Mapping and Ablation of Ventricular Fibrillation Associated With Long-QT and Brugada Syndromes

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Background—The long-QT and Brugada syndromes are important substrates of malignant ventricular arrhythmias. The feasibility of mapping and ablation of ventricular arrhythmias in these conditions has not been reported.

Methods and Results—Seven patients (4 men; age, 38±7 years; 4 with long-QT and 3 with Brugada syndrome) with episodes of ventricular fibrillation or polymorphic ventricular tachycardia and frequent isolated or repetitive premature beats were studied. These premature beats were observed to trigger ventricular arrhythmias and were localized by mapping the earliest endocardial activity. In 4 patients, premature beats originated from the peripheral right (1 Brugada) or left (3 long-QT) Purkinje conducting system and were associated with variable Purkinje-to-muscle conduction times (30 to 110 ms). In the remaining 3 patients, premature beats originated from the right ventricular outflow tract, being 25 to 40 ms ahead of the QRS. The accuracy of mapping was confirmed by acute elimination of premature beats after 12±6 minutes of radiofrequency applications. During a follow-up of 17±17 months using ambulatory monitoring and defibrillator memory interrogation, no patients had recurrence of symptomatic ventricular arrhythmia but 1 had persistent premature beats.

Conclusion—Triggers from the Purkinje arborization or the right ventricular outflow tract have a crucial role in initiating ventricular fibrillation associated with the long-QT and Brugada syndromes. These can be eliminated by focal radiofrequency ablation. (Circulation. 2003;108:925-928.)

Key Words: long-QT syndrome ■ death, sudden ■ ablation ■ arrhythmia

The long-QT syndrome (LQTS) and Brugada syndrome are established causes of sudden cardiac death associated with abnormal ventricular repolarization.1–6 The cornerstone of their management has been the implantation of a defibrillator (or β-blockers in LQTS). Recent studies have implicated the role of triggers in idiopathic ventricular fibrillation (VF) and their successful catheter ablation have been demonstrated.7 These triggers originated dominantly from the Purkinje system or right ventricular outflow tract (RVOT). The present study describes the mapping and ablation of malignant ventricular arrhythmias in patients with LQTS or the Brugada syndrome.

Methods

Seven patients with LQTS (2 men/2 women; age, 37±8 years) or Brugada syndrome (2 men/1 woman; age, 39±7 years) underwent mapping and ablation of triggers inducing polymorphic ventricular tachycardia or VF. These patients presented with documented episodes of polymorphic ventricular tachycardia or VF (1 to 21 episodes), 3 with a family history of sudden death. Whereas patients with the Brugada syndrome had 14±8 episodes of VF, those with LQTS had 6±4 episodes of VF or syncope before mapping. The LQTS was diagnosed in 4 patients on the basis of established criteria with a corrected QT interval of >460 ms; KCNQ1, SCN5A, and HERG channelopathies were excluded. The Brugada syndrome was diagnosed by abnormal QRSST complexes in leads V1 and V2 with a coved ST-segment elevation in 3 patients, one who had a familial SCN5A channelopathy (2850delT). No patient had evidence of structural heart disease according to physical examination, echocardiography, and right/left ventricular ejection fraction. Exercise testing in all and coronary angiography in 4 patients excluded myocardial ischemia.

The LQTS was diagnosed at the time of ventricular arrhythmia. Two patients with Brugada syndrome were initially asymptomatic, having undergone prophylactic insertion of a defibrillator, and later presented (9 months and 3 years, respectively) with clinical episodes of VF (5 and 17, respectively); in the third, a defibrillator was inserted after 12 episodes of syncope.

