




# Geometry of the left ventricular outflow tract assessed by 3D TEE in patients with aortic stenosis: impact of upper septal hypertrophy on measurements of Doppler-derived left ventricular stroke volume

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Received: 25 December 2017 / Revised: 14 May 2018 / Accepted: 19 May 2018 / Published online: 24 May 2018  
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## Abstract

**Background** It is unclear how upper septal hypertrophy (USH) affects Doppler-derived left ventricular stroke volume (SV) in patients with AS. The aims of this study were to: (1) validate the accuracy of 3D transesophageal echocardiography (TEE) measurements of the left ventricular outflow tract (LVOT), (2) evaluate the differences in LVOT geometry between AS patients with and without USH, and (3) assess the impact of USH on measurement of SV.

**Methods** In protocol 1, both 3D TEE and multi-detector computed tomography were performed in 20 patients with AS [aortic valve area (AVA)  $\leq 1.5$  cm<sup>2</sup>]. Multiplanar reconstruction was used to measure the LVOT short and long diameters in four parts from the tip of the septum to the annulus. In protocol 2, the same 3D TEE measurements were performed in AS patients (AVA  $\leq 1.5$  cm<sup>2</sup>,  $n = 129$ ) and controls ( $n = 30$ ). We also performed 2D and 3D transthoracic echocardiography in all patients.

**Results** In protocol 1, excellent correlations of LVOT parameters were found between the two modalities. In protocol 2, the USH group had smaller LVOT short and long diameters than the non-USH group. Although no differences in mean pressure gradient, or SV calculated with the 3D method existed between the two groups, the USH group had greater SV calculated with the Doppler method ( $73 \pm 15$  vs.  $66 \pm 15$  ml) and aortic valve area ( $0.89 \pm 0.26$  vs.  $0.73 \pm 0.24$  cm<sup>2</sup>) than the non-USH group.

**Conclusions** 3D TEE can provide a precise assessment of the LVOT in AS. USH affects the LVOT geometry in patients with AS, which might lead to inaccurate assessments of disease severity.

**Keywords** Aortic valve stenosis · Echocardiography · Three-dimensional echocardiography · Transesophageal echocardiography

## Introduction

From a public health perspective, valvular heart disease, which has a poor prognosis, affects entire communities, and presents an important public health problem in developed countries [1]. Aortic stenosis (AS) is the most common

form of valvular heart disease in developed countries and its prevalence is increasing along with the aging population [1–4]. AS is detected in 2–7% of adults aged 65 years and older and characterized by degenerative calcification and congenital valvular defects [1–4]. The accurate assessment of disease severity is critical for the appropriate treatment of patients with AS. Conventional two-dimensional (2D) transthoracic echocardiography (TTE) is the standard approach for evaluating aortic valve area (AVA) calculated by the continuity equation method. AVA derived from continuity equation method relies on geometric assumptions of the left ventricular (LV) outflow tract (LVOT) area, which can amplify errors, particularly in the presence of upper septal hypertrophy (USH). USH, which increases the LVOT velocity, is relatively common in the elderly. However, it is not clear how USH can affect continuity-equation-derived AVA from TTE results in patients with AS. The recently

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developed three-dimensional (3D) transesophageal echocardiography (TEE) has been a preferred method for the evaluation of aortic root geometry because of its greater accuracy than two-dimensional (2D) TTE and 2D TEE. Earlier studies evaluated the geometry of the aortic root from the aortic annulus to the sinotubular junction; however, the LVOT geometry was not fully elucidated [5–10]. We hypothesized that AS patients with USH have a greater stroke volume (SV) due to increased LVOT velocity despite less LVOT velocity of 1.5 m/s than the AS patients without USH and that this leads to the overestimation of AVA calculated using the continuity equation.

The aims of this study were to: (1) validate the accuracy of 3D TEE measurements of LVOT against multi-detector computed tomography (MDCT) measurements as a reference, (2) evaluate the geometric differences in LVOT geometry between AS patients with and without USH, and (3) assess the impact of USH on the measurement of SV.

## Methods

### Study population

In protocol 1, 20 patients with AS ( $AVA \leq 1.5 \text{ cm}^2$ ) who underwent both MDCT and 3D TEE within 1 month were retrospectively enrolled. Patients allergic to iodine contrast agents and those at high risk for contrast nephropathy were excluded from the analysis. In protocol 2, a total of 152 patients with more-than-moderate AS measured using continuity equation method ( $AVA < 1.5 \text{ cm}^2$ ), who underwent TEE between November 2011 and April 2014 and 30 controls were prospectively enrolled. Patients with poor quality images ( $n=5$ , 3.3%), atrial fibrillation ( $n=16$ , 10.5%), moderate or severe mitral regurgitation ( $n=0$ , 0%), and high LVOT velocity ( $> 1.5 \text{ m/s}$ ;  $n=2$ , 1.3%) were excluded from the study population. Finally, 129 AS patients and 30 controls were enrolled. The inclusion criteria for the controls in this study were: (1) no significant valvular heart disease, (2) preserved LVEF ( $\geq 60\%$ ), (3) no left ventricular wall motion abnormalities, and (4) no dilated left ventricle. This group was identified from the patients undergoing clinically indicated TEE for investigating a cardioembolic source of stroke. This study was approved by the institutional review board at St. Marianna University School of Medicine. All patients gave their written informed consent before study enrollment.

### MDCT

Twenty patients underwent retrospective electrocardiographically gated conventional scans with tube current dose modulation using an MDCT scanner (Aquilion ONE ViSION

Edition, Toshiba Medical Systems, Odawara, Japan). This system was equipped with 320-row detector arrays. Computed tomography was performed with a slice thickness of 0.5 mm, tube voltage of 120 kV, and maximum tube current of 580 mA with a gantry rotation time of 275 ms. The voltage was occasionally reduced to 100 kV in patients with thin chests. All patients with heart rates  $> 65$  beats per minute received 10 mg propranolol hydrochloride or 0.125 mg/kg landiolol hydrochloride.

