The Extracellular Matrix Speaks. But Are We Truly Listening? Left Atrial Strain, Hereditary Transthyretin Amyloidosis, and Some Reflections

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Short Editorial related to the article: Left Atrial Strain Assessment in Hereditary Amyloidosis: A Systematic Review

Left atrial strain, especially left atrial reservoir strain (LASr), is an important tool in the assessment of atrial function and diastology. It changes before remodeling becomes detectable on echocardiography and contributes to a better understanding and characterization of diastolic dysfunction and left atrial–left ventricle (LA–LV) uncoupling.[1-3] In patients with preserved ejection fraction, LASr values <18% strongly suggest elevated filling pressures.[4,5]

In amyloid cardiomyopathy, the mean values of the atrial strain components are characteristically very reduced compared with individuals without the disease, and may serve as relevant clinical clues for diagnosis.[6,7] Atrial dysfunction in amyloid cardiomyopathy results from two main mechanisms: direct infiltration of amyloid fibrils into the atrial wall, and chronic elevation of left ventricular filling pressures.[7] Characteristically, the atrial wall is thin and highly dependent on the integrity of the extracellular matrix; therefore, even small deposits of amyloid fibrils can reduce reservoir strain, before increases in atrial volume or diameter occur.[7]

The diseased extracellular matrix progresses to fibrosis, impairing atrial relaxation, reducing its compliance, increasing its stiffness, and promoting remodeling — a process known as amyloid atrial myopathy.[7] In this context, the atrium is not only a victim of ventricular dysfunction and elevated filling pressures, but also suffers directly from the deposition of amyloid fibrils within its walls. This progressively compromises its reservoir, conduit, and booster pump functions, increasing the likelihood of thromboembolic events, even in the absence of atrial fibrillation.[8]

The most prominent phenotypic expression of the degree of amyloid infiltration in the atrial wall is atrial electromechanical dissociation. This dissociation occurs when there is electrical activity in the sinus node, that is, the presence of P waves on the resting electrocardiogram, despite the absence of A waves on mitral Doppler or a very low or even absent booster pump strain value.[7] Bandera et al.[7] evaluated approximately 900 patients with heart failure due to transthyretin amyloidosis — both ATTRv (variant/hereditary transthyretin amyloidosis) and ATTRwt (wild-type transthyretin amyloidosis) — and observed this intriguing electromechanical dissociation in 22% of cases, identifying it as an independent risk factor associated with worse prognosis, similar to that seen in patients with clinical atrial fibrillation.[7] From this perspective, amyloid atrial myopathy represents a continuous remodeling process, characterized by impairment of atrial function (deformation and stiffness index), structure (volume), and electrophysiology. Atrial cardiomyopathy may present dramatically reduced strain values, reflecting extensive involvement and an advanced degree of chamber dysfunction.

In the study by Akintoye et al.,[8] cutoff values of LASr <6.4% and LASct <2.4% demonstrated good discriminatory ability to predict thromboembolic events in a mixed population of patients (50.2% AL and 49.8% ATTR).[8]

In transthyretin amyloid cardiomyopathy, particularly in patients with ventricular dysfunction and heart failure, the atrial stiffness index, calculated as the E/e' to LASr ratio, has already shown important prognostic value.[7] This index was independently associated with mortality, reflecting functional atrial impairment and providing incremental prognostic information beyond conventional echocardiographic variables.[3,7] However, its potential role in identifying subclinical cardiac involvement and in stratifying patients at earlier stages of the disease remains under investigation.

In a study titled *"Assessment of Left Atrial Strain in Hereditary Amyloidosis: A Systematic Review"*, alterations in reservoir strain were observed in amyloid cardiomyopathy (LASr 8–15%), but also in individuals with the neurological phenotype (LASr 20–25%) and, interestingly, in asymptomatic carriers of pathogenic variants in the transthyretin (TTR) gene (LASr 23–30%). These findings raise the hypothesis that this tool may function as a marker of subclinical dysfunction. However, this still appears to lack more robust evidence, as the studies with the largest sample sizes in this particular review did not include asymptomatic carriers and evaluated mixed populations, including ATTRh, ATTRwt, and AL amyloidosis.[7,9] On the other hand, when the analysis was performed specifically for hereditary ATTR and in individuals with a positive genotype and negative

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phenotype, LASr was reduced and the atrial stiffness index was increased. It is worth emphasizing, once again, that this evidence derived from small, observational studies.[10,11]

In another recent systematic review evaluating the prognostic value of strain in patients with transthyretin amyloidosis (ATTRwt and ATTRv), the atrial stiffness index emerged as the main predictor of mortality. Here, similarly, the results should be viewed with reservations, considering the significant methodological limitations of the included studies.[12]

Evaluating atrial deformation in cohorts composed exclusively of patients with hereditary ATTR remains a challenge. Most available studies predominantly include patients with wild-type ATTR or mixed populations, combining individuals with both the hereditary and wild-type forms of the disease. In addition, the assessment of strain has inherent methodological limitations, including the need for high-quality echocardiographic image acquisition, variability among different manufacturers and speckle-tracking software, and the lack of universal standardization of reference values for this specific population. These factors hinder both the routine incorporation of the technique into clinical practice and the direct comparison of available studies. Consequently, fundamental questions remain unanswered: What is the best cutoff value to define subclinical cardiac involvement? Does the alteration in atrial mechanics precede, accompany, or follow ventricular impairment?

Identifying which diagnostic test changes earliest in amyloidosis still lacks a definitive answer. The available evidence is based on multimodal comparative assessments (brain natriuretic peptide [BNP], pyrophosphate scintigraphy, and cardiac magnetic resonance imaging) and on indirect comparisons, suggesting that native T1 mapping and extracellular volume on cardiac MRI may change earlier.[13] When left atrial strain is incorporated into this scenario of subclinical diagnosis, an equally promising and physiopathologically compelling rationale emerges. It is important to emphasize that this hypothesis is also based, thus far, on indirect comparisons between studies, as no prospective investigations have simultaneously evaluated the temporal evolution of atrial strain and tissue-characterization parameters on MRI in patients with hereditary ATTR.

In the context of arrhythmias, atrial fibrillation goes beyond the concept of a simple rhythm disturbance and represents, in many cases, the clinical expression of atrial myopathy. This disease of the atrium leads patients undergoing electrical cardioversion or catheter ablation to present, classically, greater management complexity and high rates of recurrence.[14-16]Although robust evidence is still lacking, the study of atrial deformation and atrial stiffness emerges as an interesting strategy to refine the stratification of these patients, helping identify those most likely to benefit from rhythm-control interventions.

It is well established that reservoir strain and atrial stiffness are markedly altered in patients with clinically manifest amyloid cardiomyopathy and, possibly – albeit to a lesser extent – also in asymptomatic carriers of pathogenic TTR variants. However, several questions still need to be addressed by larger studies focused exclusively on hereditary amyloidosis. The interstitial space holds many secrets that may perhaps be revealed through a more accurate assessment of the integrity of the extracellular matrix, its remodeling, and its behavior over time.

In the era of disease-modifying therapies for amyloidosis, early detection of cardiac involvement has become highly relevant clinically. In this context, left atrial strain and the atrial stiffness index emerge as important functional biomarkers in the early investigation of hereditary ATTR. Confirming their true diagnostic value in the natural history of the disease will ideally depend on prospective studies specifically designed for this purpose.

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