REVIEW

Left atrial fibrosis: an essential hallmark in chronic mitral regurgitation

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Abstract: Chronic mitral regurgitation (MR) is the second valvular heart disease for incidence, which worsening severity gradually affects all cardiac chambers and leads to poor outcome if untreated. The recent development of minimally invasive surgical techniques and percutaneous intervention has reduced the operative risk, allowing a more confident referral of these patients for intervention. Therefore, there is a growing need of reliable markers to select the best therapeutic strategies and to identify the optimal timing for intervention. Myocardial fibrosis (MF) gradually occurs as a result of left atrial and ventricular (LA and LV) remodeling due to MR pressure and volume overload. It has been identified as an index of clinical outcome and arrhythmic risk in patients with MR. Particularly, the assessment of LA fibrosis not only allows to define different MR etiology, but also was associated with prognosis and atrial fibrillation (AF) burden. Nowadays, noninvasive estimation of MF is possible through the use of advanced imaging modalities, particularly cardiac magnetic resonance and speckle tracking echocardiography. This review discusses the role of LA fibrosis as a diagnostic and prognostic marker in patients with MR and its quantification by noninvasive multimodality cardiac imaging.
Keywords: left atrial, fibrosis, mitral regurgitation, speckle tracking, cardiac magnetic resonance.

Rezumat: Regurgitarea mitrală cronică (MR) este a doua boală cardiacă valvulară ca incidență, care se agravează progresiv si afectează treptat toate cavitatile cardiace cu prognostic sever în cazul netratării acesteia. Dezvoltarea recentă a tehnicilor chirurgicale minim invazive și a intervențiilor percutanate a redus riscul operator, permițând o selectie mai sigură a acestor pacienți pentru intervenție. Prin urmare, este nevoie de markeri fiabili pentru a selecta cele mai bune strategii terapeutice și pentru a identifica momentul optim pentru intervenție. Fibroza miocardică (MF) apare treptat ca urmare a remodelării atrialei și ventriculare stângi (LA și VS) din cauza presiunii MR și a supraîncărcării de volum. A fost identificat ca un indice de prognostic clinic și al riscului aritmic la pacienții cu MR. În special, evaluarea fibrozei LA nu numai că permite definirea diferită a etiologiei MR, dar a fost asociată și cu prognosticul și evoluția fibrilației atriale (FA). În zilele noastre, estimarea neinvazivă a MF este posibilă prin utilizarea unor modalități avansate de imagistică, în special rezonanța magnetică cardiacă și ecocardiografia speckle tracking. Acest review discută rolul fibrozei LA ca marker de diagnostic și prognostic la pacienții cu MR și cuantificarea acesteia prin imagistica cardiacă multimodală neinvazivă.
Cuvinte cheie: atriala stângă, fibroză, insuficiență mitrală, speckle tracking, rezonanță magnetică cardiacă.

INTRODUCTION

Chronic mitral regurgitation (MR) is the second most common valvular heart disease, due to primary (organic) or secondary (functional e.g. post-ischemic or dilative cardiomyopathy) etiology involving the mitral valve (MV). It is characterized by progressive worsening of severity and poor long-term prognosis if untreated, in terms of worse survival, quality of life and increased burden of atrial fibrillation (AF) and heart failure (HF) symptoms[1,2].

The advances in MR treatment, with the development of minimally invasive surgical techniques and percutaneous intervention, have led to a reduction in the operative risk parallel to a more confident referral

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of these patients for intervention[3]. Therefore, there is a growing need of reliable markers to accurately assess the optimal timing of surgical/percutaneous intervention.

Myocardial fibrosis (MF) is a maladaptive remodeling process which gradually occurs in cardiac chambers in response to different pathologic conditions causing direct or indirect cardiac injury. These include chronic MR, where MF could develop before the appearance of symptoms and other criteria for surgery[2]. It is the result of excessive activation of cardiac fibroblasts with high extracellular matrix deposition which leads to the lysis of myofibril and cardiomyocytes. Although the gold standard technique for the detection of MF still remains myocardial biopsy, other imaging techniques have recently been focused on the evaluation of MF[4,5] not only for the study of ischemic or non-ischemic cardiomyopathies, but also for a further characterization of cardiac damage and arrhythmic burden in patients with MR.

This review aims to highlight the usefulness of left atrial (LA) fibrosis as a key element for diagnostic and prognostic evaluation in patients with MR and to provide information on its quantification by noninvasive multimodality cardiac imaging.

