Characteristics of Recurrent Ventricular Fibrillation Associated With Inferolateral Early Repolarization

Role of Drug Therapy

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Objectives

Our purpose was to evaluate the efficacy of antiarrhythmic drugs (AADs) in recurrent ventricular fibrillation (VF) associated with inferolateral early repolarization pattern on the electrocardiogram.

Background

Although an implantable cardioverter-defibrillator is the treatment of choice, additional AADs may be necessary to prevent frequent episodes of VF and reduce implantable cardioverter-defibrillator shock burden or as a lifesaving therapy in electrical storms.

Methods

From a multicenter cohort of 122 patients (90 male subjects, age 37 ± 12 years) with idiopathic VF and early repolarization abnormality in the inferolateral leads, we selected all patients with more than 3 episodes of VF (multiple) including those with electrical storms (³3 VF in 24 h). The choice of AAD was decided by individual physicians. Follow-up data were obtained for all patients using monitoring with implantable defibrillator. Successful oral AAD was defined as elimination of all recurrences of VF with a minimal follow-up period of 12 months.

Results

Multiple episodes of VF were observed in 33 (27%) patients. Electrical storms (34 ± 47 episodes) occurred in 16 and were unresponsive to beta-blockers (11 of 11), lidocaine/mexiteline (9 of 9), and verapamil (3 of 3), while amiodarone was partially effective (3 of 10). In contrast, isoproterenol infusion immediately suppressed electrical storms in 7 of 7 patients. Over a follow-up of 69 ± 58 months, oral AADs were poorly effective in preventing recurrent VF: beta-blockers (2 of 16), verapamil (0 of 4), mexiletine (0 of 4), amiodarone (1 of 7), and class 1C AADs (2 of 9). Quinidine was successful in 9 of 10 patients, decreasing recurrent VF from 33 ± 35 episodes to nil for 25 ± 18 months. In addition, quinidine restored a normal electrocardiogram.

Conclusions

Multiple recurrences of VF occurred in 27% of patients with early repolarization abnormality and may be life threatening. Isoproterenol in acute cases and quinidine in chronic cases are effective AADs. (J Am Coll Cardiol 2009;53:612–9) © 2009 by the American College of Cardiology Foundation

Sudden death occurs in the absence of structural heart disease in 6% to 14% of cases (1–5). Primary arrhythmic syndromes, some associated with defects in the genes encoding cardiac ion channels or their regulating proteins, have been described to account for most of these deaths. These disorders can be accompanied by charac-
teristic electrophysiologic abnormalities affecting ven-
tricular repolarization such as long QT interval, short QT
interval, or ST-segment elevation in the V1 to V3
precordial leads (Brugada syndrome) or their cardiac
expression can be exclusively arrhythmic such as cate-
cholaminergic polymorphic ventricular tachycardia or
idiopathic ventricular fibrillation (VF) without identifi-
able electrocardiogram (ECG) abnormalities during sinus
rhythm despite drug provocation (6–10). A recent mul-
ticenter study has shown that early repolarization in the
inferolateral leads is associated with arrhythmic sudden
cardiac death in a subset of patients, accounting for 31%
of so-called idiopathic VF (11). In these patients, the
incidence of recurrent VF treated by an implanted defi-
brillator was 41% during a follow-up of 5 years. However,
there are scarce data on the role of antiarrhythmic drugs
(AADs) and their efficacy in preventing recurrences of
episodes of VF or treating electrical storms. The present
multicenter study reports the incidence and characteris-
tics of recurrent VF and the antiarrhythmic management
in a cohort of 122 patients.

Methods

Study population. Thirty tertiary care arrhythmia centers
participated in this study (Appendix). The population in-
cluded 122 patients with the diagnosis of idiopathic VF and
early repolarization on the ECG: 90 male and 32 female
patients after provocation with at least 1 class I AAD. Intravenous
ajmaline (1 mg/kg body weight at a rate of 10 mg/min), fleca-
ide (2 mg/kg body weight over 10 min with a maximum of 150
mg), cibenzoline (1.5 mg/kg body weight over 5 min), or procainamide (10 mg/kg at a rate of 100 mg/min) was used
determined by their availability in the participating centers.

