REVIEW

Aortic Valve Stenosis and Cardiac Amyloidosis: An Underestimated Coexistence

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Abstract

Coexistence of aortic valve stenosis (AS) and cardiac amyloidosis (CA) is frequent in the elderly as both conditions increase with age. Wild type transthyretin (TTR) amyloidosis is the most common type of amyloidosis in AS cohorts. Cardiac amyloidosis and AS share common clinical characteristics making diagnosis of dual pathology challenging. However, certain features should raise suspicion of CA presence in AS patients leading to specific imaging modalities to confirm diagnosis. Dual pathology (AS & CA) increase mortality risk and prompt diagnosis is crucial. Novel pharmacological agents targeted for TTR CA should be initiated to improve prognosis. The role of the Heart Team for decision-making in these cases regarding the optimal management of AS is crucial. Transcatheter aortic valve replacement may be the preferred procedure in these high-risk patients. ***Rhythmos 2022;17(3): 53-57.***

Key words: aortic valve stenosis; cardiac amyloidosis; transthyretin

Abbreviations: AS = aortic stenosis; AL = light-chain amyloidosis; CA = cardiac amyloidosis; TAVI = transcatheter aortic valve implantation; TTR = transthyretin

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Introduction

Aortic valve stenosis (AS) is the most common valvular heart disease, affecting life expectancy when symptoms are present, especially if left untreated. The prevalence of AS is increasing with age, reaching > 4% in patients aged >75 years old. [1] In autopsy studies, cardiac amyloidosis (CA) was found in ~ 25% of individuals ≥ 80 years old. [2] Coexistence of AS and CA is not rare and must not evade diagnosis. It is estimated that ~15% of the AS population may have CA. [3] However, the identification of patients with dual pathology (AS and CA) may be challenging due to common features that the two diseases share.

Amyloidosis is a rare systemic disease caused by extracellular accumulation of amyloid fibrils. Various organs are affected by this process including the heart. The classification incudes mainly immunoglobulin light-chain (AL) amyloidosis and transthyretin (TTR) amyloidosis (ATTR) associated with mutant (hereditary) or wild-type TTR (senile cardiac amyloidosis). The development of modern diagnostic modalities such as cardiac magnetic resonance (CMR) imaging and 99mTc-labeled 3,3-diphosphono-1,2-propanodicarboxylic acid (99mTc-DPD) bone scintigraphy have recently led to a considerable increase in the diagnosis of CA. [4] (N.B.: nomenclature uses the letter "A" for amyloid, followed by the letter(s) referring to the main protein being deposited, e.g., light-chain amyloidosis is "AL" ("A" for amyloid and "L" for light chain); transthyretin amyloidosis is "ATTR" ("A" for amyloid and "TTR" for transthyretin).

TTR amyloidosis (ATTR) is associated with a particularly poor life expectancy of 2 to 6 years after diagnosis and concomitant AS may be associated with even worse prognosis. In the last few years, novel pharmacotherapies have been developed to reverse the course of the disease with promising results. [5] Therefore, there is urgent need for CA patients to be identified and treated accordingly. The aim of this review is to present the current knowledge on AS-CA coexistence regarding epidemiology, pathophysiology, screening and therapeutic approach.

Epidemiology-Pathophysiology

Dual pathology is relatively common as CA prevalence in AS patients has been shown to be ~15%, whereas AS has been found to be present in ~9% of CA patients. [6] The higher prevalence of CA has been reported in patients undergoing transcatheter aortic valve implantation (TAVI). [7] TTR amyloidosis, specifically its wild type, is the most prevalent type of CA in patients with concomitant AS. [6, 8, 9] In contrast, the coexistence of AS and AL amyloidosis is rare as AL amyloidosis is present in younger patients with poor prognosis. [6, 9]

TTR is a liver synthesized protein which transports thyroxin and retinol to the liver, having an important role in the control of behavior, cognition, nerve regeneration and axonal growth. [10] The two common types of ATTR are the wild type and the hereditary. The former type is age-related, caused by the pathological aggregation of degenerated amyloid fibrils in various organs including heart. On the other hand, the latter type is transmitted in autosomal dominant pattern. Specifically, 120 mutations have been identified. [11] The majority of TTR mutations are responsible for a mixed clinical phenotype, where both

neurologic and cardiac manifestations are present. [12] The most common worldwide TTR variant, Val122Ile (or pV142I) manifests predominantly as cardiomyopathy. [13]

