Editorial

Cardiac Amyloidosis: Is It Truly a Hypertrophic Phenotype Cardiomyopathy?

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Cardiac amyloidosis is a classic example of an infiltrative disease whose predominant phenotype is characterized by a hypertrophic pattern of myocardial involvement.[1,2] The most relevant studies—both those focused on the development of disease-modifying therapies and cohorts evaluating diagnostic tools—have used increased ventricular wall thickness as a key criterion for suspecting cardiac amyloidosis.[1-6] Based on this concept, several diagnostic algorithms have proposed ventricular wall thickening as one of the major red flags for investigating amyloid cardiomyopathy.[1,2]

However, increased ventricular wall thickness does not appear to be a universal requirement for diagnosis. Emerging evidence suggests that both Immunoglobulin Light Chain Amyloidosis (AL) and Transthyretin Amyloidosis (ATTR) amyloidosis can be diagnosed, including through noninvasive methods, even in the absence of the classic hypertrophic phenotype.

Devesa *et al.,* reported a cohort of patients with Heart Failure with Preserved Ejection Fraction (ejection fraction > 50%) and no increased ventricular wall thickness. In this series, the prevalence of ATTR was approximately 5%. Three patients (5%) were identified with ATTR among 58 individuals; all had the wild-type form, were older than 75 years, and had a maximum wall thickness of 11 mm.[7]

In another retrospective study including 98 patients with a diagnosis of cardiac amyloidosis, participants were divided into two groups: those with increased wall thickness (defined as ≥ 12 mm) and those without (< 12 mm). Wall thickness was defined as the mean of interventricular septal and inferolateral wall measurements. Of the total cohort, nine patients (9%) did not exhibit increased wall thickness (< 12 mm), with a mean value of 10 mm. All cases corresponded to AL amyloidosis.[8]

Muller SA *et al.*, in investigating the etiology of patients with Heart Failure (HF) and extracardiac red flags suggestive of amyloidosis, analyzed a sample of 114 patients with cardiac amyloidosis. Of these, 12 (11%) did not exhibit increased wall thickness (< 12 mm), although they met other diagnostic criteria, including positive technetium-labeled pyrophosphate scintigraphy.[9]

In a large cohort of patients with cardiac amyloidosis, 1,845 individuals were evaluated between 2006 and 2024. It was observed that 13% of AL cases and approximately 7% of ATTR cases had normal or only mildly increased left ventricular wall thickness (≤ 12 mm). Notably, women tended to have lower ventricular wall thickness. Furthermore, within the subgroup with wall thickness ≤ 12 mm, approximately 70% demonstrated increased relative wall thickness (relative wall thickness [RWT] > 0.42), consistent with concentric remodeling.[10]

Case reports further illustrate this clinical scenario. In a recent publication in the European Heart Journal (2024), a 69-year-old man with heart failure and a rare pathogenic variant in the transthyretin protein (TTR) gene (p.Tyr78Phe) was described. In this case, bone scintigraphy showed no tracer uptake, and echocardiography did not reveal increased wall thickness.[11]

Thus, the absence of ventricular wall thickening does not exclude cardiac amyloidosis, whether AL or ATTR. Amyloid disease begins long before overt hypertrophy becomes manifest, and its absence may reflect early disease stages—although this is only one of several possible explanations. Interstitial infiltration by misfolded amyloid fibrils, associated with extracellular space expansion, proteotoxicity, disruption of myocardial architecture, inflammation, and fibrosis, may result in diastolic dysfunction, atrial enlargement, and heart failure with preserved ejection fraction, even before significant increases in ventricular wall thickness become apparent on echocardiography.[12,13] Moreover, a dichotomous diagnostic approach based solely on absolute cutoff values (≥ 12 mm versus < 12 mm), without considering intra- and interobserver variability, anthropometric differences, and sex-related factors, may contribute to underdiagnosis. This is particularly relevant in individuals with smaller body surface area and in women, in whom absolute ventricular wall thickness tends to be lower.[11] When echocardiography is used exclusively as a screening tool based on isolated septal and posterior wall measurements in search of values > 12 mm, its diagnostic potential may be underutilized. Echocardiographic assessment allows evaluation not only of wall thickness, but also of concentric remodeling patterns, ventricular mass, chamber dimensions, diastolic function, and myocardial strain. These parameters should be interpreted in an integrated manner in the presence of clinical suspicion of cardiac amyloidosis.[1,2]

Clinical scenarios involving rare genetic variants with atypical phenotypic presentations further reinforce that excessive reliance on the classic morphologic phenotype may delay disease recognition.[11]

Keywords

Amyloidosis without hypertrophy; cardiac amyloidosis; hypertrophic phenotype

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The presentation of cardiac amyloidosis without ventricular wall thickening should not be regarded merely as an anecdotal exception, but rather as a potential representation of earlier stages of disease, lower infiltrative burden, sex-related differences, or limitations of isolated morphologic criteria.[7-11]

This discussion does not seek to deny the hypertrophic phenotype as the most characteristic presentation of amyloid cardiomyopathy, but rather to acknowledge that it is not universal. Alternative morphological presentations need to be better understood and possibly incorporated into clinical reasoning and diagnostic workflows. This perspective can be crucial for raising early diagnostic suspicion, preventing the disease from remaining undetected until more advanced and severe stages.

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