Adding an Electrocardiogram to the Pre-participation Examination in Competitive Athletes: A Systematic Review

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Abstract: No matter how rare, the death of young athletes is a tragedy. Can it be prevented? The European experience suggests that adding the electrocardiogram (ECG) to the standard medical and family history and physical examination can decrease cardiac deaths by 90%. However, there has not been a randomized trial to demonstrate such a reduction. While there are obvious differences between the European and American experiences with athletes including very differing causes of athletic deaths, some would highlight the European emphasis on public welfare vs the protection of personal rights in the USA. Even the authors of this systematic review have differing interpretation of the data: some of us view screening as a hopeless battle against Bayes, while others feel that the ECG can save lives. What we all agree on is that the USA should implement the American Heart Association 12-point screening recommendations and that, before ECG screening is mandated, we need to gather more data and optimize ECG criteria for screening young athletes. (Curr Probl Cardiol 2009;34:586-662.)

The benefits of adding an electrocardiogram (ECG) to the preparticipation examination (PPE) of young, competitive athletes remain controversial. High public visibility of athletic deaths and the impact on families who lose an athlete in the prime of life and health

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intensify the need to determine the utility and social cost of implementing such a screening tool. Professional guidelines have not definitively settled this controversy.

B.J. Gersh: This is certainly a contentious area, and the emotional impact of the death of a young athlete in the prime of life is enormous. It is interesting that in 1982 Italy instituted a mandatory preparticipation screening program for young athletes, and this has undoubtedly resulted in a striking reduction in sudden cardiac death, particularly due to fewer deaths from hypertrophic cardiomyopathy and arrhythmogenic right ventricular dysplasia. It is difficult to extrapolate these data to the United States for a number of reasons including the fact that the death rate prior to mandatory screening in Italy was relatively high as is the reported incidence of arrhythmogenic right ventricular dysplasia in that country. Nonetheless, these data certainly suggest that this is an area that warrants further studies.[107]

The Study Group on Sports Cardiology of the European Society of Cardiology presented in 2005 a consensus statement regarding PPE for young competitive athletes.[1] Critical to their decisions was the 25-year Italian experience with a systematic and comprehensive system of competitive athletic PPE. The primary purpose of the consensus document was to demonstrate the need for PPE medical clearance in all athletes involved in organized sports by focusing on the key role of 12-lead ECG. They concluded that the ECG was essential to identify structural abnormalities such as hypertrophic cardiomyopathy (HCM) and right ventricular dysplasia as well as syndromes occurring in structurally normal hearts such as the Brugada and long QT syndromes.

Following the European Consensus statement, the American 36th Bethesda Conference and an American Heart Association (AHA) statement addressed similar issues regarding athletic PPE.[2,3] As opposed to the European approach, these documents noted that such screening efforts are complicated by the substantial proportion of false-positive test results that represent a major burden to athletes, their families, and the testing facilities. The stated obstacles to implementing obligatory government-sponsored national screening with ECGs or echocardiograms in the USA were the particularly large population of athletes needed to be screened and major cost-benefit considerations. Even after normal initial screening, it is impossible to completely eliminate the risks associated with competitive sports. Although the report did not recommend mandating nationwide screening, it did recommend that when a cardiovascular (CV) abnormality is initially suspected, the diagnostic strategy should focus on the systematic exclusion of those conditions known to cause sudden cardiac deaths (SCD) in young athletes. These approaches include history, physical examination, ECG, and echocardiography. Additional testing with cardiac magnetic resonance imaging (MRI), exercise testing, ambulatory Holter ECG recording, implanted loop recorder, tilt table examination, or electrophysiological testing can also be considered in selected patients.

Thus, after review of the evidence for the basis of initial ECG screening, European and American experts proposed different recommendations for use of the ECG in the screening of athletes. Chaitman has expertly argued for the American position.[4] While the 12-lead ECG adds to the diagnostic power of the complete CV history and physical examination, the ECG may be impractical in large population screening and, because of its relatively low specificity, may result in unnecessary additional testing and/or the exclusion of healthy individuals from participating in competitive sports unless they have the necessary resources to undergo further testing.

Methods of Review

A systematic review of the studies identified via MEDLINE that provide information regarding ECG abnormalities and causes of SCD in athletes was performed. Citations were obtained using the PubMed keywords athletes, ECG, screening, preparticipation examination, as well as manual selection of references found in these citations. We have attempted to consider all methodologically sound studies consisting of over 500 athletes or methodological studies that provide important insights into abnormal athlete ECG findings. We begin by describing the causes of death that could be identified by the ECG, separated into abnormalities that are associated with structural disease and those that are not. From these findings, an attempt is made to estimate the percentage of deaths that could be recognized by ECG screening. The remainder of the article presents the evidence supporting the addition of an ECG to the PPE and a more detailed description of the ECG abnormalities that may be detected during athlete screening. This review ends with a definition of screening, the criteria for applying a screening program, and our evidence-based conclusions. Medical conditions that may also cause sudden death in young athletes, but could not possibly be detected on cardiovascular screening, are not considered. These conditions include heat stroke, cerebral aneurysm, bronchial asthma, nonpenetrating blunt chest trauma (Commotio cordis), sickle cell trait, as well as use of nutritional supplements and illicit drugs.

There are several limitations to an attempt at a comprehensive review that are worth noting upfront. Many studies of athletic ECGs performed before contemporary imaging studies, such as an echocardiogram

(ECHO), were available for confirmation of disease or before genetic abnormalities were as appreciated as they are today. In addition, the prevalence of right ventricular cardiomyopathy or the Brugada syndrome, for example, cannot be assessed in studies that took place before these conditions were generally recognized. Nevertheless, these studies will be summarized as they form the basis of many concepts held today with regard to abnormal ECG findings.

Causes of Sudden Cardiac Death in Athletes

After 20 years of systematic use of an ECG in the PPE of young athletes in Italy, Corrado et al analyzed sudden deaths among athletes and nonathletes (35 years of age or less) in the Veneto region from 1979 to 1996. Athletes were defined as "participants in an organized sports program requiring regular training and competition."[5] The causes of sudden death in both groups were compared and the pathologic findings in the athletes were correlated with their clinical histories and ECGs. Of 269 sudden deaths in young people, 49 occurred in competitive athletes (44 male and 5 female athletes; mean age, 23 years). The most common causes of SCD in athletes were arrhythmogenic right ventricular cardiomyopathy (ARVC) (22%), coronary atherosclerosis (18%), and anomalous origin of a coronary artery (12%). HCM caused only 1 sudden death among the athletes (2%) but caused 16 sudden deaths in nonathletes (7%). HCM was detected in 22 athletes (0.07%) at the PPE and accounted for 3.5% of the CV reasons for disqualification.

In a separate cohort study, Eckart et al analyzed the causes of nontraumatic SCD among military recruits using demographic and autopsy data from the Department of Defense Recruit Mortality Registry.[6] All nontraumatic sudden deaths were analyzed during basic military training from 6.3 million men and women age 18-35 years. Descriptive analysis, mortality rates, and causes of sudden death were considered. Of 126 nontraumatic sudden deaths (rate, 13.0/100,000 recruit-years), 108 (86%) were related to exercise. The most common cause of SCD was an identifiable cardiac abnormality [64 of 126 recruits (51%)]. Although a substantial number of deaths remained unexplained [44 (35%)], autopsy reports referred to family history of premature SCD in several cases. The predominant structural cardiac abnormalities identified were coronary artery abnormalities (61%), myocarditis (20%), and HCM (13%). An anomalous coronary artery accounted for one-third (21 of 64 recruits) of the cases in this cohort, and, in each, the left coronary artery arose from the right sinus of Valsalva, coursing between the pulmonary artery and aorta. In this cohort study, a cardiac abnormality was the leading identifiable cause of sudden death among military recruits. However, more than one-third of sudden deaths remain unexplained despite medical investigation, suggesting the presence of underlying malignant arrhythmic or conduction system diseases.

Based on this last study, it is plausible that the proportion of CV pathologies responsible for fatal events may be underestimated in population-based and cohort studies. Many lethal cardiac diseases with possible ECG findings (such as Wolff-Parkinson-White and long QT syndrome) present minimal or no anatomic findings. Histologic recognition of abnormal conduction tissue requires supplemental sections that are not necessarily part of a routine autopsy procedure.

To better define the causes of SCD in structurally normal hearts, Corrado et al prospectively studied the pathology of 273 consecutive cases of SCD in young people between 1979 and 1998.[7] The heart was examined according to a detailed morphologic protocol consisting of macroscopic and histologic examination, including study of the specialized conduction system by serial section. At macroscopic examination, 197 SCD victims (72%) were found to have an overt underlying structural heart disease such as cardiomyopathy (56), CAD (54), valve disease (32), nonatherosclerotic coronary artery disease (28), aortic rupture (13), postoperative congenital heart disease (5), and other diseases (9). The remaining 76 cases (28%) (50 males and 26 females, mean age 23 ± 5 years) had a macroscopically normal heart. Twenty-eight structurally normal hearts (37%) had experienced 1 or more of the following prodromes: syncope, palpitations, or both in 20; ECG abnormalities in 18; and arrhythmias in 10. In 79% of this group, histologic examination disclosed concealed pathologic substrates consisting of focal myocarditis in 27 cases, ARVD/D in 9, and conduction system abnormalities in 24 (leading to ventricular pre-excitation in 18 and heart block in 6). No evidence of structural heart disease was found even after histologic study in 6% of cases. This study suggests that many deaths in apparently normal structural hearts are in fact caused by CV diseases potentially detectable with an ECG.

B.J. Gersh: In a study of sudden unexpected nontraumatic death in individuals age 20-40 years in Olmstead County, Minnesota, the major causes of death were coronary artery disease, noncardiovascular disease, presumed arrhythmia, vascular disease, and myocarditis. Histological features of right ventricular dysplasia were prevalent but were not necessarily the primary cause of death, but what was interesting was a disturbing trend in that, of the 27 sudden deaths between 1980 and 1989, 33% had a history of cocaine abuse; however, the extent to which this can predispose to sudden arrhythmic death is uncertain (Shen WK, Edwards WD, Hammill SC, et al. Sudden unexpected nontraumatic death in 54 young adults: a 30-year population-based study. Am J Card 1995;76:148-52).

The US National Registry of Sudden Death in Young Athletes

Since 1985 Minnesota has mandated an insurance program for catastrophic injury or death for all student athletes engaged in interscholastic sports. Over a 12-year period, from 1985 to 1997, 3 sudden deaths due to CV disease during exertion occurred in competitive high school athletes (grades 10-12).[8] At autopsy, the causes were determined to be anomalous origin of the left main coronary artery from the right sinus of Valsalva, congenital aortic valve stenosis, and myocarditis. All 3 athletes were white and male (16 or 17 years of age): 2 competed in cross-country/track and 1 in basketball. During the study period, there were 1,453,280 overall sports participations and 651,695 student athlete participants across the 27 high school sports. The risk for sudden death was 1:500,000 participations or 0.46/100,000 annually. Over a 3-year high school career for a student athlete the estimated risk was 1:72,500. Therefore, the risk of SCD in a population of high school student athletes was small, approximately 1 in 200,000 per year.

The Minneapolis Heart Institute Foundation has also generated and maintained a unique registry of cases comprising young trained athletes who have died suddenly. Dr Barry J. Maron, MD, Director of the Hypertrophic Cardiomyopathy Center at the Minneapolis Heart Institute Foundation, has been collecting information regarding cases of sudden death in athletes that appeared in the media since 1985. This process collected information on over 600 SCD in young athletes that participated in competitive sports. These efforts have been responsible for what is currently known about rates of SCD on the athletic field in the USA. However, a system that uses news media as a primary source might be expected to underreport athletic SCD. The deaths of nonelite athletes are more likely to reach the public if they occur in a large city. Also, autopsies are not performed on all such deaths and prior medical workups are significantly varied in quality. Only a systematically assembled national registry would permit accurate assessment of the causes of sudden death in young athletes and lead to better understanding of the true magnitude of this problem.

The majority of CV deaths in US athletes $<$35 years of age are due to several congenital or acquired cardiac malformations. These deaths occur most commonly in basketball and football, sports that have the highest levels of participation and that also involve particularly intense levels of physical activity. HCM is the single most common cause of athlete deaths (responsible for approximately one-third of the cases), followed by congenital coronary artery anomalies, particularly those with aberrant aortic sinus origin. Several other CV diseases account for 5% or less of these deaths in athletes. Maron estimated that only 3% of athletic deaths occurred without an explanation and with a structurally normal heart.

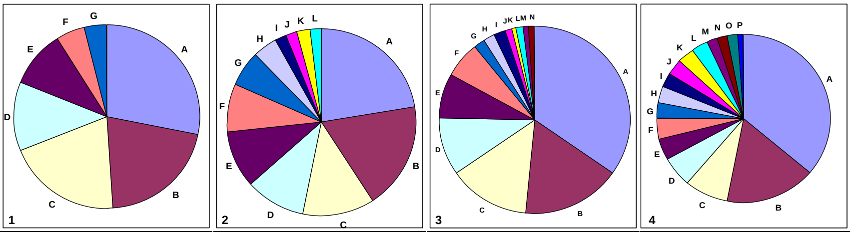
Differences in the leading causes of SCD between Italian and US athletes may be partly explained by the fact that annual screening of all athletes, starting at an early age, identifies young individuals with HCM who are prevented from participating in competitive sports and subsequent SCD.[9] Genetic predisposition to ARVC in Italians has also been suggested to explain these regional differences.

We have created pie figures including the major pathologic studies reviewed above considering what abnormalities could be discovered by adding the ECG to the PPE (Fig 1). An important issue is: what percentage of deaths occurs in structurally normal hearts? This group could provide the strongest argument for ECG screening but the results range from 3% to 33% in the athletic deaths.

Are Athletes at Higher Risk of SCD Than the Public?

The observation that SCD occurs more frequently in those who exercise vigorously vs those in the general sedentary population initially appears to be a paradox. Vigorous physical exercise may precipitate acute fatalities in both adults and young competitive athletes with concealed heart diseases. However, the risk-benefit ratio of physical exercise differs among these 2 age groups.[10,11] In adults, vigorous exertion increases the incidence of adverse coronary events in individuals who do not exercise regularly,[12,13] whereas habitual physical activity reduces the overall long-term risk of coronary events and SCD. The association between physical activity and the risk of SCD has been reported in numerous epidemiologic studies and has even been regarded as the "double-edged sword" of physical exercise. In a Rhode Island study, the exercise-related SCD rate was 7.6 times higher than that during sedentary activity.[14] In a Seattle study, the incidence of cardiac arrest during exercise was 25-fold higher than the incidence at rest or during lighter activity.[15] A similar pattern of increased risk of exercise-related acute myocardial infarction was also observed. Vigorous physical exertion has been reported within 1 hour before myocardial infarction in 4%-10% of cases.[16,17] Although these data suggest that vigorous exertion transiently increases the incidence of coronary events, the adverse event risk decreases over time with increasing amounts of physical activity in the adult group.

A



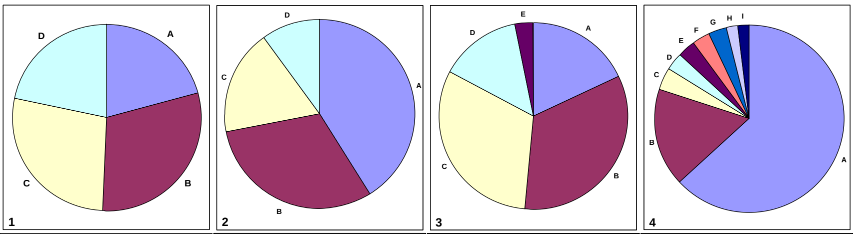
Key for Chart 1		
Corrado D, Basso C, Thiene G. Sudden cardiac death in young people with apparently normal heart. *Cardiovasc Res* 2001;50:399-408.		
A	28%	No Structural Cause
B	21%	Cardiomyopathy
C	20%	Athersclerotic Coronary Artery Disease
D	12%	Valvular Disease
E	10%	Anomalous Origin of Coronary Artery
F	5%	Miscellaneous
G	4%	Aortic Rupture

Key for Chart 2		
Corrado D, Basso C, Schiovan M, Thiene G. Screening for hypertrophic cardiomyopathy in young athletes. *N Engl J Med* 1998;339:364-9.		
A	22%	Arrhythmogenic Right Ventricular Dysplasia
B	18%	Athersclerotic Coronary Artery Disease
C	12%	Anomalous Origin of Coronary Artery
D	10%	Mitral-Valve Prolapse
E	10%	Other
F	8%	Conduction system Disease
G	6%	Myocarditis
H	4%	Myocardial Bridge
I	2%	Hypertrophic cardiomyopathy
J	2%	Dilated Cardiomyopathy
K	2%	Dissecting Aortic Aneurysm
L	2%	Pulmonary Thromboembolism

Key for Chart 3		
Eckart R, Scoville S, Campbell C, Shry E, Stajduhar K, Potter R, Pearse L, Virmani R. Sudden death in young athletes: A 25-year review of autopsies in military recruits. *Ann Intern Med* 2004;141:829-834.		
A	35%	No Structural Cause
B	17%	Anomalous Coronary Artery
C	14%	Non-Cardiac Cause
D	10%	Myocarditis
E	8%	Atherosclerotic Coronary Artery Disease
F	6%	Hypertrophic Cardiomyopathy
G	2%	Coronary Aneurysm
H	2%	Coronary Artery Hypoplasia
I	2%	Intramyocardial Coronary Bridge
J	1%	Bicuspid Aortic Valvular Stenosis
K	1%	Coronary Dissection
L	1%	Embolic Myocardial Infarction
M	1%	Idiopathic Dilated Cardiomyopathy
N	1%	Right Ventricular Dysplasia

Key for Chart 4		
Maron B, et al. Recommendation and consideration related to preparticipation screening for cardiovascular abnormalities in competitive athletes. *Circulation*2007;115:1643-1655.		
A	36%	Hypertrophic Cardiomyopathy
B	17%	Coronary Artery Anomalies
C	8%	Indeterminate LVH
D	6%	Myocarditis
E	4%	ARVC/D
F	4%	Mitral Valve Prolapse
G	3%	Aortic Stenosis
H	3%	Coronary Artery Disease
I	3%	Ion Channelopathies
J	3%	No Structural Cause
K	3%	Tunneled LAD
L	3%	Other
M	2%	Aortic Rupture
N	2%	Dilated Cardiomyopathy
O	2%	Other Congenital Heart Disease
P	1%	Sarcoidosis

B



Key for Chart 1		
ECG detectable causes of death from Corrado D, et al. *Cardiovasc Res* 2001;50:399-408.		
A	21%	**ECG Detectable**
B	30%	Coronary Artery Pathology
C	28%	No Structural Cause (risk possibly identified only by ECG)
D	22%	Misc. Cardiac Findings

Key for Chart 2		
ECG detectable causes of death from Corrado D, et al. *N Engl J Med* 1998;339:364-369.		
A	41%	**ECG Detectable**
B	31%	Coronary Artery Pathology
C	18%	Mitral Valve Prolapse
D	10%	Misc. Cardiac Findings

Key for Chart 3		
ECG detectable causes of death from Eckart R, et al. *Ann Intern Med* 2004;141:829-834.		
A	18%	**ECG Detectable**
B	33%	No Structural Cause (risk possibly identified only by ECG)
C	31%	Coronary Artery Pathology
D	14%	Non-Cardiac
E	3%	Misc. Cardiac Findings

Key for Chart 4		
ECG detectable causes of death from Maron B, et al. *Circulation* 2007;115:1643-1655.		
A	63%	**ECG Detectable**
B	17%	Coronary Artery Anomalies
C	4%	Mitral Valve Prolapse
D	3%	Coronary Artery Disease
E	3%	No Structural Cause (risk possibly identified only by ECG)
F	3%	Other
G	3%	Tunneled Left Anterior Descending
H	2%	Aortic Rupture
I	2%	Other Congenital Heart Disease

FIG 1. (A) Autopsy studies of sudden death in active young adults: four studies reviewed. (Reproduced with permission from Maron et al.[3]) (B) ECG detectable causes of sudden death in athletes. (Reproduced with permission from Eckart RE et al. Ann Internal Med 2001;141(11):829-35.) (Color version of figure is available online.)