Irrespectively of the amyloid type, deposition of the insoluble amyloid in the myocardial wall and, as a consequence, the extracellular volume expansion results in ventricular stiffness, diastolic dysfunction, restrictive physiology with late loss of systolic function, arrhythmias, and heart failure. [10] The amyloid infiltration of left ventricular (LV) basal segments precedes apical involvement. Indeed, CA patients commonly present with diastolic heart failure with preserved LV ejection fraction and impairment of longitudinal systolic function. However, in one third of cases systolic heart failure may be present. [14] Additionally, CA patients may present supraventricular arrhythmias and conduction disturbances because of atrial amyloid infiltration leading to a higher rate of thromboembolic events requiring anticoagulation therapy. [15]

Interestingly, there is evidence supporting that laboratory findings such as N-terminal pro-brain natriuretic peptide (NT-proBNP) and high-sensitive troponin T (hsTnT) values tend to be increased in patients with dual pathology compared with patients with sole aortic stenosis. Both hsTnT and NT-proBNP had a dose–response curve with the amyloid burden as estimated by the 3,3-diphosphono-1,2-propanodicarboxylic acid (DPD) Perugini grade. [16] These findings may be explained by the infiltration of the microcirculation.

On the other hand, AS is an active process which is regulated by both osteogenic and non-osteogenic mechanisms. Inflammation, lipoprotein penetration, mechanical stress and endothelial damage are major contributors to fibrocalcific stenosis. [17] The LV generates higher systolic pressures in order to preserve the cardiac output in the context of increased afterload. Therefore, increased wall stress leads to increased wall thickness according to Laplace law. These hemodynamic and structural changes lead to impaired LV relaxation and diastolic dysfunction. Eventually, systolic dysfunction occurs when LV is unable to compensate for the pressure overload.

Despite the different pathophysiology, AS and CA share common phenotypic and echocardiographic features such as the wall thickening, diastolic and systolic dysfunction complicating the diagnosis and management of AS-CA patients.

Diagnosis – Screening

Although aortic stenosis and cardiac amyloidosis share several common clinical and echocardiographic characteristics, recent studies have presented certain features (red flags) that imply the presence of CA in AS patients (**Table 1**). Diagnostic tests for ATTR confirmation and AL CA exclusion should be performed in this group of patients.

Table 1. Cardiac amyloidosis red flags in aortic stenosis.

Clinical	Older male patients Carpal tunnel syndrome Lumbar spine stenosis Biceps tendon rupture Deafness Disproportionate heart failure symptoms Predominant right heart failure
Electrocardiography	Low voltage (discordant to left ventricular hypertrophy) Pseudo infarct pattern (q waves) Conduction abnormalities
Echocardiography	Excessive LV hypertrophy Severe diastolic dysfunction Right ventricular thickness >5 Granular sparking Bilateral atrial dilatation Pericardial effusion Mitral annulus S' ≤ 6cm/sec Left ventricular global longitudinal strain ≥ -12 Paradoxical low-flow low-gradient aortic valve stenosis
Cardiac Magnetic Resonance	Excessive LGE and ECV values
Biomarkers	Excessively increased NT-proBNP and hsTnT values

Firstly, ATTR is more often found in older male patients. [18] Moreover, a clinical history of carpal tunnel syndrome [19], lumbar spinal stenosis [20], biceps tendon rupture, deafness [21], disproportionate heart failure symptoms despite non-severe AS, conduction abnormalities leading to premature pacemaker implantation may raise the suspicion of wild type ATTR. Another typical characteristic is the presence of predominant signs of right ventricular failure. Additionally, macroglossia is a common AL amyloidosis manifestation and rare feature in ATTR.

Despite the low specificity of electrocardiogram (ECG) changes in CA patients, low voltage in precordial and limb leads discordant to LV hypertrophy and a pseudo-infarct pattern (q waves) may be present. [22] Conduction abnormalities and arrythmias are more prevalent in CA patients than control groups.

