Primary Prevention of Sudden Cardiac Death in a Nonischemic Dilated Cardiomyopathy Population
Reappraisal of the Role of Programmed Ventricular Stimulation

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Background—We considered the role of programmed ventricular stimulation in primary prevention of sudden cardiac death in an idiopathic dilated cardiomyopathy population.

Methods and Results—One hundred fifty-eight patients with idiopathic dilated cardiomyopathy underwent programmed ventricular stimulation. Ventricular tachycardia/ventricular fibrillation was triggered in 44 patients (group I, 27.8%) versus 114 patients (group II), where ventricular tachycardia/ventricular fibrillation was not induced. Sixty-nine patients with idiopathic dilated cardiomyopathy underwent implantable cardioverter-defibrillator (ICD) implantation: 41/44 in group I and 28/114 in group II. The major end points of the study were overall mortality and appropriate ICD activation. Overall mortality during the 46.9 months of mean follow-up was not significantly different between the 2 groups. Patients with left ventricular ejection fraction ≤35% (n=119) demonstrated a higher overall mortality rate compared with the patients with left ventricular ejection fraction >35% (n=39; 16.8% versus 10.3%, log-rank P=0.025). Advanced New York Heart Association class (III and IV versus I and II) was the single independent and strongest prognostic factor of overall mortality (hazard ratio, 11.909; P<0.001; confidence interval, 3.106–45.65), as well as of cardiac mortality (hazard ratio, 14.787; P=0.001; confidence interval, 2.958–73.922). Among ICD recipients, ICD activation rate was significantly higher in group I compared with group II (30 of 41 patients–73.2% versus 5 of 28 patients–17.9%; log-rank P=0.001), either in the form of antitachycardia pacing (68.3% versus 17.9%; log-rank P=0.001) or in the shock delivery form (51.2% versus 17.9%; log-rank P=0.05). Induction of ventricular tachycardia/ventricular fibrillation during programmed ventricular stimulation in contrast to left ventricular ejection fraction was the single independent prognostic factor for future ICD activation (hazard ratio, 4.195; P=0.007; confidence interval, 1.467–11.994).

Conclusions—Inducibility of ventricular tachycardia/ventricular fibrillation was associated with an increased likelihood of subsequent ICD activation and sudden cardiac death surrogate. (Circ Arrhythm Electrophysiol. 2013;6:504-512.)

Key Words: dilated cardiomyopathy ■ electrophysiology test ■ implantable cardioverter-defibrillator ■ primary prevention ■ risk stratification

Sudden cardiac death (SCD) remains a major culprit of adverse long-term prognosis in patients with idiopathic dilated cardiomyopathy (IDCM), accounting for 30% to 40% of all deaths, and in most of the cases is caused by ventricular tachyarrhythmias, mainly sustained ventricular tachycardia (VT), eventually degenerating to ventricular fibrillation (VF).1 The identification of patients with IDCM who are at high risk for SCD, who could subsequently benefit from an implantable cardioverter-defibrillator (ICD) implantation, is substantial. The role of programmed ventricular stimulation (PVS) in the risk stratification of patients with IDCM remains controversial.2–11 According to the present guidelines regarding primary prevention of SCD in patients with IDCM, PVS is not included in the risk stratification assessment.1 Our objective was to investigate the prognostic value of PVS in patients with IDCM presenting to our department for electrophysiological risk stratification and management. The incidence of SCD or appropriate device activation in ICD recipients was determined. We also investigated the clinical significance of the role of PVS in the risk stratification of patients with IDCM.
of polymorphic VT/VF, considered by many authors as a nonspecific response, during an aggressive PVS protocol.6,12,13

Methods

Patient Population
A total of 158 patients with a clinical diagnosis of IDCM were the study population. All subjects were admitted to our hospital for electrophysiological risk stratification for SCD between January 1995 and March 2011. The long enrollment period reflects the strict criteria used for the IDCM diagnosis, the long time needed to gather eligible patients in a single-center study, and the fact that during the 1990s, only a few ICD devices were actually implanted in Greece.

Our cohort did not include any recent onset cases of IDCM to exclude cases of reversible myocarditis.14 Indeed, patients were not deemed eligible if they had symptomatic IDCM with impaired LV function for ≥6 months. The average time between IDCM diagnosis and the time of the study enrollment was 17.9±8 months.