In adolescents and young adults, sports activity is associated with a significant increase of the risk of SCD. This remarkable difference with adults can be explained by the differences in CV pathologies causing sport-related SCD in the 2 populations. While CAD accounts for most SCD in adults 35 years of age or older, in younger athletes, a large spectrum of CV diseases (including congenital heart disorders) has been documented. Corrado et al[18] assessed the risk of SCD in both male and female athletes (age 12-35 years) with a 21-year prospective cohort study of all young people of the Veneto region of Italy. From 1979 to 1999, 300 cases of SCD were reported, producing an incidence rate of 1 in 100,000 persons per year. Fifty-five SCDs occurred among athletes (2.3 in 100,000 per year) and 245 among nonathletes (0.9 in 100,000 per year), with an estimated all-cause SCD relative risk (RR) of 2.5 in athletes compared with nonathletes. The rates of SCD from CV diseases were 2 in 100,000 athletes per year, compared with 0.7 in 100,000 nonathletes per year (RR of 3). The risks of SCD in athletes with underlying CV disease were significantly higher, with a RR of 79 in those with congenital coronary artery anomalies, 5 in those with ARVC, and 3 in those with premature CAD.

The mechanisms of SCD differ significantly between young athletes and adults. In general, SCD results from a combination of cardiac structural lesions and transient acute abnormalities that trigger the fatal event. The mechanisms of exercise-related sudden death in young competitive athletes include several triggers such as acute myocardial ischemia, sympathetic autonomous stimulation, and abrupt hemodynamic changes leading to ventricular arrhythmias. Intensive athletic training itself may also increase the risk of SCD in the young athlete with heart disease by altering the substrate, promoting phenotypical expression, or accelerating the disease progression. For example, in Marfan syndrome, the hemodynamic challenge placed on the aorta during physical activity can accelerate the rate of aortic enlargement, thereby increasing the risk of rupture. In patients with ARVC, regular physical activity can cause right ventricular volume overload and cavity enlargement, which in turn may accelerate fibrofatty atrophy.[19] In patients with HCM, recurrent episodes of exercise-induced myocardial ischemia can produce cell apoptosis and myocardial scarring fibrosis.[20] Because of these changes, ventricular electrical instability is increased.

B.J. Gersh: Commotio cordis refers to sudden cardiac death in young athletes following low-impact precordial trauma with a projectile object such as a baseball, hockey puck, or fist. Although reported more in recent years, Commotio cordis is a rare event, but recent data from a registry suggest that Commotio cordis may be the second leading cause of sudden death in young athletes after hypertrophic cardiomyopathy (Maron BJ. Sudden death in young athletes. N Engl J Med 2003;349:1064-75).

The particular predominance of fatal events in male athletes found in the Italian experience is consistent with the findings of previous surveys of athletic field deaths. It has been explained by the fact that women participate less commonly in competitive sports than men. However, male gender was itself an independent risk for SCD in athletes in the Veneto study. Compared with women, men have a higher prevalence and/or phenotypic expression of potentially lethal cardiac diseases, such as HCM, ARVC, and premature coronary artery disease.[21-23]

This, along with the greater exposure of men to more intensive training and levels of intensity during athletic competition than women, may help explain the sex differences in SCD rates.

Conditions Associated With Preventable SCD in Athletes Identified on ECG

Structurally Normal Hearts

Brugada Syndrome. Since its introduction as a clinical entity in 1992, the Brugada syndrome has progressed from being a rare disease to 1 that is second only to automobile accidents as a cause of death among young adults in some countries.[24] It is a congenital syndrome displaying an autosomal-dominant mode of transmission in patients with structurally normal hearts. The syndrome typically manifests during adulthood with a mean age of sudden death at 42 years. The youngest patient clinically diagnosed with the syndrome was 2 days old, while the oldest was 84 years old. The disease has been linked to mutations in *SCN5A*, a gene located on the short arm of chromosome 3 (p21-24) that encodes for the alpha subunit of the sodium channel.

B.J. Gersh: It is generally accepted that Brugada syndrome demonstrates autosomal-dominant inheritance with a variable expression, although the reasons for the latter are not completely understood. Mutations of other genes including mutations of the cardiac L-type calcium channel have been described (Antzelvbitch C, Pollevick GD, Cordeiro JM, et al. Lost-of-function mutations in the cardiac calcium channel underlie new clinical entity characterized by ST-segment elevation, short-QT intervals in sudden cardiac death. Circulation 2005;115:442-9).

Brugada syndrome is characterized by right bundle branch block (RBBB) of varying degrees and dynamic ST-segment elevation (accen-

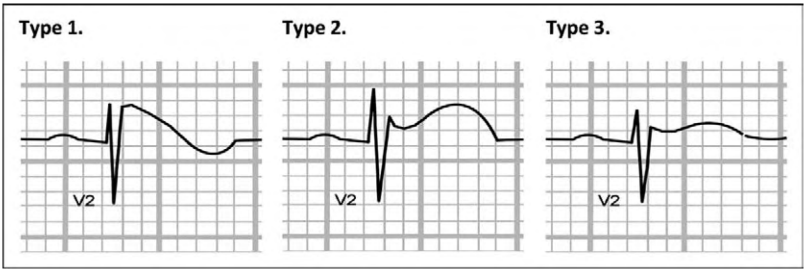


FIG 2. Example of types 1, 2, and 3 Brugada ECG patterns. Varying degrees of right bundle branch block are seen and type 1 is characterized by coved-type ST elevations, while types 2 and 3 depict a "saddleback" ST segment. Lead V2 is usually the most pronounced, although the patterns can extend from V1-V3.

TABLE 1. ECG patterns of the different Brugada types

	Type 1	Type 2	Type 3
Clinical significance	Diagnostic	Nondiagnostic	Nondiagnostic
J-wave amplitude	≥2 mm	≥2 mm	≥2 mm
T wave	Negative	Positive or biphasic	Positive
ST-T configuration	Coved-type	Saddleback	Saddleback
ST-segment	Gradually descending	Elevated ≥1 mm	Elevated <1 mm

tuated J wave) in leads V1 to V3 of the ECG followed by negative T waves (Fig 2). As was elaborated by the second Brugada syndrome consensus conference held in September 2003, each of the 3 Brugada types has a distinguishing set of electrocardiographic characteristics (Table 1). The ECG manifestations of Brugada syndrome are often dynamic or concealed and may be unmasked or modulated by sodium channel blockers, a febrile state, vagotonic agents, alpha-adrenergic agonists, beta-adrenergic blockers, tricyclic antidepressants, a combination of glucose and insulin, hypo- and hyperkalemia, hypercalcemia, and alcohol or cocaine toxicity. This syndrome is associated with syncope and a relatively high incidence of sudden cardiac death secondary to the development of polymorphic ventricular tachycardia that may degenerate into ventricular fibrillation.

Due to the dynamic and often concealed nature of the ECG patterns, it is difficult to determine the true prevalence of the disease in the general population. The syndrome is estimated to be responsible for at least 4% of all sudden cardiac deaths and at least 20% of sudden deaths in patients with structurally normal hearts. Worldwide, the prevalence of the disease is approximately 5 in 10,000 persons and, apart from accidents, is the leading cause of sudden death in men less than 40 years old, particularly in countries where the syndrome is endemic.

B.J. Gersh: The Brugada pattern is much more common in men than in women and in 1 analysis was as much as 9 times higher (Matsuo K, Akahoshi M, Nakashima E, et al. The prevalence, incidence, and prognostic value of the Brugada-type electrocardiogram: a population-based study of 4 decades. JACC 2001;38:765-70). Reasons for the predominant male preponderance are unknown, but animal models have suggested that the impact of testosterone on currents, particularly out for potassium currents, may be a contributory factor (Wylie JV, Pinto DS, Josephine MS. Brugada syndrome in sudden cardiac arrest. Up-to-Date 2008).

The Brugada syndrome is believed to be most prevalent in Asian countries. In a recent Japanese study, a type 1 ECG pattern of Brugada syndrome was identified in 12/10,000 inhabitants; type 2 and 3 ECG patterns, which are not definitively diagnostic of the Brugada syndrome, were 5 times more prevalent.[25] In another Japanese study, Yoshinaga and colleagues[26] found that of 7022 seventh grade males, 2 subjects (0.03%) met conventional criteria for Brugada. When the same subjects were re-examined 3 years later, 7 subjects (0.10%) showed Brugada's ECG pattern.

B.J. Gersh: A sudden unexpected nocturnal death syndrome (SUNDS), which has been described in young, apparently healthy males from southeast Asia, is well described, and it has been generally concluded that SUNDS and Brugada syndrome are phenotypically, genetically, and functionally the same disorder and that the management should be as for classic Brugada syndrome (Antzelebitch C, Brugada P, Borggreve M, et al. Brugada syndrome: report of the second consensus conference; endorsed by the Heart Rhythm Society (HRS) and the European Heart Rhythm Association. Circulation 2005;111:659-70).

The prevalence of Brugada syndrome among the general population in Europe and USA is thought to be much lower, although among Southeast Asian immigrants it may be as high as it is in Southeast Asia itself.[27] In Finland, Junttila et al studied the prevalence of Brugada ECG patterns in 2 populations and its clinical significance.[28] The study populations consisted of 2479 healthy male Air Force applicants (age 18-30 years), and 542 healthy middle-aged subjects (age 40-60 years). All subjects underwent a thorough physical examination and 12-lead ECG in 1980-1990 (first population) and in 1991-1992 (second population). The ECG criteria suggested by the European Society of Cardiology were used to identify subjects with a Brugada ECG pattern. Fifteen (0.6%) subjects in the first population and 3 subjects in the second population (0.6%) fulfilled the ECG criteria for type 2 or 3 Brugada pattern, with J-point elevation and a saddleback-type ST-segment configuration in the right precordial leads. Type 1 Brugada ECG abnormality (coved ST-segment elevation) was not seen in any of the subjects. No mortality or arrhythmias occurred in either study population during follow-up (20 and 10 years, respectively). They concluded that the benign natural course of Finnish patients with the Brugada pattern suggests that in asymptomatic subjects without a family history of sudden cardiac death, type 2 or 3 Brugada ECG pattern is a normal variant rather than a specific predictor of sudden death in their population.

In Canada, Lee and colleagues investigated the incidence and prognosis of spontaneous Brugada ECG pattern in a prospective cohort (the Manitoba Follow-up Study).[29] Since 1948, nearly 4000 healthy aircrew recruits were followed with routine medical examination and ECGs. Over 55 years of follow-up, clinical and ECG assessments were performed every 3-5 years, with yearly contact to monitor vital status. The mean age of the cohort at entry and the average age of the 1375 survivors in 2003 were 31 and 83 years of age, respectively. Brugada ECG pattern was defined as ST-segment elevation in at least 1 of leads V1 to V3 with J-wave amplitude of at least 2 mm, negative T waves, and generally coved ST-T configuration, in the absence of alternative explanations of these abnormalities. Serial ECGs of 273 subjects (6.9% of the cohort) with complete RBBB at any time during follow-up were reviewed. Follow-up records pertaining to clinical course and all ECGs (n = 5665) from this cohort were reviewed. Four men had an identified intermittent Brugada ECG pattern (lifetime incidence 1 per 1000). Of the 3 men, all 80 years of age or older, who received long-term follow-up, none had syncope or ventricular arrhythmias documented. The longevity of asymptomatic individuals in this cohort was not affected by spontaneous appearance of the Brugada ECG pattern.

Patients with Brugada ECG patterns who are identified because of presentation with symptoms have significantly higher event rates than those identified incidentally. In Germany, Eckardt et al identified 212 individuals (mean age, 45 years) with a type 1 Brugada ECG pattern.[30] Of these, 123 (58%) were asymptomatic, 65 (31%) had syncope of unknown origin, and 24 (11%) had to be resuscitated because of ventricular fibrillation. In 125 individuals (59%), a spontaneous type 1 ECG was recorded. In the remaining, drug challenge with a class I antiarrhythmic agent unmasked the Brugada ECG pattern. The mean ST elevation was 2 mm in symptomatic patients and slightly less in asymptomatic individuals. During a mean follow-up of 3 years, 4 of the 24 patients (17%) with aborted sudden cardiac death and 4 of 65 (6%) with prior syncope had a recurrent arrhythmic event, whereas only 1 of 123 asymptomatic individuals (0.8%) had a first arrhythmic event. Four of 9 patients with arrhythmic events during follow-up were not inducible during programmed electrical stimulation. A previous history of aborted sudden death or syncope and the presence of a spontaneous type 1 ECG were predictors of adverse outcome, while asymptomatic individuals had a very low incidence of severe arrhythmic events during follow-up.

There are other clinical conditions that may mimic the Brugada ECG patterns and make diagnosis more challenging. Among patients with ARVC, there is a subpopulation with a clinical and ECG pattern similar to that of the Brugada syndrome.[31] These cases are thought to represent an early or concealed form of the disease. Acute right-ventricular (RV) outflow tract ischemia is also known to induce a Brugada-like ECG. Di Diego and colleagues examined the electrophysiological bases for the similarities between the ECG characteristics of the Brugada pattern induced by terfenadine and the ECG manifestations of an acute transmural no-flow ischemia model.[32] For both experimental simulations, they used isolated arterially perfused canine RV wedge preparations to record transmembrane action potentials (AP) from endocardium and epicardium together with a transmural pseudo-ECG. They concluded that can modulate the ECG manifestation of acute ischemia as well as that of the Brugada syndrome, and that both clinical entities are the result of a similar electrophysiological substrate.

Brugada Syndrome in Athletes. Little is known about the association between Brugada patterns and SCD in athletes. The Brugada syndrome has not yet been implicated as a significant cause of SCD in athletes. It has been observed, however, that events in patients with a Brugada pattern typically occur more frequently at night during sleep[33] and are usually not related to exercise.[34] The prognostic and therapeutic approach in athletes with a diagnostic ECG but without any previous symptoms and family history remains controversial.

B.J. Gersh: There is considerable controversy about the optimum method of investigation and risk stratification for Brugada syndrome, and this also has an impact on the selection of the patients who should receive an ICD. Recent guidelines have supported ICD implantation in all patients with Brugada syndrome who have had a prior cardiac arrest, in patients who have had a history of syncope, and in patients with a history of VT even if this did not result in cardiac arrest. The guidelines do not address the prognostic significance of sudden cardiac death in a family member and the implications of a positive family history, and the role of electrophysiologic testing remains controversial (Epstein AE, DeMarco JP, Elenbogen KA, et al. ACC/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: a report from the American College of Cardiology/American Heart Association Task Force and Practice Guidelines (Writing Committee to Revise the ACC/AHA/NASPE 2002 guideline update; the implantation of cardiac pacemakers and antiarrhythmia devices) developed in collaboration with the American Association for Thoracic Surgery and Society of Thoracic Surgeons. JACC 2008;51:e1).

Long QT Syndrome. The congenital long QT syndrome (LQTS) is caused by cardiac ion channel mutations, which predispose young individuals to prolonged QT intervals and sudden cardiac death often related to exercise.[35] The cited article discussed 2 cases representative of the challenges brought on by this syndrome. One athlete with the diagnosis competed successfully in swimming but required that her mother sit by the pool ready with a portable defibrillator, while the other was a basketball player who had an internal cardiac defibrillator (ICD) placed for a misdiagnosis of LQTS.

One of the most challenging aspects behind the diagnosis of this condition is an accurate determination of the QT interval.

B.J. Gersh: The authors put their finger right on the root of the problem. I personally often find it very difficult to accurately determine the QT interval.

Methodologically, it is important to examine all leads and use the longest measurable QT interval. Computer algorithms are limited and one is required to check the measurements manually for an accurate determination. One must also correct the QT interval for HR using Bazett's method (QTc), although there is concern whether normalizing for heart rate is the best fit. The cutoffs for long QTc have traditionally been set at 0.44 seconds for clinical purposes, 0.460 seconds for genomic studies, while an interval greater than 0.500 seconds is clearly abnormal. Another diagnostic difficulty is that the ECG expression of this abnormality is not always active and persons with this condition can have normal QTc intervals. Some have suggested that the definitive means of diagnosing this syndrome when the history suggests it and the resting ECG is normal requires using Holter monitoring to assess for intermittent appearance of a prolonged QT.

TABLE 2. The Schwartz clinical criteria for diagnosis of long QT syndrome*

	Points
ECG findings†	
A. QTc‡	
>480 ms	3
460–470 ms	2
450 ms (in males)	1
B. Torsade de pointes	2
C. T-wave alternans	1
D. Notched T wave in 3 leads	1
E. Low HR for age§	0.5
Clinical history	
A. Syncope¶	
With stress	2
Without stress	1
B. Congenital deafness	0.5
Family history**	
A. Family members with definite LQTS††	1
B. Unexplained sudden cardiac death at younger than age 30 among immediate family members	0.5

Scoring: ≤1 point, low probability of LQTS; 2–3 points, intermediate probability of LQTS; ≥4 points, high probability of LQTS.
*Reprinted with permission.[41]
†In the absence of medications or disorders known to affect these ECG features.
‡QTc calculated by Bazett's formula, where QTc = QT/✓RR.
§Resting HR below the second percentile for age.
¶The same family member cannot be counted in A and B.
**Definite LQTS is defined by a LQTS score ≥4.
††LQTS, long QT syndrome.

Although a clearly prolonged QTc interval, in the absence of secondary causes such as drug use, can help establish the diagnosis of congenital LQTS, the clinical picture is often less obvious when the QTc interval is borderline prolonged or normal. Due to the lack of sensitivity in the ECG alone, other clinical criteria are often used to help establish the diagnosis (Table 2). The most important factors include associated clinical symptoms, such as syncope or aborted sudden death, as well as family history of LQTS or SCD.

Because of increased physician and public awareness of LQTS as well as the variability in ECG prolongation, LQTS has the potential to be overdiagnosed.[36] Taggart et al studied the agreement between the dismissal diagnosis from an LQTS subspecialty clinic and the original referral diagnosis.[37] Data from the medical record were compared with data from an outside evaluation in 176 consecutive patients (average QTc of 481 milliseconds) referred with a diagnosis of LQTS. After evaluation at Mayo Clinic's LQTS Clinic, 73 (41%) patients were categorized as no

LQTS (No-LQTS), 56 (32%) as possible LQTS (P-LQTS), and only 47 (27%) as definite LQTS (D-LQTS). The yield of genetic testing among D-LQTS patients was 78% compared with 34% for P-LQTS and 0% among No-LQTS patients ($P < 0.0001$). Determinants for discordance (ie, positive outside diagnosis vs No-LQTS) included overestimation of QTc, diagnosing LQTS by "borderline" QTc values, and interpretation of a vasovagal fainting episode as an LQTS-precipitated cardiac event. Two of every 5 patients referred with the diagnosis of LQTS departed without such a diagnosis.

LQTS is caused by several different mutations predominantly in sodium or potassium channel genes, which occur in 1 of 2500 individuals and can follow 2 different patterns of inheritance.

B.J. Gersh: As an essential first step, one has to exclude the acquired form of QT-interval syndrome due to hypokalemia, hypomagnesemia, bradycardia, and a variety of drugs including antiarrhythmic drugs, certain nonsedating antihistamines (eg, terfenadine), macrolyte antibiotics, certain antipsychotic and antidepressant medications (eg, haloperidol), and gastric motility agents such as Cisapride (Roden DM. Drug-induced prolongation of the QT-interval. N Engl J Med 2004;350:1013-22).

The first is the autosomal-dominant pattern, named the Romano-Ward syndrome (without deafness), and the second is the autosomal-recessive pattern, termed Jervell-Lange-Nielsen's syndrome, which is associated with sensorineural deafness. There are 10 different genes that have been linked to the LQTS, although only 3 account for the majority of mutations in the population (Table 3). The mutations of the LQTS-associated genes are ethnicity-specific and only LQT1 or LQT5 are associated with the Jervell-Lange-Nielsen's syndrome.

