Atrial amyloidosis: mechanisms and clinical manifestations

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Cardiac amyloidosis (CA) is now recognized as an important cause of heart failure. Increased wall thickness and diastolic dysfunction of the left ventricle are the most easily detectable manifestations of CA, but amyloid accumulates in all cardiac structures. Involvement of the left and right atria may be due to the haemodynamic effects of ventricular diastolic dysfunction, the effects of amyloid infiltration into the atrial wall, and the cardiotoxic damage of atrial cardiomyocytes by amyloid precursors. Atrial amyloidosis is an early manifestation of CA, and is associated with an increased risk of atrial fibrillation and thromboembolic events. Furthermore, atrial amyloidosis can be found even in the absence of systemic disease and ventricular involvement. This condition is named isolated atrial amyloidosis and is due to a local overproduction of atrial natriuretic peptide. In this review we summarize the evidence on the mechanisms and clinical relevance of atrial amyloidosis.

Graphical Abstract
Introduction

Amyloidosis is characterized by the extracellular deposition of misfolded proteins as insoluble amyloid fibrils. Cardiac involvement is most commonly related to the deposition of misfolded immunoglobulin light chains (AL) or transthyretin (ATTR), either in its wild-type (ATTRwt) or mutated form (variant, ATTRv). Greater disease awareness and the introduction of non-invasive diagnostic algorithms have led to an apparent increase in the prevalence of cardiac amyloidosis (CA), particularly ATTR-CA. Early diagnosis allows the prompt initiation of disease-modifying treatments, which are now available.2,3

Increased wall thickness and diastolic dysfunction of the left ventricle (LV) are the most easily detectable manifestations of CA, but amyloid accumulates in all cardiac structures. Left atrial (LA) involvement may be due to the haemodynamic effects of LV diastolic dysfunction, the effects of amyloid infiltration into the atrial wall, and the cardiotoxic damage of atrial cardiomyocytes by amyloid precursors (particularly light chains).4–6 The right atrium (RA) may be similarly affected. Atrial amyloidosis develops in early stages of AL- and ATTR-CA,7,8 and is associated with an increased risk of supraventricular arrhythmias and thromboembolic events. Furthermore, atrial amyloidosis can be found even in the absence of systemic disease and LV involvement. This condition is named isolated atrial amyloidosis (IAA) and is due to a local overproduction of atrial natriuretic peptide (ANP).9

In this review we summarize the evidence on the mechanisms and clinical relevance of AL- or ATTR-related atrial amyloidosis and IAA.

Study search

We searched the MEDLINE/PubMed database on 12 March 2022 using the keywords ‘atria’ amyloidosis’, without any restriction on language or article type. A total of 598 articles were found. The articles were screened by two authors (A.A. and V.C.); controversies were solved through discussion together with another author (G.V.). The reference lists of identified articles were screened for additional relevant papers. Given the design of this work as a narrative review, no formal criteria for study selection or appraisal were enforced.

Histological findings in atrial amyloidosis

Amyloidosis is due to a loss of protein homeostasis, which is the maintenance of an equilibrium between protein synthesis, folding and degradation, with an excess of misfolded proteins that are not removed by cellular quality control systems.10 Amyloidogenic proteins are characterized by many β-sheet regions stabilized by intermolecular hydrogen bonds, promoting monomer aggregation. β-sheet polypeptides form protofibrils, assembling into amyloid fibrils. This peculiar three-dimensional structure allows the Congo red dye to become interspersed between amyloid fibrils and causes the typical apple-green birefringence under polarized light10 (Figure 1).

Amyloid deposits in the atria may be found as focal, multifocal, or diffuse interstitial nodules surrounding cardiomyocytes and replacing normal tissue. Subendocardial and perivascular aggregates have also been described.6,16 Amyloid deposits associate with an extensive disruption of normal tissue architecture, including abnormalities of cardiomyocyte morphology, vascular remodelling and reduced capillary density.6,17 A study on atrial samples from five explanted hearts with ATTR amyloidosis reported the coexistence of amyloid nodular deposits and mild-to-moderate fibrosis in the subendocardium, while interstitial fibrosis was absent in the rest of the myocardium.6

Visualization of atrial dysfunction

Echocardiographic imaging

Standard echocardiographic examination allows to explore LA size and the patterns of transmural flow. In patients in sinus rhythm, the likelihood of atrial contractile dysfunction is high when the deceleration time of the mitral valve is normal yet the A wave is absent or diminutive (Figure 2).12 Speckle-tracking echocardiography allows to directly assess LA function, and typically reveals a progressive impairment of the reservoir and active contraction functions (Figure 3). In 124 patients with CA and sinus rhythm (68 with AL, 29 with ATTRv, and 27 with ATTRwt), these atrial functions were significantly impaired compared to 20 age- and sex-matched controls, even after adjusting for LA size, LV ejection fraction and LV filling pressures (which suggests the contribution of additional mechanisms of atrial disease beyond diastolic dysfunction). Furthermore, the same atrial functions were most severely impaired in patients...
with ATTRwt-CA than those with AL- and ATTRv-CA, even after adjusting for many variables including age, possibly reflecting a more longstanding elevation in filling pressures and a more severe diastolic dysfunction.

