

## Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Pelliccia A, Di Paolo FM, Quattrini FM, et al. Outcomes in athletes with marked ECG repolarization abnormalities. *N Engl J Med* 2008;358:152-61.

## Clinical outcome in athletes with abnormal ECGs

Of the 81 athletes with abnormal ECGs, 5 (6%) ultimately proved to have cardiac disease over the period of follow-up, including one who died suddenly at age 24 years (one-year after initial evaluation) due to clinically undetected arrhythmogenic right ventricular cardiomyopathy. Of the 80 surviving athletes, 3 developed clinical and phenotypic features of hypertrophic cardiomyopathy over an average 12.5 year follow-up, at ages 27, 32 and 50 years, including one who experienced aborted cardiac arrest (after 16 years of follow-up). The fifth athlete developed DCM over a 9-year follow-up. In contrast, none of the 229 athletes with normal ECGs, representing the control group, experienced cardiac events or had cardiomyopathies diagnosed on average 9.3 years after initial evaluation ( $p < 0.01$ ).

*Arrhythmogenic right ventricular cardiomyopathy.* One asymptomatic athlete died suddenly after one-year follow-up, at age 24 years, due to ARVC which had not been recognized clinically. At initial evaluation the ECG showed left axis deviation and diffusely inverted T waves in leads II,III,AVF and V<sub>1</sub>-V<sub>6</sub> (Figure 1 A; Table 1). Echocardiographic examination was judged consistent with physiologic cardiac remodeling of the athlete's heart, by virtue of showing only very mild right (and left) ventricular enlargement in the absence of segmental right ventricular wall motion abnormalities, thinning or aneurysm formation. Family history was unremarkable without known cardiovascular disease or premature death.

One year later, the athlete's ECG pattern was unchanged; the 24-hour ambulatory ECG Holter monitoring showed 405 premature ventricular beats, one couplet and one 3-beat burst of nonsustained ventricular tachycardia. Electrophysiologic study with programmed ventricular stimulation (2 extra-stimuli) failed to induce ventricular tachyarrhythmia. Based on the presence of arrhythmias and abnormal ECG pattern, this

athlete was disqualified from training and competition and referred for further testing, but died unexpectedly 3 months later, during a solitary training session.

At autopsy, the heart was increased in weight (550 grams) and showed mild biventricular enlargement. The LV free wall and septal thicknesses were 11 mm each, but the right ventricular wall was thinned to 2 mm. Histopathology showed extensive fibro-fatty replacement of the right ventricular wall extending into the pulmonary infundibulum (Figure 4). Focal areas of fibrous tissue replacement were also described in the LV free wall. Extramural coronary arteries were without significant atherosclerotic narrowing.

*Hypertrophic cardiomyopathy.* Three athletes developed phenotypic features consistent with HCM over a follow-up period of 12-15 years (7, 13 and 16), at ages 27, 32 and 50 years, respectively. None of these 3 athletes had a known family history of HCM.

First, an asymptomatic 34-year-old tennis player showed diffuse T-wave inversion in precordial leads V<sub>4</sub>-V<sub>6</sub> and a normal echocardiogram when initially evaluated. He maintained a physically active lifestyle after terminating his competitive career, but 16 years later, at age of 50 years, experienced unexpected cardiac arrest while driving an automobile. The ECG pattern had remained unchanged, and the probable diagnosis of HCM was made at that time based on a mildly thickened (i.e., 13 mm) and hyperdynamic LV. A cardioverter defibrillator was implanted for secondary prevention.

Second, an asymptomatic 26-year old soccer player showed diffuse deeply inverted T waves and normal echocardiogram. After 7-year follow-up, at age of 32 years, he was still engaged in professional soccer, but showed evidence of nonobstructive HCM by virtue of asymmetric LV hypertrophy (maximum thickness 16 mm) and nondilated LV cavity (end-diastolic dimension, 49 mm). ECG pattern had progressed with increased R wave voltages and deeper T wave inversion in the standard (I to III, aVL) and precordial leads (V<sub>2</sub> to V<sub>6</sub>). This athlete was, therefore, disqualified from competition.

Third, an asymptomatic 18-year old male elite rower showed diffusely inverted T waves in anterior and lateral precordial leads, associated with echocardiographic evidence of mild LV wall thickening (anterior ventricular septum = 13 mm, end-diastolic LV cavity = 50 mm). After 9 years of follow-up, at age of 27 years, he experienced multiple symptomatic episodes of nonsustained ventricular tachycardia on ambulatory Holter ECG and during exercise testing, as well as the appearance of mild systolic anterior motion of the mitral valve at rest. These findings were judged consistent with HCM and the athlete was disqualified from competition.

*Dilated cardiomyopathy.* An asymptomatic 38-year old male wheelchair athlete, competing in basketball and sprinting, showed diffusely inverted T waves in left precordial and standard leads, in association with normal systolic LV function (ejection fraction 60%; LV end-diastolic diameter = 57 mm). After a 9-year follow-up, at age of 47 years, this athlete (without a history of myocarditis or alcohol or drug abuse) developed evidence of DCM with global systolic dysfunction and ejection fraction = 40%, and also marked LV cavity dilatation (end-diastolic dimension = 62 mm). Ambulatory Holter ECG monitoring showed frequent and polymorphic PVBs (n = 1,972) and 6 couplets.

## **Authors contributions**

**Study design:** Antonio Pelliccia, Barry J Maron, Fernando M. Di Paolo

**Acquisition of the data:** Rossana De Luca, Fernando M. Di Paolo, Filippo Quattrini, Antonio Pelliccia, Antonio Spataro

**Pathological investigations:** Gloria Popoli, Cristina Basso, Gaetano Thiene

**Analysis and interpretation of the data:** Antonio Pelliccia, Barry J Maron, Fernando M. Di Paolo, Filippo Quattrini, Alessandro Biffi, Cristina Basso, Gaetano Thiene

**Statistical analysis:** Franco Culasso

**Drafting of the manuscript:** Antonio Pelliccia, Barry J Maron

**Revision of the manuscript:** Barry J Maron, Antonio Pelliccia

**Overall study supervision:** Antonio Pelliccia, Barry J Maron