Noninvasive Arrhythmia Risk Stratification in Idiopathic Dilated Cardiomyopathy

Results of the Marburg Cardiomyopathy Study

Wolfram Grimm, MD; Michael Christ, MD; Jennifer Bach, MD; Hans-Helge Müller, PhD; Bernhard Maisch, MD

Background—Arrhythmia risk stratification with regard to prophylactic implantable cardioverter-defibrillator therapy is a completely unsolved issue in idiopathic dilated cardiomyopathy (IDC).

Methods and Results—Arrhythmia risk stratification was performed prospectively in 343 patients with IDC, including analysis of left ventricular (LV) ejection fraction and size by echocardiography, signal-averaged ECG, arrhythmias on Holter ECG, QTc dispersion, heart rate variability, baroreflex sensitivity, and microvolt T-wave alternans. During 52±21 months of follow-up, major arrhythmic events, defined as sustained ventricular tachycardia, ventricular fibrillation, or sudden death, occurred in 46 patients (13%). On multivariate analysis, LV ejection fraction was the only significant arrhythmia risk predictor in patients with sinus rhythm, with a relative risk of 2.3 per 10% decrease of ejection fraction (95% CI, 1.5 to 3.3; \( P = 0.0001 \)). Nonsustained ventricular tachycardia on Holter was associated with a trend toward higher arrhythmia risk (RR, 1.7; 95% CI, 0.9 to 3.3; \( P = 0.11 \)), whereas \( \beta \)-blocker therapy was associated with a trend toward lower arrhythmia risk (RR, 0.6; 95% CI, 0.3 to 1.2; \( P = 0.13 \)). In patients with atrial fibrillation, multivariate Cox analysis also identified LV ejection fraction and absence of \( \beta \)-blocker therapy as the only significant arrhythmia risk predictors.

Conclusions—Reduced LV ejection fraction and lack of \( \beta \)-blocker use are important arrhythmia risk predictors in IDC, whereas signal-averaged ECG, baroreflex sensitivity, heart rate variability, and T-wave alternans do not seem to be helpful for arrhythmia risk stratification. These findings have important implications for the design of future studies evaluating prophylactic implantable cardioverter-defibrillator therapy in IDC. (Circulation. 2003;108:2883-2891.)

Key Words: arrhythmia ■ cardiomyopathy ■ defibrillation

Prophylactic implantable cardioverter-defibrillator (ICD) therapy has been shown to improve overall survival in selected postinfarction patients with reduced left ventricular ejection fraction (LVEF).1 In the setting of idiopathic dilated cardiomyopathy (IDC), however, arrhythmia risk stratification with regard to prophylactic ICD implantation is a completely unsolved issue.2-5 Accordingly, the Marburg Cardiomyopathy Study (MACAS) was designed to determine the clinical value of potential noninvasive arrhythmia risk predictors in a large patient cohort with IDC.

Methods

MACAS is a prospective observational monocenter study4 with patient enrollment between March 1996 and June 2001 at the Hospital of the University of Marburg, Germany, with a subsequent minimum follow-up of 18 months (Figure 1). The study protocol was approved by the ethics committee of the Philippus-University of Marburg. After informed consent had been obtained, men and women with IDC between 16 and 70 years of age were included if they had an LVEF \( \leq 45\% \) and a LV end-diastolic diameter >56 mm by echocardiography.4 Patients were excluded from the study if they demonstrated one or more of the following parameters: heart failure NYHA functional class IV; a history of sustained ventricular tachycardia (VT) or ventricular fibrillation (VF); an episode of unexplained syncope within the previous 12 months; class I or class III antiarrhythmic drug therapy that could not be withdrawn for at least 5 drug half-lives; amiodarone therapy within the previous 6 months; pacemaker dependency; coronary artery disease diagnosed by evidence of any coronary artery stenosis \( \geq 50\% \) by angiography; or a history of myocardial infarction, systemic arterial hypertension, active myocarditis, alcohol abuse, drug dependency, severe liver or kidney disease, thyroid disease, malignancies, or systemic diseases. Complete diagnostic cardiac catheterization was performed in all patients before study entry, including endomyocardial biopsy in 312 patients (91%), which did not reveal any evidence of active myocarditis or specific heart muscle disease in these patients. Comprehensive echocardiographic examinations were performed in all patients to determine LVEF and LV size. In 32 patients in whom echocardiographic determination of LVEF was difficult, LVEF was determined by radionuclide ventriculography for the purpose of this study.

