Quantitative Analysis of EEG Changes during Hypothermia

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Power spectrum analysis of 4-channel EEGs was performed during cooling and rewarming using cardiopulmonary bypass. During rewarming, linear correlations of temperature with the total power and with peak power frequency of the high-frequency band were observed in a significant number of cases (85%, P < 0.0001 and 76%, P < 0.002, respectively). The magnitude of these changes were 1,215 μV²°C⁻¹ (±150 [SEM]) and 0.39 Hz/°C (±0.04 [SEM]). Two other descriptors of the EEG power spectrum (the spectral edge and average frequencies) did not correlate with the temperature changes in a significant number of cases. Changes during cooling followed a similar trend but were more variable, presumably because of other physiologic changes associated with the start of bypass. Knowledge of the relationship of the EEG to temperature should permit distinguishing EEG changes secondary to hypothermia from those caused by acute hypoxia. (Key words: Brain; electroencephalogram. Hypothermia. Monitoring: electroencephalography.)

Because postoperative neurologic deficits continue to contribute to the morbidity following cardiopulmonary bypass, methods of monitoring the adequacy of cerebral oxygenation during cardiopulmonary bypass need to be developed and assessed. These may allow further refinement in the conduct of extracorporeal circulation which will, in turn, reduce morbidity. Electroencephalography, as a non-invasive monitor of cerebral activity, can provide important information about the adequacy of cerebral blood flow. During hypothermia, however, EEG activity slows, as it does during hypoxia, so that the differentiation of hypoxia and hypothermia during cardiopulmonary bypass may be difficult. Accordingly, we undertook a quantitative study of EEG changes during extracorporeal cooling and rewarming in order to determine the EEG changes associated with hypothermia.

Materials and Methods

Thirty-three patients participated in this study which was approved by the Committee on Studies Involving Human Beings of the University of Pennsylvania. Consent for monitoring was obtained as part of the routine preoperative visit. No changes in routine anesthetic or extracorporeal management were introduced, unless the EEG showed evidence of hypotension-induced hypoxia. In such a situation, vasoconstrictors were utilized to elevate the blood pressure. Anesthesia was maintained during extracorporeal circulation with fentanyl, isoflurane, or halothane, depending on the primary agent used in the pre-bypass period. The concentration of the anesthetic agent (or supplemental drug if fentanyl was used) was adjusted as needed by the anesthesiologist caring for the patient.

The EEG was recorded using a four-channel common reference electrode montage. Bilateral frontal (Fp1, Fp2) and central (C3, C4) electrodes were recorded to the right ear (A2), using the left ear (A1) as ground. A 6-db/octave high-pass filter at 4 Hz was used to reduce sweating and motion artifact, both of which can occur during light levels of anesthesia at the termination of bypass. An 18-db/octave low-pass filter at 45 Hz ensured adequate filtration to prevent the introduction of artifact (aliasing) during the digital sampling of the analog signals. After digitizing each channel at 128 Hz and performing a fast Fourier transformation on each two-second (256-point) epoch, the power spectrum for each channel was calculated in 0.5-Hz increments from 0.5 to 45 Hz and was stored for subsequent analysis. Data were displayed using the density-modulated display technique.

Data were recorded continuously from the initiation of bypass until a stable nasopharyngeal temperature was reached, and from the beginning of the rewarming until discontinuation of bypass. Following the establishment of extracorporeal circulation, cooling was performed rapidly, utilizing blood to nasopharyngeal temperature gradients as high as 15° C. Nasopharyngeal cooling occurred at a rate of 1–3° C/min. Rewarming was performed much more gradually, at a rate of 0.1–0.7° C/min, and the blood-body temperature gradient never exceeded 10° C and was usually less than 5° C. This more gradual change, combined with a minimum of changes in perfusion and anesthetic conditions, provided more stable conditions for EEG analysis.

