Early detection of vasospasm after acute subarachnoid hemorrhage using continuous EEG ICU monitoring

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Abstract

The neurologic morbidity of delayed ischemic deficits from vasospasm following aneurysmal subarachnoid hemorrhage (SAH) continues to be the most debilitating complication from this devastating illness. Neurologic critical care is focused on recognition and treatment of these secondary insults but often the treatment is withheld until an irreversible deficit becomes manifest. Continuous EEG (cEEG) monitoring provides a unique potential to recognize early secondary insults and offers an opportunity for early intervention. We studied 32 SAH patients using cEEG and trending of the quantitative measure, relative alpha (RA), to determine if reductions in RA variability occurred with documented vasospasm. In 19/19 patients with angiographically documented vasospasm, we found that RA variability was decreased by a mean of two grades and improved with resolution of vasospasm. In 10/19 this reduction in RA variability preceded the diagnosis of vasospasm by a mean of 2.9 days (SD 1.73). The positive predictive and negative predictive values are 76% and 100%, respectively. Non-diagnostic clinical signs at the time of RA variability reduction and vasospasm were present in 12/19 patients. Thus decreased RA variability is able to provide early detection of neurologic complications such as vasospasm in patients before clear clinical symptoms and signs occur. © 1997 Elsevier Science Ireland Ltd.

Keywords: Vasospasm; Subarachnoid hemorrhage; ICU monitoring

1. Introduction

Vasospasm is a primary source of neurologic co-morbidity after subarachnoid hemorrhage (SAH). The incidence of vasospasm after SAH is 40–70% (Kassell et al., 1985; Suzuki et al., 1985; Pahmy and Smith, 1992). Transcranial Doppler ultrasound (TCD) and cerebral angiography are the chief methods for detecting vasospasm and guiding therapy. But these methods are not used continuously. In contrast, EEG ICU (intensive care unit) monitoring can monitor cerebral activity continuously.

In our initial experience with quantitative EEG ICU monitoring in patients with SAH we observed marked reduction in relative alpha variability during vasospasm (Nuwer, 1994), as well as increased EEG variability as the vasospasm resolved. Persistently poor EEG variability and reactivity seemed to be predictors of a poor neurologic outcome after SAH. Based on these observations, we studied prospectively 32 acute SAH patients with quantitative EEG ICU monitoring. We hypothesized that decreased relative alpha variability is a marker for altered cerebral function accompanying vasospasm and that it may be present prior to documentation of vasospasm using other clinical means.

2. Methods

We assessed 32 consecutive acute aneurysmal SAH patients hospitalized at UCLA Medical Center. Patients received continuous quantitative ICU EEG monitoring with frequency analysis, periodic xenon (CBF) measures,
and cerebral angiograms, as well as repeated measures of clinical neurologic signs including Glasgow coma scores. Standardized informed consent was obtained at time of admission. Continuous ICU EEG monitoring was performed using an 8 electrode longitudinal bipolar montage with electrodes placed according to the International 10–20 System (F4-T4, T4-P4, P4-O2, F3-T3, T3-P3, P3-O1). Filters were set at 0.3 and 35 Hz. EEG was displayed and stored on optical discs at the bedside. Frequency analysis was performed automatically on each 2 s epoch of EEG. These frequency analysis results were then averaged over 2 min. These averaged relative alpha and total power values were printed and displayed as a continuous histogram over each of 8–12 h of EEG monitoring (Fig. 1). This color-coded histogram was printed periodically. Frequency band for relative alpha (RA) was actually 6–14 Hz, expressed as a percentage of 1–20 Hz activity. Artifact detection was done by daily review of recorded raw EEG and the corresponding spectral trends.

Two electroencephalographers independently reviewed the ICU EEG tracings and the frequency analysis trend displays for each patient after agreeing to rules of scoring. They were blinded to the presence, absence or timing of clinical vasospasm in the patient. Scoring of the raw EEG consisted of determining the peak background frequency and presence of any focal slowing during each 12 h period of monitoring. Artifact-free epochs were selected to evaluate trends. Trend analysis was done on each 8–12 h monitoring period and consisted of the following:

(1) Mean relative alpha was manually measured in each of the frontal, parietal and occipital scalp regions for each hemisphere.

