The Relationship between Heart Rate Variability and Heart Rate Turbulence Dynamics after Primary Coronary Angioplasty

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Background: The application of heart rate turbulence (HRT) analysis for risk assessment after pharmacologically treated myocardial infarction (MI) was described in 1999. The aim of the present study was to evaluate the dynamics of HRT changes in long-term observation after MI treated with primary coronary angioplasty (PTCA). Moreover, the usefulness was assessed of early postinfarction heart rate variability (HRV) analysis for predicting HRT dynamics.

Methods: The study group consisted of 96 patients with MI treated with primary PTCA. Holter monitoring with HRV and HRT analysis was performed 3 days after the procedure and 1 year later.

Results: Twelve months after primary PTCA, an improvement (Type I HRT dynamics) was noted in 51 patients, and the worsening of both the HRT parameters (Type II HRT dynamics) in 34 patients. Fourteen patients showed the worsening of only one HRT parameter (Type III HRT dynamics). The following HRV parameters recorded in early postinfarction Holter monitoring had a significant influence on the risk of Type II HRT dynamics: SDNN, RMSSD, Triangle Index and Δ LF/HF (mean day-time LF/HF – mean night-time LF/HF). Only the latter was found in the multivariate analysis as significantly connected with worsened HRT. During the follow-up, SDNN and Triangular Index improved in all the patients.

Conclusions: HRT after myocardial infarction treated with primary PTCA presents a significant dynamics, which is different than dynamics of HRV. An abnormal circadian pattern of autonomic activity is a finding that helps identify patients who need to have HRT analysis repeated during a long-term follow-up, due to the tendency for HRT to change with time toward the prognostically unfavorable values.

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heart rate turbulence; primary coronary angioplasty; Holter monitoring

In 1999, Schmidt et al. introduced heart rate turbulence (HRT)—a new method for risk assessment after myocardial infarction.¹ Their study, however, focused on patients receiving pharmacological treatment patients and only 50% of them had a thrombolytic therapy.

The usefulness of HRT at the time when the interventional treatment of myocardial infarction (MI) is routinely applied remains unclear. Patients regaining effective perfusion as a result of primary PTCA usually have only a slight myocardial dysfunction and their prognosis is quite good. However, as the time goes by, the risk connected with the progression of coronary artery disease increases even in

the “low-risk” patients. It would be interesting to find whether and how the HRT parameters can change in this group during a long-term monitoring after myocardial infarction. HRT (like the heart rate variability (HRV) analysis) is an electrocardiographic method for assessment of autonomic modulation. HRT is a new method while HRV presently constitutes a part of a standard Holter ECG monitoring. The relationship between HRV and HRT parameters was previously described by several authors.^{2–4} However, it is not known whether the pattern of possible HRT changes is similar to the pattern of HRV changes in postinfarction patients.

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The main aim of our study was to evaluate the dynamics of HRT changes in long-term observation after MI treated with primary PTCA. The second aim was to assess the association between HRT and HRV parameters obtained soon after myocardial infarction and the dynamics of HRT changes observed during first year following MI. We also wanted to compare the postinfarction dynamics of HRT and HRV.

MATERIAL AND METHODS

The study group comprised 96 patients (69 men, 27 women), aged 55 ± 10 years, who were admitted to the hospital with acute MI. Enrolled for the study were the subjects who had primary PTCA performed within the first 6 hours since the manifestation of chest pain and the procedure was successful (flow grade TIMI 3 in infarct-related artery). The following exclusion criteria were adopted:

1. An occurrence of the following signs and symptoms before discharge from hospital:
 - recurrent chest pain
 - renewed increase in cardiac enzymes
 - new electrocardiographic signs of ischemia
2. Implanted pacemaker or indications to implantation
3. atrial fibrillation (chronic or paroxysmal)
4. lack of ventricular premature beats in 24-hour Holter recording

Each patient had two sessions of 24-hour Holter monitoring (Pathfinder 700, DelMar Reynolds, Hartford UK) performed: the first on day 3 after primary PTCA, and the control one 12 months later. The following cardiac parameters were analyzed during both Holter sessions

1. Arrhythmia
2. ST segment
3. HRV (time- and frequency-domain parameters)
4. HRT

In arrhythmia analysis, heart rate (minimal, maximal and mean), the presence of premature ventricular and supraventricular beats as well as the complex forms of arrhythmia were assessed.

