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Analysis of dysautonomia in patients with Chagas Cardiomyopathy

M. Vizcardo[†], A. Ravelo[‡], P. Gomis[§]
[†]*Departamento Académico de Física,*
Universidad Nacional de San Agustín de Arequipa,
Av. Independencia, Arequipa, Perú,mvizcardoc@unsa.edu.pe
[‡]*Instituto for Technological Develoment and Innovation in Communications,*
Universidad Las Palmas de Gran Canaria, Spain
[§] *Valencian International University, Spain*

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, low-cost methodology, capable of detecting any alteration early on cardiaca produced by T. cruzi. We analyzed the 24 hour RR records in patients with ECG abnormalities (CH2), patients without ECG alterations (CH1) who had positive serological findings for Chagas disease and healthy (Control) matched by sex and age. We found significant differences between the Control, CH1 and CH2 groups that show dysautonomy and enervation of the autonomic nervous system.

Keywords: enervation; dysautonomy; Chagas myocarditis; Heart rate variability; principal component analysis.

1. Introduction

Chagas disease 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 people infected is approximately 6 million, with a population exposed to the risk of infection of 568,000[1]. In 40 % of the population infected with Trypanosoma cruzi (T. cruzi) there is cardiac involvement [2, 3, 6]. These estimates explain why this disease is a serious public health problem in the countries where it is endemic. In the evolution of Chagas disease we can distinguish an initial acute phase of infection and a prolonged intermediate chronic phase, in which the disease is often clinically silent, and the usual diagnostic techniques do not provide a robust criterion to predict whether a seropositive asymptomatic patient will suffer cardiac involvement. In the last two decades we have known the relationship between the autonomic nervous system and cardiovascular mortality, including sudden death. Experimental evidences of the association between the probability of having malignant arrhythmias and the increase of the sympathetic tone or the decrease of the vagal tone, have stimulated the development of quantitative markers of the activity of the autonomic nervous system. The variability of the heart rate represents one of the most promising markers. The term "Heart Rate Variability (HVR)" defines the variations in the intervals between the consecutive heartbeats or consecutive R-R interval of electricity. It is used to describe changes in the duration of cardiac cycles, as well as instantaneous variations in heart rate. During the last twenty years a close association has been observed between the functioning of the autonomic nervous system and mortality due to cardiovascular causes. The experimental evidence that the increase in sympathetic activity or the reduction of parasympathetic disease predict lethal arrhythmias, has generated the intense search for a method that quantifies the influence of the autonomic nervous system on the heart.

It is our interest to develop a non-invasive low-cost methodology, that allows to see the dysautonomia or dysfunction in the course ofthe 24 hours. We hypothesize that some kind of dysautonomia measured with HRV tecniques can early detect any cardiac alterations produced by the T. cruzi.

2. Database and Registry

The results of this work were obtained by processing the electrocardiogram (ECG) and obtaining the RR interval, from three different groups of volunteers. The following test: clinical evaluation, serological Machado-Gerreiro test, chest x-rays, echocardiogram, electrocardiogram and ambulatory Holter registration (24 hours), classify volunteers into three groups: 83 healthy people called **Control** group; 102 patients infected with only positive serology (clinical evaluation, chest x-rays, echocardiogram, electrocardiogram and Holter were normal) called **CH1** group; and 107 seropositive patients with incipient cardiac involvement first degree atrioventricular block (BAV), sinus bradycardia (BS) and or right bundle branch block of the bundle of His (BRDHH), that were not being treated with medications, called the **CH2** group. All were outpatients, and informed consent was obtained from all of them. The ECG signals were recorded at 500 Hz with 12 bits of resolution, a set of 288 framer of 5 minutes was obtained.

