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Editorial commentary: Role of cardiac magnetic resonance imaging in the evaluation of amyloidosis☆

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Cardiac amyloidosis was once perceived as a relatively rare condition, difficult to diagnose, and largely untreatable, however currently is recognized with increased frequency due to advances in cardiac imaging, and now potentially treatable with continued advances in therapy [1–3]. Cardiac amyloidosis is caused by the deposition of amyloid protein in the heart most commonly from either light chains (AL) or tranthyretin (TTR, including wild type[senile] or mutant [senile] form) [1–3]. While prognosis with therapy has been improving, early diagnosis of cardiac amyloidosis is critical, particularly AL, given high short term mortality rates if left untreated [1].

Cardiovascular magnetic resonance (CMR), a high-resolution 3D tomographic imaging technique offers the unique ability to characterize various tissue types and has emerged as an important imaging modality for diagnosis of cardiac amyloidosis [3,4]. CMR is the imaging modality of choice when the etiology of left ventricular hypertrophy (LVH) remains in doubt following echocardiography as it allows for differentiation between hypertrophic cardiomyopathy (HCM), hypertensive heart disease, athletes heart, glycogen/lysomal storage diseases (such as Fabry's or Danon disease) as well as cardiac amyloidosis by evaluation of magnitude and extent of LVH and patterns (or absence) of contrast enhancement with late gadolinium enhancement (LGE). Similarly, when evaluating individuals with systemic amyloidosis, CMR allows for detection of cardiac involvement, even in the absence of left ventricular hypertrophy [1,3,4].

This sets the stage for the article by Zhang et al., in the current edition of *Trends in Cardiovascular Medicine*, describing both the clinical utility and potential future applications of CMR in evaluation of patients with this disease [5]. This state-of-the art paper provides several critical "take-home points" regarding the clinical utility of CMR in this population:

Diagnosis. While many classic features of cardiac amyloidosis can be recognized by echocardiography, CMR plays an important role in improved detection and differentiation of cardiac amyloidosis. CMR allows for characterization of pattern of LVH and while hypertrophy is commonly concentric, it may be asymmetric, particularly in ATTR [2]. However, even when asymmetric the lateral wall in amyloid is often hypertrophied to greater extents than that typically seen with HCM. Additionally, CMR allows for identification of other common features including right ventricular hypertrophy, biatrial enlargement, pericardial and pleural effusions [1–3].

The major advantage of CMR in amyloidosis is contrast enhanced imaging with LGE to readily identify cardiac involvement in patients with systemic amyloidosis, and provides an LGE pattern virtually pathognomonic for amyloidosis in patients with unexplained LVH [3,4,6]. Typically, LGE in amyloid has a global subendocardial enhancement pattern with development of transmural LGE with disease progression [4]. A potential previous limitation of traditional LGE imaging was due to difficulty with nulling the myocardium (failure to create sufficient contrast between the enhancing and non-enhancing myocardium), a problem specific to diffuse disease processes that can confounded interpretation. However, the use of phase-sensitive inversion recovery (PSIR) technique to acquire LGE images allows for appropriate nulling to correct for this and improve detection of LGE in cardiac amyloid [4].

T1 mapping. T1 mapping is a newer CMR technique that is particularly attractive for cardiac amyloidosis as it overcomes the potential limitation of difficulty nulling myocardium in amyloid with traditional LGE imaging [4,7,8]. While these technical challenges can be overcome with the use of the PSIR technique, T1 mapping remains promising as it is based on the measurement of an absolute T1 time of a region of interest, most commonly measured either before (known as native T1) or at multiple time points before and after contrast administration to calculate the extracellular volume (ECV), and allows for a more direct assessment of abnormal

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myocardial substrate as well as total extent of expanded extracellular space [7,8].

Both native T1 values as well as ECV are substantially higher on average in cardiac amyloidosis compared to both normal as well as other disease states causing left ventricular hypertrophy [7,8]. Indeed, native T1 and ECV values may be abnormal prior to other cardiac morphologic abnormalities, signaling early cardiac involvement [4]. While both average native T1 and ECV values are higher in amyloidosis as compared to other diseases, overlap can nevertheless occur (particularly with HCM and amyloidosis), limiting diagnostic utility of T1 mapping alone for individual patients. On the other hand, other CMR variables, including LGE, in combination with T1 mapping can differentiate these disease entities for individual patients [1–4].

AL vs. ATTR. Although there has been much hope that CMR can differentiate between AL and ATTR amyloidosis, at present CMR is unable to reliably make this important phenotypic differentiation. Considerable overlap occurs between these phenotypes, for example, while transmural LGE more common in ATTR (present in 90% of patients), nearly 40% of AL patients also have this finding [9]. Similarly, both native T1 and ECV cut points are not specific to amyloid type [1,2,4]. Therefore, CMR should not be used to determine amyloid type.

Despite this short-coming by CMR, a tissue diagnosis is no longer always necessary in patients of suspected amyloidosis [10]. Evaluation for plasma cell dyscrasia (with serum protein electrophoresis, serum immunofixation and free light chain assay) can be performed as the next step after suspicion of amyloid is seen by CMR, with absence of plasma cell dyscrasia and a positive 99mTc-phosphate scan leading to a diagnosis of ATTR without a biopsy. However in patients with a plasma-cell dyscrasia, a biopsy for diagnosis (bone marrow, cardiac or otherwise) is needed [1,2,10].

Prognosis. Similar to other disease states, LGE has been strongly linked to mortality in amyloidosis. Presence of LGE has been linked to mortality while absence of LGE has been associated with improved survival in patients with systemic disease (up to 92% at 2 years) [4]. Additionally, transmural LGE patterns appear to indicate later stages of disease progression and are independently associated with mortality in both AL and ATTR amyloid [4].

T1 mapping also appears associated with disease severity and mortality in both ATTR and AL amyloidosis. Indeed, a linear increase in both native T1 and ECV values appears to correlate with severity of cardiac involvement, and both native T1 and ECV have been independently associated with prognosis in both subtypes [4,7,8].

CMR and the future. The future may continue to be even brighter for CMR in cardiac amyloidosis. Monitoring changes in native T1 or ECV may ultimately prove to play a critical role in the evaluation of cardiac response to treatment and given the independent link to mortality may prove to be a helpful clinical marker or even end-point in clinical trials [11]. Additionally, the potential for a single MR/PET clinical examination to evaluate for amyloidosis as well as diagnose subtype (i.e., ATTR) could dramatically change the landscape for clinical evaluation of this disease [12]. However, as currently there are limited clinical studies using this modality, as well as limited access and high costs, this technology is likely far from routine clinical availability.

In summary, CMR has become a key test in cardiac amyloidosis, raising suspicion for diagnosis in unexplained LVH, and identification of cardiac involvement in systemic disease. Multiple studies have now demonstrated prognostic utility of both LGE and T1 mapping in this disease, and T1 mapping may ultimately play a key role in evaluation of therapeutic effects of treatment, leading CMR to potentially become an even more essential component of disease evaluation in the future.

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