Establishing the relative contribution of increasing filling pressures and amyloid-mediated damage to atrial disease is difficult. On the other hand, a role of amyloid-mediated damage is suggested by pathophysiological considerations, and the evidence of atrial wall thickening and increased stiffness by cardiovascular magnetic resonance (CMR). We may also consider that LA size is the parameter most directly affected by filling pressures, and that LA stiffness (defined as the ratio between E/e’ and LA strain reservoir) is higher than expected based on LA size alone, again pointing to a role of atrial wall disease.

Three other studies found a significant impairment of LA-peak atrial longitudinal strain (PALS) values compared to patients with CA excluded, or healthy controls. The first study included 423 patients with suspected CA, with ATTR-CA in 34% and AL-CA in 28%. Patients with LA-PALS or LA-peak atrial contraction strain (PACS) in the first quartile (LA-PALS <6.65% or LA-PACS <3.62%) had an almost four-fold higher likelihood of CA and ATTR-CA regardless of standard echocardiographic and laboratory variables. In the second study, carried out in 136 patients (80% AL-CA, 17% ATTR-CA, 3% amyloid A type-CA), LA-PALS lower than median value (13.2%) displayed a strong, independent association with all-cause mortality. Nonetheless, in a study on 55 patients with CA (69% AL-CA, 27% ATTR-CA), a LA-PALS ≤8.05% (median value) was less predictive of a composite cardiovascular outcome than median longitudinal strain values of the LV or RA.

Another possible application of speckle-tracking echocardiography is the early detection of subclinical cardiac disease in TTR mutation carriers. Indeed, abnormalities of LA function (including LA reservoir and contractile longitudinal strain) have been characterized as markers of subclinical cardiac disease in carriers of the Val122Ile mutation with sinus rhythm.

### Cardiovascular magnetic resonance

Cardiovascular magnetic resonance typically shows dilated and dysfunctional atria, with thickened and enhanced walls. The simplest way to assess LA function is to calculate its emptying fraction, defined as (LA maximal – minimal volume)/LA maximal volume, expressed as percentage. Among 80 patients with CA, 24% displayed severe LA dysfunction, defined as LA emptying fraction ≤14% (reference values ≥49%) (Figure 4). A LA emptying fraction ≤14% showed a strong independent association with cardiac mortality, with a four-fold higher risk regardless of New York Heart Association class, N-terminal pro-B-type natriuretic peptide (NT-proBNP), RV ejection fraction, and LA size. Furthermore, patients with LA emptying fraction ≤14% in sinus rhythm had increased mortality compared to those with atrial fibrillation.

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**Figure 1** Histological features of atrial amyloidosis. Autopsy specimens from the left atrium of a 76-year-old female with kappa immunoglobulin light-chain amyloidosis with multi-organ involvement (heart, liver, pancreas, kidneys, thyroid and skin. (A) Green birefringence in polarized light after Congo red staining; (B) positive immunostaining for kappa light chains; (C) markedly positive immunostaining for kappa light chains; (D) negative immunostaining for lambda light chains. 

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Figure 2 Indirect evidence of atrial contractile dysfunction. This 60-year-old male patient with amyloid light-chain cardiac amyloidosis displayed a restrictive filling pattern (E/A ratio >2). The combination of a deceleration time within normal limits (194 ms, reference values 120–220 ms) and a severe depression of the A wave strongly suggest atrial contractile dysfunction.

Figure 3 Left atrial dysfunction in a patient with cardiac amyloidosis. Left atrial strain evaluation using two-dimensional speckle-tracking imaging. Left: severe left atrial functional impairment in the same patient as in Figure 2, with a severe reservoir function reduction (peak atrial longitudinal strain <7%; yellow arrow), and apparent electromechanical dissociation (P wave on electrocardiogram with no evidence of atrial contraction; blue arrow). Right: normal atrial function in a 50-year-old hypertensive woman with well represented peak atrial longitudinal strain (>30%) and peak atrial contraction strain (>10%).

