Risk Stratification Using Heart Rate Turbulence and Ventricular Arrhythmia in MADIT II: Usefulness and Limitations of a 10-Minute Holter Recording

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Background: We evaluated the usefulness of heart rate turbulence (HRT) parameters and frequency of ventricular premature beats (VPBs) for risk-stratifying postinfarction patients with depressed left ventricular function enrolled in Multicenter Automatic Defibrillator Trial II (MADIT II).

Methods: In 884 MADIT II patients, 10-minute Holter monitoring at enrollment was used to evaluate HRT parameters and frequency of VPBs. The primary endpoints were defined as all-cause mortality in patients randomized to conventional treatment and as appropriate therapy for ventricular tachycardia or fibrillation in patients randomized to implantable cardioverter defibrillator (ICD) therapy.

Results: The median turbulence slope was lower in patients who died in comparison to survivors in the conventional arm (2.3 vs 4.5 ms/RR; $P < 0.05$); but it was not a significant predictor of mortality after adjustment for clinical covariates (age, ejection fraction, beta-blocker use, and BUN levels). There was no association between HRT parameters and arrhythmic events in ICD patients. Conventionally treated patients who died and ICD patients who had appropriate ICD therapy had significantly more frequent VPBs than those without such adverse events. After adjustment for clinical covariates, frequent VPBs $> 3/10$ min were associated with death in the conventional arm (HR = 1.63; $P = 0.070$) and were predictive for appropriate ICD therapy in the ICD arm (HR = 1.75; $P = 0.003$).

Conclusion: In postinfarction patients with severe left ventricular dysfunction, frequent VPBs are associated with increased risk of mortality and with appropriate ICD therapy. HRT obtained from 10-min Holter ECG showed a trend toward the association with mortality in univariate analysis but HRT parameters were not predictive of the outcome in multivariate analyses.

A.N.E. 2004;9(3):270-279

ventricular arrhythmias; heart rate turbulence; implantable cardioverter defibrillator; myocardial infarction; prognosis; mortality

The Multicenter Automatic Defibrillator Implantation Trial II (MADIT II) showed a significant improvement in survival with a prophylactic therapy with an implantable cardioverter defibrillator (ICD) in patients with a prior myocardial infarction and a left ventricular ejection fraction $\leq 30\%$.¹ In 490 patients treated by conventional therapy, 97 (19.8%) died whereas in 742 patients of the ICD group 105 (14.2%) deaths occurred during a mean 20-month follow-up. The hazard ratio of 0.69 (31% reduction of mortality) between the two differently treated groups was observed on top of optimal pharmacological therapy of these patients. The primary ar-

ticle describing MADIT II also showed that there was no significant difference in the benefit of ICD in various subgroups of patients identified using demographic, clinical, and ECG criteria.¹

The MADIT II protocol did not use noninvasive ECG or invasive electrophysiology markers of electrical instability to enroll patients in the study. There is an interest in the prognostic significance of noninvasive ECG markers in such a population of postinfarction patients with a very low ejection fraction. Recently, heart rate turbulence (HRT) has been studied as a noninvasive method to identify patients at risk of cardiac death.²⁻⁴ This method

analyzes the behavior of heart rate (RR intervals) following ventricular premature beats (VPBs) and it is believed to reflect baroreflex sensitivity.^{5,6} Under normal conditions, there is short acceleration with subsequent deceleration of heart rate following VPBs, whereas abnormal response consists of a lack of such a biphasic pattern. In EMIAT, MPIP, and ATRAMI studies, impaired HRT was found to be a powerful predictor of cardiac death in postinfarction patients.^{2,3} It is important to emphasize that HRT takes advantage of VPBs, which are already recognized as well-established risk factors for predicting mortality in postinfarction patients. The purpose of this study was to evaluate the usefulness of HRT parameters and VPBs obtained from a 10-minute Holter ECG in risk-stratifying postinfarction patients enrolled in MADIT II study.