Patients were hospitalized within 2 weeks of symptoms or multiple VF episodes (in 5), and were then documented to have ventricular premature beats (11 559±13 111/24 hours, range 661 to 32 400). The triggering role of premature beats in the initiation of VF was observed by ambulatory monitoring or stored electrograms of the defibrillator. Premature beats in the LQTS had a coupling interval of 503±29 ms; they were monomorphic in 2 patients (1 with
left bundle-branch block–inferior axis typical of RVOT [Figure 1] and 1 with right bundle-branch block with superior axis), and polymorphic and repetitive (sometimes bidirectional) with a positive morphology in lead V1 in 2 patients (Figure 2). The latter had varying cycle lengths of 280 to 420 ms with repetitive beats lasting 3 to 45 beats, which were well tolerated during hospitalization. Premature beats in the Brugada syndrome were monomorphic in all, with a RVOT morphology in 2 (coupling interval of 340±20 and 408±15 ms) and with left bundle-branch block–superior axis in 1 (coupling interval 278±29 ms). The monomorphic RVOT premature beats were first observed at the time of VF in 1 patient, whereas in 2 patients, they had been documented (with a normal QRS/QT in sinus rhythm) 14 and 11 years before they triggered VF, after development of abnormal QRST. Exercise testing and isoproterenol infusion eliminated all premature beats, excluding catecholaminergic polymorphic ventricular tachycardia.

Medical treatment in the LQTS had included β-blockers alone or combined with class IC drugs (3), verapamil (2), and amiodarone (1). No drug therapy had been attempted in 2 patients with Brugada syndrome, while quinidine failed in 1 patient. A defibrillator was implanted in 5 patients but not in 2 patients with LQTS who had frequent polymorphic ventricular tachycardias.

Electrophysiological Study
Written informed consent was obtained from all patients. Mapping was performed in the fasted state with sedation using midazolam and nalbuphine. An intravenous dose of 0.5 mg/kg of heparin was administered during mapping in the left ventricle. Two to four multielectrode catheters were introduced percutaneously through the femoral vessels, including a 4-mm-tip quadripolar roving ablation catheter equipped with a thermocouple (Biosense Webster). The latter was introduced into the left ventricle by retrograde aortic or transseptal catheterization for the patients with left ventricular premature beats. Surface ECGs and bipolar endocardial electrograms were filtered at 30 to 500 Hz and recorded with a polygraph (model Laboratory system or Midas, 1 to 4 kHz and 10 kHz sampling rate, respectively).

In patients with Brugada syndrome, induction of sustained VF was attempted using 1 to 3 programmed extrastimuli at the right ventricular apex and (if negative) from the RVOT at twice the diastolic threshold.

Localization and Ablation of Triggers
Mapping the earliest electrogram relative to the onset of the ectopic QRS complex localized the triggers. An initial sharp potential (<10 ms in duration) preceding the larger and slower ventricular electrogram by <15 ms during sinus rhythm represented a peripheral Purkinje component, whereas longer intervals indicated proximal Purkinje fascicle activation. Such a potential preceding ventricular activation during premature beats indicated the latter originated from the Purkinje system.6,9 Ablation was performed using radiofrequency (RF) energy with a target temperature of 55°C to 60°C and a maximum power of 50 watts, with a duration that included the time to abolish premature beats and consolidating applications to minimize recurrence.

Results
The procedural and fluoroscopy durations were 169±57 minutes (range 90 to 240) and 42±21 minutes (range 17 to 69), respectively.

Long-QT Syndrome
In 1 patient, premature beats originated from the RVOT and were ablated by 6 minutes of RF application. In 2 patients, polymorphic ventricular beats originated from the peripheral

Figure 1. RVOT-triggered VF. A, Holter demonstrates LQTS and polymorphic ventricular tachycardia, minutes later followed by VF requiring resuscitation (not shown because of tracing artifact). B, Defibrillator interrogation demonstrates isolated monomorphic premature beats that subsequently initiate VF in Brugada syndrome. C, Twelve-lead ECG demonstrating features of Brugada syndrome and characteristic RVOT premature beat, subsequently inducing an arrhythmic storm requiring 11 shocks.
Purkinje arborization in the left ventricle, including the ramifications of anterior or posterior fascicles (which produced inferior and superior axis morphologies, respectively), and from the intervening region in intermediate morphologies (Figure 2). In 1 patient, premature beats originated from the posterior fascicle. During premature beat, the earliest Purkinje potential preceded the local endocardial muscle activation by a conduction interval of $34\pm17$ ms, whereas during sinus rhythm it preceded the ventricular muscle activity by 5 to 15 ms. Repetitive beats were also preceded by Purkinje activity (Figure 2) with a variable delay ranging from 20 to 110 ms ($52\pm24$).