The most common genetic subtypes of LQTS are associated with a distinct ECG (Fig 3) and clinical pattern. The following is a summary of the clinical and physiological characteristics associated with each of the known genes linked to the LQTS:

- LQT1 (*KCNQ1*) (40%-55% of cases): The *KCNQ1* gene product, $K_V7.1$, forms voltage-gated K channel alpha subunits to form the current channel, which slowly deactivates the delayed rectifier potassium channel. There are over 179 missense mutations in this subunit that lead to dominant-negative effects in vitro. The net effect of these mutations is a decreased outward K current during the plateau phase of the action potential, a delay in repolarization, and subsequent QT prolongation. The ECG is characterized by a tall, broad-based T wave.

TABLE 3. Summary of the genetic and clinical characteristics of the most common LQTS genotypes*

	LQT1	LQT2	LQT3
Gene	KVLQT1	HERG	SCN5A
Chromosome locus	11p15.5	7q35-36	3p21-24
Mechanism of QT prolongation	↓ IKs → delayed repolarization	↓ IKr → delayed repolarization	↑ I_{Na} → prolonged action potential
T-wave morphology	Broad based or late appearing	Bifid	Late onset or asymmetrical peaked
QTc during exercise	Prolongs	Unchanged	Shortens excessively
Specific triggers†	Exercise, swimming	Emotion, loud noise	Sleep
Incidence of a first cardiac event before age 40 (%)‡	30	46	42
Incidence of first cardiac arrest or sudden death before age 40 (%)‡	10	20	16.4
Response to beta-blocker therapy	Good	Moderate	Weak

Abbreviations: IKs, slow outward (delayed) rectifier potassium current; IKr, rapid outward (delayed) rectifier potassium current; I_{Na}, inward sodium current.

*Reprinted with permission.[35]

†Data from Schwartz et al.[30]

‡Data from Priori et al.[23] examining the cumulative incidence of cardiac events (syncope, cardiac arrest, sudden death) before the age of 40 and before therapy in patients with known LQTS genotype.

SCD in this syndrome most commonly occurs during strenuous exercise and responds best to β blocker therapy.

- LQT2 (HERG) (35%-45% of cases): Mutations in *HERG* can manifest as long or short QT (loss/gain of function). The gene product, K_V11.1, is responsible for forming K channel alpha subunits whose tetramers form Ikr, the rapidly activating and deactivating delayed rectifier K channel. There are over 198 distinct *HERG* mutations described. The ECG frequently shows notching of the T waves, which can be low amplitude. Clinical events are often associated with emotional stress or strong auditory stimuli.
- LQT3 (*SCN5A*) (8%-12% of cases): Mutations lead to prolonged opening of sodium channels (gain of function), enhancing inward flux of sodium and prolongation of the plateau phase of the action potential. The resulting lengthening of the repolarization leads to an elongated QT interval. There are over 56 mutations described in this gene, which is the same gene responsible for the Brugada syndrome. The ECG is characterized by a late-onset, peaked, often biphasic T

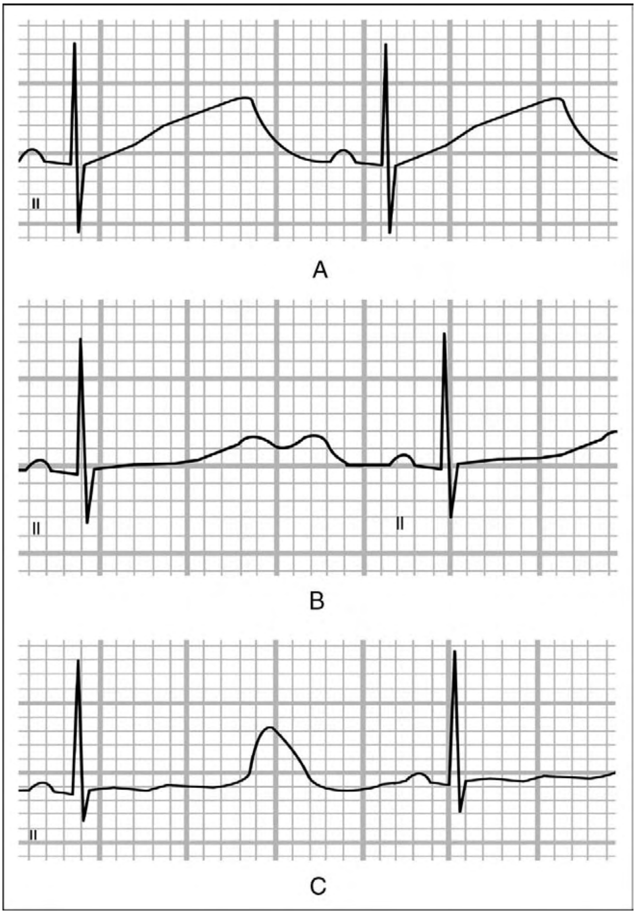


FIG 3. (A-C) Typical ECG patterns of the most common LQT syndromes.

wave. Unlike the first 2 LQTS, SCD often occurs during sleep. Although the sodium channel blocker mexilitine has been proposed as a genetically targeted drug therapy, the efficacy of this genetic-based treatment compared with β blocker use is yet to be determined in humans.

- LQT4 (*ANK2*) (1% of cases): The responsible gene encodes ankyin-B, which is responsible for anchoring Na/K ATPase, and mutations result in Na buildup and a compensatory increase in intracellular Ca. Together, this leads to a prolongation in QTc.
- LQT5 (KCNE1) (5% of cases): This gene encodes mink, the beta subunit of the current potassium channel.

- LQT6, 7, 8, 9, 10 together accounts for less than 5% of cases. Most encode potassium, calcium, or sodium channel subunits. LQT9, by contrast, encodes a Caveolar protein believed to direct the localization of the SCN5A gene product.

LQTS in Athletes. The prevalence of LQTS in athletes is estimated to be very low. In 1 Italian PPE study, QTc prolongation was a rare finding in athletes (0.03%) and no deaths related to this prolongation were reported.[38] In the USA, Maron estimated that 3% of SCD in athletes were due to ion channelopathies, and at most 6% if 1 considered SCD in structurally normal hearts.[3] Basavarajaiah and colleagues at the UK Olympic Medical Center studied 2000 elite athletes (mean age, 20 years) who underwent ECG and echocardiogram (ECHO) testing between 1996 and 2006.[39] Athletes with a QTc >460 milliseconds underwent Holter monitoring and exercise testing. All athletes with a prolonged QTc interval were offered genetic testing and first-degree relatives were invited for ECG. The QTc was prolonged in 7 (0.4%) athletes ranging from 460 to 570 milliseconds. Three athletes had a QTc value of >500 milliseconds and all exhibited paradoxical prolongation of QTc during exercise, a confirmatory genetic mutation, and/or prolonged QTc in a first-degree relative. In contrast, none of the athletes with a QTc value of <500 milliseconds had any other features to indicate LQTS. They concluded that a QTc of >500 milliseconds was highly suggestive of LQTS in athletes and that a QTc of <500 milliseconds in the absence of symptoms or familial disease was unlikely to represent a risk of sudden death.

To address the concern that physiological changes secondary to athletic training might affect the QT duration, Turkmen et al[40] compared ECGs obtained from 44 trained athletes and 35 sex- and age-matched healthy sedentary controls. QT and QTc duration did not differ significantly between the 2 groups. No association was observed between an athlete's heart and ventricular heterogeneity compared with healthy sedentary controls, despite physiological and structural changes. It appeared that the physiological ventricular hypertrophy seen with training did not result in ventricular repolarization abnormalities.

Interestingly, the genetic subtype may help determine whether an athlete may be susceptible to adverse outcomes. In Italy, Schwartz and colleagues studied the association of various "trigger" activities with syncope, aborted cardiac arrest, and sudden death in patients with LQTS.[41] They found that LQT1 patients experienced most of their arrhythmic events (62%) during exercise, and only 3% of events occurred

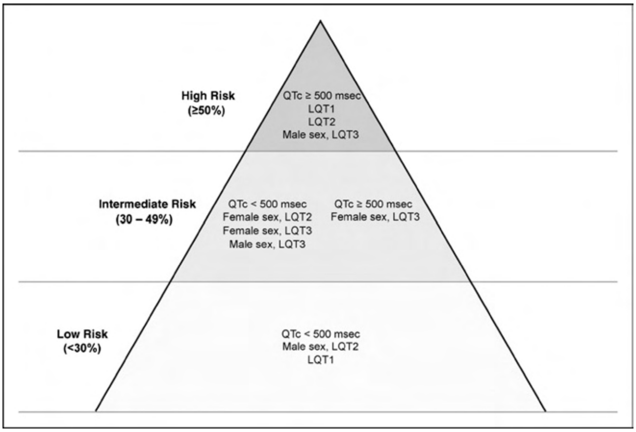


FIG 4. A proposed scheme for risk-stratification among patients with LQTS according to genotype, QT interval, and gender. The risk groups have been defined by the probability of a first cardiac event (syncope, cardiac arrest, or sudden death) before the age of 40 years and before therapy. A probability of 50% or higher defines the high-risk group; a risk of 30%-49% defines the intermediate-risk group, and a risk <30% defines the low-risk group. (Reprinted with permission from Priori SG, et al. Risk stratification in the long-QT syndrome. N Engl J Med 2003;348:1866-74.)

during rest/sleep. In LQT2 and LQT3 they found the opposite: events occurred during exercise only 13% of the time and during rest and sleep, 29% and 39%, respectively. However, the 2006 American College of Cardiology/American Heart Association/European Society of Cardiology (ACC/AHA/ESC) guidelines recommended avoidance of competitive sports or strenuous activities in all patients with LQTS, regardless of genotype.[42] Along with using genetic subtyping, the length of the QTc interval and gender can help risk-stratify athletes at risk of adverse events from LQTS (Fig 4).

Wolff-Parkinson-White Syndrome. Originally described by Wolff, Parkinson, and White in 1930, the Wolff-Parkinson-White (WPW) *syndrome* was initially defined as a functional bundle branch block with an abnormally short PR interval and paroxysms of tachycardia or atrial fibrillation.[43] Electrocardiographically, the WPW *pattern* is identified by the presence of a δ wave (Fig 5), short PR, and wide QRS complex. One may have the WPW pattern without necessarily developing the WPW syndrome. The ECG pattern is due to an accessory conduction pathway between the atria and the ventricles, permitting premature ventricular activation or pre-excitation. The most common accessory pathway is found in the left lateral free wall (10%), and patients are often found to

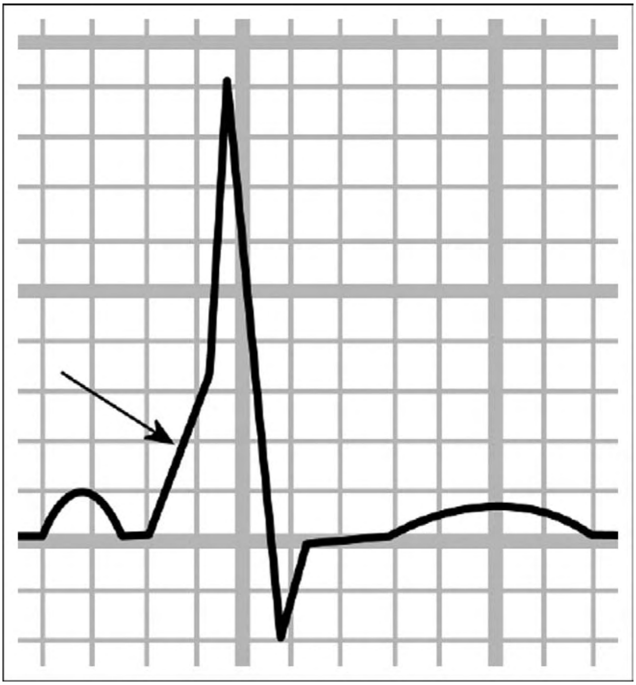


FIG 5. WPW pattern: delta wave (arrow), short PR, and wide QRS complex.

have multiple pathways.[44] Most adults with pre-excitation syndromes have structurally normal hearts, although a variety of acquired and congenital cardiac defects have been associated with this condition.[45,46]

The overall prevalence of a WPW pattern, without associated cardiac symptoms, has been reported to be 0.1%-0.3% in the general population. Its true prevalence is likely underestimated because of the dynamic nature of the δ wave, which can be modulated by the autonomic nervous system, changes in the conduction system, and age-related myocardial degeneration.[47,48]

The definitive treatment in patients with WPW syndrome is ablation of the accessory pathway; however, the management of asymptomatic subjects remains controversial. These patients are usually assumed to have a benign prognosis, although the concern is that several of these patients subsequently develop supraventricular tachycardia (SVT) and a handful of these patients present with atrial fibrillation (AF) with unopposed ventricular conduction as the first manifestation of the syndrome. The incidence of AF is estimated to be from 11% to 30% in the WPW population.[49-51] Although the pathogenesis of AF in the absence of structural heart disease is not well understood, rapid ventricular rates cause metabolic and hemodynamic changes that can play a major role in the development of ventricular fibrillation (VF) and SCD.

To help determine the appropriate treatment strategy in patients with the WPW pattern, several studies have analyzed at the clinical outcomes in these patients. In 1 population-based study, Munger et al[52] followed 113 residents of Minnesota from 1953 to 1989 with WPW pattern. Follow-up via medical record review and telephone interview was completed in 95% of subjects through 1990. The incidence of newly diagnosed cases was approximately 4 per 100,000 per year. Approximately 50% of the population was asymptomatic at the time of diagnosis, with 30% of these patients subsequently developing symptoms related to arrhythmia at follow-up. Two episodes of SCD occurred over 1338 patient-years of follow-up, yielding an overall SCD rate of 0.0015 per patient-year. None of the SCDs occurred in patients who were asymptomatic at the time of initial diagnosis. In an attempt to measure clinical consequences of WPW pattern identification, Goudevenos et al[53] also performed a prospective survey of such cases in Greece over an 8-year period (1990-1997). During the study period, 157 cases with WPW pattern were identified (49 female, 108 male). During the average 4.5 years of follow-up, clinically documented SVT was recorded in 27 (17%) patients and atrial fibrillation occurred in 12 (8%), but no SCD was documented.

In a similar study, Fitzsimmons et al[54] reviewed records of 238 consecutive military aviators with WPW pattern, of which only 42 (17.6%) were associated with SVT. Over the 22 years of follow-up, SCD occurred in 1 patient, which represents an incidence of 0.0002 per patient-year. Of the 187 patients who initially had the WPW ECG pattern only, 28 (15%) reported SVT during follow-up. Referral bias and characteristics unique to the military aviator population may partly account for these low event rates. However, these results may be more applicable to the general athletic population than those of the tertiary referral-based studies. Based on these studies, the incidence of SCD in the population based on those with the WPW pattern is very low at an approximate rate of 1 per 1000 patient-years.[55,56]

Although the primary concern in patients with WPW pattern is subsequent onset of VF, the low incidence of this arrhythmia makes this outcome difficult to study. In the 3 largest retrospective series of WPW patients with associated VF, this malignant arrhythmia was the initial presenting symptom in 3/25 patients,[57] 6/23 patients,[58] and 8/15 patients.[55] In patients over 30 years of age, VF was rarely the initial presentation of WPW. Nevertheless, a method of more invasively risk stratifying those at risk for subsequent SVT and particularly those at risk of VF has been sought.

Pappone et al[59] assessed in a cohort of asymptomatic subjects with WPW pattern the usefulness of an invasive electrophysiology study (EPS) in predicting the occurrence of arrhythmic events over a 5-year follow-up. Only 47 of the 162 patients had an inducible arrhythmia at the time of EPS. Of the 115 noninducible patients, only 4 (3.4%) developed symptomatic SVT, while 29 (62%) of the 47 inducible patients had symptomatic episodes of SVT or AF on follow-up. These patients were younger, had shorter AP anterograde refractory periods, and multiple APs compared with patients who remained asymptomatic (for all comparisons, $P < 0.0001$). Of the 8 patients with symptomatic episodes of AF and inducible sustained AF, 2 had a resuscitated cardiac arrest and 1 died suddenly. All 3 patients were inducible for AV re-entry tachycardia (AVRT) and AF at the time of initial evaluation and each had multiple APs. It was concluded that in the asymptomatic WPW population, a negative EPS with no AVRT or AF inducibility identifies subjects at very low risk for development of spontaneous arrhythmias. By contrast, inducibility of sustained pre-excited AF with fast ventricular response, particularly in the presence of multiple APs, may help to select asymptomatic WPW subjects at definite risk for dying suddenly.

To further define predictive risk factors for VF in WPW, Attoyan et al[60] conducted a retrospective study of 28 consecutive patients presenting with VF either spontaneously[20] or during EPS investigation.[8] Their clinical and EPS characteristics were compared with those of 60 consecutive patients with the WPW syndrome who had documented AF (and even reciprocating tachycardia) but never VF. No significant differences between the 2 groups were found with respect to the following clinical parameters: sex, duration of symptoms, the type of tachycardia previously recorded, and cardiac history. With respect to the EPS, there were no differences in the point of anterograde block, the effective anterograde refractory period of the accessory pathway, or the effective and functional refractory periods of the right atrium and atrial vulnerability. By contrast, patients with associated VF had a higher age (29 years vs 36 years), higher percentage of multiple accessory pathways (25% vs 7%), higher presence of a dominant localization in the postero-septal region (75% vs 47%), and greater pre-excitation during exercise testing. On multivariate analysis, the most discriminating and independent predictive factor for VF was the shorter RR interval during AF. Numerous studies have also confirmed this association.[61,62]

Similarly, Sharma et al[63] compared invasive EPS and noninvasive testing as methods for retrospectively identifying patients with WPW syndrome at risk for VF. Sixty-seven patients were studied, including 9 with a history of ventricular fibrillation. During EPS, detection of an interval between consecutive pre-excited beats of less than 250 milllisec-onds during induced AF identified 7 of 9 patients with prior VF. Continuous pre-excitation during exercise testing also identified these patients with a sensitivity of 80%, a specificity of 29%, and a predictive accuracy of 12%. Thus, both invasive and noninvasive techniques have a good sensitivity but a low specificity for identifying patients with WPW syndrome and SCD.

Better noninvasive techniques of risk stratification have also been considered. Because the intermittent loss of the δ wave at faster heart rates in some patients with the WPW pattern may result from precarious conduction over the accessory pathway, some have suggested that this could predict a benign prognosis should AF occur. Klein and Gulamhusein[64] evaluated 52 consecutive patients referred for the assessment of the WPW syndrome. Half of these patients were determined to have intermittent pre-excitation based on review of serial ECGs, ambulatory monitoring, and treadmill testing. On EPS, these patients were also found to have longer effective refractory periods of the AP and longer shortest cycle lengths maintaining 1:1 anterograde conduction than their counterparts with constant pre-excitation. In those inducible for AF, only 15% of patients with intermittent pre-excitation had shortest RR intervals between pre-excited beats less than 250 milliseconds vs 50% of patients with constant pre-excitation, supporting the hypothesis that intermittent pre-excitation is associated with a benign prognosis in the event of AF. This finding is particularly important in asymptomatic subjects because a careful search for intermittent pre-excitation may yield important prognostic information and obviate further investigation.

B.J. Gersh: Another reasonably reliable predictor of a relatively long refractory period is the "concertina" form of pre-excitation, in which the degree of pre-excitation demonstrates a cyclic pattern over the course of several cardiac cycles (German LV, Gallagher JJ. Functional properties of accessory atrial ventricular pathways in Wolff-Parkinson-White syndrome. Clinical implications. Am J Med 1994;76:1079-86).

