

Stroke

American Stroke
AssociationSM

JOURNAL OF THE AMERICAN HEART ASSOCIATION

A Division of American
Heart Association



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

Anthony J. Strong, Martin Fabricius, Martyn G. Boutelle, Stuart J. Hibbins, Sarah E. Hopwood, Robina Jones, Mark C. Parkin and Martin Lauritzen

Stroke published online Nov 14, 2002;

DOI: 10.1161/01.STR.0000043073.69602.09

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75214
Copyright © 2002 American Heart Association. All rights reserved. Print ISSN: 0039-2499. Online
ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://stroke.ahajournals.org>

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

Permissions: Permissions & Rights Desk, Lippincott Williams & Wilkins, a division of Wolters Kluwer Health, 351 West Camden Street, Baltimore, MD 21202-2436. Phone: 410-528-4050. Fax: 410-528-8550. E-mail:
journalpermissions@lww.com

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

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;33:2739-2744.)

Key Words: brain injuries ■ electroencephalography ■ head injury ■ hemorrhage ■ penumbra
■ spreading cortical depression ■ trauma

In 1944, Leão¹ described propagation, across the cerebral cortex of rabbits, of a wave of depression of electric activity: cortical spreading depression (CSD). He initiated the wave by focal stimulation of the cortex and recorded it from the electrocorticogram (ECoG). The phenomenon has been studied extensively in the laboratory, and the subject was recently reviewed thoroughly.² Perhaps the most critical of many features of CSD is a striking but transient increase in cerebral blood flow with later oligemia.³ CSD does not cause ischemic damage to the cortex if cerebral perfusion is normal,⁴ and experimental work has suggested that induction of CSD in the rat brain partially protects from subsequent ischemic insults.^{5,6}

Propagated or nonpropagated depolarizations resembling CSD (in terms of the cation transients observed) occur spontaneously in ischemic cortical boundary zones associated with experimental middle cerebral artery occlusion; they have been designated *peri-infarct depolarizations* (PIDs)⁷ or hypoxic spreading depression–like depolarizations.² PIDs are contributors to, rather than simply markers of, ischemic

damage⁸ and hence differ critically from CSD. Thus, these phenomena are of considerable potential relevance to the understanding of common human disease states,⁹ but there is no direct electrophysiological evidence to date that CSD or PIDs occur and propagate in the injured human neocortex. Resolution of this question is critical to understanding the pathophysiology of the acute phases of stroke and head injury in humans.

In this initial study in postoperative neurosurgical patients, we sought ECoG evidence of any depolarization-like events that might occur in human neocortex affected by traumatic or ischemic injury.

Subjects and Methods

Patient Recruitment and Clinical Care

The research monitoring protocol was approved by the local research ethics committee. After a clinical decision had been made that surgery was required, we obtained clinical and research consents. In 14 consecutive patients with traumatic (n=11) or spontaneous (n=1) intracranial hematomas or with intracranial aneurysms requiring

Received August 20, 2002; final revision received September 16, 2002; accepted September 24, 2002.

From the Departments of Neurosurgery (A.J.S., S.J.H., S.E.H., R.J.) and Chemistry (M.G.B., S.E.H., M.C.P.), King's College London, London, United Kingdom, and Department of Clinical Neurophysiology, Glostrup Hospital, University of Copenhagen, Copenhagen, Denmark (M.F., M.L.).

Correspondence to Anthony J. Strong, DM, Department of Neurosurgery, King's College Hospital, London SE5 9RS, UK. E-mail Anthony.strong@kcl.ac.uk

© 2002 American Heart Association, Inc.

Stroke is available at <http://www.strokeaha.org>

DOI: 10.1161/01.STR.0000043073.69602.09

craniotomy ($n=2$), 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 [Sao₂, 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 may block glial gap junctions,¹⁰ which may contribute to CSD propagation¹¹).