In patients with systemic AL amyloidosis, lower LA emptying fraction values were associated with other signs of cardiac involvement and identified patients with lower 2-year survival. In a small series of patients with ATTRv either with or without cardiac involvement (n = 16 vs. 14), the former had higher LA volumes but not significantly lower LA emptying fraction values, suggesting that LA enlargement develops before LA dysfunction. LA strain by CMR might allow a more sophisticated assessment of LA haemodynamics and function, including a separate evaluation of the three atrial functions, but does not seem to offer any advantage over echocardiographic strain analysis. Finally, CMR detects LA thrombi.

Tomographic imaging
Computed tomography can be used to evaluate LA anatomy and detect LA thrombi, but we are not aware of dedicated...
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Figure 4 Left atrial volume/time curves. Examples of left atrial volume/time curve in a healthy control (upper panel) and in a patient with cardiac amyloidosis (lower panel). AEF, atrial emptying fraction. Reprinted with permission from Aquaro et al.19

Consequences of atrial dysfunction

Amyloid fibrils accumulate between cardiomyocytes and may disrupt electrical conduction, eventually promoting supraventricular arrhythmias. Even when patients are still in sinus rhythm, the lack of effective LA contraction favours blood stasis and coagulation, and the infiltrated atrial wall may become more thrombogenic26 (Graphical Abstract).

Arrhythmias

Atrial arrhythmias seem more prevalent in CA than in the general population, with highly heterogeneous estimates because of differences in study cohorts and the type of screening for atrial fibrillation. Sanchis et al27 reported an overall AF prevalence of 44% in a cohort of 238 CA patients, compared with an estimated AF prevalence of 1% in the community; 71% of patients with ATTRwt-CA had AF compared to 19% of those with ATTRv-CA and 26% of those with AL-CA. In another study, AF was found in just 15% of patients with CA. AF was present in 40% of those with ATTRwt-CA compared with 9% in AL-CA and 11% in ATTRv-CA.28 To explain the consistent finding of a higher AF
prevalence in patients with ATTRwt-CA, the authors pointed out that patients with ATTRwt-CA are more likely to be elderly, male, and with a longer duration of heart failure. The presence of AF does not seem to impact significantly on the outcome of patients with CA.

The management of AF in patients with CA is debated. There are currently no studies comparing rhythm and rate control strategies in patients with CA. The main study about rhythm control in CA was a retrospective analysis of the Mayo Clinic registries, assessing 58 patients with CA referred for elective direct-current cardioversion for atrial arrhythmias (58% AF, 41% atrial flutter, and 1% atrial tachycardia) and 114 matched controls. A transoesophageal echocardiogram was performed in 79% of patients with CA and 69% of controls. Patients with CA had significantly lower LA appendage emptying velocities than controls, and more often a thrombus in the LA or the LA appendage (28% vs. 3%; p < 0.001). Therefore, elective cardioversion was canceled much more often in the CA group (28% vs. 7%; p < 0.001). Among the CA patients with an intracardiac thrombus, 15% had AF for <48 h, and 29% had an international normalized ratio within the therapeutic range for ≥3 weeks. Patients with AL- versus ATTR-CA and those with AF versus flutter had similar cancelation rates. As a general recommendation, patients with CA should undergo a transoesophageal echocardiogram before an elective cardioversion, including those on therapeutic anticoagulation. When patients with CA proceeded to cardioversion, the success rate (90%), the proportion of patients requiring >1 shock (33%), and median energy required (110 J) did not differ significantly from other patients with AF. Elective cardioversion after a transoesophageal echocardiogram appeared an effective and safe procedure.

If antiarrhythmic agents are needed for rhythm or rate control, drugs with a negative inotropic or chronotropic effect should be avoided or used with caution because of the risk to precipitate heart failure decompensation. Amiodarone should be the first-line antiarrhythmic drug, with a preliminary and serial assessment of lung, thyroid and liver function.

Digoxin is traditionally contraindicated in patients with CA based on a few cases of increased toxicity reported in the ‘60s, in patients receiving digoxin as an inotropic, and an in vitro study in which digoxin was found to bind to AL amyloid fibrils, which suggested an increased risk of digoxin toxicity in amyloidosis, even when the serum drug concentration is within the normal range. In a retrospective cohort of 107 patients with AL-CA receiving digoxin for rate control at the Mayo Clinic from 2000 to 2015, no patient developed major adverse effects and the continuing need for digoxin therapy should be re-evaluated periodically. Overall, digoxin in CA should be used just as a negative chronotropic drug, and digoxin therapy in patients with AF may be acceptable if used cautiously. Importantly, there are no data demonstrating its efficacy in ventricular rate control when using the scheme proposed by the Mayo Clinic.

