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Mapping and Ablation of Idiopathic Ventricular Fibrillation

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Background—Ventricular fibrillation is the main mechanism of sudden cardiac death. The feasibility of eliminating recurrent episodes by catheter ablation has not been reported.

Methods and Results—Twenty-seven patients without known heart disease (13 men, 14 women, 41 ± 14 years of age) were studied after being resuscitated from recurrent (10 ± 12) episodes of primary idiopathic ventricular fibrillation; 23 had received a defibrillator. The first initiating beat of ventricular fibrillation had an identical electrocardiographic morphology and coupling interval (297 ± 41 ms) to preceding isolated premature beats typically noted in the aftermath of resuscitation. These triggers were localized by mapping the earliest electrical activity and ablated by local radiofrequency delivery. Outcome was assessed by Holter and defibrillator memory interrogation. Premature beats were elicited from the Purkinje conducting system in 23 patients: from the left ventricular septum in 10, from the anterior right ventricle in 9, and from both in 4. The interval from the Purkinje potential to the following myocardial activation varied from 10 to 150 ms during premature beat but was 11 ± 5 ms during sinus rhythm, indicating location at peripheral Purkinje arborization. The premature beats originated from the right ventricular outflow tract muscle in 4 patients. The accuracy of mapping was confirmed by acute elimination of premature beats during local radiofrequency delivery. During a follow-up of 24 ± 28 months, 24 patients (89%) had no recurrence of ventricular fibrillation without drug.

Conclusions—Primary idiopathic ventricular fibrillation is a syndrome characterized by dominant triggers from the distal Purkinje system. These sources can be eliminated by focal energy delivery. (*Circulation*. 2002;106:962-967.)

Key Words: ablation ■ death, sudden ■ heart arrest ■ fibrillation ■ mapping

Ventricular fibrillation (VF) is the main mechanism of sudden cardiac death. Idiopathic VF in the absence of structural heart disease or surface electrocardiographic abnormalities accounts for 5% to 10% of survivors of out-of-hospital cardiac arrest.¹⁻³ Mapping during VF has shown that fibrillation is perpetuated by reentrant or spiral waves, while recent data suggest the role of specific sources triggering the arrhythmia.^{4,5} This study describes the results of ablation of these triggers in a group of 27 patients with idiopathic ventricular fibrillation.

Methods

Twenty-seven consecutive patients underwent attempted ablation of primary idiopathic VF in 6 centers. Six patients had a family history of sudden death (Table). Twenty-three had received a defibrillator but continued to suffer from recurrent VF or runs of polymorphic ventricular tachycardia (Figure 1), whereas 4 had no implanted defibrillator because they underwent early ablation with complete

abolition of ventricular arrhythmia confirmed by prolonged in-hospital monitoring and no longer warranted defibrillator insertion by the judgment of the treating clinicians. In 19 patients, VF as well as premature beats were temporally clustered within a few days (electrical storm), requiring multiple shocks, and reoccurred suddenly months or years later. The 8 remaining patients had persistent ventricular arrhythmias over long periods of time. A mean of 3.6 ± 2 (median 4) antiarrhythmic drugs were unsuccessfully tried, including Vaughan-Williams class I drugs in 22, β -blockers in 19, amiodarone in 11, and verapamil in 16 (despite effectiveness of intravenous verapamil in 7).

The first episode of documented VF occurred during daily activity in 23 patients (none during effort) and during sleep in 4; none of them was taking any medications or drugs of influence. Seventeen patients had a prior history of unexplained syncope.

