

How to differentiate athlete's heart from pathological cardiac hypertrophy?

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ABSTRACT

Left ventricular hypertrophy is defined as an increase in left ventricular mass. It can be physiological in athletes, as a result of cardiac adaptation to long-term training, or pathological in different conditions, such as chronic pressure overload (e.g. systemic hypertension, aortic stenosis), volume overload (e.g. aortic regurgitation), or myocardial disease (e.g. hypertrophic cardiomyopathy). Distinction between physiological and pathological hypertrophy might have major implications, since undiagnosed hypertrophic cardiomyopathy is one of the most common causes of sudden cardiac death in athletes, whereas identification of cardiovascular disease in an athlete may be the basis for disqualification from competitions. Conventional echocardiography is used as the standard method to assess the differentiation between physiological and pathological hypertrophy, however there are still more than 20% of cases when this remains difficult. In these ambiguous cases, new echocardiographic techniques, such as tissue Doppler, can provide new criteria that can be used for the differential diagnosis. This review will discuss main reasons to differentiate physiological from pathological hypertrophy, role of conventional echocardiography, and potentials of new echo criteria.

Keywords: athlete's heart, pathological ventricular hypertrophy, tissue Doppler imaging

ATHLETE'S HEART AND REASONS TO DIFFERENTIATE FROM PATHOLOGICAL HYPERTROPHY

Cardiac hypertrophy refers to the growth process of the cardiomyocytes, and thus to the cardiac thickening and remodeling. This process may be due to a cardiac pathology or to a long-term exercise training (1,2). Hypertension, causing chronic pressure overload, or hypertrophic cardiomyopathy (HCM), a genetic cardiac disorder, are associated with *pathological cardiac hypertrophy*, whereas sustained exercise training causes *physiological cardiac hypertrophy* (3,4).

Pathological cardiac hypertrophy is characterized not only by the growth of myocardial fibers, but also by changes in cardiac architecture and cellular metabolism and, finally, by myocardial dysfunction with increased morbidity and mortality. Specific genetic expression profiles, different from the adaptive ones involved in physiological hypertrophy, are activated (5). Pressure or volume overload causes initial hypertrophy, which represents a compensatory mechanism for maintaining cardiac function. If these stimuli persist, structural and functional cardiac anomalies develop. Thus, the cardiac sarcomers become bigger with ab-

Abbreviations:

CHD: coronary heart disease
HCM: hypertrophic cardiomyopathy
HD: heart disease
IVS: interventricular septum
LVH: left ventricular hypertrophy
LVEDD: left ventricular end-diastolic diameter
LVM: left ventricular mass

LMI: left ventricular mass index
MRI: Magnetic Resonance Imaging
PET: Positron Emission Tomography
RV: right ventricle
TDI: tissue Doppler imaging
Sn: sensitivity
Sp: specificity

normal proteins, resulting in bioenergetic deficit that affects their function. The cardiac muscular fibers are disorganized, and separated by an excessive interstitial tissue. Meanwhile, collagen metabolism is changed, resulting in decreased degradation and increased synthesis of extra cellular matrix (6). Consequently, myocardial fibrosis, localized mainly into the subendocardium layers, causes regional myocardial dysfunction (7).

On contrary, sustained exercise training is associated with physiological changes, in order to response to the specific haemodynamic requirements. "Athlete's heart" is characterized by preserved myocardial structure, with a normal pattern of gene expression and collagen metabolism, and does not progress to left ventricular dysfunction (7). Cardiac adaptation differs according to the type of the exercise training, and therefore two morphological forms of athlete's heart can be distinguished: an endurance-trained heart present in athletes involved in sports with a high dynamic component (runners), and a strength-trained heart present in athletes involved mainly in isometric exercise (e.g., weight-lifting) (7-9). During endurance training volume overload occurs (cardiac output can increase up to 40 l/min), causing *eccentric LVH* – increase of left ventricular internal diameter, with a moderate increase of the wall thickness; during strength training important pressure overload occurs (up to 48/35 cm Hg), inducing *concentric LVH* – thickening of the ventricular wall, with unchanged cavity diameter (4,7-9).