Initially, 191 patients with IDCM were assessed for eligibility. Six patients with a history of aborted SCD or spontaneous sustained VT and 9 patients with medically refractory NYHA stage IV heart failure (HF) were excluded, whereas 3 refused to undergo any invasive procedure for risk stratification. Finally, 173 patients were recruited, but 15 of them were lost during the long-term follow-up. No difference was observed between patients lost at follow-up and the final study population in any of the baseline characteristics.

Overall, the IDCM diagnosis was based on clinical, echocardiographic, and angiographic findings in the presence of global LV dysfunction of no defined pathogenesis (LVEF<50%). Absence of significant coronary artery disease was demonstrated by coronary angiography (152 patients) or by a normal stress thallium (2 patients) or stress echo response. Patients with a history of spontaneous VT or VF, myocardial infarction, myocarditis, significant valvular disease, hypertrophic or restrictive cardiomyopathy, alcohol-associated disease, cardiac toxicity, and those listed for heart transplantation were not included in the trial. A cardiac MRI was performed in selective cases with left-dominant arrhythmogenic right ventricular cardiomyopathy or a recent onset HF (6–12 months) to exclude myocarditis. We did not perform any endomyocardial biopsies because that was not an option in our center.

Complex ventricular arrhythmias were defined by ≥1 episodes of nonsustained VT on Holter monitoring (≥3 consecutive beats at a rate ≥120 bpm) or an average of ≥10 premature ventricular complexes per hour on 24-hour Holter monitoring. Before assessment for ICD implantation, all patients were requested to have at least two 24-hour Holter monitorings. An episode of transient loss of consciousness was defined as syncope of unknown origin, only if the pathogenesis of syncope remained undetermined after a thorough evaluation.

Electrophysiological Study

Although European and American guidelines for ICD implantation do not recommend PVS for risk stratification, according to the national guidelines in Greece,15 induction of sustained VT/VF is generally, but not uniformly, required to approve ICD implantation for primary prevention of SCD regardless of the severity of the coexisting LV dysfunction. ICD implantation could also be approved in patients with LVEF<35% in cases of recurrent syncope or an indication for biventricular pacing regardless of PVS findings. All patients underwent ≥1 electrophysiological study (EPS), whereas antiarrhythmic medications, except for β-blockers, were discontinued for ≥5 half lives before the study. In patients on amiodarone, the drug was interrupted ≥30 days before the EPS. All patients underwent PVS using a standardized protocol which remained constant over the whole time period. Stimulation protocol consisted of up to triple extrastimuli (S2S3S4) delivered at 2 paced cycle lengths (550 and 400 ms) at the right ventricular apex and at right ventricular outflow tract. Extrastimuli were applied after 6-beat drive trains with a 2-second interdrive pause. Ventricular extrastimuli were introduced beginning late in diastole and moved progressively earlier in 10-ms steps until either ventricular refractoriness or a coupling interval of 200 ms was reached. In cases where no sustained ventricular tachyarrhythmia was triggered, PVS was repeated after intravenous isoproterenol administration (1–4 µg/kg per minute). In case the patients complained of not tolerating the tachycardia induced by the PVS, interdrive pause was increased up to 6 seconds.

The arrhythmia induced was defined as sustained monomorphic VT when showing a uniform morphology of QRS complexes with a rate between 120 to 220 bpm, while persisting for ≥30 seconds (or shorter, if termination was necessary because of hemodynamic instability). Faster rates of regular unimorphic VT (≥220 bpm) not permitting to distinguish QRS complexes readily from T waves and without deterioration toward VF were defined as ventricular flutter, but they were included in the monomorphic VT category. Polymorphic VT was defined if constantly changing morphologies and axes were present, leading eventually to VF. According to the results of the PVS protocol, 2 subsets of patients were identified: group I, patients with IDCM with induced sustained ventricular tachyarrhythmias, and group II, patients having had a negative EPS.

Device Implantation and Programming

When sustained VT/VF was triggered during PVS, ICD implantation was subsequently performed. In addition, in cases without VT/VF induction, ICD implantation was performed in patients with recurrent syncope or the need for biventricular pacing.

All devices were programmed on 2 consecutive zones: an antiarrhythmia pacing (ATP) zone (cutoff rate for VT detection was set at a mean cycle length of 375±40 ms and a detection interval of 16 of 16 or 24 of 24 beats), and an initial shock zone (VF detection at a mean cycle length of 300±30 ms and a detection interval of 18 of 24). In the ATP zone, ventricular arrhythmias were initially attempted to be terminated by 2 to 5 bursts of ATP followed by a similar number of ramp ATP runs and, if the arrhythmia continued, by low energy cardioversion and subsequently defibrillator shocks. In the case of VF, device shocks were the initial therapy.

