Loeffler's Endocarditis: An Integrated Multimodality Approach

Maria Vincenza Polito, MD, Andreas Hagendorff, MD, Rodolfo Citro, MD, Costantina Prota, MD, Angelo Silverio, MD, Elena De Angelis, MD, Karin Klingel, MD, Michael Metze, MD, Stephan Stöbe, MD, Karl Titus Hoffmann, MD, Osama Sabri, MD, Federico Piscione, MD, and Gennaro Galasso, MD, *Salerno, Italy; and Leipzig and Tübingen, Germany*

Loeffler's endocarditis (LE) is the cardiac manifestation of hypereosinophilic syndrome, a rare systemic disease characterized by the sustained production of eosinophils leading to organ damage. Few data, principally by case reports, are available regarding the diagnostic workup in patients with suspected LE. Thus, we have performed a systematic search of the literature dealing with imaging in LE and propose an integrated multimodality imaging approach in the cardiac diagnostics of LE patients. The aim is to provide an updated state-of-the-art review focused on noninvasive and invasive imaging modalities for this rare and underdiagnosed disease. Standard and advanced echocardiography are typically the first cardiac imaging examinations when LE is suspected and they are also used later in follow-up for prognostic stratification and assessing response to treatment. Cardiac magnetic resonance provides a more detailed anatomical and functional evaluation of cardiac chambers, tissue characterization for the presence and extension of myocardial edema and fibrosis, and ventricular thrombi identification. Computed tomography scan and [18F]-fluoro-deoxy-glucose positron emission tomography may be helpful in selected cases to evaluate the cardiac involvement of LE as well as the other noncardiac manifestations of hypereosinophilic syndrome. Endomyocardial biopsy may be considered in patients with high clinical suspicion of LE if noninvasive imaging findings are confusing or not conclusive. The appropriate use of invasive and noninvasive imaging modalities, combining the available techniques with the patients' clinical features, will hopefully lead to early diagnosis, more accurate staging of disease, and timely treatment of LE that may prevent the irreversible myocardial damage of LE and adverse cardiovascular events. (J Am Soc Echocardiogr 2020;33:1427-41.)

Keywords: Hypereosinophilic syndrome, Loeffler's endocarditis, Multimodality imaging

The endocarditis parietalis fibroplastica or Loeffler's endocarditis (LE) is the cardiac manifestation of hypereosinophilic syndrome (HES), a rare systemic disease characterized by the sustained production of eosinophils, which impair tissues and organs through infiltration and release of toxins by degranulation.[1] A cardiac involvement has been described in about 50% of HES cases and is associated with a high morbidity and mortality rate.[2] Although there are no data on its prevalence, it is generally accepted that HES is an underdiagnosed disease, which affects mostly male subjects between 20 and 50 years of age, with a peak in the fourth decade of life.[3] It is considered very rare in children and is mostly seen in temperate regions.[4,5]

As reported by Shaper *et al.*,[6] the diagnosis of HES is often challenging and is based on three criteria: (1) an eosinophil count > 1,500 cells/mL for at least 6 months, (2) no other causes for eosinophilia, including eosinophilic leukemia, allergic diseases, drugs, sarcoidosis, connective tissue disorders, and parasitic infections, and (3) signs or symptoms of organ involvement by eosinophilic infiltration.[6-8] However, it has to be mentioned that LE can be detected as a local and isolated manifestation of HES in the absence of peripheral detection of eosinophils.[9]

Clinical manifestations of HES are markedly heterogeneous, ranging from asymptomatic forms to forms of acute eosinophilic myocarditis (EM) or chronic restrictive cardiomyopathy (RCM) with symptoms related to tissue damage.

The most common presenting symptoms are generally nonspecific: weakness, cough, myalgias, angioedema, dyspnea, rash, and fever.[10] Evidence of cardiac involvement includes signs and

From the Division of Cardiology, Department of Medicine, Surgery and Dentistry, University of Salerno (M.V.P., C.P., A.S., E.D.A., F.P., G.G.), Salerno, Italy; Department of Cardiology, University Hospital Leipzig (A.H., M.M., S.S.), Leipzig, Germany; Department of Cardiology, A.O.U. "San Giovanni di Dio e Ruggi D'Aragona" (R.C.), Salerno, Italy; Cardiopathology, Institute for Pathology and Neuropathology, University Hospital Tübingen (K.K.), Tübingen; and Department of Radiology (K.T.H.) and Department of Nuclear Medicine (O.S.), University Hospital Leipzig, Leipzig, Germany.

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflicts of Interest: None.

Reprint requests: Maria Vincenza Polito, MD, Department of Medicine and Surgery, University of Salerno, San Giovanni di Dio and Ruggi D'Aragona Academic Hospital, Cardiology Tower, Largo Città d'Ippocrate, 84131, Salerno, Italy (E-mail: *mvpolito@hotmail.it*).

0894-7317/$36.00

https://doi.org/10.1016/j.echo.2020.09.002

Abbreviations

18F-FDG = [18F]-fluoro-deoxy-glucose

2D-TTE = Two-dimensional transthoracic echocardiography

3D-TTE = Three-dimensional transthoracic echocardiography

CAD = Coronary artery disease

CE = Contrast echocardiography

CMR = Cardiac magnetic resonance imaging

CP = Constrictive pericarditis

CT = Computed tomography

EM = Eosinophilic myocarditis

EMB = Endomyocardial biopsy

HCM = Hypertrophic cardiomyopathy

HES = Hypereosinophilic syndrome

HF = Heart failure

LA = Left atrium

LE = Loeffler's endocarditis

LGE = Late gadolinium enhancement

LV = Left ventricle

MV = Mitral valve

PET = Positron emission tomography

RCM = Restrictive cardiomyopathy

RV = Right ventricle, ventricular

STE = Speckle-tracking echocardiography

TEE = Transesophageal echocardiography

symptoms associated with heart failure (HF), intracardiac thrombosis, arrhythmias, myocardial ischemia, and pericarditis.[11]

Loeffler's endocarditis usually follows three stages. The first is a necrotic stage, characterized by damage of the endocardium associated with myocardial infiltration with eosinophils and lymphocytes, necrosis, and abscesses. However, the evidence of the myocardial inflammation with eosinophilic infiltration, without the involvement of the endocardium, allows the diagnosis of EM. This stage is often clinically silent and may be unrecognized with the conventional diagnostic tools.

In the second stage thrombosis prevails with the formation of thrombi superimposed on the damaged endocardium of either one or both ventricles, occasionally in the atrium, or on atrioventricular valve leaflets. The major complication of intracardiac thrombus formation is the detachment and distal embolization of thrombotic material, which are a major cause of morbidity.[12] Clinical suspicion usually arises during this phase, in which a thick layer of granulation tissue replaces normal endocardium, producing a ventricular apical mass typical of LE. The third stage is dominated by fibrosis, derived from damage to cardiac myocytes, that may lead to entrapment of chordae tendineae resulting in mitral and/or tricuspid valve regurgitation due to inadequate leaflet coaptation.[13] Finally, the endomyocardial fibrosis leads to RCM, stiffened ventricular and atrial walls, increased left-sided filling pressures, and symptoms of congestive HF.

This damaging process can involve different parts of the heart, with lesions affecting the left ventricle (LV), right ventricle (RV), both or, sometimes, with patchy distribution of the fibrotic areas. The historical classification of endomyocardial fibrosis by Shaper *et al.*[6] borrowed from histologic studies during necropsies in 172 subjects can be employed to define the distribution of fibrosis by echocardiography or other imaging modalities.[6] Five patterns have been described (Figure 1): type 1, fibrosis is limited to the apex; type 2, fibrosis engages the apex and the posterior papillary muscle of the mitral and/or tricuspid valve; type 3, only the atrioventricular valves are involved (this form is difficult to differentiate from common degenerative valve disease); type 4, the apex and the atrioventricular valves are both involved, but the myocardium between them is spared; type 5, patches of fibrotic tissue are scattered all over the endomyocardium.

It is important to highlight that the stages may overlap and that the degree of cardiac involvement does not always correlate with the degree of eosinophilia.[14] It has been supposed that the persistent eosinophilic damage of the endomyocardium can foster thrombotic and fibrotic transition from acute EM to LE.[15] The development and widespread use of noninvasive imaging modalities may help to identify and better characterize LE at each stage of its natural history. Unfortunately, the vast majority of data on LE diagnosis derive from single cases or small series, and currently there is no consensus on the best diagnostic workup.

Against this background, this review aims to provide a comprehensive overview of traditional and novel imaging techniques for the assessment of the structural and functional abnormalities of LE. A more precise characterization by a multimodality imaging approach might hopefully facilitate an earlier diagnosis, a more accurate prognostic stratification, and a timely treatment of this challenging disease.

NONINVASIVE IMAGING MODALITIES

Noninvasive multimodality imaging, including echocardiography in its various modalities (two-dimensional [2D-TTE] and three-dimensional transthoracic echocardiography [3D-TTE], transesophageal echocardiography [TEE], contrast echocardiography [CE], and speckle-tracking [STE]) and cardiac magnetic resonance imaging (CMR), are useful tools in the diagnosis, risk stratification, therapeutic management, and prognostic evaluation of LE. Computed tomography (CT) scan and [18F]-fluoro-deoxy-glucose (18F-FDG) positron emission tomography (PET) may be helpful in the presence of contraindications for CMR, inadequate echocardiographic image quality, inconsistent or inconclusive findings from the previous techniques; to exclude coronary artery disease (CAD) from the differential diagnosis; and to reveal secondary noncardiac manifestations of the HES. In case of a discrepancy between clinical suspicion and noninvasive imaging findings, endomyocardial biopsy (EMB) may be considered to detect the peculiar histologic pattern of LE.

ECHOCARDIOGRAPHY

Although there are no echocardiographic pathognomonic signs for LE, peculiar atrial, ventricular, and valvular abnormalities typically associated with LE have been reported.[16-18] These findings should be evaluated, taking into account the clinical picture, since they characterize the stages and severity of LE. Beyond diagnosis, standard and advanced echocardiographic techniques allow the timely start of appropriate treatment and monitoring of the efficacy of the therapy, to identify complications and to stratify prognosis.[10]

Standard 2D-TTE

Two-dimensional transthoracic echocardiography is generally the first imaging modality to detect LE.[19] Endomyocardial thickening and mural thrombi, most frequently in the apices of both ventricles, represent the more suggestive echocardiographic findings of the disease. Other abnormalities such as atrial enlargement, valvular involvement, and diastolic dysfunction, with a typical RCM in the later stages, can also be detected.[9]

HIGHLIGHTS

- Hypereosinophilic syndrome is a rare systemic disease characterized by organ damage.
- Loeffler's endocarditis is the cardiac manifestation of disease.
- Noninvasive multimodality imaging is useful for diagnosis, management, and prognosis.
- Endomyocardial biopsy is still currently considered the gold standard for diagnosis.
- Diagnosis is crucial because prognosis is favorable if the treatment is initiated early.

Since ultrasound techniques are not adequate to detect the tissue changes related to the subendocardial necrosis, standard 2D-TTE is generally suboptimal in detecting an impairment of myocardial function during the first "necrotic stage" of LE.