Pathophysiologic background of LA fibrosis

MF arises as an adaptive process of remodeling; however, it often ends up with the distortion of myocardial architecture and the loss of myocytes, either by apoptosis or necrosis, with severe impairment of contractile function[6]. This could be primary, deriving from genetic or non-genetic causes (including dilated, hypertrophic and arrhythmogenic cardiomyopathies) or secondary to myocardial damage as in myocarditis, valvular heart disease or myocardial infarction.

The LA has an essential role both in guaranteeing a correct left ventricular (LV) filling during each diastole and in preserving pulmonary veins from volume and pressure overload. Because of its peculiar anatomy and thin walls, LA is extremely sensitive to internal and external stressors. In case of sustained atrial tachycardia, such as chronic AF, or pressure-and volume overload, as in HF or chronic MR, the diastolic dysfunction and the increase in LV filling pressures are responsible for LA maladaptive remodeling and fibrosis, which chronically lead to LA enlargement and lower distensibility[7,8].

Particularly, a transformation of the wall environment, with the activation of inflammatory cells and cytokines, takes place, causing a marked proliferation of cardiac fibroblasts and the production of collagen and other extracellular matrix (ECM) proteins[9]. Since ECM surrounds myocytes and vasculature cells as a scaffold and controls biochemical signals, its expansion causes excessive LA fibrosis with myofibril lysis and loss of intercellular junctions.

This process makes electric impulse propagation between atrial myocytes slower and favors re-entry circuits with the occurrence of AF[10]. On the other hand, when contractile and elastic fibers are replaced by fibrotic tissue, LA gradually loses its compliance, becoming uncapable to sustain chronic volume overload, as in MR. This will reflect to pulmonary circulation and finally right heart, with severe prognostic consequences if left untreated[11].

LA fibrosis in acute vs chronic mitral regurgitation

Acute mitral regurgitation (MR) is a medical and surgical emergency which usually presents with severe decompensated HF. This is due to the sudden pressure and volume load imposed on the LA. Physical examination is often inconclusive because of the severely deteriorated hemodynamic conditions leading to a soft or absent murmur. In fact, it is often misdiagnosed as acute pulmonary disease in the emergency department[12].

Thus, in doubtful cases, echocardiography should be performed as first-line exam for differential diagnosis; however, if unknown MR is found, one should determine if the trigger of hemodynamic deterioration is acute MR or if there was a pre-existing MR. First of all, normal dimensions of cardiac chambers and eccentric jets suggest an acute etiology of the mitral disease; however, these are non-specific signs. Obviously, the presence of endocarditis or papillary muscle head/tendineae chordae rupture will be conclusive, but if these signs are absent, indirect but more specific indices should be investigated. The assessment of LA fibrosis may be of help in these cases, since, due to the rapidity of the raise in LV filling pressures in acute severe MR, there is not enough time for LA remodeling for adaption to the new hemodynamic conditions, and hence, the high intracardiac pressures reflect backwards leading to pulmonary edema[12]. Therefore, the evaluation of presence/absence (or high/low grades) of LA fibrosis with quick and reliable techniques could be paramount to solve any doubt about acute or preexisting MR also in the emergency setting. Advanced echocardiographic techniques, such as speckle-tracking echocardiography (STE), could offer a noninvasive and easy assessment of the grade of LA fibrosis in these

cases, since it is performed using common 2D-scale echocardiographic images. However, even though its predictive role on LA fibrosis in chronic MR has been established, there is a lack of evidence on its use to assess LA fibrosis in acute MR.

On the other hand, in chronic MR several degrees of MF according to the etiology and stage of mitral disease can be found. As concerning LA, this could be either associated with LA enlargement („LA structural remodeling", characterized by considerable LA dilatation) or not („LA functional remodeling", characterized by subtle ultrastructural modifications, leading to impaired function and pro-arrhythmic state without overt LA dilatation)[13]. In fact, previous models showed the existence of several LA ultrastructural changes in relation to LA dilation due to chronic MR[14]. Moreover, Mary-Rabine et al. used intra-operative myocardial biopsy to prove an impaired contraction of the atria in patients with MR undergoing cardiac surgery due to myolysis and an imbalance in collagen synthesis and degradation[15].

LA fibrosis in primary vs secondary mitral regurgitation

Primary or „organic" MR is due to intrinsic valvular disease, whereas secondary or „functional" MR is caused by regional and/or global LV remodeling without structural abnormalities of the mitral valve, or by functional remodeling of the LA due to chronic AF, the so-called „atrial functional MR"[16].

