Polymorphic Ventricular Tachyarrhythmias in the Absence of Organic Heart Disease: Classification, Differential Diagnosis, and Implications for Therapy

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Different polymorphic ventricular tachyarrhythmias may cause syncope or cardiac arrest in patients with no heart disease: (1) Catecholamine-sensitive polymorphic ventricular tachycardia (VT) presents during childhood: the hallmark is the reproducible provocation of atrial and polymorphic ventricular arrhythmias during exercise, despite a normal QT. β-Blockers are the treatment of choice. (2) In the long QT syndromes (LQTS), malfunction of ion channels leads to prolonged ventricular repolarization, early afterdepolarizations, and triggered ventricular arrhythmias. Therapeutic options include: β-blockers, genotype-specific therapy, cardiac sympathetic denervation, and implantation of pacemakers or defibrillators. (3) The "short-coupled variant of torsade de pointes" is a malignant disease that shares several characteristics with idiopathic ventricular fibrillation. Although verapamil is frequently recommended, mortality rates remain high. (4) Idiopathic ventricular fibrillation (VF) with normal electrocardiogram (ECG) strikes young adults of both genders. In contrast to other polymorphic tachyarrhythmias, idiopathic VF is not generally related to stress. Also, familial involvement is rare. Therapeutic options include implantation of defibrillators and therapy with class 1A drugs. (5) The "Brugada syndrome" and the "syndrome of nocturnal sudden death" strike males almost exclusively. Right bundle branch block (RBBB) with ST elevation in the right precordial leads---the "Brugada sign"---is seen in the ECG of both patient populations. Implantation of defibrillators is recommended.

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Sustained ventricular arrhythmias generally occur in the setting of organic heart disease. When such arrhythmias arise in patients with no structural cardiac abnormalities, they are usually monomorphic.^{1,2} Although cardiac arrest may rarely occur, the idiopathic monomorphic ventricular tachycardias have, in general, a good prognosis with or without therapy.^{1,2}

Polymorphic ventricular tachycardia (VT) and ventricular fibrillation (VF) may also strike ostensibly healthy patients. Recent advances in our understanding of these more malignant polymorphic tachyarrhythmias prompt the present review.

Definitions

Polymorphic VT is a rapid VT with changing morphology of the QRS complexes. Torsade de pointes is a polymorphic VT that occurs in the setting of a long QT syndrome (LQTS). The definition of normal heart in the studies reviewed, is in conformity with the requirements considered "mandatory for ruling out organic heart disease."3 Accordingly, a "normal heart" is defined when all the following are normal: (1) clinical history (including the absence of arrhythmogenic drugs), (2) blood chemistry (except for high cardiac enzymes or brief hypokalemia ascribed to resuscitation), (3) electrocardiography and exercise testing (except for arrhythmias and specific abnormalities of the QRS, ST, and QT segments in special groups, see below), (4) echocardiography,

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and (5) cardiac catheterization with coronary angiography. The limitations of this definition of "apparently normal heart" should be noted (see "differential diagnosis" below).

Classification of Polymorphic Ventricular Tachyarrhythmias

A common characteristic of these arrhythmias is the clinical presentation with syncope and the high incidence of sudden death. Young patients with no evident heart disease are often misdiagnosed as "epileptics" when these rapid polymorphic tachyarrhythmias provoke seizures.

Inconsistent terminology has led to confusion. We propose the following classification based on clinical and electrocardiographic characteristics (Table 1).4-11

Polymorphic VT

Catecholamine-Dependent Polymorphic VT

The hallmark of this disease^{8,12} is the reproducible occurrence of polymorphic VT during stress, without QT prolongation (Fig 1). Catecholaminergic polymorphic VT mainly affects children. In the largest series,⁸ the age at the onset of symptoms (syncope or cardiac arrest during stress) was 8 ± 4 years. Infants,¹³ as well as adults,^{14,15} have been reported as affected. Familial involvement is common,8 and autosomal dominant inheritance has been suggested.14 The resting electrocardiogram (ECG; including the QT interval) is normal, but sinus bradycardia is common.^{8,13} During exercise, a reproducible sequence of events occurs (Fig 1): as the sinus rate increases, atrial

	Patient Characteristics			Arrhythmia		
Patient Group (First Series	a) b)	Age Gender	Baseline	Stress-		
Reported)	c)	Familial Hx	ECG	related	Mode of Onset	Therapy
I. Polymorphic VT						
Congenital LQTS (Jervell- Lange Nielsen ⁴ and Romano-Ward ^{5,6})	a) b) c)	21 ± 15 years† Female > male‡ Common	Long QT Abnormal TU morphology	Often§	Pause-dependent Long CI	β-blockers Pacemaker ICD, other¶
Catecholaminergic poly- morphic VT (Leenhardt ⁸)	a) b) c)	8 ± 4 years M/F = 1.3/1 Common	Normal Sinus bradycardia	Always	Typical (see text)	β-blockers
Short-coupled variant of torsade de pointes (Leenhardt ⁷)	a) b) c)	35 ± 10 years M/F = 1/1 Common	Normal	Rarely	Not pause-dependent Short Cl	ICD
II. Ventricular Fibrillation	- /					
Idiopathic VF with normal ECG (Belhassen ⁹)	a) b) c)	36 ± 16 years M/F ≈ 1.4/1 No	Normal	No	Not pause-dependent Short Cl	ICD Class 1A
Idiopathic VF with RBBB and ST↑ (Brugada ¹⁰)	a) b) c)	46 ± 7 years M/F > 10/1 Common	RBBB + ST↑	Rarely	Not pause-dependent Short Cl	ICD
Sleep-death syndrome (Aponte ¹¹)	a) b) c)	35 ± 10 years M/F = 10/1 Rare	RBBB + ST↑	Sleep	Not pause-dependent Short Cl	ICD