All patients had apparently normal heart based on established criteria,¹ which were normal physical examination and ECG, echocardiography, and right and left ventricular ejection fraction, as well as normal endomyocardial biopsy in 6 patients. Clinical history, Holter monitoring, and exercise testing showed no indication of

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Characteristics of Patients With RVOT Versus Purkinje Premature Beats

	Sex, Female/Male	Age, y	Family History of Sudden Death	Number of VF Before Ablation	Persistent/ Episodic Arrhythmias	Polymorphic/ Monomorphic Premature Beats	Ectopic QRS Durations, ms	Coupling Interval Initiating VF or Polymorphic VT, ms
RVOT (n=4)	3/1	27±8	0	2±2	4/0	1/3	145±12	355±30
Purkinje (n=23)	11/12	43±14	6	10±13	4/19	18/5	126±18	280±26
<i>P</i>	NS	0.02	NS	0.03	<0.01	0.06	0.04	0.01

RVOT indicates right ventricular outflow tract; VF, ventricular fibrillation; and VT, ventricular tachycardia.

myocardial ischemia, and coronary angiography was normal in all patients. Ergonovine provocation was negative in the 5 patients in whom it was performed, and coronary spasm was excluded in others by documentation of normal ST-segment preceding VF on ECG or Holter recording. Catecholaminergic polymorphic ventricular tachycardia was excluded by exercise testing or isoproterenol infusion. A long-QT interval was excluded based on a corrected QT interval <440 ms and no QT prolongation after a pause or during class IA drug. Normal QRST complexes were observed in all electrocardiograms before and after cardiac arrest and during oral or intravenous (n=18) class IC drug administration, thus excluding a Brugada syndrome.¹ SCN5a and HERG channelopathies were excluded in 12 patients, including 5 with familial sudden death.

ECG Morphology of Premature Beats

The 12-lead ECG showed different characteristic morphologies of premature beats (Figure 2) with a right or left bundle-branch block pattern in 10 and 13 patients and both patterns in 4. Their coupling interval was fixed in 4 but varied by 20 to 160 ms (75±42) in 23. Runs of repetitive beats or VF were initiated at the shortest coupling intervals (297±41 ms) in all but 3 patients, coinciding with the peak of preceding T wave (R on T phenomenon) in 16 patients and its descending slope in 11 patients (Figure 1). Interpolated beats were noted in 17 patients. A long-short initiating sequence of VF was not observed. During hospitalization immediately before ablation, 24 patients had frequent premature beats with an average number of 7841±9595 in 24 hours; 3 patients had no ventricular premature beats, but there was prior 12-lead documentation of spontaneous initiating beats.

Electrophysiological Study

Two to four multielectrode catheters were introduced percutaneously through the femoral vessels, including a 4-mm tip-ablation catheter. Surface ECG leads and bipolar intracardiac electrograms filtered at 30 to 500 Hz were recorded simultaneously with a polygraph (model Lab system or Midas, 1- to 4-kHz and 10-kHz sampling rate, respectively). Stimuli were twice the diastolic threshold and 2 ms in duration.

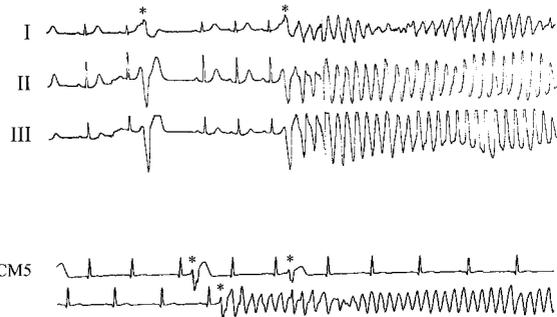


Figure 1. Examples of VF initiation by premature beats later found to originate from the right (top) or left (bottom) ventricle. The inferior panel is continuous Holter recording. In each case, the initiating beat is identical or similar to preceding isolated premature beat (*).

Localization of Arrhythmogenic Triggers

The source was localized by the earliest electrogram relative to the onset of the ectopic QRS complex. An initial sharp potential (<10 ms in duration) preceding by <15 ms the larger and slower ventricular electrogram 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 that the latter originated from the Purkinje system, whereas its absence at the site of earliest activation indicated an origin from ventricular muscle.⁵⁻⁷

Ablation was performed at the site with the earliest electrogram using radiofrequency energy with a target temperature of 55°C to 60°C and a maximum power of 50 W. In cases where maximum power delivered was limited to 30 W, an externally irrigated tip catheter (17 cm³/min, maximum 50 W) was used. The procedural end point was abolition of premature beats.

Patients with successfully eliminated premature beats were followed without antiarrhythmic drugs. The number of shocks and stored electrograms during each clinical event were provided by the data-logging capabilities of the defibrillator.

