Are they reproducible in Heart Failure Patients? the Heart Rate Turbulence Indexes

G. CORBI 1, G. D'ADDIO 2, N. FERRARA 1,2, CESARELLI M 3

1 Dpt of Medicine and Health Sciences
University of Molise
via Giovanni Paolo II - Località Tappino, Campobasso
ITALY

2 S. Maugeri Foundation, IRCCS, Rehabilitation Institute of Telese-Campoli,
via Bagni Vecchi 1, Telese Terme
ITALY

Dpt of Biomedical,
Electronic and Telecommunication Engineering,
University “Federico II”,
Naples
ITALY

e-mail address: graziamaria.corbi@unimol.it

Abstract: Cardiovascular oscillations following spontaneous ventricular premature complexes (VPC) are characterized by a short-term heart rate fluctuation known as heart rate turbulence (HRT) described by the so-called turbulence onset (TO) and slope (TS). Despite a recent written consensus on the standard of HRT measurement, reproducibility data are lacking. Aim of the paper was a reproducibility study of HRT indexes in heart failure patients (HF). Eleven HF patients underwent two 24h ECG Holter recordings, spaced 7±5 days. A paired t test was used to assess the clinical stability of patients during the study period and the number of PVC in Holter recordings’ couples. Both TO and TS indexes were calculated for each isolated VPC, and due to their skewed distribution, reproducibility of median and mean TO and TS was studied by Bland-Altman technique. Results showed that median HRT indexes might be preferred to commonly suggested mean values and that, although TO showed lower bias value than TS, TS can be considered much more reproducible than TO, comparing limits of agreements with normal values. This preliminary results suggest the use of medians instead of mean HRT indexes values and a reliability of the turbulence slope greater than the turbulence onset index.

Keywords: turbulence, heart failure, heart rate variability, baroreflex, ventricular ectopic complex, turbulence onset, turbulence slope

1 Introduction

Heart failure (HF) is characterized by neurohumoral activation with sympathetic overdrive and progressive hemodynamic deterioration, with a significantly reduced heart rate variability and impaired baroreflex sensitivity [1]. In fact the analysis of heart rate variability is a well recognized non-invasive tool to investigate the cardiovascular autonomic control especially in HF patients [2-4], but also in other pathological conditions [5-9].

Between different methods to evaluate the HRV [10,11] an indirect and noninvasive baroreflex sensitivity assessment is represented by heart rate turbulence (HRT) technique, consisting on the study of short-term sinus cycle length fluctuations following spontaneous isolated ventricular premature complexes (VPCs) [12].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 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 [13]. In the last years several trials confirm a growing interest in this technique, reporting HRT indexes strongly correlated with the severity of HF [14, 15] and as powerful independent predictor of decompensation and sudden death in this pathology [16-18].

Despite a recent written consensus on the standard of HRT measurement and clinical use has been reached [19], a number of issues still remain poorly understood and need further investigation [20]. Particularly reproducibility data are lacking and would be of clear interest [19]. Aim of the paper was the evaluation of short-term reproducibility of HRT indexes in patients with stabilized HF. Reproducibility represents a basic methodological study for clinical settings and this is the first paper addressing such issue.

2 Study Population

Eleven patients (62 ± 10 years old, males) with clinically stable HF in New York Heart Association functional class II-III, in sinus rhythm, admitted to the “Heart Failure Unit of Maugeri Foundation Institute of Telese Terme” were studied. All patients underwent two 24 hours ECG Holter recordings spaced 7±5 days. The day after the Holter recording, were performed clinical and laboratory examinations, including 2D echocardiography for left ventricular ejection fraction (LVEF) evaluation, ECG stress test for maximal oxygen consumption (VO2max) estimation and a blood sample for plasma norepinephrine assay (NPE), assessed by a single-isotope radioenzymatic method, in all selected subjects.

