Sudden cardiac death in young people with apparently normal heart

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Abstract

Objective: The aim of the present study was to assess the prevalence of subtle morphologic substrates, clinically unrecognizable, underlying sudden cardiac death (SCD) in young people with apparently normal heart. Methods: In the time interval 1979–1998, 273 consecutive cases of SCD in young people (≤35 years) which occurred in the Veneto Region of Italy were prospectively studied. Following exclusion of extracardiac causes of sudden death, the heart was examined according to a detailed morphologic protocol consisting of macroscopic and histologic examination, including study of the specialized conduction system by serial sections. Results: At macroscopic examination, 197 SCD victims (72%) had an overt underlying structural heart disease such as cardiomyopathy in 56, obstructive coronary atherosclerosis in 54, valve disease in 32, non-atherosclerotic coronary artery disease in 28, aortic rupture in 13, postoperative congenital heart disease in five, and other disease in nine. The remaining 76 cases (28%) (50 males and 26 females, aged 4–35 years, mean 23±5 years) had a macroscopically normal heart. A total of 28 of them (37%) had experienced one or more of the following prodroma: syncope, palpitations or both in 20, ECG abnormalities in 18 and arrhythmias in ten. In 79% of them, histologic examination disclosed concealed pathologic substrates consisting of focal myocarditis in 27 cases, regional arrhythmogenic right ventricular cardiomyopathy, mostly localized to RV outflow tract, in nine, and conduction system abnormalities in 24 (leading to ventricular preexcitation in 18 and heart block in six). In 16 hearts (6%) there was no evidence of structural heart disease even after histologic study. Conclusion: Macroscopic heart features were normal in nearly one-third of young SCD victims. In 79% of them, however, histologic study unmasked concealed pathologic substrates such as focal myocarditis or cardiomyopathy and conduction system diseases. A total of 16 victims (6%) had no evidence of structural heart disease and the mechanism of their SCD remained unexplained.

Keywords: Arrhythmia (mechanisms); Cardiomyopathy; Conduction system; Histo(patho)logy; Myocarditis; Sudden death

1. Introduction

A structural cardiac abnormality is found at autopsy in most cases of sudden cardiac death (SCD) [1–10]. Fatal events in adults usually occur as an arrhythmic complication of atherosclerotic coronary artery disease, in the setting of either acute coronary syndromes or previous myocardial infarction [1–6]. Other cardiovascular disorders implicated in SCD, predominantly in younger people, include cardiomyopathy, valve heart disease, congenital anomaly of coronary arteries, conduction system disease, and congenital heart disease [6–9].

SCD may occur in patients with ‘apparently’ normal heart [7,10–12]. The mechanism is usually arrhythmic, namely a rapid ventricular tachycardia or fibrillation leading to cardiac arrest with no demonstrable structural heart disease. Failure to detect structural abnormalities may depend on the unknown or concealed nature of the underlying pathologic substrates along with the the low sensitivity of currently available clinical tests [12–14]. Subtle structural heart conditions potentially at risk of sudden arrhythmic cardiac arrest include coronary artery spasm superimposed on a non-obstructive coronary artery plaque, focal myocarditis, segmental cardiomyopathy, and abnormalities of the conduction system [13,14]. The ultimate diagnosis of these structural lesions which remain

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clinically concealed may require histologic examination by endomyocardial biopsy or at postmortem.

On the other hand, life-threatening ventricular arrhythmias may be the result of a primary electrical instability of the heart (so-called ‘idiopathic’ ventricular tachycardia or fibrillation) on structurally normal heart [14,15].

The aim of the present study was to assess by histological examination of both ordinary ventricular myocardium and specialized conduction system the prevalence and nature of concealed pathologic substrates underlying SCD in a large cohort of young victims with apparently normal heart at macroscopic examination.

2. Methods

A clinico-pathologic study of sudden death in young people was carried out in the Veneto Region of Italy from 1979 to 1998. Sudden death in young people was defined as unexpected death as a result of natural causes in which loss of all functions occurred instantaneously or within 1 h of the onset of symptoms or collapse in person aged 35 years or younger; cases of sudden infant death syndrome were ruled out. The study protocol has been reported in detail elsewhere [7,9]. The heart morphology was evaluated as follows.