Statistical Analysis

Continuous variables were expressed as group mean value±SD, and median and range were compared using the nonparametrical Mann-Whitney *U* test. Qualitative variables were compared using the Fisher exact test. Statistical significance was selected at *P*<0.05.

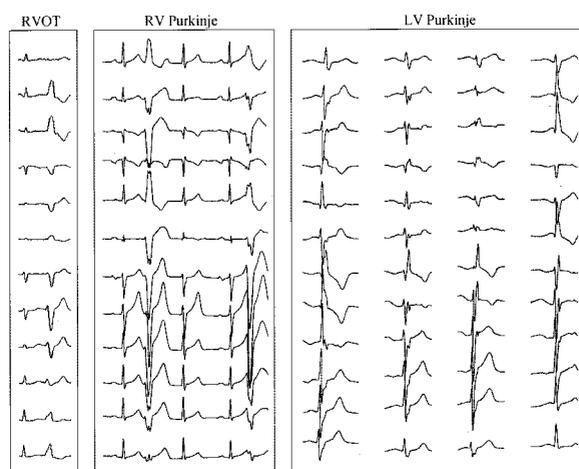


Figure 2. Electrocardiographic morphology of premature beats. Left, Morphology of premature beat from the right ventricular outflow tract. Middle, Two premature beats with minor morphological variations both originating from the mid-anterior right ventricular Purkinje system. Right, Four different morphologies of premature beats from the left ventricular Purkinje system in the same patient (first beat, superior axis; second and third beats, intermediate axis; fourth beat, inferior axis) with a short duration of QRS complexes (124±5 ms).

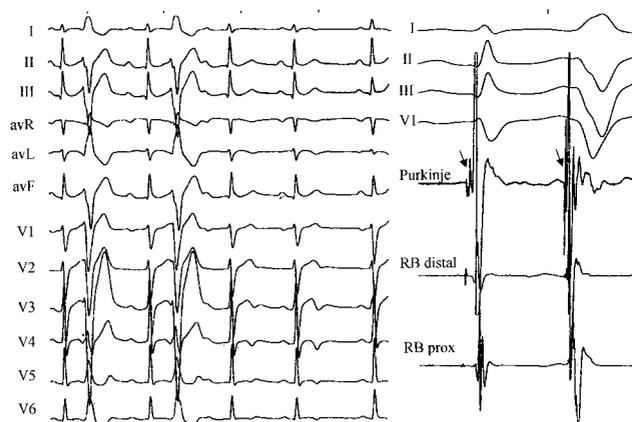


Figure 3. Electrocardiographic morphology (left) and endocardial mapping (right) of 2 identical premature beats originating from the right ventricular anterior wall. A distal Purkinje potential precedes local activation during ectopy as well as during sinus rhythm.

Results

The HV interval was 46 ± 7 ms, < 60 ms in all. VF was inducible using programmed stimulation in 10 patients.

ECG Analysis of Initiating Premature Beats

Premature beats with a positive morphology in V1 (left ventricular origin) were polymorphic in all patients except 2, exhibiting significant morphological variations predominantly in limb leads (Figure 2) with, however, a characteristically short QRS duration (115 ± 11 ms). Premature beats negative in V1 (right ventricular origin) displayed a significantly longer QRS duration (143 ± 10 ms, $P < 0.01$). They had an inferior axis in 4 patients (single morphology in 3, two morphologies in 1) later found to originate from the outflow tract or a superior axis later mapped to the anterior wall in 13. In the latter, subtle morphological differences were observed in 10 patients and a monomorphic pattern in 3; an initial rapid ventricular depolarization (r wave < 40 ms in V1, V2) was noted in 10 (Figure 2).

