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ORIGINAL INVESTIGATION

# Prognostic value of tissue-tracking mitral annular displacement by speckle-tracking echocardiography in asymptomatic aortic stenosis patients with preserved left ventricular ejection fraction

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## Abstract

**Background** Tissue-tracking mitral annular displacement (TMAD) by speckle-tracking echocardiography provides rapid and simple assessment of left ventricular (LV) longitudinal deformation. The purpose of this study was to evaluate the value of TMAD for the assessment of LV longitudinal deformation in patients with severe AS and preserved LV ejection fraction (LVEF).

**Methods** We studied 44 patients with severe AS preserved and LVEF in whom TMAD was assessed. Using TMAD analysis software, the base-to-apex displacement of automatically defined mid-point of mitral annular line in four-chamber view was quickly assessed, and the percentage of its displacement to LV length at end-diastole (%TMAD) was calculated. We investigated the association between %TMAD and the cardiac events including appearance of symptom (dyspnea on exertion and hospitalization due to heart failure), decreased LVEF (< 50%), and cardiac death.

**Results** During follow-up, the cardiac events developed in 16 (36%) of 44 patients. %TMAD was significantly impaired in patients with the cardiac events compared with those without the cardiac events (9.6 ± 1.9 vs 12.1 ± 2.6, $p = 0.002$). The cardiac events were predicted by %TMAD (HR 0.68, 95% CI 0.54–0.85; $p = 0.0012$).

**Conclusions** The present study suggests that TMAD easily and rapidly estimated by speckle-tracking echocardiography may be used as a simple method to predict occurrence of the cardiac events in asymptomatic severe AS patients with preserved LVEF.

**Keywords** Aortic stenosis · Speckle-tracking echocardiography · Mitral annulus · Longitudinal strain

## Introduction

Management of asymptomatic patients with severe aortic stenosis (AS) remains controversial. American College of Cardiology (ACC)/American Heart Association (AHA) and European Society of Cardiology (ESC) guidelines [1, 2] recommend to perform aortic valve replacement (AVR) in patients with severe AS with impairment of left ventricular (LV) ejection fraction (LVEF < 50%) even if patient has no symptom because it suggests the development of irreversible myocardial damage and AVR is needed to prevent progressive postoperative LV dysfunction and improve clinical outcome. On the other hand, the several studies demonstrated the benefits of an early AVR strategy in reducing mortality and hospitalization due to heart failure as compared with a conservative strategy [3, 4].

The histopathologic studies have demonstrated that myocardial fibrosis evaluated by cardiac magnetic resonance correlates with that by histopathology [5] and myocardial fibrosis is reflected in LV longitudinal deformation [6] in patients with AS. Recent studies using global longitudinal strain (GLS) have shown that decreased LV longitudinal deformation can predict adverse cardiac events in AS patients with preserved LVEF [7–13]. Application of speckle-tracking echocardiography to mitral annulus provides rapid and easy assessment of mid-point of mitral annulus displacement

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(TMAD) by automated tracking of the mitral annuls [14–17]. In addition, displacement of the mid-point of the annulus can be automatically determined from the line between septal and lateral annulus in four-chamber view, which may be expected to reflect the longitudinal movement of the entire LV. It was also reported that TMAD is obtained more rapidly than GLS [16, 17], and is sensitive and reproducible method for the assessment of longitudinal systolic deformation [14, 15]. However, there has been no report examining the value of TMAD for the prediction of the cardiac event in asymptomatic patients with severe AS and preserved LVEF. Thus, we proposed this study to examine the value of %TMAD to predict occurrence of the cardiac events in asymptomatic severe AS patients with preserved LVEF.

## Methods

### Study patients

We retrospectively studied 103 patients with severe AS and preserved LVEF (≥ 50%) without LV segmental wall motion abnormalities. According to the European Association of Echocardiography (EAE)/American Society of Echocardiography (ASE) guidelines [18], severe AS is defined by the following conditions; aortic velocity > 4 m/s or aortic valve area < 1.0 $cm^2$. Exclusion criteria were (1) symptomatic, (2) atrial fibrillation, (3) concomitant valve disorders (> mild aortic regurgitation, mitral valve disease or right-sided organic valve disease), (4) history of myocardial infarction, (5) LV segmental wall motion abnormalities, (6) previous cardiac surgery, (7) cardiomyopathies, (8) congenital heart disease and (9) inadequate echo images including LV foreshortening in apical four-chamber view. Coronary artery disease (CAD) was defined as history of percutaneous coronary intervention or coronary artery stenosis ≥ 75% on coronary angiography (history of myocardial infarction or LV segmental wall motion abnormalities were also excluded).

