

The electrocardiographic abnormalities in highly trained athletes compared to the genetic study related to causes of unexpected sudden cardiac death

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Abstract

Background: Electrocardiograms in elite endurance athletes sometimes show bizarre patterns suggestive of inherited channelopathies (Brugada syndrome, long QTc, catecholaminergic polymorphic ventricular tachycardia) and cardiomyopathies (arrhythmogenic right ventricular cardiomyopathy, hypertrophic cardiomyopathy) responsible for unexpected sudden cardiac death. Among other methods, genetic analyses are required for correct diagnosis.

Objective: To correlate 12-lead electrocardiographic patterns suggestive of inherited channelopathies and cardiomyopathies to specific genetic analyses.

Design: Prospective study (2004-2007) of screening 12-lead ECG tracings in standard position and higher intercostal spaces V1 to V3 precordial leads, performed in athletes and normal sedentary subjects aged match. Genetic analyses of subjects with ECG abnormalities suggested inherited channelopathies and cardiomyopathies.

Setting: All cardiologic exams and electrocardiograms were performed at „Prof. Dr. C.C. Iliescu” National Institute of Cardiovascular Diseases (Bucharest, Romania). The genetic studies were done at „Mina Minovici” National Institute of Forensic Medicine (Bucharest, Romania).

Participants: 347 elite endurance athletes (seniors - 190, juniors - 157), mean age of 20; 200 subjects mean age of 21, belonging to the control group of 505 normal sedentary population.

Results: Seniors. RSR' (V1 to V3) pattern, in 45 cases (23.68%), 5 of them with questionable Brugada sign (elevated J wave and „coved” ST segment, < 2mm in one lead, V1. Typically, Brugada 1 sign was found in one case (0.52%) with no SCN5A abnormalities. One athlete (0.52%) had normal ECG and exon1 SCN5A duplication. MRI confirmed three arrhythmic right ventricular cardiomyopathy epsilon waves (1.57%), in one case. ST-segment elevation myocardial injury like in V1-V3 precordial leads in 34 athletes (17.89%). Genetic analyses-no gene mutations.

Juniors. Upright J wave was found in 43 cases (27.38%). Convex ST segment elevation in V1-V3/V4, in 39 cases (24.84%). Bifid T wave with two distinct peaks was found in 39 cases (24.84%), 5 of them with mild prolonged QTc (0.48"-0.56") and KCN genes mutations. Nine (5.73%) of the elevated ST segment juniors had questionable Brugada sign, two of which with KCN (n=1) and SCN5A (n=1) gene mutations. Ajmaline provocative test was negative in 4 and was refused by 5 subjects.

Conclusion: Bizarre QRS, ST-T patterns suggestive of abnormal impulse conduction in the right ventricle, including the right outflow tract, associated with prolonged QTc interval in some cases were observed in highly trained endurance athletes. The genetic analyses, negative in most athletes, identified surprising mutations in SCN5A and KCN genes in some cases.

• **Key words:** endurance athlete, electrocardiography, genetic analysis •

The medical society and athletes' community are extremely interested in the precocious identification of athletes' risk of sudden cardiac death. Pre-participating screening guidelines for athletic training are formulated by many scientific medical groups [1-5,7-10]. The frequent causes of sudden cardiac death in athletes younger than

35 years old are hypertrophic cardiomyopathy (HCM) 50%, idiopathic left ventricular cardiomyopathy 18%, coronary artery abnormalities 14%, arrhythmogenic right ventricular cardiomyopathy (ARVC), 2.23-20% [11,57]. In 3%, sudden cardiac death is associated with normal structural hearts. Inherited cardiac channelopathies

(Brugada syndrome, long QT syndroms, idiopathic ventricular fibrillation, polymorphic ventricular tachycardia) could be the causes for sudden cardiac death [11-14]. In the absence of any echocardiographic structural abnormalities, establishing the diagnosis is often difficult to achieve when the electrocardiograms of trained athletes often present findings considered abnormal by usual standards. The correct management includes detailed athlete's history, 12-lead electrocardiography, additional tests (i.e. 24h heart rhythm ambulatory monitoring, Ajmaline provocative test) and sometimes, targeted genetic analysis [15-18]. A genotype - phenotype analysis based on the electrocardiographic findings in elite endurance athletes was the purpose of our study.

Material and methods

Studied population

Endurance athletes

347 intensively trained athletes (Caucasians) participants in sports activity with high cardiovascular burden were chosen [19,20]. The sports were canoeing, rowing, football, hockey, tennis, swimming, and athletics. There were 190 senior and 157 junior athletes [20]. Senior athletes had trained intensively for 20-27 h /week for > 5 years and participated in World Championships and Olympic Games. The junior primary and final selections were at the age of 12-14 years old and 17-18 years old respectively.

Sedentary healthy population (controls)

The apparently normal (asymptomatic, normal physical examination, no detectable cardiovascular risk factors) sedentary population [21,25] of 505 subjects and participants were investigated for work eligibility in our Cardiology Department (Auto/Work License). Exclusion criteria for control subjects were coronary artery disease, valvular / congenital diseases, cardiomyopathies, heart failure, and cardiovascular drug therapy. None of the athletes and controls received any drugs. The protocol was approved by the Hospital Ethical Committee and informed consents were obtained from all subjects who enrolled in the study.

Study protocol

Clinical examination

The cardiologic examination included detailed personal and family history and complete physical examination [9,11].

Standard 12 - lead electrocardiography

ECG was recorded with a digital machine (MACC 5500 GE Medical Systems, Milwaukee, Wisconsin, USA) in all athletes and controls. ECG measurements were computer - assisted and independently manually controlled by two experienced electrocardiographic readers (CM,IS) unaware of clinical data and sports categories [22-24,36]. Disagreements regarding the measurements were resolved by consensus. An average of 3-5 cardiac cycles was used. Tracings were obtained >

24 hours after the last athletic activity. Recordings in higher right precordial V1-V3 intercostal spaces (six new positions: -V1 to -V3; -2V1 to -2V3) to detect the Brugada signs were performed in all athletes and sedentary normal subjects [26,27,32]. Ajmaline provocative test in standard 12-lead ECG and upper right V1-V3 precordial leads positions was indicated according to the current guidelines [33,61]. ECG parameters were evaluated according to actual criteria [22-24,36].

Standard electrocardiographic variables. Definitions.

We used the current electrocardiographic criteria [22,23] including:

- 1) normal sinus rhythm: heart rate 60-100 bpm;
- 2) normal QTc (Bazett) ≤ 0.39 " in men , ≤ 0.44 " in women;
- 3) borderline normal ECG : RSR' or rSr' pattern in V1 lead (QRS duration < 0.10", height < 7mm; r'wave < 2mm and r' < r; juvenile T wave (inversed T in V1-V3 precordial leads; usually deep < 2mm);
- 4) Q wave (≤ 0.5 mm in lead III; normal duration ≤ 0.03 " and height ≤ 0.4 mm in all leads);
- 5) J wave (Osborn; deflection that distort the QRS-ST junction usually in II,III,V4 to V6 leads);
- 6) upright T wave (beyond normal ≤ 0.5 mm in limb leads and ≤ 0.10 mm in precordial leads);
- 7) bifid T wave (T wave with two peaks different from U wave; possible delayed right ventricular repolarization);
- 8) ST-segment, normally isoelectric (within normal limits: elevation and depression ≤ 0.1 mm in limb leads, elevation ≤ 0.3 mm in V1-V3 precordial leads; measurements at 80 ms from the J point).

