TITLE:

Complexity analysis of the cerebrospinal fluid pulse waveform during infusion studies

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ABSTRACT

PURPOSE: Nonlinear dynamics has enhanced the diagnostic abilities of some physiological signals. Recent studies have shown that the complexity of the intracranial pressure (ICP) waveform decreases during periods of intracranial hypertension in paediatric patients with acute brain injury. We wanted to assess changes in the complexity of the cerebrospinal fluid (CSF) pressure signal over the large range covered during the study of CSF circulation with infusion studies.

METHODS: We performed 37 infusion studies in patients with hydrocephalus of various types and origin (median age 71 years; interquartile range 60-77 years). After 5 minutes of baseline measurement, infusion was started at a rate of 1.5 ml/minute until a plateau was reached. Once the infusion finished, CSF pressure was recorded until it returned to baseline. We analyzed CSF pressure signals using the Lempel-Ziv (*LZ*) complexity measure. To characterize more accurately the behaviour of *LZ* complexity, the study was segmented into four periods: basal, early infusion, plateau and recovery.

RESULTS: The *LZ* complexity of the CSF pressure decreased in the plateau of the infusion study compared to the basal complexity ($p=0.0018$). This indicates loss of complexity of the CSF pulse waveform with intracranial hypertension. We also noted that the level of complexity begins to increase when the infusion is interrupted and CSF pressure drops towards the initial values.

CONCLUSIONS: The *LZ* complexity decreases when CSF pressure reaches the range of intracranial hypertension during infusion studies. This finding provides further evidence of a phenomenon of decomplexification in the pulsatile component of the pressure signal during intracranial hypertension.

KEY WORDS:

intracranial pressure, intracranial hypertension, Lempel-Ziv complexity, cerebrospinal fluid, hydrocephalus.

INTRODUCTION

Intracranial pressure (ICP) is a key signal in the care of patients with acute brain injury, hydrocephalus and other cerebrospinal fluid (CSF) circulation disorders. It was the first brain parameter to be monitored for clinical purposes, providing us with data that are useful in characterizing the mechanisms responsible for disease and assessing changes induced by treatment. The current ICP therapy in severe traumatic brain injury based predominantly on the time-averaged mean is a paradigm thereof. Taken alone, however, the mean ICP offers insufficient insight into the underlying physiological mechanisms that drive brain compliance and cerebral autoregulation. To determine ways to obtain such knowledge remains a significant research goal.

Infusion studies are routine procedures when investigating the circulation of CSF in patients with clinical and radiological features of hydrocephalus [1]. During infusion studies ICP is deliberately raised introducing fluid into the ventricular or subarachnoid space. The resulting ICP response is recorded, usually in the lumbar subarachnoid space, and CSF outflow resistance is calculated. Infusion studies are usually performed to determine if placement of a ventriculoperitoneal shunt is necessary. Besides their clinical value, infusion studies have also proved their utility in observational studies which have described the metabolic changes in the periventricular white matter [2] and the cerebral and systemic haemodynamic responses associated with the increase of ICP during infusion studies [3,4].

Recent progress in the theory of nonlinear dynamics has provided new methods for the study of physiological signals. Some of them have focused on the development of metrics to quantify the complexity of a time series with various types of entropy measures [5]. One of these strategies pursues to quantify the complexity of the biological system by evaluating the randomness of finite sequences of a given physiological signal. Lempel and Ziv proposed a useful complexity measure which can characterize the degree of predictability in a time series and that does not require long data segments to compute [6]. The Lempel-Ziv (*LZ*) complexity is related to the number of distinct substrings or patterns and the rate of their occurrence along a given sequence [7]. *LZ* complexity has been applied extensively in biomedical signal analysis. For instance, applied to electroencephalograms *LZ* estimates the depth of anaesthesia [8] and predicts movement during anaesthesia in animals [9]. Applied to the dynamics of the electrocardiogram, *LZ* complexity detects ventricular tachycardia and fibrillation [10].

Recent studies by Hornero et al. have shown that the complexity of the ICP waveform, estimated by the approximate entropy and by the *LZ* complexity metrics, decreases during acute episodes of intracranial hypertension in paediatric patients with traumatic brain injury [11,12]. In the present study, we have analysed the CSF pressure signal with the *LZ* complexity. We wanted to assess the changes in the pulse waveform complexity throughout the large pressure range covered during infusion studies performed by direct infusion of volume into the CSF compartment in patients with hydrocephalus.

