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EDITORIAL COMMENT

Aging, Aortic Stenosis, and Transthyretin Cardiac Amyloidosis

A Perfect Cardiac Storm?*

Sabahat Bokhari, MD, Rahul Gupta, MD

Systemic amyloidosis is a rare, progressive, multisystem disease characterized by extracellular deposition of insoluble amyloid fibrils. Cardiac amyloidosis (CA) occurs when these fibrils deposit within the myocardial extracellular space. If untreated, this leads to infiltrative cardiomyopathy, heart failure, and death. Advances in echocardiography, cardiac magnetic resonance (CMR), and bone scintigraphy have led to improved diagnoses of CA. These imaging advances have been accompanied by developments in therapies for CA patients.

The 2 most common types of CA are immunoglobulin light chain (AL) and transthyretin (ATTR) CA. ATTR-CA is characterized by misfolding of the transthyretin protein into insoluble amyloid fibers and its subsequent deposition in the extracellular space of the myocardium. The prevalence of dual disease (ATTR-CA and severe aortic stenosis [AS]) increases with age and is higher in patients with low-flow low-gradient severe AS. Studies have shown that the prevalence of amyloid deposits ranges from 4% to 29% in patients with severe AS undergoing valvular intervention (1). Triebel et al (10) found that 4.1% (6 of 146) of patients undergoing surgical aortic valve replacement (SAVR) have amyloid deposition on endomyocardial biopsy. Castaño et al (2) reported that approximately 1 of 7 patients currently undergoing transcatheter aortic valve replacement have cardiac amyloidosis. It is still unclear whether TTR amyloid deposition has a contributory effect in the pathogenesis of AS, or whether these are 2 separate yet overlapping diseases. The presence of concomitant diagnoses can potentially worsen the severity of AS and is associated with a worse prognosis. These patients tend to have a poor response to standard therapy, including valvular interventions in the form of transcatheter aortic valve replacement or SAVR.

ADVANCES IN NONINVASIVE IMAGING MODALITIES FOR DIAGNOSIS OF ATTR-CA AND SEVERE AS

Because ATTR-CA and severe AS share clinical, electrocardiographic, and echocardiographic parameters, the RAISE (remodeling, age, injury, system, and electrical) score was developed to predict the presence of CA in severe AS (3). A score of ≥2 initiates further screening by bone scintigraphy and serum/urine testing for monoclonal proteins. Aortic valve calcium scoring, as measured by noncontrast computed tomography (CT), may be useful in low-flow low-gradient AS, which is more prevalent in patients with CA. Advanced imaging modalities have led to early recognition and identification of ATTR-CA. Echocardiography is usually the first cardiac imaging test performed. Abnormalities include left ventricular hypertrophy, diastolic dysfunction, speckled appearance of myocardium, and impairment of longitudinal function with apical sparing. Myocardial late gadolinium enhancement, myocardial nulling, T_1 mapping, and extracellular volume mapping along with left ventricular wall hypertrophy on CMR also raise suspicion for cardiac amyloidosis. It is not possible to distinguish

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From the Lehigh Valley Heart and Vascular Institute, Allentown, Pennsylvania, USA.

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between AL-CA and ATTR-CA by echocardiography or CMR. Nuclear cardiac scintigraphy with bone seeking single photon emission computed tomography radiotracers (99m-technetium pyrophosphate [PYP], diphosphono propanodicarboxylicacid [DPD], hydroxymethylene diphosphonate [HMDP]), when used in combination with serum free light chains and serum/urine immunofixation assessment, can differentiate ATTR-CA from AL-CA with high sensitivity and specificity (4,5). These advanced noninvasive imaging techniques have allowed clinicians to diagnose and determine the amyloid type without invasive endomyocardial biopsy.

CURRENT AND FUTURE THERAPEUTICS FOR ATTR-CA AND SEVERE AS

ATTR-CA carries a poor prognosis if left untreated, and when combined with severe AS, the mortality rate increases significantly. Until recently, patients with ATTR-CA had no treatment options and care was focused on supportive therapy. In the past few years, there have been various emerging therapies for ATTR-CA. The therapies are targeted at reducing production of TTR, stabilizing circulating TTR, or removal of existing TTR. Tafamidis is a TTR stabilizer that is approved by the U.S. Food and Drug Administration for the treatment of ATTR-CA. Tafamidis causes significant reduction in mortality and rehospitalizations and is more effective when administered early in the disease course. Patisiran and inotersen are TTR silencers that decrease the synthesis of TTR protein and are approved by the U.S. Food and Drug Administration for the treatment of the polyneuropathy of hereditary TTR amyloidosis (6,7). Diflunisal is a nonselective TTR stabilizer that is under trial for ATTR-induced polyneuropathy. AG10 is another TTR stabilizer that is under development for ATTR-CA (8). TTR-LRx and vutrisiran are TTR silencers that cause reduction of serum TTR protein. PRX004 is a monoclonal antibody that targets and clears the misfolded TTR protein. Also, the combination of doxycycline and tauroursodeoxycholic acid is under study for its synergistic effects on removal of TTR deposits.