3 Holter Analysis

Twenty-four-hours ambulatory ECGs were recorded with a portable three-channel tape recorder and processed by a Oxford, Laser Holter Marquette 8000T system with a sampling frequency of 128 Hz. In order to be considered eligible for the study, each recording had to have at least 12 hours of analyzable periods [21]. Each beat was labeled as normal, VPCs or aberrant according to recognition by the algorithm for tape analysis and after an investigator’s verification.

4 Heart Rate Turbulence Analysis

Accordingly to standards of measurements [8], HRT was 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 VPCs and the last two sinus RR intervals before a VPCs. 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 VPCs. Both indexes were separately calculated for each isolated VPCs. Filtering algorithms were used to eliminate inappropriate RR intervals and VPCs 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) [19]. In addition, HRT calculation has been limited to VPCs 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) [19]. All analyses were performed by HRT-LAB, a customized Matlab [22] software toolbox developed by the authors.

5 Statistical Analysis

A paired t test has been used to assess the clinical stability of patients during the study period and the number of PVCs in Holter recordings’ couples. Since estimation of HRT indexes is sensitive to the number of VPC [23], effectiveness of pairing between number of studied VPC for each patient in the two studies was assessed by calculating the Pearson correlation coefficient, r, and a corresponding P value. The variables describing the hemodynamic status, neurohormonal activation and exercise performance were analyzed by repeated measures ANOVA.
To exclude clear outliers values, the first and last percentile of the TO and TS distributions has been cut. D’Agostino-Pearson normality test (p<0.05) was used to assess the normality of all TO and TS distributions.

Reproducibility has been studied by Bland-Altman technique [24,25], plotting the difference between the two repeated measurements against their mean value, which can be assumed as the best estimate that we have of the true value. Removing the variation between subjects, Bland-Altman plots describe the bias and the standard deviation respectively as the average and the standard deviation of the difference between the two measures. The last one was used to calculate the limits of agreement, computed as the mean bias plus or minus 1.96 times its standard deviation, accordingly to definition of repeatability coefficient [26]. Any future measure should lie within the limits of agreement approximately the 95% of the time. All statistics were performed by GraphPad Software [27].

6 Results
The study population did not show any change in clinical conditions.

The variables describing the hemodynamic status, neurohormonal activation and exercise performance, as reported in Table 1, showed relatively clinical stable conditions of the patients during the study period.

Since the HRT indexes evaluation is based on the number of isolated VPCs detected in the Holter recording, for each patient only couples of recordings with approximately the same number of VPCs and at least 50 VPCs per Holter (Table 2) were compared.

Table 1: Assessment of patients’ clinical stability during the study period

<table>
<thead>
<tr>
<th></th>
<th>Study 1</th>
<th>Study 2</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEF</td>
<td>28 ± 7</td>
<td>27 ± 4</td>
<td>0.87</td>
</tr>
<tr>
<td>NPE</td>
<td>344 ± 156</td>
<td>351 ± 160</td>
<td>0.36</td>
</tr>
<tr>
<td>V02max</td>
<td>12 ± 2</td>
<td>13 ± 2</td>
<td>0.23</td>
</tr>
</tbody>
</table>

P value for all variables in third column; Left ventricular ejection fraction [%] in the first row; plasma norepinephrine levels [pg/L] in the second row; maximal oxygen consumption [(mLxkg-1x min-1] in the third row. All data expressed as mean ± standard deviation.

Since TO and TS showed highly skewed non-gaussian distribution (D’Agostino-Pearson normality p test >0.05 for almost all recordings) their medians differed from mean values. The average median and mean TO and TS values in the two studied recordings are shown in Table 3.

Table 2: Number of isolated VPCS in the Holter recordings

<table>
<thead>
<tr>
<th></th>
<th>Study 1</th>
<th>Study 2</th>
<th>p</th>
<th>pairing r</th>
<th>pairing p</th>
</tr>
</thead>
<tbody>
<tr>
<td>205 ± 190</td>
<td>154 ± 142</td>
<td>0.10</td>
<td>0.88</td>
<td>0.0002</td>
<td></td>
</tr>
</tbody>
</table>

P value in third column; Pearson correlation coefficient between studies and related p value in fourth and fifth column. All data expressed as mean ± standard deviation.

