Hypothermia and the Approximate Entropy of the Electroencephalogram

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Background: The electroencephalogram is commonly used to monitor the brain during hypothermic cardiopulmonary bypass and circulatory arrest. No quantitative relationship between the electroencephalogram and temperature has been elucidated, even though the qualitative changes are well known. This study was undertaken to define a dose–response relationship for hypothermia and the approximate entropy of the electroencephalogram.

Methods: The electroencephalogram was recorded during cooling and rewarming in 14 patients undergoing hypothermic cardiopulmonary bypass and circulatory arrest. Data were digitized at 128 Hz, and approximate entropy was calculated from 8-s intervals. The dose–response relationship was derived using sigmoidal curve-fitting techniques, and statistical analysis was performed using analysis of variance techniques.

Results: The approximate entropy of the electroencephalogram changed in a sigmoidal fashion during cooling and rewarming. The midpoint of the curve averaged 24.7°C during cooling and 28°C (not significant) during rewarming. The temperature corresponding to 5% entropy ($T_{0.05}$) was 18.7°C. The temperature corresponding to 95% entropy ($T_{0.95}$) was 31.3°C during cooling and 38.2°C during rewarming ($P < 0.02$).

Conclusions: Approximate entropy is a suitable analysis technique to quantify the electroencephalographic changes that occur with cooling and rewarming. It demonstrates a delay in recovery that is of the same magnitude as that seen with conventional interpretation of the analog electroencephalogram and extends these observations over a greater range of temperatures.

IT is well known that the electroencephalogram changes with hypothermia; however, the quantitative relationship between the electroencephalogram and hypothermia is poorly defined. Previous attempts at defining a quantitative relationship between temperature and the processed electroencephalogram[1,2] have produced conflicting results, and more recent work[3,4] has focused on visual interpretation of the analog signal. Although this approach has yielded valuable insights regarding specific electrophysiologic events at deep hypothermia, it is not particularly applicable to the majority of the effects of hypothermia on the electroencephalogram.

Approximate entropy analysis is a method for assessing the variability of an analog signal. Unlike most univariate descriptors, it reflects changes in both frequency and amplitude in the original signal. It has been applied to the electroencephalogram by Bruhn,[5] who demonstrated good correlation with changes in anesthetic depth (end-tidal concentration). Additional work[6] modified the initial algorithm to apply to the electroencephalogram during burst-suppression activity. We hypothesized that this analytic approach would provide useful information about the relationship between the electroencephalogram and temperature and undertook this study to quantify the changes that occur in the approximate entropy of the electroencephalogram over the range of temperatures from normal to deep hypothermia.

Materials and Methods

In our institution, patients undergoing procedures involving hypothermic circulatory arrest are routinely monitored by electroencephalogram to ascertain the occurrence of electrical silence before initiating circulatory arrest. Accordingly, the institutional review board (University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania) approved collection and analysis of this routine clinical data without consent beyond the written consent required for patient care during the procedure. Electroencephalographic data were recorded from 14 subjects during the cooling and rewarming periods of cardiopulmonary bypass. A bilateral bipolar montage consisting of Fp_1T_3, Fp_1C_3, Fp_2C_4, Fp_2T_4, T_3O_1, C_3O_1, T_4O_2, and C_4O_2 was utilized. The amplifier bandwidth was 0.5–30 Hz. Data were digitized at 128 Hz and stored for subsequent analysis. Simultaneous temperature measurement was recorded from a nasopharyngeal temperature probe.

Approximate entropy of the electroencephalogram was calculated using the method described by Bruhn.[5,6] Both the epoch size (1,024 data points) and the noise level (20% of SD of the sample) were the same as in the earlier studies. Power spectrum analysis was also performed using 2-s epochs (256 data points), but univariate descriptors of the power spectrum were not derived. Approximate entropy values were sampled at intervals of approximately 1°C during cooling and rewarming unless electrical activity was contaminated by artifact. The relationship between temperature and approximate entropy was analyzed for each channel of each patient separately for cooling and rewarming by fitting to a sigmoid curve (Prism7; GraphPad, Inc., San Diego, CA), generating the usual parameters of minimum, maximum, Hill slope, and midpoint. Two additional parameters, $T_{0.05}$ and $T_{0.95}$, were defined. $T_{0.05}$ represents the tem-