(2) Variability of relative alpha in these three regions was qualitatively scored by visual inspection as excellent (4), good (3), fair (2), or poor grades (1) (Fig. 1). This qualitative visual inspection of relative alpha trends was performed as follows: First, an average baseline of the RA trend was set at the median value of relative alpha during a 12 h epoch. The size and frequency of excursions from this median value baseline were used to assign a score. Excursions from baseline occurring once per hour or of greater than 15% of the median value were given a score of excellent (4), excursions of 10% at least every 4 h were given a score of good (3), small or infrequent excursions were given a score of fair (2), and no excursions greater than 2% were scored as poor (1). The worst RA variability score from one or more monitored channels was considered the score for that 12 h epoch. A change in RA variability score from one or more monitored channels was considered a significant decrease.

(3) Variability of relative alpha in these three regions was then quantitatively calculated using the formula 

\[ \frac{\text{Peak value} - \text{Trough value}}{\text{Peak value} + \text{Trough value}} \]

where peak value is the highest value of the frequency analysis trend and trough value is the lowest value of the frequency analysis trend during the 8–12 hour monitoring period. Brief extreme values, such as an isolated brief high peak or low trough, were eliminated from both the quantitative measurements and from the qualitative determinations to avoid bias created by an outlier segment of a trend that was usually artifactual in origin.

TCD was performed every day or every other day (on weekends) after SAH to detect vasospasm. Unilateral insolation of the middle cerebral artery (MCA) and ipsilateral internal carotid artery (ICA) was performed over each side of the head using the standard temporal window and submandibular approach, respectively. Vasospasm was defined as TCD mean velocities of >120 m/s in the MCA distribution and Lindegard ratio (MCA/ICA velocity) of >3 or angiographic evidence of vasospasm. Onset of vasospasm, as determined by TCD or angiographic evidence of vasospasm, was blindly recorded and subsequently correlated with onset of focal or generalized decreased alpha variability. Glasgow coma scores at the time of TCD measurements were reviewed. Hemispheric xenon CBF studies were performed using the 133-Xe inhalation technique with recordings from 8 sodium iodide collimators. CBF was calculated from the CBF-15 using the two-compartment model described by Obrist and Wilkinson (1990). CBF values were corrected to a pCO2 of 34 torr. CBF studies done during the period of decreased RA and vasospasm were recorded and follow-up end of ICU CBF studies were also analyzed.

Fig. 1. Examples of continuous histogram RA variability trends and the corresponding scores. These are from 4 different patients. Each trend here is 8–12 h long. The amount of relative alpha (RA) EEG content is shown by the vertical lines, minute by minute, in each trend. Four types of results are displayed, with poor variability at the top and excellent variability at the bottom. These examples served as a visual template by which all trends were qualitatively scored.
Patients received customary neurointensive care, including occlusion of the aneurysm by surgery or Gugliemi detachable coil (GDC) (Target® Therapeutics, Inc., Fremont, CA) occlusion within 24 h of presentation, hourly Glasgow Coma Scale (GCS) assessment by nurses and frequent neurologic exams by the investigators. Upon diagnosing vasospasm by TCD or angiography, hypertensive hypervolemia therapy was begun with the use of phenylephrine and albumin to increase mean arterial pressure by 20%, and increase central venous pressure to 10–12 mmHg. Given the prospective nature of our project, no attempt was made to alter management based solely upon changes in EEG.

3. Results

We included 32 of 40 consecutive SAH patients in our analysis. These 32 met selection criteria as acute aneurysmal SAH and had EEG monitoring during the period of documented vasospasm. Eight patients were excluded for the following reasons: 3 did not have acute SAH; 3 did not have EEG during the period of vasospasm; two had only 1 day of EEG monitoring.

