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Analysis of Intracranial Pressure Signals Recorded During Infusion Studies using the Spectral Entropy

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Abstract—**Hydrocephalus includes a range of disorders characterized by clinical symptoms, abnormal brain imaging and altered cerebrospinal fluid (CSF) dynamics. Infusion tests can be used to study CSF circulation in patients with hydrocephalus. In them, intracranial pressure (ICP) is deliberately raised and CSF circulation disorders evaluated through measurements of the resulting ICP. In this study, we analyzed 77 ICP signals recorded during infusion tests using the spectral entropy (*SE*). Each signal was divided into four artifact-free epochs. The mean *SE*, <*SE*>, and the standard deviation of *SE*, SD[*SE*], were calculated for each epoch. Statistically significant differences were found between phases of the infusion test using <*SE*> and SD[*SE*] ($p<1.7\cdot10^{-3}$, Bonferroni-corrected Wilcoxon tests). Furthermore, we found significantly lower <*SE*> and SD[*SE*] values in the plateau phase than in the basal phase. These findings suggest that the increase in ICP during infusion studies is associated with a significant decrease in irregularity and variability of the spectral content of ICP signals, measured in terms of *SE*. We conclude that the spectral analysis of ICP signals could be useful for understanding CSF dynamics in hydrocephalus.**

I. Introduction

The term hydrocephalus encompasses a range of disorders characterized by clinical symptoms, abnormal brain imaging and derangement of cerebrospinal fluid (CSF) dynamics [1]. The study of intracranial pressure (ICP) and CSF dynamics can help in the decision about performing shunt placement surgery and can also provide valuable information for shunted patient management [2].

Infusion tests are routinely performed to study CSF circulation disorders in patients showing features of hydrocephalus. In them, CSF pressure is increased by addition of external volume. The resulting ICP is recorded, usually in the lumbar subarachnoidal space [3]. The applications of infusion studies include prediction of patient response to shunting and assessment of shunt function [4].

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Some therapies in hydrocephalus are based on the ICP time-averaged mean [3], [5]. However, this parameter does not account for all the information included in the ICP waveform and does not provide a deep insight into cerebral autoregulation mechanisms [3], [5]. Several methods have been developed in order to better understand CSF circulation disorders. Some of them rely on the non-linear [3], [6] or spectral [5], [7] analysis of ICP signals.

In this study we applied the spectral entropy (*SE*) to characterize ICP signals recorded during infusion tests in patients with hydrocephalus. *SE* was used to explore the irregularity of ICP recordings in terms of the flatness of the power spectral density (PSD) of ICP signals. Therefore, the aims of this study were: (i) to analyze the irregularity patterns in ICP signals based on *SE*, (ii) to test whether *SE* could reveal significant differences among phases of the infusion study, and (iii) to introduce an alternative framework to understand brain dynamics in hydrocephalus.

II. Materials

A. Subjects

ICP signals of 77 patients (41 male and 36 female, age 69 ± 14 years, mean ± standard deviation, SD) were recorded during infusion tests at the Department of Neurosurgery of the University Hospital of León (Spain). Patients showed features of hydrocephalus, such as poor motor balance, cognitive impairment, urinary incontinence and ventricular dilation (Evans index ≥ 0.30). Lumbar infusion tests were performed as a supplementary hydrodynamic study and as an aid in the decision on the surgical management of patients [3]. Some details regarding the population under study are shown in Table I. Patients or a close relative gave their informed consent to participate in the study, which was approved by the local ethics committee.

B. ICP Data Recording

Infusion studies were performed using a variant of the Katzman and Hussey method [8]. Under local anesthesia, patients were positioned in the lateral recumbent position and two needles were inserted in their lower lumbar region. The first one (caudal needle) was connected to an infusion pump (Lifecare® 5000, Abbott Laboratories). The second (rostral cannula) was connected to a pressure microtransducer (Codman® MicroSensorTM ICP transducer, Codman & Shurtleff). The pressure signal from the analogue output of the microtransducer monitor was amplified (ML110 Bridge amplifier) and digitized (PowerLab 2/25 Data Recording System ML825, ADI Instruments). The

