Heart Rate Turbulence for Prediction of Heart Transplantation and Mortality in Chronic Heart Failure

Beata Sredniawa, M.D.,* Sylwia Cebula, M.D.,* Jacek Kowalczyk, M.D.,* Velislav N. Batchvarov, M.D.,† Agata Musialik-Lydka, M.D.,* Anna Sliwinska, M.D.,* Aleksandra Wozniak, M.D.,* Michal Zakliczynski, M.D.,‡ Marian Zembala, M.D.,‡ and Zbigniew Kalarus, M.D.*

From the *Department of Cardiology, Congenital Heart Diseases and Electrotherapy, Medical University of Silesia, Silesian Center for Heart Diseases, Zabrze, Poland; †Division of Cardiac and Vascular Sciences, St. George's University of London, London, U.K.; and ‡Department of Cardiac Surgery and Transplantology, Medical University of Silesia, Silesian Center for Heart Diseases, Zabrze, Poland

Background: Previous studies have shown conflicting results about the value of heart rate turbulence (HRT) for risk stratification of patients (pts) with chronic heart failure (CHF). We prospectively evaluated the relation between HRT and progression toward end-stage heart failure or all-cause mortality in patients with CHF.

Methods: HRT was assessed from 24-hour Holter recordings in 110 pts with CHF (54 in NYHA class II, 56 in class III–IV; left ventricular ejection fraction (LVEF) $30\% \pm 10\%$) on optimal pharmacotherapy and quantified as turbulence onset (TO, %), turbulence slope (TS, ms/RR interval), and turbulence timing (beginning of RR sequence for calculation of TS, TT). $TO \geq 0\%$, $TS \leq 2.5$ ms/RR, and $TT > 10$ were considered abnormal. End point was development of end-stage CHF requiring heart transplantation (OHT) or all-cause mortality.

Results: During a follow-up of 5.8 ± 1.3 years, 24 pts died and 10 required OHT. TO, TS, TT, and both (TO and TS) were abnormal in 35%, 50%, 30%, and 25% of all patients, respectively. Patients with at least one relatively preserved HRT parameter (TO, TS, or TT) ($n = 98$) had 5-year event-free rate of 83% compared to 33% of those in whom all three parameters were abnormal ($n = 12$). In multivariate Cox regression analysis, the most powerful predictor of end point events was heart rate variability (SDNN < 70 ms, hazard ratio (HR) 9.41, $P < 0.001$), followed by LVEF $\leq 35\%$ (HR 6.23), $TT \geq 10$ (HR 3.14), and $TO \geq 0$ (HR 2.54, $P < 0.05$).

Conclusion: In patients with CHF on optimal pharmacotherapy, HRT can help to predict those at risk for progression toward OHT or death of all causes.

Ann Noninvasive Electrocardiol 2010;15(3):230–237

heart rate turbulence; chronic heart failure; risk stratification; heart rate variability; heart transplantation

Despite advances in medical and surgical management, chronic heart failure (CHF) continues to be a major health care problem. Its prevalence in the overall population is 2–3% and rises to 10–20% in elderly people, in whom it is the most frequent cause for hospitalization.^{1,2} The lifetime risk of developing CHF is estimated to be approximately 20%.³

The Framingham Heart Study demonstrated that the incidence of CHF is higher in men than in

women.⁴ Coronary artery disease either alone or in combination with hypertension are the two most common causes of CHF.⁴ Five-year total mortality in patients (pts) with CHF averages 50%, whereas in the end-stage CHF it may reach 75%,^{5,6} with sudden death accounting for 30–50% of the total mortality.^{7–11}

Various indices, such as left ventricular ejection fraction (EF), peak oxygen consumption, 6-minute walking test, biomarkers such as natriuretic

Address for correspondence: Beata Sredniawa, M.D., Silesian Center for Heart Diseases, Department of Cardiology, Congenital Heart Diseases and Electrotherapy, Szpitalna 2 Street, 41-800 Zabrze. Fax.: +48323733792; E-mail: bms@pro.onet.pl

Conflict of Interest: All authors state that they do not have any conflict of interest to disclose regarding this manuscript.

peptide and C-reactive protein are used in clinical practice to assess the functional class of CHF. During the last decades, various electrocardiographically derived parameters, such as heart rate and heart rate variability (HRV) have been tested as prognostic markers in CHF.^{12–15} However, it is still not clear how to reliably identify those patients with CHF who are at risk to die or progress toward orthotopic heart transplantation (OHT) using the standard electrocardiogram (ECG).

