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Spectral analysis of intracranial pressure signals recorded during infusion studies in patients with hydrocephalus

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ABSTRACT

Hydrocephalus includes a number of disorders characterised by clinical symptoms, enlarged ventricles (observable using neuroimaging techniques) and altered cerebrospinal fluid (CSF) dynamics. Infusion tests are one of the available procedures to study CSF circulation in patients with clinical and radiological features of hydrocephalus. In them, intracranial pressure (ICP) is deliberately raised and CSF circulation disorders evaluated through measurements of the resulting ICP. In this study, we analysed seventy-seven ICP signals recorded during infusion tests using four spectral-based parameters: median frequency (*MF*) and relative power (*RP*) in three frequency bands. These measures provide a novel perspective for the analysis of ICP signals in the frequency domain. Each signal was divided into four artefact-free epochs (corresponding to the basal, early infusion, plateau and recovery phases of the infusion study). The four spectral parameters were calculated for each epoch. We analysed differences between epochs of the infusion test and correlations between these epochs and patient data. Statistically significant differences ($p < 1.7 \times 10^{-3}$, Bonferroni-corrected Wilcoxon signed-rank tests) were found between epochs of the infusion test using *MF* and *RP*. Furthermore, some spectral parameters (*MF* in the basal phase, *RP* for the first frequency band and in the early infusion phase, *RP* for the second frequency band and in all phases of the infusion study and *RP* in the third frequency band and in the basal phase) revealed significant correlations ($p < 0.01$) between epochs of the infusion test and signal amplitude in the basal and plateau phases. Our results suggest that spectral analysis of ICP signals could be useful for understanding CSF dynamics in hydrocephalus.

1. Introduction

The term hydrocephalus includes a number of disorders characterised by clinical symptoms, enlarged brain ventricles (observable using available neuroimaging techniques) and alterations in cerebrospinal fluid (CSF) dynamics [1]. It can appear as a primary condition or as a secondary effect to head trauma, brain tumour or meningitis [2]. Implantation of a CSF shunt is a standard way of managing hydrocephalus [3]. However, some patients may not respond to this treatment and their condition becomes complex for neurosurgeons [2]. The study of intracranial pressure (ICP) and CSF dynamics can help in the decision about performing shunt placement surgery in a patient with hydrocephalus and can also provide valuable information for shunted patient management [3]. Several efforts have been made to find a relationship between parameters that characterise CSF dynamics and the outcome of shunting. Previous studies provided reference values that could be used for comparison when exploring disturbances in CSF dynamics. However, the recording protocol and the results vary among studies. Some authors reported a mean resting pressure of 1.38 kPa (approximately 10.35 mmHg) on 100 patients lying in the supine position for data recording [4]. In a more recent study [5], lumbar puncture was performed on patients lying on their side on the examination table. They obtained resting pressure values of 9.4 ± 4.6 mmHg in 151 patients at risk for normal pressure hydrocephalus (NPH). These values are lower than those found in another study on 40 healthy (no psychiatric or neurologic disorders) elderly subjects, where a median resting pressure of 11.6 mmHg was obtained while patients lied on the supine position during data recording [6]. These differences show that further research is needed to better understand CSF dynamics and to improve clinical management of patients with hydrocephalus.

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Infusion tests, also known as infusion studies, are routinely performed to analyse CSF circulation in patients with clinical and radiological features of hydrocephalus. In infusion studies, ICP is deliberately raised by the introduction of fluid in the ventricular or subarachnoidal space. The resulting ICP is recorded, usually in the lumbar subarachnoidal space, and CSF outflow resistance is calculated [7]. Infusion studies are commonly performed as predictive tests in patients with NPH, but its applications also include prediction of patient response to shunting and assessment of shunt function [8]. Additionally, clinical and experimental studies have relied on infusion tests to analyse metabolic changes in the periventricular white matter [9] and haemodynamic responses associated with the increase of ICP [10]. Computerised infusion tests [11,12] are a modification of the conventional constant rate infusion test, originally described by Katzman [13].

Some therapies in severe traumatic brain injury or hydrocephalus are based on the ICP time-averaged mean [7,14]. However, this parameter does not account for all the information that can be extracted from the ICP waveform and does not provide physicians with a deep insight into cerebral mechanisms of autoregulation [7,14]. Several methods have been developed in order to better understand ICP and CSF circulation disorders. Some of them rely on the non-linear analysis of ICP signals, using parameters like approximate entropy [15,16] and Lempel–Ziv complexity [7,17]. The results of these studies revealed a decomplexification in the ICP signal during episodes of intracranial hypertension in paediatric patients with traumatic brain injury [15,17] and in adults with hydrocephalus during infusion studies [7]. Spectral analysis of ICP signals recorded using different techniques has also been addressed in previous studies [10,18–20]. However, the approaches are quite different. Some authors analysed the relationship between three spectral components of the ICP waveform and the resistance to CSF outflow in infusion studies in order to explore the ability of new indexes in the prediction of the response to shunting [10]. Nevertheless, the differences among phases of the infusion test were not analysed. Other studies focused on the analysis of very low frequency components, called slow waves, and their relationship with physiological processes [18]. As a consequence, their analysis did not explore frequencies above 0.2 Hz. Several indexes that quantify the signal spectrum waveform were analysed in [19] to explore the differences in the shape of the waveform for different conditions. A continuous monitoring of ICP was required to obtain the recordings. The reconstruction of the ICP signal from the information contained in its first harmonic was addressed by Holm and Eide [20]. However, their frequential analysis relied only on the first harmonic of the Fourier transform of the signal. Further work should be developed to improve the spectral characterisation of ICP signals and to assess the potential of this approach in the clinical practise.

The present study is a new effort to explore the ability of several spectral based measures to characterise ICP signals recorded during infusion tests in patients with hydrocephalus. We studied the following spectral parameters: median frequency (*MF*) and relative power (*RP*) in three frequency bands. The aims of this study were: (i) to test whether *MF* and *RP* could reveal significant differences among phases of the infusion study, (ii) to explore the relationship between spectral parameters and some demographic, radiological and ICP-based variables recorded for the patients in our database and (iii) to introduce an alternative framework to understand brain dynamics in hydrocephalus.

