Complex analysis of intracranial hypertension using approximate entropy*

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Objective: **To determine whether decomplexification of intracranial pressure dynamics occurs during periods of severe intracranial hypertension (intracranial pressure >25 mm Hg for >5 mins in the absence of external noxious stimuli) in pediatric patients with intracranial hypertension.**

Design: **Retrospective analysis of clinical case series over a 30-month period from April 2000 through January 2003.**

Setting: **Multidisciplinary 16-bed pediatric intensive care unit.**

Patients: **Eleven episodes of intracranial hypertension from seven patients requiring ventriculostomy catheter for intracranial pressure monitoring and/or cerebral spinal fluid drainage.**

Interventions: **None.**

Measurements and Main Results: **We measured changes in the intracranial pressure complexity, estimated by the approximate entropy (ApEn), as patients progressed from a state of normal intracranial pressure (<25 mm Hg) to intracranial hypertension. We found the ApEn mean to be lower during the intracranial hypertension period than during the stable and recovering periods in all the 11 episodes (0.5158 ± 0.0089, 0.3887 ± 0.077, and 0.5096 ± 0.0158, respectively, $p < .01$). Both the mean reduction in ApEn from the state of normal intracranial pressure (stable region) to intracranial hypertension (−0.1271) and the increase in ApEn from the ICH region to the recovering region (0.1209) were determined to be statistically significant ($p < .01$).**

Conclusions: **Our results indicate that decreased complexity of intracranial pressure coincides with periods of intracranial hypertension in brain injury. This suggests that the complex regulatory mechanisms that govern intracranial pressure may be disrupted during acute periods of intracranial hypertension. This phenomenon of decomplexification of physiologic dynamics may have important clinical implications for intracranial pressure management. (Crit Care Med 2006; 34:87–95)**

KEY WORDS: brain injury; intracranial pressure; intracranial hypertension; approximate entropy; complexity

Elevated intracranial pressure (ICP) following acute brain injury may be due to cerebral edema, cerebral hyperperfusion, and/or intra- or extracranial hemorrhage. Intracranial hypertension (ICH) has been defined as elevated ICP ≥25 mm Hg for >5 mins in the absence of external noxious stimuli (1). ICH may be associated with secondary brain injury due to decreased cerebral perfusion pressure and cerebral ischemia.

Current intensive care unit (ICU) monitoring devices only allow for display of the ICP waveform with a digital variable display of the averaged 3- to 10-sec mean ICP value (2). ICP alarms are typically set for sustained periods of ICP in accordance with the preceding definition of ICH. Thus, by the time a bedside ICP alarm goes off, the ICP may have been dangerously elevated for seconds to minutes, depending on the alarm settings and type of ICP elevation. Conversely, very brief elevations in ICP lasting <3–10 secs may be missed altogether.

We have previously demonstrated that elevated ICP due to severe traumatic brain injury (TBI) is associated with changes in physiologic signal metrics derived from the electrocardiogram, arterial pressure waveform, and ICP waveform that suggests uncoupling of autonomic cardiovascular regulatory mechanisms (3–5). In addition, we reported preliminary data showing a breakdown in long-range correlation behavior of heart rate fluctuations, as measured by the nonlinear scaling exponent, α, a nonlinear complexity statistic calculated by detrended fluctuation analysis (6, 7). This line of research suggests that metrics to analyze the ICP signal other than the time-averaged mean may have physiologic and clinical significance and that there are measurable differences in signal metrics between patients with ICH.

In this study, the objective was to determine whether there were immediate changes in the ICP signal before, during, and after an acute elevation in ICP (a so-called "ICP spike") using metrics other than the time-averaged mean value. We hypothesized that measures of ICP complexity would decrease during periods of ICH compared with baseline values when the ICP was within physiologic normal ranges, providing evidence for decomplexification during an acute and finite period of severe physiologic stress (8). To test this hypothesis, we measured changes in the complexity of the ICP signal, estimated by the approximate entropy (ApEn), as patients progressed from a stable state of normal ICP (<25 mm Hg) to ICH (ICP >25 mm Hg for >5 mins in the absence of external noxious stimuli) (9), and then back toward pre-ICH levels.

***See also p. 245.**

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Table 1. Subject characteristics

Subject	Age	Gender	Mechanism and Description of Brain Injury	Admission GCS	Survival	GOS
1	9.5	F	Fall off horse Depressed skull fracture, IPH, cerebral edema	7	Y	4
2	4.5	M	MVA Skull fracture, SDH, cerebral edema	3	Y	3
3	8	F	Status post-craniosysostosis repair at age 2 yrs, ICP monitoring for headaches	15	Y	NA
4	4.75	F	MVA Skull fracture, IPH, cerebral edema	5	Y	2
5	11.5	M	MVA Skull fracture, SDH	8	Y	3
6	12.5	M	Gunshot wound IPH, SDH, cerebral edema	4	Y	4
7	15.8	M	Fall off skateboard Depressed skull fracture, IPH, cerebral edema	3	Y	3
Mean ± SD	9.5 ± 4.1			6 ± 4		3 ± 1

GCS, Glasgow Coma Scale score; GOS, Glasgow Outcome Score; IPH, intraparenchymal hematoma; MVA, motor vehicle accident; ICP, intracranial pressure; NA, not applicable; SDH, subdural hematoma.

