Reflex Versus Tonic Vagal Activity as a Prognostic Parameter in Patients With Sustained Ventricular Tachycardia or Ventricular Fibrillation

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**Background** The autonomic nervous system has been demonstrated to play a decisive role in the genesis of sudden cardiac death. The loss of protective vagal reflexes, in particular, appears to be associated with an increased incidence of malignant ventricular tachyarrhythmias. Two clinically applicable methods for assessment of cardiac autonomic control have been developed: determination of heart rate variability and evaluation of baroreflex sensitivity.

**Methods and Results** To compare the potential predictive value of both methods, two groups of patients were studied. Group 1 comprised 14 postinfarction patients who had experienced at least one episode of ventricular fibrillation or sustained ventricular tachycardia and who were studied after this event. Group 2 consisted of 14 postinfarction patients without tachyarrhythmic events after their infarct. Both groups were carefully matched with respect to age, sex, infarct location, extent of coronary artery disease, left ventricular ejection fraction, blood pressure, and heart rate at rest. Heart rate variability was assessed from 24-hour Holter recordings, and baroreflex sensitivity was determined by means of the phenylephrine method. Indices of heart rate variability were not significantly different between the two groups (SD of the mean RR interval, 84±30 milliseconds versus 103±20 milliseconds; proportion of adjacent RR intervals >50 milliseconds different, 2.8±3.2% versus 5.0±4.1% in group 1 versus 2). Baroreflex sensitivity, however, showed a striking difference: Group 1 patients had a mean value of 1.75±1.63 ms/mm Hg compared with 9.17±5.40 ms/mm Hg in group 2 (P=.0002). Eleven of 14 group 1 patients had a baroreflex sensitivity ≤3.0 ms/mm Hg. By contrast, only 1 of 14 group 2 patients had such a depressed value.

**Conclusions** The results of this study indicate that postmyocardial infarction patients who develop life-threatening ventricular tachyarrhythmias, compared with carefully matched postinfarction patients without major arrhythmic episodes, differ strikingly in terms of baroreflex sensitivity but not in terms of heart rate variability. This finding may have implications for the risk stratification of postinfarction patients and may lead to a differential therapeutic strategy based on autonomic testing. (Circulation. 1994;89:1068-1073.)

**Key Words** • nervous system • heart rate • death, sudden

Experimental and clinical studies conducted during the past two decades have convincingly demonstrated that the autonomic nervous system plays a critical role in the genesis of sudden cardiac death, particularly in the presence of ischemic heart disease. Specifically, sympathetic hyperactivity promotes the occurrence of life-threatening ventricular tachyarrhythmias, whereas augmented vagal tone exerts a protective and antifibrillatory effect. Two clinically applicable methods for assessment of the cardiac autonomic control have been developed: determination of heart rate variability from short- or long-term ECG recordings and evaluation of baroreflex sensitivity according to the phenylephrine method. An important distinction is that whereas heart rate variability determined from Holter recordings reflects primarily tonic vagal activity, baroreflex sensitivity indicates predominantly reflex vagal activity. Both of these tests have been proved to be useful in risk stratification after myocardial infarction.

Bigger et al addressed the issue of the potential redundancy of the two tests. They compared heart rate variability and baroreflex sensitivity in 32 postinfarction patients and found that only a weak statistical correlation existed between the two methods; ie, one cannot be used to predict the results obtained with the other. Moreover, the relative yield of either method with respect to prediction of future arrhythmic events in patients after myocardial infarction remains to be determined.

The present study aimed to compare heart rate variability and baroreflex sensitivity measurements in two selected groups of carefully matched postinfarction patients. One group included patients who after their index infarction experienced an episode of out-of-hospital syncope ventricular tachycardia or ventricular fibrillation, and the other group served as control subjects.

**Methods**

**Patient Population**

The study group consisted of 28 patients with coronary artery disease and a history of remote myocardial infarction that had been diagnosed by the presence of typical chest pain associated
with ECG changes and elevation of creatine kinase. All patients had undergone coronary and left ventricular angiography that confirmed both the presence of coronary artery disease and regional wall motion abnormalities corresponding to the infarct location in the surface ECG. Exclusion criteria for the study were systemic arterial hypertension, insulin-dependent diabetes mellitus, atrial fibrillation, or coexisting valvular disease. At the time of baroreflex sensitivity and heart rate variability measurements, patients had to be in stable clinical condition; in particular, without any signs of uncompensated congestive heart failure or overt angina pectoris.

