Estimating the Haemodynamic Streamline Vena Contracta as the Effective Orifice Area Measured from Reconstructed Multislice Phase-contrast MR Images for Patients with Moderately Accelerated Aortic Stenosis

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**Purpose:** In aortic stenosis (AS), the discrepancy between moderately accelerated flow and effective orifice area (EOA) continues to pose a challenge. We developed a method of measuring the vena contracta area as hemodynamic EOA using cardiac MRI focusing on AS patients with a moderately accelerated flow to solve the problem that AS severity can currently be determined only by echocardiography.

**Methods:** We investigated 40 patients with a peak transvalvular velocity > 3.0 m/s on transthoracic echocardiography (TTE). The patients were divided into highly accelerated and moderately accelerated AS groups according to whether or not the peak transvalvular velocity was ≥ 4.0 m/s. From the multislice 2D cine phase-contrast MRI data, the cross-sectional area of the vena contracta of the reconstructed streamline in the Valsalva sinus was defined as MRI-EOAs. Patient symptoms and echocardiography data, including EOA (defined as TTE-EOA), were derived from the continuity equation using TTE.

**Results:** All participants in the highly accelerated AS group (n = 19) showed a peak velocity ≥ 4.0 m/s in MRI. Eleven patients in the moderately accelerated AS group (n = 21) had a TTE-EOA < 1.00 cm². In the moderately accelerated AS group, MRI-EOAs demonstrated a strong correlation with TTE-EOAs (r = 0.76, P < 0.01). Meanwhile, in the highly accelerated AS group, MRI-EOAs demonstrated positivity but a moderate correlation with TTE-EOAs (r = 0.63, P = 0.004). MRI-EOAs were overestimated compared to TTE-EOAs. In terms of the moderately accelerated AS group, the best cut-off value for MRI-EOAs was < 1.23 cm², compatible with TTE-EOAs < 1.00 cm², with an excellent prediction of the New York Heart Association classification ≥ III (sensitivity 87.5%, specificity 76.9%).

**Conclusion:** MRI-EOAs may be an alternative to conventional echocardiography for patients with moderately accelerated AS, especially those with discordant echocardiographic parameters.

**Keywords:** aortic stenosis, cardiovascular magnetic resonance imaging, blood flow, diagnosis
Introduction

Recently, aortic stenosis (AS) has become a common comorbidity in older people, it has been increasing in number and has received attention because it causes heart failure. Moreover, transcatheter aortic valve implantation (TAVI) has become a viable option for older people. Transthoracic echocardiography (TTE) is the current standard method for assessing AS severity and plays a key role in the clinical decision-making process. Severe AS is defined by standardized clinical guidelines, including aortic valve area (AVA) ≤ 1.0 cm² calculated by the continuity equation, mean pressure gradient (MG) ≥ 40 mm Hg, and peak aortic flow velocity (Vmax) ≥ 4.0 m/s. However, up to 30% of patients with AS present with discordant echocardiographic parameters of AS severity: MG < 40 mmHg and Vmax < 4.0 m/s with AVA ≤ 1.0 cm². The discordance is associated with multiple factors, including decreased stroke volume (SV) with or without preserved left ventricular ejection fraction (LVEF) and small LV cavity, MG and Vmax do not necessarily correspond to the true AVA. In this context, the decision-making for AS patients with moderately accelerated flow, who are more likely to have discordant parameters, is challenging, and it is fair to say that multi-modality imaging should be considered in the clinical setting, raising the uncertainty of AS severity.

Echocardiography remains the first-line diagnostic tool for AS severity, as previously described. Meanwhile, cardiovascular MRI is a valid alternative to echocardiography when ultrasound images do not have a good resolution because of obesity, chronic lung disease, and having had several surgical procedures, or when echocardiographic measurements are borderline or ambiguous. More recently, time-resolved phase-contrast MRI (PC-MRI) with velocity encoding along all the three flow directions and 3D anatomic coverage, which is termed as 4D flow MRI, has been developed, although it is a relatively novel technology in cardiology and its use is not yet widespread. We introduced a simple technique using accumulated slice conventional 2D cine PC-MRI with three orthogonal velocity axes to assess AS severity by measuring the vena contracta of the stenotic jet after visualization of the Valsalva sinus flow. Vena contracta was visualized with accelerated and condensed flow streamlines around the stenotic jet. In a daily clinical setting, there is a limitation that decision-making depends on the assessment of AS severity using a single modality even while echocardiographic assessment is supported by a large number of studies, making the assessment ambiguous or inconsistent with clinical findings. We hypothesized that another noninvasive modality, such as MRI, could help us to understand the functional severity of AS. Our study aimed to evaluate the feasibility and utility of this blood-flow imaging technique for the estimation of AS severity compared with echocardiographic assessment focusing on AS patients with a moderately accelerated flow.

