Anterior Aortic Plane Systolic Excursion: A Novel Indicator of Transplant-Free Survival in Systemic Light-Chain Amyloidosis

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Background: Anterior aortic plane systolic excursion (AAPSE) was evaluated in the present pilot study as a novel echocardiographic indicator of transplant-free survival in patients with systemic light-chain amyloidosis.

Methods: Eighty-nine patients with light-chain amyloidosis were included in the post-hoc analysis. A subgroup of 54 patients with biopsy-proven cardiac amyloid infiltration were compared with 41 healthy individuals to evaluate the discriminative ability of echocardiographic findings. AAPSE is defined as the systolic excursion of the anterior aortic margin. To quantify AAPSE, the M-mode cursor was placed on the aortic valve plane in parasternal long-axis view at end-diastole. Index echocardiography had been performed before chemotherapy. Median follow-up duration was 2.4 years. The primary combined end point was heart transplantation or overall death.

Results: Mean AAPSE was 14 ± 2 mm in healthy individuals (mean age=57 ± 10 years; 56% men; BMI=25 ± 4 kg/m^2). AAPSE < 11 mm separated patients from age-, gender-, and BMI–matched control subjects with 93% sensitivity and 97% specificity. Median transplant-free survival of patients with AAPSE < 5 mm was 0.7 versus 4.8 years (P = .0001). AAPSE was an independent indicator of transplant-free survival in multivariate Cox regression (echocardiographic model: hazard ratio=0.72 [P = .03]; biomarker model: hazard ratio=0.62 [P = .0001]). Sequential regression analysis suggested incremental power of AAPSE as a marker of transplant-free survival. An ejection fraction–based model with an overall χ^2 value of 22.8 was improved by the addition of log NT-proBNP (χ^2 = 32.6, P < .005), troponin-T (χ^2 = 39.6, P < .01), and AAPSE (χ^2 = 54.0, P < .0001).

Conclusions: AAPSE is suggested as an indicator of transplant-free survival in patients with systemic light-chain amyloidosis. AAPSE provided significant incremental value to established staging models. (J Am Soc Echocardiogr 2016;■:■-■.)

Keywords: Echocardiography, Cardiomyopathy, Anterior aortic plane systolic excursion, AAPSE, Systemic light-chain amyloidosis, Survival

Amyloidosis comprises a heterogeneous group of rare disorders with an estimated annual incidence of about five to 12 affected subjects per million.[1] The majority of cases result from systemic light-chain (AL) amyloidosis related to multiple myeloma. The excessive synthesis of immunoglobulin light chains leads to deposition and formation of β pleated sheets caused by changes to secondary protein structure. These extracellular deposits of insoluble fibrillary proteins may cause organ malfunction. Up to 90% of patients with AL amyloidosis experience cardiac involvement during the course of disease.[2] The extent of cardiac impairment determines overall prognosis.[3-5] The median survival of affected patients with markedly elevated brain natriuretic peptide and cardiac troponin levels is reduced to only 8 months.[6]

Echocardiographic assessment is essential in patients with suspected amyloidosis.[7,8] The diagnosis of cardiac involvement in systemic amyloidosis requires either positive results on endomyocardial biopsy or an echocardiographic mean wall thickness ≥12 mm, excluding other causes, together with a positive biopsy of noncardiac origin.[9] However, advanced cardiac amyloidosis might even be present in patients with normal interventricular septal thickness.[10]

The value of echocardiography is not limited by its diagnostic abilities, as it also delivers crucial information for further risk stratification in patients with AL.[11] Unlike serum biomarkers, imaging parameters are independent of commonly impaired renal function in patients with AL. Typical morphologic findings include biventricular increased wall thickness, valvular thickening, and myocardial granular sparkling, particularly of the septal wall.[7,9,10,12,13] Functional contractile impairment commonly precedes these changes and may occur before

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Abbreviations

AAPSE = Anterior aortic plane systolic excursion

AL = Systemic light-chain amyloidosis

BMI = Body mass index

EF = Ejection fraction

HR = Hazard ratio

ICC = Intraclass correlation coefficient

MAPSE = Mitral annular plane systolic excursion

NT-proBNP = N-terminal prohormone of brain natriuretic peptide

TAPSE = Tricuspid annular plane systolic excursion

TnT = Cardiac troponin T

cardiac symptoms. In this context, diastolic dysfunction and left ventricular longitudinal function provide diagnostic and prognostic information in cardiac amyloidosis.[5,14-19]

There is an ongoing need to improve risk stratification and early detection of cardiac involvement in systemic amyloidosis.[8] Noninvasive surrogates ought to be easily assessable in daily practice. Previous studies provided evidence that basal left ventricular segments are most sensitive to functional changes in AL.[14,15,19,20]

Here, we introduce anterior aortic plane systolic excursion (AAPSE), which is defined as the systolic excursion of the anterior margin of the aortic root derived from M-mode echocardiography in the parasternal long-axis view. We hypothesized that AAPSE might provide additional value to established prognosticators in AL, to identify patients at risk for adverse events during follow-up.

