Community-Wide Analysis of Sudden Cardiac Death: Clinical and Research Implications

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Introduction

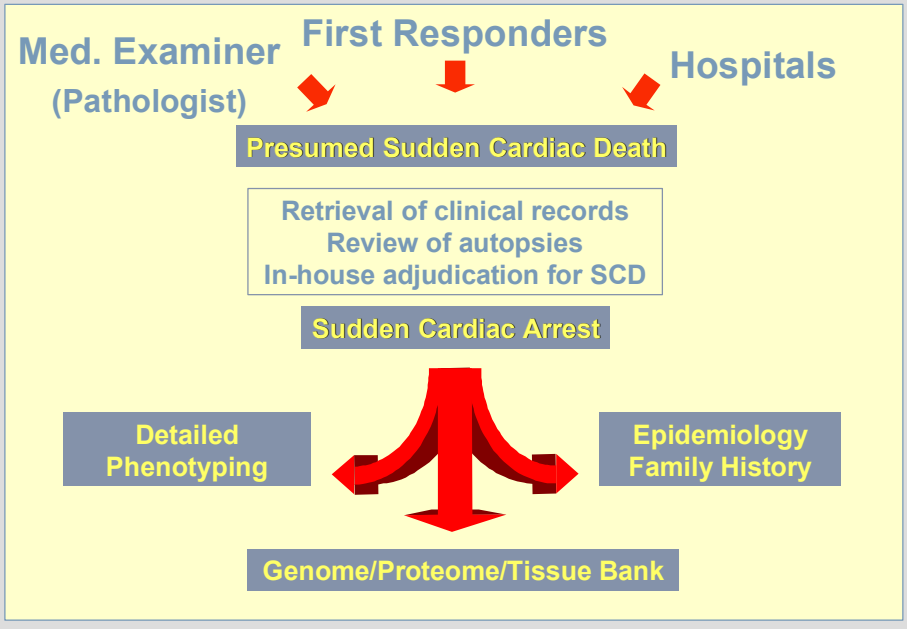
Analyses of disease progression patterns performed at the end of the last millennium predicted a globally increased incidence of heart disease by the year 2020 (1-3). Even in the first decade of the new millennium, these predictions are already being realized. In a reversal of trends, the greatest increases in prevalence of diabetes and coronary artery disease are being observed in the developing nations (4). An important consequence of this burgeoning population of patients with coronary disease and heart failure will be an increasing incidence of sudden cardiac death. As a result, sudden cardiac death (SCD) will have to be confronted as a shared and indiscriminate, worldwide public health problem. The current advancements in resuscitation science notwithstanding, survival from sudden cardiac arrest (SCA) remains low even in the developed nations (5). At the close of the 20th century, awareness of this important deficiency has focused considerable interest on mechanisms of SCD. Despite a renewed focus, the significant delay in development of effective measures of risk stratification and prevention of SCD can be attributed directly to a poor understanding of mechanisms involved in fatal arrhythmogenesis (6), particularly at the community-wide level. While longitudinal cohort studies and the multi-center trials of SCD prevention have been invaluable, there is increasing recognition of the critical need to view these observations in the context of community-wide analyses, without which discovery of meaningful and relevant risk stratification methodology may not be possible. The purpose of this review is to discuss the significance and strengths of community-wide evaluations of SCD, summarize recent observations from such studies, and finally to highlight specific potential predictors that warrant further evaluation as determinants of SCD in the general population.

Current burden of sudden cardiac death in the community

The first stage in the process of confronting any community-wide disease condition is the assessment of the magnitude of the problem. For several reasons, this has been difficult to accomplish in the case of SCD, the first of which is that a standard definition for the condition was not employed by a large number of studies. The most accepted definition is sudden and unexpected death within an hour of symptom-onset (7, 8). If un-witnessed, subjects should have been observed alive within 24 hours of their death. In addition, whenever possible, it is important to exclude subjects that are likely to have had a non-cardiac cause of sudden death, such as patients that may have had a large pulmonary embolism that lead to cardiac arrest or were known to be suffering from malignancy that is not in remission. Secondly, an accurate estimate of SCD incidence requires prospective ascertainment of cases. Studies that have used retrospective death-certificate based methodology to identify cases of SCD are likely to significantly overestimate SCD incidence by as much as 200-300 percent (5). Therefore the US estimates published by the US Centers for Disease Control and Prevention (400-450,000 per year) (9) are likely to be a significant overestimate (5). Prior to the publication of the limited number of community-wide studies that have employed the standard definition, there were several that prospectively examined the community-wide incidence of primary cardiac arrest using data collected by first responders. In these studies, the annual incidence of treated primary cardiac arrest ranged between 41 and 89/100,000 (10-13). However the major limitation of this methodology is that it does not include the significant proportion of SCD cases that are un-witnessed. In addition, due