Follow-up

Patients without ICD were regularly followed up in the outpatient arrhythmia clinic at least once every 6 months. Implanted patients were routinely followed up every 3 months or urgently if shocks occurred. For patients who died, the cause of death was determined as SCD (defined as the occurrence of death within 1 hour after symptoms onset), death caused by other acute cardiovascular events (such as aortic aneurysm dissection or massive pulmonary embolism), or death caused by progressively deteriorating HF. Other possible noncardiac causes of death were also recorded.

The major end points of the study, assessed in both patient groups, were overall mortality and SCD surrogate, representing the combination of either SCD or successful and appropriate first activation of the ICD. The time to the first appropriate ICD therapy delivery constituted the end point of analysis for each patient unless death occurred first.

Statistical Analysis

Continuous data are expressed as mean±SD; categorical data are presented as percentages. Differences at baseline were evaluated with the independent sample t test for continuous variables and χ² test for categorical variables. Cumulative incidences were analyzed by the method of Kaplan–Meier and compared using the log-rank test (patients with IDCM with induced ventricular tachyarrhythmias versus those with negative PVS, patients with LVEF≤35% versus those with LVEF>35%). Start of follow-up was marked by PVS, whereas patients with ICD activation were censored at the time of their last follow-up visit. The relation between baseline characteristics (age, history of syncope, presence
of complex ventricular arrhythmias, advanced NYHA class [III and IV versus I and II], LVEF, induced ventricular arrhythmia, and cardiac resynchronization therapy) and end points was assessed by using Cox regression analysis and described with hazard ratios (HR) and 95% confidence interval (CI). In the multivariable Cox regression analysis, adjustments were made for variables that showed a significant association with survival outcomes in univariate analysis. After NYHA class (in the model of overall mortality) and induced ventricular arrhythmia (in the model of ICD activation) entered the model in the first step of the forward selection analysis, no other variables remained statistically significant. For all tests, a P value of <0.05 was considered significant.

Results

Patients—EPS Results—ICD Implantation

Sustained ventricular tachyarrhythmia was induced in 44 of the 158 patients with IDCM (group I, 27.8%); tachyarrhythmia was not induced in 114 patients (group II; Figure 1). Sustained monomorphic VT was triggered in 20 patients (45.4%), ventricular flutter in 9 (20.5%), whereas VF or polymorphic VT leading to VF was induced in 15 patients (34.1%). The relative percentage of monomorphic VT versus ventricular flutter was ≈2:1.

Detailed parameters of the PVS protocol used are presented in the Table in the online-only Data Supplement. In 8 patients, the ventricular tachyarrhythmia was induced after intravenous administration of isoproterenol. No major complications occurred during EPS, except for small hematomas (5 patients).

There were no statistically significant differences between the 2 groups regarding sex, history of syncope, and complex ventricular arrhythmias, LVEF, NYHA class, prevalence of atrial fibrillation or left bundle branch block on the 12-lead ECG, and antiarrhythmic drug administration, whereas group I patients were older than group II patients (Table 1).

In sum, 69 patients with IDCM underwent ICD implantation in the present study: 41 of 44 in group I and 28 of 114 patients in group II, (93.2% versus 24.6%, respectively; P<0.001; Figure 1). Specifically, 12 patients received a single-chamber device, 22 patients received dual-chamber ICDs, and 35 patients (51% among ICD recipients, 15 in group I and 20 in group II) received biventricular pacemaker defibrillators (Cardiac Resynchronization Therapy-Defibrillators device) for NYHA class III and IV HF and prolonged QRS interval. Among them, 27 patients initially received a Cardiac Resynchronization Therapy-Defibrillator device, 6 had a device upgrade from a single- or dual-chamber ICD, and 2

Figure 1. Diagram showing clinical data, programmed ventricular stimulation (PVS) inducibility, and outcome in our idiopathic dilated cardiomyopathy population. CD indicates cardiac death; EF, ejection fraction; HF, heart failure; ICD, implantable cardioverter-defibrillator; CD cardiac death

SCD denotes sudden cardiac death; HF heart failure PVS programmed ventricular stimulation; ICD implantable cardioverter-defibrillator; CD cardiac death.
NYHA III patients with an EF ≤35% and initially negative PVS had an upgrade from Cardiac Resynchronization Therapy-Pacemakers to Cardiac Resynchronization Therapy-Defibrillators. These 2 patients underwent a second EP study:

ventricular flutter was induced in 1 patient and VF was induced in the other. ICDs were subsequently activated in both patients. No significant complications occurred during implantations. Small pocket hematomas, conservatively treated, were observed in 6 patients.

