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EDITORIAL COMMENT

Prognosticating in Cardiac Amyloidosis

Let Me Count the Ways*

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Increasingly, cardiac amyloidosis (CA) is recognized as a cause of common cardiovascular conditions in older adults, including heart failure with a preserved ejection fraction, low flow aortic stenosis, acute decompensated heart failure in Afro-Caribbeans, and atrial fibrillation (1-4). In addition, transthyretin CA is increasingly noticed in noncardiac cohorts, including patients with degenerative orthopedic conditions such as lumbar spinal stenosis and hip and knee arthroplasty, biceps tendon rupture, and bilateral carpal tunnel syndrome (5-8). In addition, the nihilistic belief that CA has no effective treatments is now changing. Contemporary chemotherapeutic strategies for light chain (AL) amyloidosis, pharmacological therapies to stabilize the transthyretin (TTR) tetramer and suppress TTR expression with antisense oligonucleotides or RNA interference in transthyretin CA (ATTR-CA), and improved outcomes after heart transplantation are modifying prognosis (9-12).

In this context, the work of Knight et al. (13) in this issue of *iJACC* is an important addition to the constellation of cardiac imaging parameters used to characterize cardiac amyloidosis and inform prognosis in the aforementioned cohorts. The authors used state-of-the-art echocardiographic and cardiac magnetic resonance (CMR) parameters to carefully characterize a large population of patients with AL and ATTR-CA. Blinded to prior imaging data, the investigators delineate multiple elements of cardiac architecture and function across a wide spectrum of CA burden as quantified by CMR-derived extracellular volume (ECV). Of the more than 10 parameters studied in this cross-sectional study, all were individually prognostic for mortality. Emerging from the numerous parameters evaluated, stroke volume and tricuspid annular plane systolic excursion were independent predictors of survival. Importantly, the architectural and functional parameters associated with increasing ECV also illustrate a natural history of progressive amyloid deposition. Abnormalities of left ventricular (LV) mass, diastolic (E/e') and longitudinal function (global longitudinal strain and mitral annular plane systolic excursion) were more likely to be abnormal in early stages of disease ("low ECV burden"), whereas low biventricular ejection fractions and enlarged bi-atrial area predominated in advanced stages of disease ("high ECV burden").

While biventricular ejection fractions were preserved up until higher burdens of cardiac amyloid infiltration, impairments in the myocardial contraction fraction were detected in earlier stages, highlighting the importance of the variables from which it is derived, namely stroke volume (SV) and myocardial mass as measures of amyloid burden. Decreases in SV occurred in patients with early CA and progressively declined with increasing ECV, mediated by increasing LV mass, decreasing LV cavity size, and worsening diastolic dysfunction. These findings recapitulate hemodynamic simulations of cardiac amyloidosis in which progressive amyloid infiltration in the extracellular matrix alters myocardial stiffness, resulting in an upward and leftward shift in the end-diastolic pressure-volume relationship with concomitant declines in stroke volume, cardiac output, and blood pressure (**Figure 1**). Parallel declines in SV and end-diastolic volume show why ejection fraction remains preserved during the course of progressive amyloid deposition. Declines in ejection fraction in CA were shown to be a late-phase phenomenon mediated by impairments in chamber contractile function in

