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**Author:** Debonnaire, Philippe Jean Marc Rita  
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Chapter 8

Potential role of fibrosis imaging in severe valvular heart disease

Philippe Debonnaire, Jeroen J Bax, Victoria Delgado

ABSTRACT

The increasing burden of valvular heart disease (predominantly aortic stenosis and mitral regurgitation) parallels the ageing of the population. Timing of surgery in asymptomatic patients is controversial, and is currently considered in the presence of variables (such as reduced left ventricular ejection fraction, left ventricular dilatation, pulmonary hypertension, reduced exercise capacity, increased plasma levels of biomarkers and arrhythmias) that occur relatively late in the disease progression, with suboptimal outcome after surgery. Accordingly, early markers to guide therapeutic management are needed. In both aortic stenosis and mitral regurgitation, left ventricular fibrosis can be detected in the early stage of the disease and the extent of LV fibrosis may provide an early marker for disease severity. Currently, new non-invasive imaging technology is being developed that may permit direct or indirect assessment of left ventricular fibrosis; indirect assessment of left ventricular fibrosis refers mainly to sophisticated quantification of left ventricular function (which indirectly reflects left ventricular fibrosis extent). An overview of these non-invasive imaging techniques is provided in this article, and the potential role of early detection of left ventricular fibrosis in patients with aortic stenosis or mitral regurgitation is discussed.

KEY POINTS

1. In left-sided valvular heart disease, pressure overload (aortic stenosis) is more pro-fibrotic than volume overload (mitral regurgitation)
2. Fibrosis causes adverse left ventricular remodeling, functional impairment and is associated with poor clinical outcome
3. Non-invasive imaging techniques to assess direct left ventricular fibrosis include:
   a. Contrast-enhanced cardiac magnetic resonance:
      5. Focal (replacement) fibrosis
   b. T1-weighted cardiac magnetic resonance:
      5. Diffuse fibrosis: T1-mapping, extracellular volume (ECV)
   c. Echocardiographic calibrated integrated backscatter
   d. Molecular imaging:
      5. Collagen-targeted agents with cardiac magnetic resonance
      5. Radiolabelled angiotensin converting enzyme inhibitors and angiotensin receptors antagonists with single photon emission computed tomography or positron emission tomography
4. Non-invasive imaging techniques to assess indirect left ventricular fibrosis include:
   a. Strain and strain rate imaging:
      5. Tissue Doppler imaging
      5. Speckle tracking echocardiography
      5. Tagged cardiac magnetic resonance
   b. Perfusible tissue fraction and index with positron emission tomography
INTRODUCTION

Currently, the most encountered valve diseases include aortic stenosis (AS) and mitral regurgitation (MR); data from population-based studies showed that approximately 9% of individuals aged 65 years or more have either MR or AS.\textsuperscript{1,2} While indications for surgery are well-defined in symptomatic patients, the optimal timing of surgery in asymptomatic severe AS or MR remains controversial. Currently, surgical intervention is considered in the presence of reduced left ventricular ejection fraction (LVEF), left ventricular (LV) dilatation, pulmonary hypertension, reduced exercise capacity, increased plasma levels of biomarkers (e.g. NT-proBNP) and arrhythmias (e.g. atrial fibrillation), since all these variables are associated with worse prognosis if treated medically.\textsuperscript{3,4} However, most of these variables are encountered only once AS or MR have progressed significantly, leading to suboptimal clinical outcomes after surgery.\textsuperscript{5,6}

Accordingly, markers that could identify early structural and functional abnormalities of the LV are needed to potentially facilitate the decision for timing of surgery thereby improving clinical outcomes. In both AS and MR, ultra-structural changes of the LV with expansion of the extracellular matrix and fibrosis formation may occur due to pressure and volume overload, respectively.\textsuperscript{7,8} Fibrosis causes increased LV stiffness, leading to diastolic dysfunction and subtle worsening of systolic function, whereas overt LV systolic dysfunction (reduced LVEF) will occur later in the course of AS and MR.

Focal fibrosis reflects scar tissue formation by replacement of dead myocardial cells by collagen, which is observed after myocardial infarction, for example. In valvular heart disease however, pressure or volume overload predominantly cause diffuse interstitial fibrosis, a distinct type of fibrosis.\textsuperscript{9,10} This type of fibrosis increases the interstitial collagen without notable cell loss and therefore it may be (partially) reversible.\textsuperscript{10}

Recently, a rapid development in non-invasive imaging technology has occurred which may permit direct or indirect assessment of LV fibrosis. Particularly new cardiac magnetic resonance (CMR) techniques (with or without contrast agents) permit direct assessment of LV fibrosis, whereas strain imaging with advanced echocardiographic techniques or CMR can be used to detect subtle systolic LV dysfunction (while LVEF is still normal), which provides an indirect reflection of LV fibrosis. This article provides an overview of these non-invasive imaging techniques and the potential role for early detection of structural and functional LV abnormalities in patients with AS or MR. In Table 1, a summary is provided of direct and indirect imaging techniques for quantitative or qualitative fibrosis evaluation.\textsuperscript{2} In the paragraphs below the different imaging techniques for fibrosis detection are discussed.
Table 1. Non-invasive imaging modalities and techniques for left ventricular fibrosis assessment. Adapted with permission from Jellis et al. J Am Coll Cardiol 2010;56:89-97.

