Review

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The role of advanced multimodality imaging in chronic mitral regurgitation

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Abstract

Mitral regurgitation (MR), the second most common valvular heart disease, still constitutes a major diagnostic and therapeutic challenge, due to its complex nature and to its consequences on cardiac remodelling. Life quality and expectancy are determined by the irreversibility of the left ventricular systolic dysfunction, which, despite current guidelines, remains a major drawback. In order to accurately establish "the point of no return" for left ventricular systolic function, the embedment of clinical, biological and imaging data is a requirement. The purpose of this review is to provide an overview of the current multimodal imaging techniques that are useful in correctly assessing patients with MR. Cardiac magnetic resonance strain imaging techniques and 3D echocardiography, in addition to current echocardiographic criteria may help identify the patients who will benefit from early surgery. The technical development of new transcatheter techniques in mitral valve repair could lead to the extension of current guidelines.

Keywords: mitral regurgitation; echocardiography; cardiac magnetic resonance; modular imaging

Introduction

Mitral regurgitation (MR), the second most frequent valvular heart disease after aortic stenosis [1], remains an important cause of heart failure (HF), despite correctly applying current guidelines for mitral valve (MV) intervention and the advances made in the surgical and percutaneous repair techniques [2]. The main cause of persistent HF after MV surgery is represented by the prior development of irreversible left ventricular (LV) dysfunction, which makes correct assessment of LV remodelling paramount in choosing the moment for intervention [3].

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The indication for MR repairment is based on the symptom onset and echocardiographic assessment of MR severity and its consequences, especially on the LV size and systolic function [4,5]. The severity of MR is a key point, since only severe MR represents an indication for surgery. Choosing between early intervention and watchful waiting dictates a subsequent long-term prognosis of MR patients. Recent studies have focused on using non-invasive multimodality imaging in the early detection of subclinical LV dysfunction and on potential biomarkers for identifying specific patients which might benefit from an early intervention.

The presence of symptoms must not be a prerequisite for accurate assessment of MR severity and its consequences on LV function, since they are not correlated with the severity of the MR nor with LV function [3].

The MR evaluation is closely related to the understanding of the geometry and function of mitral annulus (MA), as well as their relationship with the left atrium (LA) dilation and LV function [6]. This is now possible with the progress of multimodality imaging through three-dimensional (3D) acquisition with high temporal

and spatial resolution using 3D echocardiography (3DE) or cardiac magnetic resonance (CMR), which allows detailed quantitative analysis of MA geometry and function [7] of both LV and LA.

The purpose of this review is to provide an overview of the current multimodal imaging techniques that are useful in correctly assessing patients with MR.

I. Chronic MR and LV remodelling

In order to choose from the different imaging modalities available, a better understanding of the cardiac remodelling due to chronic MR is required. Severe chronic MR determines an increase in LA volume and LV preload, while reducing the LV forward stroke volume [8]. LV responds to the increased preload by eccentric hypertrophy, with a serial increase in myocyte sarcomeres and myofibril slippage, leading to a compensation phase with preserved afterload [9]. However, LV hypertrophy does not fully compensate the wall stress; it increases the cardiomyocyte diameter and decreases their length in comparison to the physiologically loaded muscle, suggestive of parallel rearrangement of sarcomeres, due to inadequate protein synthesis triggered by MR [10], leading to progressive myocardial dysfunction, with LV dilation and increased LV wall stress [11]. The latter results in cardiomyocyte loss due to complex inflammatory and apoptotic pathways and also to the sliding displacement of cardiomyocytes, or cell slippage, caused by myocardial extracellular matrix (ECM) disruption –integrin linkages. Initial reactive reversible fibrosis secondary to volume overload, progresses in time to irreversible replacement fibrosis with its consequences on LV's function [11].

II. MR severity assessment

1. Echocardiography

Both ESC and ASE guidelines recommend using multiple echocardiographic qualitative, semiquantitative and quantitative parameters in assessing MR severity, due to the limitations of each of them (Table I) [5,12].

