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# Left ventricular deformation and torsion assessed by speckle-tracking echocardiography in patients with mutated transthyretin-associated cardiac amyloidosis and the effect of diflunisal on myocardial function☆

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ABSTRACT

*Background:* Mutated transthyretin-associated (ATTRm) amyloidosis with heart failure is associated with decreased longitudinal left ventricular (LV) myocardial contraction, as measured by strain Doppler echocardiography. We sought to clarify whether speckle-tracking echocardiography (STE) would provide useful information in patients with ATTRm cardiac amyloidosis.

*Methods:* One hundred twenty-three consecutive patients with ATTRm amyloidosis were divided into 3 groups. Group 1 had no evidence of cardiac involvement (n = 47), group 2 had heart involvement but no congestive heart failure (CHF) and/or serum brain natriuretic peptide (BNP) levels <100 pg/mL (n = 35), and group 3 had heart involvement and CHF and/or serum BNP levels ≥100 pg/mL (n = 41). All patients underwent standard 2-dimensional (2D), Doppler echo, and STE.

*Results:* By standard 2D and Doppler echo, differences in parameters were only apparent between group 3 and groups 1 and 2. Global circumferential strains by STE at each LV level and LV torsion were different between group 1 and groups 2 and 3, but not between group 2 and group 3. In contrast, global longitudinal LV strain showed significant intergroup differences (−17.3 ± 2.3%, −13.3 ± 2.3%, −9.9 ± 3.3% for groups 1 to 3, respectively, $P < 0.0001$). Radial strain also showed significant intergroup differences for each basal LV segment. Among 41 patients who could have been followed up after 1 year, 34 patients with diflunisal treatment had shown improvement in apical rotation and torsion without deterioration in multidirectional strains.

*Conclusion:* ATTRm cardiac amyloidosis is characterized by progressive impairment in longitudinal and basal LV radial function when global circumferential shortening and torsion remain unchanged.



## 1. Introduction

Cardiac amyloidosis is a cardiomyopathy associated with thickening of all 4 chambers, with biatrial dilation, a normal or mildly dilated right ventricle, and normal or decreased left ventricular (LV) cavity size. Congestive heart failure (CHF) may occur even if LV ejection fraction is normal [1–7]. Therefore, it is generally considered that CHF in cardiac amyloidosis manifests predominantly as diastolic LV dysfunction, with systolic dysfunction only occurring late in the disease [5,8–12]. Tissue Doppler echocardiography has demonstrated that cardiac amyloidosis is characterized by early impairment of systolic function at a time when fractional shortening remains normal, and that this abnormality precedes the onset of CHF [13,14]. Speckle tracking echocardiography (STE) allows the evaluation of different components of complex cardiac motions, such as longitudinal, circumferential, and radial strain, and rotation [15–18].

Many studies have focused on light-chain associated cardiac amyloidosis, but few data concerning mutated transthyretin-associated (ATTRm) amyloidosis have been derived using strain echocardiography [19–21]. The purpose of this study was to clarify whether STE could detect early regional myocardial dysfunction in ATTRm amyloidosis, before the onset of CHF, and to determine whether change in regional myocardial deformation can be detected by STE in these patients after oral small-molecule treatment by diflunisal [20].

## 2. Methods

### 2.1. Study population

One hundred twenty-eight consecutive patients with ATTRm amyloidosis were examined at the Shinshu University Hospital between

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January 2003 and March 2011. The diagnosis of amyloidosis was made by biopsy of involved organs, which demonstrated the typical Congo-red birefringence when viewed under polarized light. ATTRm amyloidosis was diagnosed from amyloid deposition in the abdominal fat pad (n = 90), endocardium (n = 10), stomach (n = 6), duodenum (n = 5), and rectum (n = 7), skin (n = 4), sural nerve (n = 4), vitreum (n = 3), and from the biopsy of carpal tunnel (n = 1) (there are overlap in some patients). Additionally, TTR gene analysis was routinely carried out, as previously described [22,23].Patients with atrial fibrillation (n = 5) were not included. Thus the final population consisted of 123 patients.

All patients underwent a physical examination by cardiologists, with particular emphasis on the signs and symptoms of CHF, or a chest radiographic appearance of heart failure and/or the presence of elevated jugular venous pressure with peripheral edema [13,14,24–26]. Echocardiograms were reviewed by 2 readers to determine the degree of cardiac involvement, defined as a mean LV wall thickness >12 mm in the absence of hypertension, valvular heart disease, or criteria for LV hypertrophy on the electrocardiogram [6,7,13,14, 24–26]. Some patients, who were not indicated for liver transplantation (n = 41), had been prescribed diflunisal, which prevents amyloidogenesis in vitro [27], and these patients were examined before and 1 year after starting the medication. Of these 41 patients, 7 patients discontinued diflunisal administration because of transient acute deterioration of renal function. Plasma levels of brain natriuretic peptide (BNP) were measured on the day of echocardiography, as previously described [28].

