Left Ventricular Hypertrabeculation

Although left ventricular non-compaction (LVNC) was defined as a primary cardiomyopathy by the American Heart Association (AHA) in 2006,[783] the 2023 European Society of Cardiology's 'Management of Cardiomyopathies' guideline classifies this condition not as a cardiomyopathy, but as a phenotypic feature characterized by prominent left ventricular trabeculae and deep recesses. This feature can occur in isolation or in conjunction with other abnormalities, including ventricular hypertrophy, dilatation, and/or systolic dysfunction. The guideline recommends using the term "hypertrabeculation (HT)" instead of LVNC, particularly in cases where the phenomenon is reversible or clearly initiates in adulthood.[1]

While previous studies have suggested that hypertrabeculation arises due to an interruption in the transformation of non-compacted myocardium into compacted myocardium, recent evidence contradicts this hypothesis.[784] Left ventricular hypertrabeculation is known to be associated with hereditary, developmental, or congenital heart diseases.[784] It can manifest as a normal variant or result from a remodeling response to increased preload and afterload, secondary to factors such as pregnancy, sports activities, or ventricular dysfunction.[785,786] The association of hypertrabeculation with left ventricular dilatation and dysfunction sparks significant debate. The question remains whether hypertrabeculation is a secondary response to changes in preload and afterload in ventricular dysfunction or represents a very rare cardiomyopathy that triggers this dysfunction, posing a perplexing dilemma.[787,788]

Definition of Left Ventricular Hypertrabeculation

The diagnosis of left ventricular hypertrabeculation (LVHT) relies on cardiac imaging modalities. Despite the establishment of various diagnostic criteria for different modalities, which derived from studies involving small patient cohorts, these criteria lack standardization and definitive consensus. Typically, these criteria primarily emphasize morphological evaluation, disregarding functional assessment, which may result in the overdiagnosis of LVNC.[789]

While echocardiography serves as the primary imaging modality, cardiac magnetic resonance (CMR) with high resolution plays a crucial role in diagnosis, particularly in patients with limited echocardiographic windows. The role of cardiac computed tomography (CT) in diagnosis remains uncertain. However, it provides an opportunity to assess hypertrabeculation in patients who undergo CT for other indications, such as coronary artery or congenital anomaly examination.

Evaluation of Hypertrabeculation with Multimodality Imaging Methods

Echocardiography

Three separate echocardiographic criteria for diagnosing LVHT are outlined in Table 40. First, Chin et al.[790] established a criterion based on the ratio derived from the short axis view at end-diastole, obtained by dividing the distance between the epicardial surface and the intertrabecular recesses (X) by the distance between the epicardial surface and the peak of the trabeculation (Y), where a ratio of less than 0.5 is diagnostic (Figure 123). However, this criterion, developed from a study involving only 8 cases, lacks clarity regarding the level at which the measurement should be taken and is not commonly preferred in daily clinical practice.

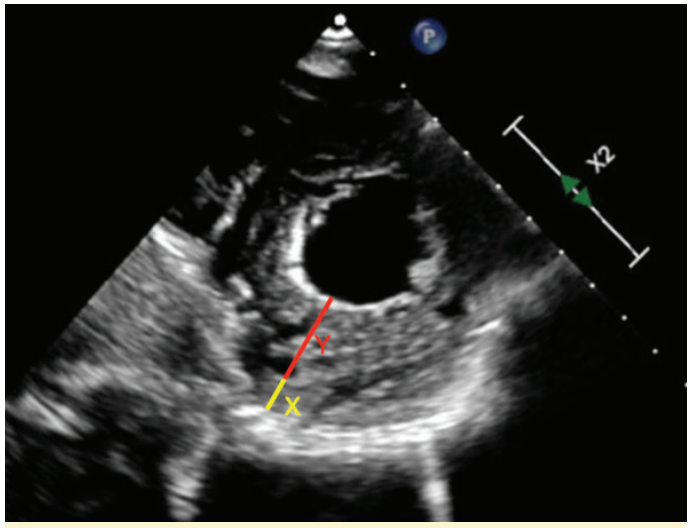

Figure 123. Chin criterion with transthoracic echocardiography: X (yellow line) / Y (red line) ≤ 0.5 in the short-axis view at end-diastole.