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 coupled, 50-Hz notch filter in operation. Data were digitized (128 Hz per channel) with a CED 1401 analog/digital converter and recorded (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) non-spreading transient depolarizations: a rapidly developing reduction of ECoG amplitude of $\geq 50\%$ 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 $\geq 50\%$, followed by gradual recovery; and (3) possible CSD: sequential onset at 2 adjacent recording sites of a rapidly developing reduction of ECoG amplitude of $\geq 50\%$, 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 Leão¹ 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 Sao₂ that preceded or accompanied ECoG suppression/depolarization events and thus might have caused them.

Summary of Clinical Electrocorticogram Data in 14 Patients

Patient	M/F	Age	Principal Lesion Site	Number of Episodes of ECoG Suppression*			Hours From Injury to First Record	Hours of Observation	ECoG Events per Hour
				Synchronous	Possible Spread	Definite Spread			
1	F	68	L frontotemporal ASDH	1			18	1.3	†
2	F	69	R frontotemporal ASDH	1	2 (3–4)		>72	42.7	0.077
3	M	67	L frontotemporal ASDH	0‡			26	6.8	0.15
4	M	53	R frontotemporal ASDH	2			21	15.4	0.13
5	M	24	L temporal ASDH	9	5	1 (2.2–2.4)	66	41.1	0.36
6	M	22	Bifrontal ASDH	2	3	1 (1.0–5.0)	39	62.7	0.10
7	M	21	Bifrontal ASDH	1			24	19.8	0.05
8	F	65	Middle cerebral artery aneurysm	1			n/a	62.3	0.02
9	F	57	Frontotemporal ASDH		6	4 (1.1–3.4)	19.2	47.1	0.21
10	M	51	ASDH	2			9	54.1	0.04
11	F	57	Hypertensive intracerebral hematoma		7 (0.43–2.1)		25	47.6	0.15
12	M	45	Clipping of aneurysm	0	0	0	4	60	
13	F	68	Frontal traumatic intracerebral hematoma	0‡	0	0	24	59.7	
14	M	65	Frontotemporal traumatic intracerebral hematoma	0‡	0	0	49	49.1	

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).

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, Leão¹ 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”¹⁵), which is well illustrated in a recent report of an experimental model of focal cerebral ischemia.¹⁶ (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.¹

