Unexplained syncope in patients with structural heart disease and no documented ventricular arrhythmias: value of electrophysiologically guided implantable cardioverter defibrillator therapy

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Aims To evaluate electrophysiologically guided implantable cardioverter defibrillator (ICD) therapy in patients with syncope, structural heart disease and no documented sustained ventricular tachycardia (sVT).

Methods and Results Programmed ventricular stimulation (PVS) was performed in 52 patients (age 62 ± 10 years): 40 patients had ischaemic and 12 patients had idiopathic dilated cardiomyopathy. On PVS sVT and ventricular fibrillation were induced in seven and four patients, respectively, and two patients spontaneously experienced symptomatic sVT. These patients received an ICD (ICD group, n = 13). Non-inducible patients were left on conventional therapy (non-ICD group, n = 39). During 5 ± 2.8 years five ICD patients received therapies, all appropriate. There were seven non-sudden deaths and overall survival analysis revealed no significant difference. Recurrent syncope occurred in five ICD and four non-ICD patients and did not correlate well with sVT. The positive and negative predictive values of PVS for tachyarrhythmias or sudden death were 36 and 98%, respectively.

Conclusion Syncope per se does not necessarily herald a bad prognosis. PVS identifies high-risk patients. Induction of ventricular fibrillation with double or triple extrastimuli is of limited value. Patients with poor left ventricular function and bad clinical condition benefit most from an ICD. Syncope and sVT are not necessarily correlated during follow-up, which may merit consideration.

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Key Words: Implantable cardioverter defibrillator, unexplained syncope, electrophysiological testing.
unexplained[10]. Although the true value of electrophysiological testing in patients with unexplained syncope, no documented ventricular arrhythmias and structural heart disease, is not precisely defined this technique is commonly used for further risk stratification and guided antiarrhythmia management. It is the purpose of this retrospective study to analyse this approach with special emphasis on electrophysiologically guided ICD therapy.

Methods

Study population

We evaluated 52 consecutive patients with unexplained syncope and structural heart disease who underwent electrophysiological testing between June 1992 and December 2000. Inclusion criteria were: (1) one or more episodes of unexplained syncope, (2) no documented ventricular tachyarrhythmias on surface electrocardiograms (ECG) or Holter recordings, (3) presence of structural heart disease and (4) electrophysiological testing. Exclusion criteria were: (1) history of any episode of tachycardia, (2) history of cardiac arrest, (3) history of inducible supraventricular and ventricular tachyarrhythmias, (4) diagnosis of long QT syndrome (5) presence of aortic valve stenosis and (6) susceptibility to neurally mediated syncope which was not found in any of the study patients using head-up tilt testing.

Measurement of left ventricular function

Left ventricular ejection fraction was calculated from radionuclide angiography (VERTEX® MCD/AC-PET®, ADAC Laboratories, California, U.S.A.), echocardiography (ACUSON Sequia C256®, Acuson, Mountain View, CA, U.S.A.) or from cardiac catheterization data (Quantcor.QCA®, V4.0, Pie Medical Imaging, Maastricht, The Netherlands and ELK CAP 35E® Cine Angio System, Medis, The Netherlands).

Electrophysiological study

After written consent was obtained studies were performed in the postabsorptive and non-sedated state. Prior to the study all antiarrhythmic drugs were discontinued for ≥5 half lives. No patient had been treated with amiodarone. Two or three multipolar electrode catheters were used. They were percutaneously inserted under local anaesthesia through the femoral vein and positioned under fluoroscopic guidance in the high right atrium, His bundle area and right ventricle. Programmed ventricular stimulation (PVS) was performed with a Biotronik® UHS 20 Universal heart stimulator (Biotronik, Berlin, Germany) with pulse duration of 2 ms at twice diastolic threshold. The programmed ventricular stimulation protocol utilized up to three extrastimuli delivered during sinus rhythm and after eight paced ventricular cycle lengths at 500, 430, 375 and 333 ms. First the right ventricular apex, then the right ventricular outflow tract was tested in case no sustained ventricular arrhythmia was induced before. Recordings were made at paper speed of 100 mm s⁻¹ (MICOR®, Siemens Elema AB, Solna, Sweden).

Definitions

Syncope: sudden transient loss of consciousness and postural tone with spontaneous recovery.

Structural heart disease: coronary artery disease (with or without prior myocardial infarction) or dilated cardiomyopathy (left ventricular ejection fraction <50% on echocardiography or radionuclide angiography).

Monomorphic ventricular tachycardia: ventricular tachycardia (VT) manifesting a beat-to-beat uniform surface ECG QRS configuration.