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TABLE I. DATA RECORDED FROM THE POPULATION UNDER STUDY

Characteristic	Value (mean ± SD)
Ventricular size (Evans index)	0.38 ± 0.06
Basal pressure (mm Hg)	8.25 ± 3.75
Basal amplitude (mm Hg)	2.67 ± 1.35
Plateau pressure (mm Hg)	25.38 ± 8.97
Plateau amplitude (mm Hg)	10.26 ± 6.20
Outflow resistance, R (mm Hg ml^{-1} min)	11.42 ± 4.88

analogue to digital converter was also connected to a computer in order to visualize and record the ICP signals. After 5 minutes of baseline recording, a Ringer solution at a constant infusion rate of 1.5 ml/min was infused until a plateau was reached. Once the infusion was stopped, CSF pressure was still recorded until it decreased towards the baseline level [3]. For each recording, a neurosurgeon selected four artifact-free epochs, representative of four phases of the infusion test:

- Epoch 0 corresponds to the basal phase of the infusion test.
- Epoch 1 is representative of the early infusion phase and usually describes an ascending slope.
- Epoch 2 corresponds to the plateau phase.
- Epoch 3 represents the recovery phase, once the infusion has stopped and the ICP signal returns slowly to basal state levels.

ICP recordings were acquired with a sampling frequency of 100 Hz. The recordings were also processed using a finite impulse response (FIR) bandpass filter with cut-off frequencies 0.1 Hz and 10 Hz. This frequency range was chosen in order to minimize the influence of the DC component and preserve the relevant spectral content.

III. METHODS

A. Calculation of Spectral Entropy

A Fourier analysis was carried out in order to characterize the spectral content of ICP signals. Initially, we computed the PSD of each recording as the Fourier transform (FT) of the autocorrelation function [9]. However, biomedical signals are intrinsically non-stationary [10]. Thus, we performed a spectral analysis of ICP signals taking into account their time-varying properties. In this case, we used the Short-Time Autocorrelation (STA) function, which extends the definition of the autocorrelation function using the time sliding window algorithm [11]. A moving window of 5 s with an overlap of 4 s was used [3]. Each ICP signal was divided into N_T segments of 5 s (with length L= 500 samples), and the PSD was computed in each segment as the FT of the STA function of each segment.

SE represents a disorder measure, which can be used to estimate the irregularity of signals in terms of the flatness of the PSD. A uniform spectrum with a broad spectral content (e.g., white noise) yields a high *SE* value. A more predictable signal with few spectral components (e.g., sum of sinusoids) would give a low *SE* value [12].

After PSD calculation, the *SE* was obtained for each 5 s segment using the definition of Shannon's entropy computed over the normalized PSD function [13]:

$$SE = -\frac{1}{\ln(L)} \sum_{f=0.1Hz}^{10Hz} PSD_n(f) \cdot \log\left[PSD_n(f)\right], \quad (1)$$

where $PSD_n(f)$ is the normalized PSD from 0.1 Hz to 10 Hz. *SE* was normalized in order to take values in the 0–1 interval. This was done by dividing Shannon's entropy by its maximum possible value, ln(L) [14].

As previously stated, *SE* was calculated for each 5-s segment of the signal. Thus, we obtained a value of *SE* for every second beyond the fifth. The mean (<*SE*>) and the standard deviation (SD[*SE*]) of *SE* were subsequently calculated from the time series formed by the temporal evolution of *SE*. The mean summarizes the average degree of temporal irregularity, while the standard deviation describes the variability in *SE* around the mean value. An average value of <*SE*> and SD[*SE*] in the four artifact-free epochs was obtained for each subject. We will denote by <*SE0*> to the average value of *SE* in the basal phase, by <*SE1*> to the mean *SE* value in phase 1, by <*SE2*> to the mean *SE* value in the plateau phase and by <*SE3*> to the mean *SE* value in the recovery phase. Similarly, SD[*SE0*], SD[*SE1*], SD[*SE2*] and SD[*SE3*] represent the value of SD[*SE*] in the basal, early infusion, plateau and recovery phases, respectively.

B. Statistical Analysis

Initially, we performed an exploratory analysis to study the data distribution. The Kolmogorov–Smirnov test with Lilliefors significance correction and the Shapiro–Wilk test were used to verify the normality of the spectral parameters in the 4 artifact-free epochs of the infusion test. Variables did not meet parametric test assumptions. Thus, the non-parametric Friedman test was used to determine whether statistically significant differences (α=0.01) could be found between epochs of the infusion test [15]. *Post hoc* analyses were carried out using the Wilcoxon signed rank test with Bonferroni correction to account for multiple comparisons (α=0.01/6=1.7·10^{-3}) [15]. Notched boxplots were also calculated to analyze the changes in <*SE*> and SD[*SE*] between phases of the infusion test.