The second criterion, defined by Jenni et al.,[791] comprises four parameters measured from the short axis view at end-systole: 1. a ratio of thick noncompacted endocardial layer (NC) to thin compacted epicardial layer (NC/C) > 2; 2. predominance of NC in mid-lateral, mid-inferior, and apical segments; 3. blood flow in the deep intertrabecular recesses detected with color Doppler; and 4. absence of accompanying cardiac abnormalities (Figure 124). It's worth noting that the Jenni criteria are often applied regardless of the absence of accompanying cardiac abnormalities.[792]

Lastly, Stöllberger et al.[793] published criteria involving five parameters observed at end-diastole in the apical four-chamber view: 1. more than three prominent trabeculations distal to the papillary muscles at the apex in a single imaging plane; 2. blood flow or perfusion in the trabecular recesses with color Doppler; 3. trabeculation and myocardium exhibiting the same echogenicity; 4. trabecular movement synchronous with ventricular contraction; and 5. NC/C ≥ 2 (Figure 125).

Table 40. Echocardiographic diagnostic criteria of left ventricular hypertrabeculation

Criteria	Chin[790]	Jenni[791]	Stöllberger[793]
Cardiac Cycle	End-diastole	End-systole	End-diastole
View	Short axis	Short axis	Apical
Cut-off Value for Hypertrabeculation	X/Y ≤ 0.5	NC/C ≥ 2; predominance of NC in mid-lateral, mid-inferior, and apical segments; blood flow in the recesses with color Doppler; No accompanying cardiac anomalies	NC/C ≥ 2; more than three trabeculation distal to the papillary muscles; flow in the trabecular space with color Doppler; trabeculation and myocardium have the same echogenicity; trabecular movement synchronous with ventricular contraction

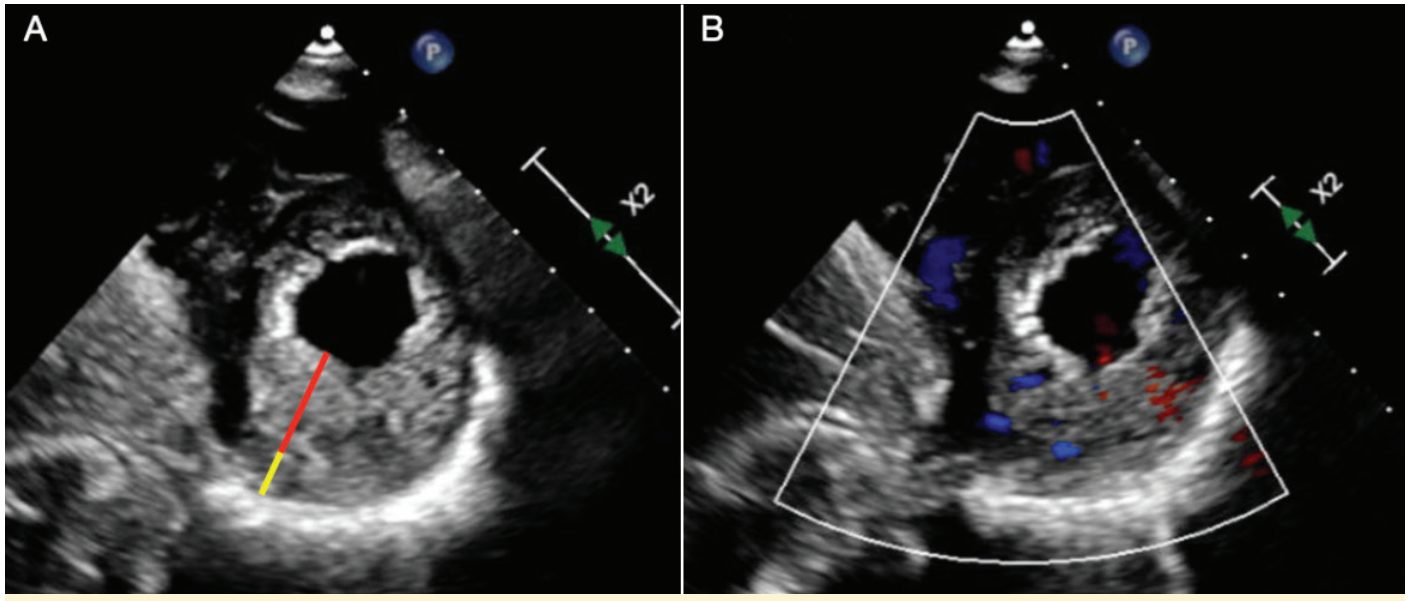

Figure 124. Jenni Criterion with Transthoracic echocardiography: (A) Noncompacted layer (red line) / compacted layer (yellow line) > 2 in the short-axis view at end-systole, with trabeculation predominance in the mid and apical segments. (B) Blood flow in intertrabecular recesses visualized with color Doppler.

