Application of the Entropy of Approximation for the nonlinear characterization in patients with Chagas Disease

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Abstract

Chagas disease American trypanosomiasis is caused by a flagellated parasite: Trypanosoma cruzi, transmitted by an insect of the genus Triatoma and also by blood transfusions. In Latin America, the number of infected people is approximately 6 million, with a population exposed to the risk of infection of 550000. It is our interest to develop a non-invasive and low-cost methodology, capable of detecting any early cardiac alteration that also allows us to see dysautononia or dysfunction within 24 hours and with this it could be used to detect any cardiac alteration caused by T early Cruzi. For this, we analyzed the 24-hour Holter ECG records in 107 patients with ECG abnormalities (CH2), 102 patients without ECG alterations (CH1) who had positive serological results for Chagas disease and 83 volunteers without positive serological results for Chagas disease (CONTROL). Approximate entropy was used to quantify the regularity of electrocardiograms (ECG) in the three groups. We analyzed 288 ECG segments per patient. Significant differences were found between the CONTROL-CH1, CONTROL-CH2 and CH1-CH2 groups.

1. Introduction

Chagas disease is an endemic disease, which is caused by a flagellated parasite: Trypanosoma cruzi (T. cruzi), transmitted by an insect of the genus Triatoma, Chagas disease can also be acquired by blood transfusions. According to WHO in Latin America, the number of infected people is approximately 6 million, with a population exposed to the risk of infection of 568,000[1]. Previous studies show that 40% of the population infected with T. cruzi have cardiac compromise[2, 3, 11]. In Chagas disease we can distinguish two phases: an initial acute phase of infection and a prolonged intermediate chronic phase, where the disease is often clinically silent and asymptomatic. It is our interest to develop a low-cost non-invasive methodology that allows to distinguish dysautononia or dysfunction in the course of 24 hours and with this it could be used as an early marker that shows cardiac alterations produced by T. cruzi

2. Database

For this work, we have used the electrocardiogram (ECG) database of the Instituto de Medicina Tropical (IMT) of the Universidad Central de Venezuela. The patients and volunteers underwent the following tests: clinical evaluation, positive Machado-Gerreiro serological test, chest x-rays, echocardiogram, electrocardiogram and Holter recording (24 hours). They were classified into three groups: 83 healthy volunteers called the Control group; 102 patients infected with only the positive serological test of Machado-Gerreiro (clinical evaluation, chest x-rays, echocardiogram, electrocardiogram and Holter were normal) called group CH1 and 107 seropositive patients with incipient heart disease, atrioventricular block (BAV) involvement first grade, sinus bradycardia (BS) or right bundle branch block of His (BRDHH), all of which were not being treated with medications, called the CH2 group. All were outpatients and informed consent was obtained from all of them.

3. Method

3.1. Preprocessed

We will use the 24-hour ECG holter register (Rozzin model 151 with two leads), which we will divide into 288 segments (framers) corresponding to 5 minutes of ECG (approximately 300 beats) for each volunteer or patient. ECG signals were recorded at 500 Hz with 12 bits of resolution, one channel was recorded. Because we will use a method based on the regularity of the data, no filter was used.

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3.2. Feature extraction

In statistics, an approximate entropy (ApEn) is a technique used to quantify the amount of regularity and the unpredictability of fluctuations over time-series data[4, 5].

The approximate entropy (ApEn) was developed by Steve Pincus[4, 5] based on the entropy of Kolmogorov-Sinai KS, proposed by Grassberger and Procaccia[6] and modified by Takens[7]. Later Richman[8] made a modification of ApEn, which is the sampling entropy (SampEn). Both ApEn and SampEn are based on comparisons of component-to-component embedment vectors ($m = 2$) and with a threshold of 20% of the standard deviation of the ECG ($r = 0.20$). The difference between the entropies is that ApEn does not take into account the parisons of the embedment vectors with itself and the way to calculate the logarithm[9]. To calculate ApEn:

$$ApEn(m, r, N) = -\frac{1}{N-m}\sum_{i=1}^{N-m}\log\left(\frac{A_i}{B_i}\right) \quad (1)$$

where B_i are the vectors of embedding dimension m and A_i are the vectors of dimension of embendding $m + 1$, r is the threshold that is typically 20% of the value of the standard deviation and N is the number of elements.
SampEn is calculated as:

$$SampEn(m, r, N) = -\log\left(\frac{\sum_{i=1}^{N-m} A_i}{\sum_{i=1}^{N-m} B_i}\right) = -\log\left(\frac{A}{B}\right) \quad (2)$$

similar a ApEn m, r and N. The ApEn and SampEn was applied at 288 framers each frame corresponds to 5 minutes per patient

3.3. Kruskal Wallis test and logistic regression

The Kruskal Wallis test will be used to find significant differences ($p - value < 0.05$) between the groups: Control-CH1, Control-CH2 and CH1-CH2 in the 288 framer respectively. A logistic regression is also used to evaluate the circadian profiles of the average values of ApEn, SampEn.