ST segment changes were evaluated for each normal cardiac evolution, and transient ischemic episodes were diagnosed according to the "1 × 1 × 1" rule.⁵

HRV was assessed according to the guidelines of the European Cardiac Society and North American Society of Pacing and Electrophysiology.⁶ In time-domain analysis, SDNN, RMSSD, and Triangular Index were calculated from the 24-hour ECG record. Spectral indexes of HRV were computed with the fast Fourier transformation model. The analysis was done using the "Step and Scan" mode, which made it possible to divide Holter recording into 5-minute fragments. The following frequency-domain parameters were assessed for each fragment:

1. low frequency—LF (0.04 to 0.15 Hz)
2. high frequency—HF (0.15 to 0.40 Hz)

LF and HF parameters were expressed in ms.² To determine the circadian pattern of autonomic modulation, the difference (Δ LF/HF) between mean LF/HF value from the daytime record and mean LF/HF from the night-time period was calculated. We assumed that Δ LF/HF < 1 reflected an impaired circadian pattern of autonomic activity.

HRT analysis was performed using an algorithm adapted from the web page on noncommercial HRT usage. Two parameters describing HRT were calculated. Turbulence onset (TO) was defined as the difference between the mean of the first two sinus RR intervals after ventricular premature beat (VPB), and the last two sinus RR intervals before VPB divided by the mean value of the last two sinus RR intervals before VPB. TO (expressed in %) was calculated for each VPB and then averaged. Turbulence slope (TS) was defined as the maximum positive value of the slope of a regression line assessed over any sequence of five subsequent sinus RR intervals within the first 20 sinus intervals after VPB. TS was calculated based on an averaged local tachogram. The TS value was expressed in ms/RR interval. Filtering algorithms was used to exclude inappropriate RR intervals and ventricular premature beats with too long coupling intervals or too short compensatory pause.

STATISTICAL ANALYSIS

All data were presented as mean $\pm$ SD. Statistical differences between groups were assessed by analysis of variance (ANOVA) and the method developed by Bonferroni (continuous variables) or² and Fisher's exact tests (discrete variables). TO and TS dynamics was determined with multivariate

analysis of variance (MANOVA) for the repeated measures. Pearson's linear correlation coefficient was used to evaluate the relationship between TO and TS. The influence of individual variables on the risk of worsening of both HRT parameters was assessed using univariate logistic regression analysis. A multivariate logistic regression model was constructed to determine the group of variables most likely to influence the TO and TS variables (parameters). P values <0.05 were considered statistically significant. Statistical software package SPSS PC (Chicago, IL, USA) was used for analysis.

RESULTS

All patients were asymptomatic during both Holter sessions (initial and after 12 months). Within the 12-month follow-up after myocardial infarction no new coronary events could be recorded in the study population.

Dynamics of HRT Changes

In early postinfarction Holter monitoring only one patient had abnormal both HRT parameters. In the control Holter monitoring, the values of both the HRT parameters changed significantly compared with the postinfarction examination. Three types of HRT dynamics could be distinguished: improvement of both parameters, worsening of both parameters and worsening of one parameter. Taking account of the prevalence of each type of HRT dynamics, the study population was divided into three groups:

Group 1: Fifty-one patients with Type I HRT dynamics: TS increase (from 8.511 ± 5.936 ms/RR to 10.83 ± 5.531 ms/RR, $P < 0.0001$) and TO decrease (from $-1.96 \pm 1.85\%$ to $-3.012 \pm 1.57\%$, $P < 0.0001$).