ECG patterns in highly trained endurance athletes [41-45,47-49,54]

A. Distinctly abnormal ECG, strongly suggesting cardiovascular disease:

- 1) striking increase in R or S wave voltage (≥ 35 mm) in any lead;
- 2) Q waves ≥ 4 mm in depth in ≥ 2 leads;
- 3) inverted T wave > 2mm in ≥ 2 leads;
- 4) left bundle branch block;
- 5) marked left ($\geq 30^\circ$) or right ($\geq 110^\circ$) QRS axis deviation;
- 6) Wolff-Parkinson-White pattern.

B. Mild abnormal ECG

- 1) increased R or S wave voltage (30 to 34mm) in any lead;
- 2) Q waves 2 to 3 mm in depth, in ≥ 2 leads;
- 3) T wave flat, minimally inverted or particularly tall (i.e. ≥ 15 mm) in ≥ 2 leads;
- 4) abnormal R wave progression in the anterior precordial leads;
- 5) left atria enlargement;
- 6) short PR interval (≤ 0.12 ").

C. Normal ECG or ECG with minor alterations (athlete's heart syndrome):

- 1) PR interval duration > 0.20";
- 2) R or S voltage, 25 to 29mm;
- 3) early repolarization;
- 4) RSR' pattern in V1 ,V2 of 0.12" in duration);

5) sinus bradycardia < 60 bpm.

For the Brugada syndrome: long QT syndrome, polymorphic ventricular tachycardia, ARVC and HCM the commonly adopted clinical and electrocardiographic criteria were used in the study [30,31,34,35,37-40,47-49].

Holter monitoring, indicated when necessary [28,29,46].

Echocardiography

Echocardiographic, standard Doppler and TDI analyses were performed by digital ultrasound machine (VIVID 3, GE Medical Systems, Milwaukee, Wisconsin, USA; Aloka α Grosound, Japan).

Measurements were done according to ASE criteria. (58)

Genetic study

Subjects with positive or questionable ECG patterns of inherited channelopathies / cardiomyopathies were enrolled.

Techniques. Genomic DNA (200µl blood) - QiAampDNA blood minikit (Qiagen).

SCN5A and KCN genetic mutations studies were performed with Multiplex Ligation-Dependent Probe Amplification (MLPA, MRC Holland). SALSA P108 for SCN5A and SALSA P114 for KCNQ1, KCNH2, KCNE1, KCNE2 , kit were used.(50,51,52,53,54,55,56)

Statistics

Results are expressed in mean value ± SD. Proportions were compared with the chi square test, where appropriate.

Results

Clinical characteristics of studied population

We examined 347 athletes (seniors 190; juniors 157).

Fig. 1 shows the athletes' distribution according to the type of sport and level of training.

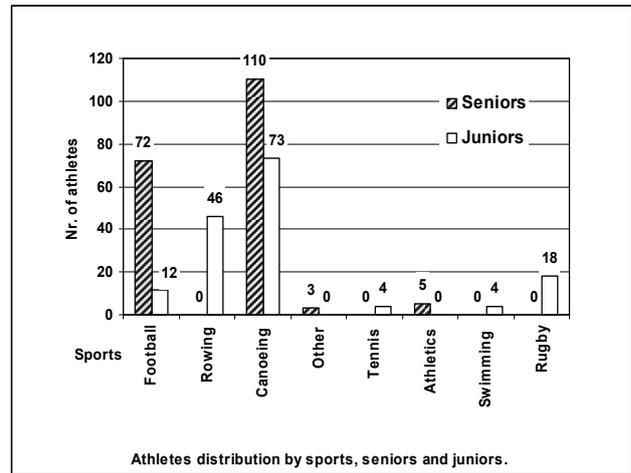


Fig. 1 190 seniors and 157 juniors athletes and their distribution according to type of sport

Athletes. There were 272 males (78.38%) and 75 females (21.6%). The athletes group characteristics: age 19.45 ± 4.82 years old (11-37), height (cm) 178.08 ± 8.99(140-200), weight (kg) 73.70 ± 12.33 (34-109), BSA (m²) 1.90 ± 0.19(1.15 - 2.37), blood pressure (mmHg) (110/65-140/85), heart rate (bpm) (32-110).

Controls. 505 normal sedentary subjects, 284 males (56.23%), 221 females (43.75%). Characteristics: age 34.93±10.88 years old (13-76), height (cm) 170.71±8.46 (134-195), weight (kg) 68.86±12.25 (29-125), BSA (m²) 1.79±0.18 (1.14 - 2.41), blood pressure (mmHg)(105/60-143/85), heart rate (bpm)(42-115).

The demographic data of the entire cohort of sedentary subjects is summarized in **Table1**, according to the decades of age.

No., number, BSA, body surface area, BP, blood pressure,systolic/diastolic; HR, heart rate.

Age (y)	No. (505)	Height (cm)	Weight (Kg)	BSA (m2)	BP(mmHg) mean	HR(bpm)
13 - 20	21	163.1±12.61	54.5±11.95	1.58±0.23	105/75	84±12
21 - 30	179	171.27±11.31	67.33±15.05	1.78±0.19	110/75	82±14
31 - 40	189	171.37±7.53	70.54±14.43	1.83±0.17	120/80	78 ±11
41 - 50	67	168.66±8.36	70.07±10.14	1.79±0.16	125/75	68 ±15
51 - 60	35	168.78±8.91	74.12±8.84	1.78±0.35	130/75	72 ±15
61 - 76	14	172±8.57	77.63±10.34	1.90±0.14	130/85	68±10

Table 1 Sedentary normal subjects group divided by decades of age

Electrocardiographic findings

All electrocardiographic parameters in athletes (n=347) are summarized in **Table 2**.

Senior athletes. RSR' pattern in high V1-V3 precordial leads in 45 athletes (23.68%) associated with ST elevation in 34 cases (17.89%). Coved ST segment elevation, suggestive for Brugada 1 sign in one lead only (standard/high V1; questionable Brugada sign) in 5 of ST elevation subjects. Provocative Ajmaline test – negative in 2 cases and refused by 3 subjects. Complex premature

ventricular beats (Holter, 24h), were found in 23 athletes (12.10%).

Brugada sign1, V1-V3 standard / high, one (0.52%) subject; EP induced ventricular tachycardia.

Epsilon wave, was found in 3 athletes (1.57%). Bifid T wave associated to prolonged QTc (0.48"± 0.09") was found in 8 athletes (4.21%).

There was a normal echocardiographic exam except for one epsilon subject and for ARVC echo data, diagnosed by MRI.

Junior athletes. RSR' (R'height 2.18 ± 0.56 mm) recorded in the V1-V3 upper precordial leads, 26 cases (16.56%); questionable Brugada sign in 9 athletes (5.73%). Ajmaline provocative test was negative in 4 cases and refused by 5 subjects. In juniors, the highest incidence of 12-leads ECG abnormalities were J wave elevation (1.32 ± 0.63 mm), 34c (27.38%) and ST-segment

convex injury elevation (elevation height 2.39 ± 0.79 mm, measured at 80ms from J point) pattern, 39c(24.84%) (Table 2). Bifid T waves associated to prolonged QTc intervals ($0.56'' \pm 0.07''$) were recorded in 5 subjects (Table 2). Long QTc associated with coved ST elevation in V1 (questionable Brugada sign) in 2 subjects.

