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CICLO 29°

NON-ISCHEMIC LEFT VENTRICULAR SCAR:

AN EMERGING CAUSE OF VENTRICULAR ARRHYTHMIAS AND SUDDEN

DEATH IN THE YOUNG AND ATHLETE.

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ABSTRACT

BACKGROUND:. The clinical relevance of isolated non-ischemic left-ventricular (LV) scar as a cause of ventricular arrhythmias and sudden death in the young and athlete remains to be established. Contrast-enhanced cardiac magnetic resonance (CE-CMR) is increasingly used in the clinical work-up of athletes with apparently idiopathic ventricular arrhythmias (VA) and can reveal LV scar in the form of late gadolinium enhancement (LGE).

AIMS: we aimed to: 1) evaluate the incidence and causes (with particular reference to non-ischemic LV scar) of out-of-hospital cardiac arrest (OHCA) in people 1-40 year-old in the Padua province in the modern era; 2) assess the clinical profile and outcome of athletes referred to our Institution for non-ischemic LV scar as suggested by LGE at CE-CMR, which was performed for evaluation of apparently idiopathic VA and/or ECG abnormalities; 3) evaluate whether a strategy consisting of 24-hours 12-leads ambulatory ECG monitoring as first-line investigation and CE-CMR as second line investigation may improve our ability to identify concealed LV scar in apparently healthy athletes.

METHODS: we performed three different studies: 1) we recorded all cases of OHCA which occurred during the period 2011-2015. The study population included all residents in the province of Padua 1-40 year-old who suffered OHCA, either resuscitated or not, of presumed cardiovascular origin. The cause of OHCA was ascertained clinically in survivors and at postmortem investigation in victims of sudden death; 2) we compared the clinical profile and outcome of 35 athletes with VA and isolated non-ischemic (subepicardial/midmyocardial) LGE on CE-CMR suggesting myocardial scar with 38 athletes with VA and no LGE and 40 healthy control athletes; 3) we offered a 12-leads 24-hours ambulatory ECG monitoring to apparently healthy athletes ≥16 year-old, who performed at least 6 hours of physical exercise per week and who have been considered eligible at preparticipation screening within 1 year. Athletes were selected to undergo CE-CMR if they showed >29 premature

ventricular beats (PVBs) of “uncommon morphology” (i.e. excluding those with a morphology suggestive of right ventricular outflow tract or fascicular origin) or repetitive VA (excluding isolated couplets with a morphology suggestive of right ventricular outflow tract origin).

RESULTS: the main results for each study were: 1) the incidence of OHCA in the Padua province was 3.5/100.000 residents/year and was significantly lower among screened athletes than among non-athletes (1.1/100.000/year vs. 3.9/100.000/year, p<0,001). A final diagnosis was reached in 40 (83%) subjects while in 8 (17%) victims of sudden death the autopsy was not performed. The most frequent diagnosis were coronary artery atherosclerosis (23%) and structurally normal heart (23%) while cardiomyopathies accounted for 10% of cases. The most frequent cardiomyopathy (3 of 7 cases) was the non-ischemic LV scar; 2) a “stria” LGE pattern with subepicardial/midmyocardial distribution, mostly involving the lateral LV wall, was found in 27 (77%) of athletes with VA versus 0 controls (p<0.001). All athletes with “stria” LGE pattern showed VA with a predominant right-bundle-branch-block morphology (suggesting LV origin) but only 5/27 (19%) showed hypokinesis of the lateral LV wall at echocardiography. During a follow-up of 38±25 months, 6/27 (22%) athletes with a “stria” LGE pattern experienced major arrhythmic events (including 1 sudden death) compared with none of athletes with no or LGE-“spotty” pattern; 3) PVBs were rare in apparently healthy athletes (median 1/day) and their number and complexity significantly correlated with age. The prevalence of frequent or repetitive PVBs with “uncommon” morphology was 28/384 (7.3%) apparently healthy. athletes. In this group, 3/28 (11%) showed non-ischemic LV scar at CE-CMR.

CONCLUSIONS: the non-ischemic LV scar with a “stria” pattern may be associated with life-threatening VA and sudden death in the young athlete and cannot be simply dismissed as a sign of a previous healed myocarditis. Because of its subepicardial/midmyocardial location, the LV scar is often undetectable by echocardiography, and athletes with PVBs with right-bundle-branch-block morphology, particularly if exercise-induced or associated with ECG abnormalities, should undergo CE-CMR to exclude an underlying pathological myocardial substrate.

Abbreviations list

1.ARVC=arrhythmogenic right ventricular cardiomyopathy

2.CE-CMR=contrast-enhanced cardiac magnetic resonance

3.HCM=hypertrophic cardiomyopathy

4.LBBB=left bundle branch block

5.LGE=late gadolinium enhancement

6.LV=left ventricle

7.OHCA=out-of-hospital cardiac arrest

8.PVBs=premature ventricular beats

9.RBBB=right bundle branch block

10.SD=sudden death

11.VA=ventricular arrhythmias

INTRODUCTION

The issue of sudden death in the athletes

Incidence

The risk of sudden death (SD) among athletes or during sports activity varies in the different series reported in the literature[1-27]. It generally increases with age and is greater in men. In apparently healthy adults (>35 years), joggers or marathon racers, the estimated rate of SD ranges from 1:15,000 to 1:50,000/year. In comparison, a significantly lower incidence of fatal events have been reported in young athletes (≤35 years), in the range of 0.5-1/100,000/year (Table 1). Van Camp et al. in a nationally based survey estimated the prevalence of SD in high school and college athletes in the United States to be 0.4 per 100,000 athletes per year between 1983 and 1993[28]. Maron et al. found a prevalence of SD in high school athletes from Minnesota (age 12 to 19 years, mean 16) over a 26-years study period of 0.7/100.000/year[23]. In contrast, Harmon et al. reported a higher (2.28/100.000/year) incidence of SD among athletes of the National Collegiate Athletic Association [14]. A prospective study in the Veneto Region of Italy reported an incidence of SD of 2.3 (2.62 in males and 1.07 in females) per 100.000 athletes per year from all causes, and of 2.1 per 100.000 athletes per year from cardiovascular diseases[1]. The different SD rate found in different studies may be explained by a variety of factors, including the age range, the proportion of men, the estimation of the denominator and the methodology of data collection (prospective collection vs. retrospective analysis of data from public media reports and insurance claims). To this regard Harmon et al. found that only 56% of SD cases would have been identified relying on media reports (including internet) only[14]. The risk of SD in athletes increases with age and is greater in men (Table 1). A recent French study reported an incidence of SD during moderate or vigorous exercise of 1/100.000/year among males and of 0.05/100.000/year among females[29].

Table 1. Main studies reporting the incidence of cardiac arrest/sudden death in the young and/or during sports activity.

Ref.	Study period	Region	Population	Results
Maron, JACC 1998	1985/1986- 1996/1997	Minnesota, USA	651.695 High School athletes 13-19 year-old	SD among athletes during competition or training: 0.46/100.000/yr.
Corrado, JACC 2003	1979-1999	Veneto, Italia	1.386.600 people 12-35 year-old 112.970 athletes 12-35 year-old	SD in the general population: 0.9/100.000/yr. SD among athletes: 2.3/100.000/yr.
Gerein, AEM 2006	1991-2002	Ontario, Canada	500.000 people 0-18 year-old	OHCA: 9.1/100.000/yr.
Corrado, JAMA 2006	1979-2004	Veneto, Italia	2.938.730 athletes 12-35 year-old 33.205.370 non athletes 12-35 year-old	Cardiovascular SD among athletes: 1.9/100.000/yr. Cardiovascular SD among non-athletes: 0.79/100.000/yr. SD rate reduction after screening implementation: 89%
Ong, Resuscitation 2006	1992-2002	Ontario, Canada	800.000 people 0-19 year-old	OHCA: 5.97/100.000/yr.
Maron, Circulation 2009	2001-2006	USA	10.700.000 athletes 13-25 year-old	Cardiovascular SD among athletes: 0.61/100.000/yr.
Chugh, Heart Rhythm 2009	2002-2005	Multnomah County, Oregon, USA	Estimated number of children 0-14 year-old	SD rate 1-13 year-old : 7.5/100.000/yr. SD rate <1 yr.: 96.0/100.000/yr.
Atkins, Circulation 2009	2005-2007	Canada	Canadian population 0-19 year-old	OHCA rate <1 yr.: 72.71/100.000/yr. OHCA rate 1-11 year-old: 3.73/100.000/yr. OHCA rate 12-19 year-old: 6.73/100.000/yr. OHCA rate 0-19 year-old: 8.04/100.000/yr.
Solberg, Eur J Prev. Cardiol 2010	1990-1997	Norway	Norwegian population 15-34 year-old	Sports-related SD: 0.9/100.000/yr.
Holst, Heart Rhythm 2010	2000-2006	Denmark	Danish population 12-35 year-old	Sports-related SD: 1.21/100.000/yr. SD in the general population: 3.76/100.000/yr.
Donohoe, Resuscitation 2010	2003-2007	London, UK	4.000.000 people 0-35 year-old	OHCA rate 0-35 year-old: 19.3/100.000/yr. OHCA rate in the general population: 131.2/100.000/yr.
Park, Resuscitation 2010	2006-2007	South Korea	South Korean population 0-20 year-old	OHCA rate <1 yr.: 67.1/100.000/yr. OHCA rate 1-11 year-old : 2.5/100.000/yr. OHCA rate 12-20 year-old: 3.5/100.000/yr. OHCA rate 0-20 year-old: 4.2/100.000/yr.

Deasy, Resuscitation 2010	1999-2007	Melbourne, Australia	810.400 people 0-16 year-old	OHCA rate: 3/100.000/yr.
Harmon, Circulation 2011	2004-2008	USA	1.969.663 athletes/year 17-23 year-old	Cardiovascular SD among athletes: 2.28/100.000/yr.
Winkel, Eur Heart J 2011	2000-2006	Denmark	2.380.000 people 1-35year-old	Cardiovascular SD rate: 2.8/100.000/yr.
Margey, Europace 2011	2005-2007	Ireland	Irish population 15-35 year-old	Cardiovascular SD rate: 2.85/100.000/yr.
Eckart, JACC 2011	1998-2008	US Military training base	US Military recruits	SD rate <20 year-old: 3.3/100.000/yr. SD rate >50 year-old: 106/100.000/yr.
Meyer, Circulation 2012	1980-2009	King County, Washington	620.000 people 0-35 year-old	Overall OHCA rate : 2.28/100.000/yr. OHCA rate 0-2 year-old: 2.1/100.000/yr. OHCA rate 3-13 year-old: 0.61/100.000/yr. OHCA rate 14-24 year-old: 1.44/100.000/yr. OHCA rate 25-35 year-old: 4.40/100.000/yr.
Roberts, JACC 2013	1993/1994- 2011/2012	Minnesota, USA	1.666.509 High School athletes	Cardiovascular SD among athletes: 0.24/100.000/yr.
Pilmer, Heart Rhythm 2013	2008	Ontario, Canada	6.602.680 people 2-40 year-old	Cardiovascular SD rate 2-18 year-old: 0.7/100.000/yr. Cardiovascular SD rate 19-29 year-old: 2.4/100.000/yr. Cardiovascular SD rate 30-40 year-old: 5.3/100.000/yr.
Berdowsky, Eur Heart J 2013	2006-2008	North Holland	2.400.000 people 10-90 year-old 1.000.000 people 10-35 year-old	Exercise related OHCA during the study period: 5.7% Exercise related OHCA rate 10-90 year-old: 2.1/100.000/yr. Exercise related OHCA rate 10-35 year-old: 0.3/100.000/yr. At rest OHCA rate 10-90 year-old: 35.5/100.000/yr. At rest OHCA rate 10-35 year-old: 2.8/100.000/yr.
Maron, Heart Rhythm 2013	1986-2011	Minnesota, USA	1.930.504 High school athletes	SD rate among athletes: 0.7/100.000/yr.
Risgaard, Circulation 2014	2007-2009	Denmark	3.470.000 people 1-49 year-old	Overall cardiovascular SD rate: 8.6/100.000/yr. Cardiovascular SD rate: 31-49 year-old: 21.7/100.000/yr. Cardiovascular SD rate: 1-35 year-old: 2.3/100.000/yr.
Pilmer, Heart Rhythm 2014	2005-2009	Ontario, Canada	14.893.860 people 1-19 year-old	Cardiovascular SD rate 1-2 year-old: 3.1/100.000/yr. Cardiovascular SD rate 2-4 year-old: 1.3/100.000/yr. Cardiovascular SD rate 5-9 year-old: 0.4/100.000/yr. Cardiovascular SD rate 10-14 year-old: 0.5/100.000/yr. Cardiovascular SD rate 15-19 year-old: 1.0/100.000/yr.

Harmon, Circulation 2015	2003-2013	USA	National Collegiate Athletic Association 17-24 year-old	SD in the athletes: 1.9/100.000/yr SD in male athletes: 2.6/100.000/yr SD in female athletes: 0.8/100.000/yr SD in black athletes: 4.7/100.000/yr SD in white athletes: 1.5/100.000/yr
Marijon, Circulation 2015	2002-2013	Portland Oregon, USA	679.348 people 35-65 year-old	Exercise-related OHCA: 2.2/100.000/yr (5% total) Relative risk in men vs. women = 18.7
Bohm, Eur J Prev Cardiol 2016	2012-2014	Germany	Exercise-related SD 10-79 year-old	SD in sports participants ≥18 year-old = 0.12/100.000/yr SD in male: 0.16/100.000/yr SD in female: 0.006/100.000/yr
Grani, Eur J Prev Cardiol 2016	1999-2010	Switzerland	Exercise-related SD 10-39 year-old	Competitive athletes: 0.9/100.000/yr Recreational athletes: 0.5/100.000/y

OHCA= out-of-hospital cardiac arrest, SD= sudden death

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The striking male predominance (male to female ratio up to 10:1) of SD in athletes has been related to the higher participation rate of male compared with female in competitive sports, the more intensive training load and level of athletic achievement of males, and the greater prevalence and/or phenotypic expression in young males of cardiac diseases at risk of arrhythmic cardiac arrest, such as cardiomyopathies and premature coronary artery disease.

Causes

Atherosclerotic coronary artery disease accounts for the vast majority of fatalities in older athletes (>35 years), while the most common causes of SD in younger athletes are genetic or congenital cardiovascular diseases, including cardiomyopathies and coronary artery anomalies (Table 2). Hypertrophic cardiomyopathy (HCM) has been reported to account for more than one third of fatal cases in the USA [28, 30], and arrhythmogenic right ventricular cardiomyopathy (ARVC) for approximately one fourth of cases in the Veneto Region of Italy [1, 3, 31]. A sizeable proportion of young people and athletes who die suddenly have no evidence of structural heart disease and the cause of their cardiac arrest in all likelihood is related to a primary electrical heart disease such as inherited cardiac ion channel defects (channelopathies), including long and short QT syndromes, Brugada syndrome and catecholaminergic polymorphic ventricular tachycardia [32]. Sudden death may also be caused by a non-arrhythmic mechanism-e.g., spontaneous aortic rupture complicating Marfan's syndrome or bicuspid aortic valve, as well as by diseases not related to the heart—e.g., bronchial asthma or rupture of a cerebral aneurysm. Blunt, non-penetrating and often innocently appearing blows to the precordium may trigger ventricular fibrillation without structural injury to ribs, sternum, or heart itself (*commotio cordis*)[33].

The risk-benefit ratio of physical exercise differs between adults and young competitive athletes because of the different nature of cardiovascular causes of death. Several epidemiologic studies have assessed the relationship between physical exercise and the risk of acute myocardial infarction/SD in the middle-aged/senior individuals engaged in leisure sports activity, in which

Table 2. Main studies reporting the cause of cardiac arrest/sudden death in the young and/or during sports activity.

Ref	Study period	Region	Population	Causes (shown if ≥5%)
Corrado, JACC 2003	1979-1999	Veneto, Italy	1.386.600 people 12-35 year-old 112.970 athletes 12-35 year-old	Cardiovascular SD: 86% CAD: 22% ARVC: 14% Myocarditis: 12% Mitral valve prolapse: 10% Conduction system disease: 10% HCM: 9% Aortic rupture: 5% Non cardiovascular SD: 14% Unexplained SD: 8%
Eckart, JACC 2004	1977-2001	US military training base	US military recruits	Cardiovascular SD: Coronary anomalies: 33% Myocarditis: 20% CAD: 16% HCM: 13%
Puranik, Heart Rhythm, 2005	1995-2004	East Sidney, Australia	2.500.000 people 5-35 year-old	Cardiovascular SD: 56% Structurally normal heart: 29% CAD: 25% Myocarditis: 12% HCM: 6% Aortic dissection: 5%
Corrado, JAMA 2006	1979-2004	Veneto, Italia	2.938.730 athletes 12-35 year-old 33.205.370 non athletes 12-35 year-old	Structural cardiovascular SD among athletes: Cardiomyopathy: 25% CAD: 20% Coronary anomalies: 13% Myocarditis: 13% Mitral valve prolapse: 11% Conduction system disease: 7% Structural cardiovascular SD among non athletes: Cardiomyopathy: 31% CAD: 20% Myocarditis: 15% Conduction system disease: 9%

				Mitral valve prolapse: 7% Coronary anomalies: 5%
Ong, Resuscitation 2006	1992-2002	Ontario, Canada	800.000 people 0-19 year-old	Cardiovascular cardiac arrest: 19% Of those: Structurally normal heart: 7%
Maron, Circulation, 2009	2001-2006	USA	10.700.000 athletes 13-25 year-old	Cardiovascular SD: Unexplained: 34% HCM: 24% Coronary anomalies: 11% Possible HCM: 5%
De Noronha, Heart, 2009	1996-2008	United Kingdom	Athletes who died suddenly	Cardiovascular SD: Structurally normal heart: 23% Idiopatic LV hypertrophy: 31% ARVC: 14% HCM: 11% Idiopatic LV fibrosis: 6% Coronary anomalies: 5%
Park, Resuscitation, 2010	2006-2007	South Korea	South Korean population 0-20 year-old	Cardiovascular cardiac arrest: 31%
Winkel, Eur Heart J 2011	2000-2006	Denmark	2.380.000 people 1-35 year-old	Cardiovascular SD: Unexplained: 43% CAD: 13% Myocarditis: 7% Aortic dissection: 7% HCM: 6% Idiopatic LV fibrosis: 6% ARVC: 5%
Eckart, JACC 2011	1998-2008	US military training base	US military recruits	Cardiovascular SD <35 year-old: Unexplained: 41% CAD: 23% HCM: 13% Myocarditis: 6% Dilated cardiomyopathy: 5% Cardiovascular SD>35 year-old: Unexplained: 11% CAD: 73%

Margey, Eur Heart J 2011	2005-2007	Ireland	Irish population 15-35 year-old	Cardiovascular SD: Structurally normal heart: 26% CAD: 20% HCM: 14% Congenital heart diease: 9% LV hypertrophy: 10% Myocarditis: 6%
Meyer Circulation, 2012	1980-2009	King County, Washington	620.000 people 0-35 year-old	Cardiac arrest of cardiovascular origin 0-35 year-old Primary arrhythmia: 22% Cardiomyopathy: 19% CAD: 29% Congenital heart disease: 15% Cardiac arrest of cardiovascular origin 0-2 year-old: Congenital heart disease: 84% Primary arrhythmia: 8% Cardiac arrest of cardiovascular origin 3-13 year-old: Congenital heart disease: 21% HCM: 18% Long QT syndrome: 14% Primary arrhythmia: 11% Myocarditis: 11% Mitral valve prolapse: 7% Cardiac arrest of cardiovascular origin 14-24 year-old: Congenital heart disease: 23% Structurally normal heart: 23% Dilated cardiomyopaty: 14% Long QT syndrome: 8% Cardiac arrest of cardiovascular origin 25-35 year-old: CAD: 43% Structurally normal heart: 14% Dilated cardiomyopathy: 11%
Pilmer, Heart Rhythm, 2013	2008	Ontario, Canada	6.602.680 people 2-40 year-old	Non-ischemic cardiovascular SD: CMD: 35% HCM:17% Myocarditis: 13% Aortic dissection: 13%