### Echocardiographic evaluation

Transthoracic echocardiography was performed using EPIQ echocardiographic system equipped with X5-1 probe, or iE33 echocardiographic system equipped with S5 probe, by sophisticated sonographers (Philips Ultrasound, Bothell, WA). Two consecutive cycles in apical long-axis, apical four-chamber, and two-chamber views were obtained. We carefully set the cross section to avoid foreshortening of LV as well as possible. Loops were digitally stored and recorded on CD. LV diameters were measured according to ASE criteria [19]. LV volumes and left atrium (LA) volumes were measured with the biplane Simpson's rule from the apical four- and two-chamber views. LVEF was derived from the LV volumes. Systolic pulmonary artery pressure was estimated from the peak velocity of tricuspid regurgitation [19]. Mitral annulus calcification (MAC) was defined by an intense echocardiograph-producing structure located at the junction of the atrioventricular groove and posterior mitral leaflet [20]. MAC was then categorized for further analysis into none, mild to moderate (1–4 mm) or severe (> 4 mm) according to the presence of MAC [21]. Maximal MAC thickness measured from the anterior to the posterior edge at its greatest width is also used to assess MAC. Speckle tracking analysis was performed to assess GLS using semiautomatic algorithm with QLAB software (10.5, Philips). Three points (two mitral annular and apical points) were positioned in each three apical cross sections (long-axis view, apical four-chamber view, and two-chamber view) enabling the software to track the myocardium semi-automatically throughout the cardiac cycle. The region of interest was adjusted to cover the thickness of the myocardium. And, careful inspection of tracking and manual correction was performed. The algorithm provided longitudinal strain curve during entire cardiac cycle in each segment. GLS was calculated by averaging the peak negative strain value during systole of 17 segments.

### Tissue mitral annular displacement (TMAD) by speckle-tracking echocardiography

Tissue mitral annular displacement was assessed in the apical four-chamber view by speckle tracking analysis with semiautomatic algorithm with QLAB software by a single certified and experienced cardiologist blinded to the other echocardiographic date. Initially, we placed three regions of interest (ROI) in each view for TMAD analysis. The septal and lateral aspects of the mitral annulus and the apex were selected in each apical four-chamber view (Fig. 1). Once we set the ROIs, the mid-point between the two annular ROIs was automatically pointed. Setting ROI was the only manual procedure we need in TMAD technique. Septal and lateral annular ROIs and mid-point between the two ROIs were tracked throughout the cardiac cycle in each view. The speckle-tracking software automatically plotted the measured mitral annular longitudinal displacement of each tracked point frame by frame. The displacement of mid-point between the two annular ROIs (TMAD), septal and lateral annular ROIs (septal and lateral MAD) was automatically measured by the software although the time–displacement curve of the mid-point between the two annular ROIs is not shown. To normalize with respect to the LV length, displacement of the mid-point between the two annular ROI was expressed as the percentage of LV length at end-diastole (%TMAD).

