Risk Stratification After Acute Myocardial Infarction by Heart Rate Turbulence

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Background—Retrospective postinfarction studies revealed that decreased heart rate turbulence (HRT) indicates increased risk for subsequent death. This is the first prospective study to validate HRT in a large cohort of the reperfusion era.

Methods and Results—One thousand four hundred fifty-five survivors of an acute myocardial infarction (age <76 years) in sinus rhythm were enrolled. HRT onset (TO) and slope (TS) were calculated from Holter records. Patients were classified into the following HRT categories: category 0 if both TO and TS were normal, category 1 if either TO or TS was abnormal, or category 2 if both TO and TS were abnormal. The primary end point was all-cause mortality. During a follow-up of 22 months, 70 patients died. Multivariately, HRT category 2 was the strongest predictor of death (hazard ratio, 5.9; 95% CI, 2.9 to 12.2), followed by left ventricular ejection fraction (LVEF) ≤30% (4.5; 2.6 to 7.8), diabetes mellitus (2.5; 1.6 to 4.1), age ≥65 years (2.4; 1.5 to 3.9), and HRT category 1 (2.4; 1.2 to 4.9). LVEF ≤30% had a sensitivity of 27% at a positive predictive accuracy level of 23%. The combined criteria of LVEF ≤30%, HRT category 2 or LVEF >30%, age ≥65 years, diabetes mellitus, and HRT category 2 had a sensitivity of 24% at a positive predictive accuracy level of 37%. The combined criteria of LVEF ≤30% or LVEF >30%, age ≥65 years, diabetes mellitus, and HRT category 1 or 2 had a sensitivity of 44% at a positive predictive accuracy level of 23%.

Conclusions—HRT is a strong predictor of subsequent death in postinfarction patients of the reperfusion era. (Circulation. 2003;108:1221-1226.)

Key Words: arrhythmia • heart rate • mortality • myocardial infarction • nervous system, autonomic

In the 2002 American College of Cardiology/American Heart Association/North American Society of Pacing and Electrophysiology guidelines, prophylactic implantation of defibrillators was recommended in postinfarction patients with left ventricular ejection fraction (LVEF) ≤30%. This statement was based on the results of the MADIT 2 trial, which showed in these patients a significant risk reduction if they received an implantable defibrillator. Analysis of the cost effectiveness indicated that 11 patients need to be treated over a 3-year period to save 1 life. Thus, the cost of primary defibrillator prophylaxis looms as a barrier to the wider use of this approach. A risk stratification strategy that combines markers of autonomic imbalance and left ventricular dysfunction was recently assumed to be more precise and, thus, may lead to a decrease of the expense.

Heart rate turbulence (HRT) is a measure of the autonomic response to perturbations of arterial blood pressure after single ventricular premature complexes (VPCs). HRT correlates significantly with baroreflex sensitivity and is simple to measure from Holter records. The goals of this study were validation of HRT as a predictor of late mortality in a large postinfarction cohort of the reperfusion era and selection of high-risk subgroups.

Methods

Recruitment and Follow-Up

Patients of either sex younger than 76 years of age were enrolled between January 1996 and December 2000 if they had survived an acute myocardial infarction within the last 4 weeks and if they presented with sinus rhythm. (Initially, the trial was designed to validate a risk stratification protocol based on LVEF, arrhythmia count, heart rate variability, and late potentials. On January 1, 1998, after the enrollment of 629 patients, we incorporated HRT into the protocol. Of note, this modification involved only the definition of risk factors and did not influence data collected or patient care. At the time of the protocol modification, no interim analysis was performed.) An infarction was diagnosed if a patient had at least 2 of the following findings: chest pain for ≥20 minutes, creatine kinase >200 U/L, and ST-segment elevation of ≥0.1 mV in 2 or more limb leads or ≥0.2 mV in 2 or more contiguous precordial leads at the time of admission. The institutional ethics committee approved the study protocol. Diabetes mellitus was considered present if a patient had been given this diagnosis and was receiving treatment (diet, tablets, or insulin) or...
if repeatedly a blood glucose concentration of ≥11 mmol/L was found.