				Cardiac tamponade: 7%
Suarez-Mier, Forensic Sc Int 2013	1995-2010	Spain	SD victims who underwent autopsy	Cardiovascular SD: CAD: 51% Unexplained: 11% ARVC: 8% HCM: 7%
Risgaard, Circulation 2014	2007-2009	Denmark	3.470.000 people 1-49 year-old	Cardiovascular SD: CAD: 36% Unexplained: 31% LV hypertrophy: 8% ARVC: 5%
Pilmer, Heart Rhythm 2014	2005-2009	Ontario, Canada	14.893.860 people 1-19 year-old	Cardiovascular SD: Myocarditis: 25% ARVC: 16% HCM: 14% Possible ARVC: 9% Other myocardial disease: 16%
Mitany, Circulation J 2014	2005-2009	Japan	Japanese children 6-12 year-old	Cardiac arrest of cardiovascular origin: Congenital heart disease: 17% Primary arrhythmia: 17% Long QT syndrome: 16% HCM: 14% Coronary anomalies: 12% WPW, CPVT: 7% Myocarditis: 5% Dilated cardiomyopathy: 5%
Young, Pediatrics 2014	1994-1997	Los Angeles e Orange County, California, US	US Children < 12 year-old	Cardiac arrest of cardiovascular origin: 8% Congenital heart disease: 5.5%
Harmon, Circulation AE 2014	2004-2008	US	National Collegiate Athletic Association 17-24 year-old	Cardiovascular SD: Unexplained 31% Coronary anomalies 14% Idiopatic LV hypetrophy: 8% Aortic dissection: 8% Myocarditis: 8% Dilated cardiomyopathy: 8% CAD: 5%

Bohm, Eur J Prev Cardiol 2016	2012-2014	Germany	10-79 year-old sports-related SD	Cardiovascular SD: 85% Unexplained: 38% CAD: 29% Considered CAD: 15% Myocarditis: 8% Non cardiovascular SD: 15%
Finocchiaro, J Am Coll Cardiol 2016	1994-2014	United Kingkdom	Athletes victims of SD referred to St. George's University of London Cardiac Pathology dpt.	Unexplained: 42% Idiopathic LV hypertrophy/fibrosis: 16% ARVC: 13% HCM: 6% Myocarditis: 5%
Grani, Eur J Prev Cardiol 2016	1999-2010	Switzerland	Exercise-related SD 10-39 year-old	CAD: 28% HCM: 14% Unexplained: 13% Valvular: 8% Coronary anomalies: 7% ARVC: 7% Idiopathic myocardial fibrosis: 7% Aortic dissection: 7% Dilated cardiomyopathy: 6%

ARVC= arrhythmogenic right ventricular cardiomyopathy, CAD=coronary artery disease; HCM=hypertrophic cardiomyopathy; LV=left ventricular; SD=sudden death; WPW=Wolff-Parkinson-White syndrome

exercise can be regarded as a "double-edged sword" [34-35]. The available evidence indicates that vigorous exercise acutely increases the incidence of both cardiac arrest and acute myocardial infarction in those who do not exercise regularly. In comparison, epidemiologic studies support the concept that habitual sports activity may offer protection against cardiovascular events over the long-term [36-38]. Adolescent and young adults involved in competitive sports activity have an estimated risk of SD approximately three times greater than that of their nonathletic counterpart [1, 3] (Fig.1). Sport acts as a trigger of arrhythmic cardiac arrest in those athletes with predisposing cardiovascular conditions.

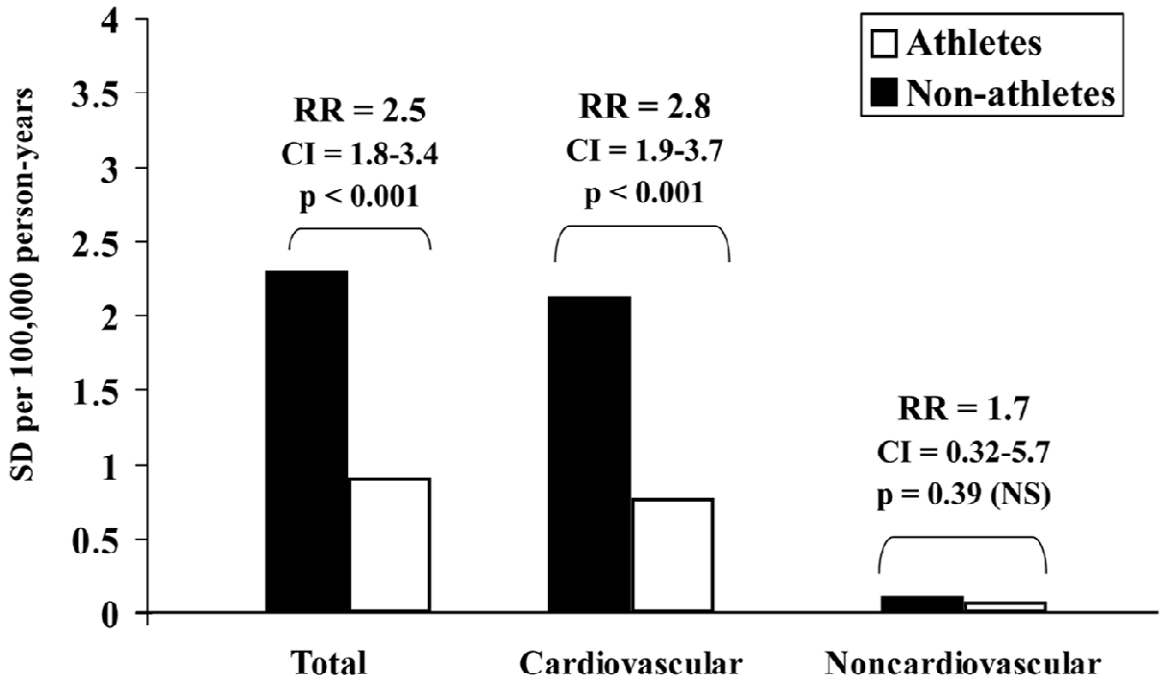

Figure 1 - Incidence and relative risk (RR) of sudden death among young athletes and non-athletes from total, cardiovascular and non-cardiovascular causes.
Adapted from Corrado et al. Herz 2006;31:553-8.

Strategies for prevention of sudden death

The catastrophic nature of SD during sports activity mandates the medical community to develop and implement effective preventive strategies [36, 39-41]. Preparticipation screening offers the potential to identify asymptomatic and apparently healthy athletes who have life-threatening

cardiovascular abnormalities and to reduce the risk of SD during sports [42-44]. However, there is a significant debate among cardiologists about the efficacy, impact of false positive results and cost-effectiveness of preparticipation screening [45-46].

Primary prevention

The primary purpose of preparticipation screening is to identify the cohort of athletes affected by unsuspected cardiovascular diseases and to prevent SD occurring during sports by appropriate interventions [42-44]. Many victims of SD did not experience symptoms before the event and, thus, pre-participation screening represents the only strategy capable of identifying the underlying cardiovascular disorder. The importance of early identification of clinically silent cardiovascular diseases at a pre-symptomatic stage relies on the concrete possibility of SD prevention by lifestyle modification, including restriction of competitive sports activity (if necessary), by prophylactic treatment with drugs and implantable defibrillator [44].

Both the American Heart Association and the European Society of Cardiology consensus panel recommendations agree that cardiovascular screening for young competitive athletes is justifiable and compelling on ethical, legal, and medical grounds [47-48]. However, there is a considerable discordance in the consensus guidelines on the pre-participation screening protocols used between European and US cardiologists/sports medicine physicians.

The American Heart Association recommends preparticipation cardiovascular evaluation by means of history (personal and family history) and physical examination alone, although this screening protocol has a recognized limited power to detect potentially lethal cardiovascular abnormalities [48-49]. Glover and Maron found that of 134 high school and collegiate athletes who suffered from SD after they underwent preparticipation screening, only 3% were suspected of having cardiac disease and, eventually, less than 1% received an accurate diagnosis [50]. Twelve-lead ECG enhances the sensitivity of the screening process by allowing early detection of cardiovascular

conditions distinctively manifesting with ECG abnormalities, such as cardiomyopathies, pre-excitation syndromes and cardiac ion channel disorders [44, 47]. Modern criteria for interpretation of the athletes ECG have led to a significant improvement in the accuracy of the ECG-based preparticipation screening[51] (Fig.2).

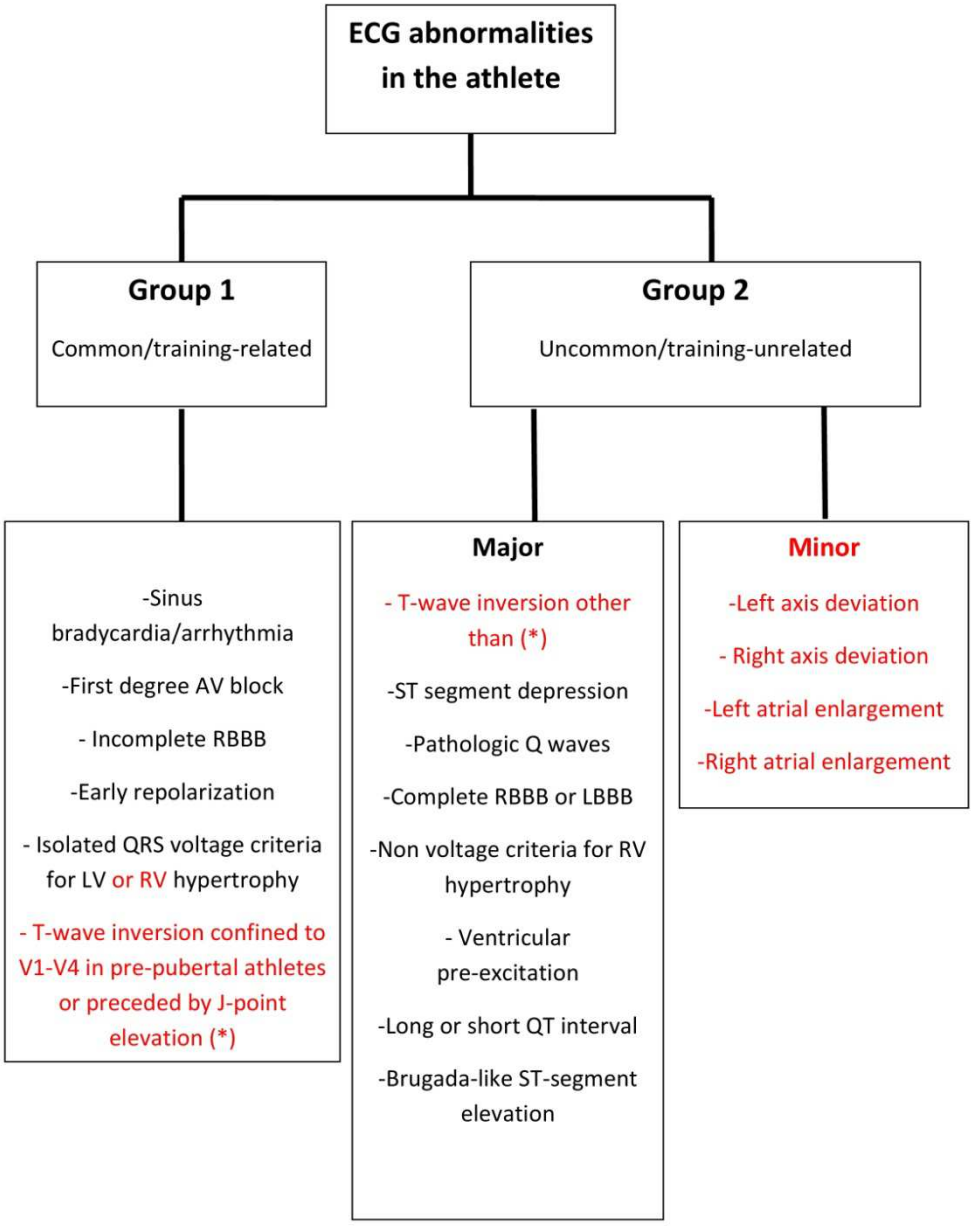

Figure 2. modern classification of ECG abnormalities in the athlete.
The main changes compared with the 2010 European Society of Cardiology guidelines are underlined in red. *Adapted from Zorzi et al., J Electrocardiology 2015; 48:283-291*

In Italy the law mandates that every subject engaged in competitive sports activity must undergo a clinical evaluation to obtain eligibility. A nationwide mass preparticipation screening program, essentially based on ECG has been in practice since 1982 (Fig.3).

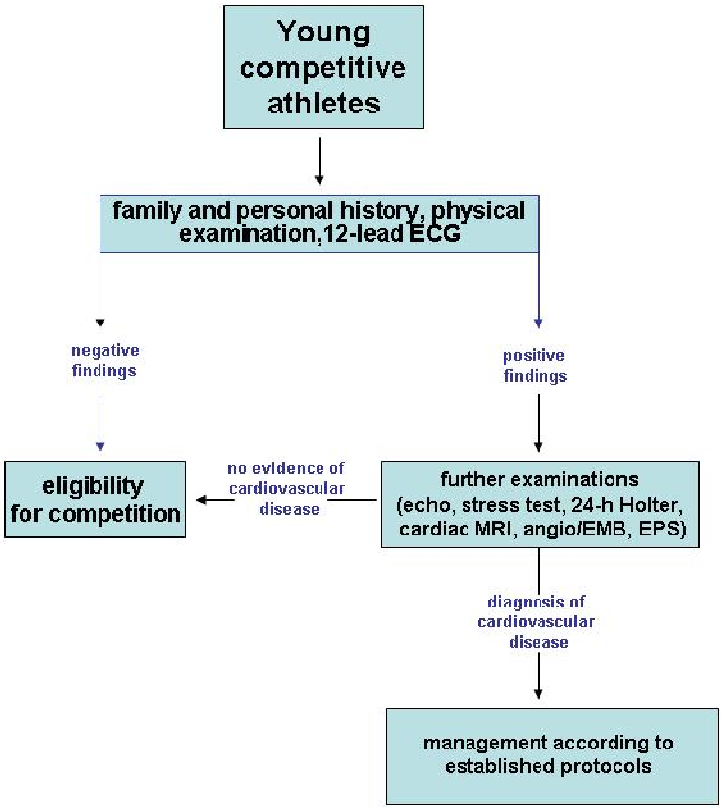

Figure 3. Flow chart of the Italian protocol of preparticipation screening.
First line examination includes family history, physical examination and 12-lead ECG; additional tests are requested only for subjects who have positive findings at the initial evaluation. The screening starts at the beginning of competitive athletic activity, which for the majority of sports disciplines corresponds to an age of 12–14 years. Athletes recognized to be affected by cardiovascular conditions potentially responsible for sudden death in association with exercise and sport participation are managed according to the available recommendations for sports eligibility. EPS=electrophysiologic study with programmed ventricular stimulation; MRI= magnetic resonance. *Adapted from Corrado et al. Eur Heart J 2005;26:516-24.*

The efficacy of ECG screening in the identification of cardiomyopathies has been demonstrated in a large population-based prospective study in the Veneto region of Italy [1, 52]. Among 33,735 athletes undergoing ECG screening at the Center for Sports Medicine in Padua, 22 (0.07%) were identified with HCM, based predominantly on an abnormal ECG [52]. An absolute value of ECG screening sensitivity for HCM cannot be derived from this study because systematic

echocardiographic findings were not available; however, this 0.07% prevalence of HCM is similar to that (0.10%) observed in a population-based study in the USA, using echocardiography[53].

A recent meta-analysis by Harmon et al.[49] aimed to evaluated the sensitivity and specificity of ECG for pre-participation screening compared with history and physical examination. The study found that the sensitivity of ECG (80%) was superior than history (50%) and physical examination (33%) and that the false positive rates of history (8%) and physical examination (10%) were higher than that of ECG (6%).

An Italian study provided the most compelling evidence of the efficacy of ECG screening to save lives by identifying and disqualifying athletes with at-risk heart diseases. A time-trend analysis of the incidence of SD in young competitive athletes in the Veneto region of Italy over 26 years (1979 to 2004) showed a sharp decline of mortality rates after the introduction of the nationwide screening program[1]. Fifty-five SDs occurred in screened athletes (1.9 deaths per 100,000 person-years) and 265 deaths in unscreened nonathletes (0.79 deaths per 100,000 person-years). The annual incidence of SD in athletes decreased by 89%, from 3.6 per 100,000 person-years in the pre-screening period to 0.4 per 100,000 person-years in the late-screening period (Fig.4).

These data have generated a number of concerns[54-56]. The main criticism is that the study was not a randomized trial comparing screening versus non-screening of young competitive athletes and, thus, definitive conclusions that the reduced mortality was solely the consequence of the screening process could not be drawn. However, the strong cause-effect relationship between ECG screening and the substantial reduction of SD in this prospective, population-based investigation is supported by the following findings: 1) there was a coincident timing between decline of SD in young competitive athletes and screening implementation in Italy; 2) most of the reduced incidence of SD was due to fewer deaths from cardiomyopathies (HCM and ARVC), and it was accompanied by the

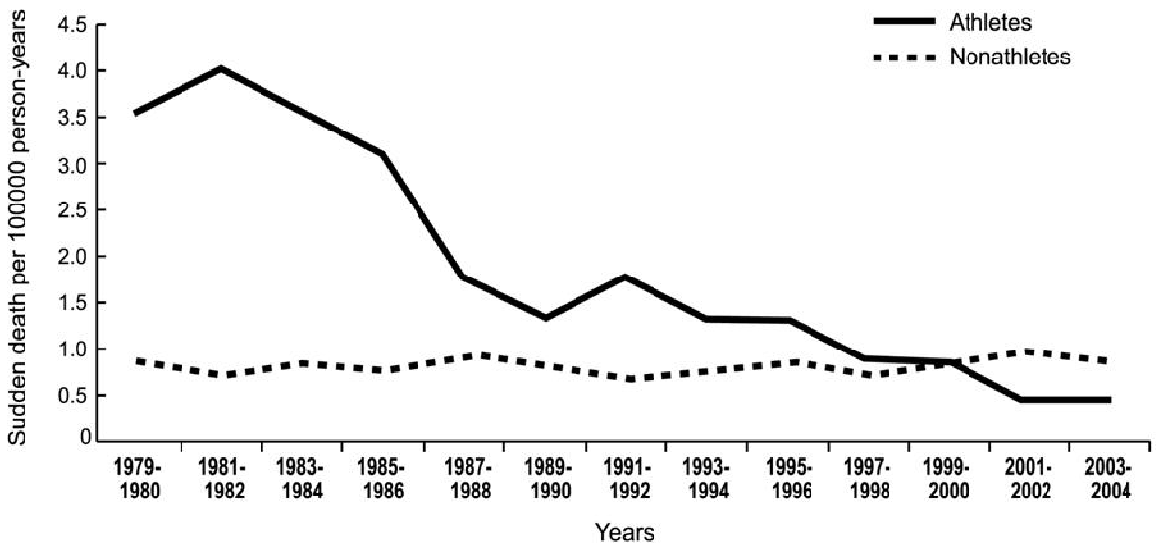

Figure 4. Annual incidence rates of SD per 100,000 person, among screened competitive athletes a unscreened nonathletes 12-35 years of age in the Veneto Region of Italy, from 1979 to 2004. During the study period (the nationwide preparticipation screening program was initiated in 1982), annual incidence of SD declined by 89% in screened athletes (P for trend <0.001). In contrast, the incidence of SD did not demonstrate consistent changes over that time in unscreened nonathletes. *Modified form Corrado et al. JAMA 2006;296:1593-1601*

concomitant increase of the proportion of young competitive athletes who were identified with these cardiomyopathies and disqualified from competition at the Center for Sports Medicine in Padua during the same time interval; and 3) during the study period, the incidence of SD did not change among the unscreened nonathletic population of the Veneto region of the same age range. Although additional factors - environmental, socio-economic or medical/surgical - may have contributed to mortality reduction over the time, such factors are expected to impact mortality similarly in screened athletes and unscreened nonathletes, and hence are unlikely to explain the declining trend in SD selectively recorded in the screened athletic population[1, 57].

