Characterisation of the complexity of intracranial pressure signals measured from idiopathic and secondary normal pressure hydrocephalus patients

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Published in Healthcare Technology Letters; Received on 1st April 2016; Revised on 2nd June 2016; Accepted on 13th June 2016

Hydrocephalus is a condition characterised by enlarged cerebral ventricles, which in turn affects intracranial pressure (ICP); however, the mechanisms regulating ICP are not fully understood. A nonlinear signal processing approach was applied to ICP signals measured during infusion studies from patients with two forms of hydrocephalus, in a bid to compare the differences. This is the first study of its kind. The two forms of hydrocephalus were idiopathic normal pressure hydrocephalus (iNPH) and secondary normal pressure hydrocephalus (SH). Following infusion tests, the Lempel–Ziv (LZ) complexity was calculated from the iNPH and SH ICP signals. The LZ complexity values were averaged for the baseline, infusion, plateau and recovery stages of the tests. It was found that as the ICP increased from basal levels, the LZ complexities decreased, reaching their lowest during the plateau stage. However, the complexities computed from the SH ICP signals decreased to a lesser extent when compared with the iNPH ICP signals. Furthermore, statistically significant differences were found between the plateau and recovery stage complexities when comparing the iNPH and SH results ($p = 0.05$). This Letter suggests that advanced signal processing of ICP signals with LZ complexity can help characterise different types of hydrocephalus in more detail.

1. Introduction: The inadequate absorption of cerebrospinal fluid (CSF) within the cranium is known to be potentially life threatening. Despite the dangers of CSF accumulation, relatively little is known about the exact mechanisms through which CSF absorption occurs. Unsurprisingly, the lack of a thorough understanding of CSF dynamics has led to conditions related to CSF dynamics, such as hydrocephalus, being somewhat misunderstood. Often, when the brain swelling condition of hydrocephalus develops following brain injuries or haemorrhages, it is covered by the umbrella term of secondary normal pressure hydrocephalus (SH), whilst hydrocephalus of no known cause, is often termed as idiopathic normal pressure hydrocephalus (iNPH) [1].

Hydrocephalus is often characterised using intracranial pressure (ICP) signals. ICP can be measured during an infusion test. Infusion tests consist of artificially elevating ICP through the infusion of fluid into the subarachnoid space, then recording the exhibited pressures [2]. Many approaches have been previously employed in the analysis of hydrocephalic ICP signals, ranging from traditional spectral analysis to newer nonlinear methods. For example, hypertensive ICP was found to consist of higher frequency components, when compared with basal ICPs [3]. Nonlinear studies of ICP signals have produced findings suggesting that following traumatic brain injury, ICP slow waves exhibit the lowest sample entropy values when the pressure values themselves are at their highest, and most dangerous [4]. The Lempel–Ziv (LZ) complexity measure has also been applied to hydrocephalic ICP signals, from which it was found that, again when ICP was at its highest, the LZ complexity values were at their lowest [2].

It is important to note that the previous signal processing characterisations of hydrocephalic ICPs have not taken aetiology into account. Thus, despite the fact that iNPH and SH clearly represent differing aetiologies, there has never before been an attempt to distinguish between the characteristics of iNPH and SH.

In this Letter, we hypothesised that LZ complexity, computed from the ICP signals recorded from iNPH and SH patients, would uncover statistically significant differences between iNPH and SH ICP signals.

2. Materials and methods

2.1. Signal acquisition and pre-processing: A total of 69 ICP signals were recorded from patients with ventriculomegaly (Evans index >0.3). Thirty three of the signals were from patients with iNPH (consisting of 20 males and 13 females, aged 76.9 ± 6.8 years) and 36 signals were from patients with SH (consisting of 16 males and 20 females, aged 63.5 ± 16.6 years). The patients were put under local anaesthesia, whilst a lumbar infusion test was carried out at the Hospital Universitario de León, Spain, in which the infusion method was slightly altered to that first described by Katzman and Hussey [5].

The infusions began with each patient placing themselves in the lateral recumbent position, before a caudal needle and a rostral cannula were inserted into the lower lumbar region; the needles were, respectively, connected to an infusion pump and a three-way stopcock [2, 3]. The three-way stopcock was in turn connected to a fenestrated male Luer lock, through which a pressure micro-transducer was pushed towards the rostral cannula and secured in place [2, 3]. Following an initial 5 min of basal ICP measurement, Ringer solution was then infused at a rate of 1.5 ml/min [2, 3]. Using a sampling rate of 100 Hz to obtain a signal, the infusions continued until it was deemed by the overseeing neurosurgeon that a plateau ICP had been reached, after which the ICP was allowed to drop back to basal levels [2, 3].

