Usefulness of Risk Stratification for Future Cardiac Events in Infarct Survivors with Severely Depressed Versus Near-Normal Left Ventricular Function: Results From a Prospective Long-Term Follow-Up Study

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Background: Although primary preventive therapy with implantable cardioverter defibrillators has recently been shown to be effective in patients with coronary artery disease and left ventricular dysfunction, further identification of patients at particularly high risk for arrhythmic death would improve the cost effectiveness of device therapy. The value of risk stratification in postinfarction patients with versus those without left ventricular dysfunction has not been investigated in detail in infarct survivors treated according to contemporary therapeutic guidelines.

Methods: Patients with acute myocardial infarction underwent coronary angiography including left ventricular angiography in an attempt to restore antegrade flow of the infarct-related artery. Additionally, patients underwent noninvasive autonomic risk stratification by means of heart rate variability (HRV) and baroreflex sensitivity (BRS) measurements prior to hospital discharge.

Results: A total of 411 patients were prospectively included in the study. The primary study endpoint of cardiac death and arrhythmic events was significantly more common in patients with LVEF $\leq 35\%$ as compared to those with preserved LV function (27% vs 4%; $P < 0.0001$). In patients with LV dysfunction, HRV and BRS were significant risk predictors on univariate ($P < 0.01$ for BRS; $P = 0.04$ for HRV) and multivariate ($P = 0.028$ for BRS; $P = 0.053$ for HRV) analyses. In contrast, in patients with preserved LV function, only patency of the infarct artery but not autonomic markers was significantly predictive of cardiac death and arrhythmic events.

Conclusion: The present study demonstrates that autonomic testing does not yield predictive power in infarct survivors with preserved left ventricular function. Accordingly, cost effectiveness of risk stratification and subsequent preventive therapy may be improved by restricting risk stratification to patients with impaired LV function.

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Primary prevention of SCD by prophylactic implantable cardioverter defibrillator (ICD) implantation has been demonstrated to benefit mainly patients with severely impaired LV function with^{1,2} or without³ inducible arrhythmias. Further identification of patients at particularly high risk for SCD would improve the cost effectiveness of device therapy.^{4,5} Previous studies on risk stratification after acute myocardial infarction (AMI) have been conducted largely before the era of widespread reperfusion therapy during the acute phase of the infarct. Accordingly, the present study aimed to evaluate the effectiveness of risk stratification in

a large cohort of MI survivors treated according to contemporary therapeutic guidelines with particular emphasis on two different patient groups, namely those with severely versus those with only moderately depressed or near-normal LV function.

METHODS

Patient Population

Patients with a confirmed diagnosis of AMI based on clinical presentation (typical chest pain for >30 minutes, unresponsive to nitrates; ST-segment

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elevation in at least two-limb leads of >0.1 mV or in at least two precordial leads of ≥ 0.2 mV; elevated Troponin, CK, and CKMB levels) were eligible for participation in this study. Prior to hospital discharge, all patients underwent selective coronary angiography including LV angiography for assessment of LV function. Patients with an initially occluded artery who were revascularized before hospital discharge were considered to have a patent vessel during the statistical analysis. Similarly, Holter monitoring was performed before discharge in all patients. Risk stratification was based on assessment of LV function, infarct-related artery patency (IRA), and measures of cardiac autonomic tone.

Heart Rate Variability (HRV)

HRV measurements were obtained as previously described.^{6,7} In brief, Holter recordings with at least 18 hours of analyzable time were accepted for HRV analysis. From these recordings only R-R cycles in which beats had a normal morphology and cycle lengths within 20% of the duration of the preceding cycle length were measured to ensure abolition of ectopic beats. In instances in which sinus rhythm was interrupted by a premature atrial or ventricular beat, 1 R-R interval preceding, and 1 following the nonsinus beat were rejected. After this labeling process, the data file was verified, manually overread, and corrected where appropriate. For each recording, the standard deviation of the mean R-R interval (SDNN) was determined. Impaired autonomic tone was defined as $SDNN \leq 70$ ms.⁶⁻⁸

Baroreflex Sensitivity (BRS)

Determination of BRS was performed according to the phenylephrine method⁹ with noninvasive assessment of blood pressure changes using the FinapresTM system (Ohmeda 2300, Ohmeda, WI, USA), as previously described.^{7,8} Patients received bolus injections of phenylephrine starting with 2 μ g/kg to achieve an increase in systolic blood pressure between 15 and 40 mmHg. BRS was calculated from the slope of the linear regression analysis of R-R intervals plotted against the preceding arterial pressure pulse. A reduced vagal reflex activity was defined if BRS was ≤ 3 ms/mmHg.^{7,8}

Follow-up

After discharge, patients were seen in the arrhythmia outpatient clinic at 4, 8, and 12 months and in 6-month intervals thereafter. All episodes of nonfatal arrhythmic events, reinfarction, and revascularization procedures were carefully recorded. Information about deceased patients was obtained from family members, their general practitioners, and from the hospitals to which they had been admitted. Particular attention was given to the circumstances of each death.

