

Risk Stratification in Congestive Heart Failure Patients Using a Model-Based Approach to Heart Rate Turbulence Characterization

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Abstract

Heart rate turbulence (HRT) is commonly assessed by two parameters: turbulence onset (TO) and turbulence slope (TS), both obtained by averaging RR tachograms following a ventricular premature beat (VPB). It has been recently shown that a model-based detection-theoretical approach results in HRT indices outperforming TO/TS in identifying the presence or absence of HRT. The aim of this work is to evaluate the risk stratification ability of this approach, as compared with the classical parameters TO and TS, in a population of 96 ischemic patients with mild to moderate congestive heart failure. We found significant differences (Mann-Whitney U test) between survivors and cardiac death groups for TS and the new parameter $T_{\Sigma}(x)$. Survival analysis showed that $T_{\Sigma}(x)$ is the HRT index with highest association to risk of cardiac death (hazard ratio=2.8, $p=0.008$). Results show improved risk stratification of the new description of HRT with respect to classical parameters.

1. Introduction

Heart rate turbulence (HRT) denotes the typical pattern of the heart rate subsequent to a ventricular premature beat (VPB). The turbulence consists of an early heart-rate acceleration followed by a deceleration [1, 2]. The mechanism of this phenomenon is not completely understood, but it is considered as a baroreflex response triggered by the blood pressure drop induced by the VPB.

Two indices are commonly used to assess HRT: turbulence onset (TO) and turbulence slope (TS), both obtained from the RR interval tachogram following a VPB. Turbulence onset measures the relative change in the RR immediately after the VPB, while turbulence slope quantifies the velocity of RR interval increase following the initial heart

rate acceleration.

Blunted or absent HRT, identified by a non-negative TO or a low TS, has been shown to be a powerful risk predictor in different populations, mainly in postinfarction [3] and congestive heart failure patients [4].

We have recently introduced a novel, model-based approach to HRT characterization [5]. This approach is based on an extension of the integral pulse frequency modulation (IPFM) model accounting for HRT. It is assumed that the total observed modulating signal is the sum of the background heart rate variability (HRV) and the HRT response triggered by each VPB. Modelling HRT as a linear combination of Karhunen-Loève (KL) basis functions, several statistics have been derived to detect the presence of HRT in the observed signal [5–7]. We have also shown on simulated and real data that those model-based indices outperform the classical TS, TO for detecting the presence of a HRT response [5–7].

In this work we will validate the applicability of this concept for risk stratification. For that purpose, the risk stratification ability of these new model-based HRT indices will be assessed and compared to that of classical indices in a population of patients with ischemic cardiomyopathy and mild to moderate congestive heart failure.

2. Study population

Our clinical population consists of 96 patients with mild to moderate (II-III NYHA class) congestive heart failure of ischemic etiology enrolled into the MUSIC (Muerte Súbita en Insuficiencia Cardíaca, Sudden Death in Heart Failure) study by one of the participating centers. Due to requirements for HRT calculation, only patients with sinus rhythm were included in the study. The study protocol was approved by institutional investigation committees, and all patients signed informed consent.

In this work, we used 24-hour Holter recordings (3 orthogonal leads, 200 Hz sampling frequency) performed at enrollment by means of SpiderView recorders and analyzed by ELA Medical Holter software (ELA Medical, Sorin Group). Automatic analysis was followed by manual verification to assure the proper classification of recorded beats. Data on RR intervals and corresponding annotations were exported for analysis of HRT.

VPBs unsuitable for HRT analysis were discarded, according to the criteria described in [8]. Six patients without any suitable VPB were excluded.

The final study population consisted of 90 patients (80 males, 89%) with mean age 64 ± 9 years. The mean LVEF was 36 ± 10 and most of the patients were in NYHA class II (72 patients, 80%). Patients were followed for a median of 44 months with endpoints defined as total mortality, cardiac mortality and sudden death.

3. Methods

Our approach to HRT detection is based on the modulating signal $x(t)$ of the extended IPFM model, which can be estimated from the RR interval tachograms after each VPB [5]. This signal, evenly sampled at 2 Hz, is denoted by the $N \times 1$ vector \mathbf{x} .

The observation vector \mathbf{x} has two components, the background HRV \mathbf{m} , and HRT, which can be present or not. HRT is modelled as a linear combination of r KL basis functions $\mathbf{B}\boldsymbol{\theta}_s$, where $N \times r$ matrix \mathbf{B} contains in its columns the r basis functions and $\boldsymbol{\theta}_s$ is the $r \times 1$ coefficient vector describing HRT.