Patients were divided into two groups according to the history of aborted sudden cardiac death, which was present in 14 individuals (group 1). In all of these patients, at least one episode of out-of-hospital cardiac arrest due to sustained ventricular tachycardia (n=7) or ventricular fibrillation (n=7) not associated with acute myocardial infarction had been documented. These episodes of cardiac arrest occurred after a median of 43 months (range, 9 to 182 months) after the index infarction. These patients were referred to the Department of Medicine at the University of Freiburg Hospital for antiarrhythmic management, including the implantation of an automatic cardioverter/defibrillator.

The other 14 patients (group 2) were a stratified sample from a larger group of 102 postinfarction patients with baroreflex sensitivity and heart rate variability who were studied at the same center as part of an ongoing international multicenter trial of postinfarction risk stratification (ATRAMI). These patients were studied within 4 weeks after their myocardial infarction.

The patients in groups 1 and 2 were carefully matched, with special attention to those demographic and clinical variables that might affect the autonomic markers under study. Baroreflex Sensitivity Study

All patients were carefully instructed about the study, and all gave informed consent to participate. The study protocol was approved by the ethics committee of the University of Freiburg. Baroreflex sensitivity determination was performed according to the phenylephrine method. The patients were placed in the supine position in a comfortable environment and were instructed to breathe regularly. A slow intravenous saline infusion was started. The ECG limb leads were used to determine RR intervals, and blood pressure was measured noninvasively during the entire test (Finapres 2300 blood pressure monitor, Ohmeda, Louisville, Colo). Thirty minutes was allowed for stabilization before basal blood pressure and heart rate measurements were started. Heart rate and blood pressure were continuously displayed on an oscilloscope (Mingoscop M 8, Siemens, Erlangen, Germany) and, after analog-to-digital conversion, were fed into a Siemens PCD-2 computer system and stored for subsequent analysis.

After the stabilization period, patients received a test bolus injection of phenylephrine (2 μg/kg) to evaluate the magnitude of the resulting increase in systolic blood pressure. In case of an increase of 15 to 40 mm Hg, phenylephrine injection was repeated at least twice at intervals of ≥10 minutes. In case of inadequate blood pressure response (<15 mm Hg increase), the dose was increased stepwise by addition of 25 μg per bolus to a maximum of 3.5 μg/kg. The dose found by this procedure was repeated at least twice. Beat-by-beat changes in baseline systolic blood pressure (in mm Hg) and in the lengths of the normal RR intervals (in milliseconds) were calculated off-line from the digital records. Each RR interval was plotted against the preceding arterial pressure pulse, and linear regression analysis was performed for all data included between the point of start of blood pressure rise and the point where it ceased to increase. Only regression lines exhibiting a significant (P<.05) correlation coefficient were accepted for analysis. The final slope represents the mean value of three or more successive determinations.

Ambulatory Monitoring and Analysis of Heart Rate Variability

All patients had baroreflex sensitivity determination and 24-hour Holter monitoring performed within a few days. All ambulatory ECG recordings were performed by means of two-channel bipolar Marquette 8500 Holter recorders. The tapes were subsequently analyzed by running the Marquette 8000 laser scanner with the Marquette arrhythmia analysis program to identify and label each QRS complex. Analysis of heart rate variability was performed as reported in detail elsewhere. In brief, the Marquette system provides R-wave detection via precise fiducial point markings. Only RR cycles in which beats had a normal morphology and cycle lengths were 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 RR 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 by one of the investigators who was unaware of the arrhythmia history of the respective patients (T.K.).

For each recording, the standard deviation of the mean RR interval (SDNN) and the proportion of adjacent RR intervals >50 milliseconds different (pNN50) were determined. In particular, pNN50 has been demonstrated to be a reliable measure of cardiovascular tone. In addition, the software provides three frequency-domain measurements of heart rate variability using fast Fourier transform, namely, the low-frequency (0.04 to 0.15 Hz), the high-frequency (HF) (0.15 to 0.40 Hz), and the total-frequency (0.01 to 1.00 Hz) components.

Statistical Analysis

All values are presented as mean±SD. Comparisons between the two patient groups were performed by means of the two-tailed Student’s t test or the χ² test for unpaired data. Correlation between two variables was evaluated by means of least-squares linear regression analysis and was expressed as the correlation coefficient (r). Statistical significance was assumed with a level of α=0.05.

