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14. ABSTRACT

This report describes year 2 progress of a multi-center study of neurosurgical TBI patients to determine the effects of spreading depression (SD) on neurologic outcome. In this year, we have initiated our final study site and have enrolled 41 patients, bringing the study total to 61. Electrocorticographic (ECoG) recordings were made in patients for an average duration of 70 hours during intensive care, and 6 month clinical outcomes were assessed. Using admission risk factors as covariates, we have found a highly significant independent association of SD with poor outcome. Combining ECoG with microdialysis, we also found that SD is associated with excitotoxicity (elevated glutamate) and metabolic crisis (elevated lactate/pyruvate). Finally, analysis of direct current ECoG potentials showed that a signficant subset of SD have prolonged durations, which is direct evidence of a harmful effect. These results suggests the study goals will be achieved and that SD should be targeted therapeutically in a future interventional trial.

15. SUBJECT TERMS
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I. INTRODUCTION

Severe TBI often results in delayed complications and deterioration of a patient‟s condition after initial stabilization. This secondary injury is life-threatening and a principal cause of permanent disabilities. *Spreading depressions* (SD) are waves of mass neuronal/astrocytic depolarization that actively propagate a breakdown of ion homeostasis and perturbations of blood flow through injured, but potentially salvageable brain tissue. A large body of pre-clinical research has shown that SD causes expansion of ischemic brain lesions and may be similarly detrimental after TBI. In our preliminary studies using electrocorticography (ECoG) to measure SD in human TBI, we have found that SD occurs in an alarming 58% of patients (18 of 31). *The objective of this study is to determine whether SDs cause secondary injury after TBI, and therefore represent an acute target for treatment to improve recovery.* The Specific Aims of the study are to determine the extent to which spreading depressions are correlated with worse neurologic outcome (6 mo. GOS-E), cerebral metabolism, and secondary physiologic insults (hypotension, high intracranial pressure, and fever).

These aims will be achieved with a prospective, observational clinical study design. Approximately 180 total patients undergoing neurosurgery for treatment of TBI will be enrolled. Subdural electrode strips will be placed during surgery and ECoG recordings will be made for at least 72 hr to measure SD events. Clinical outcome will be assessed at six months according to the extended Glasgow Outcome Scale (GOS-E). Metrics of SD activity will be assessed for their relationship with the GOS-E using a proportional odds model. This regression analysis will include standard co-variates to control for the effects of known factors that independently influence outcome, such as age, GCS score at admission, CT classification, and pupil reactivity. Physiologic variables will be acquired in co-registration with ECoG data. Relationships of SD activity with these measures will be assessed by correlations and comparisons of means and proportions.

The following abbreviations for the study sites are used throughout this report:

University of Pittsburgh	PIT
University of Miami	MIA
Virginia Commonwealth University	VCU
King‟s College Hospital	KCH
University of Cincinnati Coordinating Center	UCCC

II. BODY

OVERVIEW

In the first year, all study materials were developed, site initiation visits were conducted, and ethical approvals were obtained, so that enrollment was opened at 4 of 5 study sites. In this reporting period, a site visit was conducted at the 5th site (KCH), which obtained all ethical approvals and also opened for enrollment.

The following Table 1 summarizes progress toward enrollment at each site with patient recruitment numbers for Y1 and Y2. The main effort of Y2 was recruitment of patients, entry of clinical study data, and analysis of study data. This report elaborates on specific details of study progress and results, concluding with a summary table of progress on task/milestone completion.

Table 1. Summary of patient enrollment and progress to study inception

	UCCC	MIA	PIT	VCU	KCH
IRB submission	X	X	X	X	X
IRB approval	X	X	X	X	X
Contract signed	X	X	X	X	X
Regulatory documents filed (100%)	X	X	X	X	X
Equipment installed	X	X	X	X	X
Site Initiation Visit	X	Apr 8-9 09	Apr 29-30 09	Mar 18-19 09	Oct 1-2 09
Enrollment open	12 Jan 09	3 May 09	3 May 09	1 Apr 09	5 Oct 09
Patients enrolled Y1	6	4	8	2	-
Patients enrolled Y2	4	6	17	6	8

„X" denotes task completion.

PATIENT ENROLLMENT

Table 2 below shows the expected time course of patient enrollment to reach the study goal of 180 patients. The bottom half shows actual enrollment rates. Actual enrollment in Y2 was 41 patients, which is 63% of the expected enrollment of 65. Since inception, actual enrollment was 61patients, or 64% of expected enrollment of 95. Projecting forward to the planned closing of enrollment after Q2 2012, we would achieve total enrollment of 115 (0.64 x 180) patients if this trend continues.