METHODS

Study Population and Design

In this retrospective observational study, we included a total of 89 patients with systemic light-chain amyloidosis (mean age=59 ± 9 years; 47 men [53%]; mean body mass index [BMI]=25 ± 4 kg/m^2; mean septal wall thickness = 16 ± 4 mm; mean ejection fraction [EF], 51 ± 11%) to evaluate echocardiographic markers of survival. The discriminative value of these parameters was assessed in the "diagnostic" subgroup of 54 patients with AL amyloidosis with at least one positive left or right ventricular biopsy (mean age=57 ± 8 years; 27 men [50%]; mean BMI=24 ± 4 kg/m^2; mean septal wall thickness= 19 ± 4 mm; mean EF= 45 ± 12%) compared with 41 sex-, age-, and BMI-matched healthy individuals without medical histories (mean age= 57 ± 10 years; 23 men [56%]; mean BMI=25 ± 4 kg/m^2; mean septal wall thickness=10 ± 1 mm; mean EF=63 ± 3%). The diagnosis of AL was based on the presence of a monoclonal gammopathy by serum electrophoresis, free light-chain test, immunofixation on serum and urine, confirmed by positive Congo red staining with birefringence under polarized light of any biopsy (periumbilical fat aspiration, rectum, or affected organ), positive results on immunohistology for κ or λ in the biopsy, and on the exclusion of hereditary forms of amyloidosis. The study population was referred to our clinic for echocardiographic routine workup with diagnosed light-chain disorder between February 2006 and August 2008, before chemotherapy. The use of anonymized patient data for research purposes was approved by the institutions ethics committee to the Declaration of Helsinki.

Echocardiographic Examination

Echocardiography was performed at rest with an iE33 (Philips Medical Systems, Andover, MA). Offline analysis of echocardiographic studies was conducted on a commercially available workstation. Heart rate and blood pressure were measured in supine position before echocardiography. Digital images were obtained at optimal frame rates (50–55 frames/sec). Three cardiac cycles were stored in cine loop format for offline analysis. All measurements were acquired by two independent expert examiners who were blinded to the patients' clinical status according to current recommendations of the American Society of Echocardiography.[21] Accordingly, diastolic dysfunction was classified into three pathologic grades.[22]

Anterior Aortic Plane Systolic Excursion

AAPSE is defined as the systolic excursion of the anterior margin of the aortic root and was assessed from the parasternal long-axis view at passive end-expiration (Figure 1). The M-mode beam was placed on aortic valve plane at end-diastole. The distance from lowest (end-diastole) to highest (end-systole) excursion of the anterior aortic root margin was defined as AAPSE.

Mitral annular plane systolic excursion (MAPSE) and tricuspid annular plane systolic excursion (TAPSE) were measured from the apical four-chamber view. The systolic excursion of the lateral mitral and tricuspid annulus were measured as previously described.[23,24] EF was determined using the modified Simpson method for biplane assessment.[22]

Blood samples were drawn on the day of echocardiographic examination. Glomerular filtration rate was estimated using the Modification of Diet in Renal Diseases formula. N-terminal prohormone of brain natriuretic peptide (NT-proBNP) and cardiac troponin T (TnT) were measured using a commercially available sandwich immunoassay on a fully automated analyzer (Elecsys; Roche Diagnostics, Mannheim, Germany).

Follow-Up

Follow-up was acquired by review of patients' electronic records or telephone interviews with patients or their relatives. The primary combined end point was all-cause mortality or heart transplantation.

Reproducibility

The reproducibility of echocardiographic findings was evaluated in a subgroup of 20 randomly selected patients. For intraobserver variability, the same investigator was asked to reassess the parameters of interest 2 weeks after the first measurements had been acquired. For interobserver variability, two different investigators evaluated the echocardiographic studies separately.

Statistical Methods

Data were analyzed using SPSS version 23.0.0.2 (IBM, Armonk, NY). Continuous variables are expressed as mean ± SD. Group differences for continuous variables were tested using the independent *t* test and for ordinal variables using the Mann-Whitney *U* test, and differences between nominal variables were assessed using the Fisher exact test. Correlation analyses were performed using the Spearman coefficient. Correlation coefficients were classified as weak ($r > 0$ to $r < 0.2$), mild ($r \geq 0.2$ to $r < 0.4$), moderate ($r \geq 0.4$ to $r < 0.6$), moderately strong ($r \geq 0.6$ to $r < 0.8$), and strong ($r \geq 0.8$ to $r \leq 1.0$). Kaplan-Meier curves were used to estimate the distribution of survival as a function of follow-up duration. The association of clinical, echocardiographic, and serologic parameters with outcomes was evaluated using multivariate Cox proportional hazards regression models. Receiver operating characteristic curves were used

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