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Arrhythmogenic Right Ventricular Dysplasia and Sudden Cardiac Death in Croatians' Young Athletes in 25 Years

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A B S T R A C T

The paper deals with the sudden cardiac death during training in male athletes in Croatia. The data are a part of a retrospective study dealing with 67 sudden death due to physical activity in men in Croatia during 25 years: from January 1, 1986 to December 31, 2010. Two of them suddenly died during training due to malignant ventricular arrhythmia because of the arrhythmogenic right ventricular dysplasia. First was a short trails runner aged 24, with no any previous physical discomforts, who suddenly collapsed and died during training. The second was a soccer player aged 13, with no any previous physical discomfort, who suddenly collapsed and died during training. A sudden cardiac death due to physical exercise in young athletes in Croatia suffered of arrhythmogenic right ventricular dysplasia reached 0.07/100.000 yearly (p=0.00000), in all young athletes suffered of heart diseases reached 0.19/100 000 (p=0.00005), and in the total male population aged 15–40 engaged in sports and recreational physical exercise: 0.71/100.0000 (p=0.00001).

Key words: *athletes, training, arrhythmogenic right ventricular dysplasia, sudden cardiac death*

Introduction

In healthy young persons health-related events due to physical exercise are very rare as is sudden death[1–7]. In those young persons who died suddenly due or immediately after physical exercise, the most common reasons are cardiovascular diseases. Among those diseases, arrhythmogenic right ventricular dysplasia (ARVD) or arrhythmogenic right ventricular cardiomyopathy by some authors reached 2%–5% of all sudden deaths in young persons, with a higher death rate during exercise[8].

ARVD is primary myocardial diseases caused of genetic defect of desmosomes, i.e. area in myocardium which links together the myocardial myofibrils. Those desmosomes are composed of several proteins. In this disease we are facing with changes of cell adhesion proteins: plakoglobulin, plakophilin-2, desmoglein-2, desmoplakin[9–11]. Many of those proteins can have harmful mutations. ARVD is very often biventricular disease involving the right ventricular myocardium and typically the subepicardial region of the left ventricle characterized of myocyte vacuolization. It is replaced with fibro fatty tissue in the right ventricle leading to myocardial atrophy and with more fibrosis than fibro fatty infiltration in the left ventricle[8,12]. It could be connected with a high risk of ventricular instability and a malignant ventricular arrhythmias. Sudden cardiac death could be the only manifestation of the disease, especially in young athletes[8]. When the left ventricle is involved, a consequence could be a congestive heart failure.

The aim of this study is to analyze the course of the illness in young athletes died suddenly because of ARVD, during sport·s training in Croatia.

Sample and Methods

In a period of 25 years: from January 1,1986 to December 31, 2010, in Croatia seven sudden cardiac death due to physical exercise in young athletes were regis-

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tered. Two of them suffered of ARVD. Those data are part of a retrospective study dealing with 67 sudden and unexpected deaths due or immediately after sport or recreational exercise in persons of all ages in Croatia, collected from the whole population consisted of 4,500.000 persons. Seven of them were athletes and 60 were practicing recreative exercise. The deceased persons were found from the registry of Services of Forensic Medicine, Public Health Registry and Sport's clubs. The statistical difference was calculated using χ^2 test and Poison rates.

Results

Case 1

A male athlete aged 24, with no previous any physical discomforts, was admitted to the University Hospital in Zagreb during a heart arrest and resuscitation efforts. He was a short trails runner for years. This morning he was running due to training and suddenly collapsed and died after less than hundred meters. He was intubated and ventilated mechanically immediately by physician at the field, and after that he was resuscitated by a medical team of the Reanimation Unit. He was admitted to the regional University Hospital and resuscitated all the time during transport.

At the admittance he was unconscious, anisocoric pupils, with no respirations, no heared heart sounds, with central cyanosis, and with flat line on an ECG monitor all the time during long unsuccessful resuscitation.

The clinical diagnoses were: reanimatio facta, haemorrhagia cerebri suspecta, cardiomyopathia hypertophica suspecta, sanguinatio ex ore, ventilatio mechanica, implantatio electrostimulatori cordis facta, dissociatio electromechanica.

At autopsy, the size of the whole heart was 11×11×6.5 cm, the left ventricle wall reached 15 mm (normal finding is 11–12 mm), the right ventricle wall reached 4 mm (normal finding is 3–4 mm), both ventricles were dilated, with normal mitral, aortal, tricuspidal and pulmonary valves and no signs of coronary or aortal atherosclerosis.

