Favourable outcome in idiopathic ventricular fibrillation with treatment aimed at prevention of high sympathetic tone and suppression of inducible arrhythmias

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Abstract

Objective—In the absence of an obvious cause for cardiac arrest, patients with idiopathic ventricular fibrillation are difficult to manage. A subset of patients has inducible arrhythmias. In others sympathetic excitation plays a role in the onset of the cardiac arrest. This study evaluates a prospective stepped care approach in the management of idiopathic ventricular fibrillation, with therapy first directed at induced arrhythmias and secondly at adrenergic trigger events.

Setting—University Hospital.

Patients—10 consecutive patients successfully resuscitated from idiopathic ventricular fibrillation.

Interventions—Programmed electrical stimulation to determine inducibility, followed by serial drug treatment. Assessment of pre-arrest physical activity and mental stress status by interview, followed by β blockade. Cardioverter-defibrillator implantation in non-inducible patients not showing significant arrest related sympathetic excitation.

Main outcome measure—Recurrent cardiac arrest or ventricular tachycardia.

Results—Five patients were managed with serial drug treatment and four with β blockade. In one patient a defibrillator was implanted. During a median follow up of 2-8 years (range 6 to 112 months) no patient died or experienced defibrillator shocks. One patient had a recurrence of a well tolerated ventricular tachycardia on disopyramide.

Conclusions—Idiopathic ventricular fibrillation may be related to enhanced sympathetic activation. Prognosis may be favourable irrespective of the method of treatment. Whether the present approach enhances prognosis of idiopathic ventricular fibrillation remains to be determined. However, it may help to avoid potentially hazardous antiarrhythmic drugs or obviate the need for implantation of cardioverter-defibrillators.

(Br Heart J 1995;74:408-412)

Keywords: idiopathic ventricular fibrillation; sympathetic activation; inducible arrhythmias

In idiopathic ventricular fibrillation there is controversy about the risks for arrhythmia recurrence. One cause for conflicting data may be differences in treatment between studies. It has been suggested that if stress or exercise triggered the event, this might be a useful target of treatment and counselling of the patient. Similarly, Viskin, Belhassen and their colleagues reported that if a monomorphic tachycardia (induced at programmed electrical stimulation) can be suppressed by class I agents, prognosis may be favourable.

Other investigators have advocated implantation of an automatic defibrillator, irrespective of presumed trigger events or inducible ventricular arrhythmias. Up to now, these different strategies have not been studied sequentially. In the present study we evaluated a stepped care approach in the management of idiopathic ventricular fibrillation, combining these treatment strategies. As a first step, therapy was aimed at suppression of induced arrhythmias and secondly at prevention of adrenergic trigger events or both. The automatic implantable cardioverter-defibrillator was used in the third stage in patients not manageable within the previous two stages.

Methods

Patients

Between January 1985 and May 1993 10 consecutive patients with idiopathic ventricular fibrillation were evaluated at our department after being resuscitated. Idiopathic ventricular fibrillation was defined as previously reported, that is, ventricular fibrillation in the absence of demonstrable cardiac abnormalities. In the present study this included no family history of unexpected sudden death and no abnormalities on physical examination, 12-lead electrocardiogram, ambulatory monitoring, and exercise testing. In addition, echocardiography with Doppler measurements and coronary angiography, including ergonovine provocation and right and left ventriculography, were normal. Spasm provocation with ergonovine maleate was performed as described by Heupler et al. The baseline characteristics of the first eight patients and patient 10 (table) in the present study have been described previously.

Premonitory symptoms and pre-arrest physical and mental stress status

After resuscitation all patients had regained normal consciousness and had adequate cognitive function. After stabilisation of their clinical condition patients were carefully questioned about premonitory symptoms preceding the event, including chest pain, exertional
Favourable outcome in idiopathic ventricular fibrillation

Baseline characteristics and outcome of the 10 study patients. Patients are listed according to physical activity and mental stress status before the arrest

