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Multimodality imaging in decompensated heart failure

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KEYWORDS
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Myocardial scintigraphy

Heart failure (HF) is usually suspected by clinical history, symptoms, physical examination, electrocardiogram findings, and natriuretic peptides' values. However, echocardiography and other imaging techniques play an essential role in supporting HF diagnosis. Thanks to its non-invasiveness and safety, transthoracic echocardiography is the first-level technique of choice to assess myocardial structure and function, trying to establish the diagnosis of HF with reduced, mildly reduced, and preserved ejection fraction. The role of echocardiography is not limited to diagnosis but it represents a crucial tool in guiding therapeutic decision-making and monitoring response to therapy. Over the last decades, several technological advancements were made in the imaging field, aiming at better understanding the morphofunctional abnormalities occurring in cardiovascular diseases. The purpose of this review article is to summarize the incremental role of imaging techniques (in particular cardiac magnetic resonance and myocardial scintigraphy) in HF, highlighting their essential applications to HF diagnosis and management.

Introduction

Heart failure (HF) is a clinical syndrome characterized by dyspnoea, fatigue, and limitation of physical activity, due to reduced cardiac output and/or elevated ventricular filling pressures at rest or during stress. It has been estimated that, in the developed countries, HF affects about 1–2% of the adult population, reaching ≥10% among people >70 years of age. Once developed, HF results in significant cardiovascular morbidity and mortality. More than 1 million people are annually hospitalized for HF, with a 5-year mortality rate of ∼50%.[1]

HF is usually suspected by clinical history, symptoms, physical examination, electrocardiogram findings, and natriuretic peptides' values. However, echocardiography and other imaging techniques play an essential role in supporting HF diagnosis. Thanks to its non-invasiveness and safety, transthoracic echocardiography is the first-level technique of choice to assess myocardial structure and function, trying to establish the diagnosis of HF with reduced, mildly reduced and preserved ejection fraction (HFrEF, HFmrEF, and HFpEF, respectively) (Class I of recommendation, according to European guidelines on HF).[2] The role of TTE is not limited to diagnosis but it represents a crucial tool in guiding therapeutic decision-making and monitoring response to therapy

Over the last decades, several technological advancements were made in the imaging field, aiming at better understanding the morphofunctional abnormalities occurring in cardiovascular diseases.

The purpose of this review article is to summarize the incremental role of imaging techniques in HF, highlighting their essential applications to HF diagnosis and management.

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Imaging of LV shape, mass, and myocardial deformation

Imaging of LV morphology and function should be performed according to current American Society of Echocardiography (ASE)/EACVI recommendations.[3] LV geometry is traditionally classified based on LV mass and relative wall thickness (RWT), calculated as two times posterior wall thickness divided by LV internal diameter at end-diastole. A RWT lower than 0.42, with a normal LV mass is expression of a normal LV geometry, while if both are elevated, there is concentric hypertrophy. The echocardiographic finding of increased RWT, with a normal LV mass, results in a concentric remodelling of LV without appreciable hypertrophy. Both these abnormal geometries (concentric remodelling and hypertrophy) are prevalent in HFpEF.[2] More frequently, an increased LV mass associated with normal RWT, which define an eccentric hypertrophy, is observed in HFrEF. Although echocardiography is the most widely used method to identify abnormal LV geometry, it is important to highlight that cardiac magnetic resonance (CMR) provides the gold standard for assessment of LV morphology (even in complex cases like non-compaction cardiomyopathy) (*Figure 1*), LV mass and wall thickness. Moreover, CMR allows the evaluation of myocardial fibrosis, as well as in the discrimination of increased LV mass due to storage and infiltrative diseases, such as amyloidosis[2]

Clinical application of left ventricular speckle tracking echocardiography to heart failure with reduced ejection fraction

If in HFpEF speckle tracking strain echocardiography (STE) plays an adding value in the detection of subclinical LV systolic dysfunction, in HFrEF setting, in which LV contractile function is clearly impaired, STE has shown to be useful in risk stratification and decision-making.

Global longitudinal strain (GLS) indeed is superior to standard echocardiographic parameters in the prediction of all-cause mortality in HFrEF patients and has been shown to be an accurate predictor of ventricular arrhythmias.[4] In patients with acute HF, GLS has greater prognostic value than LVEF during a 5-year follow-up period.

Finally, strain represents a practical tool able to capture early improvement of myocardial function related to new therapies during follow-up. A recent study proved that GLS was able to detect the early benefit of sacubitril/valsartan on LV remodelling in patients with HFrEF after 3 months of treatment, while LVEF was not significantly changed.[5]

Clinical application of left ventricular speckle tracking echocardiography to heart failure with preserved ejection fraction

A reduction of LV longitudinal systolic function is a common finding among patients affected by HFpEF.[2] The underlying mechanism is that several comorbidities coexisting with HFpEF such as obesity, systemic arterial hypertension, Type 2 diabetes, history of coronary artery disease, and severe LV hypertrophy, often cause interstitial fibrosis which primarily involves LV sub-endocardial fibres. Therefore, echocardiographic features of HFpEF are not limited to isolated LV diastolic dysfunction, but include also LV systolic longitudinal abnormalities.

The isolated impairment of the sub-endocardial layer is compensated by the augmentation of function of the other layers, so that LVEF and overall LV performance remain preserved.[1] Thus, longitudinal systolic dysfunction in patients with HFpEF is counteracted by a normal rotational, circumferential and radial LV contraction. A GLS value $< 16\%$ currently falls within the minor criteria of HFpEF workup and scoring system, according to a consensus document drafted by the HF association of the ESC.[2] The lower resting values of LV GLS and myocardial work in HFpEF patients suggest an early subclinical myocardial damage, which seems to be closely associated with lower exercise capacity, greater pulmonary congestion, and blunted LV contractile reserve during effort[6] (*Figure 2*).

