

MAYO CLINIC
PROCEEDINGS

The Many Faces of Sudden Death



See also pages
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and 1617

Sudden cardiac arrest (SCA), which is characterized by abrupt and unexpected cessation of cardiac output, loss of consciousness, and often sudden cardiac death (SCD), is a major cause of death worldwide. It accounts for up to 450,000 deaths per year in the United States alone and is surpassed only by all cancers combined regarding the total number of lives lost.¹⁻³ Because of its frequency and severity, SCA is the subject of intense public health interest and research efforts.

Our understanding of SCA continues to expand. Already we can identify some patients as being at high risk for SCA, and for many we decrease that risk through the use of various medications or by placement of an implantable cardioverter-defibrillator.^{4,5} Although the largest population known to be at high risk for SCA is composed of those with depressed left ventricular ejection fraction, many other individuals experience SCA without any previous indication of risk.⁶ Contemporary research seeks to improve risk stratification for SCA not only in patients with established cardiovascular disease (CVD) but also in those without any sign of disease at all. The current issue of *Mayo Clinic Proceedings* details 4 investigations⁷⁻¹⁰ into various aspects of SCA detection, epidemiology, pathogenesis, and treatment, exhibiting several of the potential faces of SCD.

Serious CVD, and particularly SCD, in a young person or in athletes of any age participating in extreme endurance exercise (EEE) is a rare but particularly tragic occurrence, with far reaching implications for families and communities.^{11,12} In the current issue of the *Proceedings*, Harmon et al⁷ examined the incidence of SCA and SCD in high school athletes by reviewing a database that included information from 7 states and

athletes' activities during 6 school years.⁷ They reviewed more than 16 million athlete-seasons and 974,640 athlete-years of activity, within which they identified 104 cases of SCA/SCD (35 cases of SCA with survival and 69 cases of SCD). However, because identification of cases relied on media reports, the numbers of SCA and SCD were likely underestimated. The data demonstrated that the event rate was 5.3 times higher in boys than in girls. In particular, male basketball athletes had the highest rate of SCD (1 per 37,087 athlete-years), which was 2.3 times higher than the next closest group: boys who played football. Autopsies were available in 73% of cases, and—contrary to the popular belief that SCA in athletes is most frequently due to hypertrophic cardiomyopathy (HCM) or congenital coronary anomalies—the most common findings were idiopathic left ventricular hypertrophy/possible cardiomyopathy (26%), autopsy-negative SCA (18%), HCM (14%), and myocarditis (14%).

Consonant with the results of the study by Harmon et al,⁷ we recently reported that in college athletes, the group with by far the highest rate of SCD was male basketball players, especially African American Division I male basketball players.¹¹ Although ideally almost everyone could be screened to identify for treatment those at high risk for SCD, detailed screening of all youth and school-aged athletes is probably cost prohibitive. Therefore, electrocardiographic testing, especially using newer criteria, may provide the greatest cost-effectiveness, especially when applied to the highest risk groups (eg, male basketball players, especially those of African American race).^{7,11}

Likewise, although low levels of physical activity (PA) may be the greatest threat to health

in the 21st century,¹³ and great strides are needed to increase PA across the health care system (which would be extremely cost-effective), there also are risks of EEE.^{8,12-19} Maximal benefits of PA and exercise probably occur at low to moderate levels.^{12,13,16-18,20} In the current issue of the *Proceedings*, van de Schoor et al⁸ assessed the risk of athletics-associated myocardial fibrosis (MF) by reviewing the literature. They identified 65 athletes from 19 studies/series that used biopsy or magnetic resonance imaging to make a diagnosis in patients suspected to be at high risk and 14 magnetic resonance imaging-based population studies. van de Schoor et al⁸ reported that MF predominantly occurs in the intraventricular septum and right ventricle, possibly due to microinjury from repeated dilation of the relatively thin-walled right ventricle during prolonged EEE.⁸ Although this MF may increase the rate of potential cardiomyopathies and reentrant tachyarrhythmias that could increase the risk of SCD, we agree with Levine's recent commentary that these risks are not high enough to rightfully frighten competitive athletes away from competing in EEE training and related competitions.¹⁹ On the other hand, we should emphasize that from an overall health standpoint, maximal benefits occur at quite low levels of exercise, and there is no need to engage in EEE.^{12,13,16-18,20} The study by van de Schoor et al⁸ implies that avoiding EEE could lessen MF and perhaps could reduce further the rare incidence of SCD in these athletes. However, as was recently reported in the *Proceedings*, one good way to reduce the risk of SCD is by having at least a moderate to high level of cardiorespiratory fitness (CRF),²¹ and—although there is an inherited, non-PA component of CRF—by far the greatest determinant of CRF is regular PA and exercise training.^{13,17,18}

