Short-Period Heart Rate Variability in the General Population as Compared to Patients with Acute Myocardial Infarction from the Same Source Population

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Background: Our aim was to compare the distribution and determinants of heart rate variability (HRV) measures in a middle-aged population with patients of the same sex and age after an acute myocardial infarction (AMI), and to show, whether HRV values defined as abnormal from the general population are indicative for a worse prognosis even in AMI patients.

Methods: HRV was studied in a random sample of 149 middle-aged men and 137 women from the general population (45–65 years) as well as 129 consecutive AMI patients (25–74 years). Spectral analysis was used to compute low frequency (LF), high frequency (HF), and total frequency power. To the AMI population of age 45–65 years (N = 85) a sample out of the general population was matched by age and sex by 2:1 matching (N = 149). All AMI patients were followed for a median of 43 months (range 1–47) for death or malignant arrhythmia.

Results: All measures of HRV were significantly and substantially lower in AMI patients than the general population ($P < 0.001$). Expression in relative terms revealed that the proportionate contributions of HF and LF to total power were significantly different in the two populations with relatively lower LF power in AMI patients ($P < 0.01$). The negative correlation with heart rate and HRV measures was significantly more pronounced in AMI patients ($P < 0.01$). The 2.5th percentile of the LF power distribution in the general population ($3.08 \ln \text{ms}^2$) corresponds to the 25th percentile in the AMI population. Subjects of the whole AMI population with values below this LF cutpoint revealed a significant increased risk of death or malignant arrhythmia during follow-up (odds ratio 5.1; 95% confidence interval: 1.3; 23).

Conclusions: AMI patients had strongly diminished HRV compared to the general population. The relatively lower LF power indicates an alteration of the sympathico-vagal balance, and the significantly stronger correlation of heart rate with HRV may be indicative for a more pronounced effect of sympathetic activation on autonomic modulation in the case of myocardial infarction. Finally, a value below the 2.5th percentile of the population LF power distribution may identify subjects at risk and warrant further testing.

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Impaired cardiac autonomic function measured by heart rate variability (HRV) has been shown to be associated with a worse prognosis in a variety of diseases and disorders.^{1,2} Especially, in the case of acute myocardial infarction (AMI), measurement of HRV has been recognized as a noninvasive tool for the assessment of prognosis. More recently, in light of possible therapeutic implications of a recognized

impairment of autonomic balance, measurement of HRV has become more attractive.^{3–6} On the other hand, it also has been shown that impaired HRV in the general population confers a greater risk of coronary heart disease incidence and all-cause death.^{7,8} Although it has been recommended earlier to be an important research area by the American College of Cardiology⁹ very few data exist on the

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distribution and the determinants of HRV measures in subjects who have suffered a recent AMI as compared to subjects of the general population.¹⁰ We, therefore, aimed to study the distribution of HRV measures obtained in middle-aged subjects a few days after an AMI as compared to subjects of the general population matched for age and sex.

SUBJECTS AND METHODS

Study Groups

General Population

The subjects of this analysis were participants of the German sample of a tri-national population-based study.^{11,12} Age-stratified random samples of men and women aged 45–65 years were drawn from the population of Augsburg. One hundred and fifty-three men and 143 women were examined (participation rate 71%) from March to July 1995.

AMI Population

The study population consisted of 129 consecutive patients <75 years old admitted between January and July 1997 with an AMI to the Zentralklinikum Augsburg (primary care center, treating more than 75% of all AMI cases in the region of Augsburg with more than 500,000 inhabitants).¹³ Myocardial infarction was diagnosed in the presence of at least two of the following criteria: typical ECG changes, including an ST elevation of at least 2 mm in two precordial leads or 1 mm in two limb leads; chest pain persisting for more than 30 minutes and not relieved by nitrates; a two-fold or greater increase in serum creatine phosphokinase or creatine phosphokinase-MB levels.

Out of the whole AMI population a sample with the age range 45–65 years was selected (N = 85; 74 men, 11 women). To this group, a sample out of the general population (286 subjects excluding those with a history of myocardial infarction, congestive heart failure, or cardiomyopathy) was matched by age and sex in a ratio of 2:1. This resulted in a comparison group of 149 subjects (130 men) from the general population (the number is somewhat below the expected number of 170 subjects because of the lack of more cases from the general population sample fulfilling the matching criteria).