Since TO and TS showed highly skewed non-gaussian distribution (D’Agostino-Pearson normality p test >0.05 for almost all recordings) their medians differed from mean values. The average median and mean TO and TS values in the two studied recordings are shown in Table 3.

Table 3: Average median and mean to and ts values in the two studies

<table>
<thead>
<tr>
<th></th>
<th>Study 1</th>
<th>Study 2</th>
<th>Study 1</th>
<th>Study 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median</td>
<td>-0.55±0.87</td>
<td>-0.65±1.12</td>
<td>6.75±3.59</td>
<td>7.42±3.62</td>
</tr>
<tr>
<td>Mean</td>
<td>-0.38±0.93</td>
<td>-0.60±1.46</td>
<td>7.44±3.95</td>
<td>8.57±4.55</td>
</tr>
</tbody>
</table>

Mean ± standard deviation values for all variables in the two studies. P value > 0.05 for all

All bias and limits of agreement values are reported in Table 4.

Table 4: Bias and limits of agreement values of Bland Altman plots

<table>
<thead>
<tr>
<th></th>
<th>TO</th>
<th>TS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median</td>
<td>0.10</td>
<td>0.22</td>
</tr>
<tr>
<td>Mean</td>
<td>-0.68</td>
<td>-1.12</td>
</tr>
<tr>
<td>SD of Bias</td>
<td>0.75</td>
<td>1.35</td>
</tr>
<tr>
<td>95% Limits of Agreement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>From</td>
<td>-1.37</td>
<td>-2.43</td>
</tr>
<tr>
<td>To</td>
<td>1.57</td>
<td>2.87</td>
</tr>
</tbody>
</table>

In the first two rows the bias and its standard deviation between the two measures for all medians and mean TO and TS values. In the last two rows the related 95% limits of agreement.

Fig. 1 and 2 show Bland-Altman plots of TO median and mean values, and Fig. 3 and 4 of TS median and mean values.

7 Discussion
These results suggest that median values of HRT indexes might be preferred to commonly suggested mean values [19] for different reasons. In fact, since TO and TS showed highly skewed non-gaussian distribution, they are better described by median than mean values. Practically algorithms for
evaluation of HRT indexes cannot exclude singles TO and TS outliers values and the median is much less sensitive than mean to outliers. Moreover, by a methodological point of view the median TO and TS values showed higher reproducibility than means, which exhibit quite double bias and limit of agreement values. Although TO showed narrower limits of agreements than TS, the latter can be considered much more reproducible than the former. By considering the data showed in Table 3 mean TO values were between -0.60 and -0.38%, while mean TS values were between 7.44 and 8.57 ms/RR. Studies in normal healthy volunteers [28-31] reported mean TO values ranged from -2.7% to -2.3% and mean TS ranged from 11.0 to 19.2 ms/RR interval. Thus for TO, the difference between means, from Normal to HF patients, is of about 2%, which is just less than 1.5 times the standard deviation of bias reproducibility error of 1.35 shown in Table 4. Differently for TS, the difference between means, from Normal to HF patients, is of about 7 ms/RR, which is at least more than 4 times the standard deviation of bias reproducibility error of 1.62 shown in Table 4.

Consequently, the estimation of TS can be considered to show a sufficient degree of reproducibility, in contrast to what happens for TO. Moreover, the data on Bland-Altman plots did not show any difference. In fact, the variability between the two measures was consistent across the graph and the scatter around the bias line was unrelated to their average.

8 Conclusions
HRT is going to have wide and interesting clinical applications, showing very high prognostic value in several cardiac diseases. The importance of reproducibility data knowledge about this technique is at the base of a more accurate use of the information related to the HRT indexes. Preliminary results of this paper suggest the use of HRT indexes median values instead of mean values and a reliability of the turbulence slope that appears greater than the turbulence onset index. Future extension of the work should be addressed to perform similar reproducibility study toward wider and different cardiac pathological populations.
References


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


