Athlete's heart or hypertrophic cardiomyopathy

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Abstract

There is overwhelming evidence that the heart of athletes may differ from that of non-athletes, provided that the training is of sufficient intensity and duration (athlete's heart). Predominantly eccentric left ventricular (LV) hypertrophy is observed in sports with high dynamic and low static demands (e.g. running). Sports with high static demands (e.g., weight lifting) lead to predominantly concentric hypertrophy. In sports with high dynamic and high static demands (e.g., cycling) the hypertrophy is compatible with mixed eccentric-concentric hypertrophy. The role of exercise is shown by the study of athletes in different training states. LV systolic function appears to be normal in athletes, both when measured at rest and during exercise. LV diastolic function is on average normal at rest, but is enhanced during exercise, which favors adequate filling of the ventricle at high heart rates. Investigations at the cardiac cellular, molecular and metabolic level confirm that cardiac hypertrophy in response to exercise should be considered physiological. LV wall thickness may be ≥13mm in highly trained male athletes and ≥11mm in female athletes, but the upper physiological limit appears to be 15mm and 13mm, respectively. Key features in the distinction between athlete's heart and hypertrophic cardiomyopathy are the appropriately increased size of the LV internal dimension in endurance athletes, and the normal systolic and particularly diastolic LV function in endurance and strength athletes, apart from history, type of hypertrophy, exercise performance and regression of structural changes with detraining.

Keywords: athlete's heart; hypertrophic cardiomyopathy; echocardiography; endurance training; static training.

■ Heart Metab. (2012) 56:14–19

Metabolic Imaging

Cardiac enlargement in athletes had already been recognized at the end of the nineteenth century through careful percussion of the chest in cross-country skiers, and was later confirmed by use of radiography and by evidence from autopsy. The advent of echocardiography and magnetic resonance imaging (MRI) allowed investigators to gain a better insight into the heart of athletes and the impact of different sports on cardiac structure and function. However, the heart of athletes may occasionally mimic certain pathological conditions associated with sudden death, such as hypertrophic cardiomyopathy (HCM), so that the distinction between athlete's heart and HCM is of crucial importance, particularly in the grey zone of overlap of structural cardiac changes.

Athlete's heart: structure and function

There is little doubt that repeated exercise stimuli of sufficient duration and intensity may induce cardiac enlargement in response to the exercise-induced hemodynamic changes and altered loading conditions of the heart. Left ventricular (LV) hypertrophy (LVH) has been observed in athletes [1–6], but cardiac adaptations also occur in sedentary subjects in response to physical training [7]. However, there is less unanimity on the relationship between the type of exercise and the specific cardiac adaptations [1–6,8,9]. As early as 1975, Morganroth et al [1] reported that athletes participating in endurance exercise had increased LV mass (LVM) with cardiac changes similar to those in chronic volume overload (eccentric LVH) and that athletes participating in static exercise had increased LVM similar to those in chronic pressure overload (concentric LVH). These cardiac adjustments serve to counterbalance the increase in wall stress [10]. However, the "Morganroth hypothesis" has been debated because athletic conditioning is rarely purely dynamic or static and the training programs of different athletes may overlap [2–6,8,9]. The results of a first meta-analysis [2] are shown in Table 1, in which the hypothesis of divergent cardiac adaptations in different sports was tested based on echocardiographic studies involving male competitive athletes and non-athletic control subjects, matched for age and body surface area, a strong determinant of cardiac dimensions. As shown in panel A, long-distance runners, a proper example of endurance exercise, have increased LV internal diameter and wall thickness, as expected. However, the

