Sudden Cardiac Death in Young Athletes: Trying to Find the Needle in the Haystack

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ABSTRACT
Sudden cardiac death in young athletes is an infrequent, but catastrophic event. Hypertrophic cardiomyopathy, coronary artery anomalies, and arrhythmias are common identifiable causes of sudden cardiac death. Many of these disorders can be difficult to diagnose, and athletes may be completely asymptomatic prior to their sudden death event. This article reviews causes of sudden cardiac death in young athletes and current recommendations for pre-participation screening.

INTRODUCTION
Sudden death in athletes is an infrequent event, but has significant impact on families, communities, and society. Estimates of frequency of sudden death vary widely and depend on the definition of sudden cardiac death, age of the athlete, population sampled, and lack of mandatory reporting of these events. Sudden cardiac death is most often defined as death occurring from a cardiac cause within 1 hour of the onset of symptoms. However, some have broadened the definition to include those deaths occurring within 24 hours after the onset of symptoms. In the United States the incidence of sudden death in young athletes is estimated to be about 1/200,000.\(^1\) The most common non-cardiac causes of sudden death in this population include asthma, heat stroke, pulmonary embolism, and epilepsy. Cardiac causes of sudden death include structural abnormalities such as cardiomyopathy, anomalous coronary arteries, atherosclerotic heart disease, valvar abnormalities, ruptured aortic aneurysm, and myocarditis, and primary arrhythmias such as long QT syndrome, Brugada syndrome, Wolff-Parkinson-White syndrome, and familial catecholaminergic polymorphous ventricular tachycardia, and commotio cordis. Patients with repaired congenital heart disease may also be at an increased risk for cardiac sudden death but will be excluded from this review.

ETIOLOGY OF SUDDEN CARDIAC DEATH
Several studies have sought to elucidate the etiology of sudden cardiac death in young athletes and non-athletes. In Minnesota, Maron et al\(^2\) analyzed sudden death in young athletes and collected data from a 10-year period from postmortem reports and interviews with family members, witnesses, and coaches. Of 158 deaths, 134 were determined to have cardiovascular causes. Those affected ranged in age from 12 to 40 years with a mean age of 17 years. The majority were males (90%), and the deaths typically occurred during or immediately after exertion. Basketball and football were the most common sports associated with sudden death events. The majority of sudden cardiac death events occurred during afternoon and evening hours, consistent with the timing of athletic practice and competition. Hypertrophic cardiomyopathy was the primary cardiac etiology (36%); an additional 10% were due to an “unexplained increase in cardiac mass,” consistent with possible hypertrophic cardiomyopathy. The second most common etiology was an anomalous coronary artery (24%), most commonly an anomalous origin of the left main coronary artery or anomalous origin of the right coronary artery. Only 12 of the 134 athletes reported symptoms immediately prior to death, which included chest pain, dyspnea, dizziness, or weakness, and only 24 athletes had any symptoms in the 3 years prior to death.

Corrado et al\(^3\) reviewed deaths in people (both athletes and non-athletes) <35 years of age (mean age 24 years) over a 19-year period in the Veneto Region of Italy. Autopsy review of 273 deaths showed atherosclerotic coronary artery disease was the most common cause of sudden death, and was found in 54 victims (20%). Arrhythmogenic right ventricular cardiomyopathy or dysplasia (ARVC or ARVD, respectively)
Hypertrophic cardiomyopathy is characterized by abnormal hypertrophy, primarily of the left ventricle, with histologic features of myocyte hypertrophy, myofibril disarray, and interstitial fibrosis. It is the most common cause of sudden cardiac death in young athletes in the United States.\(^1\) Fifty percent of the patients with familial hypertrophic cardiomyopathy have an autosomal dominant inheritance pattern with variable penetrance that involve genes encoding cardiac sarcomeric proteins. The sporadic forms of the disease may be due to spontaneous mutations. Hypertrophic cardiomyopathy is one of the most common inherited cardiac disorders with a prevalence of 1 in 500 young adults.\(^3\) The annual mortality rate of patients with hypertrophic cardiomyopathy is variable and is as high as 6% in children referred to tertiary care centers and as low as 1% or less in unselected populations.