There were 25 (79%) females and 7 (21%) males with a mean age of 55 years. Among our patients, 19/32 (59%) developed vasospasm with onset occurring an average of 6 days after hemorrhage (range 0–16 days). In these 32 patients, the EEG tracings revealed dominant frequencies averaging 6–7 Hz. Focal hemispheric delta activity was seen in 20/32 cases, corresponding in each case to known hemispheric dysfunction. The other patients had no focal slowing. During the course of ICU monitoring all 19 patients with vasospasm had a temporally associated decrease in RA variability by EEG trend analysis. Among these, 15/19 patients had a qualitative variability decrease of two grades (e.g. from 4 to 2) at the time of vasospasm. Of these 15 patients, the RA variability decreased at the time of vasospasm in ≥4/6 monitored channels in 11/15 patients and in ≥2 monitored channels in the remainder. The other 4/19 patients had poor or fair qualitative variability from the onset of EEG monitoring, which remained static or improved after therapy. The quantitative variability scores ranged from 0.05 to 0.45 (mean 0.24, SD 0.09) and became decreased in all 19/19 patients at the time of vasospasm (mean 0.17; SD 0.06) (P < 0.0016, two-tailed t test). The decrease ranged from 0.05 to 0.32 with a mean decrease of 0.15 for the 15/19 patients with a qualitatively observed decline at time of vasospasm. With resolution of vasospasm the quantitative scores returned to values similar to those at baseline (e.g. before vasospasm occurred). Thus there was no statistical difference in values before and after vasospasm (P < 0.68, two-tailed t test).

Decreased RA variability preceded TCD or angiographic documentation of vasospasm by more than 2 days in 10/19 patients (mean 2.9 days, SD 1.73), and it occurred on the same day in 4/19 patients. In 5/19 patients EEG monitoring was begun after the TCD documentation of vasospasm, with a decreased RA variability being present from the start of monitoring. In Fig. 2 the temporal profile of RA variability demonstrates that RA variability declined in conjunction with vasospasm and later returned to excellent or good variability in 12/19 patients after resolution of vasospasm. In all cases in which RA variability changes preceded TCD diagnosis, TCD was done on a daily basis during the critical time examined. Fig. 3 demonstrates a decrease in RA variability to grade of 1 (arrowhead) 2 days prior to TCD MCA.
Fig. 3. Day-by-day trend of transcranial Doppler, middle cerebral artery (MCA) mean velocity and left hemisphere RA variability qualitative score. The RA variability decreases from good (3) to poor (1) to fair (2) by day 5 (arrowhead) after subarachnoid hemorrhage, whereas the transcranial Doppler surpasses MCA velocity 120 cm/s on day 7, 2 days later (horizontal arrow). Thus the EEG displayed a change in neuronal activity preceding the diagnosis of vasospasm. RA variability improves as hypertensive therapy is given (vertical arrow).

mean velocity reaching the vasospasm range (arrow). An example of the evolution of baseline, decreased and normalized RA variability and the corresponding raw EEG in one patient with vasospasm is shown in Fig. 4. Mean peak dominant frequency decreased at the time of decreased alpha variability from 6.6 ± 1.5 Hz (range 6–9) to 5.6 ± 1.0 Hz (range 4–9). The background EEG demonstrated increased amounts of low amplitude theta (20–25 μV, 5–7 Hz) with less abundant faster frequencies.

Thirteen of 32 patients did not have vasospasm (non-vasospasm group). Seven of these 13 patients also developed decreased variability. Five patients had grade 2 or worse variability from the beginning of monitoring and improved by the end of monitoring. A single patient had grade 4 variability and worsened to grade 1 after an embolic stroke during an endovascular procedure, while the remaining patient had a transient decrease from grade 3 to grade 2 coincident with increased ICP. In summary, decreased RA variability in the non-vasospasm group correlated with increased intracranial pressure (1), recurrent hemorrhage and herniation (1), embolic stroke during endovascular procedure (1), hemiplegia during the ICU stay (3), and recurrent hemorrhage (1). In contradistinction with the vasospasm group, no statistically significant decrease in quantitative RA variability occurred during the period of monitoring. Specifically, no significant change occurred in RA variability of the non-vasospasm group from the beginning to the middle of monitoring (two-tailed t test, P < 0.29), nor from the beginning to the end of monitoring (two-tailed t test, P < 0.31).

