Atrial amyloidosis and atrial fibrillation: a gender-dependent “arrhythmogenic substrate”?

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This editorial refers to “Amyloid deposition as a cause of atrial remodelling in persistent valvular atrial fibrillation” by O. Leone et al. on page 1237.

Atrial fibrillation (AF) is known to cause significant changes in atrial tissue architecture and electrophysiology. It has become clear over recent years that pre-existing alterations, such as autonomic dysbalance, degenerative tissue changes and fibrosis, can provide an electrophysiological and morphological substrate, which increases the likelihood of AF. In particular, alterations of the interstitial matrix in atrial tissue seem to be significant contributory factors. Increased amounts of fibrous tissue in fibrillating human atria were reported as early as 30 years ago and it is known to impair cell-to-cell coupling, thus causing heterogeneity in intra- and inter-atrial conduction. Initially, subsequent changes in atrial conduction may be subtle. However, isolated atrial amyloidosis (IAA) has recently been found to be of importance for the development of atrial conduction disturbances and AF. Amyloidosis represents a diverse group of diseases characterised by the presence of extracellular proteinaceous deposits showing characteristic structural and tinctorial properties. Amyloidoses are classified on the basis of the amyloid protein deposited and the clinical presentation and may affect the heart as part of a systemic disease, as in immunoglobulin-derived AL amyloidosis. In senile cardiovascular amyloidosis, the fibril protein consists of transthyretin (non-hereditary ATTR amyloidosis), and amyloid is observed in cardiac vessels, in the interstitium of the ventricles and in atria. Most commonly, the heart is affected by a strictly localised or organ-limited variety called IAA. The incidence of IAA increases with age, reaching more than 90% in the 9th decade.

In a prospective study, we investigated 245 right atrial appendages for the correlation between the presence of atrial amyloidosis and the prevalence of persistent AF. Analyses, including matched patient populations, demonstrated that AF is associated with significantly higher amounts of amyloid compared to sinus rhythm. Interestingly, the fibril protein deposited in the atria was atrial natriuretic peptide (ANP). Furthermore, the occurrence of amyloid correlated with patient age and P-wave duration, demonstrating the impact of amyloid on atrial conduction. Interestingly, women undergoing valve surgery had the highest amounts of amyloid.

The study presented by Leone et al. extends our knowledge about IAA and AF. They examined 128 atrial appendages (66 left and 62 right) from 72 patients with chronic persistent AF undergoing valve surgery and 104 specimens from patients in sinus rhythm. The authors found that atrial amyloid is present in approximately 30% in right atrial appendages in this cohort of patients, thus confirming previous data. In addition, they clearly showed that the incidence of IAA is higher in left atrial appendages (45%) compared to the right atrium. The authors have also analysed the distribution of amyloid within the atrial wall, demonstrating a predominant deposition along the sarcolemma of myocytes with sparse involvement of the endocardium. Interestingly, stepwise logistic regression analysis revealed that AF duration and female gender were independently related to amyloid deposition. A limitation of the study is that no immuno-histochemistry was performed to quantify or analyse the nature of the amyloid. It also remains to be determined if amyloid seen in patients with AF is the same as in the presence of severe left ventricular failure.

How can this gender-dependent impact on the development of IAA be explained? Steiner found that atrial amyloid deposits occur more frequently in women than in men, the difference being most significant in the age group between 31 and 50 years. Recently Babiker et al. have shown...
that 17β-estradiol induces ANP expression in cardiac myocytes. The oestrogen receptor may form a transcriptionally active complex with a co-factor, such as SP-1, to influence the ANP promotor. Increased ANP expression results in autocrine and paracrine stimulation of cardiac myocytes and surrounding tissue through its transmembrane guanylyl cyclase (GC)-A receptor (natriuretic peptide receptor A). Activation of this receptor increases cellular cGMP levels, thereby activating cGMP-dependent protein kinases, which mediates the anti-hypertrophic and anti-proliferative response. By contrast, the absence of the GC-A receptor is associated with marked cardiac hypertrophy and interstitial fibrosis in mice. This effect is more pronounced in the atria compared to the ventricles. Thus, chronic stimulation of the estrogen receptor by estradiol increases the expression of ANP. Persistent elevated cardiac ANP levels may increase the likelihood of amyloid formation and deposition, particularly if cardiac ANP secretion is induced by atrial dilation and atrial fibrillation.4,10,11 Valve diseases are associated with progressive atrial dilation, especially mitral valve diseases. Distension of the left atrium, and in particular that of the left atrial appendage, correlates with systemic ANP levels, which explains the significant impact of valve diseases on atrial ANP release. Another trigger for increased expression of ANP is AF. Thus, women with longstanding mitral valve dysfunction are particularly pre-disposed to a persistently high expression and release of ANP, which increases the likelihood of deposition and accumulation of IAA. This hypothesis is supported by the fact that Leone et al.6 found a higher incidence of amyloid in the left atrium compared to the right atrium in patients with mitral and aortic valve diseases. As already shown in our previous study, IAA reduces atrial conduction, which may result in atrial arrhythmias and AF. The occurrence of AF further increases ANP secretion, inducing a vicious circle for irreversible IAA deposition (Fig. 1).

Why are the presented findings of clinical importance? A therapeutic approach to the treatment of IAA still needs to be taken. Amyloid deposits remain in the tissue even after menopause, valve surgery or cardioversion of AF. Thus, the only way to treat IAA is to prevent its occurrence. Recently, several studies have shown a beneficial impact of "anti-fibrotic therapies" with ACE-inhibitors and angiotensin II receptor antagonists for AF therapy. The anti-fibrotic effects of ANP, however, may explain the significant inverse relationship between the amounts of amyloid and fibrosis.4 A patient population with persistent elevated ANP tissue levels, in which the incidence of IAA is high, develop only small amounts of atrial fibrosis, and may therefore benefit less from an anti-fibrotic therapy.

Thus, the data presented by Leone et al. are important for the understanding of the pathophysiology of AF.

They increase our knowledge of the impact of IAA as a morphological substrate for AF. Based on the presented results, further studies are necessary to assess gender-dependent differences in atrial mechanical and electrophysiological function. This may also be clinically relevant to the investigation of novel strategies for AF therapy, focussing on structural alterations as already suggested by recent findings.1,2,11

References