Approximate entropy is a metric to estimate system complexity. A low value of ApEn indicates predictability, regularity, or a quantitatively less complex state, whereas high ApEn indicates unpredictability, irregularity, and greater complexity (10). ApEn is a computable measure that can be used to determine changing system complexity from time series and is potentially capable of classifying complex systems from a relatively small amount of data. It has been used mainly in the analysis of heart rate variability (11), endocrine hormone release pulsatility (12), and the impact of pulsatility on the ensemble orderliness of neurohormone secretion (13). Furthermore, ApEn has been applied to studies discriminating atypical electroencephalograph (14) and respiratory patterns (15) from normative counterparts, to estimate depth of anesthesia (16), and to examine the time and frequency structure of Parkinson's disease tremor (17, 18). Preliminary evidence suggests that when applied to analysis of electroencephalographs, the ApEn is predictive of epileptic seizure (19). ApEn has also been used to study the connection between panic disorder and respiration dynamics (20), to investigate changes during stages of consciousness, and to associate such alterations with brain function (21). This measure of complexity, however, has not been applied directly to the ICP signal to evaluate changes in system complexity during different pathologic states of brain injury. In this article, the term *complexity* refers to the estimated complexity as measured by the ApEn metric (see Appendix 1 for definitions).

MATERIALS AND METHODS

Patients and Patient Management and Data Acquisition. The study protocol was reviewed and approved by the Institutional Review Board at Oregon Health and Science University. The requirement for informed consent was waived.

This study included 11 ICP spikes from seven patients with brain injury admitted to the pediatric ICU at Doernbecher Children's Hospital. The patients' age, gender, mechanism and description of injury, admission Glasgow Coma Scale score (22), survival, and Glasgow Outcome Score (23) are listed in Table 1. Management of the six patients with severe traumatic brain injury (TBI) followed the recently published "Guidelines for the Acute Medical Management of Severe Traumatic Brain Injury in Infants, Children, and Adolescents" (1). One patient with a history of craniosynostosis and severe headaches was admitted for ICP monitoring.

ICP Database and ICP Spike Detection. Data for this study were obtained from the physiologic signal library in the Complex Systems Laboratory (2). The database consisted of 76 GB of ICP data collected from 93 patients from 1998 to 2003. ICP was monitored continuously using a ventricular catheter or parenchymal fiberoptic pressure transducer (Integra NeuroCare, Integra LifeSciences, Plainsboro, NJ). The ICP monitor was connected to a Philips Merlin patient monitor (Philips, Best, Netherlands) that sampled the ICP and arterial blood pressure signals at 125 Hz. An HPUX workstation automatically acquired these signals through a serial data network, and they were stored in files on CD-ROM. Detailed description of the data acquisition system used in the Complex Systems Laboratory was previously reported (24).

The following criteria were used to detect ICP spikes. The criteria are specified in terms of three nonoverlapping segments of the mean ICP signal: a 300-sec stable region, a 10- to 300-sec transition zone, and a 20-sec region of ICH. Similar criteria were reported in an earlier study (25).

1. The difference between the minimum value in the critical region and the maximum value in the stable region was ≥10 mm Hg. This ensured that the detector only detected significant elevations of ≥10 mm Hg that occur over a period of ≤5 mins.
2. The minimum ICP value in the critical region was >20 mm Hg. This ensured that each ICP spike was large enough to be clinically significant (26).
3. The mean ICP was in the range of 0–100 mm Hg in the stable region and <150 mm Hg in the ICH region. These criteria were used to limit artifact from being detected as ICP spikes.
4. Each ICP spike was separated from preceding ICP spikes by ≥5 mins. This ensured that a single long elevation in ICP was not detected as two separate ICP spikes.

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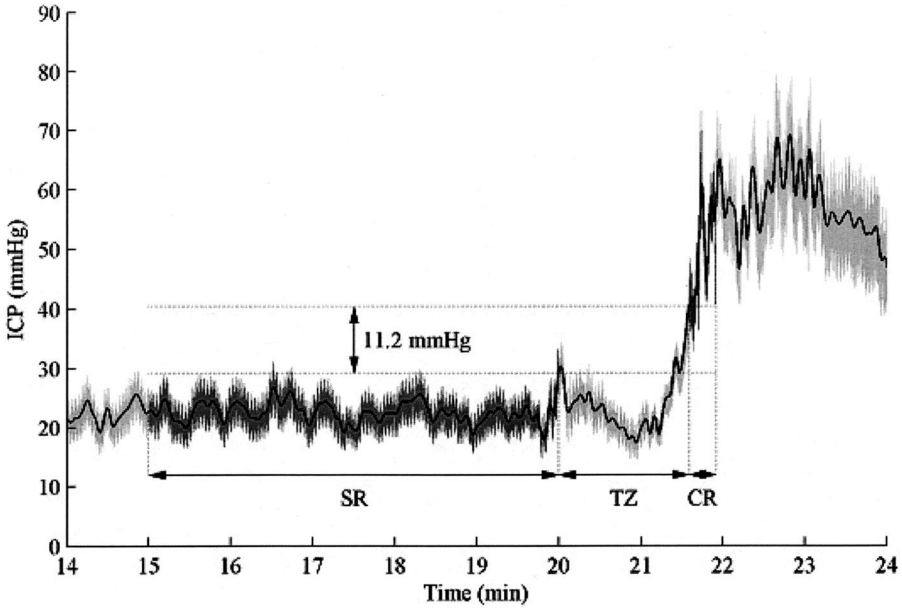

Figure 1. Illustration of the criteria for an acute elevation in intracranial pressure (*ICP*). The signal divided into three segments: a 5-min stable region (*SR*), a 10- to 300-sec transition zone (*TZ*), and a 20-sec critical region (*CR*). The stable and critical regions had a required separation of ≥10 mm Hg.

To estimate the mean ICP, a low-pass filter was applied with a cutoff frequency sufficiently low to eliminate the pulsatile components of the ICP signal due to respiration and heart beats. The noncausal low-pass filter had a cutoff frequency of 0.22 Hz and zero phase delay. To decrease the computational load, the signal was decimated by a factor of 225 using a noncausal eight-order low-pass Chebyshev type I filter. This changed the effective sampling rate from 125 Hz to 0.556 Hz. The criteria described in the previous section were then applied to every sample of the decimated signal to determine whether a spike occurred.