Sudden death in patients with hypertrophic cardiomyopathy is primarily due to ventricular arrhythmias secondary to intrinsic abnormalities in the cardiac myocytes or can occur due to dynamic outflow tract obstruction during exertion, leading to myocardial ischemia. Thus, lethal arrhythmias may occur with exertion or at rest. Physical examination of patients with hypertrophic cardiomyopathy may be completely normal since the murmur is typically due to left ventricular outflow tract obstruction (systolic murmur along the left sternal border) and may not be present at rest but only during exertion. The majority of patients (75%-95%) will have an abnormal electrocardiogram (ECG). The ECG in hypertrophic cardiomyopathy can vary greatly and may include findings of left axis deviation, ventricular hypertrophy, repolarization abnormalities, pathological Q waves, and/or bundle branch block\(^7\) (Figure 1).

The gold standard for diagnosis of hypertrophic cardiomyopathy is 2-dimensional echocardiography, illustrating ventricular hypertrophy without chamber dilation. However, the early diagnosis of hypertrophic cardiomyopathy may be difficult to make in competitive athletes. Athletic heart syndrome is a well-recognized adaptation of the cardiac muscle to daily strenuous training and conditioning. This adaptation results in increased vagal tone, manifesting in ECG findings of sinus bradycardia, junctional rhythm, and first and intermittent second degree AV block. Echocardiographic findings related to intensive isometric conditioning include concentric ventricular hypertrophy without chamber dilation, while isotonic conditioning results in concentric ventricular hypertrophy with mild left ventricular chamber dilation. Since early hypertrophic cardiomyopathy may mimic athletic heart syndrome, a 2-3 month period of athletic deconditioning may be recommended with repeat echocardiographic imaging to ensure resolution of ventricular hypertrophy due to intensive training.

Patients with hypertrophic cardiomyopathy who have the highest risk of sudden death are those with a
history of prior cardiac arrest, syncope or near syncope, hypotension with exercise, extreme left ventricular hypertrophy with a wall thickness ≥30 mm (upper limits of normal in adults is 11-12 mm), ventricular tachycardia, or a positive family history of premature death due to hypertrophic cardiomyopathy.\(^6\) Since hypertrophic cardiomyopathy is an inheritable disorder with variable penetrance, a detailed family history is an important tool for screening young athletes. While it is possible for spontaneous mutations to occur, a positive family history should lead to careful evaluations of all family members to allow for early recognition of this potentially lethal disease.

**Coronary Artery Anomalies**

Coronary artery anomalies are the second leading cause of sudden cardiac death in young athletes in the United States.\(^2\) The incidence of anomalous coronary arteries based on routine autopsies is as high as 0.17%-0.3% and even higher on coronary artery arteriography studies: 0.6%-1.55%. Clearly, the majority of these abnormalities do not result in sudden death. The most common coronary anatomy associated with a risk of sudden death is the left main coronary artery arising from the right sinus of Valsalva with an intra-arterial course between the aorta and pulmonary artery (Figure 2) or the right coronary artery from the left sinus of Valsalva with an intra-arterial course between the aorta and pulmonary artery. Sudden death in these patients is likely due to coronary ischemia secondary to a slit-like coronary ostia, abnormal angulations causing coronary artery kinking, or intramural courses (proximal coronary artery within the wall of the aorta), leading to dynamic compression during exercise, resulting in ischemia and infarction.\(^5\) Abnormal repolarization is present with peaked T waves in the lateral leads.\(^6\) Only a third of patients have symptoms prior to death.\(^1\)