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The development of microvolt T-wave alternans is critically dependent on heart rate, β-blockers were withheld for 24 hours before T-wave alternans testing whenever possible. The mean heart rate achieved at symptom-limited peak exercise was 139±18 bpm.

All T-wave alternans tracings were stored on optical disk for subsequent offline processing and classification by an independent expert reader who was blinded to the clinical data. The classifications were performed as previously described in detail by Bloomfield et al.\(^8\) In summary, a tracing was classified as positive if sustained alternans was present at the resting heart rate or had an onset heart rate ≤110 bpm. A tracing was classified as negative if the criteria for positivity were not met and if there was 1 minute of data without significant levels of noise, bad beats, or nonsustained alternans, with an interval heart rate of ≥105 bpm (maximum negative heart rate ≥105). Tracings that did not meet the criteria for positive or negative classification were classified as indeterminate.

### Results

**Predictors of Arrhythmic Events in 263 Patients With Sinus Rhythm**

Major arrhythmic events during follow-up occurred in 38 of 263 patients (14%) with sinus rhythm at study entry (Table 1). During 52±21 months of follow-up, major arrhythmic events were observed in 46 patients (13%), including sudden cardiac death in 23 patients and sustained VT or VF in another 23 patients. A total of 49 patients (14%) died during follow-up, and 10 patients (3%) underwent heart transplantation (Table 1).

**Statistical Analysis**

Univariate and multivariate Cox regression analysis was used to evaluate the association between the 2 predefined outcome measures, major arrhythmic events and transplantation-free survival, and baseline variables (as listed in Table 2 for patients with sinus rhythm and in Table 4 for patients with atrial fibrillation at study entry). The final Cox regression model was built by a stepwise procedure, with a significance level of 0.15 as criterion for entry into the model. Event-free survival probabilities were estimated with the Kaplan-Meier method. Results are expressed as mean±SD unless specified otherwise. All probability values reported are 2-sided, and a probability value of \(P<0.05\) was considered to indicate statistical significance. SAS software (SAS Institute) was used for all statistical analyses.

**Follow-Up**

All patients were followed prospectively for 52±21 months until March 2003 (Figure 1). Follow-up could be completed in 340 patients (99%). Three patients (1%) who were lost during follow-up were censored at the time of last follow-up. Predefined primary end points were major arrhythmic events, defined as spontaneous sustained VT, VF, or sudden death, ie, death within 1 hour after the onset of symptoms in a previously medically stable patient; death during sleep; or unwitnessed death. Secondary end point was heart transplantation–free survival. Both end points were analyzed without knowledge of the outcomes.
2). On univariate analysis, LV end-diastolic diameter and LVEF, nonsustained VT, and frequent ventricular premature beats on 24-hour Holter ECG and an indeterminate microvolt T-wave alternans test showed a significant association with major arrhythmic events during follow-up (Table 3, Figure 2). On multivariate analysis, only LVEF was found to be a significant predictor of major arrhythmic events during follow-up, with a relative risk of 2.28 per 10% decrease of ejection fraction (95% CI, 1.55 to 3.33). In addition, there was a tendency for an increased risk of major arrhythmic events for patients without β-blocker therapy at study enrollment (RR, 0.6; 95% CI, 0.3 to 1.2; \( P = 0.13 \)) and for patients with nonsustained VT on baseline 24-hour Holter ECG (RR, 1.7; 95% CI, 0.9 to 3.3; \( P = 0.11 \)). The combination of LVEF <30% and nonsustained VT on baseline 24-hour Holter ECG was associated with an 8.2-fold risk for subsequent major arrhythmic events (95% CI, 3.1 to 22.6; \( P = 0.0001 \)) compared with patients with LVEF ≥30% and no nonsustained VT on baseline 24-hour Holter ECG (Figure 2B).