2. Materials and methods

2.1. Subjects

A database of 77 ICP signals from patients suffering from hydrocephalus of various types and origin (41 male and 36 female, with age 74 [62–80] years, median [interquartile range, IQR]), was retrospectively analysed in this study. Data were recorded during infusion tests at the Department of Neurosurgery of the University Hospital of León (Spain). Brain imaging (computer tomography or magnetic resonance) revealed evidence of ventricular dilation (Evans index ≥ 0.30) in all of them. Patients also showed other symptoms of NPH, such as poor motor balance, cognitive impairment or urinary incontinence. The absence of a previous history indicated idiopathic NPH in 45 patients. In 24 patients, a secondary form of NPH developed as a consequence of a preceding history of subarachnoid haemorrhage, traumatic brain injury, stroke or intracranial neoplasm. In the remaining 8 cases, the infusion study was conducted to control shunt dysfunction. Lumbar infusion tests were performed on this population as a supplementary hydrodynamic study and as an aid in the decision on the surgical management of patients [7]. Clinical data of the population under study are summarised in Table 1.

Table 1
Data recorded from the population under study.

Characteristic	Value (median [IQR])
Age (years)	74 [62–80]
Ventricular size (Evans index, *E*)	0.37 [0.35–0.40]
Basal pressure (P_0) (mmHg)	7.42 [5.55–11.00]
Basal amplitude (A_0) (mmHg)	2.55 [1.54–3.48]
Plateau pressure (P_p) (mmHg)	24.91 [20.17–31.07]
Plateau amplitude (A_p) (mmHg)	9.14 [6.11–13.62]
Outflow resistance (*R*) (mmHg ml^{-1} min)	11.95 [8.12–14.53]

IQR: interquartile range.

In all cases, patients or a close relative gave their informed consent to participate in the study, which was approved by the local ethics committee.

2.2. ICP data recording

Infusion studies were performed using a variant of the method described by Katzman and Hussey [13]. Under local anaesthesia, 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). For pressure measurement, a three way stopcock equipped with a short extension line was connected to the second needle (rostral cannula). Then, a pressure microtransducer (Codman® MicroSensor™ ICP transducer, Codman & Shurtleff) was introduced through the hole of a fenestrated male Luer lock connected to the three-way stopcock. The tip of the pressure microtransducer was pushed inside the extension line towards the lumbar needle. Finally, the transducer was secured in its position, rotating the male Luer lock and tightening the fenestrated cap to avoid CSF leakage. The pressure signal from the analogue output of the microtransducer monitor was subsequently amplified (ML110 Bridge amplifier) and digitised (PowerLab 2/25 Data recording system ML825, ADI Instruments). The analogue to digital converter was also connected to a computer in order to visualise and record the ICP signals [7].

After 5 min of baseline recording, basal pressure (P_0) was determined. Then, Ringer solution at a constant infusion rate (*IR*) of 1.5 ml min^{-1} was infused until a plateau was reached. Once the infusion was stopped, CSF pressure continued to be recorded until it decreased towards the baseline level [7]. The plateau CSF pressure (P_p) and P_0 were used to obtain the CSF outflow resistance (*R*) as follows [7]:

$$R = \frac{P_p - P_0}{IR}. \quad (1)$$

For each of the 77 recordings, an experienced neurosurgeon selected four artefact-free epochs, representative of the four phases of the infusion test [7]:

- Epoch 0 corresponds to the basal phase of the infusion test. P_0 was determined in this stage.
- Epoch 1 is representative of the early infusion phase and usually describes an ascending slope.
- Epoch 2 corresponds to the plateau phase. P_p was obtained in this stage.
- Epoch 3 represents the recovery phase, once the infusion has stopped and the ICP signal returns slowly to levels of the basal state.

The four artefact-free epochs have been represented for one of the ICP signals in Fig. 1a.

ICP recordings were acquired with a sampling frequency $f_s = 100$ Hz ($T_s = 1/f_s = 0.01$ s, where T_s is the sampling period). Besides, all the recordings were processed using a finite impulse response (FIR) bandpass filter with cut-off frequencies 0.1 Hz and 10 Hz. This frequency range preserved the relevant spectral content of the signals and minimised the presence of the DC component.

2.3. Calculation of spectral parameters

The Fourier transform (FT) is commonly used to analyse the spectral content of signals. In order to establish a mathematical framework, we assume that each ICP recording is a time signal $x(t)$ sampled at frequency f_s ($f_s = 100$ Hz in this study). The resulting discrete-time signal can be denoted by $x[n] = x(n \cdot Ts)$, $n = 0, \ldots, N-1$, where $x[n]$ has N samples. The discrete-time Fourier series (DTFS) can be computed to analyse the spectral content of $x[n]$ as follows [21]:

$$X[k] = \sum_{n=0}^{N-1} x[n] \cdot e^{-jk\Omega_0 n}, \quad k = 0, \ldots, N-1, \tag{2}$$

where $\Omega_0 = 2 \cdot \pi / N$ is the fundamental frequency and k identifies the frequency of the sinusoid associated with $X[k]$. The discrete frequency can be obtained as $\Omega = k \cdot \Omega_0$ [22].

The power spectral density (PSD) is generally used instead of the DTFS to characterise the distribution of signal power with frequency [23,24]. It can be computed as the FT of the autocorrelation function of $x[n]$, as they are Fourier transform pairs according to the Wiener–Khintchine–Einstein theorem [23,25]. In the case of non-stationary signals, the spectral analysis must be performed considering their time-varying properties. Thus, the PSD is obtained in this case as the DTFS of the short-time autocorrelation (STA) function. The STA function extends the definition of the autocorrelation function using the time sliding window algorithm [26,27]. A moving window of 5 s with an overlap of 4 s was used in this study [7]. Each ICP signal was thus divided into N_T segments of 5 s, whose length was L (500 samples). The STA function of $x[n]$, $R_{xx,w}[m, u]$, was computed as follows:

$$R_{xx,w}[m,u] = \begin{cases} \frac{1}{L} \cdot \sum_{n=0}^{L-u-1} x[n+m] \cdot w'[n] \cdot x[n+m+u] \cdot w'[u+m] & , u \geq 0 \\ R^*_{xx,w}[-u] & , u < 0 \end{cases}, \quad m = 0, \ldots, N_T - 1, \tag{3}$$

where $w[n]$ is the temporal window of length L and $w'[n] = w[-n]$.

The PSD, $S_{x,w}[m, k]$, was then calculated as the DTFS of the STA [22]:

$$\begin{aligned} S_{x,w}[m,k] &= \frac{1}{L} \cdot DTFS\{R_{xx,w}[m,u]\} = \frac{1}{L} \cdot \sum_{u=0}^{2L-1} R_{xx,w}[m,u] \cdot e^{-j \cdot \Omega \cdot u} = \\ &= \frac{1}{L} \cdot \sum_{u=0}^{2L-1} R_{xx,w}[m,u] \cdot e^{-j \cdot ((2 \cdot \pi \cdot k)/(2 \cdot L - 1)) \cdot u}, \quad k = 0, \ldots, 2 \cdot L - 1; \quad m = 0, \ldots, N_T - 1 \end{aligned} \tag{4}$$

It should be noted that Bendat and Piersol's runs test, a general test for wide-sense stationarity, was used to assess stationarity in the 5-s signal segments [28].

