The Significance of Heart Rate Turbulence in Predicting Major Cardiovascular Events in Patients after Myocardial Infarction Treated Invasively

Sylwia Cebula, M.D., Beata Sredniawa, M.D., Jacek Kowalczyk, M.D., Agata Musialik-Lydka, M.D., Aleksandra Wozniak, M.D., Agnieszka Sedkowska, M.D., Andrzej Swiatkowski, 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

Introduction: The role of heart rate turbulence (HRT) related to baroreflex sensitivity in predicting mortality after myocardial infarction (MI) has been confirmed by several investigators. However, the significance of HRT in predicting major adverse cardiovascular events (MACE) following acute MI is unknown.

Purpose: To analyze the prognostic value of HRT and other independent risk factors associated with autonomic regulation of MACE.

Methods: HRT was assessed based on 24-hour Holter recordings in 500 patients (pts) with acute MI treated invasively (352 M, aged 60.58 years). Turbulence onset (TO,%), slope (TS, ms/RR interval) and timing (TT) were calculated. $TO \geq 0$, $TS \leq 2.5$ and $TT \geq 10$ were considered abnormal; classic and own categories were defined. Time domain heart rate variability (HRV) parameters were also calculated. Within 30.1 ± 15.1 months of follow-up, MACE occurred in 116 pts.

Results: Abnormal TO, TS, and TT were significantly more frequent in patients with MACE ($P < 0.05$ for each parameter, classic and own categories). In long-term follow-up, the largest differences in MACE were observed in patients with own category comprising abnormal TO, TS, and TT. Combining HRT parameters with SDNN (total HRV index) augmented their predictive value. Independent risk factors for MACE were TT, SDNN and rMSSD (a parasympathetic activity index) (HR 2.44, 1.71 and 1.69 respectively; $P < 0.05$).

Conclusion: Abnormal HRT distinguishes patients at risk of MACE after MI. Own category encompassing three abnormal HRT parameters best differentiates patients at risk of MACE. Turbulence timing is a strong independent risk factor for MACE following MI.

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heart rate turbulence; autonomic nervous system; myocardial infarction; major adverse cardiovascular events

The implementation of optimal treatment methods, both pharmacological and invasive, in acute myocardial infarction (MI) has resulted in a substantial improvement of long-term outcome in patients after MI. Nevertheless, major adverse cardiovascular events (MACE), encompassing death, urgent

revascularization due to new or recurrent acute ischemia and stroke, still remain a serious problem following MI.^{1,2}

Although numerous factors have been investigated in order to identify patients at risk of death after MI, MACE factors are much less recognized.

Address for correspondence: Beata Sredniawa, MD, Silesian Center for Heart Diseases, Department of Cardiology, Congenital Heart Diseases and Electrotherapy, M.C. Skłodowskiej 9 Street, 41–800 Zabrze, Poland. Fax: +48323733792; E-mail: bms@pro.onet.pl

Drs. Cebula and Sredniawa contributed equally to this article.

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Beside the well-known contributors to unfavorable outcome after MI, i.e., cardiogenic shock on admission and depressed left ventricular ejection fraction (EF), several noninvasive risk markers and prognostic models for fatal events after MI have been developed.^{3–5} Some markers of autonomic tone, such as heart rate variability (HRV), have a well-documented prognostic role.⁶

The announcement of heart rate turbulence (HRT) as a marker of mortality after MI was crucial for risk stratification.⁷ Although numerous subsequent studies have confirmed the prognostic value of HRT in death prediction after MI,⁸ as yet there are no data concerning its role in MACE prognosis. Whilst some HRT parameters, such as turbulence onset (TO) and turbulence slope (TS) as well as their combinations have been widely investigated,^{8,9} little attention has been paid to turbulence timing (TT).¹⁰

The aim of this study was to analyze the prognostic value of HRT and other independent risk factors associated with autonomic regulation of MACE in long term follow-up in patients after acute MI treated invasively.

