Journal of the American College of Cardiology
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Published by Elsevier Science Inc.

Vol. 34, No. 7, 1999
ISSN 0735-1097/99/$20.00
PII S0735-1097(99)00438-6

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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Manuscript received November 20, 1998; revised manuscript received June 18, 1999, accepted August 23, 1999.

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

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

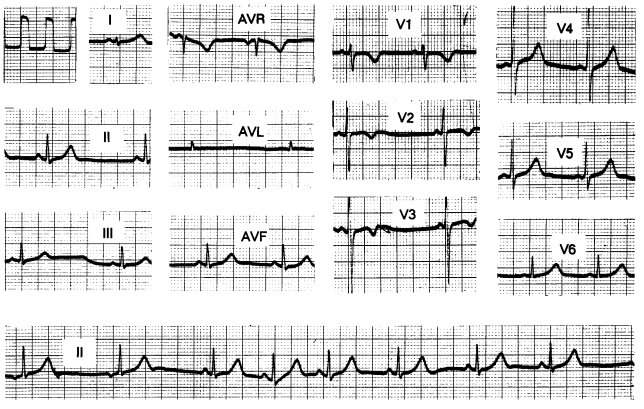

Figure 2. Electrocardiogram of the propositus.

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

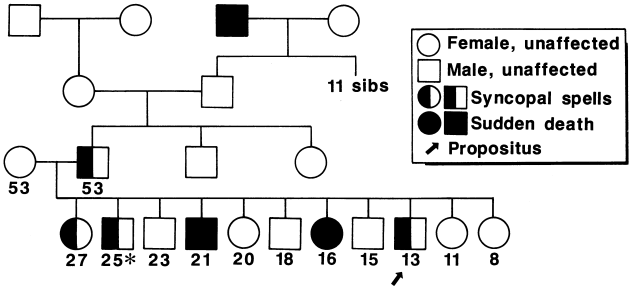

Figure 1. Family pedigree. Consistent with an autosonal dominant trait with variable penetrance. **Asterisk** indicates episodes that began by 1978 (age 30 years).

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