Reflex and Tonic Autonomic Markers for Risk Stratification in Patients With Type 2 Diabetes Surviving Acute Myocardial Infarction

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OBJECTIVE—Diabetic postinfarction patients are at increased mortality risk compared with nondiabetic postinfarction patients. In a substantial number of these patients, diabetic cardiac neuropathy already preexists at the time of the infarction. In the current study we investigated if markers of autonomic dysfunction can further discriminate diabetic postinfarction patients into low- and high-risk groups.

RESEARCH DESIGN AND METHODS—We prospectively enrolled 481 patients with type 2 diabetes who survived acute myocardial infarction (MI), were aged ≤80 years, and presented in sinus rhythm. Primary end point was total mortality at 5 years of follow-up. Severe autonomic failure (SAF) was defined as coincidence of abnormal autonomic reflex function (assessed by means of heart rate turbulence) and of abnormal autonomic tonic activity (assessed by means of deceleration capacity of heart rate). Multivariable risk analyses considered SAF and standard risk predictors including history of previous MI, arrhythmia on Holter monitoring, insulin treatment, and impaired left ventricular ejection fraction (LVEF) ≤30%.

RESULTS—During follow-up, 83 of the 481 patients (17.3%) died. Of these, 24 deaths were sudden cardiac deaths and 21 nonsudden cardiac deaths. SAF identified a high-risk group of 58 patients with a 5-year mortality rate of 64.0% at a sensitivity level of 38.0%. Multivariately, SAF was the strongest predictor of mortality (hazard ratio 4.9 [95% CI 2.4–9.9]), followed by age ≥65 years (3.4 [1.9–5.8]), and LVEF ≤30% (2.6 [1.5–4.4]).

CONCLUSIONS—Combined abnormalities of autonomic reflex function and autonomic tonic activity identifies diabetic postinfarction patients with very poor prognoses.

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D iabetes remains one of the leading causes of death in the industrialized world despite considerable recent attention. Diabetic patients with histories of myocardial infarctions (MIs) have particularly poor prognoses (1). A substantial number of deaths in these patients occur suddenly and might thus be preventable by prophylactic implantation of implantable cardioverter defibrillators (ICDs). As implanting ICDs in all diabetic post-MI patients would not be cost-effective, further risk stratification of this patient population is necessary. At present, left ventricular ejection fraction (LVEF) is the gold standard tool for post-MI risk stratification (2). However it is neither specific nor sensitive. This problem is not related to diabetic patients because risk stratification in the general post-infarction population suffers from the same shortcoming. Therefore, additional risk stratification tools, including the assessment of autonomic dysfunction, have been proposed for the general postinfarction population.

In diabetic postinfarction patients, autonomic function can be affected by both the infarction, including its complications, and the preexisting cardiac autonomic neuropathy (2–4). This might compromise risk-predictive value of the autonomic markers. Therefore, this study was undertaken to investigate whether markers of autonomic dysfunction are of prognostic value in the clinical setting of acute MI complicated by a preexisting diabetic cardiac neuropathy.

Heart rate turbulence (HRT) (5) and deceleration capacity (DC) (6) are Holter-based techniques that capture different aspects of autonomic control. HRT quantifies an autonomic reflex, namely the heart rate response to the transient fall of arterial pressure caused by ventricular premature complexes (VPCs). DC is supposed to be representative of tonic vagal activity. Coincidence of abnormal HRT and DC are suggestive of severe autonomic failure (SAF). In unselected post-MI patients, SAF indicated high risk of subsequent death (7). In the current study of diabetic post-MI patients, we tested the association of SAF with 5-year mortality and the improvement of risk prediction by adding SAF to the LVEF gold standard.