These etiologies differ in the timing of establishment of MF in the two left heart chambers. However, the important thing is that MF of both chambers could occur before the appearance of symptoms, and that these structural changes of the myocardium may be associated with subtle functional abnormalities[17].

In particular, according to the natural history of the disease, the LA is the first affected chamber from primary MR overload, consequently, it is the first chamber to develop maladaptive remodeling and fibrosis. The LV is usually involved in the advanced phases of the disease, when LA is no more capable to compensate for volume overload and dilates; as a result, LV is overwhelmed by higher filling blood volumes and pressures as well and gradually remodels, providing a considerably higher risk of malignant arrhythmias (especially in patients with MV prolapse[18]).

Conversely, in patients with secondary „functional" MR due to the traditionally known etiologies of LV ischemia or dilatation, the LV is the target chamber for myocardial injury and fibrosis (in terms of a "scar" in ischemic cardiomyopathy and of gradual fibrosis in case of dilated cardiomyopathy), while LA gradually develops MF as a consequence of newly established chronic MR[19]. Finally, patients with „atrial functional MR" will already have a certain grade of LA fibrosis when MR occurs, according to the preexistence and duration of AF itself[20,21]. This will chronically increase, and LV fibrosis will occur later as in primary MR, but all the above mentioned steps will be anticipated due to an already-damaged LA.

Accordingly, in a biopsy study, Foglieni et al. found early cellular and interstitial alterations in LA tissue in patients with chronic MR and sinus rhythm which were analogous to patients with AF, and their grade was increasingly higher in patients with LA dilatation[22].

These considerations overall suggest that the study of left heart fibrosis as additional element in patients with MR of unknown or mixed classification would help us to correctly define the etiology and the stage of the disease based on the grade of MF involving the LA and the LV, and to identify subtle cardiac dysfunction before the development of symptoms. This would have important prognostic and therapeutic implications; thus, more evidence is warranted to support these hypotheses. Figure 1 attempts to represent the expectable findings as concerns MF of the left heart chambers according to the respective time of establishment based on different etiologies of chronic MR.

Prognostic role of LA fibrosis in chronic mitral regurgitation

The assessment of LA fibrosis has been associated with the presence of heart disease and arrhythmias, including congestive HF and AF[23,24].

Daccarett et al. investigated the link between progressive LA remodeling and prognosis, showing the correlation between stroke and high levels of LA fibrosis detected by delayed enhancement CMR in patients with AF[25].

Interestingly, Kitkungvan et al. studied the presence of MF detected by cardiac magnetic resonance (CMR) in 424 patients with primary MR (229 of whom with MV prolapse), founding that diffuse interstitial fibrosis was associated with MR severity, regardless of primary MR etiology, and that its extent was independently associated with symptoms related to MR and clinical events[26].

LA strain by STE has shown to be a reliable marker atrial fibrosis. Thus, some Authors studied its potential prognostic role in patients with MR, reaching interesting results. In fact, a reduced LA strain has shown