### 2D and 3D TEE

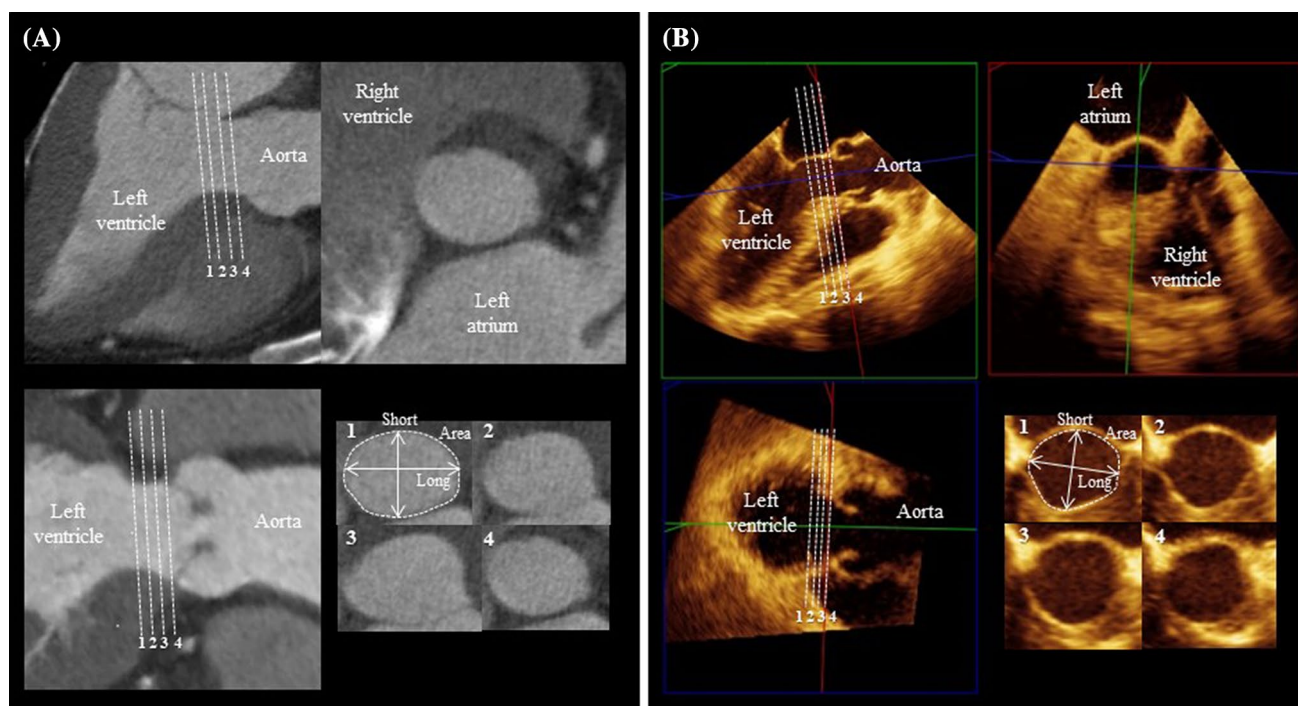
TEE was performed using an iE33 ultrasound imaging system (Philips Medical Systems, Andover, MA) equipped with a fully sampled matrix array TEE transducer that can display both 2D and live 3D images. After the application of topical anesthetics in the pharynx and intravenous sedation (propofol), the probe was advanced into the esophagus. The aortic valve was visualized from the mid-esophageal position in the zoomed 2D long-axis view (approximately  $135^\circ$ ). The 3D full-volume mode of the entire left ventricle, including the aortic root, was then acquired in four consecutive cardiac cycles (frame rate,  $23 \pm 5$  frame/s; range 16–34 frame/s) and stored digitally. The acquisition was triggered with an electrocardiogram R-wave.

### MDCT measurements of LVOT

The standard orthogonal axial and sagittal views were used for the initial orientation of the LVOT. The LVOT short and long diameters and areas were analyzed in the coronal, sagittal, and double-oblique transverse views (Fig. 1a). Image reconstruction was performed in 5% intervals from R-wave to R-wave; all 20 phases were loaded into an external workstation. For the LVOT measurements, mid-systolic data sets (20 or 30% of the RR interval) were used. The LVOT from the tip of the septum to the aortic annulus was equally sliced into four parts and each parameter was measured (LVOT 1 = tip of the septum, LVOT 4 = the aortic annulus). These measurements were performed using commercial software (zioTerm2009; Ziosoft Inc, Tokyo, Japan).

### 3D TEE measurements of LVOT

From the full-volume mode 3D data sets, the two orthogonal long-axis views of LVOT were extracted. A third plane, which was perpendicular to the two long-axis planes, was shifted to adjust the orthogonal 2D cutting plane of the LVOT with quantitative software (QLAB cardiac 3DQ, Philips Medical Systems, Andover, MA, USA). After selecting the mid-systolic frame in which maximal LVOT was visualized, the multiplanar reconstruction planes were aligned at each level of the LVOT to measure the LVOT short and



**Fig. 1** Left ventricular outflow tract (LVOT) assessed using (a) multi-detector computed tomography (MDCT) and (b) three-dimensional (3D) transesophageal echocardiography (TEE)

long axis diameters and areas (LVOT 1 = tip of the septum, LVOT 4 = the aortic annulus, Fig. 1b). The LVOT sphericity index (short/long diameter) was also assessed.

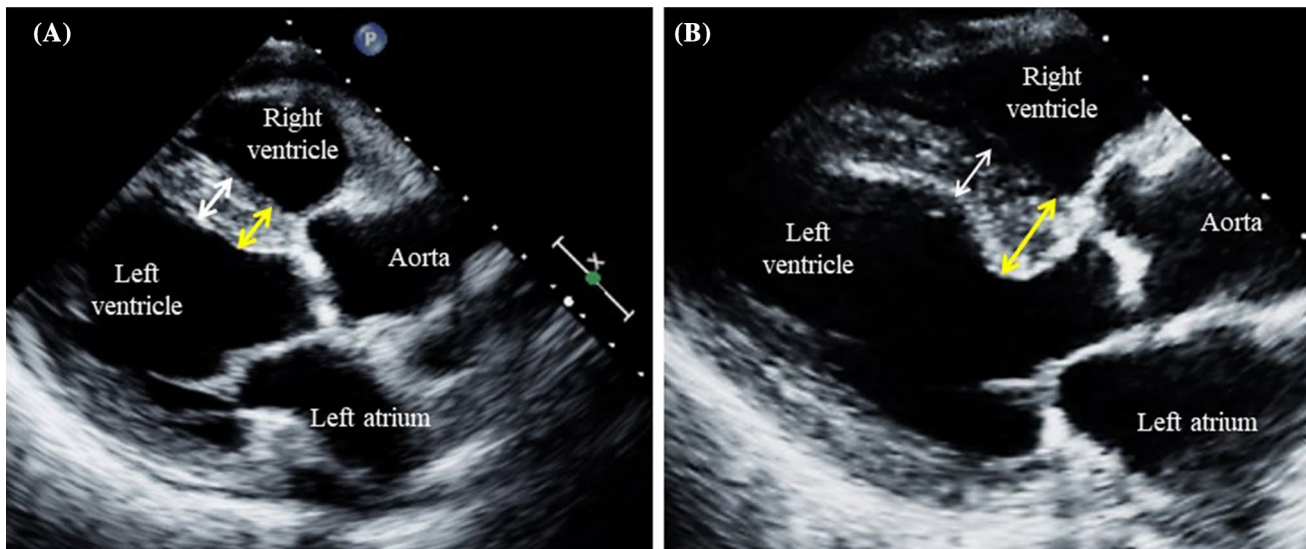
## 2D TTE

Comprehensive TTE, including 2D and Doppler echocardiography, was performed using commercially available ultrasound equipment according to the American Society of Echocardiography guidelines within 1 week before and after TEE [11]. The aortic valve jet velocity was recorded from the multiple acoustic windows to obtain the highest velocity signal. The AVA was calculated using the time–velocity integral of the aortic valve (AV) and LVOT spectral curves in the standard continuity equation. SV was determined using the velocity–time integral (VTI) from pulsed wave Doppler echocardiography at the LVOT  $\times$  LV outflow area, which was determined using the following formula:  $3.14 \times (\text{LVOT diameter}/2)^2$ . The LVOT diameters were measured carefully using the zoom mode of the parasternal long-axis view in mid-systole from the black-and-white interface at the level of the aortic annulus [12]. LVOT velocity was recorded with pulsed Doppler using an apical approach in the 5-chamber view or in the apical long-axis view. The pulsed Doppler sample volume was positioned just proximal to the aortic valve with a length of 3–5 mm. The relative wall thickness was estimated as  $2 \times (\text{diastolic LV posterior wall thickness})/$

