Differentiating Left Ventricular Hypertrophy in Athletes from That in Patients With Hypertrophic Cardiomyopathy

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Identification of hypertrophic cardiomyopathy (HC) in young athletes is challenging when left ventricular (LV) wall thickness is between 13 and 15 mm. The aim of this study was to revise the ability of simple echocardiographic and clinical variables for the differential diagnosis of HC versus athlete's heart. Twenty-eight athletes free of cardiovascular disease were compared with 25 untrained patients with HC, matched for LV wall thickness (13 to 15 mm), age, and gender. Clinical, electrocardiographic, and echocardiographic variables were compared. Athletes had larger LV cavities (60 ± 3 vs 45 ± 5 mm, p <0.001), aortic roots (34 ± 3 vs 30 ± 3 mm, p <0.001), and left atria (42 ± 4 vs 33 ± 5 mm, p <0.001) than patients with HC. LV cavity <54 mm distinguished HC from athlete's heart with the highest sensitivity and specificity (both 100%, p <0.001). Left atrium >40 mm excluded HC with sensitivity of 92% and specificity of 71% (p <0.001). Athletes showed higher e′ velocity by tissue Doppler imaging than patients with HC (12.5 ± 1.9 vs 9.3 ± 2.3 cm/second, p <0.001), with values <11.5 cm/second yielding sensitivity of 81% and specificity of 61% for the diagnosis of HC (p <0.001). Absence of diffuse T-wave inversion on electrocardiography (specificity 92%) and negative family history for HC (specificity 100%) also proved useful for excluding HC. In conclusion, in athletes with LV hypertrophy in the "gray zone" with HC, LV cavity size appears the most reliable criterion to help in diagnosis, with a cut-off value of <54 mm useful for differentiation from athlete's heart. Other criteria, including LV diastolic dysfunction, absence of T-wave inversion on electrocardiography, and negative family history, further aid in the differential diagnosis. **(Am J Cardiol 2014;114:1383−1389)**

Intensive athletic training is associated with a spectrum of morphologic and functional cardiac changes (i.e., athlete's heart), considered to be physiologic adaptations to increased hemodynamic load and neurohormonal changes.[1,2] In most athletes, morphologic cardiac changes are mild and do not raise clinical concern, but in some highly trained athletes, left ventricular (LV) remodeling may be substantial, prompting differential diagnosis with structural heart disease, most commonly hypertrophic cardiomyopathy (HC).[2,3] Indeed, accurate identification of HC in athletes has relevant clinical implications, because this disease is one of the most common causes of athletic field deaths[4−6] and usually represents the basis for disqualification from competitive or professional sports.[7,8] Distinguishing athlete's heart from HC may prove particularly difficult when absolute LV wall thickness is in the range of 13 to 15 mm, which identifies the "gray zone" of overlap between these 2 clinical entities.[1,8,9] Although previous studies have proved useful in aiding this differential diagnosis, at present, reliable identification of HC continues to be challenging in athletes with such ambiguous morphology.[8−11] Therefore, the aim of the present study was to revise the ability of simple echocardiographic and clinical variables for the differential diagnosis of HC versus athlete's heart.

Methods

From January 2008 to June 2009, 1,191 consecutive highly trained athletes were evaluated at the Institute of Sport Medicine and Science in Rome, as potential participants in the 2008 Beijing Olympic Games and/or the 2009 Pescara Pan-Mediterranean Games. Of these, 28 athletes (2.3%) were selected for the present study, on the basis of age 18 to 40 years and the echocardiographic finding of absolute LV wall thickness of 13 to 15 mm, which has been defined as the gray zone of overlap of physiologic LV hypertrophy and HC.[1,8,9] Diagnosis of physiologic LV hypertrophy was based on the presence of mild LV wall thickening, judged consistent with the intensity and duration of sport discipline participated (as previously described),[1,2,8,9] associated with normal systolic and diastolic function and in the absence of systolic anterior motion of the mitral valve and LV outflow tract obstruction, and negative family history for the disease. The athletes were asymptomatic male Caucasians aged 26 ± 4 years; each had been competing at the national or international level for ≥3 years, participating in rowing or canoeing (n = 11), cycling (n = 6), swimming (n = 4), water polo (n = 2), judo (n = 2), basketball (n = 1), wrestling

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Table 1
Morphologic and functional left ventricular characteristics detected by echocardiography in athletes with left ventricular hypertrophy and hypertrophic cardiomyopathy patients

Variable	Athletes (n = 28)	HC (n = 25)	p-Value
Anterior septum (mm)	12.5 ± 0.6	13.8 ± 1.5	<0.001
Posterior septum (mm)	13.1 ± 0.4	12.0 ± 1.7	0.002
LV Posterior free wall (mm)	11.7 ± 0.7	9.3 ± 1.5	<0.001
LV Lateral free wall (mm)	11.3 ± 0.8	8.7 ± 1.1	<0.001
LV end-diastolic diameter (mm)	60 ± 3	45 ± 4	<0.001
LV end-systolic diameter (mm)	37 ± 5	24 ± 4	<0.001
Relative wall thickness*	0.42 ± 0.03	0.62 ± 0.11	<0.001
Left atrium diameter (mm)	42 ± 4	34 ± 5	<0.001
Aortic root (mm)	34 ± 3	30 ± 3	<0.001
Ejection fraction (%)	63 ± 5	64 ± 6	0.488
E wave (cm/s)	82 ± 18	80 ± 21	0.767
A wave (cm/s)	44 ± 8	57 ± 18	0.001
E/A ratio	1.9 ± 0.5	1.6 ± 0.6	0.032
Deceleration time (ms)	207 ± 53	175 ± 30	0.011
IVRT (ms)	97 ± 16	88 ± 13	0.135
TDI e′ wave (cm/s)	12.5 ± 1.9	9.1 ± 2.4	<0.001
TDI a′ wave (cm/s)	7.3 ± 1.6	6.7 ± 2.5	0.452
TDI e′/a′ ratio	1.77 ± 0.40	1.55 ± 0.70	0.170
TDI s wave (cm/s)	9.1 ± 1.8	8.2 ± 1.4	0.087
E/e′ ratio	6.6 ± 1.2	9.2 ± 2.5	<0.001