METHODS

The study population consisted of 500 consecutive patients (352 male, mean age 60.58 ± 11.19 years) with acute MI treated with percutaneous coronary interventions (PCI) between 2004 and 2007 and who fulfilled the following inclusion criteria: clinically, electrocardiographically and laboratory confirmed MI, invasive treatment of acute MI, alive status on the 5th day after acute MI, the presence of sinus rhythm during Holter monitoring and the absence of indications for permanent stimulation. Patients aged ≥ 80 years, who died before Holter monitoring, with permanent atrial fibrillation, unable to perform rehabilitation due to poor compliance, with life expectancy <1 year and patients with <5 ventricular premature ectopic beats in 24-hour Holter monitoring were excluded from the study. All patients signed informed consent to undergo diagnostic and therapeutic procedures, including invasive treatment of MI. The local ethics committee was informed about the collection of data and Holter analysis.

All patients with MI confirmed on the basis of the commonly accepted criteria,¹¹ including elevated biomarkers of myocardial necrosis, such as troponin and/or creatine phosphokinase-MB isoenzyme, were treated invasively on admis-

Table 1. Demographic and Clinical Characteristics of the Study Population

	n (% pts) or Mean Value
Age (years)	60.58 ± 11.19
Gender (male)	352 (70.4)
Hypertension	264 (52.8)
Diabetes	144 (28.8)
Hyperlipidemia	247 (49.4)
STEMI	405 (81)
NSTEMI	95 (19)
Previous MI	95 (19)
Anterior MI	173 (35)
Inferior MI	232 (46.4)
CK-MB on admission (ng/mL)	45.7 ± 71.4
GFR < 60 mL/min/1.73m ²	70 (14)
Hemoglobin (mmol/L)	8.69 ± 1.05
Cardiogenic shock on admission	19 (3.8)
Class Killip on admission	1.25 ± 0.60
EF (5th day MI) (%)	44.24 ± 7.8
NYHA class (5th day MI) (%)	1.20 ± 0.50
TIMI before PCI	0.78 ± 1.10
TIMI after PCI	2.72 ± 0.80
Beta-adrenergic blocker	450 (90)
ACEI/ARB	380 (76)
Acetylsalicylic acid	475 (95)
Clopidogrel/Ticlopidine	460 (92)
Statins	420 (84)

STEMI = ST segment elevation myocardial infarction; NSTEMI = non-ST segment elevation myocardial infarction; MI myocardial infarction; CK-MB = creatine phosphokinase-isoenzyme MB; GFR = glomerular filtration; EF = left ventricular ejection fraction; NYHA = New York Heart Association; TIMI = thrombosis in myocardial infarction; PCI = percutaneous coronary intervention; ACEI/ARB = angiotensin-converting enzyme inhibitors/angiotensin receptor blocker.

sion. All invasive procedures and the pharmacological treatment of MI were performed according to the current guidelines.^{1,12} Eighty-one percent of patients presented MI with ST elevation (STEMI) and the remaining 19% without ST elevation (NSTEMI). Anterior wall infarction was present in 35% of patients and inferior in 46.4%. In the acute phase of MI and during in-hospital stay, the patients received optimal pharmacotherapy, including antiplatelet agents, beta-adrenergic blockers, angiotensin-converting enzyme inhibitors and statins.

The characteristics of the study group, including concomitant diseases, acute MI data, invasive treatment of acute MI and pharmacotherapy at hospital discharge are presented in Table 1.

At the end of in-hospital rehabilitation, a clinical assessment was performed including the

New York Heart Association (NYHA) functional class, EF estimated with the Simpson's method and a 24-hour, 3-lead digital Holter recording (Lifecard CF, Spacelabs Healthcare, Issaquah, WA, USA). Holter analyses were carried out with the use of Pathfinder 700 Spacelabs Healthcare and included interactive arrhythmia analysis, HRV time domain, and HRT.