LV end-diastolic diameter [13]. The LV mass was calculated using linear measurement. The maximum left atrial volume was measured according to the biplane Simpson's method and indexed to the body surface area. The peak early and late diastolic velocities of LV inflow (E and A velocity), deceleration time of early diastolic velocity, and peak early diastolic velocity on the septal corner of the mitral annulus (E') were measured in the apical four-chamber view. The ratio of the upper septal wall thickness to the mid-septum wall thickness in diastole was measured to determine the degree of USH. USH was defined according to the following criteria: (1) upper septum knuckle evaluated by visual assessment, (2) upper interventricular septum thickness  $\geq 1.4$  cm, and (3) ratio of upper septal wall thickness to mid-septal wall thickness  $\geq 1.3$  (Fig. 2) [14, 15].

## 3D TTE

3D TTE was also performed using an iE33 scanner (Philips Medical Systems) equipped with fully sampled matrix-array transducer (X3-1) for 3D data acquisition in AS patients and controls. Full-volume data sets were acquired from the apical transducer position during held respiration. To ensure the inclusion of the entire LV volumes within the pyramidal scan volume with a relatively higher volume rate, data sets throughout one cardiac cycle were acquired using the wide-angle mode, wherein four wedge-shaped sub-volumes were



**Fig. 2** Example cases of non-upper septal hypertrophy (a) and upper septal hypertrophy (b) in aortic stenosis. Case A met none of the following USH criteria: (1) upper septum knuckle evaluated with visual assessment, (2) upper interventricular septum thickness of  $\geq 1.4$  cm (1.1 cm), and (3) ratio of upper septal wall thickness to mid-septal wall thickness of  $\geq 1.3$  (1.0). Case B met all the following USH cri-

teria: (1) upper septum knuckle evaluated with visual assessment, (2) upper interventricular septum thickness of  $\geq 1.4$  cm (1.5 cm), and (3) ratio of upper septal wall thickness to mid-septal wall thickness of  $\geq 1.3$  (1.4). White arrow: mid-septal wall thickness. Yellow arrow: upper septal wall thickness

acquired with electrocardiographic gating during a single 5–7-s breath hold. A 3D volumetric assessment of LV was performed according to the biplane Simpson's method using data extracted from 3D data sets with commercially available quantitative software (3DQ, QLAB, version 9.0, Philips Medical Systems, Andover, MA).

### Statistical analysis

The results are expressed as mean  $\pm$  standard deviation (SD) or percentage unless otherwise specified. Data for the USH and non-USH groups were compared using Student's *t* test, Chi-squared test, or Fisher's exact test as appropriate. Differences were considered significant if  $P < 0.05$ . Pearson's correlation coefficient was used to evaluate the correlation between two parameters. Bland–Altman plots were used to evaluate differences in LVOT areas using 3D TEE and MDCT. The mean differences and limits of agreement were reported. Bland–Altman plots were also used to evaluate differences in SV between Doppler and 3D methods. Both the interobserver and intraobserver variabilities for LVOT areas measured with 3D TEE and MDCT were obtained according to blinded analysis of 10 random images by two independent observers at two different time points. The results were analyzed using both an intraclass correlation coefficient for absolute agreement (ICCa) and the Bland–Altman method. Statistical analyses were performed with SPSS 22.0 software (SPSS, Inc, Chicago, IL, USA).

## Results

### Protocol 1

The LVOT parameters were successfully measured on MDCT and 3D TEE in all patients. Baseline and echocardiographic findings in this protocol are summarized in Table 1. Figure 3 shows the linear correlation and Bland–Altman plot between MDCT and 3D TEE measurements in each LVOT area. All LVOT areas measured using 3D TEE were slightly, but significantly smaller than those measured using MDCT; however, a favorable correlation was found between the two imaging modalities (Fig. 3,  $r = 0.846$ – $0.941$ ).

### Protocol 2

#### Comparisons in LVOT geometry between the three groups

The baseline characteristics are summarized in Table 2. Of the study patients, 64 were men (49.6%). The mean age of patients was  $75 \pm 9$  years (range, 55–89 years), and 41 of them had USH (31.8%). No differences in the demographic findings without the prevalence of coronary artery disease were found between the USH and non-USH groups. Moreover, no differences in the prevalence of left ventricular asynergy or scar in antero-septal area were found between the two groups (6.8 vs. 4.9%,  $P = 0.523$ ). The LVOT geometries in the three groups are shown in Table 3. No differences in LVOT short and long

**Table 1** Baseline and echocardiographic characteristics in protocol 1 ( $n=20$ )

Variable	( $N=20$ )
<b>Clinical characteristics</b>	
Age (years)	$80 \pm 8$
Male (%)	51
Height (cm)	$154 \pm 10$
Body weight (kg)	$54 \pm 10$
BSA ( $m^2$ )	$1.51 \pm 0.18$
Systolic BP (mmHg)	$120 \pm 31$
Diastolic BP (mmHg)	$70 \pm 19$
HR (bpm)	$72 \pm 15$
<b>Echocardiographic findings</b>	
AVA ( $cm^2$ )	$0.68 \pm 0.26$
Indexed AVA ( $cm^2/m^2$ )	$0.45 \pm 0.16$
Peak velocity (m/s)	$4.0 \pm 1.2$
Mean PG (mm Hg)	$44 \pm 32$
Severe ( $AVA \leq 1.0 cm^2$ ) $n$ (%)	18 (90%)
SV <sub>Dopp</sub> (ml)	$67 \pm 20$
SVI <sub>Dopp</sub> ( $ml/m^2$ )	$44 \pm 13$
LVMI ( $g/m^2$ )	$117 \pm 33$
LVDd (mm)	$47 \pm 7$
LVDs (mm)	$30 \pm 7$
EDV (ml)	$96 \pm 34$
ESV (ml)	$43 \pm 31$
LVEF (%)	$62 \pm 15$
RVSP (mm Hg)	$37 \pm 16$
E/A	$0.94 \pm 0.96$
E/E'	$17.0 \pm 9.6$

BP blood pressure; HR heart rate; AVA aortic valve area; PG pressure gradient; SV stroke volume; SVI stroke volume index; LVMI left ventricular mass index; LVDd left ventricular end-diastolic diameter; LVDs left ventricular end-systolic diameter; EDV end-systolic volume; ESV end-systolic volume; RVSP right ventricular systolic pressure

diameters, area or shape were found between the non-USH group and controls. Although the USH group had smaller short and long diameters, smaller LVOT area, and lower sphericity index than the non-USH group at LVOT 1, the tip of the septum, and LVOT 2, no significant differences in LVOT area and the sphericity index at LVOT-3 and -4 or the aortic annulus were observed between the two groups. The valve annulus of peripheral side (LVOT-3 or -4) was larger than that of the left ventricle central side (LVOT-1 or -2) in the controls and non-USH group, whereas the left ventricle side was smaller than the valve annulus in the USH group. The representative cases are shown in Fig. 4.

