Clinical significance of heart rate turbulence assessment in patients with chronic heart failure

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Abstract

Background: Heart rate turbulence (HRT) is modulated by the baroreceptor reflex, and it has been suggested that it could be used as a measure of autonomic dysfunction. Impaired HRT has a significant prognostic value in patients after myocardial infarction. The usefulness of HRT parameters in CHF patients has not yet been well established.

Aim: To assess the relationship between HRT parameters, clinical course of CHF and selected biochemical markers with respect to their prognostic value in CHF patients.

Methods: A 64 of 100 consecutive CHF patients, in whom it was possible to calculate HRT, were divided into four groups according to NYHA class. Uric acid (UA) and brain natriuretic peptide (BNP) concentrations were measured. Heart rate turbulence was analysed from 24-hour Holter ECG and characterised by two parameters: turbulence onset (TO) and turbulence slope (TS). The results of 20 healthy persons served as a control group. Follow-up examinations were performed after 6 and 12 months.

Results: In patients with CHF both HRT parameters (TO and TS) were significantly impaired in comparison to TO and TS in healthy subjects. A negative correlation between these parameters was found. A strong positive correlation between TO and NYHA class and a significant negative correlation between TS and BNP and UA concentrations were observed. There were 11 deaths during one-year follow-up. Patients who died due to CHF had significantly lower TS and higher TO values in comparison to survivors.

Conclusions: Heart rate turbulence is impaired in CHF patients. HRT parameters show a significant correlation with some clinical factors: NYHA class, BNP and UA concentrations. Both HRT parameters, TO and TS, seem to be significant prognostic markers in patients with CHF.

Key words: heart rate turbulence, chronic heart failure

Kardiol Pol 2008; 66: 1289-1295

Introduction

Mortality due to chronic heart failure (CHF) and increase in the number of patients suffering from CHF are still considerably high despite the significant therapeutic progress that was made in the last few years, mostly due to the introduction of new drugs that prolong life. New methods for selecting patients with potential risk, requiring the use of advanced forms of therapy – resynchronisation, implantation of cardioverter-defibrillator or heart transplantation – are still being sought [1].

Assessment of the autonomic nervous system activity is extremely important for diagnostic and prognostic evaluation [2, 3]. Generalised activation of the sympathetic-parasympathetic axis and decrease of vagus nerve activity as well as baroreceptor response are all observed in CHF. These changes lead to alterations in the heart rhythm turbulence (HRT) [4]. Heart rhythm turbulence is a physiological response to ventricular premature beats. Fluctuation in blood pressure values caused by ventricular premature beats stimulates baroreceptors to an immediate response that results in an initial increase and subsequent decrease in heart rhythm [4-6].

The HRT assessment has been shown to be an important parameter in risk stratification after myocardial infarction [7-9]. The clinical significance of this examination in patients with CHF is still not clear [10-12]. Measurement of BNP concentration is useful in the assessment of left ventricular (LV) dysfunction [13]. It can also be helpful in predicting the progression of the disease. Moreover, increased level of uric acid in blood serum in patients with CHF has been also reported, which can also have a prognostic value [14].

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Received: 28 May 2008. **Accepted:** 08 October 2008.

Financial source: University of Medical Sciences in Poznan, grant no. 501-01-22011303-06172.

The aim of this study was to assess the relationship between HRT parameters, clinical course of CHF and selected biochemical markers with respect to their prognostic value in CHF patients.

Methods

Patients

Based on medical history, physical and radiological examination and echocardiographic CHF symptoms, 100 patients underwent initial evaluation. All patients were categorised among NYHA functional groups. Sixty four patients (24 females and 40 males) aged 33 to 82 years, mean 63±12 years, were eventually selected for the study group. The study group was formed after including factors inhibiting HRT or evaluation of other parameters. All patients, after including contraindications, received inhibitors of angiotensin-converting enzyme, beta-blockers, diuretic drugs – furosemide or thiazide, spironolactone and if needed, digitalis, nitrates, amiodarone or statins. The examinations were performed during pharmacological treatment, after stabilisation of patients' clinical condition.

Prior to the study the patients were informed of its character and gave written consent to participate in the study. The consent of the Local Bioethical Committee of Karol Marcinkowski University of Medical Sciences in Poznań was received for the study. Patients presenting with the following symptoms were excluded from the study: presence of non-sinus rhythm (paced rhythm, atrial fibrillation, atrial flutter), numerous disturbances in 24h Holter ECG examination, lack of ventricular premature beats, acute or chronic inflammatory or neoplastic process, psychiatric disease or alcohol abuse.