It has been reported that during the time interval 1993 to 2004 the annual rate of SD among screened Italian athletes was roughly similar to that of unscreened US high school and college competitors, i.e., 0.87 vs. 0.93 per 100,000 athlete-years, respectively[30]. Thus, it has been argued that SD in young competitive athletes is a low event-rate phenomenon which is unlikely to be influenced by pre-participation ECG screening. However, as discussed above, the two athletic

populations were clearly non comparable with regard to age and gender, the Italian athletes being much older and including more males. Moreover, the US mortality rates were unavoidably underestimated because of the lack of a reliable reporting system and the retrospective data collection mostly based on reviews of public media reports and insurance claims. On the contrary, the SD database in the Veneto region of Italy is unique, in so far as cases are collected according to a prospective study design with systematic investigation of all young people (≤35 years) who die suddenly and undergo a standardized investigation of the heart by a team of cardiovascular pathologists. The heart specimens, as well as the clinical records of all SD victims since 1979, are stored at the Registry of Cardiovascular Pathology, University of Padua, allowing retrieval and review of each case. This accounts for the greater reliability of data on causes and trends of SD in Italian young people and athletes, compared with reports from other countries, which are based on a less rigorous data collection.

Authors from Israel reported an incidence of SD in the athletes of 2.6/100.000/years but failed to demonstrated a decline in SD rate after preparticipation screening became mandatory by Law in 1997 in their country[58]. However, the study again used media reports as the sole source of data and this may have led to an underestimation of the true incidence of arrhythmic death among athletes in Israel[14, 59-60].

Secondary prevention

The screening ability to detect young competitive athletes with either premature coronary atherosclerosis or congenital coronary anomalies is limited by the scarcity of baseline ECG signs of myocardial ischemia[44, 47, 61]. Moreover, SD during sports may be the result of non-penetrating chest injury (*commotio cordis*) which cannot be prevented by screening[33]. This justifies the growing efforts to implement additional prevention strategy based on early external defibrillation of sudden cardiac arrest [33]. The presence of a free-standing automated external defibrillator (AED) at sporting events

may be a valuable intervention for conditions unrecognized by screening. However, AED should not be considered as a substitute of preparticipation evaluation. On-field cardiopulmonary resuscitation may be unsuccessful even if manoeuvres are started immediately and defibrillation equipment is readily available. Drezner et al. reported a 90% mortality rate from athletic-field cardiac arrest due to underlying cardiomyopathy, despite a witnessed collapse, timely cardiopulmonary resuscitation, and prompt defibrillation[62]. A subsequent report from the same authors on a cohort of 1,710 US high schools with free-standing AED program demonstrated an improved survival rate (64%) for young athletes with sudden cardiac arrest if early defibrillation is achieved[63]. Compared with previous studies, this higher survival rate reported in high school athletes may be explained by the higher proportion of sudden cardiac arrest victims treated with AED and the smaller proportion of victims with HCM.

The non-ischemic left ventricular scar as a cause of SD in the athletes

An underlying structural cardiac abnormality is found at autopsy in most cases of SD during sports[1, 3, 26, 31, 64-65]. Failure to detect structural heart abnormalities before the fatal event occurs may depend on the low sensitivity of the current preparticipation screening protocol (based on ECG as a first level examination and on echocardiography as a second level examination) for subtle structural heart conditions potentially at risk of arrhythmic events including focal myocarditis and segmental cardiomyopathies [32, 66].

Contrast-enhanced cardiac magnetic resonance (CE-CMR) imaging has become in the recent years part of clinical work-up of athletes with ventricular arrhythmias (VA)[67]. Besides evaluating the presence of morpho-functional ventricular abnormalities, CE-CMR allows myocardial tissue characterization by late gadolinium enhancement (LGE) technique, which provides information on the presence, morphology and wall distribution of pathological scar tissue otherwise overlooked[68-69]. A non-ischemic left ventricular (LV) LGE suggesting myocardial scar, characteristically localized at the

midmyocardial and/or subepicardial layers of the LV wall, can be revealed by CE-CMR in a broad spectrum of heart muscle diseases at risk of SD including myocarditis, sarcoidosis, dilated cardiomyopathy, HCM and ARVC [70].

Idiopathic myocardial fibrosis, either interstitial or replacement-type, with a predilection for the infero-lateral LV wall, has been increasingly reported at post-mortem examination of athletes who died suddenly[71-73]. A recent study about the anatomical substrates of juvenile SD reported a prevalence of non-ischemic LV scar of 1.3% among victims of SD at rest and of 25% among victims of SD during exercise. According to the study, the non-ischemic LV scar is the most common cause of SD during physical activity[74]. Another recent study which included cases of SD which were referred to the St. George's University of London Cardiac Pathology unit confirmed that an important minority (8%) of athletes who died suddenly showed idiopathic fibrosis as the underlying myocardial substrate[75].

The increasing use in the clinical practice of CE-CMR has offered the potential to identify "in vivo" potentially arrhythmogenic LV scar tissue. Isolated, non-ischemic LV LGE has been previously reported in anecdotic cases or small series of individuals and athletes presenting with repolarization abnormalities and/or life-threatening VA [76-78]. On the other hand, previous CE-CMR studies in asymptomatic athletes reported a prevalence of LV LGE ranging from 0 to 50% so that the association between the LV scar and VA remains to be proven[79-89] (Table 3).

The etiology of the LV scar is also a matter of debate. Traditionally, the presence of non-ischemic LV LGE with an epicardial/midmyocardial distribution and preferential involvement of the infero-lateral LV regions is interpreted as the consequence of a previous myocarditis [90-91]. However, other disease such as the left-dominant variant of ARVC can account for this LGE pattern at CE-CMR in the absence of the typical morpho-functional abnormalities of the right ventricle.

The classic "right dominant" ARVC phenotype is characterized by prevalent right ventricular involvement with progressive fibro-fatty substitution of the ventricular myocardium, particularly in

Table 3 - Prevalence of late gadolinium enhancement in previous cardiac magnetic resonance studies on healthy athletes

Reference	N° cases	Mean age	Males	Controls	Inclusion criteria	% LGE	LGE patterns in cases
Mousavi et al. 2009	14	33 y	57%	NO	Marathon runners, moderately trained	0 %	
Mohlenkamp et al. 2008 Breuckmann et al. 2009	102	57 y	100%	YES	Marathon runners (≥5 marathons in the last 3 years), age >50 y old,	12% (4% controls)	5: subendocardial 7: midmyocardial spot
O'Hanlon et al.2010	17	34 y	100%	NO	Marathon runners, mean 7 hours training/week	0%	
Oomah et al. 2011	15	32 y	47%	NO	Half marathon runners, non-elite	0%	
Wilson et al. 2011	12	57 y	100%	YES	Endurance elite, various sports, >50y old	50% (0% controls)	4: junctional 1: subendocardial 1: subepicardial stria
La Gerche et al. 2012	40	37 y	90%	NO	Endurance, > 10 h/training, high performance	13%	1: Junctional 4: spots in the septum
Erz et al. 2013 Mangold 2013	95	35 y	77%	NO	Endurance, >7 h/week for >2y	2.1%	1: inferior wall spot 1: lateral wall spot
Franzen et al.2013	40	41 y	100%	NO	Triathlon running, >5 h/week for >2 y	0%	
Bohm et al. 2016	33	29 y	100%	YES	Endurance athletes, >10 h/week for >10 years	3% (0% controls)	1: subepicardial stria

LGE=late gadolinium enhancement; y=years

the so-called "triangle of dysplasia" (outflow tract, apex and inflow). Electrical abnormalities secondary to the fibro-fatty scarring process are the basis for the typical ECG changes of ARVC including T-wave inversion that can be found in up to 90% of affected individuals do that ECG pre-participation screening has a high sensitivity for classic ARVC. Moreover, the physiopathological process of progressive myocyte loss causes a gradual dilation and systolic dysfunction of the right ventricle that can be demonstrated by standard echocardiography. [92].

Instead, the "left dominant" variant is characterized by an early and predominant LV involvement, as a result of a specific genetic background. At variance with the classic "right-dominant" variant, the diagnostic power of traditional investigations such ECG and standard 2-D echocardiography for "left-dominant" ARVC is limited because ECG changes and LV systolic dysfunction, either regional or global, is found in a minority of patients with this variant. The reason is that the fibro-fatty scarring process initially involves the sub-epicardial myocardial layers, which contribute marginally to the development of the contractile power and does not translate into prominent wall motion or electrical abnormalities. As a consequence, the "left-dominant" ARVC phenotype is difficult to diagnose and its incidence is probably underestimated. CE-CMR identifies non-transmural LV areas of LGE at a subepicardial and/or mid-mural level in the majority of affected patients, but the exam is expensive and not widely available and it is not routinely performed to apparently healthy young individuals and athletes[93].

Not surprisingly, the incidence of SD secondary to the classic ARVC variant has markedly decreased after the introduction of ECG pre-participation screening, while the difficult-to-diagnose "left dominant" variant is now among the most common causes of SD[94] (the most popular example being the professional soccer player Pier Mario Morosini, who died while playing a match in 2012).

As the majority of patients affected by "left-dominant" ARVC suffer from arrhythmias originating from the LV, 24-hours recording of the ECG may improve the diagnostic sensitivity for this disease among apparently healthy athletes with no suspicious findings at standard pre-participation screening, but this exam is not part of routine investigations of athletes.

AIMS

The research project includes three different studies that were performed during the three years of the PhD program.

The aim of the first study was to evaluate the incidence, relation to physical exercise and causes (with particular reference to non-ischemic left ventricular scar) of out-of-hospital cardiac arrest (OHCA) of presumed cardiovascular origin, which occurred in the Padua province in individuals 1-40 years-old. The incidence of OHCA was calculated both in the overall population and according to the athletic status. The study results are still unpublished.

The second study aimed to characterize the clinical profile and outcome of a cohort of competitive athletes with apparently idiopathic VA who showed isolated non-ischemic LGE on CE-CMR. The CE-CMR features and outcome of the index athletes were compared with those of athletes with frequent premature ventricular beats (PVBs) or complex VA and no LGE and control healthy athletes in order to assess whether the presence, specific morphologic pattern, regional localization and wall distribution of the LGE are associated with an increased arrhythmic risk. The study has been published in Circulation: Arrhythmias and Electrophysiology in 2016[95].

The third study aimed to investigate the prevalence, morphology, determinants and underlying substrate (as assessed by echocardiography and contrast-enhanced CMR) of frequent PVBs/complex VA at 24-hours 12-leads ambulatory ECG monitoring in apparently healthy athletes who have been considered eligible for competitive sports activity at preparticipation screening within 1 year. The purpose was to evaluate whether a strategy consisting of the 24-hours 12-leads ambulatory ECG monitoring as a first-line investigation and CE-CMR as a second line investigation may improve our ability to identify a concealed LV scar in apparently healthy athletes. The study results are still unpublished.

METHODS

1. Incidence and causes of OHCA of presumed cardiovascular origin in the Padua province

Inclusion criteria

The study population included all residents in the province of Padua 1-40 year-old who suffered OHCA, either resuscitated ("aborted" SD) or not ("SD"), of presumed cardiovascular origin during the period 2011-2015. Data were collected from the database of the Emergency Medical System (SUEM-118) of the Padua province, which is the only responsible for provision of first aid in Italy and that collects all emergency medical calls. At the time of the study the population of the Padua province 1 to 40 years of age was 380.866 inhabitants (48.6% males) (Data: Office of the President of the Padua Province).

Cases of SD of the infant (<1 year-old) were excluded because this represents a peculiar condition with different pathogenesis[96]. The cardiac arrest was considered "sudden" if it occurred within one hour of symptoms onset in apparently healthy individuals or in non terminally ill patients. The cardiac arrest was considered of "presumed cardiovascular origin" at the time of first medical contact if the circumstances of the event did not suggest a non natural cause (e.g. trauma, suicide, intoxication…) or evident non cardiovascular causes (e.g. hemorrhage…). Hence, subjects who suffered OHCA judged to be of "presumed cardiovascular origin" at first medical contact but with a final clinical or post-mortem diagnosis of non cardiovascular etiology were included. Finally, the OHCA was considered exercise-related if it occurred during or immediately after the cessation of exercise.

Cardiac arrest and competitive sports activity

In Italy all athletes who want to engage in competitive sports activity must undergo preparticipation screening including 12-lead ECG and the eligibility decision of the Sports Medicine doctor is recorded in a database of the Italian Health System. This database was consulted to determine if the OHCA victims underwent a preparticipation evaluation. In this case, we collected data on the type of sports activity, eligibility decision and time from the last medical evaluation to the event. Only subjects who underwent the last evaluation within an year of the event were classified as active "competitive athletes" as, according to the Italian Law, athletes engaged in competitive sports active must undergo preparticipation evaluation on a yearly basis. At the time of the study, the total number of athletes in the Padua province 40 year-old or younger was 72.567 (49.001 in the age group 12-35 year-old) (Data: National Olympic Committee – Padua district).

Diagnosis

The diagnosis was obtained clinically in victims of OHCA who were successfully resuscitated. A diagnosis of "idiopathic ventricular fibrillation" was made in patients with no evidence of structural heart disease or ion channel disease after a thorough clinical investigation (including CE-CMR and sodium channel blocker test for Brugada syndrome).

In Italy, autopsy of victims of SD (failed resuscitation) is not compulsory but can be required both by the physician who certified the death or by the judicial authority. In this case, the autopsy was performed in the Institute of Cardiovascular Pathology, Dpt. of Cardiac, Thoracic and Vascular sciences, University of Padova (director prof. G. Thiene) according to the Guidelines of the European Association of Cardiovascular Pathology [97]. Victims of SD who did not undergo autopsy and without a history of known cardiovascular disease were classified as SD of "unknown cause".

Statistical analysis

We calculated the yearly incidence of OHCA of presumed cardiovascular origin in the Padua province both in the overall population and according to age and gender.

Continuous variables were expressed as median (1^{st}-3^{rd} quartiles) and compared with the rank sum test (2 groups) or the Kruskall-Wallis test (>2 groups). Dichotomous variables were expressed as N (%) and compared with the chi square test or the Fisher exact test, as appropriate. Statistical analysis was performed with SPPS version 17 (SPSS inc. Chicago, ILN).

2. Characteristics and outcome of athletes with ventricular arrhythmias and LV scar

The Inherited Arrhythmogenic Cardiomyopathy unit of the Department of Cardiac, Thoracic and Vascular Sciences is a tertiary center for evaluation of young people and athletes with established or suspected cardiac disease at risk of life-threatening VA. The present study enrolled a series of competitive athletes with frequent PVB (>500/day) or complex VA (sustained or non-sustained ventricular tachycardia or ventricular fibrillation), which occurred in the absence of coronary artery disease, cardiomyopathy and other clinically overt heart disease and were diagnosed as "idiopathic" at routine clinical evaluation. All athletes underwent a comprehensive CE-CMR study for further imaging assessment and tissue characterization of myocardial substrate.

Breakdown of the study population

During the period 2009-2014 a total of 223 competitive athletes who had undergone pre-participation cardiovascular evaluation by a sports medicine physician were referred to our cardiology center for diagnostic evaluation of VA. One-hundred thirty eight athletes were excluded from the study because they did not fulfill the enrollment criteria of frequency and complexity of VA and did not undergo CE-CMR study. Among the other 85 athletes with frequent PVBs or complex VA, 8 were excluded because of a diagnosis of structural heart disease including partial anomalous pulmonary venous return (N=1), ARVC either definite (N=1) or borderline (N=2), apical HCM (N=1), ventricular pre-excitation (N=1) and coronary artery disease (N=2). Four athletes (all with no LGE) were lost to follow-up. The athletic study population comprised the remaining 73 athletes with frequent PVBs or complex VA and routine diagnostic work-up negative for overt heart disease who underwent additional CE-CMR study. According to the CE-CMR findings two groups were identified: Group A (N=35) including athletes with VA and evidence of isolated LV LGE and Group B (N=38) including athletes with VA and a totally negative CE-CMR study.

Controls

A group of 40 competitive athletes (Group C) with a negative family history for SCD or cardiomyopathy, normal ECG and no VA served as controls. They underwent CE-CMR for further imaging assessment of a borderline (LV wall thickness 12-14 mm) LV hypertrophy found at pre-participation echocardiography. The CE-CMR study ruled out a pathologic ventricular remodeling due to HCM or other structural heart diseases in all.

Clinical investigation

At the time of first evaluation, all athletes underwent a routine clinical evaluation including family and personal history, physical examination, resting 12-lead ECG, signal-averaged ECG (SAECG), 12-leads 24-hours Holter monitoring to evaluate morphology of VA, bicycle exercise testing with a protocol of 25-50 watt increments every 3 minutes, 2-dimensional transthoracic echocardiography. Late potentials on SAECG were defined according to previously proposed criteria[98].

Additional invasive tests such as coronary angiography (N=36), endomyocardial biopsy including molecular pathology investigation for viral genomes (N=6) or programmed ventricular stimulation (N=10) were reserved to selected cases.

All subjects gave written informed consent after counselling in accordance with the ethical standards of the Declaration of Helsinki (2001) and with recommendations given by the Institutional Ethical Committee.

Contrast-Enhanced cardiovascular magnetic resonance

All athletes were evaluated de novo, with repeated CE-CMR if performed in other Institutions, to provide independent diagnosis.

Scan protocol

CE-CMR was performed on a 1.5-Tesla scanner (Magnetom Avanto, Siemens Medical Solutions, Erlangen, Germany) using a comprehensive dedicated protocol.

All patients underwent detailed CE-CMR study protocol including post-contrast sequences. Images were acquired using a steady-state free precession sequence (true FISP) cine loops in sequential short axis views (slice thickness 6 mm, gap 2 mm; repetition time 2.5 to 3.8; echo time 1.1 to 1.6, average in-plane resolution 1.5x2.4 mm, flip angle 45° to 60°, temporal resolution 40 to 45 ms) and long- axis views (2-, 3- and 4-chamber views).

After intravenous administration of contrast agent (gadobenate dimeglumine, Multihance, Bracco, 0.2 mmol/kg of body weight) 2-dimensional segmented fast low-angle shot inversion recovery sequence after at least 10 minutes were acquired in the same views of cine images, covering the entire ventricles (repetition time 5.4 to 8.3 ms, echo time 1.3 to 3.9 ms, average in-plane spatial resolution 1.4 to 1.5 x 2.2 to 2.4 mm, 6- mm slice thickness, 2-mm gap, and flip angle 20° to 25°). Inversion times were adjusted to null normal myocardium using the Look-Locker sequence and images were repeated in 2 separate phase-encoding directions to exclude artifacts.

Image analysis

Global ventricular volumes, systolic function and LV myocardial mass were calculated from the short-axis cine images, excluding papillary muscles from the myocardium, using a dedicated software (CMR42, Circle Cardiovascular Imaging Inc). The presence, location and extent of LGE were independently assessed by two experienced observers who were blinded to patient clinical data and outcome; ambiguous cases were reviewed using a third expert. To exclude artifacts, LGE was deemed present only if visible in two orthogonal views (short-axis and long-axis views)using a signal intensity

threshold of >2SD above a remote reference region. The pattern of LGE distribution and morphology was characterized as either epicardial/midmyocardial “stria” or patchy/junctional “spotty”. If more than one pattern was present, the distribution was characterized on the basis of the predominant pattern.

Follow-up

After the enrollment, patients were followed-up for a mean duration of 38±25 months. The primary study end-point was the occurrence of any major arrhythmic events defined as SCD, arrhythmic cardiac arrest, sustained ventricular tachycardia or appropriate implantable cardiac defibrillators (ICD) intervention on ventricular tachycardia or ventricular fibrillation. Routine ICD interrogation and ECG recordings at the time of symptoms were used to document the occurrence of spontaneous ventricular tachycardia during follow-up. Sudden cardiac death was defined as any natural death occurring instantaneously or within one hour from symptoms onset. Sustained ventricular tachycardia was defined as tachycardia originating in the ventricle with rate >100 beats/minute and lasting >30 seconds or requiring an intervention for termination. Appropriate ICD intervention was defined as a device shock or antitachycardia overdrive pacing delivered in response to a ventricular tachyarrhythmia and documented by stored intracardiac ECG data.

