Pre-Ectopic Vagal Tone Affects Heart Rate Turbulence Slope in Heart Failure

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Abstract

Cardiovascular oscillations following spontaneous ventricular premature complexes (VPC) are described by the so-called heart rate turbulence (HRT) onset (TO) and slope (TS). Since HRT is a marker of baroreflex sensitivity, it can be hypothesized to be affected by the preceding VPC sympatovagal balance (pHF). The aim of this study is to investigate the relationship between HRT parameters and pHF in heart failure (HF) patients. We studied 75 24h ECG Holter recording of HF patients (62±9 years) performing a Spearman correlation analysis between TO, TS and pHF values. According to risk stratification standards, each post-VPC response was classified in 0-normal type or 1-abnormal category.

Results showed a 53%, 27%,5%,6% of post-VPC respectively 0,1a,1b,2-category, and a remaining 9% unclassified T0=0 values. pHF showed a moderate to good significant (p<0.0001) positive correlation with TS, ranging from r=0.5 to 0.6 in 0- and 1a-category, weaker correlations has been found between pHF and T0. Conclusions demonstrated that while the early HRT phase do not seem to depend on preceding VPC sympathovagal balance, pre-ectopic vagal tone affects HR late recovery slope in HF, with correlation patterns related to different post-VPC response type.

1. Introduction

Neurohumoral activation with sympathetic overdrive and progressive hemodynamic deterioration are well known main features of heart failure (HF). Cardiac autonomic control of these patients is consequently characterized by significantly reduced heart rate variability and impaired baroreflex sensitivity [1].

A very attractive noninvasive way for an indirect baroreflex sensitivity assessment has been recently proposed by the so called heart rate turbulence (HRT) technique, consisting on studying short-term sinus cycle length fluctuations following spontaneous isolated ventricular premature complexes (VPC) [2].

The physiologic pattern of HRT consists of a brief heart rate acceleration followed by a more gradual heart rate deceleration before the rate returns to a pre-ectopic level.

Available physiologic investigations confirm that the initial heart rate acceleration is triggered by transient vagal inhibition in response to the missed baroreflex afferent input caused by hemodynamically inefficient ventricular contraction.

A sympathetically mediated overshoot of arterial pressure is responsible for the subsequent heart rate deceleration through vagal recruitment. Hence, the HRT pattern is blunted in patients with reduced baroreflex [3].

Several clinical trials confirmed in the last years a growing interest in this technique, reporting HRT indexes strongly correlated with the severity of HF [4], as powerful independent predictors of decompensation and sudden death in this pathology [5-7] and showing a good reproducibility in this study population [8].

Despite a recent written consensus on the standard of HRT measurement and clinical use has been reached [9], a number of issues still remain poorly understood and in need of further investigation.

Since HRT is a marker of baroreflex sensitivity, it can be hypothesized to be affected by the state of the sympathovagal balance. A reduction of HRT has been observed at high heart rate [10] and these observation lead to the possibility of correcting HRT indexes for heart rate [11], but presently available data offer no practical guidance for such a correction.

Very few papers reported correlation studies between mean heart rate and HRT indexes over 24 hours Holter ECG recordings in normals and coronary patients [10-11]. Mean HRT indexes describe an averaged post-VPC response composed by the sum of very different types of response, each one can be related not to a global mean heart rate but to the specific starting condition of sympatovagal balance before the occurrence of the VPC episode.

There are no previous studies addressing such issue and the aim of this paper is to investigate the relationships between HRT parameters and pre-ectopic vagal tone in heart failure subjects.

2. Study population and Holter analysis

We studied 75 twenty-four-hours ECG Holter recording of clinically stable heart failure patients in sinus rhythm (see Table 1 for clinical details of the population).

All recordings were performed by a portable three-channel tape recorder and processed by a Marquette 8000 T system with a sampling frequency of 128 hertz. In order to be considered eligible for the study, each recording had to have at least 12 hours of analyzable RR intervals with at least half of the night time (from 00:00 AM trough to 5:00 AM) and half of the daytime (from 7:30 AM trough to 11:30 PM) analyzable periods [12].