Polymorphic ventricular tachycardia: VT that has no constant morphology for more than five complexes, has no clear isoelectric baseline or has QRS complexes that are asynchronous in multiple simultaneously recorded leads.

Sustained ventricular tachycardia: VT that lasts ≥30 s or that is haemodynamically intolerable and needs termination.

Non-sustained ventricular tachycardia: run of ≥3 ventricular beats terminating within 30 s.

Ventricular fibrillation: presence of irregular undulations of varying contour and amplitude and absence of distinct QRS complexes, ST segments and T waves.

The positive end-point of programmed ventricular stimulation was defined as induction of a sustained monomorphic/polymorphic VT or as induction of ventricular fibrillation.

Cardiac death: a witnessed death of cardiac nature as result of progressive heart failure and/or myocardial infarction under observation in a medical facility at the time of death.

Sudden cardiac death: a death cardiac in nature that occurs instantaneously or within 1 h after the onset of symptoms. Unwitnessed death: a death, which is unexpected and without other apparent cause including death during sleep is considered sudden cardiac death.

Non-sudden cardiac death: a death cardiac in nature that occurs >1 h after the onset of symptoms.

Non-cardiac death: all deaths that are not classified as cardiac death.

Data collection

July 1, 2002 was determined as the last day of data collection for this study. The duration of follow-up was calculated from the time of electrophysiological study. Telephone interviews were performed if patients had not been seen in the outpatient department within the previous 3 months. In case of death, physicians and family members as well as witnesses were interviewed for...
detailed circumstances. The ‘real’ follow-up end-point for the ICD treated group was the last time, when their device was interrogated, and this date was used for survival analysis. Stored ECGs with RR intervals and device settings for each patient’s ICD were used for data analysis. Only appropriately delivered therapy was permitted for analysis.

Statistics

All continuous variables are given as mean ± standard deviation and were compared using the Student’s t test or Wilcoxon’s non-parametric test, as appropriate. Nominal variables were compared using the chi-square or Fisher’s exact test, as appropriate. Statistical significance was assumed if the null hypothesis could be rejected at the 0.05 probability level. To assess predictors of recurrent arrhythmias, recurrent syncopal event, clinical condition and total mortality Kaplan-Meier analysis was performed. Comparisons between survival curves were made using the logrank test to determine statistically significant ($P < 0.05$) differences. Comparisons between induced and spontaneous detected VT cycle lengths were made using the Pearson correlation coefficient with a 95% mean predictive regression interval. Software: Statistical Analysis System, SAS® Version 8.2, Cary, NC, U.S.A.

Results

Of 423 patients with syncope, who had undergone electrophysiological testing, 52 patients (12.3%), 34 males and 18 females with a mean age of 62 ± 10 years, met the required inclusion criteria. The underlying heart disease was coronary artery disease in 40 patients (77%) and dilated cardiomyopathy in 12 patients (23%). Based on the result of the electrophysiological study 11 patients with inducible sustained ventricular tachyarrhythmias were treated with an ICD and non-inducible patients were left on best conventional therapy (non-ICD group, 39 patients). Two non-inducible patients (only non-sustained VT) spontaneously experienced symptomatic ventricular tachyarrhythmias minutes after PVS (one patient with sustained VT and one patient with ventricular fibrillation). Subsequently, both were referred for ICD implantation and enrolled in the ICD group (ICD group, 13 patients). Overall, two patients received epicardial ICD devices (Medtronic 7217B, Medtronic, Inc., Minneapolis, MN, U.S.A.), the remaining 11 patients received transvenous subpectoral ICD devices (Medtronic 7218, 7219, 7227 and 7250, Medtronic, Inc., Minneapolis, MN, U.S.A., CPI 1753, 1793 and 1851, Cardiac Pacemakers, Inc., St. Paul, MN, U.S.A.). Three patients underwent elective generator replacement during follow-up. The clinical characteristics of the two study groups are detailed in Table 1.