SR, sinus rhythm; **Arrhyth**, arrhythmias; **WPW**, Wolff- Parkinson-White; **Std RSR'**, standard RSR' in V1-V3 leads; **High RSR'**, higher intercostal spaces; **ST-segm**, ST-segment elevation myocardial injury like; **T>15mm**, positive T wave >15mm; * $p < 0.01$; NS, insignificant

12 lead ECG	Athletes, seniors N=190 (%)	Athletes, juniors N=157 (%)
SR	190 (100)	156 (99.36)
Arrhyth	23 (12.10)	19 (12.10)
WPW	1 (0.52)	1 (0.63)
Std RSR' V1-V3 (mm)	16 (8.42) NS	9 (5.73) NS
High RSR' V1-V3 (mm)	45 (23.68) *	26 (16.56) *
J>0.5 V1-V3 (V4) (mm)	50 (26.31) NS	43 (27.38) NS
ST-segm V1-V3 (V4) (mm)	34 (17.89) NS	39 (24.84) NS
T >15 mm V1-V3 (V4)	23 (12.10) NS	31 (19.74) NS
Inversed T > 2 mm	8 (4.21) NS	9 (5.73) NS
Bifid T wave	23 (12.10) NS	39 (24.84) NS
Epsilon wave	3 (1.57)	-
Brugada 1 sign	1 (0.52)	-
Osborn	47 (24.73)	37 (23.56)
QTc int ($0.48'' - 0.56''$)	8 (4.21)	7 (4.45)

Table 2 12-lead ECG parameters in senior and junior athletes

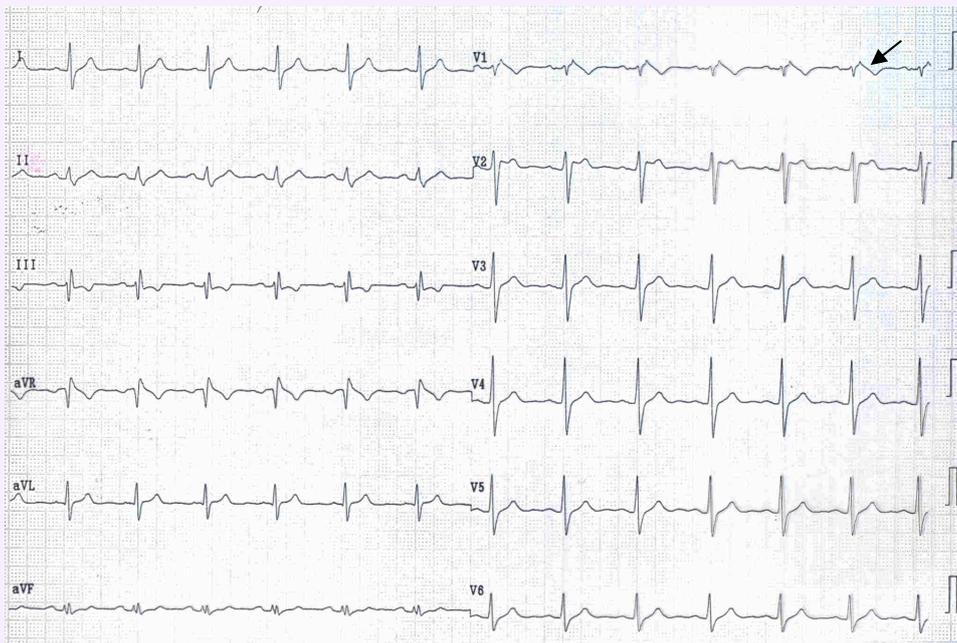


Fig. 2 Senior athlete with spontaneous Brugada sign 1 (arrow) on 12-lead ECG.

Holter method (for 24h) revealed complex premature ventricular beats (n=23 seniors), Wenckebach AV block (n=2 seniors), Wolff-Parkinson-White syndrome (one senior; one junior). Bicuspid aortic valve (n=1), HCM (n=1) and anomalous origin of the RCA from the left Valsalva sinus (n=1) recorded on echocardiography.

Normal sedentary subjects

According to the decades of age, 505 subjects' ECG characteristics are shown in Table 3. In the first 2 columns, 200 normal subjects (13-20y; 21-30y) match the athletes' age. In this subgroup (13-30 y; n=200) the ECG

abnormalities were: RSR' pattern in the V1-V3 upper precordial leads (n= 24; 12% of 200), J wave elevation (n=13; 6.5% of 200). In the decade of 31-40 years old,

one epsilon was recorded and ARVC was diagnosed on MRI. Typically Brugada 1 sign was detected in 3 cases (decade 21-50y) (Table 3).

N.B. Number, first % (related to age decade group) and second % (related to the 505 controls).

12 lead ECG	13-20y N=21	21-30y N=179	31-40y N=189	41-50y N=67	51-60y N=35	61-76y N=14
SR	21 (100) (4.15)	178 (99.44) (35.24)	189 (100) (37.42)	67 (100) (13.26)	35 (100) (6.93)	14 (100) (2.77)
WPW	2 (9.52) (0.39)	3 (1.67) (0.59)	-	2 (2.98) (0.39)	-	-
Std RSR' V1-V3 (mm)	1 (4.76) (0.19)	2 (1.17) (0.39)	6 (3.17) (1.18)	3 (4.47) (0.59)	-	-
High RSR' V1-V3 (mm)	5 (23.8) (0.99)	19 (10.61) (3.76)	24 (12.69) (4.75)	5 (7.46) (0.99)	1 (2.85) (0.19)	-
J>0.5 V1-V3 (V4) (mV)	1 (4.76) (0.19)	12 (6.70) (2.37)	18 (9.52) (3.56)	7 (10.44) (1.38)	3 (8.57) (0.59)	-
ST- segm V1-V3 (V4) (mV)	-	3 (1.67) (0.59)	-	-	-	-
T >15 mV, V1-V3 (V4)	-	2 (1.17) (0.39)	2 (1.05) (0.39)	1 (1.49) (0.19)	-	-
Inversed T >2 mm	-	8 (4.47) (1.58)	3 (1.58) (0.59)	1 (1.49) (0.19)	-	1 (7.69) (0.19)
Epsilon wave	-	-	1 (0.52) (0.19)	-	-	-
Brugada 1 sign	-	1 (0.56) (0.19)	1 (0.52) (0.19)	1 (1.49) (0.19)	-	-
Osborn	4 (19.04) (0.79)	33 (18.43) (6.53)	17 (8.99) (3.36)	9 (13.43) (1.78)	2 (5.71) (0.39)	1 (7.69) (0.19)

Table 3 Electrocardiographic findings in normal sedentary subjects divided by decades of age

Genetic analysis

227 athletes (114 seniors, 113 juniors) and 35 normal sedentary subjects were selected. The 12-lead ECG inclusion criteria for genetic analysis were:

- 1) Brugada sign;
- 2) questionable Brugada sign;
- 3) high RSR' precordial leads V1-V3 and R'>2mm >R and associated with complex PVB;

- 4) inverted T waves (>2 mm) in > 2 leads;
- 5) bifid T wave with distinct two peaks associated or not with prolonged QTc interval;
- 6) ST-segment convex elevation, injury like pattern;
- 7) epsilon waves.

In Fig. 3 the percent of the ECG abnormalities in senior and junior athletes selected for genetic analyses are presented.

