Sport Activity in Patients with Channelopathies

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Institute of Sports Medicine and Science
Italian Olympic Committee – Rome, IT
First European Course on Sports Cardiology

“ATHLETE’S HEART AND HEART DISEASE IN ATHLETES”
September 27 - 29, 2001

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Sponsors companies:
Knoll, Meffreinde, and Siemens.

The course is addressed to cardiologists, internists and sports medicine physicians who are interested in the prevention, diagnosis and management of heart disease in the athletic population.

Cardiovascular adaptations to physical training (so called “athlete’s heart”) may mimic heart disease and the differential diagnosis between the two forms is a priority objective of the course. Subclinical heart disease may dramatically degenerate to sudden cardiac death in young athletes and a medical strategy for sudden death prevention will be discussed. Furthermore, the lack of homogeneous international protocols about the preparticipation cardiovascular screening of competitive athletes, emphasizes the necessity of new guidelines for sport eligibility in athletes with cardiovascular abnormalities. The programme will include state of the art lectures, panel discussions, case studies and abstracts sessions.

European Heart House
Channelopathies

- Long QT syndrome
- Short QT syndrome
- Brugada syndrome
- Lenegre syndrome
- Cathecolaminergic polymorphic VT
- Familial atrial fibrillation
- etc.
Channelopathies: Utility of preparticipation screening

Channelopathies are rare in the general population, but are very important in Sports Cardiology because they develop the phenotype in the young age, where the sports practice is widely diffuse.

Furthermore, channelopathies can be a possible cause of sports-related sudden death.
Distribution of cardiovascular causes of sudden death in 1435 young competitive athletes

Channelopathies: Utility of preparticipation screening

Usually, the diagnostic suspicion emerges during the pre-participation screening, including 12-lead resting ECG.

That is an important preventive approach, because sports withdrawal reduces the risk of SD and allows to start with a specific therapy for the athlete and his/her family.
Channelopathies

Long QT syndrome

Jervell-Lange-Nielsen (1957)
(with deafness)

S. Di Romano-Ward (1963-1964)
(without deafness)
Long QT

1. Prolonged QT and QTc interval
2. Propensity to polymorphic VT, syncope and sudden cardiac death

*Torsade de pointe*
## Diagnostic criteria for Long QT syndrome (QTc msec)

<table>
<thead>
<tr>
<th></th>
<th>1-15 yrs</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>NORMAL</td>
<td>&lt; 440</td>
<td>≤ 440</td>
<td>≤ 460</td>
</tr>
<tr>
<td>BORDERLINE</td>
<td>440-460</td>
<td>440-450</td>
<td>460-470</td>
</tr>
<tr>
<td>PATHOLOGIC</td>
<td>&gt; 460</td>
<td>&gt; 450</td>
<td>&gt; 470</td>
</tr>
</tbody>
</table>
Risk Stratification in long QT syndrome

High Risk

Intermediate Risk

- QTc ≥ 500 msec., syncope

Low Risk

- QTc ≤ 500 msec., no-syncope

Moss, Priori, et al.
Long QT syndromes

LQT1

LQT2

LQT3
Problems in Athletes

Difficulty to precisely measure QT interval in athletes, because of the frequent presence of bradycardia and U wave
35 yrs, elite marathon runner

Sinus bradycardia 36 bpm
Bazett Formula

\[ QTc \ (msec) = \frac{QT}{\sqrt{R-R}} \ (sec) \]

\[ QTc = 400 \ msec \]

490 msec

1.54 sec (\(\sqrt{1.24}\))
29 yrs., elite cyclist

HR 42 bpm, QT 0.53 sec, QTc 0.435

U wave
19 yrs, volleyball

16 yrs, soccer
QT interval in athletes and sedentary subjects

Da P. Zeppilli, Cardiologia dello Sport, 2007
QT c in athletes and sedentary subjects

Da P. Zeppilli, Cardiologia dello Sport, 2007
Practical guidelines for suspected long QT in Athletes