Clinical and electrophysiological data. Clinical data, re-
results of pharmacological testing, and invasive electrophys-
ological testing were collected. All 12-lead ECGs showing
documentation of ventricular arrhythmias including initia-
tion of polymorphic ventricular tachycardia or VF on ECGs
were analyzed to assess the morphology of ventricular beats.

Electrophysiological study was performed using 2 or 3
multielectrode catheters introduced percutaneously through
the femoral vessels, consisting of measurement of the His-to-ventricle interval and programmed ventricular stim-
ulation. A maximum of 3 ventricular extrastimuli were
delivered from 2 ventricular sites. Patients with VF or
sustained ventricular tachyarrhythmia (lasting >30 s, caus-
ing syncope, or requiring intervention for termination) were
classified as inducible. Patients with inducible nonsustained
ventricular arrhythmias (>6 beats that terminated sponta-
neously within 30 s) were classified as noninducible.

Drug therapy, implantable cardioverter-defibrillator
(ICD) implantation, and follow-up. All patients had
ICD implantation, and subsequent follow-up was per-
formed according to local practice. In the absence of
symptoms or device therapy, patients were seen routinely
every 6 to 12 months for clinical review and device interro-
gation or as necessary in the event of symptoms or device
therapies. Appropriate shocks were defined as shocks deliv-
ered for polymorphic ventricular tachycardia or VF.

In patients with recurrent arrhythmias, the choice of
AADs was decided by individual physicians. The effect of
AAD therapy was assessed only in patients having at least 3
episodes of VF before the onset of AAD. In addition, AAD
trials were assessed if they were prescribed at least at the
following minimum daily doses: quinidine 450 mg, mexil-
etine 300 mg, flecainide 200 mg, propafenone 750 mg,
pilsicainide 450 mg, amiodarone 200 mg, and verapamil 240
mg; the doses and types of beta-blockers were variable. An
oral AAD abolishing all recurrences of VF with at least 1
year of follow-up was considered as successful.

An electrical storm was defined by ≥3 episodes of VF
occurring within 24 h. The intravenous drugs infused
during electrical storm were considered as effective if there
was no episode of VF after their administration and as
ineffective if at least 1 more episode was observed.

Statistical analysis. Continuous variables were reported as
mean ± SD or median (25th to 75th percentiles) as

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appropriate. A comparison between the groups was performed by the Student t test for independent samples. Categorical variables were compared with the Fisher exact test. All tests were 2-tailed, and a p value < 0.05 was considered indicative of statistical significance.

**Results**

**Incidence of inducible or spontaneous recurrent VF.** Table 1 shows the clinical and electrophysiological data in the total cohort. VF was inducible in only 28% of patients (despite all being resuscitated from documented VF). The majority of these patients (90%) were studied using 3 extrastimuli with the mean shortest coupling interval of the first delivered extrastimulus being 212 ± 29 ms. The HV interval was < 60 ms in all patients (mean 45 ± 9 ms).

The patients were followed for a mean of 69 ± 58 months after the initial event of cardiac arrest. From the cohort of 122 patients, 73 had no recurrence of VF, 16 had 1 to 3 recurrences, and 33 had multiple (more than 3) recurrences. The timing of the first recurrence of VF relative to the initial cardiac arrest is shown in Figure 1.

Table 2 shows the characteristics of 33 patients with multiple VF episodes compared with the characteristics of those 89 patients with lesser episodes. Patients with multiple VF more frequently had a prior history of syncope (58% vs. 24%, p < 0.001), a higher incidence of VF inducible during programmed ventricular stimulation (48% vs. 20%, p = 0.01), and a higher amplitude of J point on the baseline ECG (0.24 ± 0.12 mV vs. 0.20 ± 0.08 mV, p = 0.04).

An electrical storm was observed in 16 of the 33 patients with multiple VF (8 female subjects, 8 male subjects, age 38 ± 14 years). There was no significant difference in the clinical characteristics of 16 patients with electrical storm versus the other 17 with multiple VF.

