Unfavorable Outcome in Patients With Primary Electrical Disease Who Survived an Episode of Ventricular Fibrillation

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Background. Prognosis in patients with ventricular tachyarrhythmia without structural heart disease (primary electrical disease) has been described as excellent. However, prognosis may be less favorable in the subgroup surviving an episode of ventricular fibrillation.

Methods and Results. We prospectively followed 19 consecutive patients (age, 13 to 66 years; mean age, 33 years) who had survived an episode of documented ventricular fibrillation. Structural heart disease, preexcitation, and long QT syndromes were excluded by thorough cardiologic evaluation. All patients underwent 24-hour Holter monitoring, exercise testing, and programmed electrical stimulation according to a standardized protocol. Holter monitoring revealed episodes of ventricular tachyarrhythmia in 5 patients. Exercise testing reproducibly provoked ventricular tachycardia in 2 patients. Baseline programmed electrical stimulation yielded inducibility of rapid ventricular tachyarrhythmia in 10 patients (53%) and noninducibility in 9 (47%). Nine patients were discharged on antiarrhythmic drug therapy. A defibrillator was implanted in 10 patients. During 43-month follow-up (range, 5 to 85 months; median, 41 months), major arrhythmic events occurred in 7 patients (37%). Four of these patients had noninducibility at baseline programmed electrical stimulation. Two patients on antiarrhythmic drugs had recurrent cardiac arrest: one died suddenly and the other was successfully resuscitated from ventricular fibrillation and subsequently underwent defibrillator implantation. In the other 5 patients, termination of (pre)syncope was associated with defibrillator shocks. Termination of ventricular fibrillation was documented by Holter recording in one of these patients. Specific markers predictive of a recurrent event could not be identified, although 6 of 7 patients with recurrent events had experienced at least one episode of cardiac arrest or (pre)syncope before the index episode.

Conclusions. Patients with primary electrical disease presenting with ventricular fibrillation are at high risk of recurrence of major arrhythmic events during long-term follow-up. Noninducibility at baseline study does not predict an uneventful course. Also, early defibrillator implantation should be considered in these patients. (Circulation. 1993;88:1021-1029.)

Key Words • death, sudden • cardiac arrest • fibrillation • prognosis

Sudden unexpected cardiac arrest is due in most cases to ventricular fibrillation or rapid ventricular tachycardia.1,2 More than half the patients suffering from life-threatening ventricular tachyarrhythmias have advanced coronary artery disease, and most have a history of remote myocardial infarction. Less frequent causes are cardiomyopathies, valvular heart disease, congenital heart disease, Wolff-Parkinson-White syndrome, and long QT syndrome.3-6

In a number of patients with ventricular tachyarrhythmias, no underlying structural heart disease can be established despite extensive evaluation. Such patients are described as having primary electrical disease or idiopathic ventricular tachyarrhythmia.7 Prognosis in these patients has been described as excellent by many authors, although rare cases of sudden death have been reported.8-22 There appears to be agreement that only symptomatic patients with recurrent arrhythmia should be treated, and no particular efforts have been directed toward identification of high-risk subgroups or prevention of sudden cardiac death. It is noteworthy that many of these reports deal with patients with idiopathic ventricular tachycardia without hemodynamic deterioration.

We raised the question of whether prognosis also is favorable for the subgroup of patients with primary electrical disease who have survived an episode of ventricular fibrillation.

Methods

We prospectively evaluated the outcome in 19 consecutive patients with primary electrical disease who had survived an episode of documented ventricular fibrillation (index episode) and were referred to the Cardiac Arrhythmia Unit of the Heart-Lung Institute, Utrecht, between October 1985 and June 1992. No patient was on antiarrhythmic drugs at the time of circulatory collapse.
Diagnostic Evaluation

Diagnosis. Primary electrical disease is a diagnosis by exclusion. In our series, this diagnosis was made only when thorough clinical evaluation did not provide evidence for structural heart disease or other known causes of ventricular arrhythmia. All patients were evaluated according to a predefined protocol (baseline evaluation). In addition to the patient’s history, routine physical examination, 12-lead ECG, 24-hour two-channel Holter monitoring, exercise testing (Bruce protocol) and Valsalva maneuver, laboratory tests, and chest roentgenograms, evaluation included echocardiography with wall motion analysis and Doppler screening, cardiac catheterization with cineangiography of both the left and right ventricle, coronary angiography, nuclear scintigraphic assessment of left ventricular ejection fraction, and multiple right ventricular endomyocardial biopsies. In patients undergoing defibrillator implantation, additional transmural biopsies were taken from the right and left ventricular walls. Acute myocardial infarction was excluded. Identifiable and correctable causes of ventricular arrhythmia such as acute ischemia, metabolic or electrolyte disturbances, and drug toxicity were absent. Preexcitation patterns and long QT interval, either persistent or transient, also were excluded. Measurement of corrected QT intervals was performed according to Bazett’s formula. During hospitalization, all patients were kept in the telemetry monitoring area.

