Heart rate turbulence in patients with chronic heart failure

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Abstract

Background: Heart rate turbulence (HRT) has been shown to predict the prognosis after myocardial infarction (MI), but its prognostic value in patients with chronic heart failure (CHF) has not yet been well established.

Aim: To evaluate HRT in patients with CHF and assess the prognostic significance of HRT in this group.

Methods: The study group consisted of 82 patients with CHF and left ventricular ejection fraction (LVEF) <35%. All the patients underwent 24-hour Holter monitoring (HM). The heart rate variability (HRV) and HRT parameters were assessed using HRT view software. Two HRT parameters – turbulence slope (TS) and turbulence onset (TO), were calculated. We analysed the clinical course and survival during a two-year follow-up (mean 25±9 months).

Results: The patients were divided into three groups according to the HRT parameters. Group 1 (23 patients) with both normal TO and TS (TO <0%, TS >2.5 m/s), group 2 (30 patients) with abnormal TO or TS, group 3 (29 patients) with abnormal TO and TS (TO >0% and TS <2.5 m/s). Patients from group 1 was significantly younger. There were no differences between patients in aetiology, treatment and the frequency of ventricular premature beats. Significant correlations between HRV and HRT parameters were observed. The correlation was the strongest between TS and SDNN and LF. During the follow-up 9 patients died and 15 were hospitalised for non-fatal infarction or worsening of CHF. Using a multivariate logistic regression model, it was shown that TS <2.5 ms/RR interval, and non-sustained ventricular tachycardia (VT) significantly increased the risk of a serious cardiac events in CHF patients.

Conclusion: HRT parameters are often abnormal in patients with CHF. An abnormal turbulence slope (TS) and VT episodes are significantly associated with increased risk of cardiac complications in CHF.

Key words: cardiac heart failure, prognosis, heart rate turbulence

Introduction

In recent decades patients with chronic heart failure (CHF) are the most dynamically growing population with cardiovascular disease. Despite medical progress, the mortality rate is very high in this group, including sudden deaths in about 30-50% of patients. Therefore, risk factors of death in CHF patients have been a subject of interest for many years [1-3]. Based on ambulatory ECG monitoring traces it was documented that almost 80% of sudden cardiac arrests resulted from ventricular tachycardia (VT) or ventricular fibrillation [4]. However, the pathogenesis of sudden death has never been fully explained. Most likely the complex and multifactorial mechanisms lead to sudden death preceded by lethal arrhythmia. This unfavourable sequence of events includes significant structural abnormalities of myocardium promoting the re-entry phenomenon. In addition, the role of triggering and modifying factors must be mentioned, including an important role of disturbances of the autonomic nervous system [5].

Ambulatory ECG monitoring allows for an indirect evaluation of autonomic system impact on heart rate by means of a number of electrocardiographic parameters describing dynamics of heart rate variability (HRV) and abnormal repolarisation. In 1999 Schmidt et al. introduced heart rate turbulence (HRT) as a new non-invasive predictor of overall mortality of myocardial infarction (MI) survivors [6]. Heart rate turbulence represents the physiological biphasic sinus rhythm response to premature ventricular beats, involving a short initial acceleration followed by a deceleration of the sinus rhythm rate due to baroreflex.

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Heart rate turbulence is quantified by two parameters: (1) turbulence onset (TO), which describes the early acceleration phase of HR following a premature ventricular beat; and (2) turbulence slope (TS), which describes the dynamics of late deceleration of HR after a premature ventricular beat. Such a biphasic sinus node response is observed in healthy individuals or in low-risk patients and is disturbed in subjects with significant cardiovascular pathology.

The reports of Schmidt et al. initiated a series of studies which supported the finding that abnormal HRT is a well documented risk factor of overall mortality rate in patients with ischaemic heart disease [6-8]. There are also reports evaluating HRT in patients with non-ischaemic cardiomyopathy and CHF, but the prognostic value of HRT in this subset of patients has not yet been well established [9-11]. However, in the light of current opinions on CHF pathogenesis, highlighting the role of early neurohormonal activation, it may be speculated that dynamic ECG indices, including HRT, may have a prognostic value.

The aim of our study was to: (1) determine the prevalence of abnormal HRT in patients with CHF, (2) assess the correlation between HRT and HRV variables, (3) determine the prognostic value of classic and dynamic ECG variables such as ventricular arrhythmia, HRV and HRT in CHF patients.