TABLE 1. Characteristics of 343 Study Patients and End Points During Follow-Up

<table>
<thead>
<tr>
<th>Age and sex</th>
<th>All Patients (n=343)</th>
<th>Sinus Rhythm (n=263)</th>
<th>Atrial Fibrillation (n=80)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>49±12</td>
<td>48±12</td>
<td>54±10*</td>
</tr>
<tr>
<td>Sex, male/female</td>
<td>268/75</td>
<td>193/70</td>
<td>75/5*</td>
</tr>
<tr>
<td>New York Heart Association class, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>42 (12)</td>
<td>36 (14)</td>
<td>6 (8)</td>
</tr>
<tr>
<td>II</td>
<td>217 (63)</td>
<td>160 (61)</td>
<td>57 (71)</td>
</tr>
<tr>
<td>III</td>
<td>84 (25)</td>
<td>67 (25)</td>
<td>17 (21)</td>
</tr>
<tr>
<td>Echocardiographic study</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV end-diastolic diameter, mm</td>
<td>66±7</td>
<td>67±8</td>
<td>64±6*</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>31±10</td>
<td>30±10</td>
<td>34±10*</td>
</tr>
<tr>
<td>12-Lead ECG, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left bundle-branch block</td>
<td>96 (28)</td>
<td>91 (35)</td>
<td>5 (6)*</td>
</tr>
<tr>
<td>Right bundle-branch block</td>
<td>10 (3)</td>
<td>8 (3)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>24-Hour Holter ECG, n (%)</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Frequent VPDs (&gt;10/h)</td>
<td>131 (38)</td>
<td>89 (34)</td>
<td>42 (53)*</td>
</tr>
<tr>
<td>Nonsustained VT (≥120 bpm)</td>
<td>111 (32)</td>
<td>88 (33)</td>
<td>23 (29)</td>
</tr>
<tr>
<td>Medication at enrollment, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digitalis</td>
<td>258 (75)</td>
<td>189 (72)</td>
<td>69 (86)*</td>
</tr>
<tr>
<td>Diuretics</td>
<td>263 (77)</td>
<td>204 (78)</td>
<td>59 (74)</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>305 (89)</td>
<td>233 (89)</td>
<td>72 (90)</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>42 (12)</td>
<td>34 (13)</td>
<td>8 (10)</td>
</tr>
<tr>
<td>β-Blockers</td>
<td>178 (52)</td>
<td>132 (50)</td>
<td>46 (58)</td>
</tr>
<tr>
<td>Antiarrhythmic therapy during follow-up, n (%)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>β-Blockers</td>
<td>252 (73)</td>
<td>195 (74)</td>
<td>57 (71)</td>
</tr>
<tr>
<td>d,l-Sotalol</td>
<td>19 (6)</td>
<td>9 (3)</td>
<td>10 (13)*</td>
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<td>Amiodarone</td>
<td>42 (12)</td>
<td>33 (13)</td>
<td>9 (11)</td>
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<tr>
<td>Prophylactic ICD therapy</td>
<td>45 (13)</td>
<td>41 (16)</td>
<td>4 (5)*</td>
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<td>Follow-up duration, mo</td>
<td>52±21</td>
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<td>49±21</td>
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<tr>
<td>End points during follow-up</td>
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<td></td>
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<tr>
<td>Major arrhythmic events, n (%)</td>
<td>46 (13)</td>
<td>38 (14)</td>
<td>8 (10)</td>
</tr>
<tr>
<td>Sudden cardiac death</td>
<td>23</td>
<td>17</td>
<td>6</td>
</tr>
<tr>
<td>Sustained VT or VF</td>
<td>23</td>
<td>21</td>
<td>2</td>
</tr>
<tr>
<td>Death or heart transplantation, n (%)</td>
<td>59 (17)</td>
<td>43 (16)</td>
<td>16 (20)</td>
</tr>
<tr>
<td>Sudden cardiac death</td>
<td>23</td>
<td>17</td>
<td>6</td>
</tr>
<tr>
<td>Death from heart failure</td>
<td>18</td>
<td>12</td>
<td>6</td>
</tr>
<tr>
<td>Noncardiac death</td>
<td>8</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Heart transplantation</td>
<td>10</td>
<td>10</td>
<td>0</td>
</tr>
</tbody>
</table>