Electrophysiological study. Baseline electrophysiological study was performed off antiarrhythmic drugs in all patients and included an analysis of the sinus node recovery time and atrioventricular conduction parameters. Programmed electrical stimulation in the high right atrium was performed with the single extrastimulus technique after a basic drive cycle length of 600 or 500 milliseconds. Inducibility of ventricular tachyarrhythmias was tested at the right ventricular apex and, in case of noninducibility, also at the right ventricular outflow tract. Programmed electrical stimulation was carried out with 2-millisecond pulse width at twice-diastolic threshold current, using up to three extrastimuli during sinus rhythm and ventricular pacing at 600- and 430-millisecond basic drive cycle lengths. In addition, a long-short sequence of extrastimuli was used as described by Denker and colleagues. In case of noninducibility at a given site, burst stimulation was performed at decreasing cycle lengths until one-to-one ventricular capture was lost. If former techniques did not yield inducibility, the stimulation protocol was repeated under isoproterenol infusion (1 to 4 µg/min), aiming at a heart rate of 120 to 150 during normal sinus rhythm. End points of the procedure were completion of programmed electrical stimulation protocol or reproducible induction of ventricular tachyarrhythmia associated with hemodynamic collapse.

Treatment

Pharmacological therapy was the first option in the presence of parameters to assess antiarrhythmic efficacy (see “Definitions”). Drug efficacy was evaluated by continuous telemetry, repeated Holter recordings, exercise testing, and programmed electrical stimulation. A drug was considered efficacious if (1) sustained and nonsustained ventricular tachycardia (see “Definitions”) were completely suppressed as evidenced by noninvasive evaluation, (2) inducibility of ventricular tachyarrhythmia (at least 10 complexes) by programmed electrical stimulation was suppressed to less than five complexes, and (3) side effects requiring discontinuation were absent. Programmed electrical stimulation protocols during baseline evaluation and drug testing were similar, including the maximum number of extrastimuli. However, noninducibility at the right ventricular apex was always followed by programmed electrical stimulation at the right ventricular outflow tract. If the pharmacological approach was unsuccessful, map-guided surgical ablation or catheter ablation were considered in patients with monomorphic ventricular tachycardia. In patients with inducible polymorphic ventricular tachycardia or ventricular fibrillation or in the absence of parameters to guide drug therapy, an automatic implantable cardioverter-defibrillator (AICD) was implanted using the epicardial approach.

Follow-up

All patients were followed in the outpatient clinic by two of the authors (E.F.D.W. and R.N.W.H.) at monthly intervals for the first 3 months after discharge and every 2 to 6 months thereafter. History, physical examination, and 12-lead ECG were obtained at each visit, and chest roentgenograms and echocardiography were repeated on a yearly basis. Special attention was paid to recurrences of symptomatic arrhythmia as well as to the development of features of underlying structural heart disease that might have been latent in the previous stage.

In patients with an AICD forming of the capacitors of the pulse generator and determination of the charge time were performed every 2 months. Delivery of a shock was counted only when detected at AICD interrogation. The devices implanted were incapable of recording the ECG events leading to a discharge. Circumstantial evidence was used to classify shock delivery as appropriate or undetermined (see “Definitions”).

Definitions

For the purposes of this study, sudden death is death occurring within 1 hour of onset of symptoms. Ventricular tachycardia is at least three successive idioventricular complexes at a rate of at least 100. Rapid ventricular tachycardia is ventricular tachycardia at a mean rate of at least 200. Sustained tachycardia is tachycardia lasting at least 30 seconds or, if lasting less than 30 seconds, leading to loss of consciousness. Otherwise, a tachycardia is defined as nonsustained. Monomorphic ventricular tachycardia is ventricular tachycardia with at least six successive complexes of the same morphology. Polymorphic ventricular tachycardia is ventricular tachycardia with changing morphology of successive complexes or, in the presence of more than 10 complexes, a maximum of five successive complexes of the same morphology. Baseline inducibility by programmed electrical stimulation is reproducible induction of at least 10 successive ventricular tachycardia complexes or ventricular fibrillation. Parameters to assess efficacy of antiarrhythmic therapy include multiple spontaneous (on telemetry and Holter) or reproducibly exercise-induced ventricular tachyarrhythmia episodes and/or baseline inducibility by programmed electrical stimulation, including the maximum number of extrastimuli.
stimulation. Appropriate AICD shock is documented shock delivery preceded by a syncopal attack, sudden and transient dizziness (presyncope), or sudden onset of palpitations. Shocks under other conditions are defined as undetermined. Last, major arrhythmic event is documented ventricular fibrillation or sustained rapid ventricular tachycardia or sudden death without evidence of a nonarrhythmic cause and appropriate AICD shock.

