

# Sudden Cardiac Death With Apparently Normal Heart

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**Background**—Mechanisms of sudden cardiac death (SCD) in subjects with apparently normal hearts are poorly understood. In survivors, clinical investigations may not establish normal cardiac structure with certainty. Large autopsy series may provide a unique opportunity to confirm structural normalcy of the heart before reviewing a patient's clinical history.

**Methods and Results**—We identified and reexamined structurally normal hearts from a 13-year series of archived hearts of patients who had sudden cardiac death. Subsequently, for each patient with a structurally normal heart, a detailed review of the circumstances of death as well as clinical history was performed. Of 270 archived SCD hearts identified, 190 were male and 80 female (mean age 42 years); 256 (95%) had evidence of structural abnormalities and 14 (5%) were structurally normal. In the group with structurally normal hearts (mean age 35 years), SCD was the first manifestation of disease in 7 (50%) of the 14 cases. In 6 cases, substances were identified in serum at postmortem examination without evidence of drug overdose; 2 of these chemicals have known associations with SCD. On analysis of ECGs, preexcitation was found in 2 cases. Comorbid conditions identified were seizure disorder and obesity (2 cases each). In 6 cases, there were no identifiable conditions associated with SCD.

**Conclusions**—In 50% of cases of SCD with structurally normal hearts, sudden death was the first manifestation of disease. An approach combining archived heart examinations with detailed review of the clinical history was effective in elucidating potential SCD mechanisms in 57% of cases. (*Circulation*. 2000;102:649-654.)

**Key Words:** death, sudden ■ pathology ■ fibrillation

In the majority of cardiac arrest patients, a structural or functional abnormality can be identified, coronary artery disease being the most common.<sup>1</sup> Studies of cardiac arrest survivors indicate that in 5% to 10% of sudden cardiac death (SCD) patients, hearts are apparently normal.<sup>2-7</sup> The mechanisms of sudden cardiac death in this subset of patients are poorly understood.

Establishing structural normalcy is an essential prerequisite to making a diagnosis of this entity. However, focal manifestations of conditions such as myocarditis, cardiomyopathies, or small tumors may escape detection in survivors of SCD.<sup>8-10</sup> Furthermore, nonspecific abnormalities such as interstitial fibrosis and mild myxomatous mitral valve changes are difficult diagnoses to make in the cardiac arrest survivor. The gold standard for confirming absence or presence of a structural abnormality is the pathological examination of the patient's heart. The confirmation of structural normalcy at autopsy is thus the most suitable means to identify SCD patients with normal hearts.

The combination of a triggering event and a susceptible myocardium has evolved as a biological model for the initiation of lethal arrhythmia.<sup>1</sup> Accordingly, a search was conducted for possible abnormal myocardial substrates and triggers of fatal arrhythmia in patients with normal hearts

who died of SCD. A detailed review of anatomic and clinical findings was performed in SCD cases with normal hearts, identified from a 13-year autopsy series of 270 SCD patients.

## Methods

### Definition

For the purpose of this study, SCD was defined as death as the result of cardiac causes within 6 hours of onset of symptoms. If death was unwitnessed, patients had been observed in a normal state of health 24 hours before death.

### Archived Hearts

The Jesse E. Edwards Cardiovascular Registry (St Paul, Minn) has accessioned >14 000 archived hearts in the last 40 years. Data collected at time of original examination include a police report, family correspondence, medical examiner report, autopsy findings, toxicological screen, and available medical history; these data and results of the morphological studies in the registry are catalogued in a standardized fashion.

