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Adaptive computation of approximate entropy and its application in integrative analysis of irregularity of heart rate variability and intracranial pressure signals

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Abstract

The present study introduces an adaptive calculation of approximate entropy (ApEn) by exploiting sample-by-sample construction and update of nearest neighborhoods in an n -dimensional space. The algorithm is first validated with a standard numerical test set. It is then applied to electrocardiogram R wave interval (RR) and beat-to-beat intracranial pressure signals recorded from 12 patients undergoing normal pressure hydrocephalus diagnosis. The ApEn time series are further processed using the causal coherence analysis to study the interaction between ICP and RR interval. Numerical validation demonstrates that the proposed algorithm reproduces the known time-varying patterns in the test set and better tracks abrupt signal changes. It is also demonstrated that occurrences of large-amplitude ICP oscillation are associated with decreased ICP ApEn and RR ApEn for all 12 patients. The causal coherence analysis of ApEn time series shows that coherence between RR ApEn and ICP ApEn, after mathematically decoupling RR effect on ICP, is enhanced for the oscillatory ICP state and so is the amplitude of transfer function between ICP and RR interval. However, no enhanced coherence is observed after mathematically decoupling ICP effect on RR interval. In conclusion, the adaptive ApEn algorithm can be used to track nonstationary signal characteristics. Furthermore, interactions between dynamic systems could be studied by using ApEn time series of the direct observations of systems.

Keywords

Approximate entropy; Intracranial pressure; Causal coherence; Adaptive algorithm

1. Introduction

Approximate entropy (ApEn) was proposed by Pincus [1] as a measure of irregularity of time series of various origins. Calculation of ApEn has a modest requirement on the quality of time series in terms of data length and signal to noise ratio. This property makes it attractive for applications in biomedical signal processing as evidenced by a large number of publications pertinent to applying ApEn in heart rate variability (HRV) analysis [2,3], in electroencephalography (EEG) signal processing [4,5], and in characterizing endocrine variability [6,7]. ApEn has also been thoroughly studied using both analytical and numerical methods. For example, sample entropy (SampEn) was proposed to correct the inherent bias in

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the original definition of ApEn [8]. A comprehensive set of numerical test cases was created in [9] to study the interpretation of ApEn in terms of more traditional signal characteristics. This test set contains six time series generated with six different types of time-varying signal characteristics. These numerical test cases are particularly useful for testing whether any new regularity characterization algorithm could reproduce the time-varying patterns represented in the test cases.

The main objective of the present study is to present an adaptive algorithm of computing ApEn and its preliminary application in processing real biomedical signals. Nonstationarity exists ubiquitously in biomedical signals based on the fact that dynamics of physiological systems generating these signals are always changing because of the needs of maintaining a dynamical balance in responses to both internal and external stimuli. Considering this, the lack of adaptive algorithms for calculating ApEn may limit applications of this metric in processing of biomedical signals. To address this issue, an adaptive algorithm of updating nearest neighborhood on a sample-by-sample basis is proposed. The key idea of this algorithm has been used in our previous derivation of an adaptive algorithm of calculating generalized synchronization measures [10]. This key idea concerns a way of updating nearest neighborhoods in an n -dimensional vector space as new measurements become available. To demonstrate the algorithm, interval between consecutive electrocardiogram (ECG) R waves (RR interval) and beat-to-beat mean intracranial pressure (ICP) signals under two ICP states were analyzed. The two ICP states include a baseline state where beat-to-beat variations in ICP are small and an oscillatory state where ICP signals are characterized by irregular rhythmical large-amplitude oscillations. The resultant ApEn time series were then further processed using the causal transfer function analysis [11,12] to investigate the relationship between ApEn time series of RR interval and ICP.

In the sequel, a brief introduction of ApEn will be given and then followed by a detail presentation of the adaptive algorithm. A description of the simulation data and the patient data that were used for testing the algorithm will then be described. In Section 3, we first present the results from a numerical experiment to show the validity of the new algorithm and then show results from processing patient data. Finally, we summarize and discuss the main findings.