1.1. Qualitative assessment

Color flow Doppler is reliable in identifying mild MR with small, central jets but, in discriminating MR severity for larger or eccentric jets this technique is not reliable since the jet aria depends on MR's mechanism and it is linked to LA pressure, compliance and size, usually underestimating it [13]. The direction of the color Doppler jet may help identify the mechanism of the MR. In mitral valve prolapse, the regurgitant jet is pointing away from the prolapsed leaflet, while in secondary MR, due to tethering, the jet is pointing towards the restricted leaflet.

Continuous wave Doppler may be indicative of MR severity, with a high intensity Doppler envelope for severe MR and a faint signal or incomplete envelope for mild MR [13], but there are no criteria to differentiate between moderate and severe MR and the signal density depends on the spectral recording. However, eccentric jets are more difficult to evaluate compared to central ones.

1.2. Semiquantitative parameters

The semiquantitative parameters include VC width, pulmonary vein flow and mitral inflow.

VC is defined as the narrowest, highest velocity region of the regurgitant jet [13] and is located at or just below the regurgitant orifice. VC has shown to be correlated with the effective regurgitant orifice area (EROA),

Table I. Echocardiographic parameters for assessing mitral regurgitation severity [5,12, adapted]

	Mild MR	Moderate MR	Severe MR
Qualitative parameters			
Mitral valve morphology	normal/modified	normal/modified	mitral valve severe prolapse/flail; papillary muscle rupture or perforation
MR jet - Color Doppler	small, central	intermediate	large, central/ eccentric
Proximal convergence area	absent/small	intermediate	large
Continuous wave Doppler	low signal, parabolic shape	parabolic shape	high intensity, triangular shape
Semiquantitative parameters			
Vena contracta (mm)	<3	3-6	≥7
Pulmonary venous flow	dominant S wave	low velocity S wave (S<D)	systolic flow reversal
Mitral Doppler inflow	dominant A wave	variable	dominant E wave (>1.5 m/s)
Mitral VTI/ Aortic VTI	<1	intermediate	>1.4
Quantitative parameters			
EORA (mm2)	<20	20-39	≥40
RVol (ml)	<30	30-59	≥60

MR, mitral regurgitation; VTI, velocity-time integral; S, systolic; D, diastolic; EORA, effective orifice area; RVol, regurgitant volume

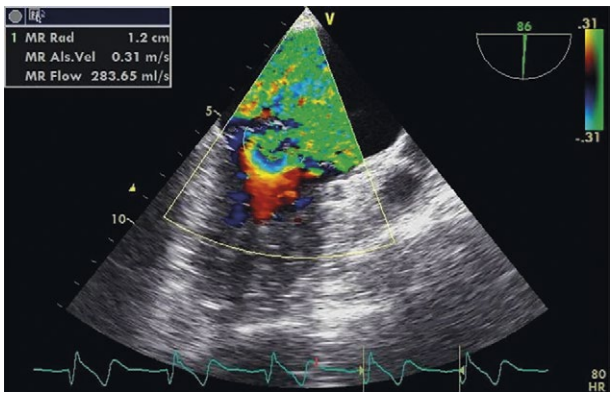

Fig 1. Representative TOE-based PISA of a 59 year old patient with severe primary mitral regurgitation due to severe Barlow's disease. Acquisition of PISA radius and continuous wave Doppler of the MR jet allows calculation of the EROA. EROA, effective regurgitant orifice area; MR, mitral regurgitation; PISA, proximal isovelocity surface area; 3D-TOE, three dimensional transoesophageal echocardiography

