Left Atrial Dysfunction in Cardiac Amyloidosis and Hypertrophic Cardiomyopathy

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Title: Left atrial dysfunction in cardiac amyloidosis and hypertrophic cardiomyopathy

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ABSTRACT
This study aims to explore the changes of left atrial function in patients with cardiac amyloidosis (CA) by speckle tracking echocardiography (STE) and identify the difference of left atrial properties between patients with CA and those with hypertrophic cardiomyopathy (HCM). In this study, 16 patients with CA, 16 patients with HCM, and 16 age-matched healthy controls were enrolled. The time-dependent strain parameters (LASr, LAScd, and LASdt) and strain rate parameters (m-SRs, m-SRe, and m-SRa) of left atrial function were measured by STE in patients with CA, then were compared with that in patients with HCM. Compared with the control group, CA group showed significantly reduced LVEDV/BSA, LVESV/BSA, A, and GLS of the left ventricle, and significantly increased heart rate, IVSd, IVPWd, E, E/A, E/e', LAd and LAV/BSA. The left atrial reserve (LASr and m-SRs), conduit (LAScd and m-SRe) and pump (LASdt and mSRa) functions of CA group were significantly reduced compared with that of controls (P<0.05). The left atrial reserve and pump functions of CA group were significantly reduced compared with that of HCM group. In the CA group, the left atrial reserve function (LASr and m-SRs), conduit function (LAScd and m-SRe) and pump function (LASdt and mSRa) were all related to left ventricular GLS and E/e'. The reserve function, conduit function and pump function of left atrial in the CA group decreased significantly than that in the health control group. When comparing with HCM group, CA group showed reduced reserve function and pump function of left atrial. STE is a qualified technique for the diagnosis of CA.

Key words: cardiac amyloidosis; speckle tracking echocardiography; left atrial function; hypertrophic cardiomyopathy

Introduction
Cardiac amyloidosis (CA) is a rare cardiomyopathy, characterized by the accumulation of the abnormal folded protein amyloid in cardiomyocytes and extracellular matrix [1]. The deposits of fibrillary protein can result in thickening of
different sections of the heart, leading to disrupted cardiac architecture and function\textsuperscript{[2]}. CA is a substantially progressive and underdiagnosed cause of heart failure\textsuperscript{[3]}. If untreated, CA is rapidly fatal, with a median survival ranging from <6 months for light chain amyloidosis\textsuperscript{[4]}. Early detection and therapeutic intervention is critical for the prognosis of patients with CA.

The diagnosis of CA is challenging and mainly relies on an endomyocardial biopsy and a combination of imaging techniques\textsuperscript{[5, 6]}. Vague symptoms in the early disease course and the diversity of ultrasonic manifestations of CA often leads to a delay in diagnosis. Whereas, current evidence identifies higher incidence than previously thought. A recent study revealed a significantly increased prevalence rate (8 to 17 per 100,000 person-years) from 2000 to 2012 in the United States\textsuperscript{[7]}, with improved amyloidosis awareness and advancements of noninvasive technologies. Specifically, as a promising new imaging modality, speckle-tracking echocardiography (STE) shows significant effect in differentiating CA from hypertrophic cardiomyopathy (HCM). It permits offline calculation of deformation parameters, such as strain and strain rate (SR). Given the various influence factors of global strain parameters, however, the potential clinical utility of STE still needs to be investigated.

In addition, previous studies mainly explored the effect of amyloid infiltration on the left ventricle\textsuperscript{[2, 8]}, and few studies focused on the specific changes of left atrial function in CA and the difference with HCM-induced myocardial hypertrophy. In this study, we performed a single-center, case-control imaging study to evaluate left atrial morphology and function in patients with CA, and compared findings with normal controls and patients with primary HCM. This study might provide important reference for the echocardiographic diagnosis of CA.

