Early and persistent impaired percent alpha variability on continuous electroencephalography monitoring as predictive of poor outcome after traumatic brain injury

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Object. Early prediction of outcomes in patients after they suffer traumatic brain injury (TBI) is often nonspecific and based on initial imaging and clinical findings alone, without direct physiological testing. Improved outcome prediction is desirable for ethical, social, and financial reasons. The goal of this study was to determine the usefulness of continuous electroencephalography (EEG) monitoring in determining prognosis early after TBI, while the patient is in the intensive care unit.

Methods. The authors hypothesized that the reduced percentage of alpha variability (PAV) in continuous EEG tracings indicates a poor prognosis. Prospective continuous EEG monitoring was performed in 89 consecutive patients with moderate to severe TBI (Glasgow Coma Scale [GCS] Scores 3–12) from 0 to 10 days after injury. The PAV was calculated daily, and the time course and trends of the PAV were analyzed in comparison with the patient’s Glasgow Outcome Scale (GOS) score at the time of discharge.

In patients with GCS scores of 8 or lower, a PAV value of 0.1 or lower is highly predictive of a poor outcome or death (positive predictive value 86%). The determinant PAV value was obtained by Day 3 after injury. Persistent PAV values of 0.1 or lower over several days or worsening of the PAV to a value of 0.1 or lower indicated a high likelihood of poor outcome (GOS Scores 1 and 2). In comparison with the combination of traditional initial clinical indicators of outcome (GCS score, pupillary response to light, patient age, results of computerized tomography scanning, and early hypotension or hypoxemia), the early PAV value during the initial 3 days after injury independently improved prognostic ability (p < 0.01).

Conclusions. Continuous EEG monitoring performed with particular attention paid to the PAV is a sensitive and specific method of prognosis that can indicate outcomes in patients with moderate to severe TBI within 3 days postinjury.

KEY WORDS • traumatic brain injury • neurosurgery intensive care unit • percentage of alpha variability • secondary insult • prognosis

To date, prognosis has been based on early clinical assessments (such as patient age, GCS score, findings on the admission CT scan, systemic variables (that is, early hypotension and elevated ICP), and lesion type (for example, acute subdural hematoma). In addition, snapshot assessments of brain function have been performed to determine functional prognosis. Formal 20-minute EEG, including evaluation of sleep potentials and quantitative measures of EEG, have been used to determine prognosis. Combinations of EEG and evoked potentials have demonstrated added prognostic value. In contrast with brain electrophysiological testing, measures of brain blood flow and oxidative metabolism have been useful in documenting ischemic events that worsen patient outcome, but have added little in terms of prognosis. Despite these advances, early direct assessment of brain function to determine prognosis is not widely performed and such testing does not influence clinical decisions.

Abbreviations used in this paper: CSA = compressed spectral array; CT = computerized tomography; EEG = electroencephalography; GCS = Glasgow Coma Scale; GOS = Glasgow Outcome Scale; ICP = intracranial pressure; ICU = intensive care unit; PA = percentage of alpha; PAV = PA variability; ROC = receiver operating characteristic; SAH = subarachnoid hemorrhage; SD = standard deviation; TBI = traumatic brain injury; TCDB = Traumatic Coma Data Bank.
Percentage of alpha variability and prognosis

The use of quantitative electrophysiological monitoring to determine prognosis has a relatively short and sparse history. Bricolo and colleagues used a form of EEG monitoring, CSA, to determine prognosis after acute brain injury. These authors’ main finding was that a monotonous CSA profile was prognostic of poor outcome (that is, a persistent vegetative state or death). In previous work in comatose patients suffering from aneurysmal SAH, our group reported monotonous trends in the PA activity in patients with vasospasm and brain infarction. This monotonous trend is termed “poor PAV.” Poor PAV has been found in patients with brain trauma who suffer from persistent coma associated with reduced brain glucose metabolism. Because poor PAV is similar to the monotonous CSA described by Bricolo and colleagues, we hypothesized that patients suffering from TBI together with impaired PAV would have a poor outcome. This paper describes a prospective observational study in which we tested the utility of the PAV, derived from continuous EEG monitoring during the early intensive-care phase of TBI treatment, in predicting patient outcome at the time of discharge.