Group 2: Thirty-one patients with Type II HRT dynamics: TS decrease (from 7.414 ± 4.23 ms/RR to 3.839 ± 2.735 ms/RR, $P < 0.0001$) and TO increase (from $-1.47 \pm 1.84\%$ to $-0.04 \pm 0.87\%$, $P < 0.0001$).

Group 3: Fourteen patients with Type III HRT dynamics (TS decrease or TO increase).

After 12 months pathologic values of both HRT parameters were found in three patients (one from Group 2 and two from Group 3). All of them initially had normal HRT.

Figure 1 presents the dynamics of changes in HRT parameters within 12 months postinfarction (Fig. 1A—TO changes, Fig. 1B—TS changes).

A strong correlation between TO and TS observed in early postinfarction period remained similar after 12 months despite significant changes in both the HRT parameters (Fig. 2).

Comparison of Study Groups

The three study groups did not differ significantly with respect to the demographic or clinical characteristics (Table 1). Patients with one-vessel coronary artery disease were the largest part of each study group. The results of coronary angiography and primary PTCA are shown in Table 2.

HRT analysis did not reveal any significant between-group differences with regard to TO and TS parameters. Figure 3 presents the comparison of HRT parameters in the three study groups.

Early Postinfarction HRV Analysis

Patients from Group 2 had significantly lower SDNN and Triangular Index than those from Group 1. The difference between RMSSD values did not reach statistical significance. In the frequency-domain analysis, only Δ LF/HF was found to differ in the study groups. This parameter assumed negative values in patients from Group 2 (Table 3).

Dynamics of HRV Changes

Table 4 shows the comparison of heart rate, SDNN, LF, HF, and Δ LF/HF values obtained at baseline and after 12 months in three study groups.

The changes in HRV parameters indicated by the comparison of early and control Holter ECG monitoring are displayed in Figure 4. All the time-domain parameters showed an increasing tendency within 12 months after MI. The difference between values obtained in first and control Holter monitoring was statistically significant only for SDNN and Triangular Index, whereas as for RMSSD it did not reach the statistical significance. It is worth noting that in patients with worsened HRT, the RMSSD value remained almost unchanged during the first year postinfarction.

Although in the univariate regression analysis, several HRV parameters significantly modified the risk of worsening HRT, the multivariable analysis indicated only one— Δ LF/HF as having influence on the unfavorable changes in TO and TS values within the first year after primary PTCA. Of note is, that the connection was inversely proportional:

Figure 1. (A) Dynamics of TO changes following 12 months after myocardial infarction. (B) Dynamics of the TS changes following 12 months after myocardial infarction.

the higher the Δ LF/HF, the lower risk of worsened HRT (Table 5).

DISCUSSION

The heart rate turbulence denotes the fluctuations in sinus cycle length after a single ventricular premature beat. Although their mechanics still remains unclear it is believed that HRT is triggered by underlying physiological alterations of cardiac autonomic modulation. The sudden drop in blood pressure, which is caused by VPB as a result of insufficient ventricular filling, produces the inhibition of the parasympathetic activity leading to sinus rate acceleration. The ensuing compensatory pause and increase in blood pressure produce the opposite effect (vagal recruitment and sympathetic withdrawal), which leads to the deceleration in sinus cycle length.^{7,8}

HRT was described by Schmidt et al. as a novel method for estimating the risk of sudden car-

diac death after myocardial infarction. Their study, however, focused on the patients receiving pharmacological treatment; only 50% had the thrombolytic therapy.¹ At present, primary PTCA is the "method of choice" in the treatment of acute myocardial infarction. The usefulness of HRT at the times when the interventional treatment of MI is routinely applied remains to be checked up. In fact, the patients with effective reperfusion gained via primary PTCA, usually present only a slight myocardial dysfunction. In our study population, only one patient had pathologic (after Schmidt et al.) TO and TS values in early postinfarction Holter ECG monitoring. Would this mean that HRT analysis is not useful in patients who had undergone successful primary PTCA? The prognosis for such patients is good enough, however, as the time goes by, the risk connected with a progression of coronary artery disease increases even in the "low-risk" patients. In view of the above, it would be interesting to investigate whether and how HRT can change