RESEARCH DESIGN AND METHODS—Between January 1996 and March 2005, survivors of acute MI (<4 weeks) were enrolled at two large university hospitals, the German Heart Centre and the Klinikum Rechts der Isar, both located in Munich, Germany. Patients were included if they suffered from type 2 diabetes, were aged ≤80 years, presented in sinus rhythm, and did not meet the criteria for secondary ICD therapy (i.e., had cardiac arrest or documented sustained ventricular tachycardia). Type 2 diabetes was considered present if a patient was already diagnosed

and was receiving treatment (diet, tablets, or insulin) or if fasting blood glucose concentration repeatedly exceeded 11 mmol/L. MI was diagnosed in the presence of at least two of the following three findings: *1*) chest pain for ≥20 min, *2*) creatine kinase-MB above the double upper normal limit of our laboratory, and *3*) ST-segment elevation of ≥0.1 mV in two or more limb leads or ≥0.2 mV in two or more contiguous precordial leads. Patients were followed up for a median of 3.9 (interquartile range 2.1–6.2) years. The Ethics Committee of Technische Universität München approved the collection of data and analysis of Holter recordings. Because the study data were noninvasive and obtained as a part of standard clinical management, the local ethics committee did not require signed informed consent. However, oral informed consent was obtained in all cases.

Assessment of reflex and tonic autonomic markers
In all patients, 24-h Holter electrocardiograms were recorded within 2 weeks of enrollment. All recordings were routinely processed using standard commercial equipment (Oxford Excel Holter system, Oxford Instruments; Pathfinder 700, Reynolds Medical; and Mortara Holter system, Mortara Instrument) to obtain the sequence of individual R-R intervals together with the distinction of sinus rhythm beats and ventricular premature complexes.

HRT is composed of an initial heart rate acceleration followed by a subsequent heart rate deceleration (8). The two phases of HRT are quantified by two numerical descriptors, turbulence onset (TO) and turbulence slope (TS). HRT was considered abnormal if both TO and TS were abnormal (TO ≥0% and TS ≤2.5 ms per heartbeat interval, respectively) (8). DC was considered abnormal if ≤4.5 ms (6).

The association of HRT and DC with autonomic abnormalities was previously reported (6,9).

Definition of categories of autonomic dysfunction
Normal autonomic function (NAF) was assumed if both HRT and DC were normal. Mild autonomic failure (MAF) was assumed if only one of HRT and DC was normal while the other was abnormal. Severe autonomic failure (SAF) was assumed if both HRT and DC were abnormal.

Other risk predictors
Other evaluated risk predictors included age, sex, history of previous MI, standard deviation of normal-to-normal heartbeat intervals (SDNN) (10), mean heart rate, arrhythmias during Holter monitoring, insulin dependency, and LVEF. LVEF was assessed by left ventricular angiography or biplane echocardiography. In the latter case, a phased-array system (Sonos 5500, Hewlett Packard) was used.

Variables were dichotomized at predefined cutoff values based on previous publications: LVEF ≤30%, age ≥65 years, SDNN ≤70 ms, mean heart rate ≥75 bpm, single VPCs ≥10 per h, and presence or absence of nonsustained ventricular tachycardia (nsVT) (11). The latter two parameters defined arrhythmia categories: negative (<10 VPCs per h and absence of nsVT) and positive (≥10 VPCs per h or presence of nsVT in 24 h). Renal impairment was defined as the estimated glomerular filtration rate (eGFR) ≤60 ml/min/1.73 m^2 (12).

Study end points
If a patient died during follow-up, the reason for death was verified from hospital and autopsy records and from either the primary physician or those witnessing the death. An independent end point committee adjudicated the mode of death. Deaths were categorized as cardiac and noncardiac. Cardiac deaths were further categorized as sudden and nonsudden. Cardiac death was defined as sudden if it was a witnessed death occurring within 60 min of the onset of new symptoms unless *1*) there was an obvious noncardiac cause, or *2*) if it was an unwitnessed death in the absence of preexisting progressive circulatory failure or other causes of death, or *3*) if it was a death during attempted resuscitation. The primary end point of the study was all-cause mortality within the first 5 years of follow-up; secondary end points were cardiac and sudden cardiac death also within the first 5 years of follow-up.