Assessment of HRV and Other Risk Factors

Mean, maximum and minimum heart rate as well as the total number of ventricular ectopic beats (VE) and the presence of complex ventricular arrhythmias were estimated. Next, HRV time domain standard parameters such as TI, SDNN, SDANN, SDNN index, and rMSSD were calculated.¹³ Based on the data from the literature, the following values were adopted as correlating with an elevated risk of sudden cardiac death: $VE \geq 10/\text{hour}$, the presence of ventricular tachycardia sustained (sVT) and nonsustained (nsVT), heart rate $\geq 70/\text{min}$, SDNN < 70 ms and rMSSD < 20 ms.^{6,9,14} SDNN and rMSSD reflect total HRV and rMSSD, the parasympathetic tone. SDNN is of well-documented prognostic value, whilst rMSSD is a weaker indicator.^{6,13}

HRT Assessment

HRT was assessed in all patients using the HRTView software program. According to the definition, two standard HRT parameters were calculated: TO in percentage and TS in ms/RR interval ratio.^{7,15} In addition, a third parameter, TT, was estimated. TT determines how quickly the sinus deceleration phase starts¹⁶ and is defined as the first beat of the RR interval sequence giving the maximal regression slope used in TS calculation.^{16–18} Thus, for example, $TT = 4$ means that the RR_4 to RR_8 interval gave the maximal TS within the first twenty sinus rhythm intervals after VE.^{16,17,19}

$TO \geq 0\%$ and $TS \leq 2.5$ ms/RR interval, previously documented by Schmidt, were considered abnormal.⁷ TT has mostly been reported in the first 10 RR intervals after VE; accordingly, in this study, $TT \geq 10$ was assumed abnormal.²⁰ A median value of $TT = 5$ was reported in 95 healthy individuals.²¹

In further analysis, the classic HRT categories, i.e., HRT 0 (both TO and TS normal), HRT 1 (TO or TS abnormal) and HRT 2 (both TO and TS ab-

normal) were used.^{9,22} In addition, own categories were established for the purpose of this study based on the combination of the three HRT parameters: HRT A (TO and TS and TT normal), HRT B (TO or TS or TS abnormal), and HRT C (TO and TS and TT abnormal).

Long-Term Follow-Up

The mean follow-up was 30.1 ± 15.1 months. MACE occurred in 116 patients (pts) and was defined as a combined end point of: death due to any cause, urgent percutaneous coronary angioplasty because of another acute coronary syndrome, urgent revascularization with coronary artery bypass grafting, or stroke. Total mortality was 7.6% (38 pts).

Statistical Methods

Continuous parameters were expressed as means with standard deviations unless otherwise specified; categorical variables were presented as numbers and percentages. A 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. Univariate Cox regression model was used to evaluate parameters such as risk for the studied end point. Log-rank tests were used to compare Kaplan–Meier curves plotted for the combined end point. All the independent risk factors were selected using multivariate logistic regression with the backward selection method. The results of multivariate Cox regression analysis were expressed as hazard ratio with a 95% confidence interval. Pearson's correlation coefficient was used to determine the correlation between continuous variables. 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 mean HRT values in the entire population were: TO $-0.71 \pm 2.34\%$, TS 6.14 ± 6.39 ms/RR interval and TT 7.10 ± 3.12 . Classic HRT categories were observed in: HRT 0 in 230 pts (46%), HRT 1 in 270 pts (54%), and HRT 2 in 75 pts (15%). The additional own categories were observed in: HRT A in 195 pts (39%), HRT B in 305 pts (61%), and HRT C in 39 pts (7.8%).