Figure 2. Correlation between TO and TS in early postinfarction Holter monitoring and 12 months after MI.

after myocardial infarction. Since now there is a little information in literature about the postinfarction dynamics of HRT values. Ortak et al. who observed patients of similar clinical characteristics to our study population did not find any changes of HRT parameters following 12 months after primary PTCA.⁹

In our study, three different types of HRT dynamics were found during a long-term period of postinfarction monitoring. The increase in TO and decrease in TS values over 12 months postinfarction compared with early postinfarction records (Type II HRT dynamics) was interpreted as the worsening of the HRT parameter while the decreased TO and increased TS (type I HRT dynamics) was assumed to be a sign of HRT improvement. Bonnemeier et al. used a similar interpretation

when describing HRT improvement within the first 24 hours after successful primary PTCA.¹⁰

However, the patients in our study were monitored for a significantly longer period of time. One year after MI, 32 of them presented a strong tendency for HRT parameters to change toward the abnormal values, with worse prognosis. In our opinion, this finding indicates that it is necessary to repeat the HRT analysis some time after myocardial infarction even in the low-risk, asymptomatic patients.

In the present study, we also found that detection of early postinfarction impairment of the circadian pattern of autonomic activity could help identify patients at a high risk of HRT worsening with time.

HRV determined from 24-hour ECG records, is well-established noninvasive marker of cardiac autonomic activity in patients recovering from acute MI.^{11,12}

In our study population the impaired circadian pattern of autonomic activity, expressed by the low $\Delta\text{LF}/\text{HF}$, modified the relative risk of HRT worsening. The results of multivariate logistic regression analysis indicated $\Delta\text{LF}/\text{HF}$ to be the only HRV parameter that had definitely influenced the risk for worsened HRT.

The stability of the circadian rhythm of HRV and the reproducibility of its measurements were described in healthy individuals as well as in patients with coronary artery disease.^{13,14} Abnormal circadian pattern of autonomic activity is a prognostically unfavorable condition. As we found in previous studies, it is related to an impaired circadian pattern of blood pressure and even more frequently with the occurrence of silent ischemia episodes in patients with a stable coronary heart disease.¹⁵ The usefulness of abnormal HRV circadian pattern in the risk assessment of coronary diabetic patients

Table 1. Demographic Characteristics, Infarct Localization and Left Ventricular Ejection Fraction (EF) in Study Groups

Parameter	Group 1	Group 2	Group 3	P
Number	51	31	14	
Age (years)	56.6 ± 10.4	56.2 ± 10.3	57.1 ± 10.9	NS
Male (%)	39 (76)	20 (65)	10 (71)	NS
Female (%)	12 (24)	11 (35)	4 (29)	NS
Anterior infarction (%)	30 (58.8)	20 (64.5)	6 (42.9)	NS
Inferior infarction (%)	21 (41.2)	11 (35.5)	7 (57.1)	NS
EF (%)	46.8 ± 7	44.9 ± 9.8	46.6 ± 8.2	NS

EF = left ventricular ejection fraction.

Table 2. Coronary Angiography and PTCA Results in Study Groups

Parameter	Number of patients			P
	Group 1 (n = 51)	Group 2 (n = 31)	Group 3 (n = 14)	
1-VD	38 (74.5%)	20 (64.5%)	10 (71.4%)	NS
2-VD	12 (23.5%)	10 (32.3%)	3 (21.4%)	NS
3-VD	1 (2.0 %)	1 (3.2%)	1 (7.1 %)	NS
PTCA RC	20 (39.2 %)	12 (38.7%)	7 (50.0%)	NS
PTCA LAD	22 (43.1%)	16 (51.6%)	5 (35.7%)	NS
PTCA Cx	12 (23.5 %)	4 (12.9%)	2 (14.3 %)	NS
Stent implantation	43 (86%)	25 (80.6%)	10 (71.4%)	NS

