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Original article

Left atrial function in patients with light chain amyloidosis: A transthoracic 3D speckle tracking imaging study☆,☆☆

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ABSTRACT

Background: Systemic light chain amyloidosis (AL) is characterized by the extracellular deposition of amyloid fibrils. Transthoracic echocardiography is the modality of choice to assess cardiac function in patients with AL. Whereas left ventricular (LV) function has been well studied in this patient population, data regarding the value of left atrial (LA) function in AL patients are lacking. In this study, we aim to examine the impact of LA volumes and function on survival in AL patients as assessed by real-time 3D echocardiography.

Methods: A total of 77 patients (67 ± 10 years, 60% men) with confirmed AL and 39 healthy controls were included. All standard 2D echocardiographic and 3D-LA parameters were obtained.

Results: Fourteen patients (18%) were in Mayo Clinic (MC) stage I, 30 (39%) in stage II, and 33 (43%) in stage III at initial evaluation. There was no significant difference among the MC stages groups in terms of age, gender, or cardiovascular risk factors. As compared to patients in MC II and MC I, those in MC III had significantly larger indexed 3D-LA volumes (MCIII: 46 ± 15 mL/m^2, MC II: 38 ± 12 mL/m^2, and MC I: 23 ± 9 mL/m^2, $p < 0.0001$), lower 3D-LA total emptying fraction (3D-tLAEF) (21 ± 13% vs. 31 ± 15% vs. 43 ± 7%, respectively, $p < 0.0001$), and worse 3D peak atrial longitudinal strain (3D-PALS) (11 ± 9% vs. 18 ± 13% vs. 20 ± 7%, respectively, $p = 0.007$). Two-year survival was significantly lower in patients with 3D-tLAEF < + 34% ($p = 0.003$) and in those with 3D-PALS < + 14% ($p = 0.034$). Both parameters provided incremental prognostic value over maximal LA volume in multivariate analysis.

Conclusion: Functional LA parameters are progressively altered in AL patients according to the MC stage. A decrease in 3D-PALS is associated with worse outcome, independently of LA volume.

Introduction

Systemic light-chain amyloidosis (AL) is characterized by the abnormal deposition in various organs of monoclonal light-chain (LC) that are produced by bone marrow abnormal clonal plasma cells. Cardiac involvement is identified in more than 50% of AL patients [1] and has a negative impact on outcomes [2,3]. Cardiac biomarkers, including amino-terminal pro-brain natriuretic peptide (NT-proBNP) and cardiac troponins (cTn) have been used since 2004 as prognostic markers in patients with AL [4]. The Mayo Clinic

☆ The results presented in this paper have not been previously published in whole or in part except in abstract forms.

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(MC) staging, based on the serum level of these two biomarkers, has since been well validated. It allows risk stratification of AL patients into low- (stage I), intermediate- (stage II), and high- (stage III) risk groups, with the more advanced stages being associated with worse outcome.

The progressive accumulation of amyloid fibrils in the myocardium leads to a restrictive cardiomyopathy characterized by an increase in left ventricular (LV) wall thickness with diastolic dysfunction and elevation in LV filling pressures [5]. Involvement of the left atrium (LA) in AL is multifactorial. Enlargement of the LA is quite common, a reflection of the severity and chronicity of the elevation in LV filling pressures similar to other disease processes. Maximal LA volume, as measured by echocardiography, is known to confer independent prognostic information in various cardiovascular conditions [6–8]. Additionally, the atrial wall myocardium is thickened in cardiac AL due to infiltration of the atrial myocardial by amyloid fibrils in a similar fashion to both ventricles [9]. This phenomenon not only leads to a decrease in LA compliance, but it may also interfere with other functions of the LA [10].

The study of various LA parameters can be readily performed by transthoracic echocardiography (TTE). As such, assessment of LA volume is traditionally derived from two-dimensional (2D) TTE [11]. Additionally, the assessment of LA functional parameters may be performed by 2D-TTE. However, data suggest that LA volume and function are better assessed using real time three-dimensional (3D) TTE (RT3D) and 3D speckle tracking imaging (STI) [12], respectively. These newer echocardiographic techniques allow the measurement of LA real-time volume curves along with 3D longitudinal wall motion tracking, thus permitting the simultaneous evaluation of 3D peak atrial global longitudinal strain (3D-PALS) and 3D LA total emptying fraction (3D-tLAEF) using the volumetric method.