ICP spikes that met the specified criteria were visually screened for artifact. This screen was based on a plot of the ICP signal spanning 20 mins before and 30 mins after the leading edge of the spike and a spectrogram of the same segment. The visual screen eliminated candidate spikes if a) they contained artifact; b) there was an abrupt drop in the ICP signal consistent with cerebrospinal fluid withdrawal; c) the signal was clipped; or d) the ICP spike was part of the preceding episode of intracranial hypertension. If there were no problems detected during the 50-min record, the ICP spike was included in the study.

The automatic spike detection algorithm found 166 ICP segments that met our criteria for an acute spike. During the visual screen we found that 31 of the segments contained artifact, 28 of were actually periods of cerebral spinal fluid drainage when the ventriculostomy catheter was turned "off" to the pressure monitor and created a "false" spike. An additional 95 segments were "clipped" at the maximum range of the patient monitor (i.e., the top or bottom of the ICP waveform was cut off creating signal artifact not suitable for analysis—this technical problem has since been resolved). One segment was identified as a second detection of a single ICH episode. The end result was 11 clean records of ICH detected from seven different patients that were used for analysis. An example of a detected ICH region is shown in Figure 1. Figure 2 shows an example of the ICP segments used for analysis including the stable, ICH, and recovering regions.

Approximate Entropy. Approximate entropy (ApEn) is a family of variables and statistics introduced as a quantification of regularity in time-series, initially motivated by applications to short and noisy data sets. It was first proposed by Pincus (10) in 1991, and its biological and physiologic applications are spreading rapidly (27, 28). Several properties of ApEn facilitate its utility for empirical time series analysis (29):

1. ApEn is nearly unaffected by noise below a *de facto* specified filter level (r).
2. ApEn can be applied to time series of ≥50 points with good reproducibility.
3. ApEn is finite for stochastic, noisy deterministic, and composite processes.
4. Increasing values of ApEn correspond to more irregularity in the time series or to intuitively increasing process complexity.

The potential uses of ApEn to provide new insights in epidemiologic settings are considerable from a complementary perspective to that given by more classic statistical methods. It appears that ApEn has potential widespread utility to practical data analysis and clinical application due to the salient features it bears. Moreover, when applied to the analysis of biomedical time series, ApEn does not show the important drawbacks (e.g., very long data sequences needed to estimate them accurately, data must be stationary) that many widely applied nonlinear methods (correlation dimension, first positive Lyapunov exponent) have. Webber (30) recently pointed out some of the limitations associated with ApEn. Even considering these limitations, for analysis of relatively short time series and intrasubject comparisons, the advantages of using ApEn compared with other nonlinear metrics suggest that it is a valid choice.

ApEn is scale invariant, is model independent, evaluates both dominant and subordinate patterns in data, and discriminates series for which clear feature recognition is difficult; notably it detects changes in underlying episodic behavior not reflected in peak occurrences or amplitudes (31). ApEn assigns a nonnegative number to a time series, with larger values corresponding to more complexity or irregularity in the data. It has two user-specified variables: a run length m and a tolerance window r. Briefly, ApEn measures the logarithmic likelihood that runs of patterns that are close (within r) for m contiguous observations remain close (within the same tolerance width r) on subsequent incremental comparisons. ApEn has two user-specified variables: a run length m and a tolerance window r. It is important to consider ApEn(m, r)—or ApEn(m, r, N), where N is the number of points of the time series—as a *family* of variables: Comparisons between time series segments can only be made with the same values of m and r (29). Appendix 2 includes a description of the algorithm used to calculate the ApEn metric.

Before ApEn estimation, the ICP signals were filtered to eliminate the low-frequency components (baseline trend) and remove the mean pressure (DC component). We used a high-pass equi-ripple FIR filter with a cutoff frequency of 0.5 Hz. This guaranteed that our ApEn estimates obtained from the ICP signal were based exclusively on the ICP pulse morphology, since both the mean ICP and the baseline trend were eliminated with by the high-pass filter. Figures 2 and 3 illustrate this methodology. Each filtered ICP signal was windowed into segments of 20 secs in duration. ApEn was estimated for each segment. We used normalized variables of $m = 1$ and $r = 20\%$ of the segments' time series SD (13). Normalizing r in this manner gives ApEn a translation and scale invariance, in that it remains unchanged under uniform process magnification, reduction, or constant shift to

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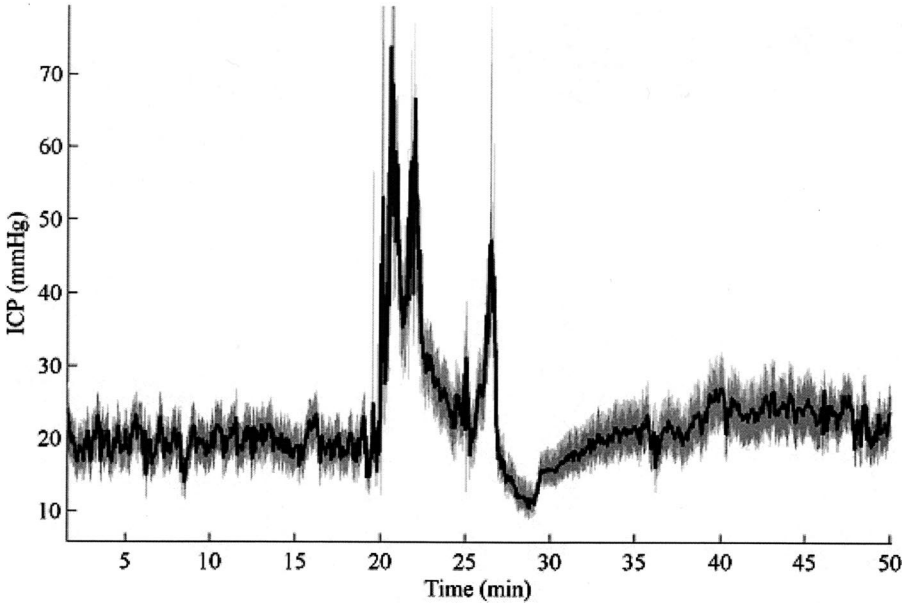