TABLE 1. Polymorphic Ventricular Arrhythmias in the Absence of Organic Heart Disease. Classification Based on Clinical and Electrocardiographic Characteristics*

NOTE. Therapy is recommended therapy based on limited data. Age is age at the onset of symptoms (mean ± standard deviation). Gender, M/F = male to female ratio. Familial Hx is familial history of syncope or sudden death. Abbreviations: CI, coupling interval of the extrasystole precipitating the tachyarrhythmia; RBBB + ST↑, RBBB with persistent ST segment elevation in the right precordial leads. *Some overlapping exists between several entities (see text). †Age at onset of symptoms in the International Long QT Registry (reports of infants abound in the literature). ‡For explanations of the female predominance in this disease with autosomal inheritance, see text. \$The incidence of stress-related arrhythmias varies according to the genotype.

Torsade de pointes that is not pause-dependent occurs in infants and patients with severe forms of LQTS.

For genotype-specific therapy, see Table 2. The "short-coupled variant of torsade de pointes"7,12 and idiopathic ventricular fibrillation⁹ may represent the same disease (see text).



Fig 1. Idiopathic catecholaminergic polymorphic ventricular tachycardia provoked by exercise. This 14-year-old girl had multiple events of stress-related syncope and developed ventricular fibrillation during isoproterenol infusion when tilt-table evaluation was performed somewhere else. Baseline ECG (left margin) is normal. Resting heart rate = 48 beats/min, QT = 0.38 s, QTc = 0.36 s. With increasing levels of exercise, the following events result: (A) atrial fibrillation begins, (B) multiple premature ventricular complexes arise, and (C,D) runs of polymorphic ventricular tachycardia appear. The patient has been asymptomatic for 4 years on 400 mg/d of metoprolol.

arrhythmias and ventricular extrasystoles appear. If the effort continues, salvos of monomorphic or bidirectional VT eventually lead to bursts of polymorphic VT. In contrast to this reproducible provocation with exercise, catecholaminergic polymorphic VT is not inducible with programmed ventricular stimulation (premature ventricular stimulation).⁸

B-Blockers are the treatment of choice. The maximal dosages that are well tolerated should be prescribed and Holter recordings and exercise tests should be repeated periodically to assure that the degree of sinus tachycardia that precedes the onset of arrhythmias is never reached. Still, 2 of 20 patients (10%) reported in the largest series8 (as well as 1 of 4 patients in a smaller series)¹⁵ died suddenly in spite of β -blocker therapy. Thus, additional modes of therapy should be considered. However, limited data suggest that class 1 drugs and amiodarone are ineffective.8 Finally, the benefits of an implantable cardioverter defibrillator (ICD) should be weighted against the potential proarrhythmic effects of such devices in these patients; stress caused by appropriate or inappropriate shocks could prove to be disastrous for patients with catecholamine-sensitive arrhythmias.

The Long QT Syndromes

In the LOTS, malfunction of ion channels leads to prolonged ventricular repolarization, early afterdepolarizations (EAD), and triggered ventricular arrhythmias.¹⁶⁻²⁰ The malfunction of ion channels may be the result of gene mutations (congenital LQTS, Table 2) or may be caused by drugs or metabolic abnormalities^{16-19,21-28} (acquired LQTS, Table 3). The abnormal repolarization (depicted in the ECG as a prolonged QT interval with odd morphology) begets malfunction of adjunct ion channels, further promoting inward currents during the late phases of repolarization. The resulting surplus of intracellular positive ions causes EADs (represented in the ECG as characteristically tall U waves), which may be of enough amplitude to depolarize the cell membrane and trigger ventricular arrhythmias. Some regions of the heart, specifically the midmyocardium, are more prone to

TABLE 2. Congenital Long QT Syndromes*					
Genotype	(Chromosome) (Gene) Ion-Channel Affected*	Basis of Prolonged Repolarization	Genotype-Specific Therapy		
LQT1	[11] (KVLQT1) Potassium channel I _{ks}	Reduced potassium outward currents	?		
LQT2	[7]: (HERG) Potassium channel I _{kr}	Reduced potassium outward currents	Spironolactone Potassium supplements Beta-blockers ^{79,80}		
LQT3	 [3]: (SCN5A) Sodium channel SCN5A (intermittent reopening) 	Sustained sodium inward current	Sodium channel blockers (mexiletine) ^{81,82}		
LQT4	[4] ?	?			
LQT5	 [21] (KCNE1)²⁶ IsK, a potassium channel subunit that regulates KVLQT1 and HERG 	Reduced potassium outward currents			

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Abbreviations: 1kr, rapid component of the delayed rectifier potassium current; 1ks, slow component of the delayed rectifier potassium current. *Detailed reviews of the molecular biology of the congenital LQTS^{16-18,20} have been published.

display prolongation of repolarization and EADs.²⁹ The resultant heterogeneity of repolarization facilitates the onset of the characteristic arrhythmia, torsade de pointes.^{29,30} Torsade is characterized by QRS complexes of changing amplitude and contour. However, these changes in contour may not be appreciable when only short bursts are recorded or when only single lead recordings are available.19 The baseline LQT interval and the mode of onset of the arrhythmia (see below) aid in establishing the diagnosis of torsade de pointes.

