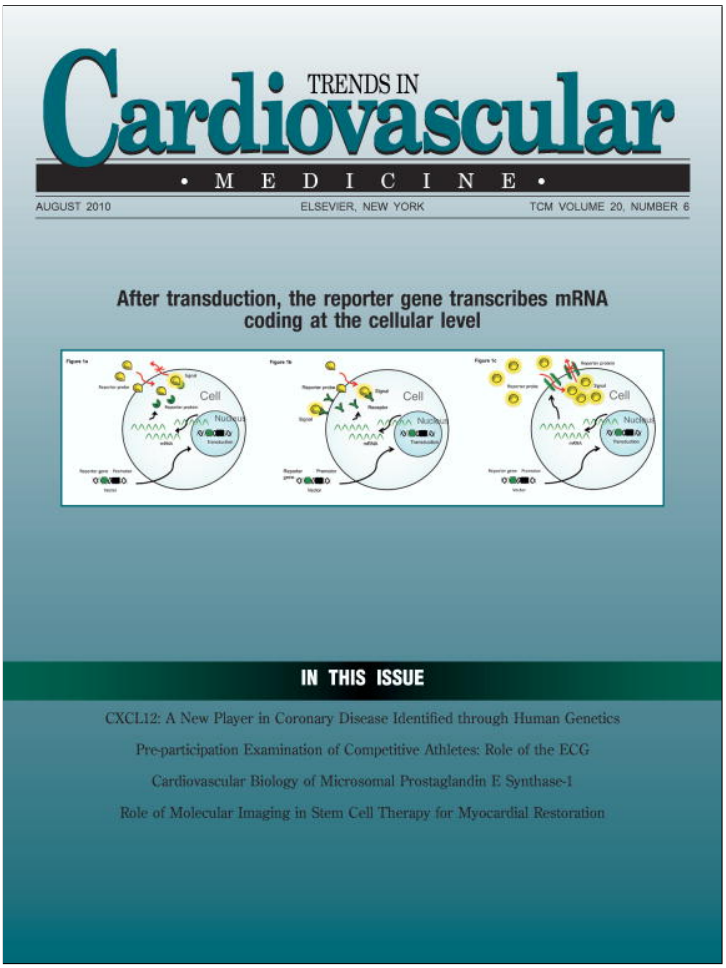

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Pre-participation Examination of Competitive Athletes: Role of the ECG

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Sudden cardiac death in athletes is rare but has a wide social impact because it confronts the general population with the paradox that athletes perceived and admired as the fittest and healthiest suddenly drop dead during their sport. Mass media coverage is guaranteed in the case of sudden cardiac death of a top athlete, while other competitive and noncompetitive athletes of all ages, team members, sponsors, as well as huge parts of society remain puzzled and frightened. Therefore, debate is ongoing regarding how to minimize the number of fatalities, and the search continues for a cost-effective preparticipation screening for competitive athletes. Despite the fact that routine ECG screening would be widely available and rather inexpensive, debate continues regarding whether this should be part of initial screening for every athlete before starting to train at high intensity as well as during annual checkups. The role of ECGs in preparticipation examinations of competitive athletes is intensively discussed because there is a lack of strict criteria for which ECG findings should generate further workup. In this article, we analyze the main publications on sudden cardiac death, focusing on the benefit of ECG screening in preparticipation examination as it has been shown to be feasible and effective in identifying athletes at risk of sudden cardiac death. (Trends Cardiovasc Med 2010;20:195–199) © *2010 Elsevier Inc. All rights reserved.*

• Introduction: Are Athletes at Higher Risk of Sudden Cardiac Death Than the General Public?

Despite the fact that exact numbers of sudden cardiac death (SCD) do not exist for athletes or for the general population, there are still several meaningful studies that have elucidated our knowledge. Corrado et al (2003) assessed the risk of SCD in all young people (aged 12-35 years) in the Veneto region of Italy and reported an estimated all-cause SCD relative risk (RR) of 2.5 in athletes compared to nonathletes. The risk of SCD in athletes with underlying cardiovascular disease was significantly higher, with an RR of 79 in those with congenital coronary artery anomalies, 5 in those with arrhythmogenic right ventricular cardiomyopathy (ARVC), and 3 in those with premature coronary artery disease (CAD). Male gender was an independent risk factor for SCD, and it has been explained by greater exercise intensity during both training and competition. Furthermore, men have a higher prevalence and/or phenotypic expression of potentially lethal cardiac diseases, such as hypertrophic cardiomyopathy (HCM), ARVC, and premature CAD (Corrado et al. 1994, 2000, Maron et al. 1996).