Methods

The study enrolled 82 patients with known systolic CHF with underlying dilated cardiomyopathy (n=37) or ischaemic heart disease (45 patients with a history of MI). Heart failure aetiology was determined based on medical history and patients’ records. This was also used for evaluation of clinical condition including NYHA class. Left ventricular ejection fraction (LVEF) was determined using echocardiography. The NT-proBNP levels were measured with the electroluminescence method. Each patient had 24-hour ECG monitoring.

The following inclusion criteria were set: (1) LVEF ≤35%, (2) heart failure NYHA class II or III, (3) stable coronary artery disease in patients with ischaemic aetiology, and (4) sinus rhythm.

Study exclusion criteria were: (1) hospitalisation due to CHF worsening within 6 months, (2) implanted permanent pacemaker, (3) permanent or paroxysmal atrial fibrillation, (4) no premature ventricular beat on 24-hour ECG monitoring.

Twenty-four hour ECG recording and analysis were performed using the Pathfinder 700, DelMar Reynolds equipment. The analysis included arrhythmia, HRV and HRT assessment.

Arrhythmia analysis typically included mean, maximum and minimum HR, presence of beats and non-sustained VT.

Heart rate variability analysis was performed according to guidelines of the European Society of Cardiology and North American Society of Pacing and Electrophysiology [12]. Heart rate variability assessment was carried out following elimination of artefacts and arrhythmias from the records. Time domain analysis was performed from the whole 24-hour ECG records and the following parameters were used: SDNN, rMSSD and triangular index. Frequency domain analysis used fast Fourier transformation to determine total power (TP), low frequency power (LF: 0.04-0.15 Hz) and high frequency power (HF: 0.15-0.4 Hz), as well as LF/HF ratio. Power spectrum for both frequencies was expressed as ms². Each ambulatory ECG monitoring hour was split into 5-minute segments. For HRV power spectrum analysis, a 5-minute strip was chosen from each hour with the lowest exclusion rate among the first 4 fragments. The LF and HF values were calculated as the mean from the analysed ECG strips.

Heart rate turbulence analysis was carried out using the HRT View software available for research from the method’s authors (the algorithm available at www.h-r-t.org). Two parameters were assessed: turbulence onset (TO) and turbulence slope (TS). TO was expressed as percentages. Normally this variable has negative values as a premature beat brings out a short lasting sinus rhythm acceleration. When TO tends above 0 it suggests lack of sinus rhythm response to ventricular beat or sinus deceleration (abnormal response). On the other hand, TS is defined as a maximum positive slope of regression line calculated for each sequence of 5 consecutive RR intervals of sinus rhythm following the ventricular beat within the first 15 sinus beats after extrasystole. TS was expressed as ms per RR interval. TO was calculated separately for each ventricular beat and then averaged for all ventricular beats. TS was calculated based on the averaged tachogram after a compensatory pause. Abnormal HRT parameters were determined according to the cut-off values suggested by the method’s authors (abnormal TO ≥0% and TS ≤2.5 ms/RR).

Based on the TS and TO values patients were divided into the following groups:

• Group 1: with both parameters within normal limits.
• Group 2: with one of the parameters abnormal (TO or TS).
• Group 3: with both parameters outside the normal limits.

Mean follow-up period was 25±9 months. The composite endpoint comprised all-cause mortality and cardiovascular hospitalisation. Deaths were classified as cardiac and non-cardiac, and the former ones were divided into sudden and non-sudden. Sudden cardiac death was defined as death due to cardiac or cardiovascular dysfunction up to one hour after acute clinical presentation. Follow-up endpoints also included hospitalisations due to MI, worsening of CHF or arrhythmia (symptomatic, poorly tolerated arrhythmia including episodes of sustained VT).
Statistical analysis

Depending on the data distribution pattern the continuous variables are presented as mean ± standard deviation (normal distribution) or median (nonparametric distribution). Categorical variables are presented as absolute value and percentages. Kolmogorov-Smirnov test was used to check for normal distribution of variables. Two-sided Student’s t-test was applied for two independent samples or univariate analysis of variance for three independent groups was applied to compare mean values of normally distributed continuous variables in the study groups. The Newman-Keuls test was used for multicomparative analysis. If the variable distribution in at least one group failed to match the normal pattern or the variable was ordinal, a Mann-Whitney test for two independent samples or the Kruskal-Wallis test for three independent samples was used. Categorical variables were compared with Fisher’s exact test or chi-square test. A multivariable logistic regression model was used to evaluate the prognostic value of analysed variables. The model included variables that differentiated groups with or without an analysed endpoint with p <0.1. The relationship between HRT and HRV parameters was assessed with Spearman correlation. A p value < 0.05 was considered significant. All analyses were performed with MedCalc software, ver. 7.4.12.