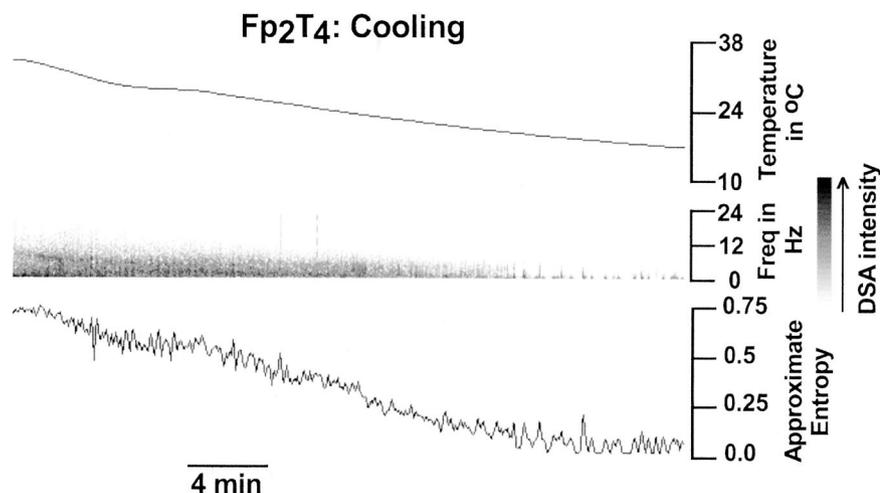---

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Fp2T4: Cooling

Fig. 1. Cooling. The power spectrum (density spectral array [DSA]) of one channel of electroencephalogram (Fp_2T_4) is shown (*middle*), together with the nasopharyngeal temperature (*top*) and approximate entropy (*bottom*). The continuous reduction in electrical activity during cooling is evident in both types of quantitative analysis. Freq = frequency.

perature (whether during cooling or rewarming) at which 95% of the hypothermia-related reduction in the approximate entropy of the electroencephalogram occurs. $T_{0.95}$ represents the temperature at which the electroencephalographic activity reaches 95% of the maximum value of approximate entropy predicted by the curve fit. Statistical analysis of the resulting parameters was performed using analysis of variance techniques (STATISTICA; StatSoft, Inc., Tulsa, OK). $P < 0.05$ was considered statistically significant.

Anesthesia was not controlled by protocol; however, all patients received fentanyl and isoflurane as the primary anesthetics with pancuronium for muscle relaxation. Psychotropic adjuvants included midazolam and scopolamine. Isoflurane was discontinued during cooling so that suppression of cortical electrical activity due to the anesthetic would not be confused with hypothermic suppression. Alpha-stat management of pH was employed during cardiopulmonary bypass, and perfusion pressure was maintained above 60 mmHg except during circulatory arrest. Retrograde cerebral perfusion *via* the superior vena cava cannula was performed during the period of circulatory arrest, and retrograde perfusion pressure was maintained below 30 mmHg measured at the internal jugular vein.

Results

Due to the extensive use of electrocautery, pump artifact, pacemaker artifact, and other types of electrical noise, obtaining adequate signal for analysis was often problematic. Adequate signal was obtained in at least one channel during cooling in all of the 14 cases; however, adequate signal was obtained from only 6 subjects during rewarming. Occipital leads were particularly troublesome, with only one patient having an adequate signal recorded from these channels. For this reason, no data from any of the four occipital channels were included in the analysis. Two patients were excluded be-

cause of problems with temperature measurement. Thus, the results presented include data from 33 frontal or temporal channels of electroencephalogram recorded in 12 patients during cooling and from 19 channels of frontal or temporal electroencephalogram recorded in 6 patients during rewarming. The patients (9 men, 3 women) had an average age of 67 yr (range, 45–80 yr), and all were undergoing surgery on the aortic arch for aneurysm or dissection. None had preoperative evidence of neurologic injury. The patients whose rewarming data were used for analysis averaged 34 min (range, 16–60 min) of circulatory arrest and did not demonstrate postoperative neurologic injury.

The data for a typical channel during cooling are shown in figure 1 and during rewarming in figure 2. Sigmoid curve fits of approximate entropy to temperature for these two data sets are shown in figure 3.