Seventy-six patients met the echocardiographic criteria for cardiac involvement, and 47 had no features of cardiac amyloidosis. The latter group was defined as group 1 (noncardiac amyloid), as we described previously [13,14,24–26]. Some patients with ATTRm had gait impairment due to peripheral nerve neuropathy, which limits behavior and masks CHF symptoms. In such patients, plasma BNP levels ≥100 pg/mL were taken as the criterion for CHF. Of the 76 patients with cardiac amyloidosis, 41 had prior or current evidence of CHF or plasma BNP levels ≥100 pg/mL [29]. These patients were defined as group 3 (CHF [+]), and the remaining 35 were defined as group 2 (CHF [−]).

Positive findings of 99mTc-PYP accumulation in the heart were also used to define groups 2 and 3 (cardiac amyloid).

### 2.2. Standard echocardiography

Ultrasound examinations were performed using a Vivid 7 System echocardiograph (General Electric Healthcare, Milwaukee, WI, USA) with a 1.5–4.0 MHz (M3S) transducer. Standard M-mode measurements of the LV were made. The LV end-diastolic and end-systolic volumes, ejection fraction, and left atrial (LA) maximum and minimum volumes were measured as previously described [30]. Transmitral, pulmonary venous, and LV outflow tract flow velocities were measured by pulsed Doppler echocardiography as previously described [13,14,24, 26–30]. Pulsed tissue Doppler imaging was performed using harmonic imaging, and the gate length of regions of interest was set at 0.59 cm. Sample volumes were placed on the basal interventricular septum and basal lateral walls, as described previously [13].

### 2.3. Speckle tracking echocardiography

Two-dimensional black-and-white cardiac cycle acquisitions were recorded in apical 2-chamber and 4-chamber views, apical long-axis view, and parasternal short-axis view (at base, mid, and apex), and stored on a hard drive. Three consecutive beats were stored in each view during breath-hold at a frame rate of 70–97 frames/s. Speckle-tracking analysis was performed offline by commercially available software (Echo Pac PC ver. 112; GE Vingmed Ultrasound, AS, Horten, Norway). After manual tracing of the endocardial border at end systole for apical and short-axis views, a region of interest was manually adjusted to include the entire myocardial thickness. The LV global and segmental longitudinal 2-dimensional strains were assessed in the apical 2-chamber, 4-chamber, and long-axis views by automated function imaging. Global and segmental longitudinal strain rates were measured from 3 apical views, and the values were averaged. LV global circumferential strain (GCS) and strain rate were measured in the parasternal short-axis view at basal, mid, and apical LV.

Segmental circumferential strain, strain rate, LV radial strain (RS), and strain rate were calculated for 6 segments (anteroseptal, anterior, lateral, posterior, inferior, and septal walls) in the parasternal short-axis view at basal, mid, and apical LV.

Measurement of LV rotation and torsion was performed as previously described [18].

Peak systolic LV torsion was calculated as the maximum instantaneous difference between peak systolic apical and basal rotation, using the R-peak in the electrocardiogram as a reference point. For LV torsion rate, the peak systolic, peak early diastolic, and peak late diastolic values were measured. In the follow-up echocardiographic assessment 1 year after the initial examination, each echocardiographic movie was recorded at the same frame rate, depth, and cut plane as with the previous picture.

### 2.4. Intraobserver and interobserver reproducibilities

To test the intraobserver reproducibility of the strain, strain rate, rotation, and torsion variables, 20 randomly selected patients were reviewed by the same observer >2 weeks after the first measurements. To test interobserver reproducibility, measurements were repeated by a second observer. The bias (mean difference) and limits of agreement between the first and second measurements were determined. To assess [18] reproducibility, the coefficient of variation was calculated as the standard deviation of the difference divided by the mean.

### 2.5. Statistical analyses

The normal distribution of continuous variables was checked using the Shapiro–Wilk W test, and all data were then expressed as mean ± standard deviation (SD). Categorical variables were expressed as absolute numbers and percentages. Statistical analyses were performed using commercially available software (JMP 9.0.2, SAS Institute, Cary, North Carolina, and Graph Pad Prism 5 for Mac OS X, GraphPad, San Diego, California, USA). Differences among the 3 groups were assessed using one-way analysis of variance, with Tukey–Kramer's HSD test for parametric variables, the Kruskal–Wallis test with Dunn's post-hoc test for nonparametric variables, and the chi-square test for categorical variables. The Bland–Altman analysis was conducted to assess intra- and interobserver agreements (expressed as absolute value of mean difference ± 1.96 SD), and intraclass correlation coefficients were calculated. Follow-up data were tested by paired t test in each group. A difference or correlation was considered significant when the probability value was <0.05.

This study was approved by the Ethics Committee of the Shinshu University School of Medicine and written informed consent was obtained from each patient.

## 3. Results

### 3.1. Patients' characteristics

The clinical characteristics are shown in Table 1. The age was greater in groups 2 and 3 compared to group 1. There were more men in group 2 than the other 2 groups. Most patients (92.7%) which entered this study had the same transthyretin mutation, involving the substitution of methionine for valine at position 30 (V30M). Other types of mutation were summarized in Table 1. Diastolic blood pressure was lower in group 3 than that in the other 2 groups. Heart rate in groups 2 and 3