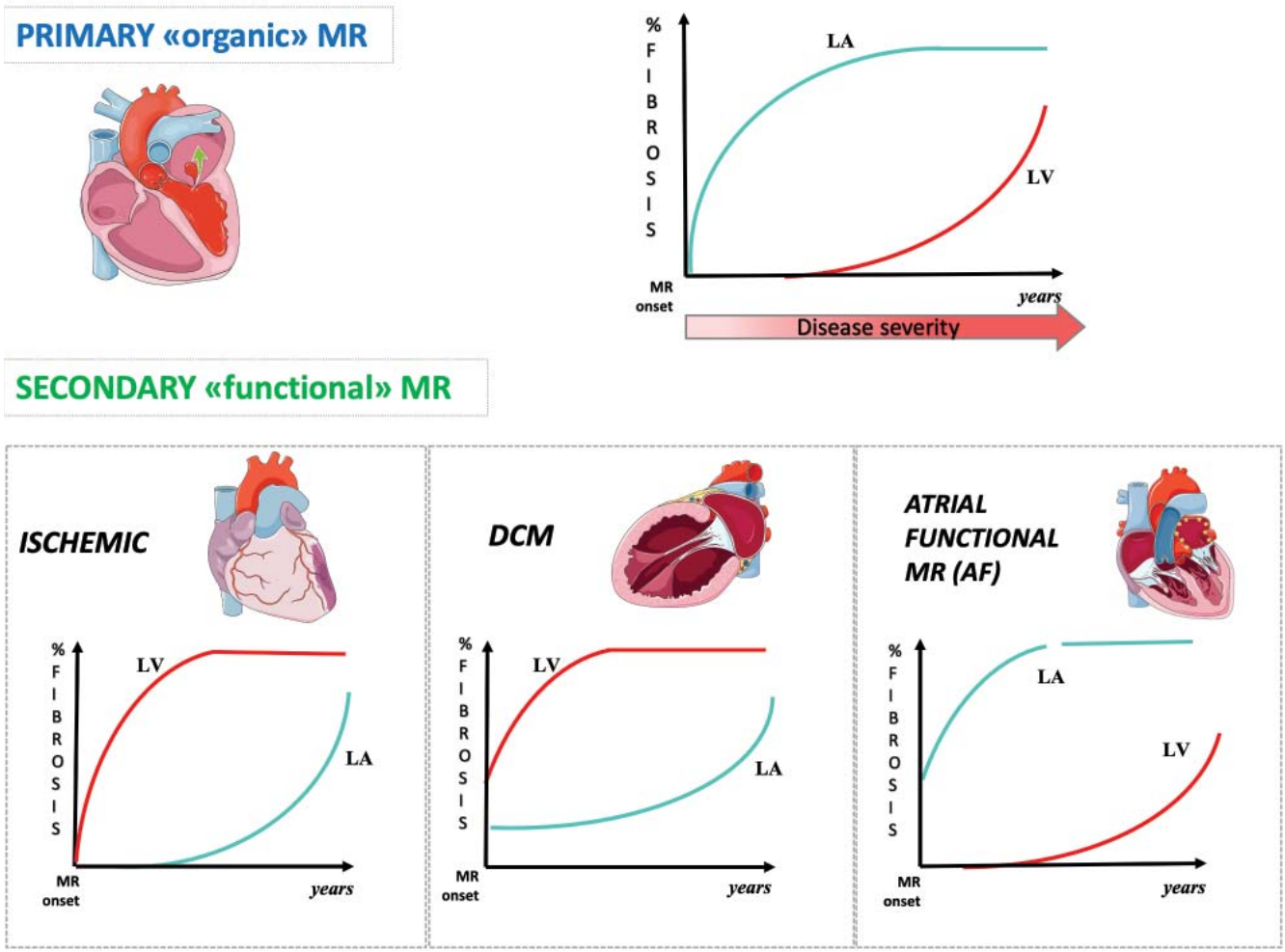

Figure 1. Graphic representation of the different timing of myocardial fibrosis of the left atrium and the left ventricle according to mitral regurgitation (MR) etiology (primary or „organic", secondary or "functional", divided into ischemic, dilated cardiomyopathy, and atrial functional MR) and the increasing severity of MR; the onset of considerable MR in considered as zero point of reference. AF, atrial fibrillation; DCM, dilated cardiomyopathy; LA, left atrium; LV, left ventricle; MR, mitral regurgitation.

to predict poor clinical outcome, in terms of survival and HF hospitalization, in patients with moderate and severe MR 10 (as discussed below). It has also been described as an important predictor of the development of paroxysmal and permanent AF in patients with MR, since the presence atrial fibrosis is gradually related to the increased risk of developing AF.

LA fibrosis and atrial fibrillation burden

To date, the association between MR and AF development has been well-established. This comes as a consequence of LA remodeling and fibrosis, which is responsible for localized wall regions of conduction slowing, with higher conduction heterogeneity providing a substrate for AF or other supraventricular arrhythmias[27].

Li et al. studied the effects of LA fibrosis in MR in pig models with the use of electroanatomic mapping and myocardial biopsy, describing that atrial fibrosis increases parallel to the duration of MR, with non-uniform degrees across different areas of the atria. Then, they hypothesized that the dispersion of atrial fibrosis may contribute to increased susceptibility to AF by influencing the conduction velocity rather than the effective refractory period[28].

Moreover, AF onset causes further LA remodeling, and the progressive increase of LA fibrosis favors the conversion to a permanent AF form[29]. In fact, AF persistence has been shown to correlate also with ECM composition and volume[30].

In a multicenter prospective observational study of persistent versus paroxysmal AF, LA fibrosis was classified into 4 severity stages based on its extent at CMR imaging („Utah stages": <10%, 10%-20%, 20%-30%, and >30%). The inclusion of LA fibrosis quantification in a

predictive model improved the ability to predict AF recurrence (C-statistic increase from 0.65 to 0.69)[31].