In some athletes who have a substantially increased left ventricular wall thickness, it may be difficult to distinguish with certainty between physiological hypertrophy due to athletic training and pathological hypertrophy due to hypertrophic cardiomyopathy or associated long-standing arterial hypertension. This discrimination is clinically important because undiagnosed hypertrophic cardiomyopathy is one of the most common causes (48%) of sudden cardiac death in young athletes (10,11) (figure 1). Moreover, left ventricular hypertrophy due to coincidental arterial hypertension is an important risk factor for coronary artery disease, which is a common cause of sudden death in older athletes (10) (Figure 1). Meanwhile, this distinction has major implications because identification of cardiovascular disease in an

athlete may be the basis for disqualification from competition. Since the clinical findings and the electrocardiographic changes may be similar in pathological left ventricular hypertrophy to those found in some athletes (12), echocardiography has an important role for making the differential diagnosis. However, echocardiographic criteria for the differential diagnosis between physiological and pathological left ventricular hypertrophy are still controversial, and despite the diagnostic potential of current ultrasound techniques, there are still cases of ambiguous myocardial hypertrophy (13,14).

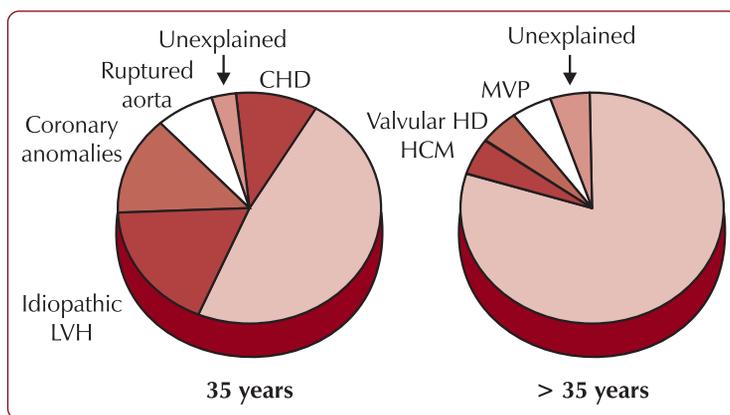


FIGURE 1. Causes of sudden death in athletes (10,11)
 CHD: coronary heart disease; HCM: hypertrophic cardiomyopathy; HD: heart disease; LVH: left ventricular hypertrophy; MVP mitral valve prolapse.

The ideal test for suspected hypertrophic cardiomyopathy might be a laboratory test for a known mutation. Unfortunately this is impractical in routine practice since many cases are sporadic and the disease may be caused by any one of 250 mutations {<http://cardiogenomics.med.harvard.edu/public-data>} (7). Thus diagnosis still depends on echocardiography, which has considerable limitations when hypertrophy is mild or uniform. More detailed information would be invaluable, so the next chapter will focus on new echocardiographic methods that may help. □

Echocardiography for the differentiation between physiological and pathological LVH

Echocardiography is still the preferred imagic technique to quantify left ventricular hypertrophy, by using an M-mode from the parasternal view and applying the well-known Devereux formula, or even better by using 3-dimensional echocardiography (1,4,6,15-17).

Usually, conventional parameters are used to discriminate between physiological and pathological hypertrophy. However, in ambiguous cases, new ultrasound methods, such as tissue Doppler imaging, might provide more valuable criteria that can be used for a better discrimination between different types of hypertrophy, and also to assess markers of subclinical cardiac dysfunction used to monitor regression (7,18).

Conventional echocardiography. There are numerous studies that use conventional echo parameters in order to establish the diagnosis of cardiac hypertrophy, or to differentiate between the two forms of remodeling (Table 1) (19,20).

patients with HCM, the pattern of hypertrophy is usually heterogeneous and asymmetrical (24). Meanwhile, HCM is sometimes characterized by the presence of the systolic anterior motion of the anterior mitral leaflet (25), or an abnormal myocardial acoustic density (16).

Furthermore, as already discussed, the exercise type influences the pattern of hypertrophy, with predominantly eccentric left ventricular hypertrophy in endurance training, and concentric left ventricular hypertrophy in strength training (26).

