Nonconvulsive Seizures after Subarachnoid Hemorrhage: Multimodal Detection and Outcomes

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Objective: Seizures have been implicated as a cause of secondary brain injury, but the systemic and cerebral physiologic effects of seizures after acute brain injury are poorly understood.
Methods: We analyzed intracortical electroencephalographic (EEG) and multimodality physiological recordings in 48 comatose subarachnoid hemorrhage patients to better characterize the physiological response to seizures after acute brain injury.
Results: Intracortical seizures were seen in 38% of patients, and 8% had surface seizures. Intracortical seizures were accompanied by elevated heart rate ($p = 0.001$), blood pressure ($p < 0.001$), and respiratory rate ($p < 0.001$). There were trends for rising cerebral perfusion pressure ($p = 0.03$) and intracranial pressure ($p = 0.06$) seen after seizure onset. Intracortical seizure–associated increases in global brain metabolism, partial brain tissue oxygenation, and regional cerebral blood flow (rCBF) did not reach significance, but a trend for a pronounced delayed rCBF rise was seen for surface seizures ($p = 0.08$). Functional outcome was very poor for patients with severe background attenuation without seizures and best for those without severe attenuation or seizures (77% vs 0% dead or severely disabled, respectively). Outcome was intermediate for those with seizures independent of the background EEG and worse for those with intracortical only seizures when compared to those with intracortical and scalp seizures (50% and 25% death or severe disability, respectively).
Interpretation: We replicated in humans complex physiologic processes associated with seizures after acute brain injury previously described in laboratory experiments and illustrated differences such as the delayed increase in rCBF. These real world physiologic observations may permit more successful translation of laboratory research to the bedside.

ANN NEUROL 2013;00:000–000

Acute brain injuries are common and a significant public health issue. Although more patients now survive the acute event due to advances in critical care and neurosurgical techniques, functional outcome is driven to a large extent by secondary complications such as brain swelling, inflammation, and seizures, most of which are potentially amenable to therapy.[1,2] Nonconvulsive seizures (NCSs) are frequent,[3,4] and associated with indicators of secondary brain injury[4–7] and poor outcome, particularly after subarachnoid hemorrhage (SAH).[4,5,7,8] Controversy about underlying mechanisms and consequences of NCSs prevails; although most believe they are potentially harmful in acute brain injury, some have suggested that NCSs are an epiphenomenon of deafferented cortex[9] or a surrogate marker for the extent of brain damage.[10,11] Treatment in the form of antiepileptic agents is available but carries risks.[12,13]

View this article online at wileyonlinelibrary.com. DOI: 10.1002/ana.23859

Received Jul 28, 2012, and in revised form Dec 18, 2012. Accepted for publication Dec 21, 2012.

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Animal models of neocortical seizures have demonstrated a strain on metabolic resources of the cortex that may result in inadequate perfusion[14–17] and lead to shunting of blood from surrounding brain regions to the seizure focus.[16] It is unclear whether similar mechanisms are at play in seizures following brain injury in humans, as baseline metabolism is altered,[18–20] waves of spreading depolarization, spreading ischemia, and spreading convulsions are frequent,[21,22] and vasoreactivity is frequently abnormal.[23] Furthermore, impairment of the autonomic nervous system,[24] including tachycardia[25] and tachypnea,[26] are common after acute brain injury, which may impair typically observed compensatory responses for seizures such as those seen in epilepsy patients.[27]

Studying systemic and cerebral physiologic effects of seizures after acute brain injury in humans has proven to be difficult due to notoriously poor signal to noise ratios in the intensive care unit (ICU).[28,29] The purpose of the current study is to illustrate the potential of investigating real world human physiology after acute brain injury obtained in an ICU. Here we test whether intracortical seizures[30] after SAH are associated with physiologic changes seen in animal models and whether isolated intracortical seizures are associated with similar physiologic responses as scalp seizures. We will investigate this by applying computational techniques to systemic and invasive brain monitoring data collected in patients with aneurysmal SAH. These insights may allow better understanding of mechanisms underlying secondary brain injury from seizures in humans, potentially help identify subjects who would benefit from prophylactic interventions (ie, choice of anesthetic or seizure prophylaxis), and estimate differences between bench and bedside pathophysiology, leading to more realistic and ultimately successful clinical trials.

Patients and Methods

Study Population

We studied all poor grade aneurysmal SAH patients admitted to the neurological ICU at Columbia University Medical Center between June 2006 and May 2011 who underwent invasive brain multimodality monitoring including minidepth electroencephalography (EEG) as part of their routine clinical care following our institutional protocol.[30,31] Multimodality monitoring was initiated in comatose patients with a Glasgow Coma Scale of $\leq$8 if patients (1) were unlikely to regain consciousness within the following 48 hours, and (2) had a high probability of surviving for the next 48 hours. This decision was made by the attending neurointensivist and head neurosurgeon. The diagnosis of SAH was established by computed tomography (CT) or xanthochromia of the cerebrospinal fluid if the CT was negative.[32] Patients were not enrolled in this observational cohort study if any of the following were met: (1) age $<$18 years, (2) pregnant, or (3) patients or families did not want to participate in the study. Patients with clinical seizures or NCSs prior to or at the start of invasive monitoring were excluded from the analysis. Data were collected as part of an ongoing prospective database approved by the local institutional review board and following recently published recommendations for core data element collection.[33]

Multimodality Monitoring

According to our protocol, invasive neuromonitoring includes measurements of intracranial pressure (Integra Neurosciences, Plainsborough, NJ), interstitial cerebral microdialysis (CMA-70 microdialysis catheter [20kDa pores], analyzed for lactate, pyruvate, and glucose using the CMA-600 [CMA, Stockholm, Sweden]; metabolic crisis was defined as lactate–pyruvate ratio [LPR] $>$ 40 and brain glucose $<$ 0.7mmol/l), partial brain tissue oxygenation ($P_{bt}O_2$) and brain temperature (using a flexible polarographic LICOX Clark-type probe; Integra Neurosciences, Kiel, Germany), and regional cerebral blood flow (rCBF; Bowman Perfusion Monitor; Hemedex, Cambridge, MA). Together with these invasive monitoring probes, we placed an EEG minidepth electrode (8-contact Spencer depth electrode [ADTech, Racine, WI], with 2.2mm center-to-center intercontact spacing, contact width = 1.32mm, 0.9mm spacing between electrodes).[30,31] This commercially available electrode is designed for clinical intracranial EEG recording and is placed at the bedside; details of the placement have been described in detail in earlier publications.[30,31]

