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Sample Entropy Analysis of Heart Rhythm Following Cardiac Transplantation

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Abstract - *Pediatric heart transplantation has become a mainstream in the treatment of end-stage heart disease in infants and children. Heart rate variability is a measure of autonomic nervous influence on the heart. After heart transplantation, the donor heart loses its nervous control. Nonlinear analysis of heart rate is a method to study the physiologic mechanisms responsible for the control of heart rate fluctuations, in which the autonomic nervous system appears to play a primary role. This work evaluated the heart rate entropy in children who has undergone heart transplantation. Patients who underwent heart transplantation showed significant decrease in entropy as assessed by sample entropy (0.63 ± 0.31 vs. 0.90 ± 0.33, $p < 0.05$). System complexity as can be assessed by entropy methods decreases in transplanted patients and this may be related to loss of the neural modulation of heart rate.*

Keywords: Transplantation, entropy, heart rate variability.

1 Introduction

Pediatric heart transplantation has become a mainstream in the treatment of end-stage heart disease in infants and children. As a last resort, heart transplantation can be a life saving measure. However, there are significant problems that can occur following transplantation. One of the problems that is encountered after heart transplantation is the loss of nervous control of the heart. Therefore, no input of sympathetic or vagal nerves can influence the heart rate, resulting in a flat power spectrum of the beat-to-beat variability.

Electrocardiogram (ECG) signals from heart beats have typical features such as P wave, QRS complex, and T wave. QRS complex represent the signal during which the ventricles are depolarized. QT interval is defined as the time interval between the onset of Q wave and the end of the following T wave in an ECG signal. Heart pump function is realized after the QRS signal stimulates the ventricles. One heart beat can be defined as a period from one R peak to the next one. ECG signals are quasiperiodic and nonstationary and heart beats have nonlinear characteristics and change over time.

Heart rate variability (HRV) is a measure of autonomic nervous influence on the heart. HRV, as assessed by linear time domain methods of HRV, was shown to be significantly reduced in patients who underwent heart transplantation [1]. HRV is characterized by a variety of linear, non-linear, periodical and non-periodical oscillations. However, to date mostly linear analysis of HRV was performed and the temporal complexity of the heart rhythm data is ignored. The aim of the present study is mainly to investigate the role played by neural mechanisms in determining non-linear and non-periodical components. Parameters that quantify non-linear dynamic behavior, in a time series, are calculated.

HRV has become a popular method for the studies of physiologic mechanisms responsible for the control of heart rate fluctuations, in which the autonomic nervous system appears to play a primary role. Depression of HRV has been observed in many clinical scenarios, including autonomic neuropathy, heart transplantation, congestive heart failure, myocardial infarction, and other cardiac and noncardiac diseases [2]. Very few of such studies involved non-linear approaches of heart rate variability, complexity assessment.

HRV may improve after several months following heart transplantation. The mechanism for HRV improvement has not been elucidated; autonomic "reinnervation", new nerve formation, of the donor heart has been proposed. However, the occurrence and the significance of reinnervation remain controversial [3].

Nonlinear analysis of heart rate can be a method to study the physiologic mechanisms responsible for the control of heart rate fluctuations, in which the autonomic nervous system appears to play a primary role [4]. Approximate entropy (ApEn) and sample entropy (SampEn) are two different methods of many of these nonlinear methods. Both are deduced from approximating the Kolmogorov entropy of a process.

Similar to HRV, change of entropy has also been observed in many clinical scenarios, including autonomic neuropathy, heart transplantation, congestive heart failure, myocardial infarction, and other cardiac and noncardiac diseases. It is shown that ApEn can be an indicator to

predict the Sudden Infant Death Syndrome (SIDS) [5]. SampEn analysis is successfully used to show that the entropy decreases before the episodes of neonatal sepsis [6]. In one study, it was possible to detect the atrial fibrillation by analyzing the previous data before the onset of atrial fibrillation [7]. Another study evaluated 53 patients with low Left Ventricular (LV) function of the heart and implantable cardioverter defibrillators (ICD), and ApEn of the QT intervals were significantly higher in patients who died compared to patients who survived ($p = 0.008$). ApEn of the repolarization phase of the cardiac electrical cycle (QT interval) was found to be an independent predictor of mortality [8].

2 Methods and Study Design

ApEn is a measure that quantifies the unpredictability in a time series data. ApEn reflects the likelihood that similar observations will *not* be followed by additional similar conditions. Lower ApEn values are assigned to more regular time series while higher ApEn values are assigned to more irregular, less predictable, time series [9]. In this method, the embedded dimension m and tolerance r can be set as $m=2$ and $r=0.20SD$ (standard deviation of signal segment). The distances among vectors are calculated as the maximum absolute distance between their corresponding scalar elements. The number of vector distance exceeding the tolerance r corresponding vector i is counted as $N^m(i)$. The counting number of different vectors are calculated, normalized and taken logarithm as

$$\phi^m(r) = \frac{1}{L-m+1}\sum_{i}^{L-m+1} \ln \frac{N^m(i)}{L-m+1} \qquad (1)$$

where L is data length. Then, ApEn is defined as

$$ApEn(m,r,L) = \phi^m(r) - \phi^{m+1}(r) \qquad (2)$$

Because of the better representation of the entropy in the analyzed signal, another method of entropy assessment, SampEn was developed in the recent years [10], [11]. SampEn has the advantage of being less dependent on time series length, and showing relative consistency over a broader range of possible r, m, and L values.