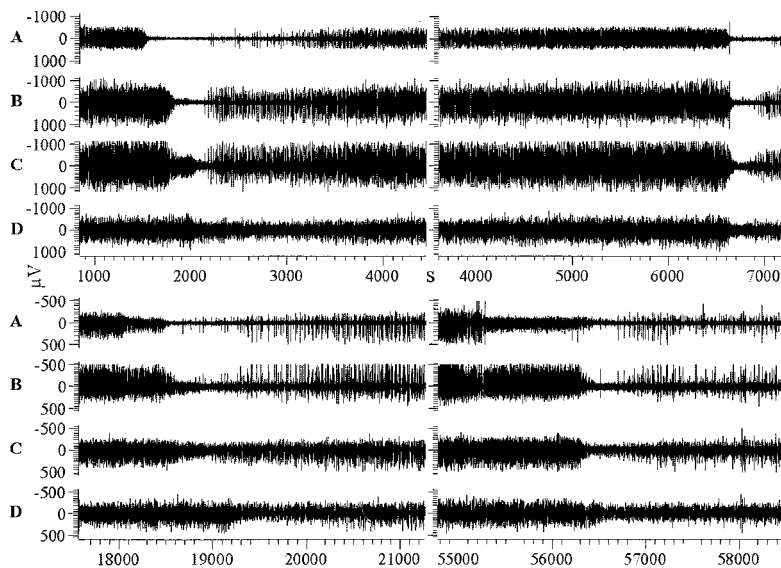


Figure 1. Time-compressed ECoG tracings from patients 5 (top) and 6 (bottom). Channel A was the differential signal between electrodes 6 and 5, channel B between numbers 5 and 4, etc. Electrode centers were 1 cm apart. Baseline ECoG showed 0.5- to 3-Hz delta activity (amplitude 500 to 2000 μ V). Several periods of depressed ECoG activity (approximately 80% reduction of amplitude) evolved over 10 to 30 seconds and lasted for 6 to 20 minutes. Patient 5: Left middle temporal gyrus recording after evacuation of a traumatic intracerebral hematoma through a small cortical incision adjacent to electrode 6. Top left, Channel A amplitude was markedly reduced at 1530 seconds followed by a similar change in channel B and moderate change in channel C at 1780 seconds and finally a further reduction in channel C and a minor change in channel D at 2040 seconds. This corresponds to depression of cortical activity at electrodes 5, 4, and 3 at the respective time points, indicating propagation at a rate of 2.4 and 2.3 mm/min. Activity recovered slowly in channel A closest to the lesion, while channels B and C recovered after 6 minutes. This indicates spread of a wave of cortical depression along the electrode

array at a rate and recovery time comparable with that described by Leão. Top right, One hour later, at end of sample, a similar event occurred, but simultaneously in all channels. No change in cerebral perfusion pressure or arterial oxygenation occurred at this point. The interpretation of synchronous changes is discussed in the text. Patient 6: Right frontal recording on viable cortex next to evacuation site of an intracerebral traumatic hematoma. ECoG amplitude was remarkably stable outside the described episodes. Bottom left, Channel A amplitude became moderately reduced at 18 050 seconds, followed by a marked reduction synchronously with channel B at 18 470 seconds, a moderate reduction in channel C at 18 590 seconds, and a subtle reduction in channel D at 19 200 seconds. This suggests a depression of cortical activity at electrodes 6, 5, 4, and 3 at the respective time points corresponding to rates of propagation of 1.4, 5.0, and 1.0 mm/min. Bottom right, At 9.4 hours later a long-lasting depression of the ECoG commenced in channel A at 55 280 seconds, followed by a synchronous depression in the other channels 18 minutes later.

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

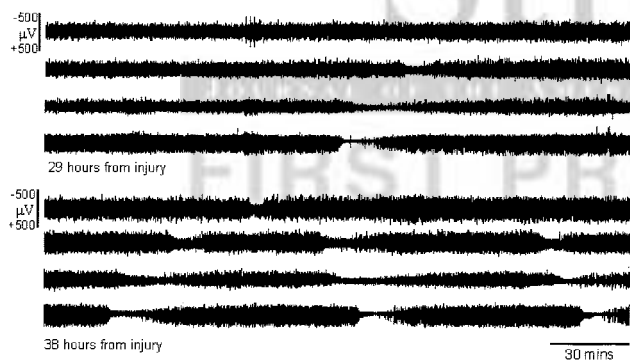


Figure 2. ECoG tracing from patient 9 (traumatic hematoma), showing multiple episodes of ECoG suppression, propagating in either direction with reference to the recording strip. Recordings commenced 19 hours after injury and continued for 47 hours: 10 events occurred, of which 4 met the criteria for definite spread; the others indicated possible spread. Speed of spread ranged from 0.6 to 3.4 mm/min, and duration of depression ranged from 7.7 to 19 minutes. The time interval between events ranged from 53 to 102 minutes. In the lower panel, the first episode spreads in one direction (upward in channel tracings) and appears to reverse direction in the region of the electrode pair recorded in the uppermost tracing. Elliptical or circular propagation of the event in the region of the electrodes is another possible interpretation, similar to the behavior of PIDs in ischemic rat cortex.²⁹

