

# Respiratory Sinus Arrhythmia Quantified with Linear and Non-Linear Techniques to Classify Dilated and Ischemic Cardiomyopathy \*

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**Abstract**— In congestive heart failure (CHF), dilated cardiomyopathy (DCM) and ischemic cardiomyopathy (ICM) are two highly related pathologies that are not fully characterized. The aim of this study is to assess respiratory sinus arrhythmia (RSA) index of the parasympathetic system, in order to discriminate between both pathologies, DCM and ICM. For this, ECG-signals of 49 subjects (12 DCM patients, 21 ICM patients, 6 ICM patients with diabetes mellitus (DM) type II and 10 control subjects) from the database HERIS II and of 173 subjects (50 DCM, 50 ICM, 15 DCM with DM type II, 15 ICM with DM type II and 47 control subjects) from the database MUSIC2 were analyzed. The RSA was quantified using linear and non-linear analysis methods (fractal dimension and entropy). The results showed a significant difference between ICM and DCM subjects ( $p=0.013$ ) with a sensitivity of 83% and specificity of 90%. Decreasing RSA values were present in CHF patients, especially in ICM patients, in comparison with healthy subjects. Alterations in the parasympathetic system due to DM were also identified.

## I. INTRODUCTION

Congestive heart failure (CHF) is a growing epidemic in Western countries with increasing incidence and prevalence. Dilated cardiomyopathy (DCM) has an incidence near to 20/10.000 new cases per annum and is responsible for almost 10.000 deaths every year in the United States [1,2]. Ischemic Cardiomyopathy (ICM) is the number one cause of death in men and the third most frequent cause of death in women. In presence of diabetes mellitus (DM), cardiovascular morbidity and mortality are increased in CHF patients compared with CHF patients without DM [3,4].

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In recent years, a higher association between CHF, DM and cardiac vagal tone has been found [5]. In addition, an increase in cardiac mortality due to an autonomic dysfunction related to cardiomyopathies was reported. Therefore, the cardiac vagal tone index, known as respiratory sinus arrhythmia (RSA), has been proposed as a parameter able to discriminate within CHF pathologies and risk levels [6].

RSA is a rhythmic fluctuation in the heart periods in the respiratory frequency, characterized by a shortening and lengthening of heart periods in phase relationship with inspiration and expirations. It is also a typical index of vagal control of the heart (parasympathetic effect) [6]. RSA can be quantified using the spectral analysis of the heart rate variability (HRV), where the high frequency component is related to the parasympathetic activity, and the low frequency is mainly related to sympathetic activity [7,8]. In this study, the main objective is the characterization of the vagal tone index using linear techniques based on the estimation of the mean and the standard deviation of the RSA and non-linear techniques such as fractal analysis by means of Higuchi Dimension, and Shannon Entropy technique. Additionally, it will be analyzed whether indices quantifying the RSA are suitable to distinguish between DCM and ICM pathologies.

## II. MATERIAL AND METHODS

### A. Datasets

In this study, two datasets (HERISII and MUSIC2) with CHF patients suffering from dilated cardiomyopathy (DCM) or ischemic cardiomyopathy (ICM), with and without diabetes mellitus (DM) type II were studied. Additionally, 57 control subjects were investigated as a reference group.

HERISII database contains high resolution ECG signals of cardiomyopathy patients recorded at the Santa Creu i Sant Pau Hospital in Barcelona, Spain. 30-minute resting (quite room, supine position, daytime) ECG recordings were acquired using a sampling frequency of 1600 Hz [9]. From the database, 49 age-matched male subjects (12 DCM patients, 22 ICM patients, 6 ICM patients with DM, and 10 control subjects), who fulfill the inclusion criteria, were selected for the RSA analyses. Due to the low number of enrolled women in the HERISII database, they were excluded from this study. Table I shows the summary of this database.

MUSIC2 database (Sudden Death in Heart Failure) contains 24-hour Holter ECGs recorded in several hospitals in Spain (200 Hz sampling frequency) [10]. From this database, an amount of 173 age-matched subjects (age was comparable to the chosen HERIS subjects) were studied (50

DCM, 50 ICM, 15 ICM plus DM type II, 15 DCM plus DM type II and 47 control subjects). Table II presents the summary of this database.