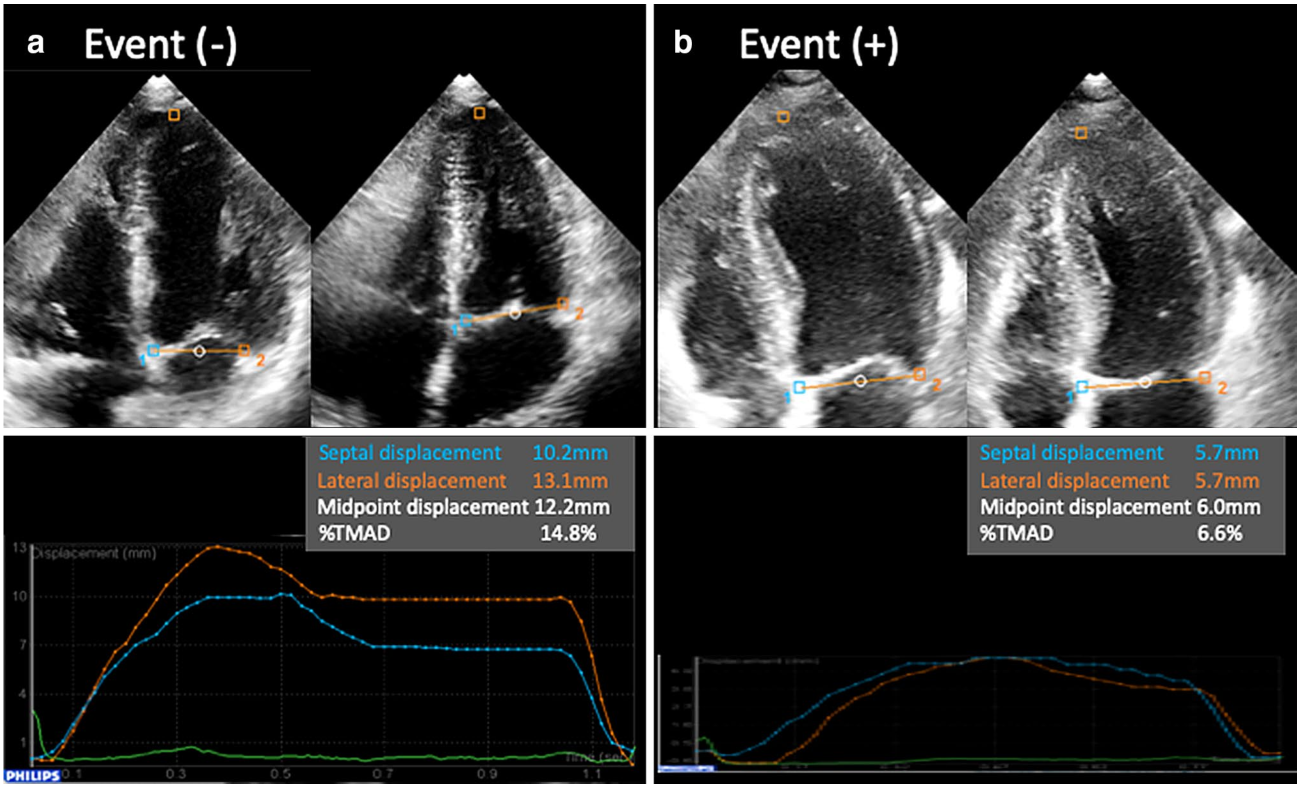


**Fig. 1** TMAD measurement. **a** Upper panel: speckle-tracking of the septal, lateral mitral annulus points and a mid-point between the two annular points were tracked during one cardiac cycle in four-chamber view. **a** Lower panel: time curve of the displacement of septal (blue line) and lateral (orange line) of the mitral annulus is displayed. %TMAD was calculated from the midpoint displacement of the septal and lateral annulus to LV length from the mid-point of mitral annulus to the apex at end-diastole and shown in the bottom. %TMAD is markedly reduced (6.6%) in the case with the cardiac events (**b**) compared with patients without the cardiac events (**a**; 14.8%)

## Analysis of TMAD data

Echocardiographic examinations were analyzed by the investigations in a blinded manner. A total of 15 patients were randomly selected for assessment of inter- and intra-observer variabilities of %TMAD measurements. The same images were examined by another observer, who was blinded to the clinical information and the results of the investigation. Inter-observer variability was calculated as the absolute difference between the measurements of two independent observers and expressed as a percentage of the average value. Intra-observer analysis was performed by the same observer at two different time points with blinding to the clinical information and the results of the other time point. Intra-observer variability was calculated as the absolute difference between the first and second determination for a single observer and expressed as a percentage of the average value. The inter- and intra-observer variabilities for %TMAD were 2.0 ± 1.3% and 5.2 ± 3.5%.

## Clinical follow-up

Patients were followed in our hospital at least 4 months after echo examination. The primary composite outcome was defined as appearance of symptoms (dyspnea on exertion and hospitalization due to heart failure), decreased LVEF (< 50%) and cardiac death. Follow-up information obtained by retrospective chart review. The composite end-point included only the first event for each patient.

## Statistical analysis

Data are expressed as mean value ± SD. Categorical variables, presented as frequency counts and percentages, were compared using the Fisher's exact test. Distribution of the continuous data was tested with the Shapiro–Wilk test. Normally distributed variables were analyzed with the Student's *t* test for differences between the two groups, whereas abnormally distributed variables were analyzed with Wilcoxon signed rank test. For the analysis of cardiac event, Cox proportional hazards analysis was utilized. To examine the association between individual relevant predictors and survival, univariable analysis was performed. Hazard ratio (HR) and 95% confidence interval (CI) were calculated. Receiver operating characteristics (ROC) curves were constructed and areas under the curves (AUC) were measured to determine cut-off values of TMAD parameters for optimal sensitivity and specificity. All statistical analyses were performed using the JMP® Pro 14 (SAS Institute Inc., Cary, NC). Values of $p<0.05$ were considered significant. This study protocol was approved by the Committee for the Protection of Human Subjects in Research at Wakayama Medical University.