Clinical Material and Methods

Patient Selection

Prospectively, all patients with moderate to severe TBI admitted to the neurosurgical ICU were enrolled into this study, under the auspices of the institutional review board consent process. The inclusion criteria were as follows: GCS scores of 14 or lower, TBI, patient age of 16 to 80 years, direct admission to the University of California at Los Angeles hospital, and abnormal findings on the admission CT scan. Patients were excluded if the admission neurological examination demonstrated brain death or if the patient’s GCS score improved to higher than 14 within 8 hours after admission. Patients receiving pentobarbital- or propofol-induced burst suppression were excluded from analysis, because burst suppression is associated with a reduction in the PAV. Other exclusion criteria included preexisting neurological disorder and overwhelming concurrent hepatic or metabolic encephalopathy.

Monitoring Protocol

Continuous EEG monitoring started within 6 hours after the patient had been admitted to the ICU and continued for 10 days after injury or until the patient was discharged from the ICU. Monitoring was performed for 24 hours each day and the EEG data were stored on a computer hard drive; monitoring was interrupted only for transportation of the patient for imaging sessions. The EEG data were continuously displayed at the bedside and were available to treating nurses and physicians for review. Specific EEG data, such as the presence of seizures, were incorporated into other diagnostic information by the treatment team and dealt with appropriately. All EEG data were then stored digitally onto a new technology (NT)-based system hard drive or to a data tape for archival purposes.

The monitoring protocol has been previously described. Briefly, a 10-electrode, 14-channel montage was used to assess electrical activity. This montage incorporates eight channels of CZ-referenced activity and eight channels of bipolar derivations. The EEG data were then further processed by fast-Fourier transform to generate spectra of the PA activity. The bandwidth for the PA used in this study was 6 to 14 Hz, which has been standardized in previous reports.

Treatment Protocol

This treatment protocol has been previously described. All patients underwent continuous EEG monitoring in the neurosurgical ICU as part of the standardized protocol. In patients requiring an initial emergency operation, the EEG monitoring was initiated after admission to the ICU. Intracranial pressure monitoring was performed using ventriculostomy and/or pressure transducer systems, and the ICP was kept below 20 mm Hg by using a stepwise management strategy that included cerebrospinal fluid drainage, hyperventilation to a PCO2 of 30 to 35 mm Hg, and administration of mannitol. Cerebral perfusion pressure was kept equal to or greater than 70 mm Hg by using phenylephrine when required. Patients with a GCS score of 8 or lower, in whom there were normal coagulation parameters, underwent jugular venous oximetry monitoring, which was performed using a No. 4 French oximetry catheter. All patients received a phenytoin loading dose (14–18 mg/kg) on admission to the emergency department and continued to receive phenytoin for at least 7 days. Daily total serum phenytoin levels were determined and additional boluses of the agent were given to maintain the level between 10 and 20 mg/dl. Sedation was maintained either by intermittent intravenous administration of midazolam and morphine or by continuous infusions of these drugs. Electroencephalography segments recorded during sedation maintained by greater than 2 mg/hour of midazolam or morphine, or during infusion of propofol at doses higher than 20 μg/kg/min were excluded from this study.

Scoring of the EEG Trend

Scoring of PA trends was identical to that used in previous reports. Histogram trends of PA were printed at an identical scale (15%/7-mm height) every 8 hours. These PA trends were then collected and later scored for their variability (PAV) by a trained technician blinded to the clinical scenario and patient outcomes. Confirmatory scoring was performed in a blinded fashion by an electroencephalographer (P.M.V.). The raw EEG waveforms were reviewed to identify artifacts that may have contaminated the trends. All artifact-based trends (3% of available trends) were excluded from scoring.

