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Prognostic Significance of Short-Period Heart Rate Variability in Patients with Acute Myocardial Infarction in the Era of Modern Infarction Therapy

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We aimed to prospectively assess the prognostic value of decreased heart rate variability (HRV) in the era of modern infarction therapy with high rates of reperfusion therapy and beta-blocker use. Short-term HRV in the frequency domain was measured in 129 consecutive patients (age < 74 years) 5 to 8 days after an acute myocardial infarction (AMI). HRV-parameters were subdivided according to predefined cut-points. Patients were followed for a mean of 38 months (range 1–47) for arrhythmic events, cardiac and noncardiac death, and recurrent nonfatal myocardial infarction or angina requiring hospitalization. The majority of patients received acute revascularization (60 %), and most were treated with β-blockers (89 %) and aspirin (95 %). Accordingly, the rate of endpoints were relatively low (9 deaths or malignant arrhythmias; 14 nonfatal reinfarctions or angina). Patients with the combined endpoint death, malignant arrhythmia or nonfatal cardiac event had significantly lower mean and median low frequency (LF) and total frequency power. Accordingly, the relative risk of reaching any endpoint of those with low LF-power was 2.3 times (Confidence Interval 1.03; 5.3) higher compared to those with normal HRV. This association persisted in the multivariate model controlling for age, ejection fraction and treatment. In conclusion, these data show that in the era of modern infarction therapy with high rates of acute reperfusion therapy and optimized medical therapy, an easily applicable test for autonomic dysfunction, ie short-term HRV-measurement, remains a significant predictor of the patients' risk for future adverse events. *J Clin Basic Cardiol 2003; 6: 23–7.*

Key words: heart rate variability, acute myocardial infarction, prognosis

For several years heart rate variability (HRV) has been recognized as a noninvasive tool for the assessment of prognosis after acute myocardial infarction (AMI) [1, 2]. More recently, the measurement of HRV has become more attractive in the light of possible therapeutic implications of a recognized impairment of autonomic balance: subgroup analysis from the EMIAT-study showed that patients after AMI with reduced ejection fraction as well as impaired HRV profited from amiodarone-therapy in contrast to patients with reduced ejection fraction but normal HRV [3]. HRV-determination is now part of the risk stratification in ongoing trials of primary prevention of sudden cardiac death after AMI with ICD-therapy (DINAMIT-trial) [4, 5] or specific antiarrhythmic therapy (ALIVE-trial) [6] because reduced HRV has been associated with a risk of arrhythmic death [7, 8]. Recent data show that low HRV is also a predictor of nonarrhythmic cardiac events, such as myocardial infarction, progression of atherosclerosis and death from heart failure in the normal population [9, 10]. Most of the data concerning HRV as a risk stratification tool after AMI come from retrospective data analysis [1, 7, 11] or, in general, originate from time periods with suboptimal AMI-therapy. In addition, the association of HRV with nonfatal cardiac events like reinfarction or angina requiring hospitalization in an AMI-population has rarely been investigated [12]. Furthermore, the rate of acute revascularization as well as the use of β-blockers and angiotensin-converting-enzyme inhibitors were rather low, even in more recent trials (eg only 20 % of patients in the ATRAMI-trial were receiving β-blockers) [13]. It is unknown if the determination of HRV is still of prognostic value in the era of modern infarction therapy with its consequence of decreasing long-term mortality and morbidity [14, 15]. We aimed to prospectively evaluate the independent value of decreased HRV in a population of AMI-patients treated with a contemporary modern infarction therapy.

Subjects and Methods

The study population was composed of 139 consecutive patients < 75 years old admitted with an acute myocardial infarction to the Central Clinic Augsburg, between January and July 1997. Written informed consent was obtained from all subjects before the study. Myocardial infarction was diagnosed as the presence of at least two of the following criteria: typical ECG-changes, including an ST elevation of at least 2 mm in 2 precordial leads or 1 mm in 2 limb leads; chest pain persisting for more than 30 minutes and not relieved by nitrates; a 2-fold or greater increase in serum creatine phosphokinase or creatine phosphokinase-MB levels. The exclusion criteria were: atrial fibrillation in 4, multiple ventricular or atrial ectopy that precluded measurement of HRV in 3, second or third degree atrioventricular block in 1 patient and unwillingness to participate in 2 patients. The resulting population of patients with analyzable tapes consisted, therefore, of 129 subjects.