In the second stage, the damaged endocardium is replaced by a thick layer of granulation tissue with concomitant activation of procoagulant factors, leading to the thrombosis. In a prospective cohort of 26 patients with HES, endomyocardial thickening was detected in 68% of cases and was progressive in untreated or inadequately treated patients.[20]

The presence of endomyocardial thickening by echocardiography in the setting of HES should prompt suspicion of LE. Standard 2D-TTE is widely available and is the first-line technique to detect mural thrombi superimposed on damaged endocardium. Thrombi usually have low echogenicity with a central brightness and usually involve the ventricular apex in the absence of wall motion abnormalities in the apical segments in LE patients (Figure 2A-2C). The thrombotic process may extend from the apex to the subvalvular regions and even involve the inflow tract of the atrioventricular valves, resulting in a reduction in ventricular cavity size and in some cases leading to a complete fibrotic obliteration of one or both ventricular chambers. Hyperdynamic contraction of the spared ventricular walls and bilateral atrial enlargement are also noted.[21] The detection of LV and/or RV apical thrombi, when the myocardial contractility is preserved, is strongly suggestive for LE and should be considered as a diagnostic clue when associated with hypereosinophilia.

The detection of small apical thrombi in the early phase of LE may be challenging with conventional TTE. Moreover, cases of isolated LV and RV apical thrombus may be confused with the apical variant of hypertrophic cardiomyopathy (HCM). The presence of layers with different degrees of reflectivity or echogenicity, along with the increase of thrombus volume over time, may be helpful for differential diagnosis. Alternatively, the employment of a second-level ultrasound technique (i.e., contrast echocardiography) and CMR should be considered, even in patients with no apparent history of hypereosinophilia.[22,23] Vegetations, resulting from a combination of organized thrombi, eosinophilis, and fibrosis, may be detected by TTE; they

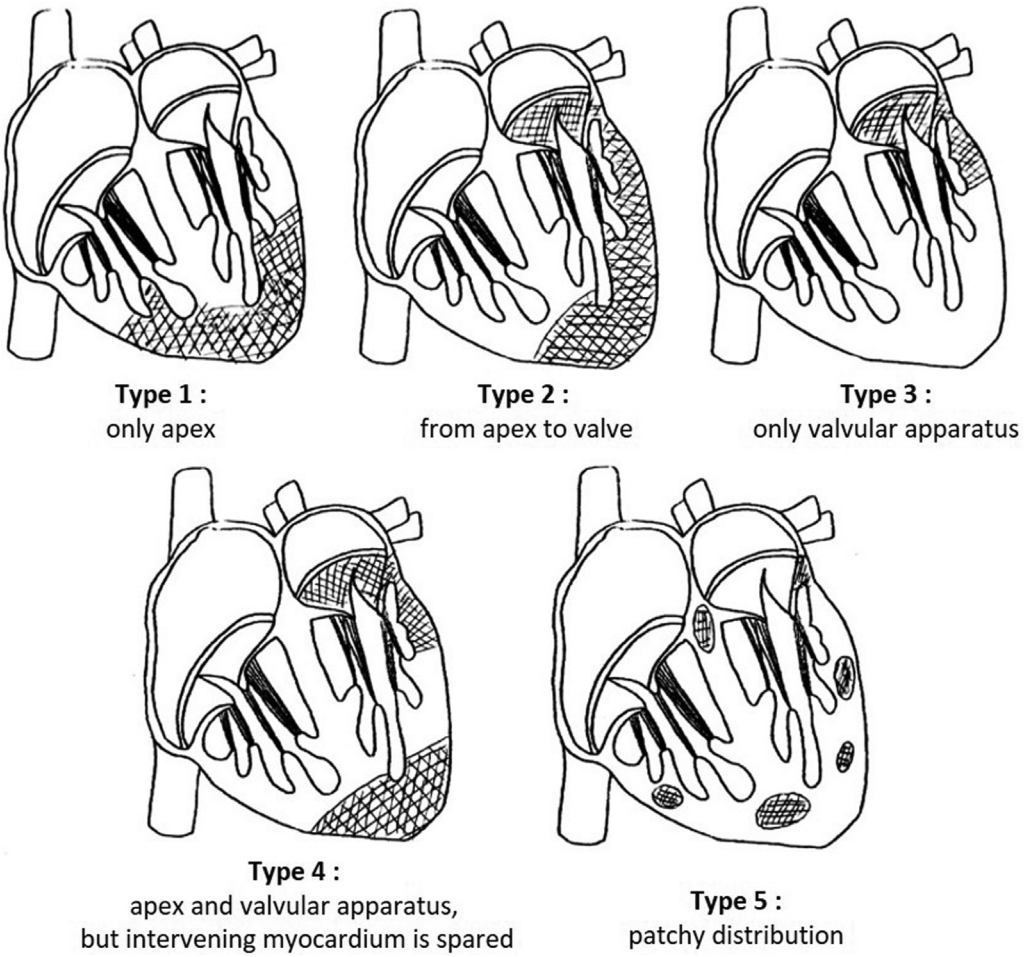

Figure 1 Classification of endomyocardial fibrosis's distribution in the LV or RV chambers proposed by Shaper *et al.*[6]

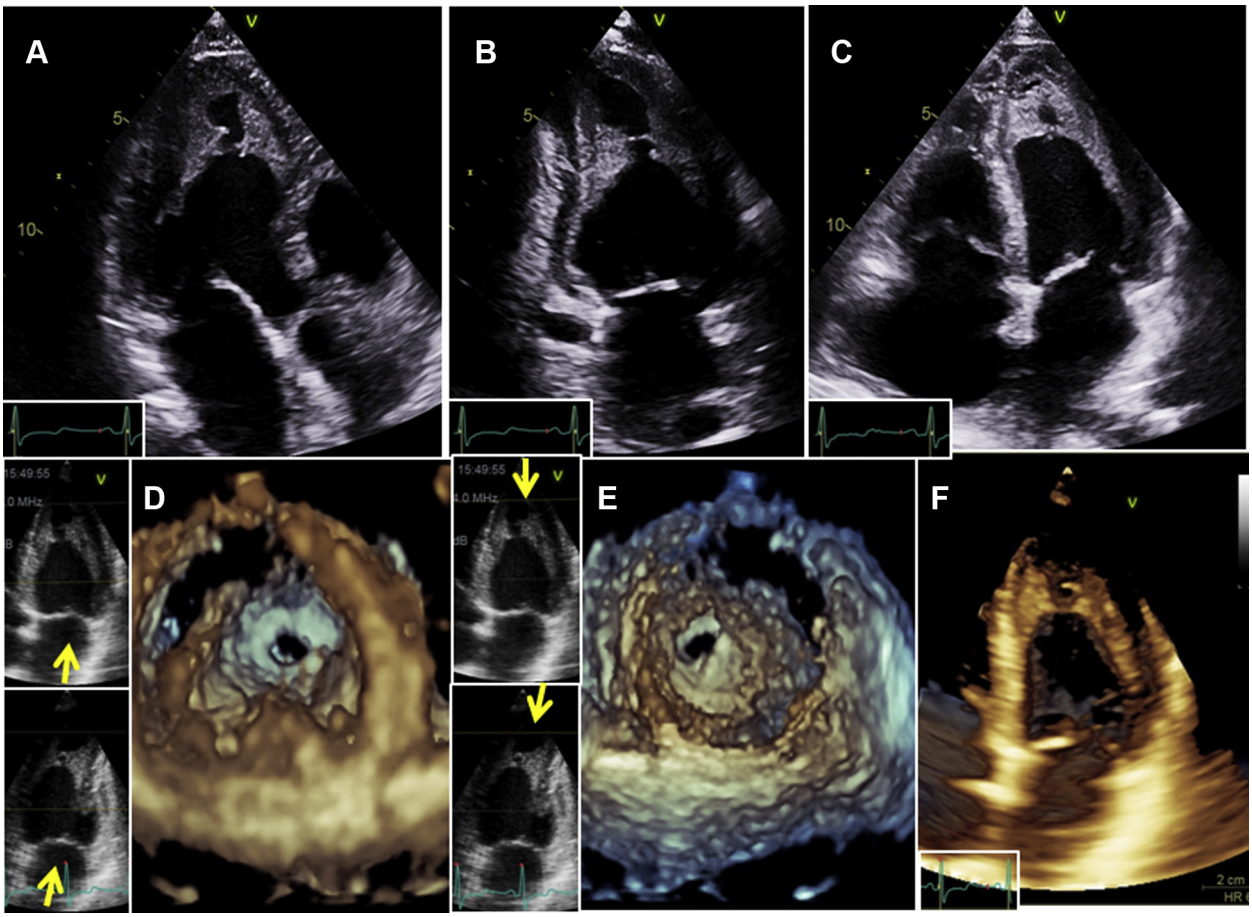

Figure 2 Standardized apical views of 2D-TEE (**A,** four-chamber view; **B,** two-chamber view; **C,** three-chamber view) in a patient with LE showing LV apical endocardial thickening and apical thrombus. Note the almost complete obliteration of the apex during systole providing the typical image of "kissing ventricle." Three-dimensional TTE showing the en face view from the center of the LV cavity into the apex **(D)** and from the apical region into the midventricular region **(E).** The direction of the views is shown by the *yellow arrows*. **(F)** Three-dimensional TTE apical four-chamber view of LV showing a diffuse LV endocardial thickening with thrombus in the apex.

typically arise from the myocardial ventricular wall with a possible extension to the valvular leaflets, leading to an increased risk of embolic events.[24]

The passage to the third fibrotic stage of LE, when the granulation tissue is changed into hyaline fibrosis, is typically characterized by a fibrosis involving both the endocardium and the subadjacent myocardium. The endomyocardial fibrosis appears as an area of greater echo intensity than the surrounding myocardium and can be better evaluated after focusing the image on the cardiac apex, image magnification, and adjustment of gain. In addition, the presence of fibrosis is highly suggested by the finding of a fibrous thrombus in the ventricular cavity.[16]

Indirect TTE findings suggestive for myocardial fibrosis include the symmetrical increase of LV wall thickness and LV mass, impaired LV filling pressure, and enlarged left atrial size.[25] In the later stage of LE, the endocardial scar results in a decrease of ventricular compliance and generates an overt RCM, which is usually characterized by LV normal or small cavity size with preserved ejection fraction, biatrial enlargement, and diastolic dysfunction. Diastolic function should be evaluated by using a multiparametric approach including mitral inflow E/A ratio $>$ 2.5, E wave deceleration time $<$ 150 msec, isovolumic relaxation time $<$ 50 msec, decreased e′ velocities (3–4 cm/sec) with a lateral e′ velocity higher than septal e′, E/e′ ratio $>$ 14, and severely increased left atrial volume index ($>$50 mL/m^2).[26] Of course, Doppler indices of LV diastolic function should be thoroughly evaluated when a ventricular compliance impairment is suspected.[27] It must be emphasized that the diagnosis of RCM, even in case of LE, does not equal the presence of restrictive physiology, although it is the most frequent; diastolic dysfunction in LE is a continuum that may present with a grade I at first and then move progressively to grade II or III diastolic dysfunction with worsening of the disease.