**Long-term Outcome—ICD Activation**

Mean follow-up period was 46.9 months, median follow-up 41.5 (29–58) months, during which 24 patients (15.2%) died: 18 patients died of deteriorating, noncompensated HF (4 were in a list for heart transplantation), 4 patients died of arrhythmic SCD, and 2 patients died of noncardiac causes. In group I, death was recorded in 13 of 44 patients (29.5%) compared with group II, where 11 of 114 patients (9.6%) died (HR, 1.694; CI, 0.732–3.922; log-rank P=0.21; Figure 2). Moreover, no statistically significant difference was observed in the incidence of SCD between group I and II (3 patients–6.8% versus 1 patient–0.9%; log-rank P=0.21), as well as in the incidence of HF death (8 patients–18.2% versus 10 patients–8.8%; log-rank P=0.76).

Among ICD recipients, the first time ICD activation rate was significantly higher in group I compared with group II (73.2% versus 17.9%; log-rank P=0.001), either in the ATP form (68.3% versus 17.9%; log-rank P=0.001) or in the shock delivery form (51.2% versus 17.9%; log-rank P=0.05; Figure 3A). No statistically significant difference occurred in the first time ICD activation rate among ICD recipients with induced VT compared with those with induced VF (78.6% versus 61.5%; log-rank P=0.48).

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**Table 1. Baseline Characteristics of the Study Population**

<table>
<thead>
<tr>
<th></th>
<th>Patients With Induced VT/VF (n=44)</th>
<th>Patients Without Induced VT/VF (n=114)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, y</td>
<td>61.3±10.5</td>
<td>55.3±16.1</td>
<td>0.023</td>
</tr>
<tr>
<td>Male sex, %</td>
<td>70.5</td>
<td>75.4</td>
<td>0.52</td>
</tr>
<tr>
<td>Syncope, %</td>
<td>31.8</td>
<td>23.7</td>
<td>0.29</td>
</tr>
<tr>
<td>Complex ventricular arrhythmias, %</td>
<td>65.9</td>
<td>65.8</td>
<td>0.98</td>
</tr>
<tr>
<td>NYHA classification, %</td>
<td></td>
<td></td>
<td>0.18</td>
</tr>
<tr>
<td>NYHA I</td>
<td>17.5</td>
<td>11.4</td>
<td></td>
</tr>
<tr>
<td>NYHA II</td>
<td>39.5</td>
<td>31.8</td>
<td></td>
</tr>
<tr>
<td>NYHA III</td>
<td>27.2</td>
<td>45.5</td>
<td></td>
</tr>
<tr>
<td>NYHA IV</td>
<td>15.8</td>
<td>11.4</td>
<td></td>
</tr>
<tr>
<td>Left ventricular ejection fraction, %</td>
<td>30.7±8</td>
<td>30.5±9</td>
<td>0.92</td>
</tr>
<tr>
<td>Diabetes mellitus %</td>
<td>18.2</td>
<td>14</td>
<td>0.51</td>
</tr>
<tr>
<td>Hypertension %</td>
<td>31.8</td>
<td>19.3</td>
<td>0.09</td>
</tr>
<tr>
<td>Atrial fibrillation, %</td>
<td>9.1</td>
<td>8.8</td>
<td>0.95</td>
</tr>
<tr>
<td>Left bundle-branch block, %</td>
<td>31.8</td>
<td>22.8</td>
<td>0.24</td>
</tr>
<tr>
<td>Medication</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RAS blockers, %</td>
<td>63.6</td>
<td>67.5</td>
<td>0.64</td>
</tr>
<tr>
<td>Diuretics, %</td>
<td>75</td>
<td>73.7</td>
<td>0.86</td>
</tr>
<tr>
<td>Aldosterone antagonists, %</td>
<td>40.9</td>
<td>36</td>
<td>0.56</td>
</tr>
<tr>
<td>Digoxin, %</td>
<td>11.4</td>
<td>13.2</td>
<td>0.76</td>
</tr>
<tr>
<td>β-Blockers, %</td>
<td>70.5</td>
<td>70.2</td>
<td>0.97</td>
</tr>
<tr>
<td>Amiodarone, %</td>
<td>25</td>
<td>22.2</td>
<td>0.6</td>
</tr>
<tr>
<td>Sotalol, %</td>
<td>13.6</td>
<td>12.2</td>
<td>0.67</td>
</tr>
</tbody>
</table>

NYHA indicates New York Heart Association; RAS, rennin angiotensin system; VF, ventricular fibrillation; and VT, ventricular tachycardia.

