PREDICTIONS OF CLINICAL APPLICATION OF THE CARDIAC DYNAMICS IN MONITORING PATIENTS WITH ACUTE CORONARY SYNDROME

Javier Rodríguez MD[1], Signed Prieto[2], Leonardo Ramírez Eng[3]

[1] INSIGHT Group. Faculty of Medicine, Universidad Militar Nueva Granada – Research Center Clínica del Country, Colombia
[2] INSIGHT Group. Research Center Clínica del Country, Colombia
[3] T1GUM Group, Faculty of Engineering. Universidad Militar Nueva Granada, Colombia

Abstract

The physical methodologies of probability and entropy, and Zipf-Mandelbrot law for quantitative evaluation of cardiac dynamics were applied simultaneously, in order to achieve a differentiation between normality and Acute Coronary Syndrome (ACS). A blind study was conducted, taking Holter monitoring tests from 50 normal subjects and 50 people with ACS who developed Acute Myocardial Infarct (AMI) and Cardiogenic Shock (CS). The maximum and minimum heart rate for each hour was taken, and the number of beats at minimum 21 hours. Probability, entropy and proportions of consecutive pairs of heart rates in numerical attractors were calculated. Zipf-Mandelbrot law was applied to cardiac frequencies grouped in ranges of 15 beats/min finding the degree of complexity of each dynamic and establishing its mathematical diagnosis. It was demonstrated that physical methodologies can evaluate more specifically the ACS, AMI and CS, with values of sensitivity and specificity of 100% and Kappa of 1.

Keywords: cardiac dynamic; probability; law; acute coronary syndrome

Introduction

Cardiovascular disease (CVD) leads the causes of mortality in North America. Efforts have been intensified to achieve an adequate analysis of heart rate variability (HRV).[1] Cases of Acute Coronary Syndrome (ACS) that developed Acute Myocardial Infarction (AMI) and Cardiogenic Shock (CS) are particularly interesting for its severity. HRV has been studied by different techniques.[2-4] However, it cannot show the dynamic properties of the fluctuations,[4] but it is possible to use entropy to measure this randomness.[5]

Recent research have revealed that cardiac dynamics have a chaotic behavior,[6-15] that has been studied with physical-mathematical methodologies differentiating normality, disease and evolution between them.[6-15]

The aim of the present paper is to apply simultaneously two methodologies, one based on probability and entropy, and the other on Zipf-Mandelbrot law, to evaluate the behaviour of the cardiac dynamics in order to confirm the clinical capacity of the methodologies.

Methods

Population

One hundred continuous electrocardiographic records were obtained through Holter monitoring from 50 normal subjects and 50 people with ACS who developed AMI and CS. The ECGs were evaluated for a minimum of 21 hours and clinical diagnosis was established by an expert cardiologist according to the standard parameters.

Procedure

Diagnoses were blinded initially. The probability of a consecutive pair of heart rates appearing within a range was defined as:

$$P(X,Y)=\frac{\text{Number of ordered pairs found in the range X, Y}}{\text{Total of ordered pairs}} \qquad Equation 1$$

The entropy of the cardiac attractor was calculated:

$$S=-k\sum_{x=1}^{n}\sum_{y=1}^{n}P(X,Y)\times LnP(X,Y) \qquad Equation 2$$

Where S is the entropy of the cardiac attractor, k is the Boltzmann's constant ($1.38\text{x}10^{-23}$ Joules/Kelvin), P(X,Y) is the defined on equation 1.

The ratio between the entropy and the Boltzmann's constant,

$$\frac{S}{K}=\sum_{x=1}^{n}\sum_{y=1}^{n}P(X,Y)\times LnP(X,Y) \quad Equation 3$$

,

These summatories can be divided:

$$\frac{S}{k}=\begin{cases}\sum_U P(U)\times LnP(U) & \text{(U) Units} \Rightarrow (1\text{-}9)\\ \sum_D P(D)\times LnP(D) & \text{(D) Tens} \Rightarrow (10\text{-}99)\\ \sum_C P(C)\times LnP(C) & \text{(C) Hundreds} \Rightarrow (100\text{-}999)\\ \sum_M P(M)\times LnP(M) & \text{(M) Thousands} \Rightarrow (1000\text{-}9999)\end{cases} \quad \textit{Equation}\ 3(a)$$

and simplified:

$$\frac{S}{K}=T=U+D+C+M \quad \text{Where } T=\frac{S}{K} \qquad \textit{Equation}\ 4$$

Where T is the totality and U,D,C,M, are the parts.