WPW in Athletes. As seen in the general population, most studies using the ECG as part of the PPE have demonstrated a prevalence of ventricular pre-excitation pattern in athletes of approximately 0.1%-0.3%. In the

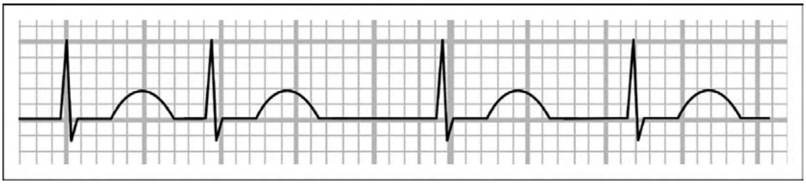


FIG 6. Atrial fibrillation is characterized on ECG by an irregular ventricular rhythm and absence of P waves (fibrillation waves are best seen in V1 and V2).

largest athletic screening study to date of 32,652 Italian athletes, Pelliccia et al[38] reported a pre-excitation pattern in only 42 ECGS (0.1%). The proportion of athletes disqualified due to the WPW syndrome was approximately 6%, which is significantly higher than what most population-based studies have reported. In an extensive systematic review of the literature to identify causes of SCD in athletes, Bille et al[65] reported that of 1101 SCDs in athletes less than 35 years of age, only 1 case of SCD was related to WPW syndrome.

Discovering a WPW pattern in an asymptomatic patient on a screening ECG represents a problem because noninvasive methods (Holter monitoring, exercise testing) are inadequate for risk stratification. Given the low specificity, routine invasive EPS for risk stratification in these patients has not been recommended by the current guidelines except for individuals who engage in high-risk occupations or those who have a pre-excitation pattern that precludes them from following their chosen career or activities.[66] The appropriate management of asymptomatic athletes identified with the WPW pattern also remains controversial.

Atrial Fibrillation. AF is characterized by disorganized atrial electrical activity leading to ineffective atrial contraction, often leads to a drop in cardiac output, and is associated with strokes. AF is characterized on ECG (Fig 6) by an irregular ventricular rhythm and absence of P waves. Lone AF, which is AF in the absence of hypertension or any structural abnormalities, is genetic and, although rare, may be the most frequent arrhythmia in athletes. An increased vagal tone in athletes resulting in bradycardia can lead to atrial repolarization dispersion, which then increases AF susceptibility.[67,68]

B.J. Gersh: Atrial fibrillation can be promoted by increased vagal tone. A clue to the role of increased vagal tone is the development of atrial fibrillation at night or while asleep, and the relatively slow ventricular response rate without additional drug therapy.[68] Not uncommonly the pattern on electrocardiogram may be atrial flutter alternating with fibrillation. Sympathetically mediated atrial fibrillation is noted in patients with underlying structural heart disease, but in some patients with lone atrial fibrillation, exercise may precipitate the arrhythmia.

AF associated with WPW, as discussed above, is even rarer and likely due to a different, less understood mechanism.

Furlanello et al[69] studied the presence of AF in a population of young elite athletes referred for arrhythmias endangering their careers. Among 146 athletes with arrhythmias, 13 (9%) had AF (paroxysmal or intermittent in 11 and permanent or chronic in 2). Three of these patients had associated WPW syndrome, 1 had ARVC/D, and 1 had myocarditis. After a follow-up of 5 years, none of the athletes with AF had died and 7 continued in their sports after radiofrequency catheter ablation or after a period of detraining. In a study that suggesting that athleticism is a trigger for AF in those susceptible to lone AF, Mont et al[70] reviewed the records of 70 patients with lone AF and found that 32 (45%) had been engaged in long-term sport practice compared with 15% in the general population. Patients with lone AF who were engaged in sports presented at earlier age and had a lower prevalence of hypertension and their episodes of AF were predominantly vagally mediated, in contrast to the sedentary patients.

One of the findings strongly associated with AF is enlargement of the left atrium (LA). Pelliccia et al[71] assessed the distribution and clinical significance of LA size in 1777 competitive athletes. The LA was enlarged (transverse dimension $\geq$ 40 mm) in 347 athletes (20%), including 38 (2%) with marked dilation ($\geq$ 45 mm). Of all the athletes studied, only 14 (0.8%) had documented, symptomatic episodes of either paroxysmal AF (0.3%) or supraventricular tachycardia (0.5%). LA enlargement was not a significant risk factor for AF in this population but rather was found on multivariate regression analysis to be associated with left ventricular cavity enlargement and participation in dynamic sports such as cycling or rowing. The authors also concluded that left atrial remodeling in competitive athletes was part of physiological adaptation to exercise conditioning, largely without adverse clinical consequences.

B.J. Gersh: In several other retrospective studies including 2 in middle-ages individuals, there is a suggestion that endurance athletes or individuals engaging in regular vigorous exercise are at a higher risk of atrial fibrillation (particularly lone atrial fibrillation) than in the general population (Karjalainen J, Kujala UM, Kaprio J, et al. Lone atrial fibrillation in vigorously exercising middle-aged men: case-controlled study. BMJ 1998;316:1784-85; Heidbüchel H, Anné W, Willems R, et al. Endurance sports as a risk factor for atrial fibrillation after ablation for atrial flutter. Int J Cardiol 2006;107:67-72; Elosua R, Arquer A, Mont L, et al. Sport practice in the risk of lone atrial fibrillation: a case-controlled study. Int J Cardiol 2006;108:332-7).

Little is known about the long-term consequences of AF in athletes and the effects of deconditioning. Hoogsteen et al[72] followed 30 well-trained athletes diagnosed with paroxysmal AF from 1993 to 2002. Paroxysmal AF remained stable in half of the athletes, became permanent in 17%, and disappeared in 7%. In a separate study of 62 former Swiss professional cyclists compared with 62 male golfers matched for equal current physical activity, Baldesberger et al[73] found that AF or atrial flutter was reported more often in former cyclists. Sinus node disease, defined as bradycardia of <40 bpm, atrial flutter, pacemaker for bradyarrhythmias, and/or maximal RR interval of >2.5 seconds, was also significantly more common in former cyclists (16%) than in controls (2%). The observed survival of all former cyclists, however, was not different from the control group. The authors concluded that among former athletes, even after cessation of training, sinus node disease occurred significantly more often compared with age-matched controls, with a trend toward more frequent ventricular tachycardias. Despite these findings, given the normal outcomes in larger populations, it does not seem appropriate to recommend the cessation of sports or exercise in athletes with AF.

B.J. Gersh: Other entities that need to be mentioned in individuals with structurally normal hearts are catecholaminergic polymorphic ventricular tachycardia and the syndromes of idiopathic monomorphic ventricular tachycardia, which include the left and right ventricular outflow tract tachycardias. All of these may be brought on by exercise. Catecholaminergic polymorphic ventricular tachycardia typically begins in childhood and adolescence, and patients may have a family history of premature sudden cardiac death or exercise-induced syncope (Priori HS, Napolitano C, Memmi M, et al. Clinical and molecular characterization of patients with catecholaminergic polymorphic ventricular tachycardia. Circulation 2002;106:69-74). Mutations on the cardiac ryanodine receptor and calsequestrin II genes have been linked to the syndrome. Prognosis of these poor and symptomatic patients should be treated with implantable defibrillator.

The outflow tract ventricular tachycardias (both right and left) plus the entity of idiopathic ventricular tachycardia should also be considered in the setting of palpitations and lightheadedness during exercise. Prognosis is generally good but a malignant variant has been described (Rahilly GT, Prystowsky EN, Zipes DP, et al. Clinical and electrophysiologic findings in patients with repetitive monomorphic ventricular tachycardia from the left ventricular outflow tract: electrocardiographic patterns consistent with the left ventricular site of origin. JACC 1997;29:1023-7). Beta blockers, verapamil, and radiofrequency ablation are effective treatment modalities.

Structurally Abnormal Hearts

Hypertrophic Cardiomyopathy. Initially described 50 years ago, HCM has undergone several name changes. It was previously known as idiopathic hypertrophic subaortic stenosis. With a better genetic understanding of the disease, however, 70% of cases lost their idiopathic nature and it was realized that subaortic stenosis did not uniformly describe the pathophysiology. The hallmark of the disease is a thickening of the myocardial wall, with patterns of concentric hypertrophy as well as asymmetric septal and apical hypertrophy. Most patients do not have a resting left ventricular outflow gradient, but the majority develops a significant exercise gradient. The pathophysiology centers on sarcomeric gene mutations and calcium cycling abnormalities leading to myocyte hypertrophy and disarray, interstitial fibrosis, microvascular intimal thickening, and mitral valve abnormalities. There have been over 450 mutations in more than 10 genes that have been linked to or associated with HCM. Mutations in *MYH7*, encoding the myosin heavy chain, are the most common, followed by the gene encoding myosin binding protein C. The patterns of inheritance are typically autosomal-dominant, although up to 50% of the identified mutations are sporadic and many demonstrate highly variable penetrance. Unfortunately, genotype-phenotype correlation is generally poor and the genotype does not necessarily correlate with prognosis. Typical ECG changes in HCM include left bundle branch block, high voltages indicating left ventricular hypertrophy with prominent septal Q waves in the lateral leads, and giant negative T waves in the precordial leads.

Although HCM occurs in 1 of 500 adults, the diagnosis can be missed. Adabag et al found that of 711 consecutive patients diagnosed with HCM, 225 (32%) were identified during routine asymptomatic medical evaluation and 27 (4%) were found during PPE.[74] Ironically, patients with extreme hypertrophy (wall thickness ≥30 mm) and those at high risk for sudden death were more often identified by routine or family screenings. The authors concluded that, although most patients with HCM were recognized clinically only after overt disease manifestations, a substantial minority were diagnosed by routine examinations while asymptomatic, including an important subset of patients with HCM recognized solely because of findings on PPE.

To assess the diagnostic efficacy of Italian preparticipation screening program in young athletes, Pelliccia et al studied the use of the ECG added to history and physical examination for identification of HCM.[75] The Italian national teams, initially judged eligible for competition because of systematic preparticipation screening across Italy (n = 4450), underwent clinical and echocardiographic examination to assess for the presence of previously undetected HCM. None showed clinical evidence of HCM. Echocardiography identified 4 athletes with borderline left ventricular wall thickness (13 mm). Only 2 (0.04%) athletes had a subsequent genetic analysis or clinical change over an average 8-year follow-up that resulted in a definitive diagnosis of HCM. In a study on sudden deaths among athletes and nonathletes (35 years of age or less) in the Veneto region from 1979 to 1996, Corrado et al reported HCM as the cause of only 1 sudden death among the athletes (2%).[5] HCM was detected in 22 athletes (0.07%) at the PPE and accounted for 3.5% of the CV reasons for disqualification. As mentioned previously, the etiologic difference in causes of SCD between the USA and Italy may reflect the fact that annual athletic screening in Italy selects out individuals with HCM.[76]

Recently, Basavarajaiah et al studied the prevalence of HCM in 3500 asymptomatic elite athletes (75% male) between 1996 and 2006, with a mean age of 21 years.[77] None had a known family history of HCM and all had a 12-lead ECG and an ECHO performed. Of the 3500 athletes, 53 (1.5%) had LVH by ECHO criteria (mean septal thickness 13.6 mm $\pm$ 0.9, range 13-16), and of these, 50 had a dilated LV cavity with normal diastolic function indicating physiological LVH. The remaining 3 (0.08%) athletes with pathologic LVH had a nondilated left ventricular cavity on ECHO and associated deep T-wave inversion on ECG that could have been consistent with HCM. However, none of these athletes had any other phenotypic features of HCM on further noninvasive testing and none had first-degree relatives with features of HCM. One of the 3 athletes agreed to detrain for 12 weeks, which resulted in resolution of ECG and ECHO changes confirming physiological LVH. The authors concluded that the prevalence of HCM in highly trained athletes is extremely rare mostly because structural and functional changes associated with HCM naturally select out most individuals from competitive sports.

It is also not clear precisely which ECG criteria are best at distinguishing the athlete heart from HCM. Dollar and Roberts compared the sensitivity of the total 12-lead QRS amplitude with the sensitivity of traditional ECG criteria for LVH in 57 necropsy patients with HCM.[78] The last technically satisfactory ECG available from each necropsy patient was used. ECG criteria employed to diagnose LVH included the Sokolow and Lyon index, the Romhilt-Estes voltage criteria, the Romhilt-Estes point score, the ratio of RV6:RV5 greater than 1, and a method using the sum of the amplitudes of the QRS complexes of all 12 leads. The total 12-lead QRS amplitude ranged from 66 to 339 mm (mean = 197 or 19.7 mm). Using 175 mm as the upper limit of normal, this technique yielded a sensitivity of 53%, which was the highest sensitivity of any criteria tested. The Sokolow-Lyon index had a sensitivity of 39%; the Romhilt-Estes voltage criteria, 37%; the Romhilt-Estes point score system, 49%; and the criterion of RV6 more than RV5, 39%. No correlation was found between total 12-lead QRS voltage and heart weight, LV free-wall thickness, LV peak systolic and end-diastolic pressures, or LV outflow tract peak systolic pressure gradient. They concluded that among patients with HCM, total 12-lead QRS amplitude of more than 175 mm was a useful indicator of LVH and is more sensitive than other more commonly employed criteria. Nevertheless, even the best of these criteria is inadequately sensitive and partly explains the low rate of HCM detection in many observational studies.

The lack of sensitivity appears even more pronounced in the African-American population. Maron et al[79] found that 55% of athletes who died of SCD due to HCM in their national registry were African American. In stark contrast, only 8% of living patients with clinically diagnosed HCM were African American. The discrepancy may either be due to a worse clinical sensitivity in identifying African-American patients at risk for SCD or that rates of SCD in African-American athletes with HCM are much higher than whites with HCM.

The terminal event in patients with HCM who die suddenly is typically a ventricular arrhythmia. Data from HCM patients who have received appropriate ICD discharges have shown that these discharges have occurred in response to sustained monomorphic ventricular tachycardia (VT), VT leading to VF, or unheralded VF. However, even in those patients in whom an ICD has been implanted because of an aborted SCD, the annual rate of appropriate ICD discharge is only 11%.[80] The onset of a malignant arrhythmia likely requires the combination of triggers (such as ischemia, hypotension, arrhythmia, or altered autonomic tone) at a critical moment in time as well as a proarrhythmic substrate (here, myocyte disarray and fibrosis).

B.J. Gersh: An example of prolonged changes in sympathetic tone causing a sinus tachycardia with ST-segment depression and presumably ischemia followed by ventricular fibrillation in a patient with hypertrophic cardiomyopathy is provided by a recent case report of a woman who had an episode of resuscitated sudden cardiac death during ambulatory monitoring (Vaglio JC, Sorajja P, Gersh BJ. Ambulatory monitoring of aborted sudden cardiac death related to hypertrophic cardiomyopathy. Nat Clin Pract Cardiovasc Med 2005;2:659-62).

Risk stratification aimed at identifying patients with HCM at high risk of ventricular arrhythmias has also been difficult. Although certain genotypes can point to a more malignant phenotype, this information alone is not sufficient to base management decisions. According to the ACC/AHA/ESC 2006 guidelines for prevention of SCD, the major risk factors for SCD in HCM, derived primarily from observational studies, include the following[81]:

1. A family history of SCD;
2. Unexplained syncope;
3. Nonsustained ventricular tachycardia on Holter monitoring (3 beats or more, >120 bpm);
4. Abnormal blood pressure response during upright exercise testing (≤25 mm Hg rise in SBP is only prognostic in patients less than 40 years of age);
5. Maximal LV wall thickness 30 mm or greater.

Other risk factors for SCD in this population include AF, myocardial ischemia, left ventricular outflow obstruction, a high-risk genetic mutation, and intense (competitive) physical exertion. The absence of any of these risk factors identifies a low-risk group. However, because of the very low positive-predictive value of 1 single positive risk factor, incorporation of multiple risk factors should be favored for stratification[82] but even that strategy can fail.[83]

The utility of ECG in predicting adverse cardiac events has also been studied in the young HCM population. Ostman-Smith et al attempted to identify clinical measures for stratification of risk in childhood HCM. In a retrospective cohort study from 6 centers of pediatric cardiology, they identified 128 patients with HCM and followed them a mean of 10.8 years.[84] Sudden death in 31 patients was independently associated with increased ECG voltage expressed as the sum of the R and S waves in the limb leads >10 mm. In the adult population, Montgomery et al studied the relationship between ECG patterns and phenotypic expression or clinical outcomes.[85] Voltages and patterns were compared with LV wall thicknesses assessed by ECHO and with clinical outcomes in 448 consecutive patients with HCM. Statistically significant, but relatively weak, correlations were evident between maximum LV wall thickness or left ventricular outflow tract gradient and ECG voltage. ECG abnormalities (2.5% in patients with SCD vs 4.5% in living patients) were not significantly associated with HCM-related death. Pelliccia et al also evaluated the relation of ECG findings to presenting features and prognosis in 125 consecutive HCM patients with a mean age of 34 years.[86] Most ECG features were similar in patients with and without a left ventricular outflow obstruction gradient. Those with obstruction had a higher prevalence of LVH according to ECG voltage criteria (54% vs 28%), whereas higher grade ventricular arrhythmias were more common in patients without an outflow gradient (20% vs 7%). In contrast to childhood HCM, ECG voltages and patterns may not be reliable markers of important clinical outcomes in adults.

ECG markers other than QRS voltage have also been studied in patients with HCM. Bongioanni et al assessed the relation between QRS duration and CV death in 241 consecutive patients with HCM.[87] During a mean follow-up of 8 years, 35 patients suffered a CV death. Multivariate Cox regression analysis confirmed that a QRS duration of 120 milliseconds or greater was independently associated with CV death (hazard ratio, 3). Finally, Yi et al examined the relation of QT dispersion on ECG to clinical outcomes and established risk factors of SCD in patients with HCM.[88] One hundred fifty-six consecutive patients with HCM were compared with 72 normal subjects. QT intervals, QTc intervals, and QT dispersion were significantly greater in patients with HCM compared with normal controls. However, no significant associations were found with SCD. Most recently, 80 athletes with marked ECG repolarization abnormalities, defined as diffusely distributed and deeply inverted T waves, were followed for an average of 12 years.[89] Three of these athletes were subsequently diagnosed with HCM and 1 of these had suffered an aborted SCD.

The reason many patients with overt HCM may present with a normal ECG remains mysterious and has been studied with MRI. Dumant et al examined the MRI in 102 HCM patients,[90] 36 (35%) of whom did not fulfill any ECG criteria for LVH. Distribution and magnitude of hypertrophy and late-enhancement were associated with ECG abnormalities. Abnormal Q waves were associated with greater upper anterior septal thickness. Conduction disturbances and absent septal Q waves were associated with late-enhancement and the depth of negative T waves was related to an increased ratio of the mean thickness between the apical and basal levels. These findings may help determine which additional ECG markers may be important for diagnostic or prognostic purposes, but these will have to be studied in large prospective athletic cohorts.

B.J. Gersh: The bottom line is that current methods of risk stratification for sudden cardiac death and implantable cardioverter-defibrillator implantation are imprecise. The positive-predictive value is low, and the complications of an ICD are substantial. Prognostication on the basis of molecular genetics has not panned out. Whether the new methods, such as cardiac MRI, will be more sensitive and specific remains to be determined.

In summary, although a low prevalence of HCM has been reported in the athletic population, it remains the most frequent cause of SCD in North America. This discrepancy can be partly explained by the low sensitivity of current ECG criteria used to identify this disease. Several studies, however, suggest that the ECG may be useful in assessment of prognosis in patients with HCM. Until further evidence on risk stratification becomes available, the 36th Bethesda Conference guidelines recommend that all athletes with probable or unequivocal clinical diagnosis of HCM be excluded from all competitive sports, independent of age, gender, phenotypic appearance, presence of symptoms, outflow tract obstruction, or prior treatment.[91]

Arrhythmogenic Right Ventricular Cardiomyopathy. Twenty-five years have elapsed from the time that the clinical profile of ARVC was first described.[92] A familial pattern of inheritance in this disease, with an autosomal-dominant pattern, was first discovered in Italy where there is a prevalence estimated at 6 in 10,000 inhabitants. Recently included among the cardiomyopathies in the revised WHO classification, ARVC appears worldwide with a prevalence of about 1 in 5000 persons and occurs predominantly in males. However, this prevalence will probably increase as the awareness for this disease among physicians rises.