METHODS

Study Population

The MADIT II study included 1232 patients, more than 21 years old, who had myocardial infarction at least 1 month prior to enrollment and a left ventricular ejection fraction $\leq 30\%$ within 3 months prior to enrollment. The patients were randomized 3:2 to an implantable defibrillator or conventional medical therapy arm. All patients, in both arms of the study, were treated with an optimal pharmacological therapy including frequent use of beta-blockers, ACE-inhibitors, and statins. The details of the study design, inclusion, and exclusion criteria are published in the primary MADIT II publication.¹

A 10-minute high resolution (1000 Hz) ECG recording (SpaceLab-Burdick 6632 recorder, Spacelab-Burdick, Milton, WI) in supine resting position was obtained at enrollment in 1197 patients. Among them, 300 patients were excluded from the analysis of VPBs and heart rate turbulence due to the absence of sinus rhythm or the technically inadequate quality of recordings. Thirteen patients did not actually receive an ICD even though they were randomized to the ICD treatment group. Thus, 884 patients with 10-minute Holter ECGs were considered for further analysis.

ECG Analyses

HRT parameters' turbulence slope (TS) and turbulence onset (TO) were calculated following the algorithm described by Schmidt et al.² Briefly, tur-

bulence onset reflecting the initial phase of sinus rhythm acceleration and turbulence slope describing deceleration phase were calculated. TO was defined as a percentage difference between the mean of the first two RR intervals after a ventricular premature beat and the two last sinus RR intervals before ventricular premature beat. TS was described by a maximum positive slope of a regression line assessed over any of the 5 consecutive RR intervals within the first 15 sinus RR intervals after a ventricular premature beat. TO was calculated for all ventricular premature beats separately and then averaged whereas TS was calculated based on an average local tachogram. Filtering algorithms were used to eliminate inappropriate RR intervals and ventricular premature beats with too long coupling intervals or a too short compensatory pause.²

The number of VPBs and the presence of couplets and episodes of nonsustained VT (≥ 3 beats in a row) in a 10-minute Holter recording were used to evaluate the electrical vulnerability of the myocardium in studied patients.

Endpoints

All-cause mortality was considered as the primary endpoint in patients randomized to conventional therapy. Sudden cardiac death, adjudicated by MADIT II endpoint committee, was considered as secondary endpoint. In patients randomized to ICD therapy, appropriate VT/VF therapy was considered as the primary endpoint.

Statistical Analysis

The HRT parameters were analyzed as continuous variables as well as dichotomized variables using cutoffs defined as in the lowest quartile for TS and the highest quartile for TO. The HRT parameters, turbulence slope, and turbulence onset were also analyzed using original cutoff points ($TS \leq 2.5$ ms/beat and $TO \geq 0\%$) identified by Schmidt et al.² The HRT parameters were analyzed as separate variables and as combined variables termed HRT category defined as category 0 (HRT0) if both TO and TS were normal; category 1 if either TO or TS were abnormal (HRT1); and category 2 if both TO and TS were abnormal (HRT2).⁴

The univariate association between heart rate turbulence parameters and cardiac events was tested using Kaplan-Meier survival analysis with log-rank test. The multivariate Cox model was used

to determinate the prognostic significance of the studied ECG parameters after adjustment for relevant clinical covariates. P value <0.05 was considered significant.

RESULTS

Heart Rate Turbulence and Ventricular Arrhythmia Analysis

The clinical characteristic of MADIT II patients analyzed in this study is shown in Table 1. They did not differ significantly from patients excluded from the analysis with the exception of a different frequency of atrial fibrillation and paced rhythm since these conditions were excluded for this analysis.

Since the ECG recordings were short (10-minute), there was limited availability of recorded VPBs that could serve to calculate HRT parameters. HRT can be evaluated only if single VPBs with 2 pre-VPB and 15 post-VPB sinus rhythm beats are present in the recording.²⁻⁴ The VPBs with too long coupling intervals or a too short compensatory pause also cannot be included in the analysis. Thus, although VPBs were found in 634 patients, HRT analysis could be performed using at least one VPB in 203 patients on conventional therapy and in 293 patients on ICD therapy. In 39 patients the coupling intervals were too long or the compensatory pause

too short. In the other 102 patients HRT could not be evaluated due to the absence of arrhythmia-free post-VPBs sequences. The analysis also was repeated while using at least 4 VPBs in a 10-minute recording in 101 patients on conventional therapy and 137 ICD patients.

Mean values of TS were 6.17 ms/RR with 193 (39%) patients having $TS \leq 2.5$ and mean values of TO were -1.5 with 155 (31%) patients with values $\geq 0\%$. Two hundred and sixteen patients (44%) had HRT category 0, 188 patients (38%) had HRT category 1, and 88 patients (18%) had HRT category 2.