3. Methods

We have used the database of the Instituto de Medicina Tropical (IMT) of the Universidad Central de Venezuela. For the detection of the QRS complex the program based on the Pan-Tomkip algorithm[4] was used, then the 288 tachograms of the RRs of 5 minutes were generated, they were made a post processed the "ada" filter[5], to eliminate the eptopic beat, and then 8 HRV indices were obtained: average RR intervals, standard deviation, pNN50, r-MSSD, LF, HF, LF/HF, VLF[8].

For the analysis of the 8 HRV indices we use the PCA Principal Component Analysis method[9] that is to say, reduce the dimension and have an uncorrelated representation. We will mention some characteristics:

- Intuitively, the technique serves to determine the number of underlying explanatory factors after a set of data explaining the variability of said data.
- The PCA seeks the projection according to which the data is best represented in terms of least squares.
- PCA involves the calculation of the decomposition in eigenvalues of the covariance matrix, normally after focusing the data on the average of each attribute.
- The calculation of the covariance matrix is based on the internal or scalar product.
- Limitations: only linearly separable problems

The standard linear PCA algorithm:

- Given a set of observations $x_i \ \epsilon \ \mathbb{R}^N \ \ i = 1, ...m$ which are centered, $\Sigma x_i = 0$, The PCA finds the main axes through the diagonalization of the covariance matrix: $C = \frac{1}{m}\Sigma x_j {x_j}^T$
- C it is a definite positive matrix, the result of the diagonalization leads to eigenvalues non-negative To perform the calculation, the equation of eigenvalues is solved: $\lambda v = Cv$ for non-negative eigenvalues and non-zero eigenvectors $\lambda \geq 0$. Replacing : $\lambda v = Cv = \frac{1}{m}\Sigma < x_j \cdot v > x_j$
- Where you can see that all the solutions v con $\lambda \neq 0$ they are in the sub-space generated by $x_1 ... x_m$, therefore for these solutions the equation of eigenvalues is equivalent to $\lambda < x_i \cdot Cv > \forall i = 1, ..., m$:

4. Results

4.1 Estimators Statistics and Frequency

With the 288 5-minute tacograms representing 24 hours for each volunteer or patient, 4 statistical indices were obtained (average of the RR intervals, standard deviation, pNN50 and r-MSDD) and 4 spectral indices (LF, HF, LF/HF and VLF). In Figure 1.1, we observe that the average values of the circadian profiles of the CH2 group are above those of the other 2 groups: Control and CH1, this is because the CH2 group is in the dilation phase. With respect to the average values of the circadian profiles: standard deviation (Fig. 1.2), LF (Fig. 1.3) and VLF (Fig. 1.4) we do not see large differences and rather much noise.

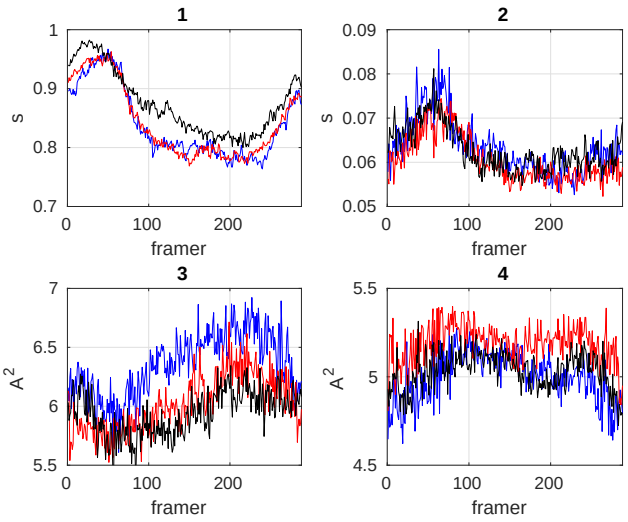

FIG. 1: Temporary and Frequency circadian profiles of the average values of: 1) RR intervals, 2) standard deviation, 3) low frequency LF, 4) very low frequency VLF. Groups: Control (blue), CH1 (red) and CH2 (black)

4.2 PCA analysis

For the PCA analysis we use the average circadian profiles and the 8 HRV indices as feature of the three groups: Control, CH1 and CH2. The covariance matrix was calculated, then its eigenvalues which were ordered from greater to less with their respective eigenvectors, the first and second eigenvalue will have the greatest variance, that is to rotate and translate two orthogonal axes in the direction of greater variance. These axes are called principal components (PC).