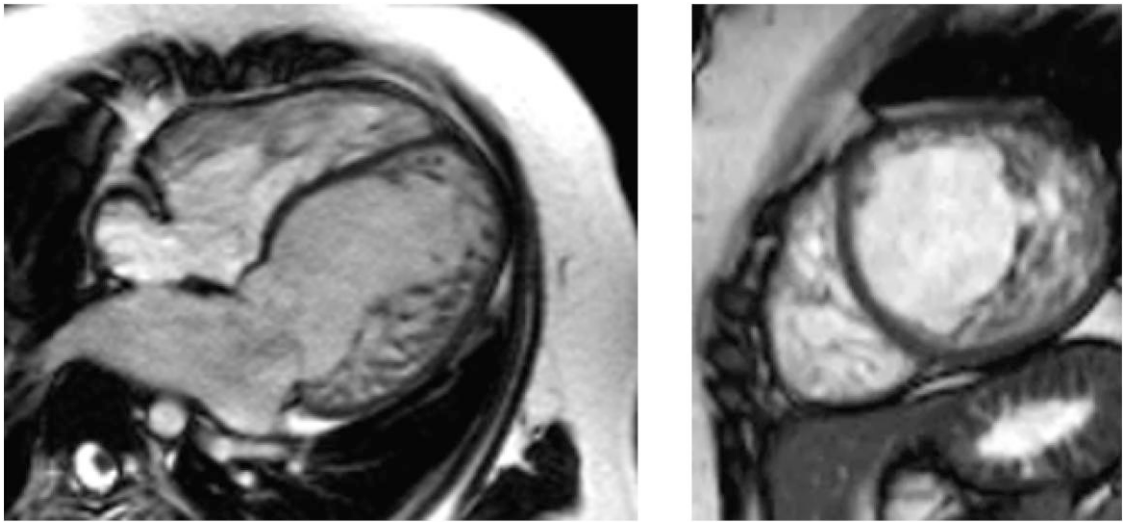

Figure 1 Cardiac MRI in non-compaction cardiomyopathy.

Beyond its diagnostic role, GLS also seems to play a prognostic role in HFpEF.[7] Impaired GLS predicts HF hospitalization, cardiovascular death, or cardiac arrest. Moreover, lower GLS values are associated with higher NT-proBNP levels, which is a proven prognostic factor in HFpEF. Further and larger multicentre studies are needed to confirm the role of STE in identifying patients with HFpEF who are at particularly high risk for cardiovascular morbidity and mortality.

Clinical application of colour Doppler flow mapping to HF

The HyperDoppler technique provides different possibilities to analyze and represent intracardiac flow data: a flow velocity vector map, where velocity vectors are displayed as arrows superimposed on the traditional colour Doppler flow images; a circulation parametric map, where vortices are represented as

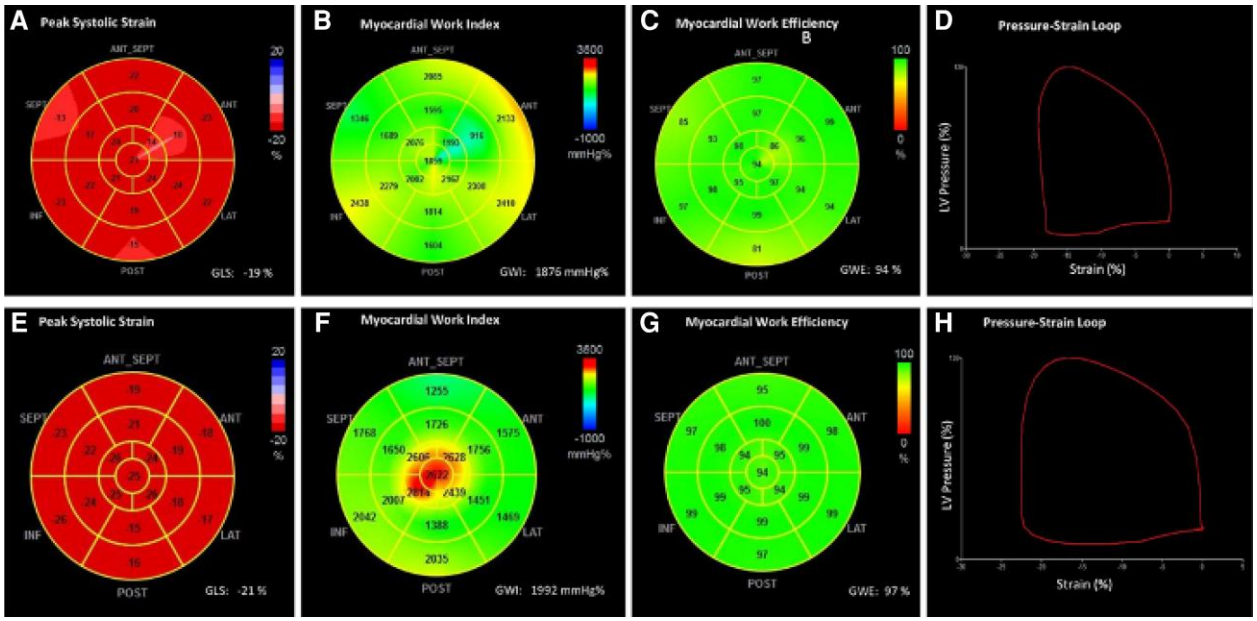

Figure 2 Representative cases showing global longitudinal strain (*A-E*), myocardial work Index (*B-F*), myocardial work efficiency (*C-G*) and pressure-strain loops in a patient with HFpEF (upper) and in a healthy subject (lower) at rest.