Endocardial Site of Origin

Premature beats observed during mapping in 24 patients originated from the right ventricular outflow tract muscle in 4, with the earliest activity preceding the QRS onset by 32 ± 15 ms and from the peripheral Purkinje system for all other sources (Purkinje beats) in 20: from the right ventricle in 7, from the left ventricle in 9, and from both ventricles in 4 (3 with a family history of sudden death). The 3 patients without premature beats were considered to have Purkinje beats (from right ventricle in 2 and left ventricle in 1) based on identical morphological characteristics of spontaneous beats previously documented on 12-lead ECG. The Table compares characteristics of patients with right ventricular outflow tract versus Purkinje beats. Patients with VF initiated from the Purkinje system were older and had more episodes of VF and polymorphic beats, and 26% had a familial history of sudden death.

The Purkinje sources were localized to the anterior right ventricle or in a wider region of the lower half of the septum in the left ventricle (Figures 3 through 5): from the ramifica-

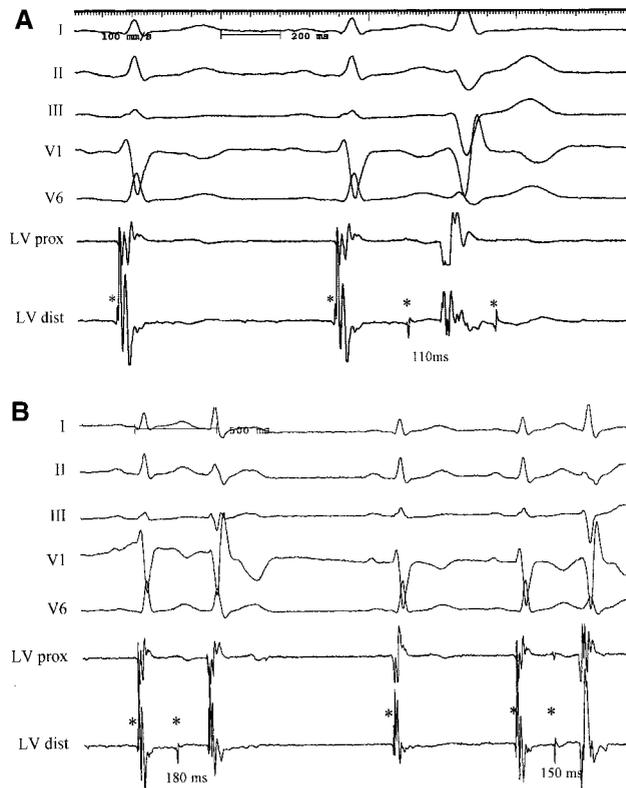


Figure 4. Endocardial electrograms before any ablation at the same Purkinje site of triggering premature beats with different morphology (mapping catheter located at left ventricular septum). A, Premature beat originating from the left ventricular Purkinje system is indicated by a sharp potential (*), which also precedes activation during sinus rhythm. The second Purkinje discharge is not conducted to the ventricle. B, Two other morphologically distinct premature beats originating from the left ventricular Purkinje system (*) with different conduction times to local muscle.

tions of anterior or posterior fascicles resulting in superior ($n=4$) and inferior ($n=10$) axis, respectively (Figure 2), and from the intervening region in intermediate morphologies ($n=12$). Recording of stable Purkinje activity was more difficult in the right than in the left ventricle because of pronounced trabeculations. During premature beat, the earliest Purkinje potential preceded the local muscle activation by a conduction interval of 38 ± 28 ms, with a greater precocity in the left than in the right ventricle (46 ± 29 versus 19 ± 10 ms, $P=0.04$). At the same site, differing conduction times were associated with varying morphologies, suggesting either changes in ventricular activation route or origin from another part of Purkinje system (Figure 4). During sinus rhythm, however, the Purkinje potential closely preceded the ventricular muscle activity by 11 ± 5 ms. Two or more Purkinje deflections were observed at the earliest site in 9 patients.

In 10 patients, 2, 3, or 4 repetitive beats were recorded, with each complex being preceded by a Purkinje potential (Figure 5) with a variable delay ranging from 15 to 120 ms (52 ± 27). Conduction block between Purkinje and ventricular muscle was also observed in 3 patients (Figure 4). Long runs or VF initiation did not occur during mapping.