Each beat was labeled as normal, VPC or aberrant according to recognition by the algorithm for tape analysis and after an investigator's verification. To avoid over- or under-estimation of HRT indexes related to the number of VPC, recordings with less than 10 VPC per 24 hours were excluded from the analysis [11].

3. Heart rate turbulence analysis

Accordingly to standards of measurements [9], HRT were estimated by two numerical descriptors: turbulence onset (TO), reflecting the initial phase of sinus rhythm acceleration and turbulence slope (TS), describing deceleration phase.

TO was defined as a percentage difference between the mean of the first two RR intervals following the compensatory pause after a VPC and the last two sinus RR intervals before a VPC.

TS was described as the maximum positive slope of a regression line assessed over any of 5 consecutive RR intervals within the first 15 sinus RR intervals after a VPC. Both indexes were separately calculated for each isolated VPC.

For each VPC, pre-ectopic vagal tone has been assessed by heart rate variability frequency domain analysis and exactly by spectral power in high-frequency band from 0.15 to 0.4Hz over 64 normal RR values preceding VPC, so in a window containing about 10 to 24 cycles of HF.

Filtering algorithms were used to eliminate inappropriate RR intervals and VPC with overly long coupling intervals or overly short compensatory pauses. Filtering algorithms excluded from the HRT calculation RR intervals with the following characteristics: <300 ms, >2000 ms, >200 ms difference to the preceding sinus interval, and >20% difference to the reference interval (mean of the 5 last sinus intervals). In addition, HRT calculation has been limited to VPC with a minimum prematurity of 20% and a post-extrasystole interval that is at least 20% longer than the reference interval (mean of last 5 sinus RR intervals).

All analysis are been performed by HRT-LAB, a customized Matlab [13] software toolbox developed by authors.

Table 1. Study population data. All data expressed as mean ± standard deviation.

Age	69±9, males
LVEF, Left Ventr. Ejection Frac.	28±7 %
NPE, plasma norepinephrine levels	344±156 pg/L
V02max, max. oxygen consumption	12±2 mL/Kg·min
NYHA, New York Heart Ass. class	II(40%)-III(60%)

Table 2. Holter analysis. All data expressed as mean ± standard deviation.

VPC number per 24 hours	169±80
HR, mean heart rate	840±148 ms
TO, turbulence onset	-0.7±3.0 %
TS, turbulence slope	9.5±8.0 ms/RR

Table 3. Post-VPC category responses. Related TO and TS values in the second column. Percentages values of studied post-VPC responses in the studied HF population in the third column.

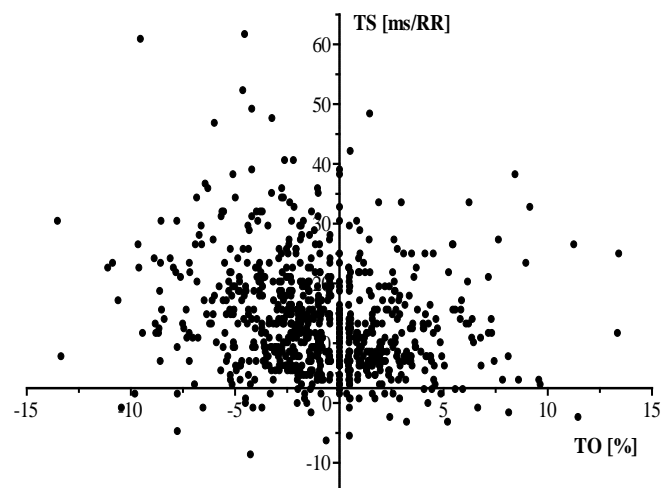| Category	Condition	%
0-category normal response	TO<0&TS>2.5	53
1a-category abnormal response	TO>0&TS>2.5	27
1b-category abnormal response	TO<0&TS<2.5	5
2-category abnormal response	TO>0&TS<2.5	6
TO=0-category abnorm. response	T0=0	9

Figure 1. Example of 24h ECG Holter analysis of HRT indexes in a HF patient. Origin of axes in TO = 0 and TS = 2.5. Post-VPC normal responses in the upper left quadrant.