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**Figure 2.** Kaplan–Meier estimates of death from any cause among patients with inducible ventricular tachyarrhythmia and those without. PVS indicates programmed ventricular stimulation.

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**Figure 2.** Kaplan–Meier estimates of death from any cause among patients with inducible ventricular tachyarrhythmia and those without. PVS indicates programmed ventricular stimulation.
Moreover, there was no statistically significant difference between groups I and II, regarding the time to the first appropriate ICD intervention (25.7 versus 30 months; \(P=0.44\)).

In addition, the incidence from PVS to the first SCD surrogate episodes in the overall population was significantly higher in group I patients (30 with ICD activation among whom 3 eventually experienced SCD 68.2%) compared with only 6 of 114 group II patients (5 with ICD activation and 1 SCD 5.3%; log-rank \(P=0.001\); Figure 3B).

**LVEF and Long-term Prognosis**

LVEF was relatively preserved in 39 patients (>35% and \(\leq\)50%; mean value, 42.9±4.4%), whereas 119 patients had low LVEF (≤35%; mean value, 26.5±5.1%). VT/VF was induced in 25.6% of patients with preserved LVEF and in 28.6% of patients with low LVEF (Figure 1). Patients with preserved LVEF compared with the low LVEF patients were younger (by 7.7 years; \(P=0.005\)), whereas there was no statistically significant difference regarding sex, history of syncope, and complex ventricular arrhythmias, as well as antiarrhythmic drug administration.

The subset of patients with low LVEF demonstrated a higher overall mortality rate (16.8% versus 10.3%; log-rank \(P=0.025\)) and a greater incidence of cardiac death compared with patients with preserved LVEF (13.5% versus 5.1%; log-rank \(P=0.02\); Figure 4), whereas both patients with preserved and low LVEF were effectively protected with ICD based on the ICD activation rates (60% among ICD recipients with preserved LVEF versus 49.2% among ICD recipients with low LVEF; log-rank \(P=0.48\)). A subset of high-risk patients with preserved LVEF was identified. Among the 10 patients with preserved LVEF and induced ventricular arrhythmias, ICD was activated in 6 of 9 ICD recipients (Figure 1).

In the multivariable Cox regression analysis, including variables such as age, LVEF, history of syncope and complex ventricular arrhythmias, NYHA class, VT/VF induction, and presence of CRT, NYHA class was the single independent and strongest prognostic factor of overall mortality (HR, 11.909; \(P<0.001\); CI, 3.106–45.65; Table 2), as well as of cardiac death (HR, 14.787; \(P=0.001\); CI, 2.958–73.922). On the contrary, VT/VF induction during PVS was the single independent prognostic risk factor for future ICD activation (HR, 4.195; \(P=0.007\); CI, 1.467–11.994; Table 3).
Discussion

The most important findings of this long-term prospective, observational study can be summarized as follows:

1. In a patient population with IDCM, inducible sustained ventricular tachyarrhythmia during PVS identified those at higher risk for a SCD surrogate, defined either as appropriate activations of the ICD or as documented SCD.

2. Overall mortality did not differ significantly between the 2 groups of patients with IDCM, defined on the basis of PVS inducibility (HR, 1.694; CI, 0.732–3.922).

3. The subset of patients with low LVEF (LVEF ≤35%) demonstrated a higher overall mortality rate compared with the subset of patients with preserved LVEF.

4. In the group of patients with IDCM with LVEF >35%, a subset of high-risk patients was recognized, when sustained ventricular tachyarrhythmia was induced. This group of patients was effectively protected with ICD implantation.

5. Among our patients with IDCM, the only independent prognostic predictor of overall mortality was the advanced NYHA class of HF.

6. Finally, the only independent prognostic predictor of ICD activation was the induction of sustained ventricular tachyarrhythmia during PVS.

PVS and Sustained Ventricular Tachyarrhythmia Induction

Sustained ventricular tachyarrhythmia was induced in 27.8% of the patients, most commonly in the form of sustained monomorphic VT or sustained ventricular flutter (65.9% of inducible cases). In the literature, there are small cohorts with similar results. It has been reported that among 13 patients with IDCM with syncope and inducibility on PVS, 10 (76.9%) appeared with inducible monomorphic sustained VT.