**Electrical storms: characteristics and effects of intravenous drugs.** Table 3 shows the characteristics of patients with electrical storms. A mean of 34 ± 47 episodes (median 19 episodes, interquartile range [IQR] 3 to 84 episodes) per patient were terminated by external or ICD shocks during the electrical storms. The storm occurred during the initial hospitalization in 10 patients: 4 were referred for resuscitated VF, 5 for syncope, and 1 patient for fever due to gastrointestinal disease (ulcerative colitis); in 2 patients referred for syncope, the electrical storm occurred at admission in the emergency unit. In 6 patients the electrical storm occurred after ICD implantation at a mean follow-up time of 33 ± 39 months (median 15 months, IQR 3 to 84 months). Twelve-lead ECGs recorded during the arrhythmic periods showed a consistent increase in the amplitude of early repolarization compared with that seen in baseline (Fig. 2). In 2 of them, J/ST-segment abnormalities were confused with myocardial ischemia so that both patients underwent a coronary angiogram that demonstrated normal vessels.

The ectopy initiating VF had positive QRS morphology in leads V1 to V2 in 8 cases indicating an origin from the left ventricle; it had a negative morphology in 5 cases and both negative and positive patterns in 3 cases. The latter 3 patients exhibited widespread abnormal repolarization on a wider territory (6 to 9 ECG leads), whereas the other 13 patients had a more localized abnormality (3 to 6 ECG leads). The coupling interval of ectopic beats triggering VF was 281 ± 39 ms (range 240 to 360 ms).

Eight patients were placed under deep sedation and mechanical ventilation during the storm. Standard intravenous AAD had a low efficacy. The electrical storm was unresponsive to verapamil (3 of 3 patients), lidocaine or mexiletine (9 of 9 patients), and beta-blockers (11 of 11 patients), while amiodarone was effective in 3 of 10 patients. Three patients were also placed under mechanical left ventricular assistance and one of them died (from mesenteric infarction 2 days after withdrawal of assistance).
Another patient died as a result of incessant VF. Rapid atrial pacing at 90 beats/min was used effectively in 1 patient.

Isoproterenol was infused in 7 patients during repetitive episodes of VF (mean 25 ± 12 episodes) at a rate of 1 to 5 μg/min and eliminated all arrhythmias when the sinus heart rate was increased above 120 beats/min. Any attempt to reduce isoproterenol infusion and heart rate was associated with recurrence of VF in 3 of the patients. Isoproterenol was infused for a period ranging from 6 h to 5 days. In addition, isoproterenol infusion reduced the early repolarization pattern or restored a normal ECG (Figs. 3 to 5). Table 3 summarizes the therapeutic history.

Effects of oral AAD on VF recurrences during long-term follow-up. The patients were followed-up over 69 ± 58 months after the initial event. Mexiletine and verapamil were ineffective in 4 of 4 patients each. Beta-blockers were ineffective in 14 patients and effective in 2 patients (follow-up 52 and 64 months, respectively). Class 1C AADs (including flecainide, propafenone, pilsicainide) were ineffective in 7 and effective in 2 patients (both with propafenone, follow-up 48 and 24 months, respectively). Amiodarone was effective in 1 patient (follow-up 19 months) and ineffective in 6 patients (in 1 during the loading phase, in 5 during chronic treatment); however, none of the patients with successful action of amiodarone during electrical storm was treated with the oral medication. The failure of AADs indicated an attempt at catheter ablation of VF triggers in 8 patients with successful outcome in 6.

Quinidine (in 3) or hydroquinidine (in 6) was totally successful in 9 of 9 patients decreasing the number of recurrent VF from a mean of 33 ± 35/median of 25 (IQR 8 to 62) episodes to nil with a current follow-up of 25 ± 18 months on therapy. The daily dose of hydroquinidine was 600 mg in 6 patients resulting in blood levels ranging from 1.7 to 4.2 μg/ml (therapeutic range 2 to 5 μg/ml). In addition, quinidine reduced the early repolarization pattern or restored a normal ECG in all patients (Fig. 6). It is notable that no other patient from the total cohort (from the groups with none or 1 to 3 VF recurrences) was prescribed quinidine.

