JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
© 2015 BY THE AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION
PUBLISHED BY ELSEVIER INC.

VOL. 65, NO. 25, 2015
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2015.04.035

Clinical Differentiation Between Physiological Remodeling and Arrhythmogenic Right Ventricular Cardiomyopathy in Athletes With Marked Electrocardiographic Repolarization Anomalies

Abbas Zaidi, BSc (Hons), MBBS, MD,* Nabeel Sheikh, BSc (Hons), MBBS,* Jesse K. Jongman, MD,† Sabiha Gati, BSc (Hons), MBBS,* Vasileios F. Panoulas, MD, PhD,‡ Gerald Carr-White, BSc (Hons), MBBS, PhD,§ Michael Papadakis, MBBS, MD,* Rajan Sharma, BSc (Hons), MBBS, MD,* Elijah R. Behr, MBBS, MD,* Sanjay Sharma, BSc (Hons), MBChB, MD*

ABSTRACT

BACKGROUND Physiological cardiac adaptation to regular exercise, including biventricular dilation and T-wave inversion (TWI), may create diagnostic overlap with arrhythmogenic right ventricular cardiomyopathy (ARVC).

OBJECTIVES The goal of this study was to assess the accuracy of diagnostic criteria for ARVC when applied to athletes exhibiting electrocardiographic TWI and to identify discriminators between physiology and disease.

METHODS The study population consisted of athletes with TWI (n = 45), athletes without TWI (n = 35), and ARVC patients (n = 35). Subjects underwent electrocardiography (ECG), signal-averaged electrocardiography (SAECG), echocardiography, cardiac magnetic resonance imaging (CMRI), Holter monitoring, and exercise testing.

RESULTS There were no electrical, structural, or functional cardiac differences between athletes exhibiting TWI and athletes without TWI. When athletes were compared with ARVC patients, markers of physiological remodeling included early repolarization, biphasic TWI, voltage criteria for right ventricular (RV) or left ventricular hypertrophy, and symmetrical cardiac enlargement. Indicators of RV pathology included the following: syncope; Q waves or precordial QRS amplitudes <1.8 mV; 3 abnormal SAECG parameters; delayed gadolinium enhancement, RV ejection fraction ≤45%, or wall motion abnormalities at CMRI; >1,000 ventricular extrasystoles (or >500 non-RV outflow tract) per 24 h; and symptoms, ventricular tachyarrhythmias, or attenuated blood pressure response during exercise. Nonspecific parameters included the following: prolonged QRS terminal activation; ≤2 abnormal SAECG parameters; RV dilation without wall motion abnormalities; RV outflow tract ectopy; and exercise-induced T-wave pseudonormalization.

CONCLUSIONS TWI and balanced biventricular dilation are likely to represent benign manifestations of training in asymptomatic athletes without relevant family history. Diagnostic criteria for ARVC are nonspecific in such individuals. Comprehensive testing using widely available techniques can effectively differentiate borderline cases.
(J Am Coll Cardiol 2015;65:2702–11) © 2015 by the American College of Cardiology Foundation.

From the *St. George's University of London, London, United Kingdom; †Isala Clinics, Zwolle, the Netherlands; ‡Imperial College Healthcare National Health Service Trust, London, United Kingdom; and the §Guy's and St. Thomas's Hospital, London, United Kingdom. Drs. Zaidi, Sheikh, Gati, and Papadakis have received research grants from the charitable organization Cardiac Risk in the Young. Dr. Sharma has been a coapplicant on previous grants from Cardiac Risk in the Young to study athletes and non-athletes. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.
Listen to this manuscript's audio summary by *JACC* Editor-in-Chief Dr. Valentin Fuster.

Manuscript received February 11, 2015; revised manuscript received March 16, 2015, accepted April 20, 2015.

Individuals engaging in regular, intensive sporting activity frequently demonstrate a constellation of electrical and structural cardiac alterations that are collectively described as the "athlete's heart." Although such training-induced changes are generally considered physiological and benign (1), they occasionally overlap with phenotypic features of inherited cardiomyopathies, in which vigorous exercise is associated with an increased risk of sudden cardiac death (SCD) (2,3). Physiological remodeling of the athlete's right ventricle (RV) may mimic changes observed in arrhythmogenic right ventricular cardiomyopathy (ARVC) (4), which is

SEE PAGE 2712

responsible for as many as 22% of SCD in young athletes (2). Accurate differentiation between physiological and pathological RV remodeling is essential because failure to identify the disease could jeopardize a young life, whereas an inappropriate diagnosis of ARVC may lead to an unnecessary exclusion from sporting activity. Whereas diagnostic algorithms to facilitate the differentiation between physiological left ventricular (LV) hypertrophy and hypertrophic cardiomyopathy are established, similar data are lacking for the RV. Furthermore, diagnostic criteria for ARVC are derived from patients with established disease (5) and may therefore not be applicable to low-risk individuals, such as athletes. The objectives of the present study were to assess the accuracy of current diagnostic criteria for ARVC when applied to athletes exhibiting phenotypic overlap with the condition and to identify clinical discriminators between RV physiology and disease.