We can formulate a detection problem where HRT can be either present (hypothesis \mathcal{H}_1) or not (hypothesis \mathcal{H}_0) in a given observation vector \mathbf{x} :

$$\begin{aligned} \mathcal{H}_0 : \quad \mathbf{x} &= \mathbf{m} \\ \mathcal{H}_1 : \quad \mathbf{x} &= \mathbf{B}\boldsymbol{\theta}_s + \mathbf{m}. \end{aligned} \quad (1)$$

In [6], the GLRT detector for the hypothesis test in (1) has been derived under the assumption that \mathbf{m} is a random vector distributed as a white multivariate Gaussian $\mathbf{m} \sim \mathcal{N}(\mathbf{0}, \sigma^2 \mathbf{I})$, with unknown variance σ^2 , and where $\boldsymbol{\theta}_s$ is assumed to be a known constant vector $\boldsymbol{\theta}_s = \boldsymbol{\mu}$, with $\boldsymbol{\mu}$ being a mean HRT shape vector estimated from a training dataset. The test statistic is then [6]:

$$T_\mu(\mathbf{x}) = \frac{\mathbf{x}^T \mathbf{x}}{(\mathbf{x} - \mathbf{B}\boldsymbol{\mu})^T (\mathbf{x} - \mathbf{B}\boldsymbol{\mu})} \quad (2)$$

An alternative detector is proposed in [7], based in the model in (1) but treating instead the coefficients $\boldsymbol{\theta}_x = \mathbf{B}^T \mathbf{x}$ as observations. The detection problem can be for-

mulated in the coefficient space as

$$\begin{aligned} \mathcal{H}_0 : \quad \boldsymbol{\theta}_x &= \mathbf{B}^T \mathbf{m} = \boldsymbol{\theta}_m \\ \mathcal{H}_1 : \quad \boldsymbol{\theta}_x &= \boldsymbol{\theta}_s + \mathbf{B}^T \mathbf{m} = \boldsymbol{\theta}_s + \boldsymbol{\theta}_m. \end{aligned} \quad (3)$$

Assuming that both the HRT and background HRV components are correlated multivariate Gaussian random vectors with means $\boldsymbol{\mu}$ and $\mathbf{0}$ respectively, we have $\boldsymbol{\theta}_x \sim \mathcal{N}(\mathbf{0}, \boldsymbol{\Sigma}_0)$ under \mathcal{H}_0 and $\boldsymbol{\theta}_x \sim \mathcal{N}(\boldsymbol{\mu}, \boldsymbol{\Sigma}_1)$ under \mathcal{H}_1 , where the mean HRT shape vector $\boldsymbol{\mu}$, and the covariance matrices $\boldsymbol{\Sigma}_0$ and $\boldsymbol{\Sigma}_1$ can be estimated from a labelled training set. This model offers a detailed characterization of the observations including not only the mean shape $\boldsymbol{\mu}$ but also the covariance of the three coefficients in the vector $\boldsymbol{\theta}_x$ with and without presence of HRT. Applying the Neyman-Pearson criterion, we obtain the equivalent detection statistic [7]

$$T_{\boldsymbol{\Sigma}}(\mathbf{x}) = \boldsymbol{\theta}_x^T \boldsymbol{\Sigma}_0^{-1} \boldsymbol{\theta}_x - (\boldsymbol{\theta}_x - \boldsymbol{\mu})^T \boldsymbol{\Sigma}_1^{-1} (\boldsymbol{\theta}_x - \boldsymbol{\mu}). \quad (4)$$

The KL basis functions were computed from the Long Term ST Database as explained in [6, 7]. As it is shown there, the 3 most important KL basis functions account for 95% of the energy of the modulating signals when HRT is present, and also 90% of the energy for spontaneous HRV. Therefore we will use $r = 3$ as the linear model dimension. The average turbulence shape $\boldsymbol{\mu}$, and the covariance matrices $\boldsymbol{\Sigma}_0$ and $\boldsymbol{\Sigma}_1$ used to compute the statistics $T_{\boldsymbol{\Sigma}}(\mathbf{x})$ and $T_\mu(\mathbf{x})$ were also estimated in the Long Term ST database [6, 7]. Thus, all parameters were obtained from a dataset independent of the clinical study group.

3.1. Statistical methods

The different HRT indices (classical and model-based) were computed from the averaged responses using all suitable VPBs. The cut-off points for dichotomization were the commonly used values of 0% and 2.5 ms/beat in the case of TO and TS, and the lower tertile in our population for the model-based indices.

The two-tailed non-parametric Mann-Whitney U test was used to test differences in parameters between patients in the different outcome groups. Kaplan-Meier survival functions were calculated to test the association of the classical and model-based HRT parameters with the endpoints of the study and compared using the log-rank test. Cox's univariate regression models were used for the survival analysis, expressing results as hazard ratios. Statistical significance was defined as $p < 0.05$.