<table>
<thead>
<tr>
<th>Pt/Age/Sex</th>
<th>Premonitory symptoms</th>
<th>Stress status before event</th>
<th>ECG</th>
<th>PES</th>
<th>Treatment</th>
<th>Follow up (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. 24/M</td>
<td>Exercise related presyncope</td>
<td>Vigorous exercise</td>
<td>Negative T in V1, V2</td>
<td>Sust VT at BCL 500 ms + 3 ES</td>
<td>Serial R,&lt;br&gt;flec + amio</td>
<td>59</td>
</tr>
<tr>
<td>2. 26/M</td>
<td>Exercise related presyncope</td>
<td>Vigorous exercise</td>
<td>Normal</td>
<td>Sust VT at BCL 430 ms + 2 ES</td>
<td>Serial R,flec + β blocker</td>
<td>47</td>
</tr>
<tr>
<td>3. 47/F</td>
<td>Exercise related chest pain</td>
<td>Moderate exercise</td>
<td>Normal</td>
<td>VF at BCL 600 ms + 2 ES</td>
<td>Serial R,flec + β blocker + amio</td>
<td>112</td>
</tr>
<tr>
<td>4. 21/M</td>
<td>Exercise related (pre)presyncope</td>
<td>Moderate exercise</td>
<td>Normal</td>
<td>Tolerated</td>
<td>β Blocker</td>
<td>96</td>
</tr>
<tr>
<td>5. 36/M</td>
<td>Stress related palpitations None</td>
<td>Extreme tachycardia*</td>
<td>iRBBB</td>
<td>Tolerated</td>
<td>β Blocker</td>
<td>25</td>
</tr>
<tr>
<td>6. 56/F</td>
<td>Stress related palpitations None</td>
<td>Moderate exercise</td>
<td>Normal</td>
<td>Non-inducible</td>
<td>β Blocker</td>
<td>36</td>
</tr>
<tr>
<td>7. 39/M</td>
<td>None</td>
<td>Moderate exercise</td>
<td>Normal</td>
<td>Non-inducible</td>
<td>β Blocker</td>
<td>24</td>
</tr>
<tr>
<td>8. 48/M</td>
<td>None</td>
<td>Rest</td>
<td>iRBBB ST in V1, V2</td>
<td>VF at BCL 430 ms + 2 ES</td>
<td>Serial R,flec + sotalol</td>
<td>18</td>
</tr>
<tr>
<td>9. 38/M</td>
<td>None</td>
<td>Rest</td>
<td>Negative T in V1, V2</td>
<td>Sust VT at BCL 600 ms + 2 ES</td>
<td>Serial R,sotalol</td>
<td>6</td>
</tr>
<tr>
<td>10. 37/F</td>
<td>None</td>
<td>Rest</td>
<td>Normal</td>
<td>Non-inducible</td>
<td>Defibrillator</td>
<td>44</td>
</tr>
</tbody>
</table>

*At the time of the episode of ventricular fibrillation, deliberately, this patient had not slept for 72 h.
Amio, amiodarone; BCL, basic drive cycle length; diso, disopyramide; ES, number of extrastimuli used after the BCL when inducing the arrhythmia; F, Female; flec, flecainide; iRBBB, incomplete right bundle branch block; PES, programmed electrical stimulation; Pt, patient; M, Male; Serial R, serial antiarrhythmic drug testing using programmed electrical stimulation; ST, ST segment elevation; Sust V1, sustained ventricular tachycardia; VR, ventricular fibrillation.

dyspnoea, palpitations, presyncope, and syncope. The patient’s activities immediately preceding the cardiac arrest were noted. The physical activity status was semiquantitatively scored as resting, moderately active, or heavily exercising. If the patient was unable to recall the immediately preceding events, bystanders were questioned concerning the circumstances of the arrest. Finally, to assess mental stress preceding the event a separate interview was held, focusing on any noteworthy psychological experiences.

**QT dispersion on the 12-lead electrocardiogram**

To estimate dispersion of refractoriness the QT intervals of all 12 leads of the standard electrocardiogram were measured by an independent observer, unaware of the patients’ diagnosis (PR). QT dispersion was measured as previously reported.† QT was measured in all 12 leads separately and dispersion was expressed as the difference between the shortest and the longest QT duration. Rate correction of the QT interval (QTc) was done using Bazett’s formula.‡ The reference values for QT and QTc dispersion at our institution are 32 (SD 12) ms (range 10–50 ms) and 36 (13) ms (range 12–60 ms), respectively. These were determined in 31 control patients (22 men), referred for minor surgical procedures. The mean age of the control group was 47 (15) years (range 19–70 years). On the basis of these data and those found previously,§ we defined QT dispersion of > 50 ms as abnormal.