TABLE 3.	Acquired	Long QT	Syndromes ³
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Etiology*	Basis of Prolonged Repolarization
Antiarrhythmic drugs (class 1A and class III)	Blockade of Ikr and other potassium outward cur- rents ^{18,21-23}
Antibiotics (erythromycin, amantadine, pentami- dine, ketoconazole, and others)	Inhibition of I _{kr} potassium outward currents ²⁴
Histamine ₁ receptor antagonists (astemizole, terfenadine)	Inhibition of I _{kr} potassium outward currents ²⁵
Cholinergic agonists (cisapride, organophos- pates) Psychiatric: antidepressants (tricyclic, tetracyclic), phenothiazines, haloperidol	Inhibition of I _{kr} potassium outward currents ²⁷
Metabolic abnormalities (hypokalemia, hypomag- nesemia) Bradyarrhythmias	Inhibition of I _{kr} potassium outward currents ²³ and other mechanisms ¹⁸ Several mechanisms ¹⁸

*Reviews of the acquired LQTS^{19,28} have been published

Classifications of the LQTS refer to the congenital LQTS as "adrenergic dependent," whereas the acquired LQTS is equated with "pause dependent" torsade de pointes.^{18,19,29} The rationale behind this grouping relates to (1) the association between "adrenergic" (stressful) states and arrhythmia precipitation in the congenital LQTS³¹ and (2) the mode of onset of torsade de pointes, which is invariably preceded by a relatively long cycle, ie, a pause, in the acquired LQTS.32,33 However, the terms "adrenergic" and "pause dependent" are not mutually exclusive.^{17,18,34} In fact, a majority of spontaneous torsade episodes, documented in adults with congenital LQTS, are actually pause-dependent (Fig 2).34-36

The age at diagnosis in the International Registry was 21 ± 15 years,³⁷ but reports of symptomatic LQTS in newborns and children abound in the literature.³⁸⁻⁴² In the Registry,³⁷ the majority of syncopal episodes occurred in association with emotional stress or vigorous physical activity. Arrhythmias that occur during swimming or after arousal by an alarm clock or the telephone ringing are more rare, but still characteristic. More recent data suggest that in some genotypes (LQT3), the majority of arrhythmias are not stress related,43 and in some families, arrhythmias occur only during sleep.^{17,44} In general, symptoms seem to be more common in females.³⁷ Explanations for this gender variability, which is unexpected for an autosomal genetic disorder, include⁴⁵: (1) the presence of modifier genes, causing more frequent symptoms in females, or alternatively,



Fig 2. Pause-dependent torsade de pointes in a 31-year-old woman with congenital long QT syndrome previously reported.³⁴ The arrhythmia occurred in the absence of drugs. R-R intervals are shown in ms. Top panel: Progressive increment in R-R interval caused by sinus arrhythmia. The eighth sinus complex follows a relatively long R-R interval (885 ms) and shows TU wave changes (arrowhead) from which the first premature ventricular complex originates (*). This extrasystole begins a series of "short-long" sequences perpetuated in the form of ventricular bigeminy (second panel), eventually escalating and leading to torsade de pointes.

premature mortality in males; and (2) overdiagnosis of LQTS in females (or underdiagnosis in males) because the clinical diagnosis is based on the QT interval, which is longer in females.⁴⁵

The diagnosis of a congenital LQTS may be confirmed with molecular biology. However, only a few specialized centers screen for all identified mutations.⁴⁶ Thus, the diagnosis remains largely a clinical one.⁴⁷ In a patient with a rate-corrected QT > 0.46 seconds and documented torsade de pointes, the diagnosis is straightforward. In that case, exclusion of secondary forms (Table 3) leads to a clinical diagnosis of congenital LQTS. Of note, before a diagnosis of "acquired" is given to a patient with drug-induced torsade, the possibility that the drug merely unmasked a congenital

LQTS^{48,49} should be excluded by close follow-up. More challenging, however, is the patient with syncope who has no arrhythmia documentation, a negative family history, and a QT in the upper normal range. In such a case, the following may aid in establishing a diagnosis of LQTS: (1) there is day-to-day variability in the QT interval, and repeated ECGs may eventually reveal a frankly abnormal trace⁵⁰; (2) attention should be focused not only on the length, but also on the morphology of the TU segment: the presence of "biphasic T waves" or "T waves humps" in the left precordial or limb leads, is a relatively specific sign of the LQTS (particularly in patients older than 15 years of age with no hypertension or heart disease)^{51,52}; (3) because the LQTS generally has

autosomal dominant inheritance, review of ECGs of family members may reveal abnormal traces; and (4) although the odds for detecting torsade de pointes during a Holter recording are small, ambulatory electrocardiographic recordings may unmask TU wave alternans or characteristic postextrasystolic TU changes.

The diagnostic yield of exercise-testing for patients with borderline QT is less clear. This is because studies emphasizing the difference in the response of QT interval to exercise or valsalva (between patients with LQTS and healthy controls)53-55 included patients who had frankly prolonged QT interval even at rest. Also, the QT response to exercise is not the same in all genotypes.⁵⁶ Finally, exercise stress testing is of low yield for arrhythmia provocation. Similarly, torsade is rarely provoked with premature ventricular stimulation.57 Therefore, the reason for performing electrophysiologic studies (EPS) in a patient with suspected LQTS is primarily to exclude other causes of arrhythmias and to record EADs with the use of special catheters.58-60 Some authors inject adrenaline or isoproterenol for arrhythmia provocation,60 but the diagnostic accuracy of this intervention is less clear.

Long-term randomized studies of the therapeutic modalities for the LQTS have not been performed and are not being conducted. It is important to remember that all the recommendations for therapy in the congenital LQTS are based essentially on observational, uncontrolled studies.

