Association of the Heart Rate Turbulence with Classic Risk Stratification Parameters in Postmyocardial Infarction Patients

Andreas Jeron, M.D., Tanja Kaiser, M.D., Christian Hengstenberg, M.D., Hannelore Löwel, M.D.,* Günter AJ Riegger, M.D., and Stephan Holmer, M.D.

*From the Klinik und Poliklinik für Innere Medizin II, Klinikum der Universität Regensburg, Germany; *GSF Forschungszentrum, Institut für Epidemiologie, München, Germany*

The heart rate turbulence (HRT) parameters were introduced for risk stratification of ventricular arrhythmias in postmyocardial infarction patients. However, the relationship of these parameters with other risk stratificators such as heart rate variability (HRV), repolarization parameters or left ventricular function is unknown. Furthermore, the influence of age and medication on HRT remains to be evaluated. Holter ECG's of 509 post-MI patients (1–10 years after MI) were screened for single ventricular extrasystole. In 196 patients the parameters' turbulence onset (TO) and turbulence slope (TS) could be computed. A pathological TO (>0%) and TS (<2.5 ms) was found in 58 and 54 patients, respectively. HRT was not related to gender, but was correlated with age (TS: $r = 0.209$, $P < 0.01$). No relationship was observed between QT interval, QTc interval or QT dispersion and HRT parameters. Individuals with a pathological HRT showed decreased HRV values (e.g., PNN50: 2.8 vs. 11.5; $P < 0.001$). Of all MI patients with systolic left ventricular dysfunction (EF < 45%, $n = 46$), 18 showed a pathological TO (39%) compared to 34 out of 142 patients (24%) with an EF > 45%. In contrast, the percentage of pathological HRT was not different between patients with left ventricular hypertrophy (16 out of 59, 27%) compared to patients without LVH (38 out of 133, 28%). The HRT was pathological in 14 out of 24 patients with diabetes mellitus (58%) compared to 40 out of 172 (23%) normoglycemic patients (TO: -0.6 ± 3.1 vs. -2.5 ± 5.5, $P < 0.02$). HRT was similar in patients with ß-blockers ($n = 96$) as in patients without ß-blockers ($n = 100$).

In stable post-MI patients, HRT is influenced by age and left ventricular function and correlates with heart rate variability. Therapy with ß-blockers has no influence on HRT, while diabetic patients may have an increased likelihood of pathological HRT. **A.N.E. 2003;8(4):296–301**

heart rate turbulence; risk stratification; myocardial infarction; diabetes mellitus

INTRODUCTION

In Europe, about 375,000 people suffer from out of hospital sudden cardiac arrest yearly, most of them being patients with previous myocardial infarction.[1,2] Risk stratification for ventricular arrhythmias and sudden cardiac death (SCD) in postmyocardial infarction patients is of enormous importance for the individual patient as well as for the health care community. The major problem in risk stratification is the relative low positive predictive value of most tests such as heart rate variability parameters,[3–5] QT dispersion,[6] late potentials,[7,8] or programmed stimulation.[9] Newer tests such as T-wave alternans have not been evaluated in prospective trials despite promising preliminary data.[10,11] While the high-risk population, i.e., survivors of SCD or patients with severely reduced left ventricular function can be identified easily, the majority of MI patients with intermediate risk is still a challenge for risk stratification. Very recently, the MADIT II trial showed a significant improvement in survival in MI patients with intermediate risk after ICD implantation.[12] To reduce the economic burden of a prophylactic ICD implantation in thousands of MI patients, new parameters for risk stratification are warranted.

Address for reprints: Andreas Jeron, M.D., Klinik und Poliklinik für Innere Medizin II, Klinikum der Universität Regensburg, Franz-Josef-Strauss-Allee 11, 93042 Regensburg, Germany. Fax: 0049-941-944-7213; E-mail: andreas.jeron@klinik.uni-regensburg.de

Recently, heart rate turbulence parameters, markers of autonomic tone control, were introduced for risk stratification. Specifically, it was shown that pathologic values predict an adverse outcome in post-MI patients by retrospective evaluation of two multicenter trials.[13] On the other hand, the association of the heart rate turbulence with other parameters of risk stratification was not investigated. Therefore, we studied the relationship of these parameters with other determinants such as heart rate variability (HRV) and repolarization parameters as well as left ventricular function, gender, age and medication in 196 chronic MI patients.

