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Can an ECG help prevent sudden death in young people?

Marcello Costantini[1], Massimo Trianni[2], Giuseppina De Benedittis[2], Cristina Tritto[2], Lorenzo Costantini[3], Luana Conte[1,4], Marco Greco[1,5], Michele Maffia[1,5,6], Michele De Benedetto[1]

[1] Interdisciplinary Laboratory of Applied Research in Medicine (DReAM), University of Salento, Lecce, Italy
[2] Cardiologia Territoriale - Distretto Socio Sanitario Lecce - ASL Lecce
[3] U.O. Cardiologia – P.O. Galatina-ASL Lecce
[4]Laboratory of Biomedical Physics and Environment, Department of Mathematics and Physics "E. De Giorgi", University of Salento, Lecce, Italy
[5]Laboratory of Physiology, Department of Biological and Environmental Sciences and Technologies, University of Salento, Lecce, Italy
[6]Laboratory of Clinical Proteomic, "Giovanni Paolo II" Hospital, ASL - Lecce, Italy

Corresponding author: Marcello Costantini
marcellocostantini9@gmail.com

Abstract
A wide spectrum of diseases or conditions (genetically based or acquired), in the presence of triggering elements, can lead to arrhythmic events, having sudden death as a common result. The substrate of fatal arrhythmia depends on age: over 35 years old it is mainly represented by the instability of coronary heart disease. Up to 35 years of age, the substrate consists mainly of electrical or structural alterations of the heart of a genetic nature the main of which are i) idiopathic hypertrophic cardiomyopathy ii) arrhythmogenic cardiomyopathy of the right ventricle iii) congenital syndrome of long QT iv) congenital syndrome of short QT;
v) Brugada syndrome. Each of these proarrhythmic genetic conditions has the prerogative of being able to be highlighted by an electrocardiogram: a simple and economical gesture that can lead directly to an important diagnosis, or at least make it suspected, addressing the subsequent evaluations. Formulating a diagnosis of this kind can minimize the risk of sudden death, through careful use of lifestyle advice, drugs, devices, procedures. It has been scientifically proved that identifying genetic conditions at risk of malignant arrhythmias in the athlete leads to a dramatic reduction in the risk of sudden death: on this basis, an electrocardiographic screening has become peremptory in many countries in order to be able to perform competitive sports (in Italy, for some years, also to be able to carry out non-competitive sports). Electrocardiographic screening should be considered for the entire youth population, regardless of participation in an organized sports activity program, as this can potentially mean saving young lives from sudden death.

Keywords: sudden death; electrocardiogram; hypertrophic cardiomyopathy; congenital long QT syndrome; Brugada's syndrome

Introduction

Sudden cardiac death (SCD) in young adults (<35 years) is an emotionally staggering event, not only for the victim's family but also for the community. Although the precise incidence of this catastrophic event is not exactly known around the world, in the USA it ranges between 0.8 and 8 deaths per 100,000/year (Vetter 2014, 688–97). As everywhere, even in Salento the SCD in young people is not a negligible event: the case of Lorenzo T., a 19-year-old male victim of SCD just as he had come out of a disco after a happy evening with friends, in which the autopsy examination revealed the presence of hypertrophic cardiomyopathy is perhaps the most sensational case, but it is only the tip of the iceberg. SCD is not a single disease, but the outcome of a wide spectrum of diseases or conditions in which a substrate (genetic or acquired) interacts with a series of physiological or pathophysiological factors (acute ischemia,

reperfusion, hyperadrenergic status, etc.) that modulate its arrhythmic propensity, in the presence of a triggering factor (Costantini 2019). This triad can lead to an intraventricular reentry (single or multiple), or result in post-potential triggered electrical activity, with the risk, in both cases, of producing a fatal arrhythmic accident. Such a paradigmatic sequence justifies most of the cases of sudden death, but the substrate is age-dependent: up to 35 years of age, the prevailing substrate is represented by electrical or structural alterations of the heart of genetic origin; above the age of 35, it is mostly represented by the consequences of a coronary heart disease (Costantini 2019). An early recognition of these arrhythmogenic conditions in the juvenile population could markedly reduce the risk of sudden death, as already evidenced in young athlete (Vetter 2014, 688–97). Below we will consider some of the characteristics related to the main hereditary proarrhythmic conditions.