In order to evaluate the behavior of univariate descriptors of the EEG as a function of temperature, an average spectrum was calculated from the 20 s preceding and the 20 s following each measurement of temperature. Four univariate descriptors of this spectrum then were computed. Total power was calculated as the sum of the power in the individual frequencies between 1 Hz and 32 Hz. The power-weighted average frequency was derived using the power measures for each individual frequency of the average spectrum. The spectral edge frequency was computed as the frequency below which 95% of the total power was found. The peak power frequency

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of the high-frequency band was computed using the algorithm in the appendix. This ensured that low-amplitude perturbations at the edge of the power spectrum would not be considered to be complete bands of activity, and selected the peak power frequency without considering the degree of modality of the spectrum. Multimodality was assessed visually because no statistical tests are generally accepted for the analysis of such complex curves. The scaling of the DSA precluded identification of bimodality of the nadir between modes exceeded 70% of either mode.

Nasopharyngeal temperature was recorded at one-minute intervals during cooling and rewarming, as were the anesthetic concentrations delivered to the oxygenator, mean blood pressure, and the presence of identifiable EEG artifact such as electrocautery or pacemaker artifact. Epochs containing known artifact were excluded from the analysis.

Statistical analysis was performed using standard linear regression and analysis of variance techniques. Significance of the changes of a descriptor in the population was tested using a binomial model.

Results

During the initiation of cardiopulmonary bypass, abrupt changes were seen in the EEG. The onset and termination of these changes did not necessarily correlate with changes in blood pressure. Figure 1 shows the EEG from a typical case, with abrupt termination of the baseline pattern as extracorporeal circulation began. Although hypotension accompanied the initial EEG change, with only minimal increases in the blood pressure, the EEG reverts to a pattern that appeared normal in both amplitude and frequency. (Whether this represents "normal" cerebral activity, and thus a safe cerebral condition, is a very different issue and one about which no information is available.)

During hypothermic bypass, burst-suppression was observed in eight subjects, five of whom were receiving isoflurane anesthesia. The short epoch utilized for this analysis (2 s) allows identification of suppression of 2 s or longer, and the pattern (fig. 2) is identified easily. During rewarming, such periods of suppression typically shortened until the EEG activity was continuous. Because the frequency distribution of the activity in the bursts seemed to exhibit the same changes as continuous activity, periods of burst suppression activity were included in the analysis. Because the univariate descriptors were computed from an average spectrum obtained over 40 s, the periods of electrical silence reduced the total power, but had no effect on the peak power frequency, the average frequency, or the spectral edge frequency.

FIG. 1. EEG changes initiating bypass. EEG changes were common during the transition from native to extracorporeal circulation. In this example, there is abrupt termination of the stable 15- to 25-Hz activity within seconds of the start of bypass. The mean blood pressure also decreased at this time (from 60 to 25 mmHg); however, the EEG returned to an apparently normal (although different) pattern of activity with a clinically insignificant increase in pressure. Nasopharyngeal temperature decreased rapidly during this time as well.
FIG. 2. DSA of burst-suppression. This pattern of burst-suppression was recorded during bypass at 26°C while the patient was receiving 1% halothane. The pattern of burst-suppression repeats approximately every 20 s.

Figure 3 shows the power spectrum analysis from the EEG of a representative subject during rewarming. The gradual increase in frequency of the high-frequency band as the temperature increases is clearly evident. Also evident in figure 3 is the bimodal character of the EEG power spectrum. Two bands of activity are identified easily, one centered in the 8- to 10-Hz range at normothermia, while the other one is at about 5 Hz. Such bimodal spectra occurred in 83% (27 of 33) of the cases; and trimodal recordings were observed in two (7%) cases. Figure 4 demonstrates the relationships between temperature and the descriptors of the power spectrum that were derived from the same subject. The relationship of the peak power with temperature was highly significant ($r = 0.90$, $P < 0.0001$). Total power also was related linearly to temperature ($r = 0.78$, $P < 0.0001$), while neither spectral edge frequency nor average frequency were related linearly to temperature in this subject.