Monitoring probes were placed ipsilateral to the aneurysm in patients who underwent aneurysm coiling and those with focal structural lesions. In patients who underwent aneurysm clipping, probes were placed contralateral to the bone flap[31] as soon as possible after securing the aneurysm, usually within 2 days of the bleed. All intracranial monitoring devices were placed at the bedside in the ICU and affixed with a bolt; for details on technical aspects of placement, please refer to our prior publication.[30] Minidepth electrodes were placed to span the cortical ribbon with the goal of having 1 electrode in the skull, 2 to 3 in the cortical gray matter, and the remaining 4 to 5 electrodes in the white matter. Location of monitoring probes was confirmed by CT scan immediately after the procedure. After removal of the monitoring probes, patients underwent CT scanning, and a subset of them also received brain magnetic resonance imaging (MRI) for clinical purposes.

Jugular venous bulb catheters (PediaSat Oximetry catheter; Edwards Lifesciences, Irvine, CA) were generally placed into the right internal jugular vein to record jugular venous oxygen saturation ($S_{jv}O_2$). Cardiovascular parameters were obtained from the arterial and central venous line catheters, and included blood pressure (systolic, diastolic, mean arterial pressure) and heart rate. Respiratory parameters such as respiratory rate and minute ventilation were obtained directly from the ventilator (840-Puritan Bennett; Nellcor Puritan Bennett, Boulder, CO) and the end tidal CO_2 (E_tCO_2) from an infrared capnometer (Respironics; Koninklijke Philips Electronics, Amsterdam, Netherlands). Body temperature was measured using a bladder temperature probe

(Bardex; Bard, Covington, GA). Scalp EEG was recorded using 21 standard scalp disk electrodes placed according to the International 10-20 system, affixed with collodion.[3]

General Management

Medical and surgical treatment followed guidelines by the American Heart Association[34] and existing management protocols at most large medical centers.[1] Patients received mechanical ventilation, external ventricular drainage (EVD), daily interruption of sedation, prophylactic oral nimodipine, and intravenous hydration according to a standardized management protocol.[1] All patients were on prophylactic phenytoin for 1 week after SAH, which was then discontinued unless seizures had been recorded on scalp EEG. Isolated scalp seizures were initially treated with levetiracetam and status epilepticus with midazolam infusions.[35] Periodic epileptiform discharges (PEDs) were not considered seizures, and there was no attempt to eliminate them with medications; however, patients with PEDs were maintained on anticonvulsants to prevent seizures. Anticonvulsants were not altered for isolated minidepth electrode findings.[30]

Data Collection

All digital physiologic data were acquired using a high-resolution acquisition system (BedmasterEX; Excel Medical Electronics, Jupiter, FL) at a sampling frequency of every 5 seconds from General Electric (Milwaukee, WI) Solar 8000i monitors and inserted into a Microsoft (Redmond, WA) SQL database. EEG was recorded using a digital video EEG bedside monitoring system (XLTEK, Oakville, ON, Canada; low-pass filter = 70Hz, high pass = 0.1Hz, sampling rate = 200Hz). Additionally, we collected a large number of clinical variables, including demographics, disease-specific variables (ie, aneurysm size), monitoring probe location, laboratory values, neurological examination findings, medications, hospital complications, and 3 months of functional outcome data as part of an ongoing, prospective observational SAH outcomes study.[32]

EEG Classification

Each minute of EEG was classified into 1 of 3 categories after visual inspection by an experienced electroencephalographer[36,37]: (1) *ictal*, defined as any spikes, sharp waves, or sharp-and-slow wave complexes lasting for 10 seconds or more at either a frequency of at least 3 per second or a frequency of at least 1 per second with clear evolution in frequency, morphology, or location; (2) *ictal-interictal continuum* (IIC), defined as repetitive generalized or focal spikes, sharp-waves, spike-and-wave or sharp-and-slow wave complexes that lasted for 10 seconds or more with a frequency between 1 and 3 per second without clear evolution in frequency, morphology, or location; and (3) *nonictal*, defined as conditions not having been met for either category 1 or category 2. All scores were recorded separately for surface and minidepth EEG recordings. Each minute of EEG was evaluated by 1 of the investigators (J.C.) blinded to the clinical course of the patient. Any minute of EEG that was controversial was independently evaluated by a second experienced electroencephalographer (L.J.H.), and scores were based on consensus.

Event Definition

EEGs often fluctuate between ictal and nonictal patterns after acute brain injury.[36] To maximize the chance of detecting physiologic changes, we aimed to identify new onset seizures defined as lasting at least 5 minutes and preceded by 30 minutes without any seizure activity. We then determined the exact second that each of these new onset seizure events started and merged EEG measures with physiologic measures.

Quantitative EEG

Quantitative EEG parameters were calculated and visualized using commercially available software (MATLAB [Mathworks, Natick, MA] and Magic Marker Insight [Persyst, Prescott, AZ]). EEG clips between 30 minutes before and 30 minutes after intracortical seizure onset were generated (Supplementary Fig 1A, B). Spectrograms representing the power in each frequency bin between 0 and 20Hz were calculated based on fast Fourier transform (FFT) analysis for every 4-second epoch of these 60-minute clips. The following procedure was then applied to transform the resulting spectrograms of individual intracortical seizures into grouped averages (see Supplementary Fig 1C): (1) a ratio was calculated between the measurement in each individual frequency bin and the average for that particular frequency bin over the entire 60-minute time series to account for interpatient and intraevent differences in overall power, (2) these normalized frequency change scores were then averaged between events to generate group averages for all intracortical seizures (see Supplementary Fig 1C).

