Late gadolinium enhancement and prognosis in cardiac amyloidosis: ready for prime time?

During the 10 years since the first study on cardiac magnetic resonance (CMR) in cardiac amyloidosis was published, (1) the technique has transformed our approach to this devastating disease, providing a second opinion on cardiac structure and function and yielding unique information through tissue characterization. Diagnostic algorithms integrating clinical presentation, ECG, echocardiography and blood biomarkers can obviate the need for myocardial biopsy in some patients, but clinical uncertainty frequently prevails and detection of early cardiac amyloidosis remains a challenging goal.

The key advantage of CMR over echocardiography is its unique ability to provide information on tissue composition.(1) After administration of an extrinsic gadolinium-based contrast agent, CMR in cardiac amyloidosis shows a characteristic pattern of global subendocardial LGE coupled with abnormal myocardial and blood pool gadolinium kinetics. Enthusiasm following the initial report has translated into wide dissemination of the technique with no standardized approaches. Varying degrees of experience have resulted in heterogeneity of the LGE patterns described, differing diagnostic accuracy and conflicting results in terms of prognosis. (2-6) Given that patterns of LGE are prognostic in most cardiac diseases, why are the results conflicting in cardiac amyloidosis?

In this issue of JACC Cardiovascular Imaging, Boynton *et al*. present a report on the prognostic impact of LGE in patients with cardiac AL amyloidosis.(7) Seventy-six consecutive patients with histological proven AL amyloidosis who underwent CMR for suspected cardiac involvement were studied. The CMR was performed

within 3 months of diagnosis. Patients were followed up for a median of 34.4 months. Forty deaths (53%) occurred, with survival probability at 1, 3, 5 years equalling 60%, 53% and 48%. The CMR protocol comprised a standard clinical scan for volumes along with LGE imaging. For the selection of the optimal IT the authors used multiple IT cine fast gradient echo sequences, where each frame in a cine sequence is acquired after an initial inversion pulse and consequently has different TI. The authors then analyzed LGE images and categorized the LGE pattern in three categories (global, focal patchy and none), using a combined approach of conventional LGE visual analysis together with inspection of differences in myocardial/blood pool nulling on the TI scout. Troponin and NT-proBNP, obtained within 3 months from diagnosis, were used to categorize patients with the Mayo staging system. Patients were also characterized by 12 lead resting ECG and transthoracic echocardiography although without longitudinal systolic strain measurements.

The principal finding of this study was the independent prognostic role of global LGE over the Mayo staging system in patients with cardiac AL amyloidosis. The Mayo staging system (8) is the current gold standard for risk stratification of patients with cardiac AL amyloidosis and influences treatment. Over the past few years, the chemotherapy options targeting monoclonal light chain production have expanded substantially, and successful free light chain suppression is associated in most cases with reduction in serum NT-proBNP concentration and improved prognosis. The rapid fall in NT-proBNP is presumed to reflect removal of any toxic effects that light chain aggregates may have, and/or the previously rapid accumulation of new amyloid deposition. This study deepens our understanding in this acute setting, supporting the independent prognostic role of LGE, a marker of

amyloid infiltration, in risk stratification of patient with cardiac AL amyloidosis and it adds nuance to the hypothesis of the pathophysiological importance of existing amyloid deposits in disease progression (9).

Although redefining the role of measuring myocardial infiltration, can we incorporate these findings into clinical practice? CMR with LGE has unique advantages over the traditional approach but also several limitations. The LGE technique utilises gadolinium chelated to diethylenetriamine penta-acetic acid (DTPA). Gd-DTPA is a pure extracellular agent, which accumulates passively in the gaps between cells. Because the interstitium is substantially expanded in amyloidosis and the kinetics are slower, a larger amount of gd-DTPA per unit volume will be present in the amyloidotic heart. The operator will than visually select a parameter (TI-inversion time) so background myocardium returns no signal - i.e. it is “nulled” and appears black on the images - and abnormal myocardium with a higher concentration of gadolinium appears white. This strategy is very effective when regional differences exist in gadolinium retention but the technique becomes very challenging in diseases where all myocardium is affected such as amyloidosis. In an attempt to overcome these problems, the authors adopted a combined approach and defined global LGE to be present when there was diffuse hyperenhancement on LGE or when the myocardium nulled before the blood pool on a multiple cine TI fast gradient echo sequence. Whilst this approach helps avoiding misclassification of the global patterns, it did not avoid the risk of images being inverted, i.e. LGE basal rather than apical, mid myocardial rather than global subepicardial. The authors also described a “patchy LGE pattern” that is thought to be related to incorrect TI settings (ref) and did not explain how uncertain situations, i.e. blood and myocardium nulling together, were solved. The timing of the TI scout was not fixed in the study protocol,

jeopardizing the validity of the interpretation since imaging too early or too late could lead to erroneous results. Perfusion heterogeneity in the dense amyloid substance makes the kinetics more complex, with potential misinterpretation of multiple perfusion defects in a global pattern with patchy LGE. Finally, no true standard was used for validation, leaving uncertainty about the effectiveness of the approach used.

A key task in the development of LGE in cardiac amyloidosis will be the transition to more robust and standardized approaches. Several option are available, including comparison with T1 or extracellular volume maps (both reflecting amyloid deposits), analysis of TI scout, the use of scanning protocol with predetermined or fixed IT, but all these strategies are time consuming and prone to errors of interpretation. Phase sensitive inversion recovery reconstruction (PSIR) is emerging as the most accurate method to assess LGE in amyloidosis, as the tissue with the least gadolinium (longest T1) is always nulled, eliminating the need of accurate inversion time selection. The wide implementation of PSIR, now available from all the CMR manufacturers, could have very favorable implications for diagnosis and prognosis. However, LGE-PSIR is unable to truly quantify myocardial infiltration, leaving a critical gap in disease characterization, ability to track changes over time and monitoring response to treatment. T1 mapping, an emerging CMR technique, can now quantify the myocardial extracellular volume, reflecting amyloid deposits.(10) We now can visualize with LGE and measure with T1 mapping the myocardial infiltration and dichotomize the myocardium into its cellular and interstitial components gaining insight in the infiltrative process but also myocyte response.(10)

Over time, tissue characterization with CMR has great potential to become an established part of the standard clinical pathway for evaluating cardiac amyloidosis. This and other work are (REF) changing our understanding of amyloidosis, moving

beyond the model of toxicity caused by pre-amyloid light chain aggregates in the pathophysiology of cardiac infiltration. Amyloid deposits within the interstitium undoubtedly have a fundamental role in the evolution of disease, and are currently the target of novel therapeutics in clinical development (9). Contemporary CMR is now well positioned to make a major contribution to the development and evaluation of new treatments and to guide clinical management of patients.

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