The prognostic role of PVS was also evaluated in 92 patients with IDCM presenting without clinical sustained VT: 36 patients without complex ventricular arrhythmias±syncope (group 2A) and 56 patients with complex ventricular arrhythmias±syncope (group 2B) underwent PVS. Group 2A patients were all noninducible, whereas 9 of 56 (16%) group 2B patients were inducible (8 of them with sustained monomorphic VT [88.8%]). All but one group 2A patients remained alive during follow-up (1 patient experienced sudden death because of hypokalemia) in comparison with inducible group 2B patients where 5 of 9 experienced VT/VF or SCD.

In our study, we investigated the long-term survival and recurrences of ventricular tachyarrhythmias in relation to PVS inducibility in a heterogeneous large group of patients with IDCM, in contrast with prior studies consisting of smaller patient populations with short follow-up periods. It is suggested that response to PVS is critically dependent on the spontaneous arrhythmia presentation. Specifically, the probability of inducing sustained VT is extremely high in patients with IDCM with clinical sustained compared with nonsustained VT, as well as the presence of syncope is accompanied by a high (51%) probability for PVS inducibility. Our study patients’ profile (66% had complex ventricular arrhythmias at baseline and 26% had experienced syncopal episodes) identified a higher risk cohort for PVS inducibility and electric instability justifying the higher incidence of inducible ventricular arrhythmias and particularly monomorphic VT. Furthermore, PVS protocols using a single or double ventricular extrastimuli at the right ventricular outflow tract had an extremely low probability of inducing sustained ventricular tachyarrhythmia. On the contrary, we have demonstrated, in agreement to previous reports, that more aggressive protocols were required in most induced cases, and sometimes after infusion of isoproterenol at the right ventricular outflow tract.

Our data clearly show that, based on the results of PVS, only 30% of patients with IDCM with clinical characteristics similar to the study group are candidates for ICD implantation, a proportion lower compared with the present recommendations based on the LVEF and the NYHA stage of HF.

Long-term Follow-up: Overall Mortality and Sudden Cardiac Death

Overall mortality was not significantly different between the 2 groups of our trial (HR, 1.694; CI, 0.732–3.922). This finding could be explained by the fact that the majority of deaths were attributed to HF deterioration, whereas SCD was observed less frequently. It might be possible that the electric instability assumed to be present in the 44 patients

Table 2. Advanced NYHA Class Is the Only Independent Predictor of Overall Mortality in 158 Patients With Idiopathic Dilated Cardiomyopathy in Multivariable Cox Regression Analysis

<table>
<thead>
<tr>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advanced NYHA class (III and IV vs I and II)</td>
<td>11.909</td>
<td>3.106–45.65</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; and NYHA, New York Heart Association.

Table 3. Induced Ventricular Arrhythmia is the Only Predictor of ICD Activation in 69 Implanted Patients in Multivariable Cox Regression Analysis

<table>
<thead>
<tr>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Induced ventricular arrhythmia</td>
<td>4.195</td>
<td>1.467–11.994</td>
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</table>

CI indicates confidence interval; and ICD, implantable cardioverter-defibrillator.
with induced VT/VF (group I) was counterbalanced by the ICD implantation in 41 of them, compared with only 28 empirically performed ICD implantations in the 114 group II patients.

Notably, ICD activation occurred in significantly higher incidence in patients with induced tachyarrhythmia. The higher rates of ICD activations may indeed reflect a greater electric instability in our high-risk population. However, the use of ICD activations as a surrogate for SCD is limited by the fact that a life-threatening ventricular arrhythmia episode interrupted by an ICD would not necessarily result in SCD otherwise. Indeed, a subanalysis of Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation (DEFINITE) trial showed that activation of ICD for terminating episodes of ventricular tachyarrhythmia overestimated the possibility of SCD. In the present study, we have used short detection intervals for VT and VF detection. Although similar ICD parameters were used in both groups, the majority of VT/VF episodes detected by the ICDs might have self-terminated spontaneously, especially in the setting of primary prevention of patients with IDCM. Nevertheless, the fact that the free of life-threatening ventricular arrhythmia survival period was significantly different between the 2 groups of patients cannot be ignored.