CLINICAL MATERIAL AND METHODS

Patient population

We retrospectively analysed 37 infusion studies performed in the Department of Neurosurgery, University Hospital of León (Spain), between June 2006 and April 2009. Patients suffered from hydrocephalus of various types and origin. All of them had evidence of ventricular dilation (Evans index >0.30) on brain imaging (computed tomography or MR imaging) and clinical symptoms of normal pressure hydrocephalus (poor motor balance, cognitive impairment and urinary incontinence). The lumbar infusion study is performed at our institution as a supplementary hydrodynamic investigation. Measurement of CSF outflow resistance aids in the decision on surgical diversion of CSF. The analysis of the complexity of the CSF pressure signal was made off line. The local ethics committee approved the study. Informed consent was obtained from either each patient or a close relative.

Lumbar infusion test

The infusion studies were performed using a variant of the original method described by Katzman and Hussey [1]. Under local anaesthesia with the patient in the lateral recumbent position, two lumbar needles (19 Gauge) were inserted in the lower lumbar region. The rostral cannula was connected via a three-way stopcock equipped with a short extension line to a pressure microtransducer (Codman® MicroSensor™ ICP transducer, Codman & Shurtleff, Raynham, MA). The presence of a pulse amplitude, indicative of proper transmission of the pressure waveform to the transducer, is mandatory to proceed with the investigation. The caudal needle was connected to an infusion pump (Lifecare® 5000, Abbott Laboratories, North Chicago, IL). A strict aseptic technique was used to keep all the prefilled tubing and the transducer sterile. The skin was carefully prepared with antiseptic solution.

Opening pressure (P_o) was determined after approximately 5 minutes of baseline measurement. Then, infusion of Ringer solution was started at a rate of 1.5 ml/minute and continued until a plateau was reached. Once the infusion was completed, CSF pressure was recorded until it returned to the baseline level. The CSF outflow resistance (R_o) was calculated as the plateau CSF pressure (P_p) minus P_o , divided by the infusion rate.

For every infusion study, we carefully selected four artefact-free epochs to characterise the behaviour of *LZ* complexity:

- LZ0 is the epoch within the basal segment.
- LZ1 is the epoch during the early infusion which usually describes an ascending slope.
- LZ2 is the epoch chosen during the plateau.
- LZ3 is the epoch selected during the recovery period, once the infusion has finished.

We also determined P_o and P_p from the LZ0 and the LZ2 epochs, respectively, for description of the traditional CSF parameters. R_o was calculated thereafter as above mentioned.

Data acquisition

Pressure was recorded with a microtransducer (Codman® MicroSensor™ ICP transducer, Codman & Shurtleff, Raynham, MA). The pressure signal from the analogue output of the Codman ICP Express™ monitor was amplified (ML110 Bridge Amp, ADI Instruments, Milford, MA) and digitized (PowerLab 2/25 Data recording system ML825, ADI Instruments, Milford, MA). The analogue-to-digital converter was fitted into a computer for real-time display, storage and processing of the digital signals (PowerLab software; ADI Instruments, Milford, MA). Pressure data were sampled at a frequency of 100 Hz.

Lempel-Ziv complexity

LZ complexity analysis is based on a coarse-graining of the measurements. Before calculating the *LZ* complexity measure $c(n)$, the signal must be transformed into a finite symbol sequence. In the context of biomedical signal analysis, the discrete-time biomedical signal $x(n)$ is converted into a binary sequence. By comparison with a threshold T_d , the original signal samples are converted into a 0–1 sequence $P = s(1), s(2), \dots, s(n)$, with $s(i)$ defined by:

$$s(i) = \begin{cases} 0 & \text{if } x(i) < T_d \\ 1 & \text{if } x(i) \geq T_d \end{cases}$$

We used the median as the threshold T_d because of its robustness to outliers [7]. Previous studies have shown that 0–1 conversion is adequate to estimate the *LZ* complexity in biomedical signals [8,10,13].

To compute *LZ* complexity, the sequence P has to be scanned from left to right and a complexity counter $c(n)$ is increased by one unit every time a new subsequence of consecutive characters is encountered. The detailed algorithm to estimate $c(n)$ can be found elsewhere [8,10,14].

In order to obtain a complexity measure which is independent of the sequence length, $c(n)$ should be normalized. In the case of a 0–1 sequence, $c(n)$ can be normalized as follows [10]:

$$C(n) = \frac{c(n)}{\frac{n}{\log_2(n)}}$$

$C(n)$, the normalized *LZ* complexity, reflects the arising rate of new patterns in the sequence, capturing its temporal structure. A larger value of *LZ* complexity means that the chance of new pattern generation is greater, so the sequence is more complex. The value of the normalized *LZ* complexity ranges between 0 and 1.