This represents a shortfall of 65 patients. To address this, we considered adding additional study sites but have decided not to pursue this option. The addition of a 6th study site or more would increase the regulatory, management, and monitoring burden of UCCC beyond its capacity and beyond the provisions of the budget. In addition, the technical procedures of the study are complex and uncommon to TBI studies. They require significant effort in personnel training, supervision, and quality control. Based on initial experience in coordinating 5 centers, it is judged best to focus on the current vested sites to obtain the best quality data and build on their experience.

In the PI‟s judgment, the best option for achieving the targeted enrollment is to seek a no cost extension of the study period. At the current enrollment rate, the projected shortfall of 65 patients could be enrolled in 1.2 years, moving the end of enrollment to Q3 2013.

Table 2. Expected and actual enrollment rates.

	Site	Q2 09	Q3 09	Q4 09	Q1 10	Q2 10	Q3 10	Q4 10	Q1 11	Q2 11	Q3 11	Q4 11	Q1 12	Q2 12	Site Total	Total
Expected	UCCC	2	3	4	3	3	3	4	3	3	3	4	3	1	39	
	VCU	0	3	4	3	3	3	4	3	3	3	4	3	1	37	
	MIA	0	2	4	3	3	3	4	3	3	3	4	3	1	36	180
	PIT	0	0	4	3	3	3	4	3	3	3	4	3	1	34	
	KCH	0	0	4	3	3	3	4	3	3	3	4	3	1	34	
Actual	UCCC	2	2	2	3	0	0	1							10	
	VCU	-	1	1	3	1	1	1							8	
	MIA	-	2	2	2	2	1	1							10	61
	PIT	-	-	8	1	5	4	7							25	
	KCH	-	-	-	2	2	2	2							8	

PATIENT CLINICAL DATA

Based on Glasgow Coma Scale scores at hospital admission, 45 patients enrolled were severe TBIs and 6 were moderates (10 not yet reported). The average age was 45 (S.D. 19) and 48/61 were male. Outcome assessments at 6 months post-injury were completed for 47 patients. Of these, 31 had poor outcomes (death, vegetative state, or severe disability) and 16 had good outcomes.

Review of ECoG Recordings

ECoG recordings of 41 have been formally reviewed and scored. The recordings of 4 patients are unusable due to poor quality or technical failures. Of the remaining 37 patients, 17 (46%) have exhibited cortical spreading depression (SD), which is close to the 53% incidence we reported in a previous patient series (J. Neurotrauma 26:1857-66, 2009). The average duration of high-quality ECoG recordings obtained per patient was 70 hr. Eleven patients had recordings more than 4 days in duration.

CLINICAL OUTCOME (*Task #1*)

In Year 1, we reported that SD was associated with clinical outcome (Shutter et al., 2009). In this year, we examined 85 patients, combining patients from the present study with those monitored in our pilot study. Data were examined not only for an association of SD with outcome, but to determine whether SD is an independent predictor of outcome, controlling for the effects of known outcome predictors.

As reported in an abstract and presentation at the meeting of the Society of British Neurological Surgeons (Hartings et al., 2010), we found that *SD was a significant independent predictor of outcome*. In univariate analysis, SD accounted for more variance in outcome than any other single factor, including admission GCS, pupil reactivity, and age (Figure 1). Addition of SD to the established set of predictors accounted for an additional 14% of outcome variance. Results are described in detail in the Appendix abstract.

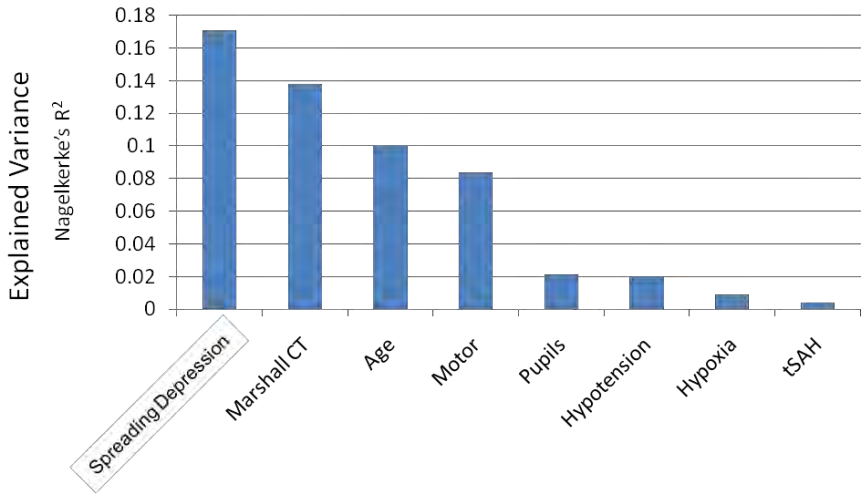

Figure 1. Variance in 6 month neurologic outcome attributable to various predictors based on univariate analysis. Only spreading depression, age, and pupils were significant predictors in multivariate analysis.

