Risk Factors and Prognostic Role of Left Atrial Enlargement in Patients with Cardiac Light-Chain Amyloidosis

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ABSTRACT

Background: Light-chain amyloidosis (AL) is a plasma cell disorder characterized by the extracellular deposition of insoluble fibril-forming monoclonal immunoglobulin, aggregating in heart and leading to cardiac amyloidosis (CA). Transthoracic echocardiography is a noninvasive method used for the evaluation of cardiac diastolic dysfunction. The left atrium (LA) plays an important role in modulating cardiovascular performance, with its function participating left ventricular filling and its size being affected by diastolic function. Therefore, we aimed to assess prognostic values of LA size measured by a simple echocardiographic parameter, LA diameter indexed to body surface area, in CA and to explore risk factors associated with LA enlargement as well as the incidence of severe heart failure (HF).

Materials and Methods: A retrospective analysis of echocardiography of patients with biopsy-proven cardiac AL amyloidosis was conducted. LA enlargement was defined as LA diameter indexed to body surface area greater than 23 mm/m^2.

Results: A total of 104 patients with CA were included in the final analysis, 61 (58.7%) of which showed a presentation of LA enlargement. Age, New York Heart Association, ejection fraction and early-to-atrial transmitral flow velocity ratio were independently associated with LA enlargement. During a mean follow-up period of 39 months, LA enlargement was strongly related with all-cause mortality (hazard ratio = 1.94; 95% CI: 1.14-3.29; $P = 0.015$) and increased risk of severe HF (hazard ratio = 2.18; 95% CI: 1.12-4.23; $P = 0.022$).

Conclusions: In cardiac AL amyloidosis, age and early-to-atrial transmitral flow velocity ratio were main independent risk factors with regard to LA enlargement. LA enlargement was strongly associated with incidence of severe HF and was also a significant predictor of all-cause mortality.

Key Indexing Terms: Amyloidosis; Echocardiography; Left atrial diameter; Prognosis. **[Am J Med Sci 2016;351(3):271–278.]**

INTRODUCTION

Light-chain amyloidosis (AL) is a plasma cell disorder characterized by the extracellular deposition and aggregation of insoluble fibril-forming monoclonal immunoglobulin in diverse organs. During this pathologic process, heart is commonly involved, and patients gradually develop into cardiac amyloidosis (CA) with restrictive cardiomyopathy.[1] Median survival for patients with AL with cardiac involvement is likely to be less than 6 months; hence, the identification of patients with CA with high risks for mortality is urgently needed.[2,3] Today in clinical settings, various noninvasive methods used for evaluating cardiac morphology and function have been applied for risk stratification and prognostic assessment. Among those, transthoracic echocardiography appears to be a desirable one, with an increased left ventricular (LV) wall thickness $\geq$12 mm and brilliant speckled appearance of myocardium as CA classical features.[4] It has been found that a preserved LV ejection fraction (EF) is not unusual in the initial stage of CA, where a diastolic dysfunction is often obvious among all these echocardiographic findings.[5] Owing to this fact, an echocardiographic parameter evaluating the diastolic function is highly needed at the early phase of disease. The left atrium (LA) plays an important role in modulating cardiovascular performance, with its function participating LV filling and its size being affected by diastolic function. The thin-walled LA is capable of enlarging when exposed to sustained elevation of LV diastolic filling pressure.[6] As reported,[6] LA size is strongly associated with cardiovascular disease and is sensitive in predicting clinical outcomes and providing accurate risk stratification. Furthermore, a continued pathologic LA enlargement, arising from increased LV filling pressures and volume overload, is more likely to contribute to the occurrence of irreversible heart failure (HF) on account of reduced reservoir and contractile pump functions.[7]

Consequently, over the past few decades, many precise measurements regarding LA size have been performed, among which, LA diameter seems to be more available and convenient in different clinical settings, especially when considering its merits of both less time-consuming and less technical requirements. Therefore, we conducted this study to assess the risk factors and prognostic significance of LA size with this simple measurement in cardiac AL amyloidosis and discuss the

possible pathophysiologic mechanisms behind these potential correlates.