4. Results

During the follow-up, 29 patients (32%) died, of which 27 from cardiovascular causes (13 of sudden cardiac death and 14 of heart failure progression). Using the common

cut-off points of 0% and 2.5 ms/beat for TO and TS, 21 patients (23%) had abnormal TO and 42 patients (47%) had abnormal TS.

Table 1 shows the differences in HRT indices and other clinical variables between patients with cardiac death and survivors. Patients who died had lower LVEF (median 33% vs 39%, $p = 0.004$) and more frequently presented higher NYHA functional class (NYHA III 44% vs 10%, $p < 0.001$).

As for parameters characterizing HRT, cardiac death victims had significantly lower values of TS and $T_{\Sigma}(\mathbf{x})$, while differences in the values of TO and $T_{\mu}(\mathbf{x})$ did not attain the significance level. Once categorized according to the previously indicated cut-off points, only the number of patients with abnormal $T_{\Sigma}(\mathbf{x})$ was significantly different between the two groups (44% vs 21%, $p = 0.030$). The rest of dichotomized indices did not achieve significance in the study group. When combining TO and TS, the number of patients with abnormal HRT (defined as at least one parameter, TO or TS, abnormal) was significantly different between the two groups (74% vs 48%, $p = 0.021$).

Patients with abnormal $T_{\Sigma}(\mathbf{x})$ index were characterized by a more than 2.5-fold higher cardiac mortality estimated at 3rd year of follow-up (45% vs 18%, $p = 0.005$). The mortality was also nearly 2-fold higher for patients stratified by TS and TO, however only in case of TS statistical significance was observed ($p = 0.043$). Kaplan–Meier curves indicating probability of cardiac death during follow-up using the respective dichotomized values are shown in Fig. 1 for $T_{\Sigma}(\mathbf{x})$ and TS. It is noteworthy that, in case of index $T_{\Sigma}(\mathbf{x})$, the Kaplan–Meier curves diverged already at the first year of follow-up (32% vs 5%), while abnormal TS was related with gradual increase in mortality risk during long-term observation.

The results of Cox’s univariate regression analysis are summarized in Table 2. Abnormal $T_{\Sigma}(\mathbf{x})$ has the strongest association with cardiac death of all the HRT indices (hazard ratio = 2.8, CI 1.32–5.97, $p=0.008$), the other index with significant but weaker association being $TS \leq 2.5$ (hazard ratio=2.2, CI 1.01–4.80, $p=0.048$). Interestingly, abnormal value of $T_{\Sigma}(\mathbf{x})$ presented also stronger hazard ratio than abnormal HRT defined as patients with at least one of the classical parameters, TO and/or TS, abnormal (HRT category 1 or 2 according to the HRT literature), indicating impaired HRT reaction according to classical approach.

5. Discussion and conclusions

In this paper, the risk stratification ability of HRT measurements has been tested in a clinical dataset of patients with ischemic cardiomyopathy and mild to moderate heart failure. We have studied classical HRT indices as well as two HRT indices based on the representation of the IPFM

Table 1. Differences in HRT indices and other clinical variables between risk groups. Data are given as mean (Median) \pm SD, or # (%). Boldface indicate significant differences.

Variable	Survivors (N=61)	Cardiac death (N=27)	<i>p</i> -value
Age (years)	63(63) \pm 8	65(68) \pm 12	0.154
Age > 65 yrs	24 (39%)	16 (59%)	0.084
Gender (males)	52 (85%)	26 (96%)	0.132
LVEF (%)	38(39)\pm10	32(33)\pm10	0.004
LVEF \leq35%	24 (39%)	20 (74%)	0.003
NYHA class III	6 (10%)	12 (44%)	<0.001
Diabetes	31 (51%)	19 (70%)	0.088
TO (%)	-1.23(-1.01) \pm 1.48	-0.62(-0.43) \pm 1.68	0.060
TO \geq 0%	11 (18%)	9 (33%)	0.114
TS (ms/beat)	4.61(3.18)\pm 4.35	3.44(1.80)\pm4.30	0.025
TS \leq 2.5	25 (41%)	17 (63%)	0.057
Abnormal HRT ¹	29 (48%)	20 (74%)	0.021
NP $T_{\Sigma}(\mathbf{x})$	2.77(0.93)\pm5.80	3.26(-0.78)\pm13.47	0.048
$T_{\Sigma}(\mathbf{x}) \leq -0.75$	13 (21%)	12 (44%)	0.030
GLRT $T_{\mu}(\mathbf{s})$	0.87(0.57) \pm 1.20	0.42(0.31) \pm 0.39	0.058
$T_{\mu}(\mathbf{x}) \leq 0.22$	18 (30%)	11 (41%)	0.301

¹ Abnormal HRT means patients with at least one abnormal classical parameter (TO \geq 0 and/or TS \leq 2.5 ms/beat).