Four spectral based measures were subsequently calculated from the PSD: the *MF* and the *RP* in three frequency bands of interest. These parameters were computed from two different points of view. Firstly, the temporal evolution of these parameters was computed from $S_{x,w}[m, k]$ to obtain a value for every second beyond the fifth. Secondly, we averaged the temporal evolution of these parameters in the four artefact-free epochs in which the infusion test was divided.

MF offers a simple means of summarising the whole spectral content of the PSD [23]. It is defined as the frequency that comprises 50% of the signal power. It can be computed as [23]:

$$0.5 \cdot \sum_{k=r_{0.1}}^{r_{10}} S_{x,w}[m,k] = \sum_{k=r_{0.1}}^{r_{MF}[m]} S_{x,w}[m,k], \quad k = 0, \ldots, L-1; \quad m = 0, \ldots, N_T - 1, \tag{5}$$

where $r_{0,1}$ represents the discrete-time frequency corresponding to 0.1 Hz linear frequency, r_{10} represents the discrete-time frequency corresponding to a linear frequency of 10 Hz and $r_{MF}[m]$ is the discrete *MF*. To obtain the continuous-time *MF*, the following relationship should be applied:

$$MF[m] = \frac{f_s}{L} \cdot r_{MF}[m], \quad m = 0, \ldots, N_T - 1. \tag{6}$$

Fig. 1b depicts the variation of *MF* along the duration of the example ICP signal in Fig. 1a.

The *RP* in several bands of interest was also calculated from the PSD. To the best of our knowledge, these bands of interest have not been standardised for ICP signals recorded during infusion studies. Thus, in a first step, we analysed the PSD of the signals in our database to experimentally determine a suitable frequency division. For this task, we obtained an average PSD for the complete data set, $\langle S_{av}[k] \rangle$. This was done by computing the mean PSD for each subject in the database i ($1 \leq i \leq 77$), $\langle S_{x\_i}[k] \rangle$, and normalising it to the range 0–1 [24], $\langle S_{n\_i}[k] \rangle$. $\langle S_{av}[k] \rangle$ was obtained as the mean of $\langle S_{n\_i}[k] \rangle$ for $1 \leq i \leq 77$. The normalisation process ensured that the PSD of all subjects was in the same range when computing $\langle S_{av}[k] \rangle$. $\langle S_{av}[k] \rangle$ showed two main peaks between 0.1 Hz and 3 Hz. The first one could be found between 0.1 Hz and 1 Hz, while the second one fell between 1 Hz and 2 Hz. We could also find some spectral components of the ICP signals in frequencies higher than

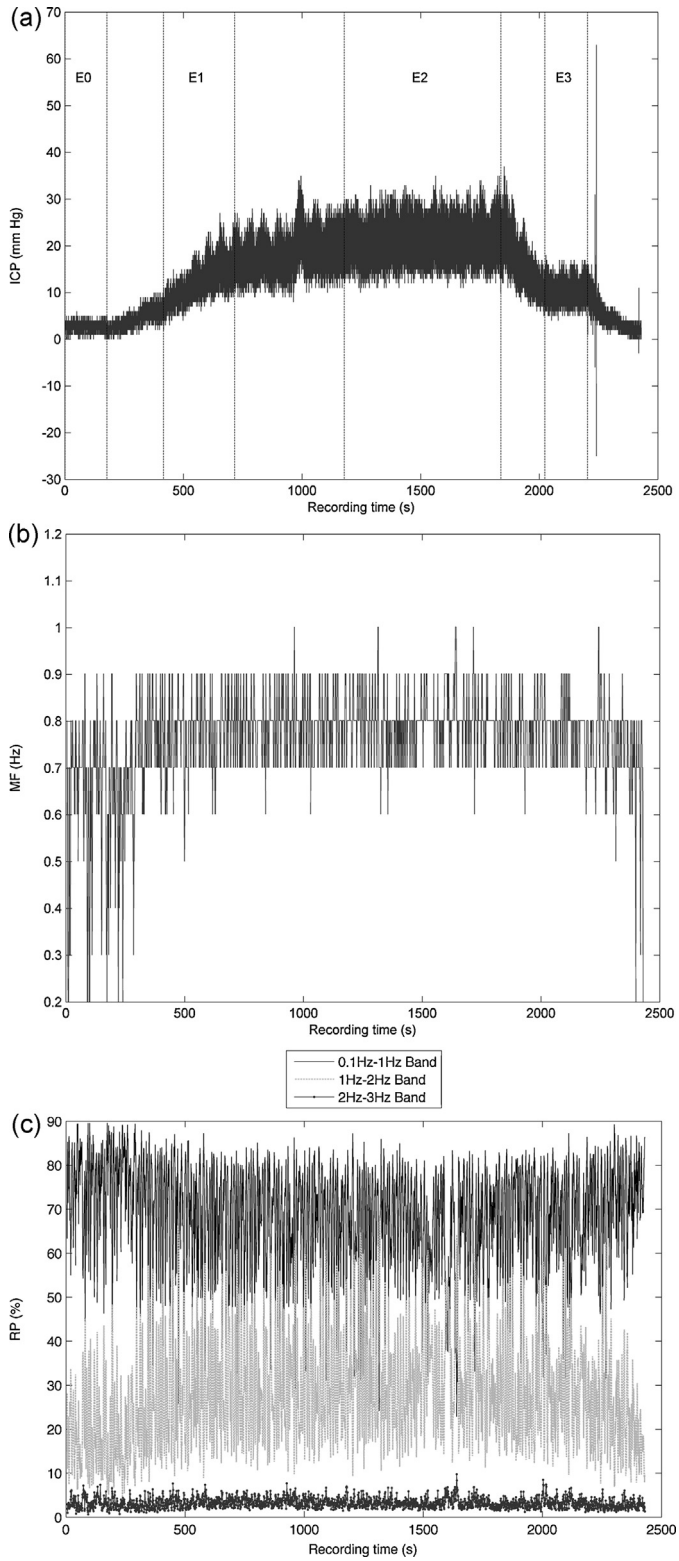

Fig. 1. (a) Evolution of the CSF pressure values in an infusion study for a patient with a proposed diagnosis of normal pressure hydrocephalus. The four artefact-free epochs selected by the neurosurgeon have been depicted (E0: epoch 0, E1: epoch 1, E2: epoch 2, E3: epoch 3). (b) Temporal variation of median frequency (*MF*) for the ICP signal shown above. (c) Temporal variation of relative power (*RP*) in the three bands of interest for the ICP signal shown above.