VPBs were found in 634 (72%) patients with frequent VPBs, defined as above median, that is, >3 VPBs/10-minute recording, in 408 patients (46%). The number of VPBs ranged from 0 to 389 beats with mean of 22 ± 46 and median of 3 (IQR:(0-19)) beats. There were 164 (19%) patients with couplets and 42 (5%) patients with episodes of nonsustained ventricular tachycardia consisting of at least three ventricular beats in a row.

HRT and Outcome

Table 2 shows HRT parameters and ventricular arrhythmias in patients with and without pre-specified endpoints separately in the conventional and in the ICD arm. Among patients eligible for HRT analysis, 40 (20%) died in the conventional arm and 82 (28%) had appropriate ICD therapy in the ICD arm. A decreased turbulence slope (≤ 2.5 ms/RR) was associated with increased mortality ($P = 0.073$) in the conventional arm in univariate analysis (Fig. 1). However, when adjusted for significant clinical covariates (age, ejection fraction, BUN level, and beta-blocker use) a decreased turbulence slope was not associated with increased mortality (hazard ratio = 1.14; $P = 0.70$). Patients with more advanced age, with lower ejection fraction, and those off beta-blockers had significantly more frequent abnormal turbulence slope than MADIT II patients without these conditions.

In the conventionally treated arm, there were 22 patients with sudden cardiac death, and they had a significantly lower turbulence slope than patients without sudden death (median 2.4 vs 4.2 ms/RR, respectively, $P < 0.05$). However, turbulence parameters were not significant for predicting sudden cardiac death in the multivariate model.

Increased turbulence onset was not associated with increased mortality in univariate or multivariate analyses. Very similar results were obtained

Table 1. Clinical Characteristics of Studied Patients

Clinical Variables	Mean (n = 884)
Mean age (years)	62.7
Age ≥ 65	46%
Female	17%
NYHA classification $\geq II$	63%
Coronary artery bypass surgery	56%
Median time between MI and enrollment (months)	50
Mean ejection fraction (%)	23%
Hypertension requiring treatment	55%
Diabetes	35%
Mean heart rate (bpm)	69
Left bundle branch block	17%
QRS > 0.12 seconds	29%
BUN > 25	26%
Medication at time of Holter	
Beta-blockers	64%
ACE-inhibitors	76%
Digitalis	54%
Diuretics	70%
Statins	63%

Table 2. Heart Rate Turbulence Parameters and Ventricular Arrhythmias in MADIT II Patients by Outcome

Parameters	Conventional Arm		ICD Arm	
	Alive	Dead	No VT/VF	VT/VF
Heart rate turbulence				
Number of patients	163	40	211	82
TO continuous (%)				
Mean	-1.4 ± 3.0	-1.1 ± 3.9	-1.3 ± 3.5	-2.2 ± 3.6
Median	-1.0	-0.4	-0.8	-1.5
$>0.31\%$ ($>Q3$)	46 (28%)	15 (38%)	48 (23%)	15 (18%)
$\geq 0\%$	55 (34%)	17 (43%)	64 (30%)	19 (23%)
TS continuous (ms/RR)				
Mean	6.9 ± 7.6	5.6 ± 11.9	6.3 ± 8.7	4.8 ± 5.2
Median	4.5	2.3*	3.8	3.3
≤ 1.5 ms/RR ($\leq Q1$)	34 (21%)	15 (38%)*	53 (25%)	22 (27%)
≤ 2.5 ms/RR	61 (37%)	22 (55%)*	78 (37%)	32 (39%)
HRT0	74 (45%)	13 (33%)	104 (49%)	43 (52%)
HRT1	62 (38%)	15 (38%)	72 (34%)	27 (33%)
HRT2	27 (17%)	12 (30%)	35 (17%)	12 (15%)
Ventricular arrhythmias				
Patients analyzed for VPBs	306	64	394	120
Patients with VPBs	204	51	278	101
Number of VPBs				
Mean	19 ± 42	39 ± 71	20 ± 45	23 ± 37
Median	2	8*	2	5.5*
Patients with VPBs >3	128 (42%)	39 (61%)*	172 (44%)	69 (58%)*
NSVT	9 (3%)	8 (13%)*	15 (4%)	10 (8%)*

The percentages are given in relation to the number of patients eligible for HRT analysis.