The ablation of Purkinje beats produced, during the first minute of local RF application, temporary exacerbation of arrhythmia (increased the number of premature beats and polymorphic ventricular tachycardia) followed by a disappearance of premature beats. Different morphologies were progressively eliminated by ablation at multiple sites using 12 to 24 minutes of RF applications. Electrograms after ablation showed the abolition of the local Purkinje potential, but the QRS complex during sinus rhythm remained unchanged.

Brugada Syndrome

In 2 patients, RVOT triggers were eliminated by 7 to 10 minutes of RF applications at the earliest site (25 and 40 ms ahead of QRS onset). Noteworthy is that VF inducibility was modified after ablation; initially, VF was reproducibly induced from the right ventricular apex with 2 extrastimuli ($S_5$, $S_4$, and $S_3$ ms in both patients), but the same repeated maneuvers after ablation were negative. Whereas 3 extrastimuli from 2 sites were negative in 1 of these patients, it ultimately induced VF in the other ($S_4$, $S_3$, and $S_1$ ms). In the third patient, premature beats with left bundle-branch block and superior axis originated from the anterior right ventricular Purkinje network and were ablated with 10 minutes of RF application. VF was not inducible in this patient.

Follow-Up

During a mean follow-up period of $17\pm17$ months (LQTS $24\pm20$ months; Brugada $7\pm6$ months), there has been no recurrence of VF, syncope, or sudden cardiac death in any patient. One patient with LQTS was maintained on a $\beta$-blocker. Another had a late recurrence of premature beats; she refused further procedures and continued $\beta$-blocker treatment. In other patients, repeated ambulatory monitoring showed none or a few (0 to 12) isolated premature beats per 24 hours.

Discussion

This study demonstrates the important role of focal triggers in the development of malignant ventricular arrhythmias associated with the LQTS and Brugada syndrome, with dramatic improvement after ablation.

These patients fulfilled established criteria for the LQTS or Brugada syndrome and presented with malignant arrhythmias that were associated with frequent isolated or repetitive premature beats and multiple VF in most. Patients were rapidly hospitalized to facilitate mapping of spontaneous triggers. Although they are consecutive patients, this cohort may represent a selected subset, and these results may not be applicable to patients with a paucity of premature beats. However, even in reports with infrequent premature beats, the morphology of these beats was similar to our patients. Triggering beats were elicited from the Purkinje system (notably in LQTS) or from the RVOT (notably in Brugada syndrome) and confirmed by elimination of triggers and malignant arrhythmia after ablation.

The present report provides new insights into the initiation of VF associated with abnormal repolarization. The finding of focal triggers is in agreement with previous observations that in 67% of patients with Brugada syndrome, initiation of VF was preceded by similar isolated premature beats. These have a right ventricular origin dominantly from the RVOT, with the latter region hypothesized to support maximal electrical gradient. However, the long coupling interval of triggers or their Purkinje origin would not support epicardial phase 2 reentry. In the LQTS, there are scarce data about morphology of beats initiating malignant arrhythmias because of their sporadic occurrence and the efficacy of $\beta$-blockers; however, narrow complex beats (“fascicular”)
occurring in isolation or in polymorphic/bidirectional runs can be recognized in previous reports.\textsuperscript{11} The initiating role of the Purkinje system may result from automaticity, reentry, or triggered activity and is sensitive to various clinical factors.\textsuperscript{6,12,13}

The cohort studied is small but involves two causes of sudden death that have been considered concurrently because they affect ventricular repolarization with similar triggers and polymorphic arrhythmia, which can be eliminated by ablation. These results are strikingly similar to those of idiopathic VF, considered implicitly not to involve an abnormal substrate, and therefore indicate a broader role of focal triggers in VF initiation. Though they need to be confirmed in a larger cohort with longer follow-up, such results have major implications as they provide new insights that may lead to a possible cure for VF.