- **To exclude acquired long QT** (drugs, ipokalema, salt-losing tubulopathies, such as Bartter-Gitelman syndrome etc)
- **Family history** (syncope, sudden death)
- **Stress-test ECG, Holter (12 leads):** paradox increase of QTc interval with exercise
- **Re-evaluation after detraining** verify a reduction of QTc
- **Genetics: is it really helpful?**
List of QT-prolonging Drugs

**Cardiovascular:** anti-arrhythmics Class I/III, diidropiridinic Ca-antagonist, sildefanil

**Antibiotics:** eritromicin and macrolides, trimetophrim-sulfamethossazole

**Antimicotics:** ketoconazole, fluconazole

**Antiistaminics:** terfenadine, difenidramine

**Antidepressive agents:** tricyclics, fluoxetine, sertraline

**Grape-fruit juice**
Genetics

Genetic tests are very important for the knowledge of the diseases and are a support for clinical test, but cannot substitute them. We have always to remember that about 20% of gene mutation are not identified by genetics.

Genetics have a clinical value:
- In “borderline” cases
- In the identification of a specific genotype (i.e. LQT1 with an increased risk during exercise)
- In the identification of a positive relative, in athletes with the gene mutation without phenotype
<table>
<thead>
<tr>
<th>SQTL</th>
<th>Locus</th>
<th>Gene</th>
<th>Prodotto</th>
<th>Ione interessato</th>
<th>Frequenza</th>
<th>Forma clinica</th>
</tr>
</thead>
<tbody>
<tr>
<td>SQTL1</td>
<td>11p15.5</td>
<td>KCNQ1</td>
<td>KvLQT1</td>
<td>Potassio</td>
<td>42-55%</td>
<td>RW/JLN (ombozigosi) (sforzo)</td>
</tr>
<tr>
<td>SQTL2</td>
<td>7q35</td>
<td>KCNH2</td>
<td>HERG</td>
<td>Potassio</td>
<td>35-45%</td>
<td>RW (sforzo/riposo)</td>
</tr>
<tr>
<td>SQTL3</td>
<td>3p21</td>
<td>SCN5A</td>
<td>Nav1.5</td>
<td>Sodio</td>
<td>8-10%</td>
<td>RW (riposo)</td>
</tr>
<tr>
<td>SQTL4</td>
<td>4q25</td>
<td>ANK2</td>
<td>Anchirina B</td>
<td>Sodio, calcio</td>
<td>Rara</td>
<td>RW</td>
</tr>
<tr>
<td>SQTL5</td>
<td>21q22</td>
<td>KCNE1</td>
<td>minK</td>
<td>Potassio</td>
<td>3%</td>
<td>RW/JLN (ombozigosi)</td>
</tr>
<tr>
<td>SQTL6</td>
<td>21q22</td>
<td>KCNE2</td>
<td>MiRP1</td>
<td>Potassio</td>
<td>2%</td>
<td>RW</td>
</tr>
<tr>
<td>SQTL7</td>
<td>17q23.1</td>
<td>KCNJ2</td>
<td>Kir2.1</td>
<td>Potassio</td>
<td>Rara</td>
<td>Sindrome di Andersen</td>
</tr>
<tr>
<td>SQTL8</td>
<td>12p13.3</td>
<td>CACNA1C</td>
<td>Cav1.2</td>
<td>Calcio</td>
<td>Rara</td>
<td>Sindrome di Timothy</td>
</tr>
</tbody>
</table>

Legenda: RW = sindrome di Romano-Ward; JLN = sindrome di Jervell e Lange-Nielsen
**LQT1**
(42-55%)

- **“normal” T wave**
- KCNQ1 gene
- K⁺ channel, slow current
- Loss of function
- Syncope or SD during exercise (swimming)

**LQT2**
(35-45%)

- **“notched” T wave**
- KCNH2 gene (Herg)
- K⁺ channel, fast current
- Loss of function
- Syncope or SD during emotional stress (alarm-clock)

**LQT3**
(8-10%)

- **“late” T wave**
- SCN5A gene
- Na⁺ channel,
- Gain of function
- SD during sleeping
Long QT syndrome and sports eligibility