METHODS

Study Population

Patients with MI prior to the age of 60 years were identified through the population-based Augsburg MONICA (Monitoring of Trends and Determinants in Cardiovascular Disease) myocardial infarction register. The diagnosis of myocardial infarction was established according to the MONICA diagnostic criteria.[14,15] Of 1254 patients contacted, 609 agreed to participate in the study (532 men, age 56.1 ± 0.3 years) and were enrolled in 1997. Standard Holter ECGs were recorded for 30 minutes and were screened for a single ventricular extrasystole. Of 609 MI patients, 196 had at least one documented PVC, enabling the calculation of the parameters turbulence onset (TO) and turbulence slope (TS) as described by others,[13] using the free software downloaded from the website http://www.h-r-t.com/index2.html. The filtering requirements we used consisted of excluding all Holter ECGs with atrial fibrillation or arrhythmias and artifacts, which disable the calculation of HRT, by carefully studying the paper printout of every single PVC. Furthermore, a prematurity of more than 20% of the PVC compared to the sinus RR interval was required. TO and TS were calculated from the first suitable PVC within 30 minutes of Holter monitoring.

The mean time after MI was 5 years (range from 1 to 10 years after MI), characterizing these patients as chronic MI patients. Therapy consisted of aspirin in 92%, beta-blocker in 74%, and ACE inhibitor in 48% at the time of evaluation. None of the MI patients had signs of acute myocardial infarction or unstable angina pectoris at the time of examination and recording of the ECG. The investigation conforms with the principles outlined in the Declaration of Helsinki and all participants gave written consent.

Electrocardiography

A 12-lead resting ECG was recorded and stored in a digitized fashion using a PageWriter XL (Hewlett Packard, Inc.). QT intervals in individual leads were computed and double-checked by an investigator blinded to the clinical data. Mean-corrected QT interval (QTc) was calculated according to Bazett's formula.[16] QT dispersion was calculated as maximal QT interval minus minimal QT interval (QTmax–QTmin) of the 12 leads if QT interval was measurable in more than seven leads (mean 8.7 ± 1.6). Individuals with an ECG showing a bundle branch block pattern with a QRS duration greater than 120 ms or atrial fibrillation were excluded from further analysis.

Echocardiography

The echocardiographic examination was carried out by a single experienced investigator blinded to the history and genotype of the patient. Left ventricular end-diastolic diameter (LVEDD) and left ventricular end-systolic diameter (LVESD) were measured in the long parasternal axis view. Left ventricular ejection fraction (LVEF) was measured in the apical 4-chamber view according to the modified Simpson method.

Statistics

All statistics were calculated by the SPSS software 10.0 for Windows (SPSS, Inc.). Student's *t*-test for comparison between two groups were applied. In addition, multiple regression analysis was performed including HRT as a dependent variable and age, gender, therapy with β-blocker, left ventricular ejection fraction, and left ventricular end-diastolic diameter as independent covariates. All numbers were calculated as mean ± SE (standard error of the mean). Differences were considered significant for $P < 0.05$.

