Detailed understating of cardiac amyloidosis by CMR – towards personalized medicine

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Cardiac amyloidosis (CA) is increasingly recognised as an underdiagnosed cause of heart failure. Current clinical care focuses on confirming the diagnosis, and assessing symptoms and prognosis to start appropriate therapies. Clinically, CA has been defined as thickened left ventricular (LV) walls (>1.2 cm) in the absence of another cause of LV hypertrophy. Over the years, more specific functional features have been recognised, such as reduction in longitudinal strain that typically spares the apex, giving the characteristic "bullseye" picture on parametric longitudinal strain polar maps. However, while echocardiography can provide an assessment of the likelihood of cardiac amyloid infiltration, it cannot be considered a definitive diagnostic test.
Histologically, amyloid deposition is associated with a wide spectrum of myocardial damage, with a variable degree of amyloid infiltration, different types of fibrils, myocardial edema, and differential myocyte response with myocyte loss in some cases and myocyte hypertrophy in others. Histology can shed light into the disease biology and shows disease complexity. However, histology is now infrequently performed to confirm the diagnosis and is never performed in early disease or during treatment. This leaves a knowledge gap of the nature of the multiple processes that compromise the myocardium, with each of the processes likely to be more or less prominent at any time-point, depending upon the individual, the disease type, response to treatment, and co-morbidities.

Technological advances in cardiovascular magnetic resonance (CMR) imaging with the introduction of mapping techniques are redefining cardiac involvement in amyloidosis. In CA, the diagnosis has been classically established using late gadolinium enhancement (LGE) imaging after intravenous administration of gadolinium-based contrast agents. A characteristic pattern of diffuse subendocardial or transmural LGE has been widely described (1) and has been demonstrated to have high diagnostic accuracy and prognostic implications. T1, T2, and ECV

mapping have been introduced in recent years, promising to detect and measure the different myocardial processes involved in the disease. However, each novel marker must prove its superior diagnostic and/or prognostic value compared to the already established markers to get wide acceptance and legitimately enter clinical/diagnostic guidelines.

In this issue of iJACC, Pan et al. present a systematic literature review and meta-analysis comparing the diagnostic and prognostic performance of native T1, ECV mapping, and LGE imaging for evaluating cardiac amyloidosis. A systematic search of electronic databases identified 18 diagnostic studies that included a total of 2015 subjects (1108 patients with cardiac amyloidosis and 907 controls) and 13 prognostic studies that included a total of 1483 subjects (72% AL, 26% ATTR and 2% another type or unspecified) with a mean follow-up period of 25 months. For diagnostic performance, bivariate comparison showed that ECV had higher diagnostic odds ratios (DOR) for CA than LGE (84.6 vs 20.1, $p = 0.03$). There was no significant difference between LGE and T1 for sensitivity, specificity, or DOR. In the meta-regression using publication year, age, gender, LVEF, LVEDVI, and LGE pattern, ECV was significantly correlated to publication year ($p = 0.03$) and LVEDVI ($p = 0.001$), and native T1 was significantly correlated to LVEF ($p = 0.038$). For prognostic performance, the hazard ratio (HR) was significantly higher for ECV (4.27) compared to LGE (2.60, $p = 0.03$ vs ECV) and T1 (2.04, $p = 0.01$ vs ECV). There was no significant difference between T1 and LGE ($p = 0.50$). In the meta-regression using publication year, follow-up duration, age, gender, NT proBNP, E/e', LVEF, and LVEDVI, only gender and follow-up duration significantly correlated with the HR of native T1 ($p < 0.01$). The selected studies had an overall low risk of bias.

The main finding of this meta-analysis is that native T1 and ECV are comparable to LGE for the evaluation of CA, with ECV being associated with a significantly better diagnostic and

prognostic performance than LGE. This work represents an important step for the field, confirming the value of native T1 and ECV across a wide range of studies and highlighting the incremental role of ECV for the diagnosis and prognostic stratification of both AL and ATTR CA.

The field should be encouraged to go beyond the models of comparison of diagnosis and prognosis employed in this meta-analysis and consider multiparametric approaches to individual patients and redefine cardiac involvement through the simultaneous assessment of myocardial processes: 1) infiltration (visualized with LGE and measured with native T1 and ECV); 2) edema (reflected in T1 and T2, with T2 being the most specific marker); 3) myocyte response (derived from LV mass and ECV); and 4) staging of the disease based on the combination of LGE and ECV. (2,3) Each of these techniques gives insight into different myocardial processes, and therefore, each parameter may have specific roles in evaluating CA, depending on the clinical situation.

The immediate clinical application for native T1 would be in patients with severe kidney dysfunction, in whom administration of gadolinium based contrast agents is relatively contraindicated. This approach is supported by the results of this study, with native T1 mapping having comparable diagnostic performance to LGE. However, because it is crucial to avoid misdiagnosis in patients with only mildly elevated native T1, macrocyclic gadolinium based contrast agent administration should still be considered, with LGE or ECV being required for a more definitive diagnosis.(4) Although native T1 had similar diagnostic performance to LGE in this meta-analysis, T1 has not been demonstrated to be an independent predictor of mortality in CA.(5) These differences are likely to represent the different biological information provided by native T1 and ECV. Native T1 is a measure of myocardial relaxation influenced by the

extracellular and intracellular compartments. The administration of contrast and ECV measurement enables us to isolate the signal from the extracellular space, providing an estimate of the amyloid deposits. The results of this meta-analysis, with ECV showing a better diagnostic and prognostic performance compared to native T1, are in line with this hypothesis of ECV being a surrogate measure of the amyloid burden within the tissue, with the degree of amyloid deposition in the myocardium being one of the major drivers of survival. This meta-analysis also confirms the better diagnostic performance of ECV compared to LGE. In CA, a spectrum of disease burden exists, ranging from small incidental amyloid deposits with no clinical consequences to very extensive deposits causing severe organ failure. Whilst with LGE we can confirm the diagnosis and divide patients into different risk categories, with ECV we can measure the continuum of amyloid infiltration, enabling the clinician to fully characterize phenotypes and track treatment response.(6) A limitation of this study is the lack of data on T2 mapping. CA, traditionally considered a disease of purely infiltration, is now emerging as one in which additional mechanisms contribute to mortality. T2 mapping, by measuring myocardial oedema, is able to identify and measure some of these additional mechanisms and redefine cardiac involvement. CA is characterized by variable degrees of infiltration and superimposed myocardial oedema, with ECV and T2 being able to define separate processes that both contribute to risk.(7)

The diagnostic and therapeutic landscape for cardiac amyloidosis has been rapidly evolving over the last few years, demonstrating that the disease is neither rare nor untreatable. Our objectives, should be to facilitate early diagnosis, prescribe the appropriate treatments, and improve outcomes by evaluating the responses of myocardial processes to treatment. CMR is uniquely

positioned to characterize cardiac involvement in patients with cardiac amyloidosis and integrate this in routine clinical practice.

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