Minimum follow-up was 12 months with clinical appointments every 6 months. Patients who failed to meet these appointments were contacted by letter or telephone at corresponding intervals.

Assessment of Risk Predictors
All risk predictors were measured during the second week after the index infarction. In addition, the following data were recorded: demographic data, history of ischemic heart disease, maximum level of creatine kinase, type of intervention immediately after admission, and therapy at the time of discharge.

Left Ventricular Ejection Fraction
Left ventriculography was performed in single-plane, 30-degree right anterior oblique projection technique using a digital angiographic system (Hicor, Siemens). LVEF was calculated by the area-length method. In 181 patients, LVEF was assessed by single-plane echocardiography using a phased-array system (Sonos 5500, Hewlett Packard). Calculation of LVEF was based on a modified Simpson rule algorithm in the apical 4-chamber view. LVEF was prospectively dichotomized at ≤30% and >30%.

Heart-Rate Turbulence
The 24-hour Holter recordings were processed by an Oxford Excel Holter system (Oxford Instruments) or by a Pathfinder 700 (Reynolds Medical). After manual review by experienced technicians, HRT onset (TO) and HRT slope (TS) were determined according to the previously published method. TO was calculated as the percentage change between the mean of the first 2 sinus RR intervals after a VPC and the last 2 sinus RR intervals before the VPC, as follows: TO = ((RR0 + RR1) − (RR2 + RR3) + (RR4 + RR5) + ... + (RR14 + RR15))/2, where RRi is the i-th sinus rhythm following (i > 0) the compensatory pause of the VPC or preceding (i < 0) the coupling interval of the VPC. These measurements were performed for each singular VPC and subsequently averaged.

TS was calculated as the maximum positive slope of a regression line assessed over any sequence of 5 subsequent RR intervals within the tachogram $RR_n$, $RR_{n+1}$, ..., $RR_{n+14}$, where $RR_i$ is the average of i-th sinus rhythm RR intervals after the compensatory pause of a singular VPB.

TO and TS were dichotomized at predefined cut points (TO <0% and ≥0%; TS ≥2.5 and ≤2.5 ms per normal-to-normal interval). Patients were classified into the following 4 HRT categories: category 0 if both TO and TS were normal; category 1 if either TO or TS was abnormal; category 2 if both TO and TS were abnormal; and category 3: if a patient had no VPCs or if HRT could not be calculated because of the absence of artifact-free and arrhythmia-free post-VPC sequences.

Assessment of Other Risk Predictors
For this study, the following risk predictors were prospectively selected: age of the patient, history of previous myocardial infarction, presence of diabetes mellitus, mean heart rate, heart rate variability triangular index (HRVI), and arrhythmia sign on Holter. The cutoff points were prospectively defined and identical to those used in our previous study, as follows: age of the patient ≥65 and <65 years, mean heart rate >75 bpm and ≤75 bpm, HRVI ≤20 U and >20 U, single VPCs ≥10 VPCs and <10 VPCs per hour, and nonsustained ventricular tachycardia (VT) ≥1 run and <1 run per 24 hours. The latter 2 parameters were used to form 2 arrhythmia categories, negative (<10 VPCs per hour and no nonsustained VT) and positive (≥10 VPCs per hour or ≥1 nonsustained VT in 24 hours).

For retrospective analyses, 3 additional HRV measures were tested. Standard deviation of normal-to-normal intervals for the entire 24-hour recording (SDNN), square root of the mean of the sum of squared differences between adjacent normal-to-normal intervals over the entire 24-hour recording (RMSSD), and standard deviation of the average normal-to-normal interval for all 5-minute segments of a 24-hour recording (SDANN), which were recently proposed by the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, were dichotomized at the lower quintiles (SDNN, 75 ms; RMSSD, 19 ms; SDANN, 63 ms).