Left ventricular diameters. Same major surveys showed that about 15-20% of the endurance athletes have an enlarged left ventricular end-diastolic diameter over 55-60 mm (16,21), which is very unusual in HCM, in

TABLE 1. Differential diagnosis between physiological and pathological hypertrophy

| Strategy | Athletes | HCM | Hypertension |
|--------------------------------------------|----------|----------|--------------|
| <i>Imagistic methods (Echo, MRI, PET)</i> | | | |
| • LVEDD | > 55 mm | 45-55 mm | >45 mm |
| • IVS thickening | < 13 mm | > 16 mm | < 16 mm |
| • Asymmetric LVH | No | Yes | No |
| • Atrial dilatation | No | Yes | Yes |
| • RV dilatation | No | Yes | Yes |
| • Diastolic dysfunction | No | Yes | Yes |
| • Systolic dysfunction (conventional echo) | No | No/Yes | No/Yes |
| • Systolic dysfunction (TDI) | No | Yes | Yes |
| <i>Thickening with deconditioning</i> | | | |
| | Yes | No | No |

HCM: hypertrophic cardiomyopathy; IVS: interventricular septum; LVEDD: left ventricular end-diastolic diameter; LVH: left ventricular hypertrophy; MRI: Magnetic Resonance Imaging; PET: Positron Emission Tomography; RV: right ventricle; TDI: tissue Doppler imaging.

Left ventricular wall thickness is the defining echo parameter for hypertrophy, used to calculate the left ventricular mass (LVM) and the left ventricular mass index (LVMI). Most of the surveys of highly trained athletes showed that the maximum thickness of the interventricular septum is <13 mm, and only 2% of the athletes develop an interventricular septum between 13-16 mm (21). However, since there are forms of HCM associated with only mild to moderate hypertrophy, these athletes are in the “grey zone”, when the suspicion of pathological hypertrophy is raised (Figure 2) (22).

Sustained exercise training determines an homogenous hypertrophy, with minor differences, in the range of 1-2 mm, between different left ventricular walls (23), whereas in

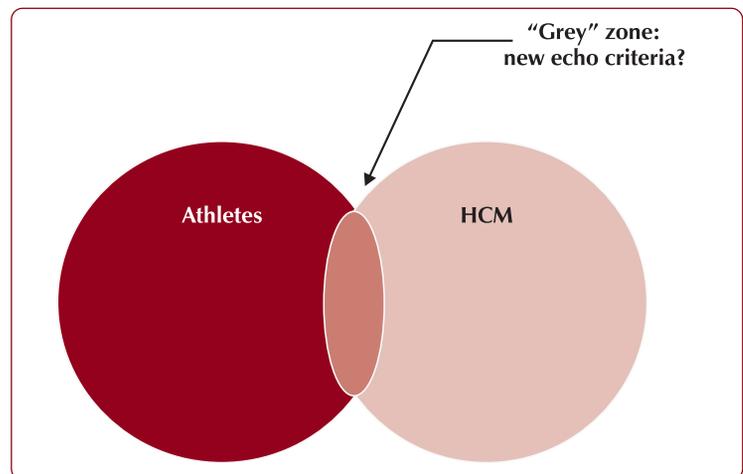


FIGURE 2. Distinguish hypertrophic cardiomyopathy from athlete’s heart (22)

which the cavity dimension is often < 45 mm, and might exceed 55 mm only in the end-stage phase, when heart failure and systolic dysfunction are present (27).

Left ventricular mass and, particularly, *left ventricular mass index* should be always calculated when we assess the athlete's heart. The upper limit of physiological hypertrophy is considered to be of 500 g (28). However, when appropriate calculations of these parameters are made, left ventricular hypertrophy, as defined by the American Heart Association (>131 g/m² in men, and >110 g/m² in women), is present only in about 50% of highly trained athletes (29).

Left atrial diameter is usually normal in athletes and increased in patients with pathological hypertrophy (25).

Right ventricular dimensions are increased in athletes, with an increase of the internal diameter and of the thickness of the free walls that are, sometime, associated with an increase of the caliber of the inferior vena cava (30). This feature characterizes only the endurance-trained athletes, not the strength-trained athletes or the patients with HCM. *Ventricular performance.* Most data suggest that left ventricular systolic function, assessed as fractional shortening of the internal diameters or as ejection fraction, is normal in athletes, both when measured at rest or during exercise (19). Meanwhile, the right ventricular performance is not different between athletes and controls (4). However, these parameters can not be used to discriminate between the different types of hypertrophy, since global systolic function is normal also in patients with HCM till the end-stage of the disease.

On contrary, left ventricular diastolic function is normal, or even "supernormal" in athletes, and impaired in pathological hypertrophy. And indeed, it was showed that left ventricular diastolic function is within normal limits in athletes at rest, but increased during exercise to favor adequate filling of the ventricle at higher heart rate. This mitral inflow pattern is called "supernormal", with an increasing of the contribution of early-diastolic phase (E-wave), and with an E/A ratio >2 (32), while in the majority of the pathological hypertrophy, the diastolic performance is impaired, by abnormality of the relaxation phase (E/A ratio <1, the deceleration time >240 ms, and isovolumic relaxation time >90 ms) (16).

