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Familial Cardiomyopathy Underlies Syndrome of Right Bundle Branch Block, ST Segment Elevation and Sudden Death

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Objectives. **We sought to assess whether structural heart disease underlies the syndrome of right bundle branch block, persistent ST segment elevation and sudden death.**

Background. **Ventricular fibrillation and sudden death may occur in patients with a distinctive electrocardiographic (ECG) pattern of right bundle branch block and persistent ST segment elevation in the right precordial leads.**

Methods. **Sixteen members of a family affected by this syndrome underwent noninvasive cardiac evaluation, including electrocardiography, Holter ambulatory ECG monitoring, stress testing, echocardiography and signal-averaged electrocardiography; two patients had electrophysiologic and angiographic study. Endomyocardial biopsy was performed in one living patient, and postmortem examination, including study of the specialized conduction system, was performed in one victim of sudden death.**

Results. **Five years before a fatal cardiac arrest, the proband had been resuscitated from sudden cardiac arrest due to recorded ventricular fibrillation. Serial ECGs showed a prolonged PR interval, right bundle branch block, left-axis deviation and persistent ST segment elevation in the right precordial leads, in the absence of clinical heart disease. Postmortem investigation disclosed right ventricular dilation and myocardial atrophy with adipose replacement of the right ventricular free wall as well as sclerotic interruption of the right bundle branch. A variable degree of right bundle branch block and upsloping right precordial ST segment was observed in seven family members; four of the seven had structural right ventricular abnormalities on echocardiography and late potentials on signal-averaged electrocardiography. A sib of the proband also had a prolonged HV interval, inducible ventricular tachycardia and fibrofatty replacement on endomyocardial biopsy.**

Conclusions. **An autosomal dominant familial cardiomyopathy, mainly involving the right ventricle and the conduction system, accounted for the ECG changes and the electrical instability of the syndrome.**

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It has been recently reported that ventricular fibrillation may occur in a subgroup of patients with a distinctive clinical and electrocardiographic (ECG) syndrome. The ECG and clinical features, previously described by Martini et al. (1) and Brugada and Brugada (2), include right bundle branch block, often with left axis deviation and a prolonged HV interval; persistent ST segment elevation in the right precordial leads, with or without T wave inversion; familial occurrence, and sudden death due to ventricular fibrillation. The etiopathogenesis of the syndrome is controversial (3). Martini et al. (1) suggested an underlying "concealed" right ventricular myocardial disease, whereas Brugada and Brugada (2) found no structural heart abnormality and stressed the nature of functional electrical disease. In the present study we present data on a family affected by this syndrome whose members had clinicopathologic evidence for a structural abnormality of both the right ventricular myocardium and the specialized conduction system.

Methods

Figure 1 shows the family pedigree. The proband died suddenly at age 35 years; 5 years earlier he had undergone detailed clinical evaluation after an episode of cardiac arrest. Postmortem macroscopic examination included measurement of heart weight and wall thickness, inspection of the coronary arteries and valves and identification of any myocardial scars or dilation. Several transmural blocks of ordinary myocardium from the free walls of both ventricles and septum were processed for histologic examination; 7-μm thick sections were stained with hematoxylin-eosin, Weigert–van Gieson and azan techniques. The study of the conduction system by serial sections was carried out according to a method previously reported (4).

All but one of the remaining living members were included in the study. The methods of clinical investigation have been previously described in detail (5). Noninvasive clinical evalua-

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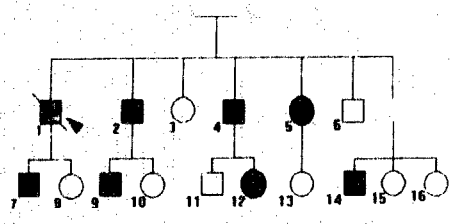

Figure 1. Family pedigree. **Numbers** indicate cases. **Circles** represent women and **squares** represent men. **Arrowhead** indicates the proband. **Diagonal bars** indicate deceased family members. Affected members are represented by **solid circles** and **squares**. Nonaffected and noninvestigated members are represented by **open** and **gray symbols**, respectively.