The PAV score was determined by visually identifying three points on the PA histogram: the PA baseline value, the PA peak value, and the PA trough value that most directly followed the peak (Fig. 1). The baseline value is the mean PA occurring during the 4 hours before a peak occurred. The PAV is calculated using the following formula: (peak PA – trough PA)/peak PA + trough PA. This yields a fractional value with a range of 0.05 to 0.5. An average of three calculations was performed on each electrode derivation each 8-hour period (nine calculations for each day). Of the 14 channels of the PA trend, two representative channels were scored for each day, yielding one value for each hemisphere for each day. The former operational scoring schema was based on the similarity of PA trends within each hemisphere and the lack of a significant SD (0.009) of PAV.
measurements between different channels. The independent hemisphere values were averaged day by day, generating a global daily PAV value. The results are reported as the daily global PAV value for each patient.

**Primary PAV Analysis**

Daily PAV values were plotted for each patient. The initial, worst, best, and final PAV values were identified from these daily global values. The worst and best PAV scores were determined by scoring those trends that first characterized the best or worst trend. Thus, if two individual trends exhibited poor variability, the trend that occurred earliest was scored as the worst. Similar rules were applied to identify and score the best PAV trend. Initial and final PAV scores were determined chronologically, rather than according to PAV trend characteristics. Once the PAV for each time point was scored, the postinjury day on which each of these scores had occurred was identified.

**Statistical Analysis**

Results are reported as the means ± SD. The daily PAV values were symmetrically distributed and no transformation was required for analysis. Note also that results of corresponding nonparametric analyses were found to agree very well with the parametric analyses reported in this paper. Two sample t-tests and a chi-square test of independence were used to examine relationships between groups for parametric PAV data. Linear regression analysis was performed among the worst, best, Day 0 through 3 average, and final PAV score, or the pattern of PAV over time, with each of the following clinical parameters: primary lesion type according to CT scanning, new brain lesion ipsilateral to the PAV, patient age and sex, admission GCS score, and discharge GOS $^{25}$ score. Logistic regression analysis was performed to examine the predictability of the GOS score by using the PAV time courses. Mixed-effects linear and logistic regression models $^{25}$ were used to classify the within-patient time courses of the PAV, as described in the text.

**Results**

**Patient Demographics**

We performed continuous EEG monitoring in 89 patients suffering from TBI who were consecutively hospitalized from October 1995 to April 1998. The group consisted of 72 men and 17 women, with a mean age of 39 ± 18.2 years. The median admission GCS score was 7 (mean 7.4 ± 4). Fifty-five patients were assigned admission GCS scores of 8 or lower, 17 patients had scores of 9 to 12, and 17 patients had scores of 13 or higher. The mean admission injury severity score was 20.4 ± 9. The mechanisms of injury were categorized in the following manner: motor vehicle accidents (27 patients), motorcycle accidents (26 patients), falls (15 patients), pedestrians struck by automobiles (eight patients), bicycle-related falls (six patients), assaults (three patients), and gunshot wounds (four patients). The types of diagnoses based on CT scanning results included the following: hemorrhagic contusion (36 patients), acute subdural hematoma (14 patients), isolated traumatic SAH (nine patients), epidural hematoma (six patients), and gunshot wounds to the head (four patients). Surgical evacuation was performed in 36 patients, whereas the remaining 53 patients underwent ventriculostomy and medical management. The mean length of stay in the hospital was 17.6 ± 11.4 days. Patient outcomes at the time of discharge, based on GOS scores, were as follows: death (21 patients), severe disability (18 patients), moderate disability (21 patients), and mild disability/good recovery (29 patients). The mortality rate was modestly higher in patients with GCS scores of 8 or less (26%) compared with that in patients with GCS scores of 9 or greater (21%; p < 0.3).

**Monitoring Details**

Continuous EEG monitoring was begun within 8 hours after admission in 80% of patients and within 24 hours after admission in the remainder. The mean interval from time of admission to the start of monitoring was 9.6 ± 5.4 hours. The mean duration of monitoring was 144 ± 66 hours. The median number of days of trend analysis was 6. Contamination of EEG waveforms by movements and electrical artifacts accounted for 11% of the entire record and consisted

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**FIG. 1.** Typical 8-hour trend of PA in three channels is shown. The peak and trough of the histogram are marked, indicating the sites used to determine the quantitative PAV score.