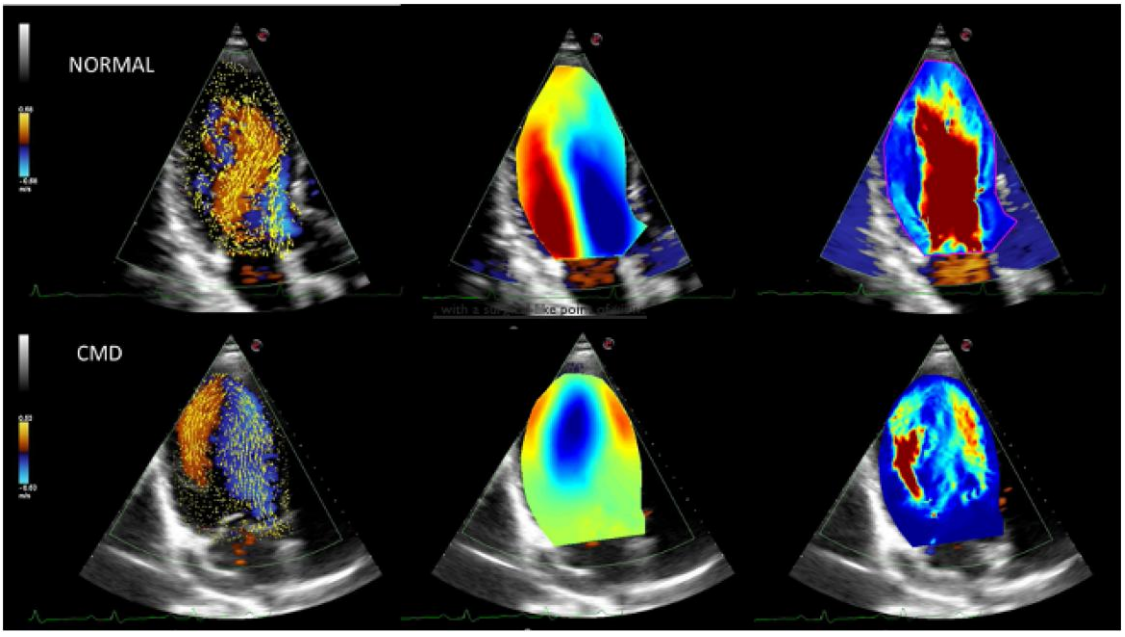

Figure 3 The HyperDoppler in a normal subject and in a dilated cardiomyopathy patient. This technique provides different possibilities to analyze and represent intracardiac flow data: vortices are represented as compacted regions in blue (clockwise rotation) or in red (counterclockwise rotation).

compacted regions in blue (clockwise rotation) or in red (counterclockwise rotation); and a steady-streaming flow map of one heart beat, which can be used for a number of quantitative measures, including vortex area, length, depth, and intensity (*Figure 3*). In addition, the software allows to evaluate kinetic energy dissipation or loss within the LV and intraventricular haemodynamic forces.

The LV vortex formation is the result of an optimal interaction between LV chamber geometry, morphology of the mitral valve apparatus, and normal electrical conduction system, which allows the harmonic contraction of the cardiac walls. If one of these elements is altered, the LV vortex formation is affected too.

In dilated cardiomyopathy, during diastole, a single vortex is generally located in the centre of the LV cavity, which is larger, rounder, and more persistent than in normal subjects, with a greater amount of kinetic energy. Kinetic energy dissipation is higher in healthy subjects than in patients with dilated cardiomyopathy or myocardial infarction and impaired LVEF and stroke volume. Finally, larger infarctions are associated with a more severe alteration in LV intracavitary blood flow dynamics. Preliminary data reported the prognostic value of vortex properties in patients with HF.[8]

Imaging and myocardial tissue characterization

CMR represents the imaging technique of choice for the tissue characterization of the myocardium and assessment of myocardial fibrosis. In particular, late gadolinium enhancement (LGE) allows identification of silent myocardial infarction (*Figures 4-5*) and provides important diagnostic information in specific cardiomyopathies, such as amyloidosis, HCM, sarcoidosis, and cardiac haemochromatosis, and in the diagnostic approach of constrictive pericarditis[9]

Besides the quantification of post-infarction focal fibrosis by LGE, CMR application includes also the quantification of diffuse myocardial fibrosis by T1 mapping, through the evaluation of extracellular volume (ECV) relative to cardiomyocyte volume. This method is based on the evidence that diffuse fibrosis increases ECV. Several pathological conditions, such as arterial hypertension and diabetes before the development of overt HF have been associated with ECV expansion. Furthermore, in patients with HFpEF, signs of myocardial fibrosis by T1 mapping and increased ECV fraction were found, and were well correlated with histologically detected fibrosis, LV stiffness, and LV diastolic dysfunction.[10] Thus, CMR is a useful advance for the diagnosis of HFpEF and in understanding the underlying aetiology. It is also an important tool for risk prediction and stratification not only in patients with established HFpEF but also in patients at risk of developing HFpEF. However, with the exception of application in cardiac amyloidosis, the clinical role of T1 mapping in HFpEF remains unclear.