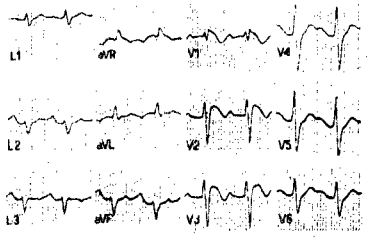

Figure 2. The 12-lead basal electrocardiogram of the proband, recorded nearly 2 years after the episode of aborted sudden death.

tion included basal electrocardiography, Holter ambulatory ECG monitoring, stress testing, two-dimensional echocardiography and signal-averaged electrocardiography. We adopted the adjustment of the definition of late potentials on the signal-averaged ECG in the presence of conduction defects proposed by Buckingham et al. (6). A sib of the proband underwent additional invasive cardiologic study (electrophysiology, angiography and right endomyocardial biopsy) after he had a presyncopal attack.

Results

Two generations of family members were studied (Fig. 1). Six subjects (4 men and 2 women, mean age 48.2 years) were in the first generation and 10 (4 men and 6 women, mean age 16.7 years) were in the second.

Findings in the proband. *Antemortem data.* The proband, a 35-year old truck driver, had been admitted to the hospital at age 30 years for evaluation of recurrent syncopal episodes. He experienced an in-hospital sudden cardiac arrest due to recorded ventricular fibrillation and required direct current cardioversion at 300 J. Results of a clinical examination were normal. Serial 12-lead ECGs showed sinus rhythm, first-degree atrioventricular (AV) block (PR interval 220 ms), right bundle branch block with left axis deviation, ST segment elevation and inverted T waves in the right precordial leads (Fig. 2). Chest roentgenogram showed a normal cardiothoracic ratio; the results of baseline hematologic and biochemical studies were within normal limits. Exercise stress testing and 24-h Holter ambulatory ECG monitoring showed no arrhythmias or ST-T wave abnormalities. Cardiac catheterization revealed normal cardiac pressures, as well as normal findings on left ventricular and coronary angiography and ergonovine testing. Right ventricular angiography was not performed. Intracardiac electrophysiologic recordings revealed a "borderline" HV interval (70 ms); programmed ventricular stimulation was not performed. The patient was given beta-adrenergic blocking therapy and his clinical course was uneventful until he died suddenly at rest 5 years later.

Postmortem data. Postmortem examination revealed a heart weight of 350 g. The coronary arteries were normal and there was no evidence of recent or healed myocardial infarction. All cardiac valves were normal. The right ventricle was moderately enlarged with dilation of the pulmonary infundibulum. Despite preserved right ventricular wall thickness (4 to 5 mm), there was significant myocardial atrophy and fatty substitution of the right ventricular anterolateral wall, infundibulum and moderator band.

Histopathologic examination of the right ventricular myocardium showed remarkable myocardial atrophy with transmural fatty replacement and slight interstitial fibrosis, in the absence of wall thinning and inflammatory infiltrates (Fig. 3A). Study of the specialized conduction system showed normal findings in the sinoatrial node, crista terminalis, atrionodal approaches, AV node and penetrating AV bundle. Conversely, there was marked fibrosis of the bifurcating His and branch bundles leading to sclerotic interruption of the proximal right bundle branch (Fig. 3B). There was also patchy fibrosis affecting the myocardium of the crest of the interventricular septum.

Findings in living members. Among the 15 surviving family members, 7 exhibited various degree of right bundle branch block, left axis deviation and ST segment elevation in the 12-lead ECG (Fig. 4A). In four of these patients (Cases 2, 4, 7 and 14), echocardiography revealed mild to moderate dilation of the right ventricle or outflow tract, or both, abnormalities in regional wall motion and structural changes of the moderator band or trabecular pattern (Table 1). These four patients also had abnormal findings on the signal-averaged ECG (Fig. 4B). The duration of the terminal QRS complex (<40 V) ranged from 47 to 67 ms, and the root-mean-square amplitude of the last 40 ms of the QRS complex ranged from 9 to 17 V; these measurements satisfied the criteria for late potentials as adjusted for the presence of conduction defects (6). Results of Holter monitoring and exercise testing were normal in all cases. During a 5-year follow-up period there was no fatal event; however, two patients (Cases 2 and 7) experienced palpitation and presyncopal episodes.

