Restricted left atrial dilatation can visually differentiate cardiac amyloidosis from hypertrophic cardiomyopathy

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Abstract

Aims Cardiac amyloidosis (CA) is an infiltrative myocardial disease that occasionally mimics hypertrophic cardiomyopathy (HCM). The aim of this study is to investigate the discriminatory ability of visual assessment of left atrial (LA) function between CA and HCM on echocardiography.

Methods and results In total, 93 patients with cardiac magnetic resonance imaging (CMR)-confirmed HCM and 34 with cardiac biopsy-confirmed CA were retrospectively assessed. LA dilatation was assessed via echocardiography in an apical four-chamber view. Visual assessment was performed to identify LA dilatation grade (preserved = 1, abnormal = 2, and restricted = 3) based on the extent of outward expansion in the LA reservoir phase. Regarding the reproducibility of visually assessing LA dilatation grade, the kappa values between intra- and inter-observer measurements were 0.82 and 0.70, respectively. Of 127 participants, 57 (45%), 42 (33%), and 28 (22%) presented with LA dilatation Grades 1, 2, and 3, respectively. All 57 patients with preserved LA dilatation (Grade 1) had HCM, and 20 of 28 patients (71%) with restricted LA dilatation (Grade 3) presented with CA. Patients with CA had a higher LA dilatation grade than those with HCM (P < 0.01). LA emptying fraction and reservoir strain were also quantitatively evaluated. The area under the curves of LA dilatation grade (0.88) and LA emptying fraction (0.88) for differentiation of these two diseases were higher than that of LA reservoir strain (0.73) (P < 0.01, respectively). During follow-up, nine patients with HCM and 16 with CA experienced cardiac event (cardiac death or hospitalization due to heart failure). In Kaplan–Meier analysis including both groups of HCM and CA, the incidence of cardiac events was higher in patients with restricted LA dilatation than in those with preserved or abnormal LA dilatation (log-rank test, P < 0.01).

Conclusions Restricted LA dilatation is an indicator for the diagnosis of CA. Further, visual assessment of abnormal LA motion may facilitate diagnosis in patients with CA and high-risk patients with HCM.

Keywords Cardiac amyloidosis; Left atrial function; Reservoir function; Echocardiography

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Introduction

Cardiac amyloidosis (CA) is an infiltrative myocardial disease that occasionally mimics hypertrophic cardiomyopathy (HCM). These conditions are managed using varying therapeutic approaches. Hence, it is important to differentiate these two phenotypes, which are characterized by a thick left ventricle.2,3 Echocardiography is the first-line screening tool for patients with CA. The apical four-chamber view allows simultaneous visualization of all four chambers of the heart, thereby facilitating an immediate evaluation of cardiac structural and...
functional abnormalities. Patients with CA and HCM have greater left ventricular (LV) wall thickness and worse diastolic dysfunction. Left atrial (LA) enlargement commonly coexists due to the burden and chronicity of LV diastolic dysfunction. However, histological changes in the LA can differ between these two phenotypes. In patients with HCM, LA dilatation and fibrosis progress due to increased afterload in the hypertrophied left ventricle. A similar LA remodelling process occurs in patients with CA. However, in this condition, abnormal amyloid proteins could infiltrate the LA wall, resulting in a more stiff left atrium. Taken together, the visual assessment of restricted LA motion might increase the diagnosis of CA. Thus, patients with CA could be differentiated from those with HCM.

Accordingly, this study investigated the discriminatory ability of visual assessment of LA function between CA and HCM on echocardiography.

**Methods**

**Patient population**

We retrospectively investigated 123 patients with HCM and 58 with CA in Ehime University Hospital and Kitaishikai Hospital. Patients with HCM were diagnosed according to the published guidelines of the European Society of Cardiology and those with HCM underwent cardiac magnetic resonance imaging (CMR) for the assessment of heterogeneous LV hypertrophy and late gadolinium enhancement (LGE). All patients with CA underwent cardiac biopsy, and the CA aetiology was histologically confirmed based on the presence of amyloid deposits. Patients with signs and symptoms of coronary artery disease, pacemaker, and poor echocardiographic images were excluded. Further, those with atrial fibrillation were not included due to the effects of the condition on LA reservoir function and difficulties in echocardiographic measurement due to an irregular heartbeat. The study was undertaken in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Ehime University Graduate School of Medicine (approval number: 1803003), and it was performed using the opt-out method of our hospital websites.

