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CMR Visualization of Cardiac Amyloid Infiltration: Challenges and Opportunities

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Cardiovascular magnetic resonance (CMR) is an indispensible clinical tool that can identify the etiology of cardiomyopathy. Unlike other non-invasive imaging modalities, CMR leverages its intrinsic capacity to characterize tissue based upon fundamental MR properties (T_1 and T_2) and in so doing can differentiate normal from diseased myocardium. Following the administration of the exogenous contrast agent gadolinium, which is retained in areas of increased interstitial space, intrinsic MR differences are accentuated permitting selective visualization of fibrosis and infarction by means of late gadolinium enhancement (LGE). LGE, arguably one of the most important innovations in the history of CMR, works best when the border between normal and abnormal is distinct and the region of abnormality is sufficiently different so as to result in significant gadolinium accumulation, thereby shortening T_1 and rendering a high signal intensity difference from normal myocardium.

In diffuse myopathic processes, as typified by cardiac amyloidosis, the discriminative capacity of LGE to differentiate the normal from the abnormal is challenged because the entire myocardium is abnormal and clear demarcation is absent. In cardiac amyloidosis, precursor proteins pathologically unfold to form amyloid fibrils that deposit in the myocardium thereby increasing interstitial space and resulting in gadolinium accumulation. While it is generally accepted that the most common types of cardiac amyloidosis, light-chain (AL) and transthyretin (ATTR), overlap in respect to their CMR manifestations[1, 2], there are no reported data to effectively disentangle amyloid type and degree/stage of amyloid infiltration. For this reason, reported LGE characteristics in cardiac amyloidosis are quite varied, with diffuse, subendocardial and transmural patterns reported[3]. Furthermore, standard LGE imaging techniques are flawed in amyloidosis as there is a requirement that the MR technologist select a key parameter from visual inspection, the inversion time (TI),

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to optimally suppresses signal from regions of normal myocardium. When nothing appears normal, TI selection can become an exercise in futility.

Diffuse myocardial processes are perhaps better assessed by CMR through T_1 mapping techniques that estimate the myocardial T_1 tissue relaxation time in a pixel-wise manner to create a T_1 map. T_1 maps measured before (i.e. native T_1 map) and after gadolinium contrast can be used to non-invasively assess the myocardial extra-cellular volume fraction (ECV). Compared to controls, abnormal T_1 and ECV differences have widely been described in various cardiomyopathies including hypertrophic, non-ischemic dilated, and amyloid[4, 5]. In practice, LGE is relatively simple to perform and interpret while T_1/ECV is not owing to heterogeneity of acquisition and post processing techniques; however, performed correctly, the two techniques measure the same T_1 variation albeit with different contrast-to-noise ratio, and thus regions of LGE should correspond spatially to abnormal T_1/ECV mapped areas.

In this issue of *Circulation*, Fontana et al. present a complete report of both T_1/ECV mapping and LGE among patients with cardiac amyloidosis[6]. This study, the largest series of CMR in cardiac amyloidosis yet reported, redefines our understanding of the continuum of infiltration in cardiac amyloidosis from early to late stage of disease, and moves beyond a simple dichotomous interpretation of imaging information. The application of LGE and T_1/ECV mapping in the same dataset unifies contemporary non-invasive CMR assessment with hard clinical outcomes for the first time, and importantly, supports the use of a widely available LGE technique, phase sensitive inversion recovery (PSIR), as the most accurate means by which to assess LGE in amyloidosis. The PSIR sequence removes the subjective TI selection variable from LGE imaging acquisition thereby improving identification of hyperenhancement and eliminating the possibility of confounding by the wrong choice of TI. The implications of this report should change the practice of CMR in amyloidosis and, potentially, other diffuse cardiomyopathic processes.

Fontana et al. recruited a cohort of 250 consecutive patients with cardiac amyloidosis of whom there were 122 with ATTR and 119 with AL. In addition, 9 patients with TTR mutations but no apparent cardiac disease manifestation (i.e., genotype positive-phenotype negative) were also recruited. Patients were followed for a 24 +/− 13 months with mortality observed in a sizable proportion (27%). CMR imaging involved pre- and post-contrast T_1/ECV determination and standard MAG-IR LGE imaging in all, as well as PSIR LGE imaging in 43% of patients. The authors then analyzed LGE images and categorized LGE pattern in a simple tri-partite classification scheme (normal, sub-endocardial, transmural) while associating the observed LGE pattern with ECV and clinical outcomes. In this way, they were able to compare standard MAGIR with PSIR, AL with TTR, and early with advanced disease. The patients were also characterized by echocardiography (though notably without longitudinal systolic strain) and serum cardiac biomarkers including nT-pro-BNP (but not troponin). To substantiate cardiac amyloidosis in the ATTR cohort, the authors reported imaging characteristics using Tc99m-DPD (3,3-diphosphono-1,2-propanodicarboxylicacid) scintigraphy.

The principal findings of this report are as follows. First, there appeared a continuum of amyloid accumulation as determined by LGE pattern progressing from normal to transmural, the latter being more prevalent in ATTR, with robust ECV cut-points that were not specific to amyloid type. Second, utilizing a subset of 100 patients with post-contrast T_1 maps as the "truth standard" for contrast accumulation in areas of presumptive amyloid deposition, the PSIR technique proved superior to conventional MAG-IR for accuracy in assignment of LGE pattern. Discordance between MAG-IR and PSIR was high (57%), an impressive observation given the expertise of this established amyloidosis and experienced CMR center, while PSIR and post-contrast T_1 maps were not discordant. Third, a transmural LGE pattern was independently associated with mortality irrespective of amyloid type and remained associated after adjustment for echo characteristics or nT-pro-BNP (HR=4.13, 95%CI: 1.30-13.07, p<0.0001). Fourth and finally, 39% of patients with no LGE and no clinical manifestations of cardiac amyloidosis as determined by CMR, echo, or nT-pro-BNP, had ECV measurements above the reported normal range (with results between 0.32 and 0.40) suggesting very early amyloid accumulation beneath the detection threshold of these other approaches.