**Methods**

**Subjects**

From January 2018 to January 2020, 16 patients with CA and 16 patients with HCM admitted to our hospital were enrolled in this study. The diagnosis of CA was in line with the consensus recommendations for multimodality imaging in cardiac
amyloidosis 2019 [9] and was confirmed by pathological biopsy or cardiac MRI. The diagnosis of HCM was in accordance with current ACCF/AHA guideline [10]. In addition, 16 gender- and age-matched healthy subjects were enrolled as a control group in the study. The exclusion criteria were as follows: systemic hypertension, ischemic heart disease or stroke, previous myocardial infarction, dilated or end-stage cardiomyopathy, severe mitral or aortic regurgitation, permanent/persistent atrial fibrillation, aortic stenosis, chronic lung disease, severe renal or liver dysfunction, and obstructive hypertrophic cardiomyopathy.

This was a single-center, case-control imaging study. All subjects underwent conventional 2D echocardiography and 2D-STE in the same examination. Clinical data of all subjects were collected at the time of examination. The study protocol was approved by local ethics review committee, and written informed consent was obtained from all subjects.

Two-dimensional echocardiography

Standard transthoracic echocardiographic examinations were performed using commercial ultrasound systems (GE vividE9 and GE vividE95, GE Medical Systems, Milwaukee, Wisconsin), equipped with a M5S two-dimensional transducer. High-resolution ultrasound images were acquired via parasternal long axis view, parasternal short axis views at mitral valve and apical levels, and apical 4-chamber and 5-chamber views. Echocardiographic measurements of left ventricular (LV) dimensions, volumes and ejection fraction was obtained in accordance with the recommendations of the American Society of Echocardiography [11].

Speckle-tracking echocardiography

The strain measurements were performed off-line using a dedicated software package (EchoPAC Advanced Analysis Technologies; GE Medical Systems). The echocardiographic images were obtained in 3 standard apical views (4-chamber, 3-chamber and 2-chamber) using 3 to 5 cardiac cycle. Images with good quality were acquired using a frame rate of 40-80 fps. AFI technology was employed to measure LV strain, and global longitudinal strain (GLS) was calculated as the average LV longitudinal strain using apical 2-, 3- and 4-chamber views [12]. The collected indexes
included GLS and left atrial reserve function, conduit function, and pump function.
The specific parameters included left atrial peak strain (LASr) and strain rate (m-SRs),
left atrial early peak strain (LAScd) and strain rate (m-SRe), and left atrial late peak
strain (LASct) and strain rate (m-SRa) (Figure 1 and 2).

![Figure 1 Left atrial strain.](image)

![Figure 2 Left atrial strain rate.](image)

**Statistical analysis**

Continuous data are summarized as mean ± standard deviation, and categorical data
as frequency (percentage). Variables were compared using Student’s t test, chi-square
test, Kruskal-Wallis test as appropriate. Statistical analyses were performed using
SPSS version 25.0 (SPSS, Chicago, IL, USA). \( P<0.05 \) was considered statistically
significant.

**Results**

Demographic and baseline clinical characteristics of the subjects are listed in Table 1.
There was no significant difference in age, gender and body surface area among controls, CA and HCM groups ($P > 0.05$). Specifically, we compared the baseline characteristics of two-dimensional ultrasound between CA group and normal controls (Table 2). Compared with normal controls, the LVEDV/BSA, LVESV/BSA, A peak, GLS, LAD and LAV/BSV of CA group were significantly lower ($P < 0.05$). Whereas, heart rate, IVS, IVPW, E peak, E/A, and E/e' of CA group were significantly higher than those of normal controls ($P < 0.05$).

| Variable                  | Control (n=16) | CA (n=16) | HCM (n=16) |
|---------------------------|----------------|-----------|------------|
| Age (years)               | 57.5±7.8       | 57.5±7.5  | 58.5±8.3   |
| Gender (male/female)      | 6/10           | 10/6      | 7/9        |
| Body surface (m²)         | 1.74±0.15      | 1.71±0.15 | 1.77±0.14  |

CA: cardiac amyloidosis group; HCM: hypertrophic cardiomyopathy group.