<table>
<thead>
<tr>
<th>Imaging Modality</th>
<th>Availability</th>
<th>Fibrosis Specificity</th>
<th>Limitations</th>
<th>Experience in AS</th>
<th>Experience in MR</th>
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<td>Echocardiography</td>
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<tr>
<td>IBS</td>
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<td>+++</td>
<td>Modest reproducibility, Angle dependent</td>
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<td>TDI</td>
<td>++++</td>
<td>+</td>
<td>Angle dependent</td>
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<td>2D speckle tracking</td>
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<td>+</td>
<td>Vendor variability, Low frame rate</td>
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<tr>
<td>Cardiac Magnetic Resonance</td>
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<td>Delayed- enhanced (replacement fibrosis)</td>
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<td>++</td>
<td>Focal fibrosis only</td>
<td>++++</td>
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<tr>
<td>T1 weighted imaging (diffuse fibrosis)</td>
<td>++</td>
<td>+++</td>
<td>Many confounders, expertise, standardization</td>
<td>++</td>
<td>-</td>
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<tr>
<td>Tissue tagging</td>
<td>+</td>
<td>+</td>
<td>Expertise</td>
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<td>+</td>
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<td>Collagen-specific contrast</td>
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<td>+++</td>
<td>Experimental</td>
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<td>Nuclear Imaging</td>
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<td>PET perfusable water index</td>
<td>++</td>
<td>+++</td>
<td>Radiation, expertise</td>
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<tr>
<td>PET molecular imaging</td>
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<td>+++</td>
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<td>SPECT molecular imaging</td>
<td>±</td>
<td>+++</td>
<td>Radiation, expertise, experimental</td>
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IMAGING TECHNIQUES FOR DIRECT ASSESSMENT OF LV FIBROSIS

1. Delayed contrast-enhanced cardiac magnetic resonance

Delayed contrast-enhanced cardiac magnetic resonance (CMR) has become the gold standard imaging technique to assess and quantify focal fibrosis in the left ventricle. Gadolinium chelates are extracellular contrast media that do not penetrate intact cell membranes and accumulate in the myocardial extracellular space. Several minutes after intravenous administration, the contrast agent is trapped into the expanded extracellular space and (after nullifying the signal of the myocardium), is visualized as increased signal intensity (white) compared to normal myocardium (black) (Figure 1).\(^3\) However, detection of diffuse LV fibrosis with delayed contrast-enhanced CMR standard techniques may be difficult since this technique relies on relative signal differences between normal myocardium and interstitial collagen.

![Image](Figure 8.1)

*Figure 8.1*

Delayed contrast-enhanced cardiac magnetic resonance patterns that can be observed in patients with severe aortic stenosis (AS). A. Absence of delayed enhancement. B. Anterior and septal sub-endocardial contrast-enhancement, similar to that noted in infarcted myocardium. C. Focal spots of contrast-enhancement in the lateral midwall (arrows). D. Linear septal midwall contrast-enhancement. E and F: Midwall contrast-enhancement of the lateral wall (arrows). With permission from Dweck et al. *J Am Coll Cardiol* 2011;58:1271-9.
2. T1 weighted cardiac magnetic resonance

For assessment of diffuse LV fibrosis, where there is no clear differentiation between normal and diseased myocardium, T1 weighted CMR imaging techniques are increasingly applied. T1 weighted techniques are based on the energy released by the tissue (protons) after applying radiofrequency pulses. This relaxation process follows an exponential formula that includes a time constant, the so-called T1 time. The shorter the T1 time constant is, the faster the relaxation process. T1 time can be assessed prior to (native T1) or after (post-contrast T1) contrast administration using a variety of possible techniques with multiple or single breath-holds (Figures 2 and 3).4

Normal native T1 values range between 900 and 1100 ms and increase in circumstances of increased density of protons (water content or edema).4 The

![Figure 8.2](image)