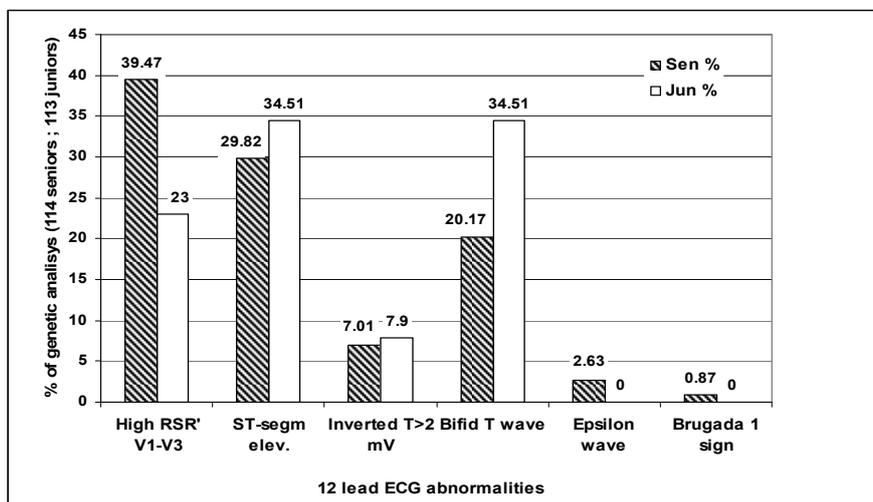


Fig. 3 ECG abnormalities percent in senior (n=114) and junior (n=113) athletes referred to genetic analysis

Seven junior athletes had mutations on KCN genes: KCNQ1 (n2), KCNE2 (n1), KCNH2 (n4); all mutations were missense (duplication) on exon 2 (n3), exon 4 (n2), exon 18 (n1) and exon 19 (n1). One of these athletes whose electrocardiograms are presented in Figure 4b,4b' had 2 mutations on 2 different KCN genes (KCNQ1, KCNH2) (Fig. 4a).

None of the senior athletes selected for genetic analysis had gene mutations except for one with SCN5 duplication, exon 1 (Fig. 6); normal clinical exam and negative specific tests for Brugada syndrome were done in this case. No SCN5A mutations in Brugada sign1 athlete and EP induced ventricular tachycardia.

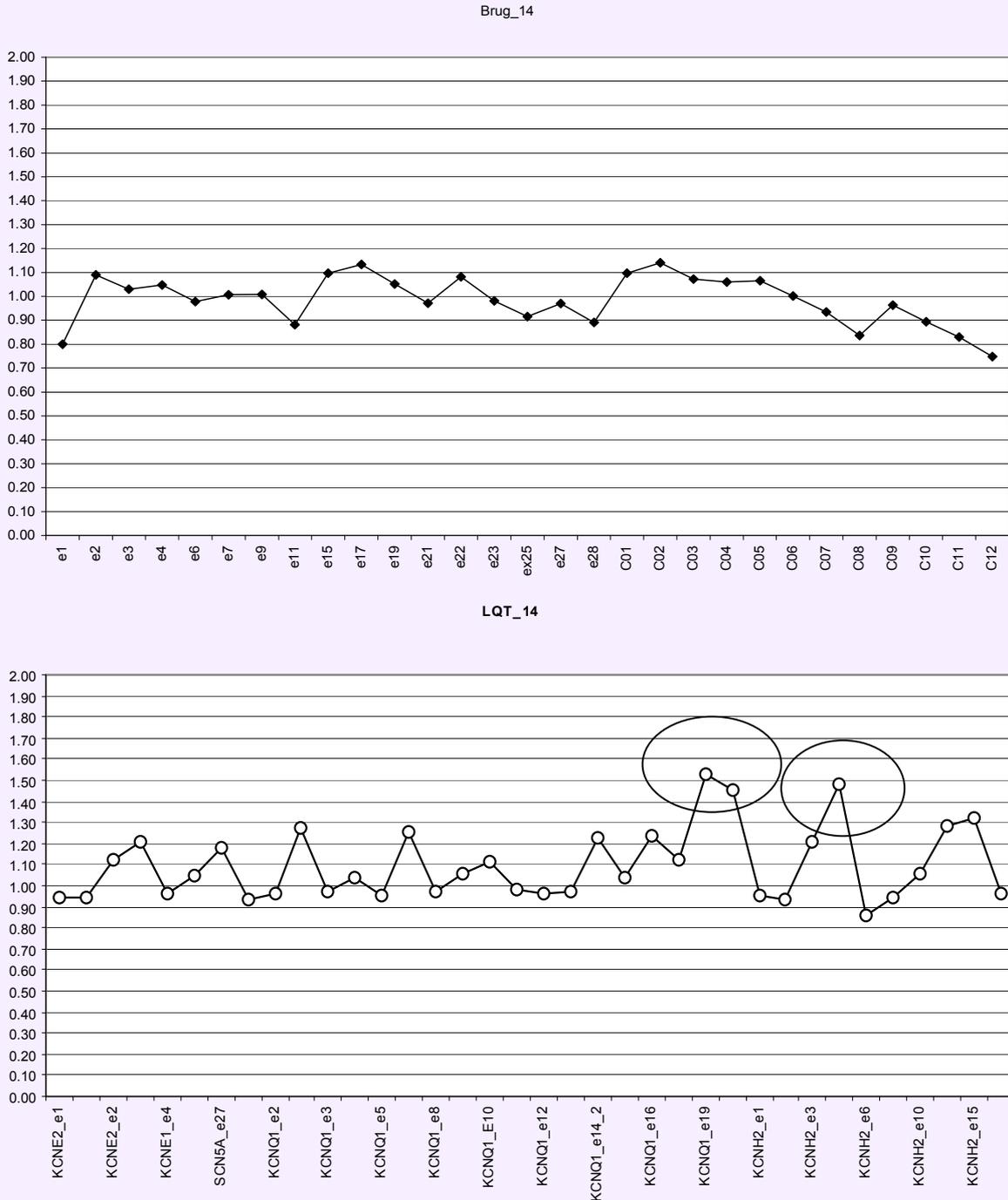
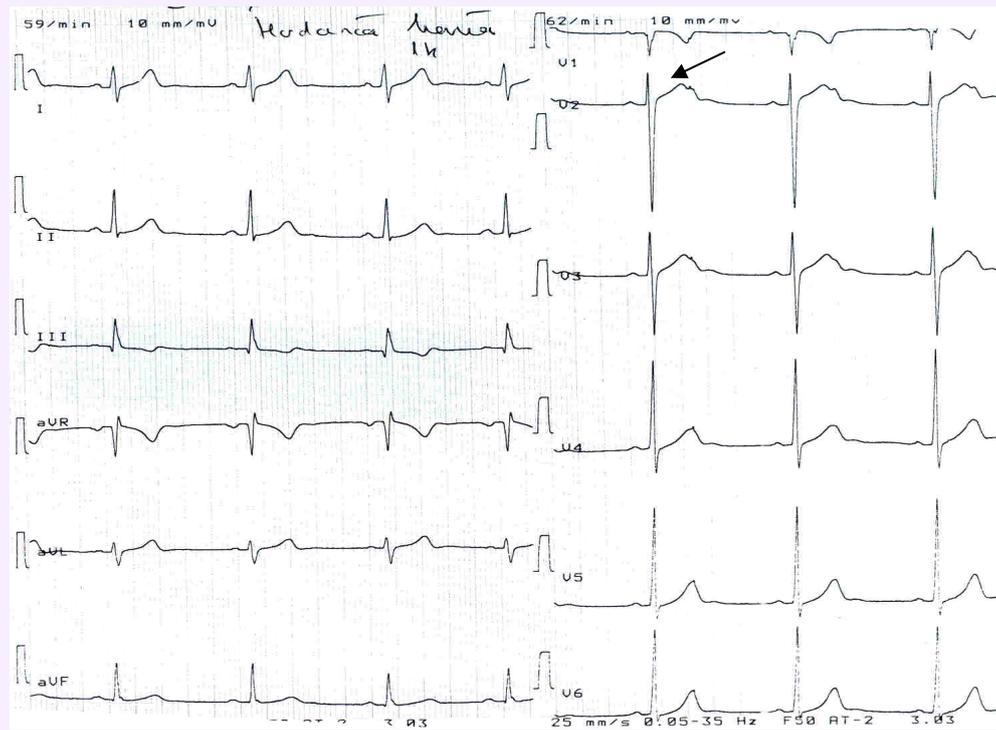
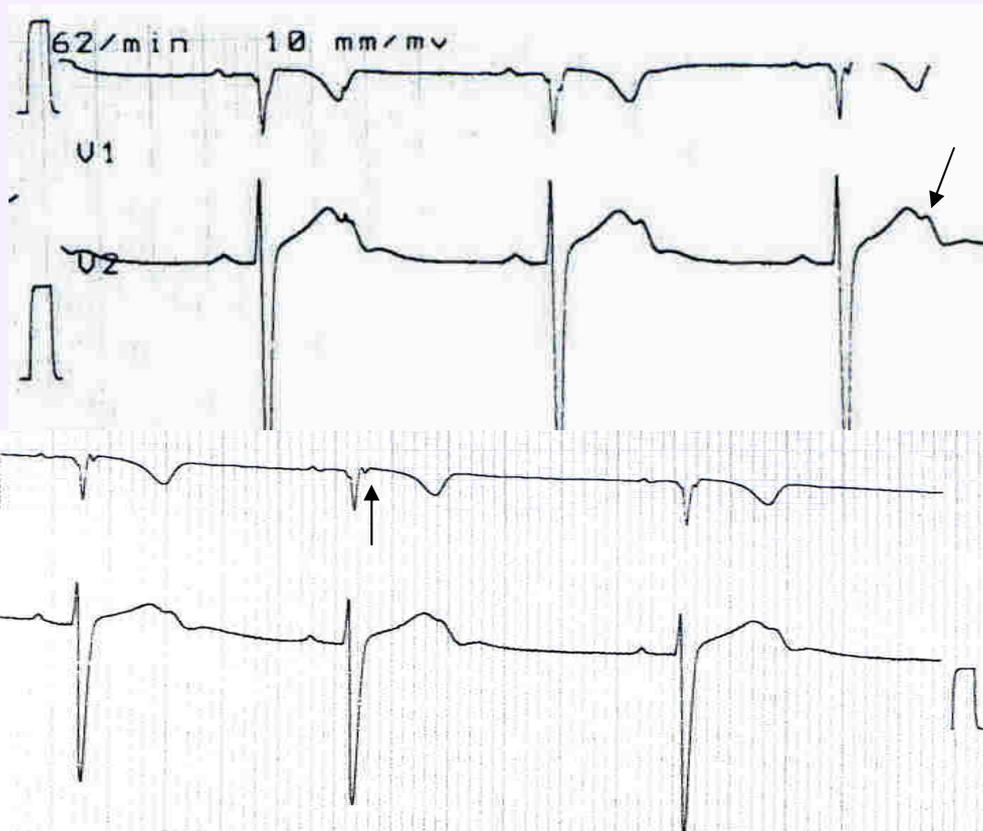