On the first principal component (1st PC) and second principal component (2nd PC) we project the 12 vectors corresponding to each hour of the three groups and are shown in Fig. 2, we do this for each hour of the 24 hours.

We calculate the centroid of each group in each hour and see its evolution in 24 hours (Fig. 3) that would be the descriptors of the dynamics of each group.

We have identified three stages in the dynamic: from 01 to 09 hours, from 09 to 20 hours and from 20 to 24

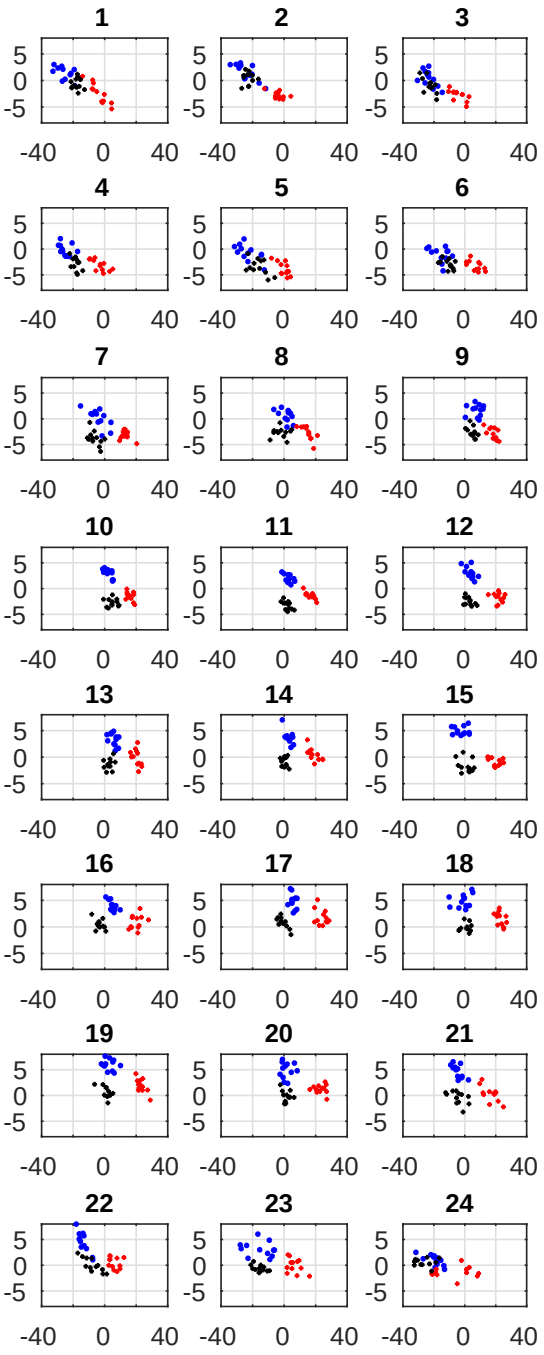

FIG. 2: First principal components vs second principal components of the 24 hours. Groups: Control (blue), CH1 (red) and CH2 (black)

hours.

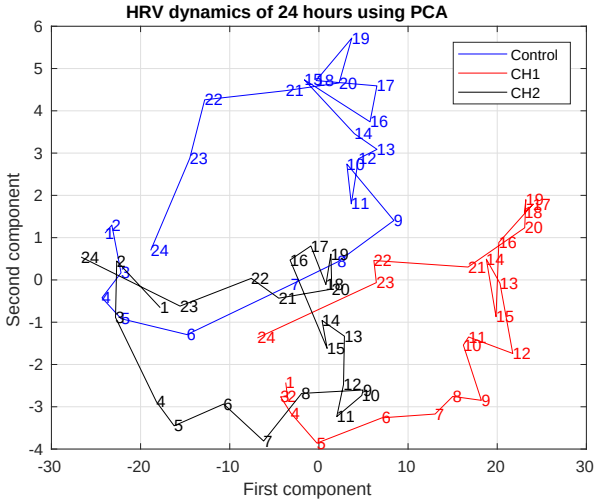

FIG. 3: First component principal versus second principal component of the 24 hour average hourly values. Groups: Control (blue), CH1 (red) and CH2 (black)