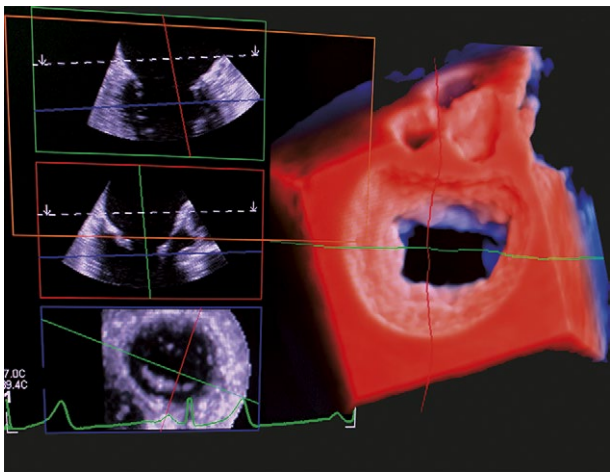

Fig 2. Illustrative image with a3D-TOE image - atrial view (EPIQ CVx) - of a severe degenerative mitral regurgitation in a 73 year old female patient.3D-TOE, 3-dimensional transoesophageal echocardiography

even for eccentric jets or acute MR, but it is not valid for multiple jets [13,14]. VC width should be measured in a long axis plane perpendicular to the mitral leaflet. Current recommendations classify a MR as mild when VC <3 mm and severe when VC >7 mm. For the intermediate values (3-7 mm) additional quantitative parameters, such as the proximal isovelocity surface area (PISA) method, are required [12].

Pulmonary venous systolic flow reversal or reduced systolic velocity in more than one pulmonary vein suggest severe MR, but when the MR jet is directed away from the pulmonary vein, such as in an eccentric MR with a dilated LA, flow reversal may be absent. Nevertheless, a small eccentric jet directed towards the pulmonary vein may also cause blunted or reversed flow [13].

Interrogating mitral filling pattern by pulse wave Doppler, a *peak mitral E wave velocity* >1.5 m/s (in the absence of mitral stenosis) indicates severe MR, whereas a dominant A wave excludes it. The regurgitant index, a mitral to aortic velocity-time integral (VTI) ratio by pulse Doppler >1.4 indicates severe MR [12].

1.3. Quantitative assessment of MR severity

The quantitative assessment of MR severity is based on the hydrodynamic principles of the non-compressibility of blood and mass conservation. The use of quantitative parameters is recommended by all current guidelines [4,5] and includes measurements of mitral *regurgitant volume* (RVol) (ml/beat)**,** *mitral regurgitant fraction* (RF) (the percentage of total LV stroke volume represented by the regurgitant volume), as well as *EROA* (the mean area of systolic regurgitant orifice).

Calculation of RVol and RF is based on the difference of the stroke volume across the MV and the aortic stroke volume (in the absence of significant aortic regurgitation) [13]. Stroke volume is calculated as the cross section area x VTI, making the geometrical assumption that both the mitral and the aortic area are circular. However, small errors in diameter measurements may result in important mismatches in cross sectional areas determination [13]. A RVol ≥60 ml for primary MR, respectively a RF ≥50% indicates severe MR, whereas RVol <30 ml and RF <30% suggest mild MR. The cut-offs for secondary MR are lower (30 ml for RVol).

The EROA is measured by the proximal isovelocity surface area (PISA) method, which is based on the convergence of flow proximal to the regurgitant orifice, observed by color Doppler, resulting in a concentric isovelocity surface area. By measuring the radius of the convergence area, assuming PISA is a hemisphere, and using CW Doppler of the MR jet, EROA is calculated (fig 1). An EROA <0.2 cm^2 indicates mild MR and an EROA over 0.40 cm^2 correlates with severe MR. This method has several limitations: being an instantaneous calculated measurement, PISA-based EROA does not reflect the average regurgitant orifice throughout the regurgitant phase [12] and it assumes that the PISA shape is hemispheric. In some cases, the PISA shape is no longer hemispheric and applying this method will estimate badly the regurgitant flow. Similar to VC, PISA is not feasible for MR with multiple jets.