Data Analysis

A Kaplan-Meier curve was used for graphic display of the occurrence of major arrhythmic events during follow-up. Analysis of potentially predictive markers of outcome included age and sex of the patients, events before index episode, abnormal 12-lead ECG, ventricular tachyarrhythmia on Holter recording or induced by exercise, and inducibility by programmed electrical stimulation. The relationship of these characteristics with the occurrence of major arrhythmic events during follow-up was statistically analyzed using Fisher’s exact two-tailed test. This relationship was also expressed as hazard ratios, which may be interpreted as relative risks. The precision of the hazard ratio estimates was described by means of 95% confidence intervals obtained from the Cox proportional-hazards model.

Results

Patient characteristics are summarized in Table 1. Information on baseline ventricular tachyarrhythmia detected during Holter recording, exercise testing, or induced at baseline programmed electrical stimulation is shown in Table 2. Fifteen men and four women were included in the study. Most of the patients were young (mean age, 33 years; range, 13 to 66 years), with 13 (68%) less than 40 years old.

Presenting arrhythmia. In 18 of the 19 patients, ventricular fibrillation was documented by ambulance personnel. The other patient (patient 17; Tables 1 and 2) was a 13-year-old girl with syncopal attacks and signs of circulatory arrest. Her Holter recording showed an episode of transient ventricular fibrillation (Fig 1). This

Table 1. Characteristics of Patients With Primary Electrical Disease Who Survived an Episode of Ventricular Fibrillation

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years), sex</th>
<th>Events before index episode</th>
<th>Index episode exercise related (+/−)</th>
<th>12-Lead ECG</th>
<th>QTc (sec1/2)</th>
<th>Serum potassium (mmol/L)</th>
<th>Serum magnesium (mmol/L)</th>
<th>LVEF</th>
<th>LVEDP (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>52, M</td>
<td>Syncope</td>
<td>−</td>
<td>Normal</td>
<td>0.36</td>
<td>4.1</td>
<td>0.90</td>
<td>0.59</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>18, M</td>
<td>Syncope</td>
<td>−</td>
<td>RAD</td>
<td>0.34</td>
<td>4.0</td>
<td>0.85</td>
<td>0.53</td>
<td>9</td>
</tr>
<tr>
<td>3</td>
<td>16, M</td>
<td>...</td>
<td>−</td>
<td>Normal</td>
<td>0.41</td>
<td>3.4 (4.2)</td>
<td>0.92</td>
<td>0.58</td>
<td>11</td>
</tr>
<tr>
<td>4</td>
<td>20, M</td>
<td>...</td>
<td>+</td>
<td>Normal</td>
<td>0.40</td>
<td>3.8</td>
<td>NA</td>
<td>0.59</td>
<td>12</td>
</tr>
<tr>
<td>5</td>
<td>27, M</td>
<td>Syncope</td>
<td>−</td>
<td>High voltage, flat T in aVF, V5-V6</td>
<td>0.40</td>
<td>4.4</td>
<td>0.85</td>
<td>0.55</td>
<td>11</td>
</tr>
<tr>
<td>6</td>
<td>27, M</td>
<td>...</td>
<td>−</td>
<td>Normal</td>
<td>0.40</td>
<td>3.3 (4.1)</td>
<td>0.80</td>
<td>0.57</td>
<td>3</td>
</tr>
<tr>
<td>7</td>
<td>54, M</td>
<td>VF</td>
<td>−</td>
<td>Normal</td>
<td>0.42</td>
<td>3.8</td>
<td>0.81</td>
<td>0.61</td>
<td>8</td>
</tr>
<tr>
<td>8</td>
<td>43, M</td>
<td>Presyncope</td>
<td>+</td>
<td>LAD, flat T in II, III, aVF</td>
<td>0.40</td>
<td>4.1</td>
<td>0.81</td>
<td>0.59</td>
<td>12</td>
</tr>
<tr>
<td>9</td>
<td>35, F</td>
<td>...</td>
<td>−</td>
<td>Low voltage, negative T in V5-V4</td>
<td>0.40</td>
<td>3.6</td>
<td>1.00</td>
<td>0.52</td>
<td>8</td>
</tr>
<tr>
<td>10</td>
<td>66, M</td>
<td>VF</td>
<td>−</td>
<td>CAF, flat T in II, III, aVF</td>
<td>0.40</td>
<td>3.9</td>
<td>0.88</td>
<td>0.52</td>
<td>5</td>
</tr>
<tr>
<td>11</td>
<td>16, M</td>
<td>Syncope</td>
<td>+</td>
<td>Negative T in V1-V5, aVF</td>
<td>0.35</td>
<td>3.5 (4.0)</td>
<td>0.85</td>
<td>0.63</td>
<td>9</td>
</tr>
<tr>
<td>12</td>
<td>53, M</td>
<td>...</td>
<td>−</td>
<td>RBBB, LAD, ST elevation in V1-V5</td>
<td>0.45*</td>
<td>3.5 (4.1)</td>
<td>1.20</td>
<td>0.56</td>
<td>10</td>
</tr>
<tr>
<td>13</td>
<td>26, M</td>
<td>...</td>
<td>−</td>
<td>Normal</td>
<td>0.39</td>
<td>3.9</td>
<td>1.28</td>
<td>0.60</td>
<td>8</td>
</tr>
<tr>
<td>14</td>
<td>30, M</td>
<td>...</td>
<td>−</td>
<td>Normal</td>
<td>0.40</td>
<td>3.8</td>
<td>0.86</td>
<td>0.56</td>
<td>7</td>
</tr>
<tr>
<td>15</td>
<td>32, F</td>
<td>Presyncope</td>
<td>−</td>
<td>Normal</td>
<td>0.43</td>
<td>4.0</td>
<td>0.64 (0.90)</td>
<td>0.52</td>
<td>10</td>
</tr>
<tr>
<td>16</td>
<td>17, F</td>
<td>...</td>
<td>−</td>
<td>Normal</td>
<td>0.40</td>
<td>3.8</td>
<td>0.75</td>
<td>0.58</td>
<td>5</td>
</tr>
<tr>
<td>17</td>
<td>13, F</td>
<td>Syncope</td>
<td>+</td>
<td>Normal</td>
<td>0.41</td>
<td>3.8</td>
<td>0.93</td>
<td>0.53</td>
<td>7</td>
</tr>
<tr>
<td>18</td>
<td>29, M</td>
<td>Syncope</td>
<td>+</td>
<td>Flat T in II, III, aVF</td>
<td>0.42</td>
<td>3.7</td>
<td>0.74</td>
<td>0.59</td>
<td>6</td>
</tr>
<tr>
<td>19</td>
<td>47, M</td>
<td>...</td>
<td>−</td>
<td>Flat T in II, III, aVF</td>
<td>0.40</td>
<td>3.7</td>
<td>0.80</td>
<td>0.70</td>
<td>12</td>
</tr>
</tbody>
</table>