The oldest sib of the proband (Case 4) was admitted for further clinical evaluation. The standard ECG showed sinus rhythm, right bundle branch block and persistent ST segment elevation with inverted T waves in the right precordial leads. Right ventricular angiography showed moderate dilation of the right ventricle (end-diastolic right ventricular volume 192 ml/m^2 [the normal value in our laboratory (5) is 79.8 ±

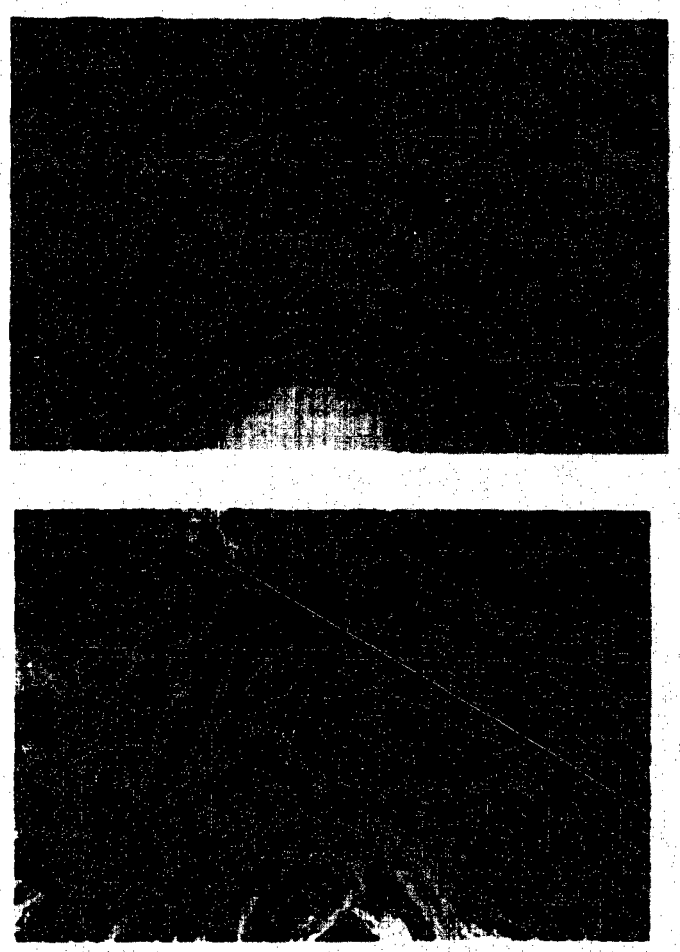

Figure 3. **A,** Histologic view of the right ventricular free wall in the proband. Note the remarkable myocardial atrophy with fatty replacement and slight interstitial fibrosis. **B,** On serial histologic section of the specialized conduction system, severe fibrosis of the bifurcating His bundle with sclerotic interruption of right bundle branch (**arrowheads**) is visible. Azan stain, original magnification ×6.

10.3 ml/m^2]), infundibular and posterobasal wall motion abnormalities and apical disarrangement of the trabecular pattern. Results of left ventricular and coronary angiography were normal. Right endomyocardial biopsy specimens revealed moderate fibrofatty replacement. Intracavitary His bundle recording showed an infra-His first-degree AV block (HV interval 80 ms); ventricular stimulation with two ventricular extrastimuli from the right ventricular outflow tract induced one episode of sustained monomorphic ventricular tachycardia, with a left bundle branch block–inferior axis pattern and cycle length of 250 ms, and runs of polymorphic ventricular tachycardia. Right ventricular endocardial mapping showed a dispersion of local activation times; the latest endocardial ventricular electrogram was recorded at the outflow tract 160 ms after the onset of the surface QRS complex, a time that coincided with the onset of the abnormal upsloping ST segment. The patient received amiodarone (200 mg/day) and has been asymptomatic for the last 3 years.

Pedigree analysis. Eight (50%) of the 16 family members exhibited some degree of right bundle branch block or ST segment elevation, or both, in the right precordial leads. When these data were included in the analysis of the pedigree, the pattern of inheritance was compatible with an autosomal dominant pattern with variable expression.

Discussion

Previous studies. In 1989 Martini et al. (1) described six patients with apparently idiopathic ventricular fibrillation, three of whom had a distinctive ECG pattern characterized by an upsloping ST segment in the right precordial leads ("early repolarization") in association with right bundle branch block and T wave inversion. In these patients, the investigators documented "subtle" underlying structural abnormalities of the right ventricle after a detailed clinical investigation.