2.1. Morphologic protocol

Sudden death (SD) victims were examined postmortem by the local pathologist or medical examiner from various medical centers in the Veneto Region of Italy which participated in the study project. Following exclusion of extracardiac causes of SD by routine autopsy as well as drug and alcohol abuse upon the postmortem toxicologic examination of blood and urine, the entire heart was fixed in formalin and forwarded to the Institute of Pathological Anatomy of the University of Padua for detailed morphological investigation.

2.1.1. Gross examination

Macroscopic examination included measurement of heart weight, chamber size and wall thickness, as well as inspection of the coronary arteries and valves. The origin and course of the coronary arteries were examined, and the patency of the four major epicardial coronary trunks was analyzed by taking transverse sections at 3-mm intervals. The following ventricular regions were systematically examined: inflow tract, outflow tract, apex, posterolateral and anterolaterals walls of both ventricles and the interventricular septum.

2.1.2. Histologic examination

Several coronary arterial segments and full-thickness blocks of myocardium were removed for histologic examination from each region of the right and left ventricles and the septum, in a plan parallel to the long axis of the ventricles. Tissue specimens were embedded in paraffin and routinely processed. All coronary artery and myocardial sections (5–7 μm thick) were stained with hematoxylin-eosin, Weigert-van Gieson, and trichromic Heidenhain (azan) techniques. Parallel sections 4–5 μm thick were stained with a panel of antibodies using avidin–biotin peroxidase complex immunohistochemical methods for cell infiltrate characterization.

Study of the specialized conduction system was carried out by serial sections according to a previously described method [16]. In brief, two blocks of tissue were excised from the heart, the first containing the sinoatrial node and its atrial approaches, the second the atrioventricular node and its atrial approaches, the His bundle, the bifurcation and the bundle branches. Blocks of lateral AV rings including atrial and ventricular myocardium were cut serially as well [17]. Entire blocks were fixed in 10% buffered formalin, embedded in paraffin and serially sectioned at 7-μm intervals. Three consecutive sections at every 100–150-μm interval were stained with hematoxylin-eosin, Weigert-van Gieson, and and trichromic Heidenhain (azan) techniques.

2.2. Pathologic substrates of SD

Obstructive atherosclerotic coronary artery disease was diagnosed by the presence of one or more major epicardial coronary arteries narrowed by more than 70% in cross-sectional luminal area [9]. Hypertrophic cardiomyopathy was diagnosed by the presence of macroscopic cardiac hypertrophy, defined with population based criteria for normal cardiac weight as well as septum and free wall thickness, either asymmetric or symmetric, in the absence of other cardiac causes of hypertrophy such as hypertensive, valvular, or congenital heart disease, and microscopic evidence of myocardial disarray that involved a significant portion of the interventricular septum [18]. The diagnosis of arrhythmogenic right ventricular cardiomyopathy was made by the presence of gross and/or histological evidence of regional or diffuse fatty or fibrofatty replacement of the myocardium of the right ventricular free wall reaching the endocardium (i.e. transmural), in the absence of other known cardiac or non-cardiac causes of death [19]. Myocarditis was diagnosed according to the Dallas criteria [20] by the presence of inflammatory infiltrates of the myocardium with degeneration and/or necrosis of adjacent myocytes. Mitral valve prolapse was diagnosed on the basis of increased leaflet thickness, floppiness and redundancy with intercordal hooding and leaflet billowing towards the left atrium [21].

The heart was defined as ‘apparently normal’ in the absence at postmortem macroscopic examination of any cardiovascular pathology and cause of death such as obstructive coronary atherosclerosis, cardiomyopathy, congenital heart disease and coronary anomalies, valve
disease, aortic dissection, or pulmonary thromboembolism. The heart was defined as 'structurally normal' when histologic examination of both ordinary myocardium and specialized conduction system definitively ruled out any structural abnormalities.

