Review

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Franz Duca , Christina Kronberger , Robin Willixhofer , Philipp Bartko , Jutta Bergler-Klein , Christian Nitsche *

Posted Date: 14 November 2023

doi: 10.20944/preprints202311.0922.v1

Keywords: aortic stenosis; mitral regurgitation; tricuspid regurgitation; AL; ATTR

Review

Cardiac Amyloidosis and Valvular Heart Disease

Franz Duca, MD, PhD [1]; Christina Kronberger, MD [1]; Robin Willixhofer, MD [1]; Philipp E. Bartko, MD, PhD [1]; Jutta Bergler-Klein, MD [1]; Christian Nitsche, MD and PhD [1]

[1] Department of Internal Medicine II, Medical University of Vienna, Austria;

* Correspondence: to: Christian Nitsche, MD PhD, Department of Internal Medicine II, Medical University of Vienna, Waehringer Guertel 18-20, A-1090 Vienna / Austria, Tel. +43-1-40400-46140; Fax +43-1-40400-42160; Email: christian.nitsche@meduniwien.ac.at

Abstract: Growing interest has accrued in the co-existence of cardiac amyloidosis and valvular heart disease. Amyloid infiltration from either transthyretin (ATTR) or light chain (AL) origin may affect any structure of the heart, including the valves. Recent literature has mainly focused on aortic stenosis and cardiac amyloidosis, improving our understanding of epidemiology, diagnosis, treatment and prognosis of this dual pathology. Even though of high clinical relevance, data on mitral/tricuspid regurgitation and cardiac amyloidosis is rather scarce and mostly limited to case reports and small cases series. It is the aim of this review article to summarize the current evidence of concomitant valvular heart disease and cardiac amyloidosis including epidemiology, diagnostic approaches, screening possibilities, therapeutic management, and prognostic implications.

Introduction

Cardiac amyloidosis (CA) is an infiltrative myocardial disease and causes heart failure and death by deposition if amyloid fibrils. The two predominant amyloid proteins deposited in the heart are transthyretin (ATTR) and immunoglobulin light chain (AL). Formerly believed to be a rare condition, recent diagnostic advances and disease awareness have resulted in a significant increase in the number of patients diagnosed with CA. (1) The diagnosis of ATTR-CA was facilitated by the introduction of a non-invasive diagnostic algorithm, which allows a non-biopsy diagnosis in the majority of patients with suspected CA. (2) Increased diagnosis of CA has spurred in-depth characterization of this condition, which – among other things – has unveiled a frequent co-existence with significant valvular heart disease (VHD). VHD may impact the clinical manifestation, therapeutic management strategies, and prognosis of patients with CA. While many issues have been addressed by recent research, there still exist essential gaps of knowledge which warrant investigation by prospective trials.

This research article therefore aims to a) summarize our current understanding of concomitant CA and the most frequent forms of valvular heart disease – aortic stenosis, mitral regurgitation, and tricuspid regurgitation, and to b) highlight gaps of knowledge which should stimulate the conduction of prospective studies. Topics discussed include epidemiology, pathophysiological considerations, screening possibilities, prognosis, and management options. For this review, we searched relevant studies in PubMed/Medline (updated October 2023) using the following terms: amyloidosis, cardiac amyloidosis, valve, valvular, stenosis, and regurgitation. Given the design of this work as a narrative review, no formal criteria for study selection or appraisal were enforced.

Aortic stenosis

Epidemiology

The coexistence of CA and AS was described for the first time in prospective patient populations in 2016 and has since then experienced fast growing interest. (3,4) These two preliminary studies found a prevalence of 12% (in elderly patients with a median age of 85 years) and 6% (in patients undergoing surgical aortic valve replacement receiving intraprocedural biopsy with a mean age of 75 years), respectively. Another study by Castano et al. of elderly AS patients undergoing transcatheter aortic valve replacement (TAVR) even described a prevalence of 16%, which may have been a slight overestimation since patients were not recruited consecutively. (5) Further studies with

