Entropy in description of vasovagal syndrome

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Abstract

In this paper we present an example of application of Approximate Entropy and Sample Entropy in analysis of vasovagal syndrome. In our research we conducted an analysis based on three types of data: RRI (RR intervals), SBP (systolic blood pressure) and TPR (total peripheral resistance), which were measured simultaneously with the head up tilt table test $(HUTT)$. The $HUTT$ tests were preformed with Task Force Monitor device. In the tilt test we examined 30 *patients recommended to diagnosis of vasovagal syncope (VVS) because of their faint episodes.*

1. Introduction

Syncope is a temporary self-regressing loss of consciousness, usually resulting in a fall. It is assumed that the direct cause of syncope is short-term reversible general brain ischaemia. Therefore, one must differentiate syncope of actual or apparent losses of consciousness having a non-ischeamia related cause, e.g. epilepsy, hyperventilation with hypocapnia, hypoglycaemia, poisoning, psychogenic reaction that are often mistakenly diagnosed as syncopes. Syncopes can be divided into three groups. The first group is neucocardiogenic, including vasovagal syncopes (caused by upright tilt or fear, pain, sight of blood or syringe procedure), situational syncopes [1]. The second group is orthostatic, resulting from primary or secondary autonomic failure. The third group is cardiac (cardio-vascular) the cause of which are arrhythmia with slow or fast heart beat rhythm, or organic heart disease [2].

Patients suffering from the cardiac cause of syncopes, require insightful diagnostics due to the worse prognoses and, thus, necessity to provide faster and more aggressive treatment.

Most patients faint due to non-cardiological causes, most frequently neuro-cardiogenic. This is the least threatened group, but concurrently the most difficult in terms of treatment. Neurocardiogenic syncope is a short-term loss of consciousness caused by excessive reflexive response of the autonomic nervous system. The mechanism resulting in sudden cardiac arrest and/or decrease of arterial blood pressure is still under discussion. It seems that their mutual reaction: stimulation or inhibition of the sympathetic or parasympathetic system centers, results in vasovagal syncope.

There are two physiological theories attempting to explain the occurrence of vasovagal syncope. According to the central theory of van Lieshout and partners, the beginning of the reflex depends on activation of the cortical-subcortical centres, participated by the neurohormones and neurotransmitters which lead to the bradycardia-hypotensia reflex due to such factors as pain, fear or emotions. The peripheral theory of Oberg and Thoren assumes causing the reflex by means of stimulation of the mechanoreceptors of the cardiac and pulmonary system in the left ventricle, cardiac atriums, aortic arch and peripheral chemoreceptors within the region of blood vessels due to long-term maintenance of upright body position.

In practice, the vasovagal syndrome is diagnosed on the basis of specific medical history and result of the tilt test (head-up tilt test, $HUTT$). In the second section of this paper we present the most popular protocols used in diagnosis of syncope. In the section 3 we describe the data used for the calculation of the entropy. The brief description of entropy is presented in the section 4. The results of our numerical experiments we show in the section 5. In section 6 we draw conclusions.

2. Diagnostics of syncopes - upright tilt testing

Vasovagal syncope takes place usually due to long-term upright tilt, especially in right stuffy rooms or after vein puncture, strong stress or emotions (pain, fear). Loss of consciousness might be preceded with sensation of sudden, strong weakening, occurrence of floaters, nausea, headache or dizziness, sweating, heart palpitation sensation. Common symptoms include seizures reflecting deep brain ischaemia, secondary to hypotonia and bradycardia. In order to confirm the preliminary diagnosis of syncope, it might be necessary to perform the tilt test (head-up tilt test,

$HUTT$). According to the standards, the test is performed in the morning, in a quiet room with dimmed illumination and on an empty stomach. It is recommended that lying time before upright tilting takes at least 5 minutes if no venipuncture is projected or at least 20 minutes in case of projected venipuncture. Next, the tilt table, equipped with a feet support, is raised to the angle of 60 degrees. ECG and arterial blood pressure are monitored in a continuous manner.