**Echocardiography**

Echocardiographic examination was performed by experienced cardiologists and sonographers using a commercially available ultrasound system (Vivid E9 or Vivid E9S; GE Vingmed, Horten, Norway). Conventional echocardiographic parameters were assessed according to the recommendation of the American Society of Echocardiography. LV and LA volumes and LV ejection fraction were evaluated with the biplane method of disks using two-dimensional images. Transmitial early diastolic velocity (E) was obtained using a pulsed-wave Doppler at the level of the mitral valve tip during diastole. The early diastolic mitral annular tissue velocity (e') was calculated at the septal mitral annulus, and E/e' was also assessed.

**Visual assessment of left atrial dilatation from an apical four-chamber view**

In an apical four-chamber view, an experienced observer without any knowledge on the patients’ clinical information performed a visual assessment of LA dilatation. The LA dilatation grades are shown in Figure 1. LA dilatation Grade 1 (preserved) was defined as good and smooth outward dilatation in the reservoir phase when the LA area expands from minimum to maximum. LA dilatation Grade 2 (abnormal) was defined as reduced and delayed outward dilatation. Finally, LA dilatation Grade 3 (restricted) was defined as restricted outward dilatation. From the same apical four-chamber view, the maximum and minimum LA volumes and emptying fraction were measured. LA emptying fraction was calculated using the following formula: 

\[
\text{LA emptying fraction} = \frac{\text{LA maximum volume} - \text{LA minimum volume}}{\text{LA maximum volume}} \times 100.
\]

Furthermore, LA reservoir and pump strains, and LV longitudinal strain were evaluated using the raw data of the same apical four-chamber images with a dedicated software (EchoPAC PC BT13: GE Healthcare). Shortening strain was presented as positive value.

**Cardiac magnetic resonance imaging**

Cardiac magnetic resonance imaging examinations were performed using a clinical 3.0-Tesla magnetic resonance imaging scanner (Achieva 3.0 T Quasar Dual; Philips Healthcare, Best, the Netherlands). To evaluate myocardial fibrosis, LGE was evaluated at 5–10 min after the injection of 0.2 mmol/kg gadopentetate dimeglumine (Magnevist, BAYER Healthcare Pharmaceuticals, USA). Experienced radiologists diagnosed the presence of LGE in both the LA and LV walls.

**Definition of cardiac event**

Cardiac event was defined as the composite incidence of cardiac death and hospitalization due to heart failure during the follow-up period. The outcomes were judged by each physician who engaged in treatment and confirmed through medical chart review.
Statistical analysis

Categorical variables were presented as n (%), and the \( \chi^2 \) test was used in the analysis. Continuous variables were presented as the median values and interquartile range. The Mann–Whitney \( U \) test was used for continuous variables. A receiver operating characteristic curve analysis for differentiating patients with CA from those with HCM was performed. The impact of LA dilatation grade on cardiac event was assessed using the Kaplan–Meier curves. Two observers who were blinded to the study assessed the reproducibility of the visual assessment of LA dilatation grade using the kappa statistic in 25 patients who were randomly selected. A \( P \) value of <0.05 was considered statistically significant. Statistical analyses were performed using the Statistical Package for the Social Sciences software (IBM Corp., version 25.0. Armonk, NY) and R software version 3.3.2 (R Foundation for Statistical Computing, Vienna, Austria).\(^{10}\)

