Longitudinal Strain Imaging in Light-Chain Cardiac Amyloidosis

Can it Help to Refine the Approach to Treatment?*

C. Cristina Quarta, MD, Rodney H. Falk, MD
Boston, Massachusetts

The systemic amyloidoses are a group of uncommon diseases characterized by extracellular accumulation of fibrillar proteins, leading to loss of normal tissue architecture and function (1). Light-chain (AL) amyloidosis, which is probably the most frequent form, can potentially involve any organ, but when the heart is affected, the outcome is particularly poor, with a median survival of 4 to 6 months (2). Over the past few years, the chemotherapeutic options for treating AL amyloidosis have expanded considerably, but the more aggressive therapies, such as high-dose melphalan with autologous stem cell transplantation, are limited in many patients with cardiac involvement (3,4).

It is therefore essential to carefully address the risk-benefit profile of the various therapies when faced with a therapeutic decision in AL amyloidosis, because aggressive therapies, although possibly associated with a higher remission rate, can result in early treatment-related mortality if cardiac involvement is present.

Myocardial strain echocardiography is a sensitive tool for studying left ventricular (LV) function in many cardiac diseases, including cardiac amyloidosis. Early studies, using Doppler-derived strain and strain rate imaging, found that global longitudinal deformation was more sensitive in detecting early systolic dysfunction than was standard tissue Doppler imaging (5). Subsequent studies showed the superior prognostic value of strain imaging, but these did not evaluate the relative prognosis of strain imaging over standard non-Doppler parameters (6). In their large cohort of patients with AL amyloidosis, Buss et al. (7), in this issue of the Journal, have expanded on these studies and used speckle strain imaging, a technique that is simpler to use and more reproducible than Doppler-derived strain imaging. In a multivariate analysis, they confirmed that reduced LV longitudinal function is an independent predictor of survival, but they also showed that it appears to offer incremental information beyond both standard clinical parameters and commonly used prognostic serological parameters in AL amyloidosis, specifically serum troponin and N-terminal pro-B-type natriuretic peptide (NT-proBNP).

The study has several strengths, but it also has important limitations that are worthy of consideration before the results can be put into clinical practice. As pointed out by the investigators, all the imaging analyses were done with a single system. Although this is appropriate for such a study, there is considerable inter-manufacturer variability and lack of standardization for strain imaging, both using two-dimensional speckle tracking and the newer three-dimensional systems (8). Thus, the investigators’ cutoff values for determining prognosis are only of value when obtained by the analysis equipment that they used, and cannot be extrapolated to other systems until validated across different analysis platforms. Perhaps more important is the manner in which the data were collected. Although referred to as a “prospective observational study,” the collection of the echocardiographic, clinical, and biochemical measurements, was obtained at the patient visits, whereas the analysis was performed retrospectively. Thus, the speckle tracking strain parameters determined to be optimal for separating survivors from nonsurvivors still need to be validated in a prospective study of untreated patients.

In addition to analyzing the whole cohort, the investigators looked at subgroups and concluded that their cutoff parameters remained robust, both among patients who had not been previously treated and in those with an ejection fraction (EF) > 50% and <50%, respectively. EF in cardiac amyloidosis may be near-normal until late in the disease, even if significant heart failure is present, and impaired longitudinal strain in such patients underscores that there is a definite systolic component to heart failure even in the presence of a normal EF. It is critical to recognize, however, that the group of patients with the normal and/or near-normal EF was not homogenous, because this study was not limited to patients with AL amyloidosis involving the heart, but included any patient with AL amyloidosis of any organ evaluated at the investigators’ institution. As such, those with a normal EF might or might not have had cardiac amyloidosis. Because the presence of cardiac involvement in AL amyloidosis is an adverse prognostic factor, one would anticipate that an abnormal longitudinal strain would be associated with a worse prognosis in this group, as it simply identifies patients with cardiac amyloidosis as opposed to those free of heart involvement. Strain imaging analysis of patients with an EF >50% and evidence by other criteria...
of cardiac involvement was not reported, but would be of interest.

Despite these shortcomings, the paper by Buss et al. (7) provides new insights into the mechanisms of LV dysfunction in cardiac amyloidosis. Both NT-proBNP and cardiac troponin are accepted as useful markers of prognosis in AL amyloidosis (9), and NT-proBNP elevation may reflect more than simply an increased ventricular wall stress due to high filling pressures (10). The investigators found a strong correlation between NT-proBNP levels and longitudinal strain values, with a weaker correlation with troponin levels. However, in multivariate analysis, NT-proBNP was no longer a prognostic factor, whereas longitudinal strain and troponin levels remained significant. The association of myocardial strain values with NT-proBNP has been noted in other cardiac diseases, and raises some intriguing avenues for future research (11). It is now well recognized that a hematologic response to chemotherapy in AL amyloidosis is associated with an early decrease in NT-proBNP in association with clinical improvement, even when wall thickness remains unchanged. These data raise the possibility that improvement in longitudinal strain may be an early feature of hematologic remission. As hematologic remission is defined as normalization of elevated free serum light chains and, because the latter have been shown to be cardiotoxic in vitro, strain imaging might turn out to be a sensitive marker of changes in cardiac function related to chemotherapy. It has the potential to give insight into mechanisms of clinical improvement after chemotherapy if improved strain correlates with normalization of an abnormal free light chain ratio.

Finally, it should be recognized that treatment in AL cardiac amyloidosis is a fast-moving field, and a once universally fatal disease is now treatable, with long-term remission and a good quality of life achievable in many patients if they are treated in skilled centers. Although the investigators did not give details of the therapy used in their patients, they mentioned high-dose chemotherapy with autologous stem cell transplant, which, although highly effective in some patients, carries a high mortality rate when used in patients with AL amyloidosis involving the heart (3). Since 2008, when their study enrollment ended, there has been increasing use of bortezomib-based regimens for the treatment of AL amyloidosis, with evidence that it is well tolerated in cardiac amyloidosis; potentially >40% of previously untreated patients can achieve a relatively rapid hematologic remission (12). This therapy may, therefore, represent an advance over current therapies for AL amyloidosis involving the heart. Whether the use of bortezomib as an early or first-line therapy in AL cardiac amyloidosis will affect the potential prognostic value of strain imaging remains to be seen, and will require further study.

Given these limitations, and the changing face of cardiac amyloidosis treatment, it is unlikely that the strain values described in this paper will show prognostic value if applied exactly as defined. However, the observations are interesting and demonstrate that with further refinement, LV longitudinal strain is likely to be integrated in the therapeutic decision making and, eventually, the evaluation of the response to treatment of this serious, but now treatable, disease.

Reprint requests and correspondence: Dr. Rodney H. Falk, Department of Cardiology, Harvard Vanguard Medical Associates, 133 Brookline Avenue, Boston, Massachusetts 02215. E-mail: rfalk@partners.org.

REFERENCES


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