Functional Cardiac Recovery and Hematologic Response to Chemotherapy in Patients With Light-Chain Amyloidosis (from the Stanford University Amyloidosis Registry)

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Cardiac involvement is common in patients with light-chain (AL) amyloidosis and portends a poor prognosis, although little is known about the changes in cardiac mechanics after chemotherapy. We sought to explore the relation between amyloidosis staging and baseline cardiac mechanics and to investigate short-term changes in cardiac mechanics after chemotherapy. We identified 41 consecutive patients from the Stanford Amyloid Center who had echocardiograms and free light-chain values before and after chemotherapy, along with 40 age- and gender-matched controls. Echocardiographic assessment included left ventricular global longitudinal strain, E/e' ratio, and left atrial (LA) stiffness. Hematologic response to chemotherapy was defined as ≥50% reduction in the difference between the involved and the uninvolved free light chain (dFLC). The mean age was 66.9 ± 8.4 years and 66% were men. Before chemotherapy, global longitudinal strain, E/e' ratio, and LA stiffness were impaired in patients with amyloidosis compared with controls, and the severity of impairment worsened with advanced staging. After chemotherapy, hematologic response was observed in 30 (73%) patients. There was a significant association between the change in dFLC and cardiac function (E/e' ratio: r = –0.43, p = 0.01; LA stiffness: r = –0.35, p = 0.05). There was no significant improvement in cardiac mechanics in patients without a hematologic response to chemotherapy. In conclusion, amyloidosis stage correlated with noninvasive measurements of cardiac mechanics, and improvement in dFLC correlated with cardiac improvement on short-term follow-up echocardiography. **(Am J Cardiol 2017;120:1381–1386)**

Systemic light-chain (AL) amyloidosis is characterized by the production of amyloidogenic immunoglobulin light chains with subsequent tissue infiltration and multiorgan dysfunction. Infiltration of the heart causes a primarily restrictive cardiomyopathy. Cardiac dysfunction is observed in up to 60% of patients with AL amyloidosis and portends a poor prognosis.[1] Chemotherapy has been shown to improve heart failure symptoms and survival rates, although few studies have explored the change in cardiac mechanics after chemotherapy.[2] A better understanding of the relation between hematologic response and change in myocardial function can provide insight into the clinical trajectory of patients with AL amyloidosis. Several metrics have recently been proposed to better assess myocardial function in patients with heart failure. The Lagrangian global longitudinal strain (GLS) assesses the longitudinal shortening of the ventricle and is more sensitive than ejection fraction in detecting ventricular dysfunction.[3,4] Left atrial (LA) stiffness has been proposed as a sensitive marker of diastolic dysfunction that combines a measurement of LA function, LA strain, and a surrogate of left ventricular (LV) filling, E/e' ratio.[5] In the present study, our first objective was to explore the relation between amyloid staging and baseline cardiac mechanics using metrics of GLS and LA stiffness.[6,7] Our second objective was to describe the change in myocardial and atrial structure and function after chemotherapy in AL amyloidosis. Finally, we sought to explore whether improvement in cardiac mechanics after chemotherapy is associated with hematologic response.

Methods

We screened 189 patients for study enrollment from the Stanford Amyloid Center database who were seen in October 2007 to June 2014. Patients with AL amyloidosis were selected if they (1) underwent chemotherapy treatment for at least 3 months,[8] (2) had an echocardiogram before chemotherapy, (3) had an echocardiogram performed ≥3 months after starting chemotherapy, and (4) had documented free light-chain (FLC) levels corresponding to the timing of the echocardiograms. Patients were excluded if they did not have

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evidence of cardiac amyloid at the start of chemotherapy (n = 14), underwent a heart transplant (n = 7), or were in atrial fibrillation during the echocardiograms (n = 3). Cardiac involvement was defined by evidence of amyloid deposits on endomyocardial biopsy (available in 20% of patients) or by the presence of low voltage on a 12-lead electrocardiography (all limb leads <0.5 mV) with echocardiographic evidence of a mean LV wall thickness of more than 12 mm in the absence of hypertension or other potential causes of LV hypertrophy.[9] Amyloid involvement in other major organ systems was included if it was diagnosed at the time of the initial echocardiography. We also randomly recruited 40 age- and gender-matched healthy volunteers from our healthy-aging database.

Patients were stratified according to the revised 4-point Mayo staging system.[6,7] The Stanford laboratory uses troponin I (Siemens, Erlangen, Germany), where a value of <0.1 ng/mL reflects the 99th percentile of healthy donors. Although the revised Mayo staging uses troponin T, we based our cut-off troponin value of ≥0.1 ng/mL on the original 3-point Mayo staging, which used troponin I. A score of 1 was assigned for each of the following variables[6,7]: troponin I ≥0.1 ng/mL, N-terminal pro-B-type natriuretic peptide (NT-proBNP) ≥1800 pg/mL, dFLC ≥ 18 mg/dL, where dFLC equals the difference between the involved FLC and uninvolved FLC. The patients were categorized into stages 1 through 4 based on scores of 0, 1, 2, and 3, respectively.