Another common TTE finding in LE is atrioventricular valve involvement. Conversely, aortic and pulmonic valves are rarely compromised.[28,29] Among the mechanism leading to valvular regurgitation, the most frequent is the fibrotic or thrombotic involvement of subvalvular apparatus. An abnormal endomyocardial thickening of the posterolateral LV wall associated with thrombus or fibrosis may entrap the chordae and tether the mitral valve (MV) posterior leaflet leading to eccentric regurgitation (Figure 3), which is a common finding in advanced stages of LE.[30]

Pericardial effusion may also be detected in association with myocarditis. Its prevalence ranges from 10% to 32% of patients with HES.[22] Other TTE findings include paradoxical movement of

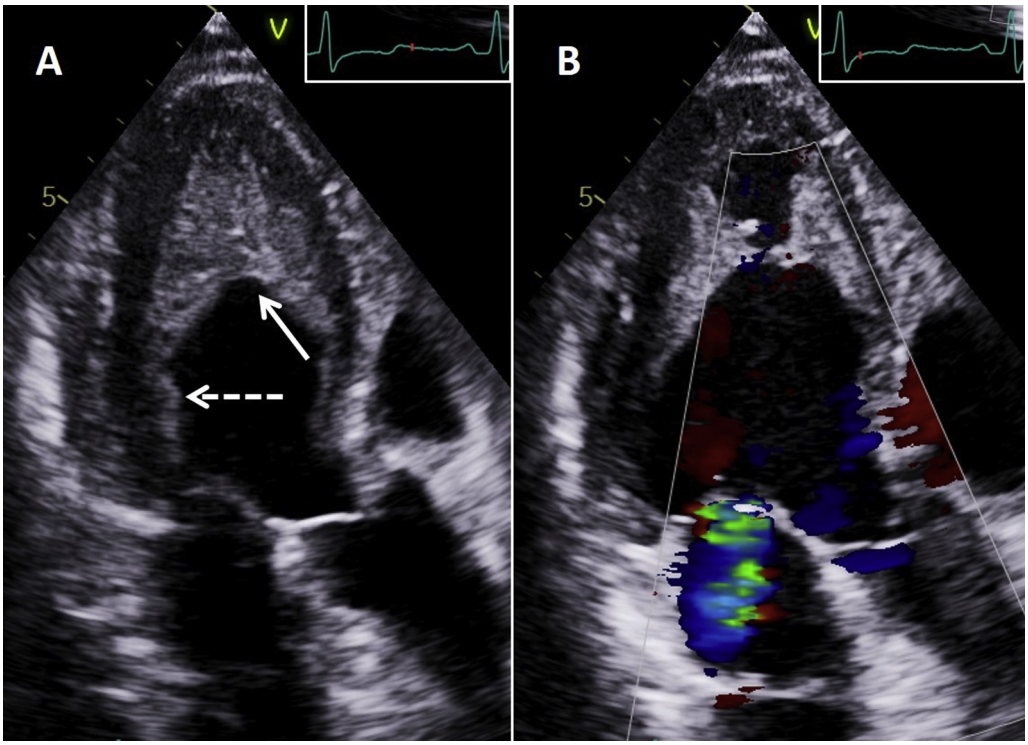

Figure 3 **(A)** Two-dimensional TTE apical long-axis view depicting thrombus (*solid arrow*) involving the posteromedial papillary muscle and entrapping the chordae (*dotted arrow*) in a patient with LE. Color Doppler showed mild, new-onset, mitral regurgitation as a consequence of the tethering of the MV leaflets **(B)**.

interventricular septum and diastolic checking of the anterior MV leaflet against the interventricular septum and enhanced echogenicity of the moderator or other bands; these features alone are not specific signs for LE.[25] The main TTE findings of LE are summarized in Table 1. For the reader's knowledge, Table 2 reports the major and minor echocardiographic criteria for diagnosis and severity assessment of endomyocardial fibrosis proposed by Kleinfeldt *et al.*[10] Nevertheless, it is the current opinion that diagnosis and prognostic stratification of LE cannot be based only on standard TTE but requires a multimodality imaging approach including advanced echocardiography, CMR, CT, and nuclear imaging. Eventually, all findings of multimodality imaging have to be interpreted in light of the patient's history and clinical data to achieve a more comprehensive evaluation of this challenging disease.

Transesophageal Echocardiography

Transesophageal echocardiography may be a valid option in patients with poor transthoracic acoustic window, especially in the presence of a high suspicion of LE and when other second-level imaging modalities are not promptly available.[31] Transesophageal echocardiography is the most accurate tool to assess the severity and mechanisms of MV regurgitation.[19]

In addition, TEE allows a more precise study of pulmonary veins; in the advanced stages of LE, pulmonary veins show a high diastolic ("D") wave and a broad atrial reversal ("A") wave caused by an increased end-diastolic LV pressure. The difference in height between the forward systolic S and diastolic D waves is also higher in RCM than in constrictive pericarditis (CP), and low S/D values may help for differential diagnosis between these two entities.[32,33] The main limitation of TEE relates to the assessment of ventricular apex, essential in LE, and may need many adjustments of image—especially the reduction of ultrasound frequency—and transgastric views to better focus and visualize the apical region.

Contrast Echocardiography

Contrast echocardiography is a highly sensitive technique to detect ventricular thrombi in patients with suspected LE. The use of contrast agents overcomes the possible image quality limitations of standard 2D-TTE and assists in identifying the apical thrombus, which will appear as a filling defect in the opacified ventricular lumen.[31]

Contrast echocardiography can help distinguish between the preserved wall motion of the ventricular apex associated with the mural thrombus often noted in LE and the presence of regional wall motion abnormalities in the LV apex associated with apical mural thrombus as a complication of myocardial infarction (Figure 4).[8]

Moreover, LV opacification with echocardiographic contrast may help to differentiate LE from the apical forms of HCM and LV noncompaction. Myocardial perfusion contrast may be very useful in controversial cases to show the degree of perfusion of myocardial walls underlying the thrombus.

In HCM, the LV apical lumen is visualized in diastole and produces the typical "Ace of Spades" configuration of LV during systole, whereas a persistent apical obliteration visualized as an opacification defect can be found in LE.[31] Moreover, the absence of prominent ventricular trabeculations and deep intertrabecular recesses allows the exclusion of LV noncompaction.[7]

Speckle-Tracking Echocardiography

Speckle-tracking echocardiography (STE) is a more recent ultrasound-based tool for quantifying global and segmental myocardial deformation and for identifying early ventricular dysfunction.[34] However, due

Table 1 Echocardiographic features of LE

Structure	Echocardiographic findings	Level of suggestion
LV	Endomyocardial thickening, most commonly at apex	+++
	Mural thrombus or spontaneous echo contrast, most frequently in apex, which appears normal or hyperkinetic	+++
	Small ventricular cavity due to endocardial thickening and mural thrombi	+++
	Systolic function generally preserved but can be reduced in advanced disease	+
	Restrictive flow pattern across MV	++
	LV apical thrombi that may extend to the LV outflow tract and MV annulus	++
RV	Endomyocardial thickening, most commonly at apex	+++
	Mural thrombus or spontaneous echo contrast, most frequently in apex, which appears retracted	+++
	Small ventricular cavity due to endocardial thickening and mural thrombi	+++
	Systolic function generally preserved	+
	Enhanced echogenicity of the moderator band	+
Valves	Diffuse thickening of mitral and/or tricuspid leaflets	+
	Entrapment of chordae tendineae with restricted motion of mitral and/or tricuspid leaflets leading to mitral and/or tricuspid regurgitation	++
	Significant stenosis may occur but less common than regurgitation	+
	Pulmonary and/or aortic valve thickening	+
	Superimposed thrombi on atrioventricular or semilunar valves	++
	"Vegetations" may be detected on the valves (echogenic masses on the leaflets)	+
	Nodular echo densities consistent with fibrosis	+
Atria	Biatrial enlargement from RCM and MV/tricuspid valve regurgitation	+
Pericardium	Pericardial effusion	+

+Low level of suggestion.
++Midlevel of suggestion.
+++High level of suggestion.

to the low incidence of LE, only anecdotal reports are available on the use of STE for the assessment of these patients.[35,36]

Layer-specific strain analysis has been proposed to elucidate the myocardial mechanics in different stages of disease, since it is more sensitive than conventional TTE in identifying subtle myocardial dysfunction in asymptomatic patients as well.

Yamamoto *et al.*,[37] in a cohort of 32 clinically stable HES patients without apparent cardiac involvement at TTE, demonstrated that global longitudinal strain was significantly lower than that of a cohort of 31 age-, gender- and LV ejection fraction–matched normal subjects (−16.2% ± 3.3% vs −19.3% ± 2.9 %, $P < .001$). Conversely, global radial and circumferential strain were not statistically different between groups. In addition, they identified a global longitudinal strain ≤ −17.0% as the best cutoff value for early identification of LV endocardial dysfunction in HES patients. This finding provides evidence that LV endocardial dysfunction occurs very early in the natural history of HES, albeit in the absence of impairment in LV ejection fraction or other conventional echocardiographic parameters.

Nemes *et al.*,[38] in a small cohort of 10 HES asymptomatic patients, also reported an impairment of left atrium (LA) strain values; peak LA circumferential strain was decreased compared with controls, suggesting a reduced reservoir function and remodeling of the LA.

Conversely, the same investigators showed no differences in terms of global and mean segmental right atrial strains between 11 HES patients and 22 age- and gender-matched healthy controls.[39] These preliminary results, although limited by the small cohort sizes, seem to support the role of STE in early detection of myocardial damage in HES. Whether STE should be routinely employed in HES patients soon after the diagnosis needs confirmation by larger prospective studies.

Three-Dimensional Transthoracic Echocardiography

Three-dimensional TTE provides a comprehensive assessment of the LV performance displaying all myocardial segments simultaneously in multilevel slices.[40] In patients with LE, 3D-TTE may be performed to evaluate both the RV and LV apical segments, even if there is not a large amount of data on this topic (Figure 2D-2F). Concomitant administration of contrast agents may lead to improved visualization of the apex and possibly more easily detect a small thrombus and evaluate all of the motion of the normally perfused myocardial walls (Figure 5).[8]

The use of contrast combined with 3D-TTE may contribute significantly to the diagnosis of LE, because it is able to identify the interface between the apical thrombus and the inner myocardium layer as a thin network of microvessels.[7]

Utilizing cropping and multiple planes and angulations, 3D-TTE provides a more detailed assessment of cardiac structures by additional nonconventional views, such as the en face view, for the assessment of morphologic alterations of the atrioventricular valve apparatus and consecutive functional impairment.[41]

To date, there are no studies evaluating the role of three-dimensional echocardiography in addition to standard 2D-TTE for LE diagnosis, encouraging its use for future research in the near future.

Cardiac Magnetic Resonance

Although not available in every center, CMR may be crucial for the diagnosis of LE due to the higher sensitivity and specificity than echocardiography in detecting subtle myocardial lesions as well.[42] It allows an accurate morphologic and functional evaluation of cardiac chambers and provides the unique opportunity to characterize myocardial

Table 2 Echocardiographic criteria for the diagnosis and assessment of severity of endomyocardial fibrosis

Criteria	Score*
Major:	
Endomyocardial plaques > 2 mm thickness	2
Thin (≤1 mm) endomyocardial patches affecting more than one ventricular wall	3
Obliteration of the RV or LV apex	4
Thrombi or spontaneous contrast without severe ventricular dysfunction	4
Retraction of the RV apex	4
Atrioventricular valve dysfunction due to adhesion of the valvular apparatus to the ventricular wall	1-4†
Minor:	
Thin endomyocardial patches localized to one ventricular wall	1
Restrictive flow pattern across MV or tricuspid valve	2
Pulmonary valve diastolic opening	2
Diffuse thickening of the anterior mitral leaflet	1
Enlarged atrium with normal size ventricle	2
M-movement of the septum and flat posterior wall‡	1
Enhanced density of the moderator or other bands	1

*A definite diagnosis of endomyocardial fibrosis can be made in the presence of two major criteria or one major criterion associated with two minor criteria. A total score <8 indicates mild endomyocardial fibrosis; 8-15, moderate disease; and >15, severe disease.

†The score is assigned according to the severity of atrioventricular regurgitation.

‡M-movement of the interventricular septum refers to a pattern of movement observed on M-mode echocardiography that is thought to be due to obliteration or restriction of the LV apex combined with mitral regurgitation.

Reproduced from Kleinfeldt *et al.*[10]

tissue for the presence of edema, fibrosis, or necrosis, as well as to identify ventricular thrombi.