METHODS

SUBJECTS. All participants provided written consent, and ethical approval was obtained from the local research ethics committee in accordance with the Declaration of Helsinki. In the United Kingdom, the charity Cardiac Risk in the Young subsidizes cardiovascular evaluations for several elite sporting organizations that mandate pre-participation screening of all member athletes. The screening protocol consists of a health questionnaire, physical examination, and 12-lead electrocardiogram (ECG). In order to facilitate a study group exhibiting diagnostic overlap with ARVC, 45 athletes with ECG T-wave inversion (TWI) were recruited between 2011 and 2013 for further detailed assessment (TWI^+ athletes). The TWI^+ athletes were required to exhibit anterior or lateral TWI as a minimum inclusion criterion, as per the 2010 Task Force Criteria (TFC) for the diagnosis of ARVC (5). A cohort of athletes without TWI (TWI^- athletes), matched for age, sex, ethnicity, and sporting category, was recruited to act as a control group. The athletic cohorts were between 14 and 35 years of age and competed at international, national, or regional levels. Sporting disciplines were categorized as predominantly endurance or strength, and as high-dynamic/high-static or non-high-dynamic/high-static disciplines, according to accepted criteria (6). Athletes with any previous history of cardiac or pulmonary disease, systemic hypertension, or diabetes mellitus were excluded. The ARVC cohort consisted of patients between 14 and 35 years of age presenting to 2 U.K. tertiary cardiac referral centers with a new diagnosis of "definite" ARVC by 2010 TFC (5).

ASSESSMENT PROTOCOL. All study participants underwent resting ECG, signal-averaged electrocardiography (SAECG), transthoracic echocardiography, cardiac magnetic resonance imaging (CMRI), and exercise testing, and they were assessed with reference to the 2010 TFC (5). Tissue characterization of the RV wall was not performed in any case. Genetic testing was offered only to the ARVC patients.

12-LEAD ELECTROCARDIOGRAM. A standard 12-lead ECG was performed in the supine position using either a MAC 5000 or MAC 5500 digital resting ECG recorder (GE Medical Systems, Milwaukee, Wisconsin). Measurements were made using calipers. The normal frontal cardiac axis was considered to be $>-30°$, but $<120°$. Left ventricular hypertrophy (LVH) and right ventricular hypertrophy (RVH) were defined according to the Sokolow-Lyon voltage criteria (LVH = $SV_1 + RV_{5/6} >3.5$ mV; RVH = $RV_1 + SV_{5/6} >1.05$ mV). TWI $\geq$-0.1 mV in 2 or more contiguous leads was considered significant. Deep TWI was defined as $\geq$-0.2 mV. Leads V_1 to V_4 were subclassified as anterior precordial leads. Biphasic T waves were defined as those with components above as well as below the PR-segment. TWI in leads V_1 to V_3 or beyond, in the absence of complete right bundle branch block (RBBB), was considered a major diagnostic criterion for ARVC. TWI in leads V_1 to V_2, or V_4, V_5, or V_6 was considered a minor diagnostic criterion in the absence of complete RBBB, or in leads V_1 to V_4 with complete RBBB. Partial right bundle branch block was defined as QRS duration >100 ms, but <120 ms, with rSR′ morphology in lead V_1 and qRS in V_6. Early repolarization was defined as J-point elevation $\geq$0.1 mV in 2 or more consecutive leads. A novel index of maximal QRS amplitude in the

ABBREVIATIONS AND ACRONYMS

ARVC = arrhythmogenic right ventricular cardiomyopathy

CMRI = cardiac magnetic resonance imaging

ECG = electrocardiography

EDV = end-diastolic volume

LV = left ventricle

LVH = left ventricular hypertrophy

RBBB = right bundle branch block

RV = right ventricle

RVH = right ventricular hypertrophy

RVOT = right ventricular outflow tract

SAECG = signal-averaged electrocardiography

SCD = sudden cardiac death

TFC = Task Force Criteria

TWI = T-wave inversion

V-Amp$_{max}$ = maximal QRS amplitude in the precordial leads

VE = ventricular extrasystole(s)

WMA = wall motion abnormality