Echocardiographic studies were performed using commercially available echocardiography systems (Sonos 7500, iE33, and EPIQ 7C; Philips Medical Imaging, Eindhoven, The Netherlands), and viewed on the offline Xcelera workstation (Philips Medical Systems, Best, The Netherlands). Standard measurements of ventricular dimension, diastolic parameters, and ejection fraction were made according to the guidelines of the American Society of Echocardiography.[10] Lagrangian longitudinal strain was calculated by manually tracing the length of the ventricular midwall in end-diastole (peak of QRS, L_0) and end-systole (L_1) as strain (%) = $100 \times (L_1 - L_0)/L_0$ as previously described by our team.[11] GLS represents the average of the longitudinal strain measured in the apical 2-chamber, 3-chamber, and 4-chamber views. Quality control for longitudinal strain measurements included keeping the apical reference point stable to avoid overestimating strain due to apical foreshortening, and tracing the mitral annular plane for better delineation. Endocardial strain and epicardial circumferential strain were measured in the parasternal short-axis view after manually tracing the endocardial and epicardial surfaces, respectively, in end-diastole (peak of QRS, C_0) and end-systole (C_1) as circumferential strain (%) = $100 \times (C_1 - C_0)/C_0$. LA emptying fraction and LA strain were obtained from the apical 4-chamber view. LA emptying fraction was calculated as LA emptying fraction (%) = 100 × (maximum LA volume − minimal LA volume)/maximal LA volume. LA strain was calculated as LA strain (%) = 100 × (minimal LA length − maximal LA length)/maximal LA length, where LA length represents the LA wall length obtained at the point of maximal and minimal LA volume.[12] We evaluated the LA stiffness as LA stiffness = E/e' ratio/LA strain.[5] For intraobserver variability, the coefficient of variation was 2.2 for LV LS and 7.6 for LA strain. For interobserver variability, the coefficient of variation was 7.6 for LV LS and 12.6 for LA strain in our Stanford Biomarker and Phenotypic Core Laboratory.[10,12]

Hematologic response to chemotherapy was assessed by the change in dFLC. For part of the analysis, patients were classified into 2 groups: hematologic responders, if there was a ≥50% reduction in dFLC, and nonresponders, which included all other patients. A cut-off value of 50% corresponds to a partial hematologic response based on consensus guidelines[9,13] and has been used in previous studies.[14] Cardiac response to chemotherapy was defined as a relative change of ≥10% in GLS, E/e' ratio, or LA stiffness based on a predefined threshold determined at the beginning of the study corresponding to the intervariability of measurements in our laboratory. The change in NT-proBNP was defined as a relative change of ≥20% in log-transformed NT-proBNP values.

Continuous variables are presented as mean and standard deviation or median and interquartile range if not normally distributed. Normality of the continuous variables was confirmed with the Shapiro-Wilk test. Categorical variables were compared using Pearson's chi-square test or Fisher's exact test, as appropriate. Comparisons of continuous variables between baseline and follow-up were performed using either a paired *t* test or the Wilcoxon signed-rank sum test, as appropriate. One-way analysis of variance test was used for comparison of GLS, E/e' ratio, and LA stiffness among Mayo stages; patients in stages 3 and 4 were combined into 1 group due to the low number of patients in stage 4. Fisher's exact test was performed to analyze the change of echocardiographic parameters according to the hematologic response to chemotherapy. A 2-sided p value of <0.05 was considered significant. All analyses were performed using SPSS 21 software (SPSS Inc., Chicago, Illinois).

Results

Baseline patient characteristics are summarized in Table 1. Of the 41 patients with AL amyloidosis, 32 (78%) had a lambda subtype. Cardiac biomarkers were positive in 29 patients (81%) for NT-proBNP and in 10 patients (29%) for troponin. Changes in vital signs, volume status, and cardiac medications before and after chemotherapy are presented in Table 2.

Standard echocardiographic parameters are featured in Table 3. All metrics of ventricular size, function, and deformation were significantly worse in the AL amyloidosis cohort compared with the control group with the exception of circumferential strain, which demonstrated a trend toward worsening in the AL amyloidosis cohort. The amyloidosis cohort also had significant impairment in all measurements of atrial size and function. Among echocardiographic parameters, GLS, E/e' ratio, LA stiffness, and relative wall thickness (RWT) were the most sensitive in identifying cardiac impairment in AL amyloidosis: GLS (area under the curve [AUC] = 0.93 [0.83 to 0.99]), E/e' ratio (AUC = 0.90 [0.83 to 0.97]), LA stiffness (AUC = 0.86 [0.77 to 0.94]), and RWT (AUC = 0.995 [0.99 to 1.00]).

Figure 1 shows the distribution of GLS, E/e' ratio, and LA stiffness in patients with AL amyloidosis. The majority of patients showed abnormalities in GLS (90%), E/e' ratio (95%), and LA stiffness (86%). All parameters needed to assess diastolic dysfunction[15] were available for 36 patients. Diastolic