CEREBRAL BLOOD FLOW MONITORING (*Task #2*)

As reported in the previous annual report, the study investigators were awarded a grant from CODMAN based on submission of an investigator-initiated study application. CODMAN agreed to make 5 Bowman Perfusion Monitors available to the study sites (1 per site) and to donate 120 Hemedex probes for use in study patients.

The purpose of using this technology is to study the cerebral blood flow response to SD. As we reported previously, the vascular coupling to SD is likely to be an important determinant of SD's effects on the brain and may account for some variability in the electrophysiologic characteristics of SD (e.g. duration of depression period). This is the basis for Task #2.

Unfortunately, in this reporting period little progress was made on this task. This is due to the fact that CODMAN decided to drop the Bowman Perfusion Monitor from their product portfolio. In addition, Hemedex, Inc. has updated the user interface and software on the monitor. These developments have caused a significant delay in delivery of the monitors from Hemedex, Inc. to the study sites.

To date, we have performed Hemedex CBF monitoring in 8 of the study patients at KCH and UCCC. We anticipate that approximately 30 additional patients will be monitored through the remainder of the study as PIT and MIA begin using Hemedex in Year 3.

SPREADING DEPRESSION AND SECONDARY INSULTS *(Task #3)*

We have previously reported that hypotension, low cerebral perfusion pressure, and fever are associated with an increased incidence of SD and have described the dose-response relationships (Hartings et al., 2009a). We continue to collect data on these variables to further elucidate these relationships. The programs we have already written for this data analysis, based on hourly nursing chart documentation of physiologic values, will be used to analyze the larger data set once patient enrollment is complete.

In addition, we are collaborating with Dr. Ian Piper and Brain-IT (www.brainit.org) through COSBID to develop more advanced routines to assess and score the burden of secondary insults (e.g. hypotension, fever, intracranial hypertension) based on collection of continuous, rather than hourly, data.

SUMMARY OF MILESTONE AND TASK COMPLETION

The following Table summarizes study progress according to the SOW tasks/milestones. Milestone completion/progress is denoted by green bars.

TIMETABLE FOR THE RESEARCH PROGRAM		Prior	YR1	YR2	YR3	YR4
Task #1:	Spreading depressions as independent predictors of worse neurologic outcome					
Milestone #1.	***Complete regulatory review and obtain approval for human use protocols***					
Milestone #2.	***Implementation of online database***					
Milestone #3.	***Final protocol briefing by P.I. to each medical center team***					
Milestone #4.	***Patient enrollment and electrocorticography***					
Milestone #5.	***Score ECoG recordings and quantitate SD activity by defined metrics***					
Milestone #6.	***Assessment of neurologic outcomes at 6 months post-TBI***					
Milestone #7.	***Statistical analysis and publication***					
Task #2:	Association of CBF and spreading depression activity					
Milestone #1.	***Patient enrollment: simultaneous ECoG and CBF measures***					
Milestone #2.	***Data analysis and publication***					
Task #3:	Association of spreading depression and secondary physiologic insults					
Milestone #1.	***Patient enrollment: simultaneous ECoG and physiologic parameter monitoring***					
Milestone #2.	***Write custom data processing programs for analysis***					
Milestone #3.	***Data analysis and publication***					

COORDINATION WITH COSBID

12th Meeting: The 12th meeting of the COSBID consortium took place on 6-8 May 2010 in Barcelona, Spain. Drs. Hartings and Wilson attended and made presentations on the topics listed separately below. It was agreed by the COSBID steering committee that the 13th COSBID meeting would be held in July 2011 in Cincinnati, OH as a joint meeting with the Vasospasm conference (www.vasospasm11.com).