to the unavailability of detailed clinical records, important diagnoses that exclude patients (such as a diagnosis of terminal malignancy) could not be made. A prospective study in the Maastricht area of the Netherlands reported an annual incidence of sudden out-of-hospital cardiac arrests of 90-100/100,000 residents age 20-75 years (14). On the other hand, a retrospective study of SCD among residents of southern Okinawa, Japan, that employed multiple sources, reported a crude annual incidence rate of 37 per 100,000 residents (15). The Oregon Sudden Unexpected Death Study (Ore-SUDS) is an ongoing prospective community-wide evaluation of SCD that employs the widely accepted, standard definition of SCD (5, 16). Originally underwritten by the US Centers for Disease Control and Prevention, this study is now in its fifth year and tracks all cases of SCD that occur in Multnomah County Oregon (Portland, Oregon metropolitan area) among a population of approximately 700,000 residents. A multiple source method of ascertainment is used, in order to capture all cases of sudden cardiac death (Figure 1). Cases are reported by first

Fig. 1. **The Oregon Sudden Unexpected Death Study**



responders (ambulance and emergency medicine personnel, 70%), the State Medical Examiner or Coroner (25%) and from the area hospitals (approximately 5%). In the first year of this study, the annual incidence of SCD was 53 per 100,000 residents and accounted for 5.6 percent of overall deaths (5). Taken together, if these studies are used to extrapolate an estimated annual incidence of SCD in the US (total population approx. 300,000,000), it would range between 180,000 – 250,000 cases per year. For the world (total population approx. 6,540,000,000), the estimated annual burden of SCD would be in the range of 4-5 million cases per year.

Spectrum of etiologies of sudden cardiac death

The most common clinical finding associated with SCD is coronary artery disease and approximately 80% of sudden cardiac deaths are attributed to this disease condition (5, 8, 17, 18). Another 10-15% occur in patients who have cardiomyopathies such as hypertrophic cardiomyopathy, dilated cardiomyopathies, arrhythmogenic right ventricular dysplasia and the myocardial infiltrative diseases (sarcoid, amyloidosis). The remaining 5-10% are composed of either structurally abnormal congenital cardiac conditions (coronary anomalies, cyanotic/non-cyanotic diseases) or patients with structurally normal but electrically abnormal heart. Besides the relatively rare genetic diseases such as long QT syndrome, Brugada syndrome and catecholaminergic polymorphic ventricular tachycardia, patients with autopsy-negative SCD (no genetic abnormalities identified) may comprise a larger part of this subgroup than previously anticipated (19). Despite the broad spectrum of etiologic conditions, in the overwhelming

majority of cases sudden cardiac death results from a fatal cardiac arrhythmia, either ventricular tachycardia/fibrillation or severe bradycardia/pulseless electrical activity (4, 5).