2.3. Clinical data

Retrospective clinical information of SCD victims included age and gender, family history, sport activity, prior symptoms, 12-lead electrocardiographic (ECG) changes, arrhythmias, and echocardiographic findings, drug therapy, and circumstances of death.

2.4. Control group

A total of 20 hearts from age- and sex-matched subjects who died suddenly of drug abuse or extracardiac causes served as controls.

2.5. Statistical analysis

Continuous variables were expressed as mean±S.D. The χ² or Fisher’s exact test was used to assess the significance of differences between subgroups. A two-tailed P-value of less than 0.05 was considered statistically significant.

3. Results

From January 1979 to June 1998, 273 consecutive cases of SCD in young people (218 males and 82 females, aged 1–35 years, mean 24±8) which occurred in the Veneto Region of Italy underwent detailed morphologic investigation of the heart.

3.1. Grossly abnormal heart

At macroscopic examination, an overt structural heart disease was identified in 197 of 273 (72%) SCD victims (Table 1). In 17 cases the mechanism of cardiac arrest was clearly mechanic and consisted of aortic rupture in 13 and pulmonary thromboembolism in four. In the other 180, death was probably caused by an arrhythmic cardiac arrest due to cardiomyopathy in 57 (arrhythmogenic right ventricular cardiomyopathy (ARVC) in 27, hypertrophic cardiomyopathy in 18, dilated cardiomyopathy in 12), obstructive coronary atherosclerosis in 54, valve disease in 31, non-atherosclerotic coronary artery disease in 28, postoperative congenital heart disease in five, and other causes in five.

3.2. Apparently normal heart

The remaining 76 cases (28%) had an apparently normal heart at macroscopic examination (Fig. 1). A total of 28 of them (37%) had experienced one or more of the following prodroma: syncope, palpitations or both in 20, ECG abnormalities in 18 and arrhythmias in ten. The following two subgroups were identified.

3.2.1. Concealed structural abnormalities

In 60 (79%) SCD victims with apparently normal heart, histologic examination of both ordinary ventricular myocardium and specialized conduction system unmasked concealed pathologic substrates such as focal myocarditis in 27 cases, segmental ARVC in nine cases, and conduction system diseases in 24 (Fig. 1). 3.1. Grossly abnormal heart

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3.2.1.1. Myocarditis

A total of 27 SCD victims (20 males and seven females, aged 6–35 years, mean 21±3) showed histopathologic evidence of myocarditis. Death occurred at rest in 21 patients (in two during sleep) and during effort in six (three of whom were competitive athletes). Prodromal symptoms were present in nine and consisted of a history of a flu-like illness 2–15 days before the fatal event in six, syncopal episodes in two, chest pain in one. A 12-lead ECG, available in three patients, showed

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Table 1

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<td>Apparently normal hearts</td>
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Fig. 1. Apparently normal heart: subgroup identification.
normal findings, pathologic ‘q’ waves in anterior precordial leads, and isolated premature ventricular beats, respectively.

The gross appearance of the heart was not distinctive, and the weight ranged within normal values (230–470 g, mean 350±125). In all cases, histological examination showed a patchy interstitial inflammatory infiltrate (at least three foci, at magnification 6×) associated with degenerative changes and/or necrosis of adjacent myocytes (Fig. 2). According to histologic and immunohistochemical characterization of inflammatory cells, myocarditis was polymorphous in 16 cases, lymphocytic in nine, giant cell in one, and rheumatic in one. In four cases the inflammatory process was subacute-healed and associated with areas of replacement-type fibrosis.

3.2.1.2. Segmental ARVC The nine patients with segmental ARVC consisted of seven males and two females with an age range of 16–30 years (mean 23±5 years). At the time of the fatal event, seven patients were engaged in sedentary activity, while the other two died during effort (one during sport activity). Three patients had a family history of premature sudden death. Two patients were asymptomatic; the other seven had palpitations that were associated with syncopal episodes in four. A 12-lead ECG was available in five of nine patients and showed precordial T wave inversion beyond V1 in only two (40 vs. 94% of patients with diffuse ARVC from the same series, P<0.05). Ventricular arrhythmias with a left bundle branch block morphology had been documented in two cases. No patients underwent two-dimensional echocardiography or any other imaging technique during life.