Written informed consent was obtained from all subjects before the study.

Interview and Physical Examination

Interview questionnaires were used to assess smoking habits, use of medication, and the medical history. Body weight was measured in light clothing with precision to the nearest 0.1 kg. Body height was measured without shoes to the nearest 0.5 cm. Body mass index (BMI) was calculated as weight (in kg) divided by height (in m) squared.

Blood pressure was measured differently between the study groups: in the general population blood pressure was measured three times on the right arm of sitting subjects by an oscillometric automated sphygmomanometer (BOSO Oscillomat) after a resting period of at least 5 minutes. The average of the second and third measurement was used for this analysis.

In the AMI population blood pressure was measured one time on the right arm of sitting subjects by sphygmomanometry after a resting period of at least 5 minutes.

Analysis of Heart Rate Variability

For the recording of HRV signals care was taken in applying the same investigation conditions for the general as well as the AMI population. Accordingly, the measurements were made at the same time of day (during the morning hours between 7.30 and 12.00 AM) and under the same standardized conditions. Holter recording was carried out using a Marquette 8500 recorder. The recordings were undertaken in a quiet room after a resting period of at least 10 minutes. According to the recommendations of The European Society of Cardiology and The North American Society of Pacing and Electrophysiology the recordings of the AMI patients were undertaken for 5–8 days after the index infarction. For the AMI patient current medication was not stopped before recording for two reasons: (1) withdrawal of medication with proven prognostic benefit seems unethical, (2) we tried to figure out if there still exist differences in autonomic modulation in infarction patients despite optimal treatment (79% of the AMI patients received beta-blockers, 86% received ace inhibitors, and 65% have been treated with acute revascularization) as compared to subjects of the general population.

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 the same system for the two study populations) using two channels: a modified V5 lead and a modified V1 lead. The cassettes of both study populations were analyzed in the same laboratory as described earlier.¹² 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.¹⁴ Subjects with atrial fibrillation, excessive ectopic beats, or technically inadequate recordings were excluded. Five-minute epochs of heart rate as a function of time were used for power spectrum (power) analysis. Power analysis was performed with a 16th order autoregressive model and by solving the Yule-Walker equations by the Levinson algorithm.¹⁵ 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,¹⁶ its use in short-term recordings (<5 minutes) generally has not been recommended.¹⁷ In the present article we, therefore, report the area of the low frequency band (LF), the high frequency band (HF), and the total power between 0.0033 Hz and 0.40 Hz (total power) in ms^2 . To express the relative contribution of the respective frequency bands to total power, normalized units (NU) were calculated as the ratio between the power of each component and the total power less the very low component multiplied by 100.^{18,19} In addition, we calculated the ratio of LF to HF (LF/HF) power, a measure that has also been used as an indicator for sympathicovagal balance.¹⁷ Two time-domain measures, the standard deviation (SD) of RR intervals, and the root mean square of successive differences in RR intervals (RMSSD) were also calculated. Because of their high correlation with frequency-domain parameters ($r = 0.99$ and $r = 0.99$ between total power and SD in AMI patients and in the general population, respectively; and $r = 0.94$ and $r = 0.94$ between HF and RMSSD in AMI patients and in the general population, respectively; P for all < 0.0001) the focus in the present report was on frequency-

domain parameters and less on time-domain measures.

Follow-Up of the AMI Population

To allow prognostic information about impaired HRV parameters, arbitrarily selected cutpoints for diminished HRV in the general population (2.5th lowest percentile) were applied on the whole AMI population (including the age group 66–75 years, $N = 129$). Patients were checked over at least 3 years with a median follow-up of 43 months (range 1–47). Details of follow-up process have been described earlier.¹³ Briefly, data were gathered from patients' charts, telephone interviews, and municipal death certificate files. During the follow-up, the following endpoints were recorded: cardiac death ($N = 6$), noncardiac death ($N = 1$ with stroke as the cause of death), and malignant arrhythmia ($N = 2$; both requiring defibrillation). For the present analysis the combined endpoint death or arrhythmia (cardiac death or noncardiac death or malignant arrhythmia) was used.