VPD indicates ventricular premature depolarization; VT, ventricular tachycardia. *\( P < 0.05 \) for patients with sinus rhythm vs patients with atrial fibrillation.
Predictors of Transplantation-Free Survival in 263 Patients With Sinus Rhythm

Thirty-three patients (13%) died and 10 patients (4%) underwent successful heart transplantation during follow-up (Table 3). On univariate analysis, NYHA class III heart failure, digitalis use, LV end-diastolic diameter and LVEF, absence of a normal signal-averaged ECG, frequent ventricular premature beats on 24-hour Holter ECG, decreased heart rate variability, and decreased baroreflex sensitivity showed a significant association with death or the need for heart transplantation.
transplantation during follow-up (Figure 2). On multivariate analysis, only LVEF remained as a significant predictor of transplantation-free survival, with a relative risk of 2.51 per 10% decrease of ejection fraction (95% CI, 1.65 to 3.85; \( P=0.0001 \)). In addition, there was a tendency toward a higher transplantation-free survival rate in patients with \( \beta \)-blocker therapy at study entry (RR, 0.51; 95% CI, 0.24 to 1.11; \( P=0.08 \)). A reduced baroreflex sensitivity was associated

### TABLE 3. Predictors of Transplantation-Free Survival in 263 Patients With IDC and Sinus Rhythm

<table>
<thead>
<tr>
<th></th>
<th>Transplantation-Free Survival</th>
<th>Univariate and Multivariate Cox Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes (n=220)</td>
<td>No (n=43)</td>
</tr>
<tr>
<td>Age and sex</td>
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<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>47±12</td>
<td>51±13</td>
</tr>
<tr>
<td>Sex, male/female</td>
<td>158/62</td>
<td>35/8</td>
</tr>
<tr>
<td>New York Heart Association class, n (%)</td>
<td>174 (79)</td>
<td>22 (51)</td>
</tr>
<tr>
<td>I or II</td>
<td></td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>46 (21)</td>
<td>21 (49)</td>
</tr>
<tr>
<td>Medication at enrollment, n (%)</td>
<td>171 (78)</td>
<td>24 (56)</td>
</tr>
<tr>
<td>Digitalis</td>
<td>149 (68)</td>
<td>40 (93)</td>
</tr>
<tr>
<td>Diuretics</td>
<td>166 (75)</td>
<td>38 (88)</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>194 (88)</td>
<td>39 (91)</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>28 (13)</td>
<td>6 (14)</td>
</tr>
<tr>
<td>( \beta )-Blockers</td>
<td>116 (53)</td>
<td>16 (37)</td>
</tr>
<tr>
<td>Antiarrhythmics during follow-up, n (%)</td>
<td>171 (78)</td>
<td>24 (56)</td>
</tr>
<tr>
<td>Class I antiarrhythmics</td>
<td>1 (0.5)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>d,l-Sotalol</td>
<td>9 (4)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>24 (11)</td>
<td>9 (21)</td>
</tr>
<tr>
<td>Echocardiographic study</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV end-diastolic diameter, mm</td>
<td>66±7</td>
<td>70±8</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>31±10</td>
<td>23±8</td>
</tr>
<tr>
<td>Bundle-branch block on ECG, n (%)</td>
<td>71 (32)</td>
<td>20 (47)</td>
</tr>