QTc indicates corrected QT interval duration; LVEF, left ventricular ejection fraction; LVEDP, left ventricular end-diastolic pressure; VF, ventricular fibrillation; RAD, right-axis deviation; LAD, left-axis deviation; CAF, chronic atrial fibrillation; NA, not available; and RBBB, right bundle branch block configuration.

Normal values of serum magnesium: 0.70 to 1.40 mmol/L; serum potassium: 3.6 to 4.8 mmol/L. Values of serum magnesium and potassium are measurements on admission; numbers in parentheses represent values obtained within 1 day after the first measurement (no suppletion).

*After QRS width of 0.16 second.
Table 2. Baseline VT or VF Detected During Holter Recording, Exercise Testing, or Induced at Programmed Electrical Stimulation; Antiarrhythmic Treatment at Discharge; and Major Arrhythmic Events During Follow-up

<table>
<thead>
<tr>
<th>Patient</th>
<th>VT/VF on Holter recording</th>
<th>VT/VF during exercise testing</th>
<th>VT/VF inducibility at baseline programmed electrical stimulation</th>
<th>Antiarrhythmic treatment at discharge</th>
<th>Follow-up events</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>...</td>
<td>...</td>
<td>VF (1)</td>
<td>Flecainide</td>
<td>VF*</td>
</tr>
<tr>
<td>2</td>
<td>NS-PVT</td>
<td>NS-PVT</td>
<td>VF (3)</td>
<td>Quinidine</td>
<td>Sudden death</td>
</tr>
<tr>
<td>3</td>
<td>...</td>
<td>...</td>
<td>VF (LS)</td>
<td>Flecainide</td>
<td>...</td>
</tr>
<tr>
<td>4</td>
<td>...</td>
<td>...</td>
<td>NS-PVT (2)</td>
<td>Quinidine</td>
<td>...</td>
</tr>
<tr>
<td>5</td>
<td>...</td>
<td>...</td>
<td>VF (2)</td>
<td>Quinidine</td>
<td>...</td>
</tr>
<tr>
<td>6</td>
<td>...</td>
<td>...</td>
<td>NIN</td>
<td>AICD</td>
<td>Shock</td>
</tr>
<tr>
<td>7</td>
<td>...</td>
<td>...</td>
<td>NIN</td>
<td>AICD</td>
<td>Shocks†‡</td>
</tr>
<tr>
<td>8</td>
<td>...</td>
<td>...</td>
<td>NIN</td>
<td>AICD</td>
<td>Shocks‡</td>
</tr>
<tr>
<td>9</td>
<td>NS-PVT</td>
<td>...</td>
<td>S-MVT (2)</td>
<td>Flecainide</td>
<td>...</td>
</tr>
<tr>
<td>10</td>
<td>NS-PVT</td>
<td>...</td>
<td>NS-PVT (2)</td>
<td>AICD</td>
<td>Shock</td>
</tr>
<tr>
<td>11</td>
<td>...</td>
<td>...</td>
<td>VF (LS)</td>
<td>Quinidine</td>
<td>...</td>
</tr>
<tr>
<td>12</td>
<td>...</td>
<td>...</td>
<td>NS-MVT (3)</td>
<td>AICD</td>
<td>...</td>
</tr>
<tr>
<td>13</td>
<td>...</td>
<td>...</td>
<td>VF (2)</td>
<td>Amiodarone</td>
<td>...</td>
</tr>
<tr>
<td>14</td>
<td>...</td>
<td>...</td>
<td>NIN</td>
<td>AICD</td>
<td>...</td>
</tr>
<tr>
<td>15</td>
<td>NS-PVT</td>
<td>...</td>
<td>NIN</td>
<td>AICD</td>
<td>Shock</td>
</tr>
<tr>
<td>16</td>
<td>...</td>
<td>...</td>
<td>NIN</td>
<td>AICD</td>
<td>...</td>
</tr>
<tr>
<td>17</td>
<td>VF</td>
<td>NS-PVT</td>
<td>NIN</td>
<td>Propranolol</td>
<td>...</td>
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<tr>
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<td>...</td>
<td>...</td>
<td>NIN</td>
<td>AICD</td>
<td>...</td>
</tr>
<tr>
<td>19</td>
<td>...</td>
<td>...</td>
<td>NIN</td>
<td>AICD</td>
<td>...</td>
</tr>
</tbody>
</table>