The consecutive heart rates were graphed and over the graph, the numerical attractor for each registry was observed.[6] Then, based on equation 1, the probabilities of occupation with respect to the total were evaluated to determinate the regions of the attractor. Equation 2 was used to calculate the entropy of each attractor. The S/k ratio was calculated with equation 3, and the ratio between the parts was shown in equation 4. Finally, the diagnosis was made using previously established parameters.[6]

Taking the absolute value of the difference between the normality limits established,[6] and the ratios from equation 4 that were outside of these limits, and then adding the orders of the magnitudes, the level of severity of the disease was quantified, where for higher values, the pathology was in a more acute state.

Also, through a logarithmic linearization of the heart rate frequency in ranges of 15 beats/min,

$$D=\frac{\log(\sigma+V)}{\log\left(F/P\right)} \qquad \textit{Equation 5}$$

Where D= statistical dimension

V = 1 / n - 1, where n is the number of frequencies obtained on each register.

P = frequency of occurrence for each range.

F= secondary factor associated to the intersection point with the vertical axis in the obtained linearization.

The Zipf-Mandelbrot law was applied using the same registers. Heart rates were grouped in ranges of 15 beats/min, ordered according to its frequency from higher to lower and represented in a graph, showing a hyperbolic behaviour, therefore, the fractal statistical dimension was obtained through a linearization (equation 5). Finally, the mathematical diagnosis was made with previously established parameters.[16]

Results

Both entropy and S/k ratios quantitatively differentiate patients with acute coronary syndrome who developed AMI and cardiogenic shock. For normal cases, a proportion outside the normal range was obtained for normal cases, and for the cases with acute pathology, values outside the limits of normality were presented from 2 to 13 times, confirming the previous results.

The sums of the subtractions of the proportions outside the limits of normality of the order of thousands were found between 1.4536 and 1.976, and for the order of hundreds between 0.1782 and 3.610, evidencing the acute character of the dynamics with acute coronary syndrome that developed AMI and cardiogenic shock. (Table 1)

For statistical fractal dimensions, it was found that both normal cases and acute cases presented values within the previously established ranges, obtaining values between 0.7157 and 0.9492 (table 2) for normal Holter monitoring tests and between 0, 4339 and 0.6677 for Holter tests with acute pathology. The R^2 values were between 0.8516 and 0.9932.

The sensitivity and specificity values for both methodologies were 100%, with a Kappa coefficient of 1, confirming the concordance between physical-mathematical diagnosis and the Gold Standard.

Table 1. Entropy values, S / k ratio, proportions of entropy and sums of the subtractions of the order of units (U), tens (D), hundreds (C) and thousands (M) corresponding to some of the studied Holter monitoring tests.

Discussion

This is this first work comparing the methodology of proportional entropy with a methodology based on Zipf-Mandelbrot law for the evaluation of cardiac dynamics in patients with acute coronary syndrome. The first one showed its diagnostic predictive capacity in cardiac dynamics, its ability to differentiate adequately evolution states towards disease, its clinical application and its capacity to establish severity, which would provide new follow-up tools for patients.

The methodology based on Zipf-Mandelbrot law showed its capacity to differentiate acute cardiac pathology from normality according to the degree of complexity of the system, which is higher in normal cases. Both methodologies are applicable to particular

Table 1. Entropy values, S / k ratio, proportions of entropy and sums of the subtractions of the order of units (U), tens (D), hundreds (C) and thousands (M) corresponding to some of the studied Holters.