1-VD = one-vessel coronary artery disease; 2-VD = two-vessel coronary artery disease; 3-VD = three-vessel coronary artery disease; RC = right coronary artery; LAD = left anterior descending coronary artery; Cx = circumflex branch of left coronary artery.

was also described by Burger et al.¹⁶ An impaired HRV circadian pattern may be caused by abnormal parasympathetic or sympathetic modulation.^{17,18} The relationship observed in the present study between the worsening of HRT (which is subject to parasympathetic regulation) and abnormal circadian HRV rhythm implies a significant role of vagal impairment in the latter pathology.^{8,19}

Another interesting finding was the different postinfarction dynamics of HRV and HRT parameters. All the time-domain HRV parameters improved in all the study groups after 12 months following MI. Similar observation was provided by Ortak et al. who reported the improvement of time-domain HRV parameters following 12 months after primary PTCA.⁹ However, as regards RMSSD, only a slight increasing tendency could be observed in our study population. In fact, this parameter remained almost unchanged in Group 2. It is generally agreed that RMSSD expresses mostly the vagal modulation. The lack of improvement in this parameter during the follow-up may be connected with the parasympathetic dysfunction in Group 2. These patients presented worse HRT values while RMSSD remained almost unchanged. This finding is difficult to interpret, the more so that the knowledge of HRT is still limited. One of the possible explanations is that the medications received by postinfarction patients (mainly beta-blockers and angiotensin converting enzyme inhibitors) may have a greater influence on the HRV than HRT parameters. It was previously reported that pharmacological treatment decreased the prognostic significance of HRV but not of HRT.^{1,20} If so, it is plausible that the HRT dynamics is a more sensitive marker of progressive postinfarction autonomic dysfunction than the HRV changes. Considering the results of our study, one can note the significance of Type III HRT dynamics should be discussed. Owing to the small number of patients with this condition, a detailed analysis was difficult. However, it should be stressed that the results of HRV analysis in this group were similar as

Figure 3. Comparison of HRT parameters obtained during early postinfarction Holter monitoring between study groups.

Table 3. Comparison of the Results of Early Postinfarction HRV Analysis in Study Groups

Parameter	Group 1	Group 2	Group 3	P
SDNN (ms)	86 ± 29 ^a	64 ± 26	70 ± 29	<0.005
RMSSD (ms)	34 ± 31	21 ± 10	24 ± 11	NS
Triangular index (ms)	23 ± 9 ^a	17 ± 7	19 ± 8	<0.005
LF (ms ²)	1892 ± 775	2001 ± 986	1482 ± 999	NS
HF (ms ²)	328 ± 167	199 ± 157	307 ± 195	NS
Δ LF/HF	1.64 ± 1.2 ^{a,b}	-0.52 ± 0.53	0.73 ± 0.6 ^a	<0.001

^aP < 0.05 in comparison with Group 2; ^bP < 0.05 in comparison with Group 3.

for the patients with HRT improvement (Group 1). Type III denoted the worsening of only one HRT parameter. Out of the 14 patients classified to Type III group, worse TS values were recorded in only one person. The remaining 13 presented the signs of worsened TO. It is worth noting that the subjects from Group 3 had HRV parameters indicating a better prognosis. This would imply that TS worsening more strongly determines poorer prognosis after MI than the worsened TO values. This observation is consistent with other reports. According to Cygankiewicz et al. TS is more closely associated with the presence of the risk factors in patients with coronary artery disease.²¹ Wichterle et al. also postulated a greater prognostic power of TS in the risk assessment after myocardial infarction.²²