**Programmed electrical stimulation**

Programmed electrical stimulation was conducted in the absence of antiarrhythmic medication. During the study, arterial blood pressure was recorded from the right femoral artery. If applicable, programmed stimulation was repeated during antiarrhythmic drug treatment after at least five half lives of the drug. Stimulation in the right atrium was done with one or two extrastimuli during sinus rhythm and basic drive cycle lengths of 600, 500, and 430 ms. Ventricular stimulation from the right ventricular apex was performed using up to three extrastimuli at sinus rhythm and three basic drive cycle lengths: 600, 500, and 430 ms. If by then no arrhythmias were induced, a similar stimulation protocol was continued from the right ventricular outflow tract. Subsequently, isoprenaline was given to non-inducible patients, aiming at a heart rate increase of 25% or more. Programmed stimulation was repeated during isoprenaline infusion. The study was terminated if refractoriness was reached or a sustained ventricular tachyarrhythmia was induced. Sustained ventricular tachycardia was defined as repetitive ventricular beats with a frequency above 100 beats per minute, either triggered in 30 seconds duration or requiring an intervention before that time. Patients with repetitive ventricular responses of less than six beats were considered non-inducible. A complete response to drug treatment was defined as non-inducibility.

**Treatment**

The following clinical decision algorithm containing three separate steps was used (figure). First, serial antiarrhythmic drug testing was performed if an arrhythmia related to the event was induced at programmed stimulation. Initially class I drugs (flecainide, disopyramide) were tested first, followed by class III agents (sotalol and amiodarone). More recently, sotalol was used as first line agent. Secondly, if the patient was non-inducible but exercise or emotional stress was the eliciting clinical factor, β blocker therapy was initiated. The dose was increased guided by maximum heart rate at exercise testing (peak heart rate < 130 beats/min). In addition, the patient was instructed to avoid strenuous exercise. As a third step, that is, in the absence of a trigger or an index for guiding antiarrhythmic drug therapy, a cardioverter-defibrillator was implanted. Also if arrhythmias could not be
Decision algorithm for management of idiopathic ventricular fibrillation (VF). During programmed electrical stimulation (PES) three patients were inducible to ventricular tachycardia (VT) and two had VF. These five patients were successfully managed by serial drug testing and continued on antiarrhythmic drug treatment. In four out of five non-inducible patients the event was considered adrenergic dependent and two patients received β-blockade. Only one patient did not have an inducible arrhythmia or a clear trigger and was given an implantable cardioverter-defibrillator (ICD).

Follow up
All patients were followed with regular intervals in the outpatient department by one cardiologist (HC). The length of follow up was assessed from the cardiac arrest. Among other factors, patients were checked for compliance with treatment and for daily activities.

Results
The table summarises the premonitory symptoms, arrest related activity status, ECG at admission, and results of programmed stimulation. It also shows the treatment instituted and duration of follow up. The mean age was 37 (11) years. The mean left ventricular ejection fraction was 0·63 (0·03). From all patients a detailed description of premonitory symptoms could be obtained and in all patients the activity status at the time of the event could be evaluated. Patient No 1 had presyncope while playing soccer immediately before the cardiac arrest, which occurred in connection with acute strenuous exercise. The other patient, a semiprofessional boxer, experienced recurrent syncope at times of near exhaustion during training. Patient No 3 performed fitness training on a regular basis. Before her ventricular fibrillation she was exercising moderately, but had not felt chest pain. Patient No 4 was cycling rapidly in the cold and had experienced several bouts of dizziness under similar circumstances. Patient No 6, a regular swimmer, collapsed after swimming. Case No 7, a physically inactive man, had been carrying heavy boxes upstairs before the arrest.

Two patients (numbers 4 and 8) had positive late potentials, defined as abnormality of all three indices (filtered QRS duration, D40, and V40). One and two abnormal indices on the signal averaged electrocardiogram were seen in patients 9 and 5, respectively. The mean filtered QRS was 100 (13) ms, D40 34 (10) ms, and V40 32 (20) μV.

EXERCISE TESTING
Of all patients with adrenergic drive dependent ventricular fibrillation, only in patient No 2 was the cardiac arrest reproduced during exercise testing. He developed a ventricular tachycardia with a cycle length of 205 ms, causing instantaneous unconsciousness. Degeneration into ventricular fibrillation was not recorded since the arrhythmia was rapidly cardioverted. In all other patients baseline exercise testing was unremarkable. Surprisingly, one patient (No 8) in whom the arrest was not considered to be exercise related, developed non-sustained polymorphic ventricular tachycardias during treadmill exercise while treated with flecainide 200 mg daily (see below).