In patients with HF with ischaemic aetiology, myocardial scintigraphy can detect areas of ischaemia or necrosis in the vascular territory of the coronary arteries. By use of scintigraphy it is possible the quantitative assessment of the extension of the area of altered post-stress perfusion (summed stress score, SSS) and at rest (summed rest score, SRS). The weighted difference between the two makes it possible to obtain the ischaemic risk area (summed defect score, SDS). In

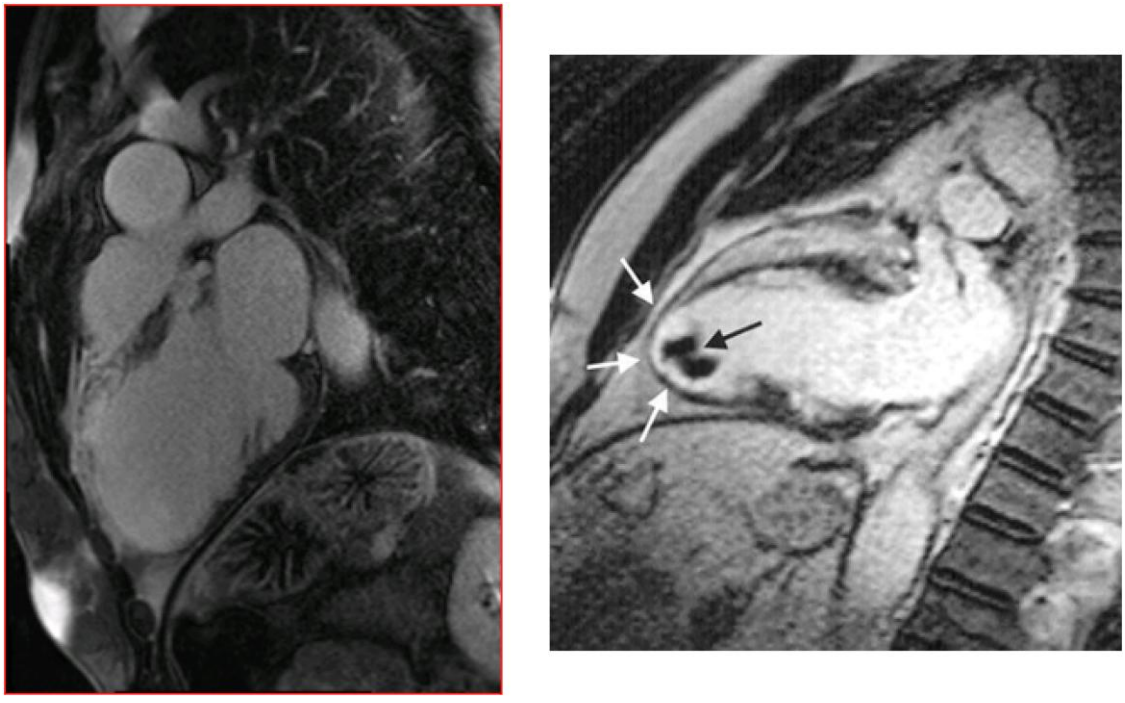

Figure 4 Cardiac MRI in a patient with ischaemic dilated cardiomyopathy. LGE shows transmural myocardial scar tissue of the anterior wall, with an apical thrombus.

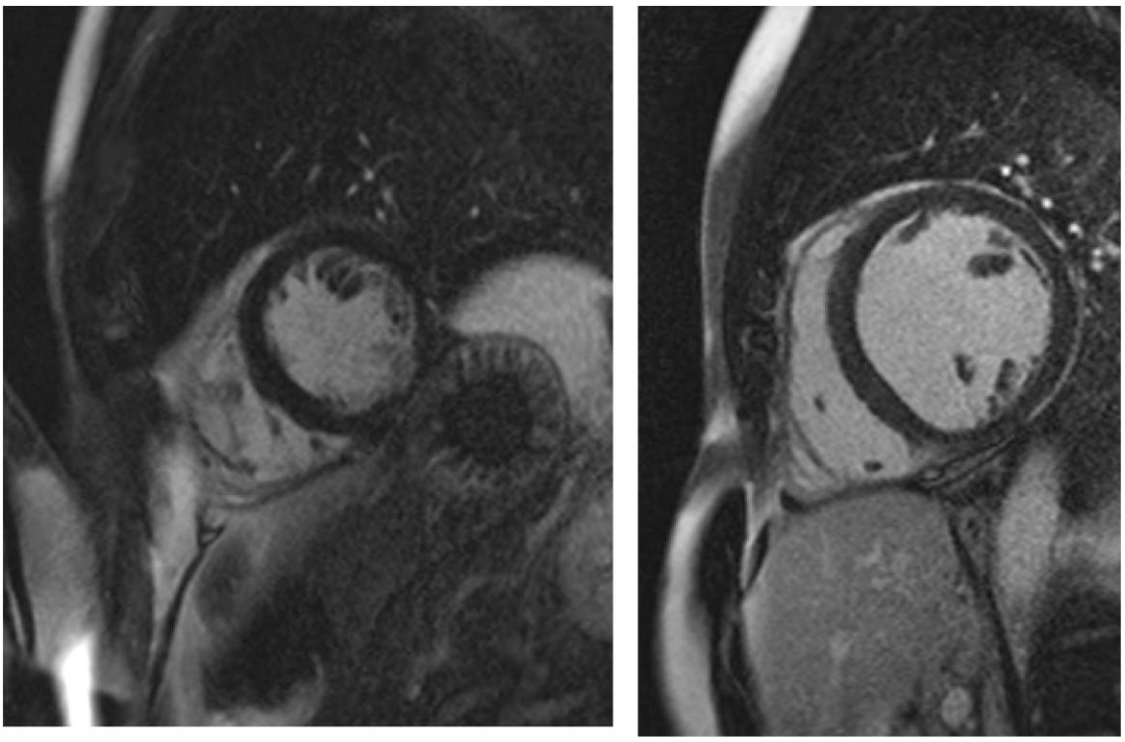

Figure 5 Cardiac MRI in a patient with previous NSTEMI (left) and in a patient with idiopathic dilated cardiomyopathy (right). LGE shows sub-endocardial myocardial scar tissue of the lateral wall in the NSTEMI patient, and absence of myocardial scar tissue in the idiopathic dilated cardiomyopathy patient.