Data analysis and statistics
We investigated both the association of the autonomic dysfunction categories with outcome and the improvement of risk prediction by adding these categories to the current LVEF-based standard of risk prediction. Continuous variables are presented as median and interquartile range; qualitative data are expressed as percentages. Mortality rates were estimated by the Kaplan-Meier method (13)

and compared by two-sided log-rank test. Secondary end points (cardiac death and sudden death) were analyzed with competing risk models (14) using *R* and compared with the procedure proposed by Gray (15). Multivariable analyses were performed using a two-sided Cox proportional hazards model with enter procedure of all risk predictors considered (Table 2). Hazard ratios (HRs) are presented with 95% CIs. The diagnostic properties of the different prognostic systems are characterized by sensitivity, specificity, and predictive values calculated to reflect the number of expected deaths in case of censored data (16). The change in the difference in the predicted probabilities of the outcome after introducing SAF to LVEF was estimated by the integrated discrimination index (IDI) (17), where a better model is reflected by a greater difference in the predicted probabilities. Differences were considered statistically significant if *P* < 0.05 (SPSS 18.0, SPSS Inc.).

RESULTS—During the recruitment period, 481 patients were enrolled. Table 1 shows the clinical characteristics of the patients. The median of creatine kinase maximum was 1,114 units/L. Median LVEF was 51%. Percutaneous coronary interventions were performed in 89% of the patients. The adjuvant medication consisted of aspirin in 99%, β-blockers

Table 1—*Patients characteristics of the study population*

Characteristic	*n* = 481
Age (years)	65 (57–72)
Female sex	137 (28)
Oral antidiabetic drugs	276 (57)
Insulin dependency	139 (29)
History of previous MI	75 (16)
CK$_{max}$ (U/l)	1,114 (494–2,400)
Creatinine (mg/dL)	1.1 (0.9–1.3)
eGFR (ml/min/1.73 m^2)	70 (55–88)
LVEF (%)	51 (42–59)
VPC (counts per h)	0.5 (0.1–3.6)
Nonsustained VT	39 (8)
Abnormal HRT	73 (15)
DC ≤4.5 ms	250 (52)
NAF	216 (45)
MAF	207 (43)
SAF	58 (12)

Data are median (interquartile range) or *n* (%). CK$_{max}$, creatine kinase maximum; VT, ventricular tachycardia; abnormal HRT, abnormality defined as coincidence of both abnormal turbulence onset and abnormal turbulence slope.

in 94%, ACE inhibitors in 94%, and statins in 85%. Two hundred seventy-six (57.4%) of the patients received oral antidiabetic drugs; 139 (28.9%) of the patients were treated with insulin. Follow-up information was collected on all patients. Six patients were lost to follow-up. They were censored at the date of last contact. During the median follow-up of 3.9 years, 83 diabetic patients died; out of these, 21 deaths were classified as nonsudden cardiac and 24 as sudden cardiac deaths. Another 28 deaths were classified as noncardiac deaths, while the mode of death could not be specified in 10 cases.

Association of autonomic dysfunction with the primary end point

Fifty-eight patients had SAF (12.1%), 207 patients had MAF (43.0% [abnormal DC in 192 patients, abnormal HRT in 15 patients]), and 216 patients had NAF (44.9%).

In univariable analysis, all risk factors with the exception of sex were significantly associated with 5-year mortality; SAF provided the highest HR of 11.2 (Table 2). In SAF patients, probability of death within 5 years was 64.0% (positive predictive value of 64% at 38% sensitivity [Table 3]). In MAF and NAF patients, the probabilities of death within 5 years were 22.6 and 8.9%, respectively (Fig. 1A).