**FIG. 2.** Bar graph showing the distribution of the predominant background rhythm frequency of the raw electroencephalogram in all patients. The most common frequency rhythm was 5 to 7 Hz.

Receiver operating characteristic curves were constructed to determine predictive values of the PAV at clinically predetermined time points. A classification tree analysis was used to determine a critical threshold value of the PAV that indicates prognosis at the earliest time after injury. $^{6}$
most often of anticipated scalp muscle activity and drug-induced burst suppression. These segments of EEG recordings were excluded from the analysis. No scalp or skin infections occurred and no patients complained of needle electrode–related pain.

**Percentage of Alpha Trends**

A total of 1208 trends of the PA were scored for variability (PAV). The number of patients and available trends on each postinjury day varied across the observation period, with most patients monitored within the first 5 days. Figure 3 provides both an overview of the number of patients who were monitored on each postinjury day and the distribution of durations of monitoring (upper and center, respectively). The mean PAV score for the entire group improved gradually over the initial 10 days after injury (Fig. 3 lower). The mean PAV scores ranged from 0.09 ± 0.05 on the day of injury to 0.19 ± 0.09 on postinjury Day 10. The large SD reflects differences among patients on each postinjury day.

The PAV scores demonstrated one of four patterns of evolution during the ICU observation period. The patterns and number of patients in each category were as follows: Pattern I, initially poor PAV scores with late improvement (31 patients); Pattern II, sustained good or excellent PAV scores from beginning to end of monitoring (28 patients); Pattern III, sustained poor PAV scores from beginning to end of monitoring (23 patients); Pattern IV, PAV scores that worsened to poor during monitoring (seven patients). No more than one pattern was found for each patient. This expert-derived classification into four patterns was statistically validated using a mixed-effects linear model to estimate individual patient trajectories of PAVs. The estimated trajectories were then categorized into one of four patterns. The agreement between the physician’s classification and the statistical classification was excellent (κ = 0.7). In Pattern I, the initial mean PAV score of 0.09 ± 0.04 improved to 0.23 ± 0.06 (p < 0.001, t-test, df = 31). In Pattern II, the initial mean PAV score did not differ significantly from the final score (0.22 ± 0.09 compared with 0.25 ± 0.08; p < 0.09, t-test, df = 28). In Pattern III, the PAV score remained poor throughout the monitoring period, with similar starting (0.06 ± 0.02) and final (0.09 ± 0.03) mean values. In Pattern IV, the mean PAV score significantly decreased from initial (0.18 ± 0.07) to final (0.09 ± 0.02) scores (p < 0.02, t-test, df = 8). These patterns are shown in Fig. 4.

The PAV patterns corresponded with eventual outcomes. The PAV Patterns I and II correlated with good outcomes in contrast to PAV Patterns III and IV; a larger percentage of patients having PAV Patterns I and II attained a good outcome (p < 0.03). These results are summarized in Table 1. Of the 31 patients with Pattern I, four died, whereas 13 attained good outcomes (GOS Score 4 or 5). The mortality rates were higher for Patterns III and IV (39% and 57%, respectively) compared with Patterns I and II (13% and 4%, respectively).

**Predictability of Outcome in Patients With GCS Scores of 8 or Lower**

The utility of the PAV in predicting outcomes in patients with GCS scores of 8 or lower was considered by evaluating the initial, worst on Days 0 through 3, best, and final PAV scores in patients with good outcomes (GOS Score 4 or 5) compared with scores in patients with poor outcomes.
(GOS Score 1 or 2). The initial PAV score was statistically lower in the poor outcome group (0.11 ± 0.08) compared with the good outcome group (0.17 ± 0.11; p < 0.02, t-test, df = 28). Similarly, the final PAV score was lower in the poor outcome group (0.13 ± 0.09) compared with the good outcome group (0.21 ± 0.09; p < 0.01, t-test, df = 28). There was a statistical difference between poor and good outcome groups with respect to the worst PAV score (p < 0.04) or the best PAV score (p < 0.02). In contrast, in patients with GCS scores of 9 or higher, no statistical relationship between the PAV and dichotomized outcome was found at any of the four target time points. Table 2 outlines differences in PAV scores at the four time points in patients with GCS scores of 8 and lower and those with scores of 9 and higher, separated by GOS scores.