Materials and Methods

Study protocol

We prospectively investigated 40 AS patients with a Vmax of ≥ 3.0 m/s, as determined by comprehensive Doppler echocardiography. The exclusion criteria were moderate or severe mitral or aortic regurgitation and standard contraindications for MRI. This study was approved by the institutional ethics committees of Kyoto Daini Red Cross Hospital (permission number: SP 2019–33) and was conducted in accordance with the Declaration of Helsinki and all its provisions regarding the investigation of human subjects. Written informed consent was obtained from all the study participants and healthy volunteers before the examinations. To test the validity of the study, especially in the image reconstruction process, two healthy volunteer cases were examined using echocardiography. The exclusion criteria were moderate or severe mitral and aortic regurgitation and standard contraindications for MRI. According to the 2014 American Heart Association and American College of Cardiology (AHA/ACC) Guideline and Echocardiographic Assessment of Valve Stenosis: European Association of Echocardiography and American Society of Echocardiography (EAEASE) recommendations, the study population was divided into two groups depending on Vmax: the moderately accelerated AS group, which included patients with a Vmax of < 4.0 m/s and ≥ 3.0 m/s; and the highly accelerated AS group, which included patients with a Vmax of ≥ 4.0 m/s. In the moderately accelerated AS group, severe AS with LF/LG was classified as follows: the classical LF/LG severe AS is defined in the guidelines and is generally defined as an SVI < 35 mL/m², LVEF < 50%, AVA < 1.0 cm², and MG < 40 mm Hg; paradoxical LF/LG severe AS has a preserved LVEF, which is defined as an LVEF ≥ 50% and the presence of LF and LG with an AVA ≤ 1.0 cm²; normal-flow LG severe AS is defined as an LVEF ≥ 50%, a normal flow state (SVI ≥ 35 mL/m²), and LG with an AVA ≤ 1.0 cm².

All patients underwent routine echocardiography. The average interval between MRI and TTE examinations was 5.9 ± 5.1 (0 to 18) days.

Echocardiographic measurements

Echocardiography was performed using standard, commercially available, equipment, the EPIQ 7 ultrasound system for cardiology (Philips, Andover, MA, USA), by one
sonographer and one cardiologist (K.N. and A.M., respectively) who had over 20 years of experience in their respective fields. LV dimensions were measured according to the recommendations of ASE.20 We recorded pulsed-wave Doppler flow profiles in the LVOT, transmitral flow, and continuous-wave Doppler flow to measure the Vmax and MG of the aortic valve, respectively. The aortic valve effective orifice area (EOA) was calculated using the continuity equation.4 These EOA determinations were defined as TTE-EOAs. The LVEF and SVI were calculated using the modified Simpson method in the apical 4-chamber view. Relative wall thickness (RWT) was calculated by dividing the sum of the septum wall thickness and the posterior wall thickness by the LV diameter in diastole.

**MR imaging**

All MR images were acquired with a clinical 1.5 Tesla MRI scanner (MAGNETOM Avanto; Siemens Healthcare, Erlangen, Germany) with a 6-channel body matrix coil and 24-channel spine matrix coil. Morphology images for contrast-free wall tracking were obtained using a 2D segmented, balanced steady-state free-precession (True FISP) cine sequence with retrospective electrocardiogram (ECG) gating.19 The True FISP cine parameters were as follows: TR 2.50 ms; TE 1.25 ms; flip angle 65°; FOV 360 × 315 mm; matrix size 192 × 192; bandwidth 930 Hz/pixel; calculated cine phase 20; segment number 15; averaging 2; parallel acquisition generalized autocalibrating partially parallel acquisitions (GRAPPA) × 2; slice thickness 6 mm; and slice gap 0. The average scan time was 3.1 ± 1.1 (1.8 to 9.0) min. Multislice 2D cine PC-MRI was performed after 2D cine True FISP imaging with retrospective ECG gating. The 2D cine PC-MRI parameters were as follows: TR 6.76 ms; TE 3.59 ms; flip angle 30°; FOV 360 × 315 mm; matrix size 192 × 192; bandwidth 501 Hz/pixel; calculated cine phase 20; segment number 3; averaging 2; parallel acquisition GRAPPA × 2; slice thickness 6 mm; and slice gap 0.

Fig. 1 Classification of the study population. AS, aortic stenosis; LF/LG AS, low-flow low-gradient severe AS; LVEF, left ventricular ejection fraction; MG, mean pressure gradient; NF/LG AS, normal-flow low-gradient severe AS; Paradoxical LF/LG AS, paradoxical low-flow low-gradient severe AS; SVI, stroke volume index; TTE-EOA, transthoracic echocardiography-derived effective orifice area; Vmax, peak aortic flow velocity.
thickness 6 mm; and slice gap 0. The average scan time was 12.1 ± 1.5 (7.6 to 14.5) min.

Both scans were performed under free-breathing conditions. 3D phase-velocity images (in phase encode, read encode, and slice directions) were obtained by 2D cine PC-MRI. For accurate turbulence estimates, the velocity encoding (VENC) must be sufficiently high to diagnose moderately accelerated flow in AS and set to detect high-flow acceleration. However, high VENC is influenced by noise to a great extent, resulting in unreliable estimates.21

The accelerated flow exceeding the VENC was corrected using 4D flow MRI postprocessing software, iTFlow, version 1.8.5 (Cardio Flow Design, Tokyo, Japan), during post-processing and the aliasing was manually corrected. During systole, the exceeding VENC pixels were found to have black and white inversion, in the shape of an island around the center of the accelerated flow, in the phase images in the through-plane direction. (b) Velocity distribution curve (on a red line). Flow velocity profiles have discontinuous regions due to the phase shift caused by aliasing in the phase images, which indicates a 2D flow velocity distribution in the through-plane direction. The pixel-by-pixel pickup in these discontinuous inverted phase images and phase correction are performed. (c) 3D reconstruction of the aortic blood flow during peak systole at the level of the vena-contract. Velocity aliasing due to the blood flow velocities exceeding VENC (4 m/s) can be seen at the opposite side of the forward flow vectors (red arrow). (d) 3D reconstructions of blood flow after anti-aliasing phase correction. (e) Aliasing signals are recognized as a black areas in 2D cine PC-MRI (red arrow), while a white area represents forward aortic blood flow velocities within VENC as MRI-EOAs (white arrow). (f) After phase correction against aliasing signals, the area in 2D cine PC-MRI as MRI-EOAs becomes larger than before (white arrow) phase correction. AS, aortic stenosis; PC-MRI, phase-contrast magnetic resonance imaging; MRI