In multivariable analysis, SAF provided the highest HR of 4.9 (95% CI 2.4–9.9, $P < 0.0001$ [Table 2]). Other multivariately independent risk predictors were age ≥65 years (3.4 [1.9–5.8], $P < 0.0001$); LVEF ≤30% (2.6 [1.5–4.4], $P = 0.001$), and history of previous MI (1.7 [1.1–2.8], $P = 0.028$).

Association of autonomic dysfunction with secondary end points

SAF was also a statistically significant predictor of cardiac death and sudden cardiac death (Fig. 1B and C). Probability of cardiac death within 5 years was 3.8% in NAF patients. In MAF and SAF patients, these numbers were 9.7 and 42.8%, respectively. Probability of sudden death within 5 years was 2.1, 5.9, and 19.5% in NAF, MAF, and SAF patients, respectively.

Improvement of risk prediction by SAF

If SAF was added to LVEF, a significant improvement in performance of the risk stratification model was observed (IDI, 0.022; $P < 0.0001$). In the large group of patients with LVEF >30%, SAF

identified a patient subgroup of similar size and mortality risk as patients with depressed LVEF (Fig. 2).

LVEF ≤30% occurred in 38 patients. Of these, 20 patients died during the follow-up period. Another 63 patients died despite having LVEF >30%. These numbers translate to a positive predictive value of 57% at a sensitivity level of 22% (Table 3).

Risk prediction was more precise if LVEF and SAF were used in combination. Eighty-two patients fulfilled the criterion "LVEF ≤30% or SAF." Out of these, 41 patients died during the follow-up period. Another 42 patients died despite having neither LVEF ≤30% nor SAF. These numbers translate to a positive predictive value of 58% at a sensitivity level of 48% (Table 3). The increase in sensitivity by adding SAF to LVEF from 22 to 48% was statistically significant ($P < 0.0001$).

Comparable improvements of sensitivity without compromising positive predictive accuracies were observed with secondary end points (Table 3).

CONCLUSIONS—In our population of diabetic post-MI patients, SAF was strongly associated with 5-year mortality.

Table 2—Uni- and multivariable analyses for prediction of total mortality within 5 years of follow-up

	Univariable analysis		Multivarible analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Age ≥65 years	3.6 (2.2–6.0)	<0.0001	3.4 (1.9–5.8)	<0.0001
Female sex	1.4 (0.9–2.2)	0.150	0.8 (0.5–1.3)	0.301
Previous MI	2.4 (1.5–3.9)	<0.0001	1.7 (1.1–2.8)	0.028
Arrhythmia	2.0 (1.3–3.2)	0.002	1.1 (0.7–1.8)	0.750
LVEF ≤30%	4.7 (2.8–7.8)	<0.0001	2.6 (1.5–4.4)	0.001
Insulin dependency	1.6 (1.0–2.5)	0.045	1.4 (0.9–2.3)	0.117
Mean heart rate ≥75 bpm	2.3 (1.4–3.5)	<0.0001	1.5 (0.9–2.5)	0.087
SDNN ≤70 ms	2.3 (1.5–3.6)	<0.0001	1.4 (0.9–2.3)	0.169
eGFR ≤60 ml/min/1.73 m^2	2.1 (1.4–3.2)	0.001	1.2 (0.8–1.9)	0.347
MAF	2.7 (1.5–4.9)	0.001	1.5 (0.8–2.8)	0.237
SAF	11.2 (6.1–20.5)	<0.0001	4.9 (2.4–9.9)	<0.0001