Critical Threshold of the PAV

Using classification tree analysis, critical thresholds that predicted outcome were determined. Within the initial 3 days after injury, a single or average PAV value of 0.1 or lower was highly predictive of poor outcome or death (86%). Death was highly likely if the mean PAV value was lower than 0.07 during the initial 3 days. In contrast, good outcome became more likely if the mean PAV value was greater than 0.15 (positive predictive accuracy = 0.75) during the first 3 days after injury. Nevertheless, the specificity of good outcome based on the mean PAV score by postinjury Day 3 was low (54%); this was caused by the incidence of later deterioration in the PAV score, which occurred in response to clinical deterioration.

Outcome Prediction: Comparison of the PAV to Traditional Prognostic Factors

The predictive value of the PAV was assessed using a structured statistical approach of all relevant data. Table 3 presents the area under the ROC curve, sensitivity, specificity, and positive predictive values resulting from logistic regression analysis of variables associated with PAV-predicted outcomes of good recovery (GOS Score 4 or 5) and death (GOS Score 1). A prediction of poor outcome or death with both a sensitivity and a specificity greater than 75% could be made using PAV scores obtained during the initial 3 days of monitoring. In contrast, a prediction of good outcome using PAV scores was less exact, with a sensitivity and a specificity ranging between 55 and 70%.

Traditional admission prognostic factors outlined in the TCD study (GCS score, pupillary response to light, patient age, CT lesion score, and early presence of hypoxia or hypotension) were compared with the predictive power of the EEG PAV. Univariate analysis between the PAV and these factors revealed statistically significant relationships: presence of multiple contusions and PAV Pattern III (p < 0.03), TCDB Grade 2 and PAV Pattern II (p < 0.01), new lesions demonstrated on delayed postinjury CT (> 48 hours) scans and PAV Pattern III (p < 0.02), and bilateral absent pupil reflexes and PAV Pattern IV (p < 0.001).

A series of logistic regression analyses were performed to determine the predictive ability of traditional clinical variables alone and in conjunction with the PAV score. The onefold cross-validated predictive accuracy of the combination of the six clinical variables for predicting death as opposed to survival was 75%, with a specificity of only 38%. With the addition of any early PAV score (initial, worst, average over the first 3 days, pattern of PAV over time, or best PAV), the predictive accuracy increased to 87 to 89% and specificity increased, ranging from 60 to 75% (Table 3). Indeed, the predictive value of the PAV in stand-alone models demonstrates that the average PAV score dur-
Percentage of alpha variability and prognosis

**TABLE 1**

Comparison of outcomes based on the pattern of the PAV over time in 89 patients

<table>
<thead>
<tr>
<th>Pattern Type</th>
<th>No. of Patients</th>
<th>% of Total</th>
<th>GOS Score (%)†</th>
<th>1 or 2</th>
<th>3</th>
<th>4 or 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>31</td>
<td>35</td>
<td></td>
<td></td>
<td>13</td>
<td>42‡</td>
</tr>
<tr>
<td>II</td>
<td>28</td>
<td>31</td>
<td></td>
<td></td>
<td>4</td>
<td>46§</td>
</tr>
<tr>
<td>III</td>
<td>23</td>
<td>26</td>
<td></td>
<td></td>
<td>60</td>
<td>8</td>
</tr>
<tr>
<td>IV</td>
<td>7</td>
<td>8</td>
<td></td>
<td></td>
<td>57</td>
<td>14†</td>
</tr>
</tbody>
</table>

* Description of PAV patterns: I = initially poor PAV score with improvement (≥ 0.2) during monitoring; II = consistently good or excellent PAV score (≥ 0.2) during monitoring; III = consistently poor PAV score (≥ 0.1) during monitoring; IV = PAV score that worsened to poor (≤ 0.1) during monitoring.
† Percentage of patients with particular pattern type.
‡ p < 0.03 (good outcome Pattern I compared with Pattern III).
§ p < 0.02 (good outcome Pattern II compared with Pattern III).
|| p < 0.06 (good outcome Pattern I or II compared with Pattern IV).

