Editorial

# Prevention of Sudden Cardiac Death in the Young: Targeted Evaluation of Those at Risk

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A common challenge for the physician, public health and sport medicine community is to realise the potential for sudden death prevention.

Sudden cardiac death (SCD) is defined as natural death due to cardiac causes, heralded by abrupt loss of consciousness within one hour of the onset of acute symptoms; pre-existing heart disease may have been known to be present, but the time and mode of death are unexpected. In public health surveillance, SCD encompasses any death from cardiac disease occurring out of hospital, in the emergency department, or upon arrival therein.[1] The annual incidence of SCD in the general population is cited as 1 in 1,000, although this is likely to be a conservative estimate as unwitnessed events may be difficult to categorise. Ischaemic heart disease accounts for the overwhelming majority of sudden deaths in the over-35 age group.[1] Inherited forms of cardiovascular disease account for the majority (70-80%) of young sudden deaths. In up to 20% no discernible abnormalities are found at forensic post mortem.[2-4] Although SCD remains a serious public health hazard, major developments in diagnosis, risk stratification and therapy make it possible to identify many of those at risk and to provide effective prophylactic treatment.[1-9] More work is needed with regard to those with no apparent heart disease.[3-5] Effective identification and treatment of high risk subsets would be expected to lead to a substantial reduction in SCD in the general population.

In Greece, within a 4-year period (1997-2001), 134 sudden cardiac deaths under the age of 35 were recorded in the area of Attica and the Cyclades, i.e. in a general population of around 2,000,000 young people. This indicates that at least 2-3 sudden deaths occur every month in this area. The most important cause of sudden death in the young in Greece are the arrhythmogenic cardiomyopathies, which account for the majority of the cases.[2] A considerable number of sudden cardiac death cases in the young in Greece, as in other European countries, also remain of unknown cause despite detailed investigation. This finding agrees with other studies.[2-4]

## Sudden arrhythmic death syndrome

In around 20% of sudden cardiac deaths no cause can be found despite examination of the heart by an expert cardiac pathologist. The cause of death is therefore described as "unascertainable". The term sudden arrhythmic death syndrome (SADS) has been applied to these deaths with a normal heart, of which many are due to the inherited arrhythmia syndromes (Brugada syndrome, long-QT syndrome and catecholaminergic polymorphic ventricular tachycardia) and subclinical forms of cardiomyopathies.[2,3] A

recent study found that cardiological and genetic examination in surviving relatives of young sudden unexplained deaths victims (<40 years of age) revealed an underlying inherited cardiac disease and probable cause of death in up to 40% of families.[4] The high diagnostic yield of clinical and genetic examination of the relatives has important value given the clinical implications.

### A feasible alternative prevention strategy

Survival rates from out-of-hospital cardiac arrests remain poor, and therefore primary prevention is the key to reducing the burden of SCD in the community. Since screening of the general population is not feasible, targeted evaluation of high-risk subgroups[2-12] is recommended, such as:

- individuals with cardiac symptoms
- families of SCD victims
- families of probands with inherited cardiovascular disease
- competitive athletes.

Selective cardiac evaluation of high-risk subgroups may offer a viable solution. Screening "at risk" groups targets the identification of silent or subclinical forms of the inherited cardiovascular diseases, enabling risk management in subjects who may be asymptomatic but are potentially in danger of sudden death. Integral to the strategy of targeted evaluation is the need to promote public awareness of cardiac symptoms and familial risk with encouragement of primary care physicians to seek a cardiology opinion. The clinical diagnosis of arrhythmogenic right ventricular cardiomyopathy (ARVC), hypertrophic cardiomyopathy (HCM) or dilated cardiomyopathy (DCM), and the inherited arrhythmia syndromes is challenging and is best conducted at specialist centres with experience in the field.

### The clinical value of the post mortem and family evaluation

When performing a post mortem on a sudden death victim, the expert pathologist will systematically attempt to rule out all structural cardiac abnormalities, including atheromatous coronary artery disease, congenital coronary anomalies, accessory pathways and conduction system defects, valve lesions, cardiomyopathies including HCM or DCM, left ventricular non-compaction, and ARVC.[2-20] This process entails rigorous macroscopic and histological assessment of the heart. The arrhythmogenic cardiomyopathies, in particular, are easily missed on autopsy without extensive sampling of both ventricles. ARVC may be the underlying pathology in a proportion of deaths ascribed to acute myocarditis; inflammatory infiltrates are present in up to 67% of ARVC hearts, and in early disease may predominate over the characteristic fibrofatty replacement.[13,14,17,18] Obtaining a complete post mortem report from the index case is the first step in conducting clinical assessment of the family. If the cardiac post mortem examination appears incomplete and details are lacking, the clinician may seek the consent of the family to release retained tissue for expert review. Re-assessment by a specialist cardiac pathologist may unmask new abnormalities in cases where the cause of death was unascertained, and/or consolidate a borderline diagnosis.[17,18,21-23] Confirmation of a non-genetic disorder, such as anomalous coronary arteries, may obviate the need for familial evaluation.[20] The presence of premature coronary artery disease may prompt familial screening for hyperlipidaemias, plasma homocysteine and lipoprotein (a) levels. Identification of an inherited cardiomyopathy facilitates subsequent evaluation of relatives along disease-specific guidelines.[4,5,9-12,21,23-26]