2. Methods

2.1. Calculation of approximate entropy

With length of template (m) given, a set of m -dimensional vectors $\mathbf{x}_i^m$ can be formulated from a scalar time series x_i , $i = 0, \dots, N-1$, such that $\mathbf{x}_i^m = [x_{i-(m-1)}, x_{i-(m-1)+1}, \dots, x_i]$. In addition, a set of $m+1$ -dimensional vectors $\mathbf{x}_i^{m+1}$ can be obtained in the similar fashion. For the i th m - and $m+1$ -dimensional vectors, the number of their neighborhood points within δ can be counted and normalized to the total number of vectors as

$$C_i^m = \frac{1}{N - (m - 1)} \sum_{|i-j| \geq \varepsilon} H(|\mathbf{x}_i^m - \mathbf{x}_j^m| - \delta) \quad (1)$$

and

$$C_i^{m+1} = \frac{1}{N - m} \sum_{|i-j| \geq \varepsilon} H(|\mathbf{x}_i^{m+1} - \mathbf{x}_j^{m+1}| - \delta) \quad (2)$$

Then ApEn can be calculated as

$$\text{ApEn}(m, \delta, N) = \frac{1}{N - (m - 1)} \sum_i \log(C_i^m) - \frac{1}{N - m} \sum_i \log(C_i^{m+1}) \quad (3)$$

where H is the Heaviside function and $|\mathbf{x}_i^m - \mathbf{x}_j^m|$ is a measure of distance between vector $\mathbf{x}_i^m$ and $\mathbf{x}_j^m$. The distance threshold δ is usually chosen based on the standard deviation of time series x_i such that $\delta = r \times \text{STD}$. The usual range for r is between 0.1 and 0.3. In later discussion, the terms δ -neighborhood or r -neighborhood of a reference vector will be used for denoting a collection of vectors whose distances to the reference are less than $r \times \text{STD}$.

For achieving brevity in later discussion, the dependency of ApEn on m and δ is dropped. In addition, considering that we deal with nonstationary data, a time stamp is introduced such that the ApEn statistic, calculated using a w -sample data segment whose last sample is measured at time n , can be denoted as $\text{ApEn}(n, w)$. A fast neighborhood searching algorithm [13] will be employed in calculating C_i^m and C_i^{m+1} and therefore a possible adaptive way of computing ApEn in a sample-by-sample fashion can be formalized by adaptively constructing neighborhood.

2.2. Adaptive computation of approximate entropy

To calculate $\text{ApEn}(n + 1, w)$ when a new sample x_{n+1} is obtained at time $n + 1$, one needs to update historical neighborhood information in addition to finding the neighborhood for the new vectors $\mathbf{x}_{(n+1)}^m$ and $\mathbf{x}_{(n+1)}^{m+1}$. An additional consideration is that the candidates for searching neighbors of $\mathbf{x}_{n+1}^m$ and $\mathbf{x}_{n+1}^{m+1}$ are only to be sought using $\mathbf{x}_i^m$ and $\mathbf{x}_i^{m+1}$, $i = (n + 1) - w + 1, \dots, (n + 1)$, respectively. This consequently becomes a short-time neighborhood search that facilitates tracking a time-varying system.

The block diagram of this adaptive algorithm is depicted in Fig. 1 that essentially contains three steps shown as three rectangles in the figure. Meanwhile, three data buffers that are necessary for executing the algorithm are shown as three cylinders in the figure including time series buffer, neighborhood indices buffer ϕ_i , and r -neighbor counters C_i^m , and C_i^{m+1} . To proceed, a new sample x_{n+1} is first pushed into the time series buffer and a short-time neighborhood search is initialized for finding the r -neighborhood for $\mathbf{x}_{n+1}^m$ and $\mathbf{x}_{n+1}^{m+1}$. This would result in an additional neighborhood indices entry ϕ_{n+1} to be saved in the ϕ buffer. As the second step, each of the historical ϕ_i , $i = n - w + 1, \dots, n$ is checked for removing the outdated sample index $n - w$ that is included in its neighborhood. This would result in an update of ϕ_i and a reduction by one in the r -neighbor counters for those updated ϕ_i . Then the latest time index $n + 1$ will be added to those ϕ_i , where i is included in ϕ_{n+1} . This results in an update of ϕ_i as well as an increase by one in the r -neighbor counters for those updated entries. Finally, ApEn_{n+1} can be calculated using C_i^m , and C_i^{m+1} , $i = n - w + 1, \dots, n + 1$ according to Eq. (3).