β-Blockers. More than 20 years ago, Schwartz observed that patients treated with β-blockers (or cardiac sympathetic denervation) had lower mortality (6%) than those treated otherwise or patients left untreated (>60% mortality).³¹ β-blocker therapy is associated with a 0.41 relative risk for syncope or cardiac arrest (95% confidence interval = 0.21 to 0.81)⁶¹ and remains the mainstay of therapy of the congenital LQTS. However, even a 6% long-term risk for arrhythmia recurrence (with β-blockers) is unacceptable for this otherwise healthy and young patient population. Therefore, additional therapy is often recommended for those considered to be at high risk.

Left cardiac sympathetic denervation (LCSD). The rationale for recommending surgical sympathetic denervation of the heart (performed as left stellectomy, left cervicothoracic sympathectomy,

high thoracic left sympathectomy, or posterior left thoracic sympathectomy) is based on the "sympathetic imbalance" hypothesis.³¹ This hypothesis states that cardiac efferent sympathetic activity--higher in the left side-causes or aggravates the LQTS. Demonstration that the LQTS is caused by mutations in genes that encode cardiac ion channels, has called this theory into question. Nevertheless, long-term, albeit uncontrolled studies, suggest that LCSD reduces the risk for arrhythmias in patients refractory to B-blocker therapy.^{31,62-64} It is plausible that rather than correcting a left versus right "sympathetic imbalance," this procedure prevents arrhythmias by maximizing the degree of β-blockade or by blocking α-adrenergic pathways as well.⁶⁴ Thus, LCSD might be particularly beneficial for patients unwilling or unable to take adequate dosages of β-blockers. It should be emphasized, however, that patients refractory to β-blockers have a 6-year sudden death rate of 8% even after sympathetic denervation.64

Cardiac pacing. Cardiac pacing was initially recommended for patients with LQT and concomitant bradyarrhythmias.42,65 Subsequently, Eldar and others showed that pacing is also beneficial for patients without bradycardia.63,66-69 The inverse relation between the heart rate and the duration of repolarization dictates that pacing at faster rates results in a shorter QT interval. In the International LQT Registry, 6 patients who had recurrent symptoms despite pacing had a programmed lower rate limit of \leq 74 beats/min.⁶⁹ Accordingly, Moss et al recommend pacing at 70 to 80 beats/min.69 Based on the cycle length preceding spontaneous arrhythmias, we recommend a lower rate limit of 80 beats/min for adults.³⁴ This pacing rate will result in a high percentage of paced beats. Therefore, single chamber ventricular pacing would not be satisfactory, and the main options are single chamber atrial pacing or dual chamber pacing. Atrial pacing, which involves implantation of less hardware, may be adequate for most patients. However, a few patients (particularly small children with very prolonged QT interval) may develop functional atrioventricular block, as a result of the prolonged ventricular repolarization, immediately before the onset of torsade.39,41,70 In such cases, single chamber atrial pacing will be valueless at the time when it is most needed. Therefore, dual chamber pacemakers are often used. Of note, when the use of pause-prevention pacing algorithms is contemplated (see below), dual chamber pacing rather than atrial pacing is mandatory. In such a case, programming a long AV delay (longer than the patient's native PR interval during β -blocker therapy) will inhibit ventricular pacing most of the time. This will result in considerable savings in battery expenditure. For example, calculations made for a typical dual chamber pacemaker with a 2.7-V battery, programmed to pace at 80 beats/min with a 3.5-V output and 0.5-ms pulse-width and assuming a 500- Ω resistance in the atrium and the ventricle. suggest the following: (1) constant pacing in both cardiac chambers will result in battery depletion by the end of 5.9 years; and (2) in contrast, programming a sufficiently long AV delay that will allow constant pacing in the atrium, but essentially sensing-only in the ventricle, will result in a 7.5-year longevity (Albert Maarse, MSc, Guidant/Cardiac Pacemakers Inc, personal communication, February 1998). This 27% increment in pacemaker longevity is an important consideration for young patients who will need several device replacements over the years.

We believe that the main role of pacing in the LOTS is to prevent the sudden pauses that facilitate the onset of torsade de pointes.34 In particular, prevention of postextrasystolic pauses is imperative to interrupt the escalating "short-long sequence" that culminates in torsade.³⁴ More rapid pacing will shorten postextrasystolic pauses, potentially reducing the risk of torsade. However, pacing at fast rates for many years may lead to a tachycardia-induced cardiomyopathy.⁷¹ Certainly, the pacing rates that prevent drug-induced pausedependent torsade (100 to 140 beats/min)⁷² are too fast to be practical for long-term management. Dilated cardiomyopathy has already been ascribed to 12 years of pacing at 110 beats/min in a child with LQTS.73 A potential alternative method for preventing pause-induced torsade involves the use of specific pause-prevention pacing algorithms (Fig 3), but experience with this approach is very limited.74,75

Implantable defibrillators. Reliance on ICDs to treat the LQTS is becoming more frequent.⁷⁶ Defibrillators are the treatment of choice when symptoms recur in spite of combined therapy. Also, many would recommend ICD implantation

for all cardiac arrest survivors. Finally, some will argue in favor of ICDs for all patients with symptomatic LQTS.⁷⁶ In fact, analysis of implantation patterns shows that in 17% of cases, the devices are being used as "first line" of therapy.⁷⁶

A preliminary report on the risk of recurrent arrhythmias in 5 of 35 (14%) high-risk patients treated with β -blockers and cardiac pacing,⁷⁷ is likely to increase the number of defibrillator implantations. It is important to remember, however, that unique characteristics of the LQTS could lead to more frequent device-related complications in this patient population. The young age of these patients will inevitably translate into more hardware-related complications in the long term (see below). Also, torsade de pointes tends to recur upon termination, and the stress and sudden pauses produced by ICD shocks may aggravate this tendency for arrhythmia recurrence. Indeed, a patient with LOTS who received 62 appropriate shocks within a short period has been described.⁷⁸ Even during β-blocker therapy, "multiple shocks" occurred in 6% of patients with LQT.⁷⁶ Programming fast (≥100 beats/min) "postshock pacing rates" may help to prevent this complication.