After reviewing 5662 death certificates of individuals aged 12–35 years, Holst et al. (2010) identified 15 sports-related SCDs with an incidence of 1.21 per 100,000 athletes per year; the incidence rate for the general population was 3.76 per 100,000 person-years. de Noronha et al. (2009) characterized the demographics and etiology of SCD in athletes in the United Kingdom. Between 1996 and 2008, 118 SCDs were reported. Twenty-one (18%) of these cases had antecedent symptoms suggestive of a cardiac disease, 20 (17%) had a positive family history for cardiac events, and 25 (21%) had a relevant previous medical history.

Overall, it has been well documented that vigorous exercise transiently increases the incidence of coronary events (Mittleman et al. 1993, Siscovick et al. 1984, Thompson et al. 1982, Willich et al. 1993), but this adverse event risk decreases over time in the habitually trained with increasing amounts of physical activity (Dahabreh and Paulus 2011). In fact, it has been documented in many studies that physical exercise and

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1050-1738/$-see front matter

physical fitness protect from all-cause as well as cardiovascular mortality (Myers et al. 2002), and thus national and international guidelines widely promote exercise training.

• Causes of Sudden Cardiac Death

The mechanisms of exercise-related SCD in young competitive athletes include a number of triggers, such as acute myocardial ischemia, sympathetic autonomous stimulation, and abrupt hemodynamic changes leading to ventricular arrhythmias. Intensive athletic training may lead to alteration of the substrate, promote phenotypical expression, or accelerate disease progression. In patients with ARVC, regular physical activity can cause right ventricular volume overload and cavity enlargement, which in turn may accelerate fibrofatty atrophy (Corrado et al. 1990). In patients with HCM, recurrent episodes of exercise-induced myocardial ischemia can produce cell apoptosis and myocardial scarring fibrosis (Basso et al. 2000). As a result of these changes, ventricular electrical instability is increased.

Corrado et al. (1998) reported that the most common reason for SCD was ARVC (22.4%); HCM was responsible for just one death (2%). de Noronha et al. (2009) identified cardiomyopathy as the most frequent and ARVC as the second most common diagnosis in the United Kingdom, and Basavarajaiah et al. (2008) reported that HCM is very rare.

Results from Italian studies differ significantly from findings reported in the United States, in which HCM was the most common cause of SCD death (Burke et al. 1991, Maron et al. 1980, Van Camp et al. 1995).

In a separate cohort study on all nontraumatic sudden deaths during basic military training, of the 126 nontraumatic sudden deaths (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%]), including coronary artery abnormalities (61%), myocarditis (20%), and HCM (13%). Anomalous left coronary arteries accounted for one-third (21 of 64 recruits) of the cases. However, more than one-third of sudden deaths remained unexplained, suggesting the presence of underlying malignant arrhythmic or conduction system diseases.

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

Maron et al. (1980) found that out of 29 unexpected or sudden deaths of U.S. athletes, 28 deaths were related to a cardiovascular abnormality. The most common causes of death were HCM in 14 cases followed by anomalous origin of the left coronary artery, CAD, and aortic rupture.

In another study, nontraumatic sports deaths in high school and college athletes were analyzed over a 10 year study period. Of the 160 athletes who died suddenly, cardiovascular causes were found in 100 (74%). HCM was again the most common cause of death (Van Camp et al. 1995).

Corrado et al. (2001) prospectively studied the pathology of 273 consecutive cases of SCD in young people. At macroscopic examination, 197 cases of SCD (72%) were found to have an overt underlying structural heart disease: cardiomyopathy (56), CAD (54), valve disease (32), nonatherosclerotic CAD (28), aortic rupture (13), postoperative congenital heart disease (5), and other diseases (9). The remaining 76 cases (28%) had a macroscopically normal heart. A total of 28 structurally normal hearts (37%) had experienced one 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, ARVC in 9, ventricular preexcitation in 18, and heart block in 6. No evidence of structural heart disease was found even after histological study in 6% of cases. This study suggests that many deaths involving apparently normal structural hearts are in fact caused by cardiovascular diseases potentially detectable with an ECG.

Differences in the leading causes of SCD between Italian and U.S. athletes may be partly explained by the fact that in Italy, 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 (Basavarajaiah et al. 2008). Genetic predisposition to ARVC in Italians has also been suggested to explain these regional differences.