Fig. 4a Junior athlete. MLPA profiles for SCN5A gene (SALSA P108, upper panel) and for KCNQ1 and KCNH2 (SALSA P114, lower panel). Possible double mutations (duplication) for exon 18 KCNQ1 and exon 4 KCNH2 (Brug. SALSA P108; LQT. SALSA P114).



4b



4 b'

Fig. 4b, 4b' Electrocardiograms of two KCN genes mutations in junior athlete. In standard 12-lead ECG sinus rhythm 62 bpm; bifid T waves and distinct two peaks in V2, V3 precordial leads. (arrow) In higher V1, V2 leads (one upper) -bifid T waves are evident in V2 (arrow); (two upper spaces) - epsilon wave in V1 (arrow)

Athlete normal genetic profile for SCN5A and KCN genes are shown in Fig. 5.

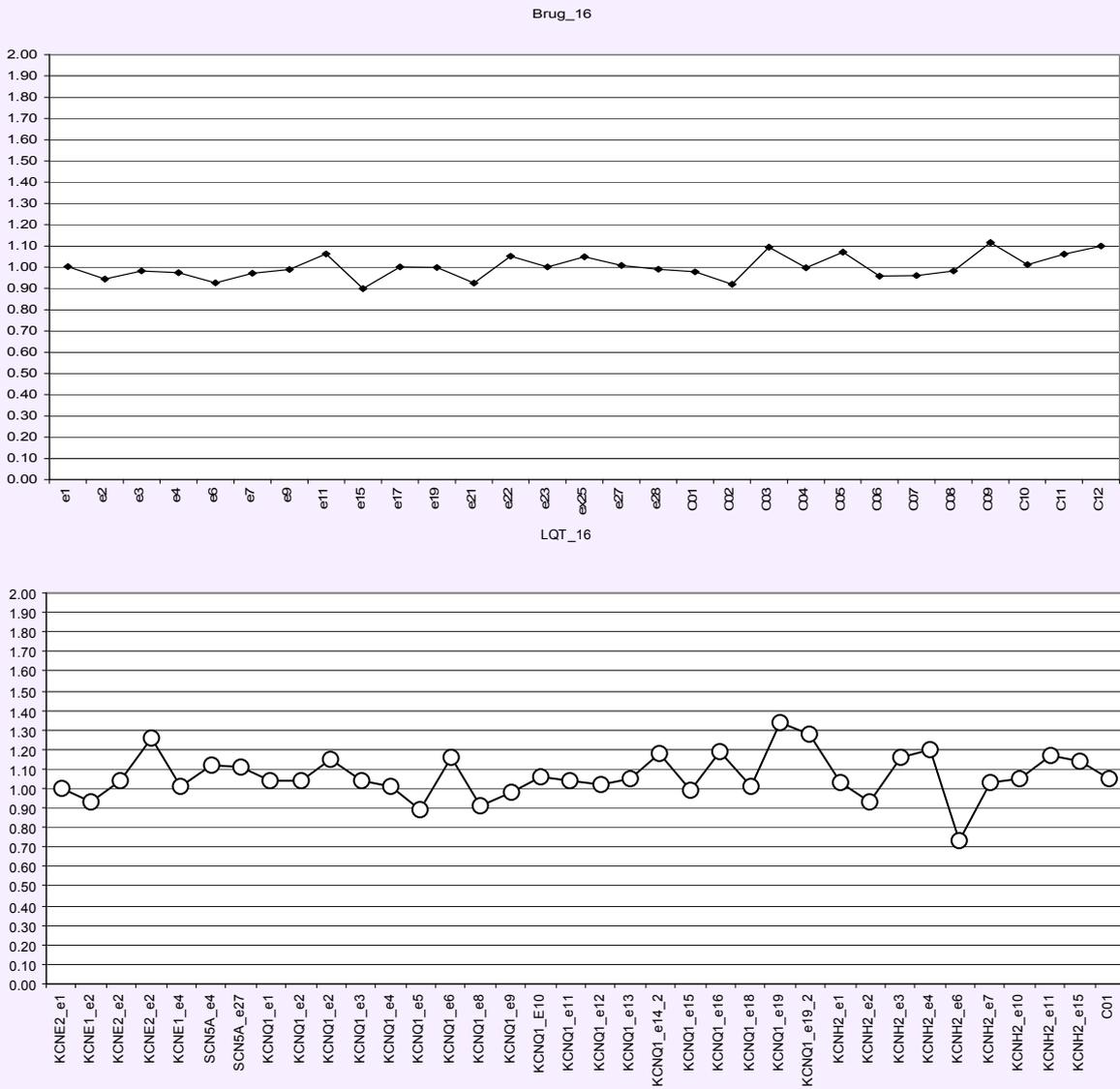
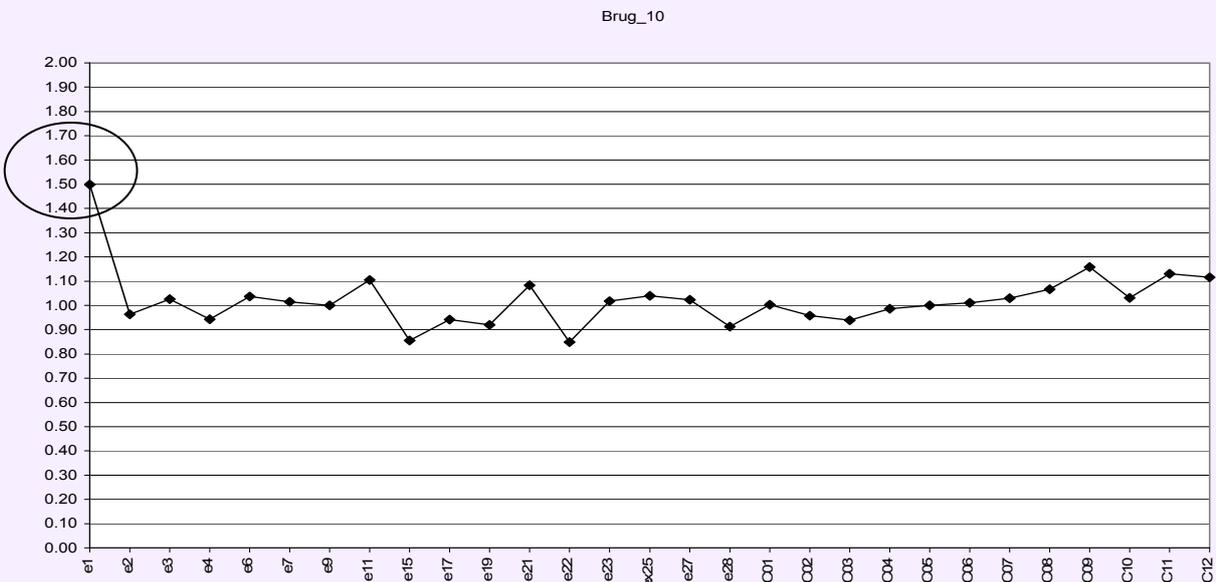