Figure 2. Illustration of the type of intracranial pressure (*ICP*) spike analyzed in this study. The light gray is the ICP signal waveform sampled at 125 Hz, and the dark line is the moving average ICP pressure. All ICP segments studied were 50 mins long, with the onset of the ICH period synchronized at minute 20.

higher or lower values (29). Several studies (10, 31, 32) have demonstrated that these input variables produce good statistical reproducibility for ApEn for time series of length $n \geq 60$, as considered herein.

Statistical Analysis. Statistical analysis was aimed at determining the statistical significance of the mean reduction in ApEn during the ICH period for each of the 11 episodes. We considered the episodes to be independent. Assuming independence is reasonable because acute spikes occur very sporadically. Having information from one spike does not provide any *a priori* information about the next spike.

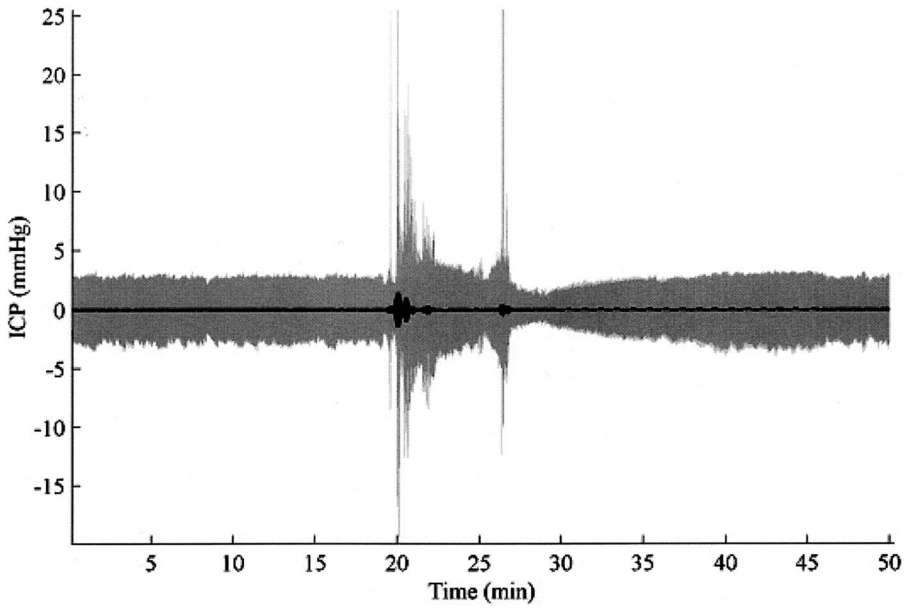

Figure 3. Before approximate entropy (ApEn) estimation, the intracranial pressure (*ICP*) signals were filtered to eliminate the low-frequency components (baseline trend) and remove the mean pressure (DC component). This figure illustrates the results of this operation. Processing the high-passed ICP signal ensures that the ApEn metric obtained is based entirely on the ICP beat morphology, since the ICP mean pressure information is eliminated in this operation.

Table 2. Mean approximate entropy of the intracranial pressure signal for the stable, intracranial hypertension, and recovering regions

Stable	Critical	Recovering
0.643	0.262	0.759
0.536	0.325	0.446
0.548	0.387	0.539
0.439	0.353	0.433
0.499	0.336	0.377
0.605	0.225	0.442
0.507	0.363	0.466
0.233	0.223	0.234
0.329	0.225	0.325
0.341	0.197	0.326
0.315	0.185	0.277

Standard errors for each of the columns are shown in Table 3.

Mean ApEn values were obtained for 2-min windows immediately before, during, and after the ICH period. We used bootstrap to estimate the standard error of the means for each of these states. We performed a nonparametric hypothesis test to determine statistically significant mean ApEn reductions based on bootstrap (33). The main advantage of using the nonparametric bootstrap technique is that it can be used to assess the statistical significance of these reductions without making any assumptions about the distribution of the mean ApEn reductions. The nonparametric bootstrap hypothesis testing involves computing a bootstrap confidence interval for the difference of mean ApEn. Equality of the mean ApEn is obtained if zero is a possible value in the confidence interval. Results were considered to be statistically significant if $p < .01$.