Results

The study involved 82 patients (30 females, mean age 53±14 years) with systolic CHF. Ischaemic cardiomyopathy was the underlying cause in 45 patients and dilated cardiomyopathy – in 37 patients. TO ranged from –4.11% to 3.53% (median –0.51), while TS ranged from 0.82 ms/RR to 10.1 ms/RR (median 3.19). Group 1 included 23 (28%), Group 2 – 30 (36.6%), and Group 3 – 29 (35.4%) patients. Thus, 72% of patients (Groups 2 and 3) had at least 1 abnormal HRT parameter.

Table I presents demographic and clinical data, including CHF cause, mean disease duration, treatment used, mean LVEF and mean NT-proBNP levels. There was a significant difference between the study groups regarding age.

Table II summarises ECG findings in the study groups. In the whole study group mean HR was 73±12 beats/min on 24-hour ECG monitoring. No significant differences were observed with respect to mean HR between patients with normal and abnormal HRT. In all patients ventricular arrhythmia was observed on ambulatory ECG monitoring. Ventricular premature beats count ranged from 270 to 6028, mean 794±1338. No significant differences were observed between the groups. Non-sustained VT was recorded in 24 (29.2%) patients, and was more common in Group 3.

The HRV parameters showed significant differences between each group. Group 3 comprised patients with considerably lower HF than groups 1 and 2 (p <0.05).
However, group 1 patients had significantly higher LF than those from group 3 (p <0.05). Comparison of results of time-domain analysis of HRV showed significantly lower SDNN in group 3, with the highest values in group 1.

Subsequently, the relationship between HRT and HRV was evaluated (Table III). The HRT indices significantly correlated with all HRV variables with the strongest relationship between TS and SDNN (r=0.6; p<0.001). Table IV lists correlation results for each study group. The strongest correlation between TS and time domain and frequency domain parameters was found in groups 2 and 3.

Nine patients died during follow-up of a mean of 25±9 months. Eight deaths were classified as cardiac deaths: two of them were sudden, two occurred in the course of acute coronary syndrome and another two during major worsening of CHF. Fifteen patients were admitted to hospital due to worsening of CHF and/or arrhythmia. Results of long-term follow-up are summarised in Table V. Adverse events were most commonly observed in group 3: 6 deaths (20.6%) and 5 (17.2%) hospital admissions due to cardiovascular events.

Table VI compares clinical data and ECG parameters in patients with respect to composite endpoint. Patients significantly differed regarding NYHA class, incidence of premature ventricular beats, episodes of nonsustained VT, SDNN and TS.

The differentiating variables were included in the multivariable regression model. The ECG parameters found to be independent predictors of increased risk of composite endpoint or single clinical events such as all-cause mortality or cardiovascular hospitalisation are listed in Table VII. Presence of non-sustained VT was associated with more than 8-fold (OR=8.6) increase of composite endpoint risk, 5-fold (OR=5.4) increase of all-cause mortality risk and 7-fold (OR=7.0) increase of cardiovascular hospital admissions risk. Moreover, decrease in TS was associated with two-fold (1/OR for OR=0.5) increase of composite endpoint risk and almost three-fold (1/OR for OR=0.3) increase of all-cause mortality risk.

Discussion

Electrocardiography is one of the basic examinations in the diagnostic approach and evaluation of risk in CHF patients [1, 2]. In addition to routine evaluation of arrhythmias and conduction disturbances, ambulatory monitoring of ECG allows assessment of autonomic nervous system status by means of HRV analysis [13, 14]. On the other hand, HRT represents the sinus node response to a premature ventricular beat. Acceleration and subsequent deceleration of sinus rhythm following a premature ventricular beat is caused by a baroreflex [15-17]. This relatively new electrocardiographic index is also helpful in evaluation of autonomic imbalance, which plays an important role in multivariable pathogenesis of death in CHF. Abnormal turbulence pattern is a docu-
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Abnormal HRT parameters and increased mortality risk in worsening and resultant deaths. A relationship between 3 ms/RR predicted the risk of hospitalisation for CHF. They found in 50 with CHF subjects with CHF that TS above was associated with adverse prognosis of CHF patients [22]. et al. also reported that decreased HRT variables were such as death or cardiovascular hospitalisation. Koyamo -sustained VT significantly influenced the risk of endpoints.