The safety and efficacy of catheter ablation for atrial arrhythmias has been evaluated in small cohorts. In a single-centre study, six patients underwent cavo-tricuspid isthmus ablation, and five underwent wide area circumferential ablation pulmonary vein isolation for AF. One- and 3-year recurrence-free survival were 75% and 60%, respectively. Complication rates were not reported. In another study, seven patients underwent catheter ablation for persistent AF or atrial tachycardia. The recurrence rate after 1 year was 83% in those with CA compared with 14% of age- and sex-matched controls (hazard ratio 5.4; 95% confidence interval 1.9–35.5; p = 0.007). A third study reported outcomes of 72 patients with ATTR-CA and AF of whom 24 underwent catheter ablation, compared with a matched control group that was medically managed. During a mean follow-up of 39 months, the recurrence rate of AF was 58%. Compared with controls, those in the ablation group had lower rates of death (29% vs. 75%; p = 0.01), and hospitalization for heart failure or arrhythmia (1.7 ± 2.4 vs. 4 ± 3.5; p = 0.005). To summarize, we have just small studies reporting high rates of AF recurrence following catheter ablation. The results are weak and heterogeneous recommendations by scientific societies.

Thromboembolism

Even when patients are still in sinus rhythm, their atrial contraction could be ineffective, a condition known as ‘atrial standstill’ or ‘atrial electromechanical dissociation’, which has been reported in up to 20% of patients with ATTR-CA. Atrial blood stasis is a powerful procoagulant factor, and might be promoted also by interatrial block related to amyloid infiltration of the Bachmann’s bundle. Furthermore, tissue infiltration by amyloid fibres might cause endothelial dysfunction, which in turn triggers the coagulation cascade.

A retrospective series of 116 autopsy or explanted cases of CA reported intracardiac thrombosis in 38 hearts (33%), with 2–5 thrombi. However, patients with AL-CA had a higher prevalence of intracardiac thrombi (51% vs. 16%, p < 0.001) and more fatal embolic events (26% vs. 8%, p < 0.03) than the other 61 patients (55 with ATTRw). Light chains are highly cytotoxic, and this might help explain the greater incidence of atrial thrombosis in AL-CA, but no specific evidence is available.

In another retrospective case series, intracardiac thrombi were present in 27% of patients undergoing a transoesophageal echocardiogram for any reason. Most thrombi were found in the LA appendage (55%). The risk of intracardiac thrombosis was particularly high in patients with AL-CA and in those with AF, but LV diastolic dysfunction predicted intracardiac thrombosis regardless
of AF. In a more recent series of 324 CA patients, the prevalence of intracardiac thrombi was 6.2% (95% confidence interval 3.5–8.8%) in the overall population, 5.2% (1.6–8.7%) in AL-CA, and 7.2% (3.3–11.2%) in ATTR-CA (p = 0.45). Out of 20 patients with intracardiac thrombi, 13 were in AF and 7 in sinus rhythm. The prevalence of thrombi in patients in AF/flutter was 9.1% in AL and 14.3% in ATTR (p = 0.52). All the patients with intracardiac thrombi in AF were on long-term anticoagulation (46% with warfarin and 54% with direct oral anticoagulants), suggesting that even anticoagulation might not be sufficient to prevent thrombus formation, as discussed above. The prevalence of intracardiac thrombi in patients in sinus rhythm and AL-CA was 4.5%, and 1.1% in ATTR-CA (p = 0.11). Most of the intracardiac thrombi were found in the LA appendage (90%), but six patients had thrombi in other sites of the LA or the RA. The presence of intracardiac thrombi was significantly higher in patients with more severe biventricular systolic dysfunction, atrial dilatation, and more extensive amyloid infiltration (as estimated through the extracellular volume). Finally, intracardiac thrombi was associated with higher levels of NT-proBNP (p < 0.01) and the AF burden (p < 0.05).