Hartings JA, "What are slow potential changes?", COSBID XII (May 6, 2010)
Hartings JA, "Spreading depolarizations as an independent predictor of poor outcome in TBI", COSBID XII (May 7, 2010)
Wilson JA, "Association of spreading depolarizations with excitotoxicity and metabolic crisis in TBI: a clinical microdialysis study", COSBID XII (May 7, 2010)

Publications: In addition to those referenced above, the following studies have been published by the COSBID group, with relevance to the present study as summarized:

Oliveira-Ferreira A, Milakara D, Alam M, Jorks D, Major S, Hartings JA, Lückl J, Martus P, Graf R, Dohmen C, Bohner G, Woitzik J, Dreier JP (2010) Experimental and preliminary clinical evidence of an ischemic zone with prolonged negative DC shifts surrounded by a normally perfused tissue belt with persistent electrocorticographic depression. *Journal of Cerebral Blood Flow and Metabolism*. 30(8):1504-1519.

This study defined the features of ECoG recordings associated with development of new brain lesions in rats. In particular, it showed that persistent depression of the ECoG is not a specific marker of terminal deterioration. The ECoG feature that distinguished brain destined for infarction was prolonged negative shifts of the direct current potential.

Eriksen N, Rostrup E, Andersen K, Lauritzen MJ, Fabricius M, Larsen VA, Dreier JP, Strong AJ, Hartings JA, Pakkenberg B (2010) Application of stereological estimates in patients with severe head injuries using CT and MR scanning images. *British Journal of Radiology.* 83(988):307-317.

This study established the feasibility of using quantitative assessment to measure the extent and progression of brain injury in computed tomographic brain scans.

Bosche B, Graf R, Ernestus RI, Dohmen C, Reithmeier T, Brinker G, Strong AJ, Dreier JP, Woitzik J; Members of the Cooperative Study of Brain Injury Depolarizations (COSBID) (2010) Recurrent spreading depolarizations after subarachnoid hemorrhage decreases oxygen availability in human cerebral cortex. *Annals of Neurology*. 67(5):607-617.

This study demonstrated that intraparenchymal measurement of brain oxygenation alongside an electrode strip is capable of capturing metabolic changes related to recordings of SD. In particular, it showed that some SD are coupled to increases in brain oxygenation, while others cause its depletion. The effects of SD on brain oxygen are related to neurovascular coupling and cortical spreading ischemia.

Nakamura H, Strong AJ, Dohmen C, Sakowitz OW, Vollmar S, Sué M, Kracht L, Hashemi P, Bhatia R, Yoshimine T, Dreier JP, Dunn AK, Graf R (2010) Spreading depolarizations cycle around and enlarge focal ischaemic brain lesions. *Brain*. 133(Pt 7):1994-2006.

This studied established a plausible explanation for the repeated occurrence of SD in patients at regular intervals. The authors found that SD can cycle around a cortical lesion, with the interval determined by the propagation velocity and circumference of the lesion. This periodicity is frequently observed in the present study patients, and similar mechanisms may be involved.

III. KEY RESEARCH ACCOMPLISHMENTS

● We have demonstrated that SD is a significant predictor of worse outcome, independent of known predictors for poor outcome at hospital admission. The role of secondary insults following admission also needs to be taken into account (see Appendix abstract).

● We have found that SD is associated with excitotoxicity and metabolic crisis. In 18 patients with cerebral microdialysis and ECoG monitoring, elevated glutamate and lactate values were more likely to occur in the ~50% of TBI patients who develop SD. In these patients, SD is more likely to occur when glutamate, lactate, and LPR are high; conversely, these values are higher when SD occurs. These results suggest a vicious cycle in which metabolic crisis and elevated glutamate trigger CSD, which in turn increases metabolic demand and failure with further excitotoxic damage (see Appendix abstract).

● Previously we developed a signal processing method to recover full-band DC waveforms from the raw, frequency-limited clinical ECoG recordings (Hartings et al., 2009b). We have now applied this method to directly assess the duration of cortical tissue depolarization associated with individual SD events. We have found that a significant proportion of SD events have pathologically prolonged durations, suggesting that they cause tissue damage. Specifically, we found that prolonged depolarizations are associated with 1) long duration depression periods, 2) lack of cortical spontaneous activity, 3) short intervals between depolarizations (see Appendix abstract).

● We analyzed pathologic features of admission CT scans in relation to the occurrence of SD and found a significant association between the degree of traumatic subarachnoid hemorrhage (tSAH) and SD. There was a progressive increase in SD incidence with Morris-Marshall tSAH grades [grade 0: 22%, grade 1-3: 45%, grade 4: 80%]. There was no association of SD with contusions, intraparenchymal or subdural hemorrhage, midline shift, or status of basal cisterns. These results show that TBI pathophysiology is diverse and varies according to features easily identified by CT, which could be used to select patients for targeted clinical trials (see Appendix abstract).