Anomalous coronary arteries can be difficult to diagnose since resting ECGs are typically normal and exercise testing may be negative. Echocardiography is a reliable method for identifying the origins of the left main coronary artery and right coronary artery. The coronary artery origins should be identified by 2-dimensional imaging as well as color Doppler, demonstrating antegrade diastolic coronary flow. However, patient size and level of cooperation, sophistication of the echocardiographic equipment, skill of the sonographer, and skill of the interpreting physician are important factors in making the correct diagnosis. Physicians ordering echocardiograms should be aware that many echocardiographic laboratories do not routinely image coronary artery origins. Therefore, physicians should request that the coronary artery origins be identified, particularly for those patients with a history of exertional symptoms. Other diagnostic options, including coronary angiography, computed tomography angiography, and magnetic resonance imaging, may also be helpful in delineating the coronary anatomy.

**Arrhythmogenic Right Ventricular Cardiomyopathy**

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is an inherited cardiomyopathy characterized by right ventricular dysfunction secondary to fibrofatty replacement of cardiac myocytes. The abnormality
causes electrical instability of the ventricle and is a common cause of sudden cardiac death in the young in Italy. There are 4 phases of the natural history of ARVC. In the first phase, patients are usually asymptomatic with subtle morphologic changes, but are already at risk of sudden death during extreme exertion. The second stage consists of symptomatic arrhythmias along with functional abnormalities of the right ventricle. During the third stage, diffuse right ventricular disease and right-sided heart failure occur, progressing to left-sided involvement in the fourth stage. The onset and duration of each phase varies widely between patients. Mortality is most often due to lethal ventricular arrhythmias or progressive heart failure. Clinically, patients may be completely asymptomatic or have symptoms such as syncope, palpitations, dizziness, or death, often with exertion. Syncope episodes are associated with a higher risk of sudden death. Up to 40% of ECGs may be normal, but characteristic abnormalities include prolonged QRS duration (>110 ms in leads V1-V3) and late potentials. Approximately a third of patients have a positive family history.

**ELECTRICAL CAUSES OF SUDDEN CARDIAC DEATH**

The most common primary arrhythmias associated with sudden death are congenital long QT syndrome, Wolff-Parkinson-White syndrome, Brugada syndrome, and catecholaminergic polymorphic ventricular tachycardia, which will be discussed in detail below. Although commotio cordis is not a primary arrhythmia, it is an electric disturbance leading to sudden cardiac death and will be described in this section. Less common causes of sudden cardiac death due to arrhythmia include severe sinus node dysfunction and complete atrioventricular node block, leading to cardiac arrest or profound bradycardia; these will not be addressed further. In addition, athletic supplements or stimulants can lead to atrial or ventricular arrhythmias, hypertension, prolongation of repolarization, or coronary vasospasm. Ultimately ischemia or lethal arrhythmias may occur. Again, these entities will not be addressed further.

**Congenital Long QT Syndrome**

Congenital long QT syndrome (LQTS) is estimated to affect 1:5000 individuals. Inherited abnormalities affecting cardiac ion channels cause abnormal repolarization, leading to *torsades de pointes*, a French term that literally means “twisting of the points” (Figure 3). This form of polymorphic ventricular tachycardia can lead to syncope, seizures, and sudden death. Approximately 9% of patients with LQTS present with sudden death and 10% present with seizures.

The QT interval is measured on an ECG, ideally in lead II, and the corrected QT interval (QTc) is calculated to correct for variations in heart rate. The QTc is often available on the computer-assisted ECG interpretation and is typically calculated using Bazett’s formula (the measured QT interval divided by the square root of the preceding R-R interval, measured in seconds). A QTc <0.44 is considered normal. Unfortunately, the computer-assisted electrocardiogram (ECG) interpretation may be inaccurate, and therefore requires careful review by the interpreting physician. QTc measurements in a single individual can vary throughout the day and may be highly dependent on heart rate. Some individuals with LQTS may have an ECG with a normal QTc calculation. Therefore, a single ECG with a normal QTc cannot completely rule out LQTS and further evaluation with 24-hour Holter monitor and exercise testing may be indicated in some patients.