Heart rate turbulence (HRT), which is marker of the autonomic regulation in the heart, has been reported to predict prognosis after myocardial infarction.^{16,17} Recently, HRT was tested as a new risk stratifier in patients with CHF with conflicting results.^{18–22}

The purpose of this single-centre prospective study was to examine the value of HRT in patients with CHF on optimal pharmacotherapy for prediction of progression toward end-stage heart failure and OHT or all-cause mortality.

METHODS

Study Population

This study group comprised 110 consecutive patients with stable CHF (16 women, 94 men; mean age 55.0 ± 10.3 years) referred to the Silesian Centre for Heart Diseases, Zabrze, Poland from February 2001 to September 2006. All patients were in sinus rhythm documented on a resting ECG, had >5 ventricular ectopic beats (VE) during 24-hour Holter monitoring¹⁷ (see below), and were in NYHA class II–IV with optimal pharmacotherapy, including angiotensin-converting enzyme inhibitors/angiotensin receptor blocker in 104 patients (94.5%), beta-adrenergic receptor antagonist in 97 (88.1%), loop diuretics in 87 (79.0%), spironolactone in 60 (54.5%), digoxin in 27 (24.5%), and amiodarone in 9 (8.2%). Patients who were hospitalized for heart failure decompensation or had received treatment with intravenous inotropic agents during the last 3 months were not included. Fifty-four patients (49%) were in NYHA class II and 56 patients (51%) were in NYHA class III–IV. The etiology of CHF was ischemic heart disease in 63 patients (57.2%) and nonischemic causes in 47 patients (42.7%). Arterial hypertension and diabetes were present in 59 patients (53.6%) and 26 patients (23.6%), respectively. Upon inclusion in the study all patients underwent physical examination,

12-lead resting ECG, cardiac ultrasound examination, 24-hour Holter monitoring, and blood tests including full blood count, serum electrolytes, and creatinine levels.

Patients were followed up for at least 2 years. They were checked in the outpatient department during their regular visits every 6 months, or during unplanned visits, if necessary. Information about death of patients was obtained from hospital documentation, patient's physicians or from family members. All patients signed informed consent to undergo diagnostic and therapeutic procedure, and a separate agreement for heart transplantation.

Analysis of HRT

All patients underwent 24-hour 3-lead ambulatory Holter recording (Pathfinder 700, Spacelabs Medical Inc., Hertford, UK) during their hospital stay. HRT was analyzed using the HRTView software program and was quantified by the following parameters:^{16–18,20}

1. Turbulence onset (TO,%) defined as the difference between the mean of the first two RR intervals after a ventricular premature beat (VPB) and the last two RR intervals before the VPB.
2. Turbulence slope (TS) defined as the maximum positive value of the slope of a regression line assessed over any sequence of five subsequent sinus-rhythm RR intervals within the first 20 sinus rhythm intervals after a VPB, expressed as millisecond per interval RR.^{16,20,23} (ms/RR).

$TO \geq 0\%$ and $TS \leq 2.5$ ms/RR, which were previously reported as predictors of sudden death in patients after myocardial infarction¹⁶ were considered abnormal. The TS value of ≤ 2.5 ms/RR was proposed by Schmidt et al.¹⁶ and its significance has been demonstrated in several studies, although $TS < 3$ has also been proposed by Koyama et al.²⁴

3. Turbulence timing (TT) defined as the first beat of the 5-beat RR-interval sequence, giving the maximal regression slope.^{25,26} It has been reported that in more than 90% of the Holter recordings TT lies within the first 10 RR intervals after a VPB.²⁷ Therefore, we accepted $TT \geq 10$ as abnormal.