QT DISPERSION
The mean QT and QTc dispersions were 56 (34) ms (range 20–140 ms) and 67 (35) ms (range 31–149 ms), respectively. Five patients had QTc dispersion larger than 50 ms (patients 1, 3, 4, 6, and 7).

PROGRAMMED STIMULATION
The induced ventricular tachycardias showed a cycle length of 215, 200, and 210 ms (patients 1, 2, and 9, respectively) and caused cardiovascular collapse instantaneously. Due to prompt cardioversion within 15 to 20 seconds, degeneration to ventricular fibrillation was not seen. All tachycardias showed a left bundle branch block morphology with either a vertical axis, an intermediate axis, or a left axis (patients 1, 2, and 9, respectively). In the non-inducible patients programmed stimulation was repeated during the administration of isoprenaline. However, no further arrhythmias were found.

The right ventricular effective refractory periods after applying one extrastimulus at basic drive cycle lengths 600, 500, and 430 ms were in the normal range and amounted to 228 (16), 220 (15), and 201 (14) ms, respectively.

TREATMENT
Patient No 1 was given 300 mg flecainide daily. However, during telemetric monitoring he showed incessant monomorphic ventricular tachycardias with the same morphology but at a slower rate as found at baseline (plasma concentration was 845 ng/l, nontoxic). Flecainide was changed to disopyramide 500 mg daily which successfully prevented tachycardia reinduction. After initiation of flecainide, patient No 8 developed non-sustained ventricular tachycardias during exercise testing. Flecainide was considered ineffective and was successfully changed to sotalol 320 mg daily.

In four out of the five non-inducible
patients there was a clear adrenergic dependence of the cardiac arrest and these were treated with β blockade. The other non-inducible patients (No 10) did not have an evident trigger for the event and received an implantable cardioverter-defibrillator. All patients with an exercise or mental stress related arrest were advised to avoid vigorous exercise or stressful situations. Counselling of patient No 5 included advice to maintain a normal day-night pattern.

**FOLLOW UP**

During a median follow up of 2-8 years there were no defibrillator discharges and only patient No 1 had a recurrence of a well tolerated monomorphic ventricular tachycardia after he had lowered his disopyramide dosage.

**Discussion**

Sudden cardiac death survivors without overt heart disease are difficult to manage, especially since in most cases the underlying arrhythmogenic mechanism is not well understood. Outcome remains uncertain in individual patients and therefore implantation of a defibrillator is often advocated. The present study suggests, however, that the clinical course may be favourable if trigger events and results of programmed electrical stimulation are considered in the management of these patients.

Viskin and Belhassen have stressed that suppression of tachycardia inducibility while on class Ia drugs indicates an excellent prognosis. Other investigators have emphasised the importance of mental stress in idiopathic ventricular fibrillation and showed a favourable outcome on β blockade. This study is the first to combine suppression of inducible tachycardia and treatment with a β blocker targeted at pre-arrest sympathetic excitation in the management of idiopathic ventricular fibrillation. In patients with inducible arrhythmias serial drug testing appeared successful and in those with adrenergic dependent arrhythmias β blockade prevented new cardiac arrests. It must be noted, however, that duration of follow up was relatively short and that our patients may have had a favourable prognosis irrespective of the type of treatment (next section).

Idiopathic ventricular fibrillation has been associated with a recurrence risk of between 25% and 37%, depending on the duration of follow up. Viskin and Belhassen, reviewing the world literature, found an 11% annual sudden death rate. Other reports have indicated a more benign course. The present study also suggests a favourable prognosis, with none of the patients dying suddenly or having defibrillator shocks, and only one suffering a recurrence of a well tolerated ventricular tachycardia during disopyramide. The following may explain the favourable prognosis in our study group. First, there was a relatively frequent association between the event and physical or emotional stress, providing a target for treatment. All these patients were advised to avoid vigorous exercise or significant mental stress and almost all of them received β blockade. Secondly, our patients were either non-inducible at baseline or became non-inducible on drug treatment. The prognostic value of non-inducibility in sudden death survivors without apparent cardiac disease is unknown. However, many previous studies have indicated a favourable prognosis in patients who were non-inducible, either with or without antiarrhythmic treatment. Thirdly, previous studies reported fewer patients with inducible monomorphic ventricular tachycardias. Obviously, monomorphic tachycardias may be more amenable to serial drug treatment than polymorphic arrhythmias or ventricular fibrillation. Fourthly, previous studies using defibrillators may have overestimated the recurrence risk, since in a few instances defibrillator shocks may have been spurious or given for non-sustained arrhythmias. Finally, it must be noted that differences between studies concerning the recurrence risk also relate to the definition of idiopathic fibrillation used, that is, the number and type of investigations performed to uncover an underlying cardiac diagnosis.