## Results

### Study population

We retrospectively studied 103 patients with severe AS and preserved LVEF (≥ 50%) in whom TMAD was measured by speckle-tracking echocardiography. Of these, 40 patients were excluded. The reasons for exclusion were symptomatic ($n=24$), chronic atrial fibrillation ($n=2$), concomitant valve disorders ($n=2$), previous cardiac surgery ($n=8$), cardiomyopathy ($n=1$) and inadequate echo images ($n=3$). After exclusion of these patients, 63 patients (age 77 ± 9 years, 38% men) were included in the study population. TMAD was successfully assessed by speckle-tracking echocardiography in 60 (95%) of 63 entered patients. Unsuccessful 3 (4.7%) patients because of poor tracking of the mitral annulus were not included in the final analysis for comparison with TMAD. Sixteen (27%) of 60 patients were excluded because of short follow-up (< 4 months). Finally, 44 patients were included as the final study patients for the follow-up study (Fig. 2).

### Baseline characteristics and echocardiographic parameters

Baseline clinical characteristics of the final study population are summarized in Table 1. It also shows data in patients with and without the cardiac events. Mean age of all patients was 77 ± 9 years and 18 (41%) patients were men. The mean follow-up duration was 603 ± 413 days. During a median follow-up, the events developed in 16 (36%) patients of 44 patients; 14 had symptoms [7 underwent aortic valve replacement (AVR) and 5 underwent transcatheter aortic valve implantation (TAVI)] and 2 decreased LVEF (1 underwent AVR). There was no significant difference in other clinical characteristics between two groups, except body surface area. Echocardiographic indexes of the final study population are summarized in Table 2. In 3 of 44 patients, it was difficult to assess GLS because of poor tracking of myocardium in more than three LV segments. There were no significant differences in echocardiographic indexes, except LV mass index, %TMAD and GLS ($p=0.02$, $p=0.002$ and $p=0.008$, respectively).

### Analysis of cardiac event-free survival

The results of univariate analysis of event-free survival are shown in Table 3. The cardiac events were predicted by %TMAD (HR; 0.68, 95% CI 0.54–0.85; $p=0.0012$) as well as GLS (HR; 0.65, 95% CI, 0.49-0.83; $p=0.0012$).

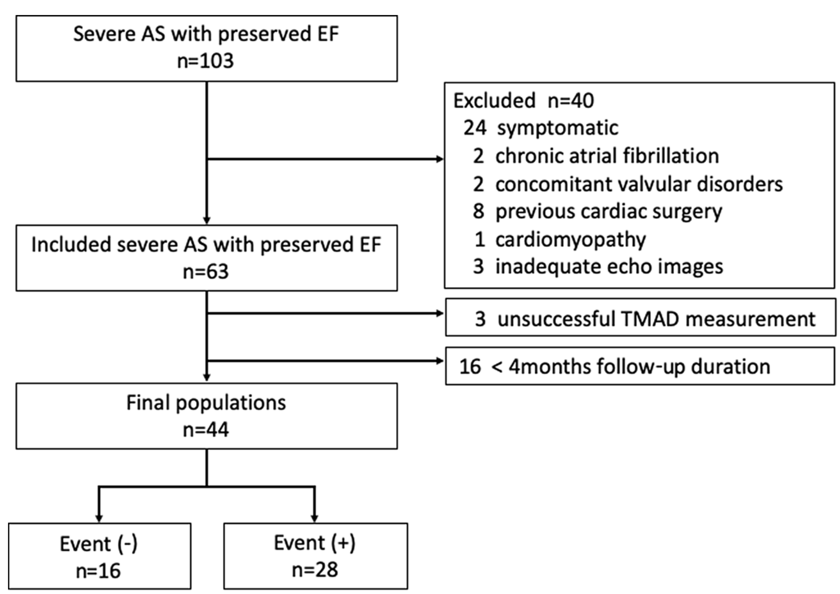


**Fig. 2** Study population. Of 103 aortic stenosis (AS) patients with preserved left ventricular ejection fraction (LVEF), the final study population consisted of 44 patients according to the inclusion criteria