Control group

The control group consisted of 20 subjects without abnormalities of the cardiovascular system, compatible with the study group in reference to age and gender, who had at least 5 ventricular premature beats in 24h Holter ECG recording.

Echocardiography

The dimension of the heart chambers, the thickness of the heart walls and LV ejection fraction (LVEF) were assessed in the echocardiographic examination (Sonos 5500 device by Hewlett Packard). The flow through the heart valves and the parameters of diastolic function of the LV were assessed using Doppler examination.

Laboratory examinations

The BNP and uric acid concentrations were measured in blood serum. The uric acid concentration was assessed by enzymatic method. The BNP concentration was assessed by radioimmunoenzymatic method.

HRT analysis

All patients selected for the study and control group underwent 24h Holter ECG monitoring (Reynolds). The results were initially analysed using the Pathfinder 700 system that evaluates arrhythmia.

Only the recordings that included at least 5 ventricular premature beats during 24 hours were chosen for the analysis. Two parameters were evaluated in the HRT analysis: turbulence onset (TO) and turbulence slope (TS). The onset of turbulence was calculated according to the formula: $TO = (RR1 + RR2) - (RR-2 + RR-1)/ (RR-2 + RR-1) \times 100\%$.

The TO was calculated by entering RR interval into the formula for each beat separately, and was subsequently averaged for all beats in an individual patient. The results are presented in percentages, with normal value <0. The TS was defined as maximal inclination of the regression line calculated from all 5 sequences of sinus rhythm RR interval occurring after VPB in the group of the first 20 beats (calculation of TS based on the analysis of 15 R-R interval was considered acceptable). The TS value was displayed in ms/RR interval. Optimal TS value was set at 2.5 ms/RR interval.

The analysis of HRT parameters was performed manually. The values of RR interval were entered into a Microsoft Excel spreadsheet. Subsequently, TO and TS were calculated according to the given formulae.

Long-term observation

The control visits were planned after 6 and 12 months. The survival was analysed and in case of death its causes were established.

Statistical analysis

Statistical analysis was carried out with STATISTICA software by StatSoft company. The quantitative values were characterised by mean, median, minimal and maximal values and standard deviations. The normality of distribution of the quantitative values was verified with the Shapiro-Wilk test. For comparison of the quantitative values between two groups nonparametric Mann-Whitney test was used. The correlation between two qualitative values or displayed in serial scale was evaluated with Spearman's rank correlation index. The observed differences or correlations were considered statistically significant if the p value was ≤ 0.05.

Results

The clinical characteristics of the studied patients are displayed in Table I.

A 36 patients out of 100 with diagnosed CHF were excluded from the study. The exclusion criterion were: lack of ventricular premature beats in 2 patients, atrial fibrillation/atrial flutter in 21 patients, paced rhythm in 4 patients, disturbances in ECG recordings/low voltage QRS in 5 patients, acute or chronic

inflammatory process in 5 patients, neoplastic process in 2 patients, alcohol abuse syndrome in 2 patients, psychiatric disease in 1 patient. In some of the patients more than one excluding factor co-existed.

Nine deaths were noted (14.0%) during a 6-month follow-up. This number increased to 11 (17.2%) after 12 months. In the group of 36 initially excluded patients, 5 (13.8%) and 6 (16.6%) deaths were noted after 6 and 12 months respectively. The percentage of deaths in the group that did not undergo HRT assessment and in the study group did not differ significantly.

HRT parameters analysis in the study and control group

The TS and TO were significantly abnormal in the study group in comparison to TS and TO in the control group. The results are displayed in Table II.

Neither TO nor TS in the study group presented a normal distribution. In 38 (60%) patients positive, improper TO values were observed. The majority of patients (45 patients – 70%) presented with significantly abnormal TS values within 0-8 ms/RR. A significant negative correlation between TO and TS values was observed (Spearman's rank correlation index r_S =–0.388; p=0.002) (Figure 1).

Correlation between HRT parameters and clinical presentation

A significant positive correlation between NYHA class and TO was observed (Figure 2). All patients with NYHA class I had negative TO values – that is, normal or close to normal. In NYHA class II almost half of patients had negative TO values. In the majority of patients in NYHA class III and IV positive TO values were observed.