4.2.1 From 01 to 09 hours

Linear regression was made between 01 and 05 hours (Fig. 4) to the three groups:
Control $y_{1-5} = -0.31x - 6.9$
CH1 $y_{1-5} = -0.31x - 3.9$
CH2 $y_{1-5} = -0.41x - 9.5$
Then between 05 to 09 hours:
Control $y_{5-9} = 0.08x + 0.38$
CH1 $y_{5-9} = 0.057x - 3.8$
CH2 $y_{5-9} = 0.038x - 2.9$

4.2.2 From 09 to 20 hours

We observe that the dynamics of each group is well defined (Fig 5) and that the linear regression of the three groups has been calculated:
Control $y_{9-20} = -0.23x + 4.5$
CH1 $y_{9-20} = 0.45x - 9.3$
CH2 $y_{9-20} = -0.47x - 0.41$

4.2.3 From 20 to 24 hours

The linear regression of the three groups (Fig. 6) was calculated:
Control $y_{20-24} = 0.16x + 4.9$
CH1 $y_{20-24} = 0.077x - 0.59$
CH2 $y_{20-24} = -0.023x - 0.38$

4.3 Test Kruskal Wallis at the PCA

The Kruskal Wallis test was used to find significant differences (p-value<0.05) between the groups: Control-

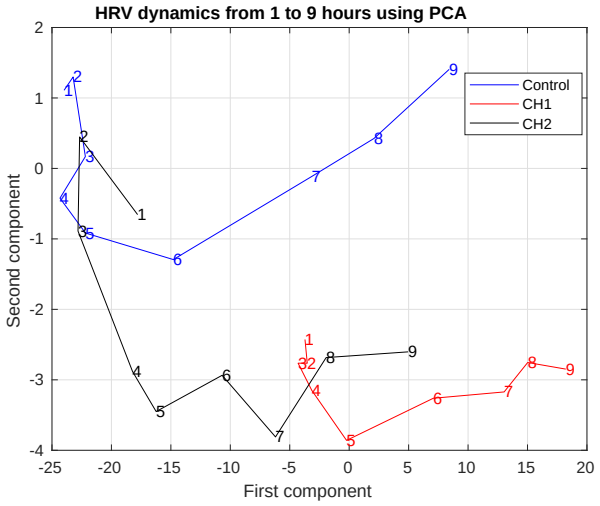

FIG. 4: First principal components vs second principal components of the 24 hours, groups: Control (blue), CH1 (red) and CH2 (black)

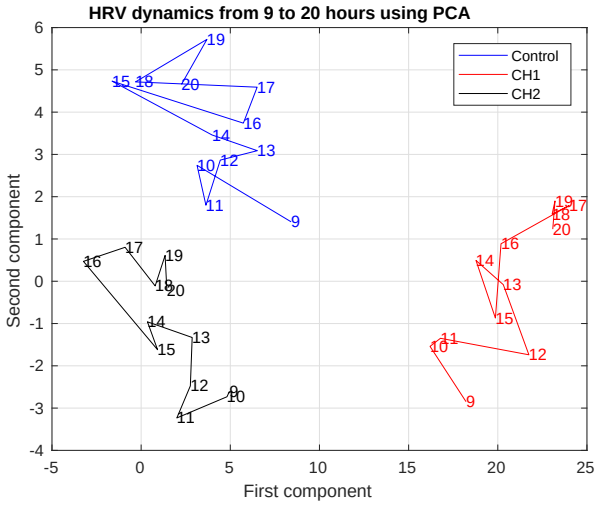

FIG. 5: First principal components vs second principal components of the 24 hours, groups: Control (blue), CH1 (red) and CH2 (black)

CH1, Control-CH2 and CH1-CH2 within 24 hours.