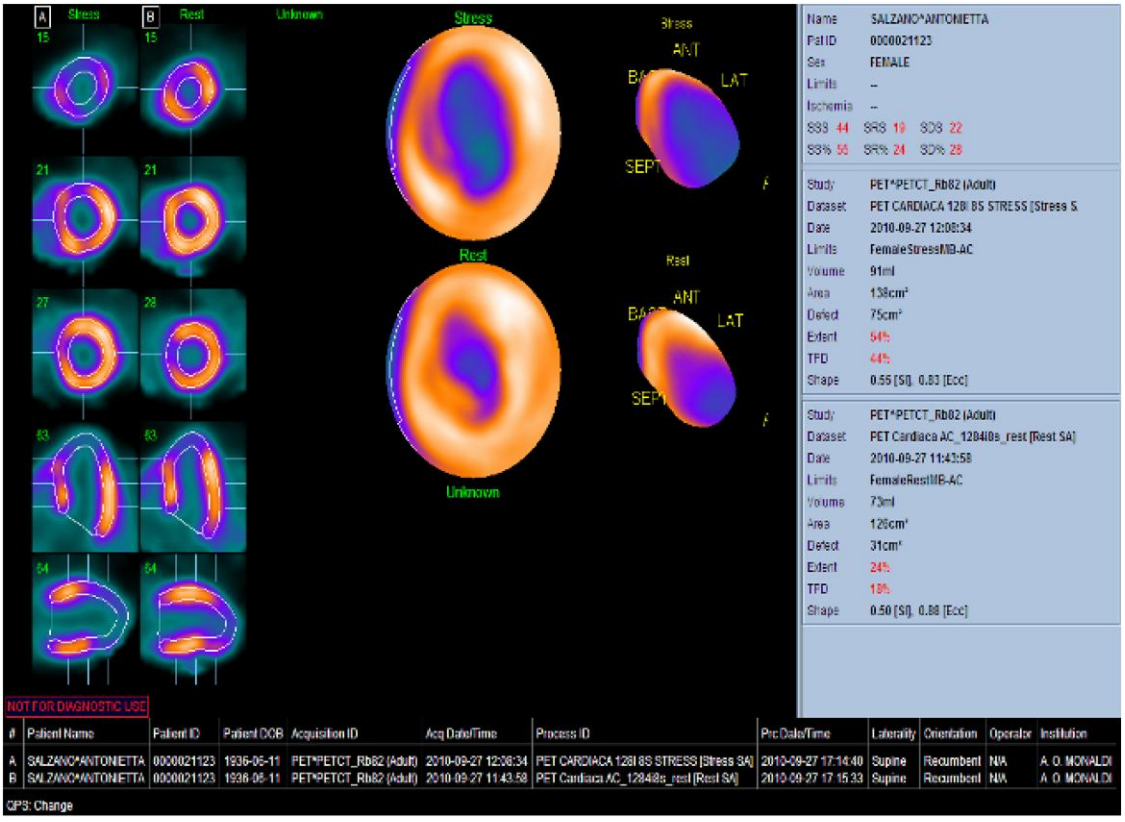

Figure 6 Myocardial scintigraphy of a patient with ischaemic heart disease. By this technique, it is possible the quantitative assessment of the extension of the area of altered post-stress perfusion (summed stress score, SSS, 44 in this case) and at rest (summed rest score, SRS, 19 in this patient). The weighted difference between the two makes it possible to obtain the ischaemic risk area (summed defect score, SDS, 22 in this patient).

addition, the gated images can quantify left ventricular function and volumes, both post-stress and at rest (*Figure 6*).

Imaging and LV diastolic function

The echocardiographic evaluation on LV diastolic function is pivotal in all patients with known or suspected HF. According to the 2016 ASE/EACVI guideline, four echocardiographic markers should be considered to identify LV diastolic dysfunction: mitral annular e' velocity (septal $e' < 7$ cm/s or lateral $e' < 10$ cm/s), average E/e' ratio >14, LAVi >34 mL/m^2, and peak TR velocity >2.8 m/s.[11] When more than half of these variables meet the cut-off values (at least 3 of 4 or 2 of 3 if one variable is missing) a diagnosis of LV diastolic dysfunction is made. Conversely, LV diastolic function is considered normal when more than half of the available variables do not meet the cut-off values.

Some patients with HFpEF have reported increased LV filling pressure only during exercise, showing low sensitivity of resting echocardiographic parameters to diagnose HFpEF.[12] In this setting, measurements of the E/e' ratio and peak TR velocity during exercise stress echocardiography have shown to be feasible and correlated with invasively estimated LV filling pressure during exercise. Moreover, adding diastolic stress testing to the standard resting echocardiography increases diagnostic sensitivity in patients suspected of HFpEF who have normal estimated LV filling pressure at rest.[13] Therefore, a diastolic stress test can be added to the echocardiographic diagnostic approach in the setting of suspected HFpEF and normal resting LV filling pressure.

Imaging of left atrial structure and function

A comprehensive echocardiographic study requires assessment of LA volume, that should be performed using dedicated LA views, measured using the biplane disk summation technique, and indexed to body surface area (LAVi). Conventionally, maximum LA volume is reported. The upper normal limit for LAVi by 2D echocardiography is defined as 34 mL/m.[3]

Enlarged left atrium is frequent in patients with both HFrEF and HFpE and, as a marker of elevated LV filling pressure, is associated with increased cardiovascular risk.