Currently, there are two tilt test protocols most popular in Poland. The first one is modified Westminster protocol (acc. to Raviele): 45 minutes of passive upright tilt, then 20 minutes upon pharmacological provocation with 0,4 mg nitro-glycerine sublingually. Second one is Italian protocol - 20 minutes of passive upright tilt and 20 minutes upon sublingual administration of nitro-glycerine. If the systolic pressure at the end of passive upright tilt is below 100mmHg, the passive phase is usually prolonged up to 60 minutes, with no pharmacological provocation. The end point of the test is causing full syncope or pre-syncope condition or test time completion.

The vasovagal syndrome is divided on the basis of behavior of blood pressure and heart rate during syncope into 3 types (according to the VASIS classification). Type 1 is mixed. The heart rate decreases during syncope, but it remains at the level of 40/min, or drops less then 40/min for less than 10 seconds with asystole less then 3sec or without asystole; arterial blood pressure drops before the heart rate decreases. Type 2A is cardio-depressive without asystole. The ventricle rhythm frequency drops less than 40/min for longer than 10 seconds, but asystole does not last longer than 3 seconds, pressure drops before the heart rate decelerates. Type 2B is cardio-depressive with asystole. Occurrence of asystole lasting more than 3 seconds, pressure drops concurrently with decreased heart rate or overtakes it. Type 3 is vaso-depressive. During a syncope, arterial pressure drops, but the heart rate does not slow down by more than 10% in comparison to its maximal value [3].

The precise differentiation of the syncope type,is taking into account its central and peripheral mechanism, the same tilt test might be insufficient. It can be combined with monitoring of changes occurring in the brain (eeg, transcranial Doppler) as well as changes in the peripheral haemodynamic parameters (impedance reography).Impedance reography is a non-invasive method allowing to determine haemodynamic parameters of the heart: stroke volume, stroke fraction, left ventricle blood stroke tipe, pre-stroke period. The patient is provided with additional 3 or 4 (depending on the system) electrodes stuck for the purpose of reographic measurements. The parameters are calculated on the basis of changes of electric resistance of tissues, measured on the surface of the chest during blood motion in the heart and large vessels occurring in the cardiac cycle.

In our tests we used The Task Force Monitor system. It allowed not only to determine the quantitative changes of haemodynamic parameters in the "beat-to-beat" systemic circulation in the cardiac cycle, but also to determine total peripheral resistance (TPR). The analysis of RRI, sBP and TPR is presented in the next Sections.

3. Data analysis

In each measurements we chose three types of data: RRI, sBP, TPR. The data were obtained during the test with the beat-to-beat method. For each patient we analyzed three segments of data (I, II, III): RRI, sBP, TPR. The width of each segment is 250 beats. The first segment (I) is located in the middle of the recording in supine position. The second segment (II) begins when the recording of tilt up started. The third segment (III) represents 250 beats just before the syncope. The plots of described segments are in the figure 1.

We made two kind of investigation. In the first

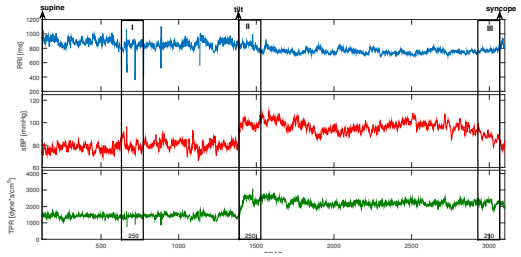

Figure 1. The plots of data: RRI blue color, sBP red color, TPR green color. The black boxes are the chosen segments numbered by I, II, III.

we calculated Approximate Entropy and Sample Entropy in each segment (I,II,II) for each data (RRI, sBP and TPR). After that we compared entropies between segments for each data separately.

In the second we calculated entropies of RRI, sBP and TPR for each segments in moving windows of width of l points. From each sequence of: RRI_L, sBP_L, TPR_L we obtained the sequence of $L - l$ values of entropies ($mApEn$, $mSampEn$). That way we could observe the changes of entropy for RRI, sBP, TPR in segments (I,II,III) during the tilt test.

4. Approximate Entropy and Sample Entropy

Entropy (Approximate Entropy - $(ApEn)$, Sample Entropy $(SampEn)$) is a statistical measure that quantifies the regularity and complexity of a time series [3].

The method is based on analysis of repetitive patterns p_m in time series $S_N = [S_1, S_2, S_3, ...S_N]$ with the fixed criterion of similarity r [4, 5].