<table>
<thead>
<tr>
<th>Table 1 Baseline characteristics</th>
<th>ICD group (n = 13)</th>
<th>Non-ICD group (n = 39)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>10 (77%)</td>
<td>24 (62%)</td>
<td>ns</td>
</tr>
<tr>
<td>Female</td>
<td>3 (23%)</td>
<td>15 (38%)</td>
<td>ns</td>
</tr>
<tr>
<td>Age (years)</td>
<td>58 ± 10</td>
<td>63 ± 10</td>
<td>ns</td>
</tr>
<tr>
<td>NYHA 1</td>
<td>5 ± 2.7</td>
<td>5.4 ± 2.7</td>
<td>ns</td>
</tr>
<tr>
<td>NYHA 2</td>
<td>10 (77%)</td>
<td>22 (56%)</td>
<td>ns</td>
</tr>
<tr>
<td>NYHA 3</td>
<td>3 (23%)</td>
<td>9 (23%)</td>
<td>ns</td>
</tr>
<tr>
<td>LV-EF</td>
<td>32 ± 8</td>
<td>48 ± 16</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CAD</td>
<td>9 (69%)</td>
<td>31 (80%)</td>
<td>ns</td>
</tr>
<tr>
<td>CM</td>
<td>4 (31%)</td>
<td>8 (20%)</td>
<td>ns</td>
</tr>
<tr>
<td>Revascularized*</td>
<td>6 (46%)</td>
<td>18 (46%)</td>
<td>ns</td>
</tr>
<tr>
<td>Medications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>9 (69%)</td>
<td>11 (28%)</td>
<td>0.005</td>
</tr>
<tr>
<td>Ca-blockers</td>
<td>1 (8%)</td>
<td>4 (10%)</td>
<td>ns</td>
</tr>
<tr>
<td>Diuretics</td>
<td>6 (46%)</td>
<td>9 (23%)</td>
<td>ns</td>
</tr>
<tr>
<td>Digoxin</td>
<td>5 (39%)</td>
<td>5 (13%)</td>
<td>0.023</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>10 (77%)</td>
<td>17 (44%)</td>
<td>0.02</td>
</tr>
<tr>
<td>Nitrates</td>
<td>10 (77%)</td>
<td>20 (51%)</td>
<td>ns</td>
</tr>
<tr>
<td>Syncope during follow-up</td>
<td>5 (39%)</td>
<td>4 (10%)</td>
<td>0.016</td>
</tr>
</tbody>
</table>

*History of myocardial infarction and interventional revascularization and/or aortocoronary bypass grafting. CAD, coronary artery disease; CM, dilated cardiomyopathy; LV-EF, left ventricular ejection fraction; NYHA, New York Heart Association.

Electrophysiological study results and spontaneous arrhythmias

ICD group. Sustained monomorphic VT was induced in six patients (five patients with coronary artery disease, one patient with dilated cardiomyopathy), sustained polymorphic VT in one patient with dilated cardiomyopathy and ventricular fibrillation was induced in four patients (three patients with coronary artery disease, one patient with dilated cardiomyopathy). During a mean follow-up period of 5 ± 2.8 years none of the patients with inducible polymorphic VT or inducible ventricular fibrillation experienced spontaneous ventricular arrhythmias. In contrast, four of six patients (three patients with coronary artery disease, one patient with dilated cardiomyopathy) with inducible monomorphic VT experienced arrhythmic events. (Table 2) To the best of our knowledge, all arrhythmias and/or syncopal events during follow-up were not related to an acute coronary syndrome. Among ICD patients who received appropriate shocks the mean time from defibrillator implantation to the first appropriate shock was 2.2 ± 3.3 years. Comparison of the cycle lengths of spontaneous ICD detected tachyarrhythmias and induced VTs in patients with appropriate ICD discharge revealed no relationship (negative correlation coefficient, $R = -0.224$, $P = ns$).

Five of 13 ICD patients (39%) had one or more recurrent syncopal event without device discharge during follow-up.
Non-ICD group. None of the patients without inducible arrhythmias experienced documented sustained ventricular arrhythmias during follow-up. During Holter monitoring four of 39 patients (10%) experienced one or more recurrent syncopal event not associated with ventricular arrhythmias during follow-up. Calculated from these data the positive and negative predicted values of programmed ventricular stimulation for tachyarrhythmias and sudden cardiac death were 36 and 98%, respectively (sensitivity, 80%; specificity, 85%).

Survival analysis

ICD group. One patient died from stroke. This death was classified non-cardiac.

Non-ICD group. Six patients died: there were two non-sudden cardiac deaths (one death was caused by pulmonary embolization and one patient died intraoperatively during coronary bypass surgery). The remaining four deaths were classified non-cardiac: one patient died from stroke, two patients died from pneumonia and the fourth patient died from Hepatitis C induced liver failure.

Kaplan–Meier analysis for overall survival between the two groups is shown in Fig. 1. After a follow-up period of 2, 5 and 7 years 90% of ICD patients and 97, 90 and 75% of non-ICD patients were still alive. The difference in survival did not reach statistical significance. After 5.2 years of follow-up virtually all patients in clinical class NYHA III had received at least one appropriate ICD discharge. Actually the same was true when patients were stratified according to the degree of left ventricular dysfunction.