Hypertrophic cardiomyopathy

It is a hereditary disease of the heart muscle, caused by mutations in the genes that encode sarcomere proteins (Pasquale et al. 2012, 10–17). The genetic abnormality results in a particular anatomical situation (myocardial hypertrophy, often asymmetric, sometimes monstrous; structural disorganization of the myofibrils, "disarray"; fibrosis) which determines a rather wide spectrum of functional and clinical alterations ranging from total asymptomaticity to myocardial ischemia, diastolic dysfunction, obstruction of left ventricular efflux, life-threatening arrhythmias and sudden death (Spirito, Quarta and Autore 2009, 1104–10). It is therefore a rather complex heart disease that has a high prevalence, estimated between 1/500 and 1/1000. The disease often remains undiagnosed. The phenotypic aspects include left ventricular hypertrophy, sometimes marked, often asymmetric, cavity of the left ventricle not dilated, conserved systolic function, dynamic obstruction in the left ventricular outflow tract (in 20% of cases), electrocardiographic changes, arrhythmias, sudden death (Spirito, Quarta and Autore 2009, 1104–10). The clinical course is extremely variable. Many patients have normal life spans, remaining completely asymptomatic. Others develop heart failure, others die suddenly, often at a young age and without any warning symptoms. Massive hypertrophy and disarray, together with fibrosis, constitute a favorable substrate for several arrhythmogenic mechanisms that can be favored by intercurrent modulating factors (autonomous nerve factors, emotional stress, acute myocardial ischemia, electrolyte disturbances, drugs), with arrhythmias of various kinds, up to malignant ventricular forms. Usually the disease is suspected for the presence of a pathological ECG, with QRS alterations (often Q of necrotic aspect) and ventricular repolarization alterations (negative T waves in anteriorior and/or lateral and/or inferior leads, figure1) , during a screening for sports activity or for family history of hypertrophic cardiomyopathy or less often for symptoms (Migliore et al. 2012, 529–38). The diagnosis is then confirmed by an echocardiogram. In a minority of cases, a clearly pathological ECG is not followed by the presence of left ventricular hypertrophy at the echocardiogram (Spirito, Quarta and Autore 2009, 1104–10). In such cases (phenotypically incomplete) cardiac nuclear magnetic resonance may help.

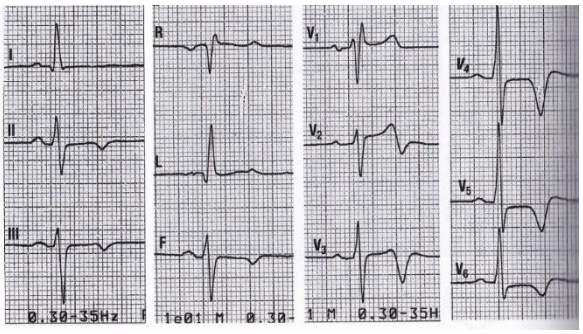

Figure 1. Classical ECG pattern in HCM

Arrhythmogenic Right Ventricular Cardiomyopathy/ Dysplasia (ARVD)

ARVD is a progressive disease of myocardial tissue clinically characterized by ventricular arrhythmias, heart failure, sudden death (Domenico Corrado and Thiene 2006, 1634–37). The distinctive character of the disease is the replacement of cardiomyocytes with fibro-adipose tissue with a particular structural and functional involvement of the right ventricle (but in more than half of the patients the left ventricle is also affected). In most cases it is a genetically determined inherited disorder with