	A. LONG-DISTANCE RUNNERS			
	N	controls	runners	P
Age (yr)	9	24.2 ± 1.06	26.9 ± 1.61	NS
HR (b/min)	8	65.7 ± 2.56	51.6 ± 0.80	< 0.001
$LVID_d$ (mm)	10	48.3 ± 0.42	53.2 ± 0.66	< 0.001
$IVST_d$ (mm)	8	9.3 ± 0.36	10.8 ± 0.27	< 0.01
PWT_d (mm)	10	8.9 ± 0.30	10.5 ± 0.29	< 0.001
LVM (g)	10	149 ± 6.2	216 ± 7.3	< 0.001
h/R	10	0.372 ± 0.015	0.398 ± 0.011	= 0.05
	B. STRENGTH ATHLETES			
	N	controls	strength athletes	P
Age (yr)	7	24.5 ± 1.49	24.5 ± 1.29	NS
HR (b/min)	7	67.2 ± 2.06	62.3 ± 1.77	NS
$LVID_d$ (mm)	7	51.9 ± 1.07	53.2 ± 0.99	< 0.01
$IVST_d$ (mm)	7	8.9 ± 0.28	10.3 ± 0.48	< 0.05
PWT_d (mm)	7	8.4 ± 0.31	9.5 ± 0.55	< 0.05
LVM (g)	7	159 ± 6.3	198 ± 7.7	< 0.01
h/R	7	0.334 ± 0.016	0.375 ± 0.026	< 0.05
	C. CYCLISTS			
	N	controls	cyclists	P
Age (yr)	4	25.2 ± 0.85	23.9 ± 0.89	NS
HR (b/min)	4	67.8 ± 2.4	52.0 ± 0.33	< 0.01
$LVID_d$ (mm)	4	50.5 ± 1.25	55.1 ± 0.6	< 0.05
$IVST_d$ (mm)	4	9.1 ± 0.32	11.7 ± 0.6	< 0.01
PWT_d (mm)	4	8.9 ± 0.48	11.6 ± 0.75	< 0.01
LVM (g)	4	159 ± 4.7	262 ± 22.0	= 0.01
h/R	4	0.357 ± 0.022	0.42 ± 0.021	< 0.05

Values are weighted means ± SE.
N *number of study groups for which the respective variables were reported or could be calculated,* HR *heart rate,* LVID *left ventricular internal diameter,* IVST *interventricular septal thickness,* PWT *posterior wall thickness,* LVM *left ventricular mass,* h/R *relative wall thickness,* d *at end-diastole.*

Table 1 *Results of meta-analyses of athletes versus non-athletic controls, matched for age and body size. Data from [2].*

meta-analysis also reveals that relative wall thickness, that is the ratio between wall thickness and internal diameter, was 8% higher than in controls, compatible with "predominantly eccentric LVH" rather than pure eccentric LVH. Several sports are categorized as predominantly static or involve power training, such as weight lifting, bodybuilding, wrestling and throwing events. As shown in panel B, relative wall thickness was 12% higher than in controls in these athletes, but there was also a small but significant 2.5% increase in LV internal diameter, compatible with "predominantly concentric LVH." Finally, cycling and rowing involve both dynamic and static exercise. As shown in panel C, LV internal diameter, wall thickness and LVM were larger in the athletes. In addition, relative wall thickness exceeded that of the control subjects by 19%, indicating that cycling is not only associated with an increase of the internal diameter but also with a substantial disproportionate thickening of the wall, compatible with "mixed eccentric-concentric LVH." In a subsequent meta-analysis, Pluim et al [3] confirmed the hypothesis of the existence of an endurance-trained and a strength-trained heart, and that divergent cardiac adaptations do occur in athletes performing dynamic and static sports. However, as suggested before [2,4,9], the classification as an endurance-trained heart or a strength-trained heart is not an absolute and dichotomous concept but rather a relative concept. In fact, in every form of endurance training, blood pressure increases (pressure load), in addition to the increase in cardiac output (volume load), just as in every form of strength training, heart rate, cardiac output and blood pressure increase [3]. Cardiac hypertrophy in athletes has in general been confirmed with MRI [5,11,12], but it was suggested that more data are needed with regard to adaptations to different types of training [5]. It is of note that, despite common use of the term LVH, LVM does not necessarily exceed normal values, so that the term "LV remodeling" may be more appropriate to describe LV adaptations in the athlete.