RESULTS

From the 196 MI patients with at least one ventricular extrasystole during the 30-minute recording, 54 had a pathological turbulence slope

Table 1. The Table Summarizes ECG, Echocardiographic and Antroprometric Parameters in MI Patients with Pathological Turbulence Slope (TS) Compared to MI Patients with a Normal TS

	TS < 2.5 ms n = 54	TS > 2.5 ms n = 142	P
Age (years)	60.6 ± 6.1	57.0 ± 7.4	0.001
Systolic RR (mmHg)	137 ± 17	134 ± 17	n.s.
Diastolic RR (mmHg)	86 ± 11	83 ± 10	n.s.
K (mmol/dL)	4.1 ± 0.4	4.2 ± 0.4	n.s.
EF (%)	49.2 ± 1.0	50.3 ± 1.1	n.s.
LVEDD (mm)	56.5 ± 8.8	55.5 ± 7.3	n.s.
LVESD (mm)	42.9 ± 8.4	40.7 ± 7.5	n.s.
Heart rate (ms)	867 ± 151	941 ± 131	0.001
PVC cycle length (ms)	555 ± 84	559 ± 92	n.s.
Post PVC (ms)	1165 ± 239	1256 ± 211	n.s.
QT (ms)	384 ± 38	395 ± 36	n.s.
QTdis (ms)	89 ± 34	91 ± 39	n.s.
SDNN (ms)	40.7 ± 15.7	59.9 ± 25.0	0.01
RMSSD (ms)	25 ± 15	42 ± 38	0.01
PNN50 (%)	2.8 ± 5.2	11.5 ± 14.8	0.001

EF: ejection fraction; LVEDD: left ventricular end-diastolic diameter; LVESD: left ventricular end-systolic diameter; PVC cycle length: coupling interval of the ventricular extrasystole; Post PVC: cycle length after the PVC; QT: QT interval; QTdis: QT interval dispersion; SDNN: standard deviation of the RR-intervals; RMSSD: root mean square of the standard deviation; PNN 50: percent of intervals outside 50 ms of the mean; P value < 0.05 is considered as significant.

Table 2. The Table Summarizes ECG, Echocardiographic and Antroprometric Parameters in MI Patients with a Pathological Turbulence Onset (TO) Compared to MI Patients with a Normal TO

	TO > 0% n = 58	TS < 0% n = 138	P
Age (years)	59.5 ± 6.8	57.3 ± 7.3	n.s.
Systolic RR (mmHg)	134 ± 17	135 ± 18	n.s.
Diastolic RR (mmHg)	83 ± 10	85 ± 10	n.s.
K (mmol/dL)	4.2 ± 0.5	4.1 ± 0.4	n.s.
EF (%)	48.6 ± 0.9	53.0 ± 0.9	0.01
LVEDD (mm)	56.4 ± 7.2	55.4 ± 8.1	n.s.
LVESD (mm)	41.9 ± 7.4	41.1 ± 7.9	n.s.
Heart rate (ms)	907 ± 155	926 ± 133	n.s.
PVC cycle length (ms)	555 ± 85	558 ± 92	n.s.
Post PVC (ms)	1193 ± 232	1247 ± 216	n.s.
QT (ms)	390 ± 37	393 ± 37	n.s.
QTdis (ms)	88 ± 36	91 ± 38	n.s.
SDNN	53.3 ± 30.3	55.2 ± 21.3	n.s.
RMSSD	45.3 ± 49.3	44.4 ± 25.6	n.s.
PNN50	9.2 ± 13.9	9.0 ± 13.1	n.s.

EF: ejection fraction; LVEDD: left ventricular end-diastolic diameter; LVESD: left ventricular end-systolic diameter; PVC cycle length: coupling interval of the ventricular extrasystole; Post PVC: cycle length after the PVC; QT: QT interval; QTdis: QT interval dispersion; SDNN: standard deviation of the RR-intervals; RMSSD: root mean square of the standard deviation; PNN 50: percent of intervals outside 50 ms of the mean; P value < 0.05 is considered as significant.

(<2.5 ms/RR), while normal values were revealed by 142 patients. The mean TS value of all 196 patients was 5.0 ± 3.6 ms/RR with a nearly Gaussian distribution. Patients with a pathological value were characterized by higher heart rate, lower heart rate variability parameters as well as a significantly higher age (Table 1). The correlation of age and TS was highly significant ($r = -0.209$, $P < 0.01$). In multivariate analysis including age, gender, and left ventricular ejection fraction, the age of the MI patients remained significantly associated to decreased TS (Table 3).