2 Hz, but the magnitude of $\langle S_{av}[k] \rangle$ was significantly lower for these frequencies, especially for frequencies above 3 Hz. This was also the average behaviour in $\langle S_{n\_i}[k] \rangle$. On the basis of the previous results, we considered three frequency bands: "band 1" between 0.1 Hz and 1 Hz (B_1), "band 2" between 1 Hz and 2 Hz (B_2) and "band 3" between 2 Hz and 3 Hz (B_3). These bands comprise most of the ICP signal spectral content (including the two maxima in $\langle S_{av}[k] \rangle$). Their width (of approximately 1 Hz) provides an exhaustive analysis of ICP signal spectrum. In a second step, we studied *RP* in B_1, B_2 and B_3. The parameter *RP* was calculated as the power of the signal in the band of interest divided by the power in the complete frequency range. Its definition can be read as [29]:

$$RP_{B_j}[m] = \sum_{k \in B_j} S_{n\_i,w}[m,k], \quad k = 0, \ldots, L-1, \quad m = 0, \ldots, N_T - 1, \tag{7}$$

where B_j denotes the band of interest (B_1, B_2 or B_3) and $S_{n\_i,w}[m,k]$ is the normalised PSD for each subject *i*. It should be noted that the frequency limits of the bands in Eq. (7) are discrete frequencies. However, a discrete frequency *k* is directly related to continuous time frequency *f* as follows: $f = f_s \cdot k/L$. The temporal variation of RP_{B_1}, RP_{B_2} and RP_{B_3} for the example ICP signal is shown in Fig. 1c.

2.4. Statistical analysis

Initially, the Kolmogorov–Smirnov test with Lilliefors significance correction and the Shapiro–Wilk test for normality were used to verify the normality of the spectral parameters in the 4 artefact-free epochs of the infusion study. After this exploratory analysis, we found that the parametric assumptions did not hold. For this reason, the non-parametric Friedman test was used to determine whether statistically significant differences ($\alpha = 0.01$) could be found in pairwise comparisons between epochs of the infusion test [30]. In the cases where these differences existed, post hoc analyses were carried out using the Wilcoxon signed-rank test with Bonferroni correction to account for multiple comparisons ($\alpha = 0.01/6 = 1.7 \times 10^{-3}$) [30]. The *Z* score and *p*-value associated to this test were obtained.

Spearman's correlation was used to analyse the relationship between phases of the infusion test and patient data in Table 1. A significance level $\alpha = 0.01$ was also considered here.

3. Results

3.1. Design considerations and notation

The first objective of this study was to determine whether the proposed spectral parameters could reveal statistically significant differences between stages of the infusion test. For this task, the spectral parameters defined in the previous section were calculated for each subject and artefact-free epoch in which the infusion test was divided. Firstly, the PSD of the ICP signals was calculated as the FT of the autocorrelation function of 5-s segments of the signal. A moving window of 5 s with an overlap of 4 s was used until the last sample of the signal was reached [23]. The stationarity of the 5-s segments of the signal was investigated using the Bendat and Piersol's runs test [28]. We found that all the segments were stationary. Thus the proposed spectral analysis is appropriate in this study. Secondly, the four spectral parameters were calculated to obtain a value for every second beyond the fifth. Finally, the spectral parameters were averaged in the four artefact-free epochs of the infusion test. Thus, a single value of *MF*, RP_{B_1}, RP_{B_2} and RP_{B_3} was obtained for each subject and artefact-free epoch. We will denote by *MF*0 the *MF* value in the basal phase of the infusion test, by *MF*1 the *MF* value in epoch 1, by *MF*2 the *MF* value in the plateau

Table 2
Median [interquartile range, IQR] values of the epoch length, CSF pressure and spectral parameters (MF, RP_{B_1}, RP_{B_2} and RP_{B_3}) for each artefact-free epoch in the infusion tests.

	Epoch 0	Epoch 1	Epoch 2	Epoch 3
Length (s)	175[150–182]	300 [300–330]	480 [420–600]	180 [180–240]
CSF pressure (mmHg)	7.42 [5.57–10.96]	16.08 [13.16–19.48]	24.91 [20.29–29.82]	16.43 [12.98–18.55]
MF (Hz)	0.91 [0.58–1.09]	0.99 [0.80–1.13]	1.02 [0.90–1.14]	1.01 [0.83–1.17]
RP_{B_1} (%)	41.74 [25.66–60.19]	33.29 [17.29–51.31]	21.76 [12.03–42.98]	28.28 [12.78–45.58]
RP_{B_2} (%)	39.41 [21.05–56.85]	55.91 [30.60–70.60]	64.01 [43.48–75.94]	60.48 [44.91–73.83]
RP_{B_3} (%)	5.97 [4.02–9.64]	6.01 [3.99–8.18]	6.24 [3.50–8.11]	6.25 [3.70–8.18]

MF: median frequency, RP_{B_1}: relative power in band B_1 (0.1–1 Hz), RP_{B_2}: relative power in band B_2 (1–2 Hz), RP_{B_3}: relative power in band B_3 (2–3 Hz).

phase and by $MF3$ the MF value in the recovery phase. Similarly, $RP_{B_j}0$, $RP_{B_j}1$, $RP_{B_j}2$ and $RP_{B_j}3$ ($j = 1, 2, 3$) represent the values of RP calculated for phases 0, 1, 2 and 3 of the infusion test, respectively.

In a second stage, we analysed whether these spectral parameters could reveal significant correlations between phases of the infusion test and the clinical data of the patients. For this task, the Spearman's correlation coefficient between spectral parameters in each artefact-free epoch and the patient data included in Table 1 was calculated.

Table 2 summarises the median [IQR] values of the epoch length, CSF pressure and spectral parameters (MF, RP_{B_1}, RP_{B_2} and RP_{B_3}) for the artefact-free epochs of the infusion test. These values were averaged over the 77 subjects in our database.

3.2. Differences in pairwise comparisons between stages of the infusion test

Our results showed that the lowest MF values were obtained in the basal epoch, then increased during infusion to reach the highest values in the plateau phase and, finally, decreased again in the recovery phase, reaching values close to those in the basal epoch (see Table 2). The Kolmogorov–Smirnov test with Lilliefors significance correction and Shapiro–Wilk test for normality revealed that $MF0$, $MF1$, $MF2$ and $MF3$ were not normally distributed ($p < 0.01$). The Friedman test revealed significant interactions among the MF values in the various stages of the infusion study ($\chi^2(3) = 44.27$, $p = 1.33 \times 10^{-9} < 0.01$). In order to explore 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: $MF0$ vs. $MF1$ ($Z = -3.42$, $p = 6.27 \times 10^{-4}$), $MF0$ vs. $MF2$ ($Z = -4.50$, $p = 6.92 \times 10^{-6}$), $MF0$ vs. $MF3$ ($Z = -4.42$, $p = 10^{-5}$) and $MF1$ vs. $MF2$ ($Z = -4.89$, $p = 1.02 \times 10^{-6}$). These results are summarised in Table 3.