ARVC is a primary heart muscle disease characterized by progressive myocardial atrophy of the RV, with transmural fatty or fibrofatty replacement, causing electrical instability and risk of life-threatening ventricular tachycardia of right-sided origin. Loss-of-function mutations mostly in desmosomal proteins (plakophilin, desmoplakin, or plakoglobin) have been associated with ARVC. Aneurysms of the RV free wall were reported in about 50% of cases in a recent pathologic investigation and are considered a pathognomonic feature of ARVC. RV enlargement to a varying degree is a prominent feature. Although initially thought of as an exclusively right-sided cardiomyopathy, involvement of the LV has been reported in almost 50% of cases. At histology, there is a transmural pattern of myocardial injury and repair. The mechanisms leading to progressive loss of myocardium and fibrofatty replacement are still unknown, although an inflammatory theory has been proposed.[93]

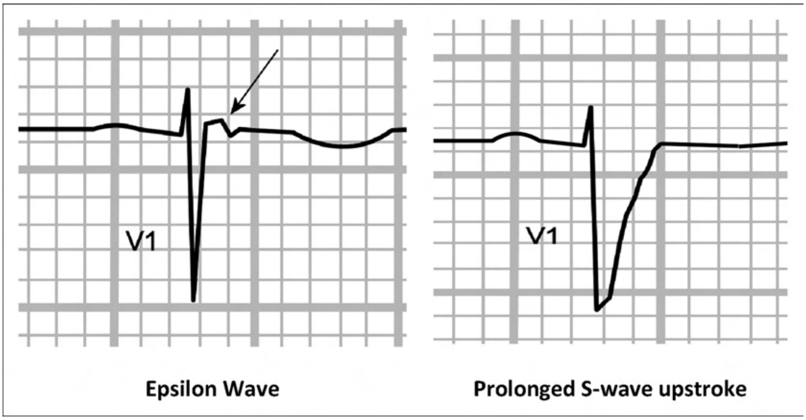


FIG 7. ECG characteristics of ARVC. Epsilon waves are distinct waves of small amplitude that occupy the initial phase of the ST segment in the right precordial leads. S-wave upstroke duration is measured from the nadir of the S wave to the end of the QRS complex in the precordial leads and can be >55 milliseconds in patients with ARVC in the absence of RBBB. They are thought to represent late and slow depolarization of RV tissue, respectively.

The usual clinical presentation of ARVC includes palpitations and VT, but SCD may be the first manifestation of the disease and most patients experience the onset of these symptoms between the ages of 20 and 40 years. On ECG, ARVC is characterized by the presence of a RBBB, T-wave inversions in V_2 through V_3, prolonged S-wave upstroke, and presence of an ε wave (Figs 7 and 8). Because diagnosis for this disease can be difficult due to the variety and intermittency of ECG and clinical manifestations, international diagnostic criteria for ARVC were proposed by an expert consensus panel in 1996 and updated in 2000 (Table 4).

These ECG diagnostic criteria are derived from early studies of patient cohorts with ARVC, such as that of Nasir et al.[94] The patient population included 50 patients with ARVC, 50 matched normal control subjects, and 28 consecutive patients with right ventricular outflow tract (RVOT) tachycardia. T-wave inversions in V1 through V3 were observed in 85% of ARVC patients in the absence of RBBB compared with none in RVOT and normal controls. Epsilon waves, thought to be due to late depolarization of islands of right ventricular myocardium, were seen in 33% and QRS duration greater than 110 milliseconds in V1 through V3 was present in 64% of patients with ARVC. Among those without overt RBBB, a "prolonged S-wave upstroke in V1 through V3" of 55 milliseconds or more was the most prevalent ECG feature (95%), was most associated with disease severity and induction of VT, and best

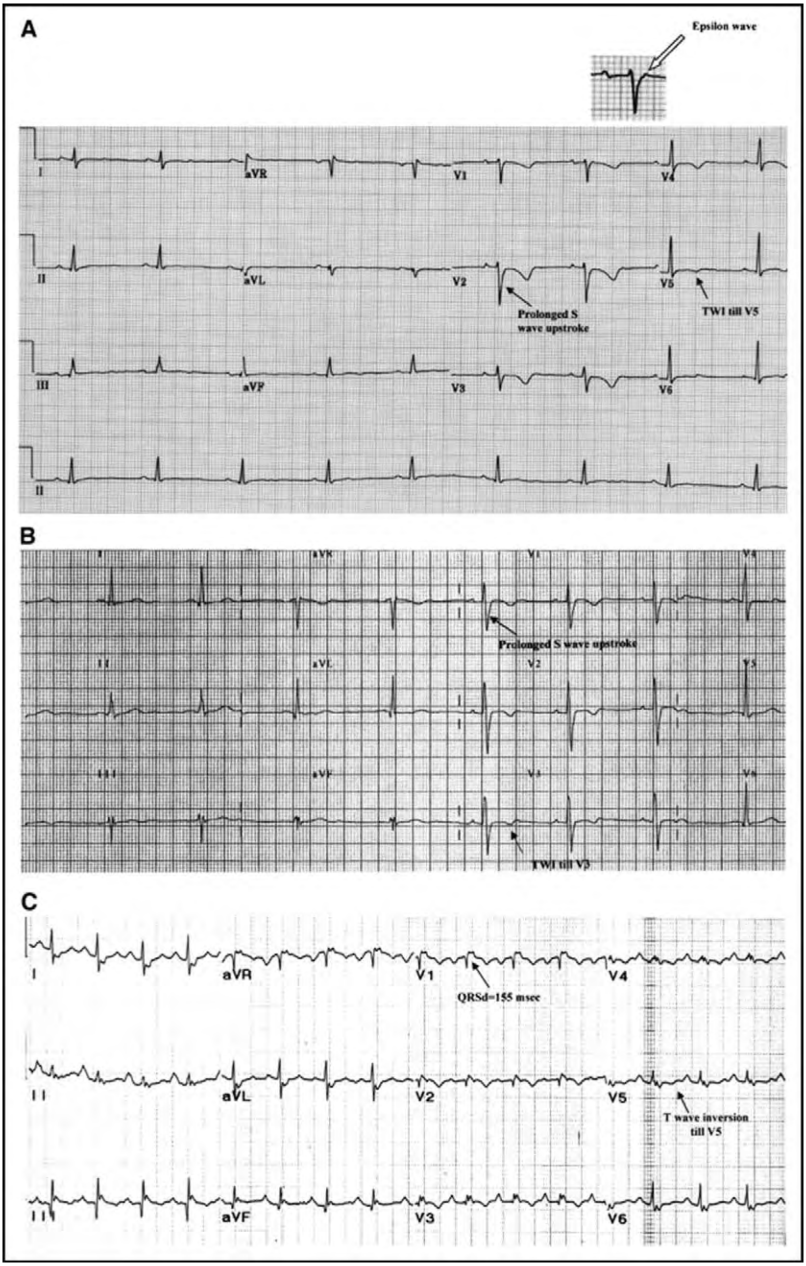


FIG 8. Sample ECGs of ARVC patients. (A) Diffuse ARVC; (B) localized ARVC; and (C) ARVC with RBBB pattern. TWI indicates T-wave inversion.

TABLE 4. Clinical characteristics of patients with ARVC according to the EU ARVC Task Force Criteria*

Clinical characteristic	ARVC (n = 50)
Family history	
Family history of ARVC confirmed by biopsy or autopsy	2 (4)
Family history of premature sudden death (age <35 years) due to suspected ARVC	1 (2)
Family history (clinical diagnosis based on present criteria)	8 (16)
ECG depolarization/conduction abnormalities	
Epsilon waves	16 (32)
Localized QRS >110 ms in V_1, V_2, or V_3(in absence of RBBB)	25/39 (64)
Late potentials on signal-averaged ECG	19 (56)
Repolarization abnormalities	
Inverted T waves in right precordial leads (V_2-V_3), >12 years old, no RBBB	34/39 (87)
Tissue characterization of walls	
Fibrofatty replacement of myocardium in endomyocardial biopsy	6/14 (43)
Structural or functional abnormalities	
Severe dilatation and reduction of RV ejection fraction with mild or no LV involvement	28 (56)
Localized RV aneurysm (akinetic or dyskinetic areas with diastolic bulging) or severe segmental dilatation of the RV	
Mild global RV dilatation and/or ejection fraction reduction with normal LV/mild segmental dilation of the RV/regional RV hypokinesis (localized RV disease)	22 (44)
Arrhythmias	
Left bundle branch block VT on ECG, Holter, or exercise tolerance test	
Sustained VT	21 (42)
Nonsustained VT	14 (28)
Frequent premature ventricular contractions (>1000/24 h on Holter)	11 (22)

*Reprinted with permission from Corrado D, et al.[21]
Abbreviation: LV, left ventricular.
All values are n (%).
Major ARVC diagnostic criteria are shown in bold. The criteria state that an individual must have 2 major, or 1 major plus 2 minor, or 4 minor criteria from different categories to meet the diagnosis of ARVC.[3]

distinguished ARVC from RVOT. In a similar study by Marcus, it was also observed that T-wave inversion in precordial leads V2 to V3 are present in less than 3% of apparently healthy young adults but is present in 87% of patients who have ARVC.[95] These studies suggests that T-wave inversions in leads V2 or V3 in a young or middle-aged patient who has no apparent heart disease should raise the suspicion of ARVC, particularly if ventricular arrhythmias of left bundle branch morphology are observed.

Recent studies have elucidated the importance of ARVD as a cause of SCD. In the USA, ARVC accounts for approximately 5% of SCD in individuals under the age of 65 and is responsible for at least 3% of deaths associated with physical activity in young athletes.[3] In Italy, ARVC is the most common cause of sudden arrhythmic deaths in individuals under the age of 35 years and an overwhelming cause of sudden death associated with exertion in young athletes in Italy.[1] The mechanism of sudden death in ARVC is, in most cases, acceleration of VT with degeneration into VF.[96] Furlanello et al studied the incidence of SCD in 1642 Italian competitive athletes referred for cardiac arrhythmias detected as part of a national PPE athletic screening program in Italy.[97] Six percent were diagnosed with ARVC using WHO criteria. During a follow-up period of 8 years, 4% of these patients suffered either a cardiac arrest or an SCD. Individuals with ARVC comprised 23% and 25% of all athletes suffering either cardiac arrest or sudden death, confirming that ARVC is the dominant cause of exercise-related sudden death among Italian athletes.

Attempts have been made to identify risk factors for SCD in patients with established ARVC. Hulot et al[98] studied 130 ARVC patients from a tertiary referral center between 1977 and 2000. After a mean follow-up of 8 years, 24 deaths were recorded, with a mean age at death of 54 years (annual mortality, 2.3%). There were 21 CV deaths, predominantly from progressive heart failure and arrhythmogenesis. All patients who died had a history of VT. After adjustment for gender, history of syncope, chest pain, VT and QRS dispersion, clinical signs of RV failure and LV dysfunction both remained independently associated with CV mortality. The combined presence of 1 of these risk factors and VT identifies high-risk subjects for CV mortality, whereas patients without VT have the best prognosis. In a study of athletes with ARVC, Furlanello et al demonstrated that all SCDs occurred during athletic activity, supporting the importance of exercise-induced adrenergic stimulation in provoking malignant arrhythmias in these patients.[97]

The mechanism behind the exercise-induced nature of SCD in ARVC is not clear. It has been suggested that regular physical activity (particularly running and bicycling) can cause RV volume overload and cavity enlargement by increasing heart rate and contractility. Because of its thinner wall, the RV is more vulnerable than the LV to cellular disruption. All these changes may in turn accelerate fibrofatty atrophy and increase electrical instability.[19] Kirchhof et al studied the cardiac effects of heterozygous plakoglobin deficiency and training in mice.[99] Ten-month-old heterozygous plakoglobin-deficient mice (plakoglobin+/−) had increased RV volume, reduced RV function, and spontaneous ventricular ectopy while the LV size and function were not altered. Isolated, perfused plakoglobin+/− hearts had spontaneous VT of RV origin and prolonged RV conduction times compared with wild-type hearts. Endurance training accelerated the development of RV dysfunction and arrhythmias in plakoglobin+/− mice. This finding strongly suggests a functional role for plakoglobin and training in the development of ARVC and a potential target to stop expression of this disease. Further evidence for this was provided by Daubert et al,[100] who found that humans with ARVC who trained intensely had manifestations (palpitations, syncope, and SCD) more frequently and at a younger age.

In conclusion, ARVC is increasingly recognized as a cause of malignant ventricular arrhythmias among apparently healthy young subjects and individuals engaged in vigorous exercise. Because of the high risk of SCD in patients of ARVC and the potential adverse effect of excessive training on the phenotypical expression of the disease, young subjects with probable or definite diagnosis should be prohibited from vigorous athletic competition.[91] Physicians should consider this condition in young subjects with cardiac arrhythmias or unexplained cardiomyopathy and should screen for this disease in young adults wishing to engage in competitive sports.

B.J. Gersh: The clinical course is unpredictable with progression of a mild to moderate or moderate to severe disease noted in 5% and 8%, respectively, in 1 series of asymptomatic patients (Nava A, Bauce B, Basso C, et al. Clinical profile and long-term follow-up of 37 families with arrhythmogenic right ventricular cardiomyopathy. JACC 200;36:2226-33). In high-risk patients including those with documented syncope or prior hemodynamically unstable ventricular arrhythmia, those with a strong family history of sudden cardiac death, and in patients presenting at a young age and those with extensive disease with signs of right ventricular and left ventricular involvement the weight of opinion support the use of an ICD (Zipes D, Camm AJ, Borggrefe M, et al. ACC/AHA/ESC 2006 guidelines for the management of patients with ventricular arrhythmias in the prevention of sudden cardiac death: a report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to develop guidelines for management of patients with ventricular arrhythmias in the prevention of sudden cardiac death). JACC 2006;48:e247).

The ECG as Part of the Preparticipation Examination in Athletes

Although there is intense debate regarding the effectiveness of using the ECG as part of the PPE in athletes, to date there have been no randomized trials of ECG screening performed in athletes. While the cost-effectiveness of routine use of the ECG in this population has not been adequately studied, proponents and opponents engage in heated debates regarding the social implications of mandating such programs. The remainder of this

TABLE 5. Characteristics of the PPE screening studies that included an ECG

Study	Year published	Year(s) data collection	Sample size	Population	Age (years)	Gender (% male)
Maron, Bodison, Wesley et al; Results of screening a large group of intercollegiate competitive athletes for cardiovascular disease	1987	1984–1985	501	Intercollegiate student athletes from the University of Maryland (total 540 but 27 refused, 12 had undergone previous cardiologic evaluations)	Mean 19.3 (range, 17–30)	71% (n = 357)
Fuller, McNaulty, Spring et al; Prospective screening of 5615 high school athletes for risk of sudden cardiac death	1997	1991–1994	5615	5615 student athletes at 30 selected high schools in Northern Nevada	13–19	60% (n = 3375)
Sharma, Whyte, Elliott et al; ECG changes in 1000 highly trained junior elite athletes	1999	1995–1998	1300	1000 postpubertal junior elite athletes in UK with negative family and medical history; 300 nonathletic controls matched for age, gender, and body surface area	16 y (range, 14–18)	72% (n = 940)
Choo, Abernathy, and Hutter; ECG in professional football players	2002	1996–1999	1282	National Football League players reporting for spring training	22 ± 0.9 y	100% (n = 1282)

TABLE 5. Continued

Ethnicity	ECG technology	Sports	PPE components	ECG variables analyzed
76% (n = 381) white, 23% (n = 114) black, 1% (n = 6) Asian/Hispanic	Burdick ek-5A instrument	14 sports: football 30%, track 25%, soccer 13%, lacrosse 9%, swimming 6%, basketball 6%, field hockey 6%	Personal/family history, physical examination, 12-lead ECG	R wave ≥30 mm in V5 or V6 or standard lead, S wave ≥30 mm in V1 and V2, ST dep or TW flat or TWI in ≥2 leads, pathologic Q waves (≥0.04 s or ≥3 mm deep in ≥ leads except V1/V2), PR ≥0.25 or <0.12, 2nd or 3rd degree AVB, LAE (depth × duration of negative portion of P wave in V1 >−0.03) or RAE (P wave in lead II or III or V1 peaked and ≥2.5 mV), QRS axis ≥120 or ≤−30, prolonged QTc, LBBB or RBBB or RSR′ in V1 or V2, PVCs
NA	NA	NA	Personal/family history, physical examination, 12-lead ECG	BBB, PVCs, SVTs, ventricular preexcitation, ventricular tachycardia, 2nd and 3rd degree AV block, prolonged QT interval, Q waves (≥ 0.04 s, ≥3 mm deep, and present in ≥2 leads except V1 or V2), ST shifts ≥1 mm in ≥2 leads, TWI/flattening in ≥2 leads except V1-V3, LVH (SV1+RV5 ≥50 mm for males, SV1 + RV5 ≥40 mm for females
99% (n = 1281) white	Marquette Hellige ECG recorder, Milwaukee, MN	9 sports: 41% soccer/rugby, 23% tennis, 10% cycling, 7% swimming, 18% misc	12-lead ECG only after negative PPE elsewhere	HR, rhythm, PR interval, QRS duration, QTc >460 ms in all except >450 ms in boys over 25 y, QRS axis, voltage, LAD <−30, radio >+120, RAE (P in V1 >0.25 mV), LAE (biphasic P in V1 with terminal portion ← 0.1 mV and ≥0.04 s), LVH/RVH using Sokolow-Lyon/Romhilt-Estes, Q wave >0.04 s or 25% of R-wave height, ST and T-wave abnormalities
65% (n = 833) black	NA	American football	NA	Rate, rhythm, QRS axis, presence of ectopic beats, conduction disturbances, ventricular hypertrophy, repolarization changes, pathologic Q waves

TABLE 5. Continued

Study	Year published	Year(s) data collection	Sample size	Population	Age (years)	Gender (% male)
Tanaka, Yoshinaga, Anan, et al; Usefulness and cost-effectiveness of cardiovascular screening of young adolescents	2006	1989–1997	68,503 initially screened; 37,807 with 6-y follow-up; 632 excluded at enrollment due to previously diagnosed CV	Enrollment on entering 7th grade in Kagoshima, Japan	NA	NA
Pelliccia, Maron, Calasso et al; clinical significance of abnormal ECG patterns in trained athletes	2000	1993–1995	1005	Italian national team members from 38 sporting disciplines; 785 routine evaluation and 220 referred for suspected CV disease	24 + 6 (median, 23, range, 9-55)	74% (n = 745)
Pelliccia, Culasso, DiPaolo et al; prevalence of abnormal electrocardiograms in a large, unselected population undergoing PPE	2007	2003	32,652	32,652 unselected subjects prospectively examined in 1 of 19 sports clinics associated with the Italian Sports Medicine Federation	22.3 + 12.5 y (range, 8–78, median, 17)	80% (n = 26,050)

TABLE 5. Continued

Ethnicity	ECG technology	Sports	PPE components	ECG variables analyzed
Japanese	NA	NA	Personal/family history questionnaire to be completed by parents, 12-lead ECG	NA
Italian	NA	38 different national sports	Personal medical history, physical examination, 12-lead ECG, CXR, and ECHO	"Distinctly abnormal": R or S ≥35 mm in any lead, Q wave ≥4 mm in ≥2 leads, inverted T >2 mm in ≥2 leads, LBBB, QRS axis ≤−30 or ≥110, WPW; "Mildly abnormal": R or S wave 30–34 mm in any lead, Q waves 2-3 mm in ≥2 leads, repolarization with flat, minimally inverted, or tall T (≥15 mm) T waves in ≥2 leads, abnormal R wave progression in precordium, RBBB (RSR' with QRS ≥120 ms in V1-V2), RAE (P >= 2.5 mm in II, III, or V1), LAE (P prolonged in II or deep/prolonged in V1), PR ≤0.12 s
Italian	NA	Soccer 39%, volleyball 8%, basketball 8%, cycling 5%, swimming 4%, gymnastics 6%, and misc	Personal/family history, physical examination, 12-lead ECG	HR, rhythm, ectopy, LVH: S1 + R5/R6 ≥35 mm in precordial leads or R >15 mm in lead I or AVL >12 mm, ST depression or TWI in >2 precordial or standard leads (except III), LAE: P >0.12 s in I or II with negative portion of P ≥1 mm and ≥0.04 s in V1, RBBB: RSR′ with QRS >= 0.12 s in anterior precordium, LAFB: QRS axis ≤−30, LBBB: QRS ≥0.12 s, preexcitation: PR <0.12 s with delta wave, QTc >0.44 s in males and >0.46 s in females, first-degree AVB: PR >0.2 s, IRBBB: RSR′ with QRS <0.12 s, early repolarization

TABLE 5. Continued

Study	Year published	Year(s) data collection	Sample size	Population	Age (years)	Gender (% male)
Wilson, Basavarajaiah, Whyte et al; Efficacy of personal symptom and family history questionnaire when screening for inherited cardiac pathologies? The role of ECG	2007	2000–2006	2720	1074 national and international junior athletes from the UK; 1646 physically active schoolchildren from the UK	National and international junior athletes: 15.8 ± 0.7 y (range, 10–27); physically active schoolchildren: 16.1 ± 2.1 y (range, 14–20 y)	NA
Magalski, Maron, Main et al; Relation of race to ECG patterns in elite American football players	2008	2000–2005	1959	Male athletes attending the American National Football League invitational camp	23 ± 0.9 y (range, 20–29)	100% (n = 1959)

Abbreviations: ECG, electrocardiogram; TW, T wave; TWI, T wave inversion; AVB, atrioventricular block; LAE, left atrial enlargement; RAE, right atrial enlargement; LBBB, left bundle branch block; RBBB, right bundle branch block; PVC, premature ventricular contraction; BBB, bundle branch block; SVT, supraventricular tachycardia; LVH, left ventricular hypertrophy; CXR, chest x-ray; LAD, left axis deviation; RAD, right axis deviation; WPW, Wolff-Parkinson-White; PPE, pre-participation examination; HR, heart rate; LAFB, left anterior fascicular block; IRBBB, incomplete right bundle branch block; RVH, right ventricular hypertrophy.

review focuses on the data that have been collected in studies that have performed ECGs on athletes for screening or descriptive purposes. A summary of the largest studies referred to in this document that specifically included the ECG as part of a formal PPE program is presented in Tables 5, 6, and 7.