Let us name the set of all patterns as $P_m = [p_m(1), p_m(2), p_m(3), ..]$. The parameter m is the length of pattern. Two patterns are similar if the difference between any pair of S_N fills a criterion:

$$|S_{i+k} - S_{j+k}| < r, \tag{1}$$

where $0 \leq k \leq m$.

The fraction of m-length patterns, that resembles the pattern of the same length is define:

$$C_{im}(r) = \frac{n_{im}(r)}{N - m + 1}, \tag{2}$$

where $n_{im}(r)$ is the number of patterns similar to $p_m(i)$ and

$$C_m(r) = \frac{\sum_{i=1}^{N-m+1} C_{im}(r)}{N - m + 1} \tag{3}$$

Approximate Entropy is defined as:

$$ApEn(S_N, m, r) = ln \frac{C_m(r)}{C_{m+1}(r)} \tag{4}$$

High value of $ApEn$ characterizes a less predictable and more complex systems. The values depend on the values of parameters r and m, that are chosen arbitrary. In cardiological measurements typical choice is: $m = 2$ and $r = 0.2 \cdot SD$, where SD is the standard deviation of analyzed time series sequence. In our investigation: $S_N = RRI_N$, $S_N = sBP_N$, $S_N = TPR_N$

Sample Entropy $(SampEn)$ is similar to $ApEn$.The brief code for calculating Sample Entropy is based on two calculations: firstly the algorithm calculates the count number of m-length patterns that are similar with the criterion (1). Let's name it as B_i, secondly the algorithm calculates the count number of $m+1$-length patterns that are similar with the criterion (1). Let's name it as A_i. Sample Entropy is calculated as:

$$SampEn = -\ln(\frac{A_i}{B_i}) \tag{5}$$

Sample Entropy does not count self-matching and does not depend on the data size as much as $ApEn$ does. That is why $SampEn$ is recommended to applications for short data size [6]. In our investigation we calculated $ApEn$ and $SampEn$.

5. Results

We analyzed 30 recordings of: RRI, sBP, TPR obtained during tilt table test. In the figure II we show the comparison of $ApEn(RRI)$, $ApEn(sBP)$ and $ApEn(TPR)$ in segments: I, II, III. The multipair comparison were preformed using Friedmann test and post hoc Dunn test at significance level $\alpha = 0.05$. In the figure 2 we show the box plots for the analyzed segments for each data. We also put the p-values obtained in statistical analysis.

We preformed similar calculation for Sample

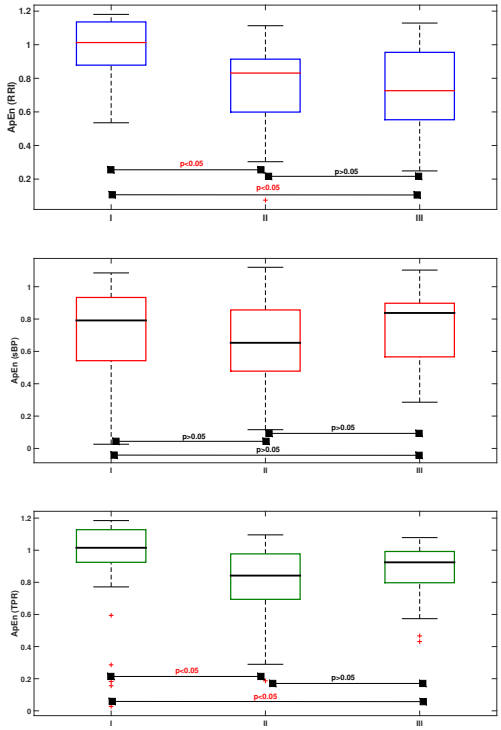

Figure 2. Approximate Entropy of (from the top): RRI, sBP, TPR. The black lines correspond to median values and the boxes correspond to first and third quartiles.

Entropy and we determined and compared the values of $SampEn(RRI)$, $SampEn(sBP)$ and $SampEn(TPR)$ in segments: I,II,III. The result are showed in figure 3.

We also analyzed the values of the entropies: $ApEn(RRI)$, $ApEn(sBP)$, $ApEn(TPR)$ and $SampEn(RRI)$, $SampEn(sBP)$, $SampEn(TPR)$ in moving windows of width of $l = 100$ points. In the figure 4 we show an example of such calculations for $mSampEn$ in segment III.

