Cardiac amyloidosis (CA) is part of a systemic disease characterized by the deposition of amyloid in multiple tissues. Although the heart is often the predominant organ involved in systemic amyloidosis, this is not always the case, as CA of varying severity may be present when a patient with amyloidosis presents with symptoms related to another organ. Thus, in familial amyloidosis, CA may accompany a painful neuropathy; in AL amyloidosis it may be found when a patient presents with nephrotic syndrome, whereas in senile systemic amyloidosis it is almost invariably responsible for the presenting symptom. Although the presence of CA is often the major prognostic factor, the heterogeneity of presentation makes analyses of prognostic factors that are limited to the cardiovascular system difficult because other organ system disease can affect outcome and should ideally be taken into account.

The biochemical constituents of amyloid vary between the various types. All amyloid deposits have a similar structure on light and electron microscopy, and all share certain biochemical components. However, there are many individual precursor proteins that can form amyloid deposits, and these differ greatly one from another and define the nature of the disease in the individual patient (1). For example, the precursor protein transthyretin (TTR) in a mutant form is responsible for familial amyloidosis, and wild-type TTR can cause senile amyloid. These proteins are completely different from the abnormal light chain responsible for AL amyloidosis, and the consequences of cardiac deposition are considerably different in the 2 diseases. Specifically, it is likely that TTR amyloidosis of the heart represents an almost pure infiltrative cardiomyopathy with cardiac dysfunction related to the extent of amyloid deposition, whereas AL amyloidosis has, in many cases, an additional cardiotoxic component mediated by circulating free light chains (2). Thus, attempts to combine AL and TTR amyloidosis patients, as done in the paper by Ternacle et al. (3) in this issue of JACC, to provide a prognostic marker should be viewed with caution. This is particularly so because AL patients can undergo therapy that may alter disease outcome in a high percentage of patients, whereas therapies for TTR are still in the early stages of clinical trials. Nevertheless, this paper does provide some interesting insights into certain noninvasive aspects of CA in general.

The key points of this study are that the unusual pattern of longitudinal strain (LS), namely a much greater impairment at base than apex, exists in all 3 types of amyloidosis, that late gadolinium enhancement (LGE) on cardiac magnetic resonance (CMR) correlates with LS, and, in a small clinicopathological correlate, that the degree of amyloid deposition in 3 explanted hearts is said to correlate strongly with the degree of LGE on CMR. The authors confirmed the findings of a recent larger study (4) that apical sparing was present not only in AL amyloidosis but also occurred in TTR-derived disease. However, they suggest, based on the definition of apical sparing proposed by of Phelan et al. (5) (apical sparing = apical strain basal LS + midcavity LS) = >1) that it is an insensitive finding, seen in only 52% of their cohort. Recent data show an absolute difference between apical and basal strain of only −2.2% in the normal population in the sixth decade, increasing to −3.8% in the over-60s,
representing a 10.5% and 17% relative difference respectively (6). The authors’ Table 2 shows a marked difference between mean basal and mean apical strain in all groups of CA, markedly exceeding normal values. It is possible that a looser definition, perhaps only comparing apical and basal strain, may still be highly specific for amyloidosis, yet with an increased sensitivity. This might be a simple and interesting line of investigation in the future.

The association of LGE with LS is intriguing. Initial reports of LGE suggested that amyloidosis had a distinct pattern of uptake characterized by a predominantly subendocardial, noncoronary distribution (7), but subsequently it became apparent that several patterns may be seen (8). The presumption is that LGE in all these cases reflects expansion of the extracellular space, predominantly by amyloid deposition. An additional assumption made by the authors is that increase in left ventricular mass (indirectly reflected by septal thickness) represents infiltration of the ventricle by amyloid. Such an assumption is challenged by indirect evidence and recently by direct imaging evidence. The indirect evidence is the paradox that wild-type TTR cardiac amyloidosis patients have thicker walls than do AL amyloid patients but, despite this, have a much better prognosis (9). Although some of the poorer prognosis in AL amyloidosis reflects the toxicity of circulating light chains, the lower prevalence of low voltage in ATTR compared with AL could be interpreted as representing relative preservation of cardiomyocytes (10). Using equilibrium contrast material-enhanced CMR, Fontana et al. (11) showed that TTR patients have, in addition to an expansion of extracellular volume, an average of 18% greater cardiac cell volume than healthy volunteers and patients with AL amyloidosis. This suggests that TTR amyloidosis is associated with a compensatory degree of hypertrophy. Given this, the observation in Figure 2 in the paper by Ternacle et al. (3) that the negative correlation of LV strain with septal thickness appears to be stronger in AL amyloidosis than in TTR can be understood because increased wall thickness in TTR is partially due to myocyte hypertrophy, whereas, in AL, it reflects purely amyloid infiltration.

The prognostic factors for major cardiac adverse events suggested by the authors were N-terminal pro-B-type natriuretic peptide >4,000 pg/ml, apical LS of <−14.5%, and New York Heart Association functional class III to IV heart failure. The finding that functional class III to IV heart failure has a poor prognosis is anticipated, and, as the authors point out, although they found a prognostic cutoff factor for LS in the apical segments, other authors have found other segments to be more predictive of major adverse cardiac events, suggesting a considerable variability based most likely on chance and on patient population. As noted above, attempting to predict prognosis in a heterogeneous population that includes TTR and AL amyloid is problematic. It is therefore unclear whether the authors’ cutoff values of N-terminal pro-B-type natriuretic peptide and apical strain can be applied prospectively, particularly in individual patients.

Despite being limited by only 3 cases, the clinicopathological findings are novel and add to our understanding of the strain gradient seen in amyloid cardiomyopathy. However, the hypothesis that regional differences in amyloid deposition are responsible for regional differences in LS may not be the full story because 1 of the 3 (Patient #1 in Figure 4B of Ternacle et al. [3]) showed only a weak correlation. Thus, the jury remains out as to whether amyloid burden is the primary cause of impaired LS or whether there may be a contribution from another factor, for example, microvascular dysfunction. Overall, the findings of this study present new findings in the pathophysiology of cardiac amyloidosis, while highlighting some of the difficulties in studying an uncommon disease with varying pathophysiology. We are now entering an era in which AL amyloidosis can be successfully treated and in which novel agents are in clinical trials for TTR amyloidosis. Any advance in understanding in the mechanisms of cardiac dysfunction in amyloidosis is thus of great interest, as it allows us to better understand whether and how new therapies affect the heart in this previously universally fatal disease (13,14).

**REFERENCES**


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