Results

Patient Characteristics

The two groups were well matched with respect to demographic and clinical data (Table 1). Of particular note is that the average left ventricular ejection fraction did not differ between the two patient groups (31±9% in group 1 versus 33±5% in group 2). In group 1, 8 of 14 patients (57%) exhibited a left ventricular ejection fraction of ≤35% compared with 7 of 14 (50%) in group 2. Left ventricular ejection fraction of the 14 group 2 patients was similar to that of the total postinfarction patient population (n=102) from which these patients were selected. There were also no significant differences between the two groups with respect to infarct location or extent of coronary artery disease. The medications potentially relevant for the autonomic measures and prescribed to the patients at the time of the study are listed in Table 2. Of note, there was no difference between the number of patients receiving β-blockers and angiotensin-converting enzyme inhibitors; however, more group 1 patients were treated with digitalis.

Heart Rate Variability

Heart rate variability indices were not significantly different among patients in groups 1 and 2, although they tended to be lower among group 1 patients: SDNN,
TABLE 1. Clinical Characteristics of the Patients Studied

<table>
<thead>
<tr>
<th></th>
<th>Group 1, Patients With VF/VT</th>
<th>Group 2, Control Patients</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>58±8</td>
<td>61±8</td>
<td>NS</td>
</tr>
<tr>
<td>Men: women</td>
<td>12:2</td>
<td>12:2</td>
<td>NS</td>
</tr>
<tr>
<td>Anterior MI, n (%)</td>
<td>7 (50)</td>
<td>8 (57)</td>
<td>NS</td>
</tr>
<tr>
<td>Inferior MI, n (%)</td>
<td>7 (50)</td>
<td>6 (43)</td>
<td>NS</td>
</tr>
<tr>
<td>CAD, one-vessel</td>
<td>7</td>
<td>6</td>
<td>NS</td>
</tr>
<tr>
<td>CAD, two-vessel</td>
<td>3</td>
<td>6</td>
<td>NS</td>
</tr>
<tr>
<td>CAD, three-vessel</td>
<td>4</td>
<td>2</td>
<td>NS</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>31±9</td>
<td>35±6</td>
<td>NS</td>
</tr>
<tr>
<td>NYHA class</td>
<td>2.1±0.6</td>
<td>1.7±0.6</td>
<td>NS</td>
</tr>
<tr>
<td>BP&lt;sub&gt;syst&lt;/sub&gt;, mm Hg</td>
<td>124±18</td>
<td>118±15</td>
<td>NS</td>
</tr>
<tr>
<td>BP&lt;sub&gt;diast&lt;/sub&gt;, mm Hg</td>
<td>69±4</td>
<td>68±8</td>
<td>NS</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>72±10</td>
<td>71±7</td>
<td>NS</td>
</tr>
</tbody>
</table>

VF indicates ventricular fibrillation; VT, ventricular tachycardia; MI, myocardial infarction; CAD, coronary artery disease; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association classification; BP, blood pressure; systolic; diastolic; bpm, beats per minute.

84±30 versus 103±20 milliseconds (P=NS); pNN50, 2.8±3.2% versus 5.0±4.1% (P=NS); and HF, 7±3 versus 8±3 milliseconds, respectively (Fig 1). Two considerations can be made in examining Fig 1. The first is that for all the three measures of heart rate variability, there is a considerable degree of overlap between groups 1 and 2. The second relates to the single patient in group 1 who had a very high value of SDNN. Without this outlier, the difference between the two groups would have reached statistical significance, but only for SDNN. Indeed, his presence or absence does not modify the lack of statistical difference for pNN50 or HF.

Baroreflex Sensitivity

In contrast to heart rate variability, baroreflex sensitivity differed significantly between the two groups. Specifically, as shown in Fig 2, it was much lower in group 1 than in group 2 (1.75±1.63 versus 9.17±5.40 ms/mm Hg; P=.0002). In group 1, 11 of 14 patients (79%) had a baroreflex sensitivity of ≤3.0 ms/mm Hg. This represents the usual cutoff value between normal and depressed baroreflex sensitivity.15,18 The highest value observed in this group was 4.4 ms/mm Hg. In group 2, a value of ≤3.0 ms/mm Hg was observed in only 1 of 14 patients (7%).

To rule out the possibility of selection bias, the mean baroreflex sensitivity value of the 14 group 2 patients was compared with that of the total cohort of 102 consecutive postinfarction patients of which these patients represented a stratified sample. The total cohort of 102 patients exhibited an average baroreflex sensitivity value of 8.51±6.40 ms/mm Hg, indicating that the 14 patients selected represent the whole patient population evaluated by the phenylephrine test.