In all cases, there was histopathologic evidence of localized myocardial atrophy with fatty (five cases) or fibrofatty (four cases) replacement of the RV wall, in the absence of cardiomegaly (heart weight range 270–430 g), global RV dilatation, or aneurysms. The most common regions of RV involvement included the outflow tract (five cases), anterolateral wall (two cases), apex (one case), and posterobasal wall (one case). In the affected areas, myocardial depletion was so deep as to involve transmurally the RV wall (Fig. 3a). The outer epicardial border of the original heart musculature was still defined by a residual rim of myocardial fibers. Fibrosis was observed in every case: it was predominantly located in the subendocardium and appeared tiny interstitial in five cases and replacement-type in four (Fig. 3b). Pachy lymphomononuclear infiltrates were seen in four cases; the left ventricular myocardium was spared.

3.2.1.3. Specialized conduction system diseases Histologic examination of the specialized conduction system by serial sections disclosed abnormalities in 24 patients (18 males and six females, aged 4–35 years, mean 24±4).

A total of 18 patients had congenital accessory pathways leading to ventricular preexcitation (that was documented by 12-lead ECG in ten). Six patients had a history of paroxysmal supraventricular tachycardia, associated with syncope in two. Sudden death occurred at rest in all but one (during sleep in four). Pathologic substrates of ventricular preexcitation included atrio-ventricular accessory pathways in ten cases, which were left lateral in six and right septal in four (two of whom in the setting of a mild Ebstein anomaly of the tricuspid valve); nodoventricular accessory pathways (Mahaim fibers) in six, right-sided atrio-Hissian tract in one, and AV node hypoplasia in one.

Six patients had acquired lesions of the specialized
conduction system leading to heart block. Three patients experienced previous symptoms such as syncope in two cases and recurrent presyncopal episodes in one. A 12-lead ECG, available in four patients, was normal in one and showed isolated right bundle branch block in two and right bundle branch block associated with left axis deviation in one. Pathologic substrates consisted of fibrotic interruption of both right and left bundle branches in three (Fig. 4) (with involvement of AV node in one), adipose insulation of the AV node resulting in atrionodal discontinuity in two, and a highly innervated sinus node probably leading to sick sinus syndrome in one.

3.2.2. Structurally normal hearts

The remaining 16 SCD victims (21% of victims with apparently normal hearts and 6% of overall SCD) included ten males and six females, aged 1–34 years (mean 20±8 years), who had no evidence of structural abnormalities even after detailed histologic examination of both ordinary ventricular myocardium and specialized conduction system, and the cause of their cardiac arrest remained unexplained (Fig. 1). Sudden death was exercise-unrelated in 14 cases (87%). One patient was grossly obese and four patients had a history of seizure disorder. Sudden death was the first manifestation of cardiac disease in all
Fig. 4. Sudden cardiac death in a 31-year-old man with apparently normal heart at gross examination. Serial histologic examination of the conduction system shows severe fibrosis of both the proximal left (a) and right (b) bundle branches.
but two patients who complained of syncopal episodes and recurrent palpitations due to paroxysmal supraventricular tachycardia, respectively. A 12-lead ECG was available in four patients: it was abnormal in two (borderline prolongation of QTc interval and isolated right bundle branch block, respectively) and normal in the other two.

Table 2 shows the final cause of death in the 273 SCD victims after histologic examination of ventricular myocardium and conduction system.

3.3. Controls

None of the control hearts exhibited significant coronary, myocardial, valve, or conduction system abnormalities.

4. Discussion

4.1. Background

Sudden cardiac arrest in the absence of structural heart disease is an uncommon event, although recent studies indicate that it is more common that previously recognized [1–10]. Data from large series of adult patients experiencing out-of-hospital cardiac arrest show that no clinical evidence of structural heart disease is found for 1–6% of all cardiac arrest survivors [10,15,22–24]. In a younger patient population (<40 years) the percentage of patients suffering prehospital cardiac arrest without identifiable cardiovascular disease increases up to 15% [25–27]. These patients, defined as having 'idiopathic ventricular fibrillation' or 'unexplained cardiac arrest', must be carefully investigated in order to establish whether ventricular fibrillation is the result of an underlying concealed structural heart disease or a true primary electrical heart disease.