HRV Analysis

The following time domain parameters of HRV were analyzed from the 24-hour Holter recordings: mean RR—mean of all normal RR intervals, SDNN—standard deviation of all normal RR intervals, SDANN—standard deviation of 5-minute mean RR intervals, SDNNi—mean of the standard deviations of all intervals for all 5-minute segments of the entire recording, rMSSD—root-mean square of differences of successive RR intervals.^{23,28} In accordance with previous studies,²⁹ SDNN < 70 ms was considered abnormal for analysis of prognostic significance.

Statistical Analysis

The combined end point of the study was development of end-stage CHF requiring OHT according to current guidelines³⁰ or death from any cause. Continuous parameters were expressed as means with standard deviations unless otherwise specified, categorical variables were presented as numbers and percentages. Comparative analysis between groups was performed using Student's *t*-test for continuous variables and chi-square or Fisher's exact test, as appropriate, for dichotomous parameters. Pearson's correlation coefficient was used to determine the correlation between continuous variables. Log-rank tests were used to compare Kaplan-Meier curves plotted for the combined end point. Independent predictors of death or OHT were identified with multivariate Cox regression model and expressed as hazard ratio (HR) with 95% confidence interval (CI). Regression models were developed after the inclusion of all parameters with univariate association with appropriate end-point. All tests were double-sided. *P*-value < 0.05 was considered statistically significant. All analyses were performed using the software package Statistica (version 6.1, StatSoft Inc., Tulsa, OK, USA).

RESULTS

The average follow-up was 5.8 ± 1.3 years (range 4 to 68 months). During follow-up, 10 patients developed end-stage heart failure and after additional examination underwent OHT, whereas 24 patients died, 3 of them after OHT. The cause of death was cardiac in 22 cases (10 cases of sudden death and 12 cases of non-sudden death) and noncardiac in 2 cases.

For subsequent analysis, patients were divided into group I consisting of those who did not meet the end point of the study (*n* = 79) and group II consisting of patients (*n* = 31) who either underwent OHT (*n* = 10) or died before undergoing OHT (*n* = 21). The clinical characteristics of patients in both groups are presented in Table 1. Patients in Group II had lower LVEF and hemoglobin level, higher NYHA class, and higher minimum heart rate during Holter recording than those in Group I.

All HRV parameters SDNN, SDANN, SDNNi, and RMSSD were significantly lower (*P* < 0.05) in patients of Group II compared to those of Group I (Table 1).

Comparison of HRT between the Two Study Groups

For all patients, the HRT parameters were as follows: mean TO $-0.65\% \pm 1.58\%$, mean TS 3.93 ± 4.62 ms/RR interval, mean TT 7.26 ± 2.98 . Abnormal values of TO, TS, TT, and both (TO and TS) parameters were observed in 35%, 50%, 30%, and 25% of the patients, respectively. All HRT parameters were significantly different between the two patients groups, with more abnormal average values (e.g., higher TO, lower TS, and later TT) in patients of Group II (Table 2). The proportion of patients with abnormal TO, TS, TT, or both TO and TS were significantly higher in Group II compared to Group I (64.5% vs 24%, *P* < 0.001; 67.7% vs 43%, *P* < 0.05; 67.7% vs 15.2%, *P* < 0.001; 38.7% vs 18.9%, *P* < 0.05, respectively) (Table 2).

Relationships between HRT Parameters and Clinical Variables

Patients in NYHA class II had significantly higher TS (5.31 ± 5.67 vs 2.60 ± 2.79 ms/RR, *P* < 0.001), lower TO (-1.145 ± 1.67 vs $0.172 \pm 1.34\%$, *P* < 0.001) and earlier TT (6.67 ± 2.92 vs 7.84 ± 2.96 , *P* < 0.05) than those in class III-IV. In the whole study population, significant correlation between TT and NYHA class (*r* = 0.27; *P* < 0.05) was observed. Similarly, significant correlations for TT and EF and mean RR (*r* = -0.32; *P* < 0.05 and *r* = -0.21; *P* < 0.05, respectively) were found. Patients with VPB ≥ 30 /h had significantly smaller TS than those with VPB < 30/h (2.07 ± 1.74 vs 4.70 ± 5.20 ms/RR; *P* < 0.05).