RESULTS

Table 2 shows the estimated mean ApEn during the stable, ICH, and recovering regions for each of the 11 episodes. Table 3 shows the estimated standard errors corresponding to the ApEn means shown in Table 2. The mean ApEn was lower during the ICH period than during the stable and recovering period in all the 11 episodes ($p < .01$, Table 2). The means across all the 11 episodes during the stable, ICH, and recovering regions were estimated to be 0.5158 ± 0.0089, 0.3887 ± 0.077, and 0.5096 ± 0.0158, respectively. Both the mean reduction in ApEn from the state of normal ICP (stable region) to the ICH region (-0.1271) and the increase in ApEn from the ICH region to the recovering region (0.1209) were determined to be statistically significant ($p < .01$). Figure 4 shows histograms of the mean ApEn for the stable, ICH, and recovering regions. Figure 5 shows a plot

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Table 3. Standard error of the mean approximate entropy for the stable, intracranial hypertension, and recovering regions

Stable	Critical	Recovering
0.0157	0.0209	0.0070
0.0060	0.0358	0.0153
0.0066	0.0032	0.0122
0.0037	0.0026	0.0095
0.0048	0.0069	0.0014
0.0142	0.0078	0.0094
0.0028	0.0024	0.0035
0.0006	0.0004	0.0005
0.0023	0.0015	0.0174
0.0060	0.0032	0.0078
0.0058	0.0023	0.0047

of the normalized ApEn for each of the 11 episodes and the median ApEn across all the episodes. The estimated ApEn decreases as patients progressed from a stable state of normal ICP to ICH. The level of complexity begins to return within minutes as ICP drops below 20–25 mm Hg. Figure 6 shows the ApEn vs. ICP for two representative patients during the study period.

DISCUSSION

Our main finding was that ApEn of the ICP signal decreased as patients progressed from a state of normal ICP to a state of ICH. As larger ApEn values correspond to increased complexity or irregularity in the data, this indicates that decreased complexity of ICP coincides with episodes of ICH. We also noted that the level of complexity begins to increase and return toward baseline levels within minutes as ICP drops below 20–25 mm Hg. These findings suggest that the complex regulatory mechanisms that govern ICP are disrupted during acute rises in ICP and return toward baseline with resolution of the acute elevation in pressure. Although we only analyzed one patient without severe TBI as a cause of ICH, the results were similar in this patient, suggesting that the regulatory mechanisms that govern ICP are independent of the type of injury.

Physiologic Implications. Godin and Buchman (34) suggested that the pathogenesis of multiple organ dysfunction syndrome from the systemic inflammatory response syndrome may be due to erosion of interconnections among organ systems. Loss of variability in the heartbeat and systemic blood pressure has been demonstrated during the sepsis syndrome in experimental models and septic patients (35–37). Return of variability was reported by Ellenby et al. (38) to be associated with recoupling between the autonomic nervous and cardiovascular systems during septic shock. Our results suggest that analogous physiologic mechanisms occur during ICH, at least during short periods of observation.

Zwiener et al. (39) found evidence of impaired short-term (25- to 60-sec periods) dynamics between respiratory movements and fluctuations in heart rate and blood pressure in brain-injured patients compared with controls. Furthermore, the impairments in short-term dynamics were inversely proportional to the degree of neurologic injury and were not affected by concomitant analgesic or sedative medications. These authors concluded that the diminished coherence was indicative of organ system uncoupling or decomplexification consistent with previous reports (8, 34).

Zweiner et al. (39) further suggested that the short-term dynamics of coherence and coordination of multiple organ system activity depend on brainstem afferent activities. They pointed to research by Langhorst et al. (40) and Schulz et al. (41), who found that the degree and pattern of rhythmic fluctuations in brainstem neurons were related to respiratory or cardiovascular functions and that the joint influence on the efferent neuroautonomic activity to lung, heart, and blood vessels depended on brainstem afferent activity. As the main stimuli to the brainstem in these experiments were from peripheral somatic and visceral origins, the conclusion is that these experiments were an example of autonomic adaptations to changed external conditions, a postulated rationale for the advantages of complexity in healthy organisms (34, 39). Thus, uncoupling between lungs, heart, and the vascular system decreases their functional performances and results in worse outcome.

Zweiner et al. (39) also pointed out, and we agree, that it is not clear whether our findings of decomplexification represent a primary physiologic process or only an epiphenomenon. However, the results of the current study, using more sensitive nonlinear methodologies, suggest the former. A recent study by Rassias et al. (28) (and accompanying editorial) of decreased physiologic variability following experimental human endotoxemia seem to lend support to this interpretation and also suggest that nonlinear dynamic models of human pathophysiology may have diagnostic and therapeutic implications (28, 30).

The six patients with severe TBI had an evolving clinical course. It is clinically accepted that maximal ICP generally occurs 24–48 hrs following severe TBI. If

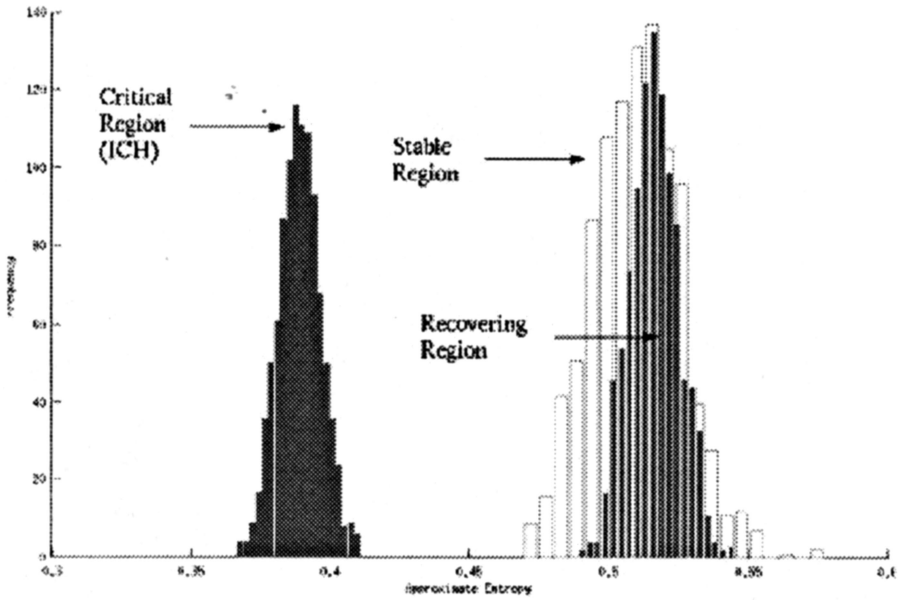

Figure 4. Histogram approximating the sampling distribution of the mean approximate entropy (ApEn) across all the patients for the stable, critical (intracranial hypertension, *ICH*), and recovering regions obtained using bootstrap. Note the statistically significance reduction in mean ApEn during the ICH period.