<tr>
<td>Left bundle-branch block</td>
<td>6 (3)</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Right bundle-branch block</td>
<td>6 (3)</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Dispersion of repolarization, ms</td>
<td>57±23</td>
<td>53±20</td>
</tr>
<tr>
<td>QTc dispersion</td>
<td>57±23</td>
<td>52±21</td>
</tr>
<tr>
<td>JTc dispersion</td>
<td>57±23</td>
<td>52±21</td>
</tr>
<tr>
<td>Signal-averaged ECG, n (%)</td>
<td>91 (41)</td>
<td>9 (21)</td>
</tr>
<tr>
<td>Normal</td>
<td>91 (41)</td>
<td>9 (21)</td>
</tr>
<tr>
<td>Abnormal</td>
<td>52 (24)</td>
<td>12 (28)</td>
</tr>
<tr>
<td>Bundle-branch block</td>
<td>77 (35)</td>
<td>22 (51)</td>
</tr>
<tr>
<td>Arrhythmias on 24-h Holter ECG, n (%)</td>
<td>69 (31)</td>
<td>19 (44)</td>
</tr>
<tr>
<td>Nonsustained VT (&gt;3 beats)</td>
<td>68 (31)</td>
<td>21 (49)</td>
</tr>
<tr>
<td>Frequent VPDs (&gt;10/h)</td>
<td>68 (31)</td>
<td>21 (49)</td>
</tr>
<tr>
<td>Heart rate variability, ms</td>
<td>790±137</td>
<td>769±145</td>
</tr>
<tr>
<td>RRm</td>
<td>790±137</td>
<td>769±145</td>
</tr>
<tr>
<td>SDNN</td>
<td>110±45</td>
<td>99±45</td>
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<tr>
<td>Baroreflex sensitivity, ms/mm Hg</td>
<td>8.1± 5.5</td>
<td>5.6±3.9</td>
</tr>
<tr>
<td>Microvolt T-wave alternans, n (%)</td>
<td>112 (51)</td>
<td>25 (58)</td>
</tr>
<tr>
<td>Positive</td>
<td>112 (51)</td>
<td>25 (58)</td>
</tr>
<tr>
<td>Negative</td>
<td>64 (29)</td>
<td>8 (19)</td>
</tr>
<tr>
<td>Indeterminate</td>
<td>44 (20)</td>
<td>10 (23)</td>
</tr>
</tbody>
</table>

VPD indicates ventricular premature depolarization.

*RR and 95% CI per 10% decrease of LVEF.
†RR and 95% CI per 5 ms/mm Hg decrease of baroreflex sensitivity.
with a tendency toward death or the need for heart transplantation during follow-up, with a relative risk of 1.42 per 5 ms/mm Hg decrease of baroreflex sensitivity (95% CI, 0.95 to 2.13; \( P < 0.08 \)) (Table 3).

Predictors of Outcome in 80 Patients With IDC and Atrial Fibrillation

Major arrhythmic events occurred in 8 of 80 patients (10%) with IDC and atrial fibrillation at study entry (Table 4). On multivariate analysis, only LVEF and lack of \( \beta \)-blocker use were found to be significant predictors of major arrhythmic events. A 10% decrease of LVEF was associated with a 4.5-fold risk for major arrhythmic events (95% CI, 1.53 to 13.2; \( P = 0.0008 \)). Patients with \( \beta \)-blocker therapy had a relative arrhythmia risk of 0.21 compared with patients without \( \beta \)-blockers (95% CI, 0.04 to 0.96; \( P = 0.03 \)). For prediction of transplantation-free survival, LVEF and lack of \( \beta \)-blocker use were also found to be the only significant predictors. A 10% decrease of LVEF was associated with a 2.5-fold risk for death or the need for heart transplantation (95% CI, 1.35 to 4.80; \( P = 0.001 \)). Patients with \( \beta \)-blockers had a relative risk for transplantation-free survival of 0.10 compared with patients without \( \beta \)-blockers (95% CI, 0.03 to 0.32; \( P = 0.0003 \)).