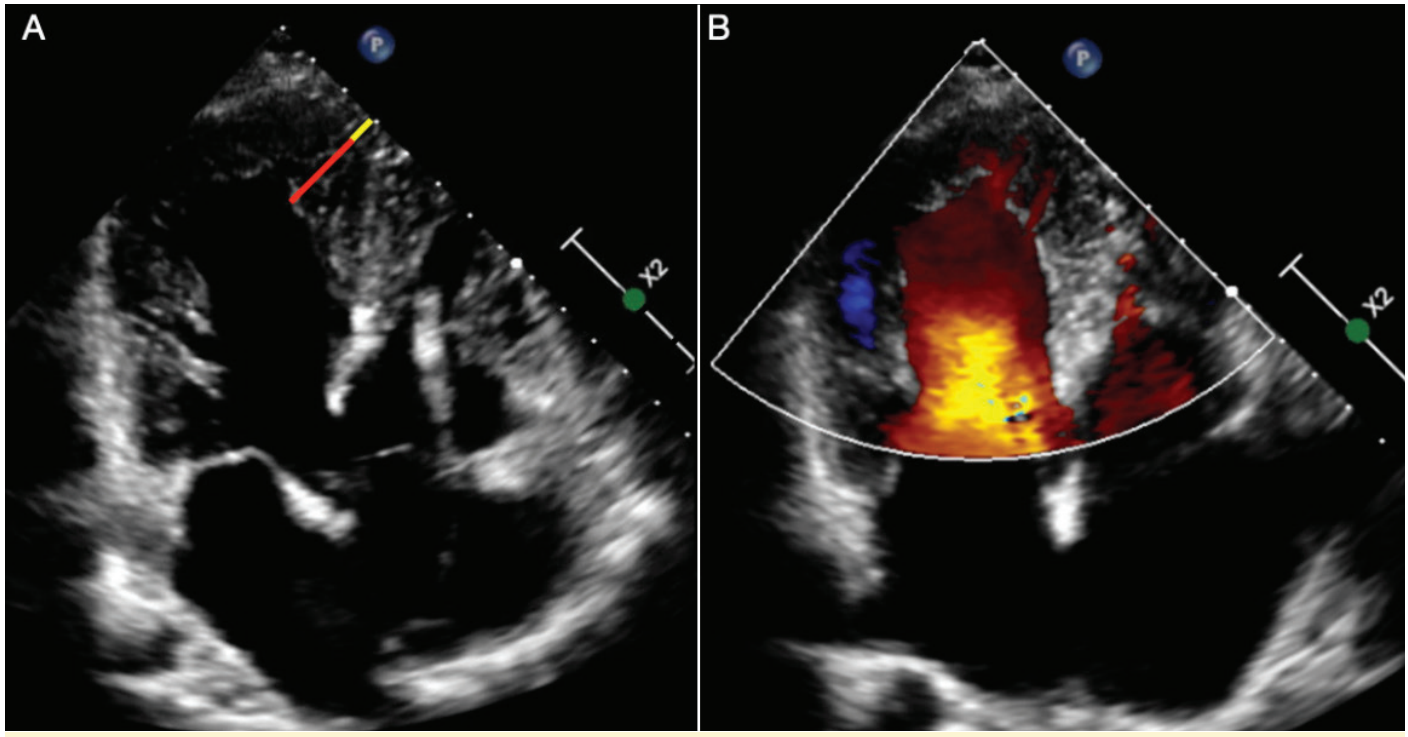

Figure 125. Stöllberger criterion with transthoracic echocardiography in a 35-year-old male patient with biventricular hypertrabeculation and systolic dysfunction who had an implantable cardioverter-defibrillator due to ventricular tachycardia. (A) In the apical view at end-diastole, the noncompacted layer (red line) / compacted layer (yellow line) ≥ 2, and trabeculations and myocardium move simultaneously with the same echogenicity. (B) Blood flow in intertrabecular recesses visualized with color Doppler.