Figure 1 is based on data from the major pathological studies reviewed previously and indicates which abnormalities could be discovered by adding the ECG to the preparticipation examination. An important question is what percentage of deaths occur in athletes with structurally normal hearts? This group could provide the strongest argument for ECG screening, but the range of SCD in athletes is 3% to 33%.

• Electrocardiogram

Athlete's heart is considered a physiologic adaptation of the heart in response to regular strenuous exercise, which results in increased left ventricular mass and/or wall thickness. Within the framework of the Italian preparticipation screening, Pelliccia et al. (2007) assessed ECG abnormalities in an unselected population of 32,652 athletes. Of these, 28,799 (88%) had a normal ECG, and 3,853 (12%) had an abnormal ECG. Sixty percent of the abnormal ECGs were associated with athlete's heart. Only a minority (approximately 5%) of these athletes had an abnormal ECG indicative of structural heart disease. There was a large proportion of abnormal ECG patterns in young athletes, as expected in this population. ECGs can be abnormal without necessarily being indicative of structural heart disease. This poses a significant challenge with regard to the differentiation between athlete's heart and, for example, hypertrophic cardiomyopathy. On the other hand, a normal ECG has been shown to be highly predictive for the absence of HCM (Corrado et al. 2006, Pelliccia et al. 2000).

The morphology of Q waves is very important for the diagnosis of HCM. Deep and very narrow Q waves are most characteristic and specific for HCM (Figure 2) (Kelly et al. 2007, Shimizu et al. 2002).

ARVC is not easy to diagnose, and it is also difficult to differentiate from right ventricular outflow tract tachycardia