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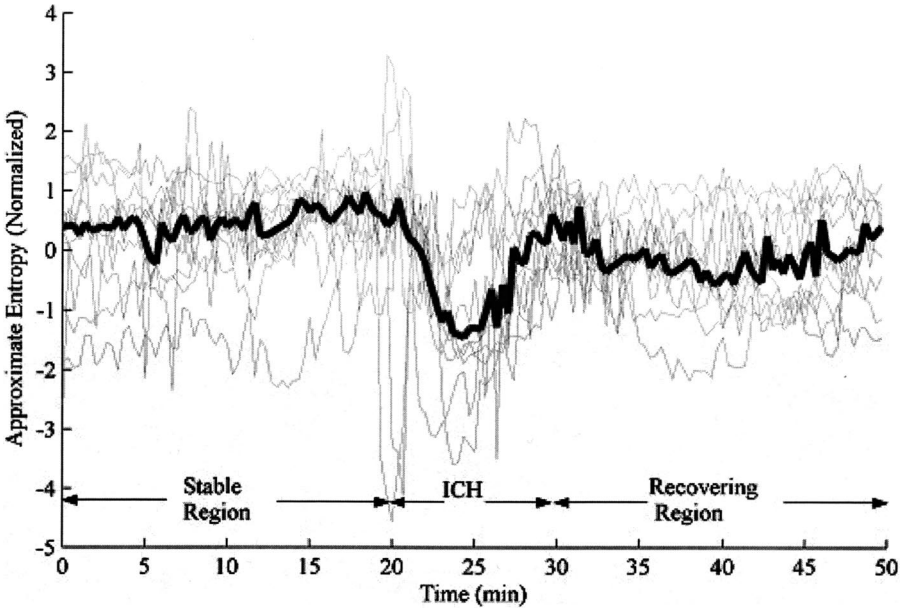

Figure 5. Approximate entropy (ApEn) (normalized) for each of intracranial hypertension (*ICH*) episodes (*light gray*) and mean and median across all ICH episodes (*dark*). ApEn decreases as patients progressed from a stable state of normal ICP to a state of ICH. This indicates that decreased complexity of ICP coincides with episodes of ICH in TBI.

the systemic inflammatory response syndrome to multiple organ dysfunction syndrome analogy applies in TBI, then future studies need to examine if repeated episodes of decreased complexity in ICP, indicative of loss of regulatory control mechanisms, result in worsening brain injury, cerebral edema, neuronal cell death, and, in extreme cases, eventually brain death. In addition, there has been much discussion about what is the best treatment threshold value of ICP to use in severe TBI (1, 26, 42). Loss of physiologic complexity of the ICP signal may be a sensitive and specific method for determining exactly at what value elevated ICP becomes physiologically dangerous.

Clinical Implications—Measures of Cerebral Autoregulation (CAR). Investigators have suggested that diminished complexity results in a decreased ability to respond to external perturbations (34, 43). Under normal conditions, cerebral autoregulatory mechanisms maintain cerebral blood flow to the brain constant over a wide range of systemic arterial pressures, with typical values between 45 and 65 mL/100 mg of brain tissue per second despite variations in blood pressure as large as 100 mm Hg (44). Local cerebral autoregulation delivers a relatively constant cerebral perfusion pressure in response to fluctuations in ICP such as with postural change and cough.

It is clear that acute ICH is a result of failure of normal cerebral autoregulatory mechanisms to compensate for overwhelming changes in cerebral volume (hemorrhage or edema), external pressure (depressed skull fractures), cerebral blood volume (cerebral hyperperfusion), or cerebral spinal fluid (obstructive hydrocephalus). Although speculative, our findings suggest that, similar to sepsis, the ICP waveform exhibits diminished complexity and increased regularity during periods of ICH when CAR has failed. Conversely, when CAR is intact, the ICP becomes more complex and irregular. Thus, our findings suggest that ApEn of the ICP waveform may provide an indirect measure of CAR.

Other investigators have proposed a number of indirect measures to determine whether CAR is intact. Physiologic stressors or challenges such as changes in Pa_{O_2}, Pa_{CO_2}, arterial blood pressure, and intracranial volume (via balloon catheter) have all been reported to correlate to various degrees with CAR. These techniques require manipulation of one or more physiologic variables with some inherent risk to the patient. More recently, investigators have examined the transfer function and phase shift between cerebral blood flow and ICP as a dynamic measure of CAR (16, 45, 46). These measures typically use Doppler blood flow velocity in the middle cerebral artery that may be difficult to maintain for continuous measurements in the ICU environment. Direct analysis of the ICP waveform using ApEn or some other nonlinear metric may provide an easier and less risky alternative for determination of CAR. Currently there are a few indexes of potential clinical interest obtained by direct analysis of the ICP signal (e.g., RAP, pressure-reactivity). The RAP index (index of compensatory reserve) is defined as the correlation coefficient (R) between the ICP pulse amplitude (AMP) and mean pressure (P). This index is obtained by calculating the linear correlation between consecutive, time average data points of AMP and ICP (usually about 40 of such samples are used) and indicates the degree of correlation between AMP and mean ICP over short periods of time ($\sim$4 mins). This can be used to estimate the state of the pressure-volume compensatory reserve. Another ICP-derived index is the pressure-reactivity index. This index has been shown to correlate well with indexes of autoregulation based on transcranial Doppler ultrasonography. In conjunction, these indexes can be use to indirectly estimate the CAR or deranged cerebrospinal compensatory reserve (47).