Table 2. The Comparison of Demographic and Clinical Data of Patients with MI in Respect to MACE Occurrence

	Pts without MACE n = 384	Pts with MACE n = 116	P Value
Age (years)	60.03 ± 11.28	62.35 ± 10.81	NS
Gender (Male) n (%)	269 (70)	81 (69.8)	NS
Hypertension n (%)	196 (51)	67 (57.7)	NS
Diabetes n (%)	100 (26)	43 (37)	<0.05
Hyperlipidemia n (%)	193 (50)	51 (43.9)	NS
STEMI n (%)	315 (82)	90 (77.6)	NS
NSTEMI n (%)	69 (18)	26 (22.4)	NS
Previous MI n (%)	57 (14.8)	37 (31.8)	<0.001
Anterior MI n (%)	136 (35.4)	37 (31.9)	NS
Inferior MI n (%)	179 (46.6)	53 (45.7)	NS
CK-MB on admission (ng/mL) ± SD	44.62 ± 71.91	49.76 ± 70.06	NS
CK-MB max (ng/mL) ± SD	181.04 ± 148.68	201.41 ± 169.0	NS
Hemoglobin (ng/mL) ± SD	8.79 ± 2.35	9.79 ± 9.06	NS
GFR < 60 mL/min/1.73m ² n (%)	38 (9.8)	29 (25)	<0.05
Class Killip on the admission ± SD	1.16 ± 0.43	1.53 ± 0.92	<0.001
Shock on admission n (%)	5 (1.3)	14 (12)	<0.001
NYHA class (5th day MI) ± SD	1.16 ± 0.47	1.30 ± 0.59	<0.5
EF (5th day MI) (%)	44.7 ± 7.44	42.64 ± 8.69	<0.05
EF < 35% (5th day MI) n (%)	35 (9.1)	21 (18.1)	< 0.05
TIMI before PCI ±SD	0.80 ± 1.10	0.67 ± 1.08	NS
TIMI after PCI ±SD	2.77 ± 0.73	2.54 ± 1.02	<0.05
TIMI < 3 after PCI n (%)	43 (11.2)	23 (19.8)	<0.05
One-vessel CAD n (%)	164 (42.8)	28 (24.1)	<0.001
Multivessel CAD n (%)	220 (57.2)	88 (75.9)	<0.001
Incomplete revascularization n (%)	167 (43.4)	79 (68.1)	<0.001
Beta-adrenergic blocker n (%)	345 (89.8)	103 (89)	NS
ACEI/ARB n (%)	287 (74.7)	88 (75.8)	NS
Acetylsalicylic acid n (%)	357 (92.9)	110 (94.8)	NS
Clopidogrel/Ticlopidine n (%)	355 (92.4)	106 (91.4)	NS
Statins n (%)	315 (82)	97 (83.6)	NS

STEMI = ST segment elevation myocardial infarction; NSTEMI = non-ST segment elevation myocardial infarction; MI myocardial infarction; CK-MB = creatine phosphokinase- isoenzyme MB; GFR = glomerular filtration; EF = left ventricular ejection fraction; NYHA = New York Heart Association; TIMI = thrombosis in myocardial infarction; PCI = percutaneous coronary intervention; ACEI/ARB = angiotensin-converting enzyme inhibitors/angiotensin receptor blocker.

MACE and the Comparison of Demographic and Clinical Data

Patients with and without MACE did not differ significantly with regard to age and gender. Diabetes and previous MI were significantly more frequent in the group with MACE ($P < 0.05$ and $P < 0.001$, respectively), and the percentage of patients with lowered GFR was higher (Table 2). This group was also characterized by a significantly higher Killip class and cardiogenic shock on admission ($P < 0.001$), higher NYHA class ($P < 0.05$), lower EF on the 5th post MI day ($P < 0.05$) and a higher percentage of patients with EF < 35% on the 5th post-MI day (Table 2). There was also a significantly greater percentage of patients with incomplete reperfusion ($P < 0.001$), revascularization

($P < 0.05$), and multivessel coronary artery disease ($P < 0.001$) in the MACE group (Table 2). The groups did not differ significantly with regard to other concomitant diseases, clinical data, and pharmacotherapy (Table 2).