 doi:10.20944/preprints202311.0922.v1

prospective consecutive screening followed reporting on disease prevalences ranging from 8 to 13%. (6-8) However, one needs to consider the different definitions of CA in these studies. Whereas CA was defined strictly according to the current expert consensus algorithm (2) in the studies by Nitsche et al. and Dobner et al., patients found to have AS-CA in the study by Scully et al. also included those with low-grade myocardial tracer uptake on bone scintigraphy confirmed by SPECT/CT (Perugini grade 1). The largest multi-center, multi-cohort study to this day reported a prevalence of 12%. (9) Here, patients with grade-1 myocardial uptake (confirmation by SPECT/CT) were included, which is believed to represent an early disease stage of ATTR. (10) One recent meta-analysis summarized the current evidence gathered from screening studies and yielded a prevalence of 11%. (11) Among AS patients with a low-flow, low-gradient phenotype, the prevalence of concomitant CA is believed to be even higher, but no study has yet evaluated this in a population restricted to low-flow low-gradient AS.

To put the disease prevalence into perspective, the prevalence of CA in the general population needs to be considered. Respective estimates are derived from bone scintigraphy referrals for non-cardiac indications, which is currently considered the most accurate way to assess ATTR prevalence in the general population. The largest comparable study to this day reported the presence of intense cardiac tracer uptake (Perugini grade ≥2) in ~3% of consecutive patients aged 80 years or older (comparable to the age of patients in TAVR screening studies). (12) Hence, the prevalence of CA is ~4 times higher in patients with AS compared to the "general population". This warrants discussion of possible underlying pathophysiological mechanisms.

Pathophysiological aspects

Underlying pathophysiological principles in dual AS-CA are currently incompletely understood and limited to hypotheses. The "chicken or egg" discussion in AS-CA refers to the question of whether a) accumulation of amyloid fibrils in the aortic valve tissue may be a driver for the progression of AS or whether b) AS primes the left ventricle for amyloid deposition. Amyloid has indeed been identified in a high proportion of surgically resected heart valve specimen. (13) However, rather than common CA subtypes (AL and ATTR), ApoA1 was found, which aggregates in the atherosclerotic and inflammatory milieu of AS. Nevertheless, data regarding the contributing role of amyloid deposition in the disease progression of AS are conflicting, as one recent study reported a surprisingly high rate of 58% of ATTR deposition in aortic valve tissue. (14) A different hypothesis of increased susceptibility of the left ventricular myocardium for amyloid formation and deposition is supported by the mechano-enzymatic cleavage process which has been proposed previously. (15) Increased biomechanical forces in the setting of increased shear stress caused by elevated left ventricular afterload may initiate the proteolysis/fibrillogenesis pathway. Finally, both AS and CA share an endo- to epicardial gradient with regards to fibrosis formation and amyloid deposition, respectively. (16) It is plausible that the ischaemic stress caused by AS creates a milieu which facilitates amyloid deposition, such as described for amyloid ß in the brain. (17) The fact that the LV mass index has been described to be lower in AS-ATTR compared to matched lone ATTR-CM patients, has also led to the hypothesis that AS-CA likely represents an early stage of amyloid infiltration. (18)

Diagnosis and screening

The diagnostic pathway of detecting concomitant CA in patients with AS does not differ from the conventional algorithm recommended by current expert consensus documents and guidelines. (2,19) The difficulty lies in the enormous volume of aortic valve replacements being performed in large valve clinics, which makes it logistically impossible to perform CA testing in every AS patient. Hence, efforts have been made to identify parameters which can be used to assess the pre-test probability for the presence of concomitant AS. Among reported parameters indicating a higher likelihood of co-existing CA are higher age, male sex, history of carpal tunnel syndrome, decreased stroke volume (low-flow pattern), poorer diastolic function, out-of-proportion LV thickening, presence of a right-bundle branch block on ECG, discordance of LV mass on ECG and echo (low