Histological finding of the right ventrical wall showed abundant subepicardial accumulation of an adipose tissue with infiltration between myocardial bundles. The left ventricular wall was not infiltrated with the mentioned process. The finding of the lungs and of the brain showed acute oedema.

The autopsy diagnoses were: dysplasia arrhythmogenes ventriculi dextri cordis (as a cause of a lethal event), dilatatio cordis totius, oedema pulmonum et cerebri acutum, cyanosis universalis.

Case 2

A male athlete-soccer player aged 13, with no any previous physical discomfort, was suddenly collapsed and died during soccer training. He was resuscitated at the field by a coach and after that by a medical team of the Reanimation Unit, with no success.

At forensic medicine autopsy, the size of the whole heart was 10×10×5 cm, the left ventricle wall reached 10 mm, the right ventricle wall reached 3 mm, both ventricles were dilated, with normal mitral, aortal, tricuspidal and pulmonary valves and no signs of coronary or aortal atherosclerosis.

Histological finding of the myocardium showed abundant subepicardial accumulation of adipose and fibrosis tissues with segmental lymphocyte infiltration between bundles of both ventricles. The finding of the lungs and of the brain showed acute oedema.

The autopsy diagnoses were: dysplasia arrhythmogenes ventriculi dextri et ventriculi sinistri cordis (as a cause of a lethal event), oedema cerebri grave, oedema pulmonum, cyanosis universalis.

A sudden cardiac death due to physical exercise in young athletes in Croatia suffered of arrhythmogenic right ventricular dysplasia reached 0.07/100.000 yearly (p=0.00000), in all young athletes suffered of heart diseases reached 0.19/100 000 (p=0.00005), and in the total male population aged 15–40 engaged in sports and recreational physical exercise: 0.71/100.0000 (p=0.00001).

Discussion

Sport's activities have protecting effect on human organism. In athletes who died suddenly because of malignant heart arrhythmias due to training, the most common reasons for such events are cardiomyopathies, coronary anomalies and myocarditis[13,14]. Among cardiomyopathies, ARVD is very often a disease with no symptoms and reached 1:2.500 to 1:5.000 of all sudden deaths during exercise in young athletes, which is lower than in our study: 2/7. Most of those persons suffering of ARVD have involved both ventricles. In our cases, in the first the right ventricle was involved, and in the second both ventricles were involved. The first symptoms could be ventricular arrhythmias and/or conduction disturbances: in about 75% of those persons the first manifestation of the disease could be sudden cardiac death due to malignant ventricular arrhythmia[8,13–19], as were cases in two deceased athletes in our study.

The right ventricular wall is relatively thin, and that is why in ARVD a subepicardial process is sometimes difficult to diagnose in vivo. Pathological anatomy finding depends on the stage of the disease and show changes in the myocardium including thinning in the some areas of the right ventricle with fibro-fatty changes[8,12,14,16,19–22]. But we are facing very often with left ventricular subepicardial involvement. Sometimes we are facing with an aneurysm of the right ventricle in a small number of these cases. Microscopic changes in myocardium showed fatty or fibro fatty replacement of the myocardium (»moth-eaten«) with inflammatory destruction of the normal myocardial cells, sometimes with inflammation of lymphocytes and macrophages and sometimes with signs of myocyte necrosis.

The aetiology of ARVD is unknown. We are facing very often with a presence with imflammatory myocardial infiltrates and progression from myocarditis to arrhythmogenic right ventricular dysplasia, and also with the discovery of the mutation in genes related to desmosomes. The is an open question: could it be an inflammatory process modified by genetic influence in desmosome-related proteins[8]? This is an autosomal dominant hereditary disease in almost 50% of all cases with variable penetrance[9], and could be located to various chromosomes, the first chromosomal locus 14q23-q24 was published 17 years ago[9,10].