Predicting risk of sudden cardiac death in the general population

Role of severe LV dysfunction: At present, a diagnosis of severe left ventricular (LV) dysfunction is the best available predictor of SCD risk. Based on data from the multi-center primary prevention trials of SCD, the presence of severe LV dysfunction is the major indication for primary prevention with the implantable cardioverter-defibrillator (ICD) (20-23). However, only 20-30% of patients that are implanted with a prophylactic ICD, actually receive appropriate therapies over a follow-up period of 4-5 years (20, 23). Therefore, when severe LV dysfunction is used as the criterion for a prophylactic ICD, it takes at least ten ICD recipients to save one life during an intermediate follow-up period. Furthermore, the high-risk SCD patients we see in our clinics and hospital wards are likely to be different from the residents in the community that have SCD, often as the very first manifestation of heart disease. Patients who present to health care providers with severely decreased LV dysfunction, constitute a high-risk group that is likely to comprise a small proportion of overall SCD cases (24). We and others have observed this to indeed be true in community-wide analyses (14, 16, 25). In the ongoing Oregon Sudden Unexpected Death Study (Ore-SUDS), severe LV dysfunction did predict SCD, but was found to affect only a third of all SCD cases in the community (16). If the current guidelines for ICD implantation were followed, at least 65% of overall SCD cases would have not met criteria for prophylactic ICDs by the current guidelines. Almost half of all SCD cases had normal LV

function and the remaining 20% had either mildly or moderately decreased LV systolic function (LV EF >0.35 and <0.50). Similar findings were reported from a community-based study in Maastricht, the Netherlands (14, 25). Among 200 cases of SCD with an assessment of LV function available, 101 (51%) had normal LVEF, defined as >0.50, and 38 (19%) had severely reduced LVEF, defined as ≤ 0.30. These findings indicate that while severe LV dysfunction remains a valuable contributor, there is an acute need identify clinical and non-clinical predictors that could enhance the process of risk stratification. What follows is a discussion of some predictors that have potential for enhancing risk stratification either independently or in combination with a diagnosis of severe LV dysfunction.

Diabetes as a potential predictor of SCD risk: The independent role of diabetes mellitus (DM) in enhancing risk of SCD has been investigated in a small number of studies. However, all have consistently identified DM as a strong predictor of SCD. An analysis was performed among >6,000 middle-aged, healthy male Parisian civil servants who were enrolled in the Paris Prospective Study and followed for over 23 years (26). There were a total of 120 SCD cases and separately, there occurred 192 non-sudden death that were related to acute myocardial infarction (MI). In a multivariate analysis, DM independently conferred the highest risk for SCD (Relative Risk [RR] 2.2) compared to all other variables (age, body mass index, tobacco use, history, heart rate, systolic pressure, cholesterol and triglyceride levels) (26, 27). The US Nurses Study and the Physicians Health Study (28, 29) as well as a retrospective clinical database analysis from a health cooperative in Seattle (30) have reported similar findings. While these findings clearly implicate DM as an important factor in pathogenesis of SCD, the relationship has yet to be

evaluated in prospective, community-wide studies of SCD. While little is known about the specific ways in which DM-related mechanisms contribute to the pathogenesis of SCD, several mechanisms have been postulated. DM increases risk of coronary artery disease, a condition that is commonly found in association with SCD. However, there may be DM-specific accelerated forms of atherosclerosis with enhanced thrombogenicity (31). In the literature, a case is being made for the existence of a distinct form of cardiac dysfunction that has been termed "diabetic cardiomyopathy" (32, 33). A universal finding among diabetics is a high prevalence of abnormal prolongation of the QT interval from the ECG (34). Earlier clinical studies of diabetics have also reported a good correlation between prolonged QTc and overall cardiac mortality (35, 36). Several studies have found a significant association between diabetic autonomic dysfunction and prolongation of the QTc (37-40). Given the recently confirmed status of prolonged QTc as a marker of SCD risk in a large, community-based cohort, this parameter has potential for increased significance among diabetics.

Prolonged ventricular repolarization and risk of SCD: The relatively rare monogenic, long QT syndromes have long constituted a human model the causative association between prolonged repolarization and increased risk of SCD (41-44). However the Rotterdam study reported that QTc was independently associated with SCD even in a cohort of unrelated individuals (45). In a cohort of 6,693 patients followed for two years patients without evidence of cardiac dysfunction and QTc >440 ms had a 2.3-fold higher risk of SCD compared to those with QTc <440 ms. This association was independent of age, gender, history of myocardial infarction (MI), heart rate and drug use. A more recent analysis from the same cohort reports that prolonged QTc was an independent risk factor for SCD in older adults followed for 6.7 years (46,

