

Editorial

Current Trends in the Classification of Sudden Cardiac Death Based on Autopsy Derived Data: A Review of Investigations Into the Etiology of Sudden Cardiac Death

Tendencias actuales en la clasificación de la muerte súbita cardiaca según los datos de autopsias: una revisión de los estudios sobre la etiología de la muerte súbita cardiaca

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In this issue, Morentin et al.¹ present a timely community based study exploring the causes of sudden cardiac death (SCD) in adults in a local population. SCD remains one of the main causes of adult mortality in the developed world. In the US alone, projections for the annual incidence of SCD range from as low as 100,000 to 250,000 cases per year in one series² to between 400,000 and 450,000 deaths per year as estimated from vital statistics data.³ Globally, the yearly burden of SCD has been estimated to reach between 4 and 5 million deaths (estimating a total global population 6,540,000,000).² The international implications regarding the impact of SCD on local populations is also underscored by the increase in the demographic and lifestyle changes implicated in the development of coronary artery disease (CAD) (namely diabetes, hypertension, hypercholesterolemia, and smoking), which have previously plagued the industrialized nations. If current trends hold true that the predominant underlying etiology in SCD is severe CAD, then this trend is projected to spur a subsequent increase in SCD worldwide, with CAD positioned to be the leading cause of death in the world by the year 2020.⁴ Given these projections, it is an understatement that gaining a thorough understanding of the underlying etiologies implicated in SCD will prove to be one of the most pressing missions in the sphere of public health, both on a community and a global scale. One obstacle in the path to effective SCD surveillance remains how researchers approach the problem. In essence, do we all agree what constitutes SCD?

As investigators such as Morentin et al.¹ (and ourselves) continue to elucidate the underlying causes of SCD, it has become evident that although many are working toward a systemized approach to the classification of SCD, one factor that has not reached international standardization is the definition of SCD. Morentin et al.¹ as well as numerous other researchers define SCD as a sudden, natural, non-violent and unexpected death occurring

within 1 h after the onset of symptoms in witnessed cases. For unwitnessed deaths, the decedent should have last been seen alive and in stable condition (with all potentially lethal non-cardiac causes ruled out) 24 h or less before being found dead. Older studies have shown how this definition can determine the incidence of SCD. Kuller et al. demonstrated that if SCD is considered to occur 2 h after onset of symptoms, 12% of cases were classified as sudden death with an overall 88% of cases considered cardiac in origin. If the time to onset of symptoms was increased to a time period of less than 24 h, 32% deaths were considered sudden, and only 75% due to cardiac causes.^{5,6} Given this data, other investigators such as Adabag et al. suggest that limiting the definition of witnessed SCD to deaths that occur within 1 h of onset maybe too restrictive.⁷ Our series of studies (Virmani et al.⁸) consider SCD to include those unexpected witnessed deaths occurring within 6 h after the onset of symptoms and use the aforementioned criterion for unwitnessed deaths, as acute myocardial infarction is not histologically evident during this time frame.

Much of our current data on the incidence of SCD continue to be collected from retrospective studies consisting of the review of medical records and death certificates. By one estimate, retrospective studies utilizing death certificate review may possibly overestimate SCD incidence by 200%–300%.⁹ In a study of out-of-hospital sudden deaths, Tavora et al.¹⁰ demonstrated that the accuracy rate of cause of death as listed on the death certificate in sudden deaths is only 50%, with CAD often used as a default diagnosis without prior history. For cases of cardiomyopathy, valvular disease, and ruptured aneurysms, under-reporting was the norm as the death certificate was accurate in less than one-third of those cases. Data from other authors support this claim of incorrect death certificates. Such data highlight a major limitation to retrospective studies of SCD incidence – the lack of autopsy findings in a significant number of cases. Prospective studies, in which collaborative efforts between researchers and medical examiner or coroners' offices identify SCD cases to undergo autopsy at the time of death, such as the one being presented by Morentin et al. have a distinct advantage as compared to

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retrospective studies. Cases suspicious for SCD can be identified early enough during the death investigation to be designated to autopsy and proper clinical investigation.

An additional factor to consider in the standardization of SCD surveillance is how the SCD investigation is conducted, including not only the post-mortem gross and histologic examination, but also what pertinent clinical data is collected. Basso et al. recently published a set of guidelines to insure at least the minimal amount of investigation into the cause of death for SCD cases (for use within the European Union).¹¹ Their work outlines in excellent detail the importance of proper documentation of clinical information relevant to the autopsy, and a structured approach not only to dissection of the heart but also to the remainder of the body. It is an unfortunate fact that not all post-mortem examinations are created equal. In our own experience as a consultative service, we have encountered SCD cases in which the heart is poorly sampled with an insufficient number of tissue blocks submitted, incomplete sections demonstrating less than the full thickness of the right or left ventricular wall, and inadequate sectioning and sampling of the coronary arteries.

