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Familial Polymorphic Ventricular Arrhythmias

A Quarter Century of Successful Medical Treatment Based on Serial Exercise-Pharmacologic Testing

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OBJECTIVES We sought to determine whether objective tests of antiarrhythmic drug efficacy could produce favorable short- and long-term outcomes in a family with idiopathic malignant ventricular arrhythmias.

BACKGROUND In 1973 a family presented with a history of several generations of syncopal spells and sudden death. Some individuals had nonspecific electrocardiographic (ECG) changes. Their QT intervals were normal at rest and with exercise. Autopsies in two young family members showed no cardiac abnormalities, specifically no evidence of arrhythmogenic right ventricular dysplasia, other cardiomyopathy, myocarditis or gross abnormality of the conduction system.

METHODS Available family members had screening ECGs. Symptomatic members had a battery of tests, including electrophysiologic studies, ambulatory ECGs, audiograms, exercise stress testing, serum catecholamine levels during rest and exercise and isoproterenol infusion. Serial exercise-pharmacologic testing was performed in symptomatic family members until induction of an arrhythmia during exercise required higher work loads or became impossible.

RESULTS Arrhythmias were not induced during electrophysiologic studies. In several family members tested, ventricular premature beats and then rapid polymorphic ventricular arrhythmias occurred whenever the sinus rate exceeded 130 beats/min. Emotional stress, isoproterenol infusion and exercise all elicited similar arrhythmias. Catecholamine levels during exercise were, however, unequivocally normal in two of three family members tested. Beta-blockers appeared to be the most effective pharmacologic agent for prevention of these arrhythmias. The efficacy of treatment has been confirmed during a follow-up of 25 years.

CONCLUSIONS This family appears to have catecholamine hypersensitivity as the basis for their ventricular arrhythmias. Guided therapy using serial exercise-pharmacologic testing provided reliable protection for this familial ventricular arrhythmia during a 25-year follow-up. (J Am Coll Cardiol 1999;34:2015–22) © 1999 by the American College of Cardiology

Familial ventricular tachycardia is usually attributable to recognized conditions such as arrhythmogenic right ventricular dysplasia (1–3), hypertrophic cardiomyopathy (4,5), familial cardiomyopathy (6) or one of the long QT interval syndromes (7–11). There are families with ventricular tachycardias in which no recognized underlying condition has been identified (12–19). Most of these families have features not shared with the others. These features differ, in turn, from those found in the family in the present report (Table 1). In this family, members developed ventricular arrhythmias during sinus tachycardia, whether induced by exercise, isoproterenol infusion or emotion. Their QT intervals were normal at rest and during exercise. This family was first identified, evaluated and treated on the basis of serial exercise-pharmacologic testing in 1973 to 1974. It is now possible to report a quarter century of apparently effective medical therapy.

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FAMILY HISTORY

The propositus presented in November 1973; he was a 13-year-old boy from a small hamlet in Lincolnshire. He had experienced syncope, often several times a week, for two and a half years, always related to exercise or to excitement such as catching a fish. The onset was sudden, with or without previous dizziness. He would fall unconscious and become pale, sometimes with gasping respiration. There were never any tonic or clonic movements or frothing. Recovery was complete within a few minutes.

There were 10 siblings, and at least six members of the family had similar attacks (Fig. 1). The paternal great-grandfather had died suddenly at an early age after having

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Abbreviations and Acronyms

A-H interval	=	atrium to His bundle interval
CSM	=	carotid sinus massage
ECG	=	electrocardiogram or electrocardiographic
H-V interval	=	interval from His bundle deflection to ventricular depolarization
ICD	=	implantable cardioverter-defibrillator
SUDS	=	sudden unexpected death syndrome (please note that the words sound rather generic, but SUDS applies to a special form of nocturnal arrhythmic sudden death in southeast Asian males)
VPC	=	ventricular premature complex

had many previous syncopal spells. The father had some reduction in his spells after being treated with phenytoin on the presumption that he had epilepsy. At times of general excitement (e.g., watching football [soccer]), several members of the family often fainted at the same time. These attacks had not been considered serious until August 1973, when the patient's 16-year-old sister died in an attack provoked by emotional stress. She had suffered as many as four attacks per week but had otherwise seemed healthy.