2.3. Numerical test

To demonstrate the adaptive algorithm, a test data set was created according to a recent publication [9]. The data set contains: (1) a constant-amplitude chirp signal with frequency increased from 0.5 Hz to 5 Hz; (2) the same chirp signal but with a sinusoidal amplitude modulation (AM); (3) a signal composed of four periodic signal with 1, 2, 4, and 7 harmonic (s); (4) an AM (at 0.2 Hz) sinusoidal signal with four different realizations of Gaussian white noise added to each consecutive 10-s segment; (5) a signal concatenated from four zero-mean Gaussian white noise; (6) a signal concatenated from passing a zero-mean Gaussian white noise through four second-order low pass filters having a normalized cutoff frequency of 0.05, 0.15, 0.25, and 0.35.

All test signals were 40 s long sampled at 100 Hz. These signals were shown on the left panel of Fig. 2. It should be noted that all simulation signals are nonstationary. The first two signals have constantly changing frequency and the later four signals are stationary in each 10-s subsegment.

The algorithm parameters to calculate ApEn are listed in Table 1. In addition, a stationary window of 4 s was chosen. To compare with this adaptive approach, the conventional way of dealing with nonstationary data with a moving-window was implemented with a window of 4 s and a 0.5 s overlap in successive windows.

2.3.1. Patient data—Twelve patients who underwent pre-operative workup for diagnosing normal pressure hydrocephalus (NPH) showed oscillatory ICP episodes in their overnight recordings. Simultaneous ICP and ECG were acquired by using a mobile cart loaded with a PowerLab™ data acquisition system that interfaced with the Codman ICP Express and the GE bedside cardiovascular monitors. Signals were sampled at 400 Hz. The insertion of ICP sensor and data acquisition were conducted with proper IRB approval and written consent from patients. Standard procedure for intraparenchymal ICP sensor insertion was followed. The patient was prepared and draped in the usual sterile fashion. A Burr hole was made through the skull at a landmark 2 cm anterior to the coronal suture and 2 cm lateral to midline. The dura was punctured and the ICP sensor was inserted to a depth about 2.5 cm. Data were recorded as soon as possible after setting up the Codman ICP Express and lasted for at least 12 h until the next morning.

Overnight recordings were reviewed using the program Chart 5.0 to locate episodes of prominent ICP oscillations (amplitude > 5 mmHg). One 5-min baseline segment that either preceded or followed the selected 5-min oscillatory segment was then exported for further processing. Consequently, the extracted segments were organized into two groups. The first group contains all segments with oscillatory ICP and the second group contains their corresponding baseline segments.

The procedure for extracting RR interval and mean ICP was described in our previous work [14]. Adaptive ApEn algorithm was then applied to these two signals with a stationary window size $w = 100$ corresponding to 50 s. Remaining algorithm parameters include $m = 2$ and $r = 0.2$. The resultant two ApEn time series were then analyzed using the parametric causal transfer function analysis following the standard procedure [12,14].

3. Results

3.1. Results from numeric experiment

Numerical results are summarized in Fig. 2 where each row displays the test data, its ApEn time series calculated using the moving-window, and that using the adaptive algorithm. Each ApEn time series from moving-window calculation resemble what were obtained in a previous validation study [9] where it was shown that ApEn correlated positively with the oscillating frequency, number of harmonics, bandwidth, and variability of signals. Similar results were reproduced by the new adaptive algorithm as shown in the figure. Furthermore, it shows that better performance of detecting the abrupt change of signal characteristics is obtained by using the adaptive algorithm. This is best illustrated in Fig. 3 where two ApEn time series, derived by using the two algorithms, for the third test case are plotted together. Each 1000 samples of the test time series has different number of harmonics indicating an abrupt change of ApEn at sample 1000, 2000, and 3000. However, it should be noted that ApEn time series produced by the adaptive algorithm has a larger variability.