Beyond the positive prognostic value of PVS, we should also point out that the percentage of ICD activation in noninduced patients was still significant (17.9%). Indeed, a high risk for SCD subgroup of patients with IDCM exist, even though no sustained VT/VF is induced because of unclear reasons. Widespread use of PVS for risk stratification has been limited by this relatively poor negative prognostic value, and future assessment of the prognostic role of the electroanatomic substrate could shed more light in the pathophysiologic substrate of these patients.

**LVEF and Long-term Follow-up**

Overall mortality was higher between the 119 patients with LVEF≤35% (mean value, 26.5%) compared with the group of the 39 patients with LVEF>35% (mean value, 42.9%). Nevertheless, the group of the 69 patients with IDCM with ICD activation could not be distinguished based on the LVEF alone. Indeed, an equivalent proportion of patients with IDCM with LVEF>35% and ≤35% presented with either episodes of nonaborted SCD or life-threatening ventricular tachyarrhythmia interrupted by the implantable device. The probability of SCD surrogate events was not higher in advanced HF compared with earlier HF stages. It seems that in addition to a low LVEF, there are other electrophysiologic parameters contributing to the generation of life-threatening ventricular tachyarrhythmias and, consequently sudden cardiac mortality. In the present study, this hypothesis was investigated by a multivariable Cox regression analysis including several factors, such as age, LVEF, history of syncope, clinical stage of HF, history of complex ventricular arrhythmia and induction of sustained VT, or polymorphic VT/VF during PVS, revealing that the only independent predictive marker for future ICD activation was the induction of sustained ventricular tachyarrhythmia.

The role of PVS in IDCM has not been clearly defined yet because it has only been studied in rather small or inhomogeneous cohorts. Contrary to our results, it has been proposed that PVS has a limited role in primary prevention of SCD in patients with IDCM. This view is based mainly on small power studies with rather small number of patients. Nevertheless, according to the results of the largest published series of patients with IDCM undergoing PVS, sustained VT induction was predictive of future sudden cardiac mortality.

In many large-scale, prospective observational trials previously performed in patients with IDCM, a low LVEF was the only predictive factor for SCD among a variety of other noninvasive clinical and laboratory risk factors assessed. However, these large-scale prospective randomized trials have focused on subjects with low LVEF at various clinical stages of HF. Despite the large number of patients recruited, only a statistically borderline survival benefit with the ICD was demonstrated. It is unknown, however, whether PVS-guided ICD implantation trials among patients with IDCM would result in improved survival, especially among patients at earlier HF stages with better preserved LVEF.

It has been stated that among the disadvantages of PVS in the risk stratification of patients with IDCM is the induction of nonspecific forms of ventricular tachyarrhythmia, such as nonsustained polymorphic VT or sustained polymorphic VT degenerating to VF. There is, indeed, enough evidence to support the low predictive accuracy of the former. It has been suggested recently that the induction of polymorphic VT or VF is associated with a high risk of subsequent ventricular arrhythmic events. Similarly, according to our findings, it is highly disputable whether induction of sustained polymorphic VT/VF represents a nonspecific response.

In the long-term follow-up of our patients, the advanced stage of HF seemed to be a stronger predictive factor for overall mortality compared with the LVEF. A multivariable survival Cox regression analysis showed that LVEF had a nonstatistically significant relation with overall mortality, whereas on the contrary advanced HF stage was the only factor with significant predictive value. It is well known that the clinical stage of HF, even though strongly related to LVEF, depends also on a variety of other clinical and laboratory parameters.

It might be speculated that improvement of SCD mortality with ICD implantation in the majority of patients presenting with sustained ventricular tachyarrhythmia during PVS is an explanation for the failure to demonstrate a strong correlation between induction of sustained VT or polymorphic VT/VF and overall mortality in the present study. Even though biventricular ICD systems were implanted in the majority of our patients, resulting in documented improvement of their functional stage, advanced HF stage represents the major aggravating factor of long-term prognosis of these patients.

**Limitations**

The major limitation of our study was the use of ICD activation as part of the surrogate point for the incidence of SCD. Depending on the initial ventricular arrhythmia detection
parameters, ICD activations may be triggered by arrhythmic events that would have been terminated spontaneously as shown by previous studies.16–19 It has been suggested that use of longer detection intervals may be accompanied by a significant delay of ICD therapies.19 However, the same conclusions of using longer detection intervals may be accompanied by a significant delay of ICD therapies. However, the same use of longer detection intervals may be accompanied by conduction of the procedure. Our rationale behind such aggressive PVS protocols relies on previous studies,6,7,25 concluding that the use of less aggressive protocols did not predict serious ventricular arrhythmias in IDCM. Another limitation of the study is the controversy of specificity of PVS. Programmed stimulation for risk stratification in patients with IDCM may be sensitive, but not specific, with a poor negative predictive value. Indeed, although lower compared with group I, the percentage of ICD activation in group II was still significant. Moreover, we acknowledge that our study sample size and subsequently the number of deaths for the mortality comparisons is relatively small, as well as the data regarding the total number of appropriate ICD activations were not available in the whole study population.