Statistical Analysis
The primary end point was death by any cause. A sample size of 1100 patients with an average follow-up of at least 1.5 years was selected based on the assumptions that the incidence of the primary end point is approximately 5 per 100 person years and that 10 end points per risk predictor investigated are on hand. To accomplish a valid analysis even in the case of a lower mortality rate than anticipated or to account for loss to follow-up, the sample size was increased by 300 patients.

Continuous variables are presented as median and interquartile range, and qualitative data are expressed as percentages. Survival curves were estimated by the Kaplan-Meier method and compared using the log-rank test. Multivariate analyses were performed using the Cox proportional-hazards model. The effects of the factors investigated are given as hazard ratios with 95% CIs. Tests in the Cox model and log-rank tests were 2-sided, and comparisons of sensitivity and positive predictive accuracy were 1-sided. Differences were considered to be statistically significant when $P<0.05$.

Results
During the recruitment period, 1942 consecutive patients were enrolled. In 487 cases, no Holter ECG was available for various reasons (no consent, early discharge or transfer to another hospital, or technical defects). A total of 1455 patients in whom a 24-hour Holter ECG was available form the actual study population. Their clinical characteristics are provided in the second column of Table 1. Median creatine kinase maximum was 553 U/L. Median LVEF was 56% (58% in patients without Holter). Percutaneous coronary interventions were performed in 90% of the patients (10% percutaneous transluminal coronary angioplasty alone, 80% percutaneous transluminal coronary angioplasty plus stenting), 6% were treated by thrombolysis, and 2% underwent acute bypass grafting. Two percent of the patients received none of these therapies because revascularization was deemed unnecessary or unreliable. The adjuvant medication consisted of aspirin in 99%, β-blockers in 93%, ACE inhibitors in 90%, and statins in 84%. Thirty-eight percent of the patients were taking diuretics; class-III antiarrhythmic drugs were administered in 1.2%. The third and fourth columns of Table 1 depict the clinical characteristics of patients in HRT categories 0, 1, and 2 and of patients in HRT category 3.

Follow-up information was collected in all patients. Six patients were lost to follow-up. They were censored at the date of latest contact. Seventy of the 1455 patients died during the follow-up period of 22±5 months (minimum, 12 months). At 2 years, the probability of death was 4.8%, which was not significantly different from patients without Holter ECG (5.7%).

Association of Risk Predictors With Mortality
On univariate analysis, LVEF and HRT category 2 were the most significant predictors of death (both $P<0.0001$, Table 2). The highest hazard ratio of 11.4 was found in patients belonging to HRT category 2; the next highest was found in patients with LVEF ≤30% (7.1).
On multivariate analysis, 5 variables were significantly associated with the primary end point (Table 2), and again, HRT category 2 was the strongest predictor, with a hazard ratio of 5.9 (P<0.0001). The second strongest was LVEF, with a hazard ratio of 4.5 (P<0.0001). The other significant predictors were presence of diabetes mellitus (2.5; P<0.0001), patient age (2.4; P<0.001), and HRT category 1 (2.4; P<0.05). There were no significant interactions between HRT and the other significant risk predictors. Substitution of HRVI by SDNN, RMSSD, or SDANN did not improve the goodness of fit of the Cox model.

Table 2 shows cumulative mortality curves for patients classified by HRT categories. In HRT categories 0, 1, and 2, the probability of death at 2 years was 2.1%, 3.0%, 7.4%, and 21.5%, respectively (P<0.0001). Because there was no significant difference in the survival probabilities of patients with HRT category 0 and HRT category 0, both categories were merged for additional analyses.

Risk Prediction in Patients With LVEF >30%

In patients with LVEF >30%, all risk predictors but 1 (history of previous myocardial infarction) were univariately associated with mortality, with HRT category 2 being the most significant predictor (Table 3; hazard ratio 8.8; P<0.0001). Multivariately, HRT categories 1 and 2, age, and presence of diabetes mellitus were significantly associated.
with the primary end point, with HRT category 2 being the strongest predictor, with a hazard ratio of 5.2 (P<0.0001).