A standard CMR examination in patients with suspected LE should include long-axis (two, three, and four chambers) and short-axis (basal, midventricular, and apical) views acquired with steady-state free precession, T1- and T2-weighted, and contrast-enhanced (first passage of gadolinium and late phase) dynamic sequences.[43]

The central role of CMR in the diagnostic work-up and clinical management of patients with LE is mostly related to the following three main applications:

1. Early detection of subendocardial thickening associated with myocardial tissue abnormalities.
2. Detection and characterization of ventricular thrombi.
3. Evaluation of RV involvement.

The typical tissue characterization of LE includes the diffusely reduced signal intensity of endocardial layers on first-pass contrast-enhanced perfusion and the subendocardial late gadolinium enhancement (LGE) in the absence of obstructive coronary lesions (Figure 6).[44] Late gadolinium enhancement is a marker of an expanded interstitial compartment with relative accumulation of gadolinium at multiple LV segments and can result from myocardial inflammation, infiltration, or fibrosis occurring at different stages of LE. The subendocardial LGE may have a patchy or diffuse distribution and usually extends from the top of the apical filling mass through the inflow tract until it reaches the subvalvular regions in some cases.[45]

Furthermore, LGE is not restricted to the territory of distribution of a single coronary artery. However, since subendocardial LGE is a hallmark of ischemic heart disease, CAD should be always excluded by using noninvasive or invasive imaging tests.

Among nonischemic cardiomyopathies, LGE may show a subendocardial distribution also in other conditions such as cardiac amyloidosis.[46,47] In the latter disease, however, subendocardial LGE is generally global, homogeneous, and associated with a diffuse increase in wall thickness and systolic dysfunction, allowing differential diagnosis with LE.[48]

Multiparametric CMR is also able to identify the eosinophil-mediated cardiac injury at different stages of the disease, by discriminating between acute and chronic lesions, acute/subacute inflammatory processes, and/or endomyocardial fibrosis (alone or in combination).[49] Owing to the linear correlation of T2 relaxation time with tissue-free water, T2-weighted sequences enable the detection of the presence and extent of myocardial edema, suggestive of an acute or subacute inflammatory process, while LGE in T1-weighted sequences in the absence of edema indicates the last stage of endocardial fibrosis.[50]

Since in cardiomyopathies and myocardial infarction CMR assessment of the extent of myocardial edema, infarct size, and myocardial scarring may be associated with adverse events (mortality, HF, arrhythmias), one might speculate that these CMR-defined parameters would also have prognostic value in LE.[51,52]

Of note, CMR has demonstrated a higher sensitivity and specificity than echocardiography in detecting thrombi in the LV and/or RV and should be performed if TTE, including CE, is not conclusive. Delayed enhancement CMR differentiates thrombi from surrounding myocardium, as thrombus is avascular and does not take up contrast (Figure 7A-7F).[44] Furthermore, it may be helpful in challenging cases to differentiate LE from apical HCM or apical tumor.

Although the majority of reports focused on LV involvement, LE shows a biventricular involvement in up to one-third of patients.[53] Owing to the intrinsic limitation of TTE in evaluating the RV in all its parts, the biventricular form of LE might also be underestimated.

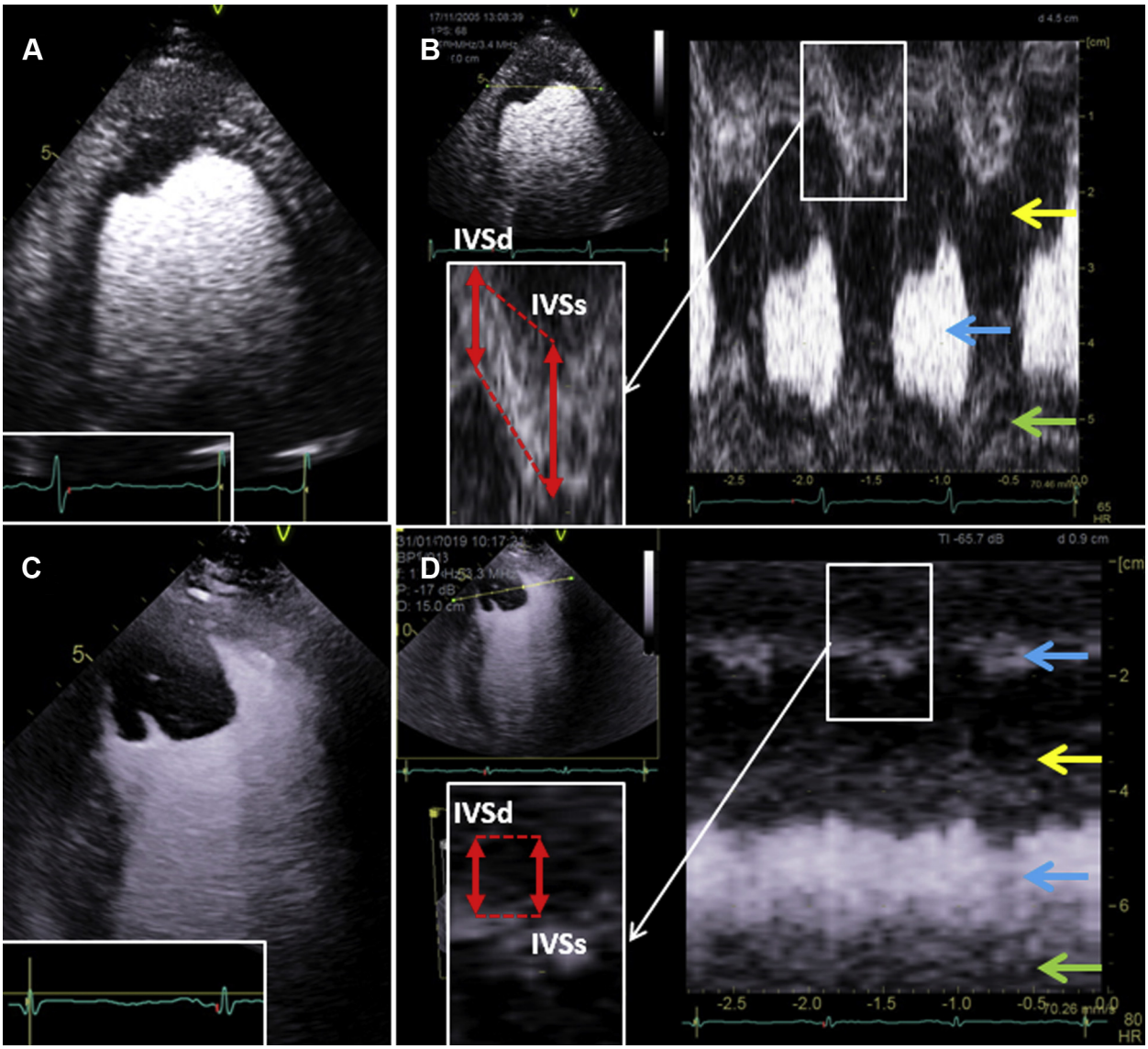

Figure 4 **(A)** Transthoracic CE showing an LV thrombus in a patient with LE. **(B)** Anatomical M-mode through the apical region illustrates the perfused septal wall with hypercontractile radial deformation. In the magnification on the *left bottom*, *red lines* show the end-diastolic and end-systolic septal wall thickness and highlight the preserved contractility of apical myocardium. The *yellow arrow* labels the dark thrombus formation, the *blue arrow* the LV cavity, and the *green arrow* the lateral wall region. **(C)** Transthoracic CE of a ventricular thrombus in a patient with recent anterior myocardial infarction. Anatomical M-mode through the apical region illustrates the nonperfused septal wall with hypo- or akinetic radial deformation **(D)**. In the magnification on the *left bottom*, *red lines* show the end-diastolic and end-systolic septal wall thickness demonstrating the absence of wall thickening of the adjacent myocardium. The *yellow arrow* labels the dark thrombus formation, the *blue arrows* label the LV cavity, and the *green arrow* labels the lateral wall region. *IVSd*, Interventricular septum thickness at end diastole; *IVSs*, interventricular septum thickness at end systole.

Cardiac magnetic resonance imaging enables visualization of RV morphology in three dimensions and provides a global assessment in terms of size, function, thrombi, and tissue characterization.[54]

Furthermore, clinical cases have suggested the usefulness of CMR to detect changes in myocardial involvement (subendocardial thickening, thrombosis, fibrosis) during follow-up to promptly start therapy and monitor the response to treatment.[55,56] Some authors also suggest its utility as anatomical guidance for targeted EMB to optimize the sampling site and reduce the need for multiple sampling.[57] In a single study that prospectively enrolled 36 patients with endomyocardial fibrosis, the endocardial fibrous tissue quantified by LGE emerged at multivariable analysis as the only independent predictor of mortality.[44] However, further studies are warranted to confirm the hypothesis of a prognostic role of CMR parameters in patients with LE. Whether CMR may improve the clinical management and outcome of patients with LE remains to be demonstrated.

CT SCAN AND 18F-FDG POSITRON EMISSION TOMOGRAPHY

The advent of multislice CT with electrocardiogram gating along with innovations in x-ray tube and detector technology has resulted in revolutionary progress in noninvasive cardiac imaging.[58] The key