IV. REPORTABLE OUTCOMES

Manuscripts in press:

Lauritzen M, Dreier JP, Fabricius M, Hartings JA, Graf R, Strong AJ. Clinical relevance of cortical spreading depression in neurological disorders: migraine, malignant stroke, subarachnoid and intracranial hemorrhage, and traumatic brain injury. Submitted to *Journal of Cerebral Blood Flow and Metabolism*.

Abstracts and Conference Presentations:

Hartings JA, Roozenbeek R, Fabricius M, Bullock MR, Okonkwo D, Mathern B, Bhatia R, Manning A, Vidgeon S, Woitzik J, Shutter L, Maas AIR, Strong AJ (2010) First evidence for an independent relationship of cortical depolarisations with adverse outcome in patients with traumatic brain injury. Society of British Neurological Surgeons Conference.

Wilson JA, Shutter L, Hartings JA (2010) A system for real-time multimodal data integration and decision support during neurologic ICU monitoring. Tomographic Physiologic Imaging and Multimodal Monitoring.

*Wilson JA, Bullock MR, Hartings JA (2010) Association of spreading depolarizations with excitotoxicity and metabolic crisis in TBI: a clinical microdialysis study. Journal of Neurotrauma 27(5): A-4.

Losiniecki AJ, Okonkwo DO, Shutter LA, Bullock MR, Strong AJ, Mathern B, Puccio A, Vidgeon S, Pahl C, Hartings JA (2010) Computed tomographic pathologies associated with cortical dysfunction after traumatic brain injury requiring surgery. Journal of Neurotrauma 27(5): A-87.

Hartings JA, Fabricius M, Dreier JP, Woitzik J, Okonkwo DO, Puccio A, Bullock MR, Strong AJ, Watanabe T (2010) Prolonged durations evidence adverse effects of spreading depolarizations in human brain trauma. Journal of Neurotrauma 27(5): A-11.

*Selected for best student abstract

Seminars at National Meetings:

Hartings JA, "Neurophysiology: spreading depression", Tomographic Physiologic Imaging and Multimodal Monitoring (August 27, 2010, Santa Fe, NM)

Hartings JA, “Neurophysiology of acute brain injury: seizures, periodic patterns, and cortical spreading depression”, American Clinical Neurophysiology Society (Feb 2010, San Diego, CA)

Hartings JA, “Secondary brain damage from non-convulsive seizures and spreading depolarizations: evidence from animals and humans”, American Epilepsy Society (Dec 2009, Boston, MA)

Funding Applications Based on Work Supported by This Award:

None

V. CONCLUSION

Here we have reported continuing progress in a challenging emergency medicine study involving the use of invasive monitoring of patients with moderate-to-severe TBI. In this year, we have initiated our final study site and have enrolled 41 patients, bringing the study total to 61. Importantly, a large volume of clinical data is being collected from these patients, including patient outcome, in our electronic case report form (eCRF) database. ECoG data quality is excellent, and patients Thusfar show a 46% incidence of SD.

Most critically, we have completed an initial assessment of the independent association of SD with clinical outcome. Using admission risk factors as covariates, we have found a highly significant and surprising association of SD with poor outcome based on a relatively small number of patients. As the most important aim of the study, this result is highly encouraging and strongly suggests that the goals of the study will be met, and perhaps with fewer patients than initially planned. Furthermore, it must be emphasized that demonstration of an independent association with outcome is the strongest possible evidence that can be provided for a candidate pathology, and represents the gold standard in clinical science. While our results are encouraging, they must be subjected to peer review and independent statistical analysis. It will also be important to incorporate measures of other secondary insults as covariates in our analysis, since presently only hospital admission factors are used, while SD is measured during intensive care.

A second critical question is whether all SDs are harmful, or only a subset? In our multivariate analysis, we found that PIDs, a putatively more pathologic form of SD, were associated with worse outcome than other SDs. However, division of depolarizations into SD and PID subtypes is somewhat simplistic, and further understanding of depolarization variants and the best methods to quantify and distinguish them is needed. We have made significant progress in this regard by analyzing DC potentials and their relationship to spontaneous ECoG activity, and also by analysis of microdialysis data.