Currently, of the 31 living patients, 22 patients have not experienced any defibrillator discharge: 8 patients are taking no medication including 6 after successful catheter ablation

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Characteristics of 33 Patients With Multiple VF Versus Other 89 Patients</th>
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<tbody>
<tr>
<td>Variables</td>
<td>n = 33</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>38 ± 13.5</td>
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<tr>
<td>Amplitude of J-wave (mm × 10)</td>
<td>24.2 ± 11.5</td>
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<tr>
<td>QRS duration</td>
<td>93.9 ± 13.5</td>
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<tr>
<td>QTc</td>
<td>393.7 ± 31.9</td>
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<tr>
<td>Men vs. women</td>
<td>21 ± 63.6%</td>
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<tr>
<td>Family history of sudden death</td>
<td>5 ± 15.6%</td>
</tr>
<tr>
<td>Syncope</td>
<td>19 ± 57.6%</td>
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<tr>
<td>EP study: VF induced</td>
<td>11 ± 47.8%</td>
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Values are mean ± SD. Bold indicates significant differences. Abbreviations as in Table 1.

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Clinical and Therapeutic Data in 16 Patients With Electrical Storm</th>
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<tr>
<td>Sex, Age (yrs)</td>
<td>VF During Storm (n)</td>
</tr>
<tr>
<td>M, 13</td>
<td>&gt;50</td>
</tr>
<tr>
<td>F, 52</td>
<td>&gt;200</td>
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<td>M, 34</td>
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<td>F, 50</td>
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Ectopy were considered as originating from the left ventricle (LV) or right ventricle (RV) when their pattern in V2 lead was positive or negative, respectively. *Patient deceased.

AAD = antiarrhythmic drugs; Amio = amiodarone; BB = beta-blocker; Bretyl = bretyllate; Cath = catheter; Fleca = flecainide; ICD = implantable cardioverter-defibrillator; Lido = lidocaine; Mexi = mexiletine; Procaï = procaïnamide; Verap = verapamil; VF = ventricular fibrillation.
of VF triggers, 9 are taking quinidine, 2 are taking beta-blockers, 2 are taking propafenone, and 1 is taking amiodarone. Nine patients have experienced at least 1 appropriate defibrillator intervention during the last 12 months (2 on no AAD, 7 on various AADs), and 4 of them are currently being considered for quinidine therapy. Four patients are followed in a rehabilitation center because of adverse neurologic sequelae of initial prolonged cardiac arrest.

Discussion

This multicenter study demonstrates the efficacy of 2 specific drugs to abolish and prevent recurrences of VF associated with early repolarization abnormality in the inferolateral leads. The infusion of isoproterenol can successfully manage electrical storms sometimes as a lifesaving therapy while the oral administration of quinidine is effective chronically on a long-term basis.

Distinct ECG entity associated with sudden death. Different electrical syndromes of arrhythmic sudden death have been described including recently a syndrome involving an early repolarization anomaly in the inferior and left precordial leads in 31% of patients resuscitated from unexplained sudden death (11). This study confirms this entity in an enlarged multicenter patient population.

The early repolarization abnormality was both variable and labile as observed in other repolarization syndromes. That repolarization was linked to arrhythmogenicity was supported by the dynamic changes affecting specifically this ECG marker, which preceded and culminated with arrhythmia and receded with their reversal; the origin of arrhythmia initiating ectopy from the region of abnormal repolarization also supported this link. Similar patients have also been previously described in case reports relating “abnormal J-wave,” however, without establishing the link with early repolarization syndrome or using a control population (13–25). The arrhythmogenicity of this syndrome is thought to be related to heterogeneity of action potentials (spike and dome morphology in epicardial tissue) across the ventricular wall at the end of phase 1. Any perturbation in the balance of currents may amplify the disparity in voltage gradient and precipitate local re-entries and polymorphic ventricular arrhythmias, providing both the trigger and substrate of VF. Experimentally, sodium and calcium-channel blockers, activation of IK-ATP, hypercalcemia, and hypothermia increase electrical gradient and are arrhythmogenic (26).

Clinically, the exogenous precipitating factors and underlying genetic abnormality are unknown; however, the incidence of death during rest or sleep indicates an augmenting role of increased vagal tone.

Acute treatment of electrical storms. Electrical storm, defined as ≥3 episodes of VF within a 24-h period, occurs in a minority of patients implanted with an ICD but may
cause death or require heroic measures such as transplantation or left ventricular assistance to save the patient’s life. Our study confirms the severity of electrical storm also in association with early repolarization abnormality and shows that continuous infusion of isoproterenol successfully treats electrical storm and consistently restores normal ECG in this particular patient population. This efficacy has also been reported in a preliminary study including the same condition (27) as well as in Brugada syndrome or in torsades de pointes associated with bradycardia (28). Isoproterenol is thought to be effective probably by increasing I Ca-L current and thus decreasing electrical gradient and possibly by increasing heart rate and reducing inactivation of Ito (26).