autosomal dominant transmission caused by mutations in the genes encoding desmosomal proteins, plakoglobin, desmoplakina, plakofilina-2, desmoglein-2 and desmocollin-2. The disease has a variable prevalence from 1/1000 to 1/5000 subjects in the general population and represents one of the main causes of sudden death in athletes and young people. Clinical manifestations generally develop between the second and fourth decades of life and include palpitations, syncope, ventricular tachycardia, sudden death (D. Corrado et al. 2009, 1097–1103). The morphological progression of the disease can lead to right or biventricular heart failure. In basal ECG, abnormalities of various kinds are found in about 90% of cases, very useful both for making the diagnosis and for establishing the prognosis and the evolution of the disease (figure 2): P wave accentuated; prolonged PR tract; extension of the QRS duration; right bundle branch block of varying degrees; presence of epsilon wave (small positive low voltage deflection in the final part of the QRS or at the beginning of the ST segment in the right precordials: it expresses delayed activation of portions of the right ventricle and corresponds to the late recordable potentials with high resolution electrocardiography); negative T waves in the right precordial leads (D. Corrado et al. 2009, 1097–1103). The arrhythmic spectrum of the disease is variegated and ranges from ventricular, isolated or repetitive extrasystoles, sustained ventricular tachycardia, and ventricular fibrillation.

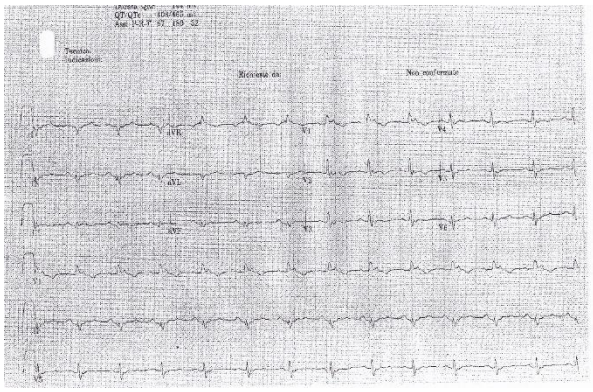

Figure 2. ECG of a subject with ARVD. Note the altered QRS, with right bundle branch block and probable epsilon wave in V1

Brugada's syndrome

It is a genetically based electrical disease that involves risk of sudden death (Brugada and Brugada 1992, 1391–96). The incidence of the condition is currently estimated around 5 cases per 10.000 (Antzelevitch et al. 2005, 429–40). Affected subjects have a defect in the gene that codes for the sodium channel: its function is depressed, leading to a transmural electrical inhomogeneity, which creates a voltage gradient between the epicardium and the endocardium. It is likely that the voltage gradient is due to an early repolarization in epicardial cells of the right ventricle: the genetic defect produces in these cells a deficit of sodium current during the phase 1 of the action potential, altering the balance between depolarizing and repolarizing forces, creating a strong predominance of the potassium repolarizing current (Ito). Since the subendocardial cells have a lower concentration of Ito channels, a clear difference in silhouette of the action potential between endocardium and epicardium takes place, producing voltage gradient, which favors the possibility of re-entry triggering in phase 2.
Classically, three different types of Brugada's patterns are derived from the basic ECG (Priori and Cerrone 2009, 1086–96):

- •Type 1: in this case it is evident a convex elevation of the ST tract (coved type) of at least 2 mm with evident J wave and negative T wave in V1 and / or V2 (figure 3);
- •Type 2: the ECG shows at V1 and / or V2 an elevation of the point J of at least 2 mm and an elevation of the ST segment of at least 1 mm and a positive or diphasic T wave;
- •Type3: there is an elevation of the point J of less than 2 mm and a saddle back elevation of ST of less than 1 mm with a positive T wave in V1 and/or V2.

Experts agree that only type 1 is diagnostic of syndrome (or pattern). Pattern 1, if not present in basal, can be disclosed by a pharmacological test, with flecainide or ajmaline, intravenously injected with great caution and under strict electrocardiographic and clinical control. Sometimes the typical ECG alteration in right precordial derivations is absent or just mentioned but appears or becomes more striking if the electrodes of the precordial right V1 and V2 are