## Impact of USH on measurement of left ventricular SV and AVA

The results of standard 2D TTE are shown in Table 2. No significant difference in the measured SV was found between Doppler echocardiography and 3D TTE in the controls ( $58 \pm 9$  vs.  $55 \pm 16$  ml,  $P=0.314$ ) and the non-USH group ( $56 \pm 15$  vs.  $56 \pm 16$  ml,  $P=0.264$ ; Fig. 5). However, the USH group revealed a significantly greater SV calculated with the Doppler method than that obtained with the 3D TTE method (Fig. 5). Moreover, no differences in peak velocity or mean pressure gradient between the USH and the non-USH groups were found; however, the USH group had greater AVA than the non-USH group ( $0.89 \pm 0.26$  vs.  $0.73 \pm 0.24 cm^2$ ,  $P=0.002$ ).

## Reproducibility

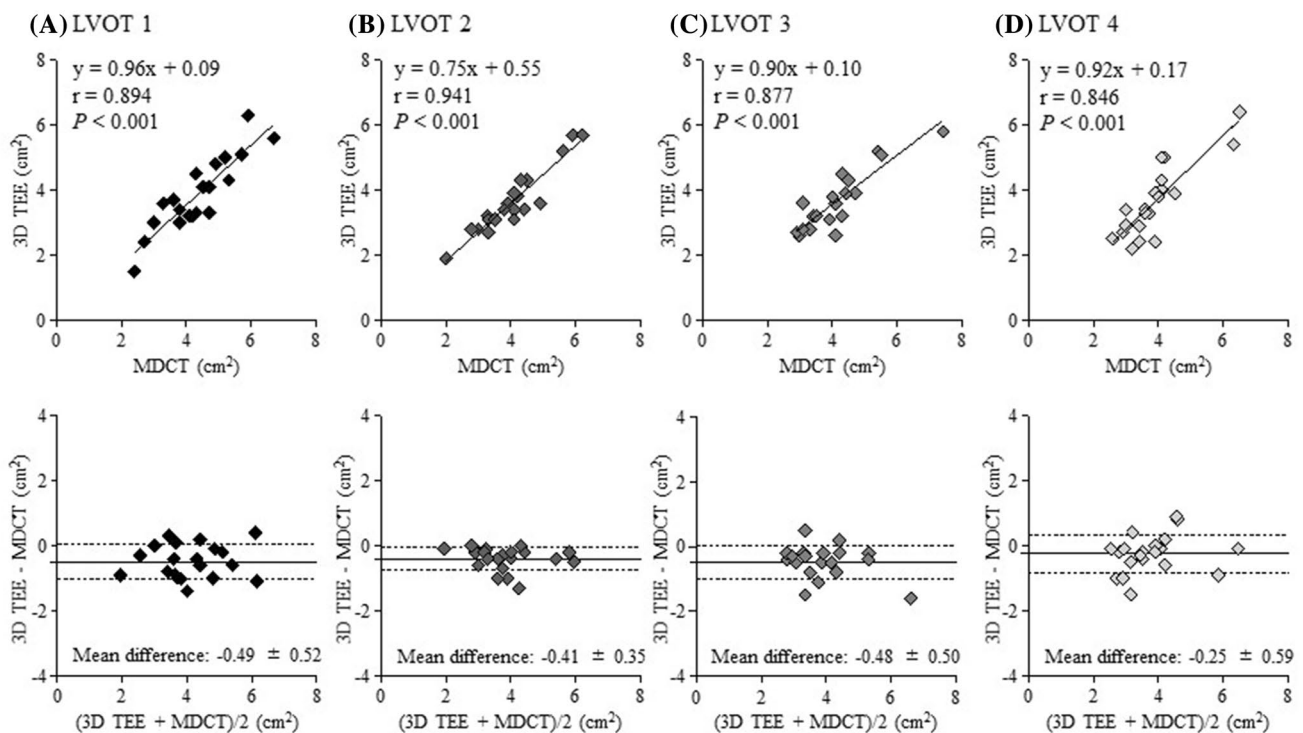
The intraobserver variabilities assessed using the ICCa were 0.89–0.93 for LVOT areas measured with 3D TEE and 0.90–0.94 for LVOT areas measured with MDCT. The interobserver variabilities were 0.87–0.92 for LVOT areas measured with 3D TEE and 0.88–0.93 for LVOT areas measured with MDCT. The Bland–Altman method showed that interobserver and intraobserver variabilities were  $0.32 \pm 0.10$  and  $0.34 \pm 0.11 cm^2$  for the LVOT areas measured with 3D TEE, and  $0.30 \pm 0.11$  and  $0.32 \pm 0.10 cm^2$  for the LVOT areas measured with MDCT, respectively.

## Discussion

The main findings of this study were as follows: (1) the LVOT parameters obtained by 3D TEE were well-correlated with those by MDCT, (2) more than 30% AS patients had USH, (3) USH affected not distal, but proximal LVOT geometry, and (4) the Doppler method overestimated SV in AS patients with USH, which might lead to an underestimation of the AS severity.

## Comparison of LVOT morphology between the USH and non-USH groups

The evaluation of aortic root geometry is increasingly important for decision-making in patients with AS and usually performed using MDCT [6–10, 16]. The earlier studies defined the aortic root from the aortic annulus to the sinotubular junction, not including LVOT [5–10]. 3D imaging techniques have provided the unique anatomic views of cardiac structures and improved the definitions of spatial relation in complex abnormalities. To the best of our knowledge, this study first reports the use of 3D TEE to compare the LVOT geometry in AS patients with and without



**Fig. 3** Linear correlations (upper panel) and Bland–Altman analysis (lower panel) of LVOT parameters on MDCT and 3D TEE. **a** LVOT 1, **b** LVOT 2, **c** LVOT 3, and **d** LVOT 4

USH as well as controls. The LVOT areas measured with 3D TEE were slightly, but significantly smaller than those with MDCT; the results of our study consisted with those of earlier studies [6–10, 16]. This underestimation might be related with lower temporal resolution of 3D TEE images. The presence of calcification might also affect smaller 3D TEE planimetric measurements. The USH group revealed shorter LVOT short diameters and smaller areas at the tip of the septum than the non-USH group, resulting in a more elliptical LVOT shape. Our study result was consistent with the result of an earlier study demonstrating an association between the sigmoid-shaped septum versus the left ventricle and the ascending aorta, which might lead to shorter anterior–posterior diameters (short-diameter) and more elliptical shape of the LVOT [15].