In a first step, we estimated *LZ* complexity on detrended CSF pressure signals using a moving window of 5 seconds with 4 seconds of overlapping between consecutive windows. This analysis displays *LZ* values throughout the whole length of each infusion study as the trend of the CSF pressure values are usually displayed (figure 1). In the second step, we quantified the complexity value of the four epochs in which each infusion study was segmented.

RESULTS

Baseline characteristics and CSF parameters

The median age among patients (15 men and 22 women) was 71 years (interquartile range [IQR] 60-77 years). The absence of preceding history indicated the idiopathic form of the disease in 17 patients, while 16 patients developed a secondary form of normal pressure hydrocephalus with an earlier history of subarachnoid haemorrhage, traumatic brain injury, stroke or previous surgery for an intracranial neoplasm. In the remaining 4 patients the study was conducted to rule out shunt dysfunction. The median ventricular size according to the Evans index was 0.37 (IQR 0.35-0.40). P_o and R_o values from the infusion studies are given in table 1.

Characteristic	Value
<i>Sex (No.)</i>	
Male	15
Female	22
<i>Age (median [IQR])</i>	
Years	71 (60-77)
<i>Etiology (No.)</i>	
Idiopathic normal pressure hydrocephalus	17
Secondary normal pressure hydrocephalus	16
Shunt dysfunction	4
<i>Ventricular size (median [IQR])</i>	
Evans index	0.37 (0.35-0.40)
<i>CSF pressure parameters (median [IQR])</i>	
Opening pressure (mm Hg)	8.96 (6.41-11.39)
Plateau pressure (mm Hg)	27.23 (21.16- 32.16)
CSF outflow resistance (mmHg ml-1 min)	12 (8.90-15.56)

TABLE 1. Baseline characteristics of the patients and CSF parameters during the infusion studies.

No., number; *IQR*, interquartile range.

Lempel-Ziv complexity

Top graph in figure 1 shows a characteristic trend of the CSF pressure signal throughout a constant-rate infusion study. First, there is a short period of baseline measurement. Once infusion has begun, the

pressure signal rises with a variable slope. Then, a steady state in the range of intracranial hypertension is reached, often with pronounced vasogenic activity. Finally, once the infusion has been interrupted, the CSF pressure drops approaching its initial values. The bottom graph displays *LZ* complexity values of the detrended CSF pressure signal using a moving window of 5 seconds with 80% of overlapping (4 seconds) between consecutive windows. During the basal period the pressure signal is more complex and it oscillates over a broad range. As CSF pressure increases with the infusion, the value of the complexity counter decreases. *LZ* complexity tends to stabilize during the steady state within a narrow band until the infusion is interrupted. At this point, the value of *LZ* complexity increases coinciding with a descent of the CSF pressure. This behaviour, although not constant, is common among the patients analysed. The *LZ* complexity graph resembles an inverse image of the graph with the trend of the CSF pressure signal.

In a next step, we quantified the complexity value of the four epochs in which each infusion study was segmented. Table 2 summarizes the average values of the sequence length, CSF pressure and *LZ* complexity of the four different epochs. *LZ* complexity values are higher in the basal epoch, decreasing during the infusion to reach the lowest values in the steady state. *LZ* complexity increases in the LZ3 epoch, reaching in some cases mean values close to those of the basal period (LZ0). To assess these differences we applied Student's t test, which showed that the decrease in *LZ* complexity of the CSF pressure signal was significant ($p = 0.0018$) when comparing LZ0 (0.27 ± 0.13 [median $\pm$ standard deviation]) and LZ2 (0.19 ± 0.10). Other comparisons of the complexity values between different pairs of epochs did not show statistically significant differences. The chosen level of significance was $p < 0.01$.

A box plot provides a visual summary of many important aspects of the distribution. The box has lines at the lower quartile, the median and the upper quartile values and therefore contains the middle half of the scores in the distribution. We can detect differences in the distributions graphically by observing if the notches of the box plots do not overlap. Figure 2 shows that this occurs in the distributions of LZ0 and LZ2, the basal and the plateau epochs, respectively.

	LZ0	LZ1	LZ2	LZ3
Sequence length (s.)	180 $\pm$ 43	330 $\pm$ 35	480 $\pm$ 109	200 $\pm$ 47
ICP (mm Hg)	8.96 $\pm$ 3.66	17.22 $\pm$ 5.02	27.23 $\pm$ 8.87	17.13 $\pm$ 6.04
<i>LZ</i> complexity	0.27 $\pm$ 0.13	0.22 $\pm$ 0.12	0.19 $\pm$ 0.10	0.21 $\pm$ 0.10

TABLE 2. Values of the sequence length, ICP and *LZ* complexity in the different periods of the infusion study. Data are presented as median $\pm$ standard deviation.

