Cardiovascular Magnetic Resonance in Clinically Suspected Cardiac Amyloidosis

Diagnostic Value of a Typical Pattern of Late Gadolinium Enhancement*

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Late gadolinium enhancement (LGE) cardiovascular magnetic resonance (CMR) imaging is a tool for noninvasive evaluation of myocardial viability that has the advantage over other imaging techniques of being able to directly visualize nonviable myocardium with excellent contrast and spatial resolution. In addition to use in patients with coronary artery disease, this imaging technique has diagnostic value in the setting of nonischemic cardiomyopathy.

Variable patterns of LGE have been described in a wide variety of cardiomyopathies. These patterns are usually quite distinct from LGE seen after myocardial infarction and may even be disease specific. Mid-myocardial enhancement is found in hypertrophic cardiomyopathy at the site of collagen deposition (1), and small patches of predominantly subepicardial enhancement may be seen with acute myocarditis (2). Hence, CMR is a tool for differentiation between ischemic and nonischemic cardiomyopathy and for identification of disease-specific patterns of enhancement. Going beyond diagnosis, there is interest in comparing the pattern and extent of LGE with patient risk and outcome in nonischemic cardiomyopathies. For example, the presence of mid-myocardial LGE has been associated with increased rates of adverse events and worse outcomes in dilated cardiomyopathy (3).

In this issue of the Journal, Vogelsberg et al. (4) describe the use of LGE-CMR in comparison to myocardial biopsy for diagnosis of cardiac amyloidosis in a clinically routine setting. The authors conclude that LGE-CMR can be used for diagnosis of cardiac amyloidosis in patients presenting with diastolic heart failure and suggest that cardiac amyloidosis may occur more frequently in the absence of systemic amyloid disease than currently suspected.

Amyloidosis is the extracellular accumulation of fibrillar proteins, certain forms of which may involve the heart. Early detection of cardiac involvement is desirable to optimize survival through aggressive treatments. In immunoglobulin light-chain and transthyretin-related amyloidosis, the presence of cardiac involvement is a major factor influencing both prognosis and treatment options.

Echocardiography is commonly used to screen for the presence of cardiac involvement in systemic disease, but definitive diagnosis of cardiac involvement hinges on the “gold standard” of endocardial biopsy. Cardiac involvement can be the presenting feature of systemic amyloidosis or the sole feature of disease in wild-type transthyretin-related amyloidosis (senile cardiac amyloidosis). In the absence of systemic disease, or when left ventricular hypertrophy from other causes exists, the differentiation of cardiac amyloidosis from other causes of restrictive cardiomyopathy by echocardiography may be challenging.

Nuclear techniques have been used for the noninvasive detection of cardiac amyloidosis. The 2 main types of radiolabeled tracers studied are bone tracers, particularly 99mTc-pyrophosphate and 123I-labeled serum amyloid P protein (SAP). Scintigraphic features associated with cardiac amyloidosis are influenced by the type of protein deposition, the choice of radionuclide tracer, and the extent of disease. Bone tracer data are extensive, with 99mTc-pyrophosphate most widely studied, but sensitivity appears limited; binding is nonspecific for amyloid type and not quantifiable. 123I-labeled SAP binds to all types of amyloid and is retained in the body in proportion to amyloid deposition, permitting noninvasive monitoring of amyloid regression during therapy (5).

The presence of LGE in cardiac amyloidosis has been previously reported. Perugini et al. (6) described CMR of a selected group of 21 patients with a “definite diagnosis” of cardiac amyloidosis. They found LGE in 16 of 21 patients, without apparent relationship between LGE and clinical, functional, or histologic characteristics. In the same year, Maceira et al. (7) published CMR findings in a selected group of 29 patients with echocardiographic criteria for cardiac amyloidosis in the setting of confirmed systemic amyloidosis. The CMR protocol was adjusted during this study, owing to the appreciation of abnormal gadolinium kinetics in these patients. Overall, 20 of 29 patients had LGE, and the pattern was subendocardial and global in all cases.

Vogelsberg et al. (4) describe the correlation between LGE-CMR and cardiac biopsy in a group of 33 patients presenting with diastolic heart failure in combination with either myocardial hypertrophy (n = 24) and/or other conditions often associated with cardiac amyloidosis (n = 18). Unlike previous reports of LGE in patients with known cardiac amyloidosis, this study describes an experience that
is taken from routine clinical practice and compares the diagnostic performance of LGE-CMR with biopsy.

In their population, a “typical pattern” of circumferential subendocardial LGE was observed in 12 of 15 patients with subsequent biopsy-proven cardiac amyloidosis. The agreement between LGE-CMR and biopsy was optimized by the routine sampling of both the right and left ventricles and the fact that cardiac biopsy was guided by the location of abnormalities on CMR. This circumstance could be considered a source of bias in a study that seeks to compare a noninvasive imaging test with a gold standard, as it can be hypothesized that a biopsy performed blinded to CMR findings and limited to the right ventricular side of the interventricular septum would have resulted in less accurate sampling of diseased myocardium and thus a higher “false positive” rate of CMR. However, 2 points can be made in defense of the approach taken. First, the authors aim to describe the performance of CMR in a “clinical routine setting” and, with routine practice, the results of noninvasive imaging are available before biopsy. Second, by virtue of this study design, the authors have demonstrated that CMR can guide cardiac biopsy in suspected cardiac amyloidosis, as seen by the excellent correlation between imaging and histologic abnormalities. This is the same approach taken by this group in its previous report of CMR for diagnosis of acute myocarditis (2), where biopsy was also guided by LGE-CMR.

This study does not suggest that CMR should replace cardiac biopsy; however, a “typical pattern” of LGE may be sufficient to allow an assumption that a patient probably has cardiac amyloidosis as the cause for diastolic heart failure. Biopsy may be required to define the type of amyloidosis but can potentially be obtained from extracardiac tissue, obviating the need for higher risk myocardial biopsy. There were 3 patients without the typical pattern of LGE-CMR in whom cardiac biopsy demonstrated amyloid protein. The authors suggest that CMR features may not be seen early in cardiac amyloidosis or may occasionally be atypical. With respect to clinical management, cases such as this will require cardiac biopsy for diagnosis.

Another point of interest with this study is the observation that 11 of 15 patients diagnosed with cardiac amyloidosis had cardiac involvement as a first manifestation of disease. Cardiac involvement has been considered as a late manifestation of systemic amyloidosis, but this may be in part related to limited sensitivity and specificity of echocardiographic and nuclear techniques and late appearance of symptoms relative to cardiac disease burden.

It appears that LGE-CMR is a new, noninvasive means of identifying patients with cardiac amyloidosis that has the potential to reshape the current understanding of the natural history of systemic amyloidosis. Is it as easy as recognizing white from black? Not quite: the performance of LGE-CMR in cardiac amyloidosis requires understanding of the numerous variables that influence image quality, most importantly, the altered gadolinium kinetics with amyloidosis and the likelihood of very diffuse involvement of the myocardium—points that these authors clearly appreciate and elegantly illustrate.

Further study of LGE-CMR in cardiac amyloidosis is needed to define the relationship between the CMR appearance and the histologic type of amyloidosis, the changing cardiac burden of disease with treatment, and, possibly, the risk of disease-related complications such as arrhythmia. With this publication, there is evidence to suggest that LGE-CMR has clinical utility for the noninvasive detection of cardiac amyloidosis in patients presenting with diastolic heart failure.

**REFERENCES**