Catheter manipulation produced transient bundle-branch block in 4 patients (right in 3, left in 1); as a result, peripheral

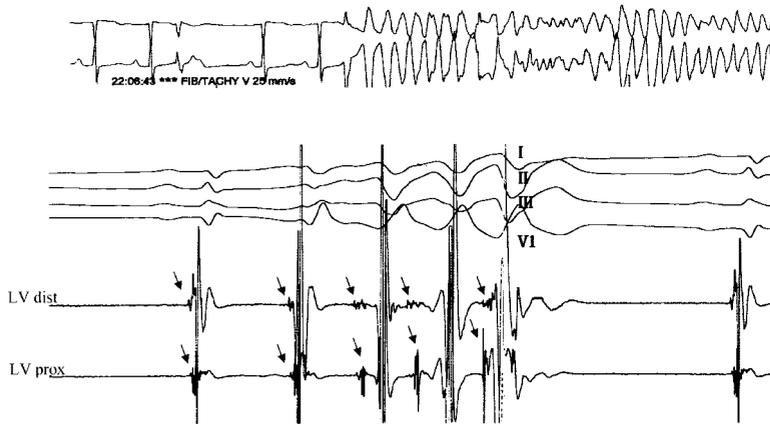


Figure 5. Top, Initiation of VF during Holter recording. Note that the initiating beat is different from the preceding isolated premature beat. Bottom, In the same patient, run of premature beats originating from the left ventricular Purkinje system. Each QRS complex is morphologically different but preceded by a Purkinje potential (arrow) with a varying conduction time. The same activity is also present during sinus rhythm with a short conduction time.

Purkinje potentials no longer preceded the local ventricular activation in sinus rhythm, although activation during ectopy remained unchanged.

Radiofrequency Ablation

The procedural and fluoroscopic durations were 190±71 and 35±20 minutes. The 4 sources mapped to right ventricular outflow tract were acutely eliminated with 4 to 10 (median, 7) energy applications.

Ablation of Purkinje beats initially produced in all patients temporary exacerbation of arrhythmia (including VF in 1 requiring defibrillation) followed by a disappearance of premature beats. Different morphologies were progressively eliminated by ablation at multiple sites with early Purkinje potential using a mean of 9±5 (median, 8; range, 2 to 19) RF applications. Electrograms recorded after ablation showed the abolition of the local Purkinje potential and slight delay in the occurrence of the local ventricular electrogram (Figure 6). In 3 patients, abrupt QRS widening suggestive of left anterior or posterior hemiblock was observed during inadvertent catheter movement. The QRS complex recovered immediately on interruption of RF delivery, and local recording showed a Purkinje-muscle interval >15 ms, indicating catheter displacement toward the proximal Purkinje system. Within the next days, 2 patients had recurrent premature beats with a

newly documented morphology and underwent successful reablation at another part of the Purkinje system.

The QRS complex during sinus rhythm was prolonged by 20 ms in 3 patients after right (2) or left (1) ventricular ablation (Figure 7). The HV interval remained unchanged in all but 1 patient (10-ms prolongation).

In the 3 patients without spontaneous arrhythmias during the procedure, the putative source of premature beats was ablated in sinus rhythm based on initial pace mapping reproducing their previously documented 12-lead ECG morphology followed by RF delivery at local sites exhibiting Purkinje potentials. Six, 10, and 12 RF applications were delivered, respectively, to abolish local Purkinje potentials. Nonsustained polymorphic ventricular tachycardia was triggered in 2 and VF in 1. The QRS complex was prolonged in 2 patients by 20 and 30 ms.

Follow-Up

Three patients had a late recurrence of premature beats (with the same morphology as preablation, 2 left and 1 right ventricular origin) and received an antiarrhythmic drug. Two of them had recurrence of VF and shocks documented by the device log (1 and 6 episodes, respectively); one had a single presyncope attributable to polymorphic VT lasting 6 seconds without defibrillator discharge. They did not undergo a repeat