Interpretation of Approximate Entropy. Since it is not possible to directly measure the complexity of individual organ systems, approximate measures must be used. There are several methods to estimate the complexity of systems from analysis of time series. In this work, the meaning of the term *complexity* is restricted to the estimated complexity by the ApEn metric (10). We chose to use ApEn because it was specifically designed as a technique to determine changing system complexity from short time series. Furthermore, contrary to the frequently used correlation dimension measure of complexity, ApEn does not assume an underlying deterministic model or chaos and is capable of classifying complex systems that include chaotic, stochastic, and composite processes; these last processes are likely models for complicated biological data sets. In the general stochastic, noisy deterministic, or composite setting, the statistical accuracy of the correlation dimension measure of complexity is typically very poor (10, 48). Because dynamic mechanics of most biological signals remain undefined, a suitable statistic of complexity for these signals must be more cautious to accommodate general classes of processes and their much more diffuse re-

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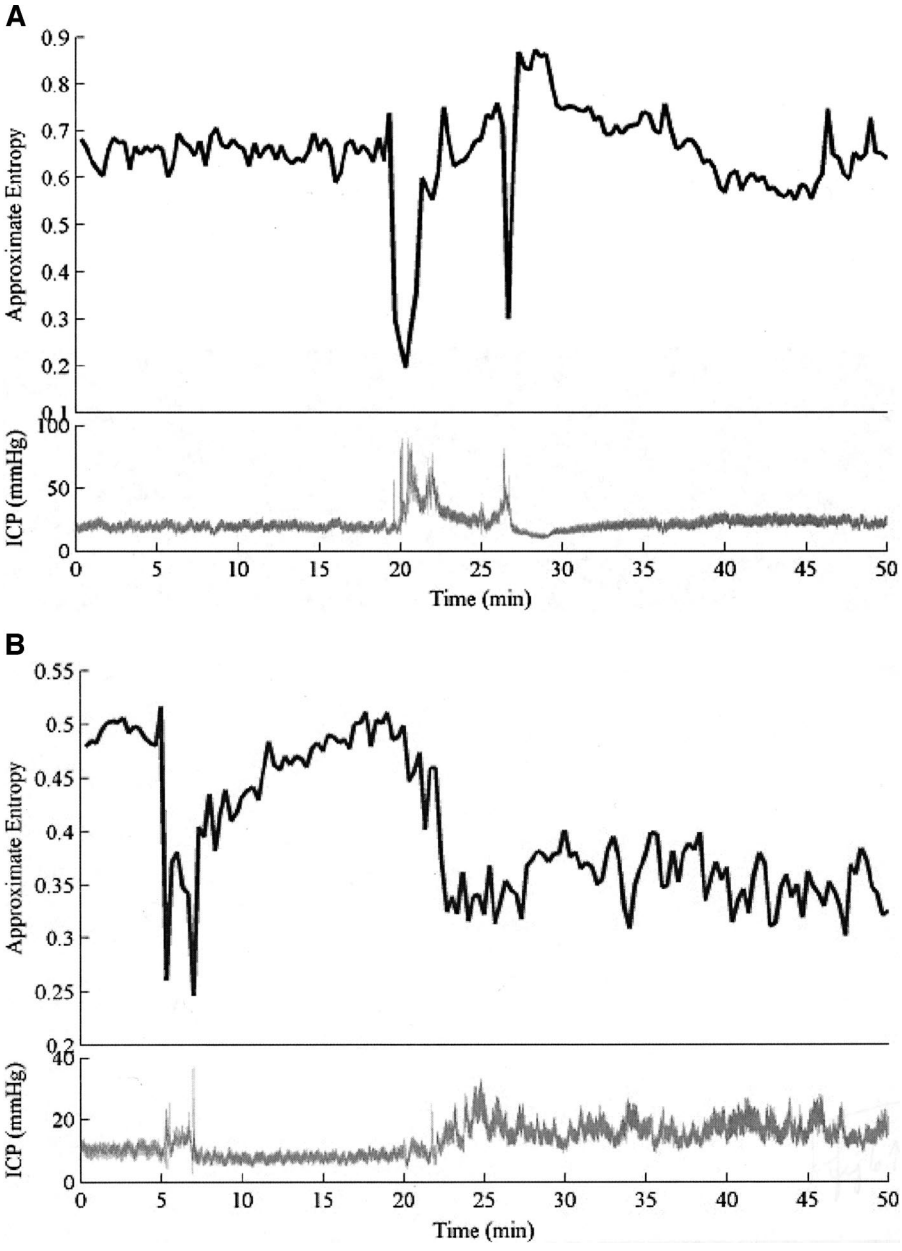

Figure 6. *Top*, approximate entropy (*ApEn*) vs. intracranial pressure (*ICP*) for patient 1, episode 1. Note decreased *ApEn* associated with both ICP spikes in pressure >20 mm Hg. *Bottom*, *ApEn* vs. ICP for patient 3, episode 1. Note decrease in *ApEn* during ICP spikes with return to baseline levels during normal ICP.

constructed dynamics (26). Moreover, a robust estimate of ApEn can be obtained by using a number of points several orders of magnitude lower than that needed to estimate accurately the correlation dimension or the first positive Lyapunov exponent (27).