### Referral Sources

For SCD, the major sources of referral are local medical examiners (coroners) from Hennepin, Ramsey, and Anoka counties, which constitute the Minneapolis–St Paul greater metropolitan area. A significant number of local cases of sudden death at age <60 years are examined by the county coroners. The coroners, in turn, refer all

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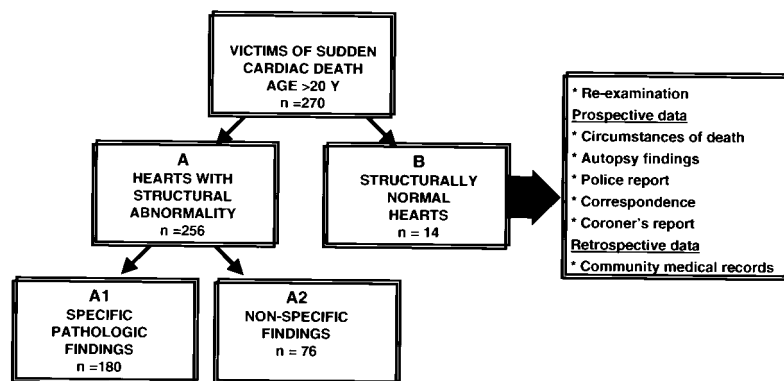


Figure 1. Study design and identification of subgroups.

cases attributable to cardiac causes to the Edwards Registry in a consistent fashion.

**Experimental Design**

All locally referred cases of SCD, age  $\geq 20$  years, during a period of 13 years (1984 to 1996) were studied. These constituted 81% (270 cases) of the 333 cases classified as SCD in the Registry during this period. All these cases were reviewed to distinguish structurally abnormal hearts (group A) from structurally normal hearts (group B) (Figure 1). Structurally abnormal hearts were further classified as subgroup A1 if specific pathological findings were present or subgroup A2 if only nonspecific findings were identified. Detailed reexamination of all hearts reported to be structurally normal (group B) was done. In addition to repeat pathological examination, this included consideration of clinical and morphological data in the registry files and detailed review of the clinical histories of the patients by analysis of all available community medical records for each patient.

**Detailed Method of Pathological Examination**

For the duration of the 13 years of this study, all 270 SCD hearts were examined by the same cardiovascular pathologist (J.L.T.) in a standardized fashion. Specimens were weighed, with normal heart weight criteria, based on body mass index. After external analysis to ascertain size and shape of cardiac chambers, the coronary arteries were cut into 4- to 5-mm sections and the cross-sectional diameter measured. To ensure exclusion of coronary artery disease in morphologically normal hearts, the criterion for pathological diagnosis of significant coronary artery disease was stenosis of  $\geq 50\%$  cross-sectional diameter in at  $\geq 1$  major epicardial coronary artery.<sup>11</sup> Subsequently, the heart was excised open in a conventional line of flow. If no gross abnormality was identified, routine sampling included standard, full-thickness sections from the posterobasal, mid-anterior, lateral, and septum regions, including portions of relevant cardiac valves. From each block, hematoxylin and eosin-stained, trichrome-stained, and elastic van Gieson-stained slides were prepared and examined. In selected cases, when no other pathological abnormality was identifiable, a conventional study of the cardiac conduction system with sections at 4- to 5-mm intervals

was also performed. Nonspecific cardiac findings were defined as myocardial hypertrophy (increased heart weight for body surface area and/or  $>1.6$ -mm thickness of compact myocardium of the left ventricle), nonspecific interstitial fibrosis, and mitral valve prolapse. The association between mitral valve prolapse and sudden death has been controversial, and the increase in risk of sudden death with this condition is probably very small.<sup>12-14</sup> For the purpose of the present study, when pathological criteria for lone mitral valve prolapse were met, hearts were considered to have a nonspecific structural abnormality.<sup>15</sup>

**Results**

**Age and Sex Distribution**

The mean age of SCD patients was  $42 \pm 14$  years. The percent frequency of male and female cases according to age by decade for the 270 Minnesota-referred cases is shown in Figure 2; overall, 70% were men and 30% were women. The frequency of SCD varied with age. The majority of patients (66%) were  $>35$  years of age; younger adults (20 to 34 years) formed 33% of the total population.