Clinical variables recorded included patient age, history of previous myocardial infarction, presence of diabetes, location of infarction, left ventricular ejection fraction (determined by angiography, radioventriculography or, if neither of both was available, by echocardiography), medication during HRV-measurement and at the end of hospital stay, and acute revascularization (either by thrombolytic therapy, percutaneous revascularization or both). Physicians taking care of the patients were unaware of the results of HRV-measurements.

Analysis of Heart Rate Variability

We used the determination of short-term-HRV, because it can be easily obtained under standardized conditions and it has been previously shown to be a valuable predictor of future adverse events [16]. Holter recording was carried out using a Marquette 8500 recorder. The recordings were per-

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formed 5 to 8 days after the index-infarction during the morning hours in a quiet room under standardized conditions after a resting period of at least 10 minutes. After connection of chest leads in the supine position, the recordings were performed during 6 minutes of silent supine free breathing. Holter cassette tapes were analyzed on a Marquette series 8000 analysis system using two channels: a modified V5 lead and a modified V1 lead.

Heart rate variability parameters were analyzed by two methods: 1. By Fast-Fourier transformation (FFT) with the use of a commercial software program (Marquette Electronics, Milwaukee, Wisconsin; Mars 8000 Sun workstation, version 3.0 a). All QRS labeling was manually edited by an experienced observer blinded to clinical outcomes. Spectral indexes of heart rate variability were computed by FFT on each 2-minute segment of the recording, with application of a Hanning window to minimize spectral leakage. Five minute epochs of heart rate as a function of time were used for power spectrum (power) analysis. 2. By autoregressive modeling (AR); methods were described earlier [17]. Briefly, files with RR intervals and their annotations (normal beats, ectopic beats and artifacts) were transferred to a 486 personal computer through an RS-232 serial port using the XMODEM protocol. RR intervals were calculated utilizing a computer program and editing routines developed by Sapoznikov et al. [18]. Five minute epochs of heart rate as a function of time were used for power spectrum (power) analysis. Power analysis was performed with a 16^{th} order autoregressive model and solving the Yule-Walker equations by the Levinson algorithm [19].

Three frequency bands were computed: 0.0033 to < 0.04 Hz (very low), 0.04 to < 0.15 Hz (low), and 0.15 to 0.40 Hz (high). Although the very low frequency band is computed and it has been shown to be reliably measured in 5-minute recordings [20], its use in short-term recordings (< 5 minutes) has not been generally recommended [2]. In the present paper we therefore report the area of the low frequency band (LF) in milliseconds squared (ms^2), the area of the high frequency band (HF) in ms^2 and the total power between 0.0033 and 0.40 Hz (total power) in ms^2. Because the correlation between the two methods (FFT and AR) was very high (0.81 for the LF, 0.84 for the HF and 0.82 for the TF bands, respectively, p for all < 0.0001), in the present paper we report only the results for the AR method.

Table 1: Characteristics of the study population (n = 129)

Age (mean ± SD; years)	59.6 ± 9.1
Male (n)	84 % (108)
Diabetes (n)	15.5 % (20)
Recurrent MI (n)	19.4 % (25)
Anterior MI (n)	58.6 % (75)
LVEF < 40 % (n)	23.3 % (30)
Acute revascularization*	60.5 % (78)
Beta-blocker#	89 % (115)
Aspirin#	94.6 (122)
ACE inhibitors#	30.2 % (39)
Diuretics#	20.9 % (27)
Calcium antagonists#	23.2 % (30)

*Thrombolysis and/or PCR (percutaneous revascularization)
#Pharmacological treatment at the time of HRV-recording

Reproducibility

In 9 patients recordings were done twice (first or second day after the initial recording) and analyzed separately. The Pearson correlation coefficients were 0.87 for the LF, 0.93 for the HF, and 0.75 for the TF bands, respectively.

