Time-dependent change of relative apical longitudinal strain index in patients with wild-type transthyretin amyloid cardiomyopathy

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ABSTRACT

Aim: This study was conducted to investigate the meaning of left ventricular (LV) apical sparing in patients with wild-type transthyretin amyloid cardiomyopathy (ATTRwt-CM). Methods and results: 165 patients who were diagnosed with ATTRwt-CM at Kumamoto University Hospital from January 2002 to December 2020 and had sufficient data for two-dimensional speckle tracking echocardiography were enrolled. Of these, 86 patients (52 %) had LV apical sparing (relative apical longitudinal strain index (RapLSI) > 1.0). Multivariable logistic regression analysis revealed the following variables were significantly associated with LV apical sparing: interventricular septal thickness in diastole (odds ratio (OR), 1.19; 95 % confidence interval (CI), 1.01–1.41; p < 0.05); E/e′ ratio (OR, 1.06; 95 % CI, 1.00–1.11; p < 0.05); and heart-to-contralateral ratio by 99mTc-labeled pyrophosphate scintigraphy (OR, 3.40; 95 % CI, 1.07–10.83; p < 0.05). Next, we compared RapLSI at the time of diagnosis with that during the follow-up period (396 days (346–458) after diagnosis) in 92 patients. RapLSI increased significantly during the follow-up period compared with RapLSI at diagnosis in the non-LV apical sparing group (0.89 ± 0.32 vs 0.74 ± 0.18, p < 0.01) but not in the LV apical sparing group (1.33 ± 0.53 vs 1.39 ± 0.45, p = 0.46). A total of 12 patients (29 %) in the non-LV apical sparing group developed LV apical sparing and 11 patients (22 %) in LV apical sparing group diminished LV apical sparing during the follow-up period. Conclusion: Approximately half of ATTRwt-CM patients did not have LV apical sparing at diagnosis. Because RapLSI in ATTRwt-CM significantly changed over time, repeated two-dimensional speckle tracking analysis is important for suspected ATTRwt-CM patients.

1. Introduction

Amyloid cardiomyopathy is a clinical disorder in which the interstitial deposition of amyloid fibrils causes morphological and functional abnormalities of the heart [1]. Amyloid cardiomyopathy is divided into three main types: amyloid light-chain amyloidosis; mutant transthyretin (TTR) amyloidosis (ATTR); and wild-type ATTR (ATTRwt) [1]. Wild-type transthyretin amyloid cardiomyopathy (ATTRwt-CM) is becoming increasingly recognized because of advancements in diagnostic imaging [2] and the potential benefits of emerging therapies [3].

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Left ventricular (LV) thickness, left atrial (LA) enlargement, and reduced systolic and diastolic LV function are widely known to be typical findings of amyloid cardiomyopathy [4,5]. However, these echocardiographic findings are also present in other cardiac diseases.

LV apical sparing, which is described as a high relative apical longitudinal strain (LS) index (RapLSI), is impaired deformation in the basal and middle segments of the LV compared with the apical segments [6]. The LV apical sparing pattern is an accurate and reproducible method of differentiating amyloid cardiomyopathy from other causes of LV hypertrophy [6].

Although we previously reported the usefulness of LV apical sparing to diagnose ATTR-CM, some ATTR-CM patients present without LV apical sparing [7]. To our knowledge, however, no previous reports have compared the clinical characteristics between ATTRwt-CM patients with or without LV apical sparing. In addition, little is known about the time-dependent change in RapLSI in patients with ATTRwt-CM. Therefore, this study was conducted to clarify the meaning of, and time-dependent change in, LV apical sparing in patients with ATTRwt-CM.