The importance of preventing sympathetic excitation seems obvious, at least in patients with a clear relation between vigorous exercise or extreme psychological disturbances and the fatal arrest. In their review of published reports on idiopathic fibrillation Viskin and Belhassen noted that in 40 patients the circumstances immediately preceding the arrest were known. Physical and mental stress were present in six (15%) and nine (22%) of 40 cases, respectively. In the study by Reich et al., mental stress was present in six out of nine patients (67%) representing a subgroup with idiopathic ventricular fibrillation in that study. We found a higher incidence of physical stress (50%) and a lower incidence of mental stress (10%) as a trigger, which may relate to different methodology in identifying the subtypes of clinical sympathetic excitation. In most of the studies reviewed by the Tel Aviv group trigger events were not considered primary targets for patient management. The present study lends further support for the notion that these items may be important in management, with counselling concerning stress on the one hand, and medical treatment consisting of β blockade on the other.

In approximately 50% of patients surviving idiopathic ventricular fibrillation sustained arrhythmias can be induced with programmed electrical stimulation. This indicates that the approach adopted herein is feasible since many patients may be amenable to treatment guided by serial drug testing using programmed electrical stimulation. Recently sotalol appeared useful in the management of sustained arrhythmias. It therefore seems justified to institute sotalol as a first line treatment in those patients showing inducible ventricular arrhythmias and we advocate assessment of efficacy with programmed stimulation.
In agreement with previous studies\(^1\), we found that ventricular fibrillation in the apparently normal heart can be caused by a monomorphic ventricular arrhythmia with an excessively short cycle length. Very rapid ventricular tachycardias may deteriorate into ventricular fibrillation, especially in the setting of a too large dispersion of refractoriness, as reflected in the abnormally large QT dispersion found in five of our patients. As has been suggested previously,\(^2\) the presence of a monomorphic tachycardia supports the view that a reentrant pathway as a substrate for the arrhythmia is present. In this respect it is noteworthy that in two patients spontaneous or exercise induced tachycardias were present only after the initiation of flecainide, which may have provided sufficient conduction slowing to set the stage for reentry. As such, flecainide or other 1c agents might appear useful as a test to uncover the presence of such reentrant substrates.

The tachyarrhythmia associated with the arrest was reproduced with bicycle exercise in only one patient. In our view this does not argue against adrenergic dependence of the cardiac arrest in the other patients. It is well known that reproducibility of ventricular arrhythmias in patients with proven exercise induced tachycardias is low.\(^3\) In addition, despite absence of a clear sympathetic excitation, many patients show a circadian variation in onset of ventricular tachycardia, suggesting adrenergic dependence.\(^4\) Meredith et al showed that patients with ventricular tachycardia or fibrillation and without clearly evident sympathetic stimulation may have raised plasma noradrenaline levels, potentially enhancing tachycardias.\(^5\) This is further supported by the fact that β-blockade may effectively prevent sustained arrhythmias even in patients without overt sympathetic excitation at the time of tachycardyas.\(^6\)

In conclusion, this study lends further support to the notion that idiopathic ventricular fibrillation may be related to an enhanced sympathetic activation. Irrespective of the method of treatment, prognosis of idiopathic ventricular fibrillation may be favourable, especially in patients with avoidable stress and in patients without inducible tachycardias. Whether the approach presented herein further enhances the prognosis in the very long term remains to be determined. However, this approach may help to avoid potentially hazardous antiarrhythmic treatment. In addition, it may obviate the need for implantation of costly cardioverter-defibrillators.

We acknowledge the contributions of Tom J M Tobé.

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Br Heart J 1995 74: 408-412
doi: 10.1136/hrt.74.4.408