**Table 1** Clinical characteristics of the study patients

| Variable | Whole cohort ($n=44$) | Event (−) ($n=28$) | Event (+) ($n=16$) | $p$ |
|---|---|---|---|---|
| Age, year | 77 ± 9 | 77 ± 9 | 75 ± 8 | 0.35 |
| Men, *n* (%) | 18 (41) | 11 (39) | 7 (44) | 0.57 |
| Body surface area, $m^2$ | 1.5 ± 0.2 | 1.5 ± 0.1 | 1.6 ± 0.2 | 0.02 |
| Clinical history | | | | |
| Hypertension, *n* (%) | 34 (77) | 20 (71) | 14 (88) | 0.21 |
| Diabetes mellitus, *n* (%) | 14 (31) | 8 (29) | 6 (37) | 0.54 |
| Hyperlipidemia, *n* (%) | 17 (39) | 10 (36) | 7 (44) | 0.60 |
| Coronary artery disease, *n* (%) | 11 (25) | 5 (18) | 6 (38) | 0.15 |
| Chronic kidney disease, *n* (%) | 11 (25) | 6 (21) | 5 (31) | 0.47 |
| COPD, *n* (%) | 4 (0.1) | 0 (0) | 4 (14) | 0.05 |
| Medication | | | | |
| ACEi/ARBs, *n* (%) | 19 (43) | 15 (53) | 4 (25) | 0.56 |
| β-Blockers, *n* (%) | 7 (15) | 4 (14) | 3 (18) | 0.30 |
| Dicretics, *n* (%) | 11 (25) | 10 (36) | 1 (6) | 0.70 |
| CCB, *n* (%) | 21 (48) | 17 (61) | 4 (25) | 0.46 |
| Laboratory results | | | | |
| Serum hemoglobin, g/dl | 12.0 ± 2.0 | 11.9 ± 2.0 | 12.0 ± 2.1 | 0.87 |
| Serum BNP, pg/ml | 67 ± 42 | 75 ± 48 | 58 ± 37 | 0.09 |

Data are expressed as mean value ± SD

*COPD* chronic obstructive pulmonary disease, *ACEi/ARB* angiotensin converting enzyme inhibitor/angiotensin receptor blockers, *CCB* calcium channel blocker, *BNP* brain natriuretic peptide

### Comparison of %TMAD between with and without cardiac events

Echocardiographic characteristics of the overall populations and the study subgroups are summarized in Table 2. %TMAD was significantly impaired in patients with the cardiac events compared with those without the cardiac events (9.6 ± 1.9 vs 12.1 ± 2.6%, $p=0.002$). Representative cases in each group are shown in Fig. 1a (without the cardiac events) and Fig. 1b (with the cardiac events).

According to ROC curves analysis, the best cut-off value of %TMAD < 11.9 had a sensitivity of 88% and specificity of 68% for the onset of cardiac events (AUC; 0.81). %TMAD showed a larger AUC for the predicting cardiac event occurrence compared with the septal MAD (0.67), lateral MAD (0.71) and mid-point MAD (0.73) (Fig. 3).

## Discussion

We showed that TMAD quickly estimated by speckle-tracking echocardiography can predict the occurrence of the cardiac events in asymptomatic severe AS and preserved LVEF. To our knowledge, there is no report to evaluate the prognostic value of in asymptomatic patients with severe AS.

### Myocardial damage in severe AS with preserved LVEF

The optimal timing of surgery for patients with asymptomatic severe AS remains controversial and there is debate regarding the role of early surgery. The present guidelines [1, 2] recommend a strategy of medical follow-up until symptoms emerge for AVR in asymptomatic patients with severe AS except for patients with LV dysfunction, need for other cardiac surgery, very severe AS, or an abnormal exercise test. On the other hand, the benefits of an early AVR have been demonstrated in reducing mortality and hospitalization due to heart failure as compared with a conservative strategy [3, 4].

Azevedo et al. reported that myocardial fibrosis evaluated by CMR correlates with that by histopathology [5]. They resulted that the amount of myocardial fibrosis in patients with severe AS is a predictor of long-term survival after AVR. Weidemann et al. demonstrated that myocardial fibrosis is reflected in longitudinal strain in patients with AS [6]. They also showed that patients with AS gradually develop myocardial fibrosis and it has a profound impact on the long-term clinical outcome. Thus, it is important to identify AS patients at risk of LV dysfunction, particularly in asymptomatic patients who are judged not to be indicated for surgery.