2. Materials and methods

2.1. Study population

Supplementary Fig. 1 shows the patient population included in this study. We diagnosed 174 patients as ATTRwt-CM at Kumamoto University Hospital from January 2002 to December 2020. Of these patients, we excluded nine patients because they had insufficient data for evaluation by two-dimensional speckle tracking echocardiography. The remaining 165 patients were enrolled in this study. Baseline clinical characteristics, laboratory findings, electrocardiographic findings, echocardiographic findings, heart-to-contralateral ratio by 99mTc-labeled pyrophosphate (99mTc-PYP) scintigraphy, and treatment at diagnosis were obtained while the patients were in a clinically stable, non-congested condition. We divided these 165 patients into two groups based on whether they showed LV apical sparing and then compared the two groups. We evaluated the time-dependent change in LS in 92 patients (LV apical sparing group (n = 51), non-LV apical sparing group (n = 41)) who had sufficient data for two-dimensional speckle tracking echocardiography during the follow-up period. This study was conducted in accordance with the principles outlined in the Declaration of Helsinki. It was approved by the Institutional Review Board and ethics committees of Kumamoto University (No. 15888). The requirement for informed consent was waived because of the low-risk nature of this retrospective study and the inability to directly obtain consent from all patients. Instead, this study protocol was extensively announced at Kumamoto University Hospital and on our website (https://www2.kuh.kumamoto-u.ac.jp/tyuokensabu/index.html) and patients were provided with the opportunity to withdraw from the study.

2.2. Diagnosis of ATTRwt-CM

The diagnosis of amyloid deposition was based on Congo red staining and apple-green birefringence visualized with cross-polarized light microscopy. To confirm the presence of TTR amyloid deposition, immunohistochemical staining was performed using antibodies that react with TTR. ATTRwt was diagnosed when no mutation was identified in the TTR gene by genetic testing (n = 121, 73 %). If genetic testing was not performed, we diagnosed ATTRwt when the patient had no family history of amyloidosis (n = 44, 27 %).

In this study, ATTR-CM was diagnosed by: (1) the presence of TTR deposition in the myocardium (n = 86, 52 %); (2) the presence of TTR deposition in extracardiac tissue (gastrointestinal tract or skin) with a positive finding on 99mTc-PYP scintigraphy and exclusion of amyloid light-chain amyloidosis (n = 19, 12 %); or (3) a positive finding on 99mTc-PYP scintigraphy without confirmation of pathological TTR deposition and exclusion of amyloid light-chain amyloidosis (n = 60, 36 %).

2.3. Conventional echocardiographic parameters

Conventional echocardiography was performed using the Vivid E95 or 7 (GE Vingmed, Horten, Norway), Apio 500 (Toshiba, Tokyo, Japan), and EPIQ 7G (Philips, Bothell, WA, USA) machines. Conventional echocardiography was performed according to the recommendations of the American Society of Echocardiography (ASE) and the European Association of Cardiovascular Imaging [8,9]. LV wall thickness was acquired in the parasternal long-axis view. LV ejection fraction and LA volume index (LAVI) were calculated using a modified Simpson’s method. Peak early diastolic velocity of LV inflow (E velocity), late atrial diastolic velocity of LV inflow (A velocity), and the peak early diastolic velocity on the septal corner of the mitral annulus (e’) were measured in the apical four-chamber view. Moderate or severe valvular disease according to the ASE guidelines [10] was defined as valvular diseases in this study. To minimize bias, the echocardiography reviewers were blinded to the patients’ clinical history and data.

2.4. Two-dimensional speckle tracking echocardiography

Two-dimensional speckle tracking echocardiography was performed by one operator who was blinded to the clinical data and who was different from the operator who performed the conventional echocardiography. Two-dimensional speckle tracking echocardiography was performed using Cardiac Performance Analysis (2D-CPA): a manual vendor-independent measurement package (TomTec-Arena, TomTec Imaging Systems, Unterscheiweisheim, Germany). LS was assessed using the apical two-, three-, and four-chamber views. Three sampling points were manually identified at the septal and lateral mitral annulus and at the apical endocardium, and the endocardial borders were traced semi-automatically at the end of systole. After tracing the LV endocardial border, the dedicated software automatically tracked the myocardium throughout the cardiac cycle. All tracking was reviewed and manually corrected if needed. The regional LS was determined in 16 segments of the LV in accordance with the ASE guidelines [8]. Strain is described in absolute values. The LV global LS was calculated as the average LS of these 16 segments. RapLSI was calculated as (average apical LS / (average basal LS + average mid LS)). In accordance with previous reports, we defined LV apical sparing as RapLSI > 1.0 [6]. The intraclass correlation coefficient (ICC) for intra-observer reproducibility of LS measurement for the 20 reassessed patients was 0.89 (95 % CI, 0.72–0.96). The ICC for inter-observer reproducibility of LS measurement for the 20 reassessed patients was 0.81 (95 % CI, 0.51–0.93).