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 studies¹⁷⁻²¹ have sug-

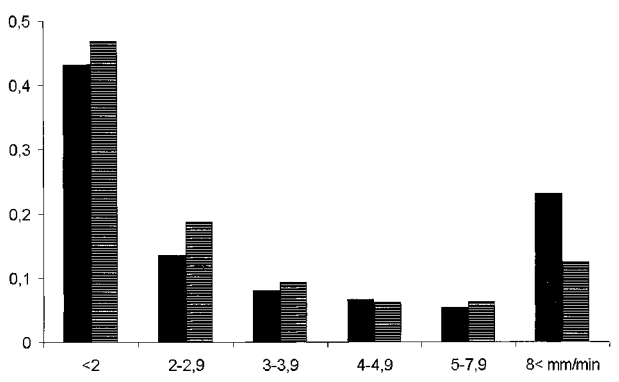


Figure 3. Solid bars show distribution of apparent velocities of spreading depressions of cortical activity. Data from all events showing possible and definite spread as well as all synchronous events in 5 patients are included. The synchronous events are represented in the $8 < (\geq 8)$ column because a direction of spread running almost perpendicular to the electrode array will make the event appear synchronous in the recording. Data are normalized first within each patient, then between patients, to correct for variation between patients in number of events. Hatched bars show theoretical distribution of apparent velocities, when a wavefront passes by 2 electrodes at a random angle between 0 and 89 degrees and at a true linear velocity of 1.5 mm/min. The concordance between observed and predicted histograms in the range < 8 mm/min supports the hypothesis that our “possibly spreading” episodes are indeed instances of actual spread. The observed $8 < (\geq 8)$ column is somewhat larger than that derived through theoretical calculation, which may indicate that both truly synchronous events as well as events spreading across the electrode array are included.

gested the possibility that spontaneous depolarizations might occur in the human cerebral cortex, and a recent review adds to this speculation (without identifying new definitive evidence).²² However, McLachlan and Girvin²³ failed to elicit CSD by electric stimulation of epileptogenic cerebral cortex in humans before its therapeutic excision.

The only evidence suggesting the occurrence of CSD-like events in the human brain after trauma is from Mayevsky et al,²⁴ 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 findings from Mayevsky and colleagues to their use of a standard recording site, which was most probably not in the perilesional region in most patients. The positive results we are able to report here required (1) planned location of an ECoG recording system in a boundary zone verified by direct vision to lie adjacent to a focal lesion, with (2) a sufficiently extended period of observation and (3) a concerted and specific effort to detect (or reliably exclude) the phenomenon.

Significance

What are the implications of these findings for our understanding of brain injury as it evolves in humans, and how will treatment strategies be influenced? The essential finding reported here is that periods of ECoG suppression strongly suggestive of depolarizations do indeed occur in the injured human neocortex and perhaps in adjacent normal cortex, thus

answering a question that has been the subject of much speculation in the context of both severe head injury and ischemic stroke. Our results also indicate clearly that the large volume of experimental studies of CSD and PIDs is indeed relevant to human disease states. The data also suggest that CSD-like events are considerably more frequent in the injured human brain than previously suggested.²⁴ The high proportion of trauma patients in whom ECoG suppressions were observed also suggests that CSD-like events may occur in other acute conditions, notably ischemic stroke, as well as subarachnoid and perhaps intracerebral hemorrhage.

Earlier, we distinguished between protection with experimentally induced CSD against subsequent ischemia, an apparently beneficial effect, and the adverse effects of PIDs (which promote infarct expansion⁸). It thus becomes important in clinical management of brain injury to distinguish between CSD and PIDs. The critical features required of a normal CSD response that might make it beneficial are transient hyperemia and tissue hyperoxia (accessible to monitoring in patients when appropriate by laser Doppler and by oxygen electrodes²⁵ or perhaps by thermal diffusion probes²⁶). Conversely, reductions in the hyperemic response and in tissue PO_2 occur in association with PIDs.²⁵

Much work will now be required to confirm and extend these observations, to validate noninvasive methods for detection of CSD/PIDs (MR diffusion-weighted imaging,²⁷ but with longer sampling sessions, and near-infrared spectroscopy²⁸), and to determine the frequency, metabolic features, and extent of propagation of these events in the acutely injured human brain and the factors, perhaps genetic as well as metabolic or hemodynamic, that determine their frequency. Comparison of the results with outcome may allow us to determine whether any, some, or all depolarization events influence, rather than simply record, the evolution of an important group of conditions whose outcome is often serious, not easily predicted, and difficult to alter favorably.