Table 41. CMR diagnostic criteria for left ventricular hypertrabeculation

Criteria	Petersen[794]	Jacquier[796]	Stacey[798]	Grothoff[799]	Captur[800]
Cardiac Cycle	End-diastole	End-diastole	End-systole	End-diastole	End-diastole
View	Long axis	Short axis stack	Short axis	Short axis stack	Short axis stack
Cut-off Value for Hypertrabeculation	NC/C > 2.3	NC mass > 20% of total LV mass	NC/C ≥ 2	Trabeculation mass > 15 g/m^2; > 25% of total LV myocardial mass; NC/C ≥ 2 in segments 4-6; NC/C ≥ 3 in segments 1–3, 7–16	Maximum apical fractal dimension ≥ 1.30

In cases with low image quality, contrast echo can enhance of the evaluation efficacy and reliability by rendering trabeculations and intertrabecular recesses more visible.

Cardiac Magnetic Resonance

In recent years, there has been an increasing utilization of CMR, particularly in the assessment of cardiomyopathies. CMR, with its high spatial resolution and intrinsic contrast, offers the opportunity to distinguish between blood and myocardium, particularly beneficial in patients with limited echocardiographic apical views. Moreover, the capability of CMR to simultaneously evaluate intrathoracic structures and potential accompanying congenital anomalies enhances its diagnostic utility. Therefore, CMR is recommended to confirm the diagnosis of LVHT.

There are five distinct CMR criteria for diagnosing LVHT (Table 41). The first criterion, defined by Peterson et al.,[794] involves measuring NC/C > 2.3 at end-diastole in any long-axis view (2-, 3-, 4-chamber) (Figure 126). However, despite the authors' claim of a sensitivity of 86% and specificity of 99% in diagnosis, the MESA study indicates that 43% of healthy individuals meet this criterion.[795]

The second criterion, proposed by Jacquier et al.,[796] entails measuring NC mass exceeding 20% of the total LV mass from short-axis stack images at end-diastole. While this criterion may seem more reliable as it assesses LVHT globally rather than regionally, the analysis requires a longer period of time. Consequently, the Peterson criterion has become the most widely used criterion in routine clinical practice.[797]

Stacey et al.[798] elucidated that an NC/C ratio of ≥ 2 on short-axis cine images at end-systole suggests LVHT (Figure 127).

Grothoff et al.[799] proposed a criterion comprising four parameters in short-axis stack images at end-diastole as follows: 1. NC mass / total LV myocardial mass > 25%; 2. NC mass > 15 g/m^2; 3. NC/C

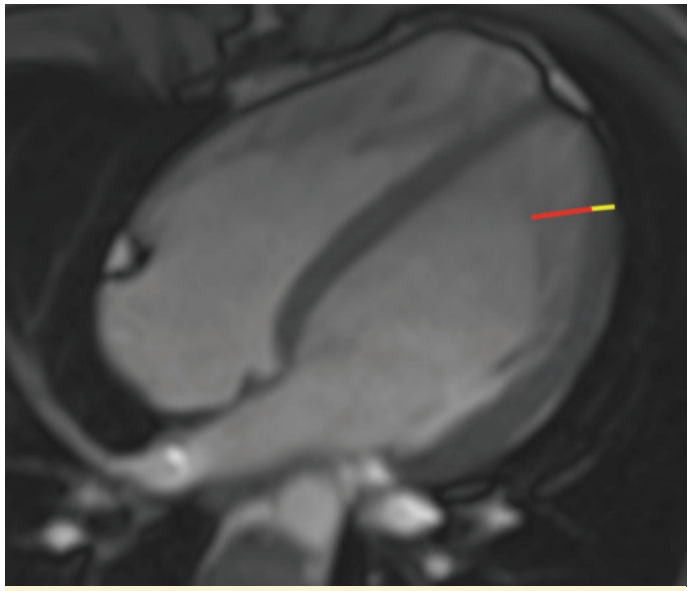

Figure 126. CMR Petersen Criterion: Noncompacted layer (red line) / compacted layer (yellow line) in the long-axis (4 chamber) cine image at end-diastole > 2.3.