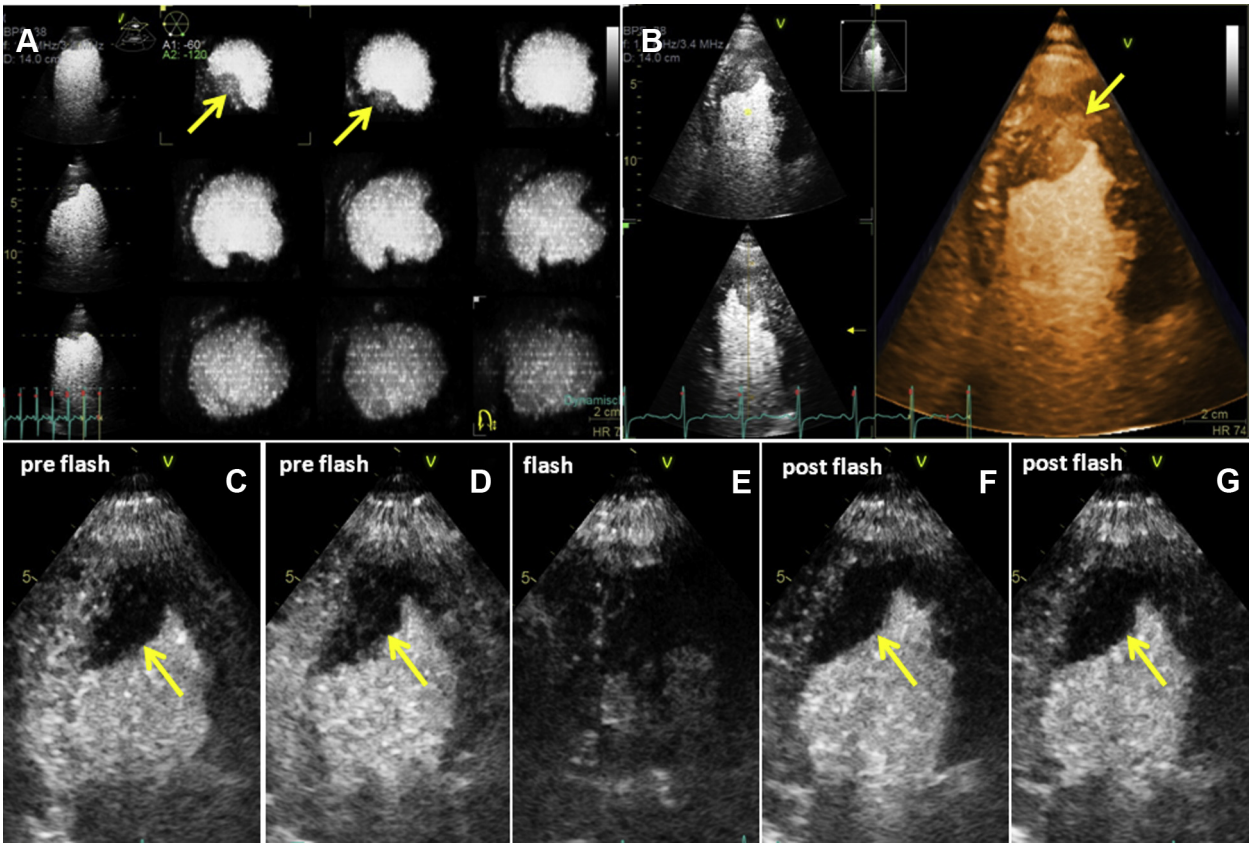

Figure 5 **(A)** 3D-TTE after contrast medium injection showing a multislice reconstruction of the LV in a patient with LE. Nine equidistant two-dimensional short-axis images are shown from LV apex (*top left*) to base (*bottom right*). The apical views illustrate precisely the LV thrombus (*yellow arrows*). **(B)** Longitudinal four-chamber view confirms the obliteration of the LV apex by the thrombus (*yellow arrow*) superimposed on the endocardium. **(C-G)** After contrast medium injection, the myocardial wall appears normally perfused, whereas a dark thrombus in the LV apex is not opacified. We used the "flash" function that, destroying the ultrasound contrast agent in myocardium (while microbubbles remained intact in the LV owing to a higher concentration), allowed the measurement of contrast replenishment velocity and the assessment of myocardial blood flow. In this case the replenishment was rapid and suggestive of normal myocardial perfusion.

advantages of CT include the high spatial resolution and high level of anatomical detail it offers. Nevertheless, significant disadvantages limit the widespread use of this imaging modality such as radiation exposure, the small risk of contrast-induced nephropathy, and the lower soft tissue and temporal resolutions compared with CMR.

Although echocardiography and CMR represent the main imaging modalities in the diagnostic work-up of LE, CT may be employed in particular patient settings. Computed tomography may overcome the limitations of echocardiography particularly in patients with poor acoustic windows, in obese patients, and in those with chronic lung disease. However, in comparison with echocardiography, CT does not allow functional assessment of LV hemodynamics, filling, or relaxation. In the suspicion of LE, CT is indicated when CMR is nondiagnostic or contraindicated, specifically in patients with claustrophobia, poor cooperation, and implanted non–magnetic resonance imaging conditional devices.

The role of cardiac CT is different in the various stages of LE.[59] Unfortunately, it does not have the necessary contrast resolution to assess myocardial inflammation in the necrotic stage. In the second stage, it enables detection of thrombotic lesions (Figure 7G-7H) within the LV or RV, which may be isoattenuating to the myocardium but demonstrates no delayed enhancement with contrast. The underlying myocardium appears morphologically normal with preserved LV function.

In the third stage characterized by endomyocardial fibrosis, CT is well suited to identify indirect anatomic features of restrictive cardiac filling and to assess myocardial extracellular volume.[60]

The indirect signs of impaired cardiac filling include atria, coronary sinus, and inferior vena cava dilatation, the presence of pulmonary congestion, and pleural effusions. However, these features are nonspecific since they are common findings of RCM as well as of CP. In this setting CT has a predominant role in distinguishing between RCM and CP, being even superior to CMR in detecting pericardial calcifications and in the accurate measurement of pericardial thickness.[61]

Computed tomography may be preferable to coronary angiography to evaluate epicardial coronary arteries, to rule out high-grade stenosis, and for differential diagnosis with chronic coronary syndrome. Moreover, when an RCM is predominately suspected, CT allows the assessment of extracardiac involvement in systemic conditions such as sarcoidosis (e.g., pulmonary nodules, pulmonary fibrosis, and lymphadenopathy) or amyloidosis (e.g., inhomogeneous

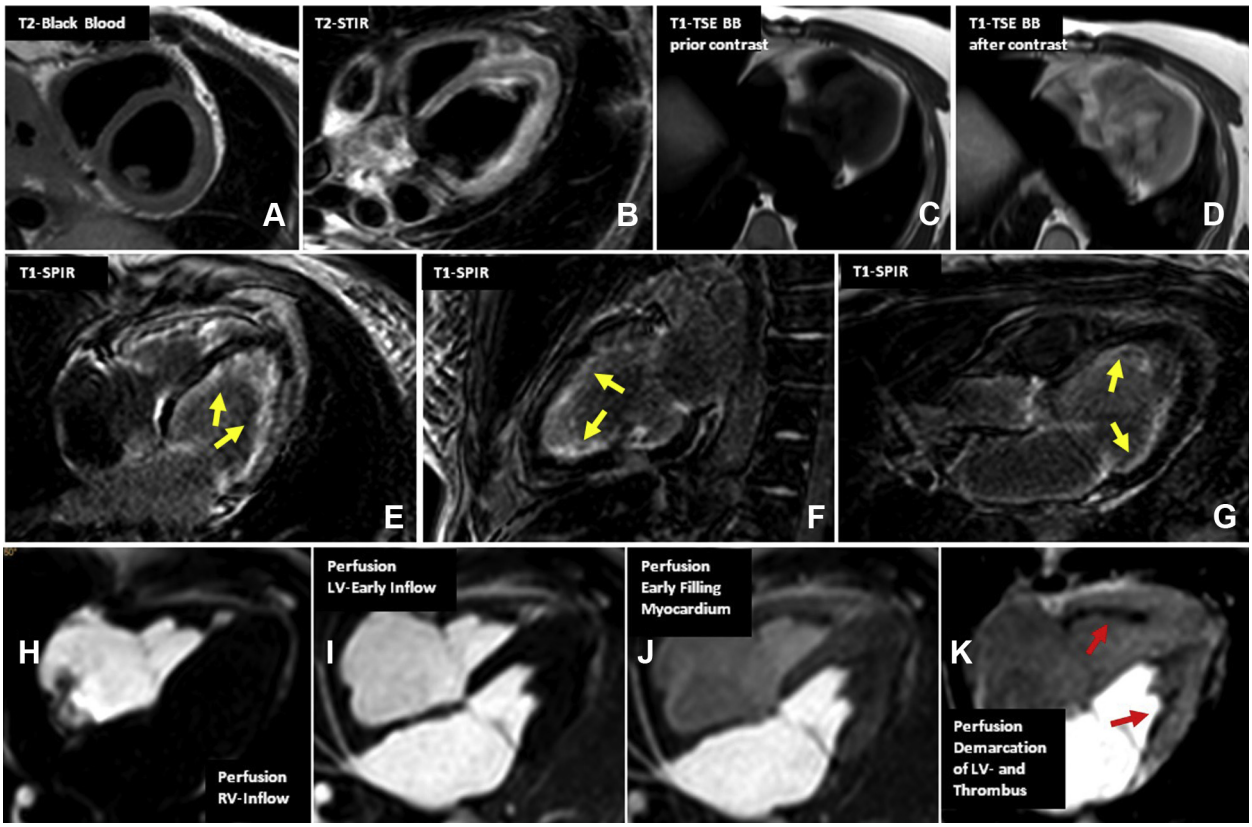

Figure 6 Cardiac magnetic resonance imaging myocardial tissue characterization by T2 black blood sequences characterizing pericardium **(A)**, T2-STIR sequences showing myocardial edema **(B)**, T1 black blood sequences prior **(C)** and directly after contrast administration **(D)** showing hyperemia, and T1-SPIR sequences of the four-chamber view **(E)**, two-chamber view **(F)**, and three-chamber view **(G)** suggestive of fibrosis through LGE (*yellow arrows*). Cardiac magnetic resonance perfusion imaging **(H-K)** documents contrast-enhanced signals in the myocardium and demarcation of subendocardial thrombus formation in the RV and LV. Thrombotic lesions show no contrast enhancement (*red arrows*).

hepatomegaly, diffuse lung parenchymal involvement, small kidneys), further aiding in the differential diagnosis.

Hepatic, pulmonary, and gastrointestinal involvement may be precisely revealed by CT, identifying possible multiorgan damage in HES.[62] Finally, CT may be also useful for a more precise evaluation of regions of replacement fibrosis, in evaluating extracellular volume fraction by equilibrium contrast-enhanced CT, which is usually increased in association with diffuse myocardial fibrosis and is a significant hallmark of pathologic remodeling.[63]

Although not widely available, 18F-FDG PET has the potential to reveal active inflammation by increased glucose metabolism in patients with suspected or confirmed LE. In several other pathologic conditions characterized by myocardial ischemia, inflammation, wall stress from pressure overload, or myocardial hypertrophy, the energy source of the myocardium shifts to glucose metabolism from fatty acids. In addition, 18F-FDG PET can be helpful to detect the earliest stages of inflammation, which may help to start medical therapy before irreversible cardiac damage occurs, as well as to show irreversible fibrosis by using perfusion imaging.[64] The degree of perfusion abnormality and 18F-FDG uptake (early stage, progressive stage, progressive myocardial impairment stage, and fibrosis stage) also provides information for clinical management during follow-up by identifying patients not responsive to medical therapy. Since 18F-FDG can be used in the case of inconclusive findings on CMR and in patients in whom CMR is contraindicated, as in those with severely impaired renal function and/or those with implanted non–magnetic resonance imaging conditional cardiac implantable devices, it has some advantages over CMR.[65-67]

Whole-body 18F-FDG PET/CT imaging can also evaluate the noncardiac systemic involvement of HES (Figure 8). Of note, the metabolic alterations related to prolonged corticosteroid therapy in LE may make 18F-FDG images challenging to interpret.

To date, we do not have sufficient data concerning the incremental value of CT and 18F-FDG PET in LE, but they should be considered as second-line imaging tools to be used in selected patients. Prospective studies are needed to elucidate their relevance in diagnosis, management, and prognosis.

INVASIVE ASSESSMENT: ENDOMYOCARDIAL BIOPSY

The 2007 American Heart Association/American College of Cardiology Foundation/European Society of Cardiology scientific statement on EMB limited its class IIa recommendations (level of evidence C) to HF associated with unexplained RCM or HF associated with a dilated cardiomyopathy of any duration associated with suspected allergic reaction and/or eosinophilia.[68] Unfortunately, because no randomized controlled data exist on the utility of EMB, the recommendations are based on case-control series and expert opinion.