A similar tendency was observed for the correlation between TS and NYHA class (r=–0.22, p=0.074). The higher the NYHA class, the lower the TS values were noted.

Correlation between average heart rate and HRT

The average heart rate in the CHF patients was 75.6±16.9/min, whereas in the control group it was 70±12/min. No significant correlations between average heart rate and HRT parameters were observed.

Relationship between uric acid, BNP concentration and HRT

A significant negative correlation between TS and uric acid (Figure 3) as well as BNP (Figure 4) was found. No correlation between TO and biochemical parameters was observed.

HRT as a prognostic factor

Significantly lower TS values were observed in patients who died due to CHF in comparison to survivors at 6 month follow-up. This difference remained also after 12 months (5.7±4.8 vs. 2.2±3.4, p <0.03).

After 6 month TO parameters were not significantly different, although a tendency towards higher TO values in patients who died was observed. After 12 months the difference between the groups reached statistical significance (–0.2±1.7 vs. 0.8±1.7, p <0.05).

Table I. Clinical characteristics of patients

Parameter	Number (%)
Age >60 years	32 (51)
Females	24 (38)
Hypertension	24 (38)
Diabetes	16 (25)
Coronary artery disease	38 (60)
Previous MI	23 (36)
Heart defect	9 (14)
Aortic stenosis	6 (10)
Mitral insufficiency	3 (5)
Dilated cardiomyopathy	15 (24)
NYHA I class	7 (10)
NYHA II class	32 (50)
NYHA III class	17 (27)
NYHA IV class	8 (13)
nsVT	23 (36)
LBBB	13 (19)
RBBB	6 (10)
LVEF (%)	38±16
LVEF <40%	36 (57)
LVEF 40-60%	19 (29)
LVEF >60%	9 (14)

Abbreviations: NYHA – New York Heart Association, nsVT – non-sustained ventricular tachycardia, LBBB – left bundle branch block, RBBB – right bundle branch block, LVEF – left ventricular ejection fraction

Table II. TO and TS values in CHF and control group

	n	Mean	Median	Minimum	Maximum	SD
TO [%]						
CHF	64	0.13	0.26	–5.80	6.91	2.37
Control group	20	–0.021*	–0.01	–0.07	0.04	0.03
TS [ms/RR]						
CHF	64	4.55	3.19	–6.83	25.63	5.66
Control group	20	21.825**	19.7	2.8	53.8	16.22