		Normales				Agudos					
	No.	1	2	3	4	5	6	7	8	9	10
	Entropia:	6,49968E-23	6,50678E-23	6,966E-23	6,531E-23	4,95E-23	4,95E-23	4,67E-23	4,86E-23	4,95E-23	5,04E-23
	Proporción	-4,709915136	-4,71505472	-5,04796879	-4,73233212	-3,58900412	-3,58497092	-3,38425773	-3,52075125	-3,58473073	-3,65365695
AREA 1	U/T:	5,98221E-05	0,00013787	0,00014523	0	0	0	2,68E-04	9,58E-05	6,15E-04	0
	D/T:	0,090322532	0,039425037	0,0817603	0,08965866	0,02504938	0,02588014	0,06975647	0,08544938	0,01555893	0,02766302
	C/T:	0,491477683	0,484504439	0,55012422	0,4842443	0,23279142	0,23172311	0,20357368	0,20983659	0,21154302	0,25820016
	M/T:	0,312153664	0,456906293	0,16300967	0,30872871	0,58806463	0,58977187	0,64126295	0,6030037	0,62350686	0,70610468
	C/M:	1,574473538	1,060402201	3,37479499	1,56851072	0,39586026	0,39290296	0,31745743	0,34798557	0,33927938	0,36566839
	D/C:	0,183777484	0,08137188	0,14862152	0,18515171	0,10760441	0,11168563	0,34265958	0,40721867	0,07354973	0,1071379
AREA 2	U/T:	0,009202007	0,006621746	0,00828154	0,00842282	0	3,62E-04	0	0	0	0
	D/T:	0,070906021	0,012404615	0,13457161	0,08242433	0,0043558	0,00347227	0,00471588	0,00352535	0,00784115	0,00803213
	C/T:	0,02587827	0	0,04085761	0,02652118	0,0818476	0,08101446	0,06445728	0,06291133	0,07468482	0
	M/T:	0	0	0	0	0,03900598	0,03924987	0	0	0,03161433	0
	C/M:					2,09833461	2,06406988			2,3623724	
	D/C:	2,739983003		3,29367292	3,10786797	0,05321846	0,04285984	0,07316284	0,05603686	0,10498988	
AREA 3	U/T:				0	2,14E-04	3,26E-04	0	0	6,51E-04	0
	D/T:					0,00629025	0,00888882	0,00677282	0,01280636	0,01261568	0
	C/T:					0,02238094	0,0193123	0,00919333	0,02237152	0,02136961	0
	M/T:					0	0	0	0	0	0
	C/M:										
	D/C:					0,28105403	0,4602671	0,73670998	0,5724403	0,59035625	
SUMAS	U:					2,14E-04	3,26E-04	5,20E-05	0	0,00104996	0
	D:					0,02019044	0,02195824	0,00677282	0,01280636	0,03600632	0,01128654
	C:					3,00160261	3,18834083	3,58822533	3,51101005	3,27938928	0,22425907
	M:					1,78591814	1,75656183	1,85871112	1,78992373	1,13458739	1,87534189