TABLE 5. Continued

Ethnicity	ECG technology	Sports	PPE components	ECG variables analyzed
NA	Marquette Hellige ECG recorder, Milwaukee, MN	NA	Personal/family history questionnaires, physical examination, 12-lead ECG	LAD: QRS axis ← 30, radio: QRS axis >+120, QTc >450 ms in males and >460 ms in females, RAE: P ≥0.25 mV, LAE: biphasic P in V1 with terminal portion ← 0.1 mV and ≥0.04 s, LVH: Sokolow-Lyon criteria and Romhilt-Estes score ≥5, RVH: R in V1 + S in V6 ≥10.5 mm, Q wave ≥ −0.04 s or >25% of R wave, TWI ≤−0.2 mV in any lead except aVR or V1 or III, ST depression, ε waves, BBB
Black 67% (n = 1321), white 31% (n = 598), other races 2% (n = 40)	Hewlett Packard Sonos 2500 and 5500 instruments (Andover, MA)	American football 100%	Personal/family history, physical examination, 12-lead ECG	"Distinctly abnormal": R or S ≥35 mm in any lead, Q wave ≥4 mm in ≥2 leads, inverted T >2 mm in ≥2 leads except AVR, LBBB, QRS axis ≤−30 or ≥ 110, WPW, atrial fibrillation; "Mildly abnormal": R or S wave 30–34 mm in any lead, Q waves 2–3 mm in ≥2 leads, repolarization with flat, minimally inverted, or tall T (≥15 mm) T waves in ≥2 leads except AVR, abnormal R-wave progression: R >S in V5-V6, RBBB (rsR' with QRS ≥120 ms in V1), RAE (P ≥2.5 mm in II, III, or V1), LAE (P prolonged in II or deep/prolonged in V1), PR ≤0.12 s

One of the first prospective screening evaluations of intercollegiate student athletes that included an ECG was accomplished at the University of Maryland by Maron et al.[101] Of the 501 subjects that were screened, abnormal ECGs were found in 57 athletes, who were then referred for

TABLE 6. ECG findings in the PPE screening studies that included an ECG

Study	L/RBBB	PVCs	LAD/Radio	LVH	RVH	Diagnostic Q wave
Maron, Bodison, Wesley et al; Results of screening a large group of intercollegiate competitive athletes for cardiovascular disease	LBBB 0%/RBBB 0.3% (n = 2)	0.2% (n = 1)	LAD 1% (n = 5)/ radio 0%	8.3% (n = 42) by voltage only	NA	1% (n = 6)
Fuller, McNaulty, Spring et al; Prospective screening of 5615 high school athletes for risk of sudden cardiac death	NA	NA	NA	0.6% (n = 31)	NA	0.2% (n = 6)
Sharma, Whyte, Elliott et al; ECG changes in 1000 highly trained junior elite athletes	Athletes: LBBB 0/RBBB 0.6% (n = 6); nonathletes: 0/0%	NA	Athletes: LAD 0%/ radio 16% (n = 160); nonathletes: LAD 0%/radio 6% (n = 18)	Athletes Sokolow-Lyon: 45% (n = 450); nonathletes Sokolow-Lyon: 23% (n = 69); athletes Romhilt-Estes: 10% (n = 100); nonathletes Romhilt-Estes: 0%	athletes Sokolow: 12% (n = 120); non-athletes Sokolow: 10% (n = 30)	Athletes and nonathletes: 0%
Choo, Abernathy, and Hutter; ECG observations in professional football players	LBBB 0/RBBB 0.4% (n = 5); IRBBB 6% (n = 77)	NA	NA	0.7% (n = 9)	0.6% (n = 8)	0.9% (n = 12)
Tanaka, Yoshinaga, Anan et al; Usefulness and cost-effectiveness of cardiovascular screening of young adolescents	NA	NA	NA	NA	NA	NA
Pelliccia, Maron, Calasso et al; Clinical significance of abnormal ECG patterns in trained athletes	LBBB 0.2% (n = 2)/RBBB 0.2% (n = 2); IRBBB 12% (n = 122)	NA	LAD 1% (n = 11)/ radio 0.8% (n = 8)	R or S ≥35 mm in 9% (n = 92); R or S-30-34 mm in 14% (n = 141)	NA	Q wave ≥4 mm in ≥2 leads in 1.7% (n = 17), Q wave 2-3 mm in ≥2 leads in 6.9% (n = 69)
Pelliccia, Culasso, DiPaolo et al; Prevalence of abnormal electrocardiograms in a large, unselected population PPE	LBBB 0.06% (n = 19)/ RBBB 0.01% (n = 351)	1.1% (n = 349) PVCs, 0.1% (n = 40) polymorphic PVCs	LAFB 0.5% (n = 162)	0.8% (n = 247)	NA	NA

TABLE 6. Continued

QT prolonged	ST depression	T-wave changes	LAA/RAA	QRS duration	WPW syndrome	Brugada or ARVC
0	4% combined ST depression/T wave abnormality (n = 19)	4% combined ST depression/T wave abnormality (n = 19)	1/0% (n = 6), all LAE	0.3% (n = 2) RBBB	NA	NA
0	1.6% (n = 94) combined ST/T wave changes	1.6% (n = 94) combined ST/T wave changes	NA	0.03% (n = 4) RBBB	0.1% (n = 6)	NA
Athletes: 0.3% (n = 3); nonathletes: 0%	Athletes and nonathletes: 0%	Athletes tall T waves: 22% (n = 220); nonatheletes tall T waves: 6% (n = 18); athletes inverted T waves 4% (n = 44); nonathletes inverted T waves 4% (n = 12)	Athletes LAE: 14% (n = 140); nonathletes LAE: 1.2% (n = 4); athletes RAE: 16% (n = 160); nonathletes RAE: 2% (n = 6)	Athletes: 0/0.6% (n = 6 RBBB); non-athletes: 0/0%	NA	NA
NA	15.5% (n = 199) combined ST depression and T-wave abnormalities	15.5% (n = 199) combined ST depression and T-wave abnormalities	NA	19.3% (n = 247)	NA	NA
Long QT syndrome diagnosed in 0.0026% (n = 1)	NA	NA	NA	NA	0.0026% (n = 1) diagnosed with long QT syndrome	NA
NA	NA	Inverted T in 2.6% (n = 27); tall/flat T in 5.9% (n = 59)	LAE 0.9% (n = 9)/ RAE 0.2% (n = 2)	LBBB 0.2% (n = 2)/RBBB 0.2% (n = 2); IRBBB 12% (n = 122)	0.3% (n = 3)	1.6% (n = 16) with deeply inverted T waves in V1-V4 with IRBB but workup negative for ARVC
0.003% (n = 1)	NA	2.3% (n = 751)	NA	LBBB 0.06% (n = 19)/ RBBB 0.01% (n = 351)	0.1% (n = 42)	NA

TABLE 6. Continued

Study	L/RBBB	PVCs	LAD/Radio	LVH	RVH	Diagnostic Q wave
Wilson, Basavarajaiah, Whyte et al; Efficacy of personal symptom and family history questionnaire when screening for inherited cardiac pathologies? The role of ECG	NA	NA	NA	NA	NA	NA
Magalski, Maron, main et al; Relation of race to ECG patterns in elite American football players	NA	NA	Combined LAD/ radio: White 1.2% (n = 7), Black (n = 16)	White 0.2% (n = 1), Black 2% (n = 26)	NA	Q wave ≥4 mm: White 0%, Black 0.2% (n = 3)

Abbreviations: ECG, electrocardiogram; LBBB, left bundle branch block; RBBB, right bundle branch block; PVC, premature ventricular contraction; LAD, left axis deviation; RAD, right axis deviation; LVH, left ventricular hypertrophy; RVH, right ventricular hypertrophy; LAA, left atrial abnormality; RAA, right atrial abnormality; WPW, Wolff-Parkinson-White; ARVC/D, arrhythmogenic right ventricular cardiomyopathy/dysplasia; LAE, left atrial enlargement; IRBBB, incomplete right bundle branch block; LAFB, left anterior fascicular block.

further cardiology evaluation and echocardiography; all of which was negative. In fact, their initial screening protocol identified no athletes with HCM, Marfan's syndrome, or any other CV disease. The failure to identify such diseases was possible because athletes with these conditions had been discovered before college or previously dropped out of sports because of symptoms. It is important to consider that the prevalence of sudden death in athletes is typically lower than 1 in 500. Thus, large studies will be needed to demonstrate the screening efficacy of the ECG.

Professional athletes have also been examined for distinct differences in the ECG. Choo et al presented the results of screening 1282 NFL players reporting for spring training from 1996 to 1999.[102] Sinus bradycardia and sinus arrhythmias were common, found in 25% and 17% of athletes, respectively. Athletes were also screened for first-degree AV block (2.6%), Q-wave pathologies (0.9%), left ventricular hypertrophy (0.7%), and right ventricular hypertrophy (0.6%), ST and T-wave abnormalities (9% of white athletes, 20% of black athletes), ventricular conduction delay (28% white, 16% black), early repolarization frequency (12% white, 19% black), and nonspecific intraventricular conduction delay (19% white, 11% black). Although abnormal ECGs were highly prevalent in American professional football players, no sudden deaths were recorded during the course of the study. Perhaps these specific abnormalities are not contraindicative to sport participation and, as was the case in the intercollegiate study, most problematic cardiac pathologies had already been previously recognized from earlier screening processes.

TABLE 6. Continued

QT prolonged	ST depression	T-wave changes	LAA/RAA	QRS duration	WPW syndrome	Brugada or ARVC
Long QT syndrome type 1 diagnosed in 0.1% (n = 3)	NA	NA	NA	NA	0.1% (n = 4)	ARVC/D 0.04% (n = 1)
NA	NA	White 0.2% (n = 1), Black 2.6% (n = 34)	NA	NA	White 0.2% (n = 1), Black 0%	NA

There has been a recent influx of research pertaining to the ECG screening in younger populations. Fuller et al[103] performed ECGs in 5615 high school athletes (60% male, aged 13-19 years) as part of a PPE. The ECGs were performed on-site in groups of 50-300 high school athletes at a time by a cardiac technician without a physician present. ECHOs were performed for an abnormal ECG. An abnormal ECG was defined per 16th Bethesda Conference guidelines, including Q-wave, ST-T wave abnormalities, and flattened or inverted T waves. A total of 146 (2.5%) athletes had an abnormal ECG identified over the 3-year course of the study. Of the athletes with abnormal ECGs, 65% had ST-wave and/or T-wave abnormalities, 21% had LVH, 4% had abnormal Q waves, and 10% were found to have rhythm or conduction abnormalities, including premature ventricular beats (PVCs), ventricular pre-excitation, RBBB, or SVT. Of the 146 ECHOs performed for these abnormal ECGs, none demonstrated any other serious cardiac abnormality. Of all athletes with LVH by ECG, only 1 had minimal LVH by ECHO. Thus, the ECG screening abnormalities identified in this study were considered false-positive findings. Of the 5615 athletes tested, 16 were not approved for sports participation because of an abnormal ECG. Six of these athletes had ventricular preexcitation, 5 had PVCs, 4 had RBBB, and 1 had SVT. During the 3-year study period, no athlete experienced sudden death during sports. Only 1 athlete developed VF during track practice but was successfully resuscitated. Coronary angiography revealed an anomalous right coronary artery and subsequent treatment with coronary artery bypass surgery was

TABLE 7. Screening results in the PPE screening studies that included an ECG

Study	"Abnormal" ECGs	Required follow-up examination after PPE/ECG	Follow-up test results
Maron, Bodison, Wesley et al; Results of screening a large group of intercollegiate competitive athletes for cardiovascular disease	13% (n = 63)	102 [11% ECG only (n = 57), 2.4% ECG plus PPE (n = 12), 6% PPE only (n = 31)]	Three with anterior and basal ventricular septal thickness of 14–15 mm and LAE (none with SAM, 14 with mild MVP), 1 with HBP
Fuller, McNaulty, Spring et al; Prospective screening of 5615 high school athletes for risk of sudden cardiac death	2.5% (n = 146)	10% (n = 582)	Normal echo in 538; minor abnormalities in 43 including mild TR in 17, mild MR in 16, bicuspid AV in 4, minimal LVH with LV wall thickness of 12 mm in 3, mild AR, PR, PS, and severe AR 1 each
Sharma, Whyte, Elliott et al; ECG changes in 1000 highly trained junior elite athletes	NA	NA	NA
Choo, Abernathy, and Hutter; ECG observations in professional football players	55%	NA	NA
Tanaka, Yoshinaga, Anan et al; Usefulness and cost-effectiveness of cardiovascular screening of young adolescents	NA	2.7% of 37,807 (n = 1876); 632 students with previously diagnosed CV disease excluded	0.024% (n = 9) "high-risk" subjects: 5 HCM, 1 dilated cm, 1 WPW with tachycardic episodes, 1 primary pulmonary hypertension, and 1 long QT syndrome; 1.3% (n = 497) "low risk"
Pelliccia, Maron, Calasso et al; Clinical significance of abnormal ECG patterns in trained athletes	40% (n = 402); "distinctly abnormal" 14% (n = 145) and "mildly abnormal" 26% (n = 257)	Echocardiogram and CXR performed on all subjects regardless of history and ECG results	5% (n = 53) of all subjects with clinical/echo abnormalities: MVP with MR 1.9% (n = 19), bicuspid AV with AR 1% (n = 10), ASD/VSD 0.6% (n = 6), dilated cm 0.4% (n = 4), WPW 0.3% (n = 3), systemic hypertension 0.1% (n = 1), mild PA stenosis 0.2% (n = 2), myocarditis 0.2% (n = 2), aortic prosthesis for valvular stenosis, CAD, pericarditis all 1 each
Pelliccia, Culasso, DiPaolo et al; Prevalence of abnormal ECGs in a large, unselected population undergoing PPE	11.8% (n = 3853)	4.8% (n = 1541) of the total study population; 40% (n = 1541) of "abnormal" ECGs	NA

successful. This student had a normal screening examination. The inclusion of an ECG allowed a greater number of CV abnormalities requiring further testing to be identified than history and physical examination alone. ECG screening has a sensitivity of 60%-70% and a specificity of 97% with a false-positive rate of 2.6% for all the common

TABLE 7. Continued

Follow-up for events	Breakdown of ECG abnormalities by sport	Not approved for athletic participation
0%	NA	0.6% (n = 3); all exclusions unrelated to ECG
Followed through 1994: 1 VF successfully resuscitated on track subsequently found to have anomalous RCA (normal PPE/ECG)	NA	Total 0.4% (n = 22): severe AR 0.02% (n = 1), severe HTN 0.09% (n = 5), pre-excitation 0.1% (n = 6), PVCs 0.09% (n = 5), RBBB 0.07% (n = 4), SVT 0.02% (n = 1)
NA	NA	0%
NA	100% American football	NA
Three sudden cardiac deaths over 6 y follow-up; 1 had HCM, was disqualified from kendo but died jogging; 2 had normal screenings but died during athletic activity	HCM: 3 nonathlete, 1 kendo, 1 tennis; dilated cm: 1 baseball; LQTS: 1 nonathlete; WPW: 1 nonathlete; primary pulmonary hypertension: 1 nonathlete	0.024% (n = 9) "high-risk" subjects identified (only 3 were athletes); all asked to limit athletic participation
Follow-up of 1-11 y (mean, 3) of 145 with "distinctly abnormal"; disqualified HCM patient became symptomatic with atrial fibrillation; no deaths	"Distinctly abnormal": cycling 35%, cross-country skiing 30%, tennis 28%, rowing/canoeing 19%, basketball 20%, rugby 16%, track 15%, soccer 15%, swimming 15%, boxing 12%, volleyball 11%, baseball 11%, fencing 10%, gymnastics 10%, water polo 8%, ice hockey 4%, shooting 2%	0.1% (n = 1 with HCM)
NA	Early repolarization, prolonged PR, IRBBB common for basketball, volleyball, soccer; R/S wave voltages, IVCD, inverted T-wave common for cyclists	NA

causes of SCD in young athletes. Importantly, this study demonstrated the feasibility of a program implementing large-scale ECG screening in athletes.

Sharma et al[104] performed screening ECGs on 1000 junior elite athletes (73% male, aged 16). Compared with matched nonathlete controls,

TABLE 7. Continued

Study	"Abnormal" ECGs	Required follow-up examination after PPE/ECG	Follow-up test results
Wilson, Basavarajaiah, Whyte et al; Efficacy of personal symptom and family history questionnaire when screening for inherited cardiac pathologies? The role of ECG	Athletes 2.3% (n = 25), schoolchildren 0.9% (n = 15)	Athletes 4% (n = 45), schoolchildren 3.8% (n = 62)	Long QT 0.1% (n = 3), WPW 0.1% (n = 4), ARVD/C 0.04% (n = 1), right ventricular outflow tract ventricular tachycardia 0.04% (n = 1)
Magalski, Maron, Main et al; Relation of race to ECG patterns in elite American football players	25% (n = 480); "distinctly abnormal" 5% (n = 88), "mildly abnormal" 20% (n = 392)	10% (n = 203)	0.3% (n = 6) with septal thickness 13-14 mm but no other findings suggestive of HCM

Abbreviations: ECG, electrocardiogram; PPE, pre-participation; LAE, left atrial enlargement; SAM, systolic anterior motion; MVP, mitral valve prolapse; HBP, high blood pressure; TR, tricuspid regurgitation; MR, mitral regurgitation; AV, aortic valve; LVH, left ventricular hypertrophy; LV, left ventricle; AR, aortic regurgitation; PR, pulmonic regurgitation; PS, pulmonic stenosis; VF, ventricular fibrillation; RCA, right coronary artery; HTN, hypertension; PVC, premature ventricular contraction; SVT, supraventricular tachycardia; CV, cardiovascular; HCM, hypertrophic cardiomyopathy; CM, cardiomyopathy; WPW, Wolff-Parkinson-White; LQTS, long QT syndrome; ASD/VSD, atrial septal defect/ventricular septal defect; PA, pulmonary artery, CAD, coronary artery disease; IRBBB, incomplete right bundle block; IVCD, intraventricular conduction delay.

athletes had a significantly higher prevalence of sinus bradycardia (80% vs 19%) and sinus arrhythmia (52% vs 9%). PR interval, QRS duration, and QT duration were more prolonged in athletes than nonathletes. Athletes met Sokolow (45%) and Romhilt-Estes (10%) criteria for left ventricular hypertrophy (LVH) more often than nonathletes; however, none of the athletes with LVH had left-axis deviation, ST segment depression, deep T-wave inversion, or pathologic Q waves. ST segment elevation was common in athletes (43%) and minor T-wave inversion was present in only 0.4% of athletes. The absence of other findings could be attributed to the young age of these athletes, as they may not have been mature enough to manifest certain pathologic cardiac abnormalities.