Deconditioning. Serial echocardiographic assessment demonstrated that hypertrophy secondary to exercise training regresses after interruption of physical activity, with a reduction

in the wall thickness of about 2-5 mm within 3 months of deconditioning (31). These findings are not present in patients with HCM (Table 1).

Unfortunately, conventional echo methods proved to have low accuracy for the differentiation between physiological and pathological left ventricular hypertrophy; rest and/or post-exercise left ventricular diastolic dysfunction, measured by reversal of the E/A ratio and/or a prolongation of the E wave deceleration time, an increase in the thickness of the left ventricular wall to >16 mm, and an increase of the ratio of (septum + posterior wall) to end-diastolic diameter to more than 0.6, have all been proposed as markers of pathological left ventricular hypertrophy, however, in our experience, their sensitivities was rather low (40-73%) (32). Therefore, new echocardiographic approaches has been developed in order to evaluate left ventricular hypertrophy, from which tissue Doppler is the most promising (7,17, 24,32-36).

Tissue Doppler imaging (TDI) is an ultrasound technique, available on the majority of commercially available echo machines, which allows rapid measurements of myocardial velocities of contraction and relaxation, and mechanical activation times, thus allowing assessment of ventricular synchrony. The principle of differentiation between physiological and pathological hypertrophy by this technique is based on the fact that in the heart there are two morpho-functional muscular layers, the subepicardial layer, which is concentrically disposed and is responsible for the radial function of the heart, and the subendocardial layer, which is longitudinally disposed and is responsible for the long axis function of the heart. The subendocardial, longitudinal, muscular fibers are the most susceptible to ischemia and fibrosis and consequently they are the first affected by the pathological processes, such as hypertension or HCM (7). Meanwhile, ventricular function depends not only on the myocardial contraction force, but also on the synchronous contraction of different myocardial segments, which might be impaired in patients with mild HCM (33).

Thus, recent studies that used TDI for the assessment of the long axis function of left ventricle showed that athletes have higher systolic and early diastolic mitral annular velocities than the patients with pathological hypertrophy (Figure 3 and 4) (7, 32-36). Using univariate analysis, the best differentiation of physiological from pathological left ventricular hypertrophy (due to hypertension

or mild obstructive HCM) was provided by a mean systolic annular velocity <9 cm/s or a mean early diastolic annular velocity <9 cm/s (Figure 3) (32). Actually, the criteria given by TDI performed much better than conventional echo parameters,

amongst which the best diagnostic accuracy was found for a ratio of (septum + posterior wall) to end-diastolic diameter >0,6 (sensitivity 63%, specificity 100%, accuracy 82%) (figure 5).

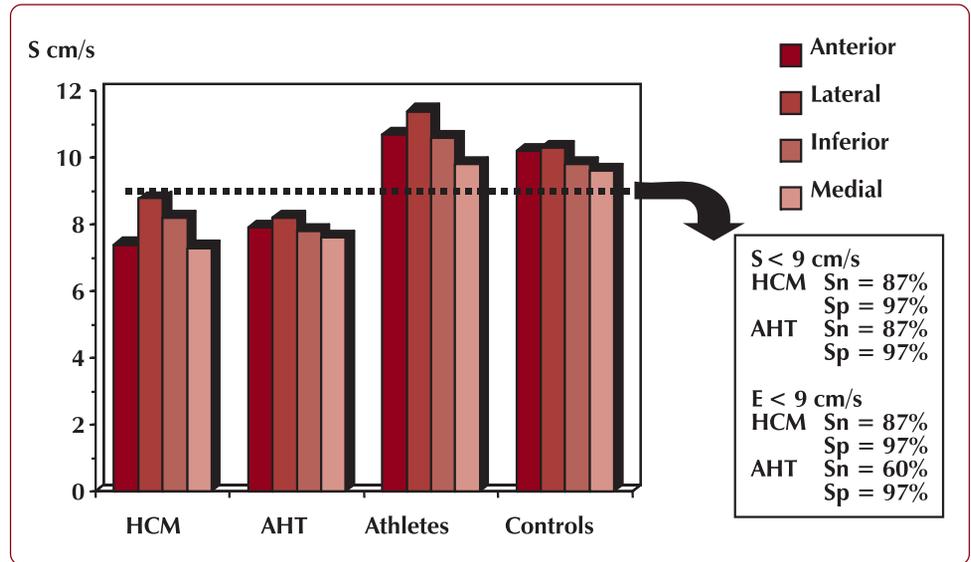


FIGURE 3. Accuracy of the assessment of long-axis function for the differential diagnosis between physiological and pathological left ventricular hypertrophy (32) HCM: hypertrophic cardiomyopathy; AHT: arterial hypertensive; Sn: sensitivity; Sp: specificity. Anterior, lateral, inferior, and medial refers to the corresponding sites of the mitral annulus from the 4-chamber view.