Table 1. Clinical Parameters and Noninvasive Prognostic Markers of the Patients

	Group I n = 79	Group II n = 31	P-Value
Clinical variables			
Age (years)	55.0 ± 10.3	54.5 ± 10.5	0.82
Gender (male)	69 (87.3%)	27 (87.0%)	0.76
Hypertension	43 (54.4%)	16 (51.6%)	0.68
Diabetes	17 (21.5%)	9 (29.0%)	0.40
Hemoglobin [mmol/l]	8.49 ± 1.21	7.78 ± 0.90	<0.05
NYHA class (mean)	2.40 ± 0.49	3.0 ± 0.68	<0.001
LVEF [%]	31.83 ± 9.98	24.67 ± 7.57	<0.001
Heart rate			
Mean heart rate (bpm)	72.12 ± 9.63	75.71 ± 11.55	0.10
Max. heart rate (bpm)	102.53 ± 15.6	99.0 ± 16.6	0.30
Min. heart rate (bpm)	52.2 ± 6.72	59.1 ± 10.29	<0.001
Ventricular ectopics/24 h			
All	1453 ± 2489	1078 ± 2662	0.50
Filtered ^a	732 ± 1274	551 ± 1085	0.46
HRT parameters			
TO [%]	-0.969 ± 1.70	0.163 ± 0.74	<0.001
TS [ms/RR interval]	4.85 ± 5.16	1.61 ± 0.92	<0.001
TT	6.27 ± 2.63	9.8 ± 2.26	<0.001
HRV "time domain" parameters			
Mean RR [ms]	895.6 ± 111.6	809.0 ± 121.1	<0.001
SDNN [ms]	131.7 ± 88.6	75.6 ± 13.5	<0.001
SDANN [ms]	106.89 ± 34.13	64.6 ± 14.77	<0.001
SDNNi [ms]	50.66 ± 18.8	31.97 ± 9.57	<0.001
rMSSD [ms]	34.33 ± 27.42	21.68 ± 12.0	<0.01

HRT = heart rate turbulence; HRV = heart rate variability; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; Mean RR, SDNN, SDANN, SDNNi, rMSSD = heart rate variability parameters; TO = turbulence onset; TS = turbulence slope; TT = turbulence timing; ^aFiltered ventricular ectopics = ectopic ventricular beats accepted by the HRT software.

Patients with abnormal TO, TT, as well as those with abnormal values of both TO and TS had significantly lower SDNN compared to those with normal values of TO, TT, or both TO and TS 129.0 ± 95.7 vs 92.7 ± 24.3 ms; ($P < 0.01$), 127.7 ± 91.2

vs 88.3 ± 25.3 ms; ($P < 0.05$), and 128.6 ± 41.9 vs 95.8 ± 41.9 ms; ($P < 0.001$), respectively.

Association of HRT with End-Stage CHF or Total Mortality

The end point-free rates stratification using one of the HRT parameters (TO, TS, or TT) is shown in Figure 1. Patients with abnormal TO, TS, or TT had significantly lower 5-year end point-free rates (59% vs 87%; 67% vs 87%; 42% vs 92%, respectively) compared to those with normal parameters (Fig. 1). TT was the most powerful single parameter.

Figure 2 presents the end point-free rates of the patients stratified by combined HRT parameters. Patients with normal TO (<0%) and/or TS (>2.5 mm/RR) ($n = 83$) had 5-year end point-free rate of more than 80% compared to less than 70% of those with abnormal values of both TO and TS ($n = 27$) ($P < 0.05$) (Fig. 2).