**p=0.007 study group vs. control group*
***p=0.0001 study group vs. control group*

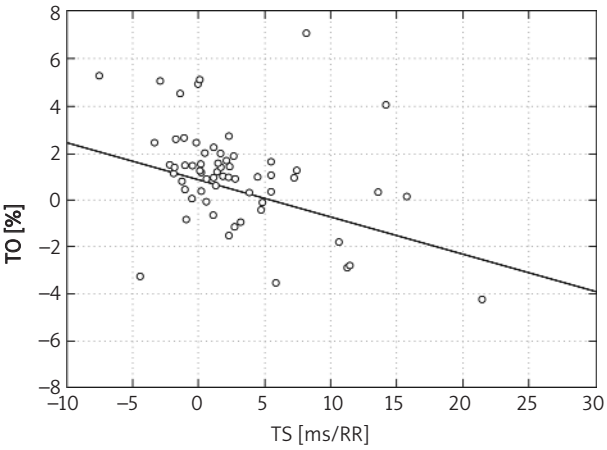

Figure 1. Correlation between TO and TS values

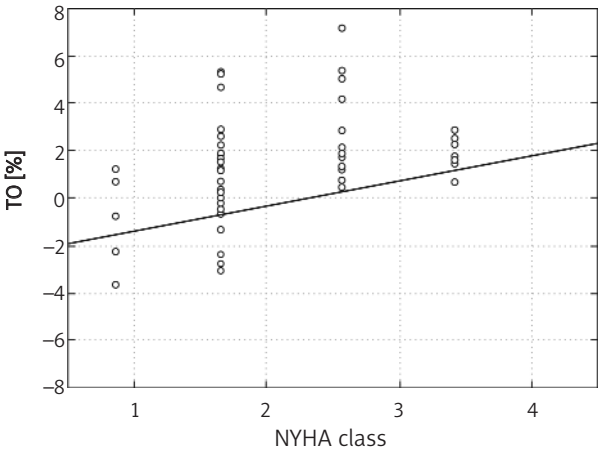

Figure 2. Correlation between NYHA class and TO values

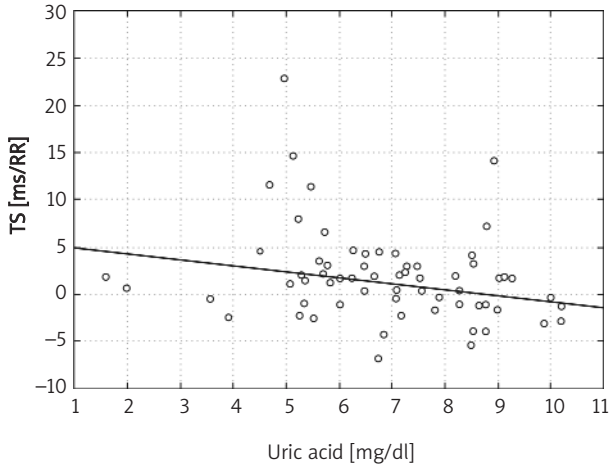

Figure 3. Correlation between TS values and uric acid concentration

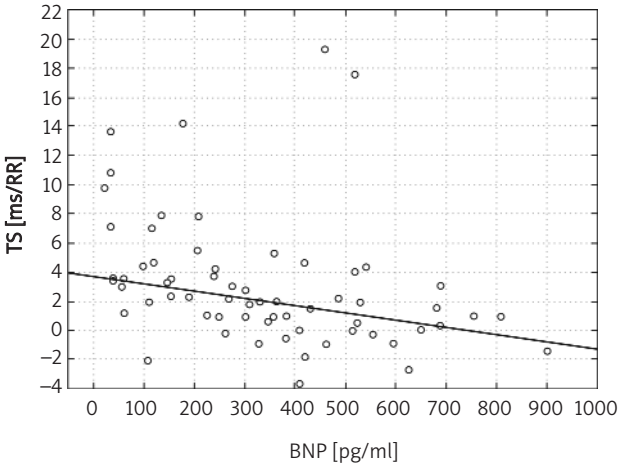

Figure 4. Correlation between TS values and BNP concentration

The mean values of baseline HRT parameters in survivors and non-survivors are compared in Figure 5.

Discussion

It is well known that ventricular premature beats can influence the frequency of impulses sent from the sinus node [15-17]. In the last years it was shown that abnormal HRT is a strong prognostic factor of cardiac death in patients after myocardial infarction [7-9]. In the MPIP (Multicenter Postinfarction Program) and EMIAT (European Multicenter Amiodarone Trial) studies, which enrolled about 1200 subjects, prognostic value of the HRT parameters was assessed [9]. In the univariate analysis of the EMIAT study, TO values over 0% occurred to be the strongest prognostic factor of sudden cardiac death, along with LVEF, triangular index (TI) <20, heart rhythm >75/min, age >65 years, number of ventricular premature beats (VPB) in 24h ECG Holter recording and previous myocardial infarction. In the MPIP study, TO was the second – after decreased LVEF values – most powerful prognostic factor. In the multivariate analysis, TO and TS values were the strongest risk factors of sudden cardiac death in both studies.

In the multicentre ATRAMI (Autonomic Tone and Reflexes After Myocardial Infarction) study, which included 1212 patients with a follow-up over 20 months, TS values <2.5 ms/RR occured to be an independent prognostic factor [18, 19]. The prognostic value of TS in predicting sudden cardiac death in patients after myocardial infarction was also confirmed in the Makikallio et al. study [20]. In 2130 patients improper TS values increased the risk of sudden cardiac death in patients with slightly abnormal or normal LVEF (>35%). In the group with significantly altered LVEF these Holter parameters proved to be of insignificant predictive value.

In the recommendations of the European Society of Cardiology from 2006 concerning evaluation of risk and prevention of sudden cardiac death, HRT assessment was described as a useful method, but as yet little documented – indications of II B class [21].

In our study we demonstrated that TS and TO values in patients with CHF are significantly altered. Malberg et al. [3] in a group of 167 healthy subjects found the TS values at 21.30 ms/RR, and TO – 4.34%, in comparison to values of TS=6.75 ms/RR and TO=1.8% in 37 patients with dilated cardiomyopathy. Grimm et al. [11] observed abnormal TO and TS values in patients with CHF. In the Kawasaki et al. [22] study, 104 patients with hypertrophic cardiomyopathy, 44 patients after myocardial infarction and 56 controls were examined. Abnormal TO and TS value, were found in post-infarction patients but not in those with hypertrophic cardiomyopathy.