The left atrial function parameters measured by speckle-tracking echocardiography are listed in Table 3. The left atrial reserve function (LASr, m-SRs), conduit function (LAScd, m-SRe), and pump function (LASct, m-SRa) of both HCM and CA groups were significantly lower than those of normal controls ($P < 0.05$). However, compared with HCM group, the left atrial reserve function and pump function in CA Group were significantly reduced (Table 3 and Figure 3).
Table 3 Comparison of left atrial function among controls, CA, and HCM groups.

| Parameter      | Controls     | CA           | HCM          |
|----------------|--------------|--------------|--------------|
| **Reserve function** |              |              |              |
| LASr (%)       | 32.74±5.77   | 13.96±5.93\textsuperscript{ab} | 20.00±6.57\textsuperscript{c} |
| m-SRs (S\textsuperscript{-1}) | 1.99±0.21   | 0.85±0.28\textsuperscript{ab} | 1.18±0.16\textsuperscript{c} |
| **Conduit function** |              |              |              |
| LAScd (%)      | 17.90±3.59   | 7.12±3.07\textsuperscript{a}  | 9.68±4.34\textsuperscript{c} |
| m-SRe (S\textsuperscript{-1}) | 1.54±0.27   | 0.67±0.39\textsuperscript{a}  | 0.78±0.31\textsuperscript{c} |
| **Pump function** |              |              |              |
| LASct (%)      | 15.30±2.79   | 7.91±4.02\textsuperscript{ab} | 11.19±3.56\textsuperscript{c} |
| m-SRa (S\textsuperscript{-1}) | 2.11±0.29   | 0.94±0.46\textsuperscript{ab} | 1.56±0.32\textsuperscript{c} |

a: $P<0.05$ vs. controls; b: $P<0.05$ vs. HCM; c: $P<0.05$ vs. controls.
Figure 3 Comparison of left atrial reserve function and pump function among control, CA, and HCM groups. A: Left atrial pump function (m-SRa); B: Left atrial reserve function (m-SRs). CA: cardiac amyloidosis group; HCM: hypertrophic cardiomyopathy group.

Finally, we compared the correlation between left atrial function and left ventricular strain in the CA group (Table 4). In the CA group, left atrial reserve function (LASr, m-SRs), conduit function (LAScd, m-SRe) and pump function (LASct, m-SRa) were significantly correlated with left ventricular GLS. m-SRs, LASct, and m-SRa were correlated with E peak and e'. LASr, LASct, and m-SRa were correlated with A peak. LASr, m-SRs, m-SRe, LASct, and m-SRa were correlated with E/ e'.

Table 4 Correlation between left atrial function parameters and left ventricular function parameters in the CA group.

| Parameter   | Reserve function | Conduit function | pump function |
|-------------|------------------|------------------|--------------|
|             | LASr (%)         | LAScd (%)        | LASct (%)    |
|             | m-SRs (S⁻¹)      | m-SRe (S⁻¹)      | m-SRa (S⁻¹)  |
GLS: global longitudinal strain; E: the peak of early diastolic blood flow; A: the peak of late diastolic blood flow; e’: lateral mitral early relaxation velocity; E/e’: mitral inflow to mitral relaxation velocity ratio.

Discussion

This work confirms potential value of STE in evaluating left atrial morphology and function in patients with CA, which is significant for the early detection and differential diagnosis.

For patients with CA, myocardial longitudinal systolic dysfunction may precede heart failure. This characteristic of CA can be easily detected by strain imaging. Previous studies have focused on this characteristic of CA through various strain imaging techniques, especially in left ventricular strain parameters \[13, 14\]. STE can overcome the angle dependence of conventional strain Doppler imaging, and accurately measure the strain and strain rate of each segment and the whole heart \[15, 16\]. Under STE examination, the left ventricular GLS in patients with CA was significantly reduced, and the longitudinal strain in the basal segment was significantly lower than that in the apical segment, which could be used to differentiate with HCM.
In various causes of left ventricular diastolic dysfunction, the pump function of left atrium plays an important role, and the change of left atrial function can reflect that of left ventricular diastolic function to a certain extent. Left atrium participate in left ventricular filling by three ways, including reserve, conduit, and pump functions. CA and HCM are accompanied by the enlargement of left atrial or both atrial, may due to the decreased left ventricular diastolic function and the increased left atrial afterload [17].