 doi:10.20944/preprints202311.0922.v1

"voltage/mass ratio"), and out-of-proportion troponin elevation. (5,6,8,9,20) Some of these measures have been combined to form an additive score (RAISE-score) including proposed optimal cut-off values for continuous metrics. (9) Here, each parameter is assigned a specific score if present. Higher scores indicate a higher pre-test probability of concomitant CA, and patients with a score of 3 points or higher are advised to receive further testing by bone scintigraphy and light chain assessment. It is important to mention that this score has been developed in a patient population with severe AS referred for TAVR and should therefore be applied to this specific group only. It is currently unknown how the RAISE score would perform in other clinical scenarios, such as a) patients with AS of moderate or mild severity, b) patients with a history of AS who have already received an aortic prosthesis, or c) patients without AS. AS patients may also be suspected of concomitant CA by the presence of red flags from other tests (e.g., polyneuropathy, deafness) or imaging modalities (e.g., characteristic pattern of late gadolinium enhancement or elevated T1 relaxation times/extracellular volume fraction on cardiac magnetic resonance imaging). Finally, patients awaiting TAVR require a cardiac computed tomography (CT) scan as part of their pre-procedural planning. Just like contrast agents used in cardiac magnetic resonance, CT contrast agents also represent extracellular agents, not entering myocardial cells. This feature can be exploited to acquire and quantify extracellular volume fraction by CT. Significantly higher CT-ECV values have been described for AS-CA compared to lone AS and CT-ECV therefore represents a highly attractive marker for screening all AS patients undergoing TAVR work-up for concomitant CA. (21)

Treatment and outcomes

Given the high prevalence of comorbidities and advanced age of AS-CA, TAVR was previously thought to be futile. (22) These assumptions were also based on initial reports of higher mortality in AS-CA patients compared to lone AS. (4,20) However, these were preliminary studies that either investigated younger patients receiving surgical aortic valve replacement or selected patients of whom only ~50% underwent aortic intervention. Further studies assessing short-term mortality and hospital admissions for heart failure post-TAVR followed. (6,23) Both of these studies reported similar hazard of mortality and heart failure hospitalisations post-interventional for dual AS-CA and lone AS. However, in the study by Rosenblum et al. a higher hospitalization rate (*n* per person years) within the first year after TAVR was found for AS-CA compared to lone AS. (23) Similar mortality for both groups up until 3 years post-TAVR was confirmed by the largest cohort study to this day, and also by one recent study. (7,9) Importantly, the conception of treatment futility of severe AS in patients with dual pathology was disproven by the study of Nitsche et al., which demonstrated clear survival benefit for AS-CA receiving TAVR compared to those with conservative care. (9) Besides valvular treatment, amyloid-specific therapies should also be discussed for AS-CA. The question of whether patients with AS-CA should receive amyloid-specific treatment on top of valve replacement currently represents a gap of evidence as patients with significant valve disease were excluded from large ATTR-CM drug trials. (24,25) Also, AS-CA cohort studies were underpowered to address this issue, and patients with AS-CA receiving ATTR-specific treatment were underrepresented. (6,9) A large inter-national, multi-center, multi-cohort registry currently tries to address the potential benefit of ATTR-specific therapies in dual AS-CA (NCT06129331).

Despite the lack of convincing evidence, surrogate markers may suggest possible benefits through ATTR-specific treatment in AS-CA. One study reported trajectories of functional capacity, laboratory makers, and echocardiographic parameters in AS-CA compared to lone AS at one-year after TAVR. (26) Patients with AS-CA remained more symptomatic, with higher residual NT-proBNP values and higher LV mass. Also, a pattern of apical sparing developed in AS-CA only after TAVR. These features indicate that at one-year after TAVR AS-CA resembles a lone ATTR-CM phenotype by symptoms, biomarkers, morphology, and contractility pattern, making benefit through ATTR-specific drugs very likely.