**Structurally Abnormal Hearts**

Group A comprised 256 hearts (95% of total), with 180 (67% of total) and 76 (28% of total) hearts in subgroups A1 and A2. In subgroup A1, coronary artery disease was the most common finding (65% of cases), followed by congenital conditions in 14% (Figure 3). The latter group comprised 11 patients with anomalous coronary arteries and 15 patients with other congenital cardiac conditions (aortic valve malformations, 5; corrected transposition, 2; atrial septal defect, 1; pulmonary atresia, 1; cleft tricuspid/mitral valve, 2). The incidence of myocarditis was 11%; arrhythmogenic right ventricular dysplasia and hypertrophic cardiomyopathy were

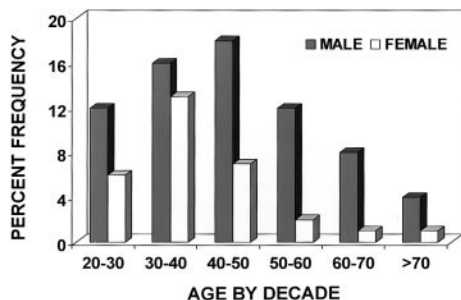


Figure 2. Age and sex distribution in entire autopsy series.

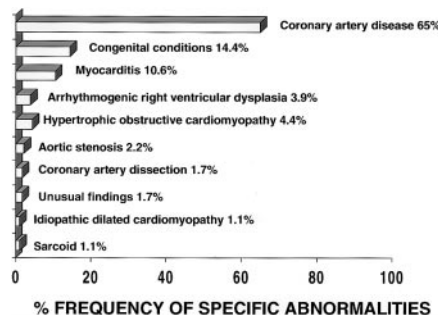


Figure 3. Group A1: structurally abnormal hearts with specific pathological findings.

## Details of Clinical Findings in Subjects With Structurally Normal Hearts

| Subject | Age, y | Sex | Time From Symptom-Onset to Death, h | Associated Conditions     | ECG Findings        | Serum Findings                        |
|---------|--------|-----|-------------------------------------|---------------------------|---------------------|---------------------------------------|
| 1       | 21     | F   | 0                                   | Pregnant, 27 wk           | Preexcitation       | Negative                              |
| 2       | 30     | M   | 0–6                                 | None                      | N/A                 | Negative                              |
| 3       | 33     | F   | 0                                   | Obesity                   | Preexcitation       | Negative                              |
| 4       | 37     | M   | 0                                   | Micronodular cirrhosis    | N/A                 | Negative                              |
| 5       | 33     | F   | 0–1                                 | Postpartum <1 wk          | N/A                 | Negative                              |
| 6       | 43     | F   | 0–6                                 | None                      | N/A                 | Benzoylcegonine, 0.21 mg/L            |
| 7       | 37     | M   | 0–1                                 | Family history of SCD     | N/A                 | Negative                              |
| 8       | 51     | M   | 0–12                                | Pervasive mental disorder | Normal              | Haloperidol, 43 $\mu$ g/mL            |
| 9       | 30     | F   | 0                                   | None                      | N/A                 | Negative                              |
| 10      | 22     | F   | 0                                   | Seizure disorder          | Normal              | Negative                              |
| 11      | 45     | F   | 0–1                                 | Schizophrenia             | Normal              | Valproate, 70 $\mu$ g/mL              |
| 12      | 32     | F   | 0–24                                | Seizure disorder          | Atrial fibrillation | Phenobarbital, 13.6 $\mu$ g/mL        |
| 13      | 45     | F   | 0                                   | None                      | N/A                 | Unidentified peak (mass spectrometry) |
| 14      | 32     | F   | 0–24                                | Obesity                   | Normal              | Negative                              |

present in  $\approx$ 4% each; other abnormalities occurred in  $\leq$ 2% cases (Figure 3). Findings in 3 cases were relatively unusual: 1 patient died of a ruptured sinus of Valsalva aneurysm, 1 had mycotic aneurysm with left ventricular rupture, and 1 had coronary arteritis.