When could we diagnose ARVD? This disease is uncommon under ten years of age, and rare appeared in the elderly[20–22]. The major criteria for ARVD are: 1. global or regional dysfunction and structural alterations (severe dilatation and reduction of right ventricular – RV ejection fraction with no or only mild left ventricular impairment; localized RV aneurysms: akinetic or dyskinetic areas with diastolic bulging; severe segmental dilatation of the RV; 2. tissue characterization of wall (fibro fatty replacement of myocardium on endomyocardial biopsy); 3. repolarization abnormalities (inverted T waves in right precordial leads: V_1, V_2, and V_3 or beyond in individuals >14 years of age in the absence of complete right bundle branch block – RBBB QRS ≥120 ms); 4. depolarization/conduction abnormalities (epsilon waves or localized prolongation >110 ms of the QRS complex in right precordial leads V_1 to V_3); 5. arrhythmias (nonsustained or sustained VT of left bundle branch – LBBB morphology with superior axis (negative or indeterminate QRS in leads II, III, and aVF and positive in lead aVL); 6. family history (familial disease confirmed at necropsy or surgery). The minor criteria are: 1. global or regional dysfunction and structural alterations (mild global RV dilatation and/or ejection fraction reduction with normal LV; mild segmental dilatation of the RV; regional RV hypokinesia); 2. tissue characterization of wall (residual myocytes 60% to 75% by morphometric analysis or 50% to 65% if estimated, with fibrous replacement of the RV free wall myocardium in ≥1 sample, with or without fatty replacement of tissue on endomyocardial biopsy); 3. repolarization abnormalities (inverted T waves in right precordial leads V_2 and V_3 – people age >12 years, in absence of RBBB; inverted T waves in leads V_1 and V_2 in individuals >14 years of age in the absence of complete RBBB, or in V_4, V_5, or V_6; inverted T waves in leads V_1, V_2, V_3, and V_4 in individuals >14 years of age in the presence of complete RBBB; 4. depolarization/conduction abnormalities (late potentials by signal averaged electrocardiogram in ≥1 of 3 parameters in the absence of a QRS duration of ≥110 ms on the standard ECG; filtered QRS duration ≥114 ms; duration of terminal QRS <40 μV – low-amplitude signal duration ≥38 ms; root-mean-square voltage of terminal 40 ms ≤20 μV; terminal activation duration of QRS ≥55 ms measured from the nadir of the S wave to the end of the QRS, including R´, in V_1, V_2, or V_3, in the absence of complete RBBB; 5. arrhythmias (LBBB--type ventricular tachycardia – VT sustained and nonsustained by ECG, Holter, exercise; frequent VPB >1000 *per* 24 hours – Holter; nonsustained or sustained VT of RV outflow configuration, LBBB morphology with inferior axis (positive QRS in leads II, III, and aVF and negative in lead aVL) or of unknown axis; >500 ventricular premature beats *per* 24 hours – Holter; 6. family history of premature sudden death <35 years of age, due to suspected ARVD; familial history clinical diagnosis based on present criteria; history of ARVD in a first-degree relative in whom it is not possible or practical to determine whether the family member meets current Task Force criteria; premature sudden death <35 years of age due to suspected ARVD in a first-degree relative; ARVD confirmed pathologically or by current Task Force criteria in second-degree relative.

By the Task Force criteria of this disease[20,21], the following criteria are necessary for definitive diagnosis of this disease: two major, or one major plus two minor, or 4 minor criteria; the borderline diagnosis consists of one major plus one minor, or three minor criteria; the possible diagnosis consists one major, or two minor criteria from different categories. The ECG indicating ARVD shows an epsilon wave – a terminal notch in the QRS complex due to slowed i.v. conduction[10]. This wave is presented in only 33–50% of patients suffering of ARV[23,24]. In our two presented young athletes we cannot use the mentioned criteria, because they were without symptoms and died suddenly at the field during training.

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ARITMOGENA DISPLAZIJA DESNE KLIJETKE I NAGLA KARDIJALNA SMRT U MLADIH SPORTAŠA U HRVATSKOJ U 25-GODIŠNJEM RAZDOBLJU

S A Ž E T A K

Prikazane su nagle kardijalne smrti za vrijeme treninga u Hrvatskoj, kao dio retrospektivnog istraživanja u koje su uključeni podaci 67 muškaraca naglo i neočekivano umrlih za vrijeme tjelovježbe u Hrvatskoj tijekom 25 godina: od 1. siječnja 1986. do 31. prosinca 2010. g. Dva su umrla tijekom treninga, zbog maligne aritmije srca tijekom aritmogene displazije desne klijetke. U mladih sportaša aritmogena displazija desne klijetke često je asimptomatska i njeno jedino ispoljavanje može biti nagla smrt. Prvi bio je trkač kratkih pruga dobi 24 g., nije imao somatskih tegoba, a naglo je kolabirao i umro za vrijeme treninga. Drugi bio je nogometaš kadet dobi 13 g., nije imao somatskih tegoba, a naglo je kolabirao i umro za vrijeme treninga. U obojice svi su reanimacijski postupci bili neuspješni. U Hrvatskoj nagla smrt zbog aritmogene displazije desne klijetke iznosi 0,07/100 000 (p=0,00000), u svih mladih sportaša koji su bolovali od bolesti srca iznosi 0,19/100 000 (p=0,00005), dok u ukupnoj populaciji muškaraca dobi 15–40 g. koji su uključeni u takmičarsku ili rekreacijsku tjelovježbu iznosi 0,71/100 000 godišnje (p=0,00001).