Results

Finally, 93 patients with HCM and 34 with CA who met the inclusion criteria were included in the analysis. The characteristics of the participants, conventional echocardiographic parameters, and magnetic resonance imaging findings are summarized in Table 1. Patients with CA were significantly older than those with HCM (median age: 76 vs. 67 years). Moreover, patients with CA had a lower blood pressure than those with HCM. There was no significant difference in interventricular septum thickness between patients with HCM and those with CA. However, the posterior wall thickness was significantly greater in patients with CA than in those with HCM. Patients with CA had a lower LA volume index than those with HCM. Patients with CA had a higher LA volume index than those with HCM. Patients with CA experienced a significant decrease in LV ejection fraction, LA emptying fraction, LV longitudinal strain, and LA reservoir and pump strains. CMR revealed that most patients had LGE in the left ventricle irrespective of the two phenotypes of HCM and CA (85% vs.
Table 1 Characteristics of the participants, conventional echocardiographic parameters, and magnetic resonance imaging findings

| Variables                                         | Patients with HCM  | Patients with CA  | P value |
|---------------------------------------------------|--------------------|-------------------|---------|
| Age (years)                                       | 67 [56, 73]        | 76 [69, 81]       | <0.01   |
| Male sex                                          | 66/93 (71%)        | 26/34 (76%)       | 0.70    |
| Body surface area (m²)                            | 1.7 [1.5, 1.8]     | 1.6 [1.4, 1.7]    | <0.05   |
| Heart rate (beats/min)                            | 63 [56, 69]        | 66 [62, 79]       | <0.05   |
| Systolic blood pressure (mmHg)                    | 131 [118, 147]     | 107 [96, 120]     | <0.01   |
| Diastolic blood pressure (mmHg)                   | 70 [62, 79]        | 59 [53, 72]       | <0.01   |
| Echocardiographic parameters                      |                    |                   |         |
| Left ventricular end-diastolic diameter (mm)      | 47 [43, 50]        | 45 [40, 49]       | 0.23    |
| Left ventricular end-systolic diameter (mm)       | 27 [25, 32]        | 32 [27, 35]       | <0.01   |
| Interventricular septum thickness (mm)            | 14 [11, 17]        | 14 [12, 17]       | 0.78    |
| Posterior wall thickness (mm)                     | 10 [8, 11]         | 12 [10, 15]       | <0.01   |
| Left ventricular end-diastolic volume index (mL/m²)| 37 [33, 46]        | 43 [38, 52]       | <0.05   |
| Left ventricular end-systolic volume index (mL/m²)| 13 [10, 16]        | 21 [17, 24]       | <0.01   |
| Left ventricular ejection fraction (%)            | 67 [61, 72]        | 53 [46, 59]       | <0.01   |
| E velocity (cm/s)                                 | 59 [51, 75]        | 77 [68, 90]       | <0.01   |
| A velocity (cm/sec)                               | 65 [53, 79]        | 59 [32, 74]       | 0.07    |
| E/A                                              | 0.8 [0.7, 1.2]     | 1.4 [1.0, 2.2]    | <0.01   |
| E/e (cm/s)                                        | 4.0 [3.4, 5.0]     | 3.0 [2.4, 3.7]    | <0.01   |
| Left ventricular longitudinal strain (%)          | 14 [11, 17]        | 9 [7, 12]         | <0.01   |
| Left atrial parameters                            |                    |                   |         |
| Left atrial volume index (mL/m²)                  | 40 [32, 50]        | 47 [38, 65]       | <0.01   |
| Left atrial emptying fraction (%)                 | 48 [41, 57]        | 25 [17, 35]       | <0.01   |
| -Maximum left atrial volume (mL)                  | 56 [47, 71]        | 56 [40, 74]       | 0.84    |
| -Minimum left atrial volume (mL)                  | 27 [22, 42]        | 40 [28, 56]       | <0.01   |
| Left atrial reservoir strain (%)                  | 14 [11, 18]        | 10 [6, 14]        | <0.01   |
| Left atrial pump strain (%)                       | 9 [6, 12]          | 5 [2, 7]          | <0.01   |
| Cardiac magnetic resonance imaging findings       |                    |                   |         |
| Late gadolinium enhancement in the left ventricle | 78/92 (85%)        | 18/18 (100%)      | 0.17    |
| Late gadolinium enhancement in the left atrium    | 1/92 (1%)          | 18/18 (100%)      | <0.01   |

Values were expressed as median [interquartile range] or percentage (number of observations/total number of patients).

100%). By contrast, LGE in the left atrium was more commonly observed in patients with CA patients than in those with HCM (100% vs. 1%).