In subgroup A2 hearts, a nonspecific abnormality was present, but a definite pathological diagnosis could not be made. These nonspecific abnormalities included left ventricular hypertrophy (left ventricular wall thickness of compact myocardium  $>$ 1.6 cm) found in two thirds of the cases (50 of 76 hearts), pathological criteria for mitral valve prolapse in approximately one third (28 of 76 hearts), and nonspecific interstitial fibrosis in the absence of discrete postinfarction scars identified in nearly one third of hearts (22 of 76 hearts) in this subgroup.

In the hearts with nonspecific fibrosis, the mean age of patients was identical to the average age for the entire series ( $42 \pm 12$  versus  $42 \pm 14$  years). Fibrosis/left ventricular hypertrophy and fibrosis/mitral valve prolapse coexisted in 11 of 22 and 8 of 22 hearts, respectively. A special conduction system examination was performed in 9 of these hearts, and fibrosis was found to extend to the atrioventricular node, His bundle, or either bundle branch in 8 patients. Comorbid conditions included seizure disorder (1, same patient had systemic lupus erythematosus), obesity (2, 1 patient had sleep apnea syndrome), noncardiac sarcoidosis (1), and emphysema (1). Only 2 patients had evidence of mild coronary disease (40% stenosis). Two patients were known to have manifested prior arrhythmia (ventricular tachycardia in 1 and supraventricular tachycardia 1).

### Structurally Normal Hearts

Group B contained 14 structurally normal hearts (5% of total). Among these cases, in addition to existing registry records, past medical records were available from 13 patients; 1 subject did not appear to have had any healthcare visits. ECGs were available in 6 of the 14. The mean age was  $35 \pm 9$

years (median age 33 years), and 10 of the 14 patients were women. A significant noncardiac abnormality was present in only 1 of the 14 cases; the patient had micronodular cirrhosis. Repeat cardiac examination (gross morphological and microscopic study) did not yield additional cardiac abnormalities.

### Details of Clinical History

From review of the 13 medical records (Table), sudden death was the first manifestation of disease in 7 cases. Six patients had a history of prior symptoms, of which 2 had syncope, 3 had a history of palpitations, and 1 had chest pain. Two patients had a family history of sudden death. Obesity was a comorbid condition in 2 patients, and 2 patients had a history of a seizure disorder.

The circumstances of death varied. One subject (patient 2, Table) had been exercising vigorously, having just completed his first jog of the spring. A 37-year-old man (patient 4, Table, with autopsy findings of micronodular cirrhosis) was consuming alcohol at a bar when he collapsed. One person was bathing, and 4 were sedentary. Four subjects died in their sleep.

Chemical analysis of serum collected at the time of autopsy did not show evidence of drug overdose in any of the cases; in 9, the findings were negative. In the remaining 5 cases, however, serum tested positive for some compound. One subject had nontoxic levels of a cocaine metabolite (benzoylcegonine) in the blood and another had therapeutic levels of haloperidol (Table). The 2 patients with seizure disorder were taking valproic acid and phenobarbital. A 37-year-old woman of Southeast Asian origin, who had been previously healthy, had an unidentified peak on mass spectrometry of the serum. With the exception of the patient with findings of cocaine in the serum, no other patients had a history of drug abuse.

### ECG Analysis

Of the 6 ECGs available, 3 were normal, without evidence of QT prolongation. The other 3 were abnormal; patients 1 and

3 (Table) had evidence of preexcitation on the ECG. An ECG from patient 12 (Table), taken 6 months before death, showed atrial fibrillation with a rapid ventricular response and narrow QRS complexes.

### Discussion

Of the 270 archived hearts, 256 (95%) had evidence of structural abnormalities, but in up to 30% of cases, these abnormalities were nonspecific. Fourteen (5%) patients, of which 10 were women, had structurally normal hearts. In this subset, a possible substrate or trigger for SCD could be identified in 8 cases. Of the remaining 6 cases, none had identifiable conditions that may be associated with SCD. Seven patients had a history of syncope, palpitations, or chest pain before SCD. In the remaining 7 cases, sudden death was the first presentation of an illness.