MACE and the Assessment of HRT and Other Noninvasive Predictors

All HRT parameters were significantly worse in patients with MACE than in patients without such events: TO $-0.28 \pm 1.85\%$ vs $-0.82 \pm 2.44\%$; $P < 0.05$, TS -4.16 ± 4.67 ms/RR vs 6.73 ± 6.72 ms/RR interval; $P < 0.001$ and TT 8.87 ± 3.08 vs 6.57 ± 2.93 ; $P < 0.001$.

The percentage of patients with abnormal TO did not differ significantly between the group with

Table 3. Heart Rate Turbulence Parameters and Other Noninvasive Predictors in Patients with and without MACE

	Pts with MACE n = 384	Pts without MACE n = 116	P Value
Heart rate turbulence			
TO $\geq$ 0% n (%)	138 (35.9)	50 (43.1)	NS
TS $\leq$ 2.5 ms/RR interval	92 (23.9)	65 (56)	<0.001
TT $\geq$ 10 n (%)	80 (20.8)	63 (54.3)	<0.001
HRT category 0 n (%)	203 (52.8)	24 (20.6)	<0.001
HRT category 1 n (%)	180 (46.8)	91 (78.4)	<0.001
HRT category 2 n (%)	49 (12.7)	25 (21.5)	<0.05
HRT category A n (%)	171 (44.5)	23 (19.8)	<0.001
HRT category B n (%)	211 (54.9)	93 (80.1)	<0.001
HRT category C n (%)	16 (4.2)	23 (19.8)	<0.001
Heart rate			
Mean heart rate beats/min $\pm$ SD	67.50 $\pm$ 8.89	73.47 $\pm$ 10.79	<0.001
Max. heart rate beats/min $\pm$ SD	87.71 $\pm$ 21.68	95.35 $\pm$ 20.78	<0.001
Min. heart rate beats/min $\pm$ SD	62.40 $\pm$ 18.14	65.44 $\pm$ 15.48	NS
Ventricular arrhythmias			
VE/24h $\pm$ SD	202.48 $\pm$ 1040.89	434.09 $\pm$ 1882.52	NS
VE $\geq$ 10/h n (%)	40 (10.4%)	19 (16.4%)	NS
nsVT n (%)	27 (7.0%)	8 (6.8%)	NS
HRV, "time domain"			
Mean RR [ms] $\pm$ SD	891.85 $\pm$ 122.35	825.90 $\pm$ 117.89	<0.001
Mean RR $\leq$ 857 ms ($\geq$ 70 beats/min) n (%)	153 (39.8)	70 (60.3)	<0.001
24 TI $\pm$ SD	21.41 $\pm$ 11.88	17.44 $\pm$ 9.70	<0.001
SDNN [ms] $\pm$ SD	100.41 $\pm$ 26.99	84.63 $\pm$ 31.40	<0.001
SDANN [ms] $\pm$ SD	85.42 $\pm$ 24.98	75.65 $\pm$ 29.23	<0.001
SDNNi [ms] $\pm$ SD	45.58 $\pm$ 17.36	33.99 $\pm$ 17.14	<0.001
SDNN < 70 [ms] n (%)	44 (11.4)	46 (39.7)	<0.001
rMSSD [ms] $\pm$ SD	26.80 $\pm$ 17.65	19.09 $\pm$ 9.97	<0.001
rMSSD < 20 [ms] n (%)	146 (38.0)	73 (62.9)	<0.001

HRT = heart rate turbulence; TO = turbulence onset; TS = turbulence slope; TT = turbulence timing; VE = ventricular ectopic beat; nsVT = nonsustained ventricular tachycardia; HRV = heart rate variability; Mean RR = mean RR intervals; 24 TI, SDNN, SDANN, SDNNi, rMSSD = heart rate variability parameters.

and without MACE after MI, however, the percentage of pts with abnormal TS and TT was higher in the MACE group (Table 3). The investigated groups differed with regard to HRT category. MACE patients significantly more frequently fell into categories including at least one, two or three abnormal HRT parameters (Table 3). HRT category 2 (abnormal TO and TS) was observed in 12.7% patients without MACE and in 21.5% with MACE ($P < 0.05$), whilst the additional HRT category C (abnormal TO, TS, and TT) was noted in 4.2% versus 19.8%, respectively (Table 3).