Antiarrhythmic therapy to prevent recurrences of VF. This study demonstrates that most AADs including beta-blockers, class 1C, and verapamil are ineffective in patients with early repolarization abnormality. Previous studies have shown the efficacy of quinidine to prevent clinical recurrences in idiopathic VF, Brugada syndrome, and HERG-linked short QT syndrome (29–31). Belhasse et al. (2) also showed the efficacy of quinidine in reducing inducibility of VF. The present study demonstrates that quinidine is effective in prevention of recurrence of VF associated with early repolarization abnormality. The patients had a particularly high number of VF episodes and a long-term follow-up free of ICD interventions that strongly support the efficacy of this drug. Such results have also been reported in case reports (13,15,27). Quinidine inhibits several currents including an effect in blocking Ito, which is pivotal in endo-epicardial electrical gradient and the related arrhythmogenic risk.
Nosological frontiers with Brugada syndrome. Early repolarization is reported as a differential diagnosis of Brugada syndrome by the consensus committee (10). The former condition is distinct because of the following features: the ECG marker is absent in the right precordial leads, insensitive to sodium channel blockers, and not associated with conduction defect or SCN5A mutation; additionally, VF originating from multiple locations in the right or left ventricle contrasts with Brugada syndrome defined as a right ventricular (outflow tract) disease (10). However, our patients share some characteristics with Brugada syndrome in that the ECG abnormality occurs at the early phase of repolarization and is associated with potential arrhythmogenicity. In addition, the efficacy of isoproterenol and quinidine are also reminiscent of their efficacy in Brugada syndrome. Though both conditions are manifestations of electrical heterogeneity during phase 1 of the action potential, they may express specific ionic current density/function in different regions of the heart while sharing a common element (for example acting in synergy with Ito current). The nosological frontier between these conditions and confusion caused by phenotypic overlap (16–25) will certainly benefit from genetic studies as well as studies using molecular or morphological imaging.

Clinical implications. The present clinical study improves recognition and treatment of individuals with malignant arrhythmias. The incidence of early repolarization as a potential cause of unexplained death may be underestimated because of spontaneous fluctuation in the J-wave inscription and the rare opportunity to document arrhythmia initiation when repolarization changes are maximal; in addition, early repolarization may be present but temporally cancelled within the depolarization. The study shows that use of isoproterenol can be lifesaving in individuals with incessant VF. Though failure of most AADs indicates the need for an implantable defibrillator, the role of quinidine relative to an ICD strategy warrants further investigation.

Study limitations. Drug testing was not uniform between centers. In addition, this study did not provide information to identify the few patients at high arrhythmia risk within...
the broad population of asymptomatic patients with similar ECG patterns.

**Conclusions**

This multicenter study shows that recurrences of VF are frequent in association with early repolarization abnormality in the inferolateral leads. Isoproterenol (in acute cases) or the oral administration of quinidine are effective in correcting the ECG pattern and suppressing recurrence of arrhythmias.

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**REFERENCES**


**Key Words:** early repolarization • sudden cardiac death • ventricular fibrillation • electrical storm • antiarrhythmic drugs.

**APPENDIX**

In addition to the list of authors, the following physicians have contributed to data collection. From France: Laurence Jesel (Strasbourg); Christian De Chillou (Nancy); Patrice Scanu (Caen); Philippe Mabo (Rennes); Paul Milliez, Jerome Lacotte, Thomas Lavergne (Paris); Guillaume Laurent (Dijon); Dominique Lacroix (Lille); Dominique La-maison (ClermontFerrand); Frederic Anselme (Rouen); Philippe Maury (Toulouse). From Switzerland: Juerg Schlae-ffer (Lausanne); Marc Zimmermann (Geneve). From Germany: Thomas Rostock (Hamburg); R. Grove (Bonn); M. Borggreffe (Munster). From Czech Republic: Josef Kautzner, Piotr Neuyl (Prague). From Belgium: Yvan Blankoff (Antwerp). From Sweden: Anders Englund (Orebro). From England: Mark O’Neill (London). From Poland: Kukla Piotr (Gorlice).