To aid in interpretation of the ApEn values obtained in this study, we performed a series of tests with synthetic signals with known characteristics. From these test we concluded that a) the ApEn increases as the frequency and the number of harmonics of a sinusoidal signal increase; b) ApEn is correlated with noise bandwidth, increasing as the noise bandwidth increases (ApEn is lower in the case of colored noise than for white noise); c) typical values of ApEn for sinusoidal signals range from 0.001 to 0.07 (increasing as the numbers of harmonics increases) and 1.4 to 2 for white noise; and d) the ApEn of ICP ranges from 0.05 to 1.5, correlating with heart rate variability, noise power, and pulse morphology changes.

Our results indicate that decreased complexity of intracranial pressure coincides with periods of intracranial hypertension in brain injury.

The fact that ApEn correlates with the number of harmonics in periodic and quasi-periodic signals has important implications in the context of ICP analysis, since the number of harmonics of the signal directly relates to the morphology of the ICP beats. Investigators have documented specific variations in the ICP beat morphology, which correspond to specific alterations in the cerebral vascular system, CSF circulation, and respiration. These morphology variations may be used to measure the progression of disease. For instance, Pornoy and Choop (48) stated that in patients who do not have a cerebral edema or expanding mass, the ICP beat shows an initial sharp rise and subsequent downward slope similar to the arterial pulse, but as the expanding mass or edema develops, the ICP pulse becomes more rounded. As the ICP pulse becomes more rounded, the amplitude of the higher frequency sinusoidal components also decreases.

In the light of our results, ApEn can be interpreted as a "summarizing metric" that combines information such as heart rate variability, number of harmonics, and time morphology variability. Our results support the hypothesis that ApEn is inversely related and negatively correlated to acute elevations in ICP. Furthermore, our results also support the hypothesis that there is information in the ICP pulse that correlates with severity of disease, since ApEn was calculated from high-pass filtered ICP signals where the mean ICP trend was removed prior to ApEn calculation.

Limitations. The data presented in this study came from only seven patients. Moreover, in our statistical analysis we assumed the 11 ICH episodes were independent. Further study is warranted in a larger and more diverse population of patients with ICH from a variety of diseases and injuries. Additionally,

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there was no direct or indirect measure of cerebral autoregulation during periods of ICH. Finally, the dataset was blinded to treatments used in response to ICH, so it is not possible to differentiate what effects, if any, therapies such as osmotic diuresis, cerebral spinal fluid drainage, mild hyperventilation, or elevation of the head-of-the bed may have had on ICP analysis.

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APPENDIX 1: GLOSSARY OF TERMS

Approximate entropy: A metric that quantifies the regularity or unpredictability of a time series.

Aliasing: The apparent conversion of high-frequency signals to low-frequency signals due to an insufficient sample rate.

Bandpass filter: A filter that eliminates low- and high-frequency components of a signal but retains an intermediate range.

Bandwidth: The range of frequencies spanned by a signal. When applied to bandpass filters, this describes the range of frequencies that are allowed to pass through the filter.

Bootstrap: A computer-based method introduced in 1979 as a computational technique for estimating the standard error of an estimator.

Complexity: In this context of this article, complexity is defined as the approximate entropy (*ApEn*) of a signal segment.

Deterministic: Signals or systems that can be described by an explicit mathematical relationship.

Harmonics: Frequencies that are integer multiple of the fundamental frequency.

High-frequency noise: Many types of artifact in physiologic signals contain significant power at high frequencies. This noise is often emitted by medical equipment near the patient.

High-pass filter: A filter that eliminates low-frequency components of a signal but retains high-frequency components.

Linear interpolation: The process of estimating a value of a signal or function between two intermediate values using a line between the two points.

Low-pass filter: A filter that eliminates high-frequency components of a signal but retains low-frequency components.

Lyapunov exponent: Metric used to quantify the divergence of a dynamical system from perturbed initial conditions.

Noncausal filter: Filter that uses future values of the input.

Nonlinear: Any system or device whose behavior is governed by a set of nonlinear equations. These systems do not produce an output that is proportional to the input, in general.

Stochastic: Signals that cannot be described to any reasonable accuracy by explicit mathematical relationships and must be studied statistically.

APPENDIX 2: ALGORITHM

Given N data points from a time series $<x(n)> = x(1), x(2), \ldots, x(N)$, to compute ApEn, the following steps are taken:

1. Form m-vectors $X(1)\sim X(N-m+1)$ defined by: $X(i) = [x(i), x(i+1), \ldots, x(i+m-1)]$, $i = 1\sim N-m+1$. These vectors represent m consecutive x values, commencing with the ith point.
2. Define the distance between $X(i)$ and $X(j)$, $d[X(i),X(j)]$, as the maximum absolute difference between their respective scalar components:

$$d[X(i),X(j)] = \max_{k = 1,2,\ldots m}(|x(i+k-1) - x(j+k-1)|) \quad [1]$$

3. For a given $X(i)$, count the number of j ($j = 1\sim N-m+1, j\neq i$) such that $d[X(i), X(j)]\leq r$, denoted as $N^m(i)$. Then, for $i = 1\sim N-m+1$,

$$C_r^m(i) = N^m(i)/(N-m+1) \quad [2]$$

The $C_r^m(i)$ values measure within a tolerance r the regularity, or frequency, of patterns similar to a given one of window length m.

4. Compute the natural logarithm of each $C_r^m(i)$ and average it

$$\Phi^m(r) = \frac{1}{N-m+1}\sum_{i=1}^{N-m+1}\ln C_r^m(i) \quad [3]$$

over i φm (r) represents the average frequency that all the m point patterns in the sequence remain close to each other.

5. Increase the dimension to $m+1$. Repeat steps 1 to 4 and find $C_r^{m+1}(i)$ and $\varphi^{m+1}(r)$.
6. Approximate entropy is then defined by:

$$ApEn(m, r, N) = \Phi^m(r) - \Phi^{m+1}(r) \quad [4]$$

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