The influence of left ventricular ejection fraction and clinical condition on arrhythmic events in the ICD group is shown in Fig. 3. After 3 years of follow-up about half the patients in clinical class NYHA II and two-thirds of the patients in clinical class NYHA III have received at least one appropriate ICD therapy. After 5.2 years of follow-up virtually all patients in clinical class NYHA III had received ICD therapies. The results of this study provide further evidence that in patients with unexplained syncope, underlying structural heart disease and no documented arrhythmias electrophysiological testing with induction of sustained ventricular tachyarrhythmias is of diagnostic value. Using this technique in 21% of our patients potentially life-threatening tachyarrhythmias could be induced and were considered potentially causative of syncopal episodes. Similar results are reported in the literature with induction of sustained ventricular tachyarrhythmias in 21–50% of patients with unexplained syncope and structural heart disease[11–13]. Considering patients with positive test results at high risk for sudden arrhythmic death[16–20] all patients inducible into sustained ventricular tachyarrhythmias received implantable devices whereas non-inducible patients received no antiarrhythmia therapy at all.

**Discussion**

<table>
<thead>
<tr>
<th>PNR</th>
<th>Diagnosis</th>
<th>NYHA class</th>
<th>LV-EF %</th>
<th>EP-study arrhythmia (ms) [extrastimuli]</th>
<th>ICD arrhythmia (ms)*</th>
<th>Follow-up syncope</th>
<th>Follow-up (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CM</td>
<td>III</td>
<td>22</td>
<td>mVT (300)[2]</td>
<td>smVT (290)</td>
<td>No</td>
<td>9.5</td>
</tr>
<tr>
<td>2</td>
<td>CAD</td>
<td>II</td>
<td>39</td>
<td>sVF[3]</td>
<td>No events</td>
<td>Yes</td>
<td>8.9</td>
</tr>
<tr>
<td>3</td>
<td>CM</td>
<td>II</td>
<td>42</td>
<td>nsVT[3]/sVF†</td>
<td>No events</td>
<td>Yes</td>
<td>1.5</td>
</tr>
<tr>
<td>4</td>
<td>CM</td>
<td>II</td>
<td>23</td>
<td>nsVT[3]/smVT (280)†</td>
<td>smVT (300)</td>
<td>No</td>
<td>6.7</td>
</tr>
<tr>
<td>5</td>
<td>CAD</td>
<td>II</td>
<td>33</td>
<td>smVT (220)[3]</td>
<td>smVT (290)</td>
<td>No</td>
<td>6.4</td>
</tr>
<tr>
<td>6</td>
<td>CAD</td>
<td>II</td>
<td>32</td>
<td>smVT (220)[3]</td>
<td>No events</td>
<td>No</td>
<td>6.5</td>
</tr>
<tr>
<td>7</td>
<td>CAD</td>
<td>II</td>
<td>35</td>
<td>smVT (220)[3]</td>
<td>No events</td>
<td>No</td>
<td>6.5</td>
</tr>
<tr>
<td>8</td>
<td>CAD</td>
<td>III</td>
<td>39</td>
<td>smVT(240)[3]</td>
<td>smVT (226)</td>
<td>No</td>
<td>5.7</td>
</tr>
<tr>
<td>9</td>
<td>CAD</td>
<td>II</td>
<td>31</td>
<td>sVF[3]</td>
<td>No events</td>
<td>No</td>
<td>3.2</td>
</tr>
<tr>
<td>10</td>
<td>CAD</td>
<td>III</td>
<td>21</td>
<td>smVT (350)[3]</td>
<td>spVT (263)/sVF (224)</td>
<td>No/Yes</td>
<td>3.1</td>
</tr>
<tr>
<td>11</td>
<td>CAD</td>
<td>II</td>
<td>22</td>
<td>sVF[2]</td>
<td>No events</td>
<td>Yes</td>
<td>2.5</td>
</tr>
<tr>
<td>12</td>
<td>CAD</td>
<td>II</td>
<td>27</td>
<td>spVT (220)[2]</td>
<td>No events</td>
<td>No</td>
<td>2.0</td>
</tr>
<tr>
<td>13</td>
<td>CM</td>
<td>II</td>
<td>44</td>
<td>sVF[3]</td>
<td>No events</td>
<td>Yes</td>
<td>2.0</td>
</tr>
</tbody>
</table>

*All arrhythmias were appropriately sensed and all therapies were appropriately delivered. CAD, coronary artery disease; CM, dilated cardiomyopathy; LV-EF, left ventricular ejection fraction; m, monomorphic; ns, non-sustained; NYHA, New York Heart Association; p, polymorphic; s, sustained; VF, ventricular fibrillation; VT, ventricular tachycardia.
†Minutes after programmed ventricular stimulation.
Figure 1  Overall survival between the two groups. ICD patients, dashed line; non-ICD patients, solid line. Each circle represents a censored event.

