Staging cardiac amyloidosis with CMR: understand the different phenotypes.

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Cardiac involvement is the leading cause of morbidity and mortality in systemic amyloidosis [1]. It occurs in about 50% of patients with systemic light chain (AL) amyloidosis and is the dominant clinical feature in patients with wild-type transthyretin (ATTR) amyloidosis and many genetic variant forms of the latter. Accurate identification and staging of cardiac amyloidosis is the crucial first step in management of these patients, involving confirmation of amyloid deposits, identification of fibril type, and evaluation of the extent and severity of amyloid related organ damage.

Cardiovascular magnetic resonance (CMR) has unique advantages in identifying cardiac involvement in systemic amyloidosis. CMR provides information about cardiac structure and function but most importantly informs us on tissue composition. CMR leverages its intrinsic capacity to characterize tissue on the basis of fundamental MR properties (T1 and T2), and these intrinsic properties can be accentuated by administration of gadolinium-based contrast agents. The latest MR techniques for evaluating late gadolinium enhancement (LGE) provide images that are virtually pathognomonic in AL and ATTR cardiac amyloidosis [2] with excellent diagnostic accuracy. Recently the role of CMR in systemic amyloidosis has evolved beyond just diagnostic utility [3-7]. CMR tracks the continuum of amyloid accumulation as determined by the transmurality of LGE pattern, progressing from normal through subendocardial to transmural LGE. This has greatly elucidated how amyloid infiltration leads to dysfunction and has highlighted the potential role of LGE as a new prognostic marker that is directly linked to the basic pathogenic mechanism underlying amyloid cardiomyopathy [3-7].

In this issue of *iJACC*, Raina et al [8] present a systemic review and meta-analysis evaluating the prognostic role of LGE imaging in patients with cardiac amyloidosis. Studies were included that incorporated patients with systemic amyloidosis with known or suspected cardiac involvement undergoing CMR with LGE assessment and minimum follow up of 12 months. A systematic search of electronic databases identified 7 studies with a total of 425 patients, 149 events and a mean follow-up of 25 months. Five of these studies were prospective, single center studies, with the remainder being retrospective. All-cause mortality was recorded in all studies. Overall, the prevalence of LGE in these studies was 73% (range 28% to 84%). Twenty per cent of patients had positive endomyocardial biopsies. The patients with LGE had increased mortality compared to those without (pooled odds ratio 4.96; 95% confidence interval [CI]: 1.90 to 12.93, p=0.001). The pooled death rate for the LGE-negative group was significantly lower than for the LGE-positive group (0.07 [95% CI: 0.03-0.19] vs. 0.25 [95% CI: 0.16-0.39] events per year). The proportion of patients with cardiac biopsy within each study ranged from 3% to 68%, but the relationship between LGE status and death did not vary according to cardiac biopsy proportion across studies. Although 240 of 425 patients were from 1 center [6], the analyses were not significantly influenced by any 1 individual study.

The main finding of this meta-analysis is confirmation of the prognostic role of LGE in patients with known or suspected cardiac amyloidosis and the absence of relationship between study-specific odds ratios relating LGE status to death and the proportion of patients with cardiac biopsy.

The reference standard for the diagnosis and subtyping of amyloid is histology, but cardiac biopsy has associated risks and does not provide information beyond the presence or absence and type of amyloid in a tiny tissue specimen. Amyloid deposits only cause organ dysfunction when the amyloid burden exceeds a certain threshold; therefore, a spectrum of disease burden exists ranging from small incidental deposits with no clinical consequence to very extensive deposits causing severe organ failure, typically presenting as restrictive cardiomyopathy with biventricular involvement and low cardiac output. Cardiac biopsy may confirm the diagnosis, but it cannot determine disease burden because of the patchy nature of amyloid. Instead, the clinician requires different tools to characterize phenotypes, their stages of evolution, and understand the myocardial response and the clinical implication of amyloid deposition. CMR with tissue characterization (LGE, but also new imaging techniques such as T1 mapping) could have a unique role in cardiac amyloidosis, providing information on the impact upon cardiac structure and function in addition to tissue composition.

The association of amyloid burden represented by the LGE and mortality is intriguing, but amyloid infiltration alone does not necessarily provide all the answers. A subanalysis was performed to assess the association of LGE and events separately in AL and ATTR types. Patients with AL amyloidosis were more likely to die compared to ATTR, although the difference did not reach statistical significance. Furthermore, the results in AL were consistent with the preliminary analysis of increased mortality in LGE-positive patients, although the information provided by the studies and the number of events was not sufficient to carry out the same analysis in ATTR.

However when analyzing the differences in LGE between AL and ATTR, the transmural LGE pattern was more prevalent in ATTR than AL, yet the mortality was different across patients with similar degrees of infiltration: patients with AL amyloidosis and transmural LGE were more likely to die than ATTR patients with the same LGE extent. This has important implications. Cardiac amyloidosis is an exemplar of infiltrative disease: amyloid deposits can account for more than one-half of total myocardial mass, but amyloid cardiomyopathy is not just about infiltration. The observation that mortality is greater in AL than ATTR in the face of an apparently similar degree of amyloid infiltration suggests there are additional processes contributing to cardiac dysfunction and events in AL type. ATTR fibrils are derived from transthyretin, a normal plasma transport protein, whereas AL fibrils are composed of unique monoclonal immunoglobulin AL proteins that differ in each patient. Although all amyloid fibrils have essentially similar structure, the amyloid fibril precursor proteins in AL and ATTR are very diverse and may confer the fibrils differing biophysical properties. Recent imaging findings from T1 mapping support this hypothesis. T1 mapping is emerging as a tool that allows a more comprehensive understanding of the myocyte response and the additional mechanisms of myocardial damage in AL amyloidosis, with the potential to become an important step in disease characterization.

CMR has great potential to reshape assessment of patients with cardiac amyloidosis through LGE and T1 mapping. These biomarkers are key to understanding the pathophysiology of cardiac amyloidosis and to characterizing the evidently differing effects of ATTR and AL amyloid deposition. The next challenge will be to implement the transition of these

biomarkers into more standardized methodologies and then assess their robustness in the wider clinical environment.

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