For this, it was carried out between the 1st PC of the three groups in each hour, then it was done in the 2nd PC, Table 1 shows the p-values less than < 0.05 and with an "NS" where the values are greater. It can be seen that it is sufficient that one of the main components has < 0.05 to be significantly different, as can be seen between the Control-CH2 groups in 4 to 23 hours in Fig. 2 and Table 1. Of the 144 p-value there are only 4 that correspond to the hours of 2 and 3 Control-CH2 that are not significantly different.

5. Discussion and conclusions

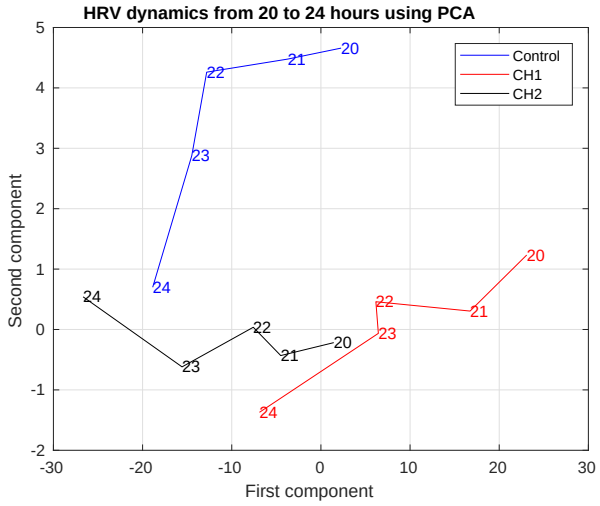

FIG. 6: First principal components vs second principal components of the 24 hours, groups: Control (blue), CH1 (red) and CH2 (black)

The circadian profiles of the HRV indices do not show significant differences, this may be due to the noise present in the ECGs.

The use of PCA with the HRV index achieves significant differences, except in two hours of Control-CH2.

We have identified three stages in the 24-hour dynamic; the first where there is a change to the right of the three groups. a second has short displacements and in a defined area and a third where the three groups move to the left. The displacements to the right and to the left are due to the hours of rest (parasympathetic), while the zone of short displacements to the hours of activity (sympathetic)

The PCA can be used to obtain HRV dynamics descriptors in 24 hours.

We note that in the slope of 1 to 5 hours and from 20 to 24 hours a decrease between the Control Groups, CH1 and CH2, this could use me as a measure of variability.

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Conflicts of Interest
The authors declare no conflict of interest

	1 CP	2 CP	1 CP	2 CP	1 CP	2 CP
Hours	C-CH1	C-CH1	C-CH2	C-CH2	CH1-CH2	CH1-CH2
1	0.001	0.001	NS	0.040	0.001	NS
2	0.001	0.001	NS	X	0.001	0.001
3	0.001	0.001	NS	X	0.001	0.026
4	0.001	0.001	NS	0.001	0.001	NS
5	0.001	0.001	NS	0.006	0.002	NS
6	0.001	0.001	NS	0.027	0.001	NS
7	0.001	0.001	NS	0.001	0.001	NS
8	0.001	0.001	NS	0.001	0.001	NS
9	0.003	0.001	NS	0.001	0.001	NS
10	0.001	0.001	NS	0.001	0.001	NS
11	0.001	0.012	NS	0.001	0.001	0.022
12	0.001	0.001	NS	0.001	0.001	NS
13	0.004	0.004	NS	0.001	0.001	NS
14	0.006	0.006	NS	0.001	0.001	NS
15	0.001	0.001	NS	0.001	0.001	NS
16	0.015	0.001	0.015	0.001	0.001	NS
17	0.013	0.004	0.018	0.001	0.001	NS
18	0.001	0.008	NS	0.001	0.001	NS
19	0.001	0.002	NS	0.001	0.001	NS
20	0.001	0.005	NS	0.001	0.001	NS
21	0.001	0.001	NS	0.001	0.001	NS
22	0.001	0.002	NS	0.001	0.002	NS
23	0.001	0.001	NS	0.001	0.001	NS
24	NS	0.001	0.033	NS	0.001	0.002