In 1992, Brugada and Brugada (2) described eight addi-

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Table 1. Findings in the Four Family Members With Echocardiographic Right Ventricular Abnormalities

	RV EDV (ml/m²)	RV OT (mm)	RV EF (%)	Regional Dysfunction	Structural Abnormalities
Case					
2	55	34	69	Infundibular akinesia	
4	96	40	58	Infundibular akinesia, posterobasal dyskinesia	Highly reflective and irregularly shaped moderator band
7	77	34	60	Infundibular akinesia, apical dyskinesia	Apical disarrangement of the trabecular pattern
14	56	37	60	Infundibular and apical akinesia	Apical disarrangement of the trabecular pattern and highly reflective moderator band
Normal*	58 ± 4	25 ± 4	6 ± 4		

*Normal values for these echocardiographic measurements in our laboratory (5). EDV = end-diastolic volume; EF = ejection fraction; OT = outflow tract; RV = right ventricular.

tional patients with the preceding ECG changes who experienced cardiac arrest due to ventricular fibrillation. These investigators introduced the term "right bundle branch block, ST segment elevation and sudden death syndrome" to describe a new clinical entity that, in their view, could not be explained on the basis of currently known diseases and conditions. They stressed the concept of a primary electrical disease as, in their experience, the ECG changes and the ventricular electrical instability were not explainable by structural heart disease, myocardial ischemia or electrolyte disturbances. However, they did not provide quantitative details regarding echocardiography and angiography and the patient who died suddenly did not undergo autopsy. Moreover, they included the syndrome among the functional electrical disturbances, even though four of their eight patients had right bundle branch block with a prolonged HV interval that strongly suggested a structural His-Purkinje system disease.

The present study. The major finding of the current study was that a familial cardiomyopathy, mainly involving the right ventricular myocardium and the specialized conduction system, may account for ECG changes and electrical instability in the syndrome of right bundle branch block, ST segment elevation and sudden death.

Autopsy in the proband revealed right ventricular cardiomyopathic changes consisting of myocardial atrophy and adipose replacement of the right ventricular free wall. The morphologic pattern resembled that observed in the "adipose" variant of right ventricular cardiomyopathy, with preservation of wall thickness and absence of replacement fibrosis (7–9). Moreover, among seven surviving family members with ECG changes, four exhibited echocardiographic signs of structural and functional right ventricular abnormalities as well as late potentials on signal averaged electrocardiography. Finally, Patient 4 had fibrofatty replacement on right endomyocardial biopsy and inducible ventricular tachycardia with a left bundle branch block configuration during programmed right ventricular stimulation.

A familial conduction system disease probably accounts for the conduction abnormalities found in the affected family members. Histologic examination of the conduction system showed marked degenerative changes in the His and branch bundles, leading to right bundle branch interruption. These features correlated with the proband's ECG findings of first-degree AV block, right bundle branch block and QRS left axis deviation. The oldest sib of the proband showed complete right bundle branch block and a prolonged intracavitary HV interval, which suggested widespread pathologic changes of the His bundle and branches.

The familial occurrence of the syndrome in our study and that of the Brugadas (2) suggests a genetic basis for the disease. Pedigree analysis in our study was consistent with an autosomal dominant mode of inheritance with variable expression. Similarly, familial progressive AV conduction defects are usually inherited in an autosomal dominant manner (10–12). In the present family, the pathologic changes of the right ventricular myocardium and His bundle and branches may have been inherited together, in the setting of a "heritable cardiac conduction and myocardial disease" (13–15).

The most distinctive ECG feature of the syndrome is persistent ST segment elevation in the right precordial leads. This ECG abnormality, also known as "prominent J wave" (16,17), has been previously observed in different clinical and experimental settings (18–22). A possible explanation for both the right bundle branch block and the ST-T wave changes we observed is that the coexistence of right bundle branch and right myocardial disease may result in both ECG abnormalities. Epicardial mapping studies during sinus rhythm (23) demonstrated that patients with a right ventricular muscle disease have a "right parietal" intraventricular conduction defect that entails a prolongation of QRS duration mostly in the right precordial leads. Accordingly, in our patients the ST segment elevation was localized to the right precordial leads, suggesting a regional right ventricular conduction defect. The presence of an additional "right septal" conduction defect, as