Follow-Up

Patients were checked over at least three years with a median follow-up of 43 months (range 1–47). Follow-up was complete until the first check after 12 months, thereafter 9 patients were lost to further follow-up. During the follow-up, the following data were recorded: recurrence of nonfatal myocardial infarction (n = 6), recurrent angina pectoris requiring hospitalization (n = 8), cardiac death (sudden cardiac death (n = 3) which was defined as death within an hour of the onset of new symptoms according to the Cardiac Arrhythmia Pilot study [21] and fatal myocardial infarction (n = 3), noncardiac death (n = 1; cause of death: stroke), and malignant arrhythmia (n = 2; both requiring defibrillation). Data were gathered from patients charts, telephone interviews, and municipal death certificate files. The following endpoints were defined: nonfatal cardiac event (nonfatal myocardial infarction or recurrent angina pectoris requiring hospitalization), cardiac death (sudden cardiac death or fatal myocardial infarction), death or arrhythmia (cardiac death or noncardiac death or malignant arrhythmia), sudden death or arrhythmia (sudden cardiac death or malignant arrhythmia), and all events combined (death of any cause or nonfatal myocardial infarction or recurrent angina pectoris requiring hospitalization).

Statistical analysis

The power spectral measures of HRV were transformed into natural logarithms (Ln) since their distributions were positively skewed. The data are given as the mean ± SD of the Ln transformed data. Groups were compared with Student's two-tailed unpaired t-test for continuous variables. Medians

Table 2: Endpoints and measures of HRV (mean ± SD and median)

	Death + Arrhythmia		Cardiac Death		Nonfatal cardiac event		Sudden death + Arrhythmia		All events	
	+ (n = 9)	– (n = 120)	+ (n = 6)	– (n = 123)	+ (n = 14)	– (n = 115)	+ (n = 5)	– (n = 124)	+ (n = 23)	– (n = 106)
LF-power										
Mean ± SD	3.27 ± 1.4	3.85 ± 1.3	3.35 ± 1.6	3.83 ± 1.4	3.43 ± 1.1	3.86 ± 1.4	2.84 ± 1.2	3.85 ± 1.3	3.36 ± 1.2	3.91* ± 1.4
Median	2.67	3.88*	2.71	3.88	3.64	3.88	2.64	3.88*	3.13	3.91*
HF-power										
Mean ± SD	3.16 ± 1.2	3.50 ± 1.3	3.10 ± 1.4	3.49 ± 1.3	3.14 ± 1.2	3.51 ± 1.3	2.66 ± 0.8	3.51 ± 1.3	3.15 ± 1.2	3.54 ± 1.3
Median	2.88	3.35	2.82	3.34	3.32	3.31	2.61	3.34	3.04	3.54
TF-power										
Mean ± SD	4.91 ± 1.4	5.39 ± 1.1	4.95 ± 1.5	5.38 ± 1.1	4.96 ± 1.0	5.41 ± 1.1	4.48 ± 0.8	5.40 ± 1.1	4.94 ± 1.1	5.45* ± 1.1
Median	4.77	5.39	4.53	5.37	5.10	5.37	4.48	5.39	4.85	5.42*

LF-power = the area at low frequency (0.04 to < 0.15 Hz); HF-power = the area at high frequency (0.15 to < 0.40 Hz); TF-power = total power spectrum (0.0033 to < 0.40 Hz); the values for the areas and total power are natural log transformed and expressed in ln ms^2; * statistically significant + vs. – with p < 0.05 or at the 95 % confidence level (for median comparisons)