TABLE I: p-value < 0.05 the Kruskal Wallis test

References

[1] World Health Organization The World Health Report 2017; 2:75,9–16 http://www.who.int/wer

[2] F. Moleiro and I. Mendoza, Circulation, 113 (1978).

[3] Moleiro F, Mendoza I Miocardiopatia Chagásica Crónica. Estudio Epidemiológico Acta Cient. Venez. 1980;31:66

[4] J. Pan and W. Tompkins, A Real-Time QRS Detection Algorithm IEEE Transactions on Biomedical Engineering, Vol. BME-32, NO. 3, March (1985).

[5] N Wessel, A Voss, Renormalised Entropy: A New Method of Non-Linear Dynamics for the Analysis of Heart Rate Variability, Computers in Cardiology 1994

[6] J. M. Hagar and S. H. Rahimtoola, N. Eng. J. Med., 325, 763 (1991).

[7] K. Mott and J. Hagstrom, Circulation, 31, 273 (1965).

[8] Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, Circulation, 73, 5, 1044 (1996).

[9] B. Schlkopf, S. Mika, C. J. Burges, P. Knirsch, K. R. Mller, G. Rtsch, & A. J. Smola, (1999). Input space versus feature space in kernel-based methods. IEEE transactions on neural networks, 10(5), 1000-1017.

[10] H. Tsuji, et.al., Jour. of Am. Coll. Cardiol. 28, 6, 1539 (1996).

[11] S. Guzzetti, D. Iosa, M. Pecis, L. Bonura, M. Prosdocimi and A. Malliani Impaired heart rate variability in patients with chronic Chagas' disease. Am. Heart J. 1991;121:1727

[12] Loyo J, Barroyeta R, Puigbó JJ, Moleiro F, Braun I, Ruggiero A, Pérez DV:Effect of postural changes in the autonomic balances in latent or indeterminate phase of Chagas Disease Chest 1995; 3:108

[13] Lombardi F, Sandrone G, Mortara A, Torzillo D, La Rovere MT, Signorini MG et al. Linear and nonlinear dynamics of heart rate variability after acute myocardial infarction with normal and reduced left ventricular ejection fraction. Am J Cardiol 1996; 77: 1283-1288.

[14] Bigger JT Jr, Steinman RC, Rolnitzky LM, Fleiss JL, Albrecht P, Cohen RJ. Power law behavior of RR interval variability in healthy middle-aged persons, patients with recent acute myocardial infarction, and patients with heart transplants. Circulation 1996; 21: 2142-2151.

[15] Huikuri HV, Mkikallio TH, Peng CK, Goldberger AL, Hintze U, Moller M, for the Diamond Study Group. Fractal correlation properties of R-R interval dynamics and mortality in patients with depressed left ventricular function after an acute myocardial infarction. Circulation 2000; 101: 47-53.

[16] Urbina J, Payars G, Molina J, Sanoja C, Liendo A, Lazardi K et al. Cure of short-and long term experimental Chagas disease using D0870. Science 1996; 273: 969-970.

[17] Sgambati de Andrade AL, Zicker F, De Oliveira RM, Almeida e Silva S, Luquetti A, Travassos L et al. Ran-

domised trial of efficacy of benzomidazole in treatment of early trypanosoma Cruzi infection. The Lancet 1996; 348: 1407-1412.