Statistical Analysis

Data are expressed as mean±standard deviation or median with 25 to 75 percentiles for normally distributed and skewed variables, respectively. Normal distribution was assessed using Shapiro-Wilk test. Categorical differences among groups were evaluated by the chi-square test or the Fisher exact test as appropriate. Differences among continuous variables were evaluated with the Kruskal-Wallis test. Kaplan-Meier analysis was used to estimate the survival distributions of the arrhythmic end-point and to show the differences in survival among groups of patients. Kaplan-Meier

curves were compared with the logrank test. Start of follow-up was defined as the date of the initial CE-CMR. Patients were followed until the time of their first event or until the time of their last clinical follow-up. A value of $P<0.05$ was considered significant. Statistics were analyzed with SPSS version 19 (SPSS Inc, Chicago, IL).

3. Prevalence, predictors and clinical significance of VA in athletes

The "Ventricular Substrates at Cardiac magnetic resonance in Athletes with ventricular ARrhythmias (V-SCAAR)" study was carried out at the Center for Sports Medicine, ULSS 16, Padova (Director Dr M. Schiavon) during the period August 2015 – September 2016. Volunteers were recruited with advertisements in the local sports medicine doctors' offices, in the social media and in local sports society headquarters. The study was reviewed and approved by the Institutional Ethical Committee.

Inclusion criteria

1) age ≥ 16 years-old;
2) considered eligible to competitive sports activity at preparticipation screening within 1 year of the study. According to the Italian Law, the preparticipation screening includes history, physical examination and 12-lead ECG. Maximal exercise testing is also required in athletes ≥ 35 year-old;
3) at least 6 hours of exercise per week;
4) written consent to participated in all stages of the study (including echocardiography and CE-CMR if indicated). If below the age of 18 years, consent of both parents or guardians;

Exclusion criteria

- engaged in a low static/low dynamic component sport according to the Mitchell classification;
- pregnancy;
- CE-CMR in the last three years or contraindication to CE-CMR;
- cognitive impairment;
- known cardiac disease (excluding mild valvular disease; previous myocarditis or pericarditis which was considered clinically healed or known PVBs in the absence of overt structural heart disease).

Personal data

At the time of enrollment, the following data were collected: age, gender, sport practiced (in case of multiple sports, the one which accounted for the majority of hours of training was considered, hours of training per week during the sporting season; estimated number of hours of training per year (calculated as mean hours of training/week x number of weeks of activity), years of sports practice; personal history and family history of coronary artery disease, premature SD (<40 year-old in male and <50 year-old in female) or cardiomyopathy.

12 leads, 24-Hours ECG monitoring

All volunteers underwent a 12 leads, 24 hours ambulatory ECG monitoring (H12+™, Mortara Instrument Inc, Milwaukee, USA).

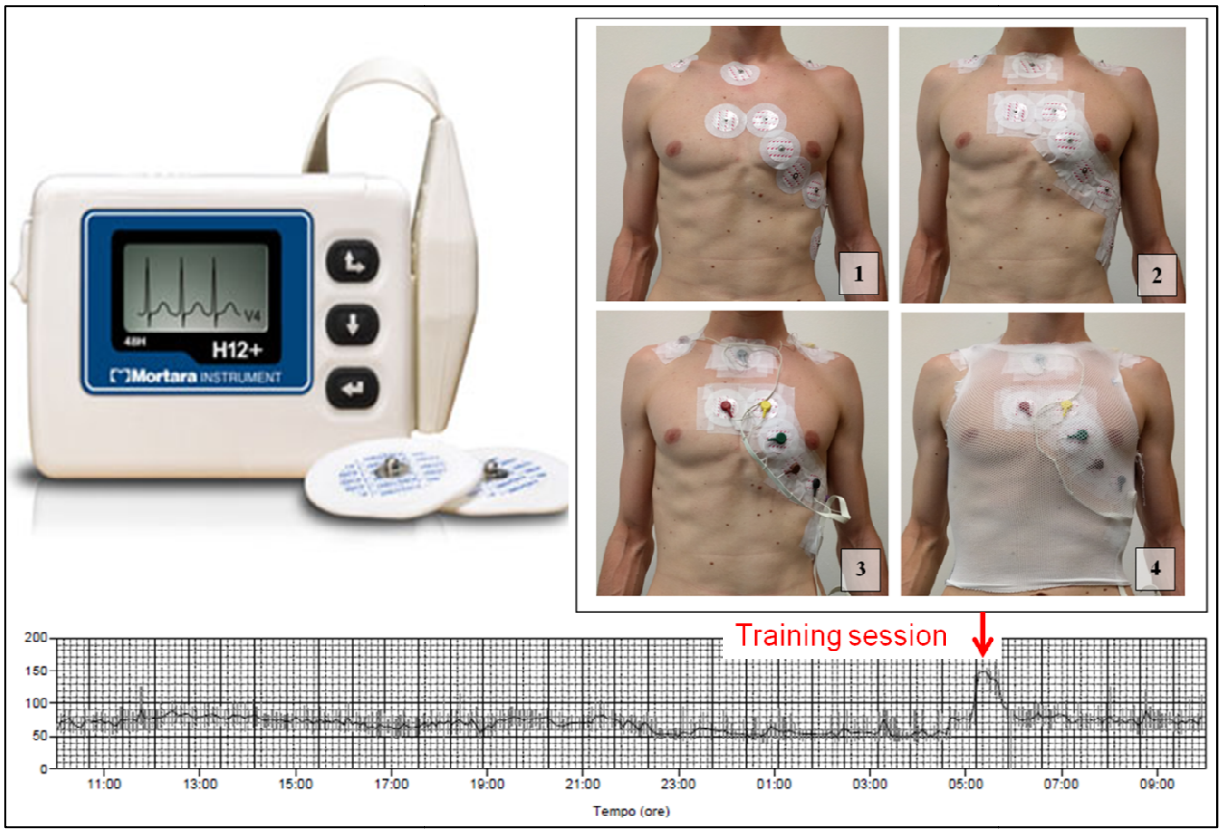

Figure 5. Methods of the V-SCAAR study

Top left: type of ambulatory ECG holter monitoring used in the study. Top right: methodology of ECG leads application to minimize the risk of artifacts. Bottom: 24-hours heart rate trend

Athletes were instructed to undergo an aerobic training session, possibly of the same sport they habitually perform, of at least one hour during the recording. To limit the burden of movement artifacts during exercise, the ECG leads were fixed with adhesive tape (Fig. 5).

Only recordings of at least 20 hours excluding artifacts and periods of no signal were included in the study: in case of <20 hours of recording, the athlete was invited to repeat the study and was excluded if he/she denied. The recordings were analyzed with the HScribe 5 software (Mortara Instrument Inc, Milwaukee, USA) by the same physician (A. Z.). All families of normal beats and every single supraventricular or ventricular ectopic beat were reviewed manually. PVBs were classified according to the morphology on the 12 ECG leads as follows:

- right bundle branch block (RBBB) like (mainly positive QRS complex in V1) or left bundle-branch-block (LBBB) like (mainly negative QRS complex in V1);
- superior axis (positive QRS complex in 1 and negative QRS complex in aVF), intermediate axis (positive QRS complex in 1 and positive QRS complex in aVF) or inferior axis (negative QRS complex in 1 and positive QRS complex in aVF).

Two distinct ventricular ectopic beats morphologies, that are recognized to be benign in the vast majority of cases [99], were identified:

1) LBBB/inferior axis, suggestive of origin from the right (or left) ventricular outflow tract;
2) RBBB/left anterior hemiblock or RBBB/left posterior hemiblock and QRS duration ≤130 ms, suggestive of fascicular origin.

Second-line clinical investigations

Athletes were selected to undergo further diagnostic investigations including echocardiography and CE-CMR if they showed:

1) >29 PVBs, excluding those with morphologies suggestive of right ventricular outflow tract or fascicular origin. The cut-off was arbitrarily chosen to balance the limited availability of CE-CMR studies that could be performed and the need of a low threshold for CE-CMR prescription to

evaluate whether there is a relationship between the number of PVBs count and the risk of an underlying LV scar. Patients with distinctively exercise-induced "atypical" PVBs were offered CE-CMR regardless of the PVBs count;

2) ≥1 ventricular couplet (excluding isolated couplets with a morphology suggestive of right ventricular outflow tract origin), triplets (any morphology) or non-sustained ventricular tachycardia (any morphology).

For each athlete with one of the above conditions, a control athlete with no arrhythmias matched for gender, age group and type of sports activity according to the Mitchell classification was selected and offered echocardiography and CE-CMR.

Athletes with frequent PVBS with a morphology suggestive of right ventricular outflow tract or fascicular origin or with right ventricular outflow tract couplets were offered echocardiography, while CE-CMR was performed only in case of positive findings at echocardiography.

Regardless of PVBs count/complexity, clinical investigation such as echocardiography, stress echocardiography or CE-CMR were offered to athletes in case of other positive findings suggesting of cardiovascular disease (e.g. family history of SD; ECG abnormalities; supraventricular tachycardia; dynamic ST-segment depression...) unless they had already undergone CE-CMR within 3 years.

The design of the study is summarized in figure 6.

Statistical analysis

Data are expressed as median (25^{th}-75^{th} percentile). Categorical differences among groups were evaluated by the chi-square test or the Fisher exact test as appropriate. Differences between continuous variables were evaluated with the Rank sum test (2 groups) or the Kruskal-Wallis test (multiple groups). A binomial logistic regression analysis model was built to identify independent predictors of high PVBs count. Variables associated with a p-value <0.15 at univariate analysis were entered as covariates in the multivariable model. A value of P<0.05 was considered significant. Statistics were analyzed with SPSS version 19 (SPSS Inc, Chicago, IL).

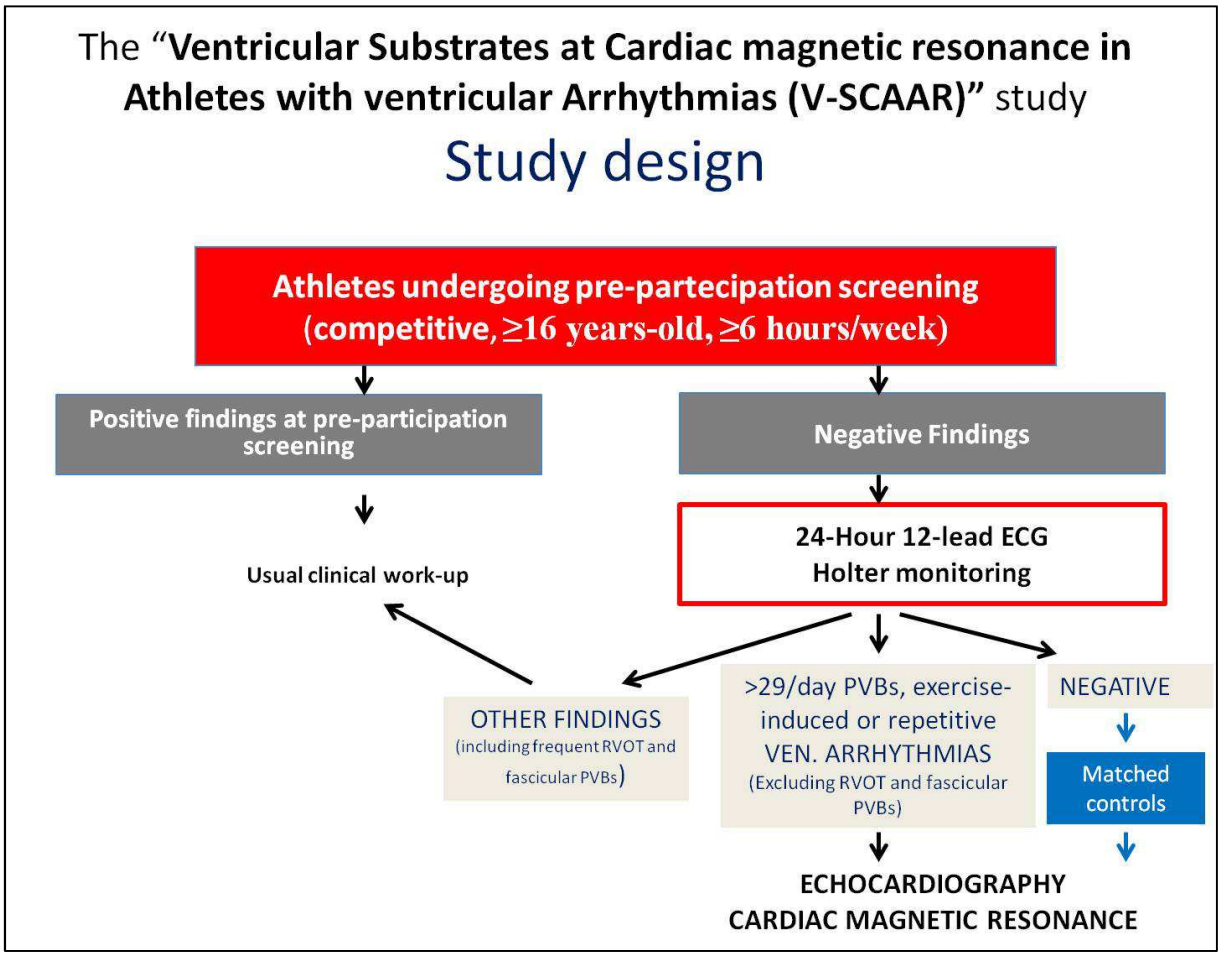

Figure 6: design of the V-SCAAR study.

RESULTS

1. Incidence and causes of OHCA of presumed cardiovascular origin in the Padua province

Incidence and outcome

Over the 44 months study period 53 cases of OHCA of presumed cardiovascular origin occurred in the Padua province in people 1-40 year-old. Two cases were excluded because they occurred in non-residents and 3 because the OHCA circumstances could not be fully established. The final study sample included 48 subjected [median age 29 (22-38) year-old]: of those 37 (77%) could not be resuscitated and 11 (23%) were admitted alive to the hospital. Eight (17%) were discharged, all without neurological impairment.

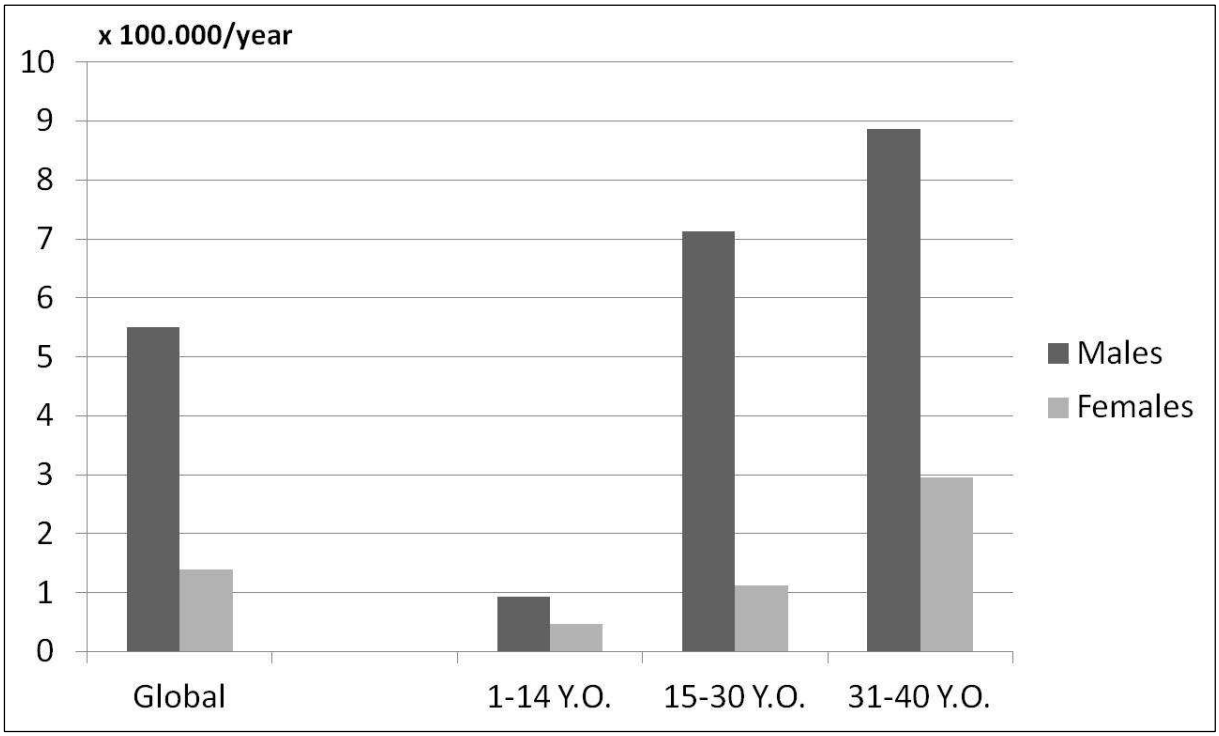

Figure 7. Incidence rate of out-of-hospital cardiac arrest of presumed cardiovascular origin per 100.000/inhabitants/year among different age classes and according to gender.

Y.O.=year-old

The incidence of OHCA in the Padua province was 3.5/100.000 residents/years. The incidence of OHCA was significantly higher in men (5.5/100.00/year) compared with females (1.4/100.000/year, p<0.001). Moreover, there was a statistically significant association between the incidence of OHCA and increasing age (p<0.001) (Fig. 7). The incidence of out-of-hospital SD in the age class 12-35 years-old (24 cases) was 2.2/100.000/year.

Causes

A final diagnosis was reached in 40 (83%) subjects while in 8 (17%) victims of SD with no known cardiovascular disease the autopsy was not performed. The causes of OHCA are listed in table 4. The most frequent causes were coronary artery atherosclerosis (23%) and structurally normal heart (23%). In this last subgroup, a post-mortem family screening allowed to reach a diagnosis of Brugada syndrome in 1 while in another 1 the ECG showed short PR interval in the absence of ventricular pre-excitation. Seven (10%) subjects were affected by a cardiomyopathy, including 3 cases of non-ischemic LV scar:

- a 38 year-old male who died suddenly during exercise. Few months before he underwent CE-CMR for chest pain with troponin release and no stenosis of coronary arteries at angiography. The CE-CMR study revealed no sign of acute pericarditis (no myocardial edema, no signs of pericardial inflammation) but disclosed LV LGE suggesting myocardial scar with a “subepicardial/midmyocardial stria pattern” in the infero-lateral LV wall (Fig.8). Autopsy was not performed;

- a 27 year-old who suffered cardiac arrest after an emotional stress (he was attending the funeral of a relative). He was resuscitated and suffered no neurological damage. CE-CMR revealed LV LGE with a “subepicardial/midmyocardial stria pattern” in the basal segments of the infero-lateral LV wall. Endomyocardial biopsy from the right ventricular apex revealed foci of fibrofatty substitution that however, did not fulfill the criteria for the diagnosis of ARVC. He was diagnosed with idiopathic non-ischemic LV scar (Fig.9);

Table 4: causes of out-of-hospital cardiac arrest in the overall sample and in the subgroup of patients who died suddenly (failed resuscitation attempts) in the age group 12-35 years-old.