If on a hand maximal LA volume is an adequate parameter to estimate the chronic effect of increased LV filling pressure on the LA, it shows scarce sensitivity in the detection of early raises of LV filling pressure.[11]

The main role of LA is to modulate LV filling and cardiovascular performance. For this purpose, LA works as reservoir during ventricular systole, when it receives blood from pulmonary veins and its volume increases, as conduit during early ventricular diastole, passively allowing the passage of blood into the ventricle, and as booster pump during late ventricular diastole, when it actively contracts to complete LV filling.

Recent findings have shown that combining LAVi with a sensitive LA functional parameter, such as LA reservoir strain leads to a significant increase in the rate of detection of LV diastolic alterations and elevated LV filling

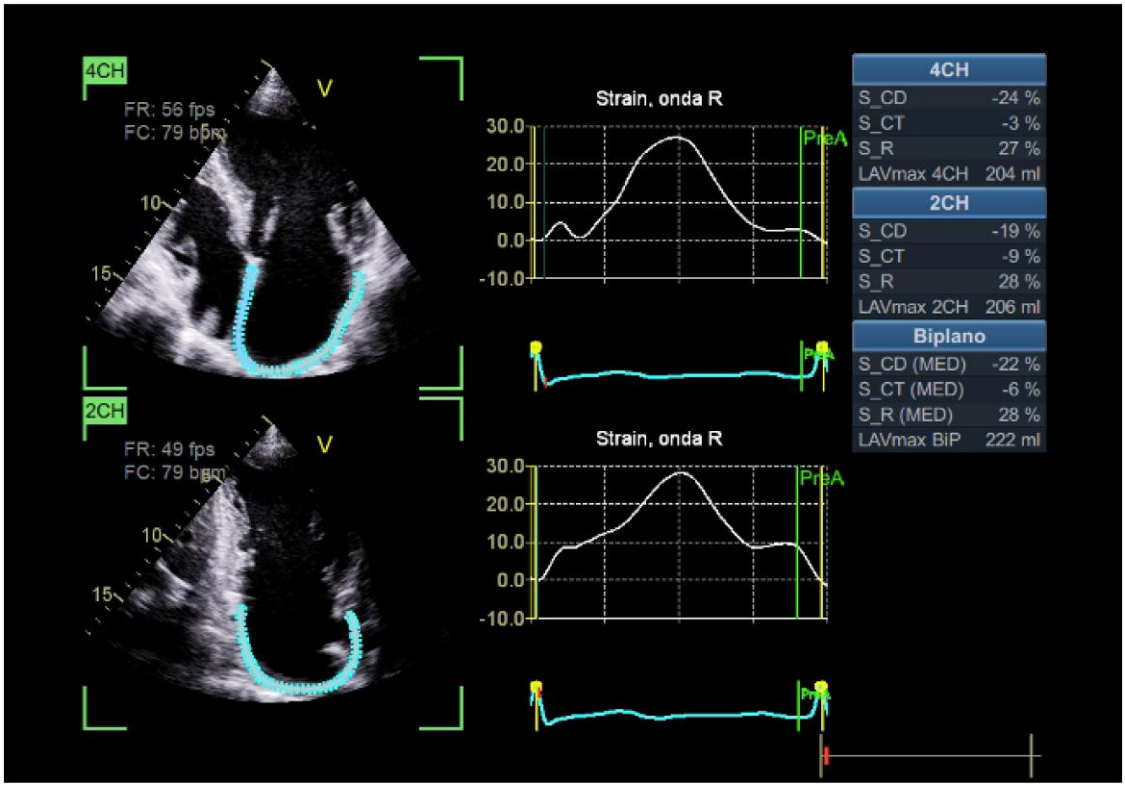

Figure 7 Peak atrial longitudinal strain (PALS) detects the maximum elongation of the LA during LV systole, at the end of the reservoir phase.

pressure than using only LAVi in patients with preserved EF.[14] Longitudinal strain curves are generated for each of the 6 atrial segments, obtained from apical 4– and 2-chamber views. Anyway, atrial curves show an opposite morphology than ventricular curves, since that atria and ventricles move in opposite directions during the cardiac cycle. Analogous to the concept of LVGLS, where longitudinal systolic myocardial deformation is quantified, peak atrial longitudinal strain (PALS) detects the maximum elongation of the LA during LV systole, at the end of the reservoir phase (*Figure 7*). Any condition with adverse eject on the LV longitudinal myocardial function will also reduce PALS. Severe LA wall remodelling, like in long-standing atrial fibrillation, leads to progressive LA fibrosis and dilatation, with reduced PALS. The mean value of PALS in healthy subjects is 42% and for LVGLS around 21%. LA reservoir dysfunction may reflect a diastolic dysfunction of the LA, likely caused by ischaemia. LA conduit dysfunction may be, rather, due to ischaemia-related LV compliance impairment during diastole. In patients with CAD and LA enlargement, even LA booster pump function, assessed during late diastole, is significantly impaired, likely due to several factors, such as LV compliance alteration, LV filling pressures elevation, LV systolic dysfunction, and LA myocardial injury. These findings may prove that LA diastolic dysfunction occurs prior to LA systolic dysfunction in patients affected by ischaemic heart disease.

Imaging of functional mitral regurgitation and myocardial dyssynchrony

Two-dimensional and three-dimensional assessment by transthoracic echocardiography (TTE) supplemented by transoesophageal echocardiography (TOE) are the methods of choice for imaging the pathognomonic changes to the mitral leaflets, annulus, chordae and papillary muscles in ischaemic functional mitral regurgitation (FMR).