**Figure 8.2**
T1 relaxation time assessment by cardiac magnetic resonance. A. Sequential images at the same cardiac phase of different heartbeats are acquired after an inversion pulse, thereby obtaining a multitude of different inversion times. T1 recovers secondary to longitudinal magnetization paralleled by inversion time increment. B. T1 relaxation curves are constructed after data sorting by inversion time. Post-contrast shorter T1 relaxation time is seen in areas of myocardium with increased interstitium (fibrosis, inflammation) (red curve) versus normal myocardium (green curve). C. Epicardial inflammation is seen on the T1 map (red region and yellow arrows). D. By inverting the pixel values, an R1 map (1/T1) can be generated providing visualization of regions of fibrosis similar to conventional LGE images (bright). With permission from Salerno et al. *JACC Cardiovasc Imaging* 2013;6:806-22.
measurement of native T1 time is also highly dependent on the magnetic field strength and acquisition techniques.\textsuperscript{5,7} Post-contrast T1 weighted techniques have been used more frequently to assess diffuse LV fibrosis. After continuous or bolus gadolinium contrast administration, the volume distribution of contrast media is higher within the interstitium or fibrotic myocardium than in normal myocardium, resulting in a shortened T1 time.\textsuperscript{4,7} The relative shortening in T1 time is related to the extent of myocardial fibrosis. Renal clearance, acquisition protocol, contrast dose, body composition and hematocrit may significantly affect the absolute post-contrast T1 value.\textsuperscript{5} To partially overcome these limitations, quantification of extracellular volume (ECV) has been developed.\textsuperscript{4,7} The ECV is estimated by calculating the volume distribution of gadolinium in the extracellular myocardial space relative to the blood in a dynamic steady state. In the myocardial tissue, the contrast exchange rate with the blood is higher than the net clearance of the contrast from the blood, which defines the dynamic steady state. This dynamic steady state can be achieved with continuous intravenous infusion of gadolinium (until the T1 in the myocardium and blood pool are constant) or following an intravenous bolus of gadolinium (assuming equilibrium between the concentration of contrast in blood pool and

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**Figure 8.3**

Native T1 relaxation mapping in aortic stenosis. Mid-ventricular short-axis color-coded T1 maps (upper row) and corresponding delayed contrast-enhanced cardiac magnetic resonance images. Examples (from left to right) of a normal individual (T1=944 ms), a patient with moderate AS and moderate left ventricular hypertrophy (T1=951 ms), and a patient with severe AS and severe hypertrophy (T1=1020 ms). With permission from Bull et al. *Heart* 2013;99:932-7.
myocardium at each time point after the bolus). The T1 time is then calculated according to the formula: $(1 - \text{Hematocrit}) \times (\text{post} \ 1/T_{1_{\text{myocardium}}} - \text{pre} \ 1/T_{1_{\text{myocardium}}}) / (\text{post} \ 1/T_{1_{\text{blood}}} - \text{pre} \ 1/T_{1_{\text{blood}}})$ where the factor $(1 - \text{Hematocrit})$ represents the volume distribution of gadolinium in blood pool. Normal ECV values range between 24% and 28% of the myocardium. Both myocardial T1 and ECV can be visually represented by color-coded maps of the left ventricle. ECV represents a very promising biomarker of diffuse myocardial fibrosis closely correlated with collagen extent. However, its assessment is technically challenging and needs further standardization to allow accurate and reproducible measurements during single-breath-hold without confounding effects of heart-rate and through-plane motion. To optimize T1 scan planning and acquisition, and to standardize analysis, a recent expert consensus document has been produced.

3. **Calibrated integrated backscatter with echocardiography**

Collagen and water content affect myocardial tissue reflectivity of ultrasound waves. Dedicated off-line cardiac ultrasound software permits evaluation of tissue reflectivity amplitudes, sampled at the pericardium and the LV myocardium at different locations. Subsequently, calibrated integrated backscatter (IBS) is calculated by subtraction of mean backscatter intensity of the pericardium from the LV myocardium (Figure 4). Higher IBS values (less negative) suggest larger diffuse fibrosis burden, as validated by in vivo biopsy specimens. Echocardiographic IBS offers relatively easy and fast assessment of LV fibrosis, but the main limitations include reduced inter- and intra-observer reproducibility due to noise, confounding effects of the location of the sample volume, artefacts and dependence on the settings of the ultrasound systems.