Regarding RP, the behaviour was different for each band of interest. In the case of RP_{B_1}, values in the basal epoch were the highest (41.74[25.66–60.19]%, median[IQR]), then decreased during infusion to reach the lowest values in the plateau phase (21.76[12.03–42.98]%, median[IQR]) and increased again in the recovery phase (28.28[12.78–45.58]%, median[IQR]) to values that were closer to those in the basal epoch. However, for RP_{B_2} the trend was different. RP_{B_2} values in the basal epoch were the lowest (39.41[21.05–56.85]%, median[IQR]), then increased during infusion and reached the highest values in the plateau phase (64.01[43.48–75.94]%, median[IQR]). They decreased again in the recovery phase (60.48[44.91–73.83]%, median[IQR]) to values that were closer to those in the basal phase. In the case of RP_{B_3}, we could not determine a clear tendency, as the values of RP_{B_3} were very similar in all phases (5.97[4.02–9.64]% for the basal phase, 6.01[3.99–8.18]% for the early infusion phase, 6.24[3.50–8.11]% for the plateau phase and 6.25[3.70–8.18]% for the recovery phase, all the values given as median[IQR]).

The Kolmogorov–Smirnov test with Lilliefors significance correction and Shapiro–Wilk test revealed that the normality hypothesis did not hold for these variables. Therefore, we carried out a Friedman test to determine whether differences between stages of the infusion study could be found using RP_{B_1}, RP_{B_2} and RP_{B_3}. The results revealed significant interactions for RP_{B_1} ($\chi^2(3) = 58.08$, $p = 1.51 \times 10^{-12}$) and RP_{B_2} ($\chi^2(3) = 107.99$, $p = 2.97 \times 10^{-23}$), whereas no significant interaction was found for RP_{B_3} ($\chi^2(3) = 2.03$, $p = 0.57$). Consequently, post hoc analyses were carried out only for RP_{B_1} and RP_{B_2}. The results of the Wilcoxon signed-rank tests for these parameters are included in Table 3. Significant differences could be found among all epochs of the infusion test with both parameters. The magnitude of these differences ranged from $Z = -5.71$ ($p = 1.13 \times 10^{-8}$) for the comparison $RP_{B_1}1$ vs. $RP_{B_1}2$ to $Z = -3.36$ ($p = 7.70 \times 10^{-4}$) for $RP_{B_1}1$ vs. $RP_{B_1}3$, in the case of B_1. Regarding B_2, the minimum Z score was $Z = -6.95$ ($p = 3.69 \times 10^{-12}$) for $RP_{B_2}0$ vs. $RP_{B_2}2$ and the maximum Z score reached $Z = -3.98$ ($p = 6.94 \times 10^{-5}$) in the case of $RP_{B_2}1$ vs. $RP_{B_2}3$.

3.3. Correlation with patient data

We also wanted to know whether the spectral parameters calculated in this study could reveal any relationship between phases of the infusion tests and some demographic, radiological and ICP-based parameters recorded for the 77 patients that participated in the study. They are summarised in Table 1 and include: age, Evans index (E), P_0, basal amplitude of the CSF pressure signal (A_0), P_p, plateau amplitude of the CSF pressure signal (A_p) and R.

The correlation between the spectral parameters ($MF0$, $MF1$, $MF2$, $MF3$, $RP_{B_j}0$, $RP_{B_j}1$, $RP_{B_j}2$ and $RP_{B_j}3$, with $j = 1, 2, 3$) and patients data was analysed using the Spearman's correlation coefficient, r. The results are summarised in Table 4. Only a few significant correlations ($p < 0.01$) were found. In the case of MF, only the correlation A_0 vs. $MF0$ was statistically significant ($r = -0.3164$, $p = 0.0051$). Similarly, only one significant correlation was found for RP_{B_1} and RP_{B_3}, with the pairs A_p vs. $RP_{B_1}1$ ($r = -0.2960$, $p = 0.0090$) and A_0 vs. $RP_{B_3}0$ ($r = -0.3599$, $p = 0.0013$). Finally, statistically significant

Table 3
Z statistics and p-values associated to the Wilcoxon tests for MF, RP_{B_1} and RP_{B_2}. The significant values ($p < 1.7 \times 10^{-3}$, Bonferroni-corrected) have been highlighted.

	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
MF	−3.42	$\mathbf{6.27 \times 10^{-4}}$	−4.50	$\mathbf{6.92 \times 10^{-6}}$	−4.42	$\mathbf{1.00 \times 10^{-5}}$	−4.89	$\mathbf{1.02 \times 10^{-6}}$	−3.04	2.40×10^{-3}	−1.90	5.79×10^{-2}
RP_{B_1}	−3.93	$\mathbf{8.59 \times 10^{-5}}$	−5.58	$\mathbf{2.44 \times 10^{-8}}$	−4.95	$\mathbf{7.31 \times 10^{-7}}$	−5.71	$\mathbf{1.13 \times 10^{-8}}$	−3.36	$\mathbf{7.70 \times 10^{-4}}$	−3.85	$\mathbf{1.20 \times 10^{-4}}$
RP_{B_2}	−6.07	$\mathbf{1.28 \times 10^{-9}}$	−6.95	$\mathbf{3.69 \times 10^{-12}}$	−6.80	$\mathbf{1.04 \times 10^{-11}}$	−6.80	$\mathbf{1.07 \times 10^{-11}}$	−3.98	$\mathbf{6.94 \times 10^{-5}}$	−4.44	$\mathbf{8.99 \times 10^{-6}}$

E0: epoch 0, E1: epoch 1, E2: epoch 2, E3: epoch 3, MF: median frequency, RP_{B_1}: relative power in band B_1 (0.1–1 Hz), RP_{B_2}: relative power in band B_2 (1–2 Hz).

Table 4
Correlation coefficients (r) and p-values obtained for the Spearman test to analyse the relationship between spectral parameters and patient data. Values with a significance level $p < 0.01$ are highlighted.