were compared using notched Box- and Whisker plots provided by the statistical software Medcalc [22]. The notched Box- and Whisker plots allow a pairwise comparison of the medians at the 95 % confidence level [23]. Linear regression modeling was used for multivariate analysis. Prespecified dichotomization of the respective frequency bands was used to compare patients below a cut-point (expected to be at high risk) with those above it (expected to be at low risk). In accordance with the literature, where most of the optimal discrimination in the prognostic value of HRV parameters was seen to be around the lowest tertile of the respective HRV distribution [11, 12], we used the lowest tertiles of the respective frequency bands as cut-points (ie < 3.258 ms^2 for LF power; < 2.76 ms^2 for HF power; < 4.83 ms^2 for TF power). Survival analysis was performed using the log rank test. Cox proportional hazards model was used to study the independent effect of HRV on endpoints. P-values < 0.05 were considered as statistically significant. All analyses were carried out with Medcalc [22] and the SAS® System for Windows, Release 6.11; SAS Institute Inc., Cary, NC.

Results

Patient characteristics are summarized in Table 1. In more than 60 % of the patients acute revascularization was performed, the majority of patients was treated with beta-blockers and aspirin. Mean HRV-indices did not differ significantly between patients who suffered from isolated events as compared to those who remained event free. However, comparing patients who suffered any event (death of any cause or nonfatal myocardial infarction or recurrent angina pectoris requiring hospitalization) with those who remained event free revealed significantly lower mean and median LF- and TF power in those with an event. In addition, the median LF-power was significantly lower in subjects who died and/or had an arrhythmic event or in patients with sudden death and/or arrhythmia (Table 2).

Figure 1 shows the results of the Cox analysis according to the predefined cut-points for low HRV. The relative risk for suffering death or arrhythmia, sudden death or arrhythmia or any event combined was significantly increased for patients with low LF-power. The same tendency was seen for patients below the TF-power cut-point, however, without reaching significance. Figure 2 shows the respective Kaplan-Meier-curve for survival/being free of any event-probability in rela-

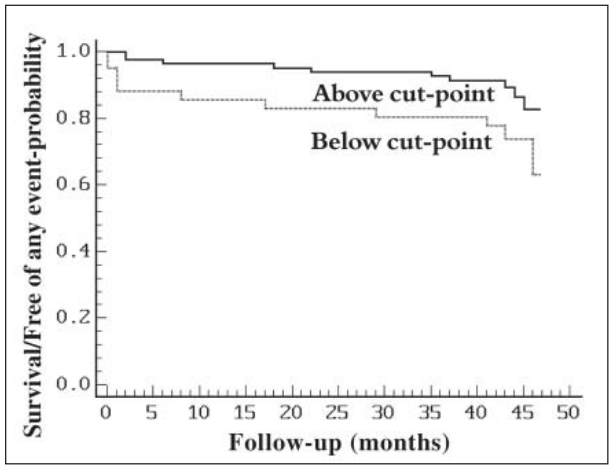

Figure 2. Cumulative survival or being free of any event (death of any cause or nonfatal myocardial infarction or recurrent angina pectoris requiring hospitalization) for patients with below vs. above the cut-points for LF-power (log rank test $p < 0.01$)