The differences between ApEn and SampEn result from 1) defining the distance between two vectors as the maximum absolute difference between their components; 2) excluding self-matches, i.e., vectors are not compared to themselves; and 3) given a time series with L data points, only the first $L-m$ vectors of length m are considered. SampEn is precisely equal to the negative of the natural logarithm of the conditional probability that sequences (epochs) close to each other for m consecutive data points will also be close to each other when one more point is added to each sequence. Having all these features makes SampEn to be a useful tool for investigating the dynamics of heart rate and other time series.

The algorithm builds up runs of points matching within the tolerance r until there is not a match, and keeps track of template matches in counters $A(k)$ and $B(k)$ for all lengths k up to m. If a particular run ends up being of length 4, for example, then that means that 1 is added to the count for template matches of length 4. In addition, there are 2 template matches of length 3, 3 of length 2, and 4 of length 1 that need to be added to the corresponding counts. A special case is needed when a run ends at the last point in the data, where the $A(k)$ counters are incremented but the $B(k)$ counters are not. Once all the matches are counted, the sample entropy values are calculated by $SampEn(k,r,L) = -\ln(A(k)/B(k-1))$ for $k=0,1,...,m-1$ with $B(0)=L$, the length of the input series.

The algorithm to find runs starts by finding all points that match the first point within a tolerance r. The points that match begin a run of length 1 and those that don't match have runs of length 0. If the points after those with runs of length 1 match the second point, the runs are now of length 2; otherwise, the run is ended. If the points after those with runs of length 0 match the second point, the runs are now of length 1. This procedure of finding runs is continued until the end of the data. Open source software from PhysioNet developed for SampEn analysis is used in this study [12].

The study involved 13 children who have undergone heart transplantation and 20 healthy controls. Total of 5 patients in transplantation group had signs of rejection as was documented by heart muscle biopsy. Electrocardiogram signals are collected during 24 hour Holter rhythm assessments close to the time of biopsy. Beat to beat intervals of cardiac cycle are then extracted from the Holter Analysis System (Delmar, Inc.) and using Matlab, SampEn (for m=2) of each patient`s beat to beat intervals are calculated.

Statistical Analysis: Results are expressed as mean values ± SD. Independent-samples T test is used to assess for differences between two groups. Correlations between variables were assessed with Pearson's correlation coefficient. A p value less than 0.05 is considered to be statistically significant.

3 Results

SampEn is significantly lower in the transplant group compared to the control group (0.63 ± 0.31 vs. 0.90 ± 0.33, $p < 0.05$) (Figure 1).

In order to evaluate for signs of possible reinnervation, the time elapsed from transplantation to the acquisition of Holter is obtained. After that, the correlation between this period and SampEn was assessed. No significant relationship was found between the two variables ($p = 0.98$) (Figure 2).

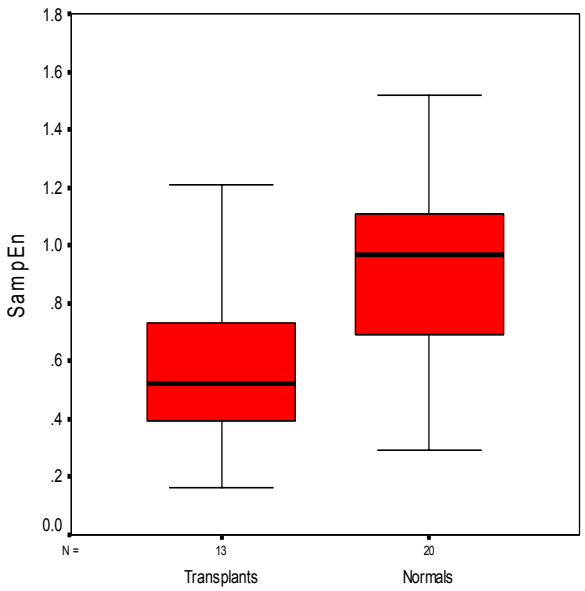

Figure 1. Boxplot representation of SampEn results of two groups ($p < 0.05$).

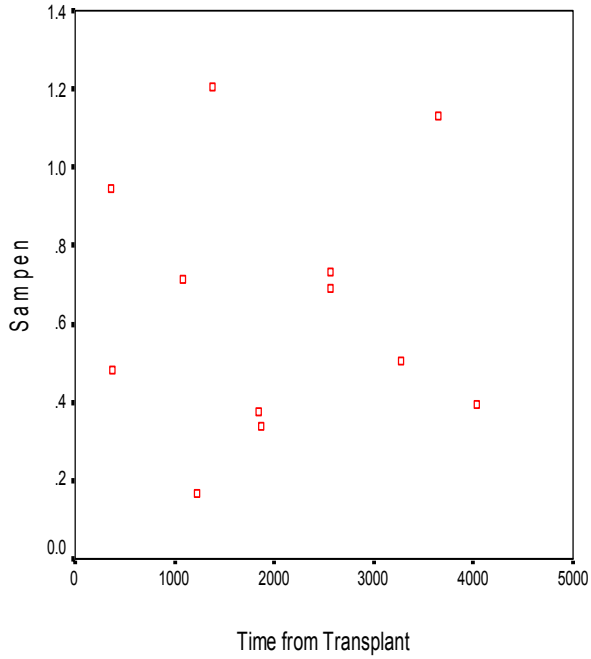

Figure 2. Relationship between duration from transplantation and SampEn. No significant correlation is found between these two factors (p=0.98).