For the patients with specific structural abnormalities, our findings are similar to published reports. In older adults (age >45 years), 80% to 90% of sudden cardiac death patients have significant coronary artery disease.<sup>16,17</sup> Coronary artery disease is also associated with 58% to 70% of sudden cardiac deaths in the young adult population.<sup>18–20</sup> In our study (mean age  $42 \pm 14$  years), 65% of SCD patients with specific pathological findings had significant coronary artery disease. Findings of congenital anomalies, myocarditis, arrhythmogenic right ventricular dysplasia, and hypertrophic cardiomyopathy in our study are consistent with earlier studies in the young adult population.<sup>5,21–25</sup>

In 5% of cases we studied, no structural abnormalities were identified after repeated pathological examinations. In an earlier 30-year, population-based study of young adults from the same region as the cases we studied, a potential cause of SCD could not be identified in 13% cases<sup>20</sup>; in that study, however, nonspecific findings such as left ventricular hypertrophy were not included as structural abnormalities.

The significant frequency (30%) of nonspecific structural abnormalities in SCD patients, in the absence of other cardiac abnormalities, has not been reported previously. Heart weight (indexed by body surface area) is not increased in patients of comparable age to the present study who die of causes unrelated to the heart.<sup>26</sup> From clinical trials, left ventricular hypertrophy has been established as an independent predictor of overall mortality.<sup>27,28</sup> In addition, in patients with left ventricular hypertrophy, the risk of ventricular arrhythmia is increased  $\geq 2$ -fold.<sup>29</sup> Observations in animal models suggest that cardiac myocytes from hypertrophied hearts develop abnormalities of repolarization, which could predispose to fatal arrhythmogenesis.<sup>30</sup> Similarly, it is conceivable that nonspecific interstitial fibrosis could contribute to the initiation of ventricular arrhythmias through a functional reentrant mechanism.<sup>31</sup> The presence of fibrosis in some component of the conduction system in 8 of 9 hearts subjected to a detailed conduction system examination suggests a propensity for bradycardia in some of these patients. The nature of factors responsible for the presence of interstitial fibrosis in this group remains uncertain. As the mean age of patients with nonspecific fibrosis was identical to the average age for the entire series ( $42 \pm 12$  versus  $42 \pm 14$  years), this is unlikely to be related to the process of aging. We are not aware of

autopsy series examining the prevalence of nonspecific interstitial fibrosis in this age range in the general population.

### Possible Causes of SCD in Patients With Structurally Normal Hearts

In 2 cases, Wolff-Parkinson-White (WPW) syndrome may have been the abnormal substrate for SCD. Long QT syndrome cannot be excluded for cases in which ECGs were not available; 2 of the patients had a family history of sudden death. In addition, this syndrome may often not be recognized on a single ECG. Rare and newly described conditions such as the Brugada syndrome (sudden cardiac death with right bundle-branch block and ST elevation on ECG)<sup>32</sup> were not identified. Subject 2 (Table) was a 30-year-old man of Southeast Asian origin who may have died of sudden nocturnal death syndrome.<sup>33</sup> Inability to define a cause in cases of SCD may have placed several subjects in the category of idiopathic ventricular fibrillation. In several cases, drugs may have been triggers for SCD of susceptible individuals.