4. Results

In Figure 1 we can see that, on average, the three groups have an increase in the values of ApEn and SampEn of frame 50 that would correspond to 4:00 hours and then a decrease of frame 250 corresponding to 20:00 hours, This result coincides with[9] where tachograms are used.

4.1. Approximate Entropy (ApEn)

- The average values of the circadian profiles of the ApEn of group CH1 (red) always remain below the average values of the control group (blue)
- We observe that the average values of the circadian profiles of ApEn of the control and CH1 groups show the greatest difference in framer 50 and 175 corresponding to 5:00 and 14:00 hours.
- As for the average values of the circadian ApEn profiles of the CH2 group (black) they remain below the average values of the control group (blue) after the framer 90
- We also observe that the average values of the circadian ApEn profiles of the control and CH2 groups show the greatest difference in framer 100 and 175 corresponding to 8:00 and 14:00 hours.

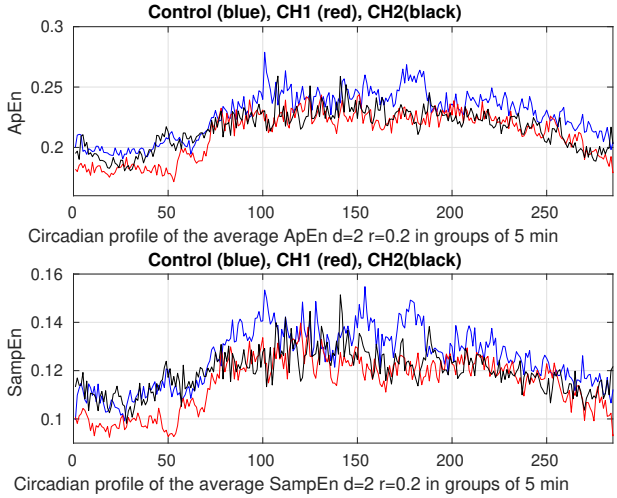

Figure 1. The average values of ApEn and SampEn of 24 hours (288 frames)

As for the Kruskal Wallis test figure 2
- We found significant differences between the Control and CH1 groups in several frames, but we can highlight in frames 50, 100 and 150-180 corresponding to 4:00, 8:00 12:00-15:00 hours.
- With respect to the control and the CH2 group, there are significant differences in several frames, we can highlight the 100 and 175 frames corresponding to 8:00 and 14:00 hours.
- For CH1-CH2 there are significant differences in the frame of 50 corresponding to 4:00 hours

We have used logistic regression to discriminate between the Control and CH2 groups of ApEn for this, 50% of the frames are chosen at random (144) for training and the other 50% for validation, finding 80% specificity and 60% sensitivity in framers 100 and 175 corresponding to 8:00 and 14:00 hours respectively figura 4