Multiple analyses were performed to assess regional variation. No statistically significant differences were identified between channels or hemispheres during cooling or rewarming. Accordingly, the individual curves were averaged to calculate a single curve for each patient, and these parameters were used to calculate the results shown numerically in table 1. Only the $T_{0.95}$ during warming was demonstrated to be statistically significantly different from the corresponding value during cooling. The graphs described by these parameters are shown in figure 4.

Discussion

The finding of a sigmoid relationship between temperature and the approximate entropy of the electroencephalogram is a novel observation, although not one that is totally surprising. Many physiologic or pharmacologic relationships can be described in this fashion, and it is perhaps more surprising that the observation has not been reported previously for the electroencephalogram. The mid temperature is entirely analogous to the ED_{50} of

Fp2T4: Warming

Fig. 2. Warming. The temperature, power spectrum (density spectral array [DSA]), and approximate entropy of the electroencephalogram are displayed during rewarming after circulatory arrest. The data are from the same channel (Fp_2T_4) of the same patient as in figure 1; however, the time scale is different. Note the erratic behavior of the approximate entropy during the periods of burst suppression that occur when the temperature is in the mid-20°C range. Freq = frequency.
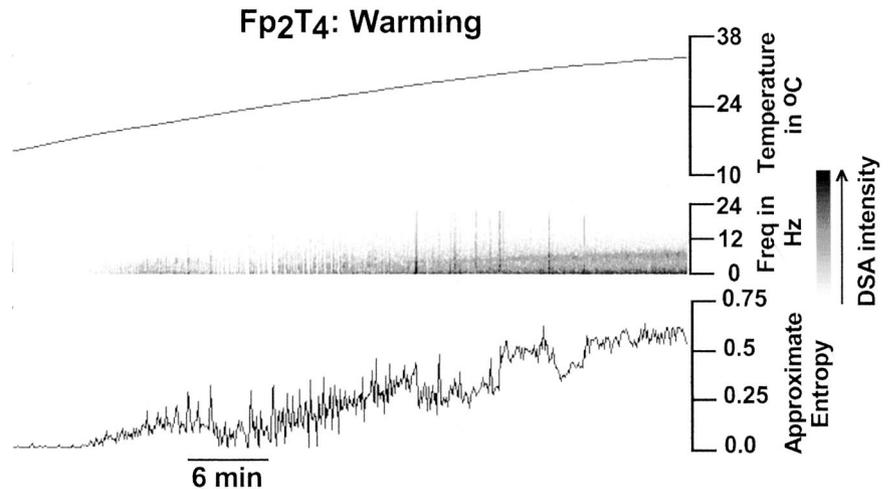
a pharmacologic dose–response relationship, while the $T_{0.05}$ and the $T_{0.95}$ are analogous to the ED_{95} of effect and recovery, respectively.

Taken in this way, the findings of a mid temperature of 24.7°C and a $T_{0.95}$ of 31.3°C provide an explanation for the different results obtained by previous investigators. Bashein,[2] in a study examining the electroencephalogram during hypothermic cardiopulmonary bypass, was unable to relate temperature and the electroencephalogram. The observations by Bashein were confined to rectal temperatures above about 30°C. Rectal temperatures are a notoriously poor indication of brain temperature,[7] and even if it were possible to extrapolate from rectal to brain temperatures, the bulk of the measurements in that study would have occurred at temperatures at which we observed less than 5% of the total thermal effect on the electroencephalogram. The earlier

observations by Levy,[1] in which a linear relationship was proposed for the electrocortical response to cooling, involved temperatures as low as 26°C, which would include nearly half the range of change seen in this study; however, the use of a less complete data set and linear, rather than curvilinear, analysis resulted in the different conclusion.

An extensive study of the changes in the analog electroencephalogram and evoked potentials during hypothermic circulatory arrest and rewarming has been published by Stecker.[3,4] The average value of $T_{0.05}$ measured during cooling (18.7°C) corresponds closely to the average temperature at which electrocerebral silence was determined to occur by Stecker.[3] There was considerable variation in the $T_{0.05}$ among our patients (13.5–21.5°C), a characteristic that was also observed by Stecker. This suggests that the $T_{0.05}$ defines an electrophysiologic state that may be equivalent to Stecker's definition of electrocerebral silence, and thus, one could objectively determine the occurrence of electrical silence using approximate entropy calculations. This process, however, would require not only the real-time analysis of the electroencephalogram but the derivation of the entropy–temperature relationship as cooling progressed. Alternatively, one could choose to cool to a specific value of the approximate entropy, which would be about 0.1, based on the data presented earlier. The reliability of such an approach should be validated against conventional electroencephalogram observations before proceeding to use approximate entropy as a means of determining electrical silence for cerebral protection during hypothermic circulatory arrest.