Clinical Considerations

For the total patient population studied, there was no significant correlation between baroreflex sensitivity and left ventricular ejection fraction (r=.27; P=NS).
Similarly, measures of heart rate variability were not significantly correlated to left ventricular ejection fraction (r = .28 for SDNN, r = - .02 for pNN50, and r = .09 for HF). The 14 patients with an inferior myocardial infarction had an average baroreflex sensitivity value of 4.55 ± 5.13 ms/mm Hg compared with a mean value of 6.40 ± 5.75 ms/mm Hg compared with a mean value of 4.55 ± 5.13 in patients with anterior myocardial infarction (P = NS). The three different heart rate variability indices showed weak correlations to baroreflex sensitivity that failed to reach statistical significance (SDNN, r = .31, NS; pNN50, r = .33, P = .08; HF, r = .23, NS).

**Patient Follow-up**

The 14 patients in group I were treated by means of an automatic implantable cardioverter/defibrillator. They were followed for 13 ± 6 months. During this time, 9 of 14 patients (64%) received appropriate shocks from the device for treatment of ventricular fibrillation or sustained hemodynamically compromising ventricular tachycardia. The 14 group 2 patients were also followed for 13 ± 7 months. None of these individuals experienced major arrhythmic episodes during this time period.

**Discussion**

The results of the present study indicate that post-myocardial infarction patients who develop a cardiac arrest, compared with carefully matched postinfarction patients who do not experience major arrhythmic episodes, differ strikingly in terms of baroreflex sensitivity but not in terms of heart rate variability. This finding may have implications for the risk stratification of postinfarction patients and may lead to a differential therapeutic strategy based on autonomic testing.

**Baroreflex Sensitivity and Heart Rate Variability After Myocardial Infarction**

After myocardial infarction, both baroreflex sensitivity and heart rate variability decrease in the majority of individuals (approximately 75% of patients). This information can be obtained only by internal control analyses with measurements made before and after a myocardial infarction, implying that these data have to come from experimental studies. Clinically, only group comparison between patients with and without myocardial infarction can be performed. Nonetheless, there is convergent evidence that, within a few months after myocardial infarction, there is a progressive return of depressed baroreflex sensitivity and heart rate variability toward values similar to those present in the non-infarcted population. In some patients, however, vagal activity remains depressed for a considerable amount of time. Before the present study, it was not known whether this would be associated with a greater risk for life-threatening arrhythmias.

The mechanism involved in the well-documented transient depression in vagal activity after myocardial infarction remains speculative. We favor the hypothesis that involves a cardiocardiac sympathovagal reflex. The necrotic scar alters the geometry of the beating heart, resulting in an increased activity of sympathetic afferent fibers secondary to distortion of their sensory endings; as previously demonstrated, this produces an inhibition of cardiac vagal efferent activity. Indeed, it has recently been shown that the reflex increase in vagal efferent traffic secondary to a blood pressure rise (the baroreceptor reflex) is largely blunted by the presence of intact cardiac sympathetic afferents.

**Prognostic Value of Autonomic Markers**

The first hint that analysis of autonomic reflexes might provide prognostic information came from experimental studies dealing with baroreflex sensitivity in conscious dogs. These findings indicated a predisposition toward lethal arrhythmias in individuals at the lower end of the normal distribution of vagal reflex responses. It was also demonstrated that this prognostic value was present not only after but also before myocardial infarction. By contrast, analysis of heart rate variability before myocardial infarction did not discriminate between high- and low-risk animals. This finding was further supported by studies that used direct recording of single cardiac efferent fibers in cats. In these animals without myocardial infarction, only the reflex responses to increases in arterial blood pressure (baroreceptor reflex) and not tonic vagal activity correlated with risk of ischemia-induced ventricular fibrillation.

These experimental findings were rapidly confirmed by two clinical studies. With regard to baroreflex sensitivity, La Rovere et al demonstrated in 78 patients with a first myocardial infarction that mortality increased strikingly when baroreflex sensitivity was depressed, ie, < 3.0 ms/mm Hg. As far as heart rate variability is concerned, Kleiger et al, using 24-hour Holter monitoring, found that depressed heart rate variability, as indicated by a low SDNN, correlated with mortality in 808 postinfarction patients. Subsequently, Farrell et al, in a series of postinfarction patients, examined the predictive value of both baroreflex sensitivity and heart rate variability. They found that baroreflex sensitivity was the best predictor for induction of ventricular tachycardia by programmed electrical stimulation and for spontaneous arrhythmic episodes. These results were obtained by a group comparison analysis between patients with and those without arrhythmic events.