Table 3—Mortality rates, sensitivities, and specificities for prediction of all-cause mortality, cardiac mortality, and sudden cardiac death in high-risk groups

|	LVEF ≤30%	SAF	LVEF ≤30% or SAF	LVEF ≤30% and SAF
n	38	58	82	14
Prediction of all-cause mortality at 5 years				
All-cause deaths	20	31	41	10
Mortality rate (%)	57.2	64.0	58.2	76.2
Sensitivity (%)	21.7	38.0	47.7	10.6
Specificity (%)	95.7	94.6	90.9	99.1
PPV (%)	57.2	64.0	58.2	76.2
Prediction of cardiac mortality at 5 years				
All-cause deaths	12	21	28	5
Mortality rate (%)	40.5	48.1	43.3	55.9
Sensitivity (%)	28.3	49.2	65.3	14.1
Specificity (%)	94.7	92.9	88.8	98.5
PPV (%)	40.5	48.1	43.3	55.9
Prediction of sudden cardiac mortality at 5 years				
All-cause deaths	6	10	15	1
Mortality rate (%)	25.2	24.2	25.9	14.3
Sensitivity (%)	30.9	44.7	69.0	6.7
Specificity (%)	93.7	90.2	86.2	97.3
PPV (%)	25.0	24.2	25.9	14.3

PPV, positive predictive value.
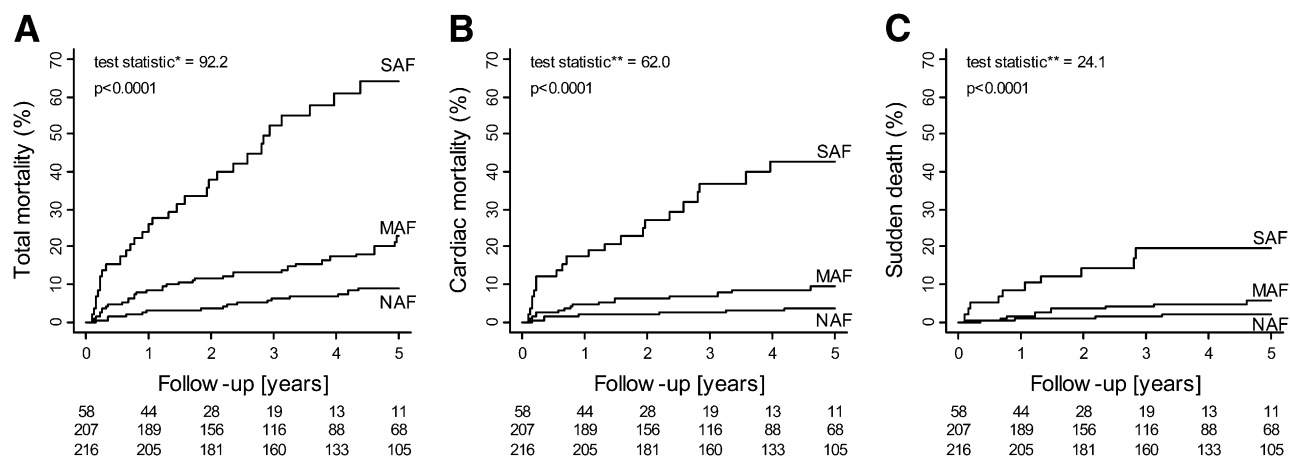
Figure 1—*Cumulative rates of deaths, cardiac deaths, and sudden deaths in patients of the study population stratified according to the degree of autonomic dysfunction (NAF, MAF, SAF). The numbers of patients of the individual groups involved in the analysis at 0, 1, 2, 3, 4, and 5 years are shown below each graph; the order of the rows corresponds to the order of the mortality curves. *Test by log-rank statistics; **test according to Gray's method.*

Twelve percent of all patients showed signs of SAF and had a very poor prognosis; two out of three of these patients died within 5 years. SAF was also strongly associated with cardiac death and sudden death. Surprisingly, almost half of the population was in the NAF category with no signs of autonomic failure. Their 5-year mortality rates were low at 8.9% for death by any cause, 3.8% for cardiac death, and 2.1% for sudden death.
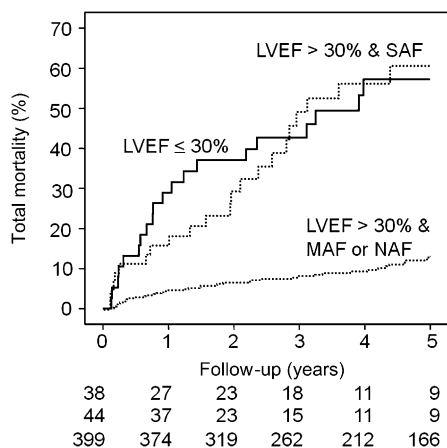