It is premature to extrapolate to the LQTS the excellent results achieved with ICDs in patients with organic heart disease. Nevertheless, in a small series of LQT patients with ICDs, sudden death has not occurred.⁷⁶ The availability of defibrillators with dual chamber pacing capabilities and pause-preventing pacing algorithms⁷⁵ is a very important addition to our therapeutic options.

Genotype-specific therapy. Recent studies⁷⁹⁻⁸² advocate genotype-specific therapy (Table 2). It should be emphasized that these encouraging data are based on a small number of patients with short-term follow-up.

Short-Coupled Variant of Torsade de Pointes

Terms like "short-coupled variant of torsade de pointes"^{7,12} or "inducible torsade with normal QT"⁸³ have been used to describe rapid nonsustained tachycardia—of "twisting of the points" morphology—in patients with strictly normal QT. Genotyping of families with LQTS has shown overlapping in the duration of the QT interval between patients affected with a long QT gene



Fig 3. Use of a pause-preventing pacing algorithm (rate smoothing) to prevent postextrasystolic pauses in a 14-year-old girl with pause-dependent torsade de pointes.74 (A) Sinus rate 76 beats/min; a premature complex is followed by a postextrasystolic pause. The ensuing sinus complex has marked post-pause U wave changes (arrow). Ventricular bigeminy (long-short sequence) supervenes. (B) Dual-chamber pacing (C.P.I. Vigor 1230, Guidant/ Cardiac Pacemakers Inc, St Paul, MN). There is atrial capture with atrioventricular conduction. Rate smoothing is off. Spontaneous extrasystoles reset the pacemaker and cause short-long sequences (perpetuated as ventricular bigeminy). Note the marked postextrasystolic TU changes after each long interval (small arrows). (C) Ratesmoothing down is programmed to 18%. This dictates that successive R-R intervals cannot increase by more than 18%. After 3 sinus complexes there is a spontaneous extrasystole. Because of rate smoothing, pacing occurs at a rate faster than the programmed lower rate: the first paced cycle is 18% longer than the coupling interval of the extrasystole. The next three complexes show atrial pacing with normal atrioventricular conduction. Each paced cycle is 18% longer than the previous one. Note the absence of pauses and the absence of TU changes. (D) An extrasystole occurs during dual chamber pacing at 60 beats/min. As a result of rate smoothing, two relatively fast paced beats ensue and the rate decreases by 18% each cycle. (E) Pacing at 80 beats/min and rate-smoothing down of 15%. An extrasystole is followed by more rapid pacing (each paced cycle increases by 15%). SR, sinus rate; LRL, programmed lower rate limit (beats/min); AV AV delay (ms); RSD, rate-smoothing-down (expressed as "percentage of the previous R-R interval"). (Reprinted with permission.74)

and unaffected relatives.⁸⁴ Thus, it could be argued that patients with these variant forms of torsade are affected by a LQTS. However, several observations suggest that this is not the case: the extrasystoles initiating torsade in the LQTS have long coupling intervals ($586 \pm 89 \text{ ms}$)³⁴ and appear to originate from the U wave or the terminal aspect of a bizarre QTU complex. However, the extrasystoles initiating the polymorphic VT in the torsade variants have a short coupling interval ($245 \pm 28 \text{ ms}$) and rise from the peak of the T wave.⁷ Also, the "long-short" sequence that often precedes the onset of torsade in the LQTS^{17,18,34} is absent in the torsade variants.⁷

Overlapping exists between the short-coupled variant of torsade^{7,12,83} and idiopathic VF^{2,9,85} (see below): (1) both conditions affect young adults of both genders (age, 36 ± 16 years)^{7,85}; (2) the morphology and the very short coupling interval of the extrasystoles initiating nonsustained polymorphic VT in the torsade variants^{7,12,83} are strikingly similar to those that precipitate sustained arrhythmias in idiopathic VF⁸⁶; and (3) patients with short-coupled torsade have a high

incidence of sudden death (presumably caused by VF),⁷ whereas episodes of nonsustained polymorphic VT are observed in idiopathic VE^{85,86} However, a positive family history is relatively common in the short-coupled torsade,^{7,83} and absent in idiopathic VF with normal ECG.^{2,85}

The short coupled variant of torsade is a malignant disease. In one series, 7 of 14 patients had recurrent arrhythmias within 5 years.⁷ Although verapamil is often recommended,⁷ the recurrence rate during verapamil therapy is high: in the series by Leenhardt, 27% of patients (3 of 11) treated with verapamil died suddenly or had appropriate ICD-shocks, despite verapamil therapy.⁷ In the same series, 2 patients received β -blockers and both died.⁷ In view of the similarities between the short-coupled variant of torsade and idiopathic VF, it is of interest to see if the beneficial effects of class 1A drugs on idiopathic VF (see below) can be reproduced in the torsade variants.