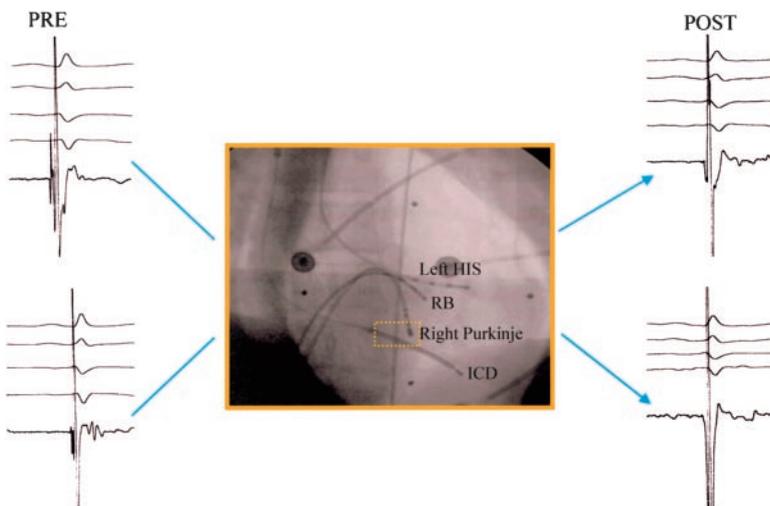


Figure 6. Middle, Anterior-posterior radiographic image showing the ablation area in the right ventricle as well as the location of the right bundle and left sided His (to reduce the risk of mechanical injury to the right bundle) recordings. Right and left panels show 2 recording sites before and after local RF delivery in the right Purkinje network. Besides abolition of the local Purkinje potential, note the slight delay in the local ventricular electrogram with regard to the QRS onset.

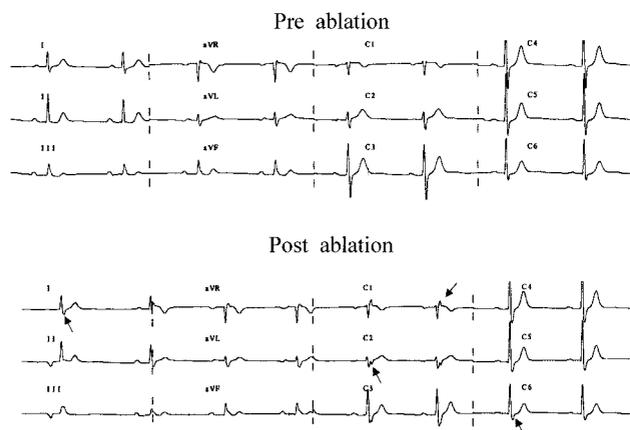


Figure 7. ECG before and after ablation showing a subtle change in QRS duration and morphology (arrows). In this patient, Brugada syndrome was excluded by pharmacologic testing.

procedure. In other patients, Holter recordings showed no or few (28 ± 49 to 0 to 145) isolated premature beats per 24 hours (without antiarrhythmic drug), with a longer coupling interval. During a follow-up of 24 ± 28 months, there was no sudden death, syncope, or recurrence of VF in 24 of 27 patients (89%), including all 3 without premature beats during mapping. No additional change in morphology or duration of the QRS complex was observed.

Discussion

This study demonstrates the feasibility of eliminating or decreasing the incidence of idiopathic VF by catheter ablation of the sources, dominantly originating from the specialized intraventricular conducting system.

Most patients were referred for VF recurring despite antiarrhythmic drugs and requiring multiple defibrillating shocks. During periods of arrhythmia, they had isolated or repetitive premature beats with a morphology identical or similar to that triggering VF, allowing mapping of their common origin. Two groups of arrhythmia origins could be distinguished. Four cases originated from the myocardium of the right ventricular outflow tract. The premature beats exhibited the classic morphology of left bundle-branch block inferior axis, which was persistent over long periods of time and had a longer coupling interval; similar malignant forms have been reported and ablated.⁹ In most, VF was initiated by different premature beat morphologies, which were mapped to various locations in the Purkinje system, indicated by specific potentials preceding local muscle activity. Both right and left Purkinje tissue was involved in 4 patients, including 3 with familial sudden cardiac death. These Purkinje beats were capricious in their occurrence, were usually of short coupling interval, and had characteristic morphologies similar to the patterns encountered in fascicular tachycardias from the left ventricle⁶ or with left axis from the right ventricle. In 3 patients, the 12-lead documentation of premature beat morphologies during a period of arrhythmia storm, even if months earlier, allowed localization in sinus rhythm based on initial pace mapping followed by RF delivery at sites exhib-

iting local Purkinje potential. Ablation produced a minor modification of QRS complex in 5 patients.