Statistical Analysis

Results are given as mean values. The power spectral measures of HRV were transformed into natural logarithms ($\ln$) since their distributions were positively skewed. Univariate relations were assessed by Pearson's product-moment correlation. Groups were compared with Student's 2-tailed unpaired t -test for continuous variables and by chi-square tests for prevalences. Linear regression modeling was used for multivariate analysis. In order to assess differences between the populations in terms of correlations with cardiovascular risk factors, we tested the population difference by use of an interaction term in a linear regression model encompassing the data of both populations. Survival analysis was performed using the log rank test. Cox proportional hazards model was used to study the independent effect of HRV on the combined endpoint in the AMI population. P values < 0.05 were considered as statistically significant.

All analyses were carried out with the SAS® System for Windows Release 6.11 (SAS Institute Inc., Cary, NC).

RESULTS

According to the matching process, the gender and age distribution was equal among the general

Table 1. Characteristics of the Study Population

	General Population (N = 149)	AMI Population (N = 85)	P Value for Difference
Systolic blood pressure (mmHg)	131 ± 18	119 ± 17	<0.05
Diastolic blood pressure (mmHg)	81 ± 7	75 ± 10	<0.05
BMI (kg/m ²)	28.0 ± 4	27.0 ± 4	n.s.
Heart rate (b/min)	68 ± 10	67 ± 12	n.s.
Age (years)	56.4 ± 6	57.1 ± 6	n.s.

population and AMI patients (85.2% vs 87.1% men, $P = 0.7$; Table 1). Table 1 also shows the baseline characteristics of the two study populations. No significant differences existed between the two populations in BMI or heart rate. The differences in blood pressure, however, have to be interpreted with caution, because blood pressure measurement was not equally standardized in the two populations and was measured differently. In addition, 88% of the AMI population had been treated with antihypertensives during HRV recording (vs 18.9% in the general population). Table 2 shows that the differences in HRV measures were highly significant for all parameters between the two populations with highly impaired HRV measures in AMI patients. By controlling for beta-blocker and ace-inhibitor use in the multivariate model the significant differences in the absolute values persisted, while the differences in the relative terms (NU) and the LF/HF ratio disappeared (NU LF power controls vs AMI patients 65 vs 61, respectively, $P = 0.37$, NU HF power 35 vs 39, $P = 0.37$, respectively, and LF/HF ratio 2.6 vs 2.2, $P = 0.43$, respectively).

Figure 1 again shows that the two populations not only differ in their absolute differences in total power ($P < 0.01$), in addition, expression in relative terms also revealed that the proportionate contributions of HF and LF to total power were significantly different in the two populations with relatively lower LF power in AMI patients ($P < 0.01$). However, as stated above, this difference did not reach significance after controlling for the use of beta-blockers.

Figure 2 shows, exemplary for the LF power, the distribution of HRV in the general population versus the AMI population by a Box and Whisker Plot. The 2.5th percentile of LF power in the general population (3.08 ms²) corresponds to the 25th percentile in the AMI population.

In Table 3, correlations between cardiovascular risk factors and HRV parameters are shown. While in the general population, but not in AMI patients, age and BMI were negatively correlated with HRV, in neither group was blood pressure associated with HRV parameters. Testing the differences in the association with age and BMI between the two

Table 2. Comparison Between the General Population and the AMI Population of HRV Measures

	General Population (N = 149)	AMI Population (N = 85)	P Value for Difference	Percent Difference AMI Versus General Population
LF power (ms ²)	5.00 ± 0.94	3.80 ± 1.36	<0.001	-24%
NU LF power	66 ± 15	59 ± 18	<0.002	-10.7%
HF power (ms ²)	4.27 ± 1.01	3.39 ± 1.32	<0.001	-20.6%
NU HF power	34 ± 15	41 ± 18	<0.002	±17%
LF/HF ratio	2.67 ± 1.9	2.09 ± 1.77	<0.02	-21.7%
TF power (ms ²)	6.19 ± 0.81	5.34 ± 1.09	<0.001	-13.7%
SD	37 ± 16	25 ± 15	<0.001	-32.4%
RMSSD	22 ± 11	17 ± 10	<0.001	-22.7%

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); 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 ms². NU LF power and NU HF power, respectively, represent LF and HF components expressed in NU (ratio between the power of each component and the total power less the very low component multiplied by 100). SD, the standard deviation of RR intervals; RMSSD, the root mean square of successive differences in RR intervals.