HC = hypertrophic cardiomyopathy; IVRT = isovolumic relaxation time; LV = left ventricle; TDI = tissue Doppler imaging.

* Relative wall thickness = ratio of the septal and free wall thickness normalized to LV cavity.

(n = 1), and hammer throwing (n = 1). According to our medical program, cardiovascular evaluation included personal and family history, physical examination, 12-lead and exercise electrocardiography, and 2-dimensional Doppler echocardiography.

For comparison, a group of 25 patients with nonobstructive HC, matched for age (range 18 to 40 years) and gender (all men) from the HC center at Tufts University Medical Center (Boston, Massachusetts) was selected for this analysis, on the basis of the presence of mild LV hypertrophy (i.e., wall thickness 13 to 15 mm), in the absence of systolic anterior motion of the mitral valve and LV outflow tract obstruction. They were Caucasian (n = 23 [92%]) or African American (n = 2 [8%]), and diagnosis of HC was based on the 2-dimensional echocardiographic (and/or cardiac magnetic resonance) demonstration of a hypertrophied, nondilated left ventricle in the absence of any cardiac or systemic disease that should lead to LV hypertrophy of the extent evident.[12] None of the patients with HC had evidence of systemic hypertension (i.e., blood pressure >140/90 mm Hg), and none was engaged in competitive sports or systematic exercise training programs (i.e., <3 hours of exercise per week). Diagnosis of HC was supported, indeed, by a positive family history of HC (n = 11 [44%]) and/or identification of pathogenic sarcomere protein mutation (n = 4 [16%]).[12]

Athletes and patients with HC were followed up for the subsequent 4 years after baseline evaluation, to assess the incidence of cardiac events, symptoms, or echocardiographic evidence of HC. The requirement for written informed consent was waived for all subjects, and the study design was approved by the local ethics committees.

Echocardiographic examinations were obtained at the 2 institutions by using Philips iE33 machines (Philips Medical Systems, Andover, Massachusetts) equipped with S3 probes (2 to 4 MHz). All acquisitions and measurements were performed by expert cardiologists (S.C., A.P., M.S.M., and N.G.P.), who were aware of patients' histories and clinical findings. The imaging protocol was defined at Tufts University Medical Center, where the Italian investigators (S.C. and A.P.) were trained in echocardiography. Specifically, 2-dimensional assessment of LV cavity diameters, wall thickness, the left atrium, and the aortic root was performed according to European Association of Cardiovascular Imaging and American Society of Echocardiography criteria.[13] The LV ejection fraction was calculated by the biplane Simpson's rule.

To assess LV diastolic function, early (E) and late (A) pulsed-wave Doppler diastolic peak-flow velocities were measured in the apical 4-chamber view, with the sample volume placed at the tip of the mitral leaflets; E-wave deceleration time and isovolumic relaxation time were measured in a standard fashion.[14] Tissue Doppler imaging (TDI) measurements of mitral annular motion were achieved in the apical 4-chamber view, with a 10-ml sample volume placed at the septal border of the mitral annulus. Early (e′) and late (a′) diastolic peak velocities and their ratio were recorded.[14]

Standard 12-lead electrocardiography was performed with the subject in the supine position and recorded at 10 mV and 25 mm/second. Analysis of the electrocardiographic tracings was performed according to widely used criteria.[15] Standard treadmill or bicycle exercise testing was performed in athletes and patients with HC under continuous 12-lead electrocardiographic and blood pressure monitoring. Twenty-four-hour Holter monitoring was selectively performed in athletes and patients in whom ≥3 premature ventricular beats were present at baseline or during exercise electrocardiography.[16]

Continuous data are expressed as mean ± SD. Categorical data are expressed as frequencies. Statistical significance was set for a 2-tailed p value <0.05. Differences between groups in terms of continuous variables were calculated by means of unpaired-samples Student's *t* tests. Differences between proportions were calculated by chi-square tests. Receiver-operating characteristic curve analysis was used to test the sensitivity and specificity of those variables that showed significant differences on unpaired Student's *t* tests. Sensitivity and specificity were reported when the p value was <0.05.[17] Data were analyzed by using PASW Statistics version 18 (SPSS, Inc., Chicago, Illinois).

Results

Comparative echocardiographic and Doppler LV findings in athletes and patients with HC are listed in Table 1. The distribution of LV hypertrophy was different in the 2 groups, in that anterior ventricular septum was thicker in patients with HC compared with athletes, whereas the posterior ventricular septum, posterior free wall, and anterolateral wall were thicker in athletes.