In our study abnormal HRT parameters were found in 72% of subjects. The MUSIC study reported an impaired turbulence response in 66% of participants [20]. This percentage is significantly lower in post-infarction patients and equals to 20-45% [8, 21].

A strong relationship between HRT and HRV is supported by other reports [21–23]. In our study turbulence parameters, in particular TS, correlated with HRV. Other investigators showed that particularly reduced TS was correlated with low SDNN [22]. The MUSIC study showed the most potent correlation between TS and LF power, supporting the theory that HRT may reflect a baroreflex [20]. It has been also shown that HRT parameters correlate with a number of clinical indices of CHF. The relationships observed mainly refer to correlations between TS and NYHA class, LVEF or NT-proBNP [20, 24, 25].

No significant correlation between HRT and LVEF was observed in our study group. This was most likely due to the enrolment pattern adopted in our study. Only patients with LVEF ≤35% were included. It was also affected by the small number of patients and high rate of subjects with abnormal HRT.

During the follow-up, 9 patients died, including 8 cardiovascular deaths, and 1 non-cardiovascular death. Fifteen patients were admitted to hospital for cardiovascular events such as MI, worsening of heart failure and/or arrhythmia. Data analysis confirmed a major role of selected ECG parameters in evaluation of prognosis in heart failure patients. A multivariable regression model was used to show that reduced TS and episodes of non-sustained VT significantly influenced the risk of endpoints such as death or cardiovascular hospitalisation. Koyamo et al. also reported that decreased HRT variables were associated with adverse prognosis of CHF patients [22]. They found in 50 with CHF subjects with CHF that TS above 3 ms/RR predicted the risk of hospitalisation for CHF worsening and resultant deaths. A relationship between abnormal HRT parameters and increased mortality risk in individuals with CHF progression was also documented by Moore et al. [18]. In addition, Grimm et al. showed a relationship between anomalous HRT pattern and worsening of CHF in patients with idiopathic cardiomyopathy [26].

In our study decreased TS was associated with both risk of composite endpoint and risk of death and cardiovascular hospitalisation alone. One of the assumptions of the MUSIC study was evaluation of prognostic value of dynamic electrocardiographic parameters in prediction of all-cause mortality and both sudden deaths and deaths associated with worsening of CHF. It was found that abnormal HRT parameters enabled the prediction of sudden deaths in patients with relatively maintained LV systolic function [20].

Arrhythmias are common in patients with CHF. Complex ventricular arrhythmias are among classic factors used for mortality risk assessment in patients with previous MI [27]. Findings on the prognostic value of ventricular arrhythmia in CHF subjects are not so clear-cut; however, a relationship between arrhythmias and unfavourable prognosis was documented in many studies [28, 29]. The MADIT II study , involving patients with low LVEF, showed that implantable cardioverter-defibrillator therapies for life-threatening arrhythmias were observed mainly in patients with CHF progression during follow-up [30]. In our study, the presence of non-sustained VT was an independent risk factor multiplying the probability of endpoint. The other analysed ECG parameters had no significant influence on the prognosis in the study group. Other studies found that accelerated HR increased risk of all-cause as well as cardiovascular mortality both in normal individuals and patients with cardiovascular disease, including CHF [31, 32]. In our study the mean HR based on 24-hour ECG monitoring had no prognostic impact. Increased HR in CHF is associated with haemodynamic changes and activation of the adrenergic system, particularly in the treatment-naive patients. It seems that this finding may play a minor role in patients on optimal treatment as in our study population.

The HRV parameters are reduced in the case of enhanced adrenergic activation, as observed in CHF. Many reports on prognostic values of HRV in CHF patients have been published [33-35]. In our study time-domain

### Table VII. Parameters showing an independent relationship with composite endpoint as well as death or cardiovascular mortality in multivariate regression analysis

<table>
<thead>
<tr>
<th>Follow-up endpoints</th>
<th>Non-sustained VT episodes</th>
<th>TS (ms/RR)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR 95% confidence interval</td>
<td>p</td>
</tr>
<tr>
<td>Follow-up composite endpoint (death or cardiovascular hospitalisation)</td>
<td>8.6 (2.51-34.75)</td>
<td>0.003</td>
</tr>
<tr>
<td>Total deaths</td>
<td>5.4 (1.87-19.11)</td>
<td>0.006</td>
</tr>
<tr>
<td>Cardiovascular hospitalisations</td>
<td>7.0 (2.87-23.43)</td>
<td>0.005</td>
</tr>
</tbody>
</table>

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parameters (SDNN) were significantly lower in patients reaching composite endpoint during follow-up. However, no statistical significance was met for these parameters in multivariable analysis. The comparison of different studies on prognostic value of HRV is complicated due to dissimilar methodology, recording durations and reference ranges.