For prediction of dichotomized GOS scores (scores of 1 and 2 compared with scores of 4 and 5), the combined six clinical predictors reached a onefold cross-validated predictive accuracy of 67% (specificity 80%, sensitivity 55%). Several of the PAV-related predictors demonstrated considerable improvement. The initial 3-day average PAV score or the PAV pattern (I–IV) increased predictive accuracy to 83% or 79%, respectively, largely due to increased specificity. Thus, the PAV added predictive accuracy of prognosis of dichotomized GOS scores.

**Discussion**

Overview of Results

In this paper we report on a large series of consecutive patients monitored with the quantitative EEG parameter PAV. The PAV was monitored continuously for 10 days following TBI, during the phase of illness in which the patient was kept in the ICU. The main findings of the study should be reiterated. 1) A poor PAV score corresponds with a poor 30-day outcome and a high mortality rate. 2) The PAV score may change from day to day in one of four patterns, with the patterns of change associated with patient outcome. 3) The PAV offers a useful, robust indicator of outcome as early as 3 days after TBI. 4) The PAV is a more sensitive and specific predictor of outcome than the admission GCS score, and adds predictive accuracy and specificity to prognosis when combined with traditional clinical predictors of GCS score, pupillary response to light, patient age, CT scan–demonstrated lesion type, and the presence of early hypotension or hypoxemia. 5) The critical threshold of the PAV is 0.1 and lower. Persistent values below this threshold predict a poor outcome. This method is easy to perform and may assist in improved prognosis in patients with GCS scores of 8 or less.

Limitations of the Study

The prospective observational design of this study inadvertently permits many factors to affect both the EEG and patient outcome. Certainly, many of the sedative agents rou-

**TABLE 2**

Comparison of PAV scores at four time points, segregated by initial GCS score and discharge GOS score *

<table>
<thead>
<tr>
<th>Time Point</th>
<th>GOS Score</th>
<th>p Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 or 2</td>
<td>3</td>
<td>4 or 5</td>
</tr>
<tr>
<td>GCS score ≤ 8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>initial PAV score</td>
<td>0.11 ± 0.08</td>
<td>0.10 ± 0.04</td>
</tr>
<tr>
<td>worst PAV score</td>
<td>0.06 ± 0.03</td>
<td>0.09 ± 0.04</td>
</tr>
<tr>
<td>best PAV score</td>
<td>0.20 ± 0.08</td>
<td>0.20 ± 0.10</td>
</tr>
<tr>
<td>final PAV score</td>
<td>0.13 ± 0.09</td>
<td>0.19 ± 0.13</td>
</tr>
<tr>
<td>GCS score ≥ 9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>initial PAV score</td>
<td>0.09 ± 0.05</td>
<td>0.16 ± 0.10</td>
</tr>
<tr>
<td>worst PAV score</td>
<td>0.06 ± 0.02</td>
<td>0.11 ± 0.06</td>
</tr>
<tr>
<td>best PAV score</td>
<td>0.18 ± 0.14</td>
<td>0.23 ± 0.08</td>
</tr>
<tr>
<td>final PAV score</td>
<td>0.13 ± 0.13</td>
<td>0.20 ± 0.08</td>
</tr>
</tbody>
</table>

* These results demonstrate that for patients with GCS scores of 8 or lower, the PAV score corresponds with patient outcome at the time of discharge. The initial and worst PAV score (by Day 3) discriminates between good outcome and death for patients with GCS scores of 8 and lower, but not for those patients with GCS scores of 9 and higher. All values are expressed as the means ± SD.
† Probability values reflect comparisons of GOS Scores 1 or 2 with GOS Scores 4 or 5.