In the vasospasm group, other possible confounding causes of altered EEG were considered to be present in 5 patients. Intraparenchymal hemorrhage in the frontal lobe was found in one patient who developed decreased RA variability during vasospasm. Elevated intracranial pressure occurred concomitantly in one patient with vasospasm. Hydrocephalus was found in 7 patients at the time of admission and in 27 patients may have independently contributed to initial decreased variability. However, during vasospasm, no clear cases of combined hydrocephalus and vasospasm occurred that could easily explain a decrease in RA variability. In fact, in one patient who had worsening of hydrocephalus on post-bleed day 2 had excellent RA variability on that day. These patients had no temporally related occurrences of meningitis, hepatic insufficiency or metabolic coma. One of 32 patients had late onset ventriculitis, which began 14 days after subarachnoid hemorrhage after the study period ended. The mean serum sodium on the day of decreased RA variability in the vasospasm group was 139.9 mEq/l (SD 4.81).

The raw EEG during vasospasm showed decreased amplitude across all frequencies. However, it was difficult to see the difference in raw EEG when comparing a 30 s segment taken during vasospasm with a similar segment taken before. In contrast, changes in RA variability were easily appreciated. After resolution of vasospasm, the fronto-temporal and temporal-parietal derivations have more bilateral slowing and increased amplitude seen in the raw EEG tracing. In contrast, the increased variability of the relative alpha trends were more easily appreciated. By visual inspection of EEG tracings alone, the raw EEG during a peak in the variability histogram was not easily distinguishable from that taken during a trough in the histogram.

Inter-rater agreement on qualitative visual scoring was 100% for qualitative visual scores of poor (1) and good
(4), while scoring between scores 2 and 3 revealed 10% disagreement. There was 100% agreement between readers for calculated RA variability within an error of ±2%. In all cases the onset of decreased RA variability was agreed upon between the two readers.

Mean global xenon CBF measurements during the period

Fig. 4. An example of individual continuous histogram RA trends and corresponding EEGs before vasospasm, during vasospasm and after resolution of vasospasm for one patient who had vasospasm after SAH. RA trends of 8–12 h for each EEG electrode are plotted right hemisphere over left hemisphere sequentially. Prior to vasospasm the patient had good (3) RA variability, and during vasospasm the RA variability declines to poor (1). After hypervolemic, hypertensive therapy the RA variability improved to excellent (4). This patient made a full neurologic recovery. Technicians' annotations and labels are present.
of decreased RA variability was 38.8 ml per 100 g per min (SD 10.6). This is at the lower limit of our laboratory normal values. The xenon CBF measurements were performed within 48 h of RA variability change but were performed after vasospasm had been documented and hypervolemic hypertensive therapy had begun. Follow-up global XeCBF studies that were done in 7 patients after RA variability had improved by at least 1 grade, revealed bilateral increases in CBF to 47.4 ml per 100 g per min (SD 13.7). While not statistically significant (P < 0.08), the increase over time was biologically meaningful in that patients improved overall to within the normal range of cerebral blood flow when RA variability improved.

GCS mean at the time of decreased variability was 11 and GCS mean motor score was 5. Clinical exam revealed 6/19 patients having focal hemiparesis, 7/19 with a decreased level of consciousness, 1/19 with a non-fluent aphasia and 5/19 without focal deficits. Symptomatic vasospasm was considered to be present in 7/19 patients, whereas the remaining patients had neurologic deficits due to other causes, such as primary hemorrhage or edema. Table 1 summarizes these data. Ultimately, by time of discharge, 1/19 died, 4/19 were left in a minimally responsive state, 8/19 had mild or moderate deficits and 6/19 had no deficits. Glasgow Outcome Scale scoring (GOS) at discharge revealed good outcome (GOS 4–5) in 6 patients, moderate disability (GOS 3) in two patients, severe disability (GOS 2) in two patients and death (GOS 1) in two patients. Three patients developed reduced RA variability that persisted until the end of monitoring and had evidence on final CT scan of infarction (2/3) and new hemorrhage with herniation (1/3). CT scans performed at time of discharge revealed infarction secondary to initial insult in 3 patients, edema and resolving subarachnoid hemorrhage in 7 patients, residual intracranial hemorrhage in two patients, and a new cerebellar hemorrhage and herniation in one patient.