Physiologic Data Preparation

Clinically recorded physiological data may have gaps due to device malfunction or loss of connectivity between the recording and data storage location. For analysis purposes, we inferred interobservation values with linear interpolation.[38] Outlier removal can be challenging, because brief deviations from the mean may be the very signal that needs to be detected. We first removed physiologically implausible outliers (ie, mean arterial pressure [MAP] of 0)[28] and extracted the raw data for all monitoring values for a 60-minute time window surrounding intracortical seizure onset (see Supplementary Fig 1D). We then normalized all monitoring parameters to individual patient averages for this window and represented the time series as deltas from individual patient means (see Supplementary Fig 1E). We then employed an additional step for outlier removal based on Chauvenet's criterion[39] to account for the distribution of a physiologic variable at a specific time relative to seizure onset (see Supplementary Fig 1F).

Statistical Analysis

Once filtered, time series windows for all measurements were aggregated, and the mean and standard error were estimated based on a bootstrap procedure (see Supplementary Fig 1G). To evaluate the significance of these changes from baseline, we

TABLE 1. Follow-up Bias Analysis among Patients Eligible for Invasive Brain Monitoring (N = 90)

Characteristic	Minidepth EEG, n = 48	No Minidepth EEG, n = 42
Demographics		
Age, yr	53 ± 15	53 ± 15
Female	31 (65)	30 (71)
White	17 (35)	15 (36)
Admission findings		
Hunt–Hess score	4 (3–5)	4 (2–5)
APACHE II score	21 ± 7	22 ± 8
SAH sum score	19 ± 8	15 ± 11
IVH	4 ± 4	4 ± 4
Global cerebral edema	38 (83)	34 (74)
Aneurysm treatment		
Aneurysm clipping	32 (67)	20 (49)
Aneurysm coiling	10 (21)	14 (33)
Not protected[a]	6 (13)	8 (19)
Hospital course		
Delayed cerebral ischemia	13 (28)	12 (30)
Worse Hunt–Hess	5 (4–5)	5 (4–5)
Functional outcome at 3 mo		
Modified Rankin score	4.5 (1.5–6.0)	5.0 (2.0–6.0)
Dead or severely disabled	17 (50)	18 (51)

Data are represented as No. (%), mean ± standard deviation, or median (interquartile range).
[a]Did not undergo angiography, were angiographic negative, or were left unprotected. None of the comparisons was significantly different.
EEG = electroencephalography; IVH = intraventricular hemorrhage; SAH = subarachnoid hemorrhage.

constructed a permutation test where we resampled by patient and evaluated a Monte Carlo estimate of the significance level.[40–42] The null distribution for this permutation test considers the time at which seizure onset occurs for all seizures to be random while preserving the number of seizures observed per patient. The test statistic was the area under the standard deviation–weighted mean time series for all time points in the window. This approach is a slight modification of lagged linear correlation.[43] Building on animal experiments,[14–17,44] we tested the hypotheses that changes observed in each of the variables surrounding seizure onset are different from chance and specifically that NCSs are associated with increases in heart rate (HR), MAP, respiratory rate (RR), minute ventilation (MV), intracranial pressure (ICP), cerebral perfusion pressure (CPP; calculated by subtracting ICP from MAP), global brain metabolism (indicated by a drop in the $S_{jv}O_2$), rCBF, and brain tissue hypoxia (indicated by a drop in $P_{bt}O_2$). To determine the significance of isolated intracortical seizures, we compared events with and without IIC or seizures on scalp recordings. Comparisons between baseline and follow-up microdialysis measurements as well as between seizure subgroups were made using generalized estimating equations with an autoregressive (AR-1) working correlation matrix.

Inter-rater reliability testing of EEG coding was performed by calculating weighted Kappa scores[45] on a random sample of 127 one-minute surface and minidepth EEG clips by comparing scores of 2 study physicians (J.C., L.J.H.).

All analyses were made using commercially available software (Python [Python Software Foundation, Wolfeboro Falls, NH], R [Institute for Statistics and Mathematics, Vienna, Austria], SPSS 18 [SPSS, Chicago, IL], MATLAB). After Bonferroni correction (13 experiments) only probability values <0.0038 were considered statistically significant, resulting in a familywise error rate of 5%.

Results

Between June 2006 and May 2011, 434 aneurysmal SAH patients were screened for possible enrollment, and 344 did not meet inclusion criteria (238 with Glasgow Coma Scale score > 8, 51 who were predicted to be dead, 37 predicted to have woken up within 48 hours of