**TABLE 3**

Sensitivity, specificity, and positive predictive values of the PAV and traditional clinical indicators *

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Area Under ROC Curve</th>
<th>PP Value</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>predicting alive compared with dead (GOS Score 5 compared w/ 1)</td>
<td>initial PAV score</td>
<td>0.75</td>
<td>0.70</td>
<td>0.70</td>
</tr>
<tr>
<td>worst PAV score</td>
<td>0.78</td>
<td>0.74</td>
<td>0.75</td>
<td>0.73</td>
</tr>
<tr>
<td>best PAV score</td>
<td>0.82</td>
<td>0.77</td>
<td>0.75</td>
<td>0.78</td>
</tr>
<tr>
<td>final PAV score</td>
<td>0.84</td>
<td>0.78</td>
<td>0.80</td>
<td>0.78</td>
</tr>
<tr>
<td>TCD B standard indicators</td>
<td>0.75</td>
<td>0.75</td>
<td>0.87</td>
<td>0.38</td>
</tr>
<tr>
<td>TCD B + PAV mean 3 days</td>
<td>0.87</td>
<td>0.78</td>
<td>0.83</td>
<td>0.63†</td>
</tr>
<tr>
<td>PAV Pattern I or II</td>
<td>0.77</td>
<td>0.78</td>
<td>0.79</td>
<td>0.75</td>
</tr>
</tbody>
</table>

predicting good outcome (GOS Score 4 or 5) compared with bad outcome (GOS Score 1 or 2)

| initial PAV score | 0.68 ± 0.64 | 0.55 ± 0.69 |
| worst PAV score   | 0.69 ± 0.55 | 0.62 ± 0.52 |
| best PAV score    | 0.65 ± 0.62 | 0.69 ± 0.59 |
| final PAV score   | 0.70 ± 0.55 | 0.55 ± 0.52 |
| PAV mean 3 days   | 0.72 ± 0.63 | 0.63 ± 0.62 |
| TCD B standard indicators | 0.76 ± 0.67 | 0.80 ± 0.55 |
| TCD B + PAV mean 3 days | 0.83 ± 0.73 | 0.81 ± 0.65‡ |
| PAV Pattern I or II | 0.67 ± 0.67 | 0.84 ± 0.51 |

* PAV mean 3 days = the mean value of the PAV during the first 3 days after injury; PP = positive predictive; TCD B standard indicators = pupillary response to light, CT scan lesion score, GCS score, patient age, early hypotension and/or hypoxemia.
† p < 0.01 for TCD B clinical indicators alone compared with added PAV score.
‡ p < 0.05 for TCD B clinical indicators alone compared with added PAV score.
that lesions of the thalamus play a role in the PAV. A third limitation is the variable periods of observation among patients. Initial and final PAV values do not correlate with the same postinjury day in all patients. This factor may have skewed values toward lower PAVs for Days 6 through 10. A fourth limitation is that death from causes other than primary brain dysfunction may have altered the relationship between the PAV and mortality. Last, we limited determination of clinical outcome to the patient’s state at 30 days because of a predetermined intent to focus on the acute state and the uncertainty of factors that may influence outcome after the acute hospital period. A comparison of the PAV and outcomes at 6 months and 1 year is underway, with more detailed outcome and psychometric testing planned.

The PAV as a Robust and Easy EEG Parameter

The PAV provides a histogram of brain activity and requires little training to read. The use of EEG to predict outcome in a comatose patient is a well-established concept that has been difficult to apply to patients suffering from brain trauma. Several cardinal, raw EEG characteristics may assist in prognosis, namely, sleep activity, responsiveness of the EEG to noxious stimulation, and spontaneous variability.2,17,22,24,26,28,37,38,46,48,55 Other measures of this monitoring system, namely quantitative EEG1,4,47,51 and combinations of EEG and evoked potentials,8,36,20,21,27,41,42 have been used to improve prognosis in comatose patients. Despite these studies, which establish the prognostic significance of EEG, incorporating EEG results into the medical decision-making process has been restricted. This restriction has been due to a lack of confidence in the EEG method by treating physicians, in part due to a lack of familiarity with this modality of monitoring. In contrast, the PAV trend method incorporates a large amount of EEG data and expresses it in an easy-to-interpret histogram that can be tracked over time, similar to other ICU physiological parameters. In this study we have established the critical threshold of the PAV to be 0.1 and lower. Thus, the PAV may become a useful EEG method because it is easy to interpret, the threshold for poor outcome is clear, and the method can be applied by neurosurgeons without EEG training.