TABLE I. HERIS II DATABASE SUMMARY

	DCM	ICM	ICM+DM
N	12	21	6
Age (years)	62,22±10,12	64,23± 9,60	64,43± 9,59
BMI (kg/m <sup>2</sup> )	28,10± 4,97	27,97± 4,99	27,95± 4,65
LVDD (mm)	61,40± 6,84	61,40± 6,76	61,30± 7,12

TABLE II. MUSIC2 DATABASE SUMMARY

	DCM	ICM	DCM+DM	ICM+DM
N	50	50	15	15
Age (years)	59,8±9,7	60,2±9,4	66,4± 10,2	66,1± 8,1
BMI (kg/m <sup>2</sup> )	27,6±4,8	28,5±4,5	29,0±3,9	30,2±5,7
LVDD (mm)	66,4±10,2	61,2±7,6	65,4±7,1	61,7±4,4
<b>Female</b>				
N	20	20	5	5
Age (years)	60,1±9,1	59,5±10,2	70,8±4,8	70,6±4,8
BMI (kg/m <sup>2</sup> )	26,0±3,2	27,9±4,0	28,4±3,3	30,6±6,4
LVDD (mm)	63,7±9,1	60,0±6,2	71,4±8,0	63,2±3,8
<b>Male</b>				
N	30	30	10	10
Age (years)	60,7±9,0	61,8±8,7	61,9±11,4	61,6±11,4
BMI (kg/m <sup>2</sup> )	28,6±5,3	28,9±4,7	29,3±4,1	30,1±5,3
LVDD (mm)	68,1±10,4	62,0±8,4	62,4±5,1	61,0±4,9

### B. Estimation of Respiratory Sinus Arrhythmia

From each ECG record, a time series consisting on successive beat-to-beat (RR) intervals, the so-called tachogram, was automatically extracted using in-house software, based on threshold-based algorithms. Using an adaptive filtering algorithm, ventricular premature beats and artefacts were automatically detected and replaced by interpolated “normal” beats. After this, each tachogram was manually sighted for correctness in relation to the original ECG. Tachograms with ectopic beats and artefacts whose percentage was higher than 5% related to the total number of heartbeats have already been excluded in the run-up to this study. Due to different signal durations in both databases (HERIS: 30-min tachograms, MUSIC2: 24-hour tachograms), an in-house software algorithm searching for and saving the 30-min most stationary phase within each tachogram, which come closest to the tachograms extracted from the resting ECG recordings in HERIS, was applied on the MUSIC2 tachograms. Afterwards, on basis of the pre-processed 30-min tachograms several RSA indices were estimated.

#### – RSA extraction of the spontaneous respiratory band

To get equidistant time series, the tachograms were linear interpolated using 2 Hz as sampling frequency. After this, the tachograms were detrended to remove periodic and aperiodic cardiac variations unrelated to respiration from the tachograms. A moving polynomial filter (MPF) of 21 points and order 3 was used to filter the signals, obtaining a template [11]. This template was extracted from the original signal to obtain a mean-zero residual series. This residual series was then, filtered by Chebychev Type II pass-band filter using respiratory band frequencies (0.12 – 0.4 Hz).

Finally, the signal was analyzed considering segments of 30 seconds without overlapping [12].

#### – RSA estimation by Porges equation

To estimate the RSAML (RSA mean-log) index the average of each 30-s segment was performed, to minimize the impact of any distortion. The RSA value represents the vagal tone which affects the regulation of the heart and it is modulated by the respiration [13]. Then, the natural logarithm was determined to reduce distribution disorder. The RSALM (RSA log-mean) index was inverting the process, applying in first term the logarithm transforms and then estimating the average for each 30-s segment, given by

$$RSALM = \log\left(\text{mean}\left(RR_{epoch}^2\right)\right) \quad (1)$$

According to Porges [13], RSApsd was estimated using spectral analysis. The sum of the variances associated with the frequency band of spontaneous respiratory was desired. This sum was calculated with spectral analysis by summing the spectral densities associated.

#### – Non-linear estimators

The *Higuchi Dimension* (HD) is able to estimate the fractal dimension from a given time series using the parameter D, which allows the classification of the series according to their fractal characteristics. In severe cardiovascular events, like arrhythmias or heart attacks, a reduction in the fractal complexity results in a good predictor of mortality. The Higuchi algorithm follows the steps [14,15]:

The original time series is defined by

$$X(1), X(2), X(3), \dots, X(N) \quad (2)$$

new time series are constructed by  $X_k^m$ , being  $k$  the interval time ( $m = 1, 2, \dots, k$ ) and  $m$  the initial time.  $[\bullet]$  represents the Gauss notation.

$$X_k^m; X(m), X(m+k), X(m+2k), \dots, X\left(m + \frac{N-m}{k} k\right) \quad (3)$$

For each new time series is estimate the length of the curve by

$$Lm(k) = \frac{1}{k} \left( \sum_{i=1}^{\lfloor \frac{N-m}{k} \rfloor} (X(m+ik) - X(m+(i-1)k)) \right) \left( \frac{N-1}{\lfloor \frac{N-m}{k} \rfloor k} \right) \quad (4)$$

where  $\frac{N-1}{\lfloor \frac{N-m}{k} \rfloor k}$  is a normalization factor.