Discussion

This prospective study investigated prediction of major arrhythmic events as primary end point in a relatively large, homogeneous group of patients with IDC on the basis of echocardiography, 12-lead ECG, signal-averaged ECG, arrhythmias, and heart rate variability on digital 24-hour Holter ECG, baroreflex sensitivity, and microvolt T-wave alternans. By multivariate analysis, we found that LVEF was the only significant arrhythmia risk predictor in this patient population. In addition, lack of \( \beta \)-blocker use and presence of nonsustained VT on Holter were significant univariate pre-

![Figure 2. Kaplan-Meier estimates for arrhythmia-free survival and transplantation-free survival of 263 patients with sinus rhythm at study entry stratified for (A) LVEF <30% vs EF >30%, (B) LVEF =30% and no nonsustained VT on Holter (group A), either LVEF <30% or nonsustained VT on Holter (group B), and LVEF <30% and nonsustained VT on Holter (group C). (C) Negative T-wave alternans test (TWA–), positive T-wave alternans test (TWA+), and indeterminate T-wave alternans (TWA±). \( P = 0.04 \) for arrhythmia-free survival in patients with an indeterminate T-wave alternans test compared with patients with a determinate T-wave alternans test. \( P = 0.14 \) for transplantation-free survival in patients with a negative T-wave alternans test compared with patients without a negative T-wave alternans test.]

![Figure 2. Kaplan-Meier estimates for arrhythmia-free survival and transplantation-free survival of 263 patients with sinus rhythm at study entry stratified for (A) LVEF <30% vs EF >30%, (B) LVEF =30% and no nonsustained VT on Holter (group A), either LVEF <30% or nonsustained VT on Holter (group B), and LVEF <30% and nonsustained VT on Holter (group C). (C) Negative T-wave alternans test (TWA–), positive T-wave alternans test (TWA+), and indeterminate T-wave alternans (TWA±). \( P = 0.04 \) for arrhythmia-free survival in patients with an indeterminate T-wave alternans test compared with patients with a determinate T-wave alternans test. \( P = 0.14 \) for transplantation-free survival in patients with a negative T-wave alternans test compared with patients without a negative T-wave alternans test.]

With a tendency toward death or the need for heart transplantation during follow-up, with a relative risk of 1.42 per 5 ms/mm Hg decrease of baroreflex sensitivity (95% CI, 0.95 to 2.13; \( P < 0.08 \)) (Table 3).
dictors of major arrhythmic events. When LVEF and arrhythmias on Holter were combined, the combination of LVEF <30% and nonsustained VT revealed a 8-fold arrhythmia risk compared with patients with LVEF ≥30% without nonsustained VT (Figure 2B). The potential clinical usefulness of the combination of LVEF <30% and nonsustained VT for selection of patients for prophylactic ICD therapy, however, is limited by a positive predictive value for arrhythmic events of <50% during 72 months of follow-up according to the Kaplan-Meier estimate in Figure 2B.