1.4. Role of 3D echocardiography in assessing MR severity

3DE ensures the evaluation of both atrial and ventricular aspects of the MV. It allows the detailed assessment of the MV apparatus, the geometry and measurements of the MV annulus (diameter, area and dynamics), the

measurements of its leaflets (length, area, volume and height of prolapse) and, in functional MR, the calculation of the mitral tenting (distance and volume) [9,14]. The "en face" visualization of the MV permits accurate measurements of the VC area in a short axis view and a direct measurement of the anatomic regurgitant orifice area, as well as improved accuracy of the EROA calculation by avoiding geometric assumption due to direct visualization of PISA. Regardless of MR's etiology, a 3DE VC area of 0.41 cm² defines severe MR. 3DE also allows accurate quantification of stroke volume along the entire cardiac cycle (fig 2) [15]. Comparison between 2D versus 3DEparameters has shown that RVol is underestimated by 2DE, especially in eccentric jets and asymmetrical regurgitant orifice [16].

2. CMR in assessing chronic MR

CMR compared to echocardiography has lower spatial and temporal resolution, which makes it difficult to detect vegetations and provides suboptimal assessment of the subvalvular mitral apparatus [17]. Dedicated cine images can assess MV morphology and identify prolapse or flail segments [18]. Imaging the MV in three planes according to the coaptation of the individual scallops, CMR is able to identify the site of regurgitation or prolapse. There are several studies comparing 2D TTE or 2D transesophageal echocardiography (TOE) with CMR in terms of identifying MV prolapse [19] with promising results but with lower spatial resolution for CMR.

Using the native contrast between the blood pool and the myocardium in the steady state free procession (SSFP) imaging and the possibility to choose the imaging plane independent of body habitus, CMR is able to evaluate MR independent of the jet characteristics that limit echocardiography. A basal short slice axis through the MV commissure is used to plan subsequent imaging planes. Two techniques are employed for MR quantification by CMR: SSFP imaging for LV forward volume and phase contrast imaging for LV forward volume. Unlike echocardiography, which requires the integration of multiple parameters in assessing MR severity, CMR relies on quantitative parameters, mainly RVol and RF [12,20].

Direct planimetry of the anatomical orifice area from cine images can be performed [21,22], but it is a laborious technique that requires correct plane alignment and angulation. An EROA ≥40 mm² carries prognostic value and has been proposed as an indication for surgery [23].

Quantitative assessment of mitral RVol is the preferred method and can be derived using direct or indirect techniques [24].

The indirect approach is preferred by calculating mitral RVol as the difference between LV stroke volume and aortic forward volume (LV stroke volume is calculated from de short axis cine-SSFP stack). The aortic forward volume is obtained from the phase-contrast velocity encoded cine-SSFP images (fig 3) [24]. This is a reproducible method, not affected by the eccentricity and direction of the regurgitant jet, the concomitant aortic regurgitation or geometrical assumptions [24]. Another indirect method used to calculate RVol is represented by the difference between LV and right ventricular (RV) stroke volumes (SV), but this is not applicable in the case of multiple valvular lesions [24].