In occasional cases, the pathologist cannot identify a cardiac or other cause of death and the death will be recorded as SADS**.** The work-up for relatives of SADS victims should therefore aim to identify both primary myocardial diseases (typical and subclinical forms) and inherited arrhythmia syndromes.[3-5,19,21] Data from a Dutch and English series indicate that inherited forms of arrhythmia are often (~40%) identified in family members, but that ARVC and HCM may also be found and presumably have been missed at post mortem.

### Recommended baseline work-up

The following recommended evaluation is designed to identify significant occult cardiac disease in a young, symptomatic patient or a family with a history of SCD. This preliminary work-up is more extensive than that advised for familial assessment in HCM or DCM, where a 12-lead ECG and two-dimensional echocardiogram will suffice as screening investigations. *The recommendations presume that there is no known cardiac history in the family, precluding the use of disease-specific guidelines*. The recommended preliminary work-up includes a 12-lead ECG, transthoracic echocardiogram, cardiopulmonary exercise test, ambulatory ECG

monitoring and signal averaged ECG. Cardiovascular magnetic resonance has a role in the assessment of ARVC and anomalous coronary arteries, while provocation during testing is of value in unmasking the ECG changes of Brugada syndrome or CPVT. When a diagnosis is made, the next step is to risk stratify the patient and the affected relatives in order to establish appropriate treatment and lifestyle modification.[7,9,14,18,22,24-26]

### Molecular genetic analysis

Single-gene disorders predominate as causes of SCD in the young and recent studies indicate that molecular genetic analysis facilitates familial assessment.[1] The past decade has seen elucidation of the genetic basis of the primary myocardial diseases and inherited arrhythmia syndromes.[1,9,16,22,24,25] The absence of a mutation in one of the known disease-causing genes does not exclude the disease, since many genes remain to be identified. However, isolation of a causative mutation in an affected individual allows cascade screening of families based on gene testing to identify the estimated 50% who will be at risk and the remainder who will not carry the mutation and need no further evaluation or follow up.

Overall, molecular genetic analysis is highly useful:

- for reconfirmation of the diagnosis.
- it increases the diagnostic yield in cases where the phenotype is not so prominent (subclinical form).
- molecular genetics facilitates the identification of preclinical disease and other disease carriers in the family (normal carriers).

### Therapy

The majority of patients with inherited arrhythmia and cardiomyopathy do not die suddenly. Implementation of prophylactic treatment for SCD depends on the patient's level of risk for sudden death**.** Arrhythmic risk in the cardiomyopathies and inherited arrhythmia syndromes may be significant without concurrent systolic dysfunction or debilitating symptoms. The implantable cardioverter defibrillator affords optimal protection against SCD in patients who are found to be at high risk, based on clinical non-invasive and invasive evaluation. Antiarrhythmic therapy has been shown to confer a survival benefit in certain contexts, such as the use of amiodarone in HCM and ß-blockers in the LQT1 subtype of long QT syndrome.[1,9,18,25] Most cardiac arrhythmias and structural defects that may cause sudden death in the young are identifiable and treatable. With treatment, people with these conditions often have normal or near-normal life spans and lifestyles.

### Conclusion

*Sudden cardiac death in the general population* may occur, mainly, as a consequence of atherosclerotic coronary diseases. *Sudden cardiac death in the young and athletes*, on the other hand, is due to genetically determined diseases affecting key proteins of the heart related to mechanical and electrical cardiac function.

Management requires an evaluation of not only the patient but the whole family. This is the main parameter that needs decoding when dealing with such diseases. Besides clinical/symptomatic forms, there are silent or subclinical forms of these diseases in families. Since screening of the general population is not a tenable proposition, targeted evaluation of high-risk subgroups is recommended. Screening the target groups permits identification of silent or subclinical forms of the inherited cardiovascular diseases, enabling risk management in subjects who are in potential danger of sudden death. With improvement in risk stratification algorithms and the availability of effective therapies, the prevention of SCD in the young is becoming a reality.

Inherited cardiovascular disease is the major cause of sudden death in the young. Screening the target groups is a feasible way to eliminate the "majority" of sudden cardiac death in the young in every country.

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