Using the judgement of the presiding neurosurgeon, each ICP recording was split into four epochs; baseline, infusion, plateau and recovery. Table 1 summarises the resulting mean ICPs and pulse amplitudes from the different epochs and resistances to CSF outflow for each group, whilst Fig. 1 shows a representative ICP signal.

Two separate band-pass filters were then used in the pre-processing of the ICP signals. Each signal was passed through a 0.005–10 Hz and a 0.045–10 Hz filter such that there would be two copies of each signal; one would contain slow wave components, whilst the other would not. Both filters were finite impulse response filters with Hamming windows and orders of 41424.

Table 1 Average ICPs and pulse amplitudes from the different epochs of the infusion tests and resistances to CSF outflow for both groups

		iNPH	SH
baseline, mmHg	ICP	7.70 ± 3.14	8.70 ± 4.12
	pulse amplitude	2.76 ± 1.51	2.76 ± 1.21
infusion, mmHg	ICP	16.34 ± 4.40	16.43 ± 6.13
	pulse amplitude	6.28 ± 3.12	6.03 ± 3.90
plateau, mmHg	ICP	26.65 ± 8.02	24.79 ± 9.61
	pulse amplitude	11.35 ± 6.62	9.76 ± 6.17
recovery, mmHg	ICP	16.93 ± 5.60	15.98 ± 6.23
	pulse amplitude	7.09 ± 4.56	5.50 ± 2.95
resistance to CSF outflow, mmHg/ml/min		12.62 ± 4.57	10.72 ± 5.07

Results are presented as mean ± standard deviation.

2.2. LZ complexity: The LZ complexity was first introduced as a method with which to calculate complexity within a finite sequence [6]. The method requires converting the signal into a sequence with a finite number of symbols before estimating the number of different patterns within the sequence. In this Letter, the ICP signals were converted into binary sequences and LZ complexity values were computed in 5 s sliding windows with overlaps of 4 s; a 5 s window was found to be sufficient when computing the LZ complexity, whilst still ensuring computational efficiency.

The first step used in the computation of the LZ complexity was to use the median, M_n as a threshold to convert each sample from the ICP signal, $x(i)$, into a binary sequence [2]

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

Scanning the binary sequence from left to right, each new subsequence of symbols increased a complexity counter $c(n)$ by one [2]. The LZ complexity values in this Letter were defined as the normalised complexity counters. The normalisation ensures that the complexity value is independent of sequence length [2, 7]

$$C(n) = \frac{c(n)}{n/\log_2(n)} \quad (2)$$

Fig. 1 Representative plot of ICP, measured during an infusion test, from a patient with iNPH

Fig. 2 shows a plot of the LZ complexities computed from the ICP signal shown in Fig. 1.

2.3. Statistical analyses: The mean of the LZ complexities from each epoch were calculated and then a range of statistical tests were performed. Following a Lilliefors test to determine the distribution of LZ complexity values (significance level of 0.05), the correlations between the complexities from different epochs were computed for each aetiology, before the complexities underwent the Wilcoxon signed rank test to ascertain which pairs of epochs produced complexities with a median difference of zero. To account for the six epoch comparisons in the Wilcoxon signed rank analyses (e.g. baseline versus infusion, baseline versus plateau etc.), a Bonferroni corrected significance level of 0.0083 was used, representing 0.05/6 [3, 8]. One-way analysis of variance (ANOVA) was also carried out to enable a pairwise assessment of which epochs pertaining to the two aetiologies were significantly different to one another (a significance level of 0.05 was used); for example, the iNPH baseline LZ values were compared with the SH baseline LZ values.

3. Results: Overall, the LZ complexities computed from both the iNPH and SH ICP signals exhibited the same trend of peaking during the baseline epoch, decreasing during the infusion epoch, reaching their lowest point during the plateau epoch and increasing during the recovery epoch. Fig. 3 shows box plots of the LZ complexities.

It can be seen from Fig. 3 that the median LZ complexities from both the iNPH and SH ICP signals displayed a similar trend of peaking during the baseline epoch and reaching their lowest during the plateau epoch. The basal iNPH complexities, however, had a much larger interquartile range when compared with those of the SH complexities. The results for the analysis of the signals which were filtered using the 0.005–10 Hz filter showed a similar trend.

The correlation analyses (which were preceded by the Lilliefors tests) were computed using a significance level of 0.05 and revealed some common trends. Both the LZ complexities computed from the 0.045–10 Hz and the 0.005–10 Hz filtered iNPH ICP signals contained significant correlations between the baseline and infusion, the infusion and plateau, the infusion and recovery, and the plateau and recovery epochs. Of the complexities computed from the 0.045–10 Hz and the 0.005–10 Hz filtered SH ICP signals, significant correlations were found amongst every pair of epochs.