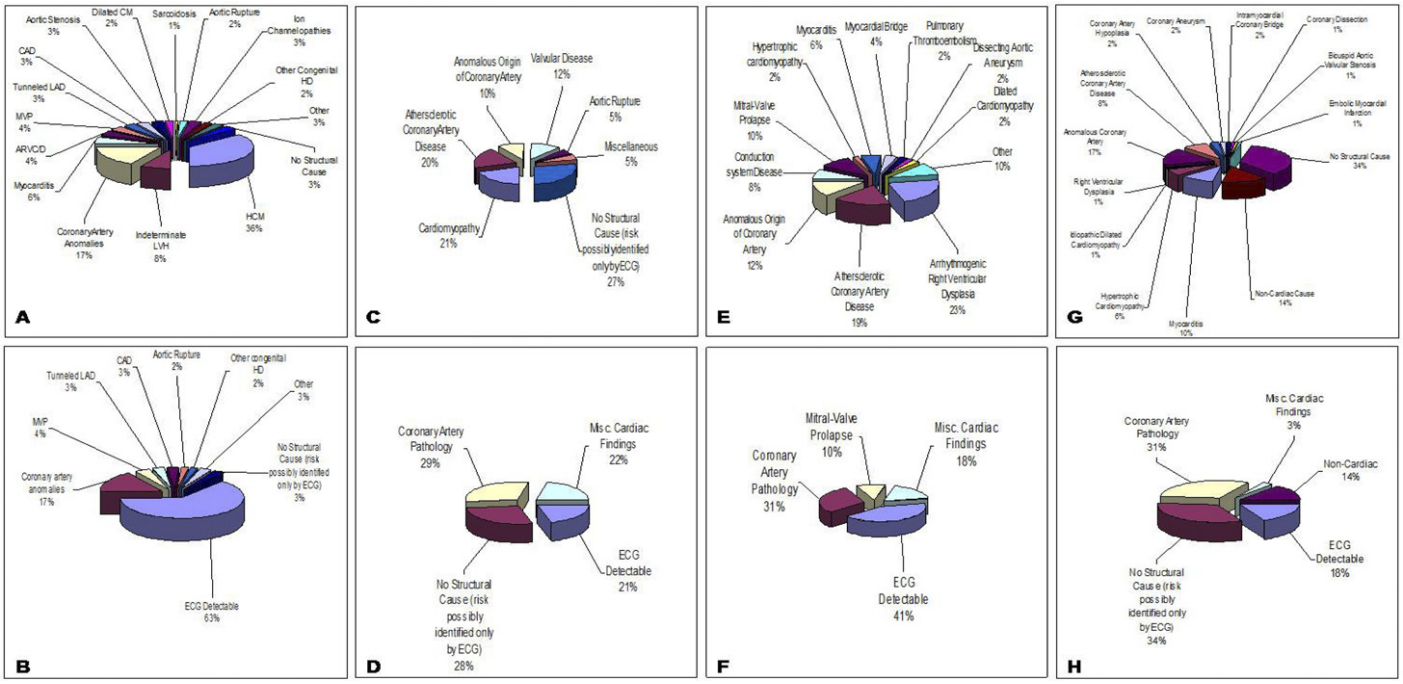

Figure 1. Autopsy studies of sudden death in active young adults. **(A)** Data from Maron et al. (2007). **(B)** Data from **A** compiled to represent ECG-detectable causes of death. **(C)** Data from Corrado et al. (2001). **(D)** Data from **C** compiled to represent ECG-detectable causes of death. **(E)** Data from Corrado et al. (1998). **(F)** Data from **E** compiled to represent ECG-detectable causes of death. **(G)** Data from Eckart et al. (2004). **(H)** Data from **G** compiled to represent ECG-detectable causes of death.

(Whyte et al. 2008). However, it has been shown that the right precordial QRS prolongation has a sensitivity of 98%. Combined with the prolonged S wave upstrokes in V1-V3 (sensitivity of 84%) and epsilon potential (sensitivity of 23%; highly amplified and modified recording technique sensitivity of 77%), these are useful noninvasive techniques for the detection of ARVC (Peters et al. 2007).

Italy was the first country to introduce a nationwide systematic preparticipation athletic screening program by national law. Since 1982, athletes wanting to compete in nationwide or international competitions have had to undergo an annual checkup. This clinical evaluation consists of family and personal history, physical examination, and a 12-lead ECG. In 1979, the annual incidence of SCD in athletes was 3.6/100,000, whereas in 2004 it was 0.4/100,000—a decrease of 89% (Corrado et al. 2006).

These findings have been challenged by a systematic newspaper search in Israel, which reported an incidence of SCD among athletes in a similar range but found that mandatory screening with ECG did not have an apparent effect on athletes' risk of SCD (Steinvil et al. 2011). Note, however, that the latter study did not provide exact but only estimated numbers of competitive athletes, and these were solely based on SCD reported in the two main newspapers.

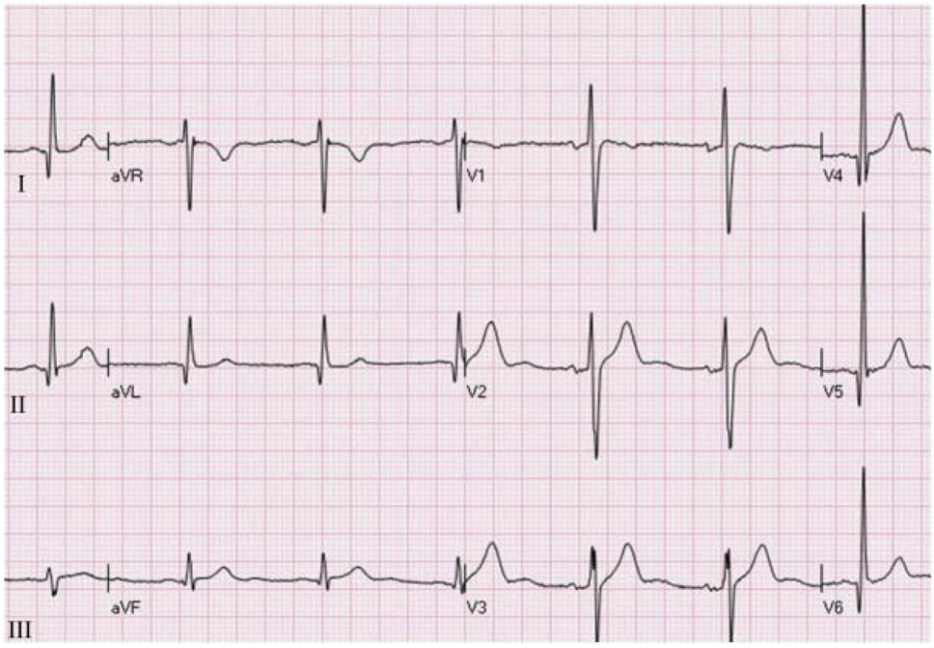

Figure 2. Twelve-lead ECG of patient with HCM. Deep and narrow Q waves are present in leads I, II, aVL, and V4-V6.

• Practical Challenges of Adding ECG to Preparticipation Examinations

By law, the Italians benefit from a cadre of physicians trained in screening athletes. Such a law is unlikely in the United States even though mandatory ECGs may be cost-effective (Wheeler et al. 2010). In addition, the physician/population ratio is greater in Italy than in the United States, which allows for easy access to qualified physicians.