Even though data were accumulating to suggest that patients with depressed baroreflex sensitivity were at greater risk for subsequent arrhythmic events or cardiac mortality, the type of analysis performed (group comparison) and the small number of patients with...
clinical events did not allow the possibility to be ruled out that additional abnormalities were contributing to the depression in the markers of vagal activity. For instance, although left ventricular ejection fraction does not directly correlate with baroreflex sensitivity,15,22 the data by Farrell et al20 indicate that patients with sudden death or arrhythmic events had a left ventricular ejection fraction significantly lower than that of the survivors (33±9% versus 52±14%). Similarly, in the study by La Rovere et al,15 most of the victims also had a depressed left ventricular ejection fraction. It was for these reasons that we decided to perform a case-control study with accurate matching for those variables most likely to affect both patient outcome and vagal activity.

Accordingly, we examined a consecutive series of postinfarction patients surviving an episode of out-of-hospital ventricular fibrillation or sustained ventricular tachycardia. We then proceeded to a rigorous matching using the relatively large population enrolled in the ATRAMI study at the Freiburg centre. Thus, the patients enrolled in ATRAMI served only as a source for appropriate control subjects. This allowed us to match the cases with the control subjects by age, sex, infarct location, extent of coronary artery disease, left ventricular ejection fraction, blood pressure, and heart rate at rest. The two well-matched groups presented a striking difference with respect to baroreflex sensitivity. This did not apply, however, to heart rate variability, which was only slightly and not significantly lower in the group with life-threatening arrhythmias.

The only difference between the two groups relates to the more frequent use of digitalis glycosides in patients with a history of life-threatening arrhythmias. However, it has been demonstrated in experimental studies26 as well as in clinical trials involving healthy volunteers27 or patients with hypertension28 or congestive heart failure29 that digitalis augments baroreflex mechanisms via a direct sensitization of baroreceptors with vagal afferents. Thus, if it had any effect, digoxin should have caused an improvement in baroreflex sensitivity in group 1 patients.

Finally, another important aspect of the present study deserves comment. Although myocardial infarction had occurred in group 1 patients months to years before the occurrence of life-threatening arrhythmias, all individuals exhibited markedly depressed baroreflex sensitivity values. The fact that baroreflex sensitivity was markedly depressed in the ventricular tachycardia/ventricular fibrillation patients months after the infarct compared with the matched control subjects soon after the myocardial infarction argues that the difference might have been greater had baroreflex sensitivity been measured at a similar time after the remote infarction in the two groups. Furthermore, this indicates that failure of the baroreflexes to recover after myocardial infarction identifies patients with a persistent high risk for the development of ventricular fibrillation or syncopal ventricular tachycardia. Importantly, this implies that during follow-up, baroreflex sensitivity can be usefully determined at various times after myocardial infarction without losing its predictive power.

**Difference Between Baroreflex Sensitivity and Heart Rate Variability**

In the present study, baroreflex sensitivity, and not heart rate variability, distinguished between postinfarction patients with and without ventricular fibrillation and ventricular tachycardia. In the absence of a definite explanation, a tenable hypothesis can be postulated. The main difference between baroreflex sensitivity and heart rate variability is that the former informs on the capability of the autonomic nervous system to respond to a stimulus with a given increase in acetylcholine release, whereas heart rate variability informs about the level of acetylcholine released on a continuous basis, ie, tonic activity. This concept involves some degree of oversimplification, because heart rate changes reflect the sympathetic-parasympathetic interaction at the level of the sinus node, ie, the combined effects of norepinephrine and acetylcholine and not only the vagal component.

When acute myocardial ischemia occurs, there is a reflex increase in sympathetic efferent activity.30 To counteract the arrhythmogenic influence of this reflex, it is necessary to increase the amount of acetylcholine released (eg, via a reflex vagal activation) over that released by tonic activity. If one assumes that a considerable portion of the life-threatening arrhythmias in the present study population might have been related to a transient ischemic episode,32 then it becomes easier to understand why it is the impairment in baroreflex sensitivity, and only to a much lesser extent that in heart rate variability, that identifies the individuals at high risk for cardiac arrest.

**References**

Reflex versus tonic vagal activity as a prognostic parameter in patients with sustained ventricular tachycardia or ventricular fibrillation.
S H Hohnloser, T Klingenstein, A van de Loo, E Hablawetz, H Just and P J Schwartz

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