### Associations between LVOT geometry and Doppler-derived SV

The primary parameters proposed for the clinical evaluation of AS severity are: (1) peak velocity, (2) mean pressure gradient, and (3) AVA calculated with the continuity equation. Some recent studies have reported decreased peak velocity and mean pressure gradient regardless of ejection fraction [17–19]; thus, AVA calculated by the continuity equation is vital in the assessment of disease severity. The calculation

of the valve area by the continuity equation requires three measurements as follows: (1) AS jet velocity evaluated with continuous wave Doppler, (2) LVOT diameters for the calculation of a circular cross-sectional area, and (3) LVOT velocity recorded with pulsed Doppler echocardiography. Its pitfalls are well-known due to inherent assumptions and simplifications. Some studies demonstrated that the calculations of continuity equation-derived AVA using 2D TTE underestimated AVA because of the elliptical shape of LVOT with its shorter anteroposterior diameters [20, 21]. Garcia, et al. conducted a subsequent assessment study using multimodal imaging and reported that the underestimation of LVOT area with TTE was compensated by the overestimation of LVOT VTI, thereby resulting in a good concordance between TTE and cardiac magnetic resonance for the estimation of AVA [22]. In our study, no difference in SV was found between the Doppler and 3D TTE methods in the non-USH group; however, the USH group had greater SV calculated by Doppler echocardiography than 3D TTE because of the greater VTI in this group. This difference is assumed not due to an oval-shaped LVOT, but faster blood flow in the USH group. Figure 6 shows the prevalence of a low-flow status (SV index,  $\leq 35$  ml/m<sup>2</sup>) in the non-USH and USH groups. No significant differences in the prevalence of the low-flow status between the two methods were found in the non-USH group (19.5 vs. 23.7%,  $P = 0.624$ ); however,

**Table 2** Baseline characteristics

	Controls (N=30)	Non-USH (N=88)	USH (N=41)	P value non-USH versus USH	P value non-USH versus controls	P value USH versus controls
<b>Clinical characteristics</b>						
Age (years)	61 ± 13	74 ± 10	76 ± 9	0.214	< 0.001	< 0.001
Male n (%)	22 (54)	47 (53)	17 (42)	0.174	0.519	0.321
BSA (m <sup>2</sup> )	1.65 ± 0.18	1.53 ± 0.17	1.54 ± 0.19	0.889	0.022	0.016
Systolic BP (mmHg)	128 ± 26	129 ± 26	136 ± 24	0.927	0.928	0.137
Diastolic BP (mmHg)	75 ± 15	74 ± 15	73 ± 15	0.911	0.133	0.414
Heart rate (bpm)	70 ± 14	73 ± 20	70 ± 12	0.912	0.718	0.882
Hemoglobin (g/dl)	13.6 ± 6.6	13.7 ± 6.5	14.8 ± 4.3	0.567	0.933	0.213
<b>Medical history n (%)</b>						
Hypertension	–	52 (59)	30 (73)	0.128	–	–
Dyslipidemia	–	23 (34)	15 (37)	0.913	–	–
Diabetes mellitus	–	25 (28)	12 (29)	0.788	–	–
Coronary artery disease	–	29 (33)	6 (15)	0.009	–	–
Chronic kidney disease	–	27 (31)	15 (37)	0.824	–	–
<b>2D transthoracic echocardiographic findings</b>						
AVA (cm <sup>2</sup> )	–	0.73 ± 0.24	0.89 ± 0.26	0.002	–	–
Indexed AVA (cm <sup>2</sup> /m <sup>2</sup> )	–	0.46 ± 0.21	0.58 ± 0.15	0.003	–	–
Peak velocity (m/s)	–	4.0 ± 1.1	4.1 ± 0.9	0.172	–	–
Mean PG (mm Hg)	–	39 ± 25	33 ± 18	0.115	–	–
Severe (AVA ≤ 1.0 cm <sup>2</sup> ) n (%)	–	76 (86)	34 (83)	0.821	–	–
LVOT VTI (cm)	18 ± 6	20 ± 3	23 ± 4	0.001	0.003	< 0.001
LVOT peak velocity (cm/s)	82 ± 24	86 ± 16	101 ± 43	0.028	0.072	0.014
SV <sub>Dopp</sub> (ml)	58 ± 9	56 ± 15	73 ± 15	0.027	0.103	0.012
SVI <sub>Dopp</sub> (ml/m <sup>2</sup> )	35 ± 10	36 ± 15	47 ± 12	0.016	0.007	0.001
SV <sub>Simpson</sub> (ml)	57 ± 15	61 ± 14	57 ± 11	0.239	0.284	0.434
LVMI (g/m <sup>2</sup> )	72 ± 21	115 ± 31	113 ± 29	0.933	< 0.001	< 0.001
Aortic annulus diameter (cm)	2.0 ± 0.3	2.0 ± 0.2	2.0 ± 0.2	0.462	0.762	0.323
LVDd (mm)	45 ± 4	47 ± 6	46 ± 5	0.190	0.053	0.434
LVDs (mm)	29 ± 4	31 ± 7	28 ± 5	0.014	0.052	0.822
EDV (mL)	90 ± 20	100 ± 30	87 ± 22	0.047	0.053	0.821
ESV (mL)	33 ± 11	39 ± 21	30 ± 11	0.022	0.034	0.391
LVEF (%)	63 ± 6	61 ± 8	68 ± 8	0.043	0.651	0.201
RVSP (mm Hg)	25 ± 4	31 ± 10	31 ± 11	0.726	0.001	0.002
E/A	0.97 ± 0.42	0.94 ± 0.64	0.78 ± 0.33	0.216	0.283	0.101
E/E′	7.3 ± 2.0	17 ± 9	15 ± 7	0.014	< 0.001	0.004
<b>3D transthoracic echocardiography</b>						
EDV (ml)	91 ± 22	100 ± 31	93 ± 30	0.028	0.041	0.202
ESV (ml)	36 ± 10	44 ± 14	32 ± 16	0.001	0.001	0.121
SV (ml)	55 ± 16	56 ± 16	60 ± 18	0.340	0.433	0.223
SVI (ml/m <sup>2</sup> )	33 ± 11	37 ± 12	39 ± 10	0.328	0.243	0.101
EF (%)	60 ± 5	56 ± 9	65 ± 9	0.018	0.092	0.081

USH upper septal hypertrophy; LVOT left ventricular outflow tract; VTI velocity–time integral; the other abbreviations are shown in Table 1

the USH group had a lower prevalence rate of low-flow status calculated using the Doppler method than 3D TTE method (7.3 vs. 18.4%,  $P < 0.001$ ). In addition, measurement errors of SV directly affected AVA estimation calculated using a continuity equation as the gold standard method.