Definition of Study Endpoints

The primary endpoint of the study was prospectively defined as a composite endpoint of cardiac mortality, documented sustained VT, and resuscitated VF. A secondary endpoint of the study was arrhythmic events (defined as sudden cardiac death, documented sustained VT, and resuscitated VF). Sudden death was defined as instantaneous, unexpected death, or death within 1 hour of symptoms onset not related to circulatory failure.¹⁰ Sustained VT was defined as a documented tachycardia of ventricular origin at a rate of ≥ 100 beats/min and lasting for more than 30 seconds or resulting in hemodynamic deterioration.

Statistical Methods

A cut-off value of 35% was defined to stratify patients according to LVEF. For further statistical analysis, subgroups of patients with an LVEF $\leq 25\%$, 26–35%, 36–50%, and $>50\%$ were evaluated prospectively.¹¹⁻¹³ Continuous variables are reported as mean $\pm$ standard deviation. All data were analyzed using the Statistical Package for the Social Sciences (SPSS; Vs 9.0). Comparisons between patients with and without events during follow-up were performed by means of the unpaired Student's *t*-test for normally distributed continuous variables (two-sided) or the χ^2 test for categorical data. Multivariate analysis using Cox hazard proportional analysis was performed to determine the independent correlation of various risk stratifiers to events during follow-up. Statistical significance was considered with a two-sided P value ≤ 0.05 .

Figure 1. Outcome of patients with respect to LVEF at the time of hospital discharge.

RESULTS

Clinical Characteristics and Outcome of Patients

Four hundred and eleven consecutive MI survivors form the basis of this report. Of these, 332 patients (81%) had an LVEF > 35% at hospital discharge. The percentage of patients within the various predefined LVEF subgroups is shown in Figure 1. At the time of discharge, 80% of the patients had an open IRA (Table 1). Total mortality in the first year after MI was 2.7% in the entire patient population, and 10.9% in patients with LVEF ≤ 35%. During a mean follow-up of 33 ± 21 months,

the prospectively defined primary endpoint occurred in 35 patients (8.5%). There were 23 patients (5.6%) with arrhythmic events of whom 12 (2.9%) suffered sudden death or resuscitated ventricular fibrillation.

Left Ventricular Function and Clinical Endpoints During Follow-up

The incidence of endpoints differed significantly in the various LVEF subgroups. Whereas a primary endpoint event was documented in only 4% of patients with LVEF > 35%, an almost seven-fold higher incidence (27%) was noted in patients with LVEF ≤ 35% ($P < 0.0001$). A similar dependence on LV function was observed for the occurrence of arrhythmic events. The highest incidence of both endpoints was observed in patients with LVEF < 26% with 48% of patients having cardiac events (10/21 patients) and 29% having arrhythmic events (6/21 patients; Fig. 2).

IRA Patency and Clinical Endpoints During Follow-up

At the time of hospital discharge, only 31 patients (14%) had a permanently occluded IRA. Twenty-three out of 328 patients with a patent IRA reached a primary study endpoint (7%), and 12 patients (3.5%) had an arrhythmic event during follow-up. The respective numbers in patients with an

Table 1. Demographic Data and Distribution of Endpoints in Different Patient Subsets Defined According to Left Ventricular Function

	All pts (n = 411)	Pts with LVEF ≤ 35% (n = 79)	Pts with LVEF > 35% (n = 332)	P Values
Age (years)	58 ± 11	60 ± 13	58 ± 11	NS
Male gender (% of pts)	79	79	80	NS
Anterior MI (% of pts)	50	71	44	0.002
LVEF (%)	48 ± 12	30 ± 5	52 ± 9	0.005
IRA patent (% of pts)	80	72	82	NS
β-BL therapy (% of pts)	76	67	78	NS
FU (months)	33 ± 21	23 ± 20	36 ± 20	0.002
SDNN (ms)	93 ± 30	75 ± 27	98 ± 29	0.003
BRS (ms/mmHg)	6.1 ± 4.9	3.7 ± 3.4	6.7 ± 4.9	0.002
Primary endpoint	35 (8.5%)	21 (26.6%)	14 (4.2%)	<0.0001
Secondary endpoint	23 (5.6%)	12 (15.2%)	11 (3.3%)	0.0001

β-BL = beta-blockers; BRS = baroreflex sensitivity; FU = follow-up; IRA = infarct-related artery; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NS = not significant; Pts = patients; SDNN = standard deviation of NN intervals.