	Age		E		P_0		A_0		P_p		A_p		R	
	r	p	r	p	r	p	r	p	r	p	r	p	r	p
$MF0$	0.0625	0.5895	0.0571	0.6220	−0.1072	0.3533	−0.3164	**0.0051**	0.0314	0.7862	0.0872	0.4509	0.1143	0.3214
$MF1$	−0.0932	0.4203	0.0147	0.8993	0.1240	0.2826	−0.0574	0.6203	−0.0162	0.8888	−0.0214	0.8534	−0.0442	0.7026
$MF2$	−0.0382	0.7413	0.0357	0.7579	0.1095	0.3430	0.0270	0.8154	−0.0665	0.5655	−0.1137	0.3247	−0.0916	0.4282
$MF3$	0.0500	0.6656	0.0414	0.7209	0.0539	0.6412	0.0562	0.6276	−0.0226	0.8450	−0.0022	0.9847	−0.0201	0.8619
$RP_{B_1}0$	−0.0223	0.8470	0.0859	0.4578	0.0163	0.8879	0.1663	0.1483	−0.1439	0.2113	−0.2418	0.0341	−0.1904	0.0971
$RP_{B_1}1$	0.0359	0.7564	0.0570	0.6227	−0.1794	0.1185	−0.0406	0.7262	−0.2271	0.0472	−0.2960	**0.0090**	−0.1922	0.0940
$RP_{B_1}2$	0.0611	0.5978	0.1156	0.3167	−0.2101	0.0667	−0.0562	0.6273	−0.2227	0.0518	−0.2610	0.0219	−0.1653	0.1505
$RP_{B_1}3$	0.0185	0.8730	0.0616	0.5946	−0.1534	0.1829	0.0230	0.8425	−0.1617	0.1597	−0.2093	0.0677	−0.1277	0.2678
$RP_{B_2}0$	0.2159	0.0594	−0.1682	0.1436	−0.0501	0.6655	0.1333	0.2479	0.1338	0.2456	0.4132	**0.0002**	0.1736	0.1309
$RP_{B_2}1$	0.1538	0.1817	−0.1495	0.1944	0.1439	0.2120	0.1782	0.1210	0.2322	0.0423	0.4438	**0.0001**	0.1942	0.0906
$RP_{B_2}2$	0.0587	0.6124	−0.1864	0.1046	0.2040	0.0752	0.1244	0.2812	0.1955	0.0885	0.3436	**0.0022**	0.1196	0.2995
$RP_{B_2}3$	0.1544	0.1799	−0.1459	0.2054	0.1456	0.2064	0.0828	0.4738	0.1604	0.1630	0.3496	**0.0018**	0.1142	0.3219
$RP_{B_3}0$	−0.1312	0.2552	−0.1185	0.3046	−0.0737	0.5243	−0.3599	**0.0013**	0.0944	0.4134	0.1236	0.2842	0.1612	0.1610
$RP_{B_3}1$	−0.1929	0.0929	−0.0689	0.5517	0.0106	0.9274	−0.1013	0.3809	0.0211	0.8552	0.0926	0.4230	0.0491	0.6712
$RP_{B_3}2$	−0.1802	0.1168	−0.1241	0.2821	0.0276	0.8116	−0.0735	0.5251	0.0118	0.9191	0.0825	0.4755	0.0313	0.7865
$RP_{B_3}3$	−0.1614	0.1608	−0.1031	0.3722	−0.0961	0.4057	−0.1393	0.2270	−0.0438	0.7047	0.0678	0.5577	0.0195	0.8662

MF: median frequency, RP_{B_1}: relative power in band B_1 (0.1–1 Hz), RP_{B_2}: relative power in band B_2 (1–2 Hz), RP_{B_3}: relative power in band B_3 (2–3 Hz), E: Evans index, P_0: basal pressure, A_0: basal amplitude, P_p: plateau pressure, A_p: plateau amplitude, R: cerebrospinal fluid outflow resistance.

correlations could be also found for the pairs A_p vs. $RP_{B_2}0$ ($r = -0.4132$, $p = 0.0002$), A_p vs. $RP_{B_2}1$ ($r = -0.4438$, $p = 0.0001$), A_p vs. $RP_{B_2}2$ ($r = -0.3436$, $p = 0.0022$) and A_p vs. $RP_{B_2}3$ ($r = -0.3496$, $p = 0.0018$).

4. Discussion and conclusion

In this study, a spectral characterisation of ICP signals recorded during infusion tests in patients suffering form hydrocephalus was carried out. The four phases in which infusion tests in our database were divided were analysed by means of four spectral parameters: MF, RP_{B_1}, RP_{B_2} and RP_{B_3}. Although ICP has been previously analysed from different points of view, this is, to the best of our knowledge, the first study that addresses the spectral analysis of ICP signals recorded during infusion studies using parameters like MF or RP.

Spectral parameters were computed from the PSD of the ICP signals. This is a useful tool to analyse the spectral content of signals. In this study, the PSD was calculated as the DTFS of the STA function, as the signals under analysis were non-stationary. However, it should be noted that this is not the only available procedure to calculate the PSD [31]. The Welch's method, based on the averaging of modified periodograms, has been also used with this purpose [31,32].

Firstly, we assessed whether the spectral parameters could reveal differences among phases of the infusion study. Results for MF in Table 3 show that significant differences were found between all phases of the infusion test, except in the comparisons $MF2$ vs. $MF3$ and $MF1$ vs. $MF3$. 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 MF values in the recovery phase may not be too different from those in the plateau phase or early infusion phase (see Table 2).

Regarding RP, significant differences were found among all phases of the infusion study using RP_{B_1} and RP_{B_2}, but differences were not statistically significant in the case of RP_{B_3}. These results suggest that low frequency components of the ICP signal (bands B_1 and B_2) change significantly during stress episodes, such as the increase in ICP produced by infusion studies. On the contrary, high frequency components (band B_3) are not sensitive to ICP variations. Some authors [10,14] indicate that the ICP signal is formed by three overlapping components in the time domain with different frequencies. The first one is the pulse wave, with a fundamental frequency equal to the heart rate and several harmonics, all of them usually above 1 Hz [10,14]. The second component is related to the respiratory cycle and can be generally found between 0.05 Hz and 0.2 Hz [10]. Finally, the third component is related to slow waves, with frequencies between 0.0055 Hz and 0.05 Hz [10,14]. Our findings support the notion that the components in bands B_1 and B_2 might be related to the respiratory wave and, especially, the pulse wave. Indeed, some authors have reported a heart rate above 60 beats per minute (bpm), corresponding to a frequency equal to 1 Hz (1 beat per second), for patients suffering from hydrocephalus. A baseline heart rate of 70 ± 10 bpm, mean ± standard deviation (SD) was found in 34 patients suffering from NPH [33]. Similarly, a heart rate of 73 ± 15 bpm (mean ± SD) was reported for a database of 13 patients [34]. Heart rate has been also modelled as having a frequency of 70 bpm on a study on hydrocephalus valves [35]. These results indicate that the frequency of the pulse wave may be above 1 Hz in patients suffering from hydrocephalus and, thus, would mainly correspond to band B_2 (1–2 Hz) in this study. Respiratory waves have lower frequencies [3,10] and, thus, would be primarily related to band B_1 (0.1–1 Hz).