*VT indicates ventricular tachycardia; VF, ventricular fibrillation; NS, nonsustained; LS, induction by long-short coupling interval of extrastimuli; PVT, polymorphic ventricular tachycardia; NIN, noninducibility; S, sustained; MVT, monomorphic ventricular tachycardia; and AICD, automatic implantable cardioverter-defibrillator.

In parentheses, number of extrastimuli required for induction by programmed electrical stimulation.

*Successful resuscitation.
†Documented PVT/VF terminated by shock.
‡Recurrent episodes with shocks.

episode was provoked by exertion and emotional stress and was preceded by premature ventricular complexes occurring in bigemini, followed by rapid polymorphic ventricular tachycardia deteriorating into fibrillation.

Exercise as precipitating factor. In 5 patients, the index episode was exercise related.

Previous events. Ten patients had a history of either cardiac arrest or (pre)syncope. Two patients had been resuscitated in the past for ventricular fibrillation: patient 7 twice, 1 and 3 years before inclusion, and patient 10 had been resuscitated 15 years before inclusion in this study. Both patients had been on antiarrhythmic drugs temporarily after these events. Six patients had a previous history of syncope, and two other patients had experienced presyncope attacks associated with palpitations.

Diagnostic Evaluation

Twelve-lead ECG. Ten of the 19 patients had a normal ECG during sinus rhythm (Table 1). One patient had chronic atrial fibrillation. Another patient had a wide QRS complex with right bundle branch block morphology, left-axis deviation, and ST-segment elevation in the right precordial leads. Patient 5 had a high R-wave voltage in the left precordial leads, suggestive of left ventricular hypertrophy. However, this could not be confirmed by echocardiography and cineangiography. Most repolarization abnormalities were minor and nonspecific. Measurement of corrected QT intervals showed normal values in all patients (see Table 1).

Holter monitoring. Episodes of ventricular tachyarrhythmia were recorded in 5 patients (26%). Four had ventricular tachycardia of three to nine complexes, and the other had transient ventricular fibrillation (see Table 2 and Fig 1). In only one of the patients (patient 2) were frequent early premature ventricular complexes recorded. Recordings did not show any evidence of QT prolongation.

Exercise testing. Treadmill testing reproducibly provoked ventricular tachycardia in only 1 (patient 17) of the 5 patients with an exercise-related index episode. Episodes of nonsustained polymorphic ventricular tachycardia (maximally, seven complexes at rates of 220 to 240) were recorded in this patient. In patient 2, nonsustained polymorphic tachycardia episodes (maximally, four complexes at a rate of 220) were provoked, although the index episode itself was not exercise related. Signs of QT interval prolongation or ischemia, however, were absent in both patients. No abnormalities were revealed in the other 17 patients.

Other diagnostic investigations. Underlying structural heart disease was not identified with any of the methods mentioned previously. Data on serum potassium, serum magnesium, left ventricular ejection fraction, and left ventricular end-diastolic pressure are shown in Table 1. In 4 patients with borderline low serum potassium on admission, repeated measurements within 1 day after admission yielded normal values without suppletion. Serum magnesium on admission was not available in 1 patient. Measurement at a later stage showed a normal
value. One patient had borderline low serum magnesium on admission that was normal within 1 day without supplementation. Nuclear scintigraphic left ventricular ejection fraction was 0.57 (0.52 to 0.70). Histological examination of myocardial biopsy specimens revealed findings classified as completely normal or within normal limits.