IV. RESULTS

We calculated the *SE* of the 5-s segments in which each ICP recording was divided using the definition of Shannon's entropy in (1). Finally, we calculated the mean values (<*SE0*>, <*SE1*>, <*SE2*> and <*SE3*>) and the standard deviations (SD[*SE0*], SD[*SE1*], SD[*SE2*] and SD[*SE3*]) of *SE* in the four artifact-free epochs.

Table II summarizes the mean values of the epoch length, CSF pressure, <*SE*> and SD[*SE*] for each epoch of the infusion test. These values were averaged over the 77 subjects in our database. These results show that the highest <*SE*> and SD[*SE*] values were obtained in the basal epoch, then decreased during infusion to reach the lowest values in

the plateau phase and, finally, increased in the recovery phase, reaching values closer to those in the basal phase.

The Friedman test revealed significant interactions among <*SE*> values ($\chi^2(3)=96.79$, $p=7.62\cdot10^{-21}<0.01$) and SD[*SE*] values ($\chi^2(3)=16.28$, $p=9.94\cdot10^{-4}<0.01$) in the four phases of the infusion test. In order to analyze these interactions, *post hoc* analyses were carried out using the Wilcoxon signed rank test with Bonferroni correction. Statistically significant differences were found between the following pairs: <*SE0*> vs. <*SE1*>, <*SE0*> vs. <*SE2*>, <*SE0*> vs. <*SE3*>, <*SE1*> vs. <*SE2*>, <*SE2*> vs. <*SE3*>, SD[*SE0*] vs. SD[*SE2*] and SD[*SE0*] vs. SD[*SE3*]. These results are summarized in Fig. 1 and Table III, where the boxplots and statistical results correspond to pairwise comparisons between stages of the infusion test. The statistically significant values in Table III have been highlighted.

V. Discussion

In this study, we assessed the changes produced in *SE* during infusion studies in patients with hydrocephalus. <*SE*> and SD[*SE*], were calculated for the four artifact-free epochs in which the infusion study was divided.

Our results show that significant differences were found between all phases of the infusion test using <*SE*>, except for the pair <*SE1*> vs. <*SE3*>. A possible explanation could be that, in the recovery phase, the ICP signals tend to gradually return to the basal state. However, the recording time may not be long enough for the ICP signals to exactly match the characteristics in the basal phase. Therefore, the <*SE*> values in the recovery phase may not be too different from those in the plateau phase or early infusion phase.

It is noteworthy that a significant decrease in <*SE*> was found in the plateau phase with respect to the basal phase. Additionally, the <*SE*> change between these two phases was the highest (Fig. 1a). This suggests that intracranial hypertension due to volume loading leads to decreased temporal irregularity measured in terms of *SE*. This result correlates with the decrease in complexity between the plateau and basal phases of infusion studies found in [3], using Lempel-Ziv (LZ) complexity. Decreased complexity during episodes of intracranial hypertension has been also found in pediatric patients with traumatic brain injury [6]. Irregularity and complexity are linked, focusing on different signal characteristics. They can be regarded as complementary measures to quantify the degree of disorder in infusion tests.

Results in Table II also show that SD[*SE*] decreased in the plateau phase with respect to the basal phase. Fig. 1b shows that the highest difference in SD[*SE*] was found between the plateau and basal phases. These results suggest that there is a significantly lower variability in the spectral content when CSF pressure reaches the range of intracranial hypertension. This variability decrease could be linked to the decrease in data dispersion found in previous studies on infusion tests [3]. In this study, the SD in LZ complexity values was lower in the plateau phase than in the basal phase. It should also be noted that previous studies reported an increased variability in the ICP signal during the plateau phase of infusion tests [16]. However, variability was measured in terms of data dispersion using central tendency measure (CTM). SD[*SE*] differs from CTM, since it measures temporal variability as the homogeneity in *SE* values along phases of the infusion test.

The decreased irregularity and variability during finite episodes of intracranial hypertension found in this study might be explained from an early Cushing response mediated by a moderate rise in ICP during infusion studies [3], [17]. This early Cushing response produces a moderate rise in arterial blood pressure, a mild decrease in cerebral perfusion pressure, a reduction of cerebral blood flow and an increase in the heart rate variability without a modification of its mean value [17]. These processes could affect the shape of the ICP waveform in the plateau phase and influence the irregularity and variability of ICP signals. It has also been suggested that decreased irregularity is associated with greater system isolation [18]. Some authors stated that increased hypertension and severity of brain injury produce physiological uncoupling among the cardiovascular and the autonomic system [19] and, thus, decreased irregularity. These mechanisms have been suggested as a possible explanation of the decreased plateau phase complexity found in [3], which is related to the lower variability found here.