In 1993, Schwartz et al published criteria for diagnosing LQTS based on a point-scale for various ECG findings, patient history, and family history. Since then, genotyping has allowed for more definitive diagnoses in many cases. Variable penetrance is common in genotype-positive patients with some family members completely asymptomatic throughout their lives while others with the same genotype die suddenly in infancy or early childhood. Initially LQTS was characterized as 2 types, an autosomal dominant form (Romano-Ward) and an autosomal recessive form (Jervell and Lange-Neilsen) associated with congenital hearing loss. Currently, 10 distinct genes and several hundred mutations are associated with the diagnosis of LQTS.

The majority of LQTS patients who are genotype-positive have abnormalities in the genes encoding for
sodium or potassium ion channels. The genes involved with LQTS have been numbered LQT1-9 in the chronological order in which they were identified. LQT1-3 account for over 95% of those with identifiable mutations. LQT1 (also known as KCNQ1 and KvLQT1) accounts for approximately 55% of those identified. LQT2 (also known KCNH2 and human ether-a-go-go-related or the H sorting gene) accounts for approximately 35% of genotype positive LQTS patients. These mutations lead to a loss of function in potassium ion channels that ultimately result in prolonged repolarization. LQT3 (also known as SCN5A) accounts for approximately 10% of genotype positive LQTS patients and results in a gain of function affecting sodium ion channels, resulting in prolonged repolarization. LQT4-10 genotypes make up less than 1% of genotype positive patients. Patients with LQT1 are more likely to experience symptoms or sudden death events during exertional activities, with swimming being a particularly high-risk activity. Patients with LQT2 are most likely to have events triggered by auditory stimuli, and those with LQT3 are more likely to have events during rest or sleep.

Commercial genotyping for the 5 most common cardiac ion channel genes has been available for the past several years. Genotyping is expensive: the 5-gene comprehensive screen costs approximately $5400. If a specific gene is identified, the cost for screening subsequent family members for that particular gene is approximately $900. (C Fontanella, Familion Inc, personal communication, July 17, 2007.) Once a specific genotype has been identified, genotyping of other family members can be done relatively quickly, thus providing a definitive genotype diagnosis for patients who may have atypical phenotypes. Genotyping may also identify a polymorphism, defined as a genetic variant found in at least 1% of the population. Some polymorphisms may have clinical relevance and test results may require interpretation by a specialist with a good understanding of inherited arrhythmias. In addition, a frank discussion with the patient or patient’s parents regarding the spectrum of possible test results and expected yield of the test should be undertaken prior to ordering these tests.

**Wolff-Parkinson-White Syndrome**

Wolff-Parkinson-White (WPW) syndrome is the most common cause of supraventricular tachycardia in children with structurally normal hearts. During sinus rhythm, antegrade conduction down the accessory pathway causes ventricular preexcitation, resulting in a delta wave on ECG. Most patients who develop symptoms have palpitations and are hemodynamically stable. Rarely, sudden death can occur in patients with WPW if spontaneous atrial fibrillation occurs and there is rapid antegrade conduction down the accessory pathway, resulting in ventricular fibrillation. Non-invasive risk stratification can be done with Holter monitors and exercise testing to determine the rate at which the accessory pathway conducts, also known as the accessory pathway antegrade effective refractory period. These methods for risk stratification are not completely reliable, and many pediatric and adult electrophysiologists favor risk stratification with invasive electrophysiology testing for patients with symptomatic and asymptomatic WPW.

