JACC: CARDIOONCOLOGY VOL. 2, NO. 5, 2020

EDITORIAL COMMENT

Atrial Involvement in Cardiac Amyloidosis

Beyond Dilatation*

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Cardiac amyloidosis (CA) is present in 50% of cases of systemic light-chain amyloidosis (AL) and is the major determinant of morbidity and mortality (1). Cardiac involvement in AL amyloidosis is associated with a high burden of cardiac arrhythmia including atrial fibrillation (AF), which is typically poorly tolerated. In compliant ventricles, diastolic filling predominantly occurs in early diastole, whereas in CA, characterized by small noncompliant ventricles, there is increased dependence on the late diastolic filling mediated by atrial contraction. Therefore, the occurrence of AF in CA can have a major impact on patients' clinical stability, as the loss of synchronized atrial contraction will result in both a significant drop in stroke volume and increase in atrial pressure, which is commonly associated with new or worsening heart failure symptoms.

Although left atrial (LA) enlargement has been traditionally associated with AF, new-onset AF often occurs in its absence, suggesting a complex pathophysiology of AF in CA, in which multiple processes differentially compromise LA structure, function, and mechanics, increasing the risk of AF. Remarkably, LA remodeling in CA differs from the typical changes observed in heart failure or mitral regurgitation, where LA dilatation is the predominant characteristic. In CA, the typical phenotype of LA remodeling includes significant infiltration of the atrial walls with progressive loss of atrial function and increased stiffness, often in the absence of significant LA dilatation. These findings mirror the accepted pathophysiological model associated with ventricular amyloid infiltration, in which progressive extracellular amyloid infiltration increases myocardial stiffness, resulting in concentric remodeling and small noncompliant chambers (2).

Recently, advances in echocardiographic imaging have improved our ability to phenotype LA remodeling in CA, with the ability to assess LA mechanics throughout the different phases of the cardiac cycle. LA function can be subdivided into 3 phases. The "reservoir phase" reflects LA filling from pulmonary veins during left ventricular (LV) systole. The "conduit phase" follows, reflecting the passive filling of the LV from the LA during LV diastole. The "booster phase" represents active LA contraction during the final stage of diastole. Previous studies have demonstrated significant impairment of the 3 phasic components of LA function, with a high correlation with LV dysfunction, suggesting that amyloid infiltration progressively impairs both LV and LA function in parallel (3,4). In this issue of *JACC: Cardio Oncology*, Lohrmann et al. (5) present a study with the aim to assess the association of LA mechanics and development of AF in patients with AL undergoing high-dose melphalan and autologous stem cell transplantation (HDM/SCT). HDM/SCT treatment has been shown to induce durable hematologic and clinical remission in selected patients with systemic AL amyloidosis. However, HDM/SCT can precipitate the development of clinically significant AF (6), which, in this setting, is associated with longer hospitalization and intensive care admissions. Current literature in predicting AF development in this patient cohort offers little clarity, with standard echocardiographic parameters such as LA size unable to distinguish those at high risk (7). Lohrmann et al. (5) retrospectively studied 91 patients with systemic AL amyloidosis (42 with cardiac involvement) before HDM/SCT.

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

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

ISSN 2666-0873 https://doi.org/10.1016/j.jaccao.2020.11.005

LA function analysis was performed using speckle tracking echocardiography. LA strain, LA strain rate, LA volumes, and phasic functions were obtained and averaged from the 4-chamber and 2-chamber views, using the R-wave as the reference point. The assessment also included time to peak strain rate index (TPSRI), which represents the time from QRS onset to peak strain rate during LV ejection (LA reservoir phase) indexed to the patient's R-R interval. All patients were in sinus rhythm at the time of their echocardiograms. To summarize the results, in the total cohort, cardiac wall thickness, LA diameter, diastolic grade, and LV systolic function did not differ among individuals who did and did not develop AF; however, LA reservoir strain and TPSRI were found to be significantly altered in patients developing AF after HDM/SCT in both the overall cohort and the subgroup with cardiac involvement. TPSRI was the only parameter associated with AF development, irrespective of cardiac involvement. They concluded that TPSRI, being a parameter of mechanical dispersion in the early reservoir phase of LA function, is significantly associated with AF development among individuals undergoing HDM/SCT for AL amyloidosis. The conclusion is in line with previous studies, as this report confirms the importance of assessing LA function and mechanics over more traditional parameters and adds further nuance to this hypothesis, focusing on the role of TPSRI in predicting AF in a cohort of patients at high risk of decompensation associated with the development of AF.

There are a number of caveats to consider when drawing conclusions from these data. The most immediately evident critique is the retrospective nature of the study and the limited sample size, with 91 patients included in the study assessed over a 5.5-year period. Furthermore, the target endpoint of AF development in the peri- or post-SCT period was found in only 12 patients, with even fewer having cardiac involvement ($n = 4$). This represents a higher percentage when compared with larger studies of AF occurrence after SCT (13% vs. 7%) (8); albeit in a cohort of patients with hematological malignancies and unmatched cardiac comorbidities. The limited number of patients who developed AF has also precluded the possibility of performing multivariable models, limiting the possibility of drawing conclusion on the role of TPSRI in predicting development of AF after adjusting for other relevant variables. The definition of cardiac involvement for inclusion in this analysis must also be considered. The use of either an unexplained wall thickness $\geq$12 mm or abnormal cardiac biomarkers (B-type natriuretic peptide or cardiac troponin) are very sensitive but poorly specific for the diagnosis of CA (9). Use of cardiac magnetic resonance may have offered a more robust method for the diagnosis without the need of a cardiac biopsy and with the use of T1-mapping would have also given insight into the degree of infiltration (10,11). Cardiac involvement in patients with systemic AL amyloidosis represents a spectrum of disease with varying degrees of severity ranging from amyloid deposits, with no significant functional consequences, to severe cardiac amyloid infiltration, where more than half of the LV mass is represented by amyloid deposits (10,11). Cardiac magnetic resonance tissue characterization with T1-mapping and quantification of extracellular volume have been well-established as noninvasive approaches to assess the degree of cardiac involvement (11) in amyloidosis and could have supported a better patient classification in disease subclasses. The analysis was performed by a single operator performing offline and blinded strain analysis. This approach, although appropriate for the study design, does not address the issues of intraoperator variability if multiple sonographers were used for image acquisition, limiting the applicability of the findings to clinical practice.

In summary, this study from Lohrmann et al. (5) offers us further insight into the concept of abnormal LA mechanics being related to AF development in patients with systemic AL amyloidosis. This study has implicated novel parameters of atrial function and supports the unique phenotype of cardiac remodeling in patients with CA, where progressive loss of atrial function and increased stiffness have a predominant role compared with atrial dilatation in the pathogenesis of atrial remodeling in CA. Using advanced atrial imaging techniques to risk assess patients continues to be an emerging area of study, and further research will be needed to explore the relative contribution of the different parameters at different disease time points, depending on the individual (age, gender differences), the disease type, and comorbidities.

AUTHOR DISCLOSURES

Dr. Fontana has consulted for Alnylam, Akcea, Eidos, Intellia, Pfizer, and Alexion; is funded from the British heart foundation fellowship FS/18/21/33447; and has received a research grant from Pfizer. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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KEY WORDS amyloidosis, atrial fibrillation, echocardiography, left atrial strain, light-chain amyloidosis, mechanical dispersion, strain