In FMR, mitral leaflets are generally normal and the main determinant of the valve regurgitation is 'systolic tenting', with displacement of the leaflets coaptation point away from mitral annulus towards the LV cavity. This phenomenon, together with mitral annulus dilation and decreased LV contractility, generates an incomplete mitral valve (MV) closure.[15]

Different tethering vectors may generate different tethering patterns, depending on global or local LV remodelling. In particular, two typical echocardiographic patterns have been described: 'asymmetric' and 'symmetric', on the basis of the disposition of the mitral leaflets with respect to their point of coaptation (moved posteriorly and apically, respectively). In addition, LV dyssynchrony causes a less efficient myocardial fibres contraction reducing the closing forces, and increasing tethering force. In fact, in the context of LV dyssynchrony, two opposing myocardial segments contract with different timing during the same systolic phase. It can generate two effects increasing tethering forces. First, the compensative LV dilation due to dyssynchrony is a major determinant of increased tethering forces, since it displaces away PM with consequent lack of leaflets coaptation. Secondly, when one segment is contracting in advance of the not-yet-contracting opposite segment, it generates important tethering vector forces distorting MV apparatus. Also, AV dyssynchrony, with during diastole improper timing of AV relaxation-contraction cycles, may create a positive pressure gradient through the MV, generating diastolic MR.[16]

D'Andrea et al. evaluated the increase in LV dyssynchrony during exercise with the increase of FMR in patients with HF and narrow QRS. Sixty patients with some degree of FMR in the context of idiopathic dilated cardiomyopathy, in NYHA Class II–III refractory HF and narrow QRS interval (<120 ms) were studied by standard Doppler echo and colour Doppler myocardial imaging at rest and during stress.[17] The results showed a significant increase in intraventricular delay during stress with systolic dyssynchrony and a concomitant stress-induced increase in FMR. A subsequent prospective longitudinal study showed that echocardiographic dyssynchrony during exercise was the strongest predictor of adverse event even in patients with idiopathic dilated cardiomyopathy with narrow QRS.[17]

Imaging of mitral leaflets

Although the classical definition of FMR requires that the MV leaflets are normal, it is now known that changes occur in response to the stresses exerted upon the tented leaflets that counteract the loss of leaflet coaptation. These compensatory changes include progressive leaflet lengthening, thickening and fibrosis. 2D TTE is the main modality for anatomic assessment of leaflet thickness (normal or increased), motion (normal, restricted or increased) and presence and distribution of calcification (none, mild, moderate, severe). 3D TOE however, is the gold standard method for full assessment of the valve and scallops compared to surgical findings, and offers quantification of leaflet geometry throughout the cardiac cycle, with a surgical-like point of view (*Figure 8*).[18] Leaflet configuration can influence likelihood of successful surgical repair. The following configurations are shown to be predictors of failure of repair: Leaflet coaptation distance > 1 cm, tenting height > 6 mm, tenting area > 2.5 cm^2 on TTE and > 1.6 cm^2 on TOE and posterior leaflet angle > 45°. If these factors are present, this may influence the decision: mitral valve repair vs. replacement or whether intervention should proceed at all.

Imaging of mitral annulus

The normal mitral annulus is elliptical shaped in cross-section and saddle-shaped in three dimensions. The highest points are near the superolateral commissure while the lowest points are located at the base of P2 and P3. The annulus changes configuration throughout the cardiac cycle to maintain leaflet coaptation, from D-shaped in mid-systole to a more circular shape in early diastole, reducing annular area by 20–30% across the cardiac cycle. The annulus also moves away from the apex of the heart in diastole, although motion of the posterior aspect is more marked than the anterior annulus, and there is conformational change with accentuation of the saddle shape in systole. All of these movements are affected by ischaemia, which tends to reduce the dynamic change in area. These changes can be tracked by high spatial and temporal resolution imaging using 3D TOE (*Figure 9*).[15]

Selection for ventricular assist devices

In patients with refractory HF, the use of ventricular assist devices is increasing, not only as a bridge to heart