![Figure 8.4](image)

**Figure 8.4**
Calibrated integrated backscatter (IBS) in aortic stenosis. A. Normal subject: with values of calibrated IBS of the septum and posterior wall of -26.9 dB and -29.3 dB, respectively (after subtracting the value of the pericardium, in red). B. Patient with severe aortic stenosis shows increased calibrated IBS (less negative) of the septum (-7.5 dB) and posterior wall (-9.3 dB), suggestive of diffuse fibrosis.
4. Molecular imaging

Molecular imaging of fibrosis comprises direct visualization and quantification of radionuclide tracers that bind to specific molecular or cellular compounds involved in the pathogenesis of myocardial fibrosis. Integrins, matrix metalloproteinases, angiotensin converting enzyme (ACE) inhibitors, angiotensin II receptor antagonist, factor XIII and collagen constitute the main targeted agents for molecular imaging of fibrosis. So far, the studies evaluating the role of molecular imaging to assess fibrosis have focused on animal models of myocardial infarction and ischemic heart failure and there are no data on fibrosis associated to valvular heart disease. The use of integrins, matrix metalloproteinases and factor XIII as targeted agents permits assessment of early inflammatory response and wound healing process of the infarcted tissue and therefore may predict LV remodeling. In contrast, collagen-targeted CMR contrast agents or radiolabeled ACE-inhibitors or angiotensin receptor antagonists have been developed to characterize postinfarction myocardial fibrosis and LV remodeling. In mouse models of chronic myocardial infarction, the use of gadolinium-based collagen-targeted contrast agent (EP-3533) for in vivo CMR imaging of myocardial fibrosis has shown feasible. On dynamic T1-weighted CMR data, the washout time constants of the targeted agent (EP-3533) was significantly longer than those for gadolinium alone in the regions of scar (194.8±116.8 min vs 25.5±4.2 min and 45.4±16.7 min vs 25.1±9.7 min, respectively, p<0.05 for both) which suggest improvement in visualization and characterization of scar. The cardiac renin-angiotensin system is enhanced in cardiac hypertrophy and fibrosis and the development of targeted radiolabeled agents have permitted in vivo imaging of angiotensin converting enzyme activity in the myocardium with positron emission tomography (PET) and single photon emission computed tomography (SPECT). By using a high-affinity analog of lisinopril radiolabelled with Technetium, the tissue upregulation of angiotensin converting enzyme in heart failure may be visualized with SPECT-CT. This molecular imaging may help to identify the patients at high risk to develop overt heart failure in whom a more aggressive therapeutic strategy may be needed to improve the prognosis. However, molecular imaging of fibrosis is currently restricted to research and further histological validation is needed.
1. Strain and strain rate imaging with echocardiography and cardiac magnetic resonance

Deformation imaging comprises quantitative assessment of the magnitude of myocardial fiber contraction and relaxation (myocardial mechanics). Strain refers to the relative change of myocardial fiber length over time and is expressed as a percentage with positive and negative values reflecting myocardial shortening or thickening and lengthening or thinning, respectively. Strain rate refers to change of strain per unit of time. Deformation imaging is highly sensitive to detect subtle changes in systolic LV function, even before LVEF becomes reduced (Figure 5) or LV dilatation occurs.

Early loss of longitudinal deformation is observed in the majority of cardiac disorders and is inversely associated to the presence and extent of fibrosis (reduced elasticity) in both ischemic and non-ischemic cardiomyopathies. Intrinsic contractility, loading conditions as well as chamber geometry influence myocardial deformation. Accordingly, deformation imaging represents an indirect and non-specific measure of fibrosis.

Quantitative deformation analysis can be performed with echocardiographic imaging techniques such as tissue Doppler imaging (TDI) or 2-dimensional speckle tracking echocardiography (STE), but also with CMR using tissue tagging. TDI assesses myocardial tissue velocities to calculate strain (rate). However (as with any Doppler technique), TDI-derived strain is dependent on the insonation angle and

Figure 8.5
Differences in left ventricular strain in patients with normal ejection fraction. A. Normal subject with normal global longitudinal strain (GLS, -21.5%) and left ventricular ejection fraction (LVEF 65%). B. Patient with severe aortic stenosis, LV hypertrophy and subclinical LV dysfunction shown by reduced GLS (-11.3%) despite preserved LVEF (62%). C. Impaired GLS (-18.6%) in a patient with LV dilatation, due to severe organic mitral regurgitation, despite high normal LVEF (67%).
strain can only be assessed accurately in those LV segments which are properly aligned along the ultrasound beam. STE, developed more recently, assesses myocardial displacement to calculate deformation, based on 2-dimensional (or even 3-dimensional) spatial tracking of ‘speckles’ (natural acoustic markers present in bimodal echocardiographic images) throughout the cardiac cycle. This technique operates at lower frame rates and is angle-independent. Therefore comprehensive function analysis including longitudinal, circumferential and radial function as well as rotational mechanics can be studied for all myocardial segments. Recent advances also allow differentiation between epicardial and endocardial layers. High quality grey-scale images are required for proper tracking and definition of the region of interest confined to the LV myocardium. Absolute values might differ between software vendors due to different speckle tracking algorithms.