It is also noteworthy that the minimum approximate entropy attained during cooling was slightly but statistically elevated above zero; however, the comparable value computed from the rewarming data were not statistically different from zero. This suggests that the visual inspection criteria used to determine electrocerebral silence actually allowed a small amount of electrical activ-
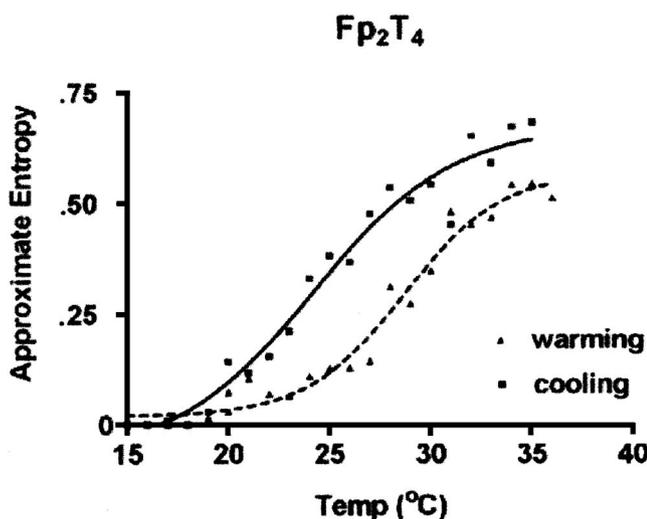
Fp2T4

Fig. 3. Dose–response. The approximate entropy data from figures 1 and 2 have been extracted at intervals of approximately 1°C and plotted to demonstrate the curvilinear relationship. The rightward shift during rewarming is clearly evident, as is the similarity of the slopes of the two curves. Temp = temperature.

Table 1. Results

Parameter	Cooling	Warming	*P*
Minimum entropy	0.035 ± 0.019	0.009 ± 0.015	NS
Maximum entropy	$0.937 \pm 0.0\,61$	0.741 ± 0.035	NS
Mid temperature	24.7 ± 0.5	28 ± 0.5	NS
Hill slope	0.26 ± 0.053	0.17 ± 0.017	NS
$T_{0.05}$	18.7 ± 1.55	16.9 ± 1.3	NS
$T_{0.95}$	31.3 ± 1.0	38.2 ± 1.5	<0.02

NS = not significant.

ity to be present and that this activity was subsequently suppressed by the ischemia of circulatory arrest or further cerebral cooling induced by hypothermic retrograde cerebral perfusion. Without further study, it is not possible to determine whether the criteria currently used to determine electrocerebral silence should be modified or whether such a change would improve patient outcome.

Stecker[4] demonstrated a significant thermal lag in the return of electroencephalographic activity following circulatory arrest. In his study, the occurrence of continuous electrical activity was delayed by nearly 5°C during rewarming. Similarly, burst-suppression activity did not resume until patients were 3.5°C warmer than the temperature at which burst suppression ceased during cooling. In this study, the mid temperature during rewarming was elevated by a comparable amount (3.3°C), but the small sample size precluded demonstration that this was statistically significant. There was, however, a statistically significant difference between $T_{0.95}$ during cooling and rewarming, with a temperature difference approaching 7°C. These findings suggest that there is a recovery process occurring in addition to the thermal recovery during rewarming and that this process lasts throughout the period of rewarming. It seems likely that this is related to the preceding period of circulatory arrest, as Stecker[4] demonstrated, but this study cannot validate

this observation. Alternatively, changes in anesthetic depth might account for these differences; however, anesthetic is usually lightest during rewarming as preparations are made to terminate cardiopulmonary bypass, and this should result in a more active electroencephalogram (and greater entropy), not a less active one.