**Table 2** Echocardiographic characteristics of the study patients

| Variable | Whole cohort ($n=44$) | Event (−) ($n=28$) | Event (+) ($n=16$) | $p$ |
|---|---|---|---|---|
| LV Dd, mm | 45 ± 5 | 44 ± 1 | 47 ± 1 | 0.02 |
| Ds, mm | 29 ± 5 | 28 ± 4 | 31 ± 6 | 0.09 |
| EDVI, ml/m$^2$ | 57 ± 11 | 56 ± 10 | 59 ± 12 | 0.28 |
| ESVI, ml/m$^2$ | 23 ± 6 | 22 ± 5 | 24 ± 6 | 0.09 |
| EF, % | 61 ± 4 | 61 ± 4 | 59 ± 3 | 0.14 |
| Mass index, g/m$^2$ | 133 ± 34 | 188 ± 47 | 228 ± 62 | 0.02 |
| LAVI, ml/m$^2$ | 40 ± 10 | 41 ± 11 | 37 ± 9 | 0.43 |
| *E*, cm/s | 75 ± 19 | 73 ± 17 | 78 ± 20 | 0.29 |
| Mean *e*', cm/s | 5.2 ± 1.4 | 5.3 ± 1.6 | 5.0 ± 1.0 | 0.48 |
| *E*/*e*' | 15 ± 4 | 13 ± 4 | 15 ± 3 | 0.26 |
| *E*/*A* | 0.78 ± 0.33 | 0.80 ± 0.37 | 0.75 ± 0.26 | 0.57 |
| AV AVA, cm$^2$ | 0.8 ± 0.2 | 0.8 ± 0.1 | 0.8 ± 0.2 | 0.30 |
| Mean PG, mmHg | 41 ± 14 | 39 ± 13 | 44 ± 16 | 0.27 |
| $V_{max}$, m/s | 4.1 ± 0.6 | 4.0 ± 0.6 | 4.2 ± 0.7 | 0.38 |
| SPAP, mmHg | 29 ± 6 | 29 ± 7 | 28 ± 6 | 0.81 |
| MAC | | | | 0.15 |
| None, *n* (%) | 16 (36) | 13 (46) | 3 (18) | 0.06 |
| Mild–moderate, *n* (%) | 16 (36) | 8 (28) | 8 (44) | 0.16 |
| Severe, *n* (%) | 12 (27) | 7 (25) | 5 (31) | 0.66 |
| \|GLS\|, % | 18.0 ± 2.6 | 18.8 ± 2.7 | 16.6 ± 1.7 | 0.008 |
| %TMAD | 11.2 ± 2.6 | 12.1 ± 2.6 | 9.6 ± 1.9 | 0.002 |

Data are expressed as mean value ± SD

*LV* left ventricular, *EDVI* end-diastolic volume index, *ESVI* end-systolic volume index, *EF* ejection fraction, *IVS* interventricular septum, *PW* posterior wall, *LAVI* left atrium volume index, *AV* aortic valve, *AVA* aortic valve area, *V* aortic velocity, *PG* pressure gradient, *SPAP* systolic pulmonary artery pressure, *MAC* mitral annulus calcification, *GLS* global longitudinal strain, *TMAD* tissue-tracking mitral annular displacement

## Assessment of longitudinal LV deformation

Fibrotic changes induced by AS start subendocardially and affect mainly longitudinal function, which is not well represented by LVEF [6]. GLS which is one of the markers in the estimation of decreased LV longitudinal deformation is useful in the detection of latent myofibrillar degeneration. Lancellotti et al. showed that reduced longitudinal contraction identified a subset of patients at higher risk of developing cardiac events and patients with GLS ≤ 15.9% had an excess risk of death, symptoms or surgery that was more than twice that of patients with preserved longitudinal function [9]. Kusunose et al. had shown that AS patients with preserved LVEF are at a high risk for mortality in the setting of GLS < − 12.1%. They also concluded that asymptomatic patients with an abnormal GLS fare significantly worse with medical therapy compared with AVR, even in the setting of a preserved LVEF [12]. Thus, longitudinal LV deformation is useful for the early detection of LV function assessment before decline in LVEF.