VF

Idiopathic VF With Normal Electrocardiogram

In 1987, Belhassen et al reported the first series of idiopathic VE⁹ Increasing awareness of this condition has led to widespread recognition. More than 160 patients have been enrolled in the Unexplained Cardiac Arrest Registry in Europe³ and a similar registry has been started in the United States. Idiopathic VF represents about 1% of cases of out-of-hospital VF, but up to 14% of VF events in patients younger than 40 years of age.^{85,87} Both genders are affected.^{2,85,88,89} Our youngest and oldest patients are 14 and 69 years old, respectively, but the majority were 25 to 55 years old at the time of diagnosis. Similar demographics have been reported by others.^{87,88,90-93}

Sudden death, with VF documented during resuscitation, is commonly the first manifestation.^{2,85} In contrast to other polymorphic arrhythmias, idiopathic VF is generally not precipitated by stress.^{85,93} One third of cases have a history of syncope, which is caused by bursts of polymorphic VT or VF that terminate spontaneously.^{85,93} In fact, many of our patients survived because cardiac arrest occurred in the emergency room, shortly after presentation for evaluation of syncope. Nevertheless, we and others have reported patients with syncopal seizures spanning over several years.^{92,94,95} Noteworthy are the "arrhythmic storms," with numerous episodes of VF clustered in the first 24 hours of hospitalization, seen in 25% of cases.^{85,92}

Idiopathic VF has a distinctive mode of onset^{85,86} (Fig 4). In all but one of our cases,⁸⁶ and in almost all published reports,89,90,93,96-101 a single extrasystole, with a very short coupling interval, initiated a rapid polymorphic VT that immediately deteriorated to VF.86 Pause-dependent polymorphic arrhythmias have exceptionally been observed.^{15,96} Also, we^{2,9} and other groups^{92,100} have reported high inducibility rates during EPS, with induction of VF in up to 78% of patients. Lower (33% to 50%) inducibility rates have been reported by others.87,88,90,93 These differences are probably related to the patient populations studied: some90 included patients with catecholaminesensitive polymorphic or idiopathic monomorphic VT (arrhythmias that are generally not inducible with programmed stimulation), beside patients with truly idiopathic VF. As discussed elsewhere,⁸⁶ differences in the protocols used are also responsible for the different inducibility rates.

The etiology of the extrasystoles with ultrashort coupling interval (Fig 4) and the mechanisms by which they trigger VF remain speculative. Studies in animals¹⁰² and humans¹⁰³ have shown a "vulnerable period" in the cardiac cycle during which a single stimulus (of appropriate strength) can reproducibly induce VF. The most vulnerable phase coincides with the upslope of the T wave, but the peak and the early phases of the T-wave downslope are also within this vulnerable phase. Some investigators have recorded fractionated endocardial potentials in patients with idiopathic VE¹⁰⁴ Nevertheless, extrapolation of the data on the "vulnerable period" suggests that spontaneous extrasystoles with very short coupling intervals may prompt VF even in the absence of cardiac pathology.

Two therapeutic options exist for idiopathic VF: (1) ICDs (the option favored by most investigators), and (2) EPS-guided therapy with class 1A drugs (the option favored by our group). EPSguided therapy is defined as a drug regimen that renders a patient, who had inducible VF in the baseline study, no longer inducible. Accordingly,



Fig 4. Idiopathic ventricular fibrillation. A 50-year-old woman referred for neurological evaluation after 10 episodes of syncope during the preceding week. (A) Baseline ECG is normal, except for the presence of multiple premature ventricular complexes with different coupling intervals. Some of these extrasystoles have a very short coupling interval and seem to arise from the peak of the T wave (arrowhead), whereas others ensue in the descending limb of the T wave (arrow). (B) Soon after hospitalization, a presyncopal episode caused by polymorphic ventricular tachycardia is documented. The tachycardia terminates spontaneously, the ensuing sinus rhythm demonstrates noise caused by presyncopal patient movements. (C) Within minutes, an episode of ventricular fibrillation requiring defibrillation occurred. All the arrhythmias started with a premature ventricular complex with very short coupling interval. No further arrhythmias occurred once therapy with quinidine was initiated.

patients with no inducible arrhythmias before the initiation of drugs are not candidates for this approach.

The rationale for selecting ICDs as first line of therapy is evident: because of the absence of organic heart disease, the risk of nonsudden cardiac death is nil. Thus, the mortality risk is entirely dependent on the risk of arrhythmia recurrence, which is high.85 Patients with idiopathic VF and implanted defibrillators have a 23% to 57% incidence of "appropriate shocks" (representing potentially lethal arrhythmias), but no overall mortality during 1 to 3.6 years of follow-up.88,90,91 However, ICDs are not problemfree. Because of their young age, patients with idiopathic VF will require repeated device replacements over the years. The risk for some complications, like infection, increases after device replacements. Therefore, the 2% infection rate reported in prospective ICD trials with only 3 years of follow-up¹⁰⁵ will lead to underestimation of the hazards faced by patients with idiopathic VF. Similarly, lead malfunction (potentially leading to oversensing and inappropriate shocks)¹⁰⁶ may be discovered only after long-term use; 5 years after implantation, such complications may be detected in 7% of systems.¹⁰⁷

Reports on the effectiveness of class 1A drugs in idiopathic VF have appeared in the literature for almost 70 years.94 An example is the patient reported by Moe in 1949¹⁰¹: following multiple syncopal attacks and VF, this 38-year-old man was treated with quinidine for 43 years until he died of noncardiac illness at the age of 81.108 Our experience with class 1A drugs for idiopathic VF dates back 18 years. By the time implantable defibrillators became readily available, our favorable experience led us to continue recommending EPS-guided therapy with class 1A drugs. This experience can now be summarized as follows: of 33 patients with idiopathic VF, 26 (79%) had inducible VF in the baseline study. All these patients had repeated evaluation after therapy with class 1A drugs and 25 (96%) of them were no longer inducible. Twenty-three of these patients received long-term therapy with class 1A drugs and all these patients are alive and have remained free of sustained arrhythmias, including 15 patients with more than 5 years of follow-up. These results contrast with the inefficacy of other drugs: recurrence may occur with class 1C drugs, 87,90,93,109 β -blockers, 87,91,93 verapamil, 93 and amiodarone. 88,91,109