LZ0, basal period; *LZ1*, early infusion; *LZ2*, plateau; *LZ3*, recovery segment; s., seconds; ICP, intracranial pressure; *LZ*, Lempel-Ziv.

DISCUSSION

In this study we have analysed the CSF pressure signal during infusion studies performed in patients with hydrocephalus by means of the *LZ* complexity, a nonparametric measure that quantifies the complexity of biomedical signals. The *LZ* complexity of the CSF pulse waveform decreased as the infusion study progressed from a state of normal baseline pressure to a steady state in the range of intracranial hypertension. We also noted that complexity increases again once the infusion is interrupted and CSF pressure drops towards its basal value. These findings occur irrespectively of the mechanism responsible for the fluctuation in ICP, and of the underlying pathology, since similar results were obtained analysing acute episodes of intracranial hypertension in paediatric patients with traumatic brain injury [12].

Quantifying complexity in a time series

Nonlinear strategies of data analysis strive to improve the diagnostic ability of the biomedical signals. Metrics to analyse the ICP waveform other than the time-averaged mean and its amplitude may have physiological and clinical significance. Lempel and Ziv proposed a useful complexity measure for characterizing the randomness of biomedical signals [6]. In the first step the signals are transformed into binary sequences by comparing the signal with a threshold value. One good choice for this threshold is the median of the signal, due to its robustness to outliers [7]. Lempel-Ziv algorithm gives the number of distinct patterns contained in the given finite sequence. After normalisation, the relative *LZ* complexity measure reflects the rate of new pattern occurrences in the investigated series. Values of *LZ* complexity close to 0 correspond to periodic signals, that is, to a rather predictable sequence of data. A value close to 1 corresponds to a signal with full bandwidth, that is, an uncorrelated stochastic process. *LZ* complexity has been applied to recognize structural regularities and to characterize DNA sequences [15,16]. This nonlinear method has also been used to measure the complexity of electroencephalogram background activity in patients with Alzheimer's disease and in control subjects [17]. Other authors have applied *LZ* complexity in electrocardiogram dynamics for the detection of arrhythmias [10].

Decomplexification in abnormal conditions

The results of our study provide further evidence of a decomplexification phenomenon in ICP dynamics related with intracranial hypertension. According to the prevalent paradigm, "normal" physiology reflects a steady state, and perturbations to the equilibrium are compensated by restorative mechanisms, which act to return the perturbed physiology to its steady state. This concept of homeostasis thus associates health with regularity and disease with sustained irregularity [18]. Irruption of nonlinear systems theory in physiology has brought a revision of the relation between normal and abnormal functioning. Whether a highly irregular behaviour constitutes evidence for pathology of a system, or whether it indicates healthy variability universally found in living organisms and nature in general, are different operating paradigms. Goldberger and West proposed the hypothesis that, in certain specific contexts, the dynamics of a healthy physiological system would produce apparently highly irregular and highly complex types of variability, whereas disease and even aging are associated with less complexity and more regularity [19]. Nonlinear regulatory mechanisms operate away from equilibrium and maintaining constancy is not the goal of

physiological control. Normal physiology includes an intrinsic variability, and the transition to a steadier state can be indicative of disease. Goldberger identified this seemingly paradoxical “steading” effect of disease on normally erratic physiology as “decomplexification” [20]. The main finding of this observational study is that the CSF pulse waveform complexity decreases during periods of intracranial hypertension compared with baseline values when the ICP is within normal physiological range, providing evidence for decomplexification during finite periods of moderate physiologic stress. This is a new approach to the analysis of the pulsatile component of ICP, which has been postulated for decades as a causative mechanism of ventricular dilation in hydrocephalus [21] and, more recently, as a predictor of outcome in normal pressure hydrocephalus [22], in traumatic brain injury [23] and in paediatric hydrocephalus [24]. Neither the mechanism leading to decreased complexity of the ICP waveform during intracranial hypertension, nor the clinical implications of this finding are clear. Two plausible mechanisms might participate in the loss of complexity in ICP dynamics during intracranial hypertension: an intracranial baroreflex and/or loss of connectivity between neuronal networks.

Intracranial baroreflex

Regardless of whether the pressure is recorded in the CSF compartment or in the brain parenchyma, the shape of the ICP pulse waveform consists of a series of time-varying components related mainly with changes in cerebral blood volume. ICP and arterial blood pressure signals are closely coupled. Hence, studies involving an ICP waveform nonlinear analysis should be interpreted in connection with the cardiovascular system to better characterize the dimensional complexity of the whole system.