Anatomically, the Purkinje system is a small fraction of the myocardial mass, consisting of specialized fibers insulated from the underlying ventricular myocardium until their peripheral arborization into muscle. It ramifies from a single branch in the anterior wall of the right ventricle, whereas in the left ventricle at least 2 fascicles are profusely interconnected over a wide area in the septum.^{7,8} Accordingly, there were relatively uniform electrocardiographic morphologies for right Purkinje sources, whereas left sources displayed more strikingly different morphologies, but with a short QRS duration. The close coupling of premature beats to the previous sinus beat (falling within the “vulnerable phase” of ventricular activation) has been remarked on since the early publications illustrating spontaneous initiation of idiopathic VF or its different eponyms^{10–25}; narrow ventricular beats initiating VF can also be recognized in published figures.^{2,17,20,24} In our patients, we could not determine how much of the complex Purkinje network was involved in each patient, and the issue of multiple foci versus differing activation routes from limited foci remains unresolved in the absence of appropriate mapping coverage. Lastly, because of our selection criteria, the true prevalence of VF arising from the Purkinje system cannot be determined but may be significant even in the presence of structural heart disease or an abnormal ECG (long-QT or Brugada syndromes).

Diseases of the His Purkinje system are the main causes of bradycardia and are usually associated with characteristic ECG markers in contrast to the normal ECGs in the present study population. Histologic abnormalities of the conduction system have been discovered in victims of sudden death either with structural heart disease or as the sole finding.^{26,27} Defects in ionic channels may be involved, particularly in patients with familial sudden death. Although SCN5A and HERG locus abnormalities were not found in our patients, other ion channel gene mutations particularly concerning calcium transport may be involved, this being supported by the efficacy of intravenous verapamil. In vitro studies have extensively shown that the Purkinje system may generate or maintain arrhythmias by automaticity, reentry, or triggered activity during multiple conditions: electrolyte imbalance, catecholamines, or other drug exposure and myocardial ischemia, during which Purkinje fibers can survive within necrotic muscle.^{28–32} Closely coupled extrasystoles and even VF-like disorganized rhythms can experimentally result from reentry involving both antidromic (muscle to Purkinje) and orthodromic activation²⁸ or scroll waves at the Purkinje-muscle junctions.^{30,31} A colony of German shepherds has genetic predisposition to sudden death induced by triggered activity from the Purkinje system.³²

The role of the Purkinje system, rather than working myocardium in initiating or maintaining VF, may be relevant to the development of selective drug therapy and may explain why patients with idiopathic VF rarely develop structural (myocardial) heart disease at follow-up.^{1,2} The effectiveness of ablation was confirmed by the device memory over several years, and, although the population study involves a selected subset of patients with idiopathic sudden cardiac death, the

same paradigm may be applicable to a broader range of patients, notably those having frequent VF estimated to 20% of patients with defibrillators,³³ provided the triggers can be localized, whatever their origin in Purkinje or muscle tissue. In patients with structural heart disease or Brugada syndrome, 2 studies showed that spontaneous initiation of VF was preceded in 67% of episodes by isolated premature beats that were identical to the triggering beat.^{34,35} Decreasing the incidence of VF with localized ablation may reduce defibrillation requirement and replacement and improve the patient's quality of life.

Appendix

The following is a list of the participating institutions and the number of patients who underwent mapping and ablation at each: Hopital Haut Lévêque, Bordeaux-Pessac, France (19); Women's Medical College, Tokyo, Japan (3); Yokohama Rosai Hospital, Kanagawa, Japan (2); Institute for Clinical Medicine, Prague, Czech Republic (1); Queen Elizabeth Hospital, Birmingham, UK (1); and Instituto de Cardiologia Laranjeiras, Rio de Janeiro, Brazil (1).

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