4.2. Apparently normal heart

The major findings of the present study are that nearly one third of young people who died suddenly had a normal heart at macroscopic examination; in the majority of these apparently normal hearts histologic investigation unmasked pathologic substrates, concealed but potentially arrhythmogenic, such as focal myocarditis or cardiomyopathy and conduction system diseases; in nearly 6% of overall young SCD victims there was no evidence of structural heart disease despite thorough cardiovascular morphologic study and the cause of cardiac arrest remained unexplained.

These results are in agreement with previous studies in which endomyocardial biopsy was used to investigate subclinical structural abnormalities in patients with life-threatening ventricular arrhythmias but apparently normal heart. Strain et al. [28] performed endomyocardial biopsy in 18 patients with ventricular tachycardia or fibrillation and apparently normal heart. The majority of patients (16 of 18; 89%) had one of more of the following histologic abnormalities: significant (although non-specific) cardiomyopathic changes such as myocardial hypertrophy, interstitial and perivascular fibrosis, and vascular sclerosis in nine; subacute inflammatory myocarditis in three; diffuse abnormalities of intramyocardial arteries in two; and fatty replacement of ventricular myocardium consistent with ARVC in two. Likewise, Sugrue et al. [29] detected histopathologic abnormalities in 11 of 12 (89%) endomyocardial biopsy specimens from patients with serious ventricular arrhythmias occurring in the setting of normal cardiac anatomy and mechanical function. Seven patients had myocardial cellular hypertrophy; five had interstitial fibrosis; two had endocardial fibrosis; and three had myocardial degenerative changes, increased interstitial cellularity, and inflammatory infiltrates, respectively.

Moreover, our findings are very similar to those recently reported by Chug et al. showing a 5% prevalence of structurally normal hearts (without any evidence of either macroscopic and histologic structural abnormalities) in a large autopsy series of SCD victims aged 42±14 years from Minneapolis-St. Paul [30].

4.3. Concealed pathologic substrates

4.3.1. Myocarditis

In our study, focal myocarditis was the most frequent pathologic substrate of SCD in those victims with apparently normal heart and accounted for 10% of overall SCDs. This figure is in agreement with previous autopsy studies, which reported a prevalence of focal myocarditis ranging from 1 to 5% of sudden death victims [31,32]. Unlike diffuse form of myocarditis which is usually associated with ventricular dysfunction and abnormal ECG findings, focal inflammatory infiltrates may precipitate fatal ventricular arrhythmias despite normal ventricular function and basal ECG and in the absence of prodromal symptoms.
Accordingly, definitive diagnosis of these subclinical cases can be obtained in vivo only by direct demonstration of inflammatory infiltrates at endomyocardial biopsy. Due to the patchy involvement of the myocardium, endomyocardial biopsy, however, is expected to have a low diagnostic sensitivity and normal bioptic findings cannot be considered a definitive criterion for excluding myocarditis.

4.3.2. Arrhythmogenic right ventricular cardiomyopathy

ARVC is a well recognized cause of arrhythmic SD, even in patients with apparently normal heart [7,8,33–35]. This disease is characterized pathologically by fibrofatty substitution of the right ventricular myocardium. Apoptosis has been recently shown to be a mode of myocyte death in ARVC and may explain the progressive myocardial loss [36,37]. Clinical features include ventricular arrhythmias such as ventricular tachycardia with left bundle branch block morphology and ventricular fibrillation which may lead to sudden death mostly in young people and athletes [7,8]; ECG abnormalities in the form of prolongation of QRS interval and inversion of T waves in right precordial leads; and morpho-functional abnormalities of the right ventricle [38]. The spectrum of clinical manifestation of ARVC ranges from a generalized involvement of the entire right ventricle with global dilatation, impaired hemodynamics, and peculiar ECG findings, to regional lesions resulting in apparently normal gross anatomy and function of the right ventricle in the absence of significant ECG abnormalities (‘concealed ARVC’) [39]. It is noteworthy that in the present study a normal 12-lead ECG was found in 60% of SCD victims with segmental ARVC as compared with only 6% of those with diffuse ARVC. Whether this localized involvement represents early cardiomyopathic changes or a distinctive form of ARVC remains to be established. It is often difficult to make a differential diagnosis between concealed ARVC and idiopathic VT or VF by means of conventional clinical testings and ultimate diagnosis may depend on demonstration of fatty replacement of the RV myocardium at magnetic resonance or endomyocardial biopsy [40].