Based on the analyses carried out we showed usefulness of HRT parameters in evaluation of prognosis in patients with CHF. Decreased TS was associated with increased risk of composite endpoint as well as mortality rate alone. However, more prospective studies need to be performed to answer the question of whether decrease in TS is another independent predictor of cardiovascular events in patients with CHF. A positive answer would make it possible to introduce HRT analysis — in addition to risk assessment — into the evaluation of effectiveness of CHF therapy.

Conclusions

1. Noticeably decreased HRT is present in a significant percentage of CHF patients. There is a correlation between HRV and HRT parameters, reflecting the autonomic status of the patient.
2. Both routine and dynamic electrocardiographic parameters are useful in predicting prognosis in patients with significantly decreased LVEF.
   a) Presence of non-sustained VT greatly increases all-cause mortality risk as well as the other endpoints such as cardiovascular hospitalisation;
   b) Turbulence slope of sinus rhythm is an independent variable linked to the risk of cardiovascular events.

References


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Turbulencja rytmu zatokowego u osób z przewlekłą niewydolnością serca

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Streszczenie

Wstęp: Osoby z niewydolnością serca są grupą o największym ryzyku zarówno nagłych zgonów sercowych, jak i zgonów w przebiegu niewydolności serca. Turbulencja rytmu zatokowego (HRT) jest nowym nieinwazyjnym wskaźnikiem w ocenie ryzyka śmiertelności całkowitej u chorych po zawale serca zaproponowanym do diagnostyki elektrokardiograficznej w 1999 r.

Cel: Analiza wartości HRT u osób z niewydolnością serca oraz określenie prognostycznego znaczenia HRT w tej grupie chorych.


 Wyniki: Zależnie od wartości TO i TS wydzieliono następujące grupy chorych: grupa 1. – 23 chorych z prawidłowymi wartościami TO i TS (TO <0% i TS >2,5 ms/RR), grupa 2. – 30 chorych z nieprawidłowymi wartościami jednego z parametrów (TO lub TS), grupa 3. – 29 chorych z nieprawidłowymi wartościami obu parametrów (TO >0% i TS <2,5 ms/RR). Chorzy w grupie 1. byli znamnie młodsze, natomiast etiologia, średni czas trwania choroby, sposób jej leczenia, wartość LVEF, częstość występowania komorowych zaburzeń rytmu nie różniły badanych grup. Odsetek chorych, u których rejestrowano epizody nieutrwalonego częstoskurczu komorowego był znamnie wyższy w grupie 3. Również średnie wartości parametrów zmienności rytmu wykazywały w tych grupach istotne zróżnicowanie. U osób z prawidłowymi wartościami turbulencji (grupa 1) rejestrowano istotnie wyższe parametry HRV w porównaniu z pozostałymi grupami (grupy 2. i 3.). Parametry HRT korelowały z parametrami HRV, przy czym w grupach 2. i 3. stwierdzono najsilniejszą korelację TS z parametrami SDNN i LF. W okresie obserwacji zmarło 9 chorych, natomiast 15 hospitalizowano z powodu innych poważnych zdarzeń sercowych. Aż 6 zgonów i 5 hospitalizacji z powodu progresji niewydolności stwierdzono w grupie 3. Dla określenia zespołu czynników mających największy wpływ na ryzyko wystąpienia złożonego punktu końcowego, jak również oddzielnym przeciwdziałania punktów końcowych sporządzono model wieloczynnikowy regresji. Obecność epizodów nieutrwalonego częstoskurczu komorowego była związana z ponad 8-krotnym (OR=8,58) wzrostem ryzyka wystąpienia złożonego punktu końcowego, jak również nieprawidłowe wartości TS miały istotny wpływ na ryzyko wystąpienia złożonego punktu końcowego oraz ryzyko zgonu ogółem. Wnioski: U znacznego odsetka osób z niewydolnością serca parametry turbulencji rytmu zatokowego mogą być nieprawidłowe. Oznaczona istotnie turbulencji oraz obecność epizodów nieutrwalonego częstoskurczu komorowego to wskaźniki związane ze wzrostem ryzyka u osób z niewydolnością serca.

Słowa kluczowe: niewydolność serca, rokowanie, turbulencja rytmu zatokowego

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