Sudden arrhythmic death and cardiomyopathies in the young: a molecular and pathology overview

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Abstract

Cardiovascular disease is a significant cause of sudden death (SD) requiring autopsy investigation. Non-ischaemic causes of SD are more prevalent in young people (<35 years of age) and conditions such as cardiomyopathies and channelopathies account for about one half of cases.

The pathologist's task is to provide the correct diagnosis and, when dealing with a genetic disease, to initiate pre-symptomatic cardiologic and genetic cascade screening of first-degree family members. Early identification is important because SD can be the first and last clinical presentation of the underlying disease and the only medical examination undertaken is the autopsy. A standardized and detailed post-mortem procedure on the SD victims, in combination with molecular testing ("molecular autopsy"), will provide vital information for the family in preventing a further tragedy. Therefore proper sampling to allow post-mortem DNA analysis as well as accurate morphological evaluation, are mandatory, as recommended in the guidelines for autopsy investigation of SD from the Association for European Cardiovascular Pathology.

Keywords autopsy; cardiomyopathies; genetics; sudden death

Sudden death (SD) is defined as an unexpected death occurring within 1 hour after the onset of symptoms (within 24 hours, when unwitnessed), in an apparently healthy subject.[1] In adolescents and young adults (<35 years) the approximate incidence is 0.01 per 1000 per year and cardiomyopathies, myocarditis, premature coronary artery disease, congenital coronary artery anomalies and channelopathies play a major causative role (Figure 1). The incidence of SD then increases, reaching about 1 per 1000 per year in the subjects 35–40 years, 2 per 1000 per year by 60 years and 200 per 1000 per year in the elderly.[2–4] In the prospective study carried out in the Veneto Region, North East Italy, among the non-athletic young people the incidence of SD was 0.9/100.000/year (0.09%/year), whereas in the athlete it was 2.3/100.000/year (0.23% year). Thus, the incidence of SD in athletes was 2.5 fold, clearly indicating that effort is a risk in people affected by hidden morbid entities.[5]

SD is usually caused by ventricular arrhythmia and more rarely by bradyarrhythmia with conduction abnormalities. When performing autopsy investigation of arrhythmic SD, the pathologist may encounter several congenital or acquired cardiovascular causes, in particular atherosclerotic coronary artery disease, especially in older people. In contrast, cardiomyopathies account for about half of SD cases in young people (Figure 1).[6–9] The cardiomyopathies at risk of electrical instability and SD, with the focus on the pathologic and molecular aspects, are discussed in this review.

Definition and classification of cardiomyopathies

The identification of novel clinico-pathological entities and the discovery of the genetic basis of several cardiovascular diseases, have necessitated a first change in definition of the original classification of cardiomyopathies published in the 1980s.[10,11] The awareness that many primary cardiomyopathies are inherited then led many researchers to ask if it is time for a genomic classification, thus distinguishing cytoskeleton (e.g., dilated cardiomyopathy), desmosomal (arrhythmogenic [ACM]), sarcomeric (as hypertrophic [HCM] and restrictive) and ion channel (channelopathies, e.g., long [LQT] or short [SQT] QT syndrome, Brugada syndrome and catecholaminergic polymorphic ventricular tachycardia [CPVT]) cardiomyopathies.[12]

Thus, a Task Force of the American Heart Association (AHA) in 2006 proposed a new definition and classification of cardiomyopathies[13] that recognized the contributions of molecular genetics, introduced several discovered entities, and included channelopathies as primary cardiomyopathies due to electrical dysfunction without morphological changes.

Accordingly, cardiomyopathies are defined as "a heterogenous group of diseases of the myocardium associated with mechanical and/or electrical dysfunction, which usually (but not invariably) exhibit inappropriate ventricular hypertrophy or dilatation and are due to a variety of causes that frequently are genetic".[13] With this definition, it was recognized that a heart affected by cardiomyopathy is not necessarily associated with cardiomegaly, that the cause can be genetic, and that cardiac dysfunction can be merely electrical. Pathological conditions in which myocardial dysfunction is a direct consequence of other cardiovascular abnormalities, such as valvular heart disease, systemic hypertension, congenital heart disease, and atherosclerotic coronary artery disease, are not included among cardiomyopathies.

The cardiomyopathies have been divided into two main categories: a) primary cardiomyopathies, when the disorder is

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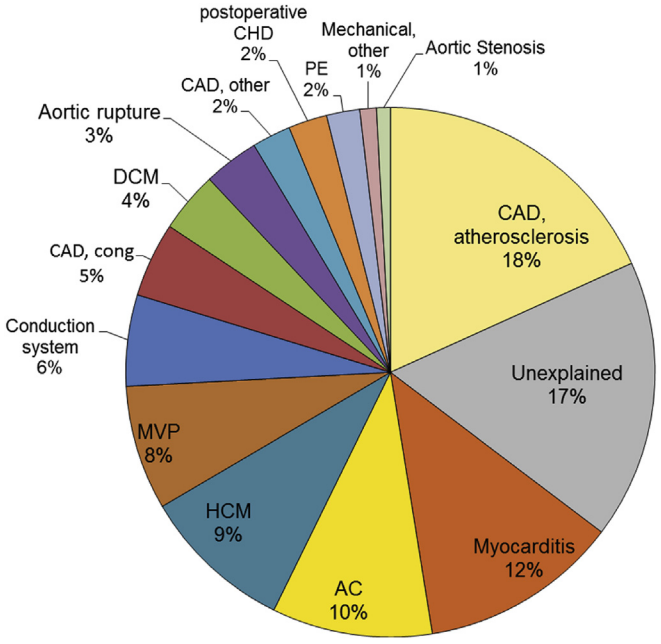