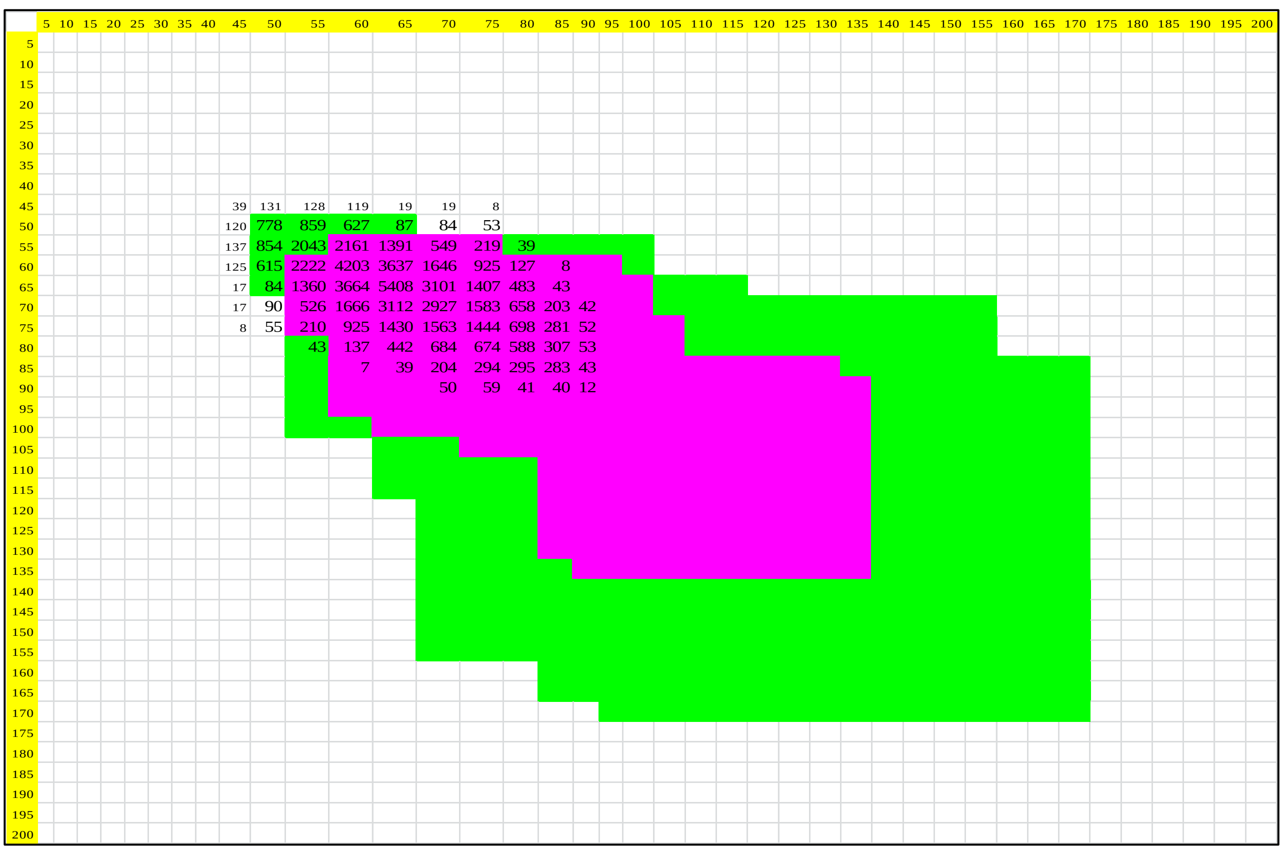

Figure 1. Numerical attractor in the phase space of the three defined regions. This attractor corresponds to the dynamic number 9 of Table 1.

Table 2. Values of the statistical fractal dimension (DF) and R^2 for some of the studied Holters, from cases of table 1.

No.	DF	R^2
1	0.8436	0.9292
2	0.8421	0.8716
3	0.9354	0.972
4	0.8908	0.9859
5	0.6207	0.9436
6	0.4887	0.9534
7	0.5959	0.8849
8	0.5057	0.8835
9	0.4409	0.9685
10	0.5036	0.9831

cases independent of other considerations such as risk factors, and their diagnostic capacity is objective and reproducible. A sensitivity and specificity of 100%, and a kappa coefficient of 1 was obtained for both methodologies.

The results found in the present study corroborate previous findings where the clinical applicability of the method based on proportional entropy was confirmed, including blind studies with 450 and 600 patients.[7,8]

Zipf-Mandelbrot law was applied in immunology,[13] where an analogy between linguistic phenomena[17-20] and the distribution of the T cell repertoire against the Poa p9 allergen in the setting of an allergic patient was evidenced.[21] It was also used in the development of a new diagnosis of foetal monitoring.[22,23] This work also confirms previous findings[16] and validates its clinical application.

Diagnoses in patients with arrhythmia,[24] ICU mortality predictions,[8] and evaluations of the neonatal cardiac system have been developed.[25] In addition, there have been achieved diagnoses and characterisations in arterial and cellular morphometry,[26-28] hematology,[29] infectology,[30] epidemic predictions[31,32] and immunology in the prediction of binding of Peptides from Plasmodium falciparum to HLA class II.[33]

Conclusion

Both methodologies allowed to establish diagnoses of cardiac dynamics, in an objective and reproducible way.

…………………………………………………………..

Corresponding author:
Leonardo Ramirez
T1GUM Group
Faculty of Engineering
Universidad Militar Nueva Granada
Colombia
eMail: leonardo.ramirez@unimilitar.edu.co

Conflict of interest. The authors declare no conflicts of interest.

Acknowledgment: We thank Universidad Militar Nueva Granada, for its support to our investigative processes, especially to Research Fund of the University, to Vice-rectory of Investigations and Faculty of Engineering. Special thanks to Doctors Yanneth Méndez and Marcela Iregui.

Financial support: Product derived from the project INV-ING 2096, funded by the Vice-Rectors Office of Investigations of the Universidad Militar Nueva Granada - Validity 2016

We also extend our thanks to the Research Center from Clinica del Country, Dr. Adriana Lizbeth Ortiz, Epidemiologist, and Silvia Ortiz, Chief Nurse, Sandra Rodríguez Nurse and Doctors Tito Tulio Roa, Director of Medical Education, Jorge Alberto Ospina, Medical Director, and Alfonso Correa, Director of the Research Center, for the support of our research group.