In addition to the cross-sectional studies, Table 2 summarizes data from studies in which competitive athletes engaged in predominantly dynamic sports were assessed in an active training period and in a period of (relative) rest [2,13]. The significantly larger LVM and its components in the active period shows that physical training per se is at least partly responsible for athlete's heart. Later on, Pelliccia et al [14] observed that LV cavity dimension, wall thickness and mass had significantly decreased after an on average 5.6-year deconditioning period. However, normalization of structural cardiac changes may not always be complete, even after many years of deconditioning. Whereas athlete's heart is at least partly due to the training per se, twin studies revealed significant heritability of LV wall thickness, so that cardiac alterations in athletes may be partly genetic [15].

With regard to the right ventricle (RV), Scharhag et al [12] showed by use of MRI that the ratio of the LV to RV end-diastolic volume was similar in endurance athletes and matched controls and concluded that regular and intensive endurance training results in a balanced enlarged heart. Similarly, atrial enlargement is proportional to the enlargement of the ventricles [6].

The meta-analysis on long-distance runners, cyclists and strength athletes, and the results from other sports, revealed that a number of indices of systolic function were usually not different between athletes at rest and matched control subjects [2,3,9]. In cyclists the

	N	Inactive	Active-Inactive	P
HR (beats/min)	11	56.8 ± 1.55	-3.3 ± 1.23	< 0.05
LVIDd (mm)	11	53.6 ± 1.01	+1.1 ± 0.45	< 0.05
IVSTd (mm)	9	10.5 ± 0.26	+0.7 ± 0.23	< 0.05
PWTd (mm)	11	10.2 ± 0.32	+0.5 ± 0.23	< 0.05
LVM (g)	11	214 ± 12.6	+25.7 ± 6.4	< 0.01
h/R	11	0.384 ± 0.0064	+0.017 ± 0.0078	= 0.05
VO_2 peak (mL/min/kg)	6	60.9 ± 2.89	+4.8 ± 0.49	< 0.001

HR *heart rate,* LVID *left ventricular internal diameter,* IVST *interventricular septal thickness,* PWT *posterior wall thickness,* LVM *left ventricular mass,* h/R *relative wall thickness,* d *at end-diastole,* VO_2 *oxygen uptake*

Table 2 *Results of the meta-analysis of longitudinal observations in 11 groups of athletes: data from the inactive period and change from the inactive to the active period. Data from [2].*

relationship between LV fractional shortening index and systolic wall stress was similar to that obtained in matched sedentary subjects [16]. In addition, the increase of fractional shortening or ejection fraction on dynamic exercise was not different from controls in endurance athletes [17]. Finally, systolic LV function remained unaltered in the longitudinal studies, in which athletes were assessed in different training states [2] and long-term deconditioning did not alter LV ejection fraction [14]. The data therefore suggest a normal LV systolic function in athletes. The overall evidence obtained with different techniques suggests that LV diastolic function at rest is similar in athletes and non-athletes [3,9,16]. However, there is evidence that LV diastolic function is enhanced in the exercising endurance-trained athlete as compared with untrained control subjects [9,17], which favors adequate filling of the ventricle when the diastolic period gets shorter at higher heart rates. Brisk filling of the athlete's ventricle may at least in part be due to the larger chamber [6].

In addition to the results from imaging studies, cardiac hypertrophy in response to exercise training is also considered physiological hypertrophy at the cellular and molecular level [18–20]. Cardiac hypertrophy is characterized by normal organization of cardiac structure and preserved or even enhanced cardiac function, whereas pathological hypertrophy associated with pressure or volume overload, such as in hypertension or valve disease, is commonly associated with up-regulation of fetal genes, fibrosis and cardiac dysfunction. Physiological and pathological hypertrophy are mediated by distinct signaling molecules. Cellular adaptations to exercise with training are due to the activation of signaling pathways, and in particular the IGF-1/IGF-1R/Akt axis appears to have a major role. In addition, Ellison et al [20] reviewed the evidence that the endurance training-induced cardiomyocyte hypertrophy is accompanied by appropriate neo-angiogenesis and that recent data suggest that physical exercise determines cardiac growth also through new cardiomyocyte formation. With regard to cardiac metabolism, myocardial fatty acid utilization [21] and myocardial high-energy phosphate metabolism [22,23] appeared to be similar in endurance-trained athletes and sedentary subjects.