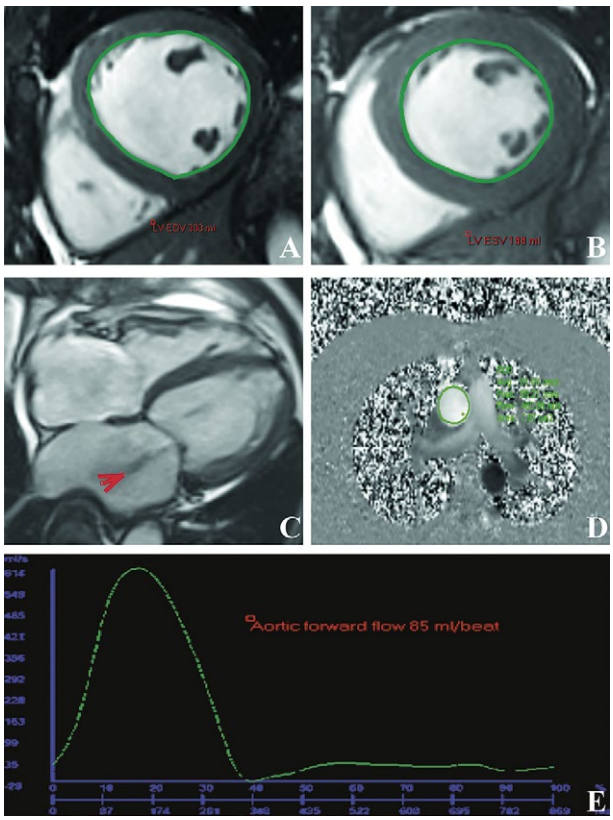

Fig 3. Representative CMR for indirect assessment of mitral regurgitation in a 54 year-old female patient with NIDCM. LVEDV (A) and LVESV (B) are evaluated using short-axis by cine-CMR imaging, and LVEF and LVSV are calculated: LVEF = 37.95% and LVSV = 115 mL/beat. The regurgitation jet is central, being visualized in long-axis by cine-CMR imaging CMR (C). The aortic flux is calculated using phase-contrast CMR imaging (D), having a value 85 mL/beat (E). Further, the RVol and RF are calculated: RVol = (LVSV-Aortic flux) = 30 mL/beat; RF = RVol/LVSV = 26%. CMR, cardiac magnetic resonance; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; LVSV, left ventricular stroke volume; NIDCM, non-ischemic dilated cardiomyopathy; RVol, regurgitant volume; RF, regurgitant fraction

The CMR cut-off values for MR severity have not been yet established. Studies comparing CMR to echocardiography show a tendency to overestimate primary

MR's severity by TTE [25]. Uretsky et al found that RVol/RF quantified by CMR were better predictors for post-surgical LV remodelling rather than by those derived by TTE, and may better predict the need for surgery [25]. Prospective studies have suggested a lower limit for RVol calculated by CMR, with a severe MR defined as RVol>55 ml and RF>40%.

Nonetheless, the usefulness of CMR in MR has been challenged in small, single center studies, but they have reported excellent reproducibility and lower interobserver variability when compared with TTE [25,26]. It remains to be established whether CMR severity parameters measured need to be used for surgical intervention and to standardize the cut-off values for these parameters.

Recently, 4D flow CMR has been supported in quantifying mitral RVol [27]. 4D flow presents several advantages over conventional multiplanar CMR, mainly that it can be prescribed as a single volume acquisition that covers the entire heart and enables direct quantification of regurgitant jets with a single measurement.

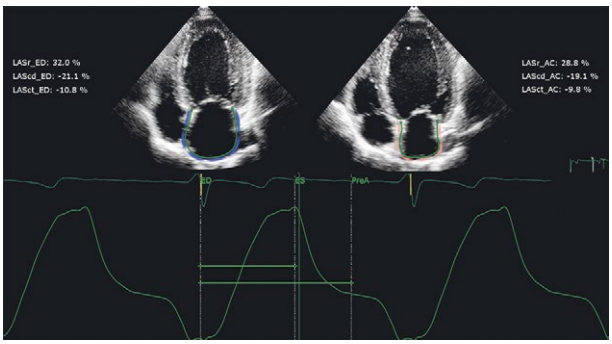

Fig 4. Representative image of LA phasic function by strain method using STI in a 65 year old male patient with moderate degenerative mitral regurgitation and diastolic dysfunction. LA longitudinal strain in apical 4-chamber view performed at LA volume at LV end-systole (ES) and at pre-atrial contraction LA volume (PreA) shows a decrease in LA reservoir, conduit and contraction strain, confirming diastolic dysfunction (EPIQ CVx).ES, end-systolic; LA, left atrium; LAScd, left atrial conduit strain; LASct, left atrial contraction strain; LASr, left atrial reservoir strain; LV, left ventricle; PreA, pre-atrial contraction; STI, speckle-tracking imaging

III. Imaging modalities for assessing cardiac remodelling in chronic MR

1. Echocardiography

1.1. Cardiac chambers dimensions

TTE is recommended for serial measurements of cardiac chambers dimensions and LVEF, every 6-12 months for patients with severe MR and preserved LVEF [5]. In current ESC guidelines [5], a dilated LA >60 ml/m^2 is IIA class indication for MV surgery. Reflecting LV dysfunction and, in consequence, a poor prognosis, an increase in LV end-diastolic diameter (LVEDD) >40 mm and a LVEF <60% are considered as class I recommendation for surgery even in asymptomatic patients.