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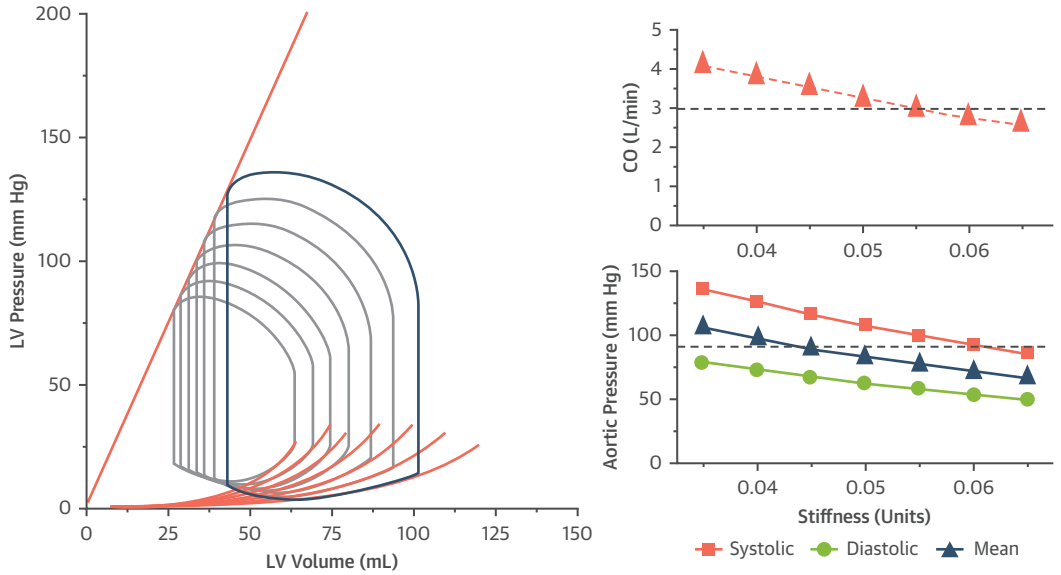
FIGURE 1 Hemodynamic Changes Occurring With Increasing Cardiac Amyloid Burden



Progressive amyloid infiltration in the extracellular matrix alters myocardial stiffness, resulting in an upward and leftward shift in the end-diastolic pressure-volume relationship with concomitant a decline in stroke volume, cardiac output, and blood pressure. CO = cardiac output; LV = left ventricular.

advanced disease. Such hemodynamic changes also show how blood pressure can "normalize" or even decline during the progression of amyloid deposition in the myocardium.

The study demographics also mirror changing trends in the epidemiology of cardiac amyloidosis. Among the 322 subjects studied, there were more subjects with ATTR than AL (n = 189 vs. 133, respectively), which is concordant with current understanding of the increasing prevalence of ATTR, driven by the escalating cases of wild-type ATTR-CA (wtATTR-CA). AL-CA is a rare condition with an estimated incidence of 10 cases per million individuals and thus ~3,000 new diagnoses per year in the United States (14). Among new cases, 30% to 50% present with symptomatic cardiac involvement. Hereditary ATTR (hATTR) is also relatively rare, with the most common mutation worldwide being Val30Met, which is not associated with significant structural cardiac changes in its early-onset form. Only 3 subjects studied harbored the Val30Met mutation, whereas the Val122Ile mutation, which almost exclusively affects individuals with West African ancestry, and the Thr60Ala mutation, which is common in those of Irish descent, were more frequent, concordant with the prevalence of mutations seen in the United States (15). The largest ATTR-CA subtype represented in the study population was wtATTR-CA (n = 105), paralleling the general epidemiologic trend of increasing prevalence of wtATTR, which will become the most commonly diagnosed CA subtype.

Several limitations of this study are worth noting. It was retrospective and performed at a single center, albeit one with tremendous expertise in CMR imaging for amyloidosis. Furthermore, this analysis was cross-sectional; therefore, inferences about longitudinal changes must be confirmed by prospective study. Integrating identified structural and functional measures that were prognostic with biomarker staging systems in larger populations will likely improve our prognostication, providing clinicians with the tools they need to better inform and treat patients (16-18). Finally, as CA is becoming treatable, expanding our understanding of the patient's journey by focusing on the significant morbidity experienced by patients and their loved ones (e.g., hospitalizations, days alive out of the hospital, functional decline, and caregiver burden) will be critical.

With the advent of effective therapies for cardiac amyloidosis, future longitudinal studies are needed to determine whether ECV can be used to track response to therapy and could be a surrogate or

biomarker of disease progression. Ultimately, the cornerstone for amyloid therapy will be early disease recognition so that cardiologists can initiate emerging therapies to actively prevent pathological structural and functional changes, which are the main determinants of prognosis.

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