[18] Maguire JH, Hoff R, Sherlock I, Guimaraes AC, Sleigh AC, Borges Ramos N et al. Cardiac morbidity and mortality due to Chagas disease; prospective electrocardiographic study of Brazilian community. Circulation 1987; 75: 1140-1145.

[19] Lopes ER. Sudden death in patients with Chagas disease. Mem Inst Oswaldo Cruz 1999; 94: 321-324.

[20] R. B. Govindan, K. Narayanan, and M. S. Gopinathan, Chaos 8, 2, 495 (1998).

[21] K. Hall, D. J. Christini, M. Tremblay, J. J. Collins, L. Glass, and J. Billette, Phys. Rev. Lett., 78, 23, 4518 (1997).

[22] K. Narayanan, R. B. Govindan, and M. S. Gopinathan, Phys. Rev. E, 57, 4, 4594 (1998).

[23] D. J. Wales, Nature 350, 485 (1991).

[24] A. G. Ravelo-García, P. Saavedra-Santana, G. Juliá-Serdá, J. L. Navarro-Mesa, J. Navarro-Esteva, X. Álvarez-López, A. Gapelyuk, T. Penzel, and N. Wessel. Symbolic dynamics marker of heart rate variability combined with clinical variables enhance obstructive sleep apnea screening, Chaos 24, 024404 (2014);

[25] Adriana Campos Junqueira de Souza and et.a Development of a risk score to predict sudden death in patients with Chaga's heart disease,l., International Journal of Cardiology 187 (2015) 700704

[26] Sofía Martín-González a, Juan L. Navarro-Mesa, Gabriel Juliá-Serdá b ,Jan F. Kraemer c ,Niels Wessel, Antonio G. Ravelo-García. Heart rate variability feature selection in the presence of sleep apnea: An expert system for the characterization and detection of the disorder,, Computers in Biology and Medicine 91 (2017) 4758

[27] Antonio G. Ravelo-García 1, Juan L. Navarro-Mesa, Ubay Casanova-Blancas, Sofia Martin-Gonzalez, Pedro Quintana-Morales, Iván Guerra-Moreno, Jos M. Canino-Rodríguez and Eduardo Hernández-Pérez, Application of the Permutation Entropy over the Heart Rate Variability for the Improvement of Electrocardiogram-based Sleep Breathing Pause Detection, , Entropy (2015), 17, 914-927; doi:10.3390/e17030914

[28] Catherine Masiel Merejo Peña and et.al., Dysautonomy in different death risk groups (Rassi score) in patients with Chagas heart disease, Pacing Clin Electrophysiol. (2018);41:238245.

[29] A. Caeiro T, Iosa D., Chronic Chagas' disease: possible mechanism of sinus bradycardia. Can J Cardiol (1994);10:765-8

[30] Goin JC, Borda ES, Auger S, Storino R, Sterin-Borda L. Cardiac M(2) muscarinic cholinoceptor activation by human chagasic autoantibodies: association with bradycardia, Heart Sep (1999);82(3):2738.

[31] Sterin-Borda L, Borda E. Role of neurotransmitter autoantibodies in the pathogenesis of chagasic peripheral dysautonomia. Ann N Y Acad Sci (2000);917:27380.

[32] D. SF, Pedrosa RC, Nascimento JH, Campos de Carvalho AC, Masuda MO. Sera from chronic chagasic patients with complex cardiac arrhythmias depress electrogenesis and conduction in isolated rabbit hearts. Circulation (1997);96:20317

[33] Octavio J, Rodríguez A, Misticchio F, Marcano A, Jiménez J, Moleiro F. Perfiles circadianos de la frecuencia cardíaca y de su variabilidad instantánea en una población de pacientes con infección chagásica crónica. Rev Esp Cardiol. (2004);57(2):130-7

[34] F. Ribeiro A, Moraes R, Ribeiro P, Ferlin E, Torres R, Oliveira E, et al. Parasympathetic dysautonomia precedes left ventricular systolic dysfunction in Chagas disease. Am Heart J (2001);141:260-5.

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