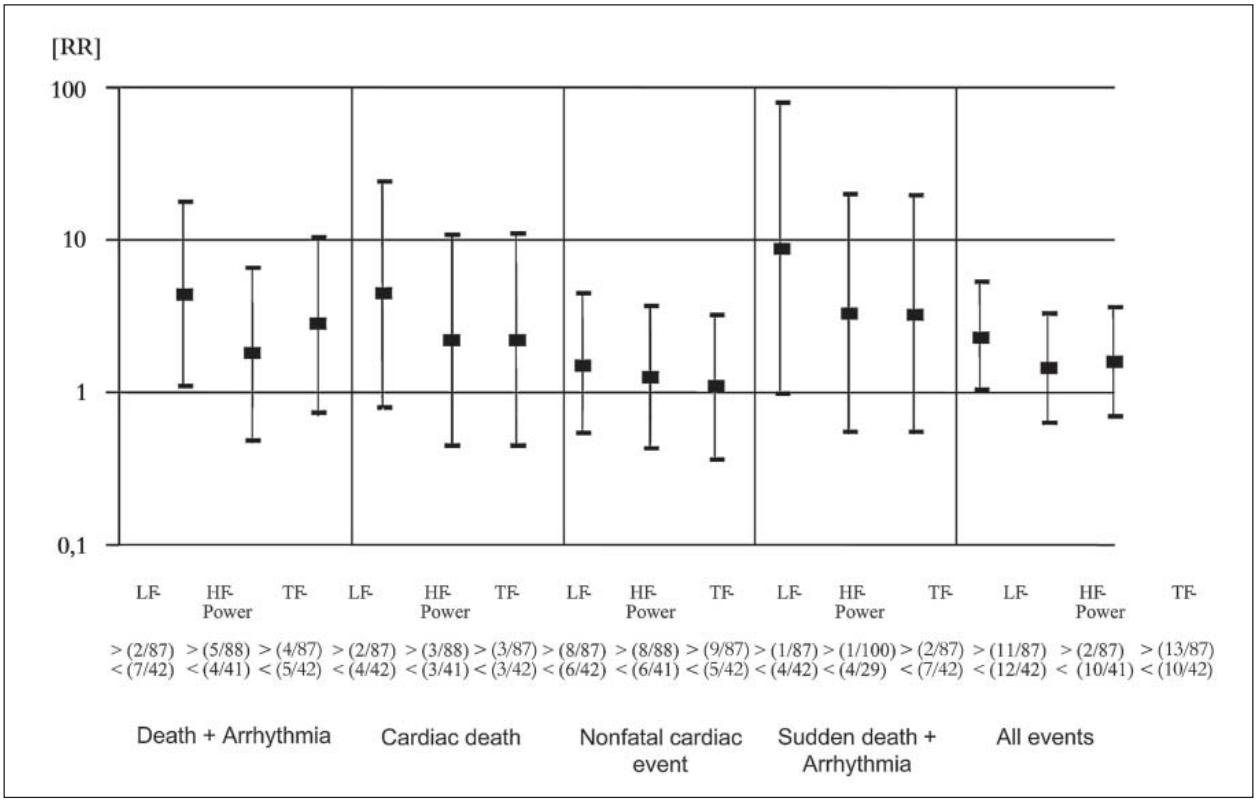

Figure 1. Relative risks (hazard ratio according to the Cox proportional model with 95 % confidence intervals) for predefined endpoints for patients below (<) vs. above (>) the respective cut-points for HRV-parameters (< 3.258 ms^2 for LF-power; < 2.76 ms^2 for HF-power; < 4.83 ms^2 for TF-power)

tion to LF-power. Table 3 shows that the increased risk of reaching an endpoint for those with low LF-power is nearly independent from other risk predictors or treatment effects. Similar results were obtained for the risk of cardiac deaths or sudden death/arrhythmia, however, with wider confidence intervals regarding the relative risk estimates for those being below the respective cut-point (data not shown).

Discussion

From earlier studies there has been compelling evidence that testing for autonomic dysfunction after myocardial infarction is a good risk predictor for future adverse events. However, those studies in part were of retrospective nature [1, 11], stemmed from selected patients groups not reflecting clinical routine reality [24] and, most important, patients were recruited at times of – from the vantage point of the present – suboptimal infarction therapy.

In the meantime, the optimized infarction therapy led to a better long-term outcome in post-infarction patients [14] raising the question whether testing for autonomic dysfunction is still of prognostic value. In particular, the underuse of beta-blockers in earlier studies (eg only 20 % of the patients in one of the most recent studies, the ATRAMI-study [13], received beta-blockers) has been criticized regarding the prognostic information obtained by testing autonomic function once more patients were treated with beta-blockers [15]. Beta-blockers are known to reduce mortality after myocardial infarction significantly [25], but it has also been shown that beta-blockers influence HRV after AMI positively [26].