ESC guidelines (2005) and recent italian guidelines (2009 –COCIS) contraindicate competitive sport activity in athletes with diagnosis of Long QT sindrome, even in absence of symptoms and of ventricular tachyarrhythmias. Sympathetic stimulation is proarrhythmogenic in patients with a congenital form.
Long QT syndrome and sports eligibility

No firm data exist concerning the exercise-related risk of silent mutation carriers. It is prudent to also disqualify them from competitive sports, especially when there is a family history of SD or a prolonged QTc interval.
Long QT syndrome and sports eligibility

Light to moderate leisure-time activity can be suggested in patients with low-risk for sudden death. Avoid sports with sudden burst of activity and of specific triggers (diving, swimming etc.)
Short QT Syndrome
A Familial Cause of Sudden Death

Fiorenzo Gaita, MD; Carla Giustetto, MD; Francesca Bianchi, MD; Christian Wolpert, MD;
Rainer Schimpf, MD; Riccardo Riccardi, MD; Stefano Grossi, MD;
Elena Richardi, MD; Martin Borggrefe, MD

Background—A prolonged QT interval is associated with a risk for life-threatening events. However, little is known about prognostic implications of the reverse—a short QT interval. Several members of 2 different families were referred for syncope, palpitations, and resuscitated cardiac arrest in the presence of a positive family history for sudden cardiac death. Autopsy did not reveal any structural heart disease. All patients had a constantly and uniformly short QT interval at ECG.

QTc < 300 msec
Short QT

QT ≤ 320 msec

- KCNH2 (Herg) gene
- $K^+$ channel, fast flow
- Gain of function
- Shortness of the AV refractory periods
- Syncope or SD, AF in young age
- Sensibility to quinidine
Short QT Syndrome
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QT = 280 msec
Short QT Syndrome
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Channelopathies

Brugada syndrome
Brugada syndrome

- Ion channel disease, in absence of structural heart disease
- Genetic disease with dominant autosomic transmission
- 18-30% SCN5A gene (Na+ channel disease); 70-82% unknown gene
- Electrophysiologic changes in RVOT
Brugada syndrome

- Rare (5/10000, 1/500 South Eastern Asia)

- Na⁺ channel, lost of function

- SD during sleeping, III-IV decades
## Rare: ECG prevalence of “coved” type 1

<table>
<thead>
<tr>
<th>Reference</th>
<th>Total subjects</th>
<th>Mean age</th>
<th>Men number</th>
<th>Total prevalence</th>
<th>Men prevalence</th>
<th>Women prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tohyou 1995</td>
<td>4092</td>
<td>46</td>
<td>78%</td>
<td>0.07%</td>
<td>0.09%</td>
<td>-</td>
</tr>
<tr>
<td>Hermida 2000</td>
<td>1000</td>
<td>39</td>
<td>63%</td>
<td>0.10%</td>
<td>0.16%</td>
<td>-</td>
</tr>
<tr>
<td>Viskin 2000</td>
<td>592</td>
<td>36</td>
<td>58%</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Miyasaka 2001</td>
<td>13929</td>
<td>58</td>
<td>27%</td>
<td>0.12%</td>
<td>0.38%</td>
<td>0.03%</td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td><strong>19613</strong></td>
<td></td>
<td></td>
<td><strong>0.11%</strong></td>
<td><strong>0.23%</strong></td>
<td><strong>0.03%</strong></td>
</tr>
</tbody>
</table>
Prevalence of abnormal electrocardiograms in a large, unselected population undergoing pre-participation cardiovascular screening

*Pelliccia: Eur H J 2007*

**Table 1** Prevalence of ECG abnormalities in an unselected population of 32,652 young individuals undergoing the pre-participation cardiovascular screening