Therefore, the continuity equation based on the 2D Doppler method may underestimate AS severity, especially in AS patients with USH. Figure 7 presents the association between VTI and SVs calculated with Doppler echocardiography and 3D TTE. A positive correlation was recognized

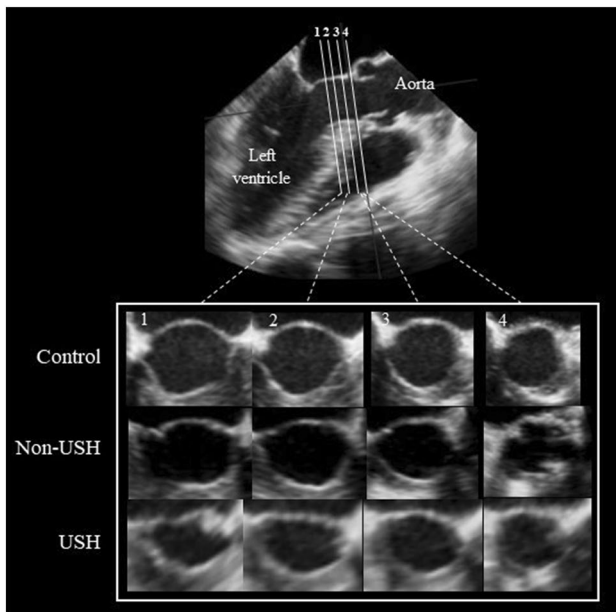
**Table 3** LVOT geometry in each group

	Controls (N=30)	Non-USH (N=88)	USH (N=41)	P value (non-USH vs. USH)
LVOT 1 short (cm)	2.08 ± 0.37	2.02 ± 0.30	1.66 ± 0.35 <sup>a</sup>	< 0.001
Long (cm)	2.76 ± 0.54	2.73 ± 0.50	2.45 ± 0.37	0.013
area (cm <sup>2</sup> )	4.64 ± 1.65	4.32 ± 1.36	3.25 ± 1.05 <sup>a</sup>	< 0.001
Sphericity index	0.76 ± 0.09	0.74 ± 0.11	0.68 ± 0.12 <sup>a</sup>	< 0.001
LVOT 2 short (cm)	1.98 ± 0.30	1.96 ± 0.28	1.67 ± 0.29 <sup>a</sup>	< 0.001
Long (cm)	2.51 ± 0.48	2.52 ± 0.45	2.35 ± 0.34	0.245
Area (cm <sup>2</sup> )	3.97 ± 1.28	3.89 ± 1.2	3.16 ± 0.87 <sup>b</sup>	< 0.001
Sphericity index	0.79 ± 0.1	0.79 ± 0.12	0.71 ± 0.11 <sup>a</sup>	0.002
LVOT 3 short (cm)	1.98 ± 0.26	1.93 ± 0.27	1.81 ± 0.28	0.081
Long (cm)	2.27 ± 0.38	2.37 ± 0.37	2.29 ± 0.40	0.438
Area (cm <sup>2</sup> )	3.59 ± 0.99	3.59 ± 1.0	3.29 ± 0.90	0.239
Sphericity index	0.88 ± 0.12	0.82 ± 0.13	0.80 ± 0.12 <sup>b</sup>	0.524
LVOT 4 short (cm)	1.97 ± 0.23	1.92 ± 0.27	1.90 ± 0.27	0.889
Long (cm)	2.22 ± 0.36	2.25 ± 0.41	2.26 ± 0.38	0.924
Area (cm <sup>2</sup> )	3.49 ± 0.88	3.41 ± 1.1	3.41 ± 0.97	0.842
Sphericity index	0.89 ± 0.1	0.86 ± 0.13	0.86 ± 0.13	0.924

Abbreviations are shown in Table 2

<sup>a</sup>P < 0.01 versus controls

<sup>b</sup>P < 0.05 versus controls



**Fig. 4** Examples of LVOT in each group

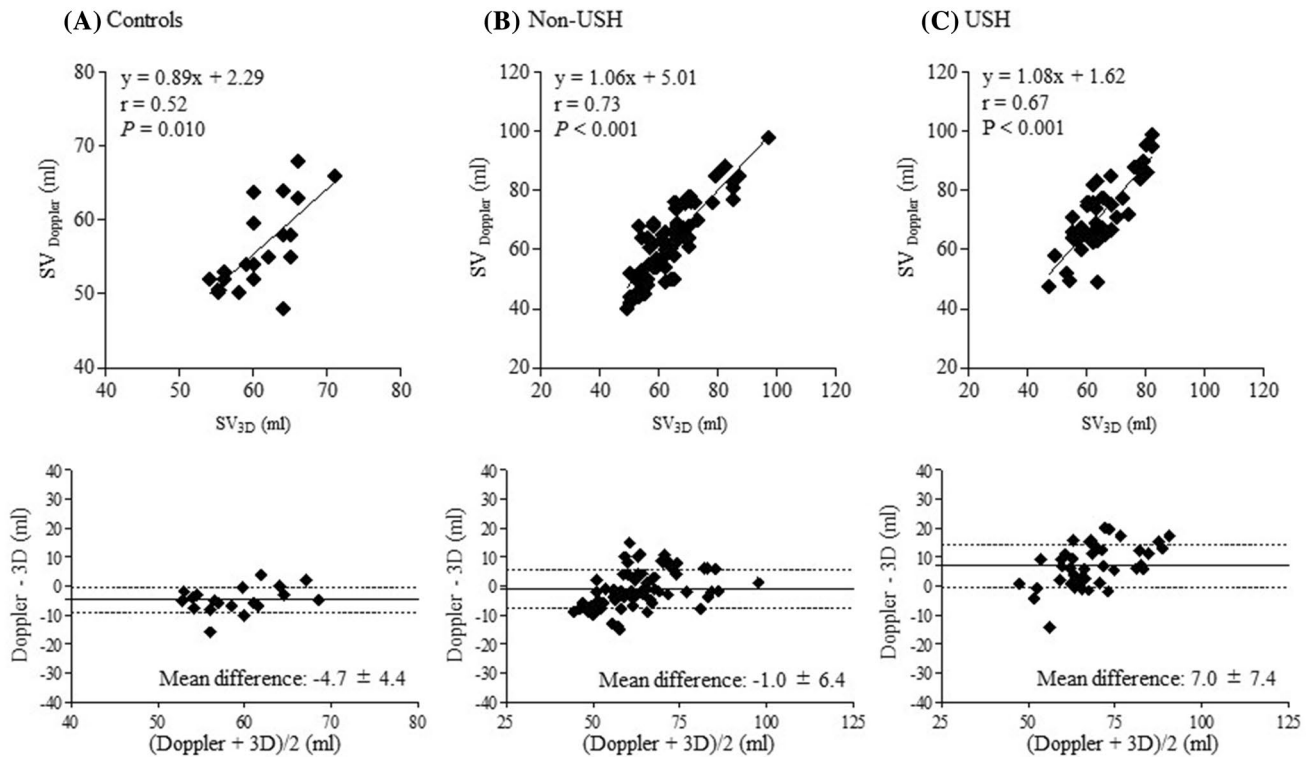
between VTI and difference in SVs (Doppler-3D). At the approximately 20 cm VTI, the SV calculated with Doppler echocardiography was consistent with that calculated with 3D TTE; in such cases, many patients in the USH group had VTI > 25 cm. Figure 8 shows the representative LVOT VTI in patients with USH and non-USH. The results of our study supported that of Garcia et al. because the mean VTI was