For the study population as a whole, total power increased linearly with temperature in 85% (28 of 33, $P < 0.0001$) of the cases. Linear changes in the peak power frequency of the high-frequency band were observed in 76% (25 of 33, $P < 0.002$) of cases. Linear changes in spectral edge frequency and average frequency occurred inconsistently, and no significant pattern of change of either frequency was noted for the study as a whole (table 1). The mean slope of the regression line for peak power frequency was $0.39 \pm 0.04$ Hz/°C (SEM) and for total power was $1,215 \pm 150 \mu V^2/°C$ (SEM) in the subjects in whom linear relationships were identified. No differences were seen among the three anesthetic agents used (table 2).
Discussion

Previous investigators have described EEG changes during hypothermic cardiopulmonary bypass; however, none have quantitated these changes in a population using a variety of anesthetic agents. Pearcy and Virtue reported on 74 patients during surface cooling (not rewarming) on cardiopulmonary bypass and saw no change in the EEG in more than one-third of these cases. In the remaining cases, "slight" slowing (5 Hz) was typically observed during 6°C of surface cooling. The high incidence of frequency changes observed in our study most likely represents the quantitative techniques utilized for assessing the EEG changes, as well as the greater range of temperatures examined. The rate of change of the frequency estimated from the earlier data is 0.5 Hz/°C, quite close to the 0.39 Hz/°C that we measured during rewarming.

The changes in power observed with rewarming, while statistically significant, were not great. Using the derived regression values, the average increase in power between 27° and 37° C was 41% (4.1%/°C). Since power is the

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**TABLE 1. Behavior of Spectral Descriptors during Rewarming**

<table>
<thead>
<tr>
<th>Descriptor</th>
<th>Increased</th>
<th>No change</th>
<th>Decreased</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total power</td>
<td>28*</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Average frequency</td>
<td>18</td>
<td>12</td>
<td>5</td>
</tr>
<tr>
<td>Peak power frequency of the high-frequency band</td>
<td>25†</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Spectral edge frequency</td>
<td>13</td>
<td>12</td>
<td>8</td>
</tr>
</tbody>
</table>

*P < 0.0001.
†P < 0.002.
square of the voltage, this represents an increase in average voltage of less than 20% overall or 2% /°C. A change of such small magnitude is difficult to detect when EEG changes are assessed visually and demonstrates the importance of quantitative EEG analysis techniques.

Not reported by Pearcy, but evident in the tracings of Cohen et al.,3 is the occurrence of a mixture of high- and low-frequency activity during hypothermia. The frequent presence of such bimodal spectra in our study explains the failure of the average or spectral edge frequencies to correlate with changes in temperature, because neither of these univariate descriptors can adequately reflect the changes in two different bands of activity. By using the average spectrum (computed over 40 s) for the generation of the univariate descriptors, the characteristic behavior of burst-suppression activity was eliminated. However, one would expect that all univariate descriptors, when computed from the individual spectra, would fail to adequately describe the nature of the changes in the EEG during burst-suppression activity.

Although this study quantifies the EEG changes resulting from hypothermia, it does not elucidate the cause of these changes. In particular, the amplitude of the change in power is markedly different from the reduction in CMRO₂ (about 7.5% /°C).4 By comparison, the EEG slowing, analyzed by linear regression techniques, averaged 5.7% /°C over the temperature range study. However, the effects of temperature change on metabolic processes are known to be logarithmic.5 Analyzing the frequency data logarithmically yields a 7% /°C reduction in frequency, suggesting that the frequency changes are closely related to the underlying changes in metabolic rate. Further studies in which CMRO₂ is modified independent of temperature and anesthetic concentration might prove helpful in elucidating this phenomenon further.

Despite the uniformity of these results during re-warming, EEG changes during cooling were not as uniform as those obtained during re-warming. While this might relate to physiologic differences between cooling and re-warming, it seems most reasonable to attribute these changes to differences in the patient’s condition at the different times. The onset of cardiopulmonary bypass, the abrupt hemodilution, hypotension, and changes in anesthetic concentration may modify the EEG independent of temperature. Also, the use of larger temperature gradients during cooling may modify the EEG response, although further study would be needed to verify this.