<table>
<thead>
<tr>
<th>ECG abnormalities</th>
<th>Athletes, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative T-waves in precordial/standard leads</td>
<td>751 (2.3)</td>
</tr>
<tr>
<td>RBBB</td>
<td>351 (1.0)</td>
</tr>
<tr>
<td>Increased R/S wave voltages (suggestive of LVH)</td>
<td>247 (0.8)</td>
</tr>
<tr>
<td>Left anterior fascicular block</td>
<td>162 (0.5)</td>
</tr>
<tr>
<td>Pre-excitation pattern</td>
<td>42 (0.1)</td>
</tr>
<tr>
<td>LBBB</td>
<td>19 (0.1)</td>
</tr>
<tr>
<td>Prolonged corrected QT interval</td>
<td>1 (0.003)</td>
</tr>
<tr>
<td>Others (incomplete RBBB, prolonged PR interval, early repolarization pattern)</td>
<td>2280 (7.0)</td>
</tr>
<tr>
<td>Total</td>
<td>3853 (11.8)</td>
</tr>
</tbody>
</table>

No case!!

RBBB, right bundle branch block; LVH, left ventricular hypertrophy; LBBB, left bundle branch block.
Does Sports Activity Enhance the Risk of Sudden Death in Adolescents and Young Adults?

Domenico Corrado, MD, PHD,* Cristina Basso, MD, PHD,† Giulio Rizzoli, MD,‡ Maurizio Schiavon, MD,§ Gaetano Thiene, MD†

Jacc 2003

### Table 2. Causes of SD by Gender and Age in Athletes and Non-Athletes

<table>
<thead>
<tr>
<th></th>
<th>Total (N = 300)</th>
<th>Athletes (n = 55)</th>
<th>Non-Athletes (n = 245)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Age (yrs)</td>
<td>Males (n = 50)</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>259</td>
<td>23.8 ± 8</td>
<td>46</td>
</tr>
<tr>
<td>Atherosclerotic CAD</td>
<td>58</td>
<td>29.1 ± 5</td>
<td>10</td>
</tr>
<tr>
<td>Arrhythmogenic RV cardiomyopathy</td>
<td>37</td>
<td>25.2 ± 7</td>
<td>12</td>
</tr>
<tr>
<td>Myocarditis</td>
<td>32</td>
<td>22.3 ± 7</td>
<td>5</td>
</tr>
<tr>
<td>Mitral valve prolapse</td>
<td>27</td>
<td>22.7 ± 6</td>
<td>4</td>
</tr>
<tr>
<td>Disease of the conduction system</td>
<td>25</td>
<td>21.5 ± 9</td>
<td>3</td>
</tr>
<tr>
<td>Hypertrophic cardiomyopathy</td>
<td>23</td>
<td>22.3 ± 7</td>
<td>1</td>
</tr>
<tr>
<td>Aortic rupture</td>
<td>12</td>
<td>21.2 ± 8</td>
<td>1</td>
</tr>
<tr>
<td>Dilated cardiomyopathy</td>
<td>11</td>
<td>22.1 ± 7</td>
<td>1</td>
</tr>
<tr>
<td>Anomalous origin of CAD</td>
<td>8</td>
<td>20.2 ± 6</td>
<td>6</td>
</tr>
<tr>
<td>Non-atherosclerotic CAD</td>
<td>7</td>
<td>21.4 ± 8</td>
<td>0</td>
</tr>
<tr>
<td>Myocardial bridge</td>
<td>6</td>
<td>21.7 ± 9</td>
<td>2</td>
</tr>
<tr>
<td>Aortic valve stenosis</td>
<td>4</td>
<td>20.7 ± 3</td>
<td>0</td>
</tr>
<tr>
<td>Postoperative CHD</td>
<td>4</td>
<td>13.2 ± 5</td>
<td>0</td>
</tr>
<tr>
<td>Pulmonary thromboembolism</td>
<td>4</td>
<td>23.4 ± 2</td>
<td>1</td>
</tr>
<tr>
<td>Long QT syndrome</td>
<td>1</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>Non-cardiovascular</td>
<td>23</td>
<td>24.1 ± 8</td>
<td>3</td>
</tr>
<tr>
<td>Asthma</td>
<td>10</td>
<td>23.2 ± 7</td>
<td>0</td>
</tr>
<tr>
<td>Cerebral berry aneurysm</td>
<td>6</td>
<td>27.8 ± 8</td>
<td>1</td>
</tr>
<tr>
<td>Cerebral embolism</td>
<td>5</td>
<td>22.2 ± 6</td>
<td>2</td>
</tr>
<tr>
<td>Other</td>
<td>2</td>
<td>24.5 ± 6</td>
<td>0</td>
</tr>
<tr>
<td>Unexplained</td>
<td>18</td>
<td>23.2 ± 8</td>
<td>1</td>
</tr>
</tbody>
</table>

Data are presented as the number of subjects and mean value ± standard deviation.

