CMR and Amyloid Cardiomyopathy

Are We Getting Closer to the Biology?*

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In cardiac amyloidosis, myocardial tissue histology reveals among its salient features, the expansion of the extracellular space, the accumulation of amyloid protein, and collagen fiber deposition. At the cellular level, cytoplasmic vacuolization and decline of myofibrils are commonly seen in endomyocardial biopsies from amyloid patients. There is evidence that human amyloidogenic light (AL) chain proteins have a cardiotoxic effect (1), which is associated with impaired cardiomyocyte contractile function and increased cell death. Of similar relevance for transthyretin-related amyloidosis (ATTR) is the fact that transthyretin (TTR) also has a cytotoxic effect (2), causing increased inflammatory and oxidative stress. How well cardiac magnetic resonance (CMR) can identify various aspects of pathological tissue remodeling in cardiac amyloidosis remains a question of intense research interest.

Over the last decade, CMR has identified a series of promising image-based markers tied to cardiomyopathic changes in amyloidosis. Initial work has focused on imaging late gadolinium enhancement (LGE), which has proven challenging in a substantial portion of patients with suspected cardiac amyloidosis because contrast enhancement tends to be diffuse. This has prompted the increasing interest in using T₁ mapping in cardiac amyloidosis, which is a method that provides a continuous measure, rather than a “binary” contrast, as sought in LGE.

In this issue of jACC, 3 separate reports tackled the challenging tasks of CMR of suspected cardiac amyloidosis. Dungu et al. (3) describe a larger LGE burden in ATTR patients than in AL patients and extended this clinical suspicion by studying a multicenter cohort of 100 patients who reached a final diagnosis of cardiac amyloidosis (50% by cardiac histology and 50% by international guidelines). The investigators derived a QALE (Query Amyloid Late Enhancement) score and reported a sensitivity of 87% and a specificity of 96% in differentiating ATTR (n = 51) from non–TTR-related cardiac amyloidosis (AL: n = 46; others: n = 3). The derivation of this score by Dungu et al. (3), though based on “real-world data,” was influenced by less-than-standardized LGE imaging protocol across 46 centers, variable scanner field strengths, and variable clinical use of endomyocardial biopsy. Sizing of LGE extent is well known to be challenging in imaging of diffusely infiltrated myocardium, and thus the results, albeit intriguing, cannot obviate the role of endomyocardial biopsy in patients with remaining uncertainty of their clinical diagnoses. Nonetheless, the QALE score developed in this pilot experience would have valuable diagnostic and prognostic implications if the results hold up in a prospective clinical trial.

White et al. (4) propose the use of a rapid, postcontrast, T₁-based visual comparison between the myocardium and blood pool, using an inversion-prepared technique, which is already being used in many centers to determine the optimal inversion time (TI) for conventional LGE imaging, and routinely referred to as “TI scout.” The criterion for the presence of diffuse left ventricular hyperenhancement was that the inversion recovery was more rapid in >50% of the myocardium compared with inversion recovery of blood, the reverse of what is typically seen in patients without infiltrative cardiomyopathies. More importantly, this study represents the largest current

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See pages 133, 143, and 157.
evidence in using CMR in characterizing the prognosis of suspected cardiac amyloid patients at a median follow-up of 29 months. The investigators found a robust association of diffuse LGE with all-cause mortality, not only in the main cohort but also in subgroup analyses. However, whereas this visual evaluation represents a practical and rapid way to assess the cardiac amyloid burden, its reliability may be influenced by variability introduced by the severity of the systemic disease burden (which affects availability of gadolinium in the blood-pool, and thus blood $T_1$), and possibly also by patient body weight, time after contrast injection, and renal function.

Furthermore, only a minority of the cohort in this study reached a histological diagnosis of cardiac amyloidosis. With the specificity of shortened $T_1$ visualization only in a moderate range, further studies will need to address whether this visual method delivers enough accuracy for tracking of disease severity and guiding any management decisions including eliminating the need for biopsy or initiation of novel medical therapy.

Fontana et al. (5) report high diagnostic accuracy for detecting ATTR or AL using native (pre-contrast) $T_1$ mapping against patients with hypertrophic cardiomyopathy as control cases. This work builds on previous observations that the native (i.e., pre-contrast) myocardial $T_1$ is abnormally high in cardiac amyloidosis, and specifically probes differences in native $T_1$ between ATTR and AL (6,7).

The investigators propose that native $T_1$ mapping reflects on a subclinical inflammatory process, and it can detect abnormal myocardial infiltration more sensitively than LGE imaging in morphologically normal gene mutation carriers. The role of native $T_1$ mapping, relative to mapping of extracellular volume (8–10) remains to be more fully defined.

All 3 studies provide new knowledge that may advance our understanding of how CMR can assist in the management of patients with suspected cardiac amyloidosis, although all of them suffer from the inherent bias of a cohort-control design, variable criteria for establishment of the diagnosis of cardiac amyloidosis, or small study size, reflecting the challenge of studying patients surrounding this clinical condition. These and other CMR studies are in part driven by the expectation that CMR can provide some form of noninvasive biopsy in cardiac amyloidosis and other cardiomyopathies (11). This presupposes that one can achieve a good understanding of the pathophysiological basis of changes in relaxographic properties of myocardial tissue.

Inflammatory stress resulting from amyloid protein deposition is a plausible cause for prolonging the native $T_1$ (and $T_2$) in the myocardium. The native, myocardial $T_1$ of patients with systemic inflammatory diseases, such as lupus erythematosus, an inflammatory autoimmune disease, is longer than in healthy control subjects (12) by an amount of similar magnitude as in the present study Fontana et al. (5). The mechanism through which inflammatory stress would increase the native myocardial $T_1$ is likely linked to an increase of free water content (edema), but inflammation is also associated with higher contrast enhancement, which may be influenced by factors other than free water content.

Some inconsistencies exist between the findings of the current reports, morphologic features, and natural histories of amyloid subtypes. Patients with TTR-type amyloidosis show significantly more pronounced ventricular hypertrophy than do patients with systemic, immunoglobulin light-chain–type amyloidosis. Consistent with this previous knowledge, Dungu et al. (3) report that late-gadolinium enhancement was pervasive in ATTR patients and less frequent in AL patients, seemingly suggesting that if one judges the disease pathology by LGE, ATTR would appear to have more severe repercussions on the left ventricle than AL would, yet median survival time from diagnosis has been known to be longer for ATTR patients than for AL patients. The exacerbated hypertrophy in ATTR raised the expectation that native $T_1$ changes would be elevated relative to normal myocardium and with $T_1$ longer in ATTR than in AL. Somewhat surprising, therefore, is the finding of Fontana et al. (5) that the native $T_1$ was not as elevated in ATTR as it was in AL.

The fact that the findings discussed here do not coalesce to an entirely coherent understanding of the different CMR parameters suggests that future studies should be more comprehensive and should integrate native $T_1$, extracellular volume, $T_2$, and LGE. In histology, one uses various stains to characterize tissue pathology, and the same can be said for CMR, where relaxation properties take on the role of virtual stains in parametric maps. Determining the best types and methods of “staining” myocardial tissue with CMR remains an important challenge and opportunity, as evidenced by the 3 referenced papers in this issue of JACC.

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