The Cushing response is a well-known pathophysiological phenomenon linking severe intracranial hypertension with an increase in arterial blood pressure [25]. It has been demonstrated to be a sympatho-adrenal systemic reaction to brainstem ischemia [26,27]. Human and animal studies have found that a moderate rise of ICP could also influence systemic haemodynamics through a putative pressure-mediated response [4,28]. The loss of waveform complexity during intracranial hypertension supports the notion that ICP can influence systemic haemodynamics via an intracranial baroreflex. Schmidt et al. described an early Cushing response mediated by a moderate rise in ICP during infusion studies in patients with hydrocephalus [4]. This response included a rise in arterial blood pressure and a drop in cerebral perfusion pressure without changes in the mean value of the heart rate. To trigger this response there should be an intracranial baroreceptor and the mechanism suggested by the authors could be an intracranial baroreflex able to influence cerebral haemodynamics and possibly the autonomic status. We postulate that a similar mechanism might be involved in complexity changes of the ICP waveform during raised ICP. Decreased complexity of the ICP waveform during intracranial hypertension might correspond to a decrease in the stochastic variability of the cardiac component, or a decrease in heart rate variability through a pressure mediated mechanism.

Uncoupling and isolation

Decreased complexity during intracranial hypertension might arise from loss of connectivity between neuronal networks. Pincus advanced the idea that greater signal regularity reflects increased system isolation [29]. Heart rate variability diminishes in proportion to the degree of neurological injury. As severity

of brain injury increases, there is a proportional degree of physiological uncoupling among the cardiovascular and the autonomic systems [30]. If alterations of the dynamical properties of physiological systems can result in pathology, then the complexity of a particular system could be a valid proxy for the “connectedness” of the whole system [18].

The decrease of *LZ* complexity during periods of intracranial hypertension may thus be regarded as a sign of uncoupling among the autonomic and cardiovascular systems. Recovery of complexity values as CSF pressure decreases is consistent with the Godin and Buchman paradigm of restoration of functional relationships, or recoupling necessary for recovery [18]. Goldstein et al. have shown that neurological recovery after acute brain injury results in restoration of heart rate variability towards healthy levels [31]. Return of heart rate variability was also reported by Ellenby et al. to be associated with recoupling between the autonomic nervous and cardiovascular systems during septic shock [32].

Some limitations of our study merit consideration. Firstly, *LZ* complexity is based on a coarse-graining measure of the measurements. The pressure data were transformed into a pattern of a few symbols, only two (0-1) in our study. Thus, it is possible that other conversions with more symbols could keep more information from the signal. Previous studies have suggested that a binary conversion is enough to study the complexity of a system [8], although a recent study seems to contradict this asseveration [17]. Secondly, the loss of complexity during intracranial hypertension is not a specific finding. As previously discussed, it occurs irrespectively of the underlying pathology and/or the mechanism leading to intracranial hypertension [12]. Ageing and age-related diseases often accompany a wide-ranging loss of physiological complexity [33]. Applied to electroencephalogram and to magnetoencephalogram signals, decreased complexity has been observed in several physiological and pathological states, including Alzheimer's disease [17,34], anaesthesia [8], schizophrenia [35], vascular dementia [36] and during seizure activity in epilepsy [7].

In summary, decreased complexity of the CSF pressure signal during intracranial hypertension adds to a growing number of biological systems recognized to undergo *decomplexification* in abnormal conditions. This phenomenon could be associated with inactivation of previously active neural networks through a pressure mediated mechanism. Our results reinforce previous research involving complexity analysis of ICP during periods of intracranial hypertension in traumatic brain injury. These findings show the possibility to analyse ICP dynamics in patients with acute brain injury, hydrocephalus and other CSF circulation disorders with *LZ* complexity.

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Figure 1. Top graph shows the trend of the CSF pressure signal in a constant-rate infusion study performed in one patient with the proposed diagnosis of normal pressure hydrocephalus. The bottom graph shows the correspondent course of the CSF pressure waveform *LZ* complexity. This illustrative case demonstrates the loss of complexity during the period of intracranial hypertension.

Figure 2. Box-plot distribution of *LZ* complexity values in the four different epochs of the infusion study. The largest values of *LZ* complexity correspond to the basal period. There is a loss of complexity with the infusion that reaches the lowest level in the plateau segment, during intracranial hypertension.

LZ0, basal period; *LZ1*, early infusion; *LZ2*, plateau; *LZ3*, recovery segment.