Fig. 2 Plot of LZ complexities, computed from an ICP signal recorded from a patient with iNPH filtered with the band-pass filter with cut-off frequencies 0.045–10 Hz

Fig. 3 Box plots of the LZ complexities computed from the 0.045–10 Hz filtered iNPH ICP signals (top) and from the 0.045–10 Hz filtered SH ICP signals (bottom)

However, the values for the correlation coefficients were consistently higher in SH.

Tables 2 and 3 show the results from the Wilcoxon signed rank tests for the LZ complexities computed from the 0.045–10 Hz iNPH and SH ICP signals, using a Bonferroni corrected significance level of 0.0083. The results show that for both aetiologies statistically significant differences between the complexities were found from all pairs of epochs, with the exception of infusion and recovery.

Tables 4 and 5 show the results from the Wilcoxon signed rank tests for the LZ complexities computed from the 0.005–10 Hz iNPH and SH ICP signals (again using a Bonferroni corrected significance level of 0.0083). Only the infusion and recovery epochs were found to contain complexities whose differences were not significantly

Table 2 Wilcoxon signed rank results from the iNPH LZ complexity values from the 0.045–10 Hz filtered signals

	<i>p</i> -value	<i>h</i> -value	<i>z</i> -value
baseline versus infusion	3.3×10^{-6}	1	4.7
baseline versus plateau	3.9×10^{-6}	1	4.6
baseline versus recovery	4.6×10^{-6}	1	4.6
infusion versus plateau	0.00017	1	3.8
infusion versus recovery	0.11	0	1.6
plateau versus recovery	0.00086	1	3.3

Table 3 Wilcoxon signed rank results from the SH LZ complexity values from the 0.045–10 Hz filtered signals

	<i>p</i> -value	<i>h</i> -value	<i>z</i> -value
baseline versus infusion	5.5×10^{-4}	1	3.5
baseline versus plateau	7.0×10^{-5}	1	4.0
baseline versus recovery	6.5×10^{-4}	1	3.4
infusion versus plateau	2.6×10^{-5}	1	4.2
infusion versus recovery	0.31	0	1.0
plateau versus recovery	0.00010	1	3.9

Table 4 Wilcoxon signed rank results from the iNPH LZ complexity values from the 0.005–10 Hz filtered signals

	<i>p</i> -value	<i>h</i> -value	<i>z</i> -value
baseline versus infusion	5.4×10^{-6}	1	4.5
baseline versus plateau	3.5×10^{-6}	1	4.6
baseline versus recovery	5.0×10^{-6}	1	4.6
infusion versus plateau	0.00017	1	3.8
infusion versus recovery	0.085	0	1.7
plateau versus recovery	0.00055	1	3.5

different to one another, as every other pair of epochs contained complexities which were significantly different to one another.

Table 6 shows the results from the one-way ANOVA of the LZ complexities (significance level of 0.05). Of the 0.045–10 Hz filtered ICP signals, statistically significant differences were found between the LZ complexities computed from the iNPH and SH signals during the recovery epochs. Of the 0.005–10 Hz filtered ICP signals, the difference between the complexities computed from the iNPH and SH plateau epochs was found to be statistically significant; this is in addition to the finding that the difference between the complexities computed from the iNPH and SH recovery epochs was also statistically significant.

4. Discussion: This Letter is believed to be first to compare the LZ complexities computed from 69 ICP signals which were recorded from iNPH and SH patients during infusion tests. Previous complexity analyses of hypertensive ICP signals have not

Table 5 Wilcoxon signed rank results from the SH LZ complexity values from the 0.005–10 Hz filtered signals

	<i>p</i> -value	<i>h</i> -value	<i>z</i> -value
baseline versus infusion	5.8×10^{-4}	1	3.4
baseline versus plateau	4.4×10^{-5}	1	4.1
baseline versus recovery	6.2×10^{-4}	1	3.4
infusion versus plateau	1.7×10^{-4}	1	3.8
infusion versus recovery	0.37	0	−0.90
plateau versus recovery	0.0015	1	3.2

Table 6 Results from one-way ANOVA of the LZ complexities from the iNPH and SH epochs

	0.045–10 Hz	0.005–10 Hz
baseline <i>p</i> -value	0.46	0.65
infusion <i>p</i> -value	0.15	0.12
plateau <i>p</i> -value	0.060	0.046
recovery <i>p</i> -value	0.045	0.032

Statistically significant differences are shown in bold.

specifically compared signals taking the aetiology of the condition into consideration [2, 4, 9]. However, with ICP dynamics remaining largely misunderstood, comparing how the complexity within iNPH and SH ICP signals differ, offers a means by which to further investigate hydrocephalus.