References

1. Mayer C, Bachler M, Hörtenhuber M, et al. Selection of entropy-measure parameters for knowledge discovery in heart rate variability data. *BMC Bioinform* 2014;15(Suppl 6):S2.
2. Rajendra Acharya U, Paul Joseph K, Kannathal N, Lim C, Suri J. Heart rate variability: a review. *Med Biol Eng Comput* 2006;44:1031–1051. doi: 10.1007/s11517-006-0119-0. doi:10.1007/s11517-006-0119-0.
3. American Heart Association Inc; European Society of Cardiology. Guidelines - heart rate variability. *Eur Heart J* 1996;17:354–381.
4. Vandeput S, Verheyden B, Aubert AE, Van Huffel S. Numerical Noise Titration analysis of heart rate variability in a Healthy Population. 5th Conference of the European Study Group on Cardiovascular Oscillations Available at:

ftp://ftp.esat.kuleuven.be/pub/sista/svandepu/reports/SISTA-08-34.pdf accessed 18 March 2017.

5. Hornero R, Aboy M, Abasolo D, McNames J, Goldstein B. Interpretation of approximate entropy: analysis of intracranial pressure approximate entropy during acute intracranial hypertension. *IEEE Trans Biomed Eng* 2005;52(10):1671–1680. doi: 10.1109/TBME.2005.855722.
6. Rodríguez J. Entropía Proporcional de los sistemas dinámicos cardiacos: Predicciones físicas y matemáticas de la dinámica cardiaca de aplicación clínica. *Rev Colomb Cardiol* 2010;17(3):115-129.
7. Rodríguez J, Prieto S, Domínguez D, et al. Mathematical-physical prediction of cardiac dynamics using the proportional entropy of dynamic systems. *J Med Med Sci* 2013;4(8):370-381
8. Rodríguez J, Prieto S, Bernal P, et al. Entropía proporcional aplicada a la evolución de la dinámica cardiaca. Predicciones de aplicación clínica. En: Rodríguez LG, Coordinador. La emergencia de los enfoques de la complejidad en América Latina: desafíos, contribuciones y compromisos para abordar los problemas complejos del siglo XXI. Tomo 1,1a ed. Buenos Aires: Comunidad Editora Latinoamericana; 2015. p. 315-44.
9. Rodríguez J, Prieto S, Correa C, et al. Proportional entropy applied to the clinical diagnostic of cardiac dynamic: blind study with 600 holter. The 61st Annual Conference of the Israel Heart Society in association with The Israel Society of Cardiothoracic Surgery. 2014.
10. Rodríguez J, Prieto S, Bernal P, Izasa D, Salazar G, Correa C, et al. Entropía proporcional aplicada a la evolución de la dinámica cardiaca Predicciones de aplicación clínica. La emergencia de los enfoques de la complejidad en América Latina. Tomo I. Argentina: Comunidad del Pensamiento complejo. 2015;247-264.
11. Rodríguez J, Mendoza F, Velásquez N. Clinical application to Arrhythmic of entropy proportion. *J Nucl Med Radiat Ther* 2015;6(4): Insue 4.
12. Rodríguez J**.** Mathematical law of chaotic cardiac dynamic: Predictions of clinic application. *J Med Med Sci* 2011;2(8):1050-1059.
13. Rodríguez J, Prieto S, Dominguez D, et al. Application of the chaotic power law to cardiac dynamics in patients with arrhythmias. *Rev Fac Med* 2014;62(4):539-546.
14. Rodríguez J, Prieto S, Correa C, Oliveros H, Soracipa Y, Méndez L, et al. Diagnóstico físico-matemático de la dinámica cardiaca a partir de sistemas dinámicos y geometría fractal: disminución del tiempo de evaluación de la dinámica cardiaca de 21 a 16 horas. *Acta Colomb Cuid Intensivo* 2016;16(1):15-22.
15. Rodríguez J. Dynamical systems applied to dynamic variables of patients from the intensive care unit (ICU): Physical and mathematical mortality predictions on ICU. *J Med Med Sci* 2015;6(8):209-220.
16. Rodríguez J, Prieto S, Correa C, et al. Physical mathematical evaluation of the cardiac dynamic applying the Zipf – Mandelbrot law. *J Modern Physics* 2015;6(13):1881-1888.
17. Mandelbrot B. Scaling and power laws without geometry. In: The Fractal Geometry of Nature. Freeman Ed. San Francisco, 1972: 344-348.
18. Mandelbrot B. Structure formelle des textes et comunication. *Word* 1954;10:1-27.
19. Zipf G. Human behaviour and the principle of least effort: an introduction to human ecology. Cambridge, Ma: Addison-Wesley, 1949.
20. Mandelbrot b. Árboles jerárquicos o de clasificación, y la dimensión. En: los objetos fractales. Tusquets eds s.a. barcelona. 2000:161-166.
21. Rodríguez J. Comportamiento fractal del repertorio T específico contra el alergeno poa p9. *Rev Fac Med Univ Nac Colomb* 2005;53:72-78.
22. Rodríguez J, Prieto S, Ortiz l, et al. Diagnóstico matemático de la monitoria fetal aplicando la ley de Zipf Mandelbrot. *Rev fac med univ nac colomb* 2006;54(2):96-107.
23. Rodríguez J. Dynamical systems theory and Zipf – Mandelbrot law applied to the development of a fetal monitoring diagnostic methodology. Xviii Figo World Congress of Gynecology And Obstetrics. Kuala Lumpur, Malaysia. November 2006
24. Rodríguez-Velásquez J, Prieto S, Bautista J, et al. Evaluación de arritmias con base en el método de ayuda diagnóstica de la dinámica cardiaca basado