**Brugada Syndrome**

Brugada Syndrome is an autosomal dominant inherited disorder that can lead to spontaneous lethal ventricular arrhythmias. Electrocardiographic findings may be transient and include a right bundle branch block pattern and ST segment elevation in the right precordial leads (V1-V3) (Figure 4). The syndrome is named after the Brugada brothers who described the syndrome and correlated clinical and ECG findings that resulted in ventricular fibrillation. The incidence of Brugada syndrome is estimated to be 5 in 10,000, but is higher in Southeast Asia, where the disorder was termed sudden unexplained nocturnal death syndrome (SUNDS). Approximately 20%-30% have a sodium ion channel defect (SCN5A), but mutations in the L-type calcium channel subunit have also been described. Brugada syndrome occurs more frequently in men than women. Syncope or sudden death events often occur at rest or night and usually first appear in the third to fourth decades of life. In children, fever may be an important precipitating factor for arrhythmic events.

Since the electrocardiographic findings may be tran-
sient, provocative testing with intravenous infusion of a sodium ion channel blocker can be useful in identifying patients with Brugada syndrome. Intravenous flecainide, ajmaline, and procainamide have been used, although only intravenous procainamide is currently available in the United States. During the drug infusion, ECG changes consistent with Brugada pattern as well as ventricular ectopy and ventricular tachycardia may appear. Invasive electrophysiology testing may be helpful in establishing the diagnosis and in risk stratification. Other features for identifying at risk patients include episodes of syncope, self-terminating polymorphic ventricular tachycardia, family history of sudden cardiac death, Brugada-pattern ECGs in family members, or nocturnal agonal respiration.

Patients at highest risk for sudden death have a spontaneously abnormal ECG, are inducible during programmed ventricular stimulation, and have experienced at least one syncopal episode. Male gender is an additional risk factor for sudden death. Patients at lowest risk have ECG findings only after drug administration, are not inducible during electrophysiology testing, and have no history of syncope.

**Catecholaminergic Polymorphic Ventricular Tachycardia**

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a bidirectional or polymorphic ventricular tachycardia induced by adrenergic stimuli. CPVT is caused by an autosomal dominant mutation in the ryanodine type 2 receptor (*RYR2*) or a recessive mutation in calsequestrin 2 (*CASQ2*). The *RYR2* gene encodes the major calcium-release channel on the sarcoplasmic reticulum in the heart, and *CASQ2* is a calcium-binding protein located in the sarcoplasmic reticulum. It most often affects children and adolescents. Untreated CPVT results in a mortality rate of 30%-50% by the age of 30 years. Resting ECG is normal, but exercise can precipitate ventricular ectopy and ventricular tachycardia. Patients may also have bradycardia relative to gender- and age-matched controls, which is more obvious in males than females.

**Commotio Cordis**

Commotio cordis is a Latin term meaning “commotion of the heart.” It is caused by blunt force precordial trauma during a vulnerable period in the cardiac cycle. Precordial impact during a critical period in ventricular repolarization causes ventricular fibrillation. Autopsies show no evidence of trauma or contusion, and the overall survival rate is only 15%. Young athletes are at risk due to their smaller chest muscle mass. Commotio cordis most often occurs in males between 4-16 years of age. Cases have occurred during a variety of athletic activities, primarily baseball, softball, and hockey, and are usually due to a projectile object. Direct bodily contact (football, the martial arts) can also cause commotio cordis.

**PRE-PARTICIPATION SCREENING AND ELIGIBILITY**

Pre-participation athletic screening is not standardized and varies tremendously throughout the nation and in the world. In Italy, routine screening of all athletes, including an ECG, began in 1982. Studies have shown a decline in the incidence of sudden cardiac death in Italian athletes with an increased ability to identify cardiomyopathies. The European Society of Cardiology recommends a thorough personal and family history and physical examination as well as routine ECG screening for all athletes. The practice of routine ECG screening has not been embraced in the United States. Opponents to a nationwide ECG-screening program suggest such a program may identify some at-risk athletes, but it would not be cost effective. False-positive ECG results may lead to temporary restrictions for these athletes until additional testing is scheduled. A screening ECG may be completely normal in the face of a potentially life-threatening cardiac abnormality such as an anomalous coronary artery. Athletic heart syndrome results in abnormal ECGs in up to 40% of athletes due to normal physiologic changes. Lastly, the screening performed for athletes would obviously not include students participating in physical education class only, since the screening is recommended for those participating in organized athletic competitions. Screening echocardiograms are not routinely recommended for athletes without abnormal physical findings or worrisome personal or family history.