Overall, data suggest that therapeutic blockade of SD/PID may be an effective strategy to improve recovery from TBI, and point toward the need for a future interventional trial. For planning of such a trial, it finally must be determined whether other important medical or pathophysiologic factors influence SD/PID occurrence. This question must be answered to optimally design an interventional trial (controls, inclusion/exclusion, protocol standardization, and treatments). It will also provide important insight into the pathophysiology of TBI and which courses of current medical management are most effective, as evidenced by this novel ECoG monitoring of evolving cerebral pathology. The current observational study will address these questions.

VI. REFERENCES

[a]Hartings JA, Strong AJ, Fabricius M, Manning A, Bhatia R, Dreier JP, Mazzeo AT, Tortella FC, Bullock MR. **Spreading depolarizations and late secondary insults after traumatic brain injury**. *Journal of Neurotrauma*. 26(11):1857-1866, 2009.

[b]Hartings JA, Watanabe T, Dreier JP, Major S, Fabricius M. **Recovery of slow potentials in AC-coupled electrocorticography by digital inverse filtering: application to spreading depolarizations in rat and human cerebral cortex**. *Journal of Neurophysiology*. 102(4):2563-2575, 2009.

Hartings JA, Roozenbeek R, Fabricius M, Bullock MR, Okonkwo D, Mathern B, Bhatia R, Manning A, Vidgeon S, Woitzik J, Shutter L, Maas AIR, Strong AJ. **First evidence for an independent relationship of cortical depolarisations with adverse outcome in patients with traumatic brain injury.** *Society of British Neurological Surgeons Conference*, 2010.

Shutter L, Strong AJ, Fabricius M, Bullock MR, Okonkwo D, Sakowitz O, Woitzik J, Hartings JA. **Association of spreading depolarizations with poor outcome after traumatic brain injury: results from a pilot study**. *Neurocritical Care* 11:S55, 2009.

VII. APPENDICES

Appendix 1	Hartings et al., British Soc. Neurol. Surgeons abstract
Appendix 2	Hartings et al., National Neurotrauma Soc. abstract
Appendix 3	Wilson et al., National Neurotrauma Soc. abstract
Appendix 4	Losiniecki et al., National Neurotrauma Soc. abstract

First evidence for an independent relationship of cortical depolarisations with adverse outcome in patients with traumatic brain injury

Authors: J.A.Hartings, R.Roosenbeek, M.Fabricius, M.R.Bullock, D.Okonkwo B.Mathern, R.Bhatia, A.Manning, S.Vidgeon, J. Woitzik, L. Shutter, A.I.R.Maas, A.J.Strong

Objective:
To determine whether spontaneous cortical spreading depolarisation (CSD) events in patients with head injury are associated with adverse outcome, independent of recognised risk factors

Design: Prospective, multicentre observational study in patients receiving intensive care following craniotomy for craniocerebral trauma.

Subjects: 64 patients with acute traumatic subdural haematoma and/or parenchymal contusion with mass effect requiring craniotomy

Methods: Prospective collection of IMPACT[1] risk factors for adverse outcome; insertion of 6-contact subdural electrode strip (Ad-Tech) at conclusion of craniotomy; continuous recording of wide band electrocorticogram (ECoG) and analysis for type of depolarization event [none (0), or CSD with (1) or without (2) recovery of spontaneous activity][2]; extended Glasgow Outcome Scale (eGOS)[3] at 6 months dichotomized to Poor (1-4) or Good (5-8); uni- and multi-variate logistic regression analysis of eGOS versus depolarisations and IMPACT risk factors.

Results: Nagelkerke's r^2*100 in multivariate regression, representing the % variance in outcome attributable to an input variable set, were as follows: IMPACT Core (Age, motor score, pupils): 29%; IMPACT Extended (Core + Marshall CT, tSAH, hypoxia, hypotension): 43%. IMPACT Extended + depolarisations: 57%. Age, pupils, and depolarizations were the only significant predictors in the full model, and of these, depolarizations had the largest r^2*100 in univariate analysis (17%).

Conclusions: Subject to independent statistical analysis, the data from this highly selected study group suggest that depolarisations in the severely injured human cerebral cortex are linked with a powerful adverse effect on outcome, independent of known admission risk factors. The role of secondary insults following admission also needs to be taken into account.