In our study 89 % of patients received beta-blockers. We show that depressed short-term HRV in the LF-power spectra is still associated with an increased risk for death, malignant arrhythmia or nonfatal cardiac events in a population treated with modern infarction therapy. The latter is reflected by a low mortality rate in our AMI population (5.4 % over the follow-up period). Although the fatal or nearly fatal (malignant arrhythmia) endpoints were even lower than previously expected (7 %) and much lower than in previous reports of similar follow-up duration (11 to 24 %) [1, 12, 27, 28], HRV remained an independent risk predictor of worse outcome.

From a clinical point of view it is important to identify post-infarction patients who are at high risk of death. In addition, it would be of interest to predict the mechanism of death. Accordingly, most studies have been focused on identifying patients with high risk of sudden or arrhythmic death [7, 8, 16], because those may preferentially be subject to specific pharmacological [3] or interventional [4] therapy. In our study, the total number of deaths and documented arrhythmic events is too low to allow specific analysis of mode of death. However, the significantly increased risk in patients with low LF-power to reach the combined endpoint of fatal and nonfatal arrhythmic events is in accordance with the suggestion that HRV may be an especially good marker for increased risk of arrhythmic events [8, 29].

HF-power which mainly depends on the effects of vagal modulation on sinus node has not been associated with either endpoint in our or in other studies [12, 27, 30]. It has been suggested that this is due to the balance of sympathetic and parasympathetic activity which is mostly expressed by LF-power and that is important in determining prognosis after myocardial infarction, and not simply the reduction in vagal tone [30]. Although it has been shown that depressed HRV may also be associated with various vascular events such as angina pectoris or myocardial infarction in the general population [9], this association has rarely been investigated in post-infarction patients. We did not find any association between low HRV and nonfatal cardiac events in our study. On the other hand, the combination of fatal or nearly fatal events with the nonfatal cardiac events revealed a significant association with low HRV. This is also in accordance with an earlier study which did not find a link between low HRV and subsequent ischaemic periods or recurrent myocardial infarction alone, however, the combined endpoint of angina pectoris, congestive heart failure, recurrent myocardial infarction, or death was significantly associated with an index of low HRV [31]. By contrast, another study reported significantly reduced HRV in patients who developed recurrent nonfatal infarctions during follow-up [12]. The findings in the general population by Tsuji et al. [9] who showed that low HRV is also a predictor of nonarrhythmic cardiac events have been explained by associations between HRV and haemodynamic factors which may – by alterations of blood flow dynamics at the arterial wall – lead to a progression of atherosclerosis [10]. However, these mechanisms may be less plausible in patients with already manifest coronary heart disease and after an AMI.

Limitations

This study is limited by the small number of deaths which is reflected by the wide range of confidence intervals and which affects the ability to distinguish more precisely the associations with HRV and mode of death. In addition, we did not determine other autonomic markers like baroreflex sensitivity or signal-averaged electrocardiogram to assess the respective meanings of those autonomic markers alone or in combination regarding their prognostic value for predicting adverse events. However, there is a tendency to use easily applicable, noninvasive methods, not needing laborious laboratory conditions at least for selecting patients for eventual further work-up [4, 32].

Table 3: Multivariate Cox-regression analysis assessing the combined endpoint of suffering any event

	P-value	RR	95 % CI
Age (> 60 years)	0.07	5.6	0.8–37
LVEF < 40 % (n)	0.07	3.4	0.88–13.4
Acute revascularization	0.90	0.91	0.22–3.8
Beta-blocker (No vs. Yes)	0.035	5.4	1.1–26.6
LnLF-cut-point	0.054	4.0	0.98–16.8

LVEF = left ventricular ejection fraction; LnLF cut-point with 1 = below the cut-point for the natural logarithm of the total frequency power; RR = relative risks or hazard ratio; 95 % CI = 95 % confidence interval

Conclusions

In this study with a relatively long follow-up period we showed that in the era of modern infarction therapy with high rates of acute reperfusion therapy and optimized medical therapy, an easily applicable test for autonomic dysfunction, ie short-term HRV-measurement, is still predictive for the patient's risk of future adverse events.

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