Myocardial Fibrosis in Asymptomatic Degenerative Mitral Regurgitation
What Does T1 Mapping Tell Us?

Seth Uretsky, MD; Linda D. Gillam, MD, MPH

Degenerative mitral regurgitation (MR), defined as that because of mitral prolapse or flail on the basis of underlying myxomatous disease or fibroelastic deficiency, is common. There is consensus that intervention is appropriate in the setting of symptoms and impaired left ventricular (LV) systolic function as gauged by LV ejection fraction (LVEF) or LV end-systolic volume, and these carry class I recommendations in the current American College of Cardiology/American Heart Association and European Society of Cardiology Guidelines.1,2 There is also support for intervening in the asymptomatic patient with atrial fibrillation or pulmonary hypertension (class II).1,2 However, in the absence of randomized control trials, there is ongoing debate as to the best approach to the management of the patient who meets none of these triggers. Those who advocate close medical follow-up with the use of stress testing to confirm the asymptomatic state until triggers develop (watchful waiting) argue that accurate identification of patients with truly severe degenerative MR can be challenging and that, even in those with unequivocally severe regurgitation, the short- and long-term risks of surgery are not outweighed by the risks of waiting until triggers develop.3 Those who favor prophylactic surgical intervention argue that for patients likely to undergo successful repair, waiting puts them at risk for poorer longer term outcomes.4

In an environment where the limitations of LVEF as a measure of systolic function are well recognized, new tools for identifying subclinical abnormalities that might be precursors to overt LVEF reduction or symptoms might prove valuable in clinical decision making. Better still would be a means of reliably identifying the onset of irreversible LV changes of which fibrosis is arguably one.

In this issue of Circulation: Cardiovascular Imaging, Edwards et al5 report a study in which MRI late gadolinium enhancement (LGE) and T1 mapping were used to identify myocardial fibrosis in patients with asymptomatic moderate to severe degenerative MR free of class I triggers for intervention. In 35 such patients, findings were compared with those in age- and sex-matched controls. The key findings of the study were that both LGE-defined fibrosis and extracellular volume (ECV) calculated from native and postcontrast T1 mapping were increased in patients with degenerative MR versus controls and that the differences in ECV between patients and controls were evident after areas of LGE consistent with previously undiagnosed infarction were excluded. Although this study must be viewed as hypothesis generating, the results are provocative because fibrosis typically represents an irreversible anatomic change and its presence might serve as an early warning of irreversible functional changes that might trigger surgical intervention.

MRI Methods for Detecting Fibrosis

LGE is a well-established tool for detecting and quantifying LV fibrosis in both ischemic and nonischemic diseases.6 Improvements in cardiac magnetic resonance techniques now permit the measurement of myocardial T1 (measured in milliseconds). T1 can be measured without the use of contrast (native T1) or after the administration of a gadolinium-based contrast agent. The role of native T1 mapping is evolving.7,8 However, differences between native and postcontrast T1 values have been reported to provide a tool for measuring myocardial ECV. The details of these calculations are provided and well illustrated in the article of Wong et al.9

The ECV calculated using cardiovascular magnetic resonance (CMR) is a measure of the myocardial space that is not taken up by myocardial cells.7 Although this might include edema or the deposition of abnormal substances, such as amyloid, increased ECV typically reflects fibrosis. Thus, T1 mapping should detect not only the patchy fibrosis detectable by LGE but also more diffuse fibrosis, a concept that has been confirmed in animal and human studies.10,11 Therefore, one construct is that although LGE is a useful tool to assess for macroscopic myocardial scar/fibrosis, T1 mapping may be helpful in identifying diffuse or microscopic scar/fibrosis.

In their study, Edwards et al1 report that LGE distributed in a noncoronary pattern was present in 11 of 35 (31%) patients with MR versus none of the controls and that both mean ECV and native T1 times were greater in MR patients than in normal controls. Using 0.297 (29.7%) as the upper limit of normal for ECV based on values for their control group, they noted that all patients with LGE and an additional 3 patients had increased ECV, suggesting that ECV might be a more sensitive test for fibrosis in these patients. However, although their cutoff of 0.297 is within the range of normal values previously reported by others,9,12 several of

© 2014 American Heart Association, Inc.
Circ Cardiovasc Imaging is available at http://circimaging.ahajournals.org
DOI: 10.1161/CIRCIMAGING.114.002700

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

From the Department of Cardiovascular Medicine, Morristown Medical Center, Morristown, NJ.

Correspondence to Linda D. Gillam, MD, MPH, Department of Cardiovascular Medicine, Morristown Medical Center, Cardiovascular Administration 5, 100 Madison Ave, Morristown, NJ 07962, E-mail linda.gillam@atlantichealth.org


(Circ Cardiovasc Imaging is available at http://circimaging.ahajournals.org
DOI: 10.1161/CIRCIMAGING.114.002700

860
their abnormal patients had values of 0.297 to 0.32, which are also within the range of values for normal subjects reported by Wong et al\textsuperscript{9} and Fontana et al.\textsuperscript{12} If all the patients with higher and more clearly abnormal ECV values also had LGE, the incremental value of ECV in these patients becomes less clear. Its relevance might also be questioned if the abnormal values were identified predominantly or exclusively in subjects with hypertension or diabetes mellitus, 2 conditions known to be associated with fibrosis. This underscores the need for additional larger studies of both normal and abnormal subjects to provide reference normal values for ECV and to explore the possibility that there may be age, sex, and racial differences. In this regard, Edwards et al\textsuperscript{5} should be commended for a control group that was age- and sex-matched to MR subjects.