Athlete's heart versus hypertrophic cardiomyopathy

Pelliccia et al [24] reported on 947 amateur competitive athletes during period of intense training and concluded that a LV wall thickness of ≥13mm is only present in about 2%, and that it is associated with an enlarged LV cavity and normal systolic and diastolic function. In addition, the upper limit to which the thickness of the LV ventricular wall may be increased by athletic training appears to be 15mm. However, LV wall thickness was between 13 and 16mm in about one third of competitive road cyclists, but it is of interest that systolic and diastolic function was normal and not different between those with and those without wall thickness of ≥ 13mm [9]. Lower upper limits of normal have been described in female [25] and adolescent junior athletes [26].

It is likely that male and female athletes with wall thickness of more than, respectively, 15mm and 13mm, and with non-dilated LV cavity, have primary forms of pathologic hypertrophy, such as HCM. However, wall thickness may be in the grey zone, that is 13–15mm in male athletes and 11–13mm in female athletes, which may overlap with patients with a mild HCM phenotype. Table 3 summarizes a number of characteristics of, respectively, HCM and athlete's heart, which may help to distinguish between the two conditions, including family history, electrocardiographic changes, characteristics of the hypertrophy, regression of structural changes with detraining, LV function and exercise performance [27,28]. Key features in the distinction between physiological LVH and HCM are the appropriately increased size of the LV internal dimension in endurance athletes, and the normal systolic and particularly diastolic LV function in endurance and strength athletes. It has been suggested, based on the comparison of group averages, that Doppler echocardiographic assessments of diastolic function may contribute to distinguish physiological from pathophysiological hypertrophy, but their value for the individual subject is limited [25,29]. Also tissue Doppler imaging may help in distinguishing athlete's heart from HCM [30]. Similarly, the myocardial velocity gradient measured across the LV posterior wall may contribute to discriminate between HCM and hypertrophy in athletes [31]. Finally, contrast-enhanced cardiovascular magnetic resonance with late gadolinium enhancement can detect areas of myocardial fibrosis, which are present in most patients with HCM but not in physiological hypertrophy [27]. Because ECG abnormalities such as abnormal QRS-pattern and repolarization changes are part of athlete's

Characteristics of hypertrophic cardiomyopathy.
- Family history positive for hypertrophic cardiomyopathy, syncope and/or sudden death
- Bizarre ECG changes, though abnormal pattern of the QRS-complex and repolarization abnormalities may also be part of athlete's heart
- Asymmetric left ventricular hypertrophy, favoring the interventricular septum
- Normal or reduced left ventricular end-diastolic diameter (<45mm)
- Abnormal left ventricular diastolic function
- Left ventricular outflow tract obstruction during stress echocardiography
- Peak oxygen uptake less than predicted by age, gender and body size
- CMR-gadolinium delayed enhancement
- Positive genetic testing
Characteristics of athlete's heart (endurance training)
- Prolonged conduction delays on ECG (sinus bradycardia; atrioventricular block)
- Enlarged left ventricular end-diastolic diameter (>55mm), with proportional and symmetric increase in wall thickness (eccentric left ventricular hypertrophy)
- Harmonious increase in right ventricular dimension
- Regression of structural cardiac changes with detraining
- Normal left ventricular diastolic function
- Peak oxygen uptake greater than predicted by age, gender and body size

Table 3 *Criteria for distinguishing between athlete's heart and mild non-obstructive hypertrophic cardiomyopathy when left ventricular wall thickness falls within the grey zone (13-15mm in males and 11-13mm in females).* ECG *electrocardiogram,* CME *cardiac magnetic resonance.*

heart [4], the ECG is not appropriate to distinguish definitively between athlete's heart and HCM, but deep Q-waves and negative T-waves are not typical for physiological hypertrophy and are therefore suspicious of HCM [28].

Conclusion

The distinction between physiological cardiac hypertrophy and HCM is important because HCM is the most common cause of sudden death in young athletes and leads to disqualification from intense competitive sports. A pre-participation screening program, including a 12-lead ECG, has been developed by the European Society of Cardiology [32], based on the 25-year experience in Italy, where the systematic pre-participation screening of competitive athletes may have led to a reduced incidence of sudden cardiovascular death [33]. •

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