Figure 2. Differences in the incidence of the primary and secondary study endpoints according to different LVEF subgroups. (a) LVEF ≤ 35% versus > 35%, and (b) LVEF ≤ 25% versus 26–35%.

occluded IRA were 18/83 patients (23%) and 11/83 patients (13%; $P < 0.001$). It is noteworthy that 45% of the patients with cardiac events had an occluded IRA, whereas IRA was patent in 83% of patients with an uncomplicated course ($P < 0.01$). The two patients with LVEF ≥ 50% who suffered sudden cardiac death had an occluded IRA. With respect to all arrhythmic events, IRA was occluded in 3/4 patients (75%).

Measures of Autonomic Tone and Clinical Endpoints

Univariate comparison of different risk markers in patients with versus those without a primary endpoint event revealed that among patients with LVEF ≤ 35%, SDNN (64 ± 21 vs 79 ± 28 ms; $P = 0.018$) and BRS (1.7 ± 2.0 vs 4.5 ± 3.7 ms/mmHg; $P < 0.001$) were significantly lower in patients reaching a primary endpoint event. Accordingly,

Figure 3. Kaplan-Meier event-free survival in patients with LVEF ≤ 35% according to the results of autonomic testing (upper graph: HRV; lower graph: BRS).

the Kaplan-Meier analysis showed a significantly better event-free survival in patients with preserved autonomic tone as compared to those with impaired HRV or BRS (Fig. 3). In contrast, among individuals with LVEF > 35%, no significant differences with respect to autonomic markers were observed among patients with or without primary or secondary endpoint events (Tables 2 and 3; Fig. 4).

Multivariate Analysis of Risk Markers

To assess independent risk factors, Cox hazard proportional analysis was performed for the entire patient population and for LVEF subgroups including the various noninvasive risk markers and IRA patency. HRV and BRS were significant predictors

Table 2. Statistical Predictors of the Primary Endpoint and of Arrhythmic Events in Patients with LVEF $\leq$ 35%

	Sens.	Spec.	PPV	NPV	RR	95% C.I.	P value
Primary Endpoint							
SDNN	0.40	0.83	0.70	0.58	1.67	1.03–2.68	0.04
BRS	0.42	0.87	0.76	0.61	1.94	1.23–3.05	<0.01
IRA	0.42	0.76	0.38	0.79	1.80	0.83–3.92	NS
Arrhythmic Events							
SDNN	0.22	0.86	0.62	0.53	1.29	0.74–2.27	NS
BRS	0.26	0.90	0.71	0.55	1.60	0.98–2.67	0.07
IRA	0.29	0.85	0.43	0.75	1.74	0.78–3.87	NS

BRS = baroreflex sensitivity; IRA = infarct-related artery; SDNN = standard deviation of NN intervals; Sens. = sensitivity; Spec. = specificity; PPV = positive predictive value; NPV = negative predictive value; RR = relative risk; C.I. = confidence interval.

of a primary endpoint event in patients with impaired LVEF (Table 4). In patients with LVEF $>$ 35%, IRA patency was the only independent predictor of the primary ($P = 0.037$) or secondary study endpoint ($P = 0.05$).

DISCUSSION

Main Study Findings

This prospective long-term follow-up study revealed a remarkably low 1 year cardiac mortality following an AMI of only 2.7% in infarct survivors treated according to contemporary therapeutic guidelines. The most important finding of our study is that in patients with preserved LV function risk stratification by means of autonomic measures did not yield predictive value. In contrast, in AMI survivors with depressed LVEF, both markers of

cardiac autonomic tone were predictive of future cardiac and arrhythmic events.

Prior Studies

Recent studies have convincingly shown that primary prevention of SCD is possible by means of defibrillator implantation.^{1–3} Most recently, in the MADIT-II trial, ICD therapy was associated with a significant survival benefit in patients with a prior MI and severe LV dysfunction (LVEF $\geq$ 30%).³ However, if prophylactic ICD therapy is performed in CAD patients with severely reduced LVEF, many patients receiving ICDs will not need the device. Considering the high costs of this treatment, further attempts of risk stratification are necessary to identify those patients who may derive the largest benefit from primary preventive strategies.⁴ As demonstrated in the present study, assessment of

Table 3. Statistical Predictors of the Primary Endpoint and of Arrhythmic Events in Patients with LVEF $>$ 35%