The use of high-pass filtration with a cut-off at 4 Hz results in the loss of substantial amounts of low-frequency activity, raising the question of bias in the results. As the component frequencies of the EEG spectrum slow, the amplitudes of the low-frequency components are reduced disproportionately, tending to increase the spectral edge and average frequency descriptors. Such a change will reduce the magnitude of the slope of the change of each descriptor with temperature (without changing the sign of the change) and increase the scatter, possibly rendering a statistically significant change insignificant. However, examination of the cases in which spectral edge frequency and average frequency did not show statistically significant changes demonstrates that such a bias would not have changed the results of this study. In order to achieve statistical significance (P < 0.05), the behavior of any univariate descriptor in this study must be similar in 23 of the 33 subjects. Of the 12 subjects who did not show a statistically significant change of spectral edge frequency with temperature, the trend of the change was toward increasing frequency with re-warming in only seven cases. Had all of these been statistically significant, the total number of subjects having increases in spectral edge frequency with re-warming (20) would still be short of the number required for statistical significance. The situation with the average frequency was entirely analogous. Only four of the 12 subjects with statistically insignificant changes showed increases in average frequency with re-warming. Had all of these been statistically significant, the total number of subjects having increases in average frequency with re-warming would still be inadequate for statistical significance.

Only one subject (80 years old) demonstrated pressure-dependent cerebral hypoxia during hypothermic perfusion. This event, shown in figure 5, exemplifies the differences between the EEG changes produced by hypoxia and those of hypothermia. An initial change in the EEG is noted at the start of bypass. As the temperature falls thereafter, gradual EEG slowing is noted. An abrupt change in the EEG occurred as the mean blood pressure fell below 60 mmHg, even though extracorporeal circulation was maintained at 2.41 · min⁻¹ · m⁻². This change reversed following the administration of a vasoconstritor and an appropriate increase in blood pressure. Extra-
corporeal flow was not changed. After recovery, the EEG continued its slowing trend. Both the abruptness of the onset and the reversal by increasing blood pressure are presumptive evidence for cerebral hypoxia caused by hypotension, even though direct measurement of the cerebral $P_{O_2}$ is impossible. Such changes have been reported previously, however, the reduction in pressure in the present case was substantially less than that of the previous ones (only 15 mmHg), and might have been thought clinically insignificant without concurrent EEG monitoring. It is also noteworthy that this episode occurred at 30°C, a temperature at which substantial hypothermic protection from ischemia would be expected.

Patients with chronic ischemia, particularly following a completed stroke, may not demonstrate EEG abnormalities, even though there may be marginal perfusion of viable tissue at the perimeter of the infarction. If EEG abnormalities are present, the recording will typically demonstrate increases in amplitude and decrease in frequency compared with unaffected areas of the brain. The areas with slowing may show further reduction in frequency if additional ischemic stress occurs; however, when slowing is present initially, identification of these changes may be more difficult.

In conclusion, we have quantitated the EEG response to hypothermia during rewarming utilizing extracorporeal circulation. Most patients demonstrated linear relationships between temperature and both power and the peak power frequency of the high-frequency band. Because of the bimodal distribution of EEG activity, neither average frequency nor spectral edge frequencies correlated with temperature in a significant number of cases. The magnitude of the changes in frequency correlated with predicted levels of hypothermic depression of cerebral metabolism, but the changes in EEG amplitude did not. The magnitude of the changes suggest that, within the temperature change studied, thermal effects should be distinguishable from acute ischemic events. EEG changes during cooling were less reproducible than those during rewarming, and further work is needed to identify the sources of variability in the EEG following the initiation of extracorporeal circulation.

References


APPENDIX

The algorithm used to compute the peak power frequency of the high-frequency band was as follows:

1. Compute total power (see methods).
2. Compute the amplitude limit as 20 times the average power in those 0.5-Hz spectral components of the average spectrum which have non-zero powers. (Arbitrarily selected and based only on empirical observation.)
3. Examine each 0.5-Hz component until one is found with an amplitude exceeding the amplitude limit calculated in step 2.
4. Beginning with the frequency identified in step 3, examine 0.5-Hz spectral components in order by descending frequency until a component is found which is smaller than the preceding (signifying that the peak has been passed.) The frequency of the preceding component is the peak power frequency. Since the analysis is done in descending order by frequency, if multiple bands are present, this technique selects the peak power of the highest frequency band.