The aim of our study is to evaluate the prognostic value of 3D-PALS and 3D-tLAEF, as assessed by 3D wall motion tracking, in patients with AL. We hypothesize that 3D-PALS and 3D-tLAEF may provide independent prognostic value in this patient population.

Methods

Patient population

This study is a single center observational report conducted between March 2011 and August 2014 by the Cardiology Department and the National French Center of Reference “AL and other Diseases due to Monoclonal Immunoglobulin Deposits” at the University Hospital of Limoges, France. Inclusion criteria included patients older than 18 years of age with confirmed AL, at any MC stage, and who underwent a comprehensive TTE at initial evaluation. The echocardiographic study included the assessment of traditional 2D parameters as well as 3D LA volumes and 3D speckle tracking imaging (STI). Additionally, healthy control subjects free from cardiovascular disease with similar age and gender distribution were enrolled and underwent identical echocardiographic evaluation. All subjects provided consent to be included in the study. The study was performed in compliance with the Helsinki Declaration.

The diagnosis of amyloid deposition using histological analysis of organ biopsy was performed as previously reported [13]. Cardiac involvement was defined according to the standard criteria defined in 2005 and updated in 2012 [14]. All patient characteristics were recorded at the time of enrollment, including demographic data, comorbid conditions, and clinical data. Additionally, biological data that were measured at the time of enrollment and within 24 h of the TTE used in this study were noted. Finally, an electrocardiogram (ECG) was obtained on the same day as the TTE and biological data.

In our population study, all patients received chemotherapeutic treatment of plasma cell dyscrasia according to their MC stage and to our standardized protocol. In case of non-response or partial response, patients were offered a second line hematologic treatment. Regarding cardiovascular protective treatment, our patients did not receive any beta-blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, or calcium channel inhibitors because of the well known bad tolerance of these medications in amyloid cardiomyopathy patients. They only received loop diuretics such as furosemide starting from 40 mg per day and up to 500 mg depending on stage of congestive heart failure. Potassium pills were added when needed. Spironolactone was added in some cases if there was no contraindication for its use.

Exclusion criteria

Patients with localized LC amyloidosis, familial transthyretin, or systemic senile amyloidosis were excluded from our study. Additionally, patients with persistent atrial fibrillation (AF) or paced rhythm during the TTE study were also excluded from analysis.

Severity and staging of AL

The severity of cardiac involvement was established using the MC staging. Stage I patients are those with normal levels of both biomarkers (NT-proBNP $<$332 ng/L and cTnT $<$0.035 μg/L); stage II are those with abnormally increased levels of a single biomarker; and stage III those with increased levels of both biomarkers. The MC staging has been recently updated incorporating two new levels in the stage III according to NT-proBNP level $<$ or $\geq$8500 ng/L (i.e. stages IIIa and IIIb) [15].

A more recent staging system published by Kumar et al. [16] incorporated the serum delta free light chains difference (FLC) allowing four stages and thus a better stratification of AL.

These two staging systems (i.e. MC updated staging and Kumar staging) were also assessed in the present study.

Echocardiographic parameters

All TTE data were obtained using the Artida 4D machine (Toshiba Medical Systems, Tustin, CA, USA, 2011) by one operator who was unaware of the patient's MC staging and biological data. A second operator, blinded to the data, performed offline 3D LA volumes and 3D-tLAEF for inter-observer variability analysis. All echocardiographic measurements were performed according to the recommendations of the American Society of Echocardiography and the European Association of Cardiovascular Imaging [11]. All classic 2D echocardiographic parameters were assessed as previously described [2].

In order to acquire 3D LA parameters, we used the 3D wall motion tracking software. This echocardiographic method associates 3D volume acquisition with time-curve derived 3D deformation analysis, thus allowing the automatic tracking of the whole volume of a given cardiac cavity over time and the generation of a time-volume curve along with phasic deformation data. 3D LA volumes are obtained by RT3D from the apical 4-chamber view using a 3D matrix-array transducer (PST-25 SX, 2.5 MHz). Generally, four cardiac cycles and a 5-s breath hold are required for the acquisition that is triggered by the electrocardiographic R-wave. The entire LA volume is included in the region of interest by manual shifting of the vertical and horizontal lines in two orthogonal apical view and short-axis views. Thereafter, the LA endocardial border is manually traced and the 3D LA volume is automatically generated. Various LA volumes are derived from the 3D volume curve at different phases of the cardiac cycle: the maximal LA volume is recorded at end systole just prior to mitral