Improvements in genetic analysis are contributing to many advances in medical diagnosis and care, including the birth of the precision medicine movement.²² Among the diseases that may be diagnosed via the appropriate use of genetic evaluation are several disorders that make up the family of inherited SCA syndromes.²³ In the current issue of the *Proceedings*, Ackerman et al⁹ present a compelling case of a tragic SCD in a young person, and the subsequent peril

of overtreatment that may be caused by undisciplined use of genomic analysis of such decedents' surviving family members. Their remarkable Special Report recounts the story in detail, demonstrating the clear investigative progression toward the correct diagnosis. This unfortunate saga reminds us that one should treat the patient (in this case, surviving family members) as a whole rather than simply treating the results of a test (here, a red herring genotype in a survivor). It also demonstrates the importance of conservation of the decedents' genetic material, as well as the utility of expert attention to the survivors' phenotype rather than merely their genetics.

Standing in contrast to Ackerman et al's⁹ tale of the potential perils of excessive reliance on genetic testing, some SCA syndromes have no known correlative genetic abnormality.²⁴ One such disorder, sudden unexplained nocturnal death syndrome (SUNDS), is touted as a distinct sudden death syndrome defined by a purely phenotypic definition occurring in predominantly healthy Asian males in the third or fourth decade of life who die unexpectedly while sleeping, often immediately preceded by brief respiratory alterations such as moaning or tachypnea. Although most of these cases have been reported to be autopsy negative, perhaps in actuality small morphologic clues could be missed, or perhaps some genetic abnormality could be at play. Some have speculated that SUNDS might be identical to Brugada syndrome (BrS), including their similarly negative history and autopsy results, as well as some variably reported degree of genetic similarity (ie, sodium channel gene mutations) and electrocardiographic similarities.^{25,26} In the current issue of the *Proceedings*, Zhang et al¹⁰ describe their morphologic and molecular examination of a cohort of 148 individuals with SUNDS, for the first time identifying slight, but statistically significant, morphologic differences between people with SUNDS and matched accidental death controls, as well as significant differences in the frequency of likely deleterious mutations between patients with SUNDS and patients with BrS. They found slightly heavier hearts and slightly larger valve circumferences in individuals with SUNDS than in controls, as well as a much lower

prevalence of *SCN5A* gene mutations in individuals with SUNDS than in patients with known BrS (4.5% vs 29%; $P=.01$).

Although Zhang et al¹⁰ should be congratulated for their contribution to our understanding of SUNDS, the study has some limitations. Foremost among these is the fairly nonspecific definition of SUNDS itself, which could be considered simply a subset of idiopathic sudden death, especially given that there presently is no known unifying cause. Many cases of sudden death are idiopathic, even after autopsy or genetic analysis, and many definite cases of known SCD syndromes are gene negative. For example, a deleterious mutation is found in only 30% to 35% of patients with diagnosed BrS.²⁷ The very definition of SUNDS includes the lack of potentially definitive clinical data, such as electrocardiographic abnormalities or echocardiographic information; thus, data that could implicate other SCA syndromes were missing from the SUNDS case pool. In the absence of a definitive “hard” sign providing a unifying pathogenesis for SUNDS, it seems likely that many cases labeled SUNDS could potentially have a different actual cause. The authors’ finding of disparate genetics between SUNDS and BrS actually supports this notion of variability, through refuting some authors’ assertions that SUNDS may be identical to BrS. In fact, genetic analysis of the SUNDS cohort showed considerable variability in cardiomyopathy-related genes: 12 of 44 individuals harbored mutations in genes that have been implicated in various other SCA syndromes. In addition, the small numbers of genetically examined SUNDS and BrS cases (44 and 17, respectively) limits genetic analysis, an arena in which there can hide many undetected causative mutations. All told, not only might SUNDS be different from BrS, but many cases labeled SUNDS may actually represent pathologically subtle instances of other SCA syndromes.

As a global epidemic, SCA has a profound effect on people from all walks of life, all around the world. Whether its victim is a patient with established CVD, an extreme athlete in the United States, or a sleeping young man in South Asia, SCD is catastrophic. The current issue of the *Proceedings* offers some novel insights into several of the many faces of SCD.

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