In spite of our favorable experience with class 1A drugs,^{2,9,85} most physicians have been reluctant to rely on drug therapy. Only 9% of the European Unexplained Cardiac Arrest Registry patients received class 1 drugs.110 This evident lack of confidence in class 1A drugs probably reflects the documented inefficacy of EPS-guided therapy in cardiac arrest patients with organic heart disease.111,112 Also, two reports of drug failure in idiopathic VF^{88,90} are frequently quoted. Thus, it is important to analyze these reports: (1) Wever⁹⁰ reported recurrent VF in 1 of 4 patients treated with quinidine; however, this fatality occurred in a patient who never underwent repeated EPS to test for quinidine efficacy; and (2) Meissner⁸⁸ reported that 46% of patients with idiopathic VF and ICDs received shocks, despite drug therapy in the majority. However, only one of these patients received class 1A drugs, and only temporarily.88

ICDs are the therapy of choice for idiopathic VF: (1) when arrhythmias are not inducible in the baseline studies, (2) when arrhythmias remain inducible despite class 1A drugs, and (3) when patients are not compliant with drug therapy. Patients who have inducible VF on presentation should be informed of the options of defibrillator implantation (an option with negligible mortality risk but small long-term morbidity) or EPSguided therapy with class 1A drugs (an option with probable small risk for arrhythmic death according to limited data). It should be emphasized that because of the limited number of patients with long-term follow-up in our series, only limited estimations of the arrhythmic risk can be offered. In other words, because only 19 patients have been treated for at least 3 years, and only 15 patients have been treated for at least 5 years, the estimated 95% confidence limits for the 3-year and 5-year arrhythmic risk are 0% to 13% and 0% to 20%, respectively.

Idiopathic VF With Right Bundle Branch Block and ST-Segment Elevation. The Brugada Syndrome

Since the description by Brugada in 1992,¹⁰ nearly 100 patients with idiopathic VF who have a peculiar pattern in their resting ECG have been reported.97,113-117 The electrocardiographic pattern (referred to as the "Brugada sign") (Fig 5) has been described as "right bundle branch block (RBBB) with ST elevation in V1-V3."10,115,116,118,119 Gussak¹²⁰ prefers the term "J-waves" to depict the same phenomenon. Experimental studies suggest that the basis for these J waves is a prominent notch--related to the spike-and-dome morphology-in the action potential of epicardial cells.¹²¹ This notch is secondary to transient outward currents, which are more prominent in the right ventricular epicardial areas. Accordingly, the prominent J waves of the Brugada syndrome could reflect variance in the duration of the spike-and-dome components of the action potential in different cardiac regions, possibly identifying patients prone to reentrant arrhythmias.¹²¹ The accentuation of J waves, observed in the Brugada syndrome after infusion of adrenergicblockers or class 1A drugs115,117 (two interventions that augment the action potential dome), is consistent with this explanation.¹²¹

Data on the prevalence of the Brugada sign in the healthy population suggest that the Brugada sign is a specific marker of arrhythmic risk. In their original description of the Brugada sign,¹⁰ none of the patients in a control group (consisting of 38 patients with RBBB but no arrhythmias) had the peculiar ST elevation.¹⁰ More recently, "an obvious Brugada sign" was found in 12% of consecutive patients with idiopathic VF, but in none of 600 healthy adults (P < 0.005, estimated 95% confidence limit for the incidence of the Brugada sign in the healthy adult population $\leq 0.5\%$ [S. Viskin, unpublished data]). Moreover, Brugada reported that malignant arrhythmias eventually occur in 27% of initially asymptomatic patients who have the Brugada sign.¹¹⁴ In contrast, in a Japanese study, all 34 asymptomatic patients with a Brugada sign remained free of cardiac events.¹¹⁶ It should be noted, however, that the follow-up in this study was only 1.2 \pm 0.2 years.

It is not clear if the Brugada syndrome and idiopathic VF with normal electrocardiogram represent different disorders or the same disease. The average age (at the time of VF) of patients with and without the Brugada sign is similar (46 ± 7 years).¹¹⁶ Also, both patient groups have a high inducibility rate with programmed ventricular



Fig 5. A 22-year-old male reported after an episode of aborted sudden death.¹¹³ (A) RBBB pattern and ST segment elevation in the right precordial leads (typical of the Brugada syndrome) are obvious. (B) Over the years, the degree of ST segment elevation varied, but the typical pattern persisted. (C) Stored endocardial electrogram retrieved from his implanted defibrillator (C.P.I., Ventak P2, 1625, Guidant/Cardiac Pacemakers Inc) during a spontaneous episode of ventricular fibrillation, which occurred 2 years after implantation in the absence of drug therapy.

stimulation: 81% of patients in the series by Brugada¹²² and 78% of our patients with normal ECG have inducible VF. Moreover, unmasking of a Brugada sign in some patients with otherwise idiopathic VF may occur during long-term follow-up or following intravenous administration of drugs.^{115,117,122} On the other hand, the Brugada syndrome affects primarily males: 89% of the patients with Brugada syndrome gathered by Brugada¹¹⁴ and all the 21 patients reported by Atarashi¹¹⁶ and our group are males. For comparison, the male to female ratio among our patients with idiopathic VF and normal ECG is 18 to 13 (P < 0.001). The male predominance of the Brugada syndrome is of interest in view of recent data¹²³ linking the Brugada sign with the "syndrome of nocturnal sudden death in Southeast Asians," another form of idiopathic VF, which almost exclusively affects males (see below). Finally, familial involvement is common in the Brugada syndrome117,118,122 and absent in idiopathic VF with normal ECG.85 Indeed, genetic studies recently performed in 6 families with the Brugada syndrome showed different mutations involving sodium channels in 3 families.¹²⁴