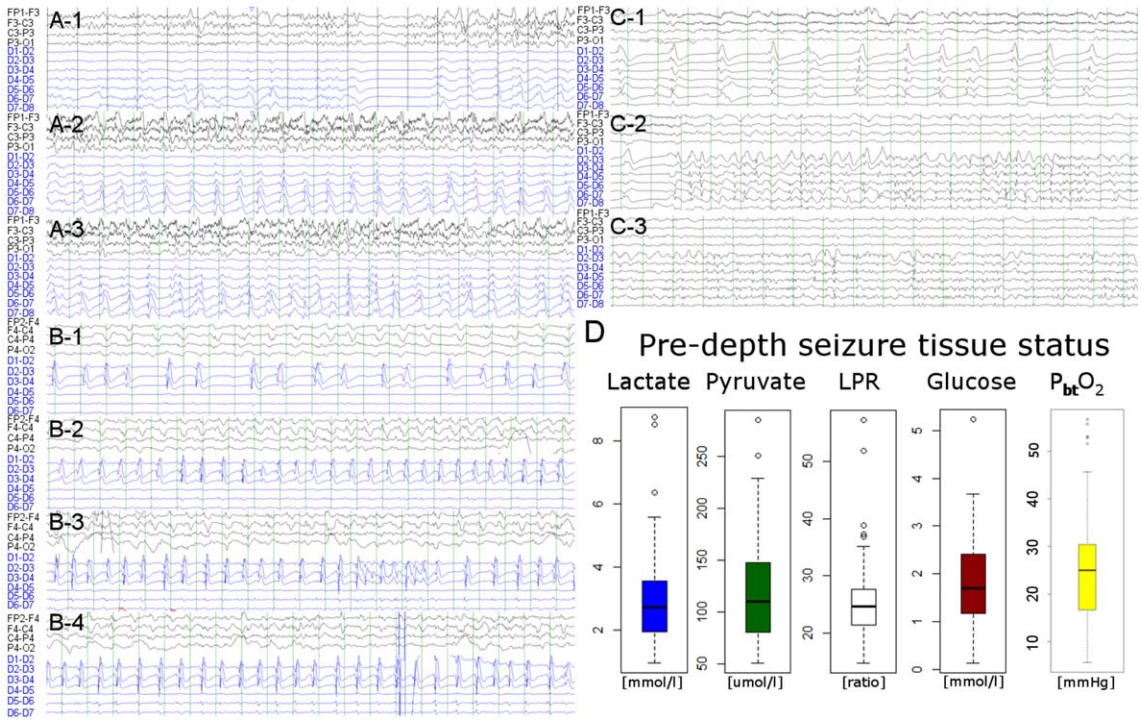

FIGURE 1: (A–C) Three illustrative intracortical seizure cases are displayed (ipsilateral scalp electroencephalogram [EEG] each in the top 4 and minidepth EEG in the bottom 6 to 7 channels; all bipolar montage). (A) Intracortical seizure with surface seizure: a 54-year-old woman with poor grade subarachnoid hemorrhage (SAH; Hunt–Hess = 5, APACHE II = 27) underwent clipping of an anterior communicating artery aneurysm. (B) Intracortical seizure with ictal–interictal continuum surface recording: a 47-year-old man with poor grade SAH (Hunt–Hess = 5, APACHE II = 14) underwent clipping of a right anterior cerebral artery aneurysm. (C) Intracortical seizure with nonictal patterns on surface recordings: a 57-year-old woman with poor grade SAH (Hunt–Hess = 4, APACHE II = 17) underwent clipping of an anterior communicating artery aneurysm. (D) Baseline tissue status based on microdialysis and partial brain tissue oxygenation averaged for all patients over 60 minutes prior to intracortical seizure onset indicating an overall nonischemic state (median glucose = 1.7mmol/l [interquartile range (IQR) = 1.2–2.4], pyruvate = 110μmol/l [IQR = 80–148], lactate = 2.8mmol/l [IQR = 1.9–3.6], lactate–pyruvate ratio [LPR] = 25 [IQR = 21–28], partial brain tissue oxygenation [$P_{bt}O_2$] = 24.4mmHg [IQR = 4.7–63.0]). Only 2 events were preceded by an LPR >40, and 9 had a cerebral glucose of 0.7mmol/l or below; no event was preceded by metabolic crisis (LPR > 40 and brain glucose < 0.7mmol/l).

admission, and 18 who had severe coagulopathy). Of 90 poor grade SAH patients who were eligible, 48 received invasive brain monitoring including minidepth EEG (26 did not based on surrogate decisions, and 16 had invasive brain monitoring without minidepth EEG). Baseline characteristics of eligible patients who did and of those who did not undergo monitoring were similar (Table).

Data Collection

Monitoring probes were placed on median post-SAH day 2 (interquartile range [IQR] = 2–3), in half of the patients into the right and the other half into the left frontal lobe (median distance between the tip of the minidepth electrode and the inner table of the skull was 14.5mm [IQR = 12.5–16.5]); monitoring probes were placed ipsilateral to the craniotomy site in 8% (n = 4) and ipsilateral to the aneurysm site in 19% of cases (n = 9). Seizure frequency did not differ by laterality of probe placement. We coded each minute of a total of 376 days of intracortical EEG into 3 categories: ictal, IIC, or nonictal. Intracortical seizures were seen in 38% (n = 18) of patients, with 12,894 minutes of cumulative seizure duration. Scalp seizures were seen in 8% (n = 4), with 3,444 minutes of cumulative seizure duration. New onset depth seizures lasted a median of 51 minutes (IQR = 17–125), with only 3% (n = 2) lasting 5 minutes and 77% (n = 59) lasting 15 minutes or more. Inter-rater reliability scores were very good for surface and minidepth EEG recordings (weighted kappa scores = 0.90 and 0.80, respectively).

Physiologic Profiles of Intracortical Seizures

We identified 77 new onset intracortical seizures (Figure 1A–C) and created physiologic profiles for recorded variables in a 60-minute time window surrounding intracortical seizure onset. Microdialysis measurements did not indicate preseizure brain tissue hypoxia or metabolic crisis (see Fig 1D). Baseline values for monitored variables at the time of seizure onset were (median, IQR): HR = 74 beats/min (69–80), MAP = 105mmHg (94–120), RR = 17 breaths/min (14–22), MV = 7.7l/min (7.2–9.3), E_tCO_2 = 32mmHg

