Different Predictive Values of Electrophysiological Testing and Autonomic Assessment in Patients Surviving a Sustained Arrhythmic Episode

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Background Recent data suggest that the electrophysiological study (EPS) has limited value in the identification of high risk patients, so the aim of the present study was to evaluate if non-invasive measurement of baroreflex sensitivity (BRS), a marker of autonomic balance, provides additional prognostic information in patients surviving a sustained arrhythmic episode.

Methods and Results The study group comprised 112 post myocardial infarction patients consecutively referred for EPS following documented ventricular fibrillation (VF) (20), sustained ventricular tachycardia (VT) (74) or a syncopal episode with subsequently documented non-sustained VT at Holter monitoring (18). BRS was assessed according to the transfer function method. A cardioverter–defibrillator (ICD) was implanted in 97 patients. During follow-up (median 315 days), appropriate ICD discharge occurred in 53 patients, and 3 more patients died suddenly. Sustained VT was induced in 84% and 77% of patients who did or did not develop arrhythmia at follow-up (p=0.34). No differences were found in age, sex, infarct site, drug therapy, resting RR interval or cycle of induced VT. Left ventricular ejection fraction (LVEF) ≤35%, New York Heart Association (NYHA) class >2 and BRS ≤3.3 ms/mmHg were found to be univariate predictors of arrhythmia recurrence. Multivariate models were obtained after grouping patients according to a moderately or severely depressed LVEF. Among the patients with LVEF ≤35%, BRS ≤3.3 ms/mmHg emerged as the only significant risk predictor of arrhythmia occurrence (sensitivity, specificity, positive and negative predictive value = 79%, 74%, 83% and 68%, respectively), whereas NYHA class >2 was a significant predictor among patients with LVEF >35%.

Conclusions Noninvasive BRS, but not EPS, is of value in predicting VT/VF episode recurrence in patients surviving a major arrhythmic event. (Circ J 2004; 68: 634–638)

Key Words: Baroreflex sensitivity; Electrophysiological study; Ventricular fibrillation; Ventricular tachycardia

Following the results of large randomized trials (AVID, CIDS, CASH)1–3 showing an improvement in survival in patients who received an implantable cardioverter defibrillator (ICD) after resuscitation from sustained ventricular tachycardia (VT) or ventricular fibrillation (VF), this treatment strategy has been included as a class I indication in the AHA/ACC Guidelines.4 However, given the high cost and invasiveness of the procedure, subsequent studies have questioned whether a subset of patients can be identified who do not require an ICD and new algorithms have been proposed.5–7 In particular, a sub-analysis from CIDS8 suggested that the cost-effectiveness of ICD therapy varied by patient risk factors, making this treatment strategy attractive in the presence of 2 of 3 risk factors including advanced age and New York Heart Association (NYHA) class and reduced left ventricular ejection fraction (LVEF).

In the AVID study, an electrophysiological study (EPS) did not properly identify high risk patients9 and its reliability in guiding therapy has been questioned10. Autonomic markers have been shown to provide significant risk prediction in patients after myocardial infarction (MI), not only identifying groups at high and low risk for total cardiac and arrhythmic mortality,11,12 but also identifying patients who could not tolerate sustained ventricular arrhythmia.13 The level of baroreflex gain may influence in turn the level of autonomic (sympathetic and vagal) balance, and hence the susceptibility of the myocardial substrate to arrhythmia. The original ‘Oxford’ method14 for testing baroreflex gain used angiotensin or phenylephrine to provoke a transient rise in blood pressure, but a more acceptable noninvasive and comparable assessment uses spontaneous blood pressure oscillations to link blood pressure changes to heart rate changes by means of the transfer function method.

Therefore, the aim of our study was to evaluate the predictive value of electrophysiological testing together with non-invasive measurement of baroreflex sensitivity (BRS) in patients surviving a sustained arrhythmic episode.
Autonomic Markers and Arrhythmia Recurrence

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Methods

Subjects

The study group consisted of 137 patients (mean age 62±8 years, 112 males, 25 females), with a previous MI, who were consecutively referred for an EPS following (i) documented VF (23 patients) or (ii) documented sustained ventricular tachycardia (SVT; 83 patients) or (iii) a syncopal episode in the presence of non-sustained VT on 24-h Holter recording (31 patients).

Twenty-five patients were excluded from the study because of atrial fibrillation (8 patients), sinus node dysfunction or/and ativoventricular block (15 patients), insulin-dependent diabetes (2 patients) or frequent (>5%) ectopic beats (6 patients). The final study included 112 patients who, at the time of the study, were clinically stable and free from angina. All of them gave their informed consent and the study was approved by the local Ethical Committee.