6. Conclusion

Approximate Entropy and Sample Entropy are useful tools for analyzing vasovagal syndrome. The comparison of $ApEn(RRI)$ and $SampEn(RRI)$ between segments I,II, III shows, that there is a sta-

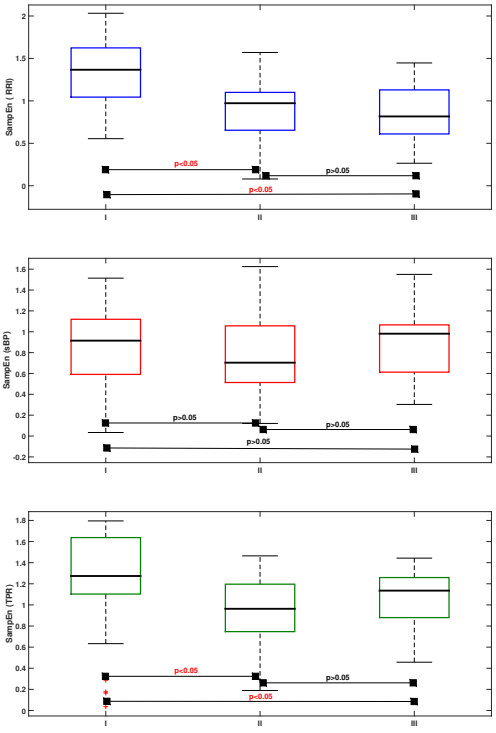

Figure 3. Sample Entropy of (from the top): RRI, sBP, TPR. The black lines correspond to median values and the boxes correspond to first and third quartiles.

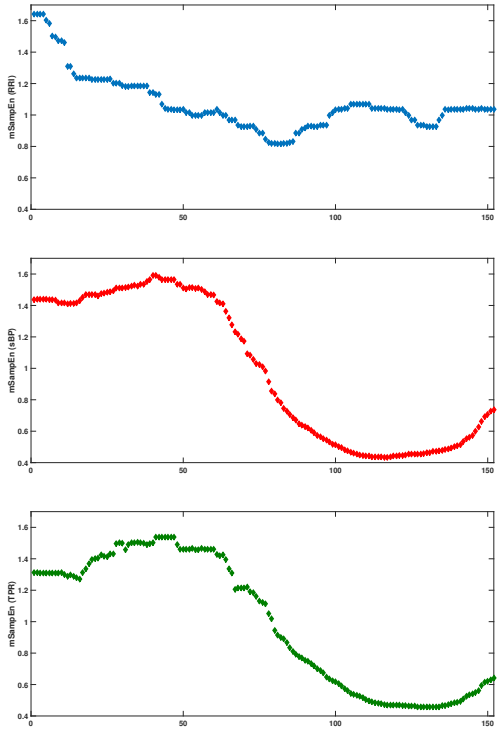

Figure 4. Sample Entropy in moving window of $l = 100$ for (from the top): RRI, sBP, TPR in segment III

tistically significant deference between entropy in segment I and II, I and III. In case of $ApEn(sBP)$ and $SampEn(sBP)$ there is not any significant difference between the segments. The comparison of $ApEn(TPR)$ and $SampEn(TPR)$ between segments I, II, III shows, that there is statistically significant deference between entropy in the segment I and II, I and III. The analysis of the entropy in the indicated segments suggests, that the regularity of RRI and TPR is different in supine position and before the syncope.

The results obtained in moving windows shows that entropy $mApEn(sBP)$ and $mApEn(TPR)$ decreases from about 0.8 to 0.4 when the syncope occurs. The $ApEn$ is more sensitive for data size, and the window of 100 points width is too small. In that case the Sample Entropy is better to analyze the complexity of the data. The values of $mSampEn(sBP)$ and $mSampEn(TPR)$ decrease from about 1.6 to 0.4 (see 4). In the presented example a decrease of the entropies occurs about 50 seconds before the syncope. The results suggest that the syncope is connected with the minimum value of the entropy of TPR and sBP, but this investigation is still in progress. We also try to determine the time between the beginning of the entropy decrease and the occurring of the syncope. We hope that the changes of entropies of sBP and TPR could be the predictors of vasovagal syndrome.

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