Figure 2A shows the LA dilatation grade of patients with HCM and CA. Regarding the reproducibility of visually assessing LA dilatation grade, the kappa values between intra- and inter-observer measurements were 0.82 and 0.70, respectively. Of 127 participants, 57 (45%), 42 (33%), and 28 (22%) presented with LA dilatation Grades 1, 2, and 3, respectively. All 57 patients with preserved LA dilatation (Grade 1) had HCM, and 20 of 28 patients (71%) with restricted LA dilatation (Grade 3) presented with CA. Patients with CA had a higher LA dilatation grade than those with HCM (P < 0.01). The relationship between LA dilatation grade and LA emptying fraction is presented in Figure 2B. The mean value and 95% confidence intervals of LA emptying fraction were 50% (47–53), 41% (36–46), and 25% (21–29) in LA dilatation Grades 1, 2, and 3, respectively. The LA emptying fraction significantly decreased with a higher LA dilatation grade. Based on the receiver operating characteristic curve analysis, in CA and HCM patients, LA dilatation grade and LA emptying fraction had a higher accuracy in obtaining a differential diagnosis than LA reservoir strain and LA volume index (Figure 3). The assessment of LA dilatation Grade 3 had a high specificity (91%) but low sensitivity (59%) in differentiating patients with CA from those with HCM. The cutoff value of LA emptying fraction (36%) could discriminate patients with CA from those with HCM, with 82% sensitivity and 80% specificity. Figure 4 shows a representative CA patient with LA dilatation Grade 3 and LGE extending in the LA wall.

During the follow-up period (median: 2.9 years, interquartile range: 0.9–5.1 years), nine patients with HCM and 16 patients with CA experienced cardiac events including death and unexpected hospitalization due to heart failure. In Figure 5, Kaplan–Meier analysis including both groups of HCM and CA, the incidence of cardiac events was higher in patients with restricted LA dilatation than in those with preserved or abnormal LA dilatation (log-rank test, P < 0.01).

**Discussion**

The current study assessed whether the visual assessment of LA dilatation on echocardiography in an apical four-chamber view could immediately identify patients with CA. These patients had a more restricted LA dilatation with LA structural abnormalities than those with HCM. Finally, in both groups, patients with restricted LA dilatation had a higher incidence...
of cardiac event than those with preserved or abnormal LA dilatation.

The characteristic echocardiographic findings of patients with CA included increased wall thickness in both the LV and LA walls and increased wall thickness indicated the deposition of abnormal amyloid fibrils. Amyloid fibrils infiltrate the extracellular matrix of the heart, causing restrictive physiology, and refractory heart failure. In contrast, patients with HCM have an asymmetrical LV wall thickness due to myocardial hypertrophy, and the LA chamber is gradually dilated to compensate for LV diastolic dysfunction in the disease process. Asymmetrical LV hypertrophy is the most common pattern in patients with HCM. However, Martinez-Naharro et al. have shown that asymmetric ventricular remodelling is common in patients with cardiac transthyretin amyloidosis. Thus, assessing LA behaviour is an alternative approach for differentiating patients with CA from those with HCM. The use of an apical four-chamber image in identifying the structure and functional abnormalities in left-sided heart disease is practical. In the current study, we introduced the visual assessment of LA reservoir function by identifying LA dilatation grade in an apical four-chamber view. LA dilatation grade refers to the wall motion score obtained while grading LV systolic dysfunction. This study showed that patients with CA had a higher LA dilatation grade than those with HCM.

Figure 2  Left atrial dilatation grade in hypertrophic cardiomyopathy and cardiac amyloidosis. (A) The number of LA dilatation grade in patients with HCM and CA. Patients with CA had a higher LA dilatation grade than those with HCM. (B) Plots of LA emptying fraction according to LA dilatation grade. Each mean value with 95% confidence intervals. When the LA dilatation grade was higher, the LA emptying fraction was lower. CA, cardiac amyloidosis; HCM, hypertrophic cardiomyopathy; LA, left atrial.