Higuchi method takes the average of  $L(k)$  considering the follow power law

$$L(k) \propto k^{-D} \quad (5)$$

Finally,  $L(k)$  is plotted against  $1/k$  (double logarithmic scale), with  $k = 1, 2, \dots, Kmax$ .  $Kmax$  is a parameter to optimize. The fractal dimension is defined as the slope of straight line in the plot. HD is estimated for each 30-s segment of signal [17].

*Shannon entropy* (SE) is extracted considering the probability of occurrence of an event, describe the level of disorder energy of the system. According to literature,

systems that describe diseases present lowest values of entropy indicating a reduction of the complexity activity, in comparison with healthy systems. The probability is calculated through

$$P(X) = \frac{\text{histogram}(X, N_{bins})}{N} \quad (6)$$

where  $X$  is the values of the vector with length  $N$ ,  $N_{bins}$  is the number of *bins* estimated by Sturges criteria [18] defined by

$$N_{bins} = 1 + 3.32 * \log(X). \quad (7)$$

Finally, SE is calculated by (with 6 as number of bins)

$$SE(X) = \sum_{x_i \in \emptyset} p(x_i) \log p(x_i) \quad (8)$$

where  $X$  represents the random variable with set of values  $\emptyset$  and probability function  $p(x_i)$ .

Differences between groups are tested by the Mann–Whitney U test and a  $p$ -value  $< 0.05$  was considered statistically significant. The quality of the results is analyzed using ROC curve (receiver operator characteristic), in terms of accuracy (Acc), sensitivity (Sn) and Specificity (Sp).

### III. RESULTS

Figure 1 shows the different RSA indices extracted from a patient. Figure 2 presents HD and SE from the same patient.

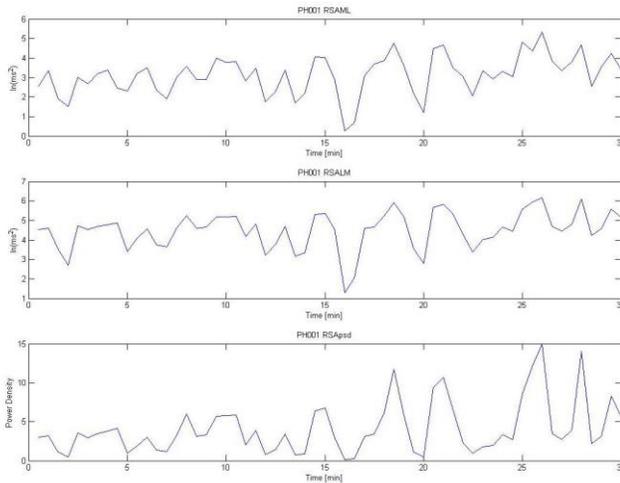


Figure 1. RSA extracted from a patient with the Porges Algorithm: Upper subplot) RSAML; Middle Subplot) RSALM; Lower subplot) RSApsd

RSAML presented statistical significance difference when comparing DCM vs ICM in HERISII database ( $p = 0.013$ ). This significance was correlated with the one obtained in MUSIC2 comparing these groups in men ( $p = 0.048$ ). Moreover, MUSIC2 presented significance ( $p = 0.04$ ) also using RSALM. These significances could be understood as the presence of a different influence of the pathology in the RSA value in men. Using ROC discriminant analysis AUC (area under the curve) = 84.4 % with a Sn=83.3% and Sp=90% were obtained in HERISII when DCM-ICM were compared.

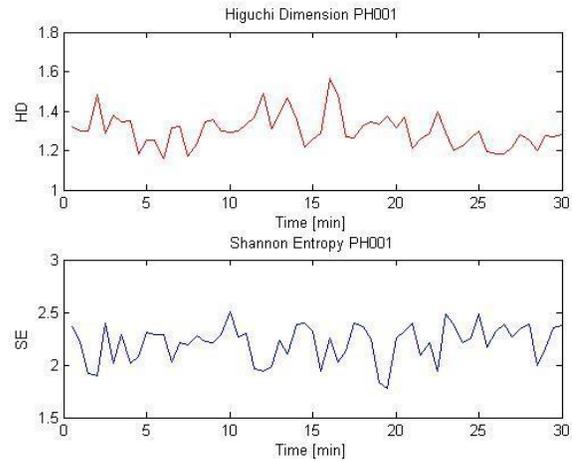


Figure 2. HD (upper) and SE (lower) of each RReepoch from the PH001 (DCM)

The presence of DM in the pathologies (DCM and ICM) resulted in a higher significant difference when both CHF pathologies were compared using RSAML ( $p = 0.009$ ) in MUSIC2. RSALM and RSApsd showed also a higher significance ( $p = 0.01$ ,  $p = 0.021$ , respectively).