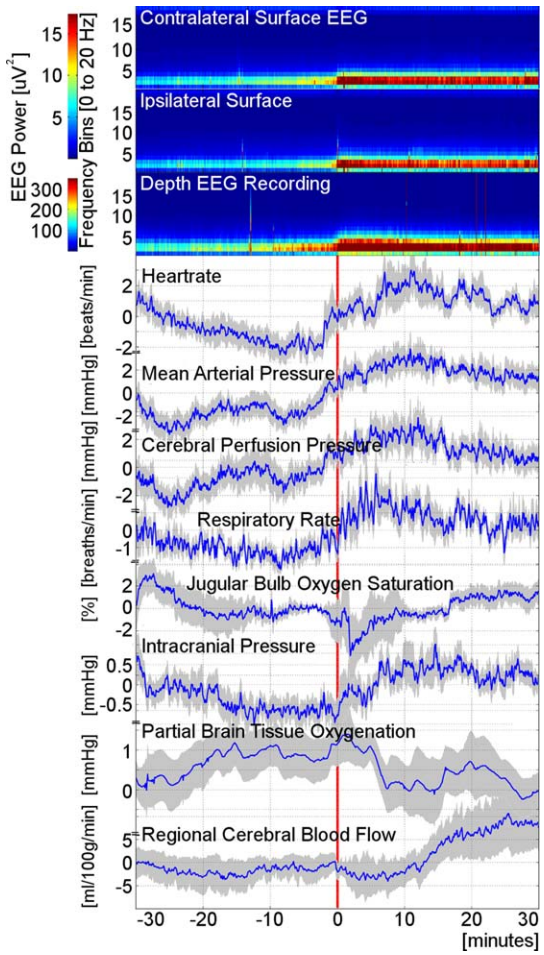

FIGURE 2: Grouped data of physiologic changes associated with the onset of intracortical seizures. Spectrograms (upper 3 panels), displayed as relative changes on a group level, demonstrate increases in electroencephalographic (EEG) power predominantly in the 2 to 5Hz frequency range, first seen in the minidepth EEG recording (third panel from top), followed by contralateral (top panel) and ipsilateral scalp (second panel from top) recordings. Spectrograms reveal clear changes in EEG power recorded from the minidepth as well as the scalp, which precedes the seizure onset determined by visual inspection of raw EEG tracings (indicated as 0 on the x-axis and by the *vertical red line*). Regarding physiological recordings, timing of increases in cardiovascular (heart rate, mean arterial pressure) and respiratory (respiratory rate, minute ventilation [not shown]) parameters coincides with detection of first intracortical spectral power changes, whereas rising intracranial pressure is only detected later, when seizures become recognizable on inspection of the raw EEG. Global brain metabolism increases sharply for a short time, as suggested by the transient drop in jugular bulb oxygenation (approximately 2 minutes after seizure onset). This lasts for several minutes followed by gradual return to preseizure baseline global metabolism (approximately 8 minutes after seizure onset). There is a small drop in partial brain tissue oxygenation starting 5 minutes after seizure onset. Whereas cerebral perfusion pressure rises with increase in mean arterial pressure at the time the first spectrogram changes are recognizable on the minidepth recording, there is a very delayed increase in regional cerebral blood flow, seen starting about 10 minutes after seizure onset. Physiology graphs are displayed as means *(blue lines)* with 1 standard error of the mean *(shaded areas)*.

(28–36), ICP = 5mmHg (2–9), CPP = 100mmHg (91–113), $S_{jv}O_2$ 84% (82–89), rCBF = 31ml/g/min (18–37), $P_{bt}O_2$ = 25mmHg (13–33), body temperature = 37.5°C (37.1–37.8), and brain temperature = 37.0°C (36.5–37.7). Prior to intracortical seizures, 70% (n = 54) of patients were on propofol, 48% on fentanyl (n = 37), and 7% on dexmedetomidine (n = 5).

Intracortical seizures were associated with an increase in HR ($p = 0.001$), MAP ($p < 0.001$), RR ($p < 0.001$), and MV ($p = 0.002$; Fig 2). A trend for higher CPP ($p = 0.03$) and ICP ($p = 0.06$) was seen. Increases in global brain metabolism ($S_{jv}O_2$ drop), transient drops in $P_{bt}O_2$ (Fig 3), and delayed increases in rCBF did not reach significance. There was no change in hourly microdialysis measurements of lactate, pyruvate, glucose, or LPR in relation to seizure onset (Supplementary Fig 2). Thirty-two percent of depth seizures were associated with an increase in HR by >20 beats/min when comparing the 30-minute median value prior to the depth seizure onset to the maximum value in the 30 minutes after seizure onset, 52% with an increase in MAP of >20mmHg, 72% with an increase in RR of >10 breaths/min, and 71% with an increase in MV of >2.0l/min. Among the intracranial monitoring parameters, ICP elevations >5mmHg were seen in 64% and >10mmHg in 28% of seizures, CPP elevations >10mmHg were seen in 88% and >20mmHg in 43%, $S_{jv}O_2$ dropped in 33% by >10% and in none by >20%, $P_{bt}O_2$ dropped in 28% by >5mmHg and in 13% by >10mmHg, and rCBF increased by >10ml/g/min in 55% and by >20ml/g/min in 36% of events.

Surface EEG

Forty-three percent (n = 29) of intracortical seizures were restricted to the minidepth electrode, whereas simultaneously recorded scalp EEG showed patterns on the IIC in 19% (n = 13) and seizures in 37% (n = 25; Fig 4). There was no adequate surface EEG available to categorize 10 of the intracortical seizure events. Overall lower baseline glucose was seen for those with seizures restricted to the minidepth electrode (median = 2.2 [IQR = 1.4–2.7] vs 1.1 [IQR = 0.6–1.6] for those with IIC or seizures on scalp vs those without, respectively, $p = 0.002$). Although baseline $P_{bt}O_2$ also appeared lower for those with isolated intracortical seizures, particularly when compared to those with seizures on the surface, these differences were not significant. rCBF did not change for those with isolated intracortical seizures, whereas there was a trend for a delayed rise starting approximately 10 minutes after onset for those with IIC or seizures on surface EEG ($p = 0.08$). Other parameters did not have significantly different responses when comparing the subgroups.

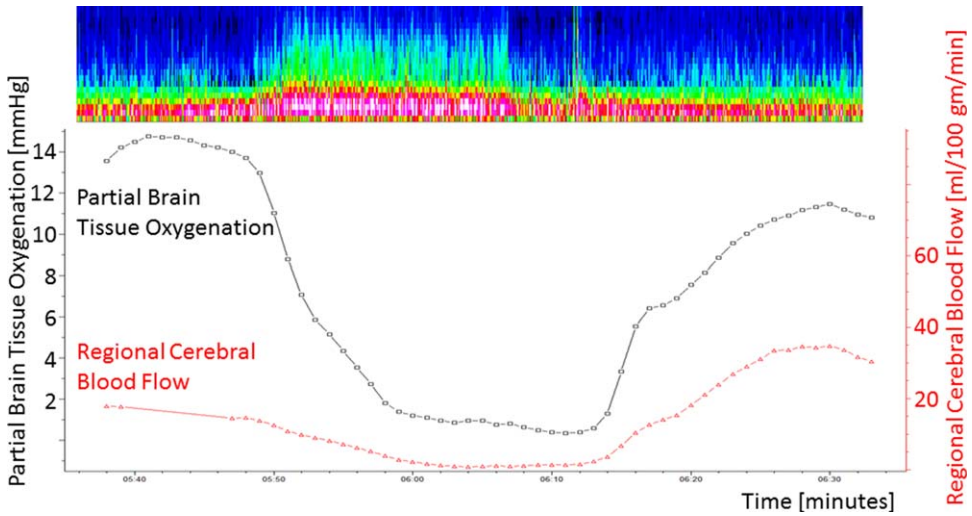

FIGURE 3: A 46-year-old man with subarachnoid hemorrhage (Hunt–Hess grade = 4, modified Fisher score = 4) who underwent clipping of an anterior communicating artery aneurysm experienced several depth and surface seizures. Displayed here is a depth seizure (spectrogram at top) on postbleed day 9 with a drop in partial brain tissue oxygenation ($P_{bt}O_2$) from 15 to 1mmHg following seizure onset and a drop in regional cerebral blood flow (rCBF). There is a delayed rise in rCBF starting approximately 15 minutes after seizure onset, accompanied by an improvement of $P_{bt}O_2$ to baseline values.

