Circulation: Cardiovascular Imaging

EDITORIAL

Echocardiography and Survival in Light Chain Cardiac Amyloidosis

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Light chain (AL) cardiac amyloidosis is a progressive restrictive cardiomyopathy marked by the extracellular deposition of amyloid fibrils composed of immunoglobulin light chain. Observed in 70% to 75% of cases, cardiac involvement is one of the most common organ manifestations of systemic AL amyloidosis and is a major determinant of survival.[1] Untreated patients with cardiac amyloidosis have historically expected a median survival of 6 to 12 months[2] while recent advances in treatments directed toward the B-cell clone of the plasma cell dyscrasia have led to tremendous improvements in overall survival.[1] The development of novel therapeutic options for patients with cardiac amyloidosis has highlighted the need for accurate prognostication to help with risk stratification and to create clinically relevant end points for clinical trials.[3]

Toward the end of the 20th century, echocardiographic parameters, such as the myocardial performance index[4] or right ventricular dysfunction,[5] were identified as conferring independent information related to survival in AL amyloidosis. A paradigm shift occurred in the early 21st century when multiple respected centers of excellence in the treatment of amyloid diseases reported that cardiac-specific serum biomarkers could provide reproducible and accurate prognostic data at the time of diagnosis.[6,7] This observation was rapidly refined in 2004 with the first reported staging system using serum cardiac troponin I and then cardiac troponin T along with NT-proBNP (N-terminal pro-B-type natriuretic peptide) as reported by clinician scientists from the Mayo clinic.[8] Using a scoring system defined by an NT-proBNP threshold of 332 pg/mL and a cardiac troponin T threshold of 0.035 ng/mL, median survival of patients with newly diagnosed AL cardiac amyloidosis ranged from 26.4 months in patients without elevation of either biomarker (Mayo stage 1 disease) to 3.5 months in patients with elevations in both biomarkers (Mayo stage 3 disease). This staging system also proved useful in the prediction of survival among AL amyloidosis patients undergoing high-dose melphalan-based chemotherapy followed by autologous stem cell transplantation.[9] Next, the recognition that the characteristics of the underlying plasma cell clone and circulating monoclonal serum-free light chain burden also affect prognosis led to a revised Mayo biomarker staging system that included the difference between involved amyloidogenic and uninvolved nonamyloidogenic serum free light chains, and subsequently stratified AL cardiac amyloidosis patients across 4 risk stages.[10] Serum biomarkers are attractive to the hematologists who treat AL amyloidosis patients because the measurement has no subjectivity, requires only a blood sample, can be determined retrospectively from stored samples, and is generalizable internationally provided identical assays are used. In fact, the search for newer biomarkers that might afford incremental prognostic value continues grounded in rationally selected candidates.

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Recently, growth differentiation factor-15, a cardiac myocyte stress response marker, was shown to have independent prognostic value beyond that imparted by NT-proBNP and cardiac troponin T among patients with AL cardiac amyloidosis.[11] It is important to recognize, however, that each of these markers, with the exception of the free light chain difference, are not specific for cardiac amyloidosis and are frequently abnormal in other myocardial diseases. Thus, while conferring clear prognostic information, their utility in the differentiation of cardiac amyloidosis from other cardiomyopathies is limited.

For this reason, despite the proven prognostic value of troponins and natriuretic peptides, interpretation must be performed with caution as serum concentrations are increased in the context of renal dysfunction, other concomitant cardiovascular diseases, and volume overload. In addition, NT-proBNP is not universally measured, and although there is some guidance as to how to interpret BNP particularly in the context of renal dysfunction,[12] no staging system exists with this marker. Although serum cardiac biomarkers likely reflect the extent of myocyte damage caused by myocardial amyloid infiltration (troponins) or direct light chain toxicity, and resultant volume overload (BNP and NT-proBNP), attention has returned to 2-dimensional echocardiography to assess the structural and pathophysiologic ramifications of this infiltrative cardiomyopathy specifically with the advent of myocardial deformation imaging. Initial observations using myocardial tissue Doppler-defined reductions in longitudinal contraction gave way to measurements of global longitudinal strain (GLS) as predictors of survival in AL amyloidosis.[13,14] Contemporary assessment of GLS involves speckle tracking methodologies, with studies showing that GLS is diminished early in the course of AL cardiac amyloidosis,[15] and may help to distinguish between early and advanced stages of the disease.[16] In addition, GLS has been shown to afford incremental prognostic utility over and above that predicted by serum cardiac biomarkers,[17] and improvements in strain may precede other echocardiographic changes after successful treatment of the underlying plasma cell disease.[18] Despite convincing data in amyloidosis and many other cardiomyopathies, strain analysis has limitations, including intervendor and interuser variability, which can limit the reproducibility of GLS measurements. Given the foundational role echocardiography holds in the diagnosis and management of patients with AL amyloidosis, there remains a need for the development and validation of simple echocardiographic metrics based on routine measurements that any clinical echocardiography laboratory can perform.