PATIENT OUTCOMES WITH DUAL DISEASE

Patients with a concomitant diagnosis of ATTR-CA and severe AS tend to have decreased survival compared with patients without ATTR-CA. Cavalcante et al (9) found that at 1 year, mortality associated with severe AS and CA was higher than that with severe AS alone (56% vs 20%; $P < 0.0001$). Treibel et al (10) evaluated 146 patients undergoing SAVR and found that patients with concomitant ATTR-CA had a higher HR for mortality at a median follow-up of 2.3 years (HR: 9.5; $P = 0.001$). Nitsche et al (3) showed that 1-year mortality in patients with severe AS-CA was worse compared with those with lone severe AS (24.5% vs 13.9%). Long-term mortality data for patients with dual diagnosis undergoing valve replacement are still lacking and highlight the need for future studies to understand the trajectory of these patients.

WHAT DID WE LEARN FROM THE CURRENT PUBLICATION?

In this issue of *JACC: CardioOncology*, Singal et al (11) studied the prevalence of dual disease (ATTR-CA and severe AS) in an elderly Indian population and identified noninvasive predictors and their impact on prognosis. They recruited 46 elderly patients ≥65 years of age with severe AS who were scheduled for SAVR. They used echocardiography, 99m-technetium PYP scan, endomyocardial biopsy from the interventricular septum (IVS), and histopathological examination of the excised native aortic valve for the diagnosis of ATTR-CA. Isolated valvular amyloidosis was noted in 71.7% (33 of 46) of the patients and isolated valvular TTR in 41.3% (19 of 46), and none of the IVS biopsies had amyloid deposits. The myocardial ATTR-CA by PYP uptake was seen in 3 of 32 (9.4%) patients. Extrapolating these results to the United Nations estimate suggests that there are 4.5 million people with a diagnosis of severe AS in India, of which ~400,000 would be expected to have dual AS-ATTR CA. The authors concluded that dual disease is not uncommon and that isolated valvular amyloidosis is much more common in the elderly Indian population with AS.

As per the study, the prevalence of ATTR-CA in patients undergoing SAVR is around 9% in the Indian population. This is similar to the previously published 6% prevalence of ATTR-CA in SAVR patients (10). One of the characteristic findings of this study is the involvement of isolated valvular amyloid in 71.7% of the patients. No prior studies have highlighted the significance of isolated valvular amyloid. Further studies are required to evaluate the role of isolated valvular amyloidosis in the pathogenesis of the disease.

To explain the possible discrepancy between PYP results and IVS biopsy, the authors hypothesized that the aortic valve accumulates TTR deposits first, which later involves the myocardium. With disease progression, there is an improved likelihood of detection on PYP scans and IVS biopsy. Also, PYP scans and the

IVS biopsy indicate involvement of myocardium; the dissociation between the PYP and the IVS biopsy results warrants further investigation. Another limitation of the study is that mass spectroscopy was not used to identify the other types of amyloid in the excised aortic valves.

Considering that isolated valvular ATTR-CA is more common and exists by itself or precedes involvement of the myocardium, early initiation of disease-modifying agents such as tafamidis may be considered in these patients. Also, this study brings up an important question as to whether early surgical intervention in these patients can potentially delay the progression of the disease process. Mortality in patients with coexisting disease seems to be driven by ATTR-CA and was not mitigated by valvular interventions. Recent studies with improved screening tools for ATTR-CA show better outcomes with valve intervention (3). Hence, aortic valve replacement should be considered in symptomatic patients with ATTR-CA who have evidence of severe AS (3).

In conclusion, early diagnosis facilitated by advanced, multimodality imaging can allow treatment to be offered at an earlier disease stage of ATTR-CA and severe AS. Patients with dual disease beyond AVR for severe AS can also be treated with therapeutics for ATTR-CA. Singal et al (11) showed that in an elderly Indian population, the coexistence of cardiac amyloidosis and severe aortic stenosis is not uncommon, as detected by PYP imaging (9.4%). They also demonstrated that there is a high prevalence of isolated valvular amyloidosis in patients with severe AS, the significance of which remains unknown. Larger dual disease studies will help to understand whether isolated valvular amyloidosis can lead to increased morbidity and mortality; valve and/or amyloid specific therapies and valvular interventions may benefit patients with concomitant disease and can potentially calm the perfect storm.

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ADDRESS FOR CORRESPONDENCE: Dr Sabahat Bokhari, Lehigh Valley Heart and Vascular Institute, 1250 South Cedar Crest Boulevard, Suite 300, Allentown, Pennsylvania 18103, USA. E-mail: Sabahat.bokhari@LVHN.org. Twitter: @Bokhari_Sabahat.

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