References:
1. Murray G. et al. J Neurotrauma 24(2): 329-37,2007

2 Strong A.J. et al:. Stroke. 2002 Dec;33(12):2738-43.

3. Wilson J.T. et al J Neurotrauma. 1998 Aug;15(8):573-85.

Prolonged durations evidence adverse effects of spreading depolarizations in human brain trauma

Jed A. Hartings, Martin Fabricius, Jens P. Dreier, Johannes Woitzik, David O. Okonkwo, Ava Puccio, M. Ross Bullock, Anthony J. Strong, and Tomas Watanabe

INTRODUCTION: Spreading depression (SD) is a pathologic wave of cortical depolarization which, when provoked experimentally in healthy animals, causes no histologic damage. By contrast, peri-infarct depolarization (PID), a variant of spreading depression occurring spontaneously in ischemic stroke, causes progressive penumbral infarction. PID is distinguished from benign SD by a prolonged duration of depolarization, measured by the extracellular DC potential. Forms of these cortical spreading depolarizations (CSD) occur in some 50% of patients with moderate-severe traumatic brain injury (TBI), but their pathogenicity remains a subject of investigation. Here we analyzed the DC potentials of CSD in TBI patients to investigate direct evidence of prolonged DC shifts analogous to PIDs in ischemic stroke. **METHODS:** In 53 TBI patients requiring neurosurgery, a subdural electrode strip was placed intraoperatively for subsequent electrocorticographic (ECoG) monitoring during neurocritical care (median duration: 71 hr). Analysis of AC-coupled ECoG recordings according to previous criteria (Fabricius et al., 2006) revealed that 30/53 (57%) patients had CSD. Ten of these (10/53, 19%) had CSD with features suggestive of PIDs (i.e. an isoelectric/silent background) and were selected for analysis. Recordings were processed off-line with a digital inverse filter to recover frequencies down to 2 mHz and reconstruct DC 'full-band' traces (Hartings et al., 2009). **RESULTS:** The durations of all 295 DC shifts of CSD in 10 patients differed significantly from a Gaussian distribution, with a positive skew reflecting longer values up to 16 min. By truncating the skew, a Gaussian fit was deciphered (mean, 2 min 5 sec; SD, 0:27) and was interpreted as the sample of typical SD. Using the 95% cutoff of this distribution (3:01) as a threshold for distinguishing two populations, 220/295 (75%) DC shifts were typical SDs and 75/295 (25%) had more prolonged durations. DC shifts occurring during silent periods of ECoG were signficantly longer [median (quartiles), 2:36 (2:07, 3:24)] than those associated with baseline activity and subsequent ECoG depression [2:10 (1:50, 2:47); M-W, $p<0.001$]. However, typical short DC shifts often occurred during ECoG silence and, conversely, prolonged DC shifts often occurred with spontaneous baseline ECoG present. The durations of ECoG depression periods were significantly correlated with the DC shift duration ($R^2=0.54$, $p<0.001$). **CONCLUSIONS:** Results demonstrate that a subset of CSDs in human TBI have prolonged DC shift durations. Resembling PIDs in ischemic stroke, these are the most pathogenic and should be prevented. Since online DC recordings are difficult, the duration of tissue depolarization can be generally inferred based on the presence/absence of baseline ECoG activity and the duration of ECoG depression periods during CSD. **REFERENCES:** Fabricius M et al: Brain 129:778-798, 2006. Hartings JA et al: J Neurophysiol 102:2563-75, 2009.

Association of spreading depolarizations with excitotoxicity and metabolic crisis in TBI: a clinical microdialysis study