The main differential diagnosis of the Brugada syndrome is arrhythmogenic right ventricular dysplasia (ARVD). In this disease, fibrous and fatty tissue replace the myocardium, initially in the right ventricle, but eventually in both ventricles.¹²⁵ In a patient with inverted T waves in the right precordial leads and diffuse ventricular involvement, the diagnosis of dysplasia is evident. However, cardiac arrest may be the first manifestation of focal ARVD.125 Ruling-out focal dysplasia may be particularly challenging when a Brugada sign is present.¹²⁶ The RBBB pattern of the Brugada sign could imply a right ventricular disorder. Also, the catecholamine-sensitive monomorphic VT, anecdotally observed in the Brugada syndrome,^{113,117} is of left bundle configuration, also suggesting right-ventricular origin. Finally, the Brugada sign has been reported in relatives of patients with documented ARVD.¹¹⁹ However,

patients with the Brugada syndrome do not develop structural abnormalities during long-term follow-up.^{10,122} In addition, the arrhythmias observed in the two groups differ: although polymorphic tachycardia has rarely been documented in ARVD,¹²⁷ the majority of arrhythmias (either spontaneous or induced) in cases of dysplasia are monomorphic.^{128,129} This contrasts with the polymorphic morphology of the arrhythmias in idiopathic VF with^{10,122} and without⁸⁶ the Brugada sign (Fig 5).

Patients with aborted sudden death and a Brugada sign are at high risk for arrhythmia recurrence.¹²² At the present time, there is no data to support the use of antiarrhythmic drugs in the Brugada syndrome,¹¹⁷ and ICD implantation is the treatment of choice.

The Syndrome of Nocturnal Sudden Death in South East Asian Males

Nocturnal death in previously healthy young men (Pokkuri disease) is a well-recognized entity in Japan. From 1959 to 1961, almost 300 cases of "sudden death of unknown etiology" were reported in Tokyo.¹³⁰ The male to female ratio was 14 to 1. Moreover, 84% of the unexplained deaths among males occurred during sleep, whereas only 8% of the female fatalities happened at night.¹³⁰ Similar "sleep-death syndromes" have been described in Laos (non-laitai or "sleep death"), the Philippines (bangungut or "arise and moan"),¹¹ and Thailand.¹³¹

Following reports of unexplained death among Laotian refugees in the United States, the Center for Disease Control began active surveillance for unexpected deaths among Asian immigrants in 1981. By 1983, 79 cases with negative postmortem examination had been identified.¹³² The same pattern was recognized: all but one of the deaths occurred in men, and all but one happened during sleep.

Epidemiological studies have attempted to explain the "sleep-death syndrome" on a nutritional basis, namely, an acquired LQTS related to thiamine deficiency.¹³³ However, this is unlikely for several reasons: (1) the QT interval of patients resuscitated from sleep-death syndrome is normal; and (2) females, who have longer QT intervals and are afflicted by acquired forms of the LQTS more commonly than males,¹³⁴ would be

expected to suffer from this predominantly male disease.

Similarities do exist between the sleep-death syndrome and other forms of idiopathic VF. These similarities include the age at the onset of symptoms (25 to 45 years),^{130,132} the mode of onset of spontaneous arrhythmias,^{123,135} and a high inducibility rate of VF during electrophysiologic studies.^{123,136,137} Moreover, according to a recent study, 82% of Thai males with sleep-death syndrome have a resting ECG indistinguishable from the Brugada sign. Interestingly, anecdotal reports suggest that class 1A drugs may prevent induction of VF in the laboratory.^{136,137}

Patients with sleep-death syndrome have a high mortality risk,^{123,135} but data on therapy is scarce.^{123,136,137} Recurrent VF, despite therapy with β -blockers or amiodarone, has been documented, and there is no data on the long-term value of class 1A drugs. ICDs are viewed as the only effective therapy.¹²³

Polymorphic Ventricular Arrhythmias Without Apparent Heart Disease: Differential Diagnosis

Onset of stress-related symptoms (syncope or cardiac arrest) during infancy or childhood favors the diagnosis of catecholaminergic polymorphic VT or a congenital LQTS. Female gender strongly points against the Brugada syndrome or a sleepdeath syndrome. Obviously, a QT interval of long duration or odd morphology is characteristic of a LOTS. Similarly, an RBBB with ST elevation is the sinequa-non of the Brugada syndrome and is apparently common in the sleep-death syndrome. Finally, documentation of the mode of onset of spontaneous arrhythmias is of importance: a long-short cycle preceding the onset of polymorphic VT favors a LQTS even in cases with borderline QT. However, arrhythmias precipitated by a single extrasystole with ultra-short coupling interval are seen in the short-coupled variant of torsade and the idiopathic VF syndromes (idiopathic VF with normal ECG, the Brugada syndrome, and the sleep death syndrome). Finally, the highly reproducible mode of onset of catecholaminergic polymorphic arrhythmias is essentially diagnostic.

Several forms of organic heart disease, which are difficult to exclude without specific testing, ought to be considered in the differential diagnosis following an episode of "cardiac arrest without apparent heart disease." These include: (1) coronary-artery spasm in patients with normal coronary angiography^{15,138}; (2) a focal ARVD^{15,118,119,139}; and (3) conditions that facilitate atrioventricular conduction of supraventricular arrhythmias to the point in which very rapid ventricular rates trigger VE¹⁴⁰ The last category includes patients with enhanced AV nodal conduction¹⁴⁰ or an atrioventricular accessory pathway that is not evident during sinus rhythm because of a left anterolateral location.141 Finally, idiopathic monomorphic VT, although usually well tolerated,^{1,2} may rarely lead to cardiac arrest, especially during strenuous effort.1,2,142

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