References


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An erratum has been published regarding this article. Please see the attached page for:
/content/111/3/378.1.full.pdf

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In the article by Huynh et al, “Aspirin, Warfarin, or the Combination for Secondary Prevention of Coronary Events in Patients With Acute Coronary Syndromes and Prior Coronary Artery Bypass Surgery,” which published in the June 26, 2001, issue (Circulation. 2001;103:3069-3074), the authors now realize errors appeared in Tables 3 and 4. The percentages of events and complications were presented on the basis of the number of patients’ visits rather than on the total number of patients.

Overall, the corrected results did not change the implication of the study. There was no benefit of warfarin alone or combined with aspirin in the secondary prevention of ischemic events in this study of patients with previous coronary artery bypass surgery and an acute coronary syndrome; there was a significant excess in minor bleeding compared with the aspirin-alone group.

Corrected versions of Tables 3 and 4 appear below.

**TABLE 3. End-Point Events According to Treatment**

<table>
<thead>
<tr>
<th>Events</th>
<th>Warfarin + Placebo</th>
<th>Aspirin + Placebo</th>
<th>Warfarin + Aspirin</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary end point, n (%)</td>
<td>18 (40.0)</td>
<td>13 (28.3)</td>
<td>11 (25.0)</td>
<td>0.27</td>
</tr>
<tr>
<td>Death, n (%)</td>
<td>1 (2.2)</td>
<td>0 (0.0)</td>
<td>2 (4.5)</td>
<td>0.34</td>
</tr>
<tr>
<td>MI, n (%)</td>
<td>4 (8.9)</td>
<td>1 (2.2)</td>
<td>2 (4.5)</td>
<td>0.34</td>
</tr>
<tr>
<td>UA, n (%)</td>
<td>16 (35.6)</td>
<td>13 (28.3)</td>
<td>10 (22.7)</td>
<td>0.41</td>
</tr>
<tr>
<td>PCI, n (%)</td>
<td>6 (13.3)</td>
<td>1 (2.2)</td>
<td>3 (6.8)</td>
<td>0.12</td>
</tr>
<tr>
<td>Repeat CABG, n (%)</td>
<td>2 (4.4)</td>
<td>2 (4.3)</td>
<td>2 (4.5)</td>
<td>0.99</td>
</tr>
</tbody>
</table>

UA indicates unstable angina requiring rehospitalization; PCI, percutaneous coronary intervention; and MI, myocardial infarction. Primary end point is any-cause mortality, MI, or UA requiring hospitalization.

**TABLE 4. Complications and Adherence to Protocol by Patients**

<table>
<thead>
<tr>
<th>Complications</th>
<th>Warfarin + Placebo</th>
<th>Aspirin + Placebo</th>
<th>Warfarin + Aspirin</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minor bleeding, n (%)</td>
<td>10 (22.2)</td>
<td>2 (4.3)</td>
<td>9 (20.5)</td>
<td>0.03</td>
</tr>
<tr>
<td>Major bleeding, n (%)</td>
<td>1 (2.2)</td>
<td>0 (0.0)</td>
<td>2 (4.5)</td>
<td>0.34</td>
</tr>
<tr>
<td>Blood transfusions, n (%)</td>
<td>2 (4.4)</td>
<td>0 (0.0)</td>
<td>2 (4.5)</td>
<td>0.34</td>
</tr>
<tr>
<td>Compliance, %*</td>
<td>90.1</td>
<td>86.7</td>
<td>86.1</td>
<td>0.66</td>
</tr>
<tr>
<td>Protocol completion, %*</td>
<td>77.6</td>
<td>78.5</td>
<td>69.9</td>
<td>0.22</td>
</tr>
</tbody>
</table>

*Compliance and protocol completion were calculated per visit.

DOI: 10.1161/01.CIR.0000155489.11621.70
In the article by Haïssaguerre et al, “Mapping and Ablation of Ventricular Fibrillation Associated With Long-QT and Brugada Syndromes,” which appeared in the August 26, 2003, issue (Circulation. 2003;108:925–928), the authors would like to note the following errors:

1. In the byline, Jerónimo Farré’s name incorrectly appeared as “Gerónimo Farre.”
2. José Angel Cabrera and Jerónimo Farré work at Fundación Jiménez Díaz in Madrid, Spain.
3. The work of Drs Cabrera and Farré was supported by Redes Temáticas de Cooperación, Red Cardiovascular C01/03.