Finally, a number of limitations merit further consideration. In this study, spectral analysis was performed on a heterogeneous group of patients who showed features of hydrocephalus. Since this study is focused on the assessment of spectral methods in deriving alternative measures form ICP signals, we consider that heterogeneity in patient

TABLE II. Mean Values of the Epoch Length, CSF Pressure, <*SE*> and SD[*SE*] for the Four Artifact-Free Epochs.

Parameter	Epoch 0	Epoch 1	Epoch 2	Epoch 3
Length (s)	175 ± 54	300 ± 49	497 ± 139	199 ± 50
CSF pressure (mm Hg)	8.247 ± 3.747	16.241 ± 5.446	25.381 ± 8.975	16.381 ± 5.978
<*SE*>	0.577 ± 0.089	0.525 ± 0.090	0.500 ± 0.081	0.514 ± 0.078
SD[*SE*]	0.047 ± 0.023	0.042 ± 0.022	0.038 ± 0.021	0.037 ± 0.017

TABLE III. *Z* Statistics and *P*-Values Associated with the Wilcoxon Tests for <*SE*> and SD[*SE*] (E0: Epoch 0, E1: Epoch 1, E2: Epoch 2, E3: Epoch 3).

Parameter	E0 vs. E1		E0 vs. E2		E0 vs. E3		E1 vs. E2		E1 vs. E3		E2 vs. E3	
	Z	*p*	*Z*	*p*	*Z*	*p*	*Z*	*p*	*Z*	*p*	*Z*	*p*
<*SE*>	-5.81	**$6.40\cdot10^{-9}$**	-6.52	**$6.94\cdot10^{-11}$**	-6.44	**$1.20\cdot10^{-10}$**	-5.84	**$5.17\cdot10^{-9}$**	-1.42	0.156	-3.87	**$1.10\cdot10^{-4}$**
SD[*SE*]	-2.50	0.012	-3.36	**$7.83\cdot10^{-4}$**	-3.80	**$1.47\cdot10^{-4}$**	-1.43	0.153	-1.82	0.070	-0.29	0.770

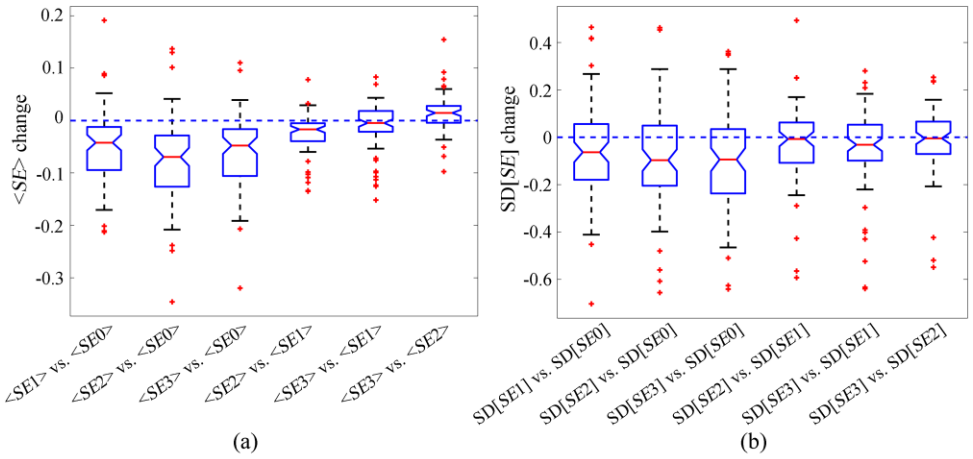

Figure 1. Notched boxplots displaying the distribution of the differences between artifact-free epochs of the infusion test in (a) <*SE*>, and (b) SD[*SE*].

population should not be regarded as a serious drawback. It should also be pointed out that it would be desirable to test the proposed method on a larger set of ICP signals.

VI. Conclusions

In summary, <*SE*> and SD[*SE*] reveal changes in the ICP signal spectrum during stress episodes. Significant differences were found among most phases of the infusion test using <*SE*>. Significant differences between the basal and plateau phases were also found using SD[*SE*]. These findings suggest that the evolution of CSF pressure in infusion studies is characterized by a significant loss of irregularity and variability. We conclude that spectral irregularity measures, such as *SE*, may help to gain further insight of brain dynamics in hydrocephalus. Future research will explore other spectral parameters and combine spectral and non-linear analysis of ICP signals, in order to obtain complementary information that helps physicians to better understand CSF dynamics in hydrocephalus.

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