CAD = coronary artery disease; CHD = congenital heart disease; RV = right ventricular.
We assessed 355 competitive athletes with ventricular arrhythmias (VAs) on a 24-h ambulatory (Holter) ECG that was obtained because of either palpitations, the presence of $\geq$ 3 premature ventricular depolarizations (PVDs) on resting 12-lead ECG, or both.

The 12-lead ECG failed to show evidence of Brugada and long QT syndromes in any athlete, although T-wave inversion in precordial leads V1–V3 raised a consideration for ARVC in four athletes, ultimately diagnosed by MRI or myocardial biopsy.
ECG variability with antiarrhythmic agents
(F, 42yrs, Familial Brugada syndrome)
AFTER FLECAINIDE

P. Delise
27 yrs., pre-syncope, ICD

25 yrs., hockey (brother)
Special Report

Brugada Syndrome

ECG variability induced by other factors

Ipokaliemia

Fever

Alcool

Cocaine

Insulin

Antidepressive

pharmacological approaches to therapy on the basis of the available clinical and basic science data. (Circulation. 2005; 111:659-670.)

Key Words: arrhythmia ■ death, sudden ■ electrocardiography ■ diagnosis
S.F. 25 yrs
25.9.07
Fever 38.5°
Syncope
Drug-Induced Brugada-Like ECG Patterns

- Antiarrhythmic drugs
- Na+ channel blockers
- Class IC drugs (Flecainide, 12, 15, 142, 207, 208
  Pilsicainide, 146, 209 Propafenone210)
- Class IA drugs (Ajmaline, 12, 211
  Procainamide, 12, 13
  Disopyramide, 4, 13 Cibenzoline212, 213)
- Ca2+ channel blockers
- Verapamil
- β-Blockers
- Propranolol intoxication214
- Antianginal drugs
- Ca2+ channel blockers
- Nifedipine, diltiazem
- Nitrate
- Isosorbide dinitrate, nitroglycerine215
- K+ channel openers
- Nicorandil

- Psychotropic drugs
- Tricyclic antidepressants216
  Amitriptyline, 217, 218 Nortriptyline, 151
  Desipramine, 149
- Clomipramine150
- Tetracyclic antidepressants
- Maprotiline217
- Phenothiazine
- Perphenazine, 217 Cyamemazine.
- Selective serotonin reuptake inhibitors
- Fluoxetine218
- Lithium157
- Other drugs
- Histaminic H1 receptor antagonists
- Dimenhydrinate152
- Diphenhydramine219
- Cocaine intoxication153, 220
- Alcohol intoxication
Brugada syndrome  
Differential diagnosis

• Aspecific ECG changes
• Arrhythmogenic RV cardiomyopathy
• Miocarditis
• Idiopathic Cardiomiopathies
• Acute coronary syndromes
• ....Athlete’s heart
Early rep. in Athletes

- **Up-sloping ST**
- **High positive T waves**
- **QRS high voltages**
- **Normal QRS duration**
- **Increase** after β-blockage, bradycardia, etc.
- **Decrease** after β-stimul., tachycardia, exercise, etc.

Brugada

- **Down-sloping ST**
- **low negative T waves**
- **QRS low voltages**
- **Prolonged QRS**
- **Increase** after β-blockage, bradycardia, etc.
- **Decrease** after β-stimul., tachycardia, exercise, etc.
A simple question.

Autonomic imbalance in BS, may account for the rarity of the event?
Antzelevich C et al., *Circulation* 2005; 111:659-670
The ECG is DUE to conduction disturbance and not repolarization abnormality.