4. HRT pattern classification

In most clinical studies, mean TO<0% and TS>2.5 ms/RR interval are considered normal. Therefore in risk stratification studies HRT values are usually classified into 3 categories: 1) HRT category 0 means TO and TS are normal; 2) HRT category 1 means 1 of TO or TS is abnormal; and 3) HRT category 2 means both TO and TS are abnormal [9]. A single TO and TS mean value over a twenty-four-hours ECG Holter recording describes an averaged HRT behavior behind which there is a complexity of different post-VPC responses. In the example of Figure 1, although the TO and TS mean value lie in the upper left quadrant, (TO<0% and TS>2.5 ms/RR) there is a significant number of different post-VPC responses lying in the remaining others three quadrants. Therefore in this study we decided to separately classify each post-VPC response as normal or abnormal according to definitions reported in the first two columns of Table 3.

5. Statistical analysis

Since the same pre-ectopic vagal level can be associated to different types of post-VPC responses, and an overall correlation analysis would obviously describe only a random behavior, we separately studied the correlation relationships in the different response categories. D'Agostino-Pearson normality test was used to assess the Gaussian distribution of all variables, and, due to the significant data skewness ($p>0.05$ for all), all the correlations have been performed by Spearman correlation analysis. All statistics have been performed by GraphPad Software [14].

6. Results

From initial 11.722 isolated VPC detected, we studied 3.890 VPC episodes matching the requirements of at least 64 preceding normal beats. Table 2 indicates the mean values of the performed HRT Holter analysis for the overall studied population. Data in Table 3 show the percentages of the different types of post-VPC episodes studied. The last row indicate a 9% of unclassified post-VPC responses with a TO value equal to zero which cannot be attributed to any of the other categories. Since the largest amount (most of the 80%) of the post-VPC episodes falls in the first two categories of Table 3, correlation analysis data reported in this paper have been limited to 0 and 1a-category cases. Looking to the results in Table 4, pHF showed a moderate to good significant ($p<0.0001$) positive correlation with TS, ranging from r= 0.5/0.6 in 0- and 1a-category, while weaker correlations has been found between pHF and T0.

Table 4. Spearman correlation analysis, r value and $p<0.0001$ for all.

	Normal responses 0-category	Abnormal responses 1a-category
TS vs. pHF	0.5***	0.6***
TO vs. pHF	- 0.3***	0.2***

7. Discussion

The study shows that pre-ectopic vagal tone affects HRT in HF patients highlighting the following three novel findings.

The first one is that pre-ectopic vagal tone affects much more TS than TO. This can be interpreted by the consideration that TO is a HRT index reflecting very instantaneous changes based over 4 RR intervals whereas TS reflect a recovering transient response over a longer 15 RR time scale. Therefore, TS is more likely to be influenced by pre-ectopic vagal tone than TO.

The second is that in normal 0-category responses pre-ectopic vagal tone affects HRT in a way that higher pre-ectopic vagal tone enhances the response resulting in a slight lowering TO and a more marked increasing TS.

The third is that in abnormal 1a-category responses this enhanced response is only due to a marked increasing TS with a negligible sign reversing increasing of the TO.

The mechanisms responsible for heart rate modulation of HRT are not completely understood. Two possible and nonexclusive explanations have been proposed [15].

First, the association of HRT and heart rate can be interpreted as a consequence of shared sympathovagal modulation. Second, heart-rate dependency of HRT may reflect intrinsic sinus nodal properties, specifically the nonlinear relationship between vagal neural activity and the rate of diastolic depolarization of pacemaker cells [16].

8. Conclusion

HRT is a very interesting baroreflex response of the autonomic system to hemodynamically inefficient ventricular contraction with wide and powerful clinical applications in several cardiac pathologies.

The study demonstrated that pre-ectopic vagal tone affects HRT with different correlation patterns related to normal and abnormal post-VPC response in HF patient and that TS is more influenced than TO values.

This associations suggests that can be difficult to compare HRT indexes in patients with substantially different vagal tone levels and that the existence of different correlation patterns related to normal and abnormal post-VPC responses must be take into account for suggested HRT adjustment algorithms for HR.