21 cm in their study. However, the USH group had higher VTI than the non-USH group, which might lead to the overestimation of SV [22]. Currently, flow-pressure status is considered crucial in the prognostic assessment [17–19, 23, 24] and it remains uncertain why normal-flow and low-gradient can be observed. A recent meta-analysis conducted by Dayan V et al. has reported that AS patients with normal-flow and low-gradient despite preserved ejection fraction have similar outcomes to those with normal-flow and high-gradient [25]. Their study discussed that the measurement error of SV might be the reason why AS patients with normal-flow low-gradient had similar outcomes to those with normal-flow high-gradient. This study suggested that the SV derived from the Doppler method should be overestimated rather than showing the real transvalvular flow in the USH group, which might be associated with errors in the measurement of SV. Of the patients in the USH group, 15% patients might be underestimated as having low-flow (SV index  $\leq 35$  ml/m<sup>2</sup>, Fig. 7). In such cases, 3D assessment of SV might be crucial for evaluating disease severity in patients with AS [26–28].

## Study limitations

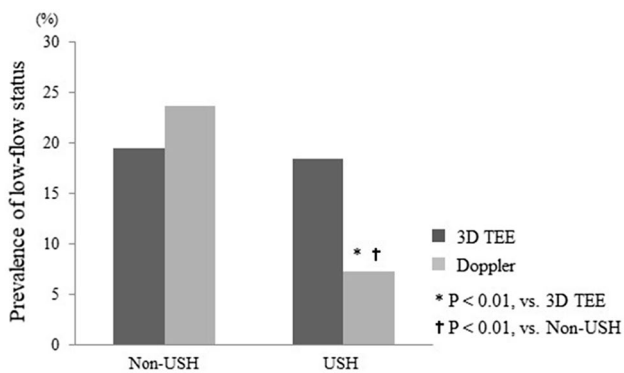
Our study has several limitations. First, the study population consisted entirely of Japanese patients, and the relevance of this study to patients of other ethnicities needs to be confirmed with future research. Second, the MDCT and TEE evaluations were not performed on the same day. Third,





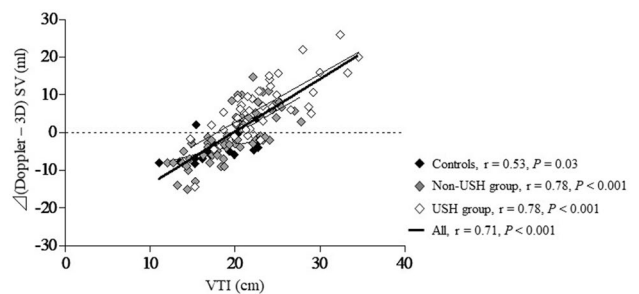
**Fig. 5** Linear correlations (upper panel) and Bland–Altman scatter plot (lower panel) determining the agreement in the measurement of left ventricular stroke volume (SV) calculated by Doppler echocardiography and 3D TTE as a gold standard. SV was underestimated by

Doppler echocardiography compared with 3D TTE in the controls (a) and the non-USH group (b); however, SV was overestimated by Doppler echocardiography compared with 3D TTE in the USH group (c)



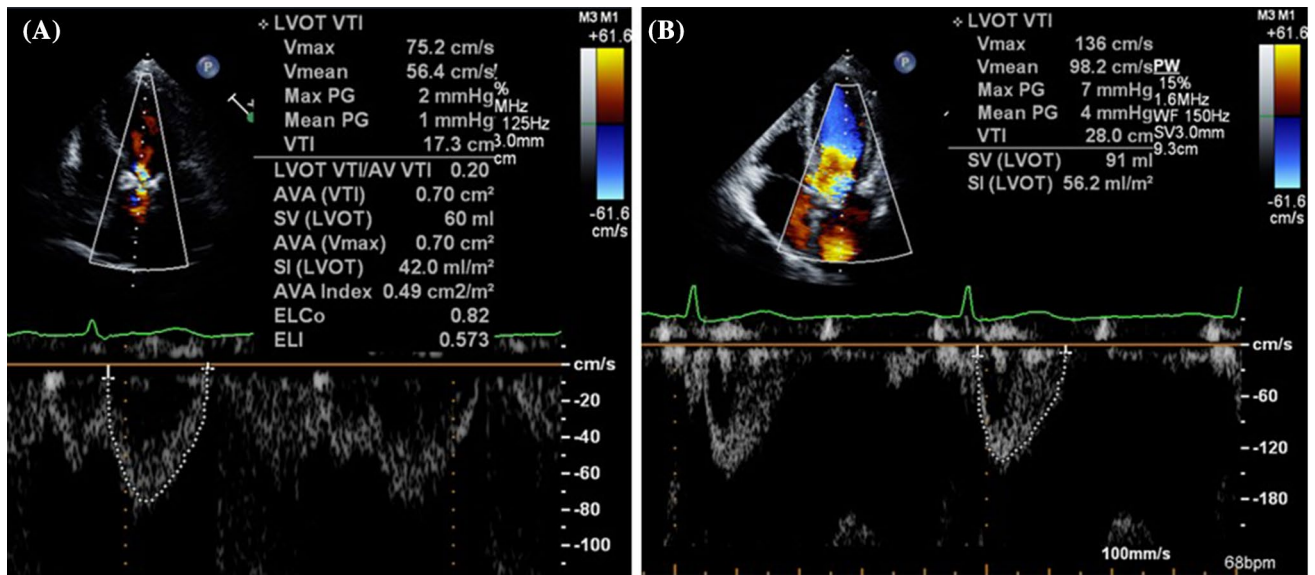
**Fig. 6** Prevalence of low-flow status ( $SV \text{ index} \leq 35 \text{ ml/m}^2$ ) in the non-USH group (left) and the USH group (right). No significant differences in the prevalence of low-flow status between the two methods were observed in the non-USH group (19.5 vs. 23.7%,  $P = 0.624$ ); however, the USH group had the lower prevalence rate of low-flow status calculated using the Doppler method than 3D TTE method (7.3 vs. 18.4%,  $P < 0.001$ )

the anesthetics used during TEE and the  $\beta$ -blockers used during MDCT might have affected the loading conditions. Forth, because of the differences in heart rate and frame rate between the MDCT and 3D TEE studies, the measurements



**Fig. 7** Linear correlation between velocity–time integral and  $\Delta(\text{Doppler} - 3\text{D}) \text{ SV}$

were not performed at exactly the same point during the cardiac cycle. Fifth, this study employed 3D TTE which was thought to be superior to two-dimensional echocardiography and regarded as a gold standard to compare SV evaluated by Doppler echocardiography between the USH and non-USH groups, we did not have invasive measurements. Sixth, the control group in protocol 2 was not a strict representation of controls because the patients had some comorbidities affecting the LVOT geometry. However, the control group in earlier MDCT and TEE studies on aortic root geometry including the LVOT also had the same prevalence of those



**Fig. 8** Examples of LVOT VTI in each group (a non-USH, b USH)

comorbidities [7–10]. Finally, this study included only AS patients; however, we found USH in not only AS patients, but also in the other population. Further investigation with a larger population is warranted

## Conclusions

3D TEE can provide a precise assessment of LVOT geometry in patients with AS. USH affects the LVOT geometry, which might lead to inaccurate assessments of AS severity.