The upper left graph of Figure 3 shows 2-year mortality rates according to HRT categories in patients with LVEF >30%. These were 15% in HRT category 2, 6% in HRT category 1, and 1% in HRT category 0, patients (P<0.0001). The bottom graph of Figure 3 additionally differentiates mortality risk of patients with LVEF >30%. The risk was lowest (1%) in patients who had all risk predictors negative (age <65 years, absence of diabetes mellitus, and HRT category 0) and gradually increased with increasing number of positive risk predictors. The highest risk (35%) was observed in patients who had all predictors positive (age ≥65 years, presence of diabetes mellitus, and HRT category 2).

### Risk Prediction in Patients With LVEF ≤30%

In patients with LVEF ≤30%, HRT category 2 was the only significant risk predictor, with a hazard ratio of 2.8 (95% CI, 1.1 to 6.9). The upper right graph of Figure 3 shows 2-year mortality rates for 3 subgroups split according to HRT category. The highest mortality risk (38.5%) was observed in patients in HRT category 2. Patients in HRT categories 0 and 1 had less than half the risk (17% and 15%, respectively).

### Different Risk Stratification Strategies

When defining a high-risk group by use of LVEF alone, as proposed by the MADIT 2 investigators, only 19 of 70 patients prone to death had a LVEF ≤30%, whereas 63 of 82 patients with a LVEF ≤30% survived the follow-up period. These figures translate to a positive predictive accuracy of 23% at a sensitivity level of 27% (Table 4).

The definition of a high-risk group was more precise if LVEF, HRT, and clinical parameters (age and presence of diabetes mellitus) were used in combination. The criterion (1) LVEF ≤30% in the presence of HRT category 2 or (2) LVEF >30% in the presence of HRT category 2, advanced age, and diabetes mellitus (black bars in Figure 3) was met by 46 patients, out of whom 17 died during follow-up. These figures translate to a positive predictive accuracy of 37% at a sensitivity level of 24%. The increase in positive predictive accuracy (from 23% to 37%) was statistically significant (P<0.05).

The criterion (1) LVEF ≤30% or (2) LVEF >30% in the presence of HRT category ≥1, advanced age, and diabetes

### TABLE 3. Association of Risk Variables With Total Mortality in Univariate and Multivariate Analysis in Patients With LVEF >30%

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate Hazard Ratio</th>
<th>P Value</th>
<th>Multivariate Hazard Ratio</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥65 y</td>
<td>4.3 (2.5 to 7.7)</td>
<td>&lt;0.0001</td>
<td>2.7 (1.5 to 5.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>4.1 (2.4 to 7.2)</td>
<td>&lt;0.0001</td>
<td>2.7 (1.5 to 4.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>History of previous MI</td>
<td>1.5 (0.7 to 3.0)</td>
<td>0.315</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>mean HR &gt;75 bpm</td>
<td>2.4 (1.3 to 4.4)</td>
<td>&lt;0.01</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>HRVI ≤20 units</td>
<td>2.9 (1.7 to 5.1)</td>
<td>&lt;0.0001</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Arrhythmia positive</td>
<td>2.4 (1.4 to 4.3)</td>
<td>&lt;0.01</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>HRT category 1</td>
<td>3.4 (1.8 to 6.4)</td>
<td>&lt;0.0001</td>
<td>2.5 (1.3 to 4.9)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>HRT category 2</td>
<td>8.8 (4.4 to 17.5)</td>
<td>&lt;0.0001</td>
<td>5.2 (2.5 to 10.7)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

HR indicates heart rate; HRVI, heart rate variability triangular index; and MI, myocardial infarction.
LVEF. Moreover, HRT category 2 remained highly significant after adjustment for LVEF and other clinical risk factors. With multivariate analysis, HRT category 2 indicated an 6-fold risk of death within the first 2 years after myocardial infarction. This figure was in a comparable range to the criterion LVEF ≤30% with its 5-fold risk. Advanced age and the presence of diabetes mellitus and HRT category 1 were other independent predictors of late mortality after myocardial infarction and indicated a 2.5-fold risk.