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 Leão's spreading depression. (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.

Acknowledgments

This study was supported by the Wellcome Trust (S.J.H., S.E.H.), HeadFirst, National Lottery Charities Board (Community Fund), EPSRC (M.C.P.), Royal Society, and King's College London. Special thanks are due to the highly skilled anesthetic and nursing staff of the King's College Hospital Intensive Care Unit for their unflinching support and cooperation. We are grateful to Dr Sue Robertson, PhD, for her careful review of the original manuscript.

References

1. Leão AAP. Spreading depression of activity in cerebral cortex. *J Neurophysiol.* 1944;7:359–390.
2. Somjen GG. Mechanisms of spreading depression and hypoxic spreading depression-like depolarization. *Physiol Rev.* 2001;81:1065–1096.
3. Lauritzen M, Jorgensen MB, Diemer NH, Gjedde A, Hansen AJ. Persistent oligemia of rat cerebral cortex in the wake of spreading depression. *Ann Neurol.* 1982;12:469–474.
4. Nedergaard M, Hansen AJ. Spreading depression is not associated with neuronal injury in the normal brain. *Brain Res.* 1988;449:395–398.
5. Kobayashi S, Harris VA, Welsh FA. Spreading depression induces tolerance of cortical neurons to ischemia in rat brain. *J Cereb Blood Flow Metab.* 1995;15:721–727.
6. Matsushima K, Schmidt-Kastner R, Hogan MJ, Hakim AM. Cortical spreading depression activates trophic factor expression in neurons and astrocytes and protects against subsequent focal brain ischemia. *Brain Res.* 1998;807:47–60.
7. Hossmann KA. Perinfarct depolarizations. *Cerebrovasc Brain Metab Rev.* 1996;8:195–208.
8. Busch E, Gyngell ML, Eis M, Hoehn Berlage M, Hossmann KA. Potassium-induced cortical spreading depressions during focal cerebral ischemia in rats: contribution to lesion growth assessed by diffusion-weighted NMR and biochemical imaging. *J Cereb Blood Flow Metab.* 1996;16:1090–1099.
9. Hansen AJ, Lauritzen M. The role of spreading depression in acute brain disorders. *An Acad Bras Cienc.* 1984;56:457–479.
10. Mantz J, Cordier J, Giaume C. Effects of general anesthetics on intercellular communications mediated by gap junctions between astrocytes in primary culture. *Anesthesiology.* 1993;78:892–901.
11. Nedergaard M, Cooper AJ, Goldman SA. Gap junctions are required for the propagation of spreading depression. *J Neurobiol.* 1995;28:433–444.
12. Cooper R, Crow HJ. Toxic effects of intracerebral electrodes. *Med Biol Eng Comput.* 1966;4:575–581.
13. Strong AJ, Harland SP, Meldrum BS, Whittington DJ. The use of in vivo fluorescence image sequences to indicate the occurrence and propagation of transient focal depolarizations in cerebral ischemia. *J Cereb Blood Flow Metab.* 1996;16:367–377.
14. Bowyer SM, Tepley N, Papuashvili N, Kato S, Barkley GL, Welch KM, Okada YC. Analysis of MEG signals of spreading cortical depression with propagation constrained to a rectangular cortical strip, II: gyrencephalic swine model. *Brain Res.* 1999;843:79–86.
15. Astrup J, Siesjö BK, Symon L. Thresholds in cerebral ischemia: the ischemic penumbra. *Stroke.* 1981;12:723–725.