## Compliance with Ethical Standards

**Conflict of interest** Dan Koto, Masaki Izumo, Takafumi Machida, Kihei Yoneyama, Tomomi Suzuki, Ryo Kamijima, Yasuyuki Kobayashi, Tomoo Harada, and Yoshihiro J. Akashi declare that they have no conflicts of interest.

**Human rights statements and informed consent** All procedure 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 revisions. The participants were well-informed prior to the test; written informed consent was obtained before enrollment.

## References

- Nkomo VT, Gardin JM, Skelton TN, et al. Burden of valvular heart diseases: a population-based study. *Lancet*. 2006;368:1005–11.
- Carabello BA, Paulus WJ. Aortic stenosis. *Lancet*. 2009;373:956–66.
- Carabello BA. Clinical practice. Aortic stenosis. *N Engl J Med*. 2002;346:677–82.
- Saikrishnan N, Kumar G, Sawaya FJ, et al. Accurate assessment of aortic stenosis: a review of diagnostic modalities and hemodynamics. *Circulation*. 2014;129:244–53.
- Delgado V, Ng AC, Schuijff JD, et al. Automated assessment of the aortic root dimensions with multidetector row computed tomography. *Ann Thorac Surg*. 2011;91:716–23.
- Tops LF, Wood DA, Delgado V, et al. Noninvasive evaluation of the aortic root with multislice computed tomography implications for transcatheter aortic valve replacement. *J Am Coll Cardiol Img*. 2008;1:321–30.
- Akhtar M, Tuzcu EM, Kapadia SR, et al. Aortic root morphology in patients undergoing percutaneous aortic valve replacement: evidence of aortic root remodeling. *J Thorac Cardiovasc Surg*. 2009;137:950–6.
- Stolzmann P, Knight J, Desbiolles L, et al. Remodelling of the aortic root in severe tricuspid aortic stenosis: implications for transcatheter aortic valve implantation. *Eur Radiol*. 2009;19:1316–23.
- Otani K, Takeuchi M, Kaku K, et al. Assessment of the aortic root using real-time 3D transesophageal echocardiography. *Circ J*. 2010;74:2649–57.
- Wu VC, Kaku K, Takeuchi M, et al. Aortic root geometry in patients with aortic stenosis assessed by real-time three-dimensional transesophageal echocardiography. *J Am Soc Echocardiogr*. 2014;27:32–41.
- Lang RM, Bierig M, Devereux RB, et al. Chamber Quantification Writing Group; American Society of Echocardiography's Guidelines and Standards Committee; European Association of Echocardiography. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr*. 2005;18:1440–63.
- Pibarot P, Clavel MA. Left ventricular outflow tract geometry and dynamics in aortic stenosis: Implications for the echocardiographic assessment of aortic valve area. *J Am Soc Echocardiogr*. 2015;28:1267–9.

13. Goor D, Lillehei W, Edwards JE. The “sigmoid septum” variation in the contour of the left ventricular outlet. *AJR Am J Roentgenol.* 1969;107:366–76.
14. Diaz T, Pencina MJ, Benjamin EJ, et al. Prevalence, clinical correlates, and prognosis of discrete upper septal thickening on echocardiography: the Framingham Heart Study. *Echocardiography.* 2009;26:247–53.
15. Funabashi N, Umazume T, Takaoka H, et al. Sigmoid shaped interventricular septum exhibit normal myocardial characteristics and has a relationship with aging, ascending aortic sclerosis and its tilt to left ventricle. *Int J Cardiol.* 2013;168:4484–8.
16. Jilaihawi H, Kashif M, Fontana G, et al. Cross-sectional computed tomographic assessment improves accuracy of aortic annular sizing for transcatheter aortic valve replacement and reduces the incidence of paravalvular aortic regurgitation. *J Am Coll Cardiol.* 2012;59:1275–86.
17. Hachicha Z, Dumesnil JG, Bogaty P, et al. Paradoxical low-flow, low-gradient severe aortic stenosis despite preserved ejection fraction is associated with higher afterload and reduced survival. *Circulation.* 2007;115:2856–64.
18. Lancellotti P, Magne J, Donal E, et al. Clinical outcome in asymptomatic severe aortic stenosis: insights from the new proposed aortic stenosis grading classification. *J Am Coll Cardiol.* 2012;59:235–43.
19. Ozkan A, Hachamovitch R, Kapadia SR, et al. Impact of aortic valve replacement on outcome of symptomatic patients with severe aortic stenosis with low gradient and preserved left ventricular ejection fraction. *Circulation.* 2013;128:622–31.
20. Doddamani S, Grushko MJ, Makaryus AN, et al. Demonstration of left ventricular outflow tract eccentricity by 64-slice multi-detector CT. *Int J Cardiovasc Imaging.* 2009;25:175–81.
21. Saitoh T, Shiota M, Izumo M, et al. Comparison of left ventricular outflow geometry and aortic valve area in patients with aortic stenosis by 2-dimensional versus 3-dimensional echocardiography. *Am J Cardiol.* 2012;109:1626–31.
22. Garcia J, Kadem L, Larose E, et al. Comparison between cardiovascular magnetic resonance and transthoracic Doppler echocardiography for the estimation of effective orifice area in aortic stenosis. *J Cardiovasc Magn Reson.* 2011;13:25.
23. Le Ven F, Freeman M, Webb J, et al. Impact of low flow on the outcome of high-risk patients undergoing transcatheter aortic valve replacement. *J Am Coll Cardiol.* 2013;62:782–8.
24. Clavel MA, Berthelot-Richer M, Le Ven F, et al. Impact of classic and paradoxical low flow on survival after aortic valve replacement for severe aortic stenosis. *J Am Coll Cardiol.* 2015;65:645–53.
25. Dayan V, Vignolo G, Magne J, et al. Outcome and impact of aortic valve replacement in patients with preserved LVEF and low-gradient aortic stenosis. *J Am Coll Cardiol.* 2015;66:2594–603.
26. Poh KK, Levine RA, Solis J, et al. Assessing aortic valve area in aortic stenosis by continuity equation: a novel approach using real-time three-dimensional echocardiography. *Eur Heart J.* 2008;29:2526–35.
27. Mehrotra P, Flynn AW, Jansen K, et al. Differential left ventricular outflow tract remodeling and dynamics in aortic stenosis. *J Am Soc Echocardiogr.* 2015;28:1259–66.
28. Sato K, Seo Y, Ishizu T, et al. Reliability of aortic stenosis severity classified by 3-dimensional echocardiography in the prediction of cardiovascular events. *Am J Cardiol.* 2016;118:410–7.