One month later, a 21-year-old brother whose single previous attack occurred in 1971, died while riding his motorcycle. He suddenly swung around in the street, drove over a curb and fell to the ground. There was no evidence of ingestion of alcohol, and his body showed no sign of injury.

Autopsies were performed on both of these victims. Autopsy of the 16-year-old girl showed lymphocytic infiltration in the portal tracts of the liver and in the lungs and brain; death was reported as being due to subacute viral encephalitis. The heart was normal on gross examination and routine histologic study. Autopsy of the 21-year-old man revealed no significant abnormality. After the family came to our attention, the cardiac material was sent to a cardiac pathologist (Dr. E. Olsen) for further analysis. In neither case did the heart prove suitable for specialized investigations of the small vessels and conducting systems, but there were no gross or general histologic abnormalities

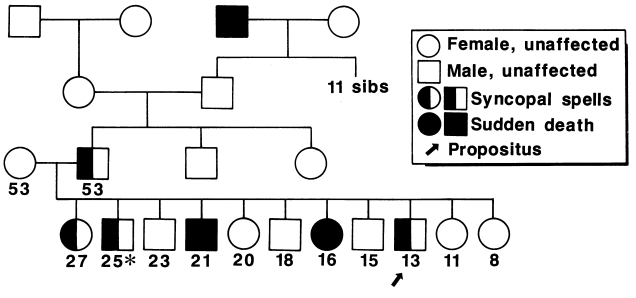

Figure 1. Family pedigree. Consistent with an autosonal dominant trait with variable penetrance. **Asterisk** indicates episodes that began by 1978 (age 30 years).

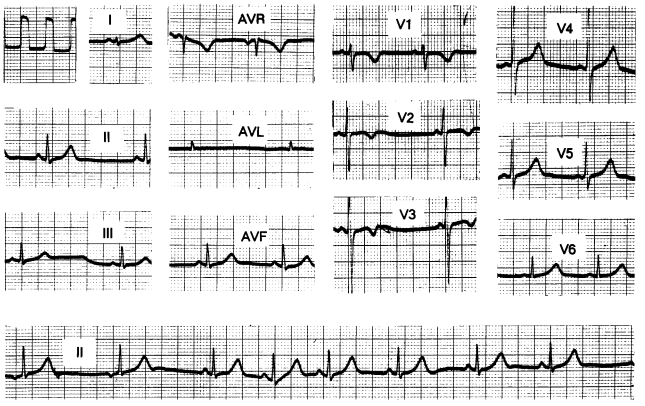

Figure 2. Electrocardiogram of the propositus.

and specifically no evidence of arrhythmogenic right ventricular dysplasia (when re-reviewed after identification of this entity), other cardiomyopathy or myocarditis.

Examination of the propositus revealed an apparently healthy, alert 13-year-old boy. Blood pressure was 115/70 mm Hg, and pulse 45 beats/min and irregular; the remainder of the physical examination was normal. Chest X-ray film, hemoglobin, white blood cell count, electrolytes (including calcium and phosphorus), urea, liver function tests, urinary vanilmandelic acid, electroencephalogram (with respiratory and photic stimulation) and audiogram were all normal. The electrocardiogram (ECG) (Fig. 2) revealed irregular sinus bradycardia with shifting atrial pacemaker, occasional junctional escapes, a short PR interval, inverted T waves in leads V_1–V_3 (normal at this age), a normal QRS complex and QTc intervals and prominent U waves.

FURTHER INVESTIGATIONS AND DEVELOPMENT OF THERAPEUTIC STRATEGY

Family members were screened for abnormalities associated with known causes of sudden cardiac death. Written, informed consent was obtained before exercise tests and invasive procedures. Systematic serial testing was still unreported in 1973 to 1974, but the finding that arrhythmias could be induced in symptomatic family members led, ad hoc, to such a protocol.