2.5. 99mTc-PYP scintigraphy protocol

99mTc-PYP scintigraphy was performed using a dual-head single-photon emission computed tomography (SPECT) / CT system (Symbia T6; Siemens Healthcare, Erlangen, Germany) with low-energy high-resolution collimators (GE Healthcare, Waukesha, WI, USA). We intravenously administered 370–740 MBq of 99mTc-PYP (Fujifilm RI Pharma, Tokyo, Japan). Anterior and lateral thoracic planar views were obtained over 3 h after the administration of the radiotracer. The acquisition parameters used for planar imaging were 256 × 256 matrix with 1.23 zoom factor. With the same system, thoracic SPECT images were acquired for each patient immediately after the planar scan. We evaluated the cardiac uptake of 99mTc-PYP using a semiquantitative visual scoring method in relation to bone (rib) (0 = no myocardial uptake; 1 = myocardial uptake less than rib uptake; 2 = myocardial uptake equal to rib uptake; and 3 = myocardial uptake greater than rib uptake). Quantitative analysis of cardiac retention was assessed by heart-to-contralateral ratio (H/CL ratio), which was calculated as the total counts in a region of interest over the heart divided by the background count of a copied and mirrored region of interest over the contralateral
2.6. Statistical analysis

Normally distributed variables are expressed as mean ± standard deviation. The hs-cTnT and BNP concentrations were not normally distributed, so natural logarithm (Ln)TnT and LnBNP were used for analysis. Categorical values are expressed as number (percentage). The clinical characteristics of the patients in each group were compared by Student’s t-test or chi-square test. Univariate logistic regression analysis was performed to identify the significant variables related to LV apical sparing. Multivariable logistic regression analysis was performed to identify independent variables. Variables with a p-value of < 0.05 in the univariate logistic regression analysis model were incorporated into the multivariable logistic regression analysis. The time-dependent change in LS was analyzed by paired t-test. All analyses were conducted with SPSS for Windows software, version 24.0 (IBM Corp., Armonk, NY, USA). Statistical significance was defined as p < 0.05.

3. Results

3.1. Distribution of RapLSI in our patient population

Supplementary Fig. 2 shows the distribution of RapLSI in the patients in this study. A total of 86 patients (52%) were parsed into the LV apical sparing group and 79 patients (48%) were included in the non-LV apical sparing group.

3.2. Comparison of clinical characteristics in ATTRwt-CM patients with or without LV apical sparing

There were no significant differences in the baseline clinical characteristics of age, sex and prior heart failure hospitalization between the two study groups (Table 1). However, in the past medical history, the rate of prior myocardial infarction was significantly lower in the LV apical sparing group than in the non-LV apical sparing group (p < 0.05). In the laboratory findings, LnTnT and LnBNP levels were significantly higher in the LV apical sparing group than in the non-LV apical sparing group (LnTnT, p < 0.05, LnBNP, p < 0.05). In the electrocardiographic findings, interventricular septal thickness in diastole (IVSTd), left ventricular posterior wall thickness in diastole (LVPWTd), E/A ratio and E/e’ ratio were significantly higher in the LV apical sparing group than in the non-LV apical sparing group (IVSTd, p < 0.01, LVPWTd, p < 0.01, E/A ratio, p < 0.01, E/e’ ratio, p < 0.01). Although there was no significant difference in the LV-global LS (GLS) between the two groups, apical LS was significantly higher and mid and basal LS were significantly lower in the LV apical sparing group than in the non-LV apical sparing group (apical LS, p < 0.01, mid LS, p < 0.01 and basal LS, p < 0.01). The H/CL ratio by 99mTc-PYP scintigraphy was significantly higher in the LV apical sparing group than in the non-LV apical sparing group (p < 0.05). There were no significant differences in treatments between the two groups.

