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Multimodality imaging for myocardial injury in acute myocardial infarction and the assessment of valvular heart disease

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Citation

Podlesnikar, T. (2022, June 28). *Multimodality imaging for myocardial injury in acute myocardial infarction and the assessment of valvular heart disease*. Retrieved from <https://hdl.handle.net/1887/3420621>

Version: Publisher's Version

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Note: To cite this publication please use the final published version (if applicable).

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Focal replacement and diffuse fibrosis in primary mitral regurgitation: a new piece to the puzzle

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JACC Cardiovasc Imaging 2021;14(6):1161-3

Mitral regurgitation (MR) is one of the most frequent valvular heart diseases. The most common etiology of primary MR is the myxomatous degeneration of the mitral valve, encompassing fibroelastic deficiency and Barlow's disease. In severe chronic primary MR, the presence of symptoms, reduced left ventricular ejection fraction (LVEF $\leq 60\%$) or increased left ventricular (LV) end-systolic diameter are indication for mitral valve repair.^{1,2} In asymptomatic patients, surgery should be considered if there is high likelihood of durable mitral valve repair, low operative risk and if there is atrial fibrillation, pulmonary hypertension, flail leaflet or dilated left atrium (LA) at sinus rhythm.^{1,2} The evidence showing the benefits of early surgery is accumulating. Data from a large cohort of 1512 patients undergoing mitral valve surgery for isolated primary MR revealed that patients who were operated based only on high likelihood of successful mitral valve repair had the best outcome.³ The rationale for an early intervention is that the longstanding volume overload caused by severe MR may lead to irreversible LV dysfunction. LVEF is considered the parameter of reference to define LV function and to base the decision making. However, LVEF is a late reflector of the structural changes that MR induces, and one fifth of the patients with preoperative LVEF $>60\%$ still develops postoperative LV dysfunction.⁴ Increased interstitial fibrosis has been confirmed on autopsy in severe primary MR and is considered to play a key role in the development of LV dysfunction.⁵

In the current issue of JACC Cardiovascular Imaging, Kitkungvan and colleges⁶ investigated the associates of extracellular volume (ECV) measured with cardiovascular magnetic resonance (CMR) T1 mapping and focal replacement fibrosis on late gadolinium contrast enhanced (LGE) CMR in 424 patients with chronic primary MR and LVEF $\geq 50\%$. Patients were divided into two cohorts: patients with mitral valve prolapse (MVP) and patients with primary MR of other etiologies. Patients with MVP were slightly older and were more frequently male than the patients with non-MVP, whereas patients with non-MVP had more frequently history of heart failure and diabetes compared to their counterparts. In terms of CMR findings, patients with MVP had larger LV and right ventricular dimensions, larger LA volumes and more severe MR as compared to patients without MVP. Patients with MVP showed more frequently replacement fibrosis on LGE-CMR and larger ECV values than patients without MVP. The location of LGE was most commonly located in the basal infero-lateral and inferior wall in patients with MVP, whereas in patients without MVP the LGE was located in the basal septum. MVP was independently associated with the presence of LGE. In contrast, ECV values increased along the mitral regurgitant fraction and volume

independently of the etiology of the primary MR and the presence of LGE. Elevated ECV was independently associated with symptoms related to MR and clinical events during follow-up. Patients with moderate and severe MR and an ECV $\geq 30\%$ had higher event rates than their counterparts with similar grade of MR and an ECV $< 30\%$.

The use of CMR in the evaluation of patients with primary MR is gaining followers. CMR has an additional value to echocardiography, since it is the reference standard to quantify chamber dimensions and, in multiple and eccentric regurgitant jets, CMR provides better estimation of the MR severity than 2-dimensional echocardiography.⁷ However, the most unique feature of CMR is its capability of noninvasive myocardial tissue characterization.

In primary MR due to MVP, Han and coworkers⁸ were the first to describe the association between focal LGE in the papillary muscles and the presence of complex ventricular arrhythmias. Furthermore, Basso *et al.*⁹ proposed a pathophysiological mechanism, in which specific morphological abnormalities of the mitral apparatus (systolic curling and mitral annular disjunction) generate regional myocardial stress that leads to hypertrophy and replacement fibrosis of the papillary muscles and adjacent myocardium providing a substrate for the development of malignant ventricular arrhythmia. The present results demonstrate that focal LV fibrosis in the inferior and inferolateral LV wall is a unique feature of MVP and is not observed in primary MR of other etiologies.⁶ However, the present study does not provide data on the association between LGE and ventricular arrhythmias.

When evaluating diffuse structural changes of the extracellular matrix, Edwards *et al.*¹⁰ described for the first time increased ECV (suggestive of diffuse interstitial fibrosis) in 35 patients with asymptomatic moderate and severe primary MR compared to the healthy individuals. In the current study,⁶ ECV was larger in patients with MVP than in patients with primary MR of other etiologies and the main determinants of larger ECV were age, male sex and larger mitral regurgitant fraction. However, it is important to note the significant overlap of the ECV values across individuals with various grades of MR.

The present study provides new knowledge in primary MR: while focal replacement fibrosis is related to the etiology of primary MR, diffuse myocardial fibrosis is associated with the severity of MR. How do we use this information in clinical practice?

The measurement of ECV may help in the timing of intervention; increased ECV has been associated with reduced exercise capacity as well as with greater perceived level of exertion in patients with primary MR.¹⁰ In addition, among asymptomatic patients with primary MR, increased ECV has been associated with adverse outcome.^{6,11} In contrast, the

presence of LGE may help to identify the patients with primary MR that are at risk of ventricular arrhythmias and who could benefit from an implantable cardioverter defibrillator. The majority of the patients with MVP who present with ventricular arrhythmias or sudden cardiac death do not present with severe MR to operate on.¹² The ongoing “Mitral FINDER” trial¹³ will provide important answers to define the role of CMR in the management of patients with primary MR.

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