Interpretation of an ECG in athletes is difficult, and there is a lack of strict criteria for which ECG findings should generate further workup (Uberoi et al. 2011). However, analysis and storage

programs are available with a 5% positive rate based on a database of thousands of athletes, and these have made it possible to improve criteria for abnormal ECGs in athletes by considering gender and sport (Mandic et al. 2010).

The European Society of Cardiology (ESC) has published recommendations for the interpretation of ECGs in athletes (Corrado et al. 2010). As part of this report, the ESC reanalyzed the 1005 highly trained athletes previously reported by Pelliccia and colleagues (Corrado et al. 2010, Pelliccia et al. 2000). Originally, 40% (N = 402) had findings possibly associated with cardiovascular disease. However, using the new recommendations, this percentage was lowered to 11%, which implies a meaningful increase in specificity. In a U.S. context, we applied this reclassification scheme to a study of Stanford collegiate athletes (Le et al. 2010) in which 63 (10%) were considered to have ECG patterns possibly associated with cardiovascular diseases. When these 63 "abnormal" ECGs were evaluated using our interpretation of the new criteria defined by the ESC, 34 were reclassified to the normal range and only 29 (4% of all ECGs) remained in the abnormal category. Thus, the achieved specificity may be greater than 95%.

These findings dispute the argument that preparticipation screening ultimately leads to unjustified costs due to false-positive findings, and they also argue against the concern that too many athletes will be banned from participating in competitions, thus having to end their careers in vain. Conversely, although ECGs are a potent and inexpensive tool to rule out cardiac disorder, SCD may still occur in athletes with normal ECGs.

• Conclusions

Sport is recommended for the entire population because people who engage in regular exercise have a reduced risk of cardiac events compared to sedentary individuals. Because CAD and structural cardiac disorders are the underlying cause of SCD, routine ECG screening before engaging in exercise training as well as annual checkups thereafter appear warranted and possibly cost-effective. Including ECGs in preparticipation examinations has been shown to be feasible and effective in identifying athletes at risk of SCD; thus, ECGs should be widely utilized and made mandatory when practical in competitive athletes.

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Regulation and Differential Role of the Tissue Factor Isoforms in Cardiovascular Biology

Andreas Eisenreich and Ursula Rauch*

Alternative pre-mRNA splicing is an essential mechanism regulating protein diversity and functional plasticity of the proteome in response to environmental changes. Several factors are involved in this regulatory mechanism, such as serine/arginine-rich (SR) proteins, the Cdc2-like kinase (Clk) family, the dual-specificity tyrosine phosphorylation regulated kinases, the SR protein kinases (SRPK) 1 and 2, the protein kinase B (PKB,Akt), and the DNA topoisomerase I (DNA topo I). Dynamic changes of the phosphorylation state of SR proteins, mediated by the kinases mentioned previously, play an important role in alternative splicing regulation. Through alternative splicing of the tissue factor (TF) pre-mRNA, two naturally occurring forms of TF, the primary initiator of blood coagulation, are expressed in humans—soluble alternatively spliced (as)TF and membrane-bound "full length" (fl)TF. Both isoforms are known to circulate in blood. flTF, rather than asTF, appears to be the major contributor to the thrombogenicity of vascular wall and blood. asTF has been linked more closely to increased cell survival and angiogenesis. We found the expression of asTF and flTF to be reduced in the myocardium of patients with dilated cardiomyopathy, indicating a role of TF in maintaining myocardial structure. Moreover, we demonstrated proinflammatory cytokines to immediately upregulate the expression of both TF isoforms, which was differentially regulated by SR proteins as well as Clks and DNA topo I. We and others have shown that asTF induces cell proliferation, survival, and angiogenesis via signaling pathways different from flTF-induced effects. These data indicate that both TF isoforms influence diverse processes in cardiovascular (patho)biology and are potential targets for antithrombotic, pro-survival, and proangiogenic therapeutic strategies. (Trends Cardiovasc Med 2010;20:199–203) © *2010 Elsevier Inc. All rights reserved.*

• Introduction

The tissue factor (TF) glycoprotein is the receptor for factor (F)VII/a and the primary initiator of the blood coagulation cascade (Giesen et al. 1999, Rauch et al. 2000). Due to alternative splicing processes, two naturally occurring TF protein isoforms are expressed in several cell types and tissues (Bogdanov et al. 2003; Table 1). Membrane-bound full-length (fl)TF is composed of an extracellular region (219 amino acids [AA]), a transmembrane domain (23 AA), and a 21-AA-long intracellular region (Bogdanov et al., 2003). flTF is a major source of procoagulant activity

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