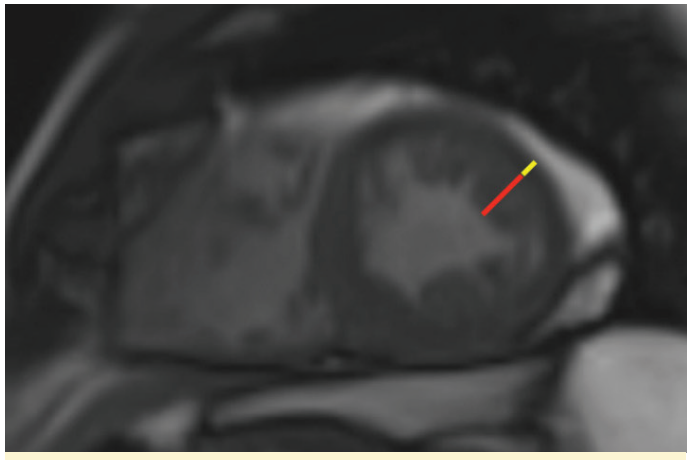

Figure 127. CMR Stacey Criterion: Noncompacted layer (red line) / compacted layer (yellow line) ≥ 2 in the short-axis cine image at end-systole.

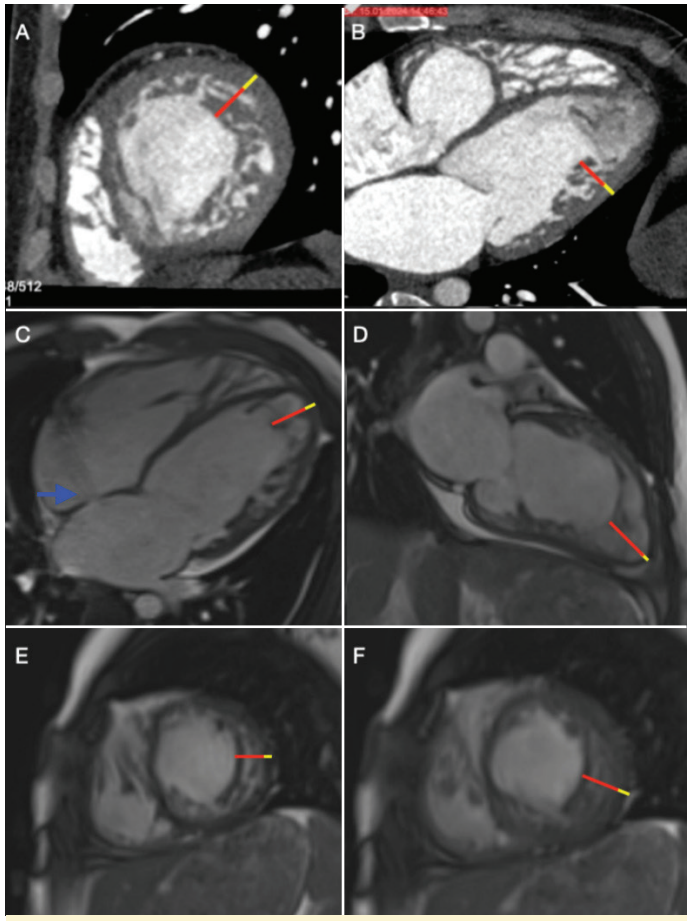

Figure 128. Detection of left ventricular hypertrabeculation by cardiac CT performed for coronary artery evaluation in a newly diagnosed dilated cardiomyopathy patient and confirmation of the diagnosis of hypertrabeculation with CMR. (A) Cardiac CT short-axis image. (B) Cardiac CT long-axis 4-chamber view. (C) CMR NC/C > 2.3 (Petersen criterion) at end-diastole on the long-axis (4-chamber) view. The blue arrow indicates a left-to-right shunt over a small atrial septal defect. (D) CMR NC/C > 2.3 (Petersen criterion) at end-diastole on the long-axis (2-chamber) view. (E) CMR NC/C ≥ 2 (Grothoff criterion parameter) on the short-axis view at end-diastole. (F) CMR NC/C ≥ 2 (Stacey criterion) on the short-axis view at end-systole. The yellow line represents the compacted layer, and the red line represents the noncompacted layer.