**Time-Domain Analysis of the Signal-Averaged ECG**

By multivariate Cox analysis, the findings of time-domain analysis of the signal-averaged ECG were not found to be helpful for arrhythmia risk stratification in our study. Like us, Turitto et al10 and Silverman et al11 did not find an abnormal time-domain analysis of the signal-averaged ECG to be helpful for arrhythmia risk prediction in patients with IDC. Mancini et al6, however, found an abnormal time-domain analysis of the signal-averaged ECG to be a good predictor for arrhythmic events during follow-up, with a sensitivity of 100% and a positive predictive accuracy of 45% in patients without bundle-branch block. This discrepancy between the study of Mancini et al and the present study may be in part because of differences in patient selection. In contrast to the study by Mancini et al, patients with a history of VT or VF, patients taking class I or class III antiarrhythmic drugs, and patients with NYHA class IV heart failure were excluded from participation in our study. In addition, 50% of patients in the series of Mancini et al had a known cause for nonischemic cardiomyopathy, including hypertensive heart disease and valvular heart disease, whereas these patients were excluded from participation in our study.

**Baroreflex Sensitivity and Heart Rate Variability**

In MACAS, we used a methodology to measure baroreflex sensitivity from the rate-pressure response to intravenous phenylephrine and heart rate variability from 24-hour Holter ECG very similar to that described previously in the multicenter ATRAMI study.7 ATRAMI enrolled 1284 patients with recent myocardial infarction and found that in addition to LVEF, both baroreflex sensitivity and heart rate variability were significant multivariate risk predictors for cardiac mortality. In contrast to ATRAMI, we observed a significant association between baroreflex sensitivity and heart rate variability with transplantation-free survival in patients with IDC only by univariate but not by multivariate analysis. As in

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**TABLE 4. Predictors of Outcome in 80 Study Patients With IDC and Atrial Fibrillation**

<table>
<thead>
<tr>
<th>Major Arrhythmic Events</th>
<th>Transplantation-Free Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes (n=8)</td>
<td>No (n=72)</td>
</tr>
<tr>
<td><strong>Age and sex</strong></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>54±15</td>
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<tr>
<td>Sex, male/female</td>
<td>8/0</td>
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<td><strong>New York Heart Association class, n (%)</strong></td>
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<td>I or II</td>
<td>7 (88)</td>
</tr>
<tr>
<td>III</td>
<td>1 (13)</td>
</tr>
<tr>
<td><strong>Medication at enrollment , n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Digitalis</td>
<td>8 (100)</td>
</tr>
<tr>
<td>Diuretics</td>
<td>7 (88)</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>7 (88)</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>1 (13)</td>
</tr>
<tr>
<td>β-Blockers</td>
<td>3 (38)</td>
</tr>
<tr>
<td><strong>Echocardiographic study</strong></td>
<td></td>
</tr>
<tr>
<td>LV end-diastolic diameter, mm</td>
<td>68±6</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>23±7</td>
</tr>
<tr>
<td><strong>Arrhythmias on 24-h Holter ECG, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Frequent VPDs (&gt;10/h)</td>
<td>5 (63)</td>
</tr>
<tr>
<td>Nonsustained VT (≥3 beats)</td>
<td>4 (50)</td>
</tr>
<tr>
<td><strong>Signal-averaged ECG, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>4 (40)</td>
</tr>
<tr>
<td>Abnormal</td>
<td>3 (37)</td>
</tr>
<tr>
<td>Bundle-branch block</td>
<td>1 (13)</td>
</tr>
</tbody>
</table>

VPD indicates ventricular premature depolarization.

*P<0.05 for patients with vs without arrhythmic events by multivariate Cox analysis.