3.3. Logistic regression analysis for LV apical sparing in patients with ATTRwt-CM

In the univariate analysis, LnTnT, LnBNP, IVSTd, LVPWTd, E/e’ ratio, and H/CL ratio were identified as significant predictors of LV apical sparing (Table 2). Considering the internal correlation of IVSTd and LVPWTd (r = 0.83, p < 0.01), we excluded LVPWTd from the multivariable logistic regression analysis. Multivariable logistic regression analysis showed that the following variables were significantly associated with LV apical sparing: IVSTd (p < 0.05); E/e’ ratio (p < 0.05); and H/CL ratio by 99mTc-PYP scintigraphy (p < 0.05).

### Table 1

| Clinical characteristics of ATTRwt-CM patients between with or without left ventricular apical sparing in this study. |
|-------------------------------------------------------------|
| **Baseline clinical characteristics** |
| Age at diagnosis, years | 78.3 ± 6.2 | 77.9 ± 7.1 | 0.65 |
| Female sex, n (%) | 10 (12) | 11 (14) | 0.66 |
| Body mass index, kg/m² | 22.4 ± 2.7 | 23.3 ± 5.2 | 0.18 |
| **Past medical history** |
| Hypertension, n (%) | 43 (50) | 42 (53) | 0.69 |
| Diabetes mellitus, n (%) | 18 (21) | 20 (25) | 0.50 |
| Dyslipidemia, n (%) | 23 (27) | 27 (34) | 0.30 |
| Prior myocardial infarction, n (%) | 0 (0) | 4 (5) | <0.05 |
| **Electrocardiographic findings** |
| Atrial fibrillation, n (%) | 45 (52) | 36 (46) | 0.39 |
| Carpal tunnel syndrome, n (%) | 32 (37) | 31 (39) | 0.79 |
| Prior heart failure hospitalization, n (%) | 37 (44) | 30 (38) | 0.51 |
| **Laboratory findings** |
| LnTnT | −2.79 ± 0.70 | −3.03 ± 0.62 | <0.05 |
| LnBNP | 5.65 ± 0.67 | 5.37 ± 0.90 | <0.05 |
| eGFR, mL/min/1.73 m² | 50.9 ± 15.5 | 52.5 ± 15.0 | 0.51 |
| Hb, g/dL | 13.3 ± 1.3 | 13.2 ± 2.0 | 0.91 |
| **Echocardiographic findings** |
| E/e’ ratio | 2.12 ± 1.49 (n = 59) | 1.41 ± 0.88 (n = 40) | <0.01 |
| E/e ratio | 22.6 ± 8.3 | 19.2 ± 6.3 | <0.01 |
| Aortic stenosis, n (%) | 8 (9) | 9 (11) | 0.66 |
| Mitral regurgitation, n (%) | 15 (17) | 14 (18) | 0.96 |
| Tricuspid regurgitation, n (%) | 14 (16) | 16 (20) | 0.51 |
| LV, % | 10.2 ± 3.0 | 10.1 ± 3.2 | 0.75 |
| Aortic reflux, % | 16.7 ± 4.4 | 12.5 ± 4.5 | <0.01 |
| Mid LS, % | 8.1 ± 3.0 | 9.6 ± 3.1 | <0.01 |
| Basal LS, % | 4.8 ± 2.2 | 7.3 ± 2.8 | <0.01 |

### Abbreviations:
- ATTRt-CM: wild-type transthyretin amyloid cardiomyopathy
- LV: left ventricular
- NYHA: New York Heart Association functional classification
- ln: natural logarithm
- Tc: technetium
- BNP: B-type natriuretic peptide
- eGFR: estimated glomerular filtration rate
- hs-cTnT: high-sensitivity cardiac troponin T
- LAVI: left atrial volume index
- ACEI or ARB: angiotensin II receptor blocker or angiotensin II receptor antagonist
- MRA: mineralocorticoid receptor antagonist
- **99m**Tc-labeled pyrophosphate scintigraphy