DO: 10.1161/01.CIR.0000155483.25082.D4

In the article by McRae and Ginsberg, “Initial Treatment of Venous Thromboembolism,” which appeared in the August 31, 2004, supplement sponsored by the Society for Vascular Medicine and Biology (Circulation. 2004;110[suppl I]:I-3–I-9), an error appeared in Table 2. The footnote of the table erroneously states that “For enoxaparin, 100 anti-Xa U/kg corresponds to a dose of 100 mg/kg.” The legend should have read, “For enoxaparin, 100 anti-Xa U/kg corresponds to a dose of 1 mg/kg.”

DO: 10.1161/01.CIR.0000155484.25082.1A

In the article by Bauer et al, “Acute Improvement in Global and Regional Left Ventricular Systolic Function After Percutaneous Heart Valve Implantation in Patients With Symptomatic Aortic Stenosis,” which appeared in the September 14, 2004, issue (Circulation. 2004;110:1473–1476), two errors of note appeared in the table on page 1474. Under “Endocardiographic data,” the rows for “LV end-systolic volume, mm Hg” and “LV end-diastolic volume, mm Hg” should have appeared as the following:

<table>
<thead>
<tr>
<th>LV end-diastolic volume, mL</th>
<th>102±36 (baseline)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV end-systolic volume, mL</td>
<td>49±25 (baseline)</td>
</tr>
</tbody>
</table>

DO: 10.1161/01.CIR.0000155485.32706/1C

Because of a typesetting error, several mathematical symbols appeared incorrectly in the article by Solomon et al, “Effect of Candesartan on Cause-Specific Mortality in Heart Failure Patients: The Candesartan in Heart failure Assessment of Reduction in Mortality and morbidity (CHARM) Program,” which appeared in the October 12, 2004, issue (Circulation. 2004;110:2180–2183). On page 2180, in the abstract and in the text of the article, there were several instances in which “LVEF≤40%” should have appeared as “LVEF≤40%.” In addition, in the last sentence of the first paragraph of the article, please note that “9% borderline risk” should read “9% borderline significant risk.” The corrected version is available online at http://circ.ahajournals.org/cgi/content/full/110/15/2180. (The previous version can be accessed by selecting the “Previous Version of This Article” link.) We regret these errors.

DO: 10.1161/01.CIR.0000155486.26868.C9

In the AHA Scientific Statement by Drew et al, “Practice Standards for Electrocardiographic Monitoring in Hospital Settings: An American Heart Association Scientific Statement From the Councils on Cardiovascular Nursing, Clinical Cardiology, and Cardiovascular Disease in the Young,” which appeared in the October 26, 2004, issue (Circulation. 2004;110:2721–2746), Figure 4 contained an error. The text in the figure refers to the “Angle of Lewis.” The correct name is “Angle of Louis.” The Association regrets this error.

DO: 10.1161/01.CIR.00001155490.19245.B0
In the article by Noujaim et al, “From Mouse to Whale: A Universal Scaling Relation for the PR Interval of the Electrocardiogram of Mammals,” which appeared in the November 2, 2004, issue (Circulation. 2004;110:2802–2808), the name of Ary L. Goldberger, MD, was misspelled as “Goldberg” in reference 12. The authors regret this error.

DOI: 10.1161/01.CIR.0000155482.89456.78

In the article by Spargias et al, “Ascorbic Acid Prevents Contrast-Mediated Nephropathy in Patients With Renal Dysfunction Undergoing Coronary Angiography or Intervention,” which appeared in the November 2, 2004, issue (Circulation. 2004;110:2837–2842), the name of author Panagiotis Iokovis was spelled incorrectly as “Panagiotis Iocovis.” The authors regret this error.

DOI: 10.1161/01.CIR.0000155487.34492.0D


DOI: 10.1161/01.CIR.0000155488.34492.E9