The echocardiographic features in AS patients suggesting CA are the following: LV hypertrophy, LV diastolic dysfunction, RV wall thickness >5 mm, bilateral atrial dilation, pericardial effusion, granular sparkling, mitral annulus S' ≤ 6 cm/sec. LV global longitudinal strain measured by speckle ≥ -12 has prognostic value while LV

longitudinal strain is often preserved at the apex in CA (apical sparing). According to Castaño et al, in patients with dual pathology, the apical sparing pattern may not be observed because of increased afterload and wall stress, [18] whereas Nitsche and colleagues demonstrated that apical sparing was a powerful marker for diagnosing AS with CA.[3]

Patients with ATTR had a higher E/A ratio (2.3 [1.10–3.10] vs. 0.9 [0.70–1.70], p = 0.001) consistent with grade III diastolic dysfunction. Moreover this group of patients present aortic valve mean pressure gradient <40 mmHg, and stroke volume index <35 ml/m^2 more frequently compared with those without CA (29.2% vs. 10.5%, p = 0.045).[8] Approximately 50% of patients with CA and low-flow, low-gradient have preserved LV ejection fraction (paradoxical low-flow, low-gradient). These findings may be attributed to severe LV concentric remodeling, impairment of diastolic filling, left atrial remodeling and dysfunction.

Cardiac magnetic resonance (CMR) imaging (mainly with late gadolinium enhancement (LGE), T1 mapping and extracellular volume (ECV) fraction) contributes to CA early diagnosis and risk stratification. However, 15% of CMR examinations may be normal in patients with CA.[23] T1 mapping has a high diagnostic accuracy for cardiac amyloid for both AL and TTR. The typical finding is circumferential LGE detected at first within the LV sub-endocardium and in basal segments. Native T1 and ECV values demonstrates a proportional increase with cardiac amyloid burden and, additionally, may indicate CA diagnosis even if LGE is normal. [23] Moreover, patients with concomitant ATTR and AS have been shown to exhibit higher native T1 and ECV values, compared to patients without ATTR.

Recently, a simple clinical score was introduced by Nitsche et al. to predict the coexistence of AS and CA. [3] The RAISE (remodeling, age, injury, systemic and electrical) score includes disproportionate myocardial remodeling (marked LV hypertrophy, septal wall thickness ≥18 mm, 1 point; marked diastolic dysfunction, E/A ratio >1.4, 1 point), age (85 years or older, 1 point), chronic myocardial injury (hsTnT >20 ng/l, 1 point), systemic disease (carpal tunnel syndrome, 3 points) and disproportionate electrical remodeling (right bundle branch block, 2 points; low voltages or Sokolow-Lyon index <1.9 mV, 1 point).[3]

Although the previous findings should raise the suspicion of AS & CA dual pathology, the diagnosis of cardiac amyloidosis in AS patients is established by bone scintigraphy with 99m technetium-labeled bisphosphonates combined with testing for monoclonal light chain in blood and urine. In particular, grade 2 or 3 uptake on scintigraphy, using the Perugini score in combination with the absence of monoclonal protein in blood and urine confirm the TTR CA diagnosis (specificity and a positive predictive value of 100%) without the need for biopsy. [4] False positive results derive almost exclusively from 99mTc-DPD uptake in patients with cardiac AL amyloidosis. Therefore, given the AL amyloidosis poor prognosis if left without chemotherapy, it should be systematically screened using serum/urine light chain protein analyses in these patients. Distinguishing wild type from hereditary TTR CA requires genotype analysis.

Importantly, differentiation between a true-severe versus a pseudo-severe AVS in a TTR CA patient may be challenging. Dobutamine stress echocardiography, which is normally used to confirm AVS severity (peak stress mean gradient ≥40 mmHg), in low-flow low-gradient AS and reduced LV ejection fraction cases may be inconclusive because of reduced contractile reserve in patients with dual pathology. Hence, the role of calcium score quantification by non-contrast computed tomography (CT) is important. However, several case reports studies support the underestimation of AS severity by this method in CA patients. [4]

Prognosis and Management

Aortic stenosis and CA are conditions associated with mortality even when they occur separately in elderly patients. In the last few years, dual pathology is being increasingly diagnosed but prognosis of these patients is not yet completely clarified as large multicenter studies are lacking. [16, 24] However, there is evidence that CA is an independent negative prognostic factor in patients with severe AS. Several studies have shown up to 35% higher mortality at 1.5 years for patients with AS-CA compared to those who suffered solely from severe AS. [16, 25-27]