**Table 3** Univariable analysis of event-free survival

| Variable | Univariate analysis HR (95% CI) | $p$ |
|---|---|---|
| Clinical characteristics | | |
| Age, year | 0.98 (0.92–1.04) | 0.46 |
| Men, *n* (%) | 0.55 (0.24–0.20) | 0.25 |
| Body surface area, m$^2$ | 9.55 (1.41–70.5) | 0.02 |
| Clinical history | | |
| Hypertension, *n* (%) | 3.26 (0.73–14.56) | 0.08 |
| Diabetes mellitus, *n* (%) | 1.02 (0.37–2.83) | 0.98 |
| Hyperlipidemia, *n* (%) | 1.14 (0.42–3.08) | 0.80 |
| Coronary artery disease, *n* (%) | 1.70 (0.61–4.74) | 0.32 |
| Chronic kidney disease, *n* (%) | 1.69 (0.57–5.03) | 0.36 |
| Medication | | |
| ACEi/ARBs, *n* (%) | 1.66 (0.60–4.60) | 0.31 |
| β-Blockers, *n* (%) | 0.88 (0.25–3.14) | 0.85 |
| Diuretics, *n* (%) | 1.56 (0.18–2.24) | 0.46 |
| CCB, *n* (%) | 1.69 (0.61–4.71) | 0.31 |
| Laboratory results | | |
| Serum hemoglobin, g/dl | 0.48 (0.13–1.47) | 0.19 |
| Serum BNP, pg/ml | 1.02 (0.99–1.06) | 0.19 |
| LV Dd, mm | 0.99 (0.91–1.06) | 0.82 |
| Ds, mm | 099 (0.91–1.06) | 0.74 |
| EDVI, ml/m$^2$ | 1.00 (0.98–1.04) | 0.59 |
| ESVI, ml/m$^2$ | 1.01 (0.94–1.08) | 0.72 |
| EF, % | 1.00 (0.89–1.12) | 0.98 |
| Mass index, g/m$^2$ | 0.99 (0.98–1.01) | 0.38 |
| LAVI, ml/m$^2$ | 1.03 (0.99–1.07) | 0.08 |
| *E*, cm/s | 1.00 (0.98–1.02) | 0.96 |
| Mean *e*', cm/s | 1.22 (0.86–1.68) | 0.26 |
| *E*/*e*' | 0.97 (0.86–1.09) | 0.62 |
| *E*/*A* | 1.90 (0.57–4.92) | 0.26 |
| AV AVA, cm$^2$ | 0.85 (0.01–15.9) | 0.91 |
| Mean PG, mmHg | 1.01 (0.98–1.05) | 0.40 |
| $V_{max}$, m/s | 1.34 (0.61–2.85) | 0.46 |
| SPAP, mmHg | 0.91 (0.91–1.09) | 0.97 |
| MAC | | |
| None, *n* (%) | 1.65 (0.77–3.56) | 0.20 |
| Mild–moderate, *n* (%) | 0.50 (0.21–1.16) | 0.09 |
| Severe, *n* (%) | 1.23 (0.51–3.02) | 0.64 |
| \|GLS\|, % | 0.65 (0.49–0.83)) | 0.0012 |
| %TMAD | 0.68 (0.54–0.85) | 0.0010 |

*HR* hazard ratio, *CI* confidence interval

## Advantages of TMAD

Longitudinal MAD can reflect the global LV longitudinal deformation of the heart because the position of the apex is

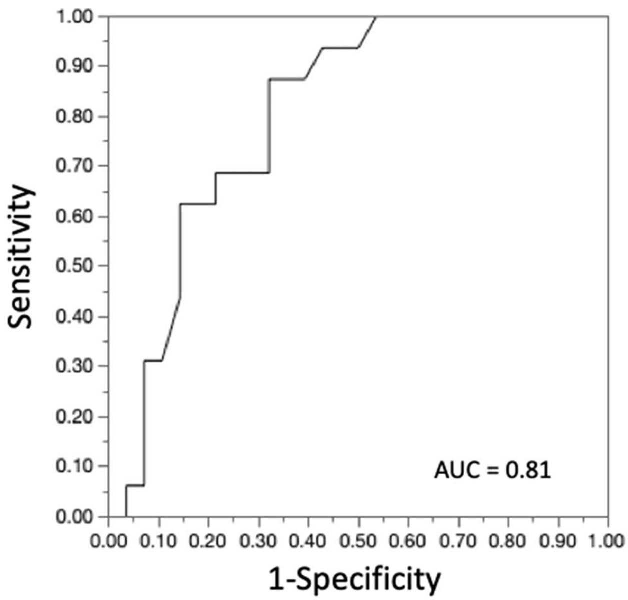


**Fig. 3** Receiver operating characteristic curve of %TMAD for the onset of cardiac events. According to ROC curve analysis, the best cut-off value of %TMAD < 11.9 had a sensitivity of 88% and specificity of 68% for the onset of cardiac events (area under the curve; 0.81)