	Sens.	Spec.	PPV	NPV	RR	95% C.I.	P value
Primary Endpoint							
SDNN	0.09	0.97	0.39	0.84	2.35	1.04–5.30	0.06
BRS	0.05	0.96	0.31	0.75	1.21	0.51–2.88	NS
IRA	0.13	0.98	0.54	0.84	3.33	1.69–6.57	<0.01
Arrhythmic Events							
SDNN	0.07	0.98	0.40	0.83	2.39	0.98–5.89	0.06
BRS	0.04	0.97	0.30	0.74	1.15	0.43–3.10	NS
IRA	0.11	0.98	0.60	0.83	3.60	1.75–7.35	<0.01

BRS = baroreflex sensitivity; IRA = infarct-related artery; SDNN = standard deviation of NN intervals; Sens. = sensitivity; Spec. = specificity; PPV = positive predictive value; NPV = negative predictive value; RR = relative risk; C.I. = confidence interval.

Figure 4. Kaplan-Meier event-free survival in patients with LVEF > 35% according to the results of autonomic testing (upper graph: HRV; lower graph: BRS).

autonomic tone is a valuable tool to identify patients within a cohort of MI survivors with impaired LV function who are at an increased risk of cardiac death and arrhythmic events. Prospective clinical trials such as the DINAMIT study are currently performed to test the hypothesis that preventive ICD therapy prolongs life in patients early after MI who have advanced LV dysfunction and impaired autonomic tone.¹⁴

Value of Assessment of IRA Patency and Cardiac Autonomic Tone

In patients with a LVEF > 35%, IRA patency was the strongest predictor of the primary (RR 3.33,

Table 4. Results of Cox Hazard Proportional Analysis with Regard to Prediction of the Primary Endpoint

	B	SE	P value
All Patients			
IRA patency	-1.1964	0.4215	0.0045
LVEF	-0.0389	0.0184	0.034
SDNN	-0.0521	0.0334	0.042
BRS	-0.1848	0.0776	0.017
Mean RR	-0.0002	0.0019	NS
Age	0.0246	0.0259	NS
Gender	0.6726	0.5084	NS
LVEF ≤ 35%			
IRA patency	-0.7765	0.5886	NS
SDNN	-0.5113	0.2896	0.053
BRS	-0.3880	0.1775	0.028
Mean RR	-0.0002	0.0026	NS
Age	-0.0181	0.0411	NS
Gender	0.6395	0.7485	NS
LVEF > 35%			
IRA patency	-1.0701	0.5135	0.037
SDNN	-0.0157	0.0120	NS
BRS	-0.0685	0.0849	NS
Mean RR	-0.0002	0.0022	NS
Age	0.0613	0.0369	NS
Gender	0.3459	0.6219	NS

BRS = baroreflex sensitivity; IRA = infarct-related artery; LVEF = left ventricular ejection fraction; meanRR = mean RR interval; SDNN = standard deviation of NN-intervals.

95% C.I. 1.69–6.57; $P < 0.01$) and secondary study endpoints (RR 3.59, 95% C.I. 1.75–7.35; $P < 0.01$). However, in patients with advanced LV dysfunction, IRA patency was not of predictive value. In this group, only autonomic risk markers were independent predictors of endpoint events. In the multicenter ATRAMI study, a prospective trial of 1284 patients conducted in the thrombolytic era, depressed HRV (SDNN ≤ 70 ms), or BRS (≥ 3.0 ms/mmHg) carried a significant multivariate risk of cardiac mortality.⁸ Association of reduced autonomic measures with impaired LVEF (≥ 35%) carried an even higher relative risk of 8.7 (95% C.I. 4.3–17.6) for BRS and 6.7 (95% C.I. 3.1–14.6) for HRV, respectively.⁸ In contrast, the present study is the first to show that autonomic measures do not yield prognostic value in MI patients with preserved LVEF. This finding can be explained at least in part by the overall low mortality in this patient group that does not allow statistical evaluation of future risk. Another important factor is the association between LV function and autonomic cardiac tone.^{15–17} It has been shown that autonomic disbalance with predominance of the sympathetic system

is particularly present in infarct survivors with decreased LV function.¹⁸⁻²⁰

Limitation of the Study

A potential limitation of the present study is the relatively low incidence of cardiac events in patients with LVEF > 35% (only 4%). This may have resulted in insufficient power to identify predictive values of the various risk stratification methods.

Clinical Implications

The data of the present study demonstrate that noninvasive risk stratification by means of assessing cardiac autonomic tone does not seem to be useful in patients with preserved LV function after MI. Only IRA patency may yield prognostic information in this subset of patients. Restricting autonomic testing only to patients with reduced LVEF will therefore increase cost effectiveness of postinfarction risk stratification and subsequent preventive treatment. In particular, such an approach may help to avoid unnecessary prophylactic ICD implants in patients who—although having LV dysfunction—will not need an ICD.

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