Another explanation for the delay in the electrocortical response to warming and cooling would be a "thermal effect compartment." Such a phenomenon might be observed if the nasal temperature changed more rapidly than the brain temperature; however, previous work does not suggest that this is occurring. In Stone's study of temperature change during deep hypothermic arrest for craniotomy,[7] he demonstrated that nasopharyngeal temperature was comparable to brain temperature for the first half of cooling (approximately 24°C) but that nasopharyngeal temperature underestimated brain temperature thereafter, particularly at the midpoint of rewarming at which point the discrepancy averaged 3.4°C. Rather than explain the difference between cooling and warming, this observation exaggerates it since it suggests that the brain temperature at the midpoint of recovery of the electroencephalogram is not 28°C but about 31.5°C, nearly 7° warmer than the temperature at the midpoint of suppression (and comparable to the 6.9° shift in $T_{0.95}$).

A thermal effect compartment might also be evident if metabolic processes did not change to temperature-normalized levels of activity immediately as temperature changed. Such a phenomenon might be unidirectional, occurring during warming but not during cooling, or bidirectional, with electrical activity maintained for a period of time after a change in temperature regardless of the direction of change. During rewarming, this phenomenon would appear indistinguishable from a residual effect of hypoxia during circulatory arrest. There is no way to choose between these alternatives based on the data presented here, and further studies would be more appropriate than speculation based on the current data. This is particularly true given the magnitude of the potential error in estimation of the brain temperature by nasopharyngeal measurements during rewarming.

Interestingly, we observed no lag in the $T_{0.05}$ values during rewarming, whereas Stecker[4] found a significant delay in the onset of burst suppression. Although this
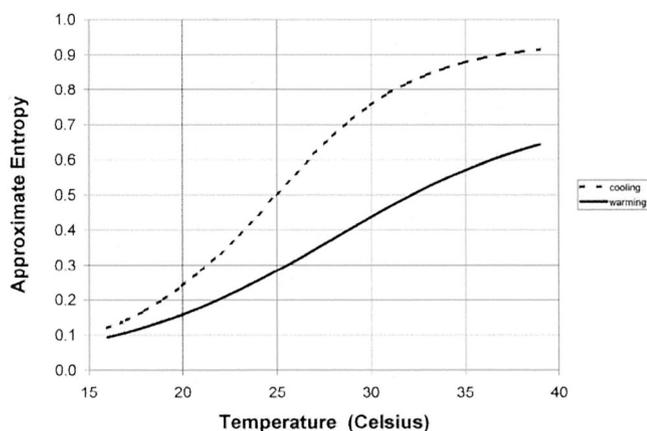

Fig. 4. Population curves. The average curves for the approximate entropy during cooling and warming were generated from the data in table 1. Unlike the example shown in figure 3, the differences in the average curves appear to be more complex than a simple shift in mid temperature.

could represent a statistical effect of the small sample size, it is also possible that this early increase in approximate entropy represents a gradual increase in very low amplitude electrical activity at the start of warming. Since burst-suppression activity represents the occurrence of synchronous activity over the entire cortex, it represents a much higher degree of interneural coordination than does a localized increase in activity, which can be identified by the approximate entropy calculations. Thus, it is reasonable to expect that small increases in electroencephalographic activity early in the rewarming period would be identified by approximate entropy calculations even though the more synchronous activity of burst suppression might be delayed. This observation would also argue against the existence of a delay in the recovery of electrical activity with warming, as would be required for a thermal effect compartment.

Patterns of oscillatory changes in the electroencephalogram were commonly observed during cooling and rewarming. Normally, these progressed to true burst-suppression activity during cooling or evolved from such activity during rewarming. The period of such oscillations was often a minute or more, and the approximate entropy appropriately tracked such changes. Sometimes, as exemplified in figure 2, the variation in approximate entropy during such oscillations was quite large. Under such circumstances, it may be more appropriate to use a longer sample of the electroencephalogram to derive a more stable estimate of the noise limit (R) for the entropy analysis.

In summary, this study demonstrated that the approximate entropy of the electroencephalogram decreases in a sigmoidal fashion during cooling, with a 50% reduction at 24.7°C and 95% activity limits of 18.7 and 31.5°C. This relationship may be useful to examine the effects of other events or therapeutic actions on the electroencephalogram during hypothermic conditions.

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