Baseline Electrophysiological Study

Functional parameters of sinus and atrioventricular node were normal in all patients. Infranodal conduction was normal in all patients except in 2: patient 12 had a right bundle branch block morphology, and patient 8 had a slightly lengthened HV interval of 65 milliseconds with a normal QRS width. However, neither rapid atrial pacing nor intravenous administration of procainamide (20 mg/kg body wt at 50 mg/min) resulted in deterioration of conduction in any of these patients. In patient 4, atrial fibrillation (cycle length, 400 to 700 milliseconds) was induced during programmed electrical stimulation at the high right atrium. Signs of longitudinal dissociation of atrioventricular nodal conduction were found in 3 patients, with inducibility of a well-tolerated atrioventricular nodal reentrant tachycardia (cycle length, 350 milliseconds) in patient 11.

Rapid ventricular tachyarrhythmias were inducible in 10 patients (53%; Table 2). In 2 patients, rapid monomorphic ventricular tachycardia episodes were induced with a left bundle branch block pattern in lead V1 of the surface ECG. In patient 9, tachycardia episodes were sustained, and in patient 12, episodes were nonsustained (11 complexes). In 8 patients (42%), either nonsustained rapid polymorphic ventricular tachycardia (patients 4 and 10; 10 to 22 complexes) or ventricular fibrillation (6 patients) was induced. Ventricular fibrillation was induced with only a single extrastimulus or with two extrastimuli in 3 of these patients (patients 1, 5, and 13). Table 2 shows the mode of arrhythmia
induction. Inducibility in all 10 patients was obtained without administration of isoproterenol. Nine patients (47%) showed noninducibility. In all of these 9 patients, programmed electrical stimulation included burst stimulation and a repeated study during isoproterenol infusion.

Treatment

Parameters to evaluate antiarrhythmic drug efficacy were present in 11 patients (58%), all of whom were given antiarrhythmic drugs as first-choice therapy. Treatment was guided by Holter monitoring and exercise testing in patients 2 and 17. In the other 9 of these 11 patients, drug efficacy was evaluated by repeated programmed electrical stimulation because of absence of assessable ventricular tachyarrhythmia episodes with Holter recording and exercise testing at baseline.

Pharmacological therapy was discontinued in patients 10 and 12 after three drug trials had failed to suppress inducibility. Nine patients were discharged on antiarrhythmic drugs.

An AICD was implanted in the other 10 patients—in 8 patients as first-choice therapy because of absence of parameters to evaluate antiarrhythmic drug therapy, including noninducibility at baseline programmed electrical stimulation, and in patients 10 and 12 after drug failure. Although 2 patients had inducible monomorphic ventricular tachycardia, ablative therapy was not carried out because of adequate drug response in patient 9 and technical reasons in patient 12.

Information on antiarrhythmic treatment at discharge is included in Table 2.

Follow-up

Duration of follow-up ranged from 5 to 85 months (mean, 43 months; median, 41 months). Major arrhythmic events occurred in 7 patients (37%; Table 2 and Fig 2). Four of these 7 patients had shown noninducibility at baseline programmed electrical stimulation. Patient 2 died suddenly (witnessed) out-of-hospital after having been on quinidine treatment for 36 months. He died within minutes after onset of dizziness. Because ventricular fibrillation was induced at baseline programmed electrical stimulation with three extrastimuli, the response had been considered nonspecific. Treatment with quinidine had subsequently been considered effective based on complete suppression of nonsustained ventricular tachycardia and frequent early premature ventricular complexes on both Holter recording and exercise testing. Patient 1, who had been on flecaïnide for 32 months, was successfully resuscitated after recurrent ventricular fibrillation and subsequently underwent AICD implantation. Shocks were associated with termination of episodes of either pre-syncope or syncope in 5 AICD patients. In all 5 patients, rate cutoff of the AICD was programmed at 200. Three of these 5 patients had recurrent episodes of (pre)syncope followed by shocks. In 1 of these patients (patient 7), Holter recording showed appropriate shock termination of ventricular fibrillation deteriorated from polymorphic ventricular tachycardia (Fig 3). No patient was on antiarrhythmic drugs after AICD implantation. Undetermined shocks did not occur in any patient.

Noninvasive follow-up examinations failed to reveal development of structural heart disease in any patient. Patient 10 died from a noncardiac cause after 30 months of follow-up.

Markers predictive of outcome could not be identified, although a history of ventricular fibrillation or (pre)syncope before the index episode appeared to indicate an increased risk (Fisher’s exact test: one-sided \( P = .04 \); two-sided \( P = .06 \); Cox proportional-hazards model: hazard ratio, 6.1; 95% confidence interval, 0.7 to 5.1).

