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Exercise testing for long-term follow-up in arrhythmogenic right ventricular cardiomyopathy

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Abstract

Objectives: We investigated arrhythmia, electrocardiography and physical work capacity (PWC) in the follow-up of ARVC.

Design: Twenty-three patients (13 men; age 41 ± 12 years) fulfilling diagnostic criteria were re-investigated after at least five years.

Results: Ventricular arrhythmia during exercise testing (ET) was present in 14 patients (61%) and showed variation between examinations. In eleven (48%), complex ventricular ectopic activity was observed at peak exercise or immediately thereafter. Mutations known to be pathogenic in ARVC were present in 13 patients (57%) of which 11 developed complex ventricular arrhythmia at ET. PWC at baseline was 190 ± 66 W (104 ± 26%) decreasing to 151 ± 61 W (91 ± 23%, $p = 0.008$) after 10.7 years.

Conclusion: The appearance of ventricular arrhythmia during exercise testing showed temporal variation but was frequent in patients with relevant genetic mutation. Physical exercise capacity decreased over time in patients with ARVC in excess to the age-related deterioration and regardless of medication.

Keywords: ARVC; Exercise testing; Arrhythmia; Follow up

Introduction

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a genetically mediated progressive myocardial disease characterized by ventricular arrhythmia, right ventricular systolic dysfunction and sudden cardiac death [1]. In young populations of athletes ARVC accounts for 4–22% of sudden cardiac deaths [2,3]. The true incidence of this disease has been difficult to establish since the clinical manifestations are quite variable. A pathogenic mutation is detected in 30–50% of all cases and mostly inherited in an autosomal dominant pattern with incomplete penetrance [4,5]. The mutation affects the desmosome and disrupts cell-to-cell contact. Cardiomyocytes are lost and replaced by fibro-fatty tissue affecting activation and repolarization of the myocardium [6,7]. ARVC primarily affects the right ventricle of the heart, but the left ventricle may also be involved [8,9].

The diagnosis of ARVC is based on major and minor Task Force Criteria [1] revised in 2010 [10]. The presence of abnormalities in the electrocardiogram (ECG) and signal averaged electrocardiogram (SAECG) as well as arrhythmia originating from the right ventricle (RV) are important parts in the diagnosis of the disease. Exercise may unmask ventricular arrhythmia but the efficacy of exercise testing (ET) in detecting arrhythmic tendency in ARVC and following the progress of the disease remains to be determined. There is a large variation in the arrhythmic burden among patients with ARVC. In the absence of arrhythmia, there is no evidence in using antiarrhythmic therapy [11], thus the detection of effort-induced ventricular arrhythmias, e.g., NSVT on exercise testing could be an indication to use beta-blockers or to assess the need for an ICD. In a large male population, the occurrence of >10% ventricular premature complexes (VPC) during heavy exercise (present in 2% of the population) predicted 2.5 times higher incidence of cardiovascular death than in those without VPCs [12]. However, Sequeira et al. [13] showed that ventricular ectopic activity during exercise testing in teenagers (<18 years) with ARVC was very unpredictable. The utility of exercise testing for long term follow-up and in general clinical decision making in ARVC in adult patients is largely unknown.

We aim to investigate whether arrhythmia and other electrocardiographic abnormalities could be induced by

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exercise testing in the follow-up of adult patients with ARVC. The hypothesis of the study was whether exercise testing could predict arrhythmic tendency and whether the presence of arrhythmia during exercise testing would predict the progress of the disease in the follow-up of patients with ARVC.

Materials and methods

Patients

All patients (n = 38) fulfilling the Task force Criteria for ARVC [10], attending our tertiary referral center are evaluated with exercise testing, ECG, SAECG, Holter and echocardiography as part of clinical follow-up. Patients with a follow-up of at least 5 years after the first examination were included in this study (n = 23, 13 men; 57%). Patient data and protocols from the different examinations were retrospectively collected.

The latest available follow-up was on average 10.7 (± 3.5) years after inclusion. Mean age at inclusion was 41 ± 12 years and that at follow-up was 51 ± 13 years. The first presentation of disease symptoms was palpitations or episodes of ventricular arrhythmia in 15 patients (65%), 3 experienced episodes of syncope and one was resuscitated after cardiac arrest. Additional reasons for referral were family history of ARVC or premature sudden death in 7 (30%) and heart enlargement at X-ray in one patient. Fourteen patients (61%) were prescribed antiarrhythmic therapy (beta-blockers in 13 and amiodarone in one patient) before the first exercise test. At the time of the last examination, all remained on their prescribed antiarrhythmic therapy with 3 additional patients receiving beta-blockers.