Non-linear indexes were useful to discriminate illness patients from healthy subjects. Using HERIS II, significance of 0.006 have been found when matching ICM vs healthy subjects using HD index (Figure 3). It was also noticeable the decrease in the RSA values (RSAML, RSALM and RSApsd) comparing patients with healthy ones. MUSIC2 presented better results comparing DCM vs Healthy and ICM vs Healthy (Figure 4).

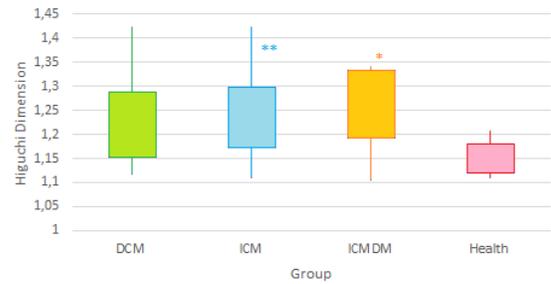


Figure 3. Comparison of HD in HERIS II between Groups. \* $p < 0.05$ , \*\* $p < 0.01$

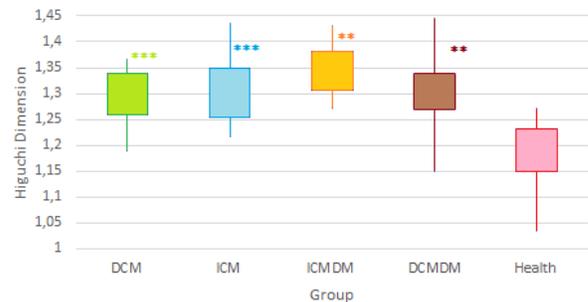


Figure 4. Box Plot HD in the different groups in MUSIC2 mixed group. \*\* $p < 0.05$ , \*\*\* $p < 0.1e-10$

Matching DCM vs healthy it was obtained significance in both non-linear indices (HD  $p = 5.41e-15$ , SE  $p=4.40e-05$ ), as well as, matching ICM vs Healthy (HD  $p=2.94e-14$ , SE  $p=4.82e-05$ ). Table III present the results obtained with the best indices.

TABLE III. AREA UNDER THE CURVE (AUC), SENSITIVITY (Sn) AND SPECIFICITY (Sp), AND P-VALUE OBTAINED WITH THE BEST PARAMETERS FOR EACH CLASSIFICATION

	Index	p-value	AUC	Sn	Sp
<b>DCM vs ICM</b>	RSAML	0.013	86.4	86.3	90.0
<b>DCM vs ICM</b>	RSAML	0.009	77.8	66.7	80.0
<b>DCM vs Healthy</b>	HD, SE	1.12e-09	86.6	88.0	85.1
<b>ICM vs Healthy</b>	HD, SE	3.64e-10	89.7	92.0	87.2
<b>DCM vs Healthy</b>	HD, SE	2.50e-03	86.7	86.7	86.7
<b>ICM vs Healthy</b>	HD, SE	1.57e-04	96.7	100.0	93.3

#### IV. DISCUSSION

In some case, decreased RSA values were present in CHF patients compared with healthy subjects. This decrease was higher in patients suffering from ICM than in DCM patients. The suggested main event that differs between ICM and DCM was the activation of the myocyte apoptosis due to ischemia. While a myocyte necrosis because of the sustained reduction in the coronary blood flow is caused by an ischemic; in DCM, there is a collagen accumulation and a fibrosis in the no infarcted myocardium that is remodeling the ventricle but not destroying it. Furthermore, greater levels of plasma noradrenaline have been reported comparing ICM against DCM, suggesting that peripheral sympathetic activation may be different and thus parasympathetic activation. Consequently, ICM seemed to present a higher risk in terms of parasympathetic dysfunction.

RSA values showed a decrease in presence of diabetes; however, no statistical significance was found between DCM with and without DM. Even in ICM patients, whose RSA decrease in presence of DM was higher, did not present significance. DM type II is associated with a heightened sympathetic tone and a decreased vagal tone.

#### V. CONCLUSION

RSA indices were used to estimate the parasympathetic dysfunction, by the vagal tone, in patients with DCM or ICM. This index demonstrated to be useful in the discrimination between pathologies and to asses a risk increase. ICM patients seemed to show a greater decrease in RSA values. The presence of diabetes mellitus type II helped to discriminate between groups and also seemed to be a risk factor in terms of autonomic dysfunction.

Non-linear techniques assessed by HD and SE showed to be useful to discriminate between patients and healthy subjects when they were studied on the RSA information from the tachogram. However, further studies are necessary to refute these conclusions.

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