relatively stationary throughout the cardiac cycle. M-mode and tissue Doppler imaging of the mitral annulus can be used as simple and image-quality independent index of systolic function [22, 23]. However, MAD by M-mode method is limited in only the direction of the ultrasound beam which is not the actual excursion of the mitral annulus. In addition, MAD obtained from only the lateral or septal side of the mitral annulus is recorded during one cardiac cycle in apical four-chamber view. Thus, M-mode-guided MAD may not reflect entire mitral motion.

There are several advantages in TMAD by speckle-tracking echocardiography. First, TMAD provides easy and quick assessment of angle-independent displacement of mid-point between the two annular ROIs. In addition, mid-point MAD was expressed as the percentage of LV length at end-diastole (%TMAD) to normalize with respect to the LV length. As shown in the previous report by Buss et al. [15], TMAD can be quickly and semi-automatically measured. The other recent study also reported TMAD is simple, sensitive and reproducible LV systolic longitudinal function evaluation [24]. Another advantage of TMAD is less dependent on image quality [14]. Buss et al. also showed very low inter- and intra-observer variabilities for TMAD which was confirmed even in patients with AS in the present study. In this study, it was difficult to assess GLS in 3 of 44 patients (7%) because of poor tracking of myocardium in more than three LV segments while TMAD was successfully measured in all the final study patients. This result suggests the feasibility of TMAD. Because the mitral annuls is usually well visualized and its motion can be easily tracked by speckle-tracking echocardiography, TMAD is less dependent on image quality compared with GLS requiring adequate visualization of most of the LV wall. In addition, the present study showed %TMAD predicted the cardiac event as well as GLS. These advantages should contribute to the application of TMAD to the assessment of LV longitudinal deformation in daily clinical practice.

### TMAD as a predictor of outcome

To the best of our knowledge, this study is the first to report that TMAD is a predictor of poor outcome in asymptomatic severe AS with preserved LVEF. We indicated that severe AS patients with preserved LVEF are at a high risk for cardiac event free in the setting of %TMAD < 11.9. TMAD is, therefore, of a high clinical value to enhance risk stratification and management in patients with asymptomatic severe AS. By improving the individual risk stratification and identifying LV dysfunction at an earlier stage, these parameters could be helpful for tailor-made therapeutic decision-making. TMAD which is a rapid, simple and reproducible echocardiographic measured should be integrated in the routine evaluation of patients with severe AS.

### Study limitations

Several study limitations should be considered in the interpretation of the present results. The study population consisted of a relatively small number of asymptomatic severe AS patients with LVEF ≥ 50%. A large cohort in multicenter research is needed for reliable statistical calculations.

Second, although the severity of the MAC was not related to cardiac events in this study, it may be at least related to annulus motion. The recent study showed that GLS was decreased and correlated with the presence and severity of MAC [25]. In addition, the three cases in whom TMAD measurement was not possible had a strong MAC and it was difficult to track the annulus. Thus, TMAD measurement may be affected in some patients with severe MAC.

Third, the patients with segmental wall motion abnormalities were not included in the present study. TMAD may be affected by the effects of "tethering" translational motion from adjacent myocardial segments, especially in the basal segments. Further studies including patients with segmental wall motion abnormalities should be considered in the future.

## Conclusions

The present study suggests that TMAD easily and rapidly estimated by speckle-tracking echocardiography may be used as a simple method to predict occurrence of the cardiac events in asymptomatic severe AS patients with preserved LVEF.

## Compliance with ethical standards

**Conflict of interest** Ikuko Teraguchi, Takeshi Hozumi, Hiroki Emori, Kazushi Takemoto, Suwako Fujita, Teruaki Wada, Manabu Kashiwagi, Yasutsugu Shiono, Kunihiro Shimamura, Akio Kuroi, Takashi Tanimoto, Takashi Kubo, Atsushi Tanaka, and Takashi Akasaka declare that they have no conflict of interest.

**Human rights statements** All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions.

**Informed consent** Informed consent was obtained from all patients for being included in the study.

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