All patients underwent clinical evaluation, electrophysiological and echocardiographic studies and BRS assessment. A cardioverter-defibrillator (ICD) was implanted in 97 patients and the remaining 15 patients were treated with either amiodarone (5 patients) or β-blocker (10 patients). Patients were followed up for a median of 315 days (range: 14–1,126).

The endpoint of the study was appropriate and documented ICD discharge for fast VT or VF or sudden (presumably arrhythmic) death, defined as death occurring within 1 h of onset of symptoms in a previously medically stable patient, death during sleep or unwitnessed death occurring within 1 h of the patient last being seen alive. Hereafter, patients who experienced an event during the follow-up will be referred to as event– group and the others as event+ group.

Electrophysiological Study

A standard protocol for VT induction was used. Briefly, electrophysiologic stimulation was performed at the right ventricular apex and right ventricular outflow tract in sinus rhythm and in paced rhythms at 3 basic rates: 550 ms, 400 ms and 330 ms. Pacing with double extra stimuli and eventually with triple extra stimuli was performed if a single stimulus failed to initiate the tachycardia. The induction of polymorphic VT or VF was considered as a non-specific endpoint. Incremental ventricular pacing, left ventricular stimulation, or provocative maneuvers such as isoprenaline infusion were not performed in any patient.

Baroreflex Sensitivity Assessment

Subjects were studied in the morning, at rest, in the supine position, in a fasting state. After instrumentation and stabilization, a 10 min recording of ECG and arterial blood pressure (Finapres 2300, Ohmeda) was performed. The heart period time series was derived from the ECG as consecutive R-R measurements with a resolution of 1 ms. Ectopic beats were linearly interpolated. The systolic pressure time series was obtained by taking the peak of the arterial blood pressure (Finapres 2300, Ohmeda) was performed. The heart period time series was derived from the ECG as consecutive R-R measurements with a resolution of 1 ms. Ectopic beats were linearly interpolated. The systolic pressure time series was obtained by taking the peak of the arterial blood pressure. Baroreflex sensitivity was assessed by the transfer function method15 Briefly, bivariate spectral analysis between spontaneous fluctuations of systolic arterial pressure and heart period time series interval was performed by the Blackman-Tuckey approach, using the software POLYAN.16 The BRS was estimated by averaging the transfer function modulus over the entire low frequency (LF, 0.04–0.15 Hz) band.

Statistical Analysis

Continuous variables in the event+ and event– groups were compared by the t-test for independent samples or, in case of violation of the normality assumption, by the Mann-Whitney test. Categorical variables were compared by the chi-square test. A p-value <0.05 was considered significant.

Table 1  Clinical Characteristics in the Overall Group and According to the Occurrence of an Event (ICD Discharge or Sudden Death)

<table>
<thead>
<tr>
<th></th>
<th>Overall group</th>
<th>Event (+)</th>
<th>Event (–)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>112</td>
<td>56</td>
<td>56</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>62±10</td>
<td>60±10</td>
<td>62±9</td>
<td>0.20</td>
</tr>
<tr>
<td>M/F</td>
<td>90/22</td>
<td>44/12</td>
<td>46/10</td>
<td>0.63</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>37±12</td>
<td>34±10</td>
<td>39±13</td>
<td>0.022</td>
</tr>
<tr>
<td>NYHA (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>21</td>
<td>16</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>42</td>
<td>38</td>
<td>46</td>
<td>0.08</td>
</tr>
<tr>
<td>III</td>
<td>37</td>
<td>46</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>No. of MI</td>
<td>1.2±0.4</td>
<td>1.2±0.5</td>
<td>1.2±0.4</td>
<td>0.78</td>
</tr>
<tr>
<td>Site of MI (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior</td>
<td>49</td>
<td>46</td>
<td>46</td>
<td></td>
</tr>
<tr>
<td>Inferior</td>
<td>33</td>
<td>29</td>
<td>38</td>
<td>0.57</td>
</tr>
<tr>
<td>Other</td>
<td>19</td>
<td>22</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Inducible VT (%)</td>
<td>80</td>
<td>84</td>
<td>77</td>
<td>0.34</td>
</tr>
<tr>
<td>CL of induced VT (ms)</td>
<td>315±59</td>
<td>321±66</td>
<td>308±51</td>
<td>0.66</td>
</tr>
<tr>
<td>Antiarrhythmic drugs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-blockers</td>
<td>28</td>
<td>27</td>
<td>29</td>
<td></td>
</tr>
<tr>
<td>Amiodarone</td>
<td>38</td>
<td>43</td>
<td>34</td>
<td>0.59</td>
</tr>
<tr>
<td>None</td>
<td>34</td>
<td>30</td>
<td>37</td>
<td></td>
</tr>
<tr>
<td>Resting RR (ms)</td>
<td>948±194</td>
<td>972±167</td>
<td>922±215</td>
<td>0.20</td>
</tr>
<tr>
<td>Resting SAP (mmHg)</td>
<td>102±18</td>
<td>102±14</td>
<td>101±21</td>
<td>0.91</td>
</tr>
<tr>
<td>BRS (ms/mmHg)</td>
<td>4.3±3.4</td>
<td>3.2±2.5</td>
<td>5.4±3.8</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

VT, ventricular tachycardia; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; SAP, systolic arterial pressure.