Conclusion
In contrast to the prevailing view, we conclude that induction of VT/VF during PVS in patients with IDCM is associated with subsequent serious arrhythmic events in this patient population. We found that patients with EP inducibility of VT or VF experienced a higher likelihood of ≥1 appropriate ICD therapies in follow-up.

Disclosures
None.

References


The role of programmed ventricular stimulation in the risk stratification of patients with idiopathic dilated cardiomyopathy (IDCM) remains controversial. We investigated the prognostic value of programmed ventricular stimulation in 158 patients with IDCM presenting to our department for electrophysiological risk stratification and management between January 1995 and March 2011. Ventricular tachycardia/ventricular fibrillation was induced in 44 patients (27.8%). Sixty-nine patients with IDCM underwent implantable cardioverter defibrillator (ICD) implantation: 41 of 44 induced patients and 28 of 114 patients without ventricular tachycardia/ventricular fibrillation inducibility. Overall mortality during the 47 months of mean follow-up was not significantly different between the 2 groups. Advanced New York Heart Association class was the single independent and strongest prognostic factor of overall and cardiac mortality. Among ICD recipients, induction of sustained ventricular arrhythmias during programmed ventricular stimulation was associated with a significantly higher ICD activation rate (73.2% versus 17.9%), either in the form of antitachycardia pacing (68.3% versus 17.9%) or shock delivery (51.2% versus 17.9%). A multifactorial regression analysis identified the induction of sustained ventricular tachyarrhythmia as the single independent prognostic risk factor for future appropriate ICD activation. It should be acknowledged that the majority of ventricular tachycardia/ventricular fibrillation episodes detected by the ICDs might have self-terminated spontaneously in the setting of primary prevention of patients with IDCM, even though programmed ICD parameters were similar in both induced and noninduced patients. In contrast to the prevailing view, we conclude that induction of ventricular tachycardia/ventricular fibrillation during programmed ventricular stimulation in patients with IDCM is associated with subsequent serious arrhythmic events in this patient population.


Primary Prevention of Sudden Cardiac Death in a Nonischemic Dilated Cardiomyopathy Population: Reappraisal of the Role of Programmed Ventricular Stimulation

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**Supplemental Table:** Stimulation protocol for induction of sustained ventricular tachyarrhythmias and mode of termination.

<table>
<thead>
<tr>
<th></th>
<th>MVT(n=29)</th>
<th>PVT/VF (n=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of extrastimuli</td>
<td>1:2</td>
<td>1:2</td>
</tr>
<tr>
<td></td>
<td>2:9</td>
<td>2:3</td>
</tr>
<tr>
<td></td>
<td>3:18</td>
<td>3:10</td>
</tr>
<tr>
<td>Pacing site</td>
<td>RVA:21</td>
<td>RVA:11</td>
</tr>
<tr>
<td></td>
<td>RVOT:8</td>
<td>RVOT:4</td>
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<tr>
<td>CL of pacing burst</td>
<td>550 ms:9</td>
<td>550 ms:3</td>
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<tr>
<td></td>
<td>400 ms:20</td>
<td>400 ms:12</td>
</tr>
<tr>
<td>Isoproterenol infusion</td>
<td>5 (17.2%)</td>
<td>3 (20%)</td>
</tr>
<tr>
<td>CL of induced ventricular</td>
<td>284±50 ms</td>
<td>201±42 ms</td>
</tr>
<tr>
<td>tachycardia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Termination of induced MVT &amp;</td>
<td>ATP:19</td>
<td>ATP:1</td>
</tr>
<tr>
<td>PVT/VF</td>
<td>DCC:10</td>
<td>DCC:14</td>
</tr>
</tbody>
</table>

MVT&PVT denotes sustained monomorphic & polymorphic ventricular tachycardia, VF ventricular fibrillation, RVA & RVOT right ventricular apex & outflow tract, CL cycle length, ATP antitachycardia pacing and DCC direct current cardioversion.