Overall, we found that 26/32 patients developed decreased RA variability, and 6 patients had preserved RA variability. Decreased variability was 100% sensitive but only 50% specific for vasospasm. The positive predictive value was 73% and the negative predictive value was 100%. Neurologic complications associated with reduced RA variability and the number of such patients are as follows: vasospasm alone (14/19), vasospasm with possible diagnostic information of the 19 patients with vasospasm, showing location of aneurysm, deficit occurring at time of vasospasm, the presence of increased intracranial pressure, motor score component of the Glasgow Coma Scale and Glasgow Outcome Scale of neurologic deficits

<table>
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<th>Patient</th>
<th>Age (years)</th>
<th>Aneurysm location</th>
<th>Deficit at time of vasospasm</th>
<th>Increased ICP</th>
<th>GCS motor</th>
<th>GOS at discharge</th>
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Eight patients had a decreased level of consciousness concurrent with vasospasm, and a total of 14/19 patients had concurrent neurologic deficits at the time of vasospasm; 12/19 patients had some degree of neurologic deficit upon discharge. A Comm, anterior communicating artery; Ant Choroid, anterior choroidal artery; P Comm, posterior communicating artery; LICA, left internal carotid artery; LMCA, left middle cerebral artery; Dec LOC, decreased level of consciousness; No, not present; Y, intracranial pressure (ICP) over 20 mmHg for over 5 min. GCS, Glasgow Coma Scale; GOS, Glasgow Outcome Scale at discharge from hospital; HP, hemiparesis.
confounding neurologic process (5/19), increased intracranial pressure (1), recurrent hemorrhage and herniation (1), embolic stroke during endovascular procedure (1), hemiplegia during the ICU stay (3), and recurrent hemorrhage (1). In total, 12/32 patients had both reduction in RA variability and defined ischemic lesions on final CT scan.

4. Discussion

Despite the recent advances in treatment, secondary injury after SAH from vasospasm remains an important cause of co-morbidity. Early identification of vasospasm using customary monitoring techniques (e.g. TCD) is imperfect because TCD testing occurs at distinct times with lengthy intervals between tests, is rarely used as a continuous monitor, and because it only indirectly monitors brain function. In addition, neurologic examination and use of the GCS are often difficult to interpret in SAH patients in the ICU setting. Discrete EEG recordings and EEG total power have been found to be abnormal in patients who develop vasospasm (Labar et al., 1991; Rivierez et al., 1991) but similarly lack continuous sampling ability. Thus detecting vasospasm and initiating therapy is often delayed until clinical deterioration has occurred or until vasospasm is documented by angiography. Despite the advances made in treating vasospasm, neurologic morbidity and mortality remain high, perhaps in part due to the delay in diagnosis.

Our previous work on continuous ICU EEG monitoring has concentrated on technical development of automated bedside trending. Trends of total power or relative alpha were used to identify complications and non-convulsive seizures in ICU patients. Bedside displays of EEG trends are an adjunct to the review of the EEG tracings themselves, which we store and review. EEG tracings themselves are often helpful in the neurologic ICU environment. Jordan found that continuous EEG monitoring contributed to the medical management in the majority of neurointensive care patients in one series and was able to detect subclinical seizures in a many patients (Jordan, 1993).

We report here finding decreased relative alpha (RA) variability using quantitative EEG monitoring with vasospasm. In all 19 of our cases of vasospasm the patients had simultaneous decreased RA variability, yielding a sensitivity of 100% and positive predictive value of 73%. Seven patients without vasospasm or neurologic dysfunction had preserved variability. Thus, the negative predictive value was 100%. In the 14 patients monitored prior to the development of vasospasm, 10/14 had decreased RA variability at least 2 days prior to TCD documentation and 4/14 had same-day changes of RA variability and TCD. Therefore, on direct comparison of daily TCD with cEEG monitoring, the RA variability detected brain dysfunction in patients with vasospasm before TCD detection in over 70% of patients. Thus the use of continuous EEG monitoring in SAH provides timely information regarding brain dysfunction in patients with vasospasm that are detected by daily TCD measurements.