VT, ventricular tachycardia; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; SAP, systolic arterial pressure.
significant.

Survival analysis was performed after categorization of continuous variables (LVEF, BRS, resting RR interval and systolic arterial pressure) into 3 levels according to the following rule: each variable was assigned to level 1 (higher risk) if its value was ≤25th percentile, level 2 (intermediate risk) if its value was between the 25th and 50th percentiles and level 3 (lower risk) for higher values. The other categorical variables considered in the analysis were NYHA class, the location of the previous MI, inducibility of VT and drug therapy; age and sex were considered as covariates (adjusting factors).

The univariate predictive value of each variable was assessed by proportional hazards regression analysis. The risks of the different risk classes (low, intermediate and high) were compared statistically and 2 contiguous classes merged together in the case of a non-significant difference. All significant univariate predictors and their interactions were analyzed jointly in a multivariate regression model. In case of significant interaction between 2 variables, the analysis was restarted after splitting the data according to the levels of either of them. Results are presented as relative risk (RR) and corresponding 95% confidence interval (CI).

Event-free curves were estimated by the Kaplan-Meier method and compared by the log-rank test. All statistical analyses were performed by the SAS-STAT statistical package, release 8.02 (SAS Institute Inc, Cary, NC, USA).

### Results

Of the 112 patients, 90 (80%) had inducible monomorphic VT in the EPS (Table 1). Of those who did not have inducible monomorphic VT, 2 had inducible VF, 2 had inducible polymorphic VT and 1 had spontaneous VF. During the observation period, 53 patients received appropriate ICD discharge (which was subsequently documented) and sudden cardiac death occurred in 3 more patients. The clinical characteristics of the overall study population as well as according to the occurrence of the arrhythmic event are reported in Table 1. No significant differences were found between the 2 event groups in mean age, sex, NYHA class (although class III patients were prevalent in the event+ group), site of MI, baseline RR interval and systolic arterial pressure and response to EPS testing. In particular, 84% and 77% of patients with and without an event at follow-up had inducible monomorphic VT, which also did not differ in cycle length (p>0.5 for all comparisons). Conversely, LVEF and BRS were significantly lower among the event+ patients (34±10% vs 39±13%, p=0.022 and 3.2±2.5 vs 5.4±3.8 ms/mmHg, p<0.001, respectively).

Of the variables described in Table 1, Table 2 reports the univariate predictors of an arrhythmic event. A depressed BRS (≤3.3 ms/mmHg) showed the strongest association with the occurrence of an event with a RR of 2.3 (95% CI 1.3–4.0).

Multivariate proportional hazard regression analysis showed a strong interaction between LVEF and BRS ($\Delta^2=18.5$, p<0.0001). As a consequence, the analysis was restarted after grouping the patients according to depressed LVEF (≤35%, n=61) or more preserved LVEF (>35%, n=51); event rates were 62% and 35%, respectively. The results of this stratified analysis are reported in Table 3. Although NYHA class >2 emerged as the only significant predictor among patients with LVEF >35%, a depressed
BRS (≤3.3 ms/mmHg) was significantly related to the occurrence of ventricular arrhythmias among patients with reduced left ventricular function with no further prognostic contribution from NYHA class (p=0.53). Fig 1 shows the event-free Kaplan-Meier curves for the combined endpoint (ICD discharge plus sudden death) according to the presence of a preserved or depressed BRS in patients with reduced LVEF. The sensitivity and specificity of BRS toward arrhythmia recurrence were respectively 79% and 74%, with positive and negative predictive values of 83% and 68%.

Discussion

This study demonstrates that electrophysiological testing in patients who have survived a sustained arrhythmic event following MI is poorly predictive of future sudden death, whereas autonomic markers together with indexes of left ventricular function can help to cost-effectively identify patients at increased risk of arrhythmia recurrence who do warrant ICD implantation.

In our study 48% of inducible patients did not experience sustained ventricular arrhythmias during follow-up. These results are well in line with a recent reanalysis from the AVID study showing that although 67% of patients had inducible sustained VT or VF, the inducibility was not predictive of VT or VF in the total group. Moreover, LeLorier et al found that in patients with coronary artery disease, left ventricular dysfunction and unexplained syncope, a negative EPS did not exclude recurrent life-threatening ventricular arrhythmias.