en la teoría de la probabilidad. *Arch Med* 2015;15(1):33-45.
25. Rodríguez J, Prieto S, Flórez M, et al. Physical-mathematical diagnosis of cardiac dynamic on neonatal sepsis: predictions of clinical application. *J Med Med Sci* 2014;5(5):102-108.
26. Rodríguez J, Prieto S, Correa C, et al. Theoretical generalization of normal and sick coronary arteries with fractal dimensions and the arterial intrinsic mathematical harmony. *BMC Medical Physics* 2010;10(1):1-6.
27. Rodríguez J, Prieto S, Correa C, et al. Geometrical nuclear diagnosis and total paths of cervix cell evolution from normality to cancer. *J Can Res Ther* 2015;11(1):98-104.
28. Prieto S, Rodríguez J, Correa C, Soracipa Y. Diagnosis of cervical cells based on fractal and Euclidian geometrical measurements: Intrinsic Geometric Cellular Organization. *BMC Medical Physics* 2014;14(2):1-9.
29. Correa C, Rodríguez J, Prieto S, et al. Geometric diagnosis of erythrocyte morphophysiology: Geometric diagnosis of erythrocyte. *J Med Med Sci* 2012;3(11):715-720.
30. Rodríguez J, Prieto S, Correa C, et al. Predictions of CD4 lymphocytes' count in HIV patients from complete blood count. *BMC Medical Physics* 2013;13(1):3.
31. Rodríguez J, Correa C. Predicción temporal de la epidemia de dengue en colombia: dinámica probabilista de la epidemia. *Rev Salud Pública* 2009;11(3):443-453.
32. Rodríguez J. Método para la predicción de la dinámica temporal de la malaria en los municipios de Colombia. *Rev Panam Salud Pública* 2010;27(3):211-8.
33. Rodríguez J, Bernal P, Prieto P, Correa C, Álvarez L, Pinilla L, et al. Predicción de unión de péptidos de Plasmodium falciparum al HLA clase II. Probabilidad, combinatoria y entropía aplicadas a las proteínas MSP-5 y MSP-6. *Archivos de alergia e inmunología clínic* 2013; 44(1): 7-14.
34. Roger VL, Go AS, Lloyd-Jones DM, et al. Heart disease and stroke statistics- 2012 update: a report from American Heart Association. *Circulation* 2012;125(1):e2-e220.
35. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2013;62:e147-e239.
36. Bacal F, Souza-Neto JD, Fiorelli AI, et al. Sociedade Brasileira de Cardiologia. II Diretriz brasileira de transplante cardiaco. *Arq Bras Cardiol* 2009; 94(1suppl1):e16-e73.
37. Bocchi EA, Fiorelli A. First Guideline Group for Heart Transplantation of the Brazilian Society of Cardiology. The Brazilian experience with heart transplantation: a multicenter report. *J Heart Lung Transplant* 2001;20(6):637-645.
38. International Registry for Heart and Lung Transplantation (ISHLT). (2016). Registries - Heart/Lung Registries. Available at: http://www.ishlt.org/registries/heartLungRegistry.asp accessed 16 January 2016.
39. Dwyer JS, Weaver A, Hughes K. Health Insurance Portability and Accountability Act. In: Reiner BI, Siegel EL, Dwyer JS Security Issues in the Digital Medical Enterprise. Jamshedpur: Society for Computer Applications in Radiology 2000;9-18.