The addition of TT further increased the predictive power of HRT: the 5-year end point-free rate

Table 2. Proportion of Patients with Abnormal TO, TS, and TT

HRT	Group I n = 79	Group II n = 31	P-Value
TO ≥ 0%	19 pts (24.1%)	20 pts (64.5%)	<0.001
TS ≤ 2.5 ms/ RR interval	34 pts (43.0%)	21 pts (67.7%)	<0.05
TT ≥ 10	12 pts (15.2%)	21 pts (67.7%)	<0.001
TO ≥ 0 and TS ≤ 2.5	15 pts (18.9%)	12 pts (38.7%)	<0.05

TO = turbulence onset; TS = turbulence slope; TT = turbulence timing.

Figure 1. Kaplan-Meier curves for end points in chronic heart failure population stratified by TO (Panel A), TS (Panel B), and TT (Panel C). TO = turbulence onset; TS = turbulence slope; TT = turbulence timing.

of patients with relatively preserved values of at least one of the three HRT parameters ($n = 98$) was 83% compared to only 33% of those with abnormal values of all three parameters ($n = 12$) (Fig. 2).

Figure 2. Kaplan-Meier curves for end points in chronic heart failure population stratified by TO and TS (Panel A) or TO, TS, and TT (Panel B). TO = turbulence onset; TS = turbulence slope; TT = turbulence timing.

In univariate analysis, the following parameters were significantly related to the end point event: NYHA class, $LVEF \leq 35\%$,³¹ hemoglobin level, $TO \geq 0\%$, $TS \leq 2.5$, $SDNN < 70$ ms, $TT \geq 10$, mean $RR \leq 857$ ms (≥ 70 bpm).³² They were entered into a multivariate regression model, which showed that NYHA class, $TO \geq 0\%$, $SDNN < 70$ ms, $TT \geq 10$, and $LVEF < 35\%$ were independent risk factors for combined end point (Table 3). The most powerful predictor was $SDNN < 70$ ms (HR 9.41, 95% CI 8.97–9.85, $P < 0.001$), followed by $LVEF \leq 35\%$ (HR 6.23, 95% CI 5.55–6.91, $P < 0.05$), $TT \geq 10$ (HR 3.14, 95% CI 2.67–3.61, $P < 0.05$), and TO (HR 2.54, 95% CI 2.14–2.94, $P < 0.05$) (Table 3).

Table 3. Independent Predictors of the Combined End point in the Study Population

Variable	Hazard ratio-HR	95% CI	P-Value
NYHA class (1 class increase)	1.97	1.63–2.31	<0.05
LVEF $\leq$ 35%	6.23	5.55–6.91	<0.05
Hemoglobin (1 mmol/l increase)	0.78	0.61–0.95	0.13
Mean RR < 857 ms (<70 bpm)	1.16	0.71–1.61	0.74
SDNN < 70 ms	9.41	8.97–9.85	<0.001
TO $\geq$ 0%	2.54	2.14–2.94	<0.05
TS $\leq$ 2.5 ms/RR interval	1.04	0.60–1.48	0.93
TT $\geq$ 10	3.14	2.67–3.61	<0.05

LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; SDNN = heart rate variability parameter; TO = turbulence onset; TS = turbulence slope; TT = turbulence timing.

DISCUSSION

The main finding of this prospective study is that in patients with CHF on optimal pharmacotherapy HRT can help to identify those who are at increased risk of progression toward end-stage heart failure necessitating heart transplantation, or death of all causes.

Previous studies have demonstrated the prognostic power of HRT for all-cause mortality in patients after myocardial infarction.^{16,33–35} Its prognostic value in patients with CHF, however, is still largely unknown, especially in terms of progression toward end-stage heart failure. Several authors have reported conflicting results about the prognostic significance of HRT in patients with CHF.^{18,20–22,24,36,37} In two studies^{18,24}, HRT slope was found to predict hospitalization because of heart failure progression and death due to end-stage CHF. In one study, TO was reported to be an independent predictor of OHT-free survival in 242 patients with idiopathic dilated cardiomyopathy followed up for 41 ± 23 months.²² On the contrary, others did not find the relation between HRT and the prognosis in patients with cardiomyopathies.²¹