Regarding management of dual pathology, in patients with heart failure, the main target is maintaining euvolemia. [28] In presence of symptoms, loop diuretics and possibly mineralocorticoid receptor antagonists may be given. The mainstay of heart failure treatment - renin-angiotensin-system inhibitors - may not be well tolerated due to hypotension. In the same line, β-blockers and digitalis may cause bradycardia and should be avoided. [29] Additionally, calcium channel blockers should not be administered due to formation of a complex with amyloid. [30] Amyloid atrial infiltration leads to atrial myopathy increasing the embolic risk. Based on that, anticoagulant treatment is recommended in all patients with CA with history of atrial fibrillation regardless of CHA_2DS_2-VASc score. [31]

Specific treatments for both AL and ATTR amyloidosis are available, making diagnosis of CA crucial in patients with AVS to improve survival in combination with aortic valve replacement. Treatment of AL amyloidosis is based on chemotherapy or autologous stem-cell transplant. In

case of ATTR amyloidosis, stabilization of TTR and reduction of its production with novel agents form the cornerstone of treatment. Accordingly, tafamidis is recommended in patients with NYHA I or II, wild type or hereditary ATTR to reduce symptoms and cardiovascular morbidity and mortality. [32] Newer drugs, such as patisiran and inotersen, have only been approved in the presence of proven polyneuropathy.[21] Specific treatment should be started as soon as ATTR CA is confirmed, regardless of the need for aortic valve replacement.

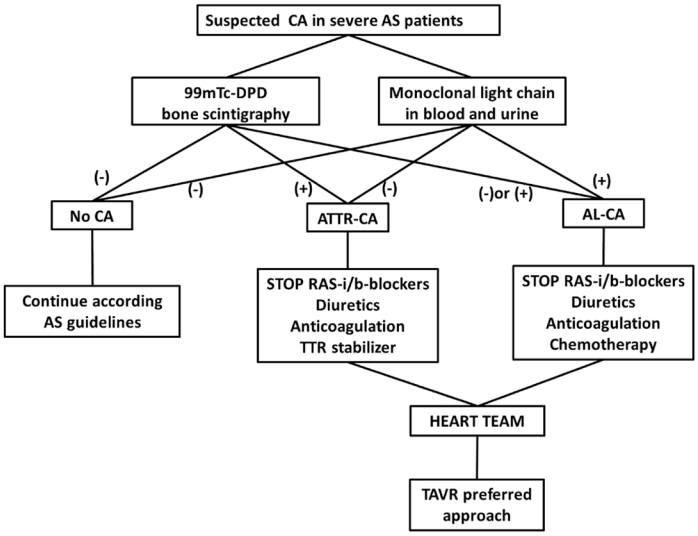

Figure 1. Heart Team approach algorithm in case of aortic valve stenosis and concomitant cardiac amyloidosis

Evidence concerning the outcome of aortic valve replacement in patients with dual pathology is limited. Some studies have shown high risk of mortality and moderate functional status improvement in patients with severe AS and CA after surgical replacement.[27, 33, 34]

Recently, TAVI has presented promising results leading to lower mortality and less HF hospitalizations in these patients compared to conservative approach and surgical replacement. [3, 16, 35, 36] Therefore, TAVI should not be denied in patients with concomitant AS and CA. On the other hand, very high-risk patients that are associated with poor prognosis and futility of aortic valve replacement may be treated conservatively. The role of Heart Team is crucial in such cases, in order to take under consideration individual comorbidities, risk factors, functional status as well as survival expectancy in each case and to finally select the optimal treatment option (**Fig. 1**).

Conclusion

Coexistence of CA in patients with AS is high reaching ~15%, with the most prevalent type being wild type ATTR CA. Specific clinical features should raise the suspicion of dual pathology leading to a series of diagnostic tests to confirm the presence of CA. Recent targeted treatment for ATTR CA may exponentially improve outcomes in these patients. The Heart Team should carefully evaluate each case individually to propose optimal approach for severe symptomatic aortic stenosis management. TAVI seems to be a more attractive option in these high-risk patients.

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