JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
VOL. 71, NO. 25, 2018

PUBLISHED BY ELSEVIER

EDITORIAL COMMENT

# Cardiovascular Magnetic Resonance in Cardiac Amyloidosis

## T1 Is Not Enough*

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Cardiac amyloidosis is currently perceived as a relatively well characterized disease. Briefly, the pathognomonic cardiovascular magnetic resonance (CMR) phenotype of cardiac amyloidosis consists of a significant increase in native myocardial T1 and extracellular volume expansion with corresponding extensive late gadolinium enhancement. The group of the authors has made several important contributions to this field with a focus on late gadolinium enhancement and myocardial T1 (1–3), but in this issue of the *Journal*, Kotecha et al. (4) add another intriguing component to this picture. The authors performed not only T1-mapping CMR, but also T2-mapping CMR in a population of 286 patients with cardiac amyloidosis. In summary, they found significantly increased myocardial T2 values in in patients with amyloidosis compared to controls. Interestingly, the degree of T2 abnormality was highest in patients with untreated light-chain (AL) amyloidosis, followed by patients with transthyretin and treated AL amyloidosis. Furthermore, the authors were able to show a potential prognostic value of myocardial T2 in patients with AL amyloidosis. In addition, they found hints for myocardial edema on histology in the majority of a subset of 16 patients who underwent endomyocardial biopsy (EMB) by using interstitial expansion as a possible surrogate for myocardial edema. The authors conclude that myocardial edema is an inherent feature of cardiac amyloidosis and hypothesize that it could be related to light-chain or fibril toxicity, but not to inflammation. This hypothesis was supported by the lack of significant cellular infiltration in their subpopulation with available EMB.

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Water constitutes the major component of myocardium, and an intact balance between intracellular and extracellular water is a prerequisite for viable cardiomyocytes (5). However, myocardial water balance is a complex, fragile system and any disturbance can result in intra- or extracellular water accumulation, which is defined as myocardial edema (6). Consequently, myocardial edema is an unspecific feature of recent or ongoing myocardial injury (6). However, it is important to note that myocardial edema is not only a symptom of myocardial injury, but also a part of a vicious circle which may further enhance myocardial injury (7). From a clinical perspective, the most common underlying conditions of myocardial edema are acute myocardial ischemia and acute myocardial inflammation in myocarditis. Therefore, myocardial edema and myocardial inflammation are often used synonymously, which is sometimes not correct because there are noninflammatory mechanisms for myocardial edema such as increased afterload (6). The post-mortal reference method for assessing myocardial edema is to calculate myocardial water content by the difference between wet and dry weight of the heart (6). However, an in vivo assessment of myocardial edema is generally challenging (7), which has therefore always been one of the major targets for CMR (8).

Briefly, CMR reveals myocardial edema by visualization of focal edema on (T1 and) T2 weighted,

*Editorials published in the *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of *JACC* or the American College of Cardiology.

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ISSN 0735-1097/$36.00
https://doi.org/10.1016/j.jacc.2018.04.025

edema-sensitive images, but even better by direct quantification of prolonged T1 and T2 relaxation times. Recently, the evolution of clinically applicable "mapping" techniques has led to several studies on the value of T1 and T2 quantification for the assessment of myocardial edema in myocardial infarction (9–12) and in myocarditis (13–16). Broadly speaking, increased myocardial T1 and T2 values are found in the presence of edema, but T2 seems to be more specific for water compared to T1, which is also increased in other conditions such as myocardial fibrosis or amyloid deposition (8,17). Thus, a comprehensive tissue characterization by CMR requires information on myocardial T1 as well as on myocardial T2.

Cardiac amyloidosis is currently perceived as a disease with poor prognosis, few therapeutic options, and predominantly irreversible injury despite adequate therapy of the underlying disease in AL amyloidosis. How could the findings of this study initiate a change in the management of patients with cardiac amyloidosis? Ultimately, the authors observed an increased myocardial water content by T2 mapping CMR in patients with cardiac amyloidosis. Histology in a small subset of patients with available EMB indicated that the mechanism of this phenomenon seems to be independent from cellular infiltration. Thus, a better understanding of this mechanism could potentially lead to novel therapeutic approaches targeting myocardial edema and subsequent injury, but this perspective is quite vague so far. Furthermore, the differences between treated and untreated AL amyloidosis patients suggest that myocardial T2 could be a marker of disease activity in amyloidosis, perhaps similar to inflammatory cardiomyopathy (14–16). Therefore, myocardial T2 could potentially be used to monitor or to guide therapeutic interventions in cardiac amyloidosis. Nevertheless, it will be difficult to show an incremental value of T2-guided therapeutic strategies in cardiac amyloidosis, considering the generally poor prognosis of this disease.

It is, therefore, worth looking beyond cardiac amyloidosis and take the findings of this study for a reason to rethink current definitions of myocardial inflammation. The arbitrary definition of cellular infiltration with ≥14 infiltrating cells/mm$^2$ for active myocarditis generally needs to be applied with caution and may not be used to exclude myocardial inflammation in a broader sense and in different diseases (18). The findings of the study by Kotecha et al. (4) could indicate that T2 mapping CMR has the ability to reveal an aspect of myocardial inflammation that is not detectable by assessing cellular infiltration on EMB. In this context, it is important to keep in mind that myocardial edema not only is a marker of acute inflammation, but also contributes to myocardial injury, and is therefore a potential therapeutic target itself (7).

In conclusion, the work by Kotecha et al. (4) provides novel insights into the mechanisms of myocardial injury in cardiac amyloidosis, but could also stimulate the discussion on current perception of myocardial inflammation and the role of myocardial edema. Furthermore, the work of Kotecha et al. clearly shows that a comprehensive evaluation of patients with cardiomyopathies by CMR requires information on not only myocardial T1, but also myocardial T2. Restricting CMR protocols to myocardial T1 carries the risk of missing unexpected and intriguing insights into disease pathogenesis.

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**KEY WORDS** cardiac amyloidosis, cardiovascular magnetic resonance, edema, myocardial T1, myocardial T2