CMR tissue tagging is a complex technique of spatial modulation of cardiac tissue magnetization. Specific magnetic field gradients and time series of radiofrequency pulses ‘tagg’ the myocardium, creating a dark line grid that can be followed during subsequent acquisitions throughout the cardiac cycle. This permits assessment of LV displacement and strain (rate) calculation. Similar to STE, it allows comprehensive analysis of longitudinal, circumferential and rotational mechanics of the LV myocardium. The technique is not widely available, requires expertise and is currently restricted for research.

2. Perfusable tissue fraction and index with positron emission tomography

Focal or diffuse myocardial fibrosis can be also detected with PET using $^{15}$O-labeled water and carbon monoxide (C$^{15}$O) as radiotracers and quantifying the perfusable tissue fraction and index of the LV. The perfusable tissue fraction is defined as the fraction of tissue capable to exchange $^{15}$O-labeled water within a region of interest while the perfusable tissue index is the proportion of $^{15}$O-labeled water-perfusable tissue within the anatomic tissue derived from the transmission scan. Increased myocardial fibrosis diminishes exchangeability of water leading to a low perfusable tissue index. A reduction in the perfusable tissue index has been correlated with increasing extent of LV fibrosis after myocardial infarction. In addition, compared with healthy volunteers, patients with hypertrophic cardiomyopathy show a decreased perfusable tissue index in the non-hypertrophied lateral wall suggesting the presence of diffuse fibrosis. In light of these observations, it would be expected that patients with severe AS and LV hypertrophy for example could also show reduced perfusable tissue index, although currently no such data are available.
RELEVANCE OF FIBROSIS IMAGING IN AORTIC STENOSIS

In AS, the increased wall stress due to pressure overload is initially compensated by concentric LV hypertrophy to maintain normal cardiac output. This structural remodeling often coincides with development of predominantly reactive (diffuse interstitial) and later replacement (focal) fibrosis as a result of a complex interplay, mainly determined by up-regulation of the renin-angiotensin-aldosterone system, transforming growth-factor β and tissue inhibitors of matrix metalloproteinases. Interestingly, the fibrotic response (similar to the extent of LV hypertrophy) may vary substantially between patients despite similar AS severity, indicating multi-factorial pathophysiology. While calcification is established as the main determinant of progressive valve narrowing, fibrosis initiates transition from compensating LV hypertrophy towards adverse LV remodeling, functional impairment and poor outcome in patients with severe AS (Table 2). The pathophysiological mechanism relating myocardial fibrosis to adverse prognosis in patients with AS is debated but probably involves deterioration of diastolic and systolic LV function as well as substrate formation for atrial/ventricular tachy-arrhythmias. Hence, fibrosis could be a strong biomarker of early cardiac dysfunction in severe AS implying increased mortality risk and may prove useful to select optimal timing for aortic valve replacement. Currently symptomatic status or LVEF<50% is considered a class I indication for valve replacement in patients with severe AS. However, most patients are asymptomatic and have normal LVEF. Moreover, few non-randomized studies demonstrated significant survival benefit with earlier intervention. These findings point out the clinical need for additional markers in patients with severe AS to optimize timing of intervention. A non-invasive imaging technique that detects and quantifies fibrosis, and correlates to outcome may be of use.

Experience with fibrosis imaging in aortic stenosis

Focal fibrosis is detected in 30% to 60% of patients with severe AS using delayed contrast-enhanced CMR and comprises between 3% and 7% of the LV myocardium, depending on the population. Often, the distribution of fibrosis is patchy, multifocal and restricted to (often basal) subendocardial or mid-wall myocardial layers (Figure 1). Excessive activation of the cardiac renin-angiotensin system, direct mechanical forces and ischemia due to an imbalance between the increased myocardial mass and the relatively reduced capillary flow reserve are proposed pathophysiological mechanisms for this replacement fibrosis. A positive correlation between fibrosis degree on the one hand, and both LV mass and valvuloarterial impedance on the other hand, partly explains the
higher fibrotic burden in the LV demonstrated in low-gradient severe AS patients, irrespective of LVEF. More extensive fibrosis on delayed contrast-enhanced CMR in AS patients is associated with heart failure symptoms and increased NT-proBNP levels. In 58 patients with symptomatic severe AS, Weidemann et al. observed that patients without fibrosis significantly improved in New York Heart Association (NYHA) functional class, LVEF and showed LV reverse remodeling after surgical valve replacement, contrary to patients who showed focal fibrosis in ≥2 LV segments. Focal fibrosis remained unchanged for all patient groups postoperatively, indicating irreversible myocardial damage (macroscopic scar formation). A more recent study (including 28 symptomatic AS patients) extended these results showing that the degree of fibrosis was independently associated with survival (irrespective of age), LVEF and symptomatic status. This independent relation was confirmed by Dweck et al. in 143 patients with moderate (40%) and severe (60%) AS. Those patients with mid-wall hyperenhancement had 5-fold increased