* $P < 0.05$ when comparing patients with and without cardiac events in respective conventionally treated and ICD-treated groups.

when TS and TO were dichotomized using quartile-determined cutoffs instead of standard values proposed by Schmidt et al.²

No significant association was found between TS or TO and appropriate ICD therapy for VT/VF in the ICD arm regardless of whether TS and TO were considered as continuous or as dichotomized variables using Schmidt's criteria or quartile-based population-specific criteria (Fig. 1).

The univariate analysis of HRT categories, similar to those used by Barthel et al.⁴ showed a non-significant trend ($P = 0.193$) of abnormal heart rate turbulence (HRT1 and HRT2) to be associated with mortality in the conventional therapy group (Fig. 2) but HRT was not predictive after adjustment of clinical covariates (hazard ratio for HRT1 vs HRT0 = 1.06; $P = 0.88$; hazard ratio for HRT2 vs HRT0 = 1.30; $P = 0.53$). There was no association of HRT categories with appropriate ICD therapy (Fig. 2).

The above analyses were repeated with at least four VPBs used to calculate HRT parameters and there was no evidence of a significant association

between HRT parameters and outcome in multivariate analyses.

VPBs and Outcome

Table 2 also shows results of ventricular arrhythmia analyses in the 372 patients studied of whom 65 (17%) died in the conventional arm and 122 (29%) of 419 had appropriate therapy in the ICD arm. The patients who died had a significantly higher number of VPBs, frequent VPBs and episodes of NSVT than survivors. When analyzing ventricular arrhythmias in 36 patients with sudden cardiac death compared to patients without sudden cardiac death, they had significantly more frequent VPBs (median 7.5 vs 2 VPBs, respectively; $P < 0.05$) and a higher number of them had NSVT (17% vs 3%, respectively; $P < 0.05$).

Similarly, patients in the ICD arm who had appropriate device therapy for VT/VF had significantly more ventricular arrhythmia than those who did not experience VT/VF. Figure 3 shows the cumulative probability of survival in the conventional

Figure 1. *Top Panel:* Cumulative probability of survival in MADIT II patients randomized to conventional therapy in relation to levels of turbulence slope (TS). *Bottom Panel:* Cumulative probability of first appropriate therapy for VT/VF in MADIT II patients randomized to ICD therapy in relation to the levels of turbulence slope.

arm and of therapy for VT/VF in the ICD arm in relation to the presence or absence of frequent VPBs. The NSVT in the 10-minute Holter was detected in 17 patients randomized to the conventional therapy arm and in 25 patients randomized to the ICD arm and the presence of such episodes also was associated with the worse outcome (Table 2).

As shown in Table 3, patients having more than three VPBs in 10 minutes were older, were enrolled in the study later after MI, had higher mean heart rate, longer QRS duration width >0.12 s, higher incidence of bypass surgery, and higher incidence of hypertension than those with VPBs frequency <3 VPBs/10 min. Patients with a less frequent incidence of VPBs were treated more

Figure 2. *Top Panel:* Cumulative probability of survival in MADIT II patients randomized to conventional therapy in relationship to the categories of heart rate turbulence levels. *Bottom Panel:* Cumulative probability of first appropriate therapy for VT/VF in MADIT II patients randomized to ICD therapy in relationship to heart rate turbulence levels. (HRT0-if both TO and TS were normal; HRT1-if either TO or TS were abnormal; HRT2-if both TO and TS were abnormal).

frequently with beta-blockers and ACE-inhibitors and less frequently with diuretics than those with VPB frequency >3 VPBs/10 min. However, there was no statistically significant association between VPB frequency and parameters reflecting severity of disease: LVEF and NYHA.

When the studied ventricular arrhythmia parameters (>3 VPBs, NSVT) were analyzed in the multivariate Cox model adjusting for imbalances in the clinical characteristics, only VPB frequency above 3 VPBs/10 min was found to be independently associated with a worse outcome (Table 4). Frequent

Figure 3. Top Panel: Cumulative probability of survival in MADIT II patients randomized to conventional therapy in relationship to presence or absence of frequent VPBs. Bottom Panel: Cumulative probability of first appropriate therapy for VT/VF in MADIT II patients randomized to ICD therapy in relationship to the presence or absence of frequent VPBs.