Clinical Implications
An important finding of our study is that HRT provides information on mortality risk on top of the information obtained by LVEF. The definition of high risk by use of LVEF alone, as proposed by the MADIT 2 investigators, was not as precise as desirable in terms of sensitivity and positive predictive accuracy. Sixty-three of 82 patients with a LVEF ≤30% survived the follow-up period, whereas 51 of 70 patients who died during the follow-up period had a LVEF >30%. These figures translate into a sensitivity of 27% at a positive predictive accuracy level of 23% (Table 4).

The assessment of HRT categories allows for identifying high-risk subgroups in patients with a LVEF below and above 30%. Patients with a LVEF ≤30% who were in HRT category 2 had a 2-year mortality risk of almost 40% (which was more than 2-fold that of patients in HRT categories 0 or 1). Patients with a LVEF >30% who were in HRT category 2, were older than 65 years of age, and suffered from diabetes mellitus showed a 2-year mortality risk of almost 35%. Merging both high-risk groups (black bars in Figure 3) resulted in a 60% increase in positive predictive accuracy (from 23% to 37%, P<0.05) at the cost of a slight decrease in sensitivity (from 27% to 24%).

Broadening the risk stratification criteria to (1) LVEF ≤30% or (2) LVEF >30%, HRT category ≥1, age >65 years, or presence of diabetes mellitus resulted in a 63% increase in sensitivity (from 27% to 44%, P<0.0001) without a change in positive predictive accuracy (unchanged at 23%).

To obtain these gains in sensitivity or positive predictive accuracy of risk assessment, HRT does not need to be assessed in all patients but only in those presenting with a LVEF ≤30% and with a LVEF >30% who are older than 65 years of age and who suffer from diabetes mellitus. In our population, 183 of 1455 patients, ie, 13%, belonged to this category.

TABLE 4. Group Sizes and Number of Primary End Points, Sensitivities, Specificities, and Positive and Negative Predictive Accuracies for Selected Subgroups Defined by LVEF and HRT Categories, Patient Age, and Presence of Diabetes Mellitus

<table>
<thead>
<tr>
<th>Risk-Stratification Criterion</th>
<th>e/n</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPA</th>
<th>NPA</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEF ≤30% alone</td>
<td>19/82</td>
<td>27.1†</td>
<td>95.5</td>
<td>23.2*</td>
<td>96.3</td>
</tr>
<tr>
<td>LVEF ≤30%/HRT 2 or LVEF &gt;30%/age ≥65 y/DM/HRT 2</td>
<td>17/46</td>
<td>24.3</td>
<td>97.9</td>
<td>37.0*</td>
<td>96.2</td>
</tr>
<tr>
<td>LVEF ≤30% or LVEF &gt;30%/age ≥65 y/DM/HRT ≥1</td>
<td>31/135</td>
<td>44.3†</td>
<td>92.5</td>
<td>23.0</td>
<td>97.1</td>
</tr>
</tbody>
</table>

DM indicates diabetes mellitus; e, No. of primary end points; n, size of subgroup; NPA, negative predictive accuracy; and PPA, positive predictive accuracy.

*P<0.05; †P<0.0001.
Limitations
The subjects included in this study were younger than 76 years of age. Therefore, the results should not be extrapolated to an infarction population of older age. Although this study shows that HRT is a potent risk stratifier in postinfarction patients, it remains to be shown that a specific treatment based on these findings will improve outcome.

Conclusion
HRT is a potent tool for postinfarction risk stratification. In patients with a LVEF $\leq 30\%$, HRT category 2 indicates an almost 40% 2-year mortality rate. In diabetic patients $\geq 65$ years of age with a LVEF $\geq 30\%$, HRT categories 1 and 2 identify additional high-risk subgroups.

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