### Table 8.2

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Positive correlation with LV fibrosis</th>
<th>Negative correlation with LV fibrosis</th>
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<td>Valve hemodynamics</td>
<td>Mean aortic valve pressure gradient</td>
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<td>Peak aortic valve pressure</td>
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<td>LA volume</td>
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<td>LV systolic function</td>
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<td>LV end systolic pressure</td>
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<td>LV stroke volume</td>
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<td>Longitudinal strain (rate)</td>
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<td>Systolic mitral annulus displacement (TDI or M-mode)</td>
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<td>LV diastolic function</td>
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<td>Variables after aortic valve</td>
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<tr>
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<td>Reverse LV remodeling</td>
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<td>Improvement LV systolic function</td>
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all-cause mortality (HR 5.35; 95% CI 1.16-24.56). Patients with mid-wall enhancement who underwent aortic valve surgery had better survival than those treated conservatively but worse compared to surgically treated patients without fibrosis. Interestingly, almost half of the deaths occurred in patients with only moderate AS and mid-wall fibrosis, underscoring the prognostic relevance of focal fibrosis.3

Focal fibrosis, however, occurs at later disease stages, while diffuse fibrosis is the predominant pattern in AS patients. Higher septal IBS values, correlating with diffuse fibrosis histology, were shown in 35 severe AS patients (Figure 4).w21 The presence of significant LV fibrosis, defined as a value of end-diastolic IBS of the septum indexed to the pericardial IBS >56.6%, permitted identification of patients with LV dysfunction. In addition, significant LV fibrosis assessed with calibrated IBS was associated with lack of LVEF improvement after valve replacement.w21 A reduction of IBS values after surgical replacement suggests at least partial reversibility of diffuse fibrosis (or reduced water content due to cell volume reduction) in AS patients and could predict LV reverse remodeling.w22 Recent development of T1 mapping techniques has renewed interest on diffuse fibrosis imaging in this group of patients. Various studies have correlated several parameters derived from native and post-contrast T1 mapping CMR techniques. In 18 patients with severe AS the correlation between contrast-enhanced T1 weighted CMR derived ECV and histological quantification of myocardial fibrosis was assessed.w23 ECV showed a strong linear correlation with histological collagen volume fraction (r² = 0.86), suggesting the potential of T1 weighted CMR for fibrosis assessment.w23 However, using native T1 mapping, Bull et al. showed a modest correlation between native T1 values and histological collagen volume fraction in 19 patients with severe AS undergoing aortic valve replacement (Figure 3).16 These findings suggest a significant variability among the different methodologies to assess diffuse myocardial fibrosis (Table 3).16,w18,w21,w23 Independently of the T1 mapping CMR technique used, all studies showed that patients with AS have increased diffuse myocardial fibrosis.16,w23 Bull et al. reported higher native T1 values in symptomatic (1014±38 ms) versus asymptomatic (972±33 ms) AS patients.16 In addition, Flett et al. showed higher ECV (18.1±8.1 versus 13.4±6.5 %, p<0.05) in 63 patients with AS as compared to 30 control patients and this parameter was an important predictor of 6-minute walking distance.14 After valve surgery ECV (as a measure of diffuse fibrosis) remained unchanged and 80% of patients who died within the first 6 months were within the upper ECV tertile.14 However, the considerable overlap of the T1 mapping results between the patients with AS versus control individuals as well as reproducibility issues may currently limit the use of this technique for individual patients.14 In addition to direct fibrosis assessment, reduction in LV function has been used as indirect marker for LV fibrosis. Impaired LVEF in patients with AS...
is inversely correlated to extensive histological fibrosis ($r = -0.57$). However, the vast majority of patients with AS have preserved LVEF, since LVEF mainly reflects radial function, which is preserved in hypertrophied hearts until end-stage of the disease. In patients with AS however, fibrosis mainly affects subendocardial to mid-wall layers of the myocardium that determine longitudinal LV function. Weidemann et al. showed an inverse relationship between the extent of fibrosis and LV longitudinal strain (rate) in patients with severe AS. Many patients with severe AS and preserved LVEF present with impaired longitudinal deformation. In more advanced disease stages, impaired LV radial and circumferential strain, corresponding to more transmural myocardial fibrosis, have been reported. The main determinants of global LV longitudinal strain in AS patients are stenosis valve severity, global afterload (valvulo-arterial impedance), LV mass, fibrosis and contractility. Since all these determinants show a significant relation with outcome in patients with AS, detection of subtle LV dysfunction by strain imaging may improve risk stratification (and therapeutic decision making). Indeed, reduced LV longitudinal function relates to exercise intolerance and was the single independent predictor of mortality or heart failure hospitalization after valve replacement in symptomatic patients with severe AS. Importantly, LV longitudinal deformation was an independent predictor of death or symptom-driven valve replacement in asymptomatic patients with severe AS and preserved LVEF. In particular, a global LV longitudinal strain value $\geq$-15% indicated worse event-free survival.