Therefore, the prevention of atrial fibrosis would be essential to prevent AF onset and progression, and the identification of advanced stages of fibrosis can guide the choice of the best therapeutic strategy.

Of note, Kuppahally et al. have demonstrated an inverse relationship between the grade of fibrosis measured by CMR late gadolinium enhancement and LA strain by STE, particularly in patients with persistent AF compared to paroxysmal forms[32].

LA strain has been described as an important index for the development of paroxysmal and permanent AF caused by MF, as it strongly affects LA deformation properties quantified by STE[33]. It also proved to be associated with AF occurrence and to be progressively more impaired in patients with MR and more episodes of paroxysmal AF[34]; moreover, it was also associated with the development of post-operative AF in patients undergoing MV surgery[35].

This was confirmed by Leung et al., showing that patients with persistent AF have longer total atrial conduction time (PA-TDI) and worse LA reservoir strain compared with patients with paroxysmal AF and controls, suggesting increasing burden of fibrosis and LA structural remodeling in the progression of AF[36]. These findings suggest that STE could have a role in the identification of patients with MR and higher extent of MF who are prone to develop AF.

Speckle tracking echocardiography for indirect imaging of LA fibrosis

The extent of adaptive or maladaptive remodeling of atrial chambers can be indirectly quantified through echocardiographic measures such as atrial emptying fraction, transmitral flow, pulmonary veins velocities, and tissue doppler analysis. However, most of these measures have some pitfalls. Speckle tracking analysis has emerged in the last years as a more reliable method which could overcome these limitations, allowing an angle-independent and objective quantification of myocardial deformation in different diseases.

STE has proved to indirectly assess the presence of MF through the analysis of intrinsic myocardial dynamics: as MF causes abnormal endocardial thickening by an increase in myocardial stiffness, this could be observed as a reduction of myocardial strain in each component of deformation analysis (i.e. longitudinal, circumferential, radial) for both LV and LA chambers[4,37].

LA strain measurement is performed on previously acquired two-dimensional grey-scale echocardiographic images, obtained using conventional two-dimensional gray-scale echocardiography, during a brief breath hold and stable ECG recording, using dedicated LA apical views (frame rate required: 60-80 fps). The operator can manually trace the LA endocardium in both four- and two-chamber (if available) views by a point-and-click approach; the system will automatically identify an endocardial region of interest of 6 segments, that can be manually adjusted in width and shape. After acceptance, the software generates the longitudinal strain curves corresponding to the deformation of all segments together with average curve which is representative of the phases of global LA deformation all over the cardiac cycle.

The application of STE to characterize atrial function allows to quantify reservoir, conduit and contractile function. The most used index is peak atrial longitudinal strain (PALS), a marker of LA reservoir function, with normality cut-off values of 39%[38], calculated using QRS as reference for its slightly higher feasibility[39,40]. The presence of fibrosis of LA walls causes a relevant decrease of PALS as a sign of reduced compliance of the atrium, and which has shown to anticipate the presence of atrial dilation[41,42]. Recent studies have demonstrated the value of LA strain analysis, especially a reduction of PALS, to predict LA wall fibrosis with a good correlation with CMR[32] and to stratify the risk of stroke in patients with AF[33].

LA strain has shown a great utility in patients with MR as potential marker of MF and of clinical outcome[43]. Particularly, in a recent prospective study we have shown a strong independent association of global PALS with the extent of LA fibrosis (Figure 2) assessed by biopsy specimens in patients with severe MR undergoing cardiac surgery; moreover, global PALS was an independent marker of post-operative clinical (cardiovascular events) and functional outcome (NYHA class-Borg scale)[44]. Furthermore, in another biopsy study conducted in a similar cohort we showed a stepwise reduction of global PALS and a close negative correlation between global and LA fibrosis grade which was superior to LA indexed volume, LA ejection fraction, and E/E' ratio. Among these indices, global PALS showed the best diagnostic accuracy to detect LA fibrosis (area under the curve 0.89)[45].