The mean turbulence onset for all 196 patients was −2.4 ± 5.6% with a perfect Gaussian distribution. A pathological turbulence onset (>0%) was computed for 58 patients. This group differed only in a significant lower left ventricular ejection fraction, while all other parameters were not different compared to patients with a normal heart rate turbulence onset (Table 2). Correlation analysis revealed a significant association of TO with age ($r = 0.169$, $P < 0.05$) and left ventricular ejection fraction ($r = -0.158$, $P < 0.05$), while only the ejection fraction was significantly associated in multivariate analysis (Table 3).

Patients with an impaired left ventricular function ($n = 48$, EF < 45%) are characterized by significantly lower TO values compared to MI patients with normal ejection fraction, while the TS values were not different (Table 4). In contrast, HRV parameters were not different between the two groups. No difference was detected in HRT parameters between MI patients with left ventricular hypertrophy and MI patients without LVH.

Standard therapy in MI patients with ACE inhibitors, diuretics, or calcium channel blockers had neither influence on turbulence onset nor on turbulence slope. Specifically ß-blocker therapy had no influence on both HRT parameters.

Table 3. Multivariate Analysis of Different Factors Associated with Pathological HRT Parameters in Chronic MI Patients

	TO β	p	TS β	P
Gender	2.3	ns (0.14)	0.8	ns
EF	2.1	0.05	1.8	ns (0.09)
Age	1.7	ns (0.12)	2.1	0.04
Gender * EF	3.7	0.03	1.0	ns
Age * EF	1.9	ns (0.06)	1.2	ns

EF: ejection fraction.

Interestingly, a quarter of all patients with pathological HRT parameters had no conventional pathological risk factor for ventricular arrhythmias such as reduced HRV, prolonged QTc interval, reduced left ventricular ejection fraction, or left ventricular hypertrophy.

Subgroup analysis in patients with diabetes mellitus demonstrated significantly lower values for both turbulence parameters. Additionally, 58% of all diabetic MI patients had a pathological turbulence onset (or slope) compared to 23% (26%) of the normoglycemic patients (Table 5).

DISCUSSION

There is an obvious necessity to develop new risk stratification parameters for ventricular arrhythmias in post-MI patients with a modest risk for sudden cardiac death. While the results of the MADIT II trial demonstrated the superiority of a prophylactic ICD implantation in MI patients with modest risk compared to best conventional therapy,[12] the economic burden for the health care systems is enormous.

Table 4. The Table Compares MI Patients with and without Reduced Left Ventricular Ejection Fraction (EF < 45%) Regarding the Distribution of Pathological Heart Rate Turbulence Values

	EF < 45% n = 48	EF > 45% n = 148	P
TO	−0.6 ± 3.1	−2.5 ± 5.5	<0.02
TS	4.6 ± 3.3	5.2 ± 3.8	n.s.
TO > 0%	18 (39%)	34 (24%)	<0.05
TS < 2.5 ms	13 (28%)	39 (27%)	n.s.

EF: left ventricular ejection fraction; TO: turbulence onset; TS: turbulence slope; P value < 0.05 is considered as significant.

Table 5. The Table Compares MI Patients with and without a Diagnosed Diabetes Mellitus Regarding the Distribution of Pathological Heart Rate Turbulence Values

	Diabetes Mellitus n = 24	No Diabetes Mellitus n = 172	P
TO	−0.6 ± 3.1	−2.5 ± 5.5	<0.02
TS	3.7 ± 3.3	5.1 ± 3.6	n.s. (0.07)
TO > 0%	14 (58%)	39 (23%)	<0.05
TS < 2.5 ms	14 (58%)	43 (26%)	<0.05

EF: left ventricular ejection fraction; TO: turbulence onset; TS: turbulence slope; P value < 0.05 is considered as significant.

HRT may be a valuable tool in the setting of risk stratification. In particular, its positive predictive value with respect to SCD equals those of left ventricular ejection fraction.[13] Furthermore, it is easy to perform without the need for additional time-consuming tests or procedures.