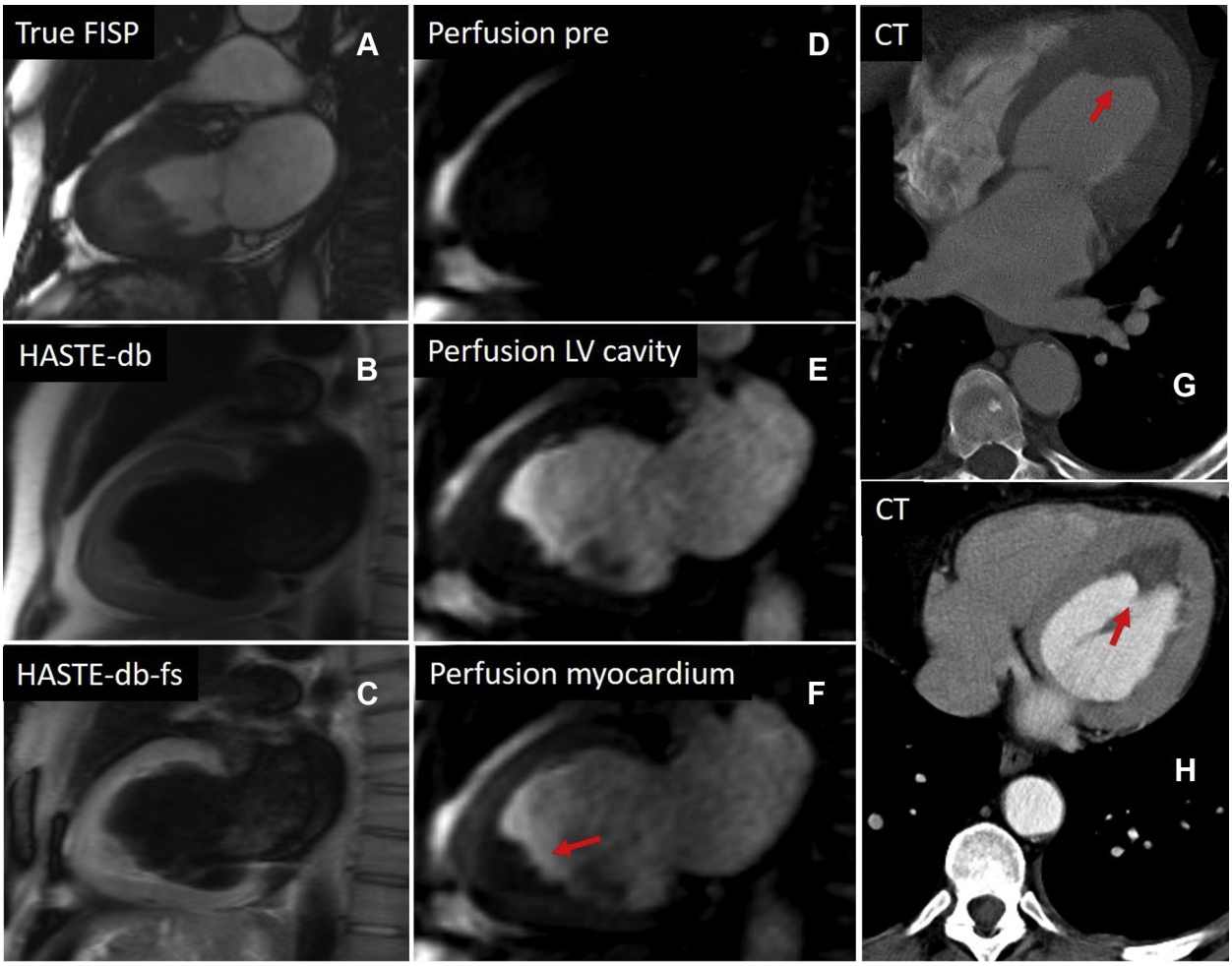

Figure 7 Cardiac magnetic resonance imaging of the two-chamber view **(A-F)** and cardiac CT of transversal views of the heart **(G, H)**. Cardiac tissue characterization by T1-weighted bright blood image **(A)** and fast-spin dark blood echo sequences without **(B)** and with fat saturation **(C)**. Cardiac magnetic resonance perfusion imaging **(D-F)** documents contrast-enhanced signals in the myocardium and demarcation of subendocardial thrombus formation (*red arrow*; **F**). Cardiac CT shows isodense signal intensity of the myocardium and apical LV thrombus (*red arrow*) without contrast **(G)** and demarcation of the subendomyocardial thrombus formation (*red arrow*) with contrast **(H)**. Thrombotic lesions show no contrast enhancement (*red arrows*). *True FISP*, fast imaging with steady-state free precession; *HASTE-db*, half Fourier acquisition single-shot turbo spin-echo - dark blood; *HASTE-db-fs*, half Fourier acquisition single-shot turbo spin-echo - dark blood - phase- symmetry.

Although noninvasive imaging modalities (particularly CMR) are effective to detect the peculiar findings of LE in the vast majority of cases, EMB still has a role in doubtful cases in which noninvasive techniques are not conclusive or, more rarely, are contraindicated.[69]

The main reasons to restrict EMB when considering the diagnosis of LE are local availability, operator experience, and the risks of the procedure. Nonetheless, if performed by experienced operators, it has been reported that EMBs have very low complication rates. In a single-center study[70] over a 28-year period, among 3,549 patients who underwent diagnostic LV EMB, either selectively or associated with an RV EMB, LE was detected in only 0.4% of the patients. It was reported that, in the entire study population, the periprocedural major complication rate (perforation with or without cardiac tamponade and embolization) was very low (0.33% for LV EMB and 0.45% for RV EMB).

Initially, in the necrotic stage of disease, eosinophilic inflammation may be detected in EMB specimens, and in some cases, it may advance to endomyocardial fibrosis. The hallmark histologic findings include interstitial infiltrates with prominent eosinophils and other immune cells, myocyte necrosis, and edema (in the acute phase; Figure 9), endocardial thrombosis containing eosinophils (in the second phase), and endocardial fibrotic thickening (several millimeters) without inflammatory infiltrates in the late stage.[71] Importantly, EMB may be capable of distinguishing on the basis of the quality of the cellular infiltrate (eosinophilic, lymphocytic, or granulomatous) hypersensitivity myocarditis from giant cell myocarditis or necrotizing EM or sarcoidosis, and thus EMB is reasonable in the setting of unexplained RCM.[72] Of note, many features of LE in the setting of RCM may also mimic those of CP. Therefore, in combination with either CMR or CT, EMB can be very helpful in differentiating these two clinical entities. However, if pericardial thickening and calcifications are

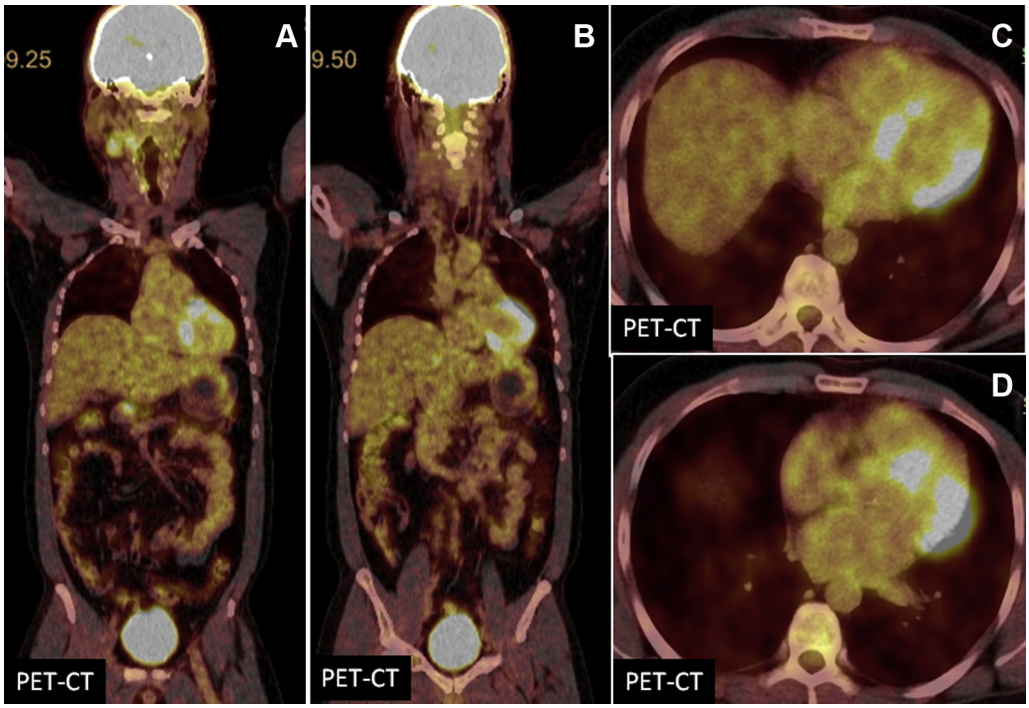

Figure 8 Fused coronal **(A, B)** and transversal **(C, D)** 18F-FDG PET/CT images after application of 276 MBq 18F-FDG in a patient with LE. Note the different signal intensity in the LV myocardium due to heterogeneous uptake related to the disease. No significant increase of metabolism is shown in other organs.

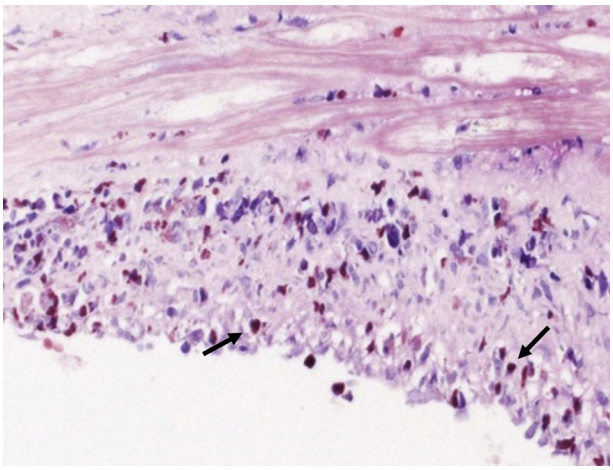

Figure 9 Histologic findings in a patient with LE. Endomyocardial biopsy shows inflammatory infiltrates, especially of eosinophils (depicted by *arrows*) in the fibrotic endocardium.

detected on CT or CMR and clinical suspicion is most consistent with CP, EMB is often not needed.[27]

In a retrospective study detecting cardiac involvement in HES, an agreement between echocardiography and EMB was found in 60% of cases; seven of 25 patients (28%) with a negative TTE were found by EMB to have LE.[73] These results suggest that, in HES patients suspected for having cardiac involvement, EMB is superior to echocardiography, and a normal TTE examination should not preclude the use of EMB, especially when the clinical suspicion is high.

Certainly, EMB may add important information about what occurs at the cellular level, elucidating the cause of the disease and subsequently influencing therapeutic decisions. Despite being a valuable tool in most cases, some drawbacks of EMB should be taken into account. Low sensitivity, low availability, and high cost limit its use in clinical practice. Notably, it has been described that EMB allows the diagnosis of LE in only about 50% of the patients mainly due to false-negative biopsies.[74] Sometimes it is not very sensitive as the infiltrates are patchy and biopsy sampling from the RV may miss the left-sided disease.[75] No data are available on the risk of thromboembolism after biopsy during the thrombotic stage, but it reasonably should be avoided during this stage.