Also, Her et al. showed that LA global strain was significantly correlated with the degree of LA fibrosis assessed by histopathology ($r=-0.55$, $p<0.001$) in patients with MV disease, independently of age, underlying

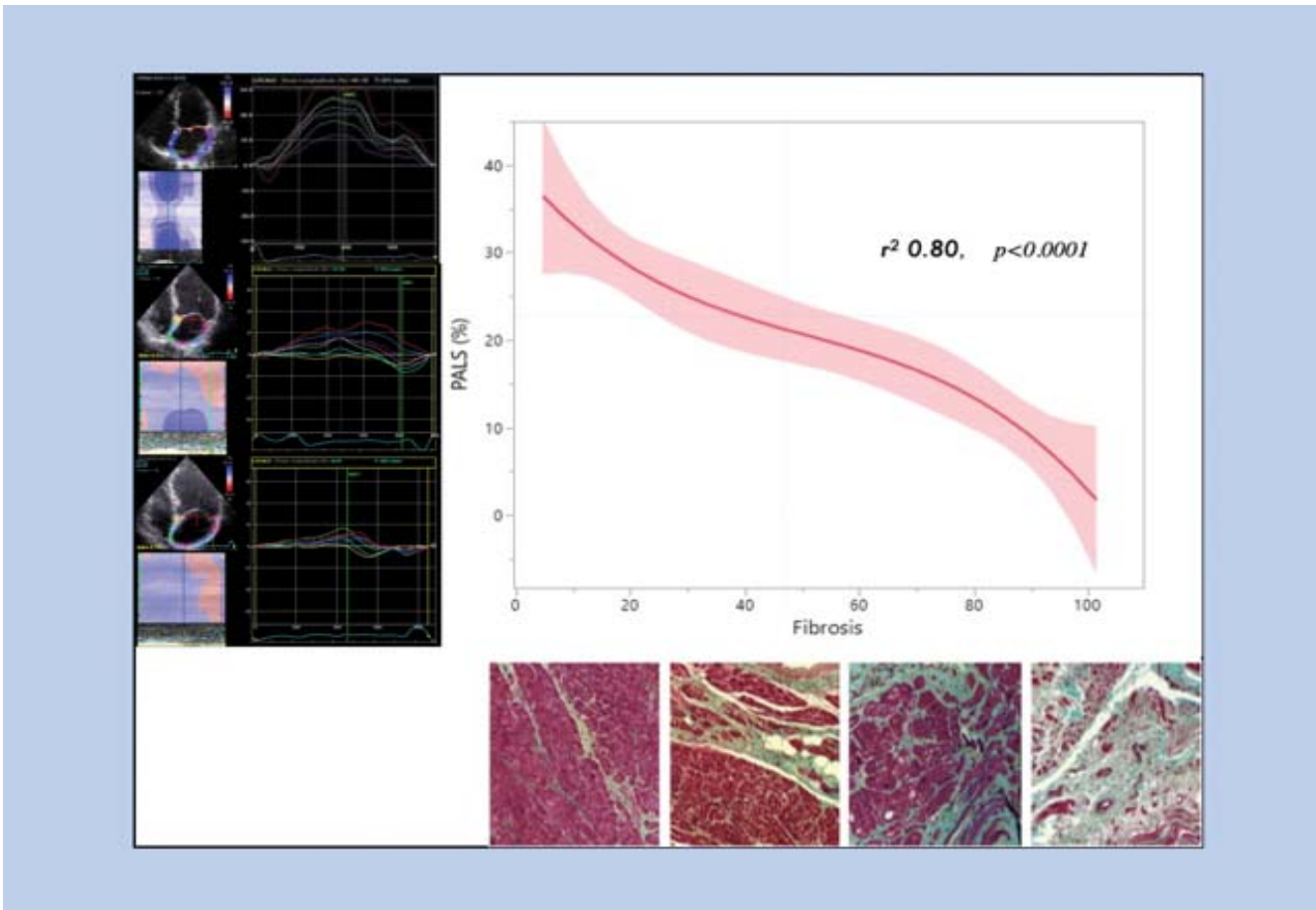

Figure 2. Correlation of peak atrial longitudinal strain (PALS) by speckle tracking echocardiography with the extent of left atrial fibrosis invasively estimated by biopsy specimens in patients undergoing cardiac surgery for severe mitral regurgitation[48].

rhythm, presence of rheumatic heart disease and type of predominant MV disease (B=-1.37, 95% confidence interval -2.32 ;-0.41, p=0.006)[46].

As concerns prognosis, global PALS reduction showed to be predictive of clinical outcome in patients with moderate and severe MR[34,47]. Moreover, a recent study showed that PALS during exercise was related to all-cause mortality and HF hospitalization in 196 with primary or secondary MR: it showed how exercise PALS could be used as a marker of LA reserve, which is somewhat preserved in primary MR, unlike secondary MR with similar severity degrees, that showed worse LA function during exercise, corresponding to lower exercise performance (measured by cardiopulmonary test parameters) and to worse clinical outcome[48].