Wilson et al also assessed the efficacy of an organized PPE that included an ECG by screening 1074 national and international junior athletes (average age, 16 years) and compared this to 1646 physically active schoolchildren matched for age.[105] A personal and family history questionnaire, physical examination, and ECG were part of the screening process. The ECG patterns considered indicative of a potentially serious cardiac disorder included inverted T waves (in all leads except aVR, V1, and III), LVH, ST segment depression, left-axis deviation plus a second abnormality, pathologic Q-wave patterns, ε waves, right ventricular hypertrophy with ST segment depression in leads V1 to V3, and complete

TABLE 7. Continued

Follow-up for events	Breakdown of ECG abnormalities by sport	Not approved for athletic participation
6 y without events	NA	0.3% (n = 9)
NA	100% American football	0%

bundle branch block. Nine individuals, all asymptomatic, were identified as having potentially serious CV conditions, including 3 cases of ECG abnormalities associated with cardiac death, 4 cases of WPW, 1 case of ARVC, and 1 case of right ventricular outflow tract ventricular tachycardia. The prevalence of cardiac disease in junior athletes was over twice (0.5%) that of schoolchildren (0.2%). The investigators argued that personal symptoms and family history questionnaires alone were inadequate for CV screening and that the ECG was critical when screening to prevent sudden death in the young.

In 1 of the largest youth screening programs, Tanaka and his colleagues in Kagoshima, Japan studied 68,503 young adolescents entering seventh grade.[106] This was part of a national screening program that included a questionnaire and an ECG for all first, seventh, and tenth grade students, regardless of athletic participation. Only half of the original cohort could be followed for 6 years. In the seventh and tenth grades, 975 and 901 students (2.7%) failed primary screening and required secondary screening by physical examination, exercise tests, or ECHO. During the follow-up period, 3 sudden deaths occurred in boys without a prior history of syncope or family history of cardiac disease. Among the 3 deaths, one 14-year-old boy had HCM identified during screening and died while jogging. The remaining 2 students, 13 and 16 years of age, died during handball and basketball, respectively. Both had had a normal ECG, and an autopsy to identify cause of death could not be performed.

The Italian PPE Experience

The largest systematic PPE program ever introduced has been that of Italy, which began in 1982. All young competitive athletes throughout the nation must be screened with family and personal history, physical examination, and 12-lead ECG. Each year, over 3 million athletes are evaluated throughout Italy and those suspected of CV disease are referred to a major medical center for further evaluation. In the Veneto area of Italy, the incidence rates and causes of SCD after initiation of the screening program were compared with the period before screening was mandated to assess the efficacy of such an ambitious undertaking.[107] There were 42,386 participants aged between 12 and 35 years followed over a 26-year period for SCD. During this period, 55 SCD occurred among the screened athletes (1.9 deaths/100,000 person-years). This rate was significantly lower than the 3.6/100,000 person-years rate of SCD in athletic population before the era of mandated screening. Most SCD reduction in this study was due to fewer cases of SCD from cardiomyopathies, including HCM and ARVC. In contrast, there were no changes in rates of SCD in a comparable, nonathletic group that did not receive screening. A parallel study examined trends in CV causes of disqualification from competitive sports in the 42,386 athletes. A total of 879 athletes (2.0%) were disqualified from competition due to CV causes including rhythm abnormalities (39%), systemic hypertension (23%), valvular disease (21%), coronary disease (1.3%), and cardiomyopathies (6.8%). The proportion of athletes who were disqualified for cardiomyopathies increased from 20 (4.4%) in the early screening period to 40 (9.4%) in the late screening period, implying that methods of detection improved during the screening program. The investigators concluded that the introduction of a nationwide systematic screening program was strongly associated with a substantial decline in SCD. Mortality reduction was predominantly due to a lower incidence of sudden death from cardiomyopathies that paralleled the improved identification of athletes with these conditions. Whether or not his degree of success can be demonstrated in other regions remains to be proven. Some have argued that because of the higher prevalence of ECG-identifiable conditions, particularly ARVC, in Italy, a screening program would be more efficacious there. It must also be pointed out that this was not a randomized trial but it remains the strongest evidence available supporting the addition of the ECG to the PPE.

To better understand the ECG abnormalities that were being observed in such a large Italian population, Pelliccia and colleagues studied 32,652 athletes from 19 clinics associated with the Italian Sports Medicine Federation.[38] Most participants were young amateur athletes, aged 8-78 years (median age, 17). The ECG patterns were considered abnormal in 3853 (12%) of the participants. The most frequent abnormalities included prolonged PR intervals, incomplete RBBB, and an early repolarization pattern. Other distinct ECG abnormalities included deeply inverted T waves in 2 leads (2.3%), evidence of LVH (247, 0.8%), conduction disorders such as RBBB (1.0%), left anterior fascicular block (0.5%), and left bundle branch block (0.1%). Rarely, cardiac pre-excitation pattern (42, 0.1%) and prolonged QTc interval (1, 0.03%) were found. They concluded that less than 5% of young athletes undergoing a PPE have markedly abnormal ECG patterns suggestive of CV disease.

Because young athletes may have abnormal ECGs without clear evidence of structural cardiac disease, Pelliccia and colleagues then considered in a separate study whether such ECG patterns may represent the initial expression of underlying cardiac disease with potential long-term adverse consequences. From a database of 12,550 Italian athletes, 123 (1%) with marked repolarization abnormalities, defined as diffusely distributed and deeply inverted T waves of >2 mm in at least 3 leads, were identified.[89] Of these, 39 had echocardiographic and clinical evidence of structural heart disease on initial evaluation. These included HCM (17), mitral-valve prolapse (6), ARVC (4), systemic hypertension (4), dilated cardiomyopathy (3), aortic stenosis with bicuspid valve (3), ischemic heart disease (1), and myocarditis (1). The 81 remaining athletes who initially had no apparent cardiac disease were followed with serial clinical, ECG, and echocardiographic studies for 10 years. Ultimately, 5 (6%) developed cardiomyopathy, including 1 subject who died suddenly at the age of 24 years from clinically undetected ARVC. Three of these athletes developed HCM, 1 of whom suffered an aborted cardiac arrest. The fifth athlete demonstrated dilated cardiomyopathy after 9 years of follow-up. In contrast, none of a control group of 229 athletes with normal ECGs had a cardiac event or received a diagnosis of cardiomyopathy 9 years after initial evaluation. It was concluded that abnormal ECGs in athletes may represent the initial expression of cardiac disease and that subjects with these abnormalities deserve clinical surveillance. However, a striking observation is the positive-predictive value of 36% for this ECG abnormality that occurs in 1% of athletes (immediate diagnosis in 39 and 5 in follow-up).

TABLE 8. ECG studies comparing athletes to nonathletes

Study	Year	Duration of study	Sample size	Population
Lee, Soni, Tate et al; The incidence and prognosis of Brugada pattern in the Manitoba Follow-up Study	2005	1948–2003	3983	Healthy aircrew recruits of the Royal Canadian Air Force during World War II
Pelliccia, Di Paolo, Corrado et al; Evidence for efficacy of the Italian national PPE for identification of HCM	2006	1990–1989	4450	Elite athletes in Italy referred consecutively to the Institute of Sport Medicine and Science
Peters, Trummel, Koehler et al, The value of different ECG criteria for ARVD/C	2006	1986–2006	395	Patients with ARVD/C (n = 343), uneffected (n = 52)
Bongioanni, Bianchi, Migliardi et al; Relation of QRS duration to mortality in a community-based cohort with HCM	2007	8 years	241	Patients with known HCM
Eckardt, Probst, Smits et al; Long-term prognosis of individuals with right precordial ST-segment-elevation Brugada syndrome	2005	30 years	212	Patients with ECG characteristic of Brugada syndrome at 4 European University hospitals
Basavarajaiah, Wilson, Whyte et al; Prevalence of HCM in highly trained athletes	2008	10 years	3500	Elite athletes in the United Kingdom

B.J. Gersh: A recent interesting case-control study concluded that the prevalence of early repolarization on the electrocardiogram is increased among survivors of idiopathic ventricular fibrillation. The mechanisms underlying this association are unknown, and what will be challenging is to identify which patients with this electrocardiographic finding, which is benign in the majority, are actually at increased risk for malignant arrhythmias (Haissaguerre M, Derval N, Sacher F, et al. Sudden cardiac arrest associated with early repolarization. N Engl J Med 2008;358:2016-23).

Testing and analysis pertaining to the Italian PPE program continues to proceed. The experience in Italy and reports such as these will help determine the efficacy of the resting ECG as part of the PPE and the justification for a new protocol in the USA. However, the sensitivity and specificity of the ECG for identifying athletes who will experience a sudden death is complicated by numerous factors. Not all used the same ECG criteria or collaborative imaging technologies. Of the 8 studies reviewed above, only 4 recorded events enabling a calculation of

TABLE 8. Continued

Population selection	Age (yr)	Gender (% male)	Types of athletics	ECG variables analyzed	Abnormal ECGs
Aircrew personnel	Mean 31 yr of age (90% between 20 and 39 yr)	100% (n = 3983)		Brugada syndrome	0.7% (n = 277) with Brugada pattern
Athletes after initial PPE referred for further testing to verify absence of HCM	24 ± 6 yr, range, 9–56	74% (n = 3293)	38 different sports	LVH (Sokoloff-Lyon), P, Q, and T wave abnormalities	0.63% (n = 28)
4 German hospitals	46 ± 13.7 yr	61% (n = 210)	N/A	Epsilon potentials and right precordial QRS prolongation ≥ 110 ms, T-wave inversions in V1-V3	N/A
Patients with HCM at Ospedale degli Infermi (Torino, Italy)	48 ± 18 yr	59% (n = 142)	N/A	QRS duration after confirmed HCM related sudden cardiac death	21% (n = 50) of HCM patients had QRS ≥120 ms
Patients with type 1 Brugada (either at baseline or with provocation)	56 ± 6 yr median 45 yr range 6–87 yr	71.7% (n = 152)	N/A	Brugada pattern, episodes of sustained VT or VF	N/A
Patients who were elite athletes and asymptomatic	21 yr 14–35 yr	75% (n = 2625)	15 different sports; 71% football, rugby, tennis, and swimming	HR, QTc, LVH, WPW, BBB, T-wave abnormalities	1.5% (n = 63) LVH, 6 WPW

sensitivity. Thus, the composite sensitivity of 70% is calculated from them and the specificity of 94% calculated from all 8 represent the best estimates we have.

Descriptive ECG Studies in Athletes

The physiological changes that occur in athletic hearts, such as hypertrophy and alterations in the conduction system, are not completely understood. One of the challenges in athletic screening is that these changes may mimic pathologic disease on ECG and even ECHO. For example, while markedly elevated voltages in the precordial leads may be considered suggestive of pathologic disease in sedentary individuals, such findings could be considered markers of physiological hypertrophy with a benign clinical course in high-endurance athletes. A better documentation and understanding of the ECG changes that can be expected in athletes, and their association with a benign prognosis, will be crucial for a successful PPE program.

Comparing Athletes to Nonathletes

Several studies have studied the ECG differences or rates of distinctive abnormalities between athletes and sedentary controls; these are summarized in Table 8. Of particular note are the seminal ECG studies of young athletes from the International Institute of Therapeutic Research at the University of Oslo by Bjornstad and colleagues. In 1991, Bjornstad et al[108] obtained ECGs on 1299 athletic students over a period of 5 years (1973-1982) and compared them with ECGs on 151 age- and sex-matched sedentary controls. The athletic population had a significantly lower heart rate, longer PR intervals, and a prolonged QTc compared with control subjects. Athletes had higher maximal Q-wave amplitudes in the precordial leads, higher R in V1, and higher indexes of right ventricular hypertrophy (RV1 + SV5) and left ventricular hypertrophy (Sokolow-Lyon and Grant indexes). Furthermore, the athletes had greater degrees of ST elevation and T-wave amplitudes in the precordial leads. It was suggested that these changes may partly be due to alterations in autonomic tone and partly to structural changes in the myocardium.

In 1993, Bjornstad et al again analyzed the ECGs from the same students and controls.[109] The athletic group was divided according to a heart rate less than 50 (bradycardia), 50-100 (normal), and above 100 (tachycardia) beats per minute. Atrioventricular conduction time, prevalence of ectopic beats and other rhythms, parameters of right and left ventricular hypertrophy, ST elevation, and T-wave amplitude were all increased in the group with sinus bradycardia. A significant negative correlation was found between heart rate and PR duration in athletes. In the group with sinus tachycardia, the PR duration was shorter and the ST depressions were more prominent than in the other groups. The subjects were also divided according to a PR interval ≥ 0.22 seconds, 0.21-0.12 seconds, and ≤0.12 seconds. Parameters of left ventricular hypertrophy were markedly increased in athletes with PR ≥ 0.22 seconds, while the heart rate was only slightly decreased, suggesting an association between prolonged atrioventricular conduction time and left ventricular hypertrophy. Incomplete RBBB was also associated with a lower heart rate, increased duration of QRS and QTc, increased voltage of precordial Q waves, indexes of right ventricular hypertrophy, and presence of negative T waves. These findings, which are typical of right ventricular hypertrophy, indicated a close relationship between incomplete RBBB and right ventricular hypertrophy. Bjornstad et al[110] then compared the ECGs and echocardiographs in 30 each of top level athletes, athletic students, and sedentary controls. As expected, resting ECGs in athletes showed increased indexes of hypertrophy compared with controls. The ECHO examination demonstrated an increase in left ventricular mass of 47% in the top athletes and of 23% in athletic students compared with controls. Highly significant correlations between ECG and echocardiographic parameters of hypertrophy were demonstrated; however, no correlation between left ventricular mass assessed by echocardiography and ventricular ectopic activity was found.

Attempts have been made to better characterize the electrocardiographic evidence of LVH that is commonly observed in athletes. Langdeau et al[111] compared resting ECGs and heart rate variability measurements between 100 athletes involved in endurance sports and 50 nonathlete controls. The athletes had significantly lower heart rates and longer QT intervals, although the difference became nonsignificant when corrected for heart rate (QTc). Among athletes, 10% exhibited LVH and 7% exhibited incomplete RBBB. In the 10% of athletes with LVH, the presence of this defect was significantly correlated with the athlete's age, but not with the number of years of training. In 2004, Turkmen et al[112] compared ECGs obtained from 44 trained athletes and 35 sex- and age-matched healthy sedentary controls. QT_{max} and QT_{min} interval durations were not statistically different between the athletic and control groups. Similarly, QT dispersion and QTcd did not differ significantly between the 2 groups. No association was observed between an athlete's heart and ventricular heterogeneity compared with healthy sedentary controls, despite physiological and structural changes. It appeared that the physiological ventricular hypertrophy seen with training does not result in ventricular repolarization abnormalities.

ECG Findings in Specific Sports or Level of Training

It is reasonable to suspect that the intensity of athletic training might correlate with the amount of hypertrophy or other physiological change and hence with the degree of ECG abnormalities. To help answer this question, Bjornstad et al[113] analyzed the ECG parameters from the 1299 athletes in their previously discussed study according to their level of fitness and type of activity. They divided the subjects into 3 fitness groups and compared their ECG changes to a control group. The most marked findings that correlated with higher fitness levels were lower heart rates, increased precordial ST segment elevation, and increased T-wave amplitudes. Only slightly increased parameters of right and left ventricular hypertrophy were found in the highly fit group. However, no correlation was found between fitness level and LVH (Sokolow index). The athletes were also subdivided according to sports activity and grouped into highly

TABLE 9. Definition of ECG abnormalities in the study by Pelliccia et al*

Distinctly abnormal ECG	Mildly abnormal ECG	ECG normal or with minor alterations
R or S ≥ 35 mm	R or S 30–34 mm	R or S 25–29 mm
Negative T wave	Flat/tall T wave	J-junction elevation
Q wave ≥ 4 mm	Q wave 2–3 mm	Incomplete RBBB
Left-axis deviation	Left atrial enlargement	PR >0.20 s
Right-axis deviation	Right atrial enlargement	Sinus bradycardia <60 bpm
WPW	Incomplete R wave	
LBBB	Progression V1 to V3	
	PR ≤0.12 s	
	RBBB	

*Reprinted with permission from Pelliccia A, et al.[115]
Left-axis deviation ≤−30°; RBBB = right bundle branch block; LBBB = left bundle branch block, right-axis deviation ≥ 110°; WPW = Wolff-Parkinson-White syndrome.

aerobic (endurance athletes or ball players) and strength-based athletes (gymnasts), and controls. Apart from a lower heart rate in highly aerobic athletes compared with strength-based athletes and gymnasts, few differences were found between the athletic groups. The heart rate was the most important parameter reflecting level of fitness and sports activity and the differences in ECG findings were relatively minor and did not distinguish type of sport activity.

In 2000, Pellicia et al[114] screened 1005 athletes engaged in 38 different sports of varying aerobic intensity. ECGs were classified as abnormal according to clinical criteria (Table 9) and the prevalence of abnormal ECG patterns in each sport is presented in Fig 9. Overall, abnormal ECGs, including markedly increased R- or S-wave voltages, flattened or inverted T waves, and deep Q waves, were found in 40% of athletes. Structural cardiac diseases were only identified with ECHO in 5% of athletes with an abnormal ECG. In the absence of cardiac disease the other causes were determined as responsible for the abnormal ECG patterns including participation in a high-endurance type of sport, cardiac remodeling, and male gender. Degree of ECG changes based on intensity of athletic training may allow one to establish thresholds that certain ECG changes may be acceptable. Further studies will be needed to help establish these thresholds.