moved higher (Priori and Cerrone 2009, 1086–96). The typical basal ECG aspect of the syndrome is not fixed, but it can suffer fluctuations (important to record ECG during fever). The sudden death is caused by a polymorphic ventricular arrhythmia and occurs especially during sleep or rest. Fever can be a factor of risk for malignant ventricular arrhythmias in affected subjects. The transmission of the condition is autosomal dominant with age penetrance and sex-dependent: clinical manifestations are more common in adult subjects and are 8 times more frequent in men than women. Ventricular fibrillation occurs at an average age of 41 ± 10 years, but can appear at any age, usually at rest or during sleep. Temperature, abuse of alcoholic beverages and large meals can reveal the ST segment elevation, with type 1 –appearance and predispose to the onset of malignant arrhythmias. Pharmacological treatments with drugs that produce an accentuation of the defect of the ion channels (such as sodium-blockers antiarrhythmics), may represent a major risk in affected patients (Priori and Cerrone 2009, 1086–96).

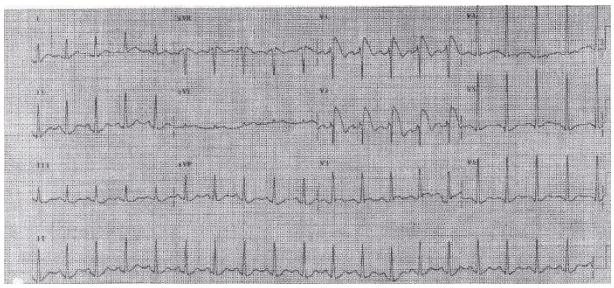

Figure 3. Classical Brugada's-Type 1 pattern

Congenital long QT syndrome (LQTS)

Genetically transmitted electrical disease, characterized by prolonged QT and high risk of malignant ventricular arrhythmias (torsade de pointes, which sometimes degenerates into ventricular fibrillation). Most arrhythmias arise in conditions of mental or physical stress. The beta-blocker therapy markedly reduces the mortality of this condition and therefore every effort is necessary for the diagnosis to be made in the affected persons (Schwartz, Periti and Malliani 1975, 378–90). The genes involved are numerous, and hence the multiplicity of the varieties already described , but the most frequent forms of LQTS are the first three varieties: the first two (LQTS 1 and LQTS 2) derive from a genetic defect of potassium channels with loss of function; variety 3 (LQTS 3) derives from a genetic defect of the sodium channel, with a gain in function (Schwartz and Crotti 2009, 1071–78).

PJ Schwartz proposed a very useful risk score for the cardiologist in diagnostic judgment (PJS score), which is based on the following elements: ECG and documented arrhythmias, medical history and family history (Schwartz and Crotti 2009, 1071–78). A PJS score ≥3.5 can be associated with a higher probability of disease presence. With a score between 1 to 3, the probability that the disease is present in the patient is intermediate, while a PJS score ≤1 can be associated with a low probability of LQTS. Often, a careful analysis of the ECG allows to differentiate between the various types of LQTS (at least among the main ones), therefore it is sometime possible to identify the genotype with a simple electrocardiogram (Schwartz and Crotti 2009, 1071–78). Thus, in type 1 a "homogeneous" elongation of the QT is classical, with evidence of very broad base T waves. In type 2 the presence of "notched" T in many derivations is characteristic (figure 4). In type 3 (the one that originates from an exalted sodium current and that responds less to beta-blocking therapy) the late manifestation of the T wave is characteristic: it occurs late, after a long ST segment often quite isoelectric. The existence of gene-specific triggers of arrhythmic events, different in the various forms of congenital long QT, is demonstrated (Schwartz and Crotti 2009, 1071–78). Thus, subjects with LQT 1 are at higher risk of arrhythmias during exercise (especially during swimming). Subjects with LQT 2 are very sensitive to loud noises, especially during sleep. Subjects with LQT 3 are more at risk during sleep or rest.