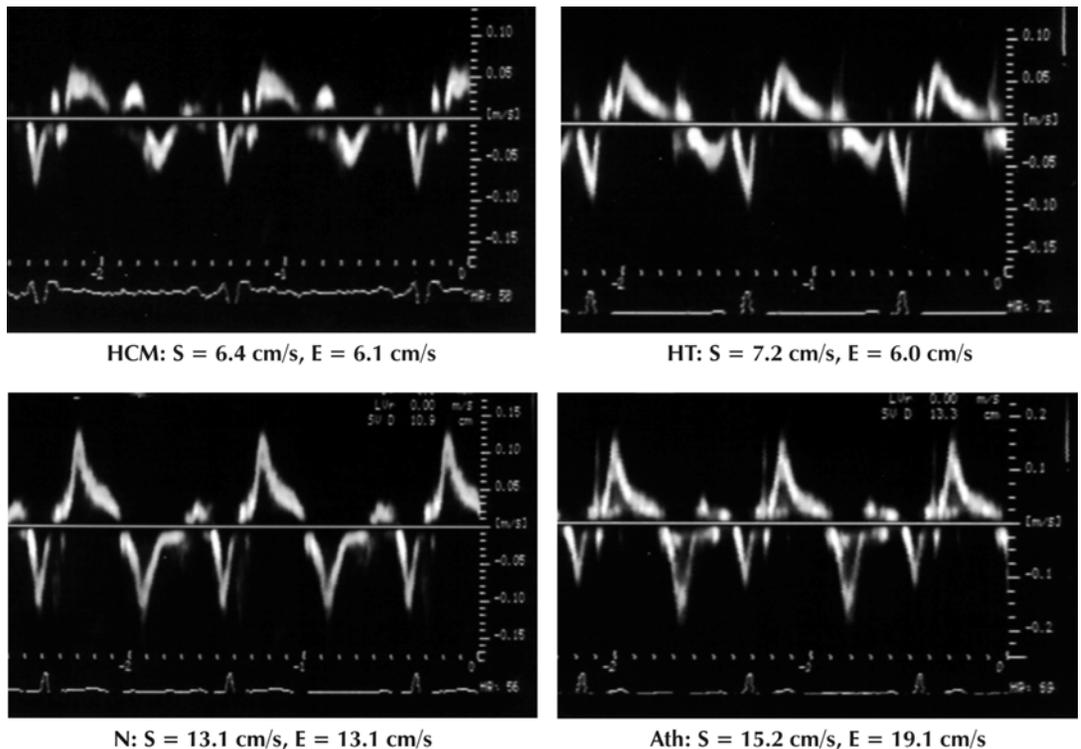


FIGURE 4. Representative examples of tissue Doppler traces of the velocities of lateral mitral annular motion in a patient with hypertrophic cardiomyopathy, a patient with hypertension, a normal subject, and an athlete with physiological hypertrophy. Note lower systolic (S) and early diastolic (E) myocardial velocities, with a reversed myocardial E/A ratio, in patients with pathological hypertrophy, and supranormal velocities in the athlete's heart (7,32).