Several studies have also considered the ECG characteristics or distinctive abnormalities found in specific sports or training. In 1976, Roeske et al[115] studied 42 active professional male basketball players and found that 11 (25%) met Romhilt-Estes ECG voltage criteria for left ventricular hypertrophy and a large number (29) exhibited 1 or more standard criteria for right ventricular enlargement. Mumford et al[116] investigated the ECG

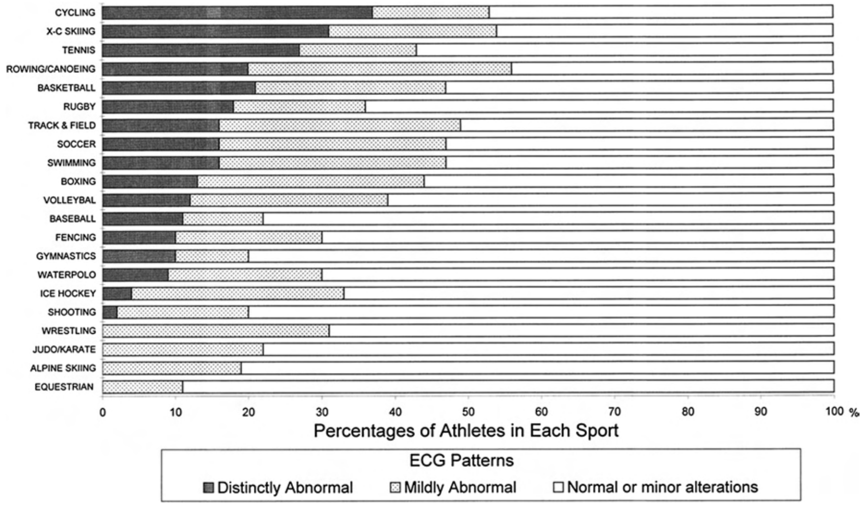


FIG 9. Relation of ECG patterns to sporting disciplines in 1005 highly trained athletes. ECGs that were distinctly abnormal (black bars), mildly abnormal (gray bars), and normal or with minor alterations (white bars) are depicted as proportions of all the athletes participating in each sporting discipline. X-C indicates cross-country. (Reproduced from Pelliccia et al with permission of the American Heart Association.[115])

and ECHO characteristics of long distance runners. Nineteen long distance runners and 19 age- and sex-matched sedentary controls were evaluated by ECHO and ECG at rest and after 12 minutes of treadmill exercise. Seven of the 10 male athletes exhibited ECG abnormalities of prominent precordial voltage and early repolarization, while 1 had evidence of right ventricle hypertrophy. Only 3 of 9 females had ECG abnormalities. The right ventricular wall thickness was equal to or greater than 6 mm in athletes vs equal to or less than 5 mm in controls. In 2001, Zakynthinos et al[117] investigated the ECG and ECHO findings in 18 athletes of the Greek national water polo team and compared them to 15 healthy sedentary male controls. The water polo players had a greater LV end-diastolic diameter index, interventricular septal thickness, and thickness of the posterior wall. LV mass index abnormalities were observed in 33% of athletes. They concluded that top water polo athletes have LV dilatation combined with LVH and normal systolic function. Finally, Langdeau et al[111] evaluated the differences in ECG findings between different sports competitors. Resting ECGs recorded in athletes from the following sports were compared: long-distance running, mountain biking, cross-country skiing, biathlon, speed skating, swimming, and triathlon. Of the 10 athletes with LVH, 6 were long-distance runners, 2 were triathletes, 1 was a swimmer, and 1 was a mountain biker. Additionally, incomplete RBBB was most prevalent in long-distance runners (57%), while 28% and 14% were found in swimming and mountain biking, respectively. The combination of LVH and incomplete RBBB was found exclusively in long-distance runners.

Gender-Specific ECG Findings in Athletes

Several studies have considered the ECG characteristics or distinctive abnormalities according to the gender of athletes. Storstein et al split their previous study group into 617 females and 833 males to analyze the influence of gender on the resting 12-lead athletic ECG.[118] Women had significantly higher heart rates, shortened conduction times (PR, ventricular activation time, and QRS), and a prolonged repolarization times (QTc). The women also had decreased P-, Q-, and T-wave amplitudes as well as indexes of right, septal, and left ventricular hypertrophy. ST elevations in precordial leads were lower in females than in males. Sinus bradycardia was more common in men, whereas sinus tachycardia was more frequent in women. Notching of R/S in V1-V2 and incomplete RBBB was less common in females.

B.J. Gersh: In studies of normals it has been shown that the rate-corrected QT interval is similar in males and females from both until late adolescence (0.37 to 0.4 seconds), but in adults, females have slightly longer QT intervals than males. A corrected QT interval of 0.44 seconds is considered prolonged in men but the normal range in females is generally extended to 0.45 to 0.46 seconds (Moss AJ. Measurement of the QT interval and the risk associated with QTc prolongation: a review. Am J Cardiol 1993;72:23B-5B).

George et al[119] examined ECG and ECHO characteristics of endurance- and resistance-trained female athletes to better understand the ECG findings in women. The subjects were 10 each of varsity-caliber endurance-trained athletes, resistance-trained athletes, and controls. Sinus bradycardia was observed in all endurance athletes and in 4 resistance-trained athletes. ECG criteria were unreliable for the prediction of left ventricular enlargement. Both female resistance- and endurance-trained athletes exhibited a lesser degree of enlargement of left ventricular wall thickness and mass than male athletes. A close relationship between skeletal and cardiac muscularity in resistance-trained athletes of both genders was demonstrated.

In the study conducted by Pelliccia et al where 1005 national athletes from 38 different sports were examined, significant differences in ECG abnormalities with respect to gender were found. Distinct abnormalities were defined according to R or S wave greater than 35 mm, repolarization pattern with inverted T wave, Q wave greater than 4 mm, marked QRS axis deviation, WPW, and left bundle branch block. Mild abnormalities were those that were compatible with the presence of CV disease. This includes increased R- or S-wave voltage (30-34 mm) in any lead, Q waves 2-3 mm in-depth and present in 2 or more leads, repolarization patterns with either flat, minimally inverted, or particularly tall T waves ($>$15 mm) in 2 or more leads, abnormal R-wave progression in the anterior precordial leads, RBBB, right atrial enlargement, left atrial enlargement, and a short PR interval. A significantly larger proportion of male athletes had either distinctly (17% vs 8%) or mildly abnormal (28% vs 14%) ECGs compared with female athletes. The majority of female athletes showed normal ECGs (78%) compared with male athletes (55%), and male athletes had greater maximum R- or S-wave voltages and more frequently exhibited abnormal Q waves. These observations suggest that different upper normal limits for ECG parameters according to gender should be applied during PPE screening.

Specialized ECG Techniques

It has been suggested that the ECG abnormalities that can help distinguish physiological vs pathologic differences in athletes may be too subtle for the normal electrocardiograph. In 1995, Moroe et al[120] performed signal-averaged electroencephalograms, a procedure whereby the electrocardiographic voltages are averaged across several heart beats, on 796 athletes (mean age, 19 years). They aimed to determine the incidence of abnormal findings and their relation to the extent and type of exercise in young healthy athletes as well as the association. Abnormal signal-averaged electroencephalograms were present in 68 (8.5%) of the athletes and were associated with a smaller left ventricular mass, which was found predominantly in athletes who performed anaerobic exercise more often. No serious ventricular arrhythmias or sudden cardiac deaths were observed on Holter monitoring or during the follow-up period of 3 years.

Lonati et al studied QT dispersion in 51 age-matched subjects: 17 hypertensive, 17 canoeists, and 17 normotensive healthy controls.[121] Echocardiographically defined LVH was observed in all athletes, while the prevalence in hypertensives was 50%. Despite large differences in LV mass, there were no significant differences in QT parameters between athletes and the control group, whereas hypertensive patients showed a significant increase in QT dispersion vs the 2 other groups. Other advanced ECG parameters, such as QRS-T spatial angle, should be studied to see if there are alternative measurements that might distinguish athletes with pathologic heart disease.

Usefulness of Diagnostic ECG Criteria in Athletes

As has been discussed, athletes display a variety of ECG abnormalities[122] that have been attributed to physiological LVH and other physiological changes induced by training. To what extent the criteria that are used to identify patients with LVH and other CV conditions can be used in the athlete is still unclear. The relationships between ECG abnormalities and ventricular mass or geometry is not completely characterized. Several studies that have compared ECG abnormalities and ECHOs in athletes to assess the prevalence of physiological left ventricular hypertrophy and the usefulness of ECG criteria for its diagnosis have been identified.

Douglas et al[123] performed ECGs and ECHOs on 44 ultra-endurance athletes. Although nearly half of the athletes studied had prolonged QRS duration, only 7 (16%) athletes met Romhilt-Estes criteria for LVH compared with none of the controls. In contrast, 26 athletes (60%) met the ECHO criteria for LVH. In addition, no correlations were found between voltage criteria and posterior wall thickness, relative wall thickness, blood pressure, or chamber diameter. The Romhilt-Estes scoring system yielded an overall accuracy rate of only 45%, while QRS prolongation was an independent predictor of hypertrophy. Additionally, voltage criteria and their individual components were not related to the geometric measures of hypertrophy or to left ventricular mass or mass index. The investigators concluded that physiological hypertrophy principally manifests itself by increased QRS voltage, while pathologic hypertrophy is suggested by the presence of marked QRS prolongation.

In the Italian population, Pelliccia et al[124] compared ECG patterns to cardiac morphology and function assessed by ECHO in their cohort of 1005 elite athletes. Forty percent had abnormal ECGs, and a subgroup of about 15% showed distinctly abnormal and often bizarre patterns highly suggestive of cardiomyopathies, such as HCM, in the absence of pathologic cardiac changes. Similarly, the group led by Bjornstad et al also studied the prevalence of hypertrophy in athletes and the correlation between hypertrophy and other ECG findings.[125] In their cohort of 1299 athletic students, they reported that an increase of Q waves of more than 0.2 mV was associated with increased indexes of both right and left ventricular hypertrophy. ECHO evidence of right ventricular hypertrophy was associated with an increased prevalence of incomplete RBBB and increased parameters of septal and left ventricular hypertrophy, while left ventricular hypertrophy was associated with bradycardia, ST elevation, and increased T-wave amplitudes but not by repolarization abnormalities.

Conclusions

Whether or not an ECG should be routinely added to the athletic PPE remains highly controversial. Much of the data presented, particularly that of the Italian experience, are supportive. However, given the lack of randomized controlled data assessing the efficacy of such an intervention in the USA, consensus groups such as those of the AHA have been unable to mandate its adoption. While we do not feel that there is sufficient evidence for a governmental mandate, we do argue that a large-scale trial in the USA is necessary. Athletic deaths may be relatively rare events, but the impact of a potentially preventable death of a youth in the public eye is sufficient as to suggest further analysis. The question of cost-effectiveness is integral to this analysis and may be affected by improvements in the accuracy of the screening ECG and by innovations leading to reduction in costs associated with ECG testing.

One critical question that had not been addressed in the studies reviewed is what percentage of conditions predisposing athletes to athletic deaths could be diagnosed premortem by the ECG? While certain cardiovascular conditions such as coronary anomalies (14%) and commotio cordis (20%) would escape detection on a resting ECG, several abnormalities indicative of conditions such as long QT syndrome and Brugada are clearly identified by the ECG before any other clinical sign. Fig 1 summarizes the causes of athletic SCD in all the large autopsy studies and illustrates the percentage of these deaths that could potentially have been identified on ECG screening. The ECG detectable causes of SCD in these studies ranged from 18% to 63%. However, the percentage of cases where no structural cause was identified varied from 3% in the Minnesota experience (highly selected as to who has autopsies) to 35% in military recruits (all of whom have autopsies). One could argue that the higher number of structurally normal hearts associated with deaths in some of these studies leaves more opportunity for the ECG to recognize the cause of athletic deaths. This particular subset, however, represents a significant challenge, and given that many of the abnormalities such as prolonged QT or ST elevations in Brugada can be transient, a percentage of these cases could remain undiagnosed even after screening.

In addition to the conditions detectable by ECG that have been discussed in this review, there are additional cardiovascular diseases that can be detected on ECG. The ECG would be able, for example, to detect myocarditis with ST segment changes or clinically significant aortic stenosis with repolarization abnormalities. The significance of other abnormalities, such as T-wave inversions, has recently been emphasized during follow-up in athletes even though the pathology that explains their association with SCD in structurally normal hearts is not yet well understood.

The sensitivity and specificity of the ECG for identifying athletes who will experience a sudden death is complicated by numerous factors. Not all the studies used the same ECG criteria or follow-up imaging technologies. Of the 8 studies reviewed that included the ECG as part of the screening process in a PPE, only 4 recorded events enable a calculation of sensitivity. Thus, the composite sensitivity of 70% is calculated from them and the specificity of 94% is calculated from all 8. These numbers are critical to any estimation of cost efficacy but, despite all their limitations, they remain the best available to date. Cost efficacy may be more decided by elements of personal choice. Would an athlete rather risk death than risk undergoing testing? Why would an athlete choose to undergo an ECG when the chance of having an abnormal ECG ranges from 5% to 20% and about 6 times out of 100 further testing is indicated? Viewed from an institutional point of view, what is the liability of restricting an athlete from playing a sport as opposed to the uncertainty of preventing athletic deaths?

The AHA (Table 10) and the European Union (Table 11) have each proposed an extensive set of well thought-out medical questions and components of the physical examination meant to capture the conditions discussed. Although some historical questions, such as a family history of premature SCD, are highly indicative of potential disease, they are far from sufficiently sensitive. We believe addition of the ECG is likely to increase the sensitivity and provide a safety net in many circumstances, particularly when an athlete and his/her family are being dishonest for personal reasons or when there is incomplete knowledge regarding these items. Unfortunately, these circumstances occur more often than appreciated in the United States due to the individual and family benefits accruing from success in sports, relatively high divorce rates or broken families, and increased geographic mobility of family members.

Improvements in the accuracy of the current PPE screening ECG recommendations (Table 12) continue to be made. An argument that is commonly made against the use of a widescale ECG program is that the financial burden and social costs of high rates of false positives would outweigh the benefits gained. A formal, well-formulated cost-benefit

TABLE 10. The 12-element AHA recommendations for the PPE CV screening of competitive athletes*

Medical history†	
Personal history	
1.	Exertional chest pain/discomfort
2.	Unexplained syncope/near syncope‡
3.	Excessive exertional and unexplained dyspnea/fatigue associated with exercise
4.	Prior recognition of a heart murmur
5.	Elevated systemic blood pressure
Family history	
6.	Premature death (sudden and unexpected or otherwise) before 50 y of age resulting from heart disease in ≥1 relative
7.	Disability from heart disease in a close relative <50 y of age
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
Physical examination	
9.	Heart murmur§
10.	Femoral pulses to exclude aortic coarctation
11.	Physical stigmata of Marfan syndrome
12.	Brachial artery blood pressure (sitting position)¶

*Reprinted with permission from Maron et al.[3]
†Parental verification is recommended for high school and middle school athletes.
‡Judged not to be neurocardiogenic (vasovagal): of particular concern when related to exertion.
§Auscultation should be performed in both supine and standing positions (or with Valsalva maneuver), specifically to identify murmurs of dynamic left ventricular outflow tract obstruction.
¶Preferably taken in both arms.

analysis has yet to be done to help answer this question. Recent studies have attempted to partially address this question by forwarding guidelines that increased the specificity of the ECG to detect the Brugada syndrome (only type 1 should be associated with pathologic changes) and long QT syndrome (a long QTc cut point in athletes should be 0.50 seconds). Similarly, recommendations that increase both the sensitivity and the specificity of detecting ARVC (adding slurred S waves to the T-wave inversion criteria in V2), HCM (adding QRS duration to voltage and repolarization criteria), and multiple causes of sudden death (T-wave inversion of 2 mm or more in 3 or more leads) have been made. There is much more to be done in the improvement of ECG criteria, particularly in the area of computerized ECG technologies to compare the ECGs of athletes to those with disease processes. Because sarcomere disarray is a feature of pathologic hypertrophy, automated spatial ECG/vector cardiogram (VCG) measurements may also be helpful in differentiating them. Furthermore, newer computerized criteria for LVH and their response to antihypertensive treatment have not been applied in athletes. Spatial

TABLE 11. Cardiovascular questions and evaluations for the PPE according to the European Union Guidelines for competitive athletes until 35 years of age

- Medical History
  - Personal History:
    - Have you ever fainted or passed out when exercising?
    - Do you ever have chest tightness?
    - Does running ever cause chest tightness?
    - Have you ever had chest tightness, cough, or wheezing that made it difficult for you to perform in sports?
    - Have you ever been treated/hospitalized for asthma?
    - Have you ever had a seizure?
    - Have you ever been told you have epilepsy?
    - Have you ever been told to give up sports because of health problems?
    - Have you ever been told you have high blood pressure?
    - Have you ever been told you have high cholesterol?
    - Do you have trouble breathing or do you cough during or after activity?
    - Have you ever been dizzy during or after exercise?
    - Have you ever had chest pain during or after exercise?
    - Do you have or have you ever had racing of your heart or skipped heartbeats?
    - Do you get tired more quickly than your friends do during exercise?
    - Have you ever been told you have a heart murmur?
    - Have you ever been told you have a heart arrhythmia?
    - Do you have any other history of heart problems?
    - Have you had a severe viral infection (eg, myocarditis or mononucleosis) within the last month?
    - Have you ever been told you had rheumatic fever?
    - Do you have any allergies?
    - Are you taking any medications at the present time?
    - Have you routinely taken any medication in the past 2 y?
  - Family history:
    - Has anyone in your family $<$50 y of age
      - Died suddenly and unexpectedly?
      - Been treated for recurrent fainting?
      - Had unexplained seizure problems?
      - Had unexplained drowning while swimming?
      - Had unexplained car accident?
      - Had heart transplantation?
      - Had pacemaker or defibrillator implanted?
      - Been treated for irregular heart beat?
      - Had heart surgery?
    - Has anyone in your family experienced sudden infant death (cot death)?
    - Has anyone in your family been told they have Marfan syndrome?
- Physical examination
  - General
    - Radial and femoral pulses
    - Marfan stigmata
  - Cardiac auscultation
    - Rate/rhythm
    - Murmur: systolic/diastolic
    - Systolic click
  - Blood pressure
- Diagnostic tests
    - 12-lead resting ECG (after the onset of puberty)

TABLE 12. Criteria for an abnormal ECG according to the European Union Guidelines for competitive athletes

Left atrial enlargement: negative portion of the P wave in lead V_1 $\geq$0.1 mV in depth and $\geq$0.04 s in duration
Right atrial enlargement: peaked P wave in leads II and III or V_1 $\geq$0.25 mV in amplitude
QRS complex
Frontal plane axis deviation: right $\geq$120° or left $-30°$ to $-90°$
Increased voltage: amplitude of R or S wave in a standard lead $\geq$2 mV, S wave in lead V_1, or V_2 $\geq$3 mV, or R wave in lead V_5 or V_6 $\geq$3 mV
Abnormal Q waves $\geq$0.04 s in duration or $\geq$25% of the height of the ensuing R wave or QS pattern in $\geq$2 leads
Right or left bundle branch block with QRS duration $\geq$0.12 s
R or R′ wave in lead V_1 $\geq$0.5 mV in amplitude and R/S ratio $\geq$1
ST segment, T waves, and QT interval
ST segment, T waves, and QT interval
ST-segment depression or T-wave flattening or inversion in $\geq$2 leads
Prolongation of heart rate-corrected QT interval >0.44 s in males and >0.46 s in females
Rhythm and conduction abnormalities
Premature ventricular beats or more severe ventricular arrhythmias
Supraventricular tachycardias, atrial flutter, or atrial fibrillation
Short PR interval (<0.12 s) with or without delta wave
Sinus bradycardia with resting heart rate $\leq$40 bpm
First- (PR $\geq$0.21 s), second-, or third-degree atrioventricular block

QRST angle, upright T waves in AVR, eigen plane thickness, and neural networks have yet to be studied in the athletic population.

For all the above reasons, we conclude that the ECG will eventually become part of the PPE of young competitive athletes. A caveat is that more research must be done to refine the ECG criteria for distinguishing physiological ECG manifestations from pathologic conditions. Furthermore, the criteria for abnormal must become specific for age, gender, and sport. This will require large computerized ECG databases in athletes and control patients. We expect that neural networks and sophisticated statistical techniques can be applied to digital ECG and VCG measurements to improve the accuracy of the screening ECG. Such studies will also lead to new ECG technologies to more effectively and less expensively screen large populations and prevent the tragic cases of SCD in athletes.

B.J. Gersh: Dr Perez and his colleagues have written a comprehensive review of the causes of sudden cardiac death in athletes and distinguished between those that could have been identified by abnormal electrocardiogram including a detailed description of the ECG abnormalities that may be detected during the screening of athletes. A major component of this review is a discussion of the evidence supporting the use of the electrocardiogram as part of the process of preparticipation evaluation. The authors certainly make a strong case for the addition of the ECG but also accept that this is highly controversial, at least in the USA.

I agree with the other conclusions that we need more data including perhaps trial and cost-effective studies, before this can be undertaken on a national scale. Another caveat is the need for more research on refining the electrocardiographic criteria for the distinction between physiological and pathologic abnormalities. In this respect, the future role of neural networks and innovative statistical approaches will be of interest. This is an excellent review of a fascinating and very controversial topic.

Addendum

A review of all sudden deaths over a 27-year period in young competitive athletes in the USA revealed 56% of deaths were predominantly due to cardiovascular disease.[126]

Analysis of the 25-year Italian data including periods before and after adding ECG screening noted an approximate 90% reduction of mortality but other factors changed during this period of observation. The most important change was the recognition of the high prevalence of ARVC in Veneto.[127]

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