### RELEVANCE OF FIBROSIS IMAGING IN MITRAL REGURGITATION

Assessment of myocardial fibrosis in patients with organic MR is of interest since early detection of associated LV and left atrial (LA) structural changes may help to...
identify patients who may benefit from surgical valve repair while still asymptomatic. In contrast, in functional (ischemic) MR, there is often extensive focal fibrosis with severe structural LV changes due to scar formation after previous infarction, and therefore detection of diffuse fibrosis may not help in the timing of surgery.

Organic MR comprises primary abnormalities of the mitral valve morphology and causes volume overload of both the LV and the LA, leading to chamber dilatation and eccentric LV hypertrophy. In contrast to concentric pressure overload LV hypertrophy (as noted with AS), the eccentric LV hypertrophy caused by chronic volume overload associated with organic MR is less pro-fibrotic.\textsuperscript{w30} A recent study involving rat surgical models of pressure and volume overload attempted to explain this phenomenon.\textsuperscript{w31} Compared with pressure overload models, volume overload models showed less myocardial ischemia and replacement fibrosis.\textsuperscript{w31} In addition, proteolytic activity in large animal models of MR, has been related to reduced support and content of extracellular matrix in eccentric hypertrophy, thereby facilitating LV dilatation.\textsuperscript{w31-w32} Although MR is less pro-fibrotic than AS, increased interstitial tissue in the LV on biopsies obtained in patients undergoing mitral valve repair/replacement is suggested to contribute to development of cardiac failure.\textsuperscript{w33} Moreover, histology revealed a larger content of subendocardial diffuse LV interstitial fibrosis in patients with MR as compared to patients without MR (18\% versus 4\%, p<0.05).\textsuperscript{w34} Similar to AS, compelling evidence points out that LV fibrosis in MR relates to LV dilatation, functional impairment and adverse outcome. These findings may impact on timing of surgery in patients with severe organic MR. Development of symptoms or LV dysfunction (LVEF ≤60\% or LV end-systolic diameter ≥40-45 mm) are class I indications for mitral valve surgery in patients with severe organic MR.\textsuperscript{w33} However, these indications should probably not be awaited for, as surgical outcome seems better in absence of these characteristics.\textsuperscript{18,w35-w36} Additional risk stratification is therefore warranted and (indirect) fibrosis imaging may be of importance.

**Experience with fibrosis imaging in organic mitral regurgitation**

In organic MR, indirect myocardial fibrosis assessment has been obtained using strain imaging. In contrast, CMR, IBS or molecular imaging studies in patients with MR are scarce. Similar to patients with AS, most MR patients have preserved LVEF. Of note, in significant MR supra-normal LVEF values defines normal systolic function due to coincidence of increased preload and reduced afterload during the initial compensated phase. Subclinical LV dysfunction despite preserved LVEF, assessed by impaired LV longitudinal strain, however, is often encountered in asymptomatic patients with severe MR (Figure 5).\textsuperscript{10} More advanced disease stages are associated with impaired LV circumferential and radial strain.\textsuperscript{w37} The main determinants
of LV longitudinal strain in MR are regurgitant volume, LV geometry (dilatation) and intrinsic contractility, related to myocardial fibrosis. Reduced strain in MR patients may therefore parallel LV geometric changes (dilatation) rather than contractility impairment, and therefore, some authors have advocated to correct the LV strain values for LV dimensions.

In a large series of 233 patients with moderate-severe MR and overall preserved LVEF, Witkowski et al. showed that impaired longitudinal LV strain together with LV end-systolic dimension predict postoperative LV dysfunction (LVEF <50%), independently of baseline LVEF ≤60%, symptoms and atrial fibrillation. In particular, a global LV longitudinal strain value ≥-19.9% predicted long-term LV dysfunction after mitral valve repair with a sensitivity and specificity of 90% and 79%, respectively. Additionally, impaired recruitment of longitudinal contractility by strain imaging during exercise was also associated with post-operative LV dysfunction in patients with preserved LVEF undergoing surgery for severe MR. Pre-operative high-normal LVEF may be misleading and mask latent LV dysfunction that is only observed post-operatively when acute preload reduction leads to LVEF decrease below normal values. Whether impaired LV longitudinal strain also predicts worse survival after valve intervention remains to be demonstrated.