Cause	All OHCA N=40	Sudden death 12-35 years-old N=19*
Coronary artery disease	9 (23)	3 (16)
Coronary stenosis >50%	*4*	*1*
Coronary occlusion	*5*	*2*
Cardiomyopathy	7 (10)	3 (16)
ARVC	*1*	*0*
Hypertrophic cardiomyopathy	*1*	*1*
Dilated cardiomyopathy	*2*	*1*
Non-ischemic LV scar	*3*	*1*
Myocarditis	3 (7)	1 (5)
Mitral valve prolapse[#]	4 (10)	1 (5)
Congenital heart disease	2 (5)	2 (11)
Surgically corrected TGA	*1*	*1*
Coronary artery anomaly	*1*	*1*
Acute pulmonary embolism	3 (7)	0
Structurally normal heart[%]	9 (23)	6 (32)
Non cardiovascular causes	3 (8)	3 (16)
Asthma	*1*	*1*
Brain hemorrhage	*1*	*1*
Lymphoma	*1*	*1*

ARVC = arrhythmogenic cardiomyopathy; LV=left ventricular; TGA=transposition of great arteries

* Inclusion criteria of the study by Corrado et al, JACC 2003
# including one case of posterior mitral leaflet flail in a patient with Marfan syndrome
% including one case of Brugada syndrome and one of accelerated atrioventricular conduction

- a 21 year-old male who suffered SD during sleep and was diagnosed with idiopathic LV scar involving the subepicardial/midmyocardial layer of the infero-lateral LV wall at autopsy.

Six people were affected by a known cardiovascular disease which was the cause of OHCA: 1) a 20 year-old male with HCM (North-African immigrant who was not regularly followed-up); 2) a 14 year-old female with surgically corrected transposition of great arteries; 3) a 3 year-old male with dilated cardiomyopathy; 4) a 35 year-old male with dilated cardiomyopathy; 5) the 38 year-old male with previous chest pain and demonstration of LV-LGE suggestive of myocardial scar at CE-CMR and 6) a 28 year-old male with mitral valve prolapse and suspected Marfan syndrome (diagnosed at sports preparticipation screening 12 years before the event) who suffered acute heart failure and ventricular fibrillation due to flail mitral valve.

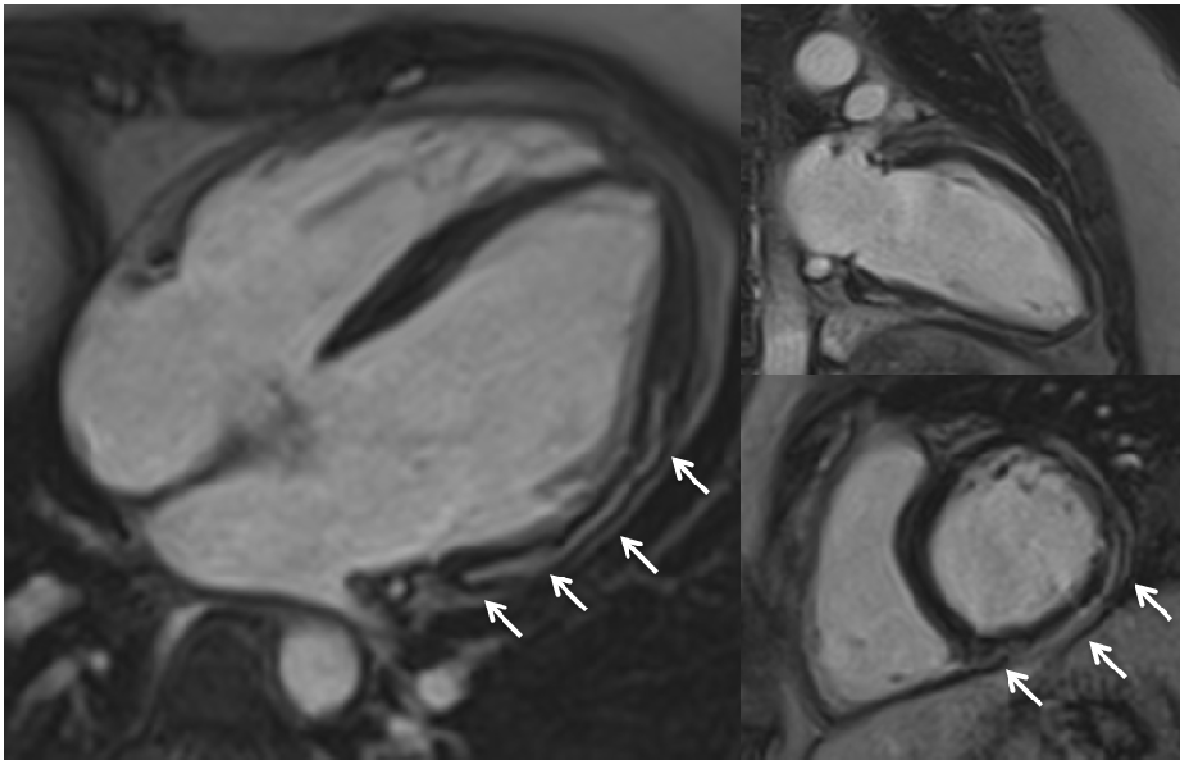

Figure 8: CE-CMR findings in a victim of sudden death during exercise.
Late post-contrast T2 weighted cardiac magnetic resonance images demonstrating non-ischemic (subepicardial/midmyocardial) left ventricular late gadolinium enhancement (suggesting myocardial scar) in the mid and basal segments of the infero-lateral wall (courtesy of dr. M. Perazzolo Marra).

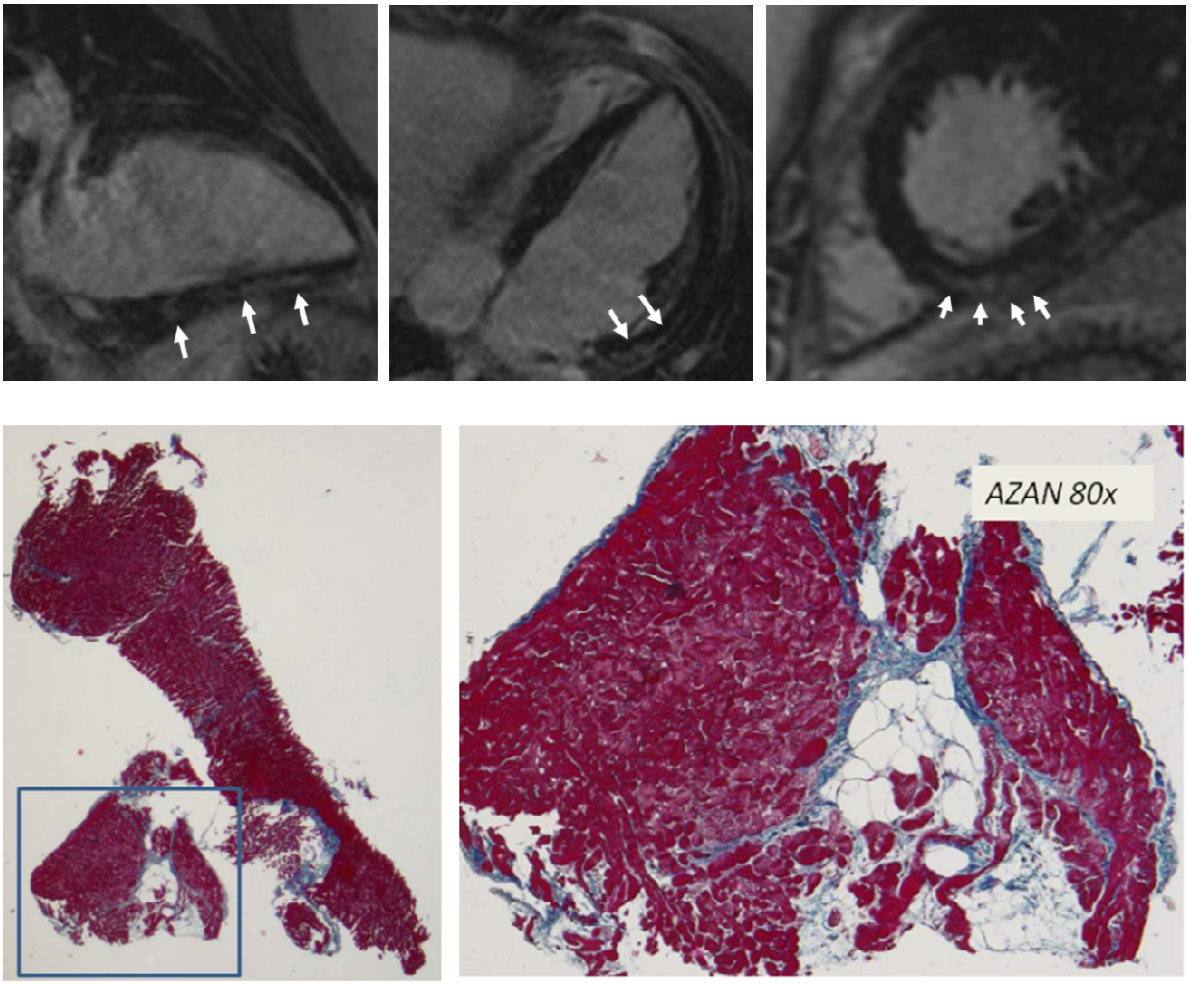

Figure 9: CE-CMR and endomyocardial biopsy in a patient who suffered resuscitated cardiac arrest. *Top:* late post-contrast T2 weighted cardiac magnetic resonance images demonstrating non-ischemic (subepicardial/midmyocardial) left ventricular late gadolinium enhancement (suggesting myocardial scar) in the mid and basal segments of the infero-lateral wall (courtesy of dr. M. Perazzolo Marra). Bottom: endomyocardial biopsy (Azan) showing foci of fibrofatty substitution which do not reach the histomorphometric criteria for the diagnosis of Arrhythmogenic cardiomyopathy (courtesy of prof. C. Basso).

Cardiac arrest and competitive sport activity

Three victims of OHCA engaged in competitive sports activity at the time of OHCA and were classified as athletes. In all three cases the OHCA occurred at rest. The first is a 29 year-old basketball player who was resuscitated from cardiac arrest while driving and was diagnosed with idiopathic ventricular fibrillation (structurally normal heart and no signs of ion channel disease). The second is a 17 year-old who was also resuscitated from cardiac arrest while sleeping. A recent preparticipation

screening revealed negative T-wave in the anterior leads V1-V2: he underwent echocardiography which revealed no signs of cardiomyopathy. During the hospitalization he underwent endomyocardial biopsy which revealed patchy fibrofatty substitution that fulfill the minor criterion for the diagnosis of ARVC. He also underwent CE-CMR that revealed mild right ventricular dilation and apical hypokinesis that did not fulfill the imaging criteria for ARVC diagnosis; however, as he had T-wave inversion in V1-V2 (minor diagnostic criterion), ventricular fibrillation (major diagnostic criterion) and patchy fibrofatty substitution at endomyocardial biopsy (minor diagnostic criterion) he received a diagnosis of ARVC[100]. The last was a 29 year-old who died while sleeping: the autopsy revealed a structurally normal heart.

Eight (17%) people, all non-athletes, suffered OHCA during physical exercise but none occurred during organized sports activity. The incidence of OHCA was significantly lower among screened athletes than among non-athletes (1.1/100.000/year vs. 3,9/100.000/year, p<0,001).

2. Characteristics and outcome of athletes with ventricular arrhythmias and LV scar

Clinical findings

The clinical characteristics of the 3 study groups are shown in Table 5. There were no statistically significant differences with regard to sex and age among groups.

Table 5: clinical characteristics of the study population

	Group A VA and LGE N=35	**Group B VA and NO LGE N=38**	**Group C Controls N=40**	**P**
Age	33 (25-40)	28 (21-41)	29 (23-36)	0.28
Sex (male)	28 (80)	27 (71)	33 (83)	0.45
Sport				
Soccer	8 (23)	7 (18)	11 (28)	0.60
Running	7 (20)	9 (24)	9 (23)	
Volleyball	7 (20)	4 (11)	6 (13)	
Swimming	3 (9)	4 (11)	6 (15)	
Cycling	4 (11)	10 (26)	3 (8)	
Other	6 (17)	4 (11)	5 (13)	
Family history				
Negative	30 (86)	37 (97)		0.10
Cardiomyopathy	2 (6)	0		0.23
Premature sudden death	3 (9)	1 (3)		0.34
Personal history				
Negative	18 (51)	23 (61)		0.43
Cardiac arrest	2 (6)	0		0.60
Sustained ventricular tachycardia	5 (14)	0		0.02
Syncope	5 (14)	0		0.02
Pre-syncope	2 (6)	2 (5)		1.0
Palpitations	8 (23)	14 (37)		0.19
Chest pain	1 (3)	0		0.48

Electrocardiogram			
Normal	22 (63)	35 (92)	0.004
Low (≤ 0.5 mV) QRS in limb leads	7 (20)	1 (3)	0.02
Intraventricular conduction delay			
QRS duration 100-120 ms	3 (9)	2 (6)	0.67
QRS duration >120 ms	0	0	-
Pathologic Q-waves	2 (6)	0	0.23
T-wave inversion in V1-V3	1 (3)	0	0.48
T-wave inversion in V4-V6 ± 1/aVL	7 (20)	0	0.004
T-wave inversion in 2/aVF/3	2 (6)	1 (3)	0.60
Late potentials at SAECG	6/15 (40)	1/20 (5)	0.03
24-Hours ECG monitoring	30 (86)	35 (92)	0.47
Frequent (>500/day) PVB	20 (57)	18 (47)	0.40
Couplets and/or triplets	8 (23)	2 (6)	0.04
Non-sustained VT (≥4 PVB)	1 (3)	0	0.48
Sustained VT/VF			
Response to exercise testing			
No/suppression	9 (26)	15 (39)	0.21
Isolated PVB	16 (46)	19 (50)	0.71
Repetitive PVB	10 (29)	4 (11)	0.07
Echocardiogram			
Normal	30 (86)	38 (100)	0.02
Regional LV wall motion abnormalities	5 (14)	0	
Inducibility at PVS	3/10 (30)	-	
Endomyocardial biopsy			
Negative	4/6 (67)	-	
Myocarditis	1/6 (17)		
Fibro-fatty replacement	1/6 (17)		
ICD implantation	9 (26)	-	

EF=ejection fraction; ICD=internal cardioverter defibrillator; LBBB=left bundle branch block, LGE=late gadolinium enhancement; LV=left ventricular; PVB=premature ventricular beats; PVS=programmed ventricular stimulation; RBBB=right bundle branch block; SAECG=signal averaged electrocardiogram; VA=ventricular arrhythmias; VF=ventricular fibrillation; VT=ventricular tachycardia

The Group A included 35 athletes (80% males, mean age 33 years, range 14-48) with frequent PVB or complex VA and LGE at CE-CMR. Thirty (86%) had a negative family history for SCD or cardiomyopathies. Seventeen athletes (49%) had a positive personal history for ≥1 of the following events/symptoms: cardiac arrest (N=2), sustained ventricular tachycardia (N=5), syncope (N=5), pre-syncope (N=5), palpitations (N=8) and/or chest pain (N=1). No patient had a prior diagnosis of acute myocarditis.

The ECG was abnormal in 13 (37%) athletes and the most common abnormalities were low QRS voltages in limb leads (20%) and T-wave inversion in infero-lateral leads (20%). Signal-averaged ECG was positive in 6/15 (40%) athletes. In 28 (80%) athletes, 12-leads 24-hours ambulatory ECG monitoring recorded frequent PVB and/or complex VA with a predominant RBBB morphology (suggestive of LV origin) with superior axis (N=23), inferior axis (N=3), or intermediate axis (N=2); the remaining 7 (20%) had frequent isolated PVBs with a predominant LBBB/inferior axis morphology. On stress testing, VA occurred or worsened at the peak of exercise in 26 (74%) athletes. Echocardiography was abnormal in 5 (14%) athletes showing hypokinesis of the infero-lateral LV wall. Sustained ventricular tachycardia was induced by programmed ventricular stimulation in 3/10 (30%) athletes.

Endomyocardial biopsy was performed in 6 athletes: histopathological findings were consistent with focal acute myocarditis in one, segmental fibro-fatty replacement in two, and were normal in the remaining 3. Molecular pathology investigation by polymerase chain reaction (PCR) and reverse-transcriptase (RT)-PCR was negative for viral genomes.

The Group B included 38 athletes with frequent PVBs or complex VA and no LGE at CE-CMR. They significantly less often showed ECG changes, non-sustained ventricular tachycardia at 24-hours ECG monitoring and echocardiographic LV wall motion abnormalities compared with athletes of Group A. The majority (71%) of athletes of group B had VA with a predominant LBBB/inferior axis pattern.

Table 6 – Contrast-enhanced cardiac magnetic resonance findings

	Group A VA and LGE n = 35	Group B VA and NO LGE N=38	Group C Controls n = 40	p
Morpho-functional CMR				
Mild LV dilatation, No. (%)	9 (26)	5 (13)	3 (8)	0.08
LV EDVi (ml/m^2), mean±SD	95 (88-110)	94 (85-108)	92 (82-101)	0.18
LV EF (%), mean±SD	62 (59-68)	61 (58-66)	60 (57-65)	0.43
LV mass (g/m^2), mean±SD	72 (65-83)	75 (63-80)	80 (69-91)	0.29
Mild RV dilatation, No. (%)	6 (17)	10 (26)	5 (13)	0.28
RV EDVi (ml/m^2), mean±SD	90 (74-102)	93 (77-105)	90 (75-103)	0.11
RV EF (%), mean±SD	60 (58-62)	60 (57-66)	58 (55-64)	0.34
Post-contrast CMR		-		
RV LGE, No. (%)	0	-	0	-
LV LGE, No. (%)	35 (100)		10 (25)	0.001
Patterns		-		
Epicardial “stria”	27 (77)	-	0	<0.001
Junctional “spotty”	11 (31)		10 (25)	0.52
Regional distribution of stria		-		
Anterior wall	4/27 (15)	-	-	-
Lateral wall	24/27 (89)	-	-	-
Inferior wall	7/27 (26)	-	-	-
Septum	3/27 (11)	-	-	-
Apex (17° segment)	3/27 (11)		-	-

*All group A athletes had LV LGE and all group B athletes had no LV LGE by study design

CMR= Cardiac Magnetic Resonance; LGE= Late Gadolinium Enhancement; LV= Left Ventricular; EDVi = End-Diastolic Volume index; EF= Ejection Fraction; RV= Right Ventricular; VA=ventricular arrhythmias.

By study design, the 40 control athletes (Group C) had no VA and a negative routine cardiovascular evaluation.

CMR features

Findings of cine CMR and tissue characterization CMR sequences are reported in Table 6.

Group A

Mild LV dilation with preserved LV ejection fraction was detected in 9 (26%) group A athletes. Mild RV dilation in the absence of RV dysfunction was detected in 6 (17%) cases. At post contrast sequences, 27 (77%) showed an epicardial/midmyocardial "stria" pattern of LGE, which was associated with a junctional "spotty" LGE (i.e. LGE spot at the insertion points of the RV free wall to the interventricular septum) in 5 (Fig. 10 and 11).

The subepicardial/midmyocardial "stria" was localized in the lateral LV region in 24/27 patients, in isolation or in association with other regions. Three patients showed isolated involvement of the LV apical segments. The remaining 8 (23%) index athletes had isolated junctional "spotty" LGE at the posterior junction (N=7) or at both the anterior and posterior junctions (N=1). No patients exhibited right ventricular LGE.

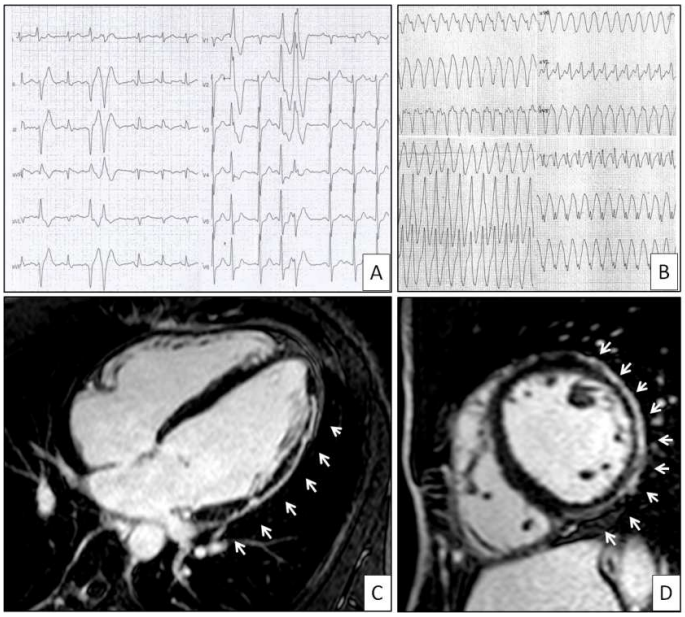

Figure 10: A 42 years-old martial art player presenting with frequent and coupled premature ventricular beats with right bundle branch block/superior axis morphology during exercise testing (A). The athlete experienced sustained ventricular tachycardia during follow-up (B). Contrast-enhanced cardiac magnetic resonance revealed a subepicardial/midmyocardial "stria" of late-gadolinium enhancement involving the antero-lateral, lateral and infero-lateral left ventricular wall (C).