16. Ohta K, Graf R, Rosner G, Heiss WD. Calcium ion transients in peri-infarct depolarizations may deteriorate ion homeostasis and expand infarction in focal cerebral ischemia in cats. *Stroke.* 2001;32:535–543.
17. Sramka M, Brozek G, Bures J, Nadvornik P. Functional ablation by spreading depression: possible use in human stereotactic neurosurgery. *Appl Neurophysiol.* 1977;40:48–61.
18. Lauritzen M, Skyhoj OT, Lassen NA, Paulson OB. Changes in regional cerebral blood flow during the course of classic migraine attacks. *Ann Neurol.* 1983;13:633–641.
19. Lauritzen M, Olesen J. Regional cerebral blood flow during migraine attacks by Xenon-133 inhalation and emission tomography. *Brain.* 1984;107:447–461.
20. Hadjikhani N, Sanchez DR, Wu O, Schwartz D, Bakker D, Fischl B, Kwong KK, Cutrer FM, Rosen BR, Tootell RB, Sorensen AG, Moskowitz MA. Mechanisms of migraine aura revealed by functional MRI in human visual cortex. *Proc Natl Acad Sci U S A.* 2001;98:4687–4692.
21. Gorji A, Scheller D, Straub H, Tegtmeier F, Kohling R, Hohling JM, Tuxhorn I, Ebner A, Wolf P, Werner Panneck H, Opiel F, Speckmann EJ. Spreading depression in human neocortical slices. *Brain Res.* 2001;906:74–83.
22. Gorji A. Spreading depression: a review of the clinical relevance. *Brain Res Rev.* 2001;38:33–60.
23. McLachlan RS, Girvin JP. Spreading depression of Leao in rodent and human cortex. *Brain Res.* 1994;666:133–136.
24. Mayevsky A, Doron A, Manor T, Meilin S, Zarchin N, Ouaknine GE. Cortical spreading depression recorded from the human brain using a multiparametric monitoring system. *Brain Res.* 1996;740:268–274.
25. Back T, Kohn K, Hossmann KA. Cortical negative DC deflections following middle cerebral artery occlusion and KCl-induced spreading depression: effect on blood flow, tissue oxygenation, and electroencephalogram. *J Cereb Blood Flow Metab.* 1994;14:12–19.
26. Vajkoczy P, Roth H, Horn P, Lucke T, Thome C, Hubner U, Martin GT, Zapletal C, Klar E, Schilling L, Schmiedek P. Continuous monitoring of regional cerebral blood flow: experimental and clinical validation of a novel thermal diffusion microprobe. *J Neurosurg.* 2000;93:265–274.
27. Back T, Hirsch JG, Szabo K, Gass A. Failure to demonstrate peri-infarct depolarizations by repetitive MR diffusion imaging in acute human stroke. *Stroke.* 2000;31:2901–2906.
28. Dirnagl U, Obrig H, von Pannwitz W, Kohl M, Kerskens CM, Doge C, Lindauer U, Wolf T, Villringer A. Cerebral blood flow, hemoglobin oxygenation, and water diffusion changes during stroke: fingerprinting with near-infrared spectroscopy and MRI. In: Fukuuchi, Y, Tomita M, Koto A, eds. *Keio University Symposia for Life Science and Medicine: Ischemic Blood Flow in the Brain.* Vol 6. Tokyo, Japan: Springer; 2001: 232–240.
29. Higuchi T, Takeda Y, Hashimoto M, Nagano O, Hirakawa M. Dynamic changes in cortical NADH fluorescence and direct current potential in rat focal ischemia: relationship between propagation of recurrent depolarization and growth of the ischemic core. *J Cereb Blood Flow Metab.* 2002;22:71–79.

JOURNAL OF THE AMERICAN HEART ASSOCIATION
 FIRST PROOF ONLY