Intracardiac thrombosis may cause systemic embolic events, manifested as stroke, transient ischaemic attack or extracranial embolic events. A multicentre retrospective study evaluated 406 patients with CA followed for a median of 19 months. Thirty-one patients (7.6%) had a thromboembolic event, with an estimated incidence of 2.2% per year. Ten patients experiencing an event (32.2%) were in sinus rhythm and had no history of AF. A substantial

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**Figure 5** Histopathological features of isolated atrial amyloidosis. (A) Gross specimen of the left atrium showing amyloid deposits (brown dots, marked by arrows) giving it the characteristic ‘sand paper’ appearance. (B) Haematoxylin and eosin stain. (C) Trichrome stain. (D) Congo red stain showing amyloid deposits within atrial tissue. Arrows in these images indicate amyloid deposits. Reprinted with permission from Krishnappa et al.9

**Figure 6** Atrial fibrillation and atrial natriuretic peptide (ANP) amyloidosis: a vicious circle. See text for details. CM, cardiomyocyte.
Isolated atrial amyloidosis

Isolated atrial amyloidosis is a different condition compared to standard CA, where LA involvement is part of the systemic involvement due to amyloidosis. IAA consists in an exclusive infiltration of the atria (i.e. without involvement of the ventricles), and has been much less studied than atrial amyloidosis in the setting of systemic amyloidosis. The main evidence derives from cardiac surgery series (intraoperative biopsy during valve heart surgery and transplanted hearts). IAA has been reported in up to 39% of atrial tissue specimens from patients with valvular heart disease and persistent AF, but only in 7% of samples from patients in sinus rhythm requiring orthotopic heart transplantation. In a series of 245 right atrial appendages from patients undergoing open-heart surgery, patients with IAA had more often a history of AF and longer P-wave duration when in sinus rhythm. IAA was an age- and sex-independent predictor of AF, and patients with AF showed a larger amyloid burden than those in sinus rhythm. Furthermore, IAA was more common in patients undergoing mitral valve replacement, which is in line with the marked atrial dilatation and higher ANP levels in patients with mitral valve disease. Figure 5 shows the main histological features of atrial amyloid deposits, which do not differ from atrial involvement in ATTR- or AL-CA. Antibody-based techniques such as immunohistochemistry or immunoelectron microscopy can demonstrate ANP deposits. ANP and ATTR may both accumulate in the same atria, but as separate deposits.

We may postulate that fibrosis is not the only substrate of atrial remodelling, but amyloid accumulation may play a role. The aging human atrium invariably develops amyloid composed of ANP and to a lower extent B-type natriuretic peptide, but this accumulation remains limited and non-clinically significant unless it is enhanced by atrial stretch due to ventricular diastolic dysfunction, mitral valve disease and/or AF. Increased ANP production is meant to normalize haemodynamics through natriuresis and vasodilatation, but ultimately becomes maladaptive as ANP tends to accumulate in the atria. It has recently been reported that pre-fibrillatory species cause cytotoxic and electrophysiological effects in atrial cells that promote arrhythmia susceptibility. The role of atrial amyloidosis as an arrhythmogenic substrate for persistent or permanent AF is well established. While the mechanisms relating atrial amyloidosis to AF (inhomogeneous impulse propagation and fragmentation of atrial activation into multiple wavelets) have not been specifically studied in relation to ANP accumulation, we may speculate that ANP atrial amyloidosis is a determinant of atrial remodelling due to AF, and a mechanism whereby AF begets AF (Figure 6 and Graphical Abstract).

Conclusions

Atrial involvement is frequently observed in patients with systemic amyloidosis and may significantly influence clinical presentation and disease progression. Atrial enlargement is typical, but impairment of atrial reservoir and contractile function is also frequently reported, and may precede the development of morphological and functional abnormalities of the LV. Advanced imaging modalities, in particular echocardiographic LA strain, seem to have additional value to standard echocardiography or LV strain analysis for the diagnosis of CA and ATTR-CA. LA strain might refine the prediction of thromboembolic events (including in patients in sinus rhythm), and might also provide a surrogate biomarker of response to disease-modifying therapies. From a clinical perspective, two questions seem particularly compelling: (1) which patients with atrial amyloidosis and no history of AF require anticoagulation?, (2) is IAA a mechanism of atrial remodelling in patients with AF? A clinical trial is needed to answer the first question, with the randomization of patients with a dilated and dysfunctional LA to anticoagulation versus no anticoagulation, and the assessment of the safety and efficacy of this strategy. Clear challenges are the nature of CA as a rare disease, the competitive enrolment in this study versus other clinical trials, the relatively low incidence of thromboembolic events, the need to screen for AF and to start anticoagulation when patients in the placebo arm develop AF. The second question is particularly intriguing as it may disclose new perspectives for the treatment of paroxysmal or persistent AF. Indeed, therapies able to degrade ANP amyloid and induce its reabsorption could blunt atrial remodelling and prevent the progression to permanent AF.

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