At first sight this is surprising, but it is likely that the catastrophic event of sudden death results from a number of complex interactions probably involving the electrolytic and intracellular environment of the myocyte, the presence of ischemia, raised sympathetic and low vagal tone, ectopic activity and ventricular conduction abnormalities, amongst other factors. It appears plausible that the effect of programmed electrical stimulation will also be powerfully dependent on these factors, which are usually not measured in routine electrophysiological tests.

In contrast autonomic tone influences many of those factors. Raised catecholamine/sympathetic activity reduces the serum potassium concentration in acute myocardial ischemia, lowers the threshold for ventricular ectopy or VF and increases oxygen demand and hence relative ischemia. Baroreflex gain is a powerful determinant of autonomic tone and is related to sympathetic activity which may be the reason why it has proven to be a powerful predictor of serious arrhythmic events when combined with other clinical measures. Clinical data also support the impact of sympathetic-vagal interaction on ventricular vulnerability. Mitranu et al have reported that a preserved response to phenylephrine-induced baroreflex activation was accompanied by an increase in the VF threshold whereas the ventricular susceptibility did not change significantly in those subjects who were not able to increase vagal activity.

Baroreflex sensitivity in humans has mainly been assessed using pharmacological methods, administering agents that cause changes in blood pressure but do not directly affect heart rate. One of these methods in particular, the one based on the use of the vasoconstrictor drug phenylephrine, has been shown to provide independent prognostic information in patients after MI. Despite this important clinical evidence and the current availability of non-invasive beat-to-beat pressure monitors as an alternative to intra-arterial cannulation, the pharmacological methods still have difficulties related to the need for repeated (usually 3) bolus injections of the drug. To overcome this, several fully non-invasive methods based on the analysis of spontaneous fluctuations of arterial pressure and RR interval have been proposed in recent years and the method of BRS assessment used in the present study is a modification of the original transfer function method proposed by Robbe et al in the late 1980s. In that approach BRS was computed by averaging the transfer function modulus only at those frequencies showing a coherence between systolic arterial pressure and heart period ≥0.5. The intention of the authors was to guarantee in this way the reliability of the measurements. Recently, however, this approach has been criticized on the grounds that (i) the reliability of the estimates depends on other parameters besides the coherence and (ii) low values of coherence are unavoidable in physiological systems owing to an impaired baroreflex brought about by a pathological condition and/or a low signal-to-noise ratio in the signals. Indeed, it has been shown that the measurability of BRS with the Robbe method in post-MI, chronic heart failure and geriatric patients the measurability is as low as <50% and 24. In the present study this index could be measured in 65 of 112 patients (58%). In order to overcome this dramatic limitation, new criteria for estimating BRS using the transfer function method have been devised. Among them, the simple average of all points of the transfer function modulus in the LF band has been shown to provide the best trade-off between measurability and accuracy. Recently, this method has been applied to 3 different groups of normal and cardiac disease patients and BRS measurements compared with those obtained by the classical phenylephrine test.

In the present study BRS was a powerful univariate predictor of sudden death. Moreover, on further analysis there was a strong interaction between BRS and LVEF. For this reason the subjects were divided into those with and without preserved left ventricular function (cut-point at the median=35%). BRS was a particularly useful predictor in those with an impaired LVEF, which is well in line with recent results from the ATRAMI study showing that among patients with a reduced LVEF and without non-sustained VT (who are generally regarded as at relatively low risk) the presence of a depressed BRS provided a 4-fold increase in the mortality risk. This may reflect the fact that patients with a poor LVEF are likely to be more unhealthy and more susceptible to rhythm disturbances and that the myocyte strain relationship is likely to be different in the failing ventricle.

A possible limitation of this study is that the 1 year follow-up may have been too short for comparison of the different methods of risk stratification. However, the population under evaluation in the present study was one at very high baseline risk, as confirmed by the high incidence of recurrence during such a short-term follow-up. Indeed, 50% of the patients developed arrhythmia during the follow-up and we think this is enough for an appropriate analysis.

Clinical Implications

Non-invasive BRS assessment by spectral analysis of spontaneous changes of systolic arterial pressure and heart period appeared to be of value in predicting the recurrence of VT/VF episode in patients surviving a sustained arrhyth-
mic event.

Although the practical value of such a finding in a high-risk group seems to be moderate, there is an argument for performing similar tests in the general population of post-MI patients because of the fact that tests in the low-risk group must be performed in a large number of patients. Such studies are always expensive and difficult to conduct.

References

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