Figure 1. Circle graphs showing comparison of total power with its relative LF and HF components. The area of each circle represents total power, the shaded regions represent the relative LF and HF components expressed in NU (ratio between the power of each component and the total power less the very low component multiplied by 100).

populations by an interaction term in the multivariate model, however, revealed no significant differences. The negative correlation of heart rate with HRV (Table 3), however, was significantly more pronounced in AMI patients (P for the interaction term with including and without including beta-

blocker use in the multivariate model, respectively <0.01).

If values below the 2.5th percentile of the HRV distribution of the general population are regarded as "abnormal," i.e., below this limit, and applying those derived cutpoints to classify the AMI

Figure 2. Box and Whisker plot for LF power showing the distribution of HRV in the general population versus the AMI population. The 2.5th percentile of LF power in the general population (3.08 ms²) corresponds to the 25th percentile in the AMI population.

Table 3. Correlation Between Cardiovascular Risk Factors and HRV Measures

	LF Power		HF Power		TF Power	
	General Pop.	AMI Pop.	General Pop.	AMI Pop.	General Pop.	AMI Pop.
Age	−0.17*	−0.13	−0.19*	−0.14	−0.20*	−0.13
BMI	−0.22¶	0.00	−0.13	−0.01	−0.24¶	0.00
Heart rate	−0.24¶	−0.51¶	−0.32¶	−0.56¶	−0.34¶	−0.59¶
Systolic blood pressure	−0.07	0.08	−0.05	0.13	−0.12	0.12
Diastolic blood pressure	−0.08	0.15	−0.07	0.12	−0.12	0.14

*P < 0.005, ¶P < 0.01.

population, we found that for LF power (2.5th percentile 3.08 ms²) 25% of the AMI population (corresponding to 29% in the whole AMI population aged 25–75 years) were classified as abnormal (Fig. 1). The respective 2.5th percentiles and corresponding percentages below this value in the AMI population were 2.18 ms² and 23.5% (18%) for HF power and 4.66 ms² and 25.9% (25.6%) for TF power.

Applying those cutpoints on the whole AMI population aged 25–75 years revealed a significant increased risk of suffering the endpoint death or malignant arrhythmia during follow-up for those being below the LF cutpoint of 3.08 ms²: Two out of 87 subjects above versus 7 out of 42 below the LF cutpoint reached an endpoint (odds ratio (OR) 5.1; 95% CI: 1.3; 23; OR 4.4; 95% CI: 1.06; 18 after controlling for heart rate and ejection fraction). In addition, the use of beta-blockers did not influence the prognostic impact of low LF HRV. The respective cutpoints for HF power or TF power were not able to distinguish those with increased risk (OR 1.3; 95% CI: 0.3; 6 for HF power and OR 2.4; 95% CI: 0.65; 9.0 for TF power, respectively). Similarly, time-domain parameters (SD, RMSSD) showed no prognostic information during follow-up.

DISCUSSION

In this study, we were able to show that HRV indices were 11–32% lower in patients 5–8 days after an AMI as compared to a sex- and age-matched sample of the general population. To best of our knowledge, after the study of Bigger et al. in the early 1990s,¹⁰ ours was the first to report such differences in patients with a recent AMI and normal subjects from the same source population and, in addition, we were able to delineate in more detail the respective determinants of the different frequency spectra of HRV.