Our two methods of measurement, qualitative visual inspection or quantitative calculation, detected this decrement equally well. The quantitative calculation lends objective credence to the method of visual scoring and permits numerical representation of variability. Future digital automation of this scoring may allow easy objective assessment and monitoring of RA variability. Decreased RA variability preceding vasospasm may represent subclinical impairment of cerebral function occurring while vasospasm is developing but is not yet readily identifiable by TCD.

Decreased RA variability usually occurred in a global fashion and correlated with hemispheric and global mildly decreased blood flow (38.8 ml per 100 g per min.). This finding further suggests that at this mild level of decreased blood flow there is cerebral dysfunction that can be identified and followed electrophysiologically in the ICU patient. When therapy for vasospasm was initiated, there was an increase in RA variability corresponding with a CBF increase from 38.8 to 47 ml per 100 g per min. Although there are data from only 7 patients and the magnitude of the change is not statistically significant, it is consistent with previous CBF studies in SAH (Jakobsen et al., 1990; Kawamura et al., 1992). It also suggests a reversible dysfunction that corresponds to relative ischemia. The persistent reduction in RA variability in the 4 patients with ischemic deficits not due to vasospasm suggests that RA variability is sensitive to ischemic injury, and the lack of 'return' to normal variability suggests that a deficit will be persistent. Confirming the prognostic value of persistent versus reversible changes in RA variability, however, would require a prospective trial with daily CBF studies and matched RA variability to determine if the return of moderate or good variability occurs with enhanced CBF. If a threshold CBF below which RA variability is decreased could be determined, then this might be used as a guide to therapy.

The corresponding decrease in EEG peak frequency from 6.6 to 5.6 Hz that occurs with vasospasm and decreased CBF corresponds to earlier work of Ingvar et al. (1976), which reported strong correlation between an EEG mean frequency index and regional CBF measures in chronically brain-injured patients. In acute and subacute stroke, the correlation between quantitative EEG measures and cerebral blood flow have been reported previously (Tagawa et al., 1978; Sainio et al., 1983; Nuwer et al., 1987; Nagata et al., 1989; Suzuki et al., 1996). The percent alpha and the power ratio index, [(delta + theta)/(beta + alpha)], correlated best with cerebral blood flow in the acute ischemic period. Oxidative brain metabolism (CMRO$_2$), however, did not correlate with any of the quantitative EEG parameters in acute ischemia (Nagata et al., 1989). Delta activity ipsilateral to the blood flow deficits have been reported by others (Tolonen and Sulg, 1981; Nagata et al., 1989). Conversely, percent alpha correlates best with cerebral blood flow in the acute and chronic stages and is best able to detect
improvement in cerebral blood flow over time. Our findings of decreased RA variability occurring with vasospasm-related decreased cerebral blood flow, as well as findings of consistent improvement in RA variability upon resolution of vasospasm, are consistent with the previous reports of reliability of percent alpha correlating with cerebral blood flow. Thus, percent alpha and RA variability may be used to detect relative changes in CBF in a continuous manner in the acute post-injury period. Nonetheless, EEG provides any direct measure of CBF or CMRO2 themselves. EEG can provide a general warning that brain ischemia may be occurring without making a formal diagnosis.

Literature regarding the ischemic penumbra supports the idea that reversible neuronal dysfunction may occur at CBF levels well above those of cell death. Traditional electrophysiologic dysfunction begins to occur at CBF below 23–25 ml per 100 g per min (Sharbrough et al., 1973). Animal models suggest that reversible neurologic deficits may occur at CBF levels that exceed the clinical threshold of ischemia (Jones et al., 1981; Mies et al., 1991; Paschen et al., 1992). Thus, decreased RA variability may represent a subclinical, reversible, change in neuronal function at CBF measures higher than could be previously detected by traditional EEG. One may speculate that decreased RA variability occurs with decreased CBF that is sufficient to alter the normal neurophysiology responsible for rhythmic fluctuation in alpha activity, namely the cortico-thalamic loop. Oligemia in the basal ganglia may affect thalamic firing patterns and perhaps decrease the variability of the thalamic discharges which in turn leads to less variability of alpha activity. Vasospasm typically develops and is most severe in the proximal intracranial arteries near the circle of Willis and possibly may affect the microcirculation to the basal ganglia prior to affecting most distal cortical structures. A theoretical construct explaining our findings would be that the small perforating vessels, such as the lenticulostriates, may be affected by subarachnoid blood and undergo vasospasm before larger vessels, such as the proximal middle cerebral artery M1 segment. This proximal vasospasm of the lenticulostriate vessels in turn may cause dysfunction of the basal ganglia and decrease alpha variability that manifests as a decrease in RA variability. Such vasospasm cannot be detected by changes in MCA velocity due to the technical inability of TCD to sample blood flow velocity in these small vessels, and thus the EEG may change prior to the MCA velocity. This theory of proximal small vessel vasospasm is also consistent with the decreased level of consciousness seen with vasospasm. In support of this speculation, 3 patients with vasospasm-associated reductions in RA variability developed basal ganglia infarctions seen on final CT scan. While it is unknown if vasospasm induced these basal ganglia infarctions or they were due to other causes (e.g. primary SAH) remains questionable, this lends anatomic support to the theory.