≥ 2 in basal and septal segments 4–6; and 4. NC/C ≥ 3 in at least one of the other segments (1–3, 7–16) except the apical segment.

Lastly, Captur et al.[800] introduced an unitless measurement value, the fractal dimension, determined by fractal analysis of all short-axis LV slices at end-diastole, assessing how thoroughly this intricate structure fills the space. The range of possible fractal dimensions for the endocardial border spans from a non-integer value of 1 (representing a solid line) to 2 (indicating complete filling of the 2-dimensional space contained by ventricular trabeculation). A maximum apical fractal dimension ≥ 1.30 serves as a diagnostic criterion for LVHT. According to the MESA study, patients with hypertension, left ventricular hypertrophy, high LV mass, and African Americans tend to exhibit higher fractal dimension values.[801]

Late gadolinium enhancement (LGE), which plays a significant role in the differential diagnosis of cardiomyopathies, does not serve as a reliable guide in the diagnosis of hypertrabeculation.

Cardiac Computed Tomography

CT, while not the preferred imaging modality due to concerns regarding radiation exposure and contrast agent use, can be utilized to assess HT in patients with limited echocardiographic windows and undergoing CT examination for other indications, such as coronary artery evaluation (Figure 128).

According to the study by Melendez-Ramirez et al.,[802] NC/C > 2.2 in at least two segments from the short axis at end-diastole confirms the diagnosis of HT.

Sidhu et al.[803] found that an NC/C value > 2.3 measured from the long axis at end-diastole is diagnostic in patients previously diagnosed with LVHT by echocardiography and CMR.

Fuch et al.[804] established a threshold value of NC/C > 1.8 at end-diastole in the short axis basal, mid, and apical segments for the early stages of hypertrabeculation and in patients with a small LV cavity. However, despite the publication of these criteria, the role of cardiac CT in the diagnosis of LVHT remains unclear.

Many publications investigating diagnostic criteria for LVHT indicate that while the sensitivity of these criteria is very high, the specificity is very low, particularly in patients with a low pre-test probability and in African American individuals.[805–807] Consequently, more healthy individuals may be misdiagnosed with LVHT.

Clinical Presentation

While asymptomatic patients are often diagnosed during routine cardiac imaging, the most common presenting symptoms of LVHT include heart failure, thromboembolism, arrhythmias, and sudden cardiac death. Thromboembolism is believed to occur due to reduced blood flow in the recesses between noncompacted trabeculae. Severe systolic dysfunction and atrial fibrillation are also contributing factors to thromboembolism.[808] Notably, thromboembolism has not been reported in individuals with asymptomatic LVHT phenotype with preserved ventricular function.[809]

Differential Diagnoses of Left Ventricular Hypertrabeculation

During the evaluation with echocardiography, which serves as the first line imaging modality, other conditions affecting the LV apical region may be mistaken for LVHT, particularly in patients with limited echocardiographic windows. These conditions may include apical hypertrophic cardiomyopathy, endomyocardial fibrosis, and thrombus. However, when the apical region of the ventricle is examined more clearly with CMR, which offers superior resolution, the potential differential diagnoses expand to include true LVHT, HT secondary to pathological remodeling due to loading conditions such as dilated cardiomyopathy, or HT secondary to physiological remodeling observed in situations such as athletes and pregnancy.[810]

Etiology

Genetic

LVHT frequently exhibits a familial pattern and is often associated with variants of genes, including those encoding sarcomere, Z-disk, cytoskeleton, and nuclear envelope proteins.[1]

Exercise

LVHT observed in athletes represents a reversible phenotype resulting from the increased cardiac preload demand associated with intense exercise.[811] The manifestation of LVHT varies depending on the specific sports discipline and the ethnicity of the athlete.[812] The prevalence of LVHT meeting echocardiography criteria among athletes ranges from 1% to 10%.[785,812]

In athletes meeting LVHT criteria, suspicion of cardiomyopathy arises only in the presence of LV dysfunction (EF <50%), a family history, and cardiac symptoms.[815] Additional echocardiographic criteria supporting cardiomyopathy diagnosis in athletes include a very thin compacted layer (<5 mm in end-diastole or <8 mm in end-systole by CMR) and impaired myocardial relaxation (E'<9 cm/s).[813,814] To ascertain whether LVHT in athletes signifies cardiomyopathy phenotype or physiological adaptation, an algorithm incorporating EF assessment, CMR imaging, presence of LGE, and family history is recommended.