Figure 2—*Total mortality in patients with LVEF ≤30%, LVEF >30% and SAF, and LVEF >30% and MAF or NAF. The numbers of patients of the individual groups involved in the analysis at 0, 1, 2, 3, 4, and 5 years are shown below the graph; the order of the rows corresponds to the order of the mortality curves. Tests were done by log-rank statistics; pairwise comparisons: 1) LVEF >30% and MAF or NAF vs. LVEF >30% and SAF, P < 0.001; 2) LVEF >30% and MAF or NAF vs. LVEF ≤30%, P < 0.001; 3) LVEF >30% and SAF vs. LVEF ≤30%, P = 0.88.*

The addition of SAF to the standard risk model improved the risk prediction in diabetic post-MI patients. Compared with the LVEF ≤30% alone, the combination of SAF or LVEF ≤30% more than doubled the sensitivity of all-cause mortality prediction while practically preserving the positive predictive value.

In a diabetic post-MI patient, autonomic function can be affected by sequelae of diabetes, by sequelae of MI, or by a combination of both. Either pathology, i.e., infarction and diabetes-related autonomopathy, has been separately linked to an increased mortality risk (18,19). A substantial fraction of diabetic post-MI patients presenting with SAF might suffer from a combination of both. We hypothesize that in every individual there is autonomic defense that has a "reserve" and thus remains functional even if partially damaged by different pathologies. When different pathologies are present at the same time, the reserve is exhausted and the autonomic defense might be lost completely.

There are examples where coincidence of different autonomopathies is associated with poor outcome. Such examples include the combination of depression and MI (20), the combination of depression and end-stage renal disease (21), or the combination of diabetes and end-stage renal disease (22).

Our study has important clinical implications. Patients with SAF should receive intensive cardiac therapy based on a multifactorial approach including tight ambulatory monitoring, regular screening for progression of coronary artery disease, optimum medical therapy of heart failure, and finally prophylactic implantation of a cardioverter defibrillator.

In this context of note, diabetic post-MI patients, who generally are sicker and at higher risk of subsequent death than nondiabetic patients, benefited equally well from ICD therapy (23). Our findings also have important implications for the majority of patients with NAF. Because these patients are at very low risk for adverse events, costly and potentially hazardous therapies can be safely avoided.

Any novel risk marker has to be tested against the accepted gold standard for its additive predictive value. In postinfarction risk assessment, LVEF is such a gold standard at present. By adding SAF to LVEF, risk prediction improved significantly. Importantly, in a subset of patients without severely impaired LVEF, SAF identified a substantial number of patients with mortality risk similar to patients with depressed LVEF. As a consequence, a twofold increase in sensitivity was gained without sacrificing specificity.

Limitations of our study should also be recognized. Because we have no information about autonomic status prior to the infarction, we cannot make definite statements about the relative contributions of diabetes-related and infarction-related autonomic damage. Moreover, we have no detailed information about glycemic status, HbA_{1c}, and changes of antidiabetic therapy after hospital discharge. We investigated diabetic survivors of myocardial infarction; we therefore cannot make statements about clinical usefulness of SAF in the general diabetic population. We did not perform reflex tests as suggested by Ewing et al. (24).

Thus, we are not able to compare their usefulness with that of SAF. Our results are limited to patients aged ≤80 years and should not be extrapolated to older patients. Finally, by its signal processing nature, SAF assessment is limited to patients in primarily sinus rhythm.

In conclusion, our study shows that among patients with diabetes and recent MI, presence of SAF is associated with an increased risk of total mortality.

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