3.2. Patient data

To demonstrate that the adaptive algorithm can track changing ICP dynamics, four examples are shown in Fig. 4 where hours of ICP and RR interval signals are shown in parallel with the corresponding ApEn time series. An oscillatory ICP episode with a series of irregular rhythmic high amplitude waves is present in each example. This episode is marked by a rectangle box on each ICP plot. A common phenomenon as observed in all 12 patients is that reduced ICP ApEn and RR ApEn are associated with this oscillatory episode. This is well represented by the four examples shown in this figure. Furthermore, adaptive ApEn algorithm enabled us to study the change of system dynamics prior to and post the oscillatory ICP episode. A consistent pattern observed in all 12 patients is the increase of ICP ApEn and RR ApEn during the recovery period from oscillatory ICP state. Furthermore, an intriguing pattern of ApEn changes prior to oscillatory ICP is also observed, i.e., there is an increase of both ICP ApEn and RR ApEn minutes before the start of oscillating ICP. These increasing regions include a 5–15 min one for panel A, 10–25, 0–15, and 30–50 for panels B, C, and D, respectively. Although this is true for all four cases presented here, it failed to be present in other cases. Due to the large variability in the ApEn time series and small number of subjects studied here, this pattern should be considered preliminary and needs further quantification and validation.

A representative example, comparing RR interval and ICP signals with their ApEn time series, for the seventh patient is shown in Fig. 5. Left panel of the figure shows the normalized raw RR interval and ICP signals for both ICP states. Their ApEn time series were shown on the right panel of the figure. The normalization of a signal was done by first subtracting its average value and then having it divided by its standard deviation. It can be seen from this figure that ApEn time series for ICP and RR interval resemble each other even though their time domain waveforms are different.

To further investigate the association of average ApEn with different ICP states and different physiological signals, two-way analysis of variance (ANOVA) was applied to the mean ApEn presented in Table 2 with different ICP states and different physiological variables as two factors. The results indicated that both factors have significant effect ($p = 0.0052$ and <0.0001 , respectively). No significant interaction of these two factors was found ($p = 0.0639$). Furthermore, paired t -test of the hypothesis that oscillatory ICP ApEn was less than that of baseline was significant ($p < 0.0001$) and so was the hypothesis that RR ApEn at oscillatory state was less than that of baseline state ($p = 0.0108$) though it is noted that the former is much more significant than the later confirming what was observed in Fig. 4. Regarding ApEn difference between different physiological signals, ICP ApEn was significantly less than that of RR interval at the oscillatory state ($p = 0.0007$). However, ApEn of ICP and RR was not significantly different ($p = 0.3857$) at the baseline.

A nonparametric spectral analysis was conducted for both signals and their ApEn time series using the Welch method with a window size of 128 s and a 50% overlap. The resultant power spectrum density (PSD) plots are shown for the seventh patient in Fig. 6. These plots are representative of those of the rest of patients. It can be seen that significant amount of energy of both ICP and RR interval signals is distributed beyond 0.1 Hz while that of their ApEn time series is confined below 0.1 Hz. PSDs of both signals and ApEn time series, at the oscillatory state, are greater compared to the baseline values.

Linear causal transfer function analysis results are summarized in Table 3. Maximal classic coherence (CC) between ApEn time series of RR interval and ICP is shown in the fourth and the fifth columns of the table for the oscillatory (OC) and baseline (BA) state, respectively. Maximal CC was searched between (0, 0.1] Hz. The frequencies where the CCs achieved maximal value are reported in the second and the third columns of the table. These maximal frequencies are not associated with the average oscillating frequency of ICP. Statistical

significance of maximal CC was assessed using the surrogate data approach with 50 surrogate time series [15]. The basic idea of surrogate data test can be referred to early articles [16–18] where it was originally designed for test nonlinearity embedded in time series. It was introduced for the purpose of assessing non-zero CC in [15] as a better approach than using a fixed zero-coherence threshold. This is then followed, from the sixth to the eleventh column, by causal coherence, including $CC_{rr \rightarrow icp}$ (coherence with only $RR \rightarrow ICP$ is activated in the bivariate AR model) and $CC_{icp \rightarrow rr}$, and amplitude of causal transfer functions. These values were obtained by evaluating the corresponding coherence and transfer functions at the frequency where maximal CC was obtained. Symbol ‘*’ was used to indicate those cases where their coherence values were significant as indicated by the surrogate data test.

Using the paired t -test, it was confirmed that variables reported in Table 3 are all significantly larger ($p > 0.05$) at the OC state as compared with those at the BA state except the variable $CC_{rr \rightarrow icp}$. Even though $TF_{rr \rightarrow icp}$ reached significance level of 0.05, its p -value is much greater than that of $TF_{icp \rightarrow rr}$.