In multivariate analysis including eight risk factors, TT and TO were independent predictors of end-stage CHF or death of all causes with a HR of 2.5 and 3.1, respectively, with narrow 95% CIs. Their predictive power was stronger than that of NYHA functional class. The strongest predictor

was depressed SDDN with an HR of 9.4. Of particular interest is the value of a relatively new HRT parameter, TT, which has previously been investigated in only few studies.^{25,26,38} While the 5-year end-event-free rate of patients with abnormal TO and TS was <70%, the addition of abnormal TT identified a subgroup of patients in whom the 5-year event-free rate was twice lower (33%). The delay in the deceleration response seems to be more important risk factor in CHF than weak response. It can be related to the tendency of faster heart rate in patients with advanced heart failure. The negative correlation between TT and sinus cycle length was documented by Watanabe in a small population of post-myocardial infarction patients.²⁶ Similar relation were found in CHF patients. Moreover, patients with abnormal TT had the lowest SDNN value. TT as heart rate-dependent parameter may be the most sensitive of all HRT parameters to altered sympathovagal balance in CHF patients and therefore the strongest predictor of unfavorable outcome.

Our results indicate that in patients with CHF autonomic dysfunction is a powerful indicator of heart failure progression. In the recent decades, it has been demonstrated that SDNN and other time domain HRV indices are not only indicators of autonomic disorders in CHF but also are closely related to fatal events.^{39–41} The mechanism responsible for HRT is closely related to the mechanisms of baroreflex sensitivity.²¹ Following a premature ventricular beat, there is an increase in blood pressure due to the prolonged filling during compensatory pause. Reflex parasympathetic activation influences heart rate.²⁷ Shifted sympathovagal balance in CHF causes the loss of baroreflex sensitivity.^{42,43} The finding of depressed SDNN in patients with abnormal HRT supports autonomic dysregulation as an underlying mechanism of abnormal HRT in CHF.

Similar to other studies of HRT in patients with CHF,^{22,37} we found one (TO or TS) or two abnormal HRT parameters (both TO and TS) in one-third and one-fourth of our patients, respectively. These figures are greater than those reported in patients after myocardial infarction (20% and 12%, respectively).¹⁶ The observation of more depressed HRT in patients with more advanced NYHA functional class is also consistent with previous reports.⁴⁴

Our results can have clear practical significance. Analysis of HRT can easily be implemented in

Holter analysis systems and could be useful for early identification of CHF patients at risk of heart failure deterioration, who would need more aggressive treatment including cardiac resynchronization therapy.

The main limitation of the study is the small sample size and the exclusion of patients with atrial fibrillation, in whom HRT cannot be assessed.

CONCLUSIONS

In patients with CHF, HRT can help to identify those at increased risk of progression toward end-stage heart failure requiring heart transplantation, or death.