Mitral regurgitation

 doi:10.20944/preprints202311.0922.v1

Epidemiology

Significant (moderate or higher) mitral regurgitation (MR) can be found in approximately one third of all patients with heart failure (HF). (27) However, the prevalence among patients with CA is much less established. The most recent study which specifically investigated MR in the context of CA included 877 patients from the United Kingdom. Chacko et al. reported a prevalence of 12.9% of at least moderate MR in patients with ATTR-CM. (28) Interestingly, an earlier study from the same UK cohort and first author found significant MR in 30.2% of their 1240 patients (29). Moreover, data from other cohorts also suggest higher prevalences of 17% and 24%, respectively (30,31). Conversely, studies investigating the prevalence of CA in patients with significant MR are scarce and of heterogeneous design. One study by Donà and colleagues systematically screened patients undergoing transcatheter edge-to-edge mitral valve repair (TEER) for the presence of CA and found a dual pathology in as many as 19.2% (whereby 11.7% had definite CA as defined according to the current guidelines). (32) Another recent study from the Cleveland Clinic by Xu et al. took a different approach and histologically analysed >7700 surgically removed mitral valve specimens. Of note, amyloid was present in only 0.2% their specimens. (33) In contrast, a German study found amyloid in 20.8% of mitral valve specimens. However, none of the common amyloid proteins (AL, ATTR) was identified by immunohistochemical analysis, and a major limitation was the small study size of only 24 MR patients. (13)

Pathophysiological aspects

From an etiological standpoint, MR in CA features aspects of primary and secondary MR. On the one hand amyloid depositions alter the structure and function of the valve leaflets and the (sub-)valvular apparatus itself. (28,33) A Japanese study from the year 2000 provides interesting insights into how amyloid infiltration changes the physical properties and subsequently the function of the mitral valve using an acoustic microscope. (34) The authors found that mitral valves from CA patients with at least moderate MR were significantly stiffer than the valves from CA patients with only mild MR or controls. Of note, also more unexpected presentations of MR in CA, such as ruptured chordae have been published. (35) Moreover, CA is associated with distinct LV geometry changes which in turn can also cause insufficient mitral valve closure. (28,36,37) Finally, left atrial enlargement represents a hallmark sign of restrictive cardiomyopathies, often leading to mitral valve annular dilatation and atrial functional MR. (32) Mixed etiologies may also occur. Thus, MR in the context of CA is indeed a rather complex disease, which is underlined by the fact that it can present as Carpentier classes I-III. (38)

Diagnosis and screening

Similar to AS in CA, the diagnostic algorithm for CA in the context of MR does not differ from current recommendations. (2,19) Given the relatively high prevalence of CA among patients undergoing TEER one could argue that systematic screening should be implemented in order to avoid missing a diagnosis of underlying CA. Again, this approach is probably not executable, especially in high-volume valvular heart disease clinics were demands for bone scintigraphy then would vastly exceed the number of available slots.

Given the unique pathophysiology and hemodynamics present in patients with CA the bigger challenge is the assessment and grading of MR itself. To date, even though regularly used it is not clear whether recommended cut-offs for the quantification for MR in the context of CA should be applied. (39) It is likely, that in the setting of low-flow conditions cut-point values of quantitative MR metrics (regurgitant volume, proximal isovelocity surface area, effective regurgitant orifice area) indicating poor clinical outcomes differ from those used in normal-flow conditions. (40) Thus, prospective studies are needed in order to establish valid cut-offs and guidelines for the quantification of MR in CA.

Treatment and outcomes

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Although numerous studies investigated the prognostic power of MR and how it should best be treated in patients with heart failure and reduced ejection fraction respective data are extremely scarce in CA. Results from a recent study of 877 ATTR-CM patients by Chacko et al. suggest that indeed MR is of prognostic relevance in this patient population. The authors found that an increase in MR severity irrespective of baseline severity was among the strongest predictors of outcome in their cohort. A 2020 study by the same authors found that a MR ≥ moderate at baseline was associated with adverse outcomes only in their univariable survival analysis, but not after adjusting for National Amyloidosis disease stage (29). Therefore, more studies dedicated to the prognostic role of MR in CA are clearly needed.

Thus far, 2 studies have investigated the feasibility of TEER as a treatment option in this patient population. (41,42) One German study included 5 CA patients (4 ATTR, 1 AL) who underwent TEER, which was demonstrated to be feasible with a procedural success rate of 100% and sustained reduction of MR severity. (42) The authors also proposed a potential survival benefit of CA patients undergoing TEER when compared to a control group of CA patients with severe MR not receiving TEER. However, this statement seems oversized as their control cohort consisted of a much sicker patient population (NTproBNP: 17,365pg/mL versus 2,928pg/mL; eGFR: 28mL/min versus 82mL/min). The second study included 120 consecutive patients who underwent TEER at two Austrian university hospitals. (32) Among those, 23 patients had concomitant CA. Again, procedural success rate was 100% and MR severity could be significantly reduced. With respect to outcomes, patients with a dual pathology had a higher risk of heart failure hospitalizations, but similar mortality when compared to lone MR.