Fig. 5 Senior athlete. MLPA profiles for SCN5A gene (SALSA P108, upper panel) and for SCN5A, KCNQ1, KCNH2, KCNE1, KCNE2 (SALSA P114, lower panel). No detectable mutations. (Brug. SALSA P108; LQT. SALSA P114)

One senior athlete had missense mutation (duplication) on SCN5A gene, exon1 (Fig. 6).



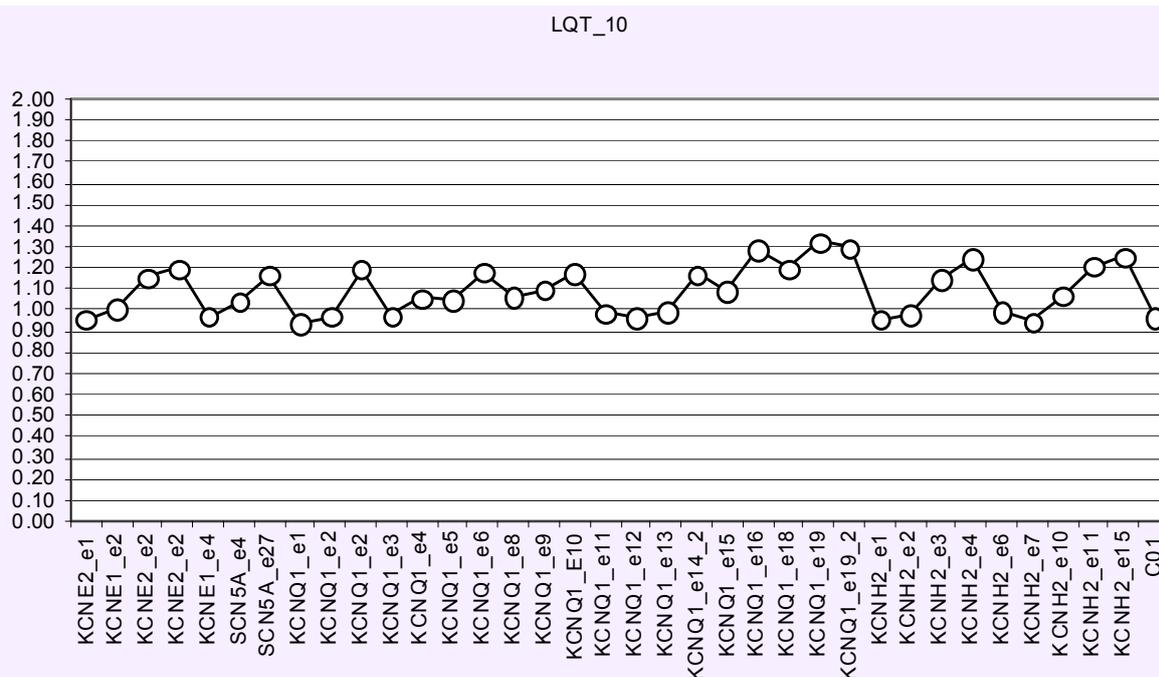


Fig. 6 Senior athlete. MLPA profiles for SCN5A (SALSA P108, upper panel) – possible exon1 duplication. SALSA P 114 (lower panel) for KCNE2, KCNE1, KCNQ1, KCNH2 normal profile. Brug. SALSA P108; LQT. SALSA P114)

Gene mutations and electrocardiographic associated abnormalities in athletes are summarized in **Table 4**.

N.B. dup, duplication; e, exon.

Athletes	KCNQ1	KCNE2	KCNH2	SCN5A	ECG
1	dup e 18	-	-	-	bifid T wave; QTc 0.52
2	-	dup e 2	-	-	bifid T wave; QTc 0.56
3	dup e 19 (19-1;19-2)	-	dup e 4	-	bifid T wave; QTc 0.48-0.50
4	-	-	dup e 4	-	QTc 0.56
5	-	-	dup e 2	-	inverted T wave; QTc 0.48
6	-	-	dup e 2	-	questionable Brugada
7	-	-	-	dup e 1	questionable Brugada

Table 4 Genes mutations and ECG abnormalities in 7 athletes.

In sedentary normal subjects, one subject with Brugada 1 sign and his healthy and electrocardiographically normal mother had similar mutations (deletion) on SCN5A gene, exon1. An epsilon sedentary normal subject (decade 31- 40y) had MRI documented ARVC; no gene mutations were detected, but his clinically and electrocardiographically normal sister had missense mutation (deletion) on SCN5A, exon1.

Discussions

Since 2004 we have been interested to evaluate the ECG patterns in highly trained athletes from different level of training (juniors, seniors) involved in sports with intensive cardiovascular burden. We observed ECG tracings with bizarre and unexpected QRS and ST-T aspects, different from the „classically” ECG patterns described in elite endurance athletes [20,58-61].

The main purpose of our study was to find out whether these ECG (V1-V3) morphologies (possible delayed impulse conduction in the right ventricle, including RVOT) were linked to genetic mutations responsible for inherited channelopathies (i.e. Brugada syndrome, RVOT ventricular tachycardias) and cardiomyopathies (i.e.ARVC). Gene mutations for HCM in subjects with specific ECG abnormalities were searched for.