Further investigation is needed in order to confirm these relationships and determine whether frequencies below 0.1 Hz can provide additional information. However, very low frequency components recorded during infusion studies may not be strictly defined as slow waves, as in a more general ICP analysis context. ICP slow waves, known as Lundberg's 'B' waves, are usually analysed in overnight ICP, since they are associated with cerebral pathological conditions [36,37]. There is evidence that frequent presence of this type of waves may result in a positive response to shunting [38]. In the case of infusion studies, the recording time is much shorter and patients are awake [10]. Therefore, very low frequency components in infusion studies may not reveal the same information as in overnight recordings [5]. Likewise, results regarding the presence of slow waves are sometimes contradictory. A reduced activity of slow waves was found to be associated with poor prognosis after traumatic brain injury [39], whereas other authors suggested that the occurrence of plateau slow waves was not directly linked to worse outcome in head injured patients [36]. Finally, 'B' waves have been also observed in healthy subjects [18,40].

Results in Table 2 also show that, during the infusion study, RP_{B_2} increased while RP_{B_1} decreased with respect to the basal phase. Therefore, under the increase in ICP induced by infusion,

the signal spectrum is shifted towards higher frequencies with respect to the basal state. As a consequence, *MF* is higher in the plateau phase (see Table 2). This result indicates that the arterial component of the pressure wave becomes more prominent in the plateau phase. This issue could be explained taking into account different effects. In the first place, it could be explained from the hypothesis of the activation of an intracranial baroreflex channelled through the autonomic system, as suggested in [33]. Results in this study showed that the moderate rise in ICP during infusion studies yielded a reversible pressure-mediated systemic response that consists in an increase in arterial blood pressure (ABP). This effect also influenced cerebral perfusion pressure (CPP), defined as the mean ABP minus ICP, which significantly decreased during infusion tests [33]. The Cushing response could compromise CPP in an advanced stage. However, before this extreme stage is reached, haemodynamic changes associated to intracranial hypertension could develop [33]. These changes are compatible with an early Cushing response: moderate rise in ABP, mild decrease in CPP, reduction of cerebral blood flow and increase in the heart rate variability without a modification of its mean value [33]. These effects might influence the ICP waveform producing an increase in RP_{B_2} during infusion.

In the second place, the rise in ICP induced by the infusion test may affect the compliance of the brain and cerebral blood vessels. Vascular compliance is important in the brain because it is surrounded by a rigid container (the skull) and an incompressible fluid (CSF) [41]. It is generally accepted that the oscillation of ICP with the cardiac cycle is a result of the cardiac-driven variations in ABP [42]. The volume of intracranial blood varies along one cardiac cycle, due to the pulsatile nature of the blood supply in the brain: it increases during systole and decreases during diastole [41,43]. The arterial pulsations are transmitted to the CSF and, thus, volume changes during the cardiac cycle result also in changes in CSF [41]. As a consequence, the morphology of the CSF waveform suffers changes that depend on the arterial input, the compliance of the cranial contents (parenchyma and cerebral wall) and the blood flow towards the venous system [41,44]. However, the relationship between ABP and ICP oscillation appears to be altered in clinically relevant conditions such as hypertension and hydrocephalus [42]. Under elevated ICP states, brain compliance decreases [14,45] and this causes small changes in intracranial volume induced by cardiac pulsations to generate large ICP wave amplitudes [46]. The increase in RP_{B_2}, together with the decrease in RP_{B_1}, in the plateau phase with respect to the basal phase observed in the present study might reflect these alterations in the ICP waveform associated to changes in brain compliance.

Finally, the increase in RP_{B_2} in the plateau phase might be related to a breakdown of the *windkessel* mechanism induced by the increase in ICP during infusion. The *windkessel* mechanism refers to a progressive dissipation of arterial pulsations, mostly through the CSF, to reach the capillary circulation almost pulseless [47]. Adequate functioning of the *windkessel* mechanism appears to be necessary for normal cerebral blood flow [47,48]. However, the increase in ICP induced by infusion tests might alter the biomechanics of the brain and cause a breakdown of the *windkessel* mechanism [47]. As a consequence, the arterial pulse pressure delivered to the capillary circulation would be stronger [47]. This effect should be reflected in changes in the arterial component during infusion, which is consistent with the increase in RP_{B_2} observed in the plateau phase.

In a second stage of the present study, the correlation between spectral parameters and several demographic, radiological and ICP-based variables was analysed. Results in Table 4 show that only a few significant correlations could be found. These were related to the amplitude of the signal in the basal and plateau phase (A_0 and A_p, respectively). It is noteworthy that, in the case of RP_{B_2}, significant correlations were found with A_p in all the artefact-free epochs of the infusion study. This result suggests that frequency components in B_2, mainly connected to the pulse component of ICP signals, are directly related to the increase in ICP produced during intracranial hypertension. The relationship between the pulse amplitude of ICP (amplitude of the first harmonic of the pulse component) and the mean pressure recorded during infusion studies has been also observed in previous studies [10,11,14]. Our findings also indicate that there is a close relationship between ICP values that can be reached during infusion studies (quantified by A_p) and the percentage of the total signal power in band B_2.

Previous studies have also addressed the characterisation of ICP signals. In previous studies from our research group [7,49], non-linear analysis of data recorded during infusion studies was accomplished. Results showed that the CSF pulse waveform complexity significantly decreased, while CSF pulse waveform variability significantly increased, during the period of intracranial hypertension (plateau phase) with respect to the basal phase. ICP signals have been also studied in the frequency domain using very different strategies. The FT of ICP signals was analysed in the context of the pulse amplitude of ICP, as a means of characterising ICP waveform [11,19]. Other researchers tried to reconstruct the ICP signal from the information in the first harmonic of the FT of the signal [20]. They compared the raw signal and the reconstructed signal in order to quantify the amount of information that was lost in this process. Slow waves have also been studied in order to separate them from other components of the ICP signal and appropriately define the frequency boundaries between different types of slow waves [18,38]. The relationship between the different vasogenic components of ICP signals and *R* was analysed in [10]. In this study, data were recorded during infusion studies for patients with hydrocephalus. However, signals in [11,18,20,38] did not come from infusion tests. Thus, a direct comparison with our study is not straightforward.