1.2. Mitral annulus dynamics and left atrial dysfunction

The risk of recurrence of MR after MR repair is linked to the progression of the MA disease [28]. Currently, antero-posterior MA diameter measured by 2D TTE in PSLAX view, with a cut-off value of 35 mm, is used as an indication for annuloplasty and is a predictor for successful MV repair [29]. MV annulus is a dynamic 3Dstructure which can be best assessed by 3DE [30,31]. Dedicated software measures several parameters of the MA, such as antero-posterior diameter, commisural diameter, circumference, height, and nonplanarity angle. MA is a highly dynamic structure, with three types of movement: "contraction" - reduction of MA area influenced by LA and LV surrounding structures, displacement with the movement of the LV base and folding across its axes, which is essential for leaflet coaptation [32,33].

In patients with primary MR, 3DE studies have shown that MA has an increased antero-posterior diameter, area, circumference and sphericity during the entire systole, and also is more planar [34]. The contraction of the MA area and diameters is decreased and delayed in patients with primary MR [34]. In patients with preserved LVEF, there is a decreased area of MA contraction, but preserved displacement, and the saddle shape conformation progressively flattens towards end systole [34].

In patients with chronic MR, LA global longitudinal strain (LA GLS) depends on the severity of the MR, with supra normal increase of LA GLS in mild MR, to strongly decreased LA GLS in severe MR and severely decreased values in patients with paroxysmal atrial fibrillation (fig 4) [35].

3DE studies have shown that MA diameter correlates with both LA and LV volumes, but there was no correlation between the MA and 3DE measured LVEF and all strain parameters of the LV by 2DSTE [35]. MA displacement showed a week correlation with LV global longitudinal strain (LV GLS). MA area reduction was associated with both maximal and minimal LA volumes by 3DE, total and active LA emptying fractions and longitudinal LA strain and strain rate by 2DSTE [32]. MA area correlated with MR severity parameters: PISA radius, EROA and the posterior leaflet area correlated with PISA radius, whereas MA fractional area chance was inversely correlated with all quantitative MR severity parameters [34,36]. MV flail, has been shown to be associated with MA's contractile dysfunction, but not with its sizwe [34].

LA and MA remodelling parameters assessed by 3DE may be used as markers of MR severity, but their role in selecting patients for early surgery are not yet established in current guidelines.

1.3. LV systolic function

Echocardiographic measured LVEF, the established parameter by the guidelines for LV systolic function and a strong predictor for mortality in MR, can remain preserved for a long period of time, even though the LV's contractility is significantly reduced [37]. Therefore, to accurately assess LV function, complementary imaging modalities are needed.

1.4. Tissue Doppler imaging, strain and strain rate

Because the LVEF is an afterload dependent parameter, it remains within the normal range even after LV dysfunction occurs [37]. Vinereanu et al showed that alterations in subendocardial fibres may constitute the mechanism of early LV dysfunction in chronic volume overload [38]. Agricola et al have demonstrated that LV longitudinal function assessed by tissue Doppler imaging measured mitral annular velocities is a more accurate marker for LV contractility and is associated with reduced contractile reserve of the LV and postoperative dysfunction after surgical repair in asymptomatic MR patients with LVEF >60% [39]. The systolic velocity of the septal MA assessed by TDI was found to be the only predictor of significant reverse remodelling, reflecting both longitudinal contraction and torsional movement [40,41], data also confirmed for secondary MR [42].