Among the 27 athletes with a "stria" pattern, 5 (19%) had a positive family history, 8 (30%) a history of sustained ventricular tachycardia or cardiac arrest, 13 (48%) ECG changes, 5 (19%) echocardiographic abnormalities compared with none of the 8 index athletes with isolated junctional

"spotty" LGE. Moreover, all 27 athletes with a "stria" pattern had VA with a predominant RBBB morphology (suggestive of LV origin) compared with 1/8 (13%) of those with an isolated junctional "spotty" pattern.

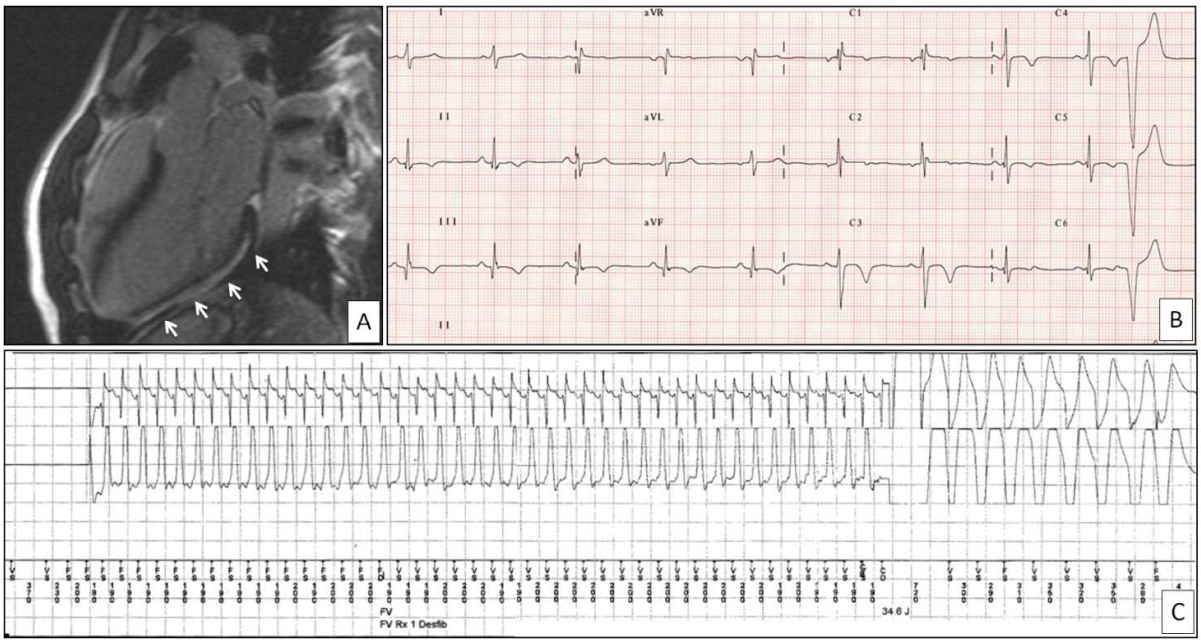

Figure 11: A 23 years-old soccer player who suffered syncope during a match.
Contrast-enhanced cardiac magnetic resonance revealed a subepicardial/midmyocardial "stria" of late-gadolinium enhancement involving the lateral left ventricular wall (A). Twelve-lead ECG showed T-wave inversion in the infero-lateral leads and premature ventricular beats (B). The patient received an ICD because of sustained ventricular tachycardia inducibility by programmed ventricular stimulation. After 13 months, he experienced an ICD shock on fast (tachycardia cycle length 200 ms) ventricular tachycardia while he was playing table tennis (C).

Group B

Mild LV and RV dilatation, in the absence of ventricular systolic dysfunction, was found respectively in 5 (13%) and 10 (26%) athletes of group B.

Group C

Mild LV dilation in the absence of LV dysfunction was found in 3 of 40 (8%) controls. Mild right ventricular dilation in the absence of right ventricular dysfunction was detected in 5 (13%) controls. At post-contrast sequences, 10 (25%) controls showed LV LGE, all with a junctional "spotty"

pattern. The junctional LGE spot was localized in the posterior junction, alone (N=8) or associated with anterior junction (N=2). No control exhibited right ventricular LGE.

Comparison among groups

At cine CMR, morpho-functional features did not significantly differ among the 3 groups. The epicardial/midmyocardial "stria" pattern was distinctively observed in athletes with VA (group A), while the prevalence of junctional "spotty" LGE was similar in athletes of Group A and controls (Fig. 12).

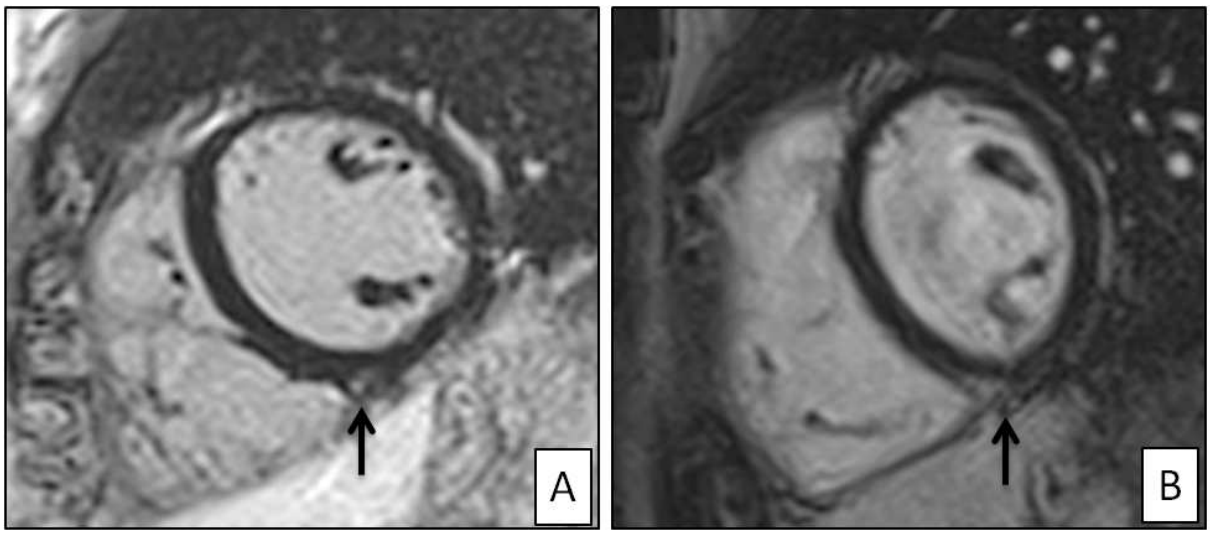

Figure 12: Short axis post-contrast cardiac magnetic resonance views of a 27 year-old rower with frequent premature ventricular beats with a left bundle branch block/inferior axis morphology (suggestive of right ventricular outflow tract origin).
(A) and in a 31 year-old healthy marathon runner without arrhythmias (B) showing late-gadolinium enhancement with a "spotty" pattern at the inferior insertion point of the right ventricular free wall to the interventricular septum.

Follow-up

Thirty-two athletes were restricted from competitive sports activity including all 27 index athletes with arrhythmias and a subepicardial/midmyocardial "stria" pattern of LGE, 1 athlete with complex VA and isolated junctional "spotty" pattern, and 4 athletes with complex, exercise-induced VA and no LGE. Twenty five athletes with demonstration of exercise-inducible LV arrhythmias and LV LGE were prescribed beta blockers and 9 group A athletes received an ICD for either secondary

prevention (cardiac arrest N=2; spontaneous sustained VT N=5) or primary prevention (syncope and inducible ventricular tachycardia by programmed ventricular stimulation, N=2).

During follow-up, 6 patients (all with a subepicardial/midmyocardial "stria" of LV LGE) experienced major arrhythmic events including appropriate ICD shocks (N=4), SD (N=1) and sustained ventricular tachycardia (N=1). Five of six events occurred during exercise. Three of them underwent programmed ventricular stimulation that was positive for sustained VT induction in 2. One patient had a progressive LV dysfunction leading over time to end-stage heart failure requiring heart transplantation 5 years after initial evaluation (Fig. 13).

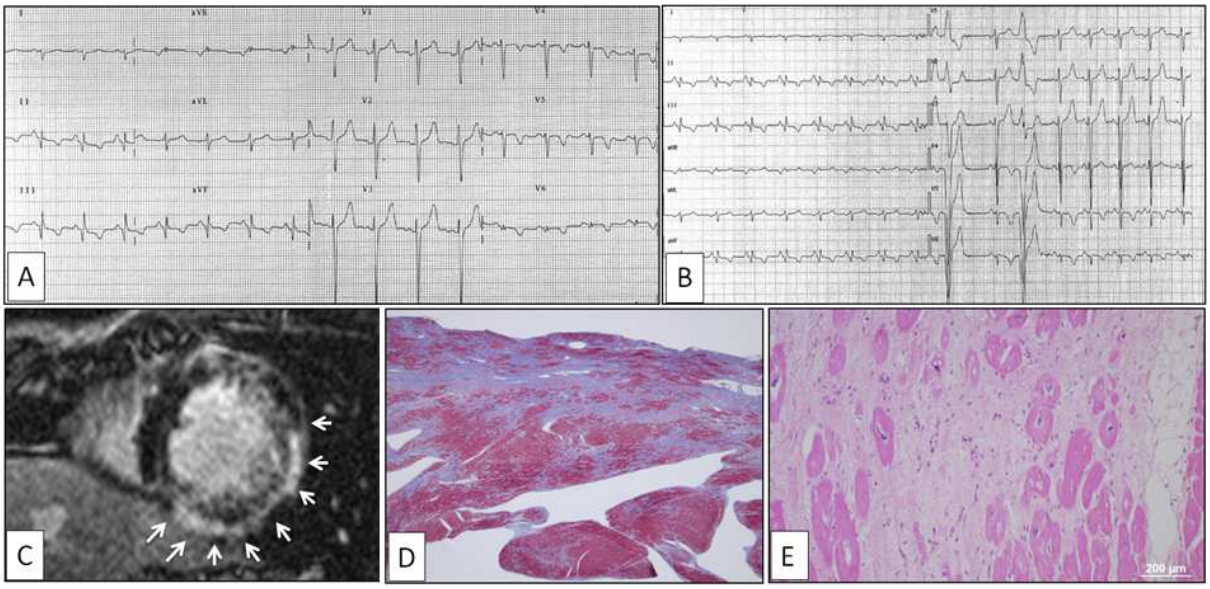

Fig. 13: A 18-years-old tennis player who underwent contrast-enhancement cardiac magnetic resonance for infero-lateral T-wave inversion at baseline 12-lead ECG (A) and frequent ventricular ectopic beats with a right bundle branch block/superior axis at exercise testing (B). Cardiac magnetic resonance revealed subepicardial/midmyocardial late-gadolinium enhancement with a "stria pattern" involving the infero-lateral left ventricular wall (C). During follow-up he developed progressive left ventricular dysfunction that led to refractory heart failure and heart transplantation. Panoramic view of the infero-lateral left ventricular wall of the removed heart showed extensive replacement-type fibrosis mostly in the subepicardial and mid-mural layers, with focal fatty infiltration (trichrome heidenhain stain) (D). At higher magnification, the residual cardiomyocytes are hypertrophic and show dysmetric and dysmorphic nuclei, with cytoplasmic vacuolization: note the diffuse fibrosis and patchy fatty infiltration (Haematoxylin-eosin stain) (E).

Both the athlete who died suddenly and the one who underwent heart transplantation had pathologic evidence of biventricular subpicardial and/or mid-mural fibro-fatty replacement, with a distribution in keeping with a diagnosis of “left dominant” ARVC.

A familial recurrence of the LV LGE was ascertained in two cases. The first was the cyclist who died suddenly. CE-CMR study demonstrated inferolateral LV LGE “stria” in his asymptomatic brother who was also a cyclist. The second was a volleyball player who sought medical attention because of frequent PVBs. The CE-CMR showed a non-ischemic LV LGE with a “stria” pattern involving both the lateral and the inferior LV free wall. The same CE-CMR features were observed in his asymptomatic identical twin brother (Fig. 14).

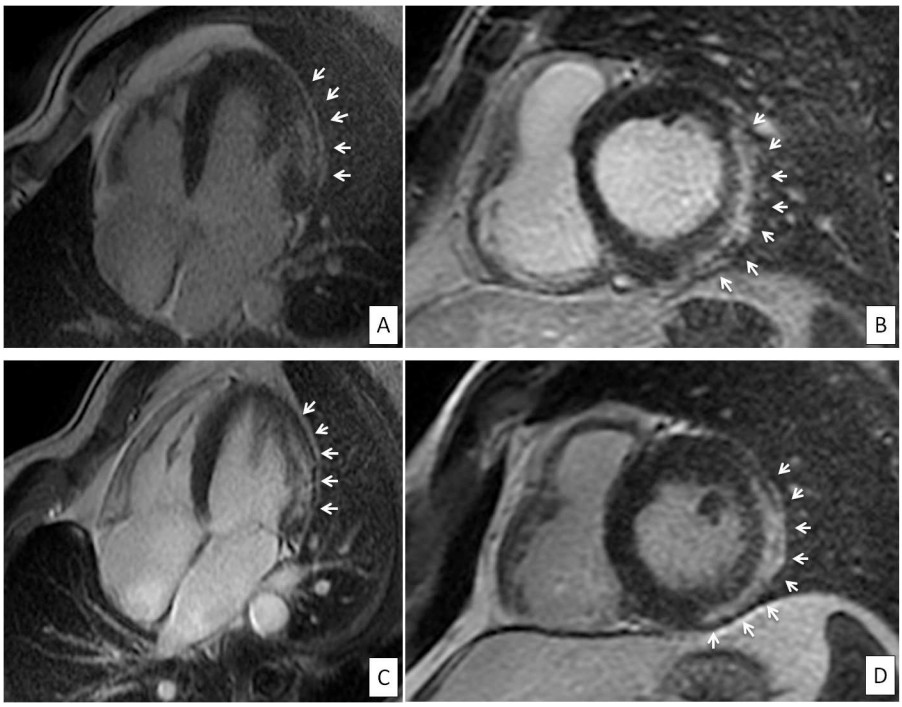

Figure 14: long axis (A,C) and short axis (B,D) post-contrast cardiac magnetic resonance views of two 34-years old identical twin brothers showing a subepicardial/midmyocardial “stria” of late-gadolinium enhancement involving the lateral and infero-lateral left ventricular wall.

Kaplan Meier analysis of freedom from malignant arrhythmias during follow-up showed that major arrhythmic events distinctively occurred in the subset of athletes with VA and a “stria” pattern of LV LGE at the time of enrollment (Fig. 15).

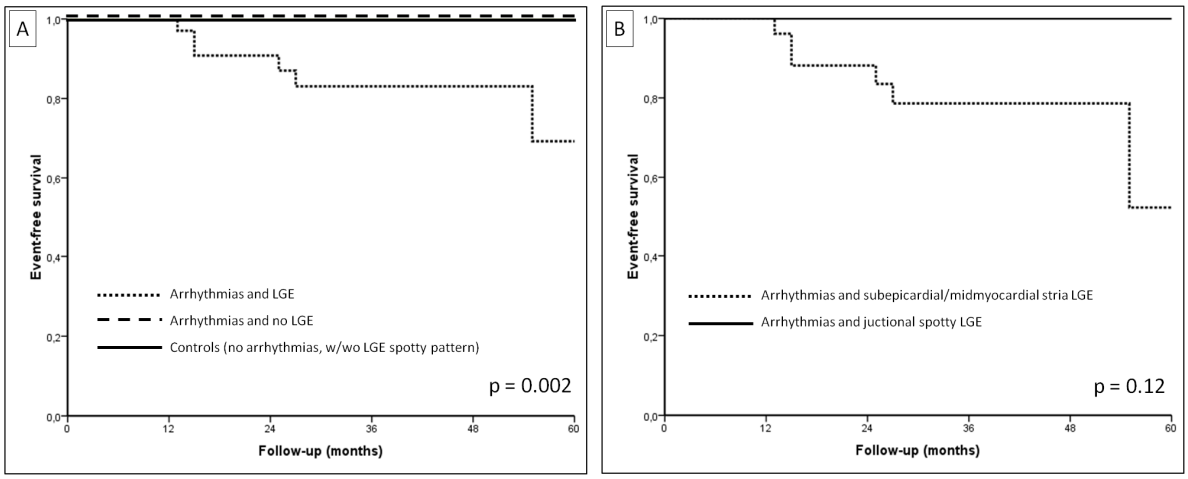

Fig. 15: Kaplan-Meier analysis for survival from major arrhythmic events

(A) Kaplan-Meier analysis for survival from major arrhythmic events in athletes with ventricular arrhythmias and late gadolinium enhancement (LGE), in athletes with ventricular arrhythmias and no LGE, and in controls (with or without “spotty” LGE) (B) Kaplan-Meyer analysis for survival from major arrhythmic events in the subgroup of athletes with ventricular arrhythmias and LGE according to specific LGE patterns (“stria” versus “spotty”).

3. Prevalence, predictors and clinical significance of VA in athletes

Characteristics of the study sample

The study population included 384 athletes with no history of structural heart disease who successfully completed at least 20 hours of recording (excluding artifacts and no-signal time) at 12-leads ambulatory ECG recording. The characteristics of the study sample are shown in table 7.

Table 7 – Characteristics of the study sample

	N=384
Median age (years)	29 (20-42)
Age classes	
16-20 year-old	116 (30.2%)
21-25 year-old	59 (15.4%)
26-35 year-old	70 (18.2%)
36-45 year-old	67 (17.4%)
>45 year-old	72 (18.8%)
Male gender	294 (77%)
Hours of practice/week	8 (6-9)
Hours of practice/week, classes	
6-9 hours/week	261 (68.0%)
10-13 hours/week	101 (26.3%)
>14 hours/week	22 (5.7%)
Hours of practice/year	350 (312-450)
Hours of practice/year, classes	
<350 hours/year	206 (53.6%)
350-600 hours/year	122 (31.8%)
>600 hours/year	56 (14.6%)
Years of sport activity	9 (5-16)
Years of sport activity, classes	
< 6 years	108 (28.1%)
6-10 years	129 (33.6%)
>10 years	147 (38.3%)
Type of sport (Mitchell classification)	

IB (low static - mod. dynamic)	31 (8.1%)
IC (low static - high dynamic)	142 (37.0%)
IIB (mod. Static - mod. dynamic)	25 (6.5%)
IIC (mod-static - high dynamic)	44 (11.5%)
IIIA (high static – low dynamic)	14 (3.6%)
IIIB (high static – mod. dynamic)	10 (2.6%)
IIIC (high static – high dynamic)	118 (30.8%)
Family history	
Negative	271 (70.6%)
Premature sudden death	16 (4.2%)
Coronary artery disease	92 (24.0%)
Cardiomyopathy	4 (1.0%)

Premature ventricular beats

The 12-leads ambulatory ECG monitoring recorded at least one PVB in 169 (56%) athletes. The distribution of percentiles of PVBs count according to the morphology is shown in table 8.