Here we demonstrated the feasibility of HRT measurements in 30-minute Holter ECGs. About a third of all screened MI patients revealed at least one PVC within the 30 minutes, enabling the calculation of HRT parameters. Nevertheless, Holter monitoring for 24 hours may be sufficient to detect PVCs in more of our MI patients, enabling the use of HRT parameters as risk stratificators in a higher percentage of MI patients.

No association of HRT parameters with the coupling interval or the compensatory pause was found, and there is no significant difference in these parameters between the groups with normal or pathological values. This confirms the results of Watanabe et al.,[17] who also found no significant variation of HRT parameters with PVC coupling interval or compensatory pause during EP study. Similar results were obtained very recently in probands without structural heart disease.[18]

Interestingly, the association of HRT with left ventricular ejection fraction and age as well as with the heart rate variability parameters is different for the two HRT parameters. This may point to an additional information of HRT parameters compared to EF and HRV parameters. It has to be acknowledged that this conclusion is limited to young MI patients like this population consisting of MI patients with their first MI prior to the age of 60 years.

Subgroup analysis revealed a higher percentage of pathological values for both HRT parameters in

case of diabetes mellitus. In contrast, patients with impaired LV function were characterized only by pathological turbulence onset values. These results may shed light on the pathophysiological mechanisms underlying the HRT parameters. Diabetes mellitus results in reduced vagal autonomic cardiac reflexes in man and rodents.[19–21] This diabetic neuropathy influences both HRT parameters, indicating vagal-mediated immediate and short-term response to a PVC. Recently, Lin et al.[18] could demonstrate by sequential autonomic blockade that the maintenance of heart rate turbulence is vagally determined. Selective parasympathetic and combined autonomic blockade diminished the correlation between turbulence slope and baroreflex sensitivity, suggesting that heart rate control after PVC is modulated by baroreflex sensitivity through a vagal mechanism. A computer simulation study also suggested that a blunted arterial baroreflex causes pathological heart rate turbulence.[22] In conclusion, loss of HRT may reflect the loss of vagal protection against life-threatening cardiac arrhythmias.

The reduced capacity of an impaired left ventricle to react to different filling and pressure conditions modifies solely the turbulence onset in this study, also indicating that a sympathetic nervous system may play a role in modulating the interaction of post-PVC heart rate acceleration. Interestingly, it was found that the correlation between turbulence onset and baroreflex sensitivity was only lost after combined autonomic blockade with atropine and the ß-blocker esmolol.[18]

Recently, Ebbehoj et al. demonstrated an improvement in HRV in post-MI patients with long-term ß-blocker therapy.[23] Here we found no significant influence of medication, specifically ß-blocker therapy, on heart rate turbulence. This is an important finding since most of MI patients receive ß-blocker within the first days after MI. Therefore, the influence of drugs on risk stratificators like T-wave-alternans or HRV variability needs to be considered during the interpretation of the obtained data, while HRT seems to be independent of medication.

No risk stratification parameter meets all requirements like a high-positive predictive value, high sensitivity and specificity as well as fast and cheap feasibility or additional information to standard parameter like left ventricular ejection fraction.[24–26] In this study, about a quarter of all MI patients with pathological HRT values have normal HRV parameters, normal LV function as well as normal repolarization parameters. This means that without HRT testing these patients would be classified as low risk patients while they may belong to a high risk group.

In conclusion, measurement of the HRT is feasible in only 30-minute Holter ECGs. No association was found between HRT parameters and repolarization parameters, while TS and HRV parameters may contain similar information. The significant association of HRT parameters to age and left ventricular ejection fraction in multivariate analysis has to be taken into consideration during interpretation of HRT parameters in chronic MI patients.

Study Limitations

The cut-offs for TS and TO were originally evaluated in the early postinfarction period of MI patients. Here we investigated chronic MI patients who suffered their first MI before the age of 60 years, so the authors cannot rule out that slightly different cut-off values for TS and TO may be more appropriate to study chronic MI patients like this population.

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