it). Given the heterogeneous distribution of the pathological lesions and the necessarily variable orientation of our electrodes in relation to traumatic lesions (tangential, radial, or intermediate), it is likely that by no means will all depolarizations that propagate do so along the axis of the electrode strip. On this basis, some of our “possibly spreading” events and even some of the synchronous events might indicate true propagation but from origins very oblique or directly lateral to the strip. However, the substantial number of synchronous events we observed lies well outside the modeled frequency distribution for propagation speeds (Figure 3), and it is therefore possible that the electrophysiological basis for synchronous ECoG suppressions is unrelated to CSD. Synchronous negative deflections of DC potentials recorded in the ischemic hemisphere of rats subjected to middle cerebral artery occlusion have been reported (J.A. Hartings, PhD, and F.C. Tortella, PhD, unpublished data, 2002). One (entirely speculative) explanation might be abrupt discharge or loss of activity in a pathway from a localized deep center projecting to the entire strip of cortex being monitored. There is clearly a need for further information, based ideally on methods with better spatial resolution, before this issue can be resolved.

Previous Studies
Our data provide for the first time unequivocal electrophysiological evidence for spread or propagation across the human neocortex of transient ECoG suppression consistent with Leão’s CSD. Several published studies have suggested
The only evidence suggesting the occurrence of CSD-like events in the human brain after trauma is from Mayevsky et al., who located their recording system at the standard (single) neurosurgical monitoring site in the right frontal convexity cortex. There were positive findings in only 1 of 14 patients. In light of our new findings from perilesional cortex in at least 11 of our 14 patients, we attribute the minimal evidence suggesting the occurrence of CSD-like events in the human cerebral cortex, and a recent review adds to this speculation (without identifying new definitive evidence). However, McLachlan and Girvin failed to elicit CSD by electric stimulation of epileptogenic cerebral cortex in humans before its therapeutic excision.

The positive results we have obtained for the first time unequivocal evidence for the spread of depression of cortical electric activity in the human neocortex and have shown that in some instances it is possible to demonstrate propagation with a velocity typical of CSD. (2) If a recording system is appropriately located, in viable tissue in the periphery of an area of brain injury, transient ECoG suppressions can be detected in the majority of patients. A significant proportion of these events represents CSD. (3) Monitoring methods are available to assess the pathogenic potential of such events and may provide relevant guidance for treatment.

Conclusions

(1) We have obtained for the first time unequivocal evidence for the spread of depression of cortical electric activity in the human neocortex and have shown that in some instances it is possible to demonstrate propagation with a velocity typical of CSD. (2) If a recording system is appropriately located, in viable tissue in the periphery of an area of brain injury, transient ECoG suppressions can be detected in the majority of patients. A significant proportion of these events represents CSD. (3) Monitoring methods are available to assess the pathogenic potential of such events and may provide relevant guidance for treatment.

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References

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