In our study TO values significantly depended on the NYHA class ($p < 0.001$). The TS values were also linked to NYHA class, but this correlation never reached statistical significance.

The negative correlation between BNP, progressive uric acid concentration and TS observed in our study may mean – along with the progression of the disease – alterations of the baroreceptors' response. It may also indicate a correlation between HRT abnormality and the advancement of the disease.

Based on the observed associations it cannot be established which of the HRT parameters may have greater importance in the evaluation of patients with CHF. The evaluation of both TS and TO seems optimal.

We found significantly lower TS values after 6 months in patients who died due to CHF. Also, a tendency toward higher TO values in patients who died was observed. After one year both parameters, TO and TS, differed significantly among survivors and non-survivors. This may indicate the usefulness of measuring HRT parameters for evaluation of death risk in patients with CHF.

Koyama et al. [10] were among the first to evaluate prognostic value of HRT in patients with CHF. They found that TS values were lower in patients who were more frequently hospitalised and in those who died. However, HRT parameters were not useful in predicting severe arrhythmias. The TS and TO values were similar in patients with or without VT.

Kawasaki et al. [22] found no usefulness of HRT in evaluation of death risk in patients with hypertrophic cardiomyopathy. Grimm et al. [11] assessed HRT in 242 patients with idiopathic dilated cardiomyopathy. A 22% of patients died or were qualified for heart transplantation during a 41-month follow-up period. In the death risk analysis the following factors were included: abnormal TO or TS values, TO along with TS, LVEF, LV diastolic dimension, functional NYHA class. In the multivariate analysis normal TO values were considered a favourable survival index

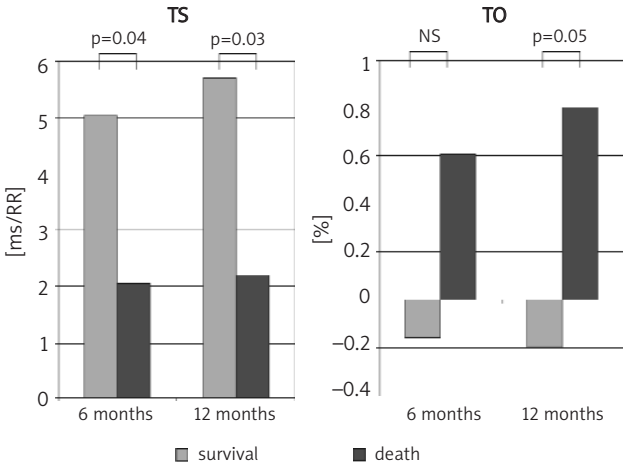

Figure 5. Compenson of baseline TS and TO values in survivors and non-survivors during 6- and 12-month follow-up

without heart transplantation. In the group of 680 patients with CHF evaluated by Moore et al. [12] TS proved to be an independent death risk factor due to decompensation of the disease. Its predictive value was greater than that of SDNN. In that study both HRT parameters correlated with the dimension of the left ventricle, level of urea and creatinine in the blood serum and the heart rhythm. No correlation was found between HRT and occurrence of sudden cardiac death. In our study we did not analyse the mode of death because in some cases the mechanisms could not be established.

The findings reported in literature during the last few years indicate that the major advantages are obtained from evaluation of many prognostic factors in CHF patients [23, 24]. Among these factors HRT parameters derived from the Holter recording should be included.

Limitations of the study

The study group was considerably small. The limitation of HRT parameters in prognostic evaluation in these patients is the necessity of presence of sinus rhythm. Frequent occurrence of atrial fibrillation disqualifies a high percentage of patients from HRT analysis.

The presented method of HRT assessment without proper software, although very time-consuming, enabled more precise selection of ventricular premature beats for analysis and avoidance of errors in their differentiation from supra-ventricular beats with aberration.

Including all factors that could influence HRT, such as age, CHF aetiology, diabetes, previous myocardial infarction, other heart diseases and drugs taken, would result in very small subgropus and difficulties in statistical analysis.

Multivariate analysis was not possible due to the small number of subjects.

Conclusions

Heart rate turbulence is impaired in CHF patients. HRT parameters show a significant correlation with some clinical factors: NYHA class, BNP and UA concentrations. Both HRT parameters, TO and TS, seem to be significant prognostic markers in patients with CHF.