†P<0.05 for patients with vs without transplantation-free survival by multivariate Cox analysis.
Microvolt T-Wave Alternans for Arrhythmia Risk Prediction in IDC

To date, only 3 studies, published by Klingenstein et al.,14 Kitamura et al.,15 and Hohnloser et al.,16 investigated the prognostic significance of microvolt T-wave alternans in patients with IDC. Klingenstein et al.14 observed 13 arrhythmic events in 107 patients with congestive heart failure of mixed pathogeneses, including 40 patients with nonischemic cardiomyopathy. Of the 13 patients with arrhythmic events during follow-up in the study by Klingenstein et al., 11 had positive T-wave alternans and 2 indeterminate T-wave alternans results, whereas a negative T-wave alternans test predicted freedom of arrhythmic events in all patients. Kitamura et al.15 investigated 104 patients with IDC and observed major arrhythmic events in 12 of 83 patients (14%) during a mean follow-up of 21 months after 21 patients with an indeterminate T-wave alternans test had been excluded from analysis. As a result, Kitamura et al. found that 11 of 12 arrhythmic events occurred in patients with a positive T-wave alternans test, with additional arrhythmia risk for patients with an onset heart rate of T-wave alternans $\leq 100$ bpm. Finally, Hohnloser et al.16 found a positive microvolt T-wave alternans analysis to be the only significant arrhythmia risk predictor by multivariate analysis in 137 patients with dilated cardiomyopathy during 14 months (mean) of follow-up. In contrast to all 3 previous studies, we did not find a positive T-wave alternans test to be associated with an increased arrhythmia risk in MACAS, whereas a negative T-wave alternans test showed a trend toward decreased arrhythmia risk by univariate analysis but not by multivariate analysis. Finally, an indeterminate T-wave alternans test was significantly associated with major arrhythmic events in MACAS by univariate analysis but again, not by multivariate analysis (Figure 2C). The discrepancy between our negative results and the positive results in previous smaller studies14–16 may be explained in part by differences in methods and patient populations. In contrast to MACAS, all 3 previous studies included much smaller patient populations with shorter follow-up durations. Furthermore, Kitamura et al.15 and Hohnloser et al.16 enrolled patients with a history of sustained VT or VF. In the study by Hohnloser et al.,16 most arrhythmic events during follow-up occurred in patients who had already received an ICD before study entry because of a history of sustained VT or cardiac arrest. Therefore, it is impossible to interpret the potential clinical value of T-wave alternans test results in the study by Hohnloser et al.16 as a potential screening tool for prophylactic ICD therapy. Patients with IDC and a history of sustained VT or VF have been shown to be at high risk for arrhythmia recurrence and to require IDC therapy without any further risk stratification.

Study Limitations

Although MACAS enrolled the largest series of patients with IDC for arrhythmia risk stratification reported so far, it must be kept in mind that the number of events in MACAS may still be too small to exclude moderate relations of some of the variables tested to outcome with certainty. Another inherent limitation of MACAS as a prospective observational study is the fact that the use of $\beta$-blockers was nonuniform and that many patients did not receive $\beta$-blockers at study entry.

Conclusions

MACAS provides clear evidence that among the clinical variables tested, LVEF is the most important arrhythmia risk predictor in patients with IDC. When combined with nonsustained VT on Holter, patients with IDC and LVEF $<30\%$ have an 8-fold arrhythmia risk compared with patients with LVEF $\geq 30\%$ without nonsustained VT on Holter. Because lack of $\beta$-blocker use at study entry is also associated with both a higher incidence of subsequent major arrhythmic events and a lower transplantation-free survival rate, optimization of medical therapy, including ACE inhibitors and $\beta$-blocker therapy, should be performed before patients with IDC are screened as potential candidates for prophylactic ICD therapy. Unfortunately, none of the remaining variables that were tested prospectively in MACAS, including signal-averaged ECG, baroreflex sensitivity, heart rate variability, and microvolt T-wave alternans, were found to be helpful for arrhythmia risk stratification or for prediction of transplantation-free survival. The results of MACAS provide useful information regarding the design of future studies evaluating the benefit of prophylactic ICD therapy in patients with IDC.

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References


Noninvasive Arrhythmia Risk Stratification in Idiopathic Dilated Cardiomyopathy: Results of the Marburg Cardiomyopathy Study
Wolfram Grimm, Michael Christ, Jennifer Bach, Hans-Helge Müller and Bernhard Maisch

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