Figure 3  Discriminatory ability of LA structural and functional parameters in patients with hypertrophic cardiomyopathy and cardiac amyloidosis. A receiver operating characteristic curve analysis was performed to assess the discriminatory ability of LA structural and functional parameters. Left atrial dilatation grade and emptying fraction had higher AUC values than LA reservoir strain and volume index. AUC, area under the curve; LA, left atrial.
Hence, LA dilatation grade can be used to screen patients with CA in clinical practice. The LA dilatation grade corresponds to LA reservoir function, which is a major clinical interest because LA reservoir strain has the largest evidence supporting its prognostic utility. According to experimental studies by Baribier et al. and Toma et al., LA reservoir function was determined by LA contraction, LV long-axis shortening through the descent of the base, and LA stiffness. Cardiac amyloidosis is a characteristic of blunted LA contractility, reduced LV longitudinal function, except in the LV apex (apical sparing), and advanced LA stiffness. In our previous clinical study, patients with CA, compared with those with hypertensive heart disease and HCM, had a fairly limited LA reservoir function. The current study supported an indirect evidence regarding the identification of LA stiffness in patients with CA because LGE was extended into the LA wall on CMR.

Quantitative parameters such as LA emptying fraction and reservoir strain can be utilized to support the visual assessment of LA reservoir function. The current study showed that compared with LA reservoir strain and LA volume index, LA emptying fraction had a discriminatory ability in patients with CA and HCM. Sugimoto et al. have reported the normal value of LA emptying fraction based on the EACVI NORRE study results, and the minimal value of LA emptying fraction among healthy individuals was 48.7%. Our study was consistent with their study showing that the 95% lower limit of LA emptying fraction was 47% in patients with LA dilatation Grade 1 (preserved). Furthermore, in differentiating patients with CA from those with HCM, the cutoff value of LA emptying fraction was 36%, and the value was close to the 95% lower limit in patients with LA dilatation Grade 1 (preserved). Moreover, in differentiating patients with CA from those with HCM, the cutoff value of LA emptying fraction was 36%, and the value was close to the 95% lower limit in patients with LA dilatation Grade 1 (preserved). Hence, LA dilatation Grade 3 (restricted) could be an echocardiographic indicator of CA, but not HCM. Moreover, patients with HCM present with LA dysfunction. In this study, about 30% and 9% of patients with HCM had LA dilatation Grades 2 (abnormal) and 3 (restricted), respectively. LA dilatation Grade 3 was associated with adverse cardiac event in all participants. Thus, LA dilatation grade might be helpful in risk stratification in patients with CA and HCM.
This study focused on LA behaviour in patients with CA and HCM. It is of course important to diagnose the two phenotypes by evaluating electrocardiographic voltage criteria and LV apical sparing pattern. The echocardiographic and CMR assessments of LA structure and function could improve a diagnostic accuracy in these patients.

This study had several limitations. First, endocardial biopsy for the diagnosis of HCM was not performed. However, we confirmed the presence of heterogenous myocardial hypertrophy and/or LGE on CMR in patients with HCM. CMR is recommended when the echocardiography finding is inconclusive. Second, the immunohistochemical classification of amyloid was not assessed in some cases. Therefore, the difference in LA function between amyloid light-chain and transthyretin amyloidoses was not identified. Third, although all echocardiographic examinations were performed by professional sonographers, the inter- or intra-rater baseline variability of echocardiographic data including speckle tracking parameters was not assessed. Finally, there was an issue in terms of the learning curve for the visual assessment of LA dilatation grade. In this study, two specialists in the field of cardiology and ultrasound medicine evaluated its reproducibility in clinical settings. The quantitative analysis of LA emptying fraction or reservoir strain was objective for the assessment of LA reservoir function. However, the visual assessment of LA reservoir function could immediately identify patients who require subsequent tests such as biopsy, CMR, and scintigraphy. This may consequently lead to early therapeutic intervention in patients with CA and HCM.

Conclusions

Restricted LA dilatation was an echocardiographic indicator of CA, but not HCM. Moreover, the visual assessment of LA dilatation grade on echocardiography could facilitate the immediate diagnosis of CA and HCM.

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Conflict of interest

None declared.

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