Moreover, hypertension-caused left ventricular wall hypertrophy can affect the left ventricular diastolic function, and then cause the left atrial function damage. In CA, extracellular amyloid protein deposition in heart leads to mechanical damage of ventricular diastolic filling, and shows progressive diastolic dysfunction. Diastolic pressure filling disorders usually result in increased left ventricular, atrial, and pulmonary vascular pressure [17]. The left atrial function is particularly affected by the severity of left ventricular diastolic function, especially in the case of chronic increase of left ventricular filling pressure, and the left atrial function can reflect the change of left ventricular diastolic function to a great extent [18]. In normal condition, left ventricular diastolic filling mainly occurs in the early diastolic period. In patients with CA, the ventricular compliance decreased. When the diastolic function decreased, the left ventricular early suction function decreased, and the late diastolic filling mediated by the atrial assist pump function increased. Therefore, left atrial function plays an important role in the diagnosis of CA. It is showed that left atrial enlargement and dysfunction are also independent predictors of poor prognosis of CA [19].

STE is an objective quantitative evaluation of the overall and local myocardial function technology. Its strain and strain rate are obtained by automatically measuring the distance change between any "spots" of interest selected frame by frame on the basis of two-dimensional echocardiography. It is a direct method to measure intrinsic myocardial deformation, which is relatively independent of load conditions and geometric assumptions of atrium, without angle dependence, and has high feasibility and repeatability [20]. STE can well detect the longitudinal myocardial strain and strain rate of left atrium, and effectively evaluate the local and overall myocardial function
of left atrium\textsuperscript{[21, 22]}. Previous studies have indicated that the left atrial function of patients with CA is damaged \textsuperscript{[17]}, and this study confirmed this viewpoint. In our study, compared with normal controls, left atrial conduit function parameters (mSRe and LAScd) in the CA group were significantly reduced, which may be due to the deposition of amyloid, resulting in the increase of left ventricular stiffness, the decrease of left ventricular compliance, the decrease of left ventricular passive diastolic function, and the increase of left ventricular diastolic filling pressure. In the early diastolic period, the left ventricle's suction to the left atrium was weakened, resulting in the decrease of LA's blood flow into the left ventricle through the mitral valve. The left atrial pump function is affected by the factors, such as left atrial pre-systolic volume and left ventricular end-diastolic pressure. According to the Frank-Starring mechanism of myocardium, the left atrial pre-systolic volume increases due to the increase of left ventricular filling pressure. In order to meet the needs of the body, the left atrial can achieve further filling of the left ventricle by increasing the active systolic force \textsuperscript{[23]}. However, the results of this study showed that mSRa and LASct of left atrium in the CA group were decreased, indicating that the left atrial pump function in CA patients was damaged. This may be due to the continuous increase of left ventricular filling pressure, which exceeded Frank-Starling's compensatory mechanism, resulting in myocardial remodeling, and the decrease of the left atrial pump function. It may also be due to the direct deposition of amyloid in the atrial wall, resulting in the decrease of the intrinsic atrial contraction function. The results of this study also showed that mSRs and LASr of CA group were significantly lower than those of normal control group, which indicated that the left atrial reserve function of CA patients decreased. This indicates that the decrease of left atrial tension during systolic period, which is related to the increase of left ventricular end-diastolic pressure, the decrease of left ventricular systolic function, and the decrease of left atrial compliance \textsuperscript{[22, 24]}. When the left ventricular filling pressure increases, the left atrial pressure increases correspondingly, resulting in the decrease of pulmonary venous return in systolic period and the decrease of left atrial reserve function. At the same time, the infiltration
of amyloid on the left ventricular wall of CA patients results in the decrease of left ventricular longitudinal contraction function, which also affects the expansion of left atrial to a certain extent. Recent studies have also suggested that the decrease of left atrial strain measured by STE is related to the histopathological changes of left atrial myocardium, that is, the decrease of left atrial strain and strain rate parameters in left ventricular systole can be used as non-invasive markers of left atrial fibrosis [25, 26]. Kwongry et al. [27] found a relatively high incidence of late gadolinium enhancement on the left atrial wall in CA patients. Therefore, it is reasonable to consider that the infiltration of amyloid directly leads to the decrease of compliance of left atrial walls, which is also a factor of the decrease of left atrial reserve function.