LV GLS was also studied for the quantitative assessment of LV contractile function, as a more sensitive marker than LVEF. Lancelloti et al assessed the reliability of strain imaging in identifying subnormal LV reserve during exercise in 71 asymptomatic patients with severe mitral regurgitation and they found that limited LV longitudinal contractile recruitment predicts postoperative LV dysfunction [41]. Furthermore, Alashi et al found that the combined use of LV GLS and brain natriuretic peptide (BNP) was associated with persistent postoperative LV dysfunction and increased mortality, independent of other clinical or echocardiographic parameters [43].

Using speckle tracking to evaluate LV reverse remodelling after MR surgery, Pandis et al found a rapid postoperative cardiac improvement, with an initial recovery of LV torsion within the first 4 to 6 weeks, followed by an improvement in longitudinal strain (fig 5) [44].

2. Cardiac magnetic resonance imaging

CMR is currently the gold standard imaging method for the evaluation of cardiac chamber dimensions, ventricular volumes and ejection fractions [41,42]. Some studies suggest that focal fibrosis should be used as an early marker of LV dysfunction [45]. The current CMR techniques for identifying fibrosis are late gadolinium enhancement (LGE) and T1 mapping.

LGE is a technique used for detecting replacement fibrosis, as gadolinium contrast agents provide a clear contrast between healthy myocardium and areas of focal extracellular matrix expansion, with slower wash out. The pattern of LGE may offer diagnostic and prognostic information, multiple studies having shown a LGE as an independent predictor of all cause and cardiovascular mortality [46]. A subendocardial pattern is suggestive of myocardial infarction, a mid-wall pattern suggests dilated cardiomyopathy, whereas subepicardial fibrosis suggest myocarditis (fig 6).

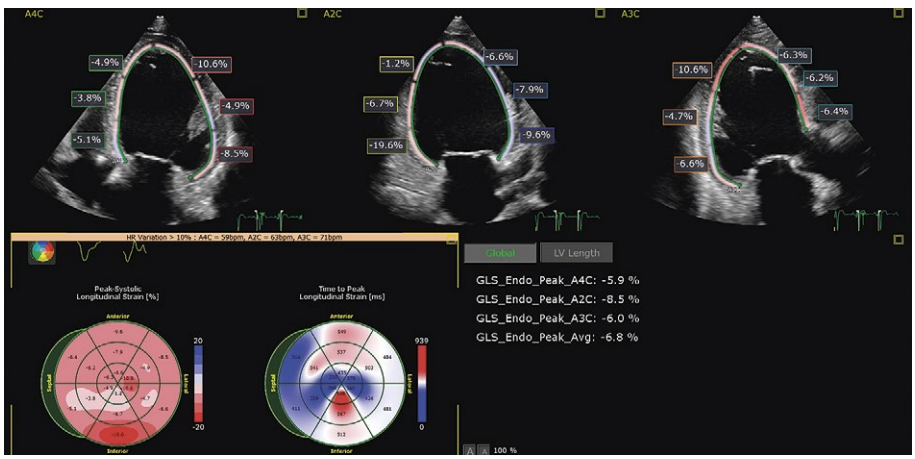

Fig 5. Illustrative image of LV global and regional strain in a 59 year-old female patient with NIDCM and severe functional mitral regurgitation with anterior leaflet asymmetric tethering. Global longitudinal strain performed in apical 2, 3 and 4 chambers by 2D-TTE shows a significantly decreased systolic function (EPIQ CVx). 2D-TTE, 2-dimensional transthoracic echocardiography; GLS, global longitudinal strain; LV, left ventricle; NIDCM, non-ischemic dilated cardiomyopathy