Discussion

The major finding of the present study is the high recurrence rate of life-threatening events during long-term follow-up in patients with primary electrical disease who presented with ventricular fibrillation. Also striking was the low mean age of the patients (33 years).
The 19 patients with idiopathic ventricular fibrillation described in this study constitute 8% of all survivors of sudden cardiac arrest due to a ventricular tachyarrhythmia who were admitted to our department between October 1985 and June 1992. Because our institute is a referral center, this percentage is unlikely to reflect the actual prevalence of the disease. Nevertheless, the data may indicate that idiopathic ventricular tachyarrhythmia is not an extremely rare cause of sudden cardiac death. Estimates in the literature vary from 1% to 14% of patients less than 40 years old who have survived an episode of sudden unexpected cardiac arrest due to ventricular tachyarrhythmia.2,3

Because primary electrical disease is a diagnosis by exclusion, considerable efforts have been made to establish or rule out underlying structural heart disease. Apart from mostly minor and nonspecific abnormalities in the resting 12-lead ECG, none of the tests mentioned in “Methods” yielded abnormal results. In 4 patients with borderline low serum potassium on admission, values were normal within 1 day. We have attributed these borderline low potassium levels to the known (lowering) effect of acute major stress (resuscitation). Serum magnesium was not analyzed in one patient on admission. Measurement at a later stage was normal. One patient had borderline low serum magnesium on admission that was normal within 1 day. All patients showed normal QT intervals, and none of these patients suffered from malnutrition; gastrointestinal, renal, or endocrine disorders; or alcoholism. Based on these factors, we concluded that neither hypokalemia nor hypomagnesemia was of etiological significance in these patients. Coronary angiography did not reveal any abnormality, and ventricular wall motion analysis was within normal limits in all patients. Also of note is the absence of demonstrable signs of structural cardiac pathology during follow-up. It therefore appears unlikely that the ventricular tachyarrhythmia was the first manifestation of an underlying but latent structural abnormality.

Previous studies have reported a considerable percentage of abnormal histological findings in right and left ventricular endomyocardial biopsies.35,36 In this study, biopsies taken randomly from several right ventricular sites and, in 11 operated patients, also from left ventricular sites, were classified as completely normal or within normal limits.

It has been well documented that coronary artery spasm may be a cause of ventricular tachyarrhythmias.37,38 However, baseline evaluation revealed no clues that spasm was of etiological significance in this study. No patient had angina, either at entry or during follow-up. In addition, documented arrhythmia episodes were never preceded by ST-segment shifts. In a recent report, Myerburg and colleagues,39 however, described the potential role of silent myocardial ischemia. Of 13 patients without overt heart disease, 5 were identified in whom focal coronary artery spasm was associated with the initiation of life-threatening ventricular arrhythmias. These findings prompted us to perform additional ergonovine tests in 11 patients in our study who were off antiarrhythmic drugs, calcium entry, or β-adrenoceptor blockers. Five of these patients had experienced major recurrent arrhythmic events during follow-up. Ergonovine was tested according to the same protocol as used by Myerburg and colleagues.39 In only 1 patient (patient 7), ergonovine caused unpleasant sensations in the epigastric region, accompanied by ST-segment elevations in the inferior leads of the 12-lead ECG and followed by nonsustained polymorphic ventricular tachycardia. This patient belonged to the group of patients who had experienced appropriate AICD shocks. Although this observation suggests a causal relationship between spasm and the index episode, correct interpretation of this finding remains uncertain because a 12-lead ECG recording of a previous spontaneous ventricular tachycardia episode was not preceded by ST-segment shifts. The ergonovine test was negative in the other patients. It is possible that the low yield may have been influenced by the time lag between the index episode and the time of ergonovine testing. On the other hand, electrical instability apparently was still present in 4 patients with recurrent events and a negative ergonovine test. The higher incidence of spasm reported by Myerburg and colleagues39 may be related to some form of coronary artery disease characterized by non-flow-limiting lesions in all of their patients with coronary spasm. In contrast, in our patients, the coronary artery system appeared completely normal angiographically.

There appears to be agreement that patients with well-tolerated idiopathic ventricular tachycardia have a good prognosis.8,9,11-17,19,21,22 However, it may not be justified to extrapolate this conclusion to the particular subgroup of patients presenting with sudden cardiac arrest. Few reports dealing with this patient category comprising small numbers of patients have been published with controversial conclusions with regard to the recurrence rate of life-threatening arrhythmias.40-43