Poor PAV Score Predictive of Poor Outcome

The data presented earlier in this paper can be used to argue that the PAV has an additive effect on predictive accuracy of prognosis, when used in combination with traditional clinical parameters. Indeed, the mean PAV value during postinjury Days 0 to 3 has a greater positive predictive accuracy and specificity (86% compared with 75% and 63% compared with 38%, respectively) than the combined traditional predictors (GCS score, pupillary response to light, CT scan–demonstrated lesion type, patient age, and presence of early hypotension or hypoxia). Clinical prognostic parameters identified in previous studies have shown variable predictive values across a number of studies,9,11–14,18,30,33,36 ranging from 60 to 75%. The predictive accuracy of the traditional clinical parameters in our study is similar to those cited in previous reports. Moreover, the mortality rates reported in our study for patients with GCS scores of 8 or lower are similar to those reported in recent placebo-controlled studies.15,43 The apparent reduction in mortality rates from values recorded in the TCDB to those specified in more recent studies may be explained by several factors including a variety of injury severity, improved critical care, and selection bias. With the addition of the PAV, predictive accuracy and specificity are improved. Thus, in the context of overall parity with previous studies and on the basis of findings in the present study we assert that the PAV is a beneficial, timely, and independent prognostic measure.

The PAV Patterns I and II (improving or consistently good PAV score over time) were associated with good outcomes (relatively few patients in this category were in a vegetative state or dead at the time of discharge). Moreover, a PAV score of 0.2 or greater was associated with good outcomes. In contrast, the PAV Patterns III and IV, both of which are defined by poor variability, are associated with poor outcomes. These patterns bear close resemblance to the monotonous CSA pattern described by Bricolo,7 Karnaze,28 and Thatcher51 and their colleagues, which also was used to predict a poor outcome in comatose patients suffering from trauma and those without trauma. The present study builds on previous observations by demonstrating that a consistently poor PAV value is a bad prognostic sign and by outlining a useful time window of PAV observation that is needed to be certain of the prognosis and a critical threshold value of PAV (<=0.1). Thus, by implementing the PAV during the initial 3 days postinjury, one can improve prognostic accuracy and specificity by using a relatively simple measurement.

Percentage of Alpha Variability as a Measure of Thalamocortical Function

The anatomical and physiological basis for the PAV is not completely understood, but it is considered a marker of thalamocortical pacemaker activity. In a previous publication,52 we reported that the PAV worsened in response to vasospasm-induced ischemia after aneurysmal SAH. A poor PAV value correlates with reduction in attention and level of consciousness. The PAV was flat in cases of stroke in the thalamus and other basal ganglia. Postanoxic brain damage leads to a loss of the variability of EEG activity and a poor PAV. In the present study, a poor PAV score was disproportionately associated with more severe CT scan–demonstrated lesion grades and with subcortical damage. Moreover, the PAV became worse (more flat) when new subcortical lesions were apparent on the CT scan. Thus, preliminary evidence indicates that the PAV is an indicator of thalamocortical function and that primary or secondary subcortical injury is associated with a poor PAV value. Disruption of this function may be one explanation of persistent coma after brain injury. Further study of the relationship between the site of injury and specific PAV patterns remains to be done.

Conclusions

Monitoring the PAV is a reliable and robust method used to track brain function in patients suffering from severe TBI (GCS Score <= 8). The PAV increases the sensitivity and specificity of prognosis during the first few days the patient spends in the ICU, in comparison with traditional prognostic variables alone. This relationship is most robust for patients with GCS scores of 8 or less, a population in which
Percentage of alpha variability and prognosis may have significant impact on clinical decisions. Given the uncertainties of prognosis and the inherent ability of the PAV to describe improvement or lack thereof over time, the PAV permits longitudinal objective assessment of the patient. Although it is recognized that most clinicians rely on experience and clinical acumen in decision making and prognosis, the present data demonstrate that the best use of the PAV is as a confirmatory or adjunctive measure to complement other clinical data. This may assist the expert clinician and novice alike. The impact of this assessment on actual decision making and outcome remains to be studied.

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