Delayed Cerebral Ischemia

Overall, 28% (n = 13) of SAH patients who underwent invasive brain monitoring including depth EEG developed delayed cerebral ischemia (DCI). Depth seizures were not more common among those with compared to those without DCI (31% of those with vs 41% of those without DCI, $p = 0.511$).

Safety

At least 1 CT scan was obtained immediately following placement of the monitoring bundle (Supplementary Fig 3). We carefully screened each CT scan performed in our patient cohort after probe placement and identified new intraparenchymal bleeds in 4 patients. Two of these appeared in the immediate proximity of the EVD distant to the monitoring site. One 2ml left frontal bleed appeared after placement and one 5ml bleed after removal of the monitoring probes, both in close proximity to the monitoring devices. None of the bleeds led to any detectable neurological worsening. Eleven patients had MRI scans performed after removal of the monitoring probes. There was a small amount of signal change seen on gradient echo sequences in 10 and a very small area of increased T2 signal on fluid attenuated inversion recovery in 9 patients. On routine surveillance cerebrospinal fluid (CSF) studies, we identified 2 positive CSF cultures (1 each with candida and *Klebsiella oxytoca*). Both patients also had EVDs placed. The former appeared 6 days after placing the EVD and monitoring bundle and was successfully treated with a 21-day course of fluconazole. The latter had CSF cultures positive for *Klebsiella* preceding the placement of the monitoring bundle and was successfully treated with a 21-day course of vancomycin and cefepime.

Outcome

Median modified Rankin score was 5.0 (IQR = 3.3–6.0) 3 months after SAH, and 52% (n = 25) of patients were severely disabled or dead (modified Rankin score of 5 or 6). Patients without surface or intracortical seizures and baseline nonattenuated intracortical EEG had a 0% risk of severe disability or death at 3 months (0 of 8), whereas the risk of poor outcome was 25% with surface (1 of 4; all of these patients also had intracortical seizures) and 50% with intracortical seizures (7 of 14, with or without background attenuation but without surface seizures), and 77% with severe background attenuation without any seizures (17 of 22; Fig 5). Intracortical EEG features (seizures and background attenuation) remained significant predictors of functional outcome (odds ratio = 5.0, 95% confidence interval = 1.7–14.2) after controlling for age, admission Hunt and Hess scale, APACHE II scores, and SAH sum score.

Discussion

Despite promising laboratory data, randomized controlled trials in acute brain injury are often disappointing and equivocal at best.[46–49] There are many reasons for this disconnect of translating research from the laboratory to the bedside, but inadequate understanding of the underlying pathophysiology and a failure of existing animal models to adequately represent the complexity of acute human brain injury are overriding themes.[50–53] We show that intracortical seizures following acute brain