MACE patients had a faster mean and maximal heart rate. Also, the percentage of patients with heart rate $\geq$ 70 beats per minute was higher in this group ($P < 0.001$). All HRV parameters were significantly lower in MACE patients. There were significantly more patients with SDNN < 70 ms in the

Mace group compared to patients without MACE ($P < 0.001$; Table 3).

The Relation between MACE and HRT Parameters in Long-Term Follow-Up after MI

Significant differences in the occurrence of MACE in patients after MI in relation to selected HRT parameters were demonstrated with the Kaplan-Meier curves. In long-term follow-up, 72% patients with normal TO and 55% with abnormal TO were MACE-free. With regard to TS, 78% patients with normal and 48% patients abnormal were MACE-free. The largest differences in MACE occurrence were observed with respect to TT values. In the 30-month follow-up, 78% of patients with normal TT and only 41% patients with abnormal TT were MACE-free (Fig. 1).

Figure 1. Differences in MACE occurrence after MI with respect to the values of selected HRT parameters.

The Kaplan-Meier curves, plotted using HRT categories, also revealed significant differences in MACE occurrence. When classic categories were used, significant differences between HRT category 0 (TO and TS normal) and the remaining categories comprising at least one abnormal parameter

($P < 0.001$) were observed; categories HRT 1 and HRT 2 differentiated patients in an identical way ($P = 0.84$ between these categories; Fig. 2).

When our own categories were incorporated, significant differences within the 30-month follow-up were observed between HRT A (TO, TS, and TT normal) and the remaining categories encompassing at least one abnormal parameter ($P < 0.001$). Significant differences were also observed between the remaining categories ($P < 0.001$). The largest differences were demonstrated between HRT C (three abnormal parameters) and HRT A (three normal parameters), with 20% versus 82% patients free of MACE, respectively (Fig. 2).

The combination of HRT parameters with the HRV parameter (SDNN) augmented the differences in MACE occurrence after MI. MACE did not occur in 70% of patients with normal TO and $SDNN \geq 70 \text{ ms}$ and in 42% of patients with abnormal TO and $SDNN < 70 \text{ ms}$ (Fig. 3). Stronger differences were demonstrated when TS and TT were combined (75% vs 18% free of MACE), as well as TT and SDNN (72% vs 14% free of MACE; Fig. 3).

Independent Predictors of MACE

The multivariate Cox regression analysis revealed incomplete revascularization, cardiogenic shock on admission, and the autonomic regulation parameters: $SDNN < 70 \text{ ms}$, $rMSSD < 20 \text{ ms}$ and $TT > 10$ to be independent risk factors for MACE (Table 4). The strongest factor was TT, which increased MACE risk 2.44-fold, closely followed by incomplete revascularization, which increased the risk 2.21-fold (Table 4).

Relationships between HRT Parameters and HRV Indices, Heart Rate and Clinical Variables

In the entire study group, weak but significant correlations between SDNN versus TO, TS, and TT were found: $r = -0.18$, $P < 0.001$; $r = 0.3$, $P < 0.001$; $r = -0.28$, $P < 0.001$, respectively. Among the HRT parameters, a weak but significant correlation was found only between $rMSSD$ and TT ($r = -0.15$, $P < 0.05$).

Significant correlations between HRT and cardiac cycle length were present for TS and TT: $r = 0.20$, $P < 0.001$; $r = -0.15$, $P < 0.05$, respectively.