Figure 2  Overall survival in non-ICD patients vs hypothetical survival in ICD patients with ventricular fibrillation-episodes. ICD patients, dashed line; non-ICD patients, solid line. Each circle represents a censored event.
Overall, mortality in the two study groups was virtually identical. In good accordance with published data\[3,12\] patients with negative results from electrophysiological testing had no documented arrhythmic events and none of the patients died suddenly during a follow-up period of 4.6 ± 2.7 years. In contrast, 39% of the ICD patients received appropriate ICD therapies due to recurrent ventricular tachyarrhythmias. To the best of our knowledge, there are only limited data available on spontaneous arrhythmic events in patients with unexplained syncope, no documented arrhythmias and positive results from electrophysiological testing\[21–26\]. In good accordance with our findings Link et al.\[25\] reported similar appropriate ICD discharge rates of 50% at 3 years of follow-up. Not all VT necessarily result in sudden cardiac death, although in patients with severely reduced LV function VT events easily may degenerate into VF. There is general agreement on the fact that VT with a heart rate of ≥ 240 bpm reflects a life-threatening condition serving as a surrogate for sudden arrhythmic death\[27\]. In our study two out of 13 patients experienced device defined VF and sudden death was immediately aborted by the implanted device. Comparison of the survival curves of the two study groups reveals that the hypothetical survival curve of the ICD group immediately diverges from the survival curve of the control group indicating the worse prognosis of high-risk patients.

A strong correlation between arrhythmic events, the degree of left ventricular dysfunction and the clinical condition of the patients was found. Overall, the worse the clinical condition of the patients and the more left ventricular function was compromised the earlier the implanted device was needed for arrhythmia intervention. After 4.5 years of follow-up virtually all patients in NYHA III class and all patients with an ejection fraction below 25% needed the implanted device.

ICDs store endocardial electrograms before and after energy discharge allowing at least discrimination between monomorphic and polymorphic VT and ventricular fibrillation.

The majority of VT detected and treated by the devices had monomorphic QRS complexes and only one patient who was inducible into monomorphic VT on programmed stimulation spontaneously developed polymorphic VT requiring device discharge.

Of note, patients with ventricular fibrillation and polymorphic VT induced on EP-testing who were considered at high risk and therefore were referred for ICD implantation, have not yet experienced any arrhythmic event during follow-up. This is in accordance with Mittal et al.\[28\], who recently showed that the long-term follow-up of patients with and without inducible VF demonstrates no difference in survival between the two groups.

In contrast to others\[21,22\] no strong relationship between induced and spontaneous VT cycle length was detected in our series. This could be due to the use of an aggressive stimulation protocol which included triple extrastimuli.

In our study, electrophysiological testing had a sensitivity and specificity of 80 and 85%, respectively, resulting in a positive predictive value of 36% and a negative predictive value of 98%.

These data support the hypothesis that only monomorphic VT induced on programmed stimulation are of predictive value. The results of our study justify aggressive prophylactic arrhythmia management in high-risk patients even in the absence of available randomized studies. In randomized prospective studies in different clinical settings\[29–32\] the superiority of ICD therapy in comparison with conventional antiarrhythmic treatment has been well established and it is only reasonable to infer comparable results in the given patient population.
Limitations of the study

A combination of a prospective evaluation with a partially retrospective investigation such as this study is subject to well-known limitations. All ‘missing data’ had to be retrieved by intensive search in several patient files or by additional calls for patients to come to the outpatient department. LV ejection fraction data could not be calculated appropriately in about 10% of the non-ICD group.

Conclusions

Syncope per se does not necessarily herald a bad prognosis in patients with structural heart disease and no documented ventricular arrhythmias. Moreover, syncope does not correlate well with potentially life-threatening arrhythmias. PVS reliably stratifies high-risk patients from low-risk patients irrespective of syncopal events. Patients with severely depressed left ventricular function and bad clinical condition benefit most from an ICD. Even after the exclusion of all possible non-arrhythmogenic diseases and the induction of sustained VT, syncope and ventricular arrhythmias do not necessarily correlate. This finding should be taken into consideration when dealing with this clinical setting.

References

[29] Prystowsky EN, Nisam S. Prophylactic implantable cardioverter-defibrillator trials: MUSTT, MADIT, and beyond.