This study greatly informs our understanding of how amyloid cardiomyopathy progresses from early to advanced stage of infiltration while affording insight into conflicting prior reports of LGE and its relationship to survival. One important observation consistent with prior reports is that among patients with transmural LGE, associated with the highest ECV and worst prognosis, myocardium retained more gadolinium than the blood pool causing blood pool signal nulling and rendering the myocardium uniformly bright (termed diffuse hyperenhancement)[7]. It is also notable that LGE pattern predicted survival irrespective of amyloidosis type, although this appeared most striking in AL. Given this high discordance of PSIR from MAG-IR, the high concordance of PSIR with post-contrast T_1 maps, and comparative simplicity and wide-spread availability of PSIR, the authors concluded that PSIR should replace MAG-IR as the LGE method of choice in cardiac amyloidosis.

It is important to note that the methodology used to assess discordance between T_1 maps, PSIR, and MAG-IR LGE was non-standard. The use of post-contrast T_1 as the "truth standard" method for visualization of extracellular space expansion is clearly challenging and subjective in cardiac amyloidosis. The low image contrast between amyloid infiltrated and healthy myocardium renders accurate detection difficult. T_1 measurements were performed using the shortened modified look-locker inversion recovery sequence (ShMOLLI) with regions of interest (ROI) drawn in the 4 chamber view at the level of the basal and mid inferoseptum. It is unclear whether the authors included or excluded areas of enhancement on LGE in these ROI for post-contrast T_1 measurements, which may have biased ECV calculations. In addition, the T_1 maps presented appear to be scaled to a broad T_1 range (300 – 3300 ms) rendering it difficult to visually identify the myocardial regional differences of up to 150 ms the authors report. Furthermore, this study utilizes an equilibrium ECV and post-contrast T_1 measurement that is rather cumbersome and somewhat out-dated. The equilibrium technique may not add additional information compared to single bolus infusion, now more commonly used in CMR studies to measure ECV. In respect to LGE transmurality assignment, it will be important to demonstrate reproducibility in a multi-center cohort given the acknowledged challenging image quality.

Finally, the limited subgroups size (PSIR vs. non-PSIR, TTR vs. AL) rendered relatively wide confidence intervals, particularly for the key association between transmural LGE and survival.

It is also notable that among the ATTR patients, those with wild-type TTR and variant (mutated) TTR were included in the same ATTR categorization. This combination of potentially different disease trajectories may be problematic for survival interpretation. In respect to amyloid deposition however, the data do suggest that DPD uptake, LGE transmurality, and ECV are all positively associated, again supporting a continuum of infiltration in ATTR. Of the few patients with LGE negative variant TTR, DPD uptake was abnormal (grade 1) in 3 of 4 with increased ECV suggesting an interesting association between DPD grade and ECV in very early stage ATTR disease – a new finding not yet reported that may have important implications for screening of cardiac involvement in genotype carriers.

While a large series, cardiac amyloidosis was determined without cardiac biopsy in the vast majority of AL patients (94%) and most of the ATTR patients (71%), the latter of which were typically identified by DPD scintigraphy. This reflects the expertise and clinical practice of this referral center, and is not dissimilar from other reports[8]. Furthermore, while we are provided with treatment regimens for AL disease and hematologic response status in broad terms, we are not provided with specific information such as free light chain or cardiac troponin concentrations, that might help elucidate the component of direct toxicity of pre-fibrillar light chain proteins in respect to ECV and LGE. Finally, as is intrinsic in all contrast-enhanced CMR studies, patients with advanced renal disease (glomerular filtration rate < 30 ml/min) were excluded, thereby affording a selection bias. For patients with advanced renal disease, native T_1 mapping (data provided here in Table 2), may provide useful prognostic and diagnostic information[9].

While arguably redefining the CMR assessment of cardiac amyloidosis, how does one incorporate the findings of Fontana et al. into the larger context of clinical assessment in systemic amyloid disease? For AL disease in particular, given the wealth of data supporting biomarker staging, treatment selection, and prognosis, CMR will probably still be viewed as an informative adjunct, utilized only in selected patients. Subsequent studies may prove that the primary utility, given the more precise and likely reproducible T_1/ECV and PSIR findings, may be in following serial changes with specific therapies. While obviously more expensive and difficult to measure, CMR biomarkers are more likely to reflect real changes in amyloid accumulation as compared to serum biomarkers, particularly nT-pro-BNP, that may fluctuate with volume status and creatinine clearance.

Fontana et al. have assembled a dataset that significantly adds to our understanding of the utility of CMR in cardiac amyloidosis. These data strongly suggest that PSIR should replace MAG-IR for LGE determination in cardiac amyloidosis, and that T_1 mapping (however, we would submit using a contrast bolus rather than equilibrium technique) affords insight into the continuum of amyloid fibril deposition that occurs in this disease. We commend the authors on their accomplishment and anticipate that these conclusions will refine clinical practice.

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