Figure 2. Differences in MACE occurrence after MI with respect to HRT categories.

In patients with incomplete reperfusion, defined as thrombosis in myocardial infarction (TIMI) grade <3 in the infarct-related artery after PCI, abnormal TS and HRT category 2 were significantly more frequent than in patients with TIMI grade > 3: 25 (42.4%) versus 129 (29.2%); $P < 0.05$, 15 (25.4) versus 59 (13.3%); $P < 0.05$, respectively.

DISCUSSION

The main finding of the presented study is that HRT has a predictive value of MACE after MI, defined as a combined end point of death due to any cause, urgent percutaneous coronary angioplasty because of another acute coronary syndrome, urgent revascularization with coronary by-pass

Figure 3. Differences in MACE occurrence after MI with respect to combined HRT parameters and the HRV SDNN index.

grafting or stroke. The largest differences in MACE occurrence were revealed when our own HRT category, comprising two classic parameters, i.e., abnormal TO and TS, and the rarely investigated TT, was used. Moreover, TT was a strong independent

Table 4. Independent Risk Factors for MACE in Patients after MI.

Variable	Hazard Ratio-HR	95% CI	P Value
Cardiogenic shock on admission	2.08	1.77–2.39	<0.05
Incomplete revascularization	2.21	2.02–2.42	<0.05
SDNN < 70 ms*	1.77	1.54–2.0	<0.05
rMSSD < 20 ms*	1.69	1.48–1.9	<0.05
TT ≥ 10*	2.44	2.25–2.63	<0.001

*HRT and HRV parameters reflecting autonomic regulation. HR = hazard ratio; CI = confidence interval; SDNN, rMSSD = heart rate variability parameters (HRV); TT = turbulence timing.

risk factor for MACE in long-term follow-up after acute MI.

The prognostic significance of HRT parameters, i.e., TO, TS, and their combinations of normal and abnormal values, in the prediction of total mortality after MI is well-documented in patients treated without reperfusion and invasively.^{7,9,23} In the FINGER postinfarction trial, together with EF and nsVT, HRT was a strong predictor of total mortality and sudden cardiac death.²⁴ In the REFINE trial, HRT category 1 combined with microvolt T-wave alternans gave a high predictive value for cardiac death, total mortality and sudden cardiac death.²⁵ In the cited studies, HRT was investigated as a marker of total mortality or sudden cardiac death, but not as a MACE factor. Our study revealed HRT to be a MACE predictor, total mortality included. Therefore, our results not only confirm the predictive value of HRT for the most fatal event, i.e., death after MI, but also increase the predictive value of HRT for stroke and acute coronary syndromes requiring urgent revascularization. We have also confirmed the values proposed by Schmidt for classic parameters in risk stratification: TO ≥ 0% and TS ≤ 2.5 ms/RR interval. Only one author proposed the value of TS ≤ 3 ms/RR interval as a predictor in heart failure.²⁶ Our study proves the importance of TT, a parameter that has not been widely investigated thus far. Beside incomplete revascularization, cardiogenic shock on admission and parameters reflecting autonomic tone, TT was the strongest independent parameter differentiating patients with regard to MACE (2.5-fold increased MACE risk). In our study, TT ≥ 10 was considered abnormal.

The mean TT values for patients with and without MACE were 8.87 and 6.57, respectively. Taking into account the median value of TT = 5 reported by Schwab in healthy individuals,²¹ the very late deceleration seems to reflect the mechanism underlying MACE occurrence.