Among the causes of left ventricular hypertrophy, HCM is most likely to be confused with CA. In clinical practice, early identification of HCM and CA is of great significance. HCM is a group of autosomal dominant inherited diseases. The main pathological changes are local cardiac hypertrophy (mainly the non-uniform thickening of ventricular septal, left ventricular diastolic dysfunction and left atrial enlargement), the disorder of myocardial fiber arrangement and myocardial fibrosis. Földeák et al. [28] compared left atrial volumetric and functional characteristics of CA with HCM by STE, and found that the left atrium had obvious damage of reserve function, conduit function and pump function, and the active contraction function of CA group showed more obvious damage compared with HCM group. In our study, the left atrial reserve and pump functions of CA group was significantly reduced compared with HCM group. Left atrial reserve function is a response of left ventricular diastolic function. The damage indicates that left ventricular stiffness is increased, suggesting that left ventricular filling pressure is transmitted to the upstream of pulmonary vein system. This may be related to the deposition of amyloid in the CA group, and leads to the more extensive and serious involvement of left ventricular function [28]. At the same time, left atrial reserve function is also related to left atrial compliance, and the direct infiltration of amyloid in the left atrial wall may aggravate the decrease of left atrial compliance in patients with CA. For left atrial pump function, the deposition of amyloid on the wall of atrium can directly affect the
intrinsic contractile function of atrium, resulting in more significant reduction in CA. Thus, our results showed that the direct deposition of amyloid played an indispensable role in the atrial dysfunction of patients with CA. Modesto et al. \cite{17} compared the left atrial function of CA patients with left ventricular enlargement and diastolic function decline, but without amyloid infiltration in the control group, and found that the left atrial systolic function was significantly reduced in the CA group. Kwong et al. \cite{27} reported that CMR strongly suggested the characteristics of left atrial infiltration, and left atrial infiltration was closely related to the impairment of left atrial emptying function. In addition, the difference of left atrium between CA and HCM provides a new perspective for us to distinguish CA from HCM.

In this study, the correlation between left atrial function and left ventricular related function were also examined. Our results indicated that left atrial storage function, catheter function, and accessory pump function were related to the indexes of left ventricular systolic function (GLS) and left ventricular diastolic function (E/e', E, and A). That is to say, the worse the systolic and diastolic function of the left ventricle is, the more serious the left atrial dysfunction will be. The association shows that left atrial function is affected by the increase of left ventricular filling pressure.

**Limitations**

The major limitation of this study is that this is a single center study with small sample size, which may limit the persuasiveness of the experimental results. Meanwhile, it is unable to propose a clear cut-off value of left atrial index between CA and HCM groups due to small sample size. In addition, the strain parameters measured by STE are limited by the differences of various machine manufacturers and analysis software, making the clinical utilization still difficult.

**Conclusions**

STE technique is qualified to measure the left atrial function of patients with CA. The left atrial reserve, conduit and pump functions were impaired in both CA and HCM groups. Relative to patients with HCM, patients with CA show more significant damage of left atrial reserve and pump functions. Early detection of CA by STE is of
great importance for the evaluation and management of patients with CA.