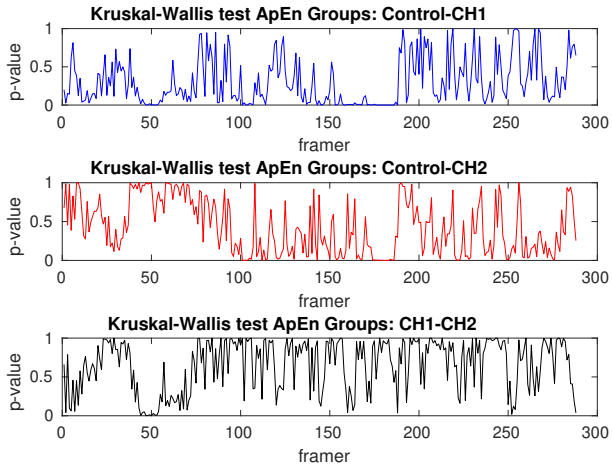

Figure 2. Kruskal-Wallis test of ApEn of the 288 framer

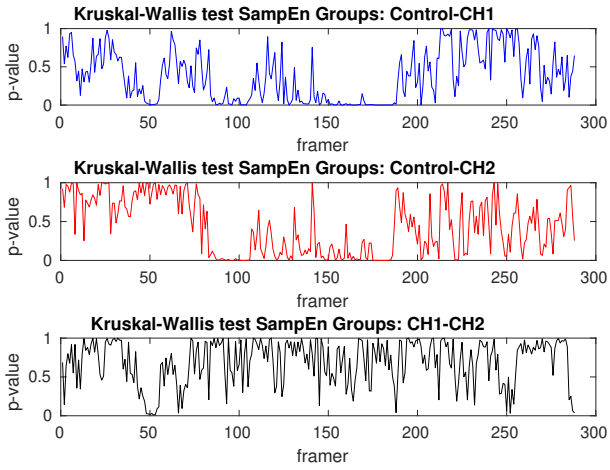

Figure 3. Kruskal-Wallis test of SampEn of the 288 framer

4.2. Sample Entropy (SampEn)

- The average values of the circadian profiles of the SampEn of group CH1 (red) always remain below the average values of the control group (blue)
- We observe that the average values of the circadian profiles of SampEn of the control and CH1 groups show the greatest difference in framer 50 and 175 corresponding to 5:00 and 14:00 hours.
- As for the average values of the circadian SampEn profiles of the CH2 group (black) they remain below the average values of the control group (blue) after the framer 75
- We also observe that the average values of the circadian SampEn profiles of the control and CH2 groups show the greatest difference in framer 100 and 175 corresponding to 8:00 and 14:00 hours.

As for the Kruskal Wallis test figure 3

- We found significant differences between the Control and CH1 groups in several frames, but we can highlight in frames 50, 100 and 150-180 corresponding to 4:00, 8:00 12:00-15:00 hours.
- With respect to the control and the CH2 group, there are significant differences in several frames, we can highlight the 100 and 175 frames corresponding to 8:00 and 14:00 hours.
- For CH1-CH2 there are significant differences in the frame of 50 corresponding to 4:00 hours

We have used logistic regression to discriminate between the Control and CH2 groups of SampEn for this, 50% of the frames are chosen at random (144) for training and the other 50% for validation, finding 80% specificity and 60% sensitivity in framers 100 and 175 corresponding to 8:00 and 14:00 hours respectively figura 5

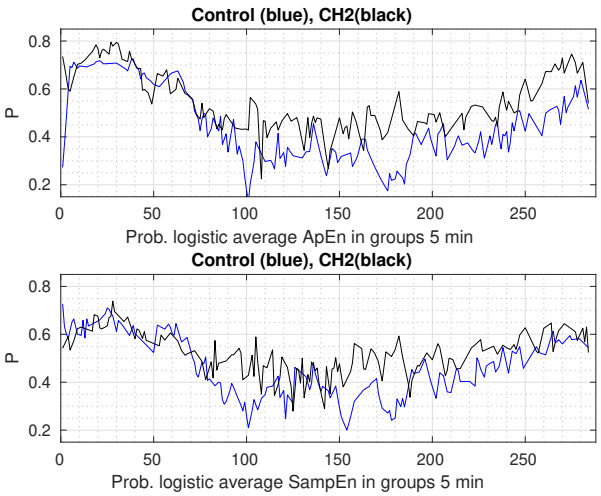

Figure 4. Logistic classifier of the average values of ApEn and SampEn of the 288 framer

5. Discussion and conclusions

The Apen and SampEn of ECG can be used as a measure of heart rate variability similar to HVR, as well as other entropies[10]

The CH1 group, its average values of ApEn and SampEn, show a decrease or enervation in their baroreflector response or autonomic nervous system.

The CH2 group its average values of ApEn and SampEn in some framers show an increase with respect to the Control group this would show a dysautonomy or lack of control of their autonomic nervous system.

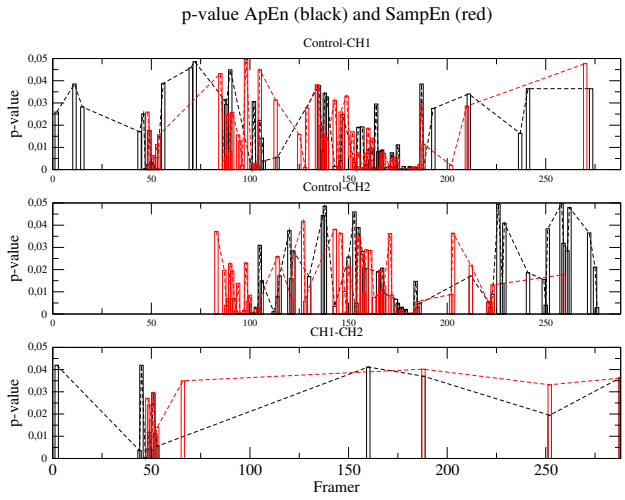

Figure 5. p-value less than 0.05 of ApEn and SampEn

Figure 5 shows the p-values less than 0.05 that would be the framers or moments where the three groups are significantly different, that is to say the Control group and the CH1 group are significantly different in 04:00 , 08:00, 10:00-14:00 hours. The Control group and CH2 are significantly different from 08:00, 12:00 and 14:00 hours. Finally there is a significant difference between the groups CH1 and CH2 only at 04:00 hours.

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Conflicts of Interest

The authors declare no conflict of interest

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