Table 8 - distribution of %iles of premature ventricular beats count according to the morphology

	5thiles	10thiles	25thiles	50thiles	75thiles	90thiles	95thiles
LBBB	0	0	0	0	1	6	49
Inferior axis	0	0	0	0	1	2	19
Interm. axis	0	0	0	0	0	0	1
Superior axis	0	0	0	0	0	2	3
RBBB	0	0	0	0	1	4	22
Inferior axis	0	0	0	0	0	1	3
Interm. axis	0	0	0	0	0	0	1
Superior axis	0	0	0	0	1	3	6
All morphologies	0	0	0	1	4	30	212
Excluding RVOT/Fascicular	0	0	0	1	2'	7	25

LBBB=left bundle branch block; RBBB=right bundle branch block; RVOT=right ventricular outflow tract

Thirty-eight athletes (9.9%) showed >29 PVBs/day and 17 (4.4%) >29 "uncommon" PVBs/day (i.e. excluding PVBs with a morphology suggestive of fascicular or right ventricular outflow tract origin). The univariate and multivariate analyses for predictors of >29 PVBs/day (both counting all morphologies and excluding morphologies suggesting right ventricular outflow tract/fascicular origin) are shown in Table 9-12.

Table 9 – characteristics of the study sample according to the presence of >29 PVBs/day (any morphology)

	≤29 PVBs/day N=346	**>29 PVBs/day N=38**	**P**
Age	26 (19-41)	43 (31-48)	<0.001
Male gender	263 (76%)	31 (82%)	0.44
Hours of practice/week	8 (6-9)	8 (6-10)	0.30
Hours of practice/year	340 (312-420)	390 (310-520)	0.09
Years of sport activity	9 (5-15)	15 (6-28)	0.009

Table 10 . multivariate analysis for predictors of the presence of >29 PVBs/day (any morphology)

	OR	**95% C.I.**	**P**
Age	1.05	1.02-1.08	0.02
Hours of practice/year	1.00	0.99-1-01	0.21
Years of sport activity	1.02	0-99-1.06	0.20

Table 11 – characteristics of the study sample according to the presence of >29 "uncommon" PVBs/day (excluding morphologies suggesting right ventricular outflow tract/fascicular origin)

	≤29 PVBs/day N=367	**>29 PVBs/day N=17**	**P**
Age	27 (19-42)	45 (36-51)	0.001
Male gender	279 (76%)	15 (88%)	0.38
Hours of practice/week	8 (6-9)	9 (7-10)	0.19
Hours of practice/year	350 (310-430)	380 (306-520)	0.21
Years of sport activity	9 (5-16)	13 (7-34)	0.07

Table 12 - multivariate analysis for predictors of the presence of >29 "uncommon" PVBs/day (excluding morphologies suggesting right ventricular outflow tract/fascicular origin)

	OR	95% C.I.	P
Age	1.05	1.02-1.08	0.002
Years of sport activity	1.03	0.99-1.06	0.14

At multivariate analysis, age was the only independent predictor of high PVBs count (Fig.16)

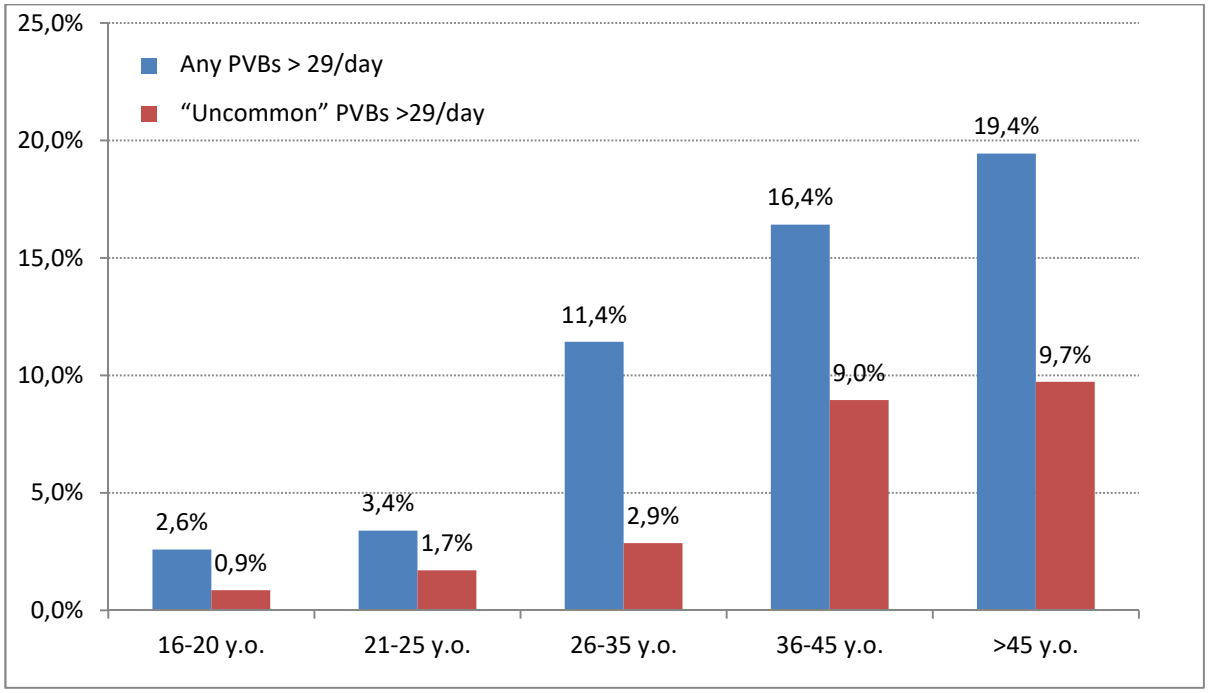

Figure 16: Prevalence of >29 PVBs/day considering any morphology and only "uncommon" morphologies (i.e. excluding morphologies suggesting right ventricular outflow tract/fascicular origin) according to age class.

Repetitive ventricular arrhythmias

Twenty-six (6.8%) athletes showed repetitive VA such as couplets (N=21, 5.5%), triplets (N=4, 1.0%) and non-sustained ventricular tachycardia of maximum 6 beats (N=8, 2.1%). Eight athletes exhibited isolated couplets with a LBBB/inferior axis morphology (suggesting origin from the right ventricular outflow tract) (Table 13). Age was the only predictor of the presence of repetitive ventricular arrhythmias at 24-hours 12-leads ECG ambulatory monitoring (Table 13 and Fig. 17).

Table 13: prevalence and type of repetitive ventricular arrhythmias such as couplets, triplets and non-sustained ventricular tachycardia (NSVT)

	N. of patients	% of patients
≥1 Couplet	21	5.5%
LBBB-like	13	3.4%
RBBB-like	9	2.3%
≥1 Triplet	4	1.0%
LBBB-like	2	0.5%
RBBB-like	2	0.5%
≥ NSVT	8	2.1%
LBBB-like	3	0.8%
RBBB-like	5	1.3%
Any repetitive VA	26	6.8%

LBBB=left bundle branch block; RBBB=right bundle branch block; VA=ventricular arrhythmias

Table 14 – characteristics of the study sample according to the presence of repetitive ventricular arrhythmias (VA)

	No repetitive VA N=358	Repetitive VA N=26	P
Age	27 (19-42)	36 (24-46)	0.04
Male gender	274 (77%)	20 (77%)	0.96
Hours of practice/week	8 (6-9)	8 (6-9)	0.17
Hours of practice/year	350 (312-450)	313 (300-426)	0.29
Years of sport activity	9 (5-16)	10 (5-26)	0.90

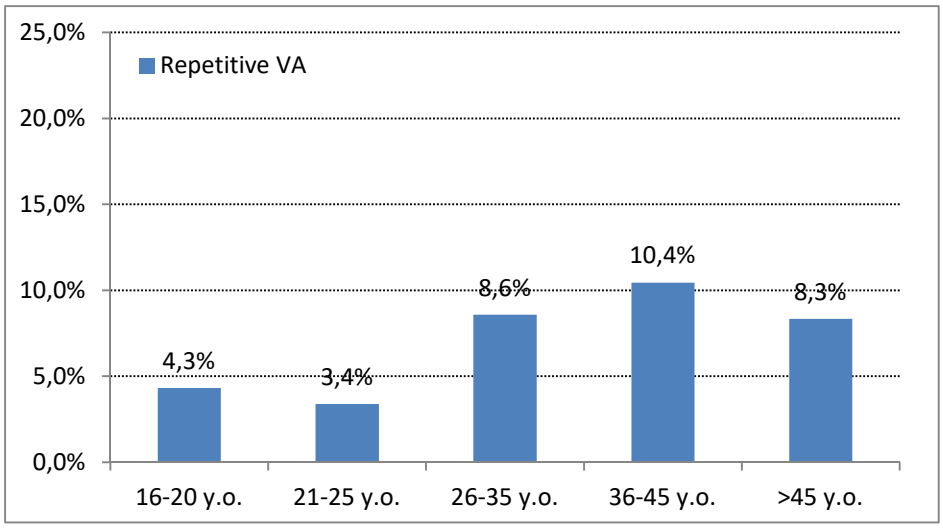

Figure 17: Prevalence of repetitive ventricular arrhythmias (VA) such as couplets, triplets and non-sustained ventricular tachycardia according to age class.

Echocardiography and CE-CMR findings

The breakdown of patients referred for second line investigations is shown in Figure 18.

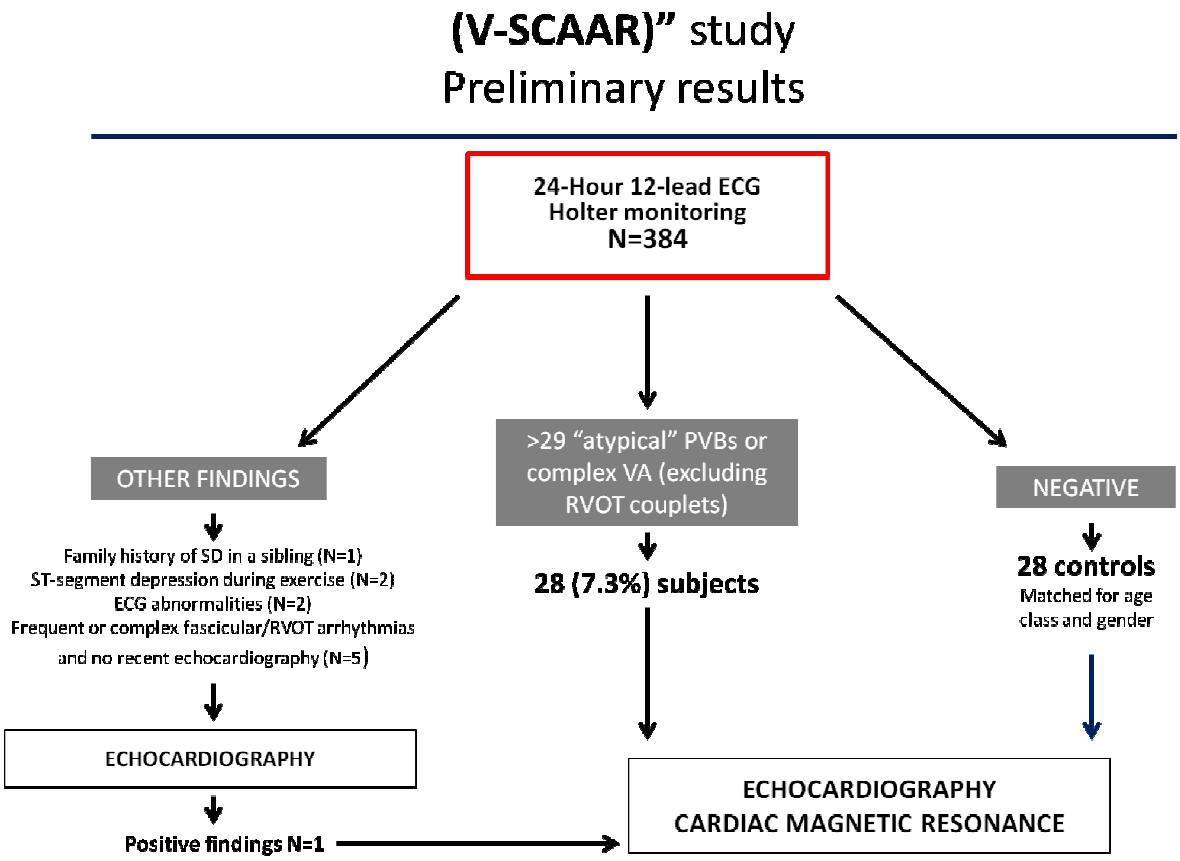

Figure 18 – Breakdown of patients undergoing second-line evaluation after 24-hour 12-lead ambulatory ECG monitoring.

Ten (2.6%) patients were offered echocardiography only (N=8) because of family history of juvenile SD (N=1), ECG abnormalities (N=2, consisting in right ventricular hypertrophy and T-wave inversion in V1-V3, respectively) and frequent PVBs/couplets with a morphology suggestive of right ventricular outflow tract/fascicular origin (N=5). Echocardiography was negative in all but one: in a 42-year old female runner with a family history of SD of unknown origin of a 35 year-old sister and of dilated cardiomyopathy in the mother, right ventricular apical akinesia was identified so that the athlete was prescribed CE-CMR, that confirmed the right ventricular apical akinesia and showed a midmyocardial "stria" of LGE involving the mid inferior LV segments (Fig. 19). She was referred for further evaluation to the Inherited Cardiomyopathy clinic. Two patients with exercise-induced ST-

segment depression during exercise underwent exercise-echocardiography that was negative for myocardial ischemia.

Twenty-eight (7.3%) athletes showed >29/day “atypical” PVBs/day and/or exercise-induced “atypical” PVBs and/or complex VA (excluding isolated couplet with a LBBB/inferior axis morphology) and thus fulfilled the criteria for undergoing echocardiography and CE-CMR. Twenty-eight athletes with no or few (<10/day) PVBs served as controls. The CE-CMR was technically satisfactory in all.

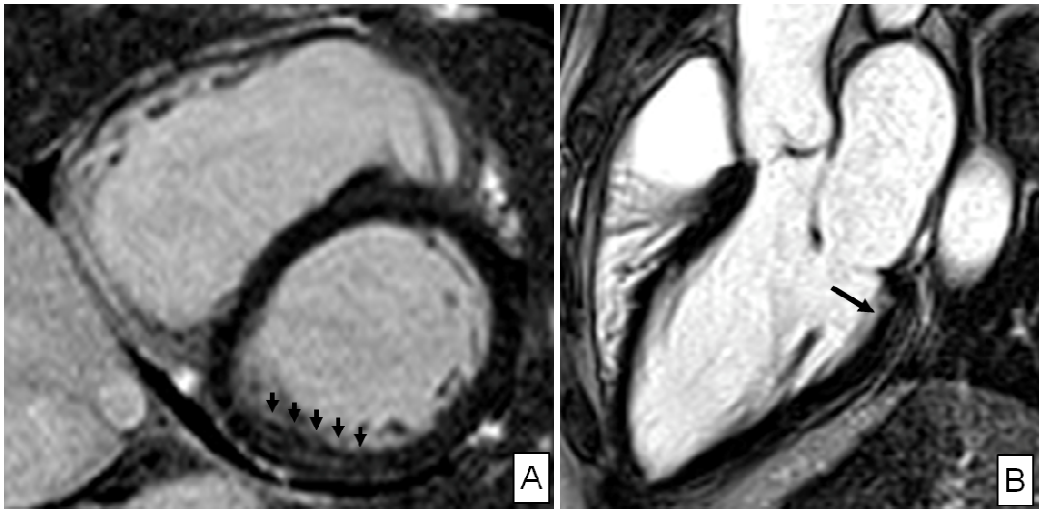

Figure 19 – Post-contrast cardiac magnetic resonance sequence, short axis (A) and three chambers long axis (B) views in a 42-year old female runner with a family history of sudden death.
The exam revealed a midmyocardial “stria” of LGE involving the mid inferior left ventricular segments. The 24-hour ambulatory ECG monitoring was negative.

Of the 28 subjects who were prescribed echocardiography and CE-CMR because of VA, none showed relevant morpho-functional abnormalities. However, in three athletes, all males and with negative family and personal history and no symptoms, LV-LGE suggestive of non-ischemic LV scar was revealed (Table 17). The CE-CMR was completely negative in all 28 controls.

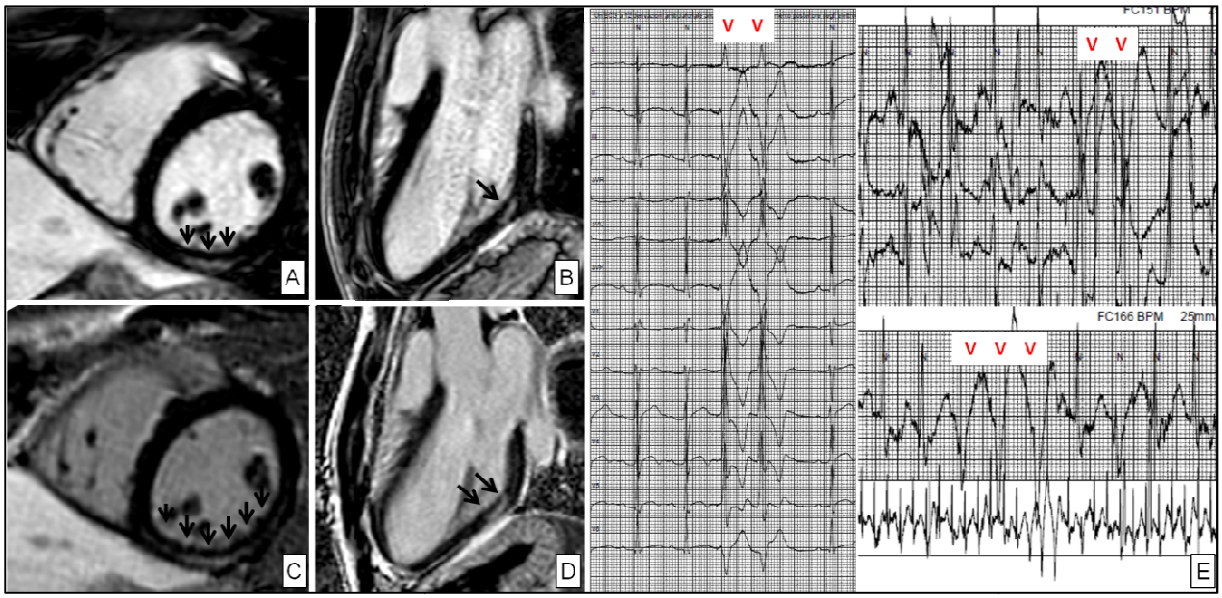

Figure 20 – Non-ischemic left ventricular late enhancement in a 17 year-old runner.
Post-contrast cardiac magnetic-resonance, short axis and three chambers long axis views at baseline (A-B) and after six months of follow-up (C-D) demonstrating a "stria" of late gadolinium enhancement with a subepicardial/midmyocardial distribution (suggesting non-ischemic origin) involving the basal portion of the infero-lateral left ventricular wall. The ambulatory ECG monitoring (E) demonstrated rare but exercise-induced ventricular arrhythmias with a right-bundle-branch-block/superior axis configuration, consistent with the origin from the scar area.