The present study encompasses a relatively large group of consecutive patients with primary electrical disease and documented ventricular fibrillation who were selected meticulously and followed prospectively at a single center. All patients followed the same diagnostic and therapeutic approaches with follow-up evaluation by two of the authors. No patient was lost to follow-up. The 37% incidence of major arrhythmic events during 43 months (range, 5 to 85 months) of follow-up is striking. Events were life threatening in at least 3 of the 7 patients. Of the 9 patients discharged with antiarrhythmic drugs, 1 died suddenly and another was successfully resuscitated out-of-hospital for the second time. The interval between index episode and recurrence of cardiac arrest was 32 and 36 months, respectively, making a proarrhythmic effect less likely. The third patient with a life-threatening event had an AICD. Holter monitoring documented polymorphic ventricular tachycardia deteriorating into ventricular fibrillation terminated by shock delivery (see Fig 3). Events in the other 4 patients consisted of defibrillator discharges without ECG documentation. We have assumed recurrence of a potentially life-threatening arrhythmia in these patients because all shocks were preceded by syncope or presyncope. Some overestimation of the risk of a recurrent event may be involved in evaluating the clinical significance of correct shock delivery (see “Study Limitations”). Nevertheless, it seems justified to state that the risk of an arrhythmic death lies between 16% (3 patients) and 37%. According to Dutch Health Care Statistics,44 the expected
3-year mortality for the Dutch population matched for age and sex would be 1.6%. Thus, the risk in the studied patients would be 10-fold to more than 20-fold higher.

Data from a recent review of idiopathic ventricular fibrillation by Viskin and Belhassen, including 14 of their patients and 40 patients from the literature, point in the same direction. These authors calculated a recurrence rate of “malignant” arrhythmias of approximately 25% for 37 patients during a follow-up ranging from 2 months to 14 years. Also, preliminary data from Siebels and colleagues for 15 survivors of sudden cardiac arrest without organic heart disease showed a 22% sudden death rate in medically treated patients and a 33% arrhythmia recurrence rate without mortality in patients with an implanted defibrillator during a mean follow-up of 19 months.

From our data, we were unable to identify specific markers predictive of a recurrent event. Although 6 of the 7 patients with a major recurrent event had suffered from previous ventricular fibrillation or (pre)syncope before the index episode, the difference from the group of patients with an uneventful follow-up did not reach statistical significance. Unlike in the study of Kuden-chuk and colleagues, younger age and the presence of ECG abnormalities did not help to stratify patients. Four patients with major events in our study had normal and 3 had abnormal 12-lead ECGs. Wells and colleagues suggested failure to suppress early and repetitive ectopic activity to be of unfavorable prognostic significance. In only 1 of our patients, frequent early premature ventricular complexes and nonsustained ventricular tachycardia episodes were seen on pretreatment Holter recording and during exercise testing. This patient, however, died suddenly despite suppression of ectopic activity with quinidine. Electrophysiological data were not helpful, either. Half of the patients had inducible ventricular tachyarrhythmia, many of which were polymorphic. Nevertheless, recurrent events were distributed approximately equally between patients with and those without inducibility. Thus, noninducibility at baseline programmed electrical stimulation did not appear to indicate a favorable outcome. This finding is at variance with earlier observations but in accordance with data reported by Roy and colleagues. Finally, easy inducibility of ventricular fibrillation with one or two extrastimuli in 3 of the 6 patients, although striking, had no predictive power.

Study Limitations

We cannot exclude that the diagnostic yield might have been higher if myocardial biopsies had been taken from selected areas, such as the site of origin of ventricular tachycardia. Possibly, some patients might then have been excluded from this study. In other series, however, biopsies showing minor nonspecific or granulomatous abnormalities were no reason to reject the diagnosis of primary electrical disease.

The defibrillators implanted were incapable of recording the ECG events leading to a discharge. AICD shock delivery might have been triggered by a nonfatal arrhythmia (eg, a supraventricular tachyarrhythmia). However, only 1 patient had chronic atrial fibrillation with maximum ventricular rate during exercise below the programmed cutoff rate of his implanted AICD. Other supraventricular tachycardia episodes were never documented in any of the AICD patients, and none of them had inducibility of these arrhythmias during programmed electrical stimulation. Theoretically, it also is possible that a ventricular tachyarrhythmia did trigger the defibrillator but ended spontaneously before its discharge. It appears that such uncertainties will be settled by the new generations of defibrillators with event-recording facilities. However, even with episodes that were truly terminated by a shock, uncertainty remains as to whether the arrhythmia would not have ended spontaneously at a later stage without leading to a fatal event.

Depression of baroreflex sensitivity and reduction of heart rate variability are known to be associated with an increased incidence of arrhythmic events, features mainly studied in postinfarction patients. These features were not studied in our patients. Also not studied was the presence of late potentials. Mehta and Camm described a low prevalence of late potentials in patients with idiopathic ventricular tachycardia.

Conclusions

Patients with primary electrical disease who present with ventricular fibrillation are at high risk of recurrence of a life-threatening arrhythmic event. Further markers to identify those at highest risk and evaluation of the most appropriate therapeutic measures clearly are needed. However, much better understanding of the mechanism of arrhythmogenesis in these patients may be required for optimum therapeutic strategy. Some of these problems will be studied by the Unexplained Cardiac Arrest Registry of Europe (U-CARE), which has just been initiated by the European Society of Cardiology. Awaiting further characterization, intensive therapy, including early implantation of a defibrillator with ECG monitoring function, is highly recommendable in all patients with primary electrical disease who have survived an episode of ventricular fibrillation.

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