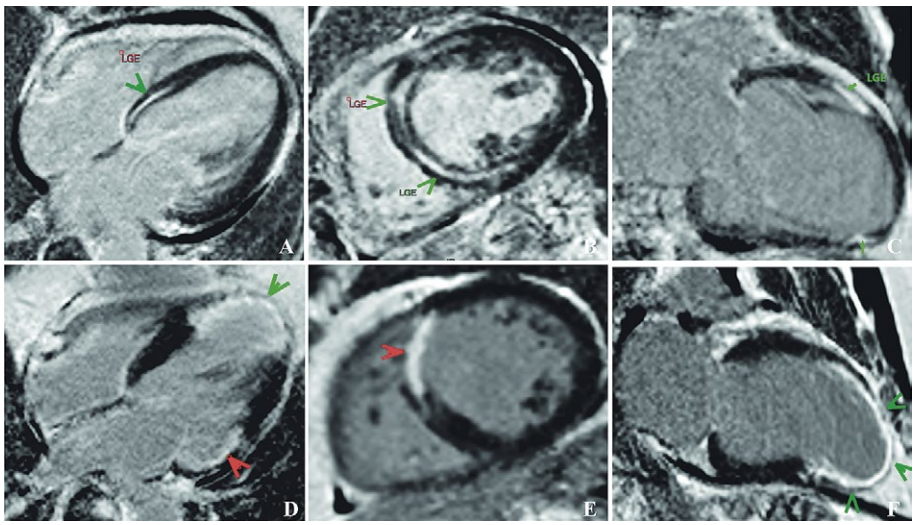

Fig 6. Representative CMR images for comparing myocardial fibrosis patterns. In myocarditis-related myocardial fibrosis, LGE usually has a LV mid-wall pattern (A, B, C), while after myocardial infarction the LGE pattern is subendocardial (D, G, E). CMR, cardiac magnetic resonance; LGE, late gadolinium enhancement; LV, left ventricle

Unlike LGE, *T1 mapping techniques* assess the extracellular compartment, and provide a noninvasive, load independent method of calculating myocardial extracellular volume, which strongly correlates with the histological collagen volume [45]. T1 mapping, in addition to feature tracking techniques, have been used to demonstrate significantly higher values of T1 and have reduced average radial and longitudinal strain in the basal and mid inferolateral wall in patients with severe MR by MV prolapse with indication for surgery [47].

Studies correlating T1 mapping in primary MR and arrhythmic risk have suggested an increased risk for ventricular arrhythmia in the presence of fibrosis. The importance of myocardial fibrosis in primary MR outcome is not yet established, but several studies have suggested a negative prognostic impact [47,48].

It has been shown that in asymptomatic patients with moderate-severe MR there is a higher ECV on CMR versus controls [46] and almost a third of the patients with MR presented a noninfarct pattern of scar on LGE. Fibrosis of the papillary muscle by LGE was described at 63% of patients with MV prolapse and the presence of fibrosis on LGE correlated with worse clinical outcomes [48].

It is also possible to evaluate atrial fibrosis by LGE techniques. LA fibrosis has been demonstrated to increase the risk for atrial fibrillation development. MR may increase LA volume, resulting in LA remodelling. There have been studies showing an association between the presence of MR and LA LGE score and LA volume, but without a direct association with MR fraction, possibly due to the small sample size [49,50]. Future larger cohort studies are required to establish the relationship between MR and LA fibrosis and its prognostic implications.

IV. Multimodality imaging in mitral regurgitation: future directions

In the presence of challenging clinical scenarios and suboptimal long-term prognosis of patients with MR, despite current guidelines, there is increasing evidence that a multimodality imaging strategy is required both for diagnosis and therapeutic strategy planning. 2DE, due to its availability, remains the principal tool in assessing MR patients, but 3DE and tissue Doppler techniques must be used to refine management and select candidates for early surgery. CMR as a valuable tool for tissue characterization should be used for identifying early LV dysfunction and fibrosis. Further studies are needed to establish the CMR cut-off values for MR severity and the prognostic implications of early fibrosis. The data on MA and LA, best assessed by 3DE and strain imaging techniques (both echo and CMR), are of paramount importance in guiding MR repair and predicting the risk of recurrence and postintervention atrial fibrillation.

Conflict of interest: none

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