3.4. Time-dependent change in LS in ATTRwt-CM patients

Next, we evaluated the change in LS over time for 92 patients who had sufficient data for two-dimensional speckle tracking.
decreased during follow-up compared with at diagnosis (LV-GLS; 8.98 ± 3.02 vs 10.21 ± 3.06, p < 0.01, basal LS; 5.09 ± 3.00 vs 5.91 ± 2.79, p < 0.01, mid LS; 8.05 ± 3.23 vs 8.91 ± 3.12, p < 0.01, apical LS; 13.01 ± 4.07 vs 14.91 ± 4.95, p < 0.01, Fig. 1A and 1B). However, RapLSl did not significantly change between diagnosis and follow-up (1.14 ± 0.50 vs 1.10 ± 0.48, p = 0.39, Fig. 1C).

3.5. Time-dependent change in LS between the LV apical sparing group and the non-LV apical sparing group

When we divided patients into two groups: the LV apical sparing group (n = 51) and the non-LV apical sparing group (n = 41) according to their RapLSI at diagnosis, RapLSI was significantly higher during follow-up compared with RapLSI at diagnosis in the non-LV apical sparing group (0.89 ± 0.32 vs 0.74 ± 0.18, p < 0.01) but not in the LV apical sparing group (1.33 ± 0.53 vs 1.39 ± 0.45, p = 0.46) (Fig. 2).

Interestingly, 12 patients (29 %) in the non-LV apical sparing group showed LV apical sparing during follow-up and 11 patients (22 %) in the LV apical sparing group had diminished LV apical sparing during follow-up. Therefore, during follow-up, 51 patients (57 %) had LV apical sparing and 40 patients (43 %) did not have LV apical sparing (Supplementary Fig. 3).

In the LV apical sparing group, the apical LS and mid LS decreased significantly during follow-up compared with values at diagnosis (apical LS; 13.64 ± 3.86 vs 16.90 ± 4.36, p < 0.01, mid LS; 7.33 ± 3.08 vs 8.31 ± 2.95, p < 0.01), however, basal LS during follow-up was not significantly different from that at diagnosis (4.31 ± 2.37 vs 4.82 ± 2.24, p = 0.46, Supplementary Fig. 4A). In the non-LV apical sparing group, basal LS was significantly lower during follow-up compared with at diagnosis (6.07 ± 3.43 vs 7.27 ± 2.83, p < 0.01). However, there were no significant differences in apical LS and mid LS between follow-up and diagnosis in this group (apical LS; 12.24 ± 4.24 vs 12.42 ± 4.53, p = 0.79, mid LS; 8.95 ± 3.23 vs 9.65 ± 3.19, p = 0.13) (Supplementary Fig. 4B).

4. Discussion

The new findings of this study are as follows. First, approximately 50 % of ATTRwt-CM patients had LV apical sparing. Second, LV apical sparing was significantly associated with LV thickness, LV diastolic dysfunction, and high H/CL ratio. Third, LS decreased in a time-dependent manner and the pattern of this LS reduction was different between the LV apical sparing group and the non-LV apical sparing group.

4.1. Rate of LV apical sparing

Several studies have reported that LV apical sparing has high sensitivity and specificity to diagnose amyloid cardiomyopathy [6,13]. Therefore, many patients with amyloid cardiomyopathy are thought to have LV apical sparing. In this study, however, only 52 % of ATTRwt-CM patients had LV apical sparing. We speculate that the low rate of LV apical sparing might depend on the ATTRwt-CM diagnostic methods used in our hospital.