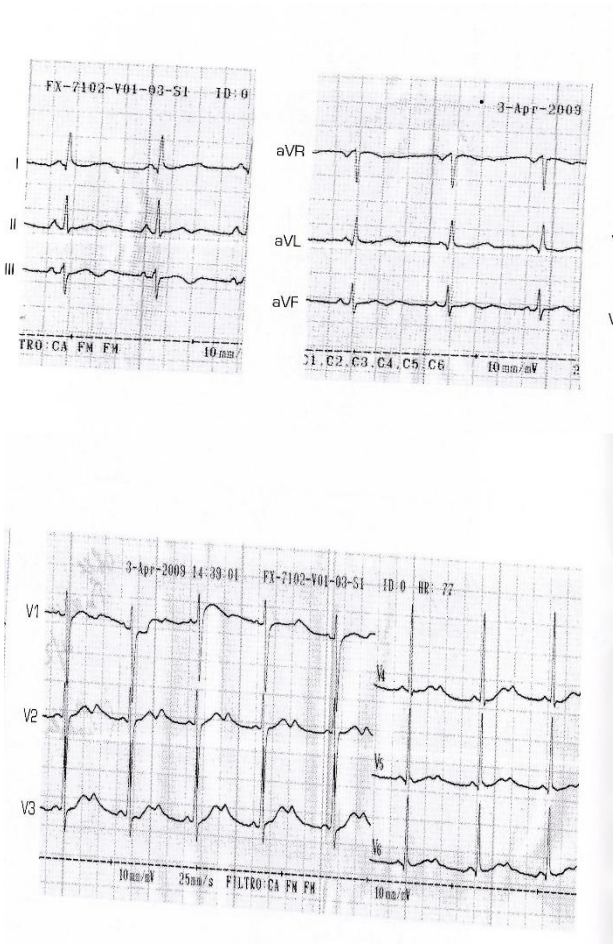

Figure 4. Type 2 congenital long QT syndrome

Short QT syndrome (SQTS)

Short QT syndrome is a genetically transmitted disease represented by the association between a very short QT to the ECG together with a propensity to develop atrial and ventricular tachyarrhythmias, in the absence of cardiac structural alterations (Gussak et al. 2000, 99–102). The mainstay of diagnosis of short QT syndrome is the 12-lead ECG: the diagnosis is made when duration of corrected QT is ≤340 ms (figure 5). Other features that may be seen on the ECG in short QT syndrome include tall, peaked T-waves and PR segment depression (Giustetto et al. 2006, 2440–47). The prevalence of SQTS in the population is likely around 0,1%. The disease appears to be associated with high lethality in all age groups, including children in early life. Criteria scientifically validated as independent risk factors for cardiac arrest are lacking, and therefore remains to be clearly defined what is the optimal primary prevention strategy in asymptomatic patients with this condition. No data are available to stratify the arrhythmic risk during competitive physical activity. Some reports show that quinidine is effective in prolonging the QTc interval and is likely to reduce arrhythmic events in these patients.

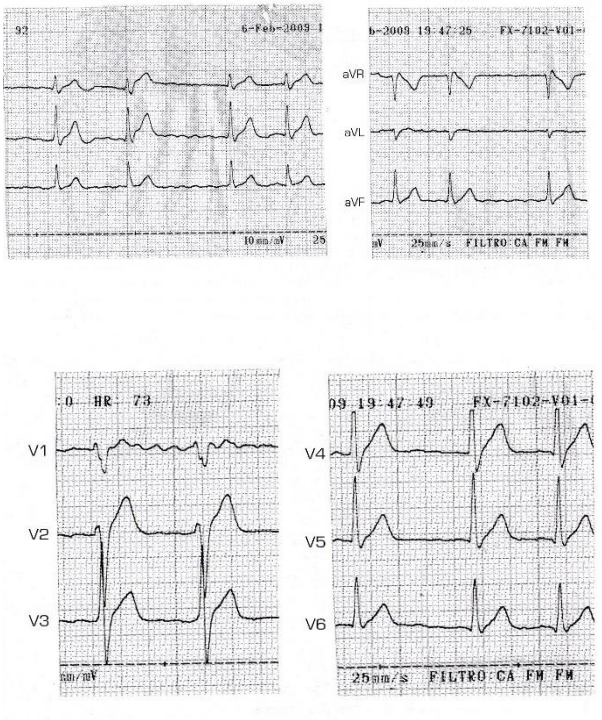

Figure 5. ECG of a subject with short QT and atrial fibrillation. Atrial arrhythmias are common in short QT syndrome.