Genetic screening had been performed in 18 patients, 2 had declined and in three patients genetic analysis had not been carried. Mutations known to be pathogenic for ARVC were present in 13 patients (57%). Plakophilin 2 (PKP-2) was affected in nine patients, desmoplakin (DSP) in 2 and desmoglein (DSG-2) in 2. Five patients did not have a known pathogenic mutation in the analyzed genes.

Clinical adverse events were defined as SCD, VT requiring antitachycardia pacing (ATP) or appropriate shock on ICD, heart failure or heart transplant. Such events were collected from the medical records.

Exercise testing

All patients included had an initial ramp exercise test on a bicycle ergometer with an increase in load of 2 watt (W) every 12 s. Women usually started at 30 W and men usually at 50 W. The initial load was selected to allow maximal physical stress to be reached without inducing premature fatigue. The Borg rating of perceived exertion (6–17) was used for exercise level guidance [14]. A rating of 6 was associated with no exertion and 17 with heavy exercise. Exercise duration of 6 to 10 min was aimed at. Physical work capacity (PWC) was measured in W and the load when the patient stopped cycling was specified. Physical exercise capacity was related to reference values based on age, weight and gender [15]. Blood pressure and heart rate were recorded at regular intervals. The exercise test was continued until exhaustion, to enable the assessment of peak work capacity and if possible to provoke symptoms. Criteria for premature interruption of exercise were general ill-being, extreme levels of effort and/or breathlessness, a decrease in blood pressure, an excessive rise in systolic blood pressure (to a level >250 mm Hg), sustained ventricular arrhythmia or ST depression (horizontal or down sloping in excess of 2 mm).

The number of VPCs of any morphology was counted per minute at three different time points: at rest before exercise testing, during one of the last three minutes of the exercise test and during one of the three minutes immediately post-exercise (the minute with most VPCs was used). VPCs were classified as none or isolated (graded 0), VPCs in trigeminy (graded 1), VPCs in bigeminy (graded 2), VPCs in couplets (graded 3) or ventricular tachycardia (VT) defined as ≥3 consecutive VPCs (graded 4). High grade ventricular ectopic activity was defined as VPCs in bigeminy, couplet or NSVT (Fig. 1).

Electrocardiogram (ECG)

The ECG was recorded with 12 standard leads at a paper speed of 50 mm/s. The QRS duration was evaluated using a manual caliper. In all precordial leads (V1–V6) the duration of the QRS-complex was measured twice and the mean value calculated. When the end of the QRS complex was difficult to define due to a gradual slope to a plateau, it was measured at the intersection of the S-wave and the isoelectric baseline [16]. The ECGs were reviewed for the following abnormalities: T-wave inversion in precordial leads (V1–V6), right bundle-branch block (RBBB), incomplete RBBB, terminal activation duration (TAD), epsilon wave and localized right precordial QRS prolongation. Localized right precordial QRS prolongation was measured as the ratio between the QRS duration in (V1 + V2 + V3) and (V4 + V5 + V6). TAD was defined as the longest QRS duration in leads V1–V3, from the nadir of the S-wave to the end of all depolarization deflections in the absence of RBBB.

Signal averaged electrocardiogram (SAECG)

SAECG was obtained using a standard 40–250 Hz filter. The filtered QRS duration (fQRS), the root-mean-square voltage of the terminal 40 ms of the filtered QRS (RMS 40) and the duration of the low-amplitude component of the fQRS signal (<40 μV, LAS40) were evaluated. According to the revised Task Force Criteria (10) the SAECG is positive if at least one of the three criteria; fQRS > 114 ms, LAS40 ≥ 38 ms or RMS40 ≤ 20 μV is fulfilled.

The follow-up protocol included Holter, using monitors that provided three channels of ECG (Marquette Electronic and Philips, USA). Twenty-four hour Holter data were analyzed for the number of VPCs: (1) none or less than 500 VPCs/24 h; (2) >500 VPCs/24 h; (3) nonsustained ventricular tachycardia (NSVT) (defined as three or more consecutive beats with rate >100 beats/min). Patients fulfilling criteria 2 or 3 were considered to have high grade ventricular ectopic activity.

Transthoracic echocardiography

Digitally stored echocardiographic data were retrieved and systolic ventricular function was assessed. Left