In the absence of a specific recommendation, some investigators suggest a preliminary CMR to guide EMB. Cardiac magnetic resonance imaging allows the detection of a focal disease process, the identification of the area of the RV or LV that would be most likely to demonstrate the underlying pathologic process and provide an optimal anatomical target for biopsy.[51,76,77] Nevertheless, this issue needs further study, particularly regarding the impact on diagnostic yield and in the selection of the best noninvasive or invasive diagnostic tool in the setting of cardiomyopathies with patchy distribution and an evolving course of myocardial involvement.[57]

MULTIMODALITY IMAGING FOR LE DIAGNOSIS

Any potential advantage of an individual imaging tool has to be balanced by the specific limitations related to the availability, bedside feasibility, contraindications, and costs. The lack of imaging pathognomonic findings and the risks related to delayed LE recognition would

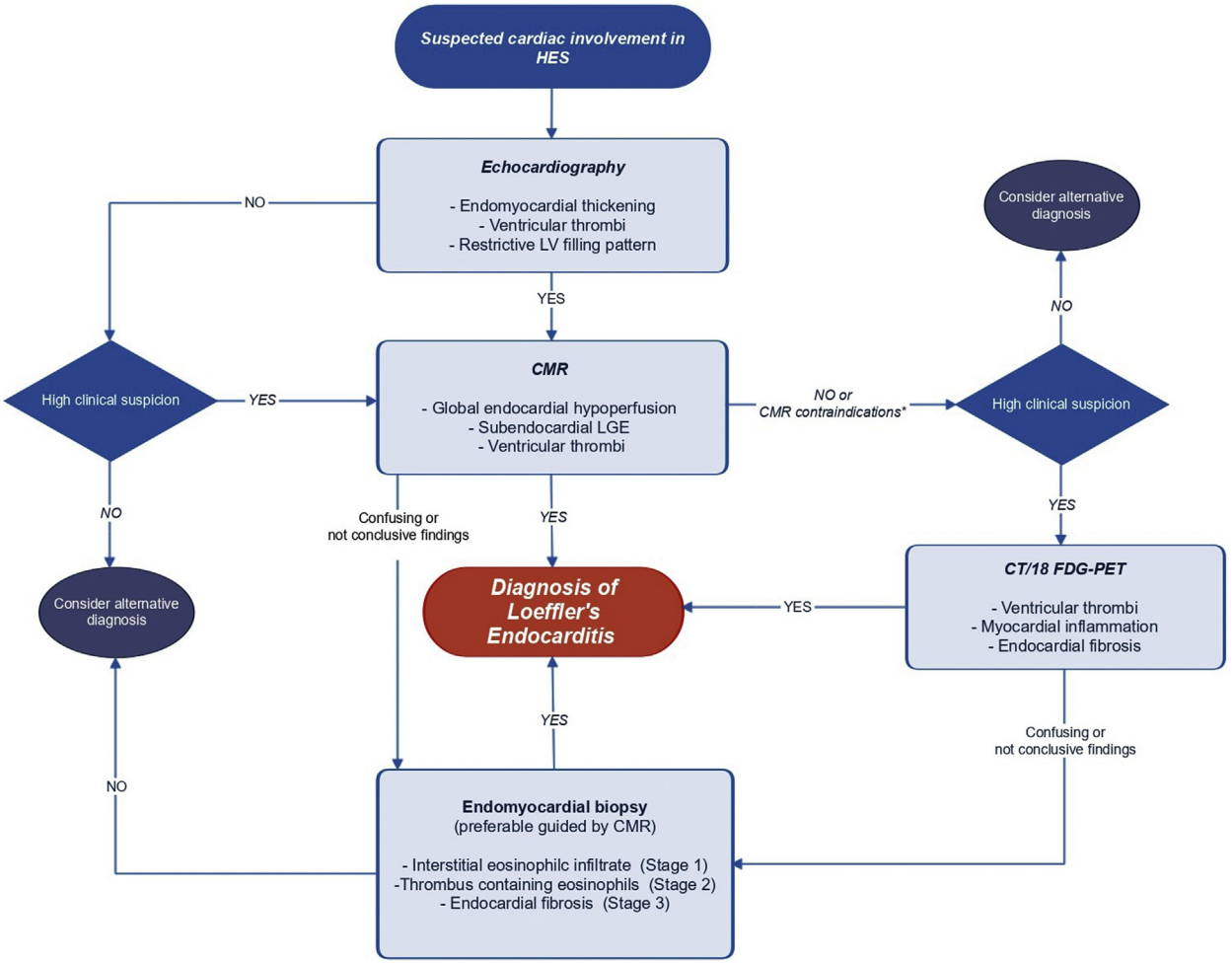

Figure 10 Flowchart showing the diagnostic work-up of LE by using the multimodality imaging approach.

suggest the use of any technology to reach a diagnosis. A stepwise approach is the most rational way to integrate different techniques and reconcile discordant findings. A diagnostic algorithm for LE diagnosis based on the multimodality imaging approach is proposed in Figure 10. After an initial comprehensive clinical evaluation of patients with HES, patients with suspected cardiac involvement should undergo TTE, including CE and other second-level ultrasound-based modalities. The evidence of endomyocardial thickening at the apex and/or ventricular thrombi is highly suggestive for LE. The coexistence of a restrictive diastolic pattern, although less specific, supports the clinical suspicion of cardiac involvement in patients with HES. Cardiac magnetic resonance imaging should be the next step in these cases as well as in patients with less suggestive findings (Table 1), when clinical suspicion is substantive. Since echocardiography has a limited sensitivity, particularly during stages 1 (necrotic) and 3 (fibrotic) of the disease, CMR should be considered also in patients with negative TTE when a high clinical risk exists. After gadolinium administration, the evidence of global endocardial hypoperfusion during the early phase, RV/LV thrombi, or LGE suggestive for endocardial fibrosis support the suspicion of LE. Cardiac CT or 18F-FDG PET should be considered in case of contraindications (i.e., non-magnetic resonance imaging conditional implantable devices) or inconclusive results from CMR. In cases where the noninvasive imaging data are discrepant or not supportive of a high clinical suspicion for LE, EMB should be considered and ideally should be guided by CMR.

CONCLUSION

A multimodality imaging approach, including noninvasive and invasive techniques, represents the current standard of care in LE. Increasingly precise characterization of LE contributes to early diagnosis, more accurate staging of disease, and timely institution of treatment, to prevent irreversible structural changes and, finally, adverse cardiovascular events.

REFERENCES

1. Tefferi A, Patnaik MM, Pardanani A. Eosinophilia: secondary, clonal and idiopathic. Br J Haematol 2006;133:468-92.
2. Parrillo JE. Heart disease and the eosinophil. N Engl J Med 1990;323:1560-1.
3. Weller PF, Bubley GJ. The idiopathic hypereosinophilic syndrome. Blood 1994;83:2759-79.
4. Niemeijer ND, van Daele PLA, Caliskan K, Oei FBS, Loosveld OJL, van der Meer NJM. Loffler endocarditis: a rare cause of acute cardiac failure. J Cardiothorac Surg 2012;7:109.

5. Libby PP, Bonow RO, Mann DL, Zipes DP. Braunwald's Heart Disease: a Textbook of Cardiovascular Medicine. 8th ed. Philadelphia: Elsevier Science; 2007. pp. 756-8.
6. Shaper AG, Hutt MS, Coles RM. Necropsy study of endomyocardial fibrosis and rheumatic heart disease in Uganda 1950-1965. Br Heart J 1968;30:391-401.
7. Del Bene MR, Cappelli F, Rega L, Venditti F, Barletta G. Characterization of Loeffler eosinophilic myocarditis by means of real time three-dimensional contrast-enhanced echocardiography. Echocardiography 2012;29:E62-6.
8. Mankad R, Bonnichsen C, Mankad S. Hypereosinophilic syndrome: cardiac diagnosis and management. Heart 2016;102:100-6.
9. Hagendorff A, Hummelgen M, Omran H, Pizzulli L, Zirbes M, Bierhoff E, et al. Loffler fibroblastic endocarditis in the thrombotic stages in isolated right ventricular tissue eosinophilia. Z Kardiol 1998;87:293-9.
10. Kleinfeldt T, Nienaber CA, Kische S, Akin I, Turan RG, Korber T, et al. Cardiac manifestation of the hypereosinophilic syndrome: new insights. Clin Res Cardiol 2010;99:419-27.
11. Ogbogu PU, Rosing DR, Horne MK 3rd. Cardiovascular manifestations of hypereosinophilic syndromes. Immunol Allergy Clin North Am 2007;27:457-75.
12. Wang S, Wang A, Guo B, Zhu S, Chi Z, Zhao X. Loffler endocarditis with multiple cerebral embolism. J Stroke Cerebrovasc Dis 2014;23:1709-12.
13. van Kessel DJW, Jerzewski A, Kardux JJ, Habets J. Loeffler's endocarditis. Eur Hear J Cardiovasc Imaging 2015;16:343.
14. Gotlib J. World Health Organization–defined eosinophilic disorders: 2017 update on diagnosis, risk stratification, and management. Am J Hematol 2017;92:1243-59.
15. Brambatti M, Matassini MV, Adler ED, Klingel K, Camici PG, Ammirati E. Eosinophilic myocarditis: characteristics, treatment, and outcomes. J Am Coll Cardiol 2017;70:2363-75.
16. Acquatella H, Schiller NB, Puigbo JJ, Gomez-Mancebo JR, Suarez C, Acquatella G. Value of two-dimensional echocardiography in endomyocardial disease with and without eosinophilia. A clinical and pathologic study. Circulation 1983;67:1219-26.
17. Lengyel M, Dekov E. Two-dimensional echocardiographic features of Loffler's endocarditis. Acta Cardiol 1982;37:59-69.
18. Davies J, Gibson DG, Foale R, Heer K, Spry CJ, Oakley CM, et al. Echocardiographic features of eosinophilic endomyocardial disease. Br Heart J 1982;48:434-40.
19. Berensztein CS, Pineiro D, Marcotegui M, Brunoldi R, Blanco MV, Lerman J. Usefulness of echocardiography and doppler echocardiography in endomyocardial fibrosis. J Am Soc Echocardiogr 2000;13:385-92.
20. Parrillo JE, Borer JS, Henry WL, Wolff SM, Fauci AS. The cardiovascular manifestations of the hypereosinophilic syndrome: prospective study of 26 patients, with review of the literature. Am J Med 1979;67:572-82.
21. Rodger JC, Irvine KG, Lerski RA. Echocardiography in Loffler's endocarditis. Br Heart J 1981;46:110-2.
22. Chang S-A, Kim H-K, Park E-A, Kim Y-J, Sohn D-W. Images in cardiovascular medicine. Loeffler endocarditis mimicking apical hypertrophic cardiomyopathy. Circulation 2009;120:82-5.
23. Sato T, Matsuyama T-A, Seguchi O, Murata Y, Sunami H, Yanase M, et al. Restrictive myocardium with an unusual pattern of apical hypertrophic cardiomyopathy. Cardiovasc Pathol 2015;24:254-7.
24. Harzy T, Allali F, Amine B, Rahmouni R, Hajjaj-Hassouni N. Cardiac manifestations of idiopathic hypereosinophilic syndrome. La Rev Med Intern 2005;26:386-92.
25. Filippetti L, Huttin O, Selton-Suty C, Voilliot D. Hypereosinophilic cardiac disease. Acta Cardiol 2017;72:9-18.
26. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF 3rd, Dokainish H, Edvardsen T, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update rrom the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr 2016;29:277-314.
27. Habib G, Bucciarelli-Ducci C, Caforio ALP, Cardim N, Charron P, Cosyns B, et al. Multimodality imaging in restrictive cardiomyopathies: an EACVI expert consensus document in collaboration with the "Working Group on myocardial and pericardial diseases" of the European Society of Cardiology endorsed by the Indian Academy of Echocardiogr. Eur Hear J Cardiovasc Imaging 2017;18:1090-121.
28. Bozcali E, Aliyev F, Agac MT, Erkan H, Okcun B, Babalik E, et al. Unusual case of aortic valve involvement in patient with Loffler's endomyocarditis: management, follow-up and short review of the literature. J Thromb Thrombolysis 2007;24:309-13.
29. Garg A, Nanda NC, Sungur A, Sharma GL, Mehta KJ, Oz TK. Transthoracic echocardiographic detection of pulmonary valve involvement in Loeffler's endocarditis. Echocardiography 2014;31:83-6.
30. Gottdiener JS, Maron BJ, Schooley RT, Harley JB, Roberts WC, Fauci AS. Two-dimensional echocardiographic assessment of the idiopathic hypereosinophilic syndrome: anatomic basis of mitral regurgitation and peripheral embolization. Circulation 1983;67:572-8.
31. Shah R, Ananthasubramaniam K. Evaluation of cardiac involvement in hypereosinophilic syndrome: complementary roles of transthoracic, transesophageal, and contrast echocardiography. Echocardiography 2006;23:689-91.
32. Klein AL, Cohen GI, Pietrolungo JF, White RD, Bailey A, Pearce GL, et al. Differentiation of constrictive pericarditis from restrictive cardiomyopathy by Doppler transesophageal echocardiographic measurements of respiratory variations in pulmonary venous flow. J Am Coll Cardiol 1993;22:1935-43.
33. Schiavone WA, Calafiore PA, Salcedo EE. Transesophageal Doppler echocardiographic demonstration of pulmonary venous flow velocity in restrictive cardiomyopathy and constrictive pericarditis. Am J Cardiol 1989;63:1286-8.
34. Voigt J-U, Pedrizzetti G, Lysyansky P, Marwick TH, Houle H, Baumann R, et al. Definitions for a common standard for 2D speckle tracking echocardiography: consensus document of the EACVI/ASE/Industry Task Force to standardize deformation imaging. Eur Heart J Cardiovasc Imaging 2015;16:1-11.
35. Eroglu E, Di Salvo G, Herbots L, Herregods MC, Sutherland GR. Restrictive left ventricular filling in hypereosinophilic syndrome as a result of partial cavity obliteration by an apical mass: a strain/strain rate study. J Am Soc Echocardiogr 2003;16:1088-90.
36. Nemes A, Kalapos A, Domsik P, Marton I, Borbenyi Z, Forster T. Three-dimensional speckle-tracking echocardiography in Loeffler endocarditis: case report from the MAGYAR-Path Study. Herz 2014;39:722-4.
37. Yamamoto T, Tanaka H, Kurimoto C, Imanishi T, Hayashi N, Saegusa J, et al. Very early stage left ventricular endocardial dysfunction of patients with hypereosinophilic syndrome. Int J Cardiovasc Imaging 2016;32:1357-61.
38. Nemes A, Marton I, Domsik P, Kalapos A, Posfai E, Modok S, et al. Characterization of left atrial dysfunction in hypereosinophilic syndrome: insights from the Motion analysis of the heart and great vessels by three-dimensional speckle tracking echocardiography in pathological cases (MAGYAR-Path) Study. Rev Port Cardiol 2016;35:277-83.
39. Nemes A, Marton I, Domsik P, Kalapos A, Posfai E, Modok S, et al. The right atrium in idiopathic hypereosinophilic syndrome: insights from the 3D speckle tracking echocardiographic MAGYAR-Path Study. Herz 2019;44:405-11.
40. Lang RM, Badano LP, Tsang W, Adams DH, Agricola E, Buck T, et al. EAE/ASE recommendations for image acquisition and display using three-dimensional echocardiography. Eur Heart J Cardiovasc Imaging 2012;13:1-46.
41. Hernandez CM, Arisha MJ, Ahmad A, Oates E, Nanda NC, Nanda A, et al. Usefulness of three-dimensional echocardiography in the assessment of valvular involvement in Loeffler endocarditis. Echocardiography 2017;34:1050-6.
42. Casavecchia G, Gravina M, Correale M, Totaro A, Macarini L, Di Biase M, et al. Cardiac magnetic resonance imaging for the diagnosis and follow-up of Loeffler's endocarditis. J Allergy Clin Immunol 2017;139:1055-7.
43. Imbriaco M, Nappi C, Puglia M, De Giorgi M, Dell'Aversana S, Cuocolo R, et al. Assessment of acute myocarditis by cardiac magnetic resonance