VPBs were associated with a 63% increase in risk of mortality in the conventional arm (HR = 1.63; P = 0.07) and with a 75% increase in risk of appropriate therapy for VT/VF in the ICD arm (HR = 1.75; P = 0.003).

DISCUSSION

Turbulence slope, evaluated in a short 10-minute Holter-ECG, was not independently associated

with all-cause mortality or sudden cardiac death in MADIT II patients randomized to conventional therapy. Turbulence onset did not show such an association. The multivariate analysis of HRT categories did not reveal HRT to be predictive for clinical outcome in both therapy groups. These results are in contrast to previous analyses from early postinfarction MPIP, EMIAT, and ATRAMI studies, which showed that impaired HRT was the strongest and independent electrocardiographic

Table 3. Clinical Characteristics of MADIT Patients with and without Frequent VPBs (>3 per 10 minutes)

Clinical Variables	VPBs $\leq$ 3 (n = 476)	VPBs > 3 (n = 408)
Mean age at randomization (years)	61	65**
Patients at age $\geq$ 65 years	39%	53%**
Median MI months before enrollment	43	65**
Mean heart rate	67	72**
QRS > 0.12 seconds	25%	34%**
Coronary bypass surgery	53%	61%*
Hypertension requiring treatment	52%	59%*
Left bundle branch block	15%	19%
Female	18%	15%
Mean LVEF (%)	24%	23%
CHF NYHA Classification $\geq$ II	63%	63%
Diabetes	35%	35%
BUN > 25	25%	26%
Medication at time of Holter		
Beta-blockers	71%	55%**
Diuretics	67%	75%*
ACE-inhibitors	78%	73%*
Digitalis	55%	53%
Statins	65%	61%

*P < 0.05; **P < 0.01 when comparing two groups.

predictor of cardiac mortality.^{2,3} The prognostic significance of HRT in post-MI patients also was confirmed in the recently published ISAR study.⁴ They enrolled patients after acute myocardial infarction with mean LVEF of 56%.⁴ However, the patients with LVEF > 30% and with LVEF $\leq$ 30% were separately analyzed in this study. The impaired HRT was found to be a strongest predictor of all-cause mortality in patients with preserved LVEF (hazard ratio = 5.2) whereas in patients with LVEF $\leq$ 30% only HRT2 was found to be predictive (hazard ratio = 2.8). There are several possible reasons for these contradictions. Different patient populations were enrolled in these studies: MADIT II enrolled patients late after myocardial infarction with very low ejection fraction whereas MPIP, EMIAT, ATRAMI, and the recent ISAR study included patients in the early postinfarction period with much better preserved left ventricular function (Table 5). In contrast to MADIT II, 82 patients with LVEF < 30% investigated in the ISAR study⁴ were enrolled at the early postinfarction phase. The VPB frequency also was substan-

tially lower in these patients (median 4.9; IQR: (0.4–30.1)/h). VPB frequency strongly correlated with altered LV architecture and function during postinfarction LV remodeling¹³ and our observation on more frequent VPBs in MADIT II patients is in agreement with this concept. These findings suggest that the progression in the severity of cardiac disease may contribute to the lack of significance of HRT in MADIT II patients.

HRT in the above-mentioned studies was measured from the 24-hour Holter recordings (with more access to VPBs) whereas in MADIT II a 10-minute recording limited the number of beats allowing for HRT analysis. We analyzed HRT parameters using all available VPBs and also while using at least four VPBs, and the results of the analyses were similar. Recently, it was shown that the analysis of HRT is not limited to 24-hour Holter recordings and it could be accomplished even from the interrogation strips recorded by an ICD.^{6–9} In other recent studies, it was demonstrated that HRT could be also evaluated when induced by intracardiac pacing in the electrophysiology lab^{5,6} or in patients with ICD.^{7,8} Since HRT is believed to reflect baroreflex sensitivity, it is expected that even a few beats should suffice to illustrate this phenomenon. The association between baroreflex sensitivity and HRT was demonstrated in several studies.^{7,10–12} Davies et al.⁵ showed a close relationship between HRT and baroreflex sensitivity in patients with chronic congestive heart failure with mean EF = 33%. They found that CHF patients with NYHA III had significantly lower TS than patients with NYHA I, II. The significant correlation between LVEF and TS ($r = .58$, $P < .05$) also was found in the study of Koyama et al.¹² Baroreflex sensitivity is vagally mediated and patients with severe left ventricular dysfunction have signs of diminished vagal activity therefore influencing the HRT parameters.⁷ As shown in Table 5, MADIT II patients had the lowest EF, the lowest values of TS, and the highest VPB frequency when compared to studies documenting predictive value of HRT parameters.