Patients with EF <50%, positive LGE, and/or a positive genetic test are more likely to be diagnosed with cardiomyopathy and should be advised to restrict sports participation. For patients with EF >50% and a positive family history, ECG abnormalities, and/or ventricular tachyarrhythmia, evaluation with CMR and genetic tests is recommended before clearing them for sports participation.[812]

When forensic data were scrutinized, none of the cases of sudden death in athletes were directly attributed to LVHT.[815] Moreover, there is no data indicating routine restriction of athletes with isolated HT and normal LV function from engaging in high-intensity exercise and competitive sports.[784] Although definitive data are lacking, the American Heart Association (AHA) and the American College of Cardiology (ACC) do not restrict asymptomatic athletes with normal ventricular systolic function, without any history of syncope or significant atrial or ventricular tachycardia, from participating in competitive sports.[816]

Furthermore, a dose-response relationship was not discovered between activity intensity and LVHT in physical activity performed by non-athletes.[817]

Pregnancy

Hypertabeculation, believed to arise secondary to increased afterload during pregnancy in patients without pre-existing cardiac problem, represents a reversible phenotype that frequently resolves within approximately 12 weeks after pregnancy.[786] This phenomenon is more prevalent among African American women, indicating that myocardial response to afterload may be influenced by genetic predisposition.[818]

Neuromuscular Diseases

Hypertrabeculation has been identified in various neuromuscular disorders, encompassing Barth syndrome, mitochondrial disorders, nuclear envelopeopathies, dystrobrevinopathy, myotonic dystrophy, zaspopathy, and myoadenylate deaminase deficiency, along with genetically determined diseases such as Duchenne and Becker muscular dystrophies.[784] Research has indicated that the co-occurrence of the LVHT phenotype and neuromuscular disease may carry clinical and prognostic implications.[819]

Renal Diseases

LVHT has been documented in cases of polycystic kidney disease. Various hypotheses suggest that this occurrence may stem from either a shared genetic basis for the two conditions[820] or an increase in preload resulting from chronic renal failure.[821]

Hematological Diseases

Hypertrabeculation has been found to be associated with β thalassemia[822], sickle cell anemia[823], hemoglobinopathies, and

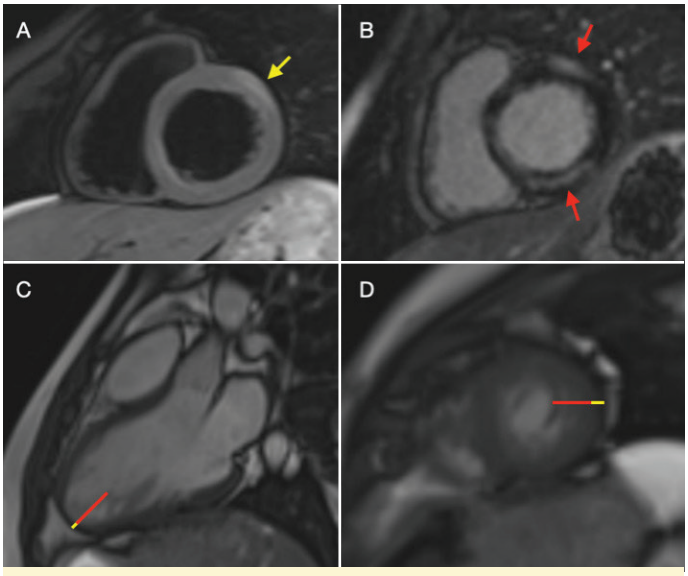

Figure 129. CMR in a 23-year-old male patient with a preliminary diagnosis of myocarditis due to chest pain, elevated troponin levels, and ventricular dysfunction following viral infection. The Updated Lake Louise criteria confirmed acute myocarditis. (A) T2-weighted image showing edema (yellow arrow) in the basal anterolateral wall. (B) T1-weighted image revealing nonischemic late gadolinium enhancement (red arrow) in the basal anterolateral, inferior, and inferolateral walls, consistent with myocarditis. (C) Cine images on long-axis 4-chamber view at end-diastole, demonstrating NC/C > 2.3 (Petersen criterion), (D) Cine images on short-axis view at end-systole, indicating NC/C ≥ 2 (Stacey criterion) hypertrabeculation. The yellow line represents the compacted layer, and the red line represents the noncompacted layer.