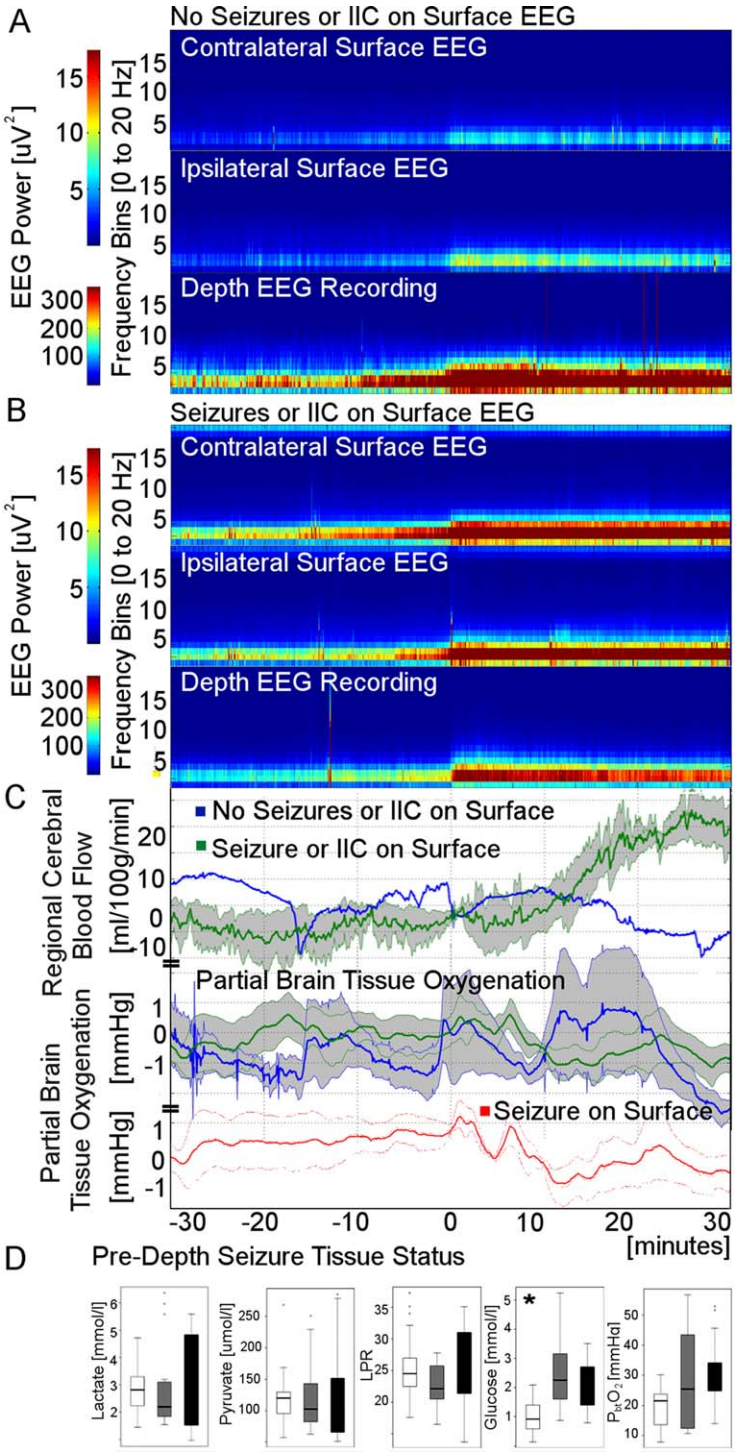

FIGURE 4: Surface electroencephalography (EEG) findings. Spectrograms for intracortical seizure events stratified into those without and those with surface EEG correlate (A and B, respectively). Regional cerebral blood flow did not change for those with isolated intracortical seizures, whereas those with IIC or seizures on the surface showed a delayed rise starting approximately 10 minutes after onset (C). For those with seizures on the surface (*red graph;* D), a brief rise in partial brain tissue oxygenation ($P_{bt}O_2$) was followed by a pronounced persistent drop, whereas a brief period of hyperoxia was not followed by a $P_{bt}O_2$ dip for those without concomitant surface seizures. Physiology graphs are displayed as means (*blue lines* = minidepth only seizures, *green lines* = ictal–interictal continuum (IIC) or seizures on surface EEG, *red line* = seizures on the surface) with one standard error of the mean (shaded area). (D) Baseline cerebral tissue status characterized by preseizure microdialysis (interstitial lactate, pyruvate, lactate–pyruvate ratio [LPR], and glucose) and $P_{bt}O_2$ averaged over 60 minutes preceding intracortical seizure onset are stratified by surface EEG findings (*white box* = no seizures or ictal interictal surface EEG findings, *light gray box* = ictal interictal surface EEG findings, *dark gray box* = seizures on surface EEG; **p* = 0.002).

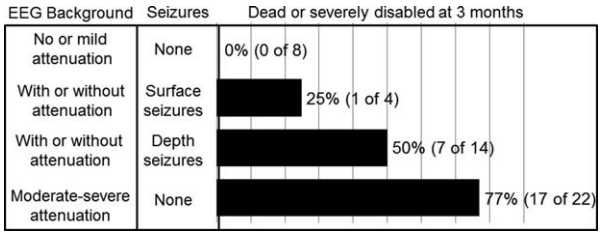

FIGURE 5: Three-month functional outcome after subarachnoid hemorrhage stratified by electroencephalographic (EEG) background activity and presence of intracortical or surface seizures.

injury are often associated with a sympathetic response reflected in tachycardia, hypertension, and tachypnea as well as trends for elevated CPP and ICP, but fail to demonstrate global hypermetabolism or brain tissue hypoxia. Rising rCBF was only present for those with surface seizures and occurred 10 minutes after seizure onset. Intracortical seizures may or may not be associated with scalp seizures, are more frequent in brain tissue with low glucose, and carry a worse prognosis than scalp seizures. We demonstrate the ability to replicate in the clinical setting findings previously made in highly controlled laboratory experiments, despite the high complexity and poor signal-to-noise ratio of physiologic data collected in patients with acute brain injury (Fig 6). These observations made in human acute brain injury confirm some of the laboratory observations but possibly even more importantly highlight discrepancies that may allow us to more successfully translate laboratory findings to the bedside.

Intracortical Seizure Model

Seizures recorded with the minidepth electrode[30] are an ideal model to gain insights into seizure-associated pathophysiology due to the spatial proximity between different monitoring probes; however, larger studies need to then correlate intracortical to scalp EEG observations. Identification of seizure onset based on minidepth EEG signals has limitations, as some of the very early particularly contralateral scalp EEG changes likely represent seizures that started remotely from the minidepth electrode and are only secondarily detected at the electrode once they have spread. This may also explain in part the observation that some physiologic responses (eg, HR) appear to precede intracortical seizure onset. Unfortunately measurements of cerebral microdialysis with currently available methodology have very poor temporal resolution and are therefore not ideally suited to study early metabolic effects of seizures. Our observations are not necessarily generalizable to all patients with SAH or other types of acute brain injury and apply only to comatose SAH patients with severe acute brain injury; however, these patients are the ones at highest risk of secondary brain injury. Safety data collected as part of the current study confirm the low risk of bleeding and infection as previously reported.[31]

Compensatory Mechanisms

The current study demonstrates that the expected seizure-related cardiac and respiratory sympathomimetic changes[27] may also be seen after acute brain injury. Interestingly, a measurable increase in rCBF, among the

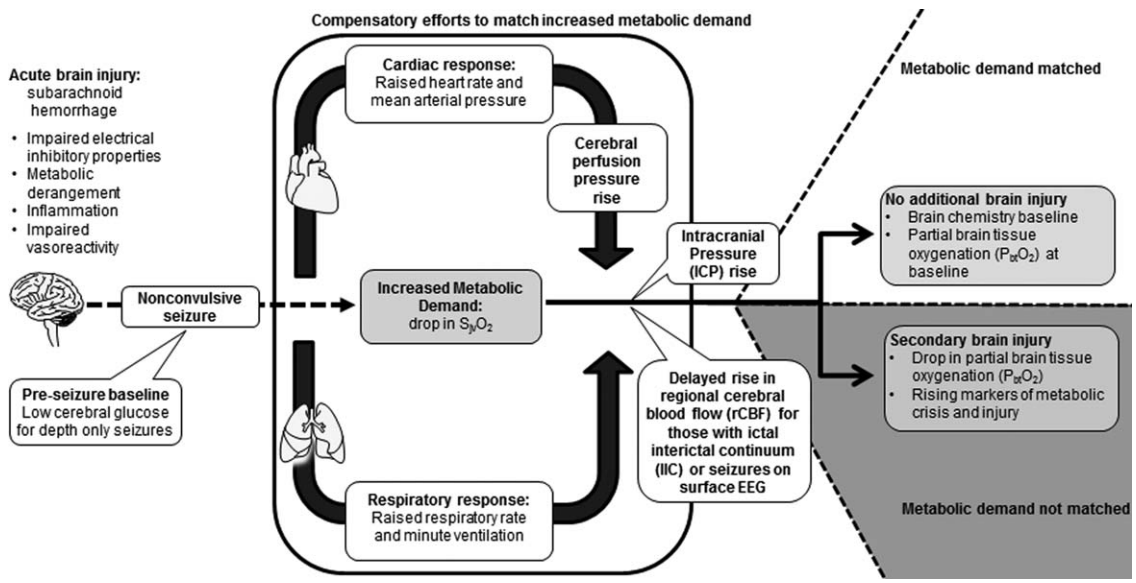

FIGURE 6: Model illustrating the relationship between acute brain injury complicated by seizures and secondary brain injury accounting for findings made in the current study. Physiologic observations supported by significant changes or trends are indicated by white boxes. Observations made in isolated cases or by visualization of grouped graphs but that were not found to be significant are kept in gray boxes. EEG = electroencephalogram; $S_{jv}O_2$ = jugular venous oxygen saturation.