With a structured, formal methodology for the investigation and documentation of SCD cases, we start to gain some clarity in the quagmire of SCD surveillance with a much more clear picture of what epidemiological data clinicians and preventative health practitioners need to be aware. In the US, current statistics indicate that 80% of SCD cases are secondary to CAD, 10%–15% secondary to cardiomyopathy (dilated or hypertrophic) and 5%–10% show no structural abnormality.¹² However, when one examines data derived from careful post-mortem investigation, a slightly different picture emerges. Data from our registry of hearts received for consultation from forensic medical examiners in the US (2348 total cases with 1891 fully characterized as sudden death cases) indicates that 57% of SCD deaths are secondary to severe CAD, 38% are secondary to non-coronary cardiac disease, and approximately 5% occurred with morphologically normal hearts (unpublished data). Similar to the data presented by Morentin et al. in our registry, 75% of all deaths secondary to non-coronary cardiac disease (i.e. cardiomyopathy, coronary anomalies, congenital disease, and mild to moderate atherosclerosis) occurred in individuals under the age of 50, and constituted 29% of total SCD cases in our database. In fact, 51% of the total non-CAD cases occurred in males 49 years of age or younger (or 20% of the total SCD cases). A recent study of SCD cases from a database of 1647 hearts in England conducted by Hill and Sheppard highlights the importance of autopsy studies in their observations concerning non-atherosclerotic CAD in SCD. In particular, they found that non-atherosclerotic disease was most prevalent in young males.¹³ In particular, the young are predisposed to experience SCD secondary to coronary artery anomalies, with the anomalous left main artery arising from right sinus of valsalva as the most fatal manifestation. Granted, data from such registries may show a bias toward younger patients, as autopsies are performed in the older population to a lesser extent. Yet, the information being gathered by various researchers is beginning to demonstrate the diversity of causes underlying SCD. In addition, the identification of morphologically normal hearts in SCD cases will continue to provide a boon to those researchers interested in histologically unapparent genetic and molecular mechanisms in the spectrum of SCD.

Separate studies conducted by Cobb et al.¹⁴ (who used electrocardiographic data from first responders) and Myerburg¹⁵ estimate that a subset of SCD cases, the sudden arrhythmic death (SAD), occurs in 185,000¹⁴ to 250,000¹⁵ individuals per year in the US alone. This is a significant number of deaths taking into consideration the aforementioned lower limit on death estimates from all causes of SCD in the United States. Behr et al.¹⁶ surveyed 117 coroners' jurisdictions in England, to describe

the characteristics of SAD affecting white Caucasians between 4 and 64 years of age in their population. During their prospective study in collaboration with the coroners' offices, 56 decedents were identified as experiencing SAD, and two-thirds of those individuals were found to have reported cardiac symptoms in the past. Their data agrees with Morentin et al. in that SAD is found predominately in young males. In addition, the true incidence of SAD may be eight times greater than previous projections for the population studied by Behr et al.¹⁶

Gathering epidemiological data is not the only advantage to the systematic characterization of SCD cases. We emphatically agree with the statement by Morentin et al.¹ that forensic autopsies can contribute histopathological and toxicological data that cannot be obtained by other methods. As such, the importance of prospective studies must be recognized also for their ability to contribute to the overall knowledge base in cardiovascular pathology. For example, using autopsy specimens from patients with SCD allowed the senior author (R.V.) to propose a modified classification of coronary atherosclerotic disease based on extensive morphological analysis of coronary artery lesions.⁸ Autopsy specimens have proven to be superior to animal models in the classification of human disease in that animal models often do not progress beyond the development of the atheroma (a well-developed fibrous cap overlying a necrotic core). It was the utilization of autopsy material from SCD cases that allowed investigation into mechanisms other than the classic atheromatous plaque rupture, and resulting occlusive thrombosis, implicated in sudden coronary death. For example, the recognition of fatal stenotic atheromatous lesions without rupture and/or thrombosis and conversely, evidence of healed plaque rupture in individuals dying of non-cardiac causes was a result of careful autopsy investigation into cases of sudden death.⁸ And we cannot forget to mention how critical the autopsy evaluation of SCD cases has been to the development of the concept of plaque erosion as a cause of fatal thrombotic lesions. Looking again at preliminary data gathered from our registry, while only 9% of SCD cases were a result of plaque erosion, 76% of all plaque erosion cases were in individuals under 50 years of age. Another important finding is that of the 123 cases of plaque erosion resulting in SCD in the less than 50-year-old age subset, 36% of these cases occurred in women. This represents a significant percentage of deaths as a sequelae of thrombosis in plaque erosion when compared to 21% of women manifesting severe CAD without thrombosis in the same age group (unpublished data).

In the final analysis, the work of Morentin et al.¹ contributes significantly to the discussion of SCD, both its causes and possible prevention strategies as we progress through the 21st century. We remain optimistic that these investigators and others will continue to add meaningful data to the knowledge base aimed at the alleviation of the death burden secondary to SCD, not only in the US, but on the global scale as well.

CONFLICT OF INTEREST

Dr. Virmani serves as a consultant for Medtronic AVE, Abbott Vascular, W.L. Gore, Prescient Medical, CardioMind, Inc., and Atrium Medical Corporation.

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