4. Discussion

An adaptive algorithm for calculating ApEn is proposed. This algorithm extends the application horizon of the ApEn metric. ApEn is a popular and efficient measure of irregularity of signals and has found applications in many areas where stationary phenomena are of interest. With the introduction of this adaptive algorithm, a rigorous way of handling nonstationary signal is available extending application ApEn to study nonstationary phenomena. In addition, a potentially useful analysis of transfer of irregularity between related signals can be carried out using ApEn time series of them that are obtainable by using the adaptive algorithm. These extended aspects of ApEn analysis are demonstrated using both simulation data and real biomedical signals including the RR interval and ICP signals recorded from normal pressure hydrocephalus patients. Implications of this exercise and its findings are discussed in the following.

4.1. Adaptive ApEn

The ApEn metric as defined in Eq. (3) needs an averaging process. Therefore, the upper limit of tracking capability as well as the time resolution of this adaptive algorithm is determined by the time span that is used in the averaging process. This concept provides the rationale for choosing an appropriate length (w) of stationary window in our algorithm. A stationary window length of 50 s was chosen in the present work for processing RR interval and ICP signals. Under the sampling rate of 2 Hz, this choice satisfies the recommended minimum sample size for reliably calculating ApEn [1,19]. This choice also confined the spectral contents of ApEn time series. Other algorithm parameters including m and r have been studied [1,19]. The recommended values for m and r seem to work well with this adaptive algorithm.

4.2. Validation using numerical simulation

A numerical validation study was performed to compare the adaptive algorithm with the standard ApEn algorithm (with a non-overlap moving-window). This was greatly facilitated by adopting a comprehensive set of numerical test cases that were designed and used in previous interpretative studies of complexity measures including ApEn [9] and Lempel-Ziv complexity [20]. The adoption of a standard test set for validation purpose is important for developing new analytical algorithms. Achieving compatible numerical results with those obtained by existing algorithms is a prerequisite for applying the proposed adaptive ApEn algorithm to the real patient data.

4.3. ApEn of ICP and RR interval signals

ApEn of ICP and RR interval signals has not been integratively studied before even though ApEn has been used in HRV analysis and in analysis of acute changes of ICP [9,21]. Our results indicated that no significant difference between ApEn of RR interval and beat-to-beat mean ICP exists at the baseline ICP state. As discussed in previous publications, interpretation of ApEn in terms of system complexity should be cautious [22] because pure random signals have a high ApEn but their complexity should be considered as low. The average ApEn values as reported in Table 2 are well below ApEn values for pure random signals. Therefore, these ApEn values may be considered as a valid indicator of the complexity of underlying physiological systems that are responsible for generating ICP and RR variations. Following this reasoning, this result indicates that physiological systems regulating beat-to-beat mean ICP and RR interval could overlap to a large extent at the baseline ICP state. The systemic arterial blood pressure variations could affect both RR interval and mean ICP variations such that ApEn of ICP and RR interval could also reflect this common effect. In addition, RR interval changes have a mechanical feedforward effect on mean ICP as discussed in our previous work [14] further supporting our observation that ApEn of these two signals is close at the ICP baseline. However, ApEn of ICP was found to be significantly smaller than that of RR interval at the oscillatory ICP state. Spontaneous oscillations of ICP could be caused by blood volume changes and (or) by the inherent nonlinearity in the ICP dynamic system as illustrated in previous modeling work [23]. These oscillations, even though not periodic, are responsible for the decrease of ICP ApEn as compared to its baseline value. Furthermore, a potential feedback effect from ICP variations on RR interval may exist based on our previous studies [14]. This feedback effect introduces oscillations in RR interval through some regulation mechanism causing decrease of ApEn of RR interval. However, the exact mechanism of ICP regulating HR remains unclear.

It should be emphasized that ApEn was calculated using pulsatile ICP in the previous study where it was found that a decrease of ApEn was associated with transient increase of ICP [9, 21]. This decrease of ApEn was rightfully attributed to the ‘rounding’ effect of ICP pulse at an elevated ICP state. In the present study, ApEn was calculated using the interpolated beat-to-beat mean ICP signal therefore the morphological change of ICP pulse cannot explain the decrease of ApEn during an oscillatory ICP state. Hence, decrease of ApEn has different physiological explanations depending on the time scale ApEn is calculated.