chronic hematological diseases.[824] As ventricular functions are preserved in the majority of patients with LVHT, it is believed that LVHT does not necessarily indicate an underlying myopathy.[784]

Cardiac Diseases

LVHT has been identified as a reversible phenomenon secondary to changing preload and afterload in myocarditis (Figure 129), coronary artery disease[825], and heart failure with reduced EF.[826] Additionally, LVHT has been observed in congenital heart diseases, most commonly associated with LVOT anomalies (46%), Ebstein anomaly (25%) (Figure 130), and tetralogy of Fallot (8%).[827]

Prognosis

Upon examining the entire cohort and subgroups of the EuroCMR registry, LVHT was not found to be associated with an increased risk of all-cause mortality, morbidity, or CMR LV indices. Consequently, it is believed that isolated LVHT does not serve as a predictor of poor prognosis.[828] Furthermore, a study involving patients with dilated cardiomyopathy revealed that clinical outcomes were linked to right and left ventricular remodeling and LGE, but not

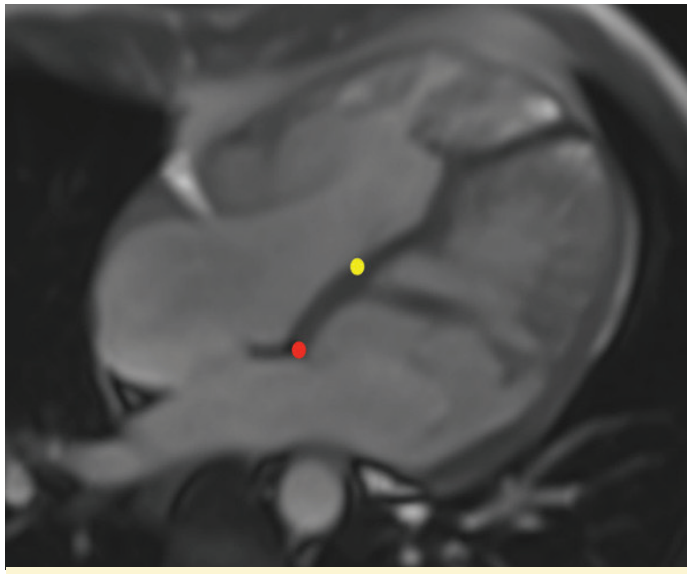

Figure 130. CMR 4-chamber cine image of a 27-year-old male patient with coexistence of biventricular hypertrabeculation and Ebstein anomaly. The red dot indicates the attachment site of the mitral valve anterior leaflet, while the yellow dot highlights the attachment site of the tricuspid valve septal leaflet, which is located more apically and is compatible with Ebstein anomaly.

to hypertrabeculation.[829] Research has demonstrated that isolated LVHT is not correlated with long-term LV remodeling[805] or poor clinical outcomes.[830,831] Therefore, based on this data, isolated LVHT with normal ventricular functions does not necessitate close follow-up concerning poor clinical outcomes.

Conclusion

Hypertrabeculation of the left ventricle represents a dynamic entity that has been the subject of numerous research studies, with ongoing updates regarding its definition. While there are accepted echocardiography and CMR criteria for diagnosis, one of the limitations of these criteria is the exclusion of functional evaluation. LVHT may have a genetic basis or may manifest as a variant of normal anatomy. Additionally, remodeling secondary to increased preload and afterload can be considered among the causes of reversible LVHT. Studies have consistently demonstrated that isolated LVHT with normal left ventricular functions is not associated with poor clinical outcomes.

The primary approach in patients with LVHT should involve comprehensive evaluation, including assessment of not only the NC/C ratios on echocardiography or CMR images, but also ventricular functions, family history, genetic testing, and clinical presentation. This holistic approach ensures a thorough understanding of the condition and guides appropriate management strategies.