

SHORT EDITORIAL

Cardiac Amyloidosis TTR: The Hidden Culprit Behind Aortic Stenosis in the ElderlySandrigo Mangini,^{1,2}  Lígia Lopes Balsalobre Trevizan² *Universidade de São Paulo, Instituto do Coração,¹ São Paulo, SP – Brazil**Hospital Israelita Albert Einstein,² São Paulo, SP – Brazil***Short Editorial referring to the article: Prevalence of Cardiac Amyloidosis in Elderly Patients With Aortic Stenosis**

Calcific aortic stenosis (AS), a condition marked by leaflet fibrosis and calcification, is driven by mechanical stress and biological stimuli that activate pro-inflammatory pathways. It results from a complex, progressive process that occurs over many years, and becomes increasingly prevalent with age. Aging itself is associated with a “low-grade inflammatory state”, which promotes and sustains various pathological conditions, including cardiac amyloidosis (CA)^{1,2} that is mostly related to wild-type transthyretin (TTR) and less commonly to variant TTR and light chain amyloidosis (AL). CA is phenotypically associated with heart failure with preserved ejection fraction (HFPEF), and wild type TTR is estimated to be prevalent in approximately 13% of elderly over 60.³ However, different from calcific AS that has a similar gender distribution, the wild-type TTR is more prevalent in men.

In a study with elderly patients, Conte et al.⁴ reported amyloid deposition in 37% of stenotic aortic valves, 10% of sclerotic valves, and no findings of amyloid in controls. Amyloid deposition was linked to greater fibrosis and calcification. Immunohistochemistry suggested involvement of serum amyloid A1 (SAA1) and TTR. These findings indicate that amyloid deposition in aortic valves may be more common and is related to aging and degenerative changes.⁴

Considering the high prevalence of wild-type TTR and AS in the elderly, their coexistence is unequivocal. High mechanical stress and valve inflammation may further promote amyloidogenesis, explaining the frequent accumulation of amyloid fibrils in stenotic valves. Singal et al.⁵ identified TTR amyloid deposits in nearly

57% of stenotic valves examined from patients without a diagnosis of systemic CA. Studies have shown that 8-16% of patients with severe AS also have coexisting TTR amyloidosis.⁶ however, it is unknown whether it varies between countries and regions.

In this issue of the International Journal of Cardiovascular Sciences, Key et al.,⁷ present their data from a pioneering study in Brazil, assessing the prevalence of CA in a population of AS patients living in Salvador (Bahia). The authors used pyrophosphate scintigraphy and found 10% of patients with moderate to severe AS of likely calcific origin with CA (three patients with wild-type TTR, and one with variant TTR - V122I), reinforcing the potential association of amyloid deposition with calcific AS.

The coexistence of AS and CA is challenging, especially in HFPEF. The hemodynamic alterations observed in AS, such as decreased cardiac output resulting from ventricular remodeling and diastolic dysfunction, are similar to those found in the restrictive cardiomyopathy characteristic of CA. This overlap can pose challenges for both diagnosis and management.⁸ Furthermore, symptoms such as heart failure and reduced exercise capacity, commonly attributed to severe AS, may be aggravated by the presence of underlying CA. As a result, therapeutic approaches like surgical intervention or transcatheter aortic valve replacement (TAVR) may lead to less favorable outcomes in patients with unrecognized CA.⁹

The detection of CA requires a high degree of suspicion, particularly in patients with AS, as conventional diagnostic tests cannot provide a definitive diagnosis. Clinical signs that may suggest CA include carpal tunnel syndrome, lumbar spine stenosis, biceps tendon rupture, hearing loss, and heart failure symptoms.

Keywords

Amyloidosis; Aortic Valve Stenosis; Amyloidosis.

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Autonomic and peripheral neuropathy are common in CA, often contributing to reduced blood pressure. Progressive amyloid deposition can also disrupt the heart's conduction system, leading to sinoatrial node dysfunction, atrial flutter, and bundle branch block. In patients with CA, features of AS may include low-flow, low-gradient hemodynamics, amyloid infiltration of the aortic valve, and accelerated progression of AS.¹⁰ In case of clinical suspicion, a multi-parametric approach is crucial for diagnosing CA in patients with AS, starting with electrocardiography and echocardiography, assessment of biomarkers and free light chains, magnetic resonance imaging, bone tracers for TTR diagnosis and genetic testing for variant or wild-type TTR definition. In doubtful cases and AL suspicion, endomyocardial biopsy and mass spectrometry can be considered. Since 2005, with studies demonstrating high sensitivity and specificity of bone tracers to TTR CA diagnosis, after excluding AL, a non-invasive approach has been defined as the standard strategy for CA diagnosis.¹¹

Early diagnosis of this condition is important, as the coexistence of both entities significantly worsens

the patient's prognosis, particularly in the absence of appropriate intervention. Current evidence indicates that patients undergoing percutaneous correction of valvular heart disease achieve better outcomes in terms of survival and cardiovascular events compared to those receiving medical therapy alone, irrespective of the presence of CA. As a result, percutaneous treatment for valvular heart disease is now considered the primary therapeutic strategy.¹² Following this intervention, consideration may be given to disease-modifying treatments for TTR amyloidosis to slow disease progression and enhance patient outcomes, although robust data on this approach remain limited.¹³

The Brazilian study by Key et al.⁷ supports the evidence that CA is not a rare, but rather an underdiagnosed condition. The presence of AS appears to be an important red flag to the prompt investigation of CA in elderly patients, particularly those with HFpEF. Furthermore, it highlights the opportunity for non-invasive diagnosis which, coupled with emerging modifying therapies and TAVR, can change the prognosis of both diseases.

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