imaging: comparison of qualitative and quantitative analysis methods. J Nucl Cardiol 2019;26:857-65.
44. Salemi VM, Rochitte CE, Shiozaki AA, Andrade JM, Parga JR, de Avila LF, et al. Late gadolinium enhancement magnetic resonance imaging in the diagnosis and prognosis of endomyocardial fibrosis patients. Circ Cardiovasc Imaging 2011;4:304-11.
45. Mahrholdt H, Wagner A, Judd RM, Sechtem U, Kim RJ. Delayed enhancement cardiovascular magnetic resonance assessment of non-ischaemic cardiomyopathies. Eur Heart J 2005;26:1461-74.
46. Polito MV, Stoebe S, Leifels L, Stumpp P, Solty K, Galasso G, et al. Cardiac sarcoidosis: a challenging diagnosis. Clin Res Cardiol 2018;107:980-6.
47. Pennell DJ. Cardiovascular magnetic resonance. Circulation 2010;121:692-705.
48. Maceira AM, Joshi J, Prasad SK, Moon JC, Perugini E, Harding I, et al. Cardiovascular magnetic resonance in cardiac amyloidosis. Circulation 2005;111:186-93.
49. Ferreira VM, Schulz-Menger J, Holmvang G, Kramer CM, Carbone I, Sechtem U, et al. Cardiovascular magnetic resonance in nonischemic myocardial inflammation: expert recommendations. J Am Coll Cardiol 2018;72:3158-76.
50. Salerno M, Sharif B, Arheden H, Kumar A, Axel L, Li D, et al. Recent advances in cardiovascular magnetic resonance: techniques and applications. Circ Cardiovasc Imaging 2017;10:e003951.
51. Pontone G, Guaricci AI, Andreini D, Ferro G, Guglielmo M, Baggiano A, et al. Prognostic stratification of patients with ST-segment-elevation myocardial infarction (PROSPECT): a cardiac magnetic resonance study. Circ Cardiovasc Imaging 2017;10:e006428.
52. Brown PF, Miller C, Di Marco A, Schmitt M. Towards cardiac MRI based risk stratification in idiopathic dilated cardiomyopathy. Heart 2019;105:270-5.
53. Mocumbi AO, Ferreira MB, Sidi D, Yacoub MH. A population study of endomyocardial fibrosis in a rural area of Mozambique. N Engl J Med 2008;359:43-9.
54. Hundley WG, Bluemke DA, Finn JP, Flamm SD, Fogel MA, Friedrich MG, et al. ACCF/ACR/AHA/NASCI/SCMR 2010 expert consensus document on cardiovascular magnetic resonance: a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents. J Am Coll Cardiol 2010;55:2614-62.
55. Debl K, Djavidani B, Buchner S, Poschenrieder F, Heinicke N, Feuerbach S, et al. Time course of eosinophilic myocarditis visualized by CMR. J Cardiovasc Magn Reson 2008;10:21.
56. Inoue T, Watanabe C, Ayukawa H, Nadahama T, Hosokawa A, Beppu K, et al. Biopsy-proven Loeffler endocarditis successfully treated with steroids. Circulation 2015;131:e353-4.
57. Syed IS, Martinez MW, Feng D-L, Glockner JF. Cardiac magnetic resonance imaging of eosinophilic endomyocardial disease. Int J Cardiol 2008;126:e50-2.
58. Halpern EJ. Clinical applications of cardiac CT angiography. Insights Imaging 2010;1:205-22.
59. Kuchynka P, Palecek T, Masek M, Cerny V, Lambert L, Vitkova I, et al. Current diagnostic and therapeutic aspects of eosinophilic myocarditis. Biomed Res Int 2016;2016:2829583.
60. Scully PR, Bastarrika G, Moon JC, Treibel TA. Myocardial extracellular volume quantification by cardiovascular magnetic resonance and computed tomography. Curr Cardiol Rep 2018;20:15.
61. Adler Y, Charron P, Imazio M, Badano L, Baron-Esquivias G, Bogaert J, et al. 2015 ESC guidelines for the diagnosis and management of pericardial diseases: the Task Force for the Diagnosis and Management of Pericardial Diseases of the European Society of Cardiology (ESC) Endorsed by: the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J 2015;36:2921-64.
62. Katre RS, Sunnapwar A, Restrepo CS, Katabathina VS, Mumbower A, Baxi A, et al. Cardiopulmonary and gastrointestinal manifestations of eosinophil-associated diseases and idiopathic hypereosinophilic syndromes: multimodality imaging approach. Radiographics 2016;36:433-51.
63. Bandula S, White SK, Flett AS, Lawrence D, Pugliese F, Ashworth MT, et al. Measurement of myocardial extracellular volume fraction by using equilibrium contrast-enhanced CT: validation against histologic findings. Radiology 2013;269:396-403.
64. Kadkhodayan A, Chareonthaitawee P, Raman SV, Cooper LT. Imaging of Inflammation in unexplained cardiomyopathy. JACC Cardiovasc Imaging 2016;9:603-17.
65. Langwieser N, Von Olshausen G, Rischpler C, Ibrahim T. Confirmation of diagnosis and graduation of inflammatory activity of Loeffler endocarditis by hybrid positron emission tomography/magnetic resonance imaging. Eur Heart J 2014;35:2496.
66. Nensa F, Poeppel TD, Schlosser T. Potential role of cardiac PET/MRI in cardiovascular disease: initial experience. In: Schindler TH, George RT, Lima JAC, editors. Molecular and Multimodality Imaging in Cardiovascular Disease. New York: Springer International Publishing; 2015. pp. 13-27.
67. Parikh A, Trivieri MG, Lala A, Mitter S, Hinohara T, Robson P, et al. PET/MRI: a novel imaging modality to guide tailored immunotherapy in eosinophilic myocarditis. J Am Coll Cardiol 2019;73(9 Suppl 1):2891.
68. Cooper LT, Baughman KL, Feldman AM, Frustaci A, Jessup M, Kuhl U, et al. The role of endomyocardial biopsy in the management of cardiovascular disease: a scientific statement from the American Heart Association, the American College of Cardiology, and the European Society of Cardiology. Endorsed by the Heart Failure Society of America and the Heart Failure Association of the European Society of Cardiology. J Am Coll Cardiol 2007;50:1914-31.
69. Dominguez F, Kuhl U, Pieske B, Garcia-Pavia P, Tschope C. Update on myocarditis and inflammatory cardiomyopathy: reemergence of endomyocardial biopsy. Rev Esp Cardiol 2016;69:178-87.
70. Chimenti C, Frustaci A. Contribution and risks of left ventricular endomyocardial biopsy in patients with cardiomyopathies: a retrospective study over a 28-year period. Circulation 2013;128:1531-41.
71. Seguela P-E, Iriart X, Acar P, Montaudon M, Roudaut R, Thambo J-B. Eosinophilic cardiac disease: molecular, clinical and imaging aspects. Arch Cardiovasc Dis 2015;108:258-68.
72. González J, Salgado F, Azzato F, Ambrosio G, Milei J. Endomyocardial biopsy: a clinical research tool and a useful diagnostic method. Chapter 4. IntechOpen 2013; https://doi.org/10.5772/54399.
73. Butterfield JH, Kane GC, Weiler CR. Hypereosinophilic syndrome: endomyocardial biopsy versus echocardiography to diagnose cardiac involvement. Postgrad Med 2017;129:517-23.
74. Burke AP, Saenger J, Mullick F, Virmani R. Hypersensitivity myocarditis. Arch Pathol Lab Med 1991;115:764-9.
75. Trachtenberg BH, Hare JM. Inflammatory cardiomyopathic syndromes. Circ Res 2017;121:803-18.
76. Metze M, Davierwala PM, Andreas H, Klingel K, Laufs U, Klöter T. Progression of left ventricular thrombus in Loeffler's endocarditis without eosinophilia-case report and review of the literature. Clin Res Cardiol 2019;108:1163-70.
77. Perazzolo Marra M, Thiene G, Rizzo S, De Lazzari M, Carturan E, Tona F, et al. Cardiac magnetic resonance features of biopsy-proven endomyocardial diseases. JACC Cardiovasc Imaging 2014;7:309-12.