The senior and junior athletes' electrocardiograms were analyzed separately and compared to sedentary normal, aged matched persons' ECG data. In seniors, the RSR' pattern dominate with R'>2mm in higher V1-V3 leads; 34% of RSR' athletes had ST-segment elevation, resembling the Brugada sign present in only one lead and V1 (questionable Brugada sign) in few cases. Possible abnormal (delayed) impulse conduction into RVOT has been considered regarding this mechanism [49].

The highest incidence of junior ECG abnormalities was elevated J wave and convex injury like ST-segment elevation in V1-V3,V4 leads (standard, high). In junior athletes, bifid T wave associated to moderately long QTc interval arose the question of a possible abnormal prolonged ventricular repolarization. Few of our controls had similar ECG abnormalities.

A molecular substratum not evident in ordinary life but exacerbated by strenuous training could be the cause of athletes' ECG abnormalities.

To support this hypothesis we focused on the relation between the ECG patterns suggestive of Brugada syndrome, long QT syndrome, HCM, ARVC and specific genetic study.

The genetic analysis referred to mutations in SCN5A and LQTS genes and genes responsible for inherited cardiomyopathies.

Junior athletes had 7 mutations in LQTS genes (KCNQ1, KCNH2, KCNE2) one of them with two KCN mutations, on KCNQ1 and KCNH2. All seven abnormalities were missense (duplication) mutations on exons 2,4, 18 and 19.

Three controls had SCN5A mutations: two of these (deletions) were in 1 Brugada person and his healthy mother. Interestingly, a family member (healthy sister) of a documented ARVC patient had a SNC5A mutation (duplication). All SCN5A mutations were missense, heterozygote type.

No specific molecular abnormalities were found in other athletes.

The mutations identified by MLPA will be detailed by complex genetic analyses such as the sequence techniques.

Conclusions

The electrocardiogram in athletes performing high endurance training is sometimes strange, looking like inherited channelopathy and cardiomyopathy ECG patterns. Specific tests for correct diagnosis are frequently necessary. Genetic analysis, the „last step” to diagnosis sometimes gives surprising and unexpected information, whose significance needs to be investigated. Complex molecular techniques could bring forward details of these genetic mutations identified in elite athletes with „frequently encountered 12-lead ECG athletics patterns”.

The next and future medical approach regarding the athletic performance is still a challenge for the scientific medical community.

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Abbreviations:

EP- electrophysiologic study

ECG = electrocardiographic/electrocardiography

HCM=hypertrophic cardiomyopathy

ARVC = arrhythmogenic right ventricular cardiomyopathy

RVOT=right ventricular outflow tract

RCA=right coronary artery

PVB=premature ventricular beats

References

- Maron BJ, Thompson PD, Ackerman MJ et al.** Recommendations and considerations related to pre-participation screening for cardiovascular abnormalities in competitive athletes: 2007 update. A scientific statement from American Heart Association council on nutrition, physical activity and metabolism. Endorsed by the American College of Cardiology Foundation. *Circulation* 2007; 115:1643-1655.
- Pelliccia A.** The pre-participation cardiovascular screening of competitive athletes: is it time to change the customary clinical practice? *Eur Heart J* 2007, 28:2703-2705.
- Corrado D, Pelliccia A, Bjornstad NH et al.** Cardiovascular pre-participation screening of young competitive athletes for prevention of sudden death: proposal for a common European protocol consensus statement of the study group of sport cardiology of the Working Group of Cardiac Rehabilitation and Exercise Physiology and Working Group of Myocardial and Pericardial Disease of the European Society of Cardiology. *Eur Heart J* 2005; 26:516-24.
- Maron BJ, Zipes DP.** 36th Bethesda Conference: eligibility recommendations for competitive athletes with cardiovascular abnormalities. *J Am Coll Cardiol* 2005; 45: 1313-75
- Crawford MH.** Screening athletes for heart disease *Heart* 2007; 93:875-879.
- Harris KM, Sporsel A, Hutler AM et al.** Cardiovascular screening practices of major North American professional sports teams. *Ann Intern Med* 2006; 145:507-11
- Maron BJ, Thompson PD, Puffer JC et al.** Cardiovascular pre-participation screening of competitive athletes. *Circulation* 1996, 94:850-6
- Fuller CW, Ojelode EO, Toyler A.** Pre-participation medical evaluation in professional sport in the UK: theory or practice? *Br J Sports Med* 2007, 41:890-896
- Corrado D, Basso C, Pavei A et al.** Trends in sudden cardiovascular death in young competitive athletes after implementation of a pre-participation screening program. *JAMA* 2006; 296:1593-601.
- Wappes JR** (executive editor) Pre-participation physical evaluation, 3rd Ed. Minneapolis; McGraw - Hill, 2005.