References

[1] Mortara A, La Rovere MT, Pinna GD, Prpa S, Maestri R, Febo O, Pozzoli M, Opasich C, Gavazzi L. Arterial baroreflex modulation of heart rate in chronic heart failure: clinical and hemodynamic correlates and prognostic implications. Circulation 1997;96(10):3450-3458.

[2] Schmidt G, Malik M, Barthel P, Schneider R, Ulm K, Rolnitzky L, Camm AJ, JT Bigger Jr JT, SchömigA. Heart-rate turbulence after ventricular premature beats as a predictor of mortality after acute myocardial infarction. Lancet 1999;353(9162):1390-1396,

[3] Voss A, Baier V, Schirdewan A, Leder U. Physiological hypotheses on heart rate turbulence. Dynamic Electrocardiography, Malik M, Camm AJ editors, Oxford: Blackwell Publishing, 2002:203–210.

[4] Cygankiewicz I, Zareba W, Vazquez R, Vallverdu M, Cino J, Cinca J, Almendral J, Gonzalez-Juanatey JR, Macaya C, Valdes M, Caminal P, Bayes de Luna A. Relation of heart rate turbulence to severity of heart failure. Am J Cardiol 2006;98(12):1635-1640.

[5] Grimm W, Schmidt G, Maisch B, Sharkova J, Muller HH, Christ M. Prognostic significance of heart rate turbulence following ventricular premature beats in patients with idiopathic dilated cardiomyopathy. J Cardiovasc Electrophysiol 2003;819-824.

[6] Moore RK, Groves DG, Barlow PE, Fox KA, Shah A, Nolan J, Kearney MT. Heart rate turbulence and death due to cardiac decompensation in patients with chronic heart failure. Eur J Heart Fail. 2006;6:585-590.

[7] Cygankiewicz I, Zareba W, Vazquez R, Vallverdu M, Gonzalez-Juanatey JR, Valdes M, Almendral J, Cinca J, Caminal P, de Luna AB. Muerte Subita en Insuficiencia Cardiaca Investigators. Heart rate turbulence predicts all-cause mortality and sudden death in congestive heart failure patients. Heart Rhythm 2008;8:1095-1102.

[8] D'Addio G, Cesarelli M, Corbi GM, Romano M, Furgi G, Ferrara N, Rengo F. Reproducibility of Heart Rate Turbulence Indexes in Heart Failure Patients, Conf Proc IEEE Eng Med Biol Soc. 2010;2573-2576.

[9] Bauer A , Malik M, Schmidt G, Barthel P, Bonnemeier H, Cygankiewicz I, Guzik P, Lombardi F, Müller A, Oto A, Schneider R, Watanabe M, Wichterle D, Zareba W. Heart rate turbulence: standards of measurement, physiological interpretation, and clinical use: International Society for Holter and Noninvasive Electrophysiology Consensus. J Am Coll Cardiol. 2008;52(17):1353-1365.

[10] Schwab JO, Eichner G, Veit G, Schmitt H, Lewalter T, Luderitz B. Influence of basic heart rate and sex on heart rate turbulence in healthy subjects. Pacing Clin Electrophysiol 2004;27:1625–1631.

[11] Cygankiewicz I, Wranicz JK, Bolinska H, Zaslonka J, Zareba W. Relationship between heart rate turbulence and heart rate, heart rate variability, and number of ventricular premature beats in coronary patients. J Cardiovasc Electrophysiol 2004;15:731–737.

[12] Kleiger RE, Bigger JT, Bosner MS, Chung MK, Cook JR, Rolnitzky LM, Steinman R, Fleiss JL. Stability over time of variables measuring heart rate variability in normal subjects. Am J Cardiol. 1991;68(6): 626-630.

[13] MATLAB® for Windows, The MathWorks, Inc. Natick, MA USA, http://www.mathworks.com

[14] GraphPad Prism for Windows, GraphPad Software, San Diego California USA, www.graphpad.com.

[15] Melenovsky V, Simek J, Sperl M, Malik J, Wichterle D. Relation between actual heart rate and autonomic effects of beta blockade in healthy men. Am J Cardiol 2005;95:999-1002.

[16] Zaza A, Lombardi F. Autonomic indexes based on the analysis of heart rate variability: a view from the sinus node. Cardiovasc Res 2001;50:434–442.

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