Total of 5 patients out of 13 heart transplant patients had signs of rejection at the time of the Holter assessment. Therefore, we analyzed possible changes in SampEn in relation to the presence of rejection.

Pearson`s moment correlation did not show any significant correlation between presence of rejection and SampEn (correlation coefficient, 0.144, $p = 0.64$) (Figure 3).

4 Discussion

This study demonstrates the decrease in system complexity as measured by SampEn, in the heart rhythm of patients who underwent heart transplantation. Even though the sinus node, where the heart rhythm originates, is intact in these patients, the external regularity control of the sinus node is interrupted. Most likely the reason for this is the lack of cardiac nerve regulation by the autonomic nervous system.

HRV using linear time domain analysis has been widely utilized. HRV was shown to be decreased in heart transplant patients. The linear analysis method of HRV has a significant methodological difference compared to the entropy assessment. Conventional methods of HRV do not assess the temporal changes that are inherent part of a time series data. Therefore temporal changes in a heart rhythm data is not evaluated with conventional HRV methods. Temporal nature of the time series data is ignored.

Entropy, however, allows one to assess the temporal complexity of time series data. Assessment of entropy in heart transplanted patients allows us to note significant changes in heart rate entropy following heart transplantation. This finding might allow us to use this method in further assessment of these patients.

One of the clinical problems that are encountered is the rejection of transplanted hearts [13]. This might occur in acute setting or even months to years after transplantation. The diagnosis of heart transplant rejection is established after obtaining heart muscle tissue biopsy. Therefore, periodic biopsies are performed in these patients in order to detect possible rejection. Since this an invasive procedure, there is a need for a noninvasive method for early and reliable detection of rejection [14].

Assessment of heart rate entropy can potentially allow one to assess the potential changes that might occur with the rejection of transplanted hearts. Eventually, it may be possible to develop methods which might allow us to establish rejection diagnosis without the the need for more invasive methods such as performing biopsy.

One of the findings of this study reveals that there is no statistically significant relationship between the heart rate entropy and the time elapsed from transplantation. This finding does not support the reinnervation theory in the transplanted hearts. There are conflicting ideas about the reinnervation following heart transplantation. One of the limiting factors of this study is the limited number of

patients. However, it is also difficult to obtain significant number of patients from any given center. Assessment of possible reinnervation, probably, requires a multicentral study to allow researchers to obtain results with statistically significant power.

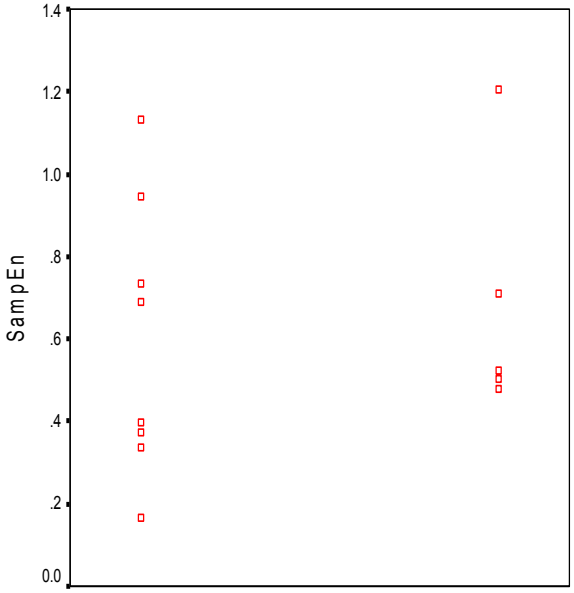

Figure 3. Sampen values for heart transplantation patients. First coloumn represents patients with no rejection and second coloumn represents patients with rejection. There is no significant difference between two groups ($p = 0.64$).

The potential role of transplant rejection on the SampEn values are also assessed. No significant correlation between presence of rejection and SampEn are shown. However, total number of patients who had rejection is 5. Also each of these patients have different degrees of rejection as is documented by heart muscle biopsy. This might have an impact on the results as well. Small number of patient group is also a limiting factor to make significant conclusions. There is a need for larger study population in order to assess the potential changes in SampEn in the event of rejection.

5 Conclusions

System complexity decreases in patients who have undergone heart transplantation. This may be related to the loss of neural modulation of heart rate. It is not clear whether new nervous control, or reinnervation develops or not following heart transplantation. Our limited series of transplanted patients do not seem to support presence of cardiac reinnervation.

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