1) *Electrocardiograms*. Electrocardiograms were obtained in 10 family members.
2) *Audiograms*. Audiograms were obtained in nine family members.
3) *Exercise tests*. Exercise tests were performed on the propositus (13 times), his 20-year-old sister (nine times), 53-year-old father (four times) and 54-year-old mother (once). Tests were first performed in the absence of medications and subsequently during trials of various medications or different doses of the same medication. With resuscitation equipment at hand, exercise was performed on a bicycle ergometer, and a modified V_5

Table 1. Some Familial Ventricular Tachyarrhythmias in the Absence of Structural Heart Disease or Associated Known Syndromes

First author (ref. no.)	ECG			Ventricular Arrhythmias Seen With						Helpful Treatment		Autopsy
	SR	PR	Other	EPS	HM	EX	EST	Emotion	Isoproterenol	Beta-Blockers	Other Rx	
Green* (12)	Nl	Nl	None	NR	NR	+	+	+	0	NR	NR	WNL except conduction system indistinct
McRae† (13)	Nl	Short	U Waves	WNL	0	+	NR	+	NR	+	NR	WNL
Sacks‡ (14)	Nl	Nl	Interior LAD	NR	NR	+	+		+	+	Quinidine	
Wren§ (15)												
A	Slow	Short	U Waves	NR	Daytime	(Rest)	0	NR	NR	(Failed)	Left cervical sympathectomy	
B	Nl	Nl	U Waves	±	+	(Rest)	Decreased	NR	NR	(Failed)	Amiodarone	
C	?Nl	?Nl	Incessant VAs	NR	+	NR	NR	NR	NR	NR	Flecainamide + AAI	WNL
D	?Nl	?Nl	SVTs Incessant VAs	Fascic VT	+	NR	NR	NR	NR	NR	Flecainamide	
Chambers (16)	Nl	Nl	Abnormal SAECG	+	NR	+	NR	NR	NR	Procainamide, Atenolol		WNL
Brookfield‖ (17)	Nl	Nl	None	−	NR	+	+	−	+	(Failed)	None	Abnormal RV septum; abnormal AV bundle, etc.
Rubin (18)	Nl	Nl	None	−	+	NR	Decreased	NR	NR	(Failed)	Procainamide	WNL
von Bernuth (19)	Slow	NR	±Ectopic A rhythm	NR	NR	+	+	+	NR	±	(Failed)	NR
Present study	Nl–Slow	Nl–Short	U Waves	−	±	+	+	+	+	+	Phenytoin	WNL

*Green: French-English stock. †McRae: white family from North Carolina. Normal VMAs and other tests. ‡Sacks: white South African. Several monomorphic ventricular tachycardias (VTs). Normal echocardiogram. §Wren: English families: Families A, B, C and D annotated separately. Some of family D had polymorphic VT, although the proband had monomorphic VT. ‖Brookfield: Structural abnormalities found at autopsy not seen with catheterization, echocardiogram, electrocardiogram, etc.

AAI = atrial pacer; AV = atrioventricular; ECG = electrocardiogram; EPS = electrophysiologic study; EST = exercise stress test; EX = exercise or effort; HM = Holter monitor; LAD = left anterior descending coronary artery; Nl = normal; NR = not reported; PR = P to R interval on ECG; RV = right ventricular; Rx = medication; SAECG = signal averaged ECG; SR = sinus rhythm; SVT = supraventricular tachycardia; VAs = ventricular arrhythmias; VMA = vanillylmandelic acid; VT = ventricular tachycardia; WNL = within normal limits; + = positive; 0 = not done; − = negative.

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lead was recorded, usually at a paper speed of 50 mm/s, although sometimes at 25 mm/s. The work load was increased by 100 kilopond meters/min (KPM/min) every 1 to 2 min to the point of fatigue or bigeminal ventricular arrhythmias. For reference, 150 KPM/min = 25 W. Some days several tests were performed after rest and return to baseline heart rate.