Currently, the American Heart Association recom-
mends 12 components for pre-participation cardiovascular screening of athletes, including physical examination findings, personal history, and family history (Table 1). An abnormality in 1 of the 12 components may be enough to warrant further evaluation, including ECG, echocardiogram, and/or referral to a pediatric cardiologist.

It is vital that parents are involved in the discussion of family history due to the possibility of an inherited arrhythmia or cardiomyopathy. Rudimentary screening physical examinations will have a low yield for these conditions. A detailed screening family history includes open-ended questions regarding family members with possible heart conditions, sudden death in relatives <50 years of age, seizures, syncope, drownings, single car accidents, sudden infant death syndrome, multiple miscarriages, congenital deafness, and history of pacemaker or implantable cardioverter defibrillator placement. Since the majority of pre-participation screening takes place in the primary care physician office, it is reasonable to have a questionnaire for the athlete and their parents to complete prior to their appointment. Absence of a positive family history does not rule out a cardiac abnormality in the face a positive physical findings or personal history. Based on this screening, further evaluation may be warranted with testing and referral to an appropriate specialist, including a pediatric cardiologist, inherited arrhythmia specialist, and geneticist or genetic counselor. Even after a sudden death event, the health care professional has an obligation to the remaining family members. Post mortem evaluations may reveal a coronary artery anomaly or inherited cardiomyopathy. Genotyping can be accomplished to rule out an inherited arrhythmia if tissue or blood is obtained in an EDTA tube. Finally, remaining family members should be thoroughly evaluated to identify others who are at risk.

### REFERENCES


### Table 1. The 12-Element AHA Recommendations for Preparticipation Cardiovascular Screening of Competitive Athletes

<table>
<thead>
<tr>
<th>Medical history</th>
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<tbody>
<tr>
<td>Personal History</td>
</tr>
<tr>
<td>1. Exertional chest pain/discomfort</td>
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<tr>
<td>2. Unexplained syncope/near-syncope</td>
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<tr>
<td>3. Excessive exertional and unexplained dyspnea/fatigue, associated with exercise</td>
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<tr>
<td>4. Prior recognition of a heart murmur</td>
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<tr>
<td>5. Elevated systemic blood pressure</td>
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<tr>
<td>Family history</td>
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<tr>
<td>6. Premature death (sudden and unexpected, or otherwise) before age 50 years due to heart disease, in equal to or less than one relative</td>
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<tr>
<td>7. Disability from heart disease in a close relative less than 50 years of age</td>
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<tr>
<td>8. Specific knowledge of certain cardiac conditions in family members: hypertrophic or dilated cardiomyopathy, long-QT syndrome or other ion channelopathies, Marfan syndrome, or clinically important arrhythmias</td>
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<tr>
<td>Physical Examination</td>
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<tr>
<td>9. Heart murmur</td>
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<tr>
<td>10. Femoral pulses to exclude aortic coarctation</td>
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<tr>
<td>11. Physical stigmata of Marfan syndrome</td>
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<tr>
<td>12. Brachial artery blood pressure (sitting position)</td>
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</tbody>
</table>

American Heart Association Recommendations for Pre-participation Cardiovascular Screening of Athletes. Medical history should be confirmed with parents. Syncope is concerning if it is judged not to be neurocardiogenic or vasovagal in etiology. Exertional syncope or exertional near-syncope is of particular concern. Auscultation of the heart should be done in both supine and standing positions (or with Valsalva maneuver) specifically to identify murmurs of dynamic left ventricular outflow tract obstruction. Ideally, blood pressures would be taken in both arms.


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