JACC: CARDIOVASCULAR IMAGING
VOL. 3, NO. 2, 2010

ISSN 1936-878X/10/$36.00
PUBLISHED BY ELSEVIER INC.
DOI:10.1016/j.jcmg.2009.10.013

EDITORIAL COMMENT

MR Imaging and Cardiac Amyloidosis

Where to Go From Here?*

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Cardiac amyloidosis describes clinically significant involvement of the heart by amyloid deposition, which may or may not be associated with involvement of other organs. Acquired systemic amyloidosis occurs in more than 10 per million person-years in the U.S. population, and cardiac involvement usually portends a poor prognosis, with or without treatment (1). As no single noninvasive test or

See page 155

abnormality is pathognomonic of cardiac amyloid, diagnosis of cardiac amyloid has usually relied on: 1) echocardiographic assessment, especially measurement of LV wall thickness, subjective assessment of myocardial appearance, and evaluation of diastolic function/restrictive physiology; and 2) histopathological findings of amyloid deposition on endomyocardial biopsy. However, both of these means of diagnosis suffer from significant limitations. Echocardiographic indicators of amyloidosis are neither sensitive nor specific, and endomyocardial biopsy is invasive, as well as being subject to potential sampling error. Cardiac magnetic resonance (CMR) has a number of appealing properties in the evaluation of suspected amyloid heart disease. Its high spatial resolution and signal-to-noise ratio permit reproducible measurement of cardiac chamber volumes and mass, as well as LV and atrial septal wall thickness. It can characterize pericardial and pleural fluid. Finally, the 'late gadolinium enhancement' technique (LGE-CMR) has an established role in 'phenotyping' various forms of cardiomyopathy (2). In this issue of *iJACC*, Syed et al. (3) report their findings from a cross-sectional study of 120 patients referred to a tertiary center with confirmed amyloidosis. CMR was performed at physician discretion. Endomyocardial biopsy was obtained in a more severely affected subset of patients, and interstitial amyloid content semiquantitatively measured. Cases without cardiac histopathology were dichotomized into those with and without evidence of cardiac amyloid on the basis of mean LV wall thickness >12 mm from end-diastolic septal and inferolateral walls by echocardiography. LGE-CMR was performed 7 to 12 min after 0.2 mmol/kg gadodiamide. The selection of optimal inversion time (TI), especially difficult in this patient group, was performed using a multi-TI cine fast echo sequence.

Among patients with histologically confirmed cardiac amyloid, increased echocardiographic wall thickness was observed in 91% and LGE in 97% of cases. The pattern of LGE was global (transmural or subendocardial) in 83%, patchy focal in 6%, while in 8% there was suboptimal nulling. Suboptimal nulling was defined where adequately nulled "black" myocardium could not be obtained despite the use of multiple TIs; these differed from diffuse LGE in that they did not have hyperenhanced myocardium. The presence of global LGE was associated with more severe interstitial cardiac amyloid deposition. Among individuals without cardiac histology but with increased echocardiographic wall thickness, there was global LGE in 53%, patchy focal LGE in 12%, suboptimal nulling in 20%, and no LGE in 14%. Of the patients without cardiac histology and with normal echocardiographic wall thickness, there was global LGE in 8%, patchy focal LGE in 22%, suboptimal nulling in 17%, and no LGE

*Editorials published in *JACC: Cardiovascular Imaging* reflect the views of the authors and do not necessarily represent the views of *JACC: Cardiovascular Imaging* or the American College of Cardiology.

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JACC: CARDIOVASCULAR IMAGING, VOL. 3, NO. 2, 2010
FEBRUARY 2010:165–7

in 53%. There was a biologically plausible association between degree of LGE and markers of disease severity, including New York Heart Association functional class, CMR measures of cardiac mass and ejection fraction, electrocardiographic parameters, and cardiac biomarkers.

The major strength of the present study by Syed et al. (3) lies in the 35 patients with histological confirmation of cardiac amyloid. It corroborates (with greater patient numbers) the findings of Perugini et al. (4), who reported similar findings in 21 patients with cardiac amyloid. Although the prevalence of LGE reported by Syed et al. (3) is similar to that observed by Maceira et al. (5), the pattern of LGE differed in that it was global subendocardial in all cases in the series of Maceira et al. (5), whereas it was more commonly transmural in those with histopathologically confirmed cardiac amyloid in the present study. Vogelsberg et al. (6) also reported a global subendocardial pattern of LGE in cardiac amyloid cases. The authors, correctly, attribute such discrepant findings to variation in the dose of contrast across these studies and timing of imaging after its administration. Allied to the timing of imaging after contrast administration is the selection of TI at which LGE is measured. The diffuse nature of cardiac amyloid, and the alteration in myocardial gadolinium kinetics in this condition make TI selection crucially important in its detection by CMR. A limitation in the widespread application of LGE-CMR in identifying cardiac amyloid is the reproducibility with which this can be performed, and a more standardized technique is desirable.

Three significant potential weaknesses of this study merit discussion. First, the key question of whether LGE-CMR can identify cardiac amyloid earlier in the disease process than detection of morphological changes (by standard echocardiography) remains incompletely answered by this study. It is this group of patients that should draw particular attention, however, because they may be most likely to benefit from disease-modifying, and potentially life-prolonging, therapy. Second, CMR was performed at a tertiary referral center at attending physician discretion, which would have introduced a significant selection bias. This makes it difficult to define the sensitivity and specificity of the LGE-CMR technique in detecting early (i.e., with normal LV wall thickness) cardiac amyloidosis from the authors' data. Third, in the patients without a cardiac biopsy (who form the majority of the study cohort), the echocardiographic criteria used to diagnose cardiac amyloid are only moderately specific. A mean LV wall thickness >12 mm is not uncommon, and can often be found in systemic hypertension, the prevalence of which is not stated in this cohort. While previous myocardial infarction was an exclusion criterion, systematic coronary angiography was not undertaken to exclude ischemic heart disease as a cause for LGE. It is conceivable that some of the LGE findings in this subgroup might represent occult coronary artery disease. The absence of endomyocardial biopsy data from patients with normal wall thickness renders this report's LGE data speculative, rather than definitive, despite the relationship between LGE presence and surrogate markers of cardiac involvement in this subgroup.

This and other recent studies also raise the question of whether a positive LGE-CMR result can obviate the need for endomyocardial biopsy for the diagnosis of cardiac involvement in patients with known amyloidosis. CMR would appear a reasonable alternative to endomyocardial biopsy in patients with tissue diagnosis from an alternate site and thought to be at high risk for invasive investigation, particularly where classic CMR findings of cardiac amyloid are identified. The advantage of an imaging modality for the recognition of cardiac amyloid is its ability to interrogate the entire heart, whereas biopsy can suffer from a sampling error (7).

The prognostic significance of the finding of LGE or suboptimal nulling cannot be determined from this cross-sectional study. Recent evidence from Maceira et al. (8), in a cohort of 29 patients, suggests that T1 mapping may have greater ability to predict outcome than LGE per se, possibly as it more accurately reflects the myocardial interstitial amyloid load. However, the additive value of this technique to existing prognostic indicators requires confirmation in larger series. Lastly, work from Rapezzi et al. (9) highlights the difference in outcome between different types of cardiac amyloidosis. Whether CMR has an independent discriminatory role across these subtypes is unknown. This is a fertile area of continuing research, and the study by Syed et al. (3) is an important step along the journey in identifying early imaging markers of cardiac amyloidosis.

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Key Words: amyloidosis ■ cardiac magnetic resonance ■ late gadolinium enhancement.