PALS has also proved a great utility during pre-surgical evaluation of primary MR for the prediction of postoperative LA reverse remodeling, also following MitraClip procedure, over conventional LV and LA echocardiographic indices[49].

All these evidence supports the introduction of LA strain as a noninvasive and easy-to-use marker of MF to include in the daily evaluation of patients with chronic MR to guide therapeutic strategies. However, these promising results require bigger studies to be generalized. Moreover, some limitation of LA strain by STE should be kept in mind, such as its dependance on loading conditions and image quality, and the lack of disease-specific reference values.

Cardiac magnetic resonance imaging for LA fibrosis assessment

CMR is considered the noninvasive gold standard method to assess MF, though limited by high costs and low availability. CMR allows the assessment of reactive fibrosis, with the use of T1 mapping techniques, and replacement fibrosis, with the use of late gadolinium enhancement (LGE). In addition, functional consequences of MF can be evaluated with myocardial tagging and feature tracking CMR, which assess the active myocardial deformation (strain). Several studies

proved that CMR techniques may be more sensitive than the conventional measures to detect these structural and functional impairment in patients with severe MR[5].

LGE CMR is considered the reference parameter to quantify myocardial replacement fibrosis and scar. The increased ECV and decreased capillary density of the fibrous tissue result in increased volume of distribution and prolonged wash-out of gadolinium in comparison to the normal myocardium. With the increase of interstitial fibrosis, longer native T1 values (without the use of gadolinium contrast) are observed while the post-contrast T1 values become shorter. By combining them, myocardial ECV fraction can be computed, which quantifies the ECM space and is a marker of myocardial fibrosis (since collagen I is the main component of the ECM)[50]. These measures are considered of added value over LGE, allowing to quantify the degree of fibrosis and, particularly, to detect diffuse interstitial fibrosis, which is often associated with early stages of the disease. However, these are not fully specific: abnormal myocardial ECV fraction can be observed in infiltrative diseases (i.e. amyloidosis) and edema, while native T1 values impairment are observed also in iron deposition and diffuse fat infiltration[51]. Furthermore, standardization of CMR T1 mapping techniques across different vendors and institutions is still lacking.

In patients with MR, CMR complements echocardiography for the study of MF, that is also a risk marker for arrhythmic complications[52]. Particularly, an important application of CMR is the estimation of arrhythmic risk in patients with MV prolapse based of the quantification of MF[53-55]. Interestingly, Basso et al. later demonstrated that arrhythmic MV prolapse was associated with fibrosis not only at the level of the papillary muscle but also within the infero-basal wall in a series of patients who experienced sudden cardiac death or presented with complex ventricular arrhythmias and without significant MR[56], suggesting an independent fibrotic role of the disease regardless of the degree of MR.

As concerning LA, its study with CMR could be operated with high-resolution LGE scans, with accurate rendering of LA wall. For 3D visualization of LA fibrosis based on the relative LGE signal intensity, a specific color coding may be used: healthy tissue is blue, whereas any tissue with LGE is green and yellow. Additionally, a color lookup-table mask may be used to better differentiate enhanced and non-enhanced tissue. The grade of LA fibrosis is then classified as one of the established 4 Utah stages, on the basis of LA wall enhancement as a percentage of the total LA wall volume: stage I=LA fibrosis <10%, stage II=10 to<20%, stage III=20 to <30%, and stage IV>30% (Fi-