Not only the LV, but also the LA has been the subject of research. Recently, a close inverse correlation between left atrial global (reservoir) strain and histological interstitial fibrosis in patients with severe organic MR (r = -0.82) was shown (Figure 6). The potential clinical relevance of such findings was explored in another study involving 121 patients with severe MR. Impaired global LA longitudinal (reservoir) strain was related to long-term mortality after mitral valve surgery, incremental to guideline based indications for mitral surgery and LA size. LA strain could potentially predict post-operative survival in patients with severe MR, without guidelines-based risk factors (Figure 7). Apart from myocardial deformation, both delayed contrast-enhancement CMR and, more recently, T1 weighted imaging of the LA have shown correlation to LA fibrosis. However, no data exist on assessment of LA fibrosis with CMR techniques in patients with severe MR.

UNRESOLVED ISSUES

Based on these experimental and clinical studies, the question remains whether fibrosis may help in the decision when to intervene in asymptomatic AS patients with preserved LVEF. Various other issues need further study to define the precise role of LV fibrosis for risk stratification and decision-making strategies. For example, is fibrosis independent from and superior to other risk factors currently
Figure 8.6
Relation between extent of left atrial fibrosis and left atrial reservoir strain in patients with severe mitral regurgitation. Four patients operated on for severe mitral regurgitation with (from left to right) progressive left atrial dilatation corresponding to more impaired left atrial function (reservoir strain, decreasing from 45% to 9%) and larger extent of fibrosis on histology of the left atrial free wall (hematoxylin-eosin and Masson’s trichrome staining). With permission from Cameli et al. Am J Cardiol 2013;111:595-601.

Figure 8.7
Prognostic value of LA strain in patients undergoing mitral valve surgery for severe organic mitral regurgitation. Dichotomizing the population based on a cut-off value of LA strain of 24%, patients with an LA strain >24% had better cumulative survival compared with patients with an LA strain ≤24%, independently of symptoms or the presence of guidelines-based surgical criteria. With permission from Debonnaire et al. J Am Soc Echocardiogr 2013;26:1053-62.
used, such as NT-proBNP? In addition, for risk estimation, should LV fibrosis be considered as a continuum or should a threshold be applied (if more than a certain percentage fibrosis is present in the LV, then surgical intervention should be considered)? Which fibrosis needs to be detected: focal or diffuse fibrosis? And which non-invasive imaging technique is optimal for assessment and quantification of LV fibrosis? And what will be the precise role of indirect fibrosis assessment using LV strain? Moreover, it is not clear whether a potential relation between fibrosis and outcome can be extrapolated to patients with different AS severity. And finally, does infarct related LV fibrosis alter predictive value in AS patients?

Similarly, for asymptomatic patients with severe organic MR, the key issue is whether strain imaging is specific enough for risk stratification of individual patients and to justify early intervention in asymptomatic patients with preserved LVEF. In addition, would LV or LA strain provide the optimal risk stratification and therapy guidance in these patients? And will strain imaging be independent and superior to other risk factors, including NT-proBNP? And, if considered for risk stratification and therapy guidance, will a threshold of LV and/or LA strain be used or a continuum? Moreover, the value of imaging techniques such as contrast-enhanced CMR or T1 mapping in MR should be explored both for the LV and the LA.

Importantly, apart from fibrosis (extracellular matrix alterations), other factors such as cell death, impaired excitation-contraction coupling due to altered calcium homeostasis and mismatch between cardiomyocyte and vascular growth contribute to transition of compensated hypertrophy towards heart failure. Molecular imaging of specific signaling pathways involved in these factors may therefore provide novel insights and ultimately contribute to risk stratification in patients with valvular heart disease.

CONCLUSION

If successfully performed prior to complications arise, surgical correction of AS or MR may reverse patients to normal life expectancy. Timing of surgery in asymptomatic patients is currently considered in the presence of reduced LVEF, LV dilatation, pulmonary hypertension, reduced exercise capacity, increased plasma levels of biomarkers or atrial fibrillation. These markers however, occur relatively late in the disease progression, and outcome after surgery is suboptimal. LV fibrosis occurs earlier, and may be a future marker to improve therapeutic decision making. Novel non-invasive imaging techniques have been developed to detect fibrosis directly or to assess subtle changes in LV systolic dysfunction (while LVEF is still preserved), secondary to LV fibrosis. Future research is needed to determine
whether LV fibrosis assessment with these imaging techniques may further refine the timing of surgery in severe AS or MR, and whether this will improve outcome after surgery.
REFERENCES


**REFERENCES (ON LINE)**