As illustrated in Fig. 4, the adaptive algorithm could track the change of ApEn for the progression of oscillatory ICP. Various patterns can be observed in this figure. The observation that reduced ICP ApEn and RR ApEn are associated with oscillatory ICP conforms with what are reported in Table 2 as expected. An increasing trend of ApEn is associated with recovery from oscillating ICP has also been observed in this cohort of patients indicating a recovery of complex regulation mechanism of ICP homeostasis. There may also exist an increase of ApEn of both ICP and RR interval minutes prior to oscillating ICP as evidenced in 4 out of 12 patients. Given the large variability, additional processing of ApEn time series in terms of smoothing and trend extraction is needed to further establish this preliminary pattern. However, a speculative cause of its existence may be associated with a transient enhancement of cerebral flow autoregulation, which has been shown in previous modeling studies to be a necessary condition in causing oscillation of ICP [24]. A short window width was adopted in calculating ApEn. This choice probably caused a large variability in the resultant ApEn time series in light of results from a recent study [25] where it was demonstrated that RR ApEn is the most unreliable one, in terms of its reproducibility at different data lengths, among the 11 evaluated heart rate metrics.

4.4. Causal transfer function analysis of ApEn

Causal transfer function analysis is a recently introduced method of studying coupled signals by mathematically decoupling the feed-forward and the feedback effects between two signals. It was chosen in the present work as a preliminary tool for studying the interaction between the physiological systems using the ApEn time series of their measurements. Major results from this analysis, as summarized in Table 3, are actually supportive of the finding that an enhanced feedback effect from ICP oscillations to RR interval variations exists, as discovered in our previous study by directly analyzing signals using the same approach. Specifically, $CC_{icp \rightarrow rr}$ and $TF_{icp \rightarrow rr}$ are shown to be significantly higher at the ICP oscillation state indicating a strengthened coupling and transferring from ICP ApEn to RR ApEn time series. However, it should be noted that absolute values of causal coherence, for a large portion of patients, did not pass the zero-coherence test using the surrogate data. This may indicate a significant nonlinear interaction between ApEn time series of RR interval and ICP or probably a low-signal to noise ratio that is caused by using a short segment of data (about 5–8 min) to study ICP oscillation with an approximate frequency of 2 cycles/min.

5. Conclusion

This work introduces a new adaptive algorithm for calculating ApEn and demonstrates its tracking ability using both simulated data and nonstationary ICP signals. Furthermore, this new algorithm enables a potentially useful way of studying interacting dynamic systems by characterizing the correlation between their entropy time series.

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Fig. 1.

Block diagram of the proposed adaptive ApEn computational algorithm. Data flow is represented using the dotted line and the procedural flow is represented using the solid line.

Fig. 2.

Numerical test results. Each row corresponds to a test case with the raw signal shown in the first column, the ApEn time series using the windowing algorithm, and the adaptive algorithm in the second and the third columns.

Fig. 3.

A detail illustration of the ApEn results for the third numerical test case as obtained using the sample-by-sample adaptive algorithm and the moving-window approach. The window width is 400 samples with a step size of 200.

Fig. 4.

Four example illustrations of ApEn time series of RR interval and ICP signals. An oscillatory ICP episode is present in each example that is associated with a decrease of both ICP ApEn and RR ApEn. An increasing trend of ApEn time series is always present after oscillatory ICP state ends.

Fig. 5.

A representative example of applying the adaptive algorithm to the data from seventh patient. The normalized signals were shown in the left panel with ICP shown in black line and RR interval in gray line. The corresponding ApEn time series are shown in the right panel. ApEn time series of both signals are similar even though their waveforms are different.

Fig. 6. Power spectrum density plots of the signals and time series shown in Fig. 5. Right panel shows results for the ApEn time series and the left panel shows results for the raw signals.