REFERENCES

- Dickstein K, Cohen-Solal A, Filippatos G, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2008. The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology. *Eur Heart J* 2008;29:2388–2442.
- Antonelli-Incalzi R, Ancona C, Forastiere F, et al. Socioeconomic status and hospitalization in the very old: A retrospective study. *BMC Public Health* 2007;7:227.
- Lloyd-Jones DM, Larson MG, Leip EP, et al. Lifetime risk for developing congestive heart failure: The Framingham Heart Study. *Circulation* 2002;106:3068–3072.
- Ho KK, Anderson KM, Kannel WB, et al. Survival after the onset of congestive heart failure in Framingham Heart Study subjects. *Circulation* 1993;88:107–115.
- Levy D, Kenchaiah S, Larson MG, et al. Long-term trends in the incidence of and survival with heart failure. *N Engl J Med* 2002;347:1397–1402.
- Rose EA, Gelijns AC, Moskowitz AJ, et al. Long-term mechanical ventricular assistance for end-stage heart failure. *N Engl J Med* 2001;345:1435–1443.
- Cleland J, Daubert JC, Erdmann E, et al. The effect of cardiac resynchronization on morbidity and mortality in heart failure. *N Engl J Med* 2005;352:1539–1549.
- Zipes DP, Camm AJ, Boorggreffe M, et al. ACC/AHA/ESC 2006 guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: A report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to develop guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death) developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. *Europace* 2006;8:746–837.
- Carson P, Anand I, O'Connor C, et al. Mode of death in advanced heart failure: The Comparison of Medical, Pacing, and Defibrillation Therapies in Heart Failure (COMPANION) trial. *J Am Coll Cardiol* 2005;46:2329–2334.
- De Maria R, Gavazzi A, Caroli A, et al. Ventricular arrhythmias in dilated cardiomyopathy as an independent prognostic hallmarks. *Am J Cardiol* 1992;69:1451–1457.
- Middlekauff HR, Stevenson WG, Stevenson LW. Prognostic significance of atrial fibrillation in advanced heart failure. *Circulation* 1991;84:40–48.
- Romeo F, Pelliccia F, Cianfrocca C, et al. Predictors of sudden death in idiopathic dilated cardiomyopathy. *Am J Cardiol* 1989;63:138–140.
- Rector TS, Cohn JN. Prognosis in congestive heart failure. *Annu Rev Med* 1994;45:341–350.
- Eichhorn EJ. Prognosis determination in heart failure. *Am J Med* 2001;110(Suppl 7A):14S–36S.
- Brouwer J, van Veldhuisen DJ, Man in't Veld AJ, et al. Prognostic value of heart rate variability during long-term follow-up in patients with mild to moderate heart failure. The Dutch Ibopamine Multicenter Trial Study Group. *J Am Coll Cardiol* 1996;28:1183–1189.
- Schmidt G, Malik M, Barthel P, et al. Heart-rate turbulence after ventricular premature beats as a predictor of mortality after acute myocardial infarction. *Lancet* 1999;353:1390–1396.
- Bauer A, Malik M, Schmidt G, et al. Heart rate turbulence: Standards of measurement, physiological interpretation, and clinical use. International Society for Holter and Noninvasive Electrophysiology Consensus. *J Am Coll Cardiol* 2008;52:1353–1365.
- Cygankiewicz I, Zareba W, Vasquez R, et al. Heart rate turbulence predicts all-cause mortality and sudden death in congestive heart failure patients. *Heart Rhythm* 2008;5:1095–1102.
- Cygankiewicz I, Zareba W, Vasquez R, et al. MUSIC Investigators. Risk stratification of mortality in patients with heart failure and left ventricular ejection fraction > 35%. *Am J Cardiol* 2009;103:1003–1010.
- Moore R, Groves DG, Barlow PE, et al. Heart rate turbulence and death due to cardiac decomposition in patients with chronic heart failure. *Eur J Heart Fail* 2006;8:585–590.
- Kawasaki T, Azuma A, Asada S, et al. Heart rate turbulence and clinical prognosis in hypertrophic cardiomyopathy and myocardial infarction. *Circ J* 2003;67:601–604.
- Grimm W, Schmidt G, Maisch B, et al. Prognostic significance of heart rate turbulence following ventricular premature beats in patients with idiopathic dilated cardiomyopathy. *J Cardiovasc Electrophysiol* 2003;14:819–824.
- American Heart Association/American College of Cardiology Foundation/Heart Rhythm Society scientific statement on noninvasive risk stratification techniques for identifying patients at risk for sudden cardiac death: A scientific statement from the American Heart Association Council on Clinical Cardiology Committee on Electrocardiography and Arrhythmias and Council on Epidemiology and Prevention. *Circulation* 2008;118:1497–1518.
- Koyama J, Watanabe J, Yamada A, et al. Evaluation of heart rate turbulence as a new prognostic marker in patients with chronic heart failure. *Circ J* 2002;66:902–907.
- Bonnemeier H, Wiegand UK, Friedlbinder J, et al. Reflex cardiac activity in ischemia and reperfusion: Heart rate turbulence in patients undergoing direct percutaneous coronary intervention for acute myocardial infarction. *Circulation* 2003;108:958–964.
- Watanabe MA, Marine JE, Sheldon R, et al. Effects of ventricular premature stimulus on blood pressure and heart rate turbulence. *Circulation* 2002;106:325–330.
- Schneider R, Barthel P, Watanabe M. Heart rate turbulence on holter. In Malik M, Camm AJ (eds.): *Dynamic Electrocardiography* A.J. New York, Blackwell Futura, Inc., 2004, pp. 190–193.
- Malik M, Bigger JT, Camm AJ, et al. Heart rate variability. Standards of measurement, physiological interpretation, and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. *Eur Heart J* 1996;17:354–381.
- La Rovere M, Bigger JT Jr, Marcus FI, et al. Baroreflex sensitivity and heart-rate variability in prediction of total cardiac