Although a preclinical genetic diagnosis of ARVC by DNA characterization is warranted, it is not yet available [41–46].

4.3.3. Conduction system diseases

Our findings indicate that clinically silent accessory pathways represent a not so rare concealed substrate in those cases of SCD with apparently normal heart. The mechanism of cardiac arrest consists in a paroxysm of atrial fibrillation which may convert to ventricular fibrillation due to the very rapid ventricular transmission (more than 300 beats per minute) in the setting of either an accessory pathway or an enhanced AV conduction [47]. Before diagnosing idiopathic ventricular fibrillation, ventricular preexcitation should be excluded by careful evaluation of its distinctive features on 12-lead ECG. In the present study, most fatal AV accessory pathways were located in the left lateral ring, a site that may account for minimal ventricular preexcitation, and are not apparent on the ECG (so-called ‘latent preexcitation’) [48]. Therefore, definitive evaluation of ventricular preexcitation in patients with aborted sudden death relies on intracardiac electrophysiology which also allows assessment of accessory pathway refractoriness which is the most important factor related to the risk of SCD.

Degenerative changes of the AV junction (premature Lev’s or Lenegre’s disease) were another concealed substrate of SCD in young people. This condition may be sporadic, associated with cardiomyopathies, either dilated or right ventricular, or may occur in the setting of a familial progressive conduction system disease. This is an autosomal dominant condition with genetic linkage to chromosome 19 [49]. It is characterized clinically by changes in the ECG conduction pattern ranging from bundle branch block to complete AV block and pathologically by progressive fibrous atrophy of the His-Purkinje system. Recurrent Morgagni-Adams-Stokes attacks and/or sudden death represent the most severe complications, which are caused by paroxysmal AV block without escape of ventricular rhythm. The progressive nature of the conduction system disease may explain our finding that even an isolated right bundle branch block on the ECG may be a marker of underlying His-Purkinje disease. Therefore, this ECG pattern should be searched for in SCD survivors and investigated by intracardiac electrophysiology.

4.4. Structurally normal heart

In the present study, nearly 6% of overall SCD victims (21% of those with apparently normal heart) had no evidence of structural abnormalities even after detailed gross and histologic examination of the heart. It is noteworthy that four victims had a history of seizure episodes and one was grossly obese. Both epilepsy and obesity are conditions predisposing to sudden death, probably due to ventricular arrhythmias precipitated by autonomic dysfunction and sympathovagal imbalance, respectively [50–52]. The cause of fatal electrical instability in the remaining cases is probably related either to primary electrical heart diseases such as long QT syndrome, or to idiopathic ventricular fibrillation [14,15]. Recently it has been reported that idiopathic ventricular fibrillation may occur in patients with a distinctive ECG pattern of right bundle branch block and ST-segment elevation in right precordial leads (V1 to V2–V3) (so-called Brugada syndrome) [53,54]. This ECG pattern and the electrical ventricular instability have been explained by dispersion of repolarization between the right ventricular epicardium and endocardium which predisposes to local reexcitation of myocytes with different action potential durations [55,56]. A missense mutation in the cardiac...
sodium channel gene SCN5A has been recently discovered in patients with Brugada syndrome [57]. Since the ECG abnormalities of Brugada syndrome may change over the time until transient complete normalization [58], this condition cannot be excluded as a cause of SCD in our series of young victims with apparently normal heart and normal or nearly normal (isolated right bundle branch block) ECG tracing. Postmortem diagnosis by DNA analysis of both long QT syndrome and Brugada syndrome will narrow the number of victims with unexplained SCD [59–61].

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References