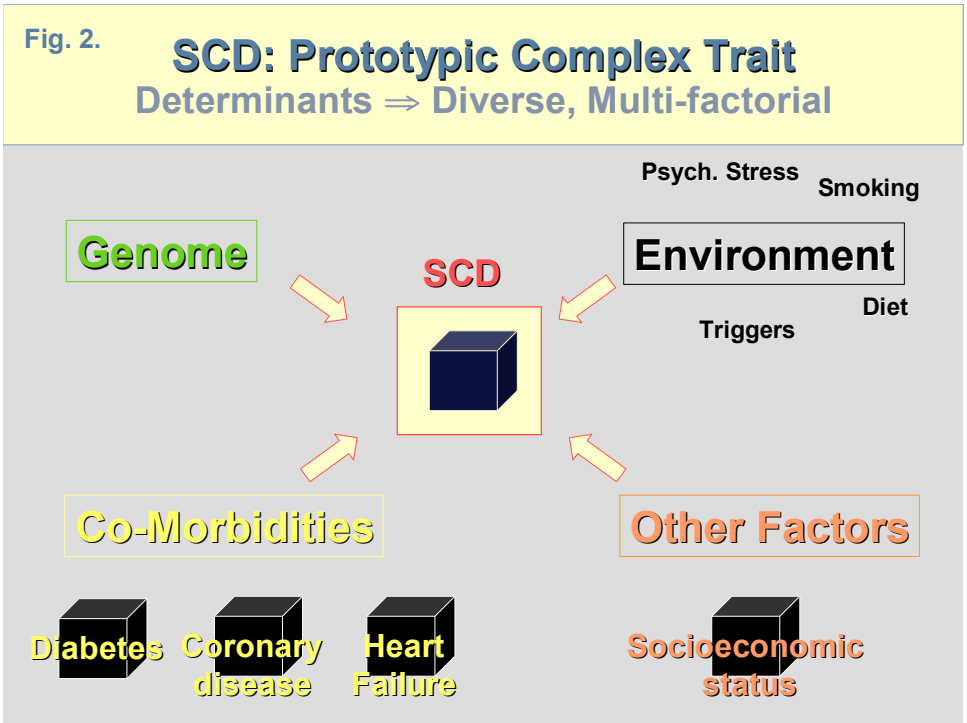
47). QTc was also found to be a predictor of increased overall cardiovascular morbidity and mortality in several cohort studies (48-52). There is significant potential for prolonged cardiac repolarization to enhance risk stratification for SCD among unrelated individuals in the general population and it clearly merits further evaluation.

Socioeconomic status and risk of SCD: Given the relatively common association between poverty and increased prevalence of human disease conditions, socioeconomic factors are likely to have significant effects on incidence of SCD (53-55). Until recently this association had not been evaluated in a prospective, community-wide study. There are some existing analyses of primary cardiac arrest cases, but again evaluation was limited to subjects that underwent resuscitation (56). As a result, the 40-50% of overall SCD cases that are un-witnessed or do not undergo attempted resuscitation may not have been included in most existing analyses. In the ongoing Oregon Sudden Unexpected Death Study (Ore-SUDS) (5), we performed a two-year prospective evaluation of the potential relationship between socioeconomic status and occurrence of SCD, evaluating both address of residence as well as specific geographic location of cardiac arrest (57). Analysis was conducted for both witnessed and un-witnessed SCD cases. In this investigation of all cases of SCD in a large urban and suburban U.S. county (Population 670,000), incidence of SCD based on address of residence was 30% to 80% higher among residents of neighborhoods in the lowest socioeconomic status quartile compared to neighborhoods in the highest socioeconomic status quartile. The gradient of socioeconomic status was significantly steeper for patients under age 65 years vs. over 65 years. Identical, as well as significant effects were observed based on geographic location of SCD. In the long term, there are likely to be multiple factors that result in the observed association between

socioeconomic status and SCD and these merit further evaluation. Risk factors for coronary artery disease such as lack of physical activity, smoking, hyperlipidemia, hypertension, obesity, and DM are more common among individuals with lower socioeconomic status (55, 58, 59). A study conducted in the UK found that incidence of out-of-hospital SCD was significantly higher in areas of socioeconomic deprivation, but the same was not true for overall CAD (60). A contributory role of psychosocial factors as direct triggers of ventricular arrhythmias and consequent SCD has also been postulated (54). Given that automated external defibrillators (AEDs) are likely to have a significant beneficial impact on survival from out-of-hospital SCA (61, 62), these findings would suggest that for the placement of AEDs in the community, neighborhood SES should be taken into consideration.