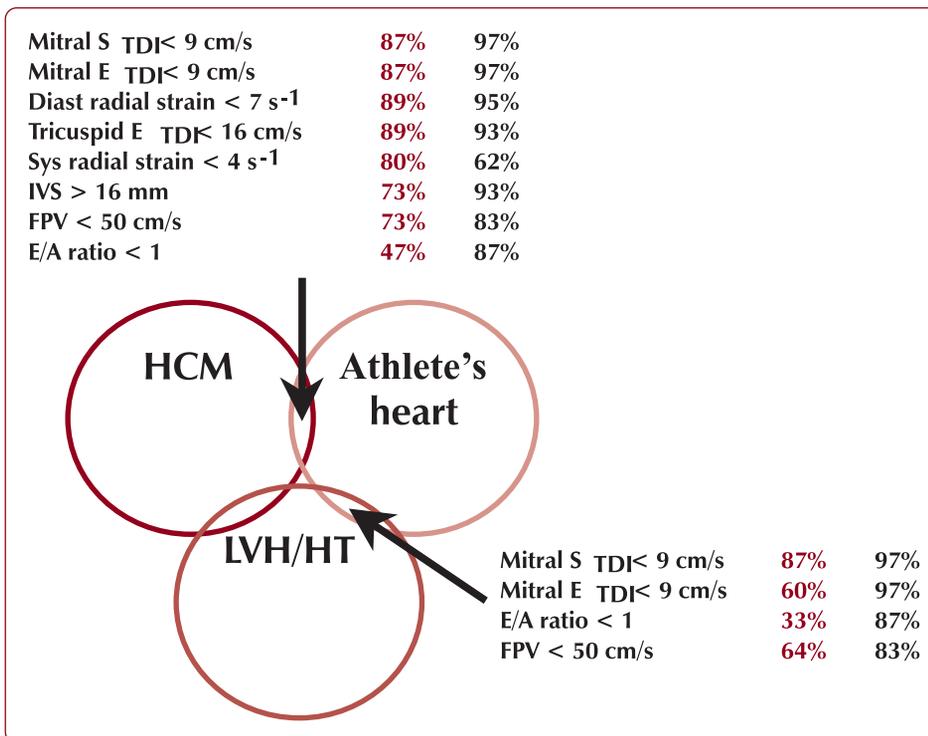


FIGURE 5. Performance of echocardiographic criteria for discriminating physiological hypertrophy in athletes from pathological hypertrophy from hypertrophic cardiomyopathy and hypertension (7).

FPV: flow propagation velocity; IVS: interventricular septum; TDI: tissue Doppler imaging.

TDI also offers informations about the right ventricular function. In our study, the best differentiation of pathological (due either to hypertension or HCM) from physiological hypertrophy was provided by an early diastolic tricuspid annular velocity <12,00 cm/s (sensitivity 77%, specificity 77%), whereas the best differentiation of HCM from physiological hypertrophy was provided by an early diastolic tricuspid annular velocity <11 cm/s (sensitivity 90%, specificity 74%) (37).

TDI allows also the measurement of myocardial velocity gradient, which is the difference between endocardial and epicardial myocardial velocities. In normal subjects, this gradient is preserved because endocardial myocardial layers moves faster than the epicardial myocardial layers (25,38). With disease, such as pathological hypertrophy, this gradient is impaired. And indeed, in an experimental study, the myocardial velocity gradient in systole and the ratio of early-to-late diastolic gradients were both decreased in pressure-induced hypertrophy, but preserved in exercise-induced hypertrophy (39). In clinical studies, differences in the

myocardial velocity gradient across the left ventricular posterior wall discriminated between HCM and physiological hypertrophy in young athletes: a myocardial velocity gradient < 7 s⁻¹, measured during rapid ventricular filling in early diastole, differentiated best, with a sensitivity of 89% and a specificity of 95%. The systolic myocardial velocity gradient was also lower in patients with HCM than in athletes, but the optimal cut-off value of 4 s⁻¹ had a lower sensitivity and specificity (80% and 62% respectively) (figure 5) (38). □

Other methods for the differentiation between physiological and pathological LVH

There are only few data regarding the use of other imaging modalities, such as *Magnetic Resonance Imaging (MRI)* or *Positron Emission Tomography (PET)*, for the assessment of left ventricular hypertrophy. MRI might be used to differentiate between pathological and physiological hypertrophy by measuring specific geometric indices (40). It may also identify regions of cardiac hypertrophy, which are not recognized

by ultrasound techniques. Using PET for the assessment of myocardial perfusion, a recent study showed that the peak global perfusion was 62% higher in athletes than in controls (41). However, these imaging techniques are expensive and time consuming and they are reserved only for selected patients.

The best future modality to diagnose mild to moderate HCM in athletes with an increase wall thickening will derive from the demonstration of genetic mutations (42). A rapid genetic test, analyzing DNA sequences muta-

tions is now available. However, because of the extensive genetic heterogeneity and the "sporadic" pattern of HCM (43), the routine availability of this technique is restricted and time consuming. □

In **conclusion**, combined use of conventional echocardiography and tissue Doppler imaging might be a rapid, simple, and non-invasive approach in order to differentiate the best physiological from pathological left ventricular hypertrophy.

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