11. **Corrado D, Basso C, Rizzoli G et al.** Does sport activity enhance the risk of sudden death in adolescents and young adults? *J Am Coll Cardiol* 2003; 42:1959-1963.
12. IOC Medical Commission, International Olympic Committee. Sudden cardiovascular death in sport: Lausanne Recommendations: Pre-participation cardiovascular screening. December 10, 2004. http://www.olympic.org/pdf/en_report_886.pdf.
13. **Maron BJ.** How should we screen competitive athletes for cardiovascular disease? *Eur Heart J* 2005; 26:428-30.
14. **Hammill SC.** Heart Disease in athletes. In: Joseph G. Murphy, Margaret A. Lloyd: *Mayo Clinic Cardiology*, 3rd Ed, Mayo Clinic Scientific Press, 2007, Ch. 38, pp 507-508
15. **Maron BJ, Pelliccia A.** The heart of trained athletes: Cardiac remodeling and risk of sports, including sudden death. *Circulation* 2006; 114; 1633-1644.
16. **Pelliccia A, Maron BJ, Culasso F et al.** Athlete's heart in women: echocardiographic characterization of highly trained elite female athletes. *JAMA* 1996; 276:211-215
17. **Corrado D, Basso C, Schiavon M et al.** Screening for hypertrophic cardiomyopathy in young athletes. *N Engl J Med*, 1998; 339:364-369.
18. **Lorvidhaya P, Stephen H.** Sudden cardiac death in athletes. *Cardiology* 2003; 100: 186-195.
19. **Fagard RH.** Athlete's Heart. *Heart* 2003; 89:1455-61.
20. **Mitchell JH, Haskell W, Snell P et al.** Task Force 8: Classification of sports. *J Am Coll Cardiol* 2005; 45:1364-1367.
21. **Blangy H, Sadoul N, Coutelour JM et al.** Prevalence du syndrome de Brugada dans une population de médecine preventive en Lorraine. A propos de 35.309 cas. *Archives des maladies du coeur et des vaisseaux*. 2005, tome 98, n 3, mars.
22. **Hammill SC.** Electrocardiographic diagnoses: criteria and definitions of abnormalities. In Joseph G. Murphy, Margaret A. Lloyd: *Mayo Clinic Cardiology*, 3rd Ed, Mayo Clinic Scientific Press, 2007, Ch. 18, pp 249-293
23. **Surawicz/Knilians.** Normal electrocardiogram: origin and description. In *Surawicz/Knilians: Chou's Electrocardiography in Clinical Practice* 5th Ed. Saunders, 2001, Ch. 1, pp 3-37
24. **Hermide JS, Lemoine JL, Bou Aoun F et al.** Prevalence of the Brugada syndrome in an apparently healthy population. *Am J Cardiol* 200; 86:91-4.
25. **Bjorntad H, Smith G, Storstein L et al.** Electrocardiographic and echocardiographic findings in top athletes, athletic students and sedentary controls. *Cardiology* 1993; 82:66-74.
26. **Nakazawa K, Sakurai T, Takagy A et al.** Clinical significance of electrocardiography recordings from a higher intercostal space for detection of the Brugada sign. *Circulation Journal* 2004, 68:1018-1022.
27. **Sangwatanaroj S, Prechawat S, Sunsaneewitajakul B et al.** New electrocardiographic leads and the procainamide test for the detection of the Brugada sign in sudden unexplained death syndrome survivors and their relatives. *Eur Heart J* 2001, 22:2290-2296.
28. **Kennedy HL.** Use of long-term (Holter) electrocardiographic recordings. In Zipes, Jalife *Cardiac Electrophysiology From Cell to Bedside* 4th Ed, Saunders 2004, Ch. 84 pp 772-785.
29. **Viitasalo MT, Kala R, Eisalo A.** Ambulatory electrocardiographic reading in endurance athletes. *Br Heart J* 1982:213-20
30. **Brugada P, Brugada J.** Right bundle branch block, persistent ST-segment elevation and sudden cardiac death: a distinct clinical and electrocardiographic syndrome. *J Am Coll Cardiol* 1992, 20:1391-1396
31. **Brugada J, Brugada R, Antzelevitch C et al.** Long-term follow - up individuals with the electrocardiographic pattern of right bundle branch block and ST - segment elevation in precordial leads V1 to V3. *Circulation* 2002; 105:73-8
32. **Shin SC, Ryu HM, Lee JH et al.** Prevalence of the Brugada - type ECG recorded from higher intercostal spaces in healthy Korean males. *Circ J* 2005; 69:1064-1067.
33. **Roef S, Bruns H-J, Witcher T et al.** The Ajmaline challenge in Brugada syndrome: diagnostic impact, safety, and recommended protocol. *Eur Heart J* 2003, 24:1104-1112.
34. **Antzelevitch C, Brugada P, Borggreffe M et al.** Brugada Syndrome Report of the Second Consensus Conference *Circulation* 2005;111/ 1-12.
35. **Brugada P, Brugada R, Antzelevitch C.** The Brugada Syndrome. In: Zipes, Jalife: *Cardiac Electrophysiology From Cell to Bedside*, Saunders 2004, Ch. 67, pp 625-632.
36. **Yan GX, Antzelevitch C.** Cellular basis for the electrocardiographic J wave. *Circulation* 1996; 93:372-379.
37. **El-Sherif N.** Polymorphic ventricular tachycardia and torsades de pointes: beyond etymology. *J Cardiovasc Electrophysiol* 2001; 12:695-696.
38. **Napolitano C, Silvia G Priori.** Catecholaminergic Polymorphic Ventricular Tachycardia and short - coupled Torsades de Pointes. In: Zipes, Jalife *Cardiac Electrophysiology From Cell to Bedside* 4th Ed, Saunders 2004 Ch. 68, pp 633-639
39. **Fontaine G, Fornes P, Hebert JL et al.** Ventricular tachycardia in arrhythmogenic right ventricular cardiomyopathies. In Zipes, Jalife *Cardiac Electrophysiology From Cell to Bedside* 4th Ed, Saunders 2004 Ch. 63, pp 588-600
40. **Maron BJ.** Ventricular arrhythmias in hypertrophic cardiomyopathy. In: Zipes, Jalife *Cardiac Electrophysiology From Cell to Bedside* 4th Ed, Saunders 2004 Ch. 64, pp 601-607
41. **Pelliccia A, Maron BJ, Culasso F et al.** Clinical significance of abnormal electrocardiographic patterns in trained athletes. *Circulation* 2000; 102:278-84.
42. **Serra Grima R, Estonch M, Carro I et al.** Marked ventricular repolarization abnormalities in highly trained athletes' electrocardiograms: clinical and prognostic implications. *J Am Coll Cardiol* 2000;36:1310-6
43. **Jordaens L, Missault L, Pelleman G et al.** Comparison of athletes with life-threatening ventricular arrhythmias with two groups of healthy athletes and a group a

- normal control subjects *Am J Cardiol* 1994;74:1124-8.
44. **Corrado D, Thiene G, Nava A et al.** Sudden death in young competitive athletes: clinicopathologic correlations in 22 cases. *Am J Med* 1990; 89:588-96.
 45. **Fagard RH.** Impact of different sports and training on cardiac structure and function. *Cardiol Clin* 1997;15:397-412
 46. **Thompson PD, Levine BD.** Protecting athletes from sudden cardiac death. *JAMA* 2006;296:1648-50
 47. **Zehender M, Meinertz T, Keul J et al.** ECG variants and cardiac arrhythmias in athletes: clinical relevance and prognostic importance. *Am Heart J* 1990;119:1378-1391
 48. **Biffi A, Moran BJ, Luisa Verdile et al.** Impact of physical deconditioning on ventricular tachyarrhythmia in trained athletes. *J Am Coll Cardiol* 2004; 44:1053-1058
 49. **Heidbuchel H, Hoogsteen J, Fagard R et al.** High prevalence of right ventricular involvement in endurance athletes with ventricular arrhythmias. Role of an electrophysiologic study in risk stratification. *Eur Feart J* 2003, 24:1473-1480.
 50. **Towbin JA, Bowles HE.** Human Molecular Genetics and the Heart. In: Zipes, Jalife *Cardiac Electrophysiology From Cell to Bedside* 4th Ed, Saunders 2004 Ch.49, pp 444-461
 51. **Silvia G Priori, Ilaria Rivalta, Napolitano C.** Genetics of Long QT, Brugada, and Other Channelopathies. In: Zipes, Jalife *Cardiac Electrophysiology From Cell to Bedside* 4th Ed, Saunders 2004 Ch. 50, pp 462-470
 52. **Di Diego JM, Cordeiro JM, Goodrow RJ.** Ionic and Cellular Basis for the predominance of the Brugada Syndrome Phenotype in males. *Circulation* 2002; 106:2004-2011.
 53. **Schwartz PJ, Silvia G Priori.** Long QT Syndrome Genotype - Phenotype Correlations In: Zipes, Jalife *Cardiac Electrophysiology From Cell to Bedside* 4th Ed, Saunders 2004, Ch. 70, pp 651-659
 54. **Bezzina C et al.** Single Na Channel Mutation Causing Both Long-QT and Brugada Syndrome. *Circulation Research*. 1999, December 3/17.
 55. **Van Langen IM et al.** The use of genotype-phenotype correlations in mutation analysis for the long QT syndrome. *J Med Genet.* 2003; 40:141-145
 56. **Schwartz PJ et al.** Genotype-Phenotype Correlation in the Long-QT Syndrome. Gene-Specific Triggers for Life-Threatening Arrhythmias. *Circulation* 2001;103:89-95
 57. **Maron BJ, Shirani J, Poliac LC et al.** Sudden death in young competitive athletes. Clinical, demographic, and pathological profiles. *JAMA* 1996; 276:199-204.
 58. **Lang RM, Bierig M, Devereux RB et al.** Recommendations for Chamber Quantification: A Report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, Developed in Conjunction with the European Association of Echocardiography, a Branch of the European Society of Cardiology. ASE Committee Recommendations. *J Am Soc Echocardiogr* 2005; 18:1440-1463.
 59. **Pelliccia A.** Rationale for implementing cardiovascular screening in elite athletes. 2nd Advanced Team Physicians Congress 23 June 2009, Stanford, California, USA.
 60. Froelicher Vic Stanford ECG&ECHO Experience for the pre-participation examination 23 June, 2009 , 2nd Advanced Team Physicians Course, Stanford, California, USA
 61. **Arthur A.M Wilde, Paul A. Friedman, Michael J. Ackerman, Win-Kuang Shen** *Electrical Diseases of the Heart*, Ed. Ihor Gussak, Charles Antzelevitch, Springer-Verlag 2008.