Brugada:pt after Ajmaline
Circulation 2000;101:510

Patient with the same ECG spontaneously
Brugada syndrome: No competitive sports
Symptomatic subjects with Brugada syndrome or with spontaneous or drug-induced type 1 ECG pattern

Although no relation between exercise and ventricular arrhythmias exists... subjects with symptomatic Brugada syndrome **should not be granted sports eligibility.**
Asymptomatic subjects with spontaneous/or drug-induced type 1 ECG pattern

The risk of SD in these subjects is low, but we do not still have safe prognostic criteria. As said, malignant ventricular arrhythmias in BS frequently occur during bradycardia/sleeping and autonomic nervous system changes induced by training could increase the arrhythmic risk related to marked sinus bradycardia in these athletes.
Sports Eligibility
(Italian Guidelines COCIS 2009)

- *Provocative test with class 1*
- *Anti-arrhythmic agents should be suggested:*
  - in athletes with type 2 or 3 ECG pattern with family history for SD or Brugada s. or syncope
  - in asymptomatic athletes with “borderline” ECG pattern
Sudden death in patients and relatives with the syndrome of right bundle branch block, ST segment elevation in the precordial leads V\textsubscript{1} to V\textsubscript{3} and sudden death

P. Brugada\textsuperscript{1}, R. Brugada\textsuperscript{2} and J. Brugada\textsuperscript{3}
A Royal Marine who collapsed and died during a rugby match in Devon last year had a rare heart condition, an inquest was told.

A routine test had shown an abnormal heart rhythm

Pathologist Dr Carl Lyons told the inquest heart specialist Dr Mary Sheppard had found apparently healthy muscle inside the organ had become fibrous.

She concluded Marine died from Arrhythmogenic Right Ventricular Cardiomyopathy, which may be linked to a genetic condition called Brugada Syndrome.
Fortuitous discovery of Brugada “syndrome” in an asymptomatic 70-year-old sportsman

Douard 1996

• The authors report an elderly sportsman presenting with the electrical signs of the BS, both during Flecaïnide because of PAF and spontaneously. The absence of any serious clinical events in this patient questions the pejorative prognosis usually reported.
• Not all the typical ECG patterns belong to the so called Brugada Syndrome.

• (expecially in some athletes!!!)
- characteristic ECG morphologies recorded in the first few hours after resuscitation or immediately after DC shock cannot be taken as diagnostic of the Brugada syndrome

Circulation 2002; 106:2514-9
Aborted Sudden Death, Transient Brugada Pattern, and Wide QRS Dysrrhythmias After Massive Cocaine Ingestion
• First conclusion

The **true** so called Brugada “syndrome”, is an anecdotal event in athlete.

• Second conclusion

• The isolated presence of an extremely rare ECG is NOT a syndrome
Syndrome

From Greek συνδρομή, “concurrence of symptoms” (Galenus, II B.C.)
From σύν = toghether, with + δρομός = run
So, as the athletes only anedoctaly suffer from the syndrome, let’s go back to the general population?
Let’s have a look to the Epidemiology of the ECG pattern published by Andrea Nava 5 years before Brugada
• specificity of sodium channel blockers, such as flecainide, ajmaline, procainamide, disopyramide, propafenone, and pilsicainide to identify patients at risk is uncertain. Drug-induced conversion of Type 3 to Type 2 ST-segment elevation is considered inconclusive for diagnosis of Brugada syndrome.
Genetic basis of Brugada syndrome

Charles Antzelevitch, PhD, FHRS  Heart & Rhythm 2007

• BrS has been associated with mutations in *SCN5A* in approximately 15% of probands. Over 100 mutations in *SCN5A* have been linked to the syndrome in recent years
Asymptomatic Brugada syndrome: a cardiac ticking time-bomb?

Viskin Europace 2007

No more indications for EPS testing in asymptomatic
So called Brugada syndrome in asymptomatic athlete

Final conclusion
it is not possible to justify the study of a patient’s genes, perform an endomyocardial biopsy, perform an MRI, perform an electrophysiological study, and perform a coronary arteriography in every patient in whom the condition is suspected.