Potential role of genetic characteristics in predicting risk of SCD: Two large retrospective cohort studies have provided evidence that genetic factors contribute to risk of SCD. The potential association between SCD and history or SCD or coronary artery disease in a first degree relative was analyzed in a cohort of men and women attended by first responders in King County, Washington (235 cases, 374 controls) (63). A separate analysis from the Paris Prospective Study was performed in a cohort of 7,746 asymptomatic middle aged males followed for a mean of 23 years, classifying cardiac deaths as either sudden deaths or non-sudden with MI (26). Multivariate analyses indicated that the occurrence of SCD in a parent or first degree relative results in a 1.6-1.8 fold increase in SCD susceptibility after controlling for conventional risk factors for coronary artery disease. In a very limited number of cases in the Paris study, where there was a history of both maternal and paternal SCD events (n=19), the offspring had a 9-fold increased risk of SCD. Familial incidence of SCD in the Paris study segregated

independently of familial incidence of death due to acute MI. These studies provide evidence of a significant genetic contribution to SCD and the next logical step is to identify specific gene defects that could be used for screening and identification of the high-risk patient. Significant advances are continuously being made in gene-finding technology, but some basic issues will need to be resolved before we can perform a search for candidate genes (64). Most patients that suffer SCD have multiple associated co-morbidities such as coronary artery disease, DM, obesity and heart failure, each one of which may have genetic risk that could be unrelated to the genetic risk of SCD (Figure 2.). Therefore genes that contribute to SCD occurrence have to be separated



from genes that lead to associated conditions. Secondly, even for the so-called "monogenic syndromes" such as the long QT syndrome, there may be additional modifier genes that are involved (65, 66). For the complex phenotype of overall SCD, it is quite likely that for an individual patient, screening may have to be conducted for a panel of genes instead of a single

gene. From a methodological standpoint, approaches that use a very high-resolution map of single nucleotide polymorphisms (SNPs) (67) to search for associations, linkage disequilibrium or a small shared genomic segment among affected individuals, are likely to be necessary (64). While the search for SCD genes had not presently employed community-wide approaches, these studies are likely to be conducted in the very near future (64).

Clinical and Research Implications

Despite significant advances in prevention and therapeutic strategies for overall heart disease, we are likely to witness an ongoing, global increase in the rates of sudden cardiac arrest. This is due in large part, to significant gaps in our current knowledge regarding SCD risk stratification. Without enhancement in risk stratification, prevention of SCD is likely to be inefficient and ineffective. Therefore discovery of novel risk stratification markers and methods has become the top priority in the field of sudden cardiac arrest investigation. We are also learning that while severe LV dysfunction is a useful predictor for a sub-group of patients who will have future SCD, the specificity of this predictor is significantly lower than anticipated and that we must extend our search beyond the ejection fraction. Among the strategies previously used to identify predictors of sudden cardiac death, there has been a significant lack of community-wide analyses. As illustrated by the findings related to severe LV dysfunction in the Portland, Oregon USA and Maastricht, the Netherlands community-wide studies, this trend will have to be reversed. Studies that employ hospital and clinic based ascertainment of SCD patients will still have a role, but meaningful predictors of SCD are most likely to be discovered by prospective, community wide investigations. There are several clinical and non-clinical predictors that have already shown promise in longitudinal cohort or community-wide studies. Specific examples from relatively recent studies are a diagnosis of diabetes mellitus, prolonged ventricular repolarization (QTc interval) on the ECG and low socioeconomic status. It is clear that genetic factors play a role in the occurrence of SCD and rapid advancements in the field of

gene finding technology indicate that availability of potential genetic predictors is imminent. For risk stratification of SCD to be comprehensive, factors as diverse as genomics and socioeconomic status may have to be taken in consideration. All of these predictors as well as those discovered in the future will require validation in multiple populations, in order to ensure relevance and applicability for global prevention of sudden cardiac death.

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