In this study, the incidence of WPW syndrome may have been underestimated. There was evidence of preexcitation on 2 of the 6 ECGs that were available for review. Both of these patients had a history of palpitations and documented tachycardia before death; supraventricular tachycardia is a risk factor for the development of ventricular fibrillation in the WPW syndrome.<sup>34</sup>

Both obesity and epilepsy were comorbid conditions in SCD patients with structurally normal hearts. The annual sudden cardiac mortality rate is reportedly increased 40-fold in morbidly obese subjects<sup>35</sup> when compared with a matched nonobese population. Sympathovagal imbalance caused by parasympathetic withdrawal in obese subjects has been implicated in the enhanced sudden death risk in obesity.<sup>36</sup> In a recent population-based study of young adults with epilepsy, the rate of sudden unexpected death was 24-fold higher than the general population.<sup>37</sup> Mechanisms remain unresolved, but precipitation of fatal arrhythmia caused by autonomic dysfunction has been postulated as a cause of sudden unexplained death in epilepsy.<sup>38,39</sup>

The electrophysiological effects of cocaine have been examined in tissue preparations, animal models, and human subjects. The drug has class I-type activity, with significant effects on myocardial refractoriness.<sup>40</sup> In addition, cocaine can have a proarrhythmic effect similar to that induced by quinidine as the result of triggered activity from early afterdepolarizations associated with a prolonged QT interval. Thus, cocaine ingestion could induce ventricular arrhythmia independent of its effects on coronary arteries<sup>41</sup> and in the absence of toxic levels. Several antipsychotic agents, including phenothiazines, have been associated with sudden death.<sup>42,43</sup> Increased susceptibility to polymorphic ventricular arrhythmia by haloperidol may be related to block of outward potassium currents in the cardiac myocyte with resultant prolongation of the QT interval.<sup>44</sup> A recent study indicated that in some families, the long QT syndrome may have a very low penetrance, with family members being prone to development of torsade de pointes when exposed to cardiac or noncardiac drugs that block potassium channels, without manifestation of a long QT interval on the ECG.<sup>45</sup> In the

present study, possible contributions of drugs to development of fatal arrhythmia cannot be ruled out in at least 2 patients despite the absence of toxic levels in the serum.

Prevention of sudden death in subjects with apparently normal hearts is a major challenge because mechanisms are not well understood. Similar to coronary artery disease,<sup>1</sup> SCD was the first manifestation of disease in 50% of patients. Identification of individuals at risk for SCD who do not have recognized structural cardiac abnormalities requires a search for substrate abnormalities, which may depend on molecular analysis, including genetic typing.<sup>46–48</sup> For the investigation of SCD, confirmation of structural normalcy of the heart at the time of autopsy likely should be combined with targeted, prospective molecular analysis of tissue as the next step in identifying causes in this group of patients.

### Possible Limitations of Study

Despite careful, methodical pathological examination of cardiac structure, atrioventricular accessory connections can be overlooked. In addition, the identification of such muscular connections may not be confirmation for the existence of a clinically relevant accessory electrical connection between the atria and ventricles.<sup>49,50</sup> In our study, detailed histological examination of the conduction system with serial histological sections cut at 4.5- $\mu$ m intervals was done in 6 of the 14 hearts; no significant abnormalities were found. Plasma or tissue analyses for molecular defects such as genetic testing for the long QT syndrome were not performed.

The referred cases were nearly all <60 years of age. For the purpose of uniformity, only locally referred cases were included, the large majority consisting of patients examined by coroners in the 3 surrounding counties. As the coroners may not have examined all local cases of sudden death, the incidence of sudden cardiac death may have been underestimated. However, there was a consistent referral pattern, ie, cases of sudden death attributable to cardiac causes and age <60 years. In addition, the sex distribution would argue against a sex bias because approximately one third of the entire group were women.

Because the major goal of our study was a detailed clinical correlation in structurally normal hearts, complete clinical correlation for hearts with nonspecific fibrosis is not available. However, we have provided all the information present in the registry records. ECGs were available in only 6 of the 14 group B cases. This is probably explained by the relatively young age of these patients as well as SCD being the first manifestation of illness in 50% patients in this group.

### Conclusions

The vast majority of SCD patients had structurally abnormal hearts, but in as many as 30%, abnormalities were nonspecific. For patients with structurally normal hearts, the autopsy–clinical history combination uncovered potential mechanisms of SCD in 57% cases.

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