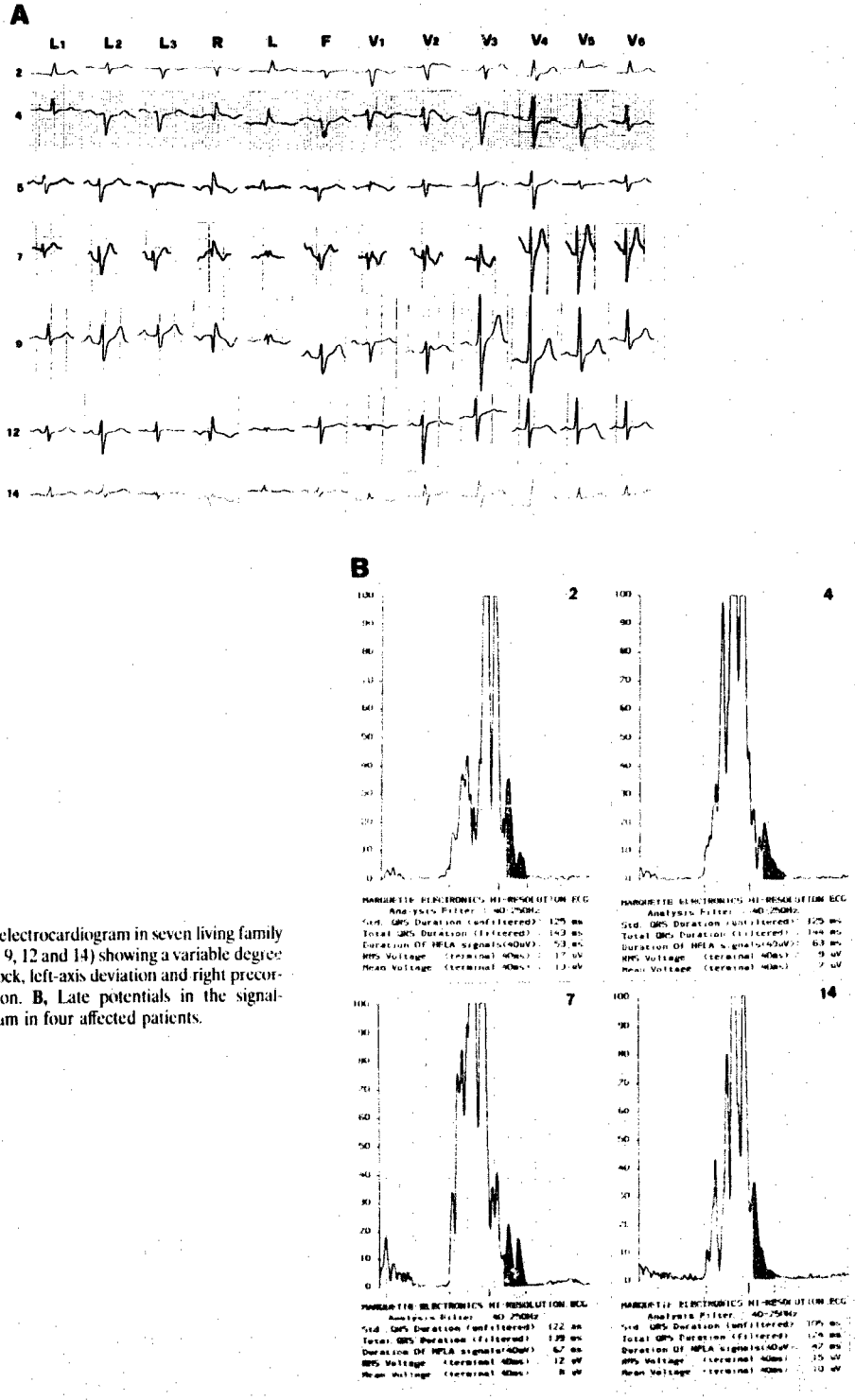

Figure 4. **A,** Twelve-lead electrocardiogram in seven living family members (Cases 2, 4, 5, 7, 9, 12 and 14) showing a variable degree of right bundle branch block, left-axis deviation and right precordial ST segment elevation. **B,** Late potentials in the signal-averaged electrocardiogram in four affected patients.

shown in the autopsy case, may account for a further delay in right ventricular depolarization, with a large R′ wave that prolongs until the onset of the T wave and mimics ST segment elevation. Right depolarization electrical activity at the time of the abnormal ST segment was recorded in four family members, either in the form of late potentials in the signal-averaged ECG or as a delayed endocardial electrogram of the right ventricular outflow tract. Therefore, the ECG pattern could reflect a marked delay in right ventricular depolarization rather than a repolarization abnormality.

The marked dispersion of ventricular activation times due to the "double" ventricular conduction defect is likely to predispose to reentrant ventricular arrhythmias and to account for the life-threatening electrical instability in the syndrome (24,25). The induction of a monomorphic ventricular tachycardia with a left bundle branch block pattern in one patient is consistent with a reentrant mechanism in the right ventricle.

Conclusions. We believe that an autosomal dominant familial cardiomyopathy, involving both the right ventricular free wall and the specialized conduction system, underlies the right bundle branch block, ST segment elevation and sudden death syndrome. The coexistence of both "septal" and "parietal" right conduction defects may account for both the ECG pattern of right bundle branch block and persistent ST segment elevation and the ventricular electrical instability.

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