Table 1

List of algorithm parameters used in the numerical experiment for each of the six simulation data

Data set index	m	r	w
1	1	0.3	400
2	1	0.3	400
3	1	0.3	400
4	2	0.2	400
5	2	0.2	400
6	2	0.2	400

Table 2

Mean approximate entropy (ApEn) and its standard deviation calculated for the ICP and RR interval signals from 12 patients under the oscillatory and the baseline states

	Oscillatory state		Baseline state	
	ICP $\pm$ STD	RR $\pm$ STD	ICP $\pm$ STD	RR $\pm$ STD
1	0.25 $\pm$ 0.10	0.27 $\pm$ 0.09	0.34 $\pm$ 0.05	0.31 $\pm$ 0.08
2	0.22 $\pm$ 0.09	0.41 $\pm$ 0.06	0.47 $\pm$ 0.08	0.37 $\pm$ 0.10
3	0.22 $\pm$ 0.09	0.33 $\pm$ 0.08	0.34 $\pm$ 0.06	0.55 $\pm$ 0.05
4	0.36 $\pm$ 0.06	0.36 $\pm$ 0.07	0.65 $\pm$ 0.05	0.57 $\pm$ 0.06
5	0.29 $\pm$ 0.09	0.26 $\pm$ 0.09	0.46 $\pm$ 0.06	0.39 $\pm$ 0.06
6	0.19 $\pm$ 0.03	0.24 $\pm$ 0.06	0.40 $\pm$ 0.10	0.54 $\pm$ 0.10
7	0.15 $\pm$ 0.10	0.36 $\pm$ 0.07	0.38 $\pm$ 0.06	0.43 $\pm$ 0.07
8	0.24 $\pm$ 0.09	0.42 $\pm$ 0.07	0.35 $\pm$ 0.09	0.31 $\pm$ 0.06
9	0.27 $\pm$ 0.08	0.31 $\pm$ 0.08	0.43 $\pm$ 0.05	0.40 $\pm$ 0.04
10	0.20 $\pm$ 0.07	0.45 $\pm$ 0.09	0.51 $\pm$ 0.09	0.51 $\pm$ 0.06
11	0.13 $\pm$ 0.08	0.38 $\pm$ 0.03	0.22 $\pm$ 0.06	0.40 $\pm$ 0.06
12	0.26 $\pm$ 0.12	0.44 $\pm$ 0.10	0.42 $\pm$ 0.06	0.51 $\pm$ 0.07

Table 3

Results of causal transfer function analysis

Freq (Hz)		CC		CC _{rr→icp}		CC _{icp→rr}		TF _{rr→icp}		TF _{icp→rr}	
OC	BA	OC	BA	OC	BA	OC	BA	OC	BA	OC	BA
1	0.001	0.008	0.85*	0.53	0.40	0.41	0.23	0.50	0.42	0.54	0.21
2	0.008	0.001	0.78*	0.40	0.54*	0.30	0.16	0.67	0.20	0.32	0.10
3	0.009	0.099	0.88*	0.54*	0.67*	0.12	0.44*	0.76	0.09	0.28	0.31
4	0.028	0.001	0.66*	0.57	0.49*	0.38	0.28	0.60	0.33	0.24	0.21
5	0.008	0.040	0.88*	0.46*	0.20	0.27	0.20	0.31	0.23	0.74	0.16
6	0.001	0.001	0.58	0.46	0.10	0.41	0.06	0.16	0.36	0.75	0.05
7	0.007	0.001	0.90*	0.67	0.53*	0.51	0.20	0.74	0.58	0.54	0.19
8	0.009	0.001	0.50	0.77	0.18	0.22	0.62	0.27	0.29	0.48	0.64
9	0.008	0.004	0.90*	0.37	0.62*	0.28	0.19	0.70	0.31	0.36	0.20
10	0.079	0.007	0.77*	0.87*	0.55*	0.54	0.46	0.33	0.67	0.15	0.42
11	0.004	0.006	0.91*	0.67*	0.28	0.36	0.37	0.72	0.37	1.21	0.32
12	0.008	0.028	0.65	0.48*	0.26	0.26	0.24	0.60	0.32	0.87	0.28

OC, oscillatory state; BA, baseline state; CC, maximal classic coherence; CC_{rr→icp}, causal coherence from RR to ICP; CC_{icp→rr}, causal coherence from ICP to RR; TF_{rr→icp}, amplitude of causal transfer function from RR to ICP; TF_{icp→rr}, amplitude of causal transfer function from ICP to RR; Symbol ‘*’, used to indicate cases where CC or causal CC is significant; Freq, the frequency at which the maximal coherence (CC) is obtained.