We showed that, in addition to the generally diminished HRV indices, expression in relative terms of the respective HRV spectra revealed that AMI patients have relatively lower LF power and, correspondingly, higher HF power than subjects of the general population (Fig. 1). LF power is suggested to be influenced by a balance of sympathetic and parasympathetic activity, while HF power is mainly influenced by parasympathetic activity. On first view this observation of a relatively less diminished HF power in AMI patients seems surprising because in acute coronary artery disease parasympathetic activity would be expected to be particularly decreased.^{20,21} In fact, contrary to our results, Lombardi et al. showed a relative increase in LF power and a decrease in HF power in postinfarction patients.²² This discrepancy, however, may be related to the high use of beta-blockers in our AMI patients, which are known to increase vagal tone in AMI patients.^{23,24} This is supported by the fact that controlling for its use in the multivariate model led to the disappearance of the difference in relative proportions of LF and HF components on the whole HRV spectrum between AMI patients and the general population. However, diminished LF power, but not HF power has been associated with an adverse prognosis during follow-up in AMI patients in earlier studies^{25–27} as well as in the present study, even after controlling for beta-blocker use in the present study. It has been suggested that prognosis is more related to the balance of sympathetic and parasympathetic activity that is mostly expressed by LF power, and which, in fact, is absolutely as well as relatively lower in AMI patients compared to the general population.

Age and BMI were inversely associated with all HRV indices in the general but not the AMI population. It may be argued that the injury of myocardial infarction itself superimposes the influences of cardiovascular risk factors on the autonomic

function of the heart. Although mean heart rate in our mainly beta-blocker-treated AMI patients did not differ from the general population, heart rate, which has been shown to be inversely related to HRV in the general population^{16,19,28,29} as well as infarction patients,^{25,30} was significantly stronger correlated to all HRV parameters in AMI patients than in the general population (P for the interaction term <0.01). Because raised heart rates commonly indicate sympathetic activation³¹ this observation may be indicative for a more pronounced effect of sympathetic activation on autonomic modulation in the case of myocardial infarction and underscores the need for treating sympathetic overactivity in AMI patients.^{23,24}

It is of interest to derive cutpoints for diminished HRV from the general population by taking values below the 2.5th percentile of the HRV distribution and applying those to the infarction population that led to corresponding percentages of 18–26% in AMI patients classified as abnormal. Also of interest in the study by Sosnowski et al. using a similar approach of defining normal values for HRV in a healthy population, was the fact that HRV values below the normal limit were found in 20–25% of postinfarction patients (>3 months after the first event).³² Applying those cutpoints to the whole AMI population in our study revealed a significant increased risk of suffering a fatal or near-fatal endpoint during follow-up for those being below the LF cutpoint. In contrast, neither HF, TF power, nor the time-domain parameters were predictive. It has been shown earlier that mortality is most strongly related to low frequency components of RR variability.^{27,33} It was interpreted that it is the balance of sympathetic and parasympathetic activity that is important in determining mortality, not simply a reduction in vagal tone.²⁷ However, because of the relatively low number of endpoints in our study interpretations regarding the differential impact of different HRV markers should be made with caution. In addition, the lack of predictive information of the time-domain parameters is not surprising because the total variance of HRV increases with the length of analyzed recording. Therefore, though SD and RMSSD of short-term recordings can be validly analyzed, they are ideal and well validated for the analysis of long-term recordings.¹⁷ On the other hand, similarly to Sosnowski et al., who demonstrated a risk prediction according to population-driven normal limits in long-term generated time-domain HRV measure-

ments, we were able to demonstrate the same for short-term measurements of HRV in the frequency domain. Accordingly, the usual derivation of cutpoints by taking the lower end of the distribution in a normal population may be useful to predict outcome in a prospective follow-up of an infarction population. Therefore, for screening purposes short-term recordings with analysis of frequency-domain parameters seem preferable.

Thus, when measures of HRV are used to screen groups of middle-aged subjects to identify individuals who have substantial risk of coronary deaths or arrhythmic events, a value below the 2.5th percentile of the HRV distribution, especially for the LF component, may be regarded as critical warranting further work-up to identify potential underlying cardiovascular disease.

In conclusion, this study showed that middle-aged subjects shortly after myocardial infarction had strongly diminished HRV compared to an age- and sex-matched control of the general population. AMI patients show relatively lower LF power and, correspondingly, higher HF power indicating an alteration of the sympathico-vagal balance with a relatively less diminished vagal influence in mainly beta-blocker treated AMI patients. The significantly stronger correlation of heart rate with HRV measures in AMI patients than in the general population may be indicative for a more pronounced effect of sympathetic activation on autonomic modulation in the case of myocardial infarction. Finally, a value below the 2.5th percentile of the population LF power distribution may identify subjects at risk and warrant further testing.

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