Autonomic dysfunction is a well-documented factor responsible for fatal events after MI.^{5,6} It has been hypothesized that HRT is related to parasympathetic tone and baroreflex sensitivity.^{27,28} Correlations have been observed between TS and baroreflex sensitivity, between TO, TS, SDNN, and rMSSD.^{27,29,30} Our results have revealed significant correlations between TO, TS, and TT with SDNN, reflecting total HRV. The correlation with the parasympathetic activity parameter confirms the dependence between HRT and parasympathetic tone. A negative correlation between TT and cardiac cycle length was described by Watanabe.¹⁷ In our population, we also found such a relation. The meaning of heart rate as a marker of cardiovascular events in coronary patients, including those after MI, has recently been investigated in detail.^{14,31,32} The influence of heart rate on HRT in healthy individuals was documented by Schwab.²¹ These data and our results indicate the existence of a relation between heart rate and TT, potentially connected with the strong predictive value of this parameter in MACE prediction after MI.

We also found that by incorporating TT, the predictive value of classic categories improved significantly. The combination of three abnormal HRT parameters, including TT, gave the best results in identifying patients at risk of MACE. When our own categories were used, after the 30-month follow-up, 82% of patients with three normal (TO, TS, and TT) parameters and only 20% of patients with three abnormal parameters were MACE-free.

Severe autonomic failure (SAF) has recently been described as a marker for unfavorable outcome after MI. Bauer defines SAF as a global dysfunction of autonomic regulation (expressed by deceleration capacity) and the presence of impaired baroreflex sensitivity (expressed by HRT).^{33,34} In the ISAR-Risk study and further meta-analysis of four independent post-infarction trials, SAF was documented as a strong independent factor for fatal events after MI.³⁵ In our study, the combination of HRT parameters with SDDN < 70 ms augmented the predictive value of selected parameters in MACE prediction, particularly when TT was combined with SDNN. With this combination, it

may be possible to evaluate cardiovascular events after MI. Moreover, three parameters reflecting different autonomic functions: SDNN < 70 ms expressing total HRV, TT ≥ 10 reflecting altered baroreflex sensitivity and rMSSD < 20 ms expressing impaired parasympathetic tone, were independent factors for such events, reflecting a serious autonomic dysfunction after MI, responsible for the unfavorable outcome after MI.

The most recent study suggests a relation between myocardial salvage, assessed by the radionuclide method, and the autonomic function in patients with acute MI treated with PCI. Low myocardial salvage index was an independent risk factor for abnormal TS and deceleration capacity.³⁶ The immediate beneficial influence of revascularization on HRT parameters in patients with acute MI treated with successful coronary angioplasty³⁷ and the prognostic significance of outcome after coronary bypass grafting are also documented.³⁸ Our results support the conception that incomplete reperfusion, defined as TIMI grade <3 in the infarct related artery after PCI, due to the presence of residual ischemia, may alter the autonomic function, as suggested by the higher percentage of patients with abnormal HRT in this group after MI. Accordingly, it may be responsible for the prognostic significance of HRT in the prognosis of MACE.

Our results can have a practical impact, since HRT may help identify patients after MI at risk of MACE, including acute coronary syndromes. The presented results also show that TT, especially when used in combination with classic parameters, is a useful predictor of unfavorable outcome after MI. As it has recently been revealed that HRT in the early post-MI period is connected with high mortality,³⁹ HRT assessment should be carried out early after MI.

Limitations of the Study

The presented method cannot be used in patients with permanent atrial fibrillation, permanent atrial stimulation or nonsinus rhythms. It is of no value in patients without VE or with only few ectopic beats. Some authors suggest that HRT parameters may change after MI and therefore, for risk stratification purposes, the assessment should be repeated one year after MI.⁴⁰ Due to the known alterations in the autonomic nervous system in the elderly, patients aged over 80 were not classified into this study.

CONCLUSIONS

Abnormal HRT after MI distinguishes patients at risk of MACEs. Our own category encompassing three abnormal HRT parameters best differentiates patients at risk of MACE. TT is a strong independent risk factor for these events following acute MI. Depressed total HRV, abnormal TT and the parasympathetic tone parameter are independent risk factors for MACE in patients after MI with serious autonomic dysfunction.

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