MATERIALS AND METHODS

Study Design

This was a retrospective analysis, including the echocardiography data of patients with histologically diagnosed cardiac AL amyloidosis, who were admitted to the Peking Union Medical College Hospital between January 2010 and December 2014. Primary systemic amyloidosis was pathologically confirmed by immunohistochemical staining or mass spectrometry–based proteomic along with proof of clonal plasma dyscrasias.[8] Cardiac involvement was evaluated according to the demonstration of amyloid deposits by the endomyocardial biopsy or the echocardiographically defined evidence of amyloid cardiomyopathy with a thickness of LV septum or posterior wall >12 mm in the absence of any potential causes of LV hypertrophy. HF was assessed with the major signs and symptoms of HF such as fatigue, exercise intolerance and lower extremity edema, which demanded a hospitalization. Hereditary or wild-type transthyretin-related amyloidosis and patients with significant valvular diseases were excluded from this study to remove confounding causes for changes in chamber size. Therefore, 104 patients with cardiac AL amyloidosis were included in the final analysis.

Data Collection

Medical records were reviewed without knowledge of histologic findings. All patients underwent a clinical evaluation, blood tests, electrocardiography (ECG) and echocardiography at the first histologic diagnosis. ECG was measured on standard definition. In all the patients, QRS, QT and QT corrected intervals were calculated. Low-voltage pattern was taken into consideration if a QRS voltage amplitude is ≤ 0.5 mV in all limb leads or ≤ 1 mV in all precordial leads. Poor R-wave progression was defined as R wave ≤ 3 mm by $V_{1\text{-}3}$.[9,10] Atrioventricular conduction delays were considered at the presence of atrioventricular block at any degree, and intraventricular conduction delays included left bundle branch block, complete and incomplete right bundle branch block and left anterior hemiblock.

Echocardiography closest to time of diagnosis was reviewed blindly to ECG, baseline characteristics and levels of cardiac biomarkers. Transthoracic echocardiography was performed with commercially available GE Vivid 7 Ultrasound machines and analyzed for wall thickness and chamber dimensions following the criteria of the American Society of Echocardiography recommendations.[11] LV fractional shortening was evaluated as the difference between the end-diastolic and the end-systolic diameters. LV EF was assessed using the biplane Simpson's equation and considered impaired at 50% by semiquantitative evaluation. Early-to-atrial transmitral flow velocity ratio (E/A ratio) was estimated by conventional pulsed Doppler in the apical 4-chamber view. LV restrictive filling pattern was taken into consideration if E wave deceleration time <150 milliseconds together with E/A ratio >2.5. LA anteroposterior diameter was measured in parasternal long-axis view. As suggested by the American Society of Echocardiography and the European Association of Cardiovascular Imaging,[6] LA diameter was indexed to body surface area (BSA) and a cutoff value of 23 mm/m^2 was used to assess the degree of LA enlargement. In the final analysis, patients were divided into 2 groups according to the LA size assessed by the diameter indexed to body surface area (LADi), whose value ≥ 23 mm/m^2 was equal to LA enlargement.

Statistical Analysis

Continuous variables are presented as median and interquartile ranges and compared on the basis of analysis of variance followed by the 2-tail Mann-Whitney test. Categorical variables were in the form of frequencies and percentages and tested by chi-square analysis using the Pearson correlation test or Fisher's exact test. Logistic models were constructed to explore the potential correlates between baseline clinical parameters and the presence of LA enlargement. We carried the follow-up through telephone, and all-cause mortality and the incidence of severe HF as the study endpoints. Survival curve regarding overall survival and survival under different New York Heart Association (NYHA) class were plotted according to Kaplan-Meier method and differences were assessed by the log-rank test. Univariate and multivariate Cox proportional hazard models were conducted to explore the association and possible interactions between baseline variables and predictors of death and severe HF. All statistical analyses were 2-sided and performed using SPSS Statistics version 20.0 (IBM). A $P < 0.05$ was considered statistically significant.

RESULTS

Baseline Clinical Characteristics

A total of 104 patients with cardiac AL amyloidosis were included in the final analysis. The mean age of patients was 55 (range: 46-63 years) years and 64.4% patients were men. A total of 64 (58.7%) patients presented with LA enlargement and 57.7% patients were accompanied with severe HF (NYHA III-IV). The baseline clinical characteristics are detailed in Table 1. The study cohort was divided into 2 groups depending on the presence ($n = 61$) or absence ($n = 43$) of LA enlargement. Comparing the baseline demographic and experimental characteristics, patients in these 2 groups were not significantly different in sex, BSA and heart rate, but in age, blood pressure, N-terminal of the pro-brain natriuretic peptide (NT-proBNP) level, B-type