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Ocena turbulencji rytmu serca u chorych z niewydolnością serca – związek z obrazem klinicznym

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Streszczenie

Wstęp: Pomiar parametrów turbulencji rytmu serca (HRT) pozwala na ocenę odruchu z baroreceptorów i pośrednio odzwierciedla funkcje autonomicznego układu nerwowego. Zjawisko HRT jest wyrazem fizjologicznej odpowiedzi ze strony serca na przedwczesne pobudzenia komorowe. Analiza parametrów HRT jest uznaną elektrokardiograficzną metodą oceny ryzyka zgonu sercowego u chorych po zawale mięśnia sercowego. Niewiele jest jednak doniesień opisujących przydatność tej metody u chorych z niewydolnością serca. Poszukiwane są stale nowe metody, które pozwoliłyby na wyodrębnienie chorych o szczególnym ryzyku, wymagających kwalifikacji do zaawansowanych form terapii.

Cel: Ocena zależności parametrów HRT od obrazu klinicznego i wybranych markerów biochemicznych ze zwróceniem uwagi na aspekty prognostyczne u chorych z niewydolnością serca.

Metody: Spośród 100 kolejnych chorych z podmiotowymi, przedmiotowymi, radiologicznymi i echokardiograficznymi objawami przewlekłej niewydolności serca, po uwzględnieniu przeciwwskazań, do badania zakwalifikowano ostatecznie 64 osoby z rytmem zatokowym w EKG, 24 kobiety i 40 mężczyzn w wieku 33–82 lat (63±12 lat). Chorych podzielono na 4 grupy w zależności od przynależności do klasy czynnościowej wg NYHA, oznaczono stężenie BNP (metodą radioimmunoenzymatyczną) i kwasu moczowego w surowicy (metodą enzymatyczną). U wszystkich chorych wykonano 24-godzinne badanie EKG metodą Holtera. Rejestrację przeprowadzano za pomocą 3-kanałowych rejestratorów cyfrowych Lifecard firmy Reynolds, stosując typowe odprowadzenia CS2, CM5 i IS. Zapis oceniano za pomocą systemu Pathfinder 700. Grupę kontrolną stanowiło 20 zdrowych osób, u których występowało co najmniej 5 pobudzeń przedwczesnych komorowych w ciągu całej doby. W obu grupach dokonano obliczeń parametrów HRT: początku turbulencji (TO) i nachylenia turbulencji (TS) zgodnie z metodą opisaną przez Schmidta. Po 6 i 12 miesiącach przeprowadzano wizytę kontrolną lub dowiadywano się o losach chorego, ewentualnie odnotowano zgon.

Wyniki: W przeprowadzonych badaniach stwierdzono, że TS i TO w grupie chorych z niewydolnością serca są istotnie upośledzone w porównaniu z TS i TO u osób zdrowych. Między tymi parametrami stwierdzono znamienną ujemną korelację. Początek turbulencji wykazywał silną dodatnią korelację z klasą NYHA. Istotną ujemną korelację obserwowano pomiędzy stężeniem BNP i kwasu moczowego a TS. Nie obserwowano korelacji między TO a tymi parametrami biochemicznymi. Już w okresie półrocznej obserwacji chorych, którzy zmarli z powodu niewydolności serca (9 chorych), odnotowano istotnie niższe wartości TS w porównaniu z chorymi, którzy przeżyli. Różnica ta utrzymywała się również po roku (11 zgonów). Wartości TO nie różniły się statystycznie po 6 miesiącach w obu grupach. Zauważono jednak tendencję do wyższego TO u chorych, którzy zmarli. Po roku różnica ta była istotnie wyższa u zmarłych osób. Odsetek zgonów wśród 36 chorych niezakwalifikowanych do analizy HRT był porównywalny.

Wnioski: Parametry HRT są znacznie upośledzone u chorych z niewydolnością serca. Turbulencja rytmu serca wykazuje istotny związek z obrazem klinicznym – wyrażający się zależnością od zaawansowania procesu chorobowego określanego przez klasę czynnościową wg NYHA, stężenia mózgowego peptydu natriuretycznego i kwasu moczowego w surowicy. Wydaje się, że oba parametry HRT – TO i TS – mają znaczenie prognostyczne w ocenie prawdopodobieństwa wystąpienia zgonu.

Słowa kluczowe: turbulencja rytmu serca, przewlekła niewydolność serca

Kardiol Pol 2008; 66: 1289-1295

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Praca wpłynęła: 28.05.2008. **Zaakceptowana do druku:** 08.10.2008.