EDITORIAL COMMENT

Prognosis in Cardiac Amyloidosis by LGE
Ready for Prime Time?*

Marianna Fontana, MD

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 disease, providing a second opinion on cardiac structure and function and yielding unique information through tissue characterization. Diagnostic algorithms integrating clinical presentation, electrocardiography, 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 late gadolinium enhancement (LGE) coupled with abnormal myocardial and blood pool gadolinium kinetics (1). Enthusiasm after the initial report has translated to 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 regarding prognosis (2–5). Given the prognostic significance of LGE patterns in a range of cardiac diseases, it is important to understand why these results are so conflicting in cardiac amyloidosis.

In this issue of *iJACC*, Boynton et al. (6) present a report on the prognostic impact of LGE in patients with cardiac light-chain (AL) amyloidosis. Seventy-six consecutive patients with histologically proven AL amyloidosis who underwent CMR for suspected cardiac involvement were studied. CMR was performed within 3 months of diagnosis. Patients were followed for a median of 34.4 months. Forty deaths (53%) occurred, with survival probabilities at 1, 3, and 5 years of 60%, 53%, and 48%, respectively. The CMR protocol comprised a standard clinical scan for the acquisition of ventricular volumes along with LGE imaging. As part of their acquisition protocol, the authors used a standard sequence to generate a set of images at different inversion time (TI) values to select the optimal TI to null normal myocardium (commonly known according to the vendor-specific nomenclature as a TI scout, cine inversion recovery, or Look-Locker sequence). The authors then analyzed LGE images and categorized the LGE pattern into 3 categories (global, focal patchy, and none) using a combined approach of conventional LGE visual analysis together with inspection of the differences in myocardial/blood pool nulling on the TI scout. Troponin and N-terminal pro-brain natriuretic peptide (NT-proBNP) levels were used to categorize patients with the Mayo staging system. Patients were also characterized by 12-lead resting electrocardiography and transthoracic echocardiography, albeit without longitudinal deformation 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 (7) is the current gold standard for risk stratifying patients with cardiac AL amyloidosis, and it consequently influences treatment. The range of chemotherapeutic options that target monoclonal light-chain production has expanded substantially in recent years. Successful free light-chain suppression is associated in most cases with a reduction in serum NT-proBNP concentration and improved prognosis. The rapid fall in NT-proBNP levels is presumed to reflect removal of any toxic effects that light-chain aggregates may have and/or

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From the National Amyloidosis Centre, University College London (UCL) Medical School, Royal Free Hospital, London, United Kingdom. Dr. Fontana has reported that she has no relationships relevant to the contents of this paper to disclose.

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cessation of the previously rapid accumulation of new amyloid deposition. This study deepens our understanding in this setting, supporting the independent prognostic role of LGE, a marker of amyloid infiltration, in the risk stratification of patients with cardiac AL amyloidosis. Furthermore, it adds nuance to the hypothesis of the pathophysiological importance of existing amyloid deposits in disease progression (8).

Although these findings redefine the role of measuring myocardial infiltration, can we incorporate them into clinical practice? CMR with LGE has unique advantages over the traditional approach but also has several limitations. The LGE technique uses gadolinium chelates. These purely extracellular agents accumulate passively in the gaps between cells. Because the interstitium is substantially expanded in amyloidosis and the gadolinium kinetics is slower, a larger amount of gadolinium per unit volume will be present in the myocardium with amyloid infiltration. The operator will then visually select a parameter (TI) so that background myocardium returns no signal—that is, 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 in which all myocardium can be affected, such as amyloidosis. In an attempt to overcome these problems, the authors adopted a combined approach and defined global LGE as being present when there was diffuse hyperenhancement on LGE imaging, when the myocardium was unable to be nulled adequately, or when the myocardium nulled before the blood pool on a TI scout. Although this approach helps in avoiding misclassification of the global patterns, it does not fully avoid the risk of misinterpreting regional localization of pathologic conditions (LGE basal rather than apical and mid-myocardial rather than global subepicardial). The authors also described a “patchy LGE pattern” that is thought to be related to incorrect TI settings (9) and did not explain how uncertain situations, such as instances when the blood pool and myocardium null simultaneously, were addressed. The timing of the TI scout relative to administration of gadolinium was not fixed in the study protocol, jeopardizing the validity of the interpretation, because image acquisition 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 imaging in cardiac amyloidosis will be the transition to more robust and standardized approaches. Several options are available, including comparison with T1 maps or extracellular volume maps (both reflecting amyloid deposits), analysis of TI scout, or the use of standardized scanning protocols with a predetermined or fixed TI (1,5,6,10). However, all of these strategies are time-consuming and prone to the inherent errors of subjective interpretation. Phase-sensitive inversion recovery reconstruction (PSIR) is emerging as the most accurate method to assess LGE in cardiac amyloidosis (9). The tissue with the least gadolinium always appears nulled using this reconstruction technique, thus eliminating the practical difficulties of accurate TI selection. The routine implementation of PSIR, now available from all CMR manufacturers, could have highly favorable diagnostic and prognostic implications. However, PSIR does not quantify myocardial infiltration, which is fundamental to track changes over time and monitor the response to treatment. T1 mapping, an emerging CMR technique, can now quantify the myocardial extracellular volume, reflecting amyloid deposits (11). A more comprehensive assessment of myocardial infiltration can now be achieved through visualization with LGE imaging and quantification with T1 mapping. This allows us to dichotomize the myocardium into its cellular and interstitial components, thus gaining insights into both the infiltrative process and the myocyte response (11).

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 (1,5,6,9) is changing our understanding of cardiac 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 therapeutic agents in clinical development (8). CMR is now well positioned to make a major contribution to the development and evaluation of new treatments and to guide the clinical management of our patients.

**REPRINT REQUESTS AND CORRESPONDENCE:**
Dr. Marianna Fontana, National Amyloidosis Centre, Division of Medicine, University College London (UCL), Royal Free Hospital, Rowland Hill Street, London NW3 2PF, United Kingdom. E-mail: m.fontana@ucl.ac.uk.
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