Complexity science itself is centred on the belief that the ability of an organism to adapt well to changes in its environment is dependent on the level of interaction between physiological structures and feedback loops [10]. Thus, in essence, the complexity theory, which was first proposed by Goldberger *et al.* [10], suggests that physiological complexity allows organisms to effectively adapt when required to do so. The results from previous complexity analyses of ICP signals support the theory, with [2, 4] both finding that hypertensive ICP signals exhibited low complexity. In this Letter, similar conclusions could be drawn, with the baseline and plateau epochs, respectively, producing the highest and lowest LZ complexities.

In terms of comparing the LZ complexities computed from the iNPH and SH ICP signals, there are very obvious visual differences in the distribution of the complexities. The iNPH complexities exhibited the same decomplexification trend as that reported in [2], with the complexities decreasing considerably from baseline to plateau, and hence representing a possible major derangement of CSF dynamics. However, the decomplexification exhibited by the SH ICP signals appeared to be less pronounced. The reduced decomplexification within the SH ICP signals is reflected by increased correlations between the SH baseline and plateau epochs, compared with the iNPH correlations.

Notably, statistically significant differences between the LZ complexities were found from all pairs of epochs, with the exception of infusion and recovery for both aetiologies. However, with the exception of the 0.045–10 Hz ‘infusion versus plateau’ and ‘plateau versus recovery’ pairs, the associated *p*-values from the iNPH signals tended to be smaller than their SH counterparts. Relating this back to the theory of physiological complexity, it could be surmised that when compared with SH, iNPH physiologies experience poorer control of ICP, which could possibly be a result of less interaction between the structures and feedback loops which control CSF dynamics.

With a 5% significance level in the one-way ANOVA assessment, the recovery epoch results and the 0.005–10 Hz plateau results show that the iNPH and SH complexities were significantly different from each other. This could therefore suggest that overall, iNPH and SH physiologies differ in their regulatory responses; this is perhaps reflected in the fact that the mean iNPH resistance to CSF outflow was larger than that of SH.

Rosner’s vasodilatory cascade theorises that arterial blood pressure is inversely proportional to ICP [11], meaning the key to ICP control may simply be blood pressure control. Applying this assumption to the results from this study, the possibility arises that the injuries which lead to forms of SH may have a reduced effect, if any, on blood pressure control, whereas the events which lead to the development of iNPH may intrinsically be a reflection of impaired blood pressure control.

In terms of comparing the way in which the frequency content of the ICP signals affected the analyses, the most noticeable differences between the results obtained from the 0.045–10 Hz filtered signals and the 0.005–10 Hz filtered signals can be found amongst the one-way ANOVA results. Not only was the *p*-value obtained from the comparison of the 0.005–10 Hz iNPH and SH plateau epoch complexities significantly different from one another, but the *p*-value obtained from the comparison of the 0.005–10 Hz recovery epochs was also noticeably smaller than the corresponding 0.045–10 Hz *p*-value. This indicates that the inclusion of the slow wave components in the analyses aids in the revelation of greater differences between the natures of the ICP signals recorded from patients with iNPH and those with SH. These results are particularly interesting given the fact that the decreases in complexity in ICP slow wave signals from patients

who have suffered traumatic brain injuries have been correlated to poorer outcomes [4].

Referring back to this Letter’s finding that there is a greater reduction in complexity within the plateau epochs of ICP signals recorded from iNPH patients, the possible effects of slow waves raises the need to further explore any differences in outcome between patients with iNPH and SH. Also, any further investigations into the complexity differences between ICP signals recorded from iNPH and SH patients would undoubtedly have to analyse larger data sets, with equal numbers of age-matched male and female patients, so as to fully discount any effects of sex or age on the complexities. The differences in the sex and age of the patients are two of the main limitations of this Letter. Another limitation could be argued to be the fact that the classifications of the aetiology of each patient’s hydrocephalus were performed retrospectively. Although out of the scope of this Letter, future studies would aim to assess the proficiency of the LZ complexity in discerning between ICP signals recorded from iNPH and SH patients, when compared with more traditional indices calculated from infusion tests. Nevertheless, our results suggest that aetiology should be taken into account when characterising ICP signals using signal processing techniques.

5. Conclusion: In this Letter, the LZ complexity was applied to 69 ICP signals measured from 33 iNPH patients and 36 SH patients. The results suggest that during hypertension, there is a greater reduction in complexity within iNPH ICP signals, when compared with the SH ICP signals. The presence of slow wave components within the ICP signals has also been found to amplify the differences between the signals recorded from iNPH patients and SH patients.

6. Funding and Declaration of Interests: Miss Adjei reports grants from Engineering and Physical Sciences Research Council and partial funding from the Doctoral Training Grant EP/K503186 was received during the conduct of the study. Conflict of interest: None declared.

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