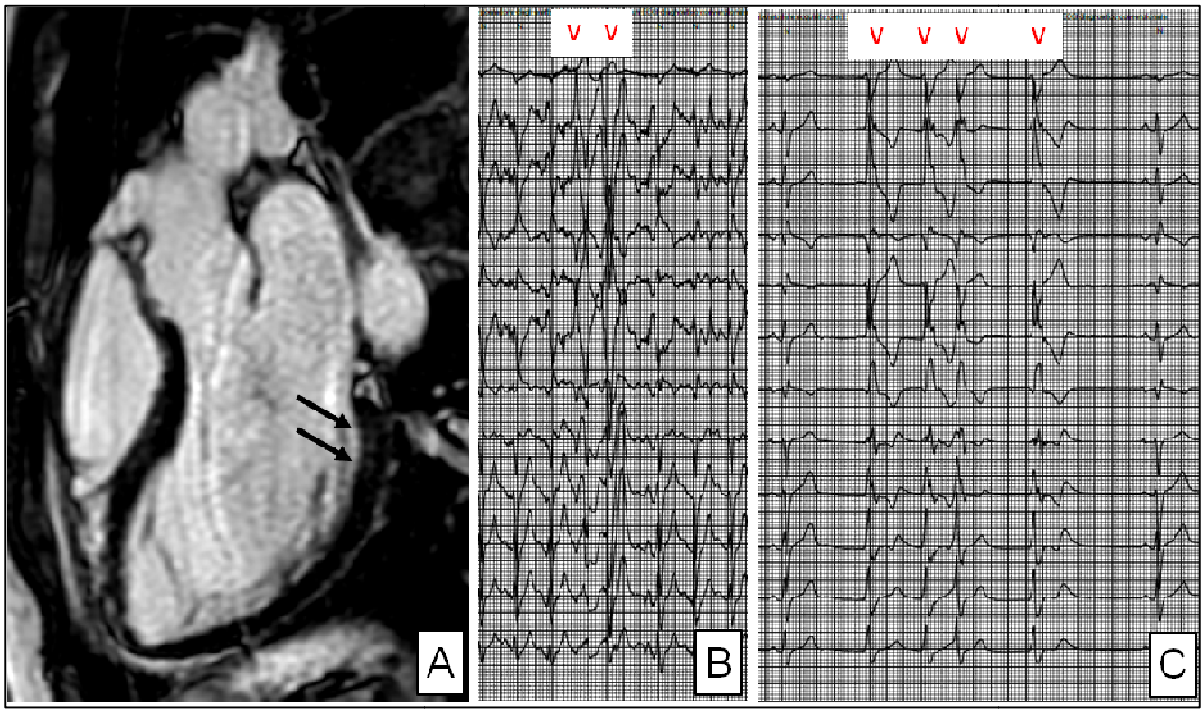

Figure 21 – Left ventricular late enhancement in a 30 year-old basketball player.
Post-contrast cardiac magnetic-resonance three chambers long axis view (A) demonstrating an intramural "stria" of late gadolinium enhancement involving the basal portion of the infero-lateral left-ventricular wall. The ambulatory ECG monitoring (B-C) demonstrated an exercise-induced ventricular couple and a run of non-sustained ventricular tachycardia of 4 beats at rest.

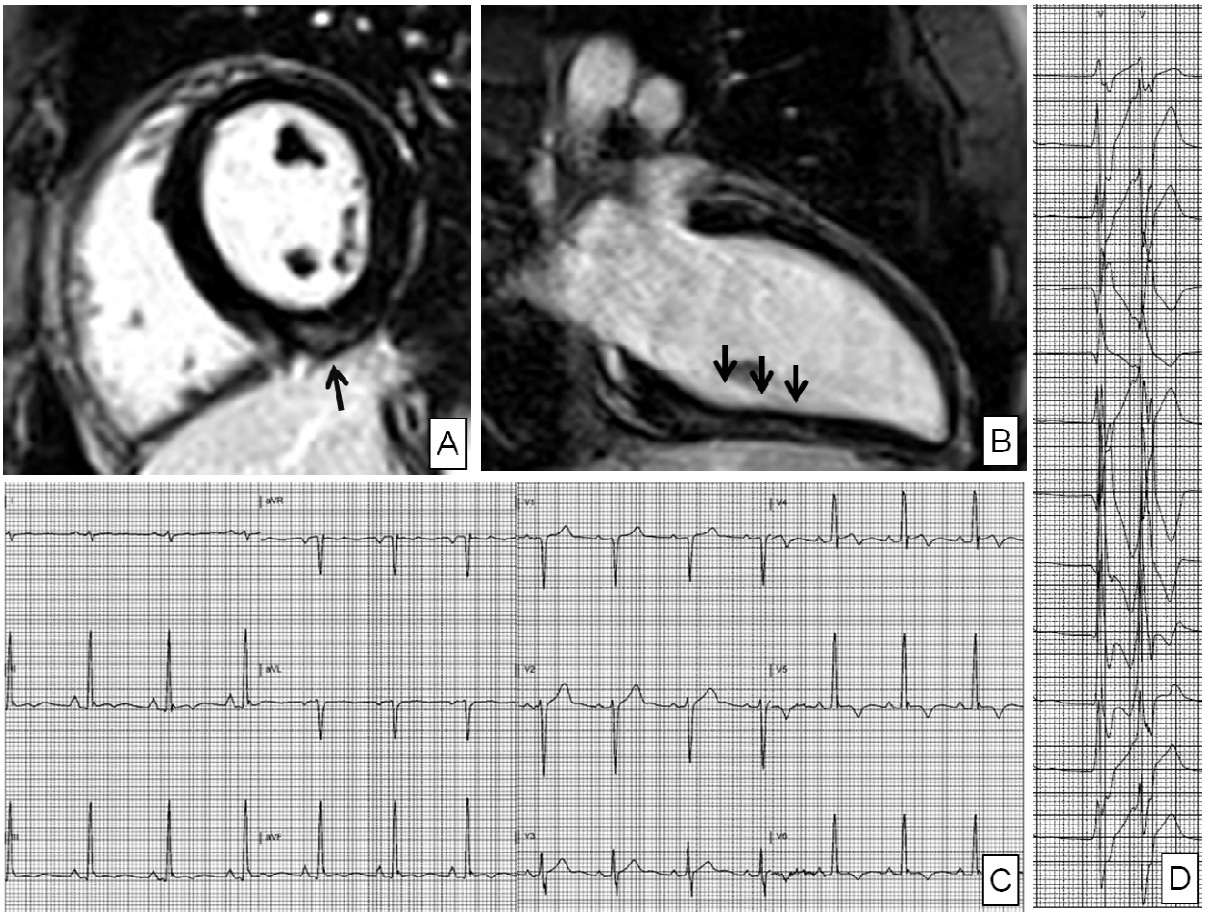

Figure 22 – Left ventricular late enhancement in a 27 year-old soccer player.
Post-contrast cardiac magnetic-resonance, short axis (A) and three chambers long axis (B) views demonstrating an intramural "stria" of late gadolinium enhancement involving the mid and basal segments of the inferior left ventricular wall. The baseline ECG demonstrated infero-lateral T-wave inversion that was considered benign at the time of preparticipation screening because of negative echocardiography. The ambulatory ECG monitoring recorded frequent isolated monomorphic premature ventricular beats and rare couples with the same morphology (right bundle branch block, inferior axis) (D) suggestive of an origin from the late enhancement site.

Table 17 – Characteristics of the three athletes with presence of non-ischemic left-ventricular scar

Age, sport	ECG	ECG monitoring	Exercise induced	Figure
17 year-old Running	Negative	Baseline: 53 isolated PVBs (RBBB/superior axis) 6-months FU: 15 isolated PVBs, 2 couples and 1 triplet (RBBB/superior axis)	Yes	20
30 year-old Basketball	Negative	1 couple (LBBB/superior axis) 1 run of 4 PVBs (RBBB/superior axis)	Yes	21
27 year-old Soccer	TWI V4-V6, II,III,aVF	747 isolated and 4 couples (RBBB/superior axis)	No	22

PVB=premature ventricular beats, LBBB=left bundle branch block, RBBB=right bundle branch block.

DISCUSSION

1. Juvenile cardiac arrest in the Padua province

The study included all cases of juvenile OHCA of presumed cardiovascular origin in the province of Padua in people 1-40 year-old, Veneto region, over a 4-years period, and demonstrated that the event is very rare under the age of 14 (0.7/100.000/year) but becomes relatively frequent between 15 and 30 year-old (4.0/100.000/year) and over 30 year-old (5.5/100.000/year).

A previous study about the incidence of SD of cardiovascular origin in the Veneto region in the age group 12-35 year-old among athletes and non-athletes during the period 1979-2004 demonstrated that at the beginning of the 80's the incidence of SD among athletes was 4.0/100.000/year. However, after the introduction of compulsory preparticipation screening in 1982, the incidence of SD among athletes progressively declined as to reach 0.4/100.000/year at the end of the study period. At the same time, the incidence of SD among non-athletes remained stable around 1/100.000/year[1].

The incidence of SD in the past and present study are not comparable because of the different age range and because the present study included all cases of OHCA (both resuscitated and not) of presumed cardiovascular origin while the past study included only cases of SD in which a cardiovascular disease was confirmed at postmortem investigation; however, it is of note that also in the present study the incidence of OHCA of presumed cardiovascular origin among screened athletes was significantly lower compared to unscreened non-athletes and that no athlete suffered OHCA during exercise.

Previous data demonstrated that cardiomyopathies were the most frequent causes of juvenile SD in the Veneto region in the 80's and 90's, particularly HCM and ARVC, followed by ischemic heart disease[1, 3]. The decrease in SD rate observed among athletes after the implementation of preparticipation screening was mainly due to the reduction of deaths due to cardiomyopathies,

which showed a decline from 36% to 16% throughout the study period[1]. The present study, which was performed in the modern era, showed that structurally normal heart and coronary artery disease were the most common causes of OHCA in the young and, in line with other recent studies, they appear to have surpassed the more traditional causes of SD (Table 2), perhaps because early identification of these conditions and risk stratification is more difficult. Moreover, it is of note that cardiomyopathies accounted for 10% (N=7) of juvenile OHCA in this study but only one case of HCM (a North-African immigrant whose previous clinical history was unknown) and one case of mild ARVC were diagnosed. Instead, the most frequent cardiomyopathy which accounted for OHCA in the Padua province in the modern era was the non-ischemic LV scar with a subepicardial/midmyocardial "stria" pattern.

2. LV scar (as suggested by LGE at CE-CMR) and ventricular arrhythmias

The analysis of morphology, regional location and wall distribution of LV LGE, both in the athletes presenting for VA and in control healthy athletes, allowed to identify two different patterns of non-ischemic LV LGE scar: "stria" and "spotty". The "stria" LGE pattern had a subepicardial/midmyocardial wall distribution, mostly (89%) the infero-lateral wall segments and was distinctively found in the group of athletes with VA. It was often associated with a history of sustained ventricular tachycardia or cardiac arrest and ECG changes such as low QRS voltages in limb leads and T-wave inversion in infero-lateral leads, and predicted a malignant arrhythmic outcome. Of note, 85% of athletes with a LGE "stria" pattern showed VA with a RBBB/superior axis configuration. This morphology is consistent with the origin of the arrhythmia from the infero-lateral LV segments, which was the region most frequently affected by LGE. The junctional "spotty" LGE pattern was typically localized in the basal segment of the inferior ventricular septum and the junction with the right ventricular free wall and was not associated with abnormal history or ECG findings and arrhythmic events during follow-up. Moreover, the majority of patients with isolated junctional

"spotty" LGE exhibited a LBBB/inferior axis arrhythmia configuration, suggesting that the arrhythmia originated from the right ventricular outflow tract and was unrelated to the LGE site. Similarly, athletes with arrhythmias but no LV LGE showed PVBs with a predominant LBBB morphology and an uneventful follow-up. Pooled together, these findings suggest that the combination of ventricular arrhythmias with a predominant RBBB morphology and LV LGE with a "stria" pattern identifies a clinical scenario at risk of malignant arrhythmic events during follow-up.

In our population of athletes with LV arrhythmias and non-ischemic LV LGE with a "stria" pattern, echocardiographic hypokinesis of the inferolateral LV segments involved by the subepicardial/midmyocardial scar as evidenced by CE-CMR was found in 5/27 (29%) patients. This finding is in keeping with the results of a previous study on a small series of athletes showing that 5 of 7 with subepicardial LGE had a normal echocardiography[78]. That non-ischemic LV scar is undetectable by echocardiography may be explained by the segmental nature of myocardial fibrosis confined to small myocardial area and involving outer wall layers without reaching the subendocardium, which is the part of the LV that contribute the most to myocardial thickening[101]. It is noteworthy that non-ischemic LV scar as evidenced by CE-CMR accounted for life-threatening arrhythmic events including SD during follow-up, despite the largely preserved global LV systolic function.

3. 12-leads ambulatory ECG monitoring for identification of concealed LV scar

The study aimed to prospectively evaluate a new protocol for pre-symptomatic diagnosis of concealed arrhythmogenic myocardial scar. The protocol consisted in offering 24-hours 12-leads ambulatory ECG monitoring (ECG-Holter) to apparently healthy athletes who have been considered eligible to competitive sports activity less than 1 year before enrollment. If the ECG-Holter recorded >29/day PVBs with uncommon morphologies (i.e. excluding fascicular and right ventricular outflow tract PVBs) or repetitive VA, CE-CMR was performed to rule out an underlying LV scar. To the best of our knowledge, this is the first study that performed 12-leads ECG-Holter to apparently healthy

volunteer athletes rather than athletes that were referred because of PVBs at preparticipation screening or palpitations[102-105].

At multivariate analysis, the presence of frequent PVBs (both of any morphology and only considering "uncommon" morphology) or repetitive VA significantly correlated with increasing age but not with the amount of sports activity.

In younger athletes (<35 year-old), even a relatively small number of PVBs may be related to an underlying LV scar and cannot be dismissed as normal finding. The results of our study suggest that in this age group more than the number, it is the morphology and relation to exercise of PVBs that may suggest the presence of a pathological myocardial substrate as suggested by the fact that all three athletes with LV scar at CE-CMR exhibited PVBs with a RBBB-like pattern (suggesting LV origin) and two of three distinctively showed exercise-induced arrhythmias. Conversely, the prevalence of frequent PVBs of uncommon morphology was higher in athletes over 35 year-old but no athletes in this age group exhibited a pathological myocardial substrate at CE-CMR. This confirms previous studies results suggesting that aging is associated with an increasing PVBs burden that does not necessarily correlate with an underlying cardiac disease[106-108].

The findings of this study, that for the first time included unselected volunteers (and not only athletes that were referred for arrhythmias at preparticipation screening), did not confirm the perspective that the amount of sports activity influences the PVBs burden[102-105]. In fact, at multivariate analysis, neither the years of sports activity nor the number of hours of practice per week significantly correlated with the presence of >29 PVBs/day at 24-hours ambulatory ECG monitoring. Further supporting this hypothesis is the comparison between the present study and the recent study by Hingorani et al.[109], who analyzed the 24-hours ambulatory ECG monitoring results of 1273 healthy volunteers <65 year-old included in phase 1 drug studies and found that the prevalence of PVBs >50/day, >100/day, >1000/day or >2000/day was comparable to that of our athletes (Table 16). Moreover, Hingorani et al. also found a higher prevalence and complexity of VA in volunteers 46-

65 year-old compared with 18-45 year-old. However, it has to be recognized that the to conclude with certainty that exercise is not related to ectopy a much larger study would be required.

Table 16 – Comparison between premature ventricular beats (PVBs) count in the present study and in the study by Hingorani et al.[109] including healthy volunteers from the general population.

	Hingorani et al. N=1273 General population	Present study N=384 Athletes	P
>0 PVB	551 (43.3%)	251 (57.3%)	P<0.001
>50 PVBs	150 (11.8%)	31 (8.1%)	0.06
>100 PVBs	116 (9.1%)	23 (6.0%)	0.07
>1000 PVBs	23 (1.8%)	8 (2.1%)	0.73
>2000 PVBs	13 (1.0%)	4 (1.0%)	1.0

Limitations of the studies

The three studies have some limitations that must be acknowledged. The main limitation of the first study (incidence and causes of juvenile OHCA) is that autopsy was not performed in 8 cases and, as a consequence, the distribution of causes of OHCA could not be precisely assessed. The second study (profile and outcome of athletes with VA and LGE at CE-CMR) observed a relatively small number of arrhythmic events during follow-up and, as a consequence, the power to detect associations was low. In particular, the small number of athletes with VA and junctional "spotty" LGE did not allow us to confidently conclude that this LGE pattern is associated with a benign outcome. The main limitation of the third study is that athletes were not consecutive but volunteers that were included only if they were considered eligible at preparticipation screening: hence, the prevalence and underlying substrate of VA in the general population of athletes cannot be reliably assessed. Although we did not find any athlete >35 year-old with LV LGE, VA may be related to coronary artery

disease that cannot be definitely rule out by a normal CE-CMR. However, none of our older athletes complained of symptoms suggestive of myocardial ischemia and all underwent maximal stress test within 1 year (required by the Italian Law as part of the preparticipation screening protocol in athletes >35 year-old) that resulted negative for ST-segment changes. Moreover, the conclusions are based on a relatively low number of athletes with arrhythmias and underlying ventricular scar and further studies are needed to confirm this findings.

Clinical implications

Taken together the results of the first two studies suggest that the non-ischemic LV scar with a “stria” morphologic pattern and subepicardial/midmyocardial distribution is an emerging cause of malignant VA and SD in the young and athlete and cannot be simply dismissed as a benign sign of a healed remote inflammatory process. In fact, this condition may be found also in cardiomyopathies (particularly the left-dominant variant of ARVC) and may represent an arrhythmic substrate regardless of its origin.

The results of these two studies raise the question as to how to identify asymptomatic and apparently healthy athletes with at-risk LV scar. The finding of a ≈50% prevalence of ECG abnormalities, either T-wave inversion in the infero-lateral leads or low QRS voltages in limb leads, in our athletes with a “stria” LGE pattern suggests the possibility that the disease may be suspected by ECG screening in some cases. However, because of its peculiar non transmural distribution which spares the subendocardial wall layer, the presence of LV scar is easily missed by echocardiography. As a corollary, in athletes presenting with frequent PVBs or complex arrhythmias (particularly with a RBBB pattern), particularly if associated with T-wave inversion in the infero-lateral leads or low QRS voltages in the limb leads, should be prescribed a CE-CMR to exclude an underlying arrhythmogenic substrate. However, many athletes with VA are asymptomatic and preparticipation screening that is

based on history, physical examination and resting 12-leads ECG, may have a limited sensitivity to detect arrhythmias. Hence, we performed a prospective study in which we enrolled volunteers athletes that were already considered eligible according to current preparticipation screening and tested the utility of 12-leads ambulatory ECG monitoring as a first-line investigation and CE-CMR as a second-line investigation (reserved to athletes with "atypical PVBs" or repetitive arrhythmias) to detect concealed LV scar. We found that this protocol may be particularly advantageous in healthy young athlete who usually show a very low arrhythmic burden and that demonstrated an high prevalence of underlying LV-scar at CE-CMR when "uncommon" PVBs (especially if exercise-induced PVBs with a RBBB configuration) are recorded. Although implementation of the 12-leads ambulatory ECG monitoring as a screening tool needs further validation, the study results suggest that the decision to perform CE-CMR in a young athlete with PVBs should be based on arrhythmia morphology (suggesting the origin) rather than the number (as benign PVBs such as fascicular and right ventricular outflow tract arrhythmias can be very frequent). As a consequence, the ambulatory 24-hours ECG monitor in an athlete should have 12-leads and the exam should include a training session, possibly of the same sport the athlete habitually performs.

The most appropriate management strategy of athletes with LV scar remains to be established. An isolated non-ischemic LV LGE is not listed by the current recommendations among the cardiac diseases at risk of SCD and requiring restriction or disqualification from competitive sports activity. Our findings indicate that, in the presence of a stria of LV LGE and VA, especially if worsened by exercise, athletes should prudentially refrain from practicing sports activity and physical exercise with high cardiovascular demand. Whether this should apply also to athletes with incidental finding of LGE in the absence of arrhythmias remains to be established. About the clinical management, by extrapolation from other arrhythmogenic disorders at risk of SD, ICD implantation is indicated in affected athletes who survived cardiac arrest due to ventricular fibrillation, experienced sustained ventricular tachycardia or had exercise-induced syncope. Successful mapping/catheter ablation of recurrent sustained ventricular tachycardia have been preliminary reported in patients

with inferolateral scar using an epicardial approach because the reentry circuit is located in the outer layer of LV wall[110]. Prophylactic beta-blocker therapy seems to be justified on the basis of the exercise test inducibility VA in the majority of our cases. However, such a therapy may not confer complete protection against life-threatening VA as shown by the significant incidence of appropriate ICD intervention on fast ventricular tachycardia during follow-up observed in our study population despite beta blockers. Of note, because the scar may be inheritable, a cascade family screening and clinical follow-up is warranted.

Finally, the results of these studies can form the basis for a number of future research projects as well as collaborative work with bigger numbers and therefore more definitive conclusions particularly on the etiopathogenesis of the LV scar, strategies for early diagnosis and risk stratification of affected individuals.

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