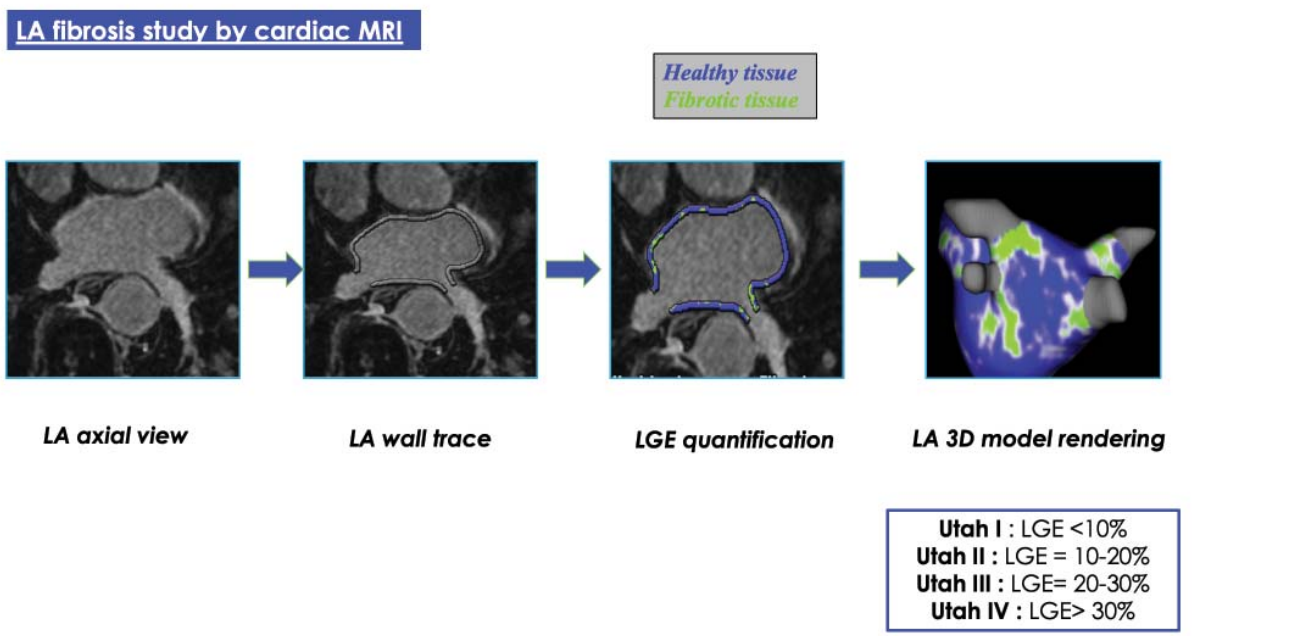

Figure 3. Assessment of left atrial (LA) fibrosis using cardiac magnetic resonance imaging (MRI) and quantification of late gadolinium enhancement (LGE) by Utah Stages. Adapted by Siebermair et al. [61].

gure 4)[57]. This approach is mostly used in patients undergoing catheter ablation; particularly, LA remodeling, measured by LGE-MRI, has shown to predict clinical outcome and AF recurrence after AF catheter ablation[58-60].

However, CMR low availability, its expense, and relative contraindication for patients with implantable medical devices (e.g. pacemakers), still limit its current clinical use in daily practice. Moreover, the evaluation of fibrosis with CMR for the LA remains time consuming and challenging for the LA due to its thin-walled structure (2-3 fold thinner that LV wall). For this reason, poor evidence currently exists on the study of LA fibrosis in patients with MR.

Cardiac computed tomography

The use of cardiac computed tomography (CT) in patients with MR with limited acoustic windows has been described in the literature. Indeed, CT offers better spatial resolution with around 84.6% sensitivity and 100% specificity for assessment of MV abnormalities[61]. Moreover, it offers a simultaneous evaluation of coronary artery disease, therefore it could be precious in case of double indication for the study of MR and coronary arteries. However, radiation exposure, poor temporal resolution and limited ability to examine each MV leaflet are some of the important limitations of cardiac CT for the diagnostic evaluation of MR. In addition, its accuracy is not comparable to that of CMR for the detection of MF.

Clinical applications of LA fibrosis assessment

LA fibrosis is a pivotal element in patients with MR, and its routine assessment would be useful to enhance the comprehension of the severity of cardiac damage consequent to MR, thus providing information on its etiology and aiding MR grading, and the accuracy in the prediction of arrhythmic risk and clinical outcome. This would lead to a more accurate evaluation of these patients and, through the application of noninvasive imaging modalities, to an improvement of the algorithms of surgical referral, e.g. including PALS or LGE quantification to the criteria for surgery. However, one should bear in mind that atrial structural remodeling is multifactorial, thus MR could represent one of the multiple factors concurring in atrial fibrosis. In fact, the presence of cardiovascular risk factors (hypertension, diabetes mellitus), of atrial involvement in different cardiomyopathies (hypertrophic cardiomyopathy, dilated cardiomyopathy, amyloidosis), all can contribute, beyond the associated MR, to atrial fibrosis occurrence. Therefore, the imaging findings should always be consciously evaluated in the overall clinical context.

CONCLUSIONS

The evaluation of MF of both LA and LV could offer important information in patients with MR.

In particular, the study of LA fibrosis using advanced imaging techniques allows an early detection of LA damage in chronic MR, providing additive value for the diagnostic and prognostic assessment in order to guide the management of these patients. The choice of imaging modality should be tailored to the specific patient and clinical indication, also considering the availability of each technique.

Conflict of interest: none declared.

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