Table 2. Univariate association of HRT risk variables with total mortality. Boldface indicates significant differences

Variable	Hazards ratio	95% CI	<i>p</i> -value
TO \geq 0%	1.79	0.81–3.99	0.152
TS \leq2.5	2.20	1.01–4.80	0.048
Abnorm. HRT¹	2.63	1.11–6.22	0.028
$T_{\Sigma}(\mathbf{x}) \leq -0.75$	2.80	1.32–5.97	0.008
$T_{\mu}(\mathbf{x}) \leq 0.22$	1.52	0.71–3.28	0.289

¹ Abnormal HRT means patients with at least one abnormal classical parameter (TO \geq 0 and/or TS \leq 2.5 ms/beat).

modulating signal after a VPB in the subspace defined by the most relevant KLT basis functions for signals with HRT, as proposed in [5, 6].

While TO and TS indices quantify the magnitude of some parts the turbulence response (the initial acceleration and the posterior recovery respectively), the model-based statistics analyse the response globally, and therefore, we can see them as HRT waveform indices.

Impaired HRT quantified by the recently proposed statistic $T_{\Sigma}(\mathbf{x})$ identified patients at high risk of cardiac death during a median of 44 months of follow-up. Patients with $T_{\Sigma}(\mathbf{x}) < -0.75$ (first tertile) had nearly 3-fold higher risk of unfavorable outcome. This is the first time when new model-based HRT indices were tested in clinical setting for predicting cardiac death and were proven to provide significant prognostic information. Our data showed that $T_{\Sigma}(\mathbf{x})$ was a stronger risk predictor than traditional HRT descriptors: TS and TO. It is worth emphasizing that abnormal $T_{\Sigma}(\mathbf{x})$ was able to determine high risk patients

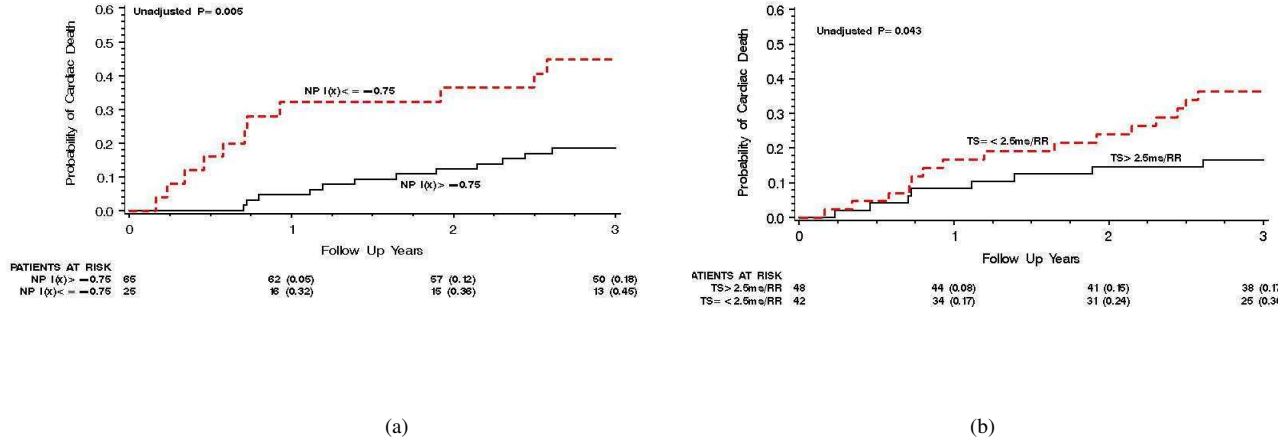


Figure 1. Kaplan–Meier mortality curves for the model-based global indices (a) $T_{\Sigma}(x)$ (b) TS. p -values are given for long-rank tests. Numbers in parenthesis below the graph represent the probability of cardiac death in the 1st, 2nd and 3rd year of the follow-up.

very early in the follow-up, identifying patients with over 6-fold higher mortality rate (32% vs 5%) in the first year of follow-up.

These promising results encourage further investigation to ascertain the predictive value of global HRT indices and its relation to other clinical variables.

Acknowledgements

This work was supported by projects TEC-2007-68076-C02-02 from CICYT, GTC T-30 from DGA (Aragon, Spain), grants from The Swedish Research Council, Gambro AB, Lund, Sweden, and CIBER de Bioingeniería, Biomateriales y Nanomedicina, which is an initiative of ISCIII (Spain).

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