presumed major compensatory mechanisms for increased metabolic demand, was primarily seen in patients with scalp seizures, suggesting that a critical volume of brain needs to be seizing to lead to a compensatory increase in rCBF. Animal work has demonstrated that increases in rCBF only occur in the seizure focus, whereas a transient decrease of flow may be seen in the surrounding tissue.[16] In our study, probes located in the seizure focus would be expected to show the most impressive increases in rCBF, whereas those in the surrounding territory may initially show a decrease.[15,16] More importantly, the time course of rising rCBF was quite different from prior reports in animal models of neocortical epilepsy. Whereas rCBF elevations were registered within seconds in these studies,[15,16] our data suggest that after acute brain injury up to 10 minutes elapse before a rise in rCBF is registered. Reasons for this discrepancy may in part be technique related, as our approach, which was validated using Xenon CT,[54] estimates blood flow based on a thermal dilution model, whereas prior animal work employed intrinsic optical imaging. However, alterations in vasoreactivity may also play a role, as small and large vessel responses are frequently abnormal after acute brain injury.[55] The observed discrepancies between animal work and human acute brain injury, if confirmed, may be of clinical relevance, as they may guide strategies to support compensatory efforts in an attempt to minimize secondary brain injury.

Metabolism and Injury

We demonstrated a trend for rising ICP with seizures, corroborating prior studies that found an overall increase in ICP in patients with traumatic brain injury[4] and a case of seizures after cardiac arrest.[56] It is unclear whether ICP elevations with seizures are primarily related to increases in blood flow or metabolism, which may be clinically relevant, as electrographic seizures after intracerebral hemorrhage have been linked to increasing midline shift and mass effect.[4,7] We were not able to demonstrate significant changes in global brain metabolism ($S_{jv}O_2$) or brain tissue hypoxia ($P_{bt}O_2$) for the group, which have previously been reported in animal models of neocortical epilepsy[14–17] and patients with temporal lobe epilepsy.[44,57] However, isolated cases (see Fig 3) and inspection of aggregated graphs (see Fig 2) suggest that transient global hypermetabolism and brain tissue hypoxia may occur after acute brain injury. Interestingly, intracortical seizures were more likely to remain localized, that is, these seizures were only detected at the minidepth electrode in hypoglycemic brain tissue. This observation implicates that adequate glucose supplies are required to allow the spread of focal seizure activity. Larger sample sizes are required to determine whether seizure duration, maximum frequency, or intactness of vasoreactivity impacts metabolism and compensatory responses. More importantly, future studies using intrinsic optical or MRI and rapid-sampling microdialysis methods[58] may more directly explore the link between seizures and regional metabolism as well as secondary brain injury.

Outcome

Patients without seizures and without moderate or severe EEG background changes had the best functional outcome, whereas those with severely abnormal EEG background activity and no seizures had the worst outcome (see Fig 5). This observation is likely primarily a reflection of the extent of the underlying brain injury and may be of importance as a strong prognostic indicator for patients with acute brain injury. Diffuse background changes may be affected by sedative medications and potentially reversible complications such as elevated intracranial pressure or hydrocephalus. However, the potential importance as a prognostic indicator may be highlighted by the recently recognized importance of absence of EEG reactivity in predicting outcome after cardiac arrest.[59]

Interestingly, functional outcome of patients with seizures was in between these 2 groups of patients, and those with seizures reflected on the surface EEG had a better outcome than those with isolated intracortical seizures. Reasons for this remain speculative at this point, but the inability of seizures to become synchronous in a sufficiently large region of cortex or to propagate and be reflected in the scalp EEG may be a sign of more extensive cortical and subcortical injury. As outlined above, alterations in baseline metabolism or substrate delivery (lower baseline cerebral glucose for those with intracortical only seizures, see Fig 4D), possibly as a direct or indirect result of brain injury, may contribute to the brain's ability to propagate seizures.

Acknowledgment

This publication was made possible by a Grant entitled "Impact of Electrographic Seizures and Periodic Epileptiform Patterns on Neuronal Function and Outcome in Brain Injured Patients" (UL1 RR024156; J.C.) from the National Center for Research Resources (NCRR), a component of the NIH, and NIH Roadmap for Medical Research. Information on the NCRR is available at the NCRR website. Information on re-engineering the clinical research enterprise can be obtained from the NIH Roadmap website. Additional support for this work included grants from the National Library of Medicine, ("Discovering and applying knowledge in clinical

databases" [R01 LM006910; G.H., D.A.] and "Training in Biomedical Informatics at Columbia University" [T15 LM007079; G.H., A.P.]), the Charles A. Dana Foundation (S.A.M.), and the National Science Foundation for the Computing Research Association CIFellows project (#1019343; S.K.). Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the NCRR, NIH, National Science Foundation, or Dana Foundation.

We thank the attending physicians, fellows, and neurology and neurosurgery residents of the Neuroscience ICU and the Epilepsy Division for their overall support of this project.

Potential Conflicts of Interest

S.K.: patents/patents pending, NYU/Abraxis. J.M.S.: grants/grants pending, Irving Institute for Clinical and Translational Research, C.S. Draper Laboratories, IBM Faculty Award, Dana Foundation; consultancy, Orsan Medical Technologies. L.J.H.: consultancy, Upsher-Smith, GlaxoSmithKline, Lundbeck; grants/grants pending, Upsher-Smith, Lundbeck, UCB-Pharma; royalties, UpToDate, Atlas of EEG in Critical Care.

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