Because little information was then available about changes in the QT interval with exercise, 44 volunteers also underwent exercise testing and served as control subjects; these subjects were normal by history, ECG and physical examination. The QT intervals in three subgroups—8 boys age 12 to 19 years, 7 young women age 19 to 26 years and 10 men age 50 to 56 years—permitted comparison to the intervals of the propositus, his sister and father, respectively.

The effects of propranolol (orally and intravenously), verapamil and isoproterenol were tested in the propositus and his 20-year-old sister; the propositus was also given oral phenytoin. The father, given phenytoin (100 mg twice a day) since 1960, was not tested while taking other medications.

4) *Plasma catecholamines*. Plasma catecholamines were measured (20) with strict attention to techniques of sampling and handling of the specimens. Samples were drawn from the propositus (twice), his 20-year-old sister and father immediately after insertion of an intravenous line, during exercise-induced arrhythmia and after the subject had rested for 1 h after exercise.
5) *Electrophysiological studies*. Intracardiac electrophysiologic recordings, including His bundle studies with programmed electrical stimulation of the atrium and ventricle, were carried out in the propositus and his 20-year-old and 27-year-old sisters using up to three ventricular extrastimuli in the absence of antiarrhythmic medications. Isoproterenol was infused at 5 μg/min without extrastimulus testing. Right and left carotid sinus massage (CSM) was done in the absence of medications and after infusions of edrophonium, 10 mg; blood pressure was measured during CSM.
6) *Ambulatory ECG monitoring*. Several ambulatory ECGs were obtained while the propositus was in the hospital and of the 20-year-old sister during a 72-h period while she toured London.
7) *Echocardiography*. The propositus underwent M-mode echocardiography.

RESULTS

1) **Electrocardiograms**. All four of the affected surviving family members had sinus arrhythmia; three had prominent U waves; and the propositus also had inverted T waves in leads V_1–V_3 (normal for his age) and a wandering atrial pacemaker. Three symptomatic members had a short PR interval (0.11 to 0.12 s). The youngest sister, 8 years old, although asymptomatic, had a PR interval of 0.11 and sinus arrhythmia. All had normal QT intervals at rest and (in those tested) during exercise (Fig. 2).

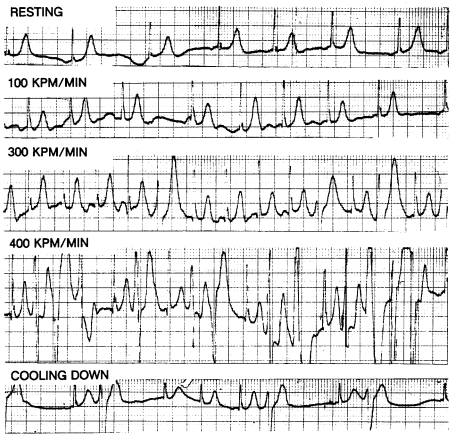

Figure 3. Exercise test in the propositus, showing increasing numbers of extrasystoles with increasing work load. At 400 kilopond meters/min (KPM/min), there were up to four successive polymorphic extrasystoles. The QTc interval remains normal.

2) *Audiograms*. Audiograms were normal in eight of nine cases. An asymptomatic 18-year-old brother whose ECG was normal had a unilateral high frequency deficit. He remains asymptomatic.
3) *Exercise tests*. The propositus, his 20-year-old sister and the father all developed ventricular tachyarrhythmias with exercise in the absence of medications. The pattern consisted of isolated ventricular premature complexes (VPCs) progressing to bigeminy, to multifocal VPCs and to symptomatic short bursts of polymorphic ventricular tachycardia, as recorded in the propositus on his initial test (Fig. 3). The father also developed two short runs of supraventricular tachycardia. Subsequently, exercise tests were stopped once ventricular bigeminy occurred. Medications and doses were considered effective if the subject was able to complete two exercise tests to fatigue without ventricular tachycardia, couplets or bigeminy. The work loads and heart rates required to produce ventricular arrhythmias in the propositus with and without medication are summarized in Figure 4. Intravenous propranolol (1.5 to 5 mg) prevented ventricular arrhythmias in the three subjects tested, even at high work loads and heart rates up to 160 beats/min. In the propositus and his sister, oral propranolol in increasing doses from 30 to 120 or 240 mg/day, respectively, was incrementally effective at suppressing the appearance of ventricular arrhythmias until higher work loads or heart rates were attained. On 120 mg/day of propranolol for the propositus and 240 mg/day for the sister, bigeminal ventricular rhythms occurred only at the point of fatigue. Verapamil and phenytoin were less effective. On phenytoin, the father had no further ventricular or