In this issue of *Circulation: Cardiovascular Imaging,* Milani et al[19] investigated the associations between stroke volume index (SVI, stroke volume divided by body surface area) and myocardial contraction fraction (MCF) with survival in a large retrospective cohort of patients with systemic AL amyloidosis that included 754 patients over a span of 19 years. Analyses of such numbers and time span in this rare disease can only be performed at a few centers worldwide. Cardiac amyloidosis was diagnosed by an endomyocardial biopsy in only 10% of the patients, with the other 90% identified by increased left ventricular wall thickness in the absence of other pathogeneses, and in the presence of elevated cardiac biomarkers (when available), based on current noninvasive diagnostic criteria.[20] It is important to note that of the 754 patients with AL amyloidosis studied, 591 (78%) were considered to have cardiac involvement, and 451 had available cardiac biomarkers. The principal finding of this report is that baseline stroke volume, defined by pulsed-wave Doppler of the left ventricular outflow tract, and the derived cardiac index (SVI multiplied by heart rate) and MCF (defined as the ratio of stroke volume to myocardial wall volume) were the strongest predictors of survival even after adjustment for biomarker stage. The authors treated each variable in separate models given that they each share a common term in their calculation (stroke volume). SVI captures the impairment of myocardial systolic and diastolic functions and thus is a logical variable to study in cardiac amyloidosis owing to the underlying pathophysiology. SVI has been previously been shown to predict mortality in patients with aortic stenosis,[21] and an SVI of <35 mL/m^2 is used to define patients with low-flow, low-gradient aortic stenosis.[22] Consistent with this observation, in the current study, an SVI <33 mL/m^2 was an independent predictor of survival in AL amyloidosis that remained predictive of mortality among patients diagnosed from 2005 to 2009 or from 2010 to 2015 despite the difference in overall mortality rates during these 2 time periods.

MCF is an uncommonly used index of stroke volume to the myocardial wall volume determined by linear dimensions, which assumes a constant left ventricular density. MCF, therefore, is also an attractive metric in cardiac amyloidosis as it accounts for the relative reduction in stroke volume that occurs as myocardial wall volume (or wall thickness) increases in the restrictive cardiomyopathy that defines AL cardiac amyloidosis, even as the left ventricular ejection fraction remains relatively stable. In fact, MCF has previously been shown to predict survival in a smaller cohort of patients with AL cardiac amyloidosis, independent of left ventricular ejection fraction.[23] In the current study, an MCF threshold of 34% independently predicted overall survival, and similar to SVI, MCF remained predictive for the 2 time periods studied.

In the cohort of 452 patients with available cardiac biomarker data, SVI and MCF remained independently predictive of mortality in multivariable models that included cardiac biomarkers; however, MCF was only

modestly predictive over biomarker stage. Furthermore, only SVI remained independently predictive of survival in a multivariable model which included left ventricular ejection fraction, systolic blood pressure, and biomarker stage. In the cohort of patients with more advanced biomarker stage disease (stages 3 and 4), SVI of >33 mL/m^2 remained predictive of improved survival. GLS was assessed in a subcohort of 238 patients with a threshold of <–14% (use General Electric EchoPAC software) also independently associated with mortality above biomarkers while the addition of SVI removed GLS from significance in the multivariable model. The authors also demonstrated that MCF and GLS were highly correlated (*R*=0.85). Therefore, this study introduces SVI as an echocardiographic predictor of survival, which, while not manifestly superior to GLS, may be similar in predicting survival. Because SVI is readily calculated from standard echocardiographic parameters without requiring additional software or experience in interpretation, these data suggest that SVI may be useful to predict survival in AL amyloidosis. Studies evaluating serial changes in SVI are now appropriate to determine whether this parameter, like left ventricular ejection fraction and wall thickness, can be used to identify improvement or decrement in cardiac function after treatment. It is also important to remember that like any echocardiographic measure, SVI and MCF are subject to error in measurement of the terms that yield the calculation. In the case of SVI, errors can occur in left ventricular outflow tract measurement or Doppler angulation, whereas in MCF, errors can occur in wall thickness, chamber diastolic dimension, or stroke volume determination. To this point, the authors measured reproducibility in 150 additional AL amyloidosis patients and found the inter- and intraobserver variation for SVI and MCF to be between 8% and 10% while for GLS it was only between 5% and 6%. Finally, regional differences in strain were not explored in this study, but previous work has demonstrated that regional specific changes can both identify cardiac amyloidosis[24] and change after effective chemotherapy.[18]

On looking at the overall survival data in this large cohort, some striking features emerge. Those patients with MCF or SVI below the threshold selected did exceptionally poorly, with median survival of 6 to 12 months with nearly all of the deaths occurring within the first year of diagnosis. However, those with values above threshold survived between 4.4 and 6.8 years, a dramatic difference. These findings persisted irrespective of era of diagnosis. According to biomarker stage, ≈15% to 20% had no evidence of cardiac amyloidosis (stage 1) while 50% to 60% most certainly did (stage 3–4), so it is clear that many patients with advanced biomarker disease had extended survival that could be predicted by SVI or MCF, as demonstrated in Figure 3. Thus, just as biomarker staging communicates, echocardiographic assessment of cardiac amyloidosis shows that the disease is by no means uniform. Likely, those with the best cardiac functional assessments were offered the most aggressive forms of chemotherapy, perhaps yielding hematologic responses that rendered the observed extended survival. This study did not include follow-up information on light chain response relative to treatment received, and thus neither the effect of treatment directed against the plasma cell clone (chemotherapy or autologous stem cell transplantation) or the depth of hematologic response on SVI and MCF could be assessed. Such information would be useful for the longitudinal management of AL amyloidosis patients undergoing contemporary therapies.

Overall, this is an important, large, retrospective cohort study of systemic AL amyloidosis patients that establishes SVI, and to a lesser degree, MCF, as reliable prognostic indicators of survival beyond cardiac biomarkers. The study also validates GLS as an important prognostic tool in this population. Further study is required to assess which of these echocardiographic measurements (SVI, MCF, or GLS) can be used to best predict survival and also identify a cardiac-specific response after contemporary treatment for systemic AL amyloidosis.

ARTICLE INFORMATION

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