Figure 1 Causes of sudden death in Veneto Region North East Italy, time interval 1980–2013 (from Thiene G, Corrado D, Basso C. Sudden Cardiac Death in the Young and Athletes. Springer 2016).

solely or predominantly confined to heart muscle; and b) secondary cardiomyopathies, when the myocardial involvement is part of a generalized systemic (multiorgan) disorder.[13] Primary cardiomyopathies are further subdivided into: a) genetic cardiomyopathies (HCM, ACM, non-compaction, glycogen storage, Lenègre disease, mitochondrial, the channelopathies such as long LQT and SQT syndromes, Brugada syndrome, CPVT); b) mixed cardiomyopathies (dilated or restrictive); c) acquired cardiomyopathies (inflammatory, peripartum, tachycardia-induced, Tako-Tsubo).

As the genetic aetiology is increasingly complex, with considerable heterogeneity and increasing numbers of causative genes, the European Society of Cardiology (ESC) Working Group on Myocardial and Pericardial Diseases in 2008 has proposed a clinically oriented classification in which cardiomyopathies were grouped according to morphology and function with subcategories of familial/genetic and non-familial/non-genetic. Cardiomyopathies are defined as "myocardial disorders in which the heart muscle is structurally and functionally abnormal, and in which coronary artery disease, hypertension, valvular and congenital heart disease are absent or do not sufficiently explain the observed myocardial abnormality".[14]

More recently, in 2013 the World Heart Federation added the genetic basis of cardiomyopathies and proposed a descriptive genotype-phenotype nosology system termed "MOGE(S)" (morphofunctional phenotype (M), organ(s) involvement (O), genetic inheritance pattern (G), aetiology (E) including genetic defect or underlying disease/substrate, and functional status (S) of the disease).[15]

Molecular genetics and pathology of cardiomyopathies at risk of sudden death

Cardiomyopathies at risk of SD include structural (HCM, ACM, myocarditis) and non-structural (mostly channelopathies) entities. Other cardiomyopathies, which may be at risk of SD, but more usually present with symptoms and signs and/or a non-arrhythmic clinical picture (i.e. dilated cardiomyopathy and spongy myocardium) will not be further considered.

Hypertrophic cardiomyopathy

Molecular genetics: HCM is the most common inherited heart disease affecting 1:200–1:500 of the population.[16] HCM is clinically heterogenous and inherited in an autosomal dominant pattern with variable expressivity and incomplete penetrance, primarily by mutations of genes encoding sarcomeric proteins: beta-myosin heavy chain (MYH7), alpha-myosin heavy chain (MYH6), myosin essential light chain (MYL3), myosin binding protein C (MYBPC3), cardiac troponin T (TNNT2), cardiac troponin I (TNNI3), cardiac troponin C (TNNC1), alpha-tropomyosin (TPM1), alpha-cardiac actin (ACTC), titin (TTN).[17–19]

Overall, the most frequent disease genes are MYH7, MYBPC3, TNNT2, TNNI3 and TPM1. For each gene several different mutations have been identified. Thus, HCM can be viewed as a sarcomeric disease and a genetic cause can be identified in 35–45% in general, and up to 60–65% when the family history is positive.

Due to genetic heterogeneity and variable phenotype, genotype-phenotype correlations remain complex. However, the degree of hypertrophy, age of onset and disease outcome have been shown to correlate with specific gene mutations. For instance, mutations in TNNT2 cause only mild hypertrophy but are associated with a poor prognosis and a high risk of SD; mutations in MYBPC3 are associated with mild disease and onset in middle age or late adult life.[20] "Malignant" mutations in the cardiac MYH7 cause a severe form of HCM with early onset, complete penetrance, and increased risk of SD. Moreover, the presence of two different mutations in the same individual, leading to compound heterozygosity, double heterozygosity, or homozygosity, is associated with a more severe phenotype.[21]

Pathology: The pathological hallmark of HCM is either asymmetrical or symmetrical left ventricular hypertrophy not explained by left ventricular pressure overload.[22–25]

The typical asymmetrical septal variant of HCM consists of thickening of the basal anterior septum with subaortic bulging leading to left ventricular outflow tract obstruction (Figure 2). Septal endocardial plaques may develop as a consequence of friction due to systolic anterior motion of a thickened mitral valve apparatus ("mirror image" impact lesion).

Hypertrophy in HCM may show wide variation in extent and distribution, from mild (13–14 mm) to severe hypertrophy (>30 mm in thickness) with virtually any portion of the left ventricle affected, including midventricular cavity obstruction and apical hypertrophy. The symmetrical form of HCM accounts for about one third of cases and is characterized by concentric hypertrophy of the left ventricle with a small ventricular cavity. Serial echocardiography during follow-up may show progression to the "end-stage" phase with a dilated left ventricular cavity.[26]

A frequent component of the HCM phenotype is the presence of myocardial bridges, or a deep intramyocardial course of the left anterior descending coronary artery (Figure 3).[27–29] The presence of this anomaly has been associated with a higher risk