STUDY LIMITATIONS

Since now a little is known about the HRT changes during long-term follow-up after MI. We found three types of HRT dynamics and we assumed that Type II was an unfavorable one. Type II of HRT dynamics was defined as the "worsening" but it should be noted that almost all the patients presenting with Type II had normal values of TO and TS both at the initial Holter monitoring and 12 months afterwards. To find an indirect evidence that Type II HRT dynamics is really an unfavorable condition, we decided to evaluate its association with the results of early postinfarction HRV analysis. Patients with HRT values that worsened within 12 months since myocardial

Table 4. Parameters Obtained from Early Postinfarction Holter Monitoring (HM) and after 12 Months

	Initial HM	HM After 12 Months	P
A. Average heart rate			
Group 1	73/min ± 9.6	67/min ± 5.4	<0.0001
Group 2	84/min ± 12.9	80/min ± 9.8	<0.0001
Group 3	73/min ± 7.6	70/min ± 6.7	<0.0001
B. SDNN			
Group 1	86 ms ± 29	128 ms ± 28	<0.0001
Group 2	64 ms ± 26	111ms ± 26	<0.0001
Group 3	70 ms ± 29	124ms ± 22	<0.0001
C. LF			
Group 1	1892 ms ² ± 775	1674 ms ² ± 675	NS
Group 2	2001 ms ² ± 986	1993 ms ² ± 899	NS
Group 3	1482 ms ² ± 999	1342 ms ² ± 992	NS
D. HF			
Group 1	328 ms ² ± 167	368 ms ² ± 146	NS
Group 2	199 ms ² ± 157	213 ms ² ± 198	NS
Group 3	307 ms ² ± 195	321 ms ² ± 201	NS
E. Δ LF/HF			
Group 1	1.64 ± 1.2	1.24 ± 0.8	0.032
Group 2	-0.52 ± 0.53	-0.62 ± 1.23	0.023
Group 3	0.73 ± 0.6	1.73 ± 0.9	0.016

Figure 4. Time-domain HRV analysis parameters in early postinfarction (1) and control (2) Holter monitoring—comparison between study groups.

Table 5. Influence of HRV Parameters Obtained from Early Postinfarction Holter Monitoring on the Relative Risk of the TO and TS Worsening during 12-Month Follow-Up

Parameter	Regression Coefficient	OR	P
Univariable logistic regression analysis			
Triangular index	-0.094	0.909	0.006
SDNN	-0.024	0.976	0.008
RMSSD	-0.045	0.956	0.029
Δ LF/HF	-2.973	0.057	0.0001
Multivariable logistic regression analysis			
Δ LF/HF	-2.274	0.238	0.001

infarction, had a lower time-domain HRV parameters in early postinfarction Holter monitoring. Many studies on postinfarction patients demonstrated that lower SDNN or RMSSD or Triangular Index values indicated poorer prognosis after MI. Thus, the results of early postinfarction HRV analysis imply that Type II HRT dynamics is also a prognostically unfavorable condition. On the other side, the pattern of postinfarction HRV changes was different from those found for HRT. The HRV parameters improved or did not significantly change in all study groups including patients with worsening of HRT.

Our study population presented no new cardiac events during the follow-up. To assess the postinfarction dynamics of HRT changes, we needed to examine the low-risk patients who were likely to survive 12 months after MI. For this reason the group of patients studied may be not representative of all postinfarction patients treated with primary coronary angioplasty.

Presumably, a longer follow-up on a larger study population will be necessary to obtain a more definite evidence for the prognostic significance of each type of HRT dynamics in a low-risk patient.

CONCLUSIONS

1. Heart rate turbulence in a low-risk patient after myocardial infarction treated with primary PTCA presents a significant dynamics with time, as revealed by long-term monitoring.
2. The patterns of HRT and HRV changes after primary PTCA are not similar
3. Abnormal circadian pattern of autonomic activity, detected soon after primary PTCA, is a finding that helps identify patients who need to have HRT analysis repeated during a long-term follow-up, due to the tendency for HRT to change toward the prognostically unfavorable values.

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