Our analysis of ventricular arrhythmias recorded in a 10-minute recording showed that frequent VPBs (defined as >3/10 min) were associated with a 63% increased risk of death in patients randomized to the conventional arm and with a 75% increased risk of appropriate ICD therapy for ventricular tachycardia or ventricular fibrillation in patients randomized to ICD therapy. The association between increased frequency of VPBs and

Table 4. Frequent VPBs in Multivariate Cox Models Predicting Outcome in MADIT II Patients Randomized to Conventional Therapy and to ICD Therapy

Variables	Hazard Ratio	95% CI	P Value
Conventional therapy (Predictors of all-cause mortality)			
Age > 65 years	2.52	1.41–4.51	0.002
Use of BB	1.70	1.03–2.78	0.040
LVEF < 25%	1.78	0.98–3.23	0.060
BUN > 25	1.65	0.98–2.78	0.070
VPBs > 3/10 min	1.63	0.98–2.71	0.070
ICD therapy (Predictors of Appropriate ICD Therapy)			
NYHA > II	1.52	1.04–2.21	0.040
VPBs > 3/10 min	1.75	1.21–2.52	0.003

mortality was reported in many studies mostly focused on postinfarction patients evaluated at hospital discharge.^{14–21} However, there are limited data regarding the predictive value of VPB frequency in patients with such a severely depressed left ventricular function as observed in MADIT II population. Since most of the studies analyzing the frequency of ventricular arrhythmias used a cutoff of >10 VPBs per hour, one could extrapolate our findings from a 10-minute to a longer recording of such conditions by calculating >18 VPBs per hour. It is likely that this somewhat increased threshold is relevant for patients with severe left ventricular dysfunction. Couplets of VPBs and episodes of nonsustained ventricular tachycardia were infrequently recorded in studied patients and they did not have predictive value.

The main propose of risk stratification is to identify high risk patients and to optimize the therapy for these patients. Our finding that frequent VPBs are predictive of arrhythmic events documented by ICD further extends previous observations reporting the associations between frequent VPBs and sudden or arrhythmic death in postinfarction patients.^{14–21} It is important to emphasize that frequent VPBs were predictive of arrhythmic events in MADIT II patients who present with very low

ejection fraction indicating that spontaneous arrhythmias are important markers of myocardial vulnerability even when there is a major left ventricular dysfunction. Although this association was described before,^{16,18} data on arrhythmic endpoints documented by ICD in the relationship to spontaneously occurring ventricular arrhythmias are very limited and we believe that our study provides important evidence documenting an additional link between ventricular arrhythmias and arrhythmic events.

In conclusion, the presence of frequent VPBs (>3 per 10 minutes) in postinfarction patients with severe left ventricular dysfunction is predictive of death and life-threatening cardiac arrhythmias. Just a 10-minute ECG recording, which could be accomplished in the physician's office, provides the basis for arrhythmia detection identifying patients with an increased risk of cardiac events. We also learned that postinfarction patients with markedly reduced ejection fraction in the course of long-term myocardial remodeling have substantially reduced heart rate turbulence and substantially increased VPB frequency. Heart rate turbulence parameters, evaluated in just a 10-minute ECG, in such patients are not predictive for future cardiac events.

Table 5. Turbulence Parameters and LVEF in Clinical Trials

Trials	LVEF (%)	TS (ms/beat)	TO (%)	VPBs*
ATRAMI	49 ± 12	12 ± 14	−1.57 ± 3.24	14 ± 61/h
MPIP	45 ± 15	8.47 ± 9.1	−1.12 ± 2.0	16 ± 49/h
EMIAT	30 ± 9	6.33 ± 8.20	−1.03 ± 2.0	48 ± 49/h
MADIT II	23 ± 6	3.94 ± 4.05	−1.33 ± 2.48	22 ± 46/10 min

The data are given in mean ± SD.

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