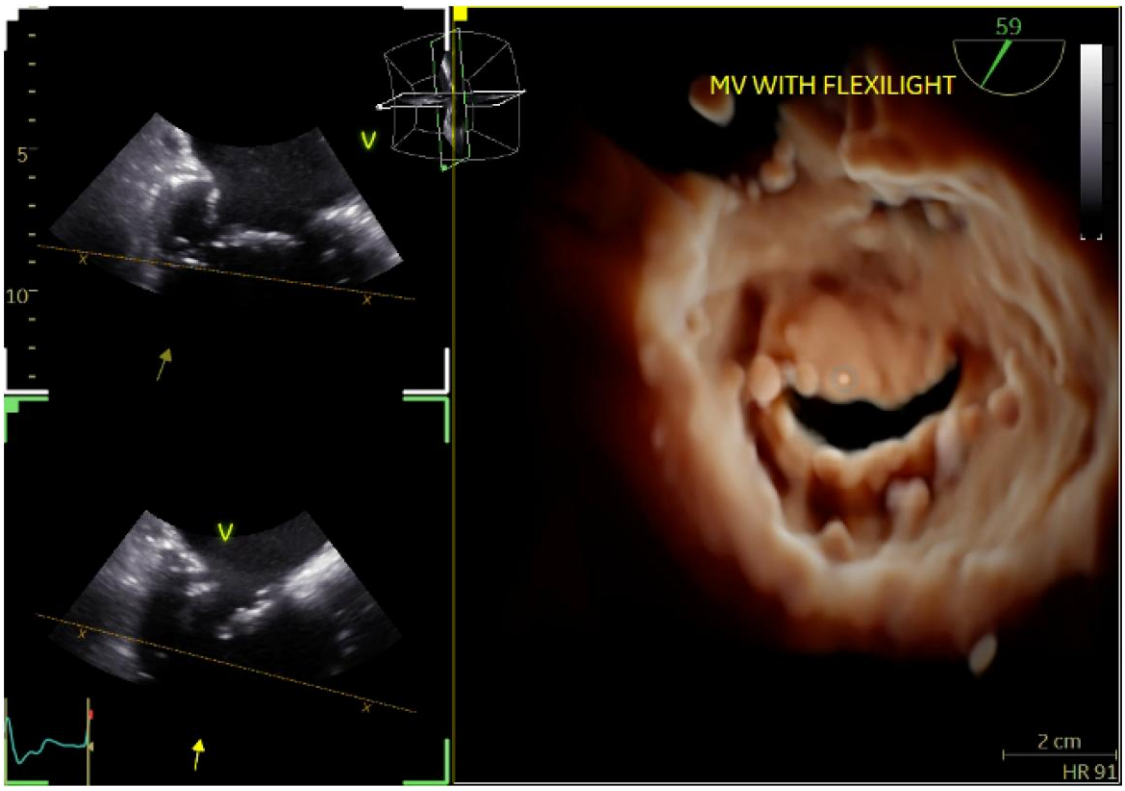

Figure 8 Three-dimensional TOE is the gold standard method for full assessment of the mitral valve and scallops compared with surgical findings and offers quantification of leaflet geometry throughout the cardiac cycle, with a surgical-like point of view.

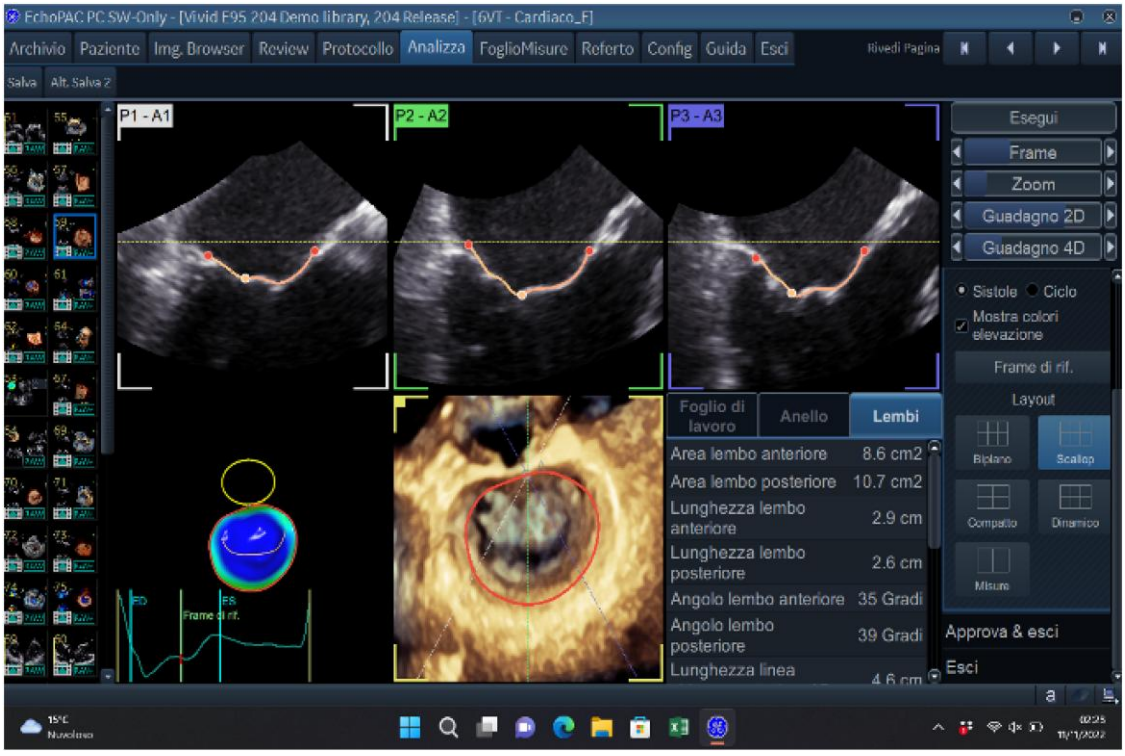

Figure 9 The mitral annulus changes configuration throughout the cardiac cycle to maintain leaflet coaptation, from D-shaped in mid-systole to a more circular shape in early diastole, reducing annular area by 20–30% across the cardiac cycle. All these changes can be tracked by high spatial and temporal resolution imaging using 3D TOE.

transplant but also as a destination therapy. In this context, the systolic function of the RV plays a critical role both in the selection of patients and in the prediction of the outcome after implantation. RV stroke work index (RVSWI), obtained with right cardiac catheterization, is considered the gold standard for evaluating RV function: its reduction is associated with the onset of RV insufficiency after implantation.[19] RV longitudinal strain (RVLS) of the free wall of the RV is able to predict a depressed RVSWI with high specificity and sensitivity[20]; patients with higher pre-implantation RVLS values undergo a progressive improvement in the deformation of VD.

Conclusions

Standard echocardiography as well other imaging modalities are essential for the management of patients affected by HF, due to their unmatched ability to combine safety with depth of diagnostic and prognostic information. The newer ultrasound technologies, which were developed over the past few decades, allowed us to better understand the morphofunctional abnormalities occurring in cardiovascular diseases. These technological advancements revealed to be promising to further expand the role of Imaging in HF diagnosis, risk stratification, management, and monitoring after cardiac pharmacological and electrical therapy, as well as after cardiac rehabilitation.

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Data availability

No new data were generated or analysed in support of this research.

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