Other indexes derived from Fourier analysis of ICP signals have been previously studied. Some researchers calculated the amplitude of the first harmonic of the pulse component and the power of slow waves after a FT analysis for the basal and plateau phases of infusion tests [10]. The pressure–volume compensatory reserve index (RAP index) has also been analysed in previous studies, as the correlation coefficient between the amplitude and mean pressure of the first harmonic of the pulse waveform [14,39]. The spectral parameters analysed in the present study are different from these. Firstly, *MF*, RP_{B_1}, RP_{B_2} and RP_{B_3} were calculated from the PSD of the signals, rather than from a direct calculation of the FT. Secondly, the PSD was calculated as the FT of the autocorrelation function using the moving window technique, more adequate for non-stationary signals [26,27]. The spectral parameters calculated in this study can be regarded as complementary measures to the previous indexes, since they provide distinct measures from the ICP waveform. The extraction of simple spectral parameters, such as *MF* and *RP*, is a necessary first step to introduce this alternative framework to understand brain dynamics in hydrocephalus. Besides, *RP* and *MF* are easy to interpret and summarise different characteristics of the PSD. Therefore, these measures provide a preliminary description of ICP signal spectra that could be extended in future studies by the inclusion of additional spectral parameters that quantify other features of the ICP signals.

Finally, some technical and clinical issues merit further consideration. The ICP waveform can be divided into several components (pulse wave, respiratory wave and slow waves) primarily related to changes in cerebral blood volume [7]. Hence, ICP signals should be studied together with ABP signals or heart rate signals in order to obtain a better understanding of their relationship in the frequency domain and the influence of these components in the bands of interest. These additional signals might also be helpful in better defining

the bands of interest for the spectral analysis of ICP signals in infusion studies. Besides, frequencies below 0.1 Hz were not analysed in this study. ICP signals were filtered below this frequency in order to avoid the influence of the DC component. Additionally, the spectral resolution of the calculated PSDs hindered the separation of the DC component from very low frequency components. Further research should be carried out to explore whether these frequencies contain useful information in signals recorded during infusion tests and their possible relationship with slow waves in overnight recordings. It should also be noted that the early infusion phase is a transient state between the basal and plateau phases. Although it is not a steady state, like the remaining phases of the infusion test, the spectral analysis in this stage provided useful information about the trend of the changes in the analysed spectral parameters between the basal and plateau phases. Another limitation of the study is related to the population under study. Spectral analysis was performed on a heterogeneous group of patients who showed clinical and radiological features of NPH. The database encompasses a wide range of ages and mechanisms leading to hydrocephalus. However, we consider that heterogeneity in patient population should not be regarded as a serious drawback, since the aim of this study was to analyse alternative spectral methods in deriving new measures from ICP signals. Finally, it should be pointed out that it would be desirable to test the proposed method on a larger set of ICP signals.

In summary, spectral parameters like *MF* and *RP* reveal changes in the ICP signal spectrum during stress episodes. Significant differences were found between most phases of the infusion test using *MF*. Besides, significant differences between all phases of the infusion study could be found using RP_{B_1} and RP_{B_2}. Differences were not statistically significant in the case of RP_{B_3}. The increase of *MF* and RP_{B_2}, together with the decrease of RP_{B_1}, in the plateau phase with respect to the basal phase indicate that the signal spectrum is shifted towards higher frequencies under raised ICP conditions. Statistically significant relationships with amplitude in the basal and plateau phases were also found using these spectral methods. More specifically, significant correlations were found for A_0 vs. $MF0$, A_0 vs. $RP_{B_3}0$, A_p vs. $RP_{B_1}1$, A_p vs. $RP_{B_2}0$, A_p vs. $RP_{B_2}1$, A_p vs. $RP_{B_2}2$ and A_p vs. $RP_{B_2}3$. These findings indicate that spectral analysis could help to understand CSF dynamics during infusion tests.

Future efforts will be aimed at studying new spectral parameters in order to determine whether they can reveal differences between stages of the infusion test, as well as more significant correlations between spectral parameters and clinical data. The use of different time–frequency representations with variable time–frequency resolution, such as *wavelets*, would also be addressed in order to appropriately study very low frequency components that might be associated with slow waves. We will also try to combine the information of spectral and non-linear analysis of ICP signals, in order to obtain complementary information that might help physicians to better understand CSF dynamics in hydrocephalus. Finally, the potential clinical applications of these results need to be further explored, since this study is a first step towards the potential use of these spectral parameters in the clinical practise. In this sense, it would be desirable to assess the utility of spectral analysis of ICP signals in the prediction of patient response to shunting and in the distinction between hydrocephalus and other pathological states with similar clinical signs.

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Ethical approval

This study was approved by the local ethics committee of the University Hospital of León, Spain.

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Appendix A. Abbreviations and symbols

A1. Abbreviations

ABP	Arterial blood pressure
CPP	Cerebral perfusion pressure
CSF	Cerebrospinal fluid
DC	Direct current
DTFS	Discrete time Fourier series
FIR	Finite impulse response
FT	Fourier transform
ICP	Intracranial pressure
NPH	Normal pressure hydrocephalus
PSD	Power spectral density
RAP	Pressure–volume compensatory reserve index
SD	Standard deviation
STA	Short-time autocorrelation
STFT	Short time Fourier transform

A2. Symbols and units

Symbol	Definition	Units
A_0	Basal amplitude of the CSF pressure signal	(mmHg)
A_p	Plateau amplitude of the CSF pressure signal	(mmHg)
B_1	Frequency band 1 (0.1–1 Hz)	(Hz)
B_2	Frequency band 2 (1–2 Hz)	(Hz)
B_3	Frequency band 3 (2–3 Hz)	(Hz)
E	Evans index	–
f_s	Sampling frequency	(Hz)
IR	Infusion rate	(ml min^{-1})
L	Length of 5-s segments	(# of samples)
MF	Median frequency	(Hz)
$MF0$	Median frequency in the basal phase	(Hz)
$MF1$	Median frequency in the early infusion phase	(Hz)
$MF2$	Median frequency in the plateau phase	(Hz)
$MF3$	Median frequency in the recovery phase	(Hz)
N	Length of discrete-time signal	(# of samples)
N_T	Number of 5-s segments in a signal	(# of segments)
P_0	Basal CSF pressure	(mmHg)
P_p	Plateau CSF pressure	(mmHg)
R	CSF outflow resistance	(mmHg ml^{-1} min)
RP	Relative power	(%)
$RP_{B_j}0$	Relative power in the basal phase and for frequency band B_j ($j = 1, 2, 3$)	(%)
$RP_{B_j}1$	Relative power in the early infusion phase and for frequency band B_j ($j = 1, 2, 3$)	(%)
$RP_{B_j}2$	Relative power in the plateau phase and for frequency band B_j ($j = 1, 2, 3$)	(%)
$RP_{B_j}3$	Relative power in the recovery phase and for frequency band B_j ($j = 1, 2, 3$)	(%)
T_s	Sampling period	(s)
α	Significance level	–
Ω_0	Fundamental frequency	(rad)
Ω	Discrete frequency	(rad)

Conflict of interest statement

None declared.

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