J. Adam Wilson, M. Ross Bullock, and Jed A. Hartings

INTRODUCTION: Microdialysis (MD) is an important clinical research tool in severe traumatic brain injury (TBI), having demonstrated an early excitotoxic glutamate surge and, more recently, a prevalence of persistent metabolic crisis. However, glutamate receptor antagonists have failed in clinical trials and MD evidence of metabolic crisis is usually unexplained by perfusion deficits or seizures. Thus, multimodal studies are needed to better understand the pathophysiology of MD trends and develop effective therapeutic countermeasures. Here we combined MD with electrocorticographic (ECoG) monitoring of cortical spreading depolarizations (CSD, or spreading depression). **METHODS:** In 18 adult TBI patients requiring neurosurgery, an electrode strip was placed on the surface of the cortex in the region of the primary injury and a MD catheter (CMA 20, 10-mm membrane length) was placed in the parenchyma within 1-2 cm alongside the electrode strip. Patients were then monitored during intensive care for 3.6 ±1.2 days. MD samples were collected hourly and analyzed on a CMA 600 Microdialysis Analyzer. Ranges for abnormal MD values were defined as: glutamate >5 μmol, glucose <200 μmol, pyruvate < 25μmol, lactate >2000 μmol, lactate/pyruvate ratio (LPR) >40. **RESULTS:** In 8/18 patients (44%), a total of 151 CSDs was observed. Patients with CSDs had significantly higher percentages of abnormal glutamate (41%) and lactate (21%) values compared to those without CSD (33% and 4.6%, resp.; χ^2, p <0.001). There was no significant difference in abnormal glucose (21% vs. 24%) or LPR (30% vs. 31%). In patients with CSD, events occurred disproportionately in association with abnormal glutamate, lactate, and LPR values (χ^2, p's <0.001). For instance, although only 41% of glutamate values were >5 μmol, 77% of CSDs occurred in this range. Similarly, 30% of LPR values were abnormal but accounted for 60.1% of CSD occurrence. Abnormal glucose and pyruvate values were not associated with higher CSD incidence. Accordingly, glutamate, lactate, and LPR values measured during a CSD event (N=80) were significantly higher (M-W *U*-test, p <0.01) than values measured when no CSD had occurred within ±90 min (N=451); glucose was significantly lower and pyruvate showed no difference (p=0.54). The daily percentages of abnormal MD values were highly correlated with the daily frequency of CSD events (r's >0.69, p's <0.02); both had a bimodal trend with peaks on days 1-3 and 6-8. **CONCLUSION:** Elevated glutamate and lactate values are more likely to occur in the ~50% of TBI patients who develop CSD. In these patients, CSD is more likely to occur when glutamate, lactate, and LPR are high; conversely, these values are higher when CSD occurs. These results suggest a vicious cycle in which metabolic crisis and elevated glutamate trigger CSD, which in turn increases metabolic demand and failure with further excitotoxic damage.

Computed Tomographic Pathologies Associated with Cortical Dysfunction after Traumatic Brain Injury Requiring Surgery

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INTRODUCTION: Unlike hemorrhagic or ischemic stroke, traumatic brain injury (TBI) consists of a variable combination of primary injury pathologies, including contusion, diffuse swelling, skull fractures, and hemorrhage in various intracranial compartments. Understanding the pathophysiologic mechanisms associated with these pathoanatomic features is considered a critical step toward successful clinical trials based on specific targeting of pathology subtypes (Saatman et al., 2008). Here we compared CT pathologies with the occurrence of electrographic seizures and cortical spreading depolarizations (CSD) measured by electrocorticography (ECoG). **METHODS:** In TBI patients requiring neurosurgery, a subdural electrode strip was placed intraoperatively for subsequent ECoG monitoring during neurocritical care. The most recent head CT prior to surgery was scored for pathoanatomic features. Thirty patients aged 18-80 with pre-surgical GCS 9-13 (n=7) or 3-8 (n=23) were studied with ECoG recordings for a median 51 hr. **RESULTS:** A total of 468 CSD were observed in 15/30 (50%) patients, and seizures were observed in 6 (20%). Primary diagnoses were similar among patients with CSD (7 SDH, 5 contusions, 1 GSW, 1 tSAH, 1 diffuse swelling) and without CSD (7 SDH, 5 contusions, 1 GSW, 1 ICH), and the occurrence/frequency of CSDs had no relationship with the presence/size of contusions, degree of midline shift, or appearance of basal cisterns. The pathologic feature most strongly associated with CSD was traumatic sub-arachnoid hemorrhage (tSAH), with progressive increase in incidence with Morris-Marshall grades [0: 2/9 (22%), 1-3: 5/11 (45%), 4: 8/10 (80%), χ^2, $p<0.05$]. Presence of sub-dural hemorrhage (SDH) was associated with a higher rate of CSD occurrence in those patients with CSD (median 17 vs. 4 CSD/day; M-W, $p=0.3$), but was not associated with the presence/absence of CSD (SDH: 10/20; no SDH: 5/10). By contrast, the occurrence of seizures was most strongly associated with SDH. All 6 patients with seizures were among those with a primary diagnosis of SDH (n=14), while no patients with other primary diagnoses had seizures (Fisher exact test, $p<0.01$). All SDH patients with seizures suffered TBI from falls and were older (mean 64 vs. 44, $p<0.05$), with higher pre-surgical GCS scores (mean 9.5 vs. 6.1, $p=0.07$), than SDH patients without seizures. **CONCLUSIONS:** While results are preliminary and require a larger sample size, they support the principle that TBI pathophysiology is diverse and varies according to features easily identified by CT. It is surprising that cortical dysfunction is not associated with parenchymal lesions and that different types of hemorrhage may lead to different forms of cortical dysfunction. Post-surgical CTs should be examined in future studies to better elucidate these associations. **REFERENCES:** Saatman KE et al: Classification of traumatic brain injury for targeted therapies. J Neurotrauma 25:719-38, 2008.