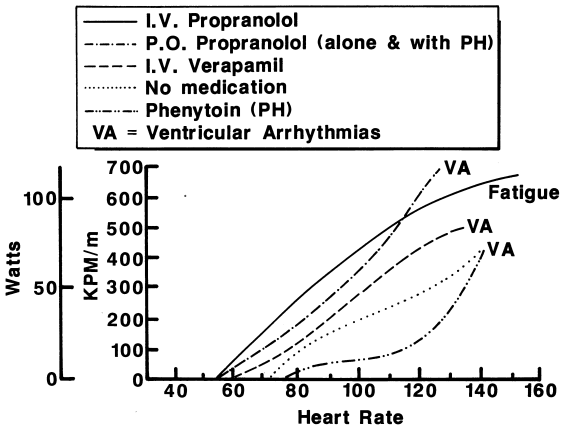

Figure 4. Serial exercise-pharmacologic testing. Effect of medications on work load–heart rate relations in the propositus. The end point was fatigue or ventricular arrhythmias (bigeminal or more). I.V. = intravenous; P.O. = oral.

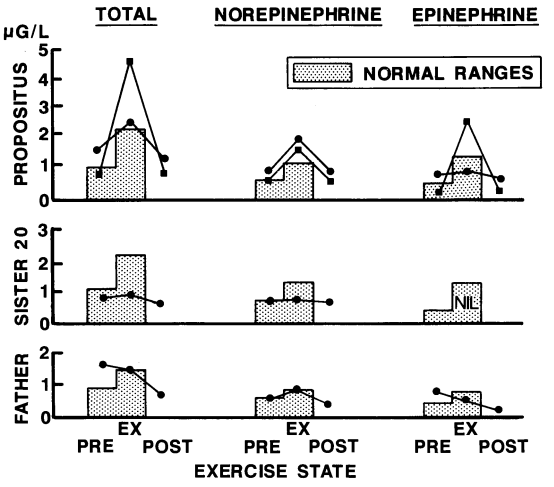

Figure 5. Plasma catecholamines before (PRE), during (EX = exercise) and after exercise (POST). The propositus had catecholamine measurements with two exercise tests. **Shaded areas** represent the normal ranges.

supraventricular tachycardia with exercise, although he did have increasing numbers of VPCs. However, he preferred to remain on phenytoin as his long-term therapy. Compared with baseline, higher work loads could be achieved before arrhythmias with oral propranolol.

Except with verapamil, the corrected QT intervals increased with exercise beyond the normal limits prescribed by Bazett's formula (21). However, the QTs remained within normal limits (±2 SD) based on the mean values established by the normal control groups used for this study (22) and others (23–25).

Ventricular arrhythmias could also be provoked by emotional stimuli. Approaching the 13-year-old propositus with a needle for an intravenous drip frequently induced sinus tachycardia and runs of VPCs and bigeminy. See additional related comments below in the section on ambulatory monitoring. Intravenous isoproterenol administered in the exercise laboratory also produced ventricular arrhythmias when the sinus rate exceeded 130 beats/min.

Plasma catecholamines. The fluctuations of the catecholamines are shown in Figure 5. It has been debated (26) whether beta-blockers can markedly increase the catecholamine levels. Because the 13-year-old and 20-year-old siblings were on beta-blockers during the tests, their "true" catecholamine levels may have been lower.