To confirm a diagnosis of amyloid cardiomyopathy, detection of amyloid deposition is necessary [1]. Therefore, endomyocardial and other tissue biopsies are needed to diagnose amyloid cardiomyopathy [6,13]. However, biopsies, particularly endomyocardial tissue biopsies, are invasive. Therefore, diagnosis of ATTRwt-CM is particularly difficult in older patients [14]. Moreover, delayed diagnosis can be a serious problem in ATTRwt-CM patients. Recently, the use of bone scintigraphy for ATTR-CM diagnosis has been proposed [2], leading to establishment of a non-biopsy diagnostic method for ATTR-CM. This method uses a semi-quantitative visual scoring of positive cardiac uptake of tracer without identifying a monoclonal protein by serum and urine testing. In this study, 36 % of enrolled patients were diagnosed with ATTR-CM only by ⁹⁹mTc-PYP scintigraphy. Use of ⁹⁹mTc-PYP scintigraphy might avoid delayed diagnosis of ATTRwt-CM and therefore, there may be more
early stage ATTRwt-CM patients in this study compared with previous reports.

4.2. Implications of LV apical sparing

Our study showed that LV apical sparing was significantly associated with LV thickness, LV diastolic dysfunction, and high H/CL ratio. Several studies have showed that certain echocardiographic findings are useful for assessing prognosis in patients with amyloid cardiomyopathy [5,15]. Cueto-Garcia et al. demonstrated that increased LV wall thickness was a significant echocardiographic predictor of poor outcome in amyloid cardiomyopathy patients [5]. Similarly, Klein et al. showed that doppler-derived LV diastolic dysfunction was an important predictor of survival in amyloid cardiomyopathy patients [15]. Therefore, LV thickness and LV diastolic dysfunction are thought to be important markers for ATTR-CM progression. The H/CL ratio is a quantitative evaluation of 99mTc-PYP scintigraphy, which is calculated as the total counts in a region of interest over the heart divided by background counts in an identical sized region of interest over the contralateral chest [16]. Castano et al. showed that an H/CL ratio of 1.6 or greater is associated with worse survival in patients with ATTR-CM [11]. Therefore, a high H/CL ratio is also an important marker of ATTR-CM progression. We believe that the significant association we found between LV apical sparing and LV thickness, LV diastolic dysfunction, and high H/CL ratio indicates that LV apical sparing is another important marker for ATTRwt-CM progression.

4.3. LV apical sparing and previous medical history

In our study, four patients had a history of myocardial infarction and did not have LV apical sparing. Since ischemic heart disease is known to affect LS [17,18], the myocardial deformation caused by myocardial infarction might obscure LV apical sparing in patients with ATTRwt-CM. Other than ischemic heart diseases, various types of cardiac diseases, such as valvular heart diseases and cancer therapeutic-related cardiac dysfunction, are known to affect LS [19,20]. Therefore, careful attention to previous medical history is needed when we use LV apical sparing to diagnose ATTRwt-CM.
4.4. The difference in the pattern of LS reduction between the LV apical sparing group and the non-LV apical sparing group

Our study also showed that all LS segments: apical LS; mid LS; and basal LS decreased over time. However, there was a significant difference between the LV apical sparing group and the non-LV apical sparing group in how LS decreased.

Although impaired basal LS is a typical finding in amyloid cardiomyopathy patients [13], a time-dependent decrease in basal LS was shown only in the non-LV apical sparing group. This result may indicate that the deleterious effect of amyloid deposition in basal segments might occur only in the early stages of ATTRwt-CM. Transthyretin-derived amyloid deposition is commonly found in high mobility organs, such as the intercarpal ligament, rotator cuff, lumbar canal, and heart [21]. In this study, however, basal LS in the LV apical sparing group was already decreased at diagnosis, indicating that the mobility of the basal segment was severely restricted at this time point. This may be the reason why basal LS did not decrease over time in the LV apical sparing group. In contrast, apical LS decreased over time in the LV apical sparing group but not in the non-LV apical sparing group. Apical LS was significantly higher in the LV apical sparing group than in the non-LV apical sparing group. Therefore, the mobility of the apical segment may have been relatively high in the LV apical sparing group, which could be the reason why the apical LS decreased over time in the LV apical sparing group. Our study results indicate that there is an order of myocardial regions in which amyloid is deposited, from the basal segment to the apical segment during ATTRwt-CM progression.