Previous Studies

There have been 2 previous reports of studies using LGE in populations with degenerative MR. In an analysis of 19 patients with mitral valve prolapse, some with only mild MR, Han et al\textsuperscript{13} noted LGE in the papillary muscles, an observation also noted in a larger study by Van De Heyning et al.\textsuperscript{14} The current study provides no data on papillary muscle LGE for comparison. Although the study of Han et al\textsuperscript{13} did not show LGE elsewhere in the myocardium, the study of Van De Heyning et al\textsuperscript{14} of 39 patients with primary MR (all but 4 of whom had degenerative MR) noted that 12 patients (31%) had LGE; 3 with an infarct pattern, 7 with a nonischemic pattern, and 2 patients with a combined pattern. These are similar to the LGE results of the study of Edwards et al\textsuperscript{5} although the latter reports a higher number of subjects with a diffuse fibrosis pattern. These differences are most likely attributable to the small sample size in both studies. Of note, no study before that of Edwards et al,\textsuperscript{5} including that of Van De Heyning et al,\textsuperscript{14} has used T1 mapping in patients with degenerative MR.

It is difficult to interpret the observations about the associations between ECV, indices of systolic function (including strain), and LV dimensions. The correlations reported are generally weak and it seems that the relationships provided were derived from groups of variable sizes at least some of which included controls and patients. Furthermore, given the greater sensitivity of strain versus LVEF in detecting LV dysfunction, it is difficult to reconcile a significant correlation between ECV and LVEF but not with any of the strain parameters.

Limitations

The major limitation of this study is the small sample size and with it the potential that confounding variables that could not be adequately addressed in the analysis have influenced the results. Notably, 31% of the MR group had hypertension and 9% had diabetes mellitus, which, as previously noted, are disease states known to be associated with LV fibrosis.\textsuperscript{15,16} Similarly, without angiography, it is impossible to exclude coronary disease as the cause for LGE and ECV positivity. Although it would be impossible to justify invasive coronary assessment in asymptomatic patients without indications for surgery, it might be feasible to perform similar magnetic resonance studies in patients free of fibrosis-associated comorbidities and who have negative computed tomographic calcium scores. Although the authors state that ECV remained elevated versus controls even after exclusion of patients with diabetes mellitus, atrial fibrillation, hypertension, and asymptomatic coronary disease, the number remaining for this analysis is not stated. The data in Table 1 suggest that it would be no \textgreater{}24 and possibly as few as 15, numbers that would be associated with an increased risk of type I error.

Another limitation relates to the control group that had unusually high LVEFs (mean, 74%) but, interestingly, without correspondingly better strain. Many of the authors’ conclusions about LV function in the MR group are, therefore, colored by comparison with a group who, at least by LVEF assessment, have hyperdynamic systolic function.

A final limitation relates to uncertainty as to severity of the MR in the study group. It is well recognized that proximal isovelocity surface area-based approaches to quantitation frequently overestimate MR severity in patients with degenerative MR particularly that which is nonholosystolic,\textsuperscript{2,7} and it is possible that the CMR determined regurgitant volumes and regurgitant fractions that identify only 8 patients as having severe MR more accurately describe the patient population. Because the hypothesis invoked to explain the MR-associated fibrosis is one that would predict a relationship between the extent of fibrosis and MR severity, it would be interesting to see data in patients with mild, moderate, and severe MR as quantified by CMR.

Clinical Implications

Should the findings of the article of Edwards et al\textsuperscript{5} be confirmed in additional studies, they would have the potential to provide an additional tool for clinical decision making. However, it would be important to do more than simply repeat the study of Edwards et al\textsuperscript{5} with a larger number of subjects free of confounding comorbidities. For example, the conclusion that fibrosis is associated with subclinical LV systolic dysfunction and, is, by inference, a precursor to dysfunction that is more severe would be strengthened by studies that demonstrated the uniform presence of fibrosis in patients with conventional class I triggers for valve surgery, particularly those related to systolic dysfunction. In this regard, it would be interesting to know the LGE and T1 mapping data on the 4 patients in this study who went to surgery based on reduced LVEF by CMR. Similarly longitudinal studies demonstrating progressive increases in LGE and T1 would be informative. In addition, there remains the challenge of demonstrating the effect of these findings on clinical outcomes again raising the imperative for randomized trials comparing prophylactic intervention versus watchful waiting for patients with degenerative MR. The inclusion of CMR assessment of fibrosis would be an interesting addition to echocardiographic and clinical measures in such a study.

The role of T1 mapping in patients with valve disease remains largely unexplored. Provocative data have been reported in patients with aortic stenosis where T1 mapping abnormalities were associated with a strain pattern on ECG, which in turn was associated with poor outcomes.\textsuperscript{8} The current study encourages us to explore the value of this new technique in patients with valvular heart disease further.
Disclosures

None.

References


Myocardial Fibrosis in Asymptomatic Degenerative Mitral Regurgitation: What Does T1 Mapping Tell Us?
Seth Uretsky and Linda D. Gillam

_Circ Cardiovasc Imaging_, 2014;7:860-862
doi: 10.1161/CIRCIMAGING.114.002700
_Circulation: Cardiovascular Imaging_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2014 American Heart Association, Inc. All rights reserved.
Print ISSN: 1941-9651. Online ISSN: 1942-0080

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circimaging.ahajournals.org/content/7/6/860

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation: Cardiovascular Imaging_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation: Cardiovascular Imaging_ is online at:
http://circimaging.ahajournals.org//subscriptions/