- mortality after myocardial infarction. ATRAMI (Autonomic Tone and Reflexes after Myocardial Infarction) Investigators. *Lancet* 1998;351:478-484.
30. Mehra MR, Kobashigawa J, Starling R, et al. Listing criteria for heart transplantation: International Society for Heart and Lung Transplantation guidelines for the care of cardiac transplant candidates-2006. *J Heart Lung Transplant* 2006; 25:1024-1042.
31. Bardy GH, Lee KL, Mark DB, et al. Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) Investigators. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. *N Engl J Med* 2005;352:225-237.
32. Fox K, Ford I, Steg PG, et al. BEAUTIFUL Investigators. Heart rate as a prognostic risk factor in patients with coronary artery disease and left-ventricular systolic dysfunction (BEAUTIFUL): A subgroup analysis of a randomised controlled trial. *Lancet* 2008;372:817-821.
33. Barthel P, Schneider R, Bauer A, et al. Risk stratification after acute myocardial infarction by heart rate turbulence. *Circulation* 2003;108:1221-1226.
34. Ghuran A, Reid F, La Rovere MT, et al. Heart rate turbulence - based predictors of fatal and nonfatal cardiac arrest (the Autonomic Tone and Reflexes after Myocardial Infarction Substudy). *Am J Cardiol* 2002;89:184-190.
35. Huikuri H, Raatikainen P, Moerch-Joergensen R, et al. Prediction of fatal or near-fatal cardiac arrhythmia events in patients with depressed left ventricular infarction. *Eur Heart J* 2009;30:689-698.
36. Sredniawa B, Lenarczyk R, Musialik-Lydka A, et al. Effects of cardiac resynchronization therapy on heart rate turbulence. *Pacing Clin Electrophysiol* 2009; 32(Suppl 1):S90-S93.
37. Cygankiewicz I, Zareba W, Vasquez R, et al. Relation of heart rate turbulence to severity of heart failure. *Am J Cardiol* 2006;98:1635-1640.
38. Watanabe MA. Heart rate turbulence slope reduction in imminent ventricular tachyarrhythmia and its implications. *J Cardiovasc Electrophysiol* 2006;17:735-740.
39. Kearney MT, Fox KA, Lee AJ, et al. Predicting death due to progressive heart failure in patients with mild-to-moderate chronic heart failure. *J Am Coll Cardiol* 2002;40:1801-1808.
40. Fauchier L, Babuty D, Cosnay P, et al. Prognostic value of heart rate variability for sudden death and major arrhythmic events in patients with idiopathic dilated cardiomyopathy. *J Am Coll Cardiol* 1999;33:1203-1207.
41. Ponikowski P, Anker SD, Amadi A, et al. Heart rhythms, ventricular arrhythmias, and death in chronic heart failure. *J Card Fail* 1996;2:177-183.
42. Davies LC, Francis DP, Ponikowski P, et al. Relation of heart rate and blood pressure turbulence following premature ventricular complexes to baroreflex sensitivity in chronic congestive heart failure. *Am J Cardiol* 2001;87:737-742.
43. Mrowka R, Persson PB, Theres H, et al. Blunted arterial baroreflex causes 'pathological' heart rate turbulence. *Am J Physiol Regul Integr Comp Physiol* 2000;279:R1171-R1175.
44. Mortara A, La Rovere MT, Pinna GD, et al. Arterial baroreflex modulation of heart rate in chronic heart failure: Clinical and hemodynamical correlates and prognostic implications. *Circulation* 1997;96:3450-3458.