4.5. The usefulness of repeated two-dimensional speckle tracking analysis to diagnose ATTRwt-CM

In this study, the rate of LV apical sparing was only 52%. Therefore, the diagnostic utility of LV apical sparing for ATTRwt-CM was considered to be lower than previously reported. However, our study showed that RapLSI significantly changed over time, particularly in the non-LV apical sparing group, where 29% of ATTRwt-CM patients had newly evident LV apical sparing during the follow-up period. These results indicate that repeated two-dimensional speckle tracking analysis is important for suspected ATTR-CM patients, especially when they did not have LV apical sparing at first.

4.6. The importance of diagnosing ATTR-CM during the early stage

Recently, a transthyretin stabilizer (tafamidis) has been used clinically. Tafamidis is reported to reduce all-cause death and cardiovascular-related hospitalizations, and improve functional capacity and quality of life [3]. Since the effectiveness of tafamidis in patients with advanced ATTR-CM has not been clarified, it is very important to diagnose ATTR-CM during the early stage of the disease. Although the usefulness of LV apical sparing to diagnose amyloid cardiomyopathy has been widely established, our study showed that ATTRwt-CM with LV apical sparing was more progressive than ATTRwt-CM without LV apical sparing. Therefore, we need further studies to establish clinical and echocardiographic methods to diagnose ATTRwt-CM in patients without LV apical sparing.

4.7. ATTR-CM patients at the further progressive stage in the non-LV apical sparing group

We determined that LV apical sparing was an important marker of disease progression, because IVSTD, E/e’ ratio and H/CL ratio were higher in the LV apical sparing group than in the non-LV apical sparing group. Therefore, many patients in the non-LV apical sparing group were thought to be at the early stage. However, there was small difference in H/CL ratio between these 2 groups. Our study revealed 22% of patients in the LV apical sparing group diminished LV apical sparing in the follow-up period. This result indicated that LV apical sparing diminished according to further progression of ATTR-CM. We previously reported the usefulness of LV apical sparing in diagnosis of ATTR-CM [7]. In the previous report, we excluded ATTR-CM patients at the further progressive stage. Because the rate of LV apical sparing was higher in the previous report than in this present study, many ATTR-CM patients at the further progressive stage might not have LV apical sparing. Thus, we thought there were many ATTR-CM patients at the early stage and some ATTR-CM patients at the further progressive stage in the non-LV apical sparing group, which might be the reason why there was small difference in H/CL ratio between LV apical sparing group and non-LV apical sparing group.

5. Study limitations

This study had several limitations. First, this was a single-center study that included a relatively small number of ATTRwt-CM patients. Second, echocardiographic images were obtained using several ultrasound machines. We performed the two-dimensional speckle tracking echocardiography analysis using vendor-independent software (TomTec Image-Arena™). Although significant correlations were shown in the LS values analyzed using vendor-independent software for paired images obtained from different ultrasound machines [22], inter-machine variability may still have affected our study results. Third, although we used a standardized protocol and the 99mTc-PYP scintigraphy images were interpreted by the same independent operators, there is a possibility of referral bias. In our present study, tafamidis was admitted to 35% of patients who time-dependent change of LS was evaluated. Because tafamidis was known to reduce all-cause death and cardiovascular-related hospitalizations, administration of tafamidis might have some effect on time-dependent change of longitudinal strain in our present study. This point was another important limitation of our present study.

Despite these limitations, our study is the first to report the significance of, and time-dependent change in, LV apical sparing in ATTRwt-CM patients.

6. Conclusion

Approximately half of ATTRwt-CM patients did not have LV apical sparing at diagnosis. Because RapLSI in ATTRwt-CM significantly changed over time, repeated two-dimensional speckle tracking analysis is important for suspected ATTR-CM patients, especially when they did not have LV apical sparing at first.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Ethics approval

This study was approved by the institutional review board and ethics committee of Kumamoto University (Reference number: 1588).