Electrophysiologic studies. In all three subjects, intracardiac electrophysiologic studies revealed normal A-H intervals that became prolonged appropriately with increasing pacing rates and in response to extrastimuli without a break in the atrium to His bundle (A-H) curve. The interval from His bundle deflection to ventricular depolarization (H-V interval) was somewhat abbreviated at 25 ms and was constant at all rates. The studies elicited no evidence of any accessory pathway. Programmed stimulation failed to initiate a tachycardia in any subject.

Isoproterenol (5 μg/min) provoked frequent VPCs in the two sisters, with up to three beats of ventricular tachycardia. These beats were all of left bundle branch block configuration, but polymorphic with right, left and normal axes. The sinus node response was somewhat blunted in the 27-year-old sister (rate 111 beats/min) and propositus (rate 110 junctional), unlike the appropriate sinus tachycardias seen with isoproterenol at the time of exercise testing. There was no significant slowing or hypotension with CSM with or without edrophonium and no significant slowing of the sinus rate with verapamil.

Ambulatory ECG (Holter) monitoring. No tachyarrhythmias or VPCs were recorded in the propositus during low level ambulatory activities in hospital. The 72 h of Holter tapes in the 20-year-old woman revealed episodes of sinus tachycardia, VPCs and bigeminy temporally related to stressful events, such as this rural inhabitant had experienced when confronted by one of the imposing escalators of the London underground railway.

Echocardiogram. The echocardiogram in the propositus was normal; in particular there was no evidence of chamber enlargement or dysfunction, septal thickening or mitral valve prolapse.

Summary of diagnostic and therapeutic strategy. No structural or chemical abnormalities were identified, and the family did not fit a known syndrome. The finding that arrhythmias could be induced by exercise led to serial testing. Three symptomatic family members underwent electrophysiologic study (negative in all); three symptomatic members had arrhythmias induced by exercise testing in the absence of drugs, but not after graded increases of medica-

tions; and an asymptomatic member had no arrhythmias induced. Other affected family members were then treated by extrapolation with beta-blockers.

Follow-up. The family has been followed continually for 25 years since the serial exercise tests. One of the authors (J.D.F.) corresponds yearly with the mother of the propositus; every three to five years she completes a detailed chart. All affected members were treated with propranolol or phenytoin, or both, or the anticonvulsant primadone (n = 1), and among these there have been no further episodes of syncope. The 20-year-old sister of the propositus has had a miscarriage of uncertain relation to propranolol therapy. A brother of the propositus began to have syncopal spells in 1978 at age 30; he was treated with propranolol and has since remained symptom-free. The son of the propositus began to have syncopal spells in 1995, at age 11, and has since remained asymptomatic on beta-blocker therapy.

DISCUSSION

Treatment based on serial exercise-pharmacologic testing appears to be effective in this family with malignant ventricular arrhythmias. The cause of the arrhythmias in this family remains unclear. The short PR interval recorded in several affected members received attention during detailed electrophysiologic studies, but these showed only normal decremental conduction. Sinus bradycardia with wandering atrial pacemaker, prominent U waves and precipitation of arrhythmias by emotional stress all occur in the prolonged QT interval syndromes (2–4). Efforts to identify intermittent QT interval prolongation were of no avail at rest, during ordinary activities using Holter monitoring or during exercise testing (25). The arrhythmias could not be definitively related to elevated plasma catecholamines at times of stress.

Similar nonfamilial arrhythmias. Very similar arrhythmias, although sporadic rather than familial, were reported by Coumel et al. (27) in four children, later expanded to a series of 21 patients (28). The arrhythmias were triggered by emotion and effort and controlled by beta-blockers, sometimes with the need for supplementary amiodarone. The authors postulated that the tachycardias arose because of an undue sensitivity to catecholamines: as with our patients, the infusion of isoproterenol induced arrhythmias exactly like those seen after emotional stress or exertion. The ventricular arrhythmias are polymorphic and therefore resemble "torsade de pointes" (29). Beta-blockers appeared effective; recurrent syncope and two deaths over a seven-year mean follow-up were attributed to lapses in therapy (28). Other reports (19) and those summarized by Vlay (30) show the spectrum of catecholamine-sensitive ventricular tachycardia. Variations or oscillations in sympathetic and parasympathetic activity have long been implicated in arrhythmogenesis (31–35). In a preliminary report, such oscillations have been recorded in a patient with idiopathic ventricular tachycardia using power spectral analysis (36). Among the series of 15 patients with sudden cardiac death and polymorphous ventricular tachycardia reported by Eisenberg et al. (37), four had their arrhythmia induced by treadmill testing or isoproterenol infusion, or both, and all were treated with the beta-blocker antenolol, but one died suddenly after 66 months. The family in our report is also reminiscent of the idiopathic ventricular fibrillation syndrome reported by Viskin et al. (38). The latter, however, was not familial and had their arrhythmias induced at electrophysiologic testing.