Abbreviations

Cardiac Amyloidosis (CA)
Hypertrophic Cardiomyopathy (HCM)
Speckle Tracking Echocardiography (STE)
Left Atrium (LA)
Left Ventricle (LV)
Left Venticular Ejection Fraction (LVEF)
Left Venticular End-diastolic Volume (LVEDV)
Left Venticular End-systolic Volume (LVESV)
Left Venticular End-diastolic diameter (LVEDd)
Interventricular Septum (IVS)
Left Venticular Posterior Wall (IVPW)
Global Longitudinal Strain (GLS)
Body Surface Area (BSA)
Left Atrial Volume (LAV)
Left Atrial Diameter (LAD)

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Table 2: General baseline characteristics of two-dimensional ultrasound between patients with CA and normal controls

| Variable                   | CA (n=16)       | Controls (n=16) | P   |
|----------------------------|-----------------|-----------------|-----|
| Heart rate (bpm)           | 76.75±12.74*    | 73.81±8.59      | 0.045 |
| LVEDd (cm)                 | 46.31±6.90      | 46.00±2.50      | 0.867 |
| IVS (cm)                   | 13.5±1.03*      | 8.87±0.88       | <0.001 |
| LVPW (cm)                  | 13.69±2.63*     | 9.01±0.72       | <0.001 |
| LVEDV/BSA (mL/m²)          | 42.35±10.20*    | 56.67±6.19      | <0.001 |
| LVESV/BSA (mL/m²)          | 17.84±5.59*     | 21.88±2.97      | 0.016 |
| LVEF (%)                   | 58.19±6.26      | 61.37±3.27      | 0.085 |
| E (m/s)                    | 0.87±0.23*      | 0.75±0.22       | 0.157 |
| A (m/s)                    | 0.57±0.25*      | 0.81±0.20       | 0.005 |
| E/A                        | 1.90±1.13*      | 0.95±0.22       | 0.040 |
| e’ (cm/s)                  | 3.66±1.16*      | 9.49±1.61       | <0.001 |
| s’ (cm/s)                  | 11.79±3.30      | 11.86±0.94      | 0.937 |
| E/e’                       | 26.63±11.70*    | 8.21±2.45       | <0.001 |
| GLS (%)                    | 10.76±3.04*     | 18.87±1.36      | <0.001 |
| LAd (cm)                   | 31.99±1.18*     | 39.62±4.40      | <0.001 |
| LAV/BSV (mL/m²)            | 24.66±3.73*     | 36.49±8.84      | <0.001 |

LVEDd: left ventricular end-diastolic dimension; IVS: interventricular septum; PW: posterior wall; LVEDV: left ventricular end-diastolic volume; LVESV: left ventricular end-systolic volume; GLS: global longitudinal strain; E/A: early to late mitral inflow velocity ratio; e’: lateral mitral early relaxation velocity; s’: lateral mitral systolic velocity; E/e’: mitral inflow to mitral relaxation velocity ratio; CA: cardiac
amyloidosis; LAd: left atrial dimension; LAV: left atrial volume.
Declarations

Ethics approval and consent to participate
The study was approved by the Ethics Committee of The Second Hospital Affiliated Hebei Medical University. Written informed consent was obtained from each patient.

Availability of data and materials
As described in the methods section.

Competing interests
The authors declare that they have no competing interests.

Funding
Not applicable.

Contributions
SC conceived and designed the experiments; YW, HB give some advices on the design; SC recruited subjects, collected clinical data, analyze the data and wrote the manuscript; YW help to translate and polish the article. All authors read and approved the final manuscript.

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Figures

Figure 1

Left atrial strain.
Figure 2

Left atrial strain rate.
Comparison of left atrial reserve function and pump function among control, CA, and HCM groups. A: Left atrial pump function (m-SRa); B: Left atrial reserve function (m-SRs). CA: cardiac amyloidosis group; HCM: hypertrophic cardiomyopathy group.

Supplementary Files
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- Table1.docx
- Table2.docx
- Table3.docx
- Table4.docx