In summary, TEER appears to be technically feasible with sustained reduction of MR severity in patients with CA. It is yet unclear whether TEER also improves quality of life and prognosis in CA, as these patients were specifically excluded from large TEER trials (MITRA-FR, COAPT). A current randomized trial tries to answer this question and is recruiting patients with ATTR-CM and significant MR who are randomized to receive either a) TEER plus optimal medical therapy or b) optimal medical therapy alone (MILLENNIAL trial, NCT06075823).

Tricuspid regurgitation

Epidemiology

Dedicated studies regarding the role of tricuspid regurgitation (TR) in patients with CA are scarce. A 2021 study by Fagot et al. from France assessed the prevalence of TR in 283 CA patients. (31) The authors reported a prevalence of TR graded as ≥ moderate of 26.2% with only a slight difference when patients were stratified according to amyloid subtype (AL: 23.4%, ATTR: 27.9%). This would suggest that the TR prevalence in CA is comparable to other heart failure entities. (43,44)

Pathophysiological aspects

Even though amyloid infiltration can be found in the tricuspid valve the fact that a significant proportion of CA patients in the study by Fagot et al. exhibited tricuspid annulus dilatation suggests that the TR mechanism in CA might be similar to other forms of heart failure (mostly secondary to elevated pulmonary pressures). (28,31,45) However, results from the UK study by Chacko and colleagues argue against this theory as only 16% had tricuspid annulus dilatation and most patients presented with thickened and restricted valve leaflets. (28)

Diagnosis and screening

Clinicians should adhere to current recommendations and guidelines for the quantification and assessment of TR, also in the context of CA. (39,46) However, once again, additional data is needed whether different cut-offs are needed in this particular patient population.

Treatment and outcomes

 doi:10.20944/preprints202311.0922.v1

The debate of whether TR is an independent predictor of adverse clinical outcomes and whether it represents a valid therapeutic target spans over decades. (47,48) Albeit much less data is available for patients with CA, this data is also conflicting. (28,31) In the studies by Chacko and co-authors a deterioration of MR but not TR was a strong outcome predictor of adverse outcome. (28,29) Conversely, in the study by Fagot et al. the presence of ≥ moderate TR was associated with increased mortality. Nonetheless, this association was found only in patients with ATTR but not AL CA. (31)

Given the general frailty and advanced age of patients with CA, a minimally invasive treatment approach seems preferrable to an open-heart surgery. The largest case series thus far was published from the Amyloidosis Center in Heidelberg. In total, 8 ATTR-CM and 21 non-CA patients underwent transcatheter tricuspid valve repair with the PASCAL Ace System. (49) Procedural success rate was 100% and after three months of follow-up TR severity and NYHA class were substantially improved. CA patients were furthermore compared to a non-matched control group of patients with severe TR and no CA, and the authors did not find any differences with respect to outcome endpoints (all-cause death/heart failure hospitalization). Randomized trials are needed to evaluate whether TR repair improves clinical outcomes in patients with CA.

Conclusion

In summary, valve disease and CA frequently coexist. While the dual pathology of AS and CA has been studied quite extensively, thereby closing significant gaps of knowledge, the coexistence of mitral/tricuspid regurgitation with CA is less well investigated. Modern imaging techniques enable a non-invasive diagnosis in a large proportion of patients with suspected CA. CA screening should therefore be widely applied in order not to miss a diagnosis of concomitant CA in patients with significant valve disease. Minimally invasive and transcatheter techniques seem most appropriate to treat valve disease in this elderly patient population with a high burden of comorbidities. This has been demonstrated for elderly patients with dual AS-amyloid. Treatment effects and associated prognosis of edge-to-edge repair in patients with mitral/tricuspid regurgitation and CA are yet to be determined.

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