Familial ventricular arrhythmias. Reports of familial tachyarrhythmias in the absence of structural heart disease or associated known syndromes have shown many variations (Table 1). Some have featured a tendency toward sinus bradycardia (15,19), U waves (13,15), a short PR interval (13,15), ventricular arrhythmias with exercise or exercise testing (12–14,16,17,19), emotion (12,13,19) or isoproterenol infusion (14,17). In some families the arrhythmias are inducible by programmed stimulation (15,16). Beta-blockers have proved effective in some (13,14,16) but not all patients (15,17,19). There seems to be a preponderance of reports from parts of the world where the population is of British or northern European background (Table 1).

Recent contributions—molecular and genetic. Recent interest in polymorphic ventricular tachycardias in the absence of structural heart disease has centered around genetic and molecular changes resulting in phase 2 reentry and early afterdepolarizations (6,39–45). These often lead to the characteristic changes seen in the Brugada syndrome (39–42,44), sudden unexpected death syndrome (SUDS) (43,44) or the long QT interval syndromes (45). Manifestation or expression of these syndromes may depend on changes in autonomic tone, including changes brought about by exercise or emotional stress. Procainamide, flecainide and other drugs may elicit the characteristic ECG changes of the Brugada syndrome (39–42,44), and this might be applicable to the ongoing follow-up of this family. Otherwise, the family in the present report does not exhibit any ECG changes characteristic of these syndromes, even subtle variations such as those described by von Bernuth et al. (46), where the QT interval is normal at rest but fails to shorten with exercise. Indeed, it has been suggested "that cardiac conditions comparable to those in the prolonged QT syndromes may exist without that ECG feature, for example with unequal sympathetic influence on areas of overlap and exclusive left-sided innervation" (47). That would amount to a kind of "long QT syndrome without a long QT interval," and we can only speculate whether this might apply to the present family.

Other data. There were no gross pathologic changes in this family. Abnormal or hypoplastic conduction systems have also been implicated in unexpected sudden death in apparently healthy young persons (17). The hearts available for

autopsy in this family were not suitable for a subsequent detailed study of the conduction system, although electrophysiologic studies of conduction and exercise heart rate response were normal. Techniques such as cardiac magnetic resonance imaging were not available during the investigation of this family.

Measures of efficacy: serial testing and time. In the treatment of potentially lethal arrhythmias, it is essential to assess the effectiveness of any proposed therapy before discharge from the hospital. Serial exercise-pharmacologic testing has had favorable short-term results in a mixed group of patients with exercise-induced ventricular arrhythmias (48–50). Verapamil (51) was not as effective as beta-blockers in the present family.

The early favorable response of the family in this report led directly to the use of serial electrophysiologic-pharmacologic testing in patients with arrhythmias inducible in the electrophysiology laboratory (52). There is at present a degree of skepticism regarding the effectiveness of therapy based on serial exercise testing, serial Holter monitoring or serial electrophysiologic studies. As a consequence, many patients with potentially fatal cardiac arrhythmias are treated with an implantable-cardioverter defibrillator (ICD), and indeed both the efficacy of the ICD and the increasing ease of implantation make the ICD the current gold standard. The effective long-term management of this family, continuing beyond two decades, indicates that alternatives to the ICD may be appropriate in selected instances. Serial exercise testing, similar to what we report, may be useful in some rhythm disorders provoked by emotion, catecholamines or exercise.

Acknowledgments

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