All the conditions considered above have the prerogative of being able to be highlighted with an electrocardiogram: a simple and inexpensive gesture can therefore lead directly to the diagnosis or can make it suspect. Diagnostic assessment can minimize the risk of fatal events, through appropriate use of behavioral advice, drugs, devices, procedures. There is a scientific evidence that ECG screening identifies athletes who are harboring potentially serious arrhythmic events and that this strategy strongly reduces the incidence of SCD in competitive athlete (Domenico Corrado et al. 2003, 1959–63); for these reasons, ECG screening in athletes is endorsed by learned scientific and sporting organizations. Why then is a similar approach not extended to the entire youth population regardless of participation in an organized sports activity program? Something is indeed forgotten: although intense exercise in individuals

harboring quiescent cardiac pathology leads a 3-fold greater risk of SCD in elite athletes compared with non athletes, the majority of SCD in the young affect the general population because a lower incidence acts on a broader population (Domenico Corrado et al. 2003, 1959–63). In most countries, young people are not offered cardiac screening unless they are engaged in top-level competitions, but this is in contrast, both ethically and legally, with the fundamental principle of equality of all individuals. Perhaps, it is time to reflect on the ECG screening of the entire youth population, not only of the athletes. In the 1960s the World Health Organization (WHO) adopted scientific criteria for the evaluation of health screening programs (A.a.v.v. 1968, 318).

According to these criteria, a screening program is justified if:

1) the morbid condition to be identified is relevant from a public health point of view;
2) there is a proven efficacy test for the early identification of the morbid condition, to allow early treatment;
3) there are effective therapeutic measures for the morbid condition if diagnosed at an early stage;
4) there is evidence that such therapies, if started in the presymptomatic phase, improves the clinical course and the prognosis of the morbid condition.

We believe that all these criteria are met by an electrocardiographic screening in youth age and that also the cost-effective ratio would be advantageous (Domenico Corrado et al. 2011).

But a few important issues arise:

1) What about false negatives? Some congenital conditions at risk of sudden death are not accompanied by alterations in the basic electrocardiogram. Among these, we must mention the Catecholaminergic Polymorphic Ventricular Tachycardia, the congenital anomalies of coronary origin, the aortopathies. It should also be considered that even in the ECG-evident proarrhythmic conditions the diagnosis can escape due to the dynamic character of the ECG-changes, which may be elusive at the time of screening (Priori and Cerrone 2009, 1086–96; Schwartz and Crotti 2009, 1071–78).

2) What about false positives? The ECG is dynamic by nature: up to 7 years, T waves in the right precordials are physiologically negative; successively, they gradually positivize. When the T waves remain negative beyond V1 after the age of 14, is it necessary to question whether one is dealing with a juvenile pattern or ARVD (18). Furthermore, regular and long-term intensive exercise is associated with several electrical manifestations that reflect enlarged cardiac camber size and increase vagal tone (Chandra et al. 2014, 2028–34). To facilitate the interpretation of the ECG in athlete, the European Society of Cardiology has produced guidelines able to differentiate the normal ECG scheme belonging to the trained subject, from the one relative to a subject with an underlying heart disease, although a certain overlap can still be observed in some cases (Chandra et al. 2014, 2028–34).

In addition to these, other issues of non-negligible importance emerge, such as the amount of subjects considered positive at screening, who need further investigations or eventually therapeutic measures and follow-up , with relative costs and assumption of responsibility by the health system and operators. Last but not least, there is a subtle question regarding the psychological impact of screening: discovering an arrhythmic condition certainly has markedly positive aspects, but we should ask ourselves what psychological impact it could have on an asymptomatic individual and his family, learning from an unknown doctor that his heart is at risk of serious arrhythmias.

In conclusions, prevention of SCD in young people, athletes and not, remains a high priority for the medical community.

We have the task of overcoming the difficulties and defining the most appropriate strategies to reach such an ambitious goal.

Disclosure

The authors declare that do not have a conflict of interest and that do not have a financial relationship with any commercial entity that has an interest in the subject of this manuscript.

Contributors

All authors participated to review. All authors were involved in writing and revising the article prior to submission.

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