An alternative cause of early decreased RA variability is distal spasm of pial-cortical vessels that give rise to EEG abnormalities prior to vasospasm detection in the proximal MCA trunk. Distal spasm is difficult to detect using TCD, although an increase in the pulsatility index may signal the development of distal spasm. Our study was not designed to specifically determine pulsatility indices in our patients so this remains an open question. Another possible explanation of decreased RA variability is a direct toxic effect of blood products on neuronal pathways. This possibility is difficult to test given the difficulty in quantitating the volume of subarachnoid blood and testing the effect of this volume on EEG over time.

It is important to point out that the results of our study are limited in several ways. First, the effects of sedative agents could not be well controlled for given the experimental design and the ethical necessity to treat patients. Secondly, it is difficult to separate the effects of confounding neurologic complications from those of vasospasm on RA variability. In 5 vasospasm patients other concurrent processes such as hydrocephalus or raised intracranial pressure possibly may have contributed to some extent to RA variability. In 5 of the 19 cases the changes in RA variability may have been due to these other neurologic complications alone, although the temporal course of RA variability changes suggests otherwise. Third, the effect over time of the initial neurologic insult from SAH (e.g. cytotoxic edema) may have contributed to a reduction in RA variability in the first week after hemorrhage that may be unrelated to vasospasm but have a similar time course and thus influence our results. The study sample is too small to adequately control for effects of any of these possible confounders in a meaningful way. Thus a careful assessment of all possible causes of neurologic compromise still needs to be performed when reduction in RA variability is found.

Despite these reservations, these findings are the first to delineate a decrease in RA variability that is temporally associated with vasospasm. Given that delayed ischemic neurologic deficits continue to occur in 15–20% of SAH patients who are treated using conventional TCD diagnosis of vasospasm (Dorsch, 1995), one could pose the question whether to monitor RA variability in all patients after SAH. In our vasospasm group, 9/19 patients had a large volume of subarachnoid blood on initial CT and were considered high risk for vasospasm whereas 10 were not. Perhaps a strategy to decide which SAH patients should undergo RA variability monitoring may be devised based on clinical grounds, such as initial risk of vasospasm, but this remains to be studied. A second question that arises is, once other causes of decreased RA variability are excluded, should specific treatment for vasospasm be begun prior to documenting either the TCD or angiogram criteria for vasospasm to avoid any possible ischemic complication? Our data suggest that reduced RA variability is associated with ischemic complications of SAH (as confirmed by final CT scan) in a total of 12/32 patients, but we have not studied the efficacy of hypertensive, hypervolemic, hemodilutional therapy (HHH) on improvement of RA variability or specifically...
on the prevention of final CT ischemic lesions. This remains to be studied.

Presently one cannot recommend beginning HHH therapy at the onset of altered RA variability alone, but rather one needs to exclude other causes of decreased RA variability (e.g. increased intracranial pressure) and then confirm the presence of vasospasm. The use of HHH therapy after detecting decreased RA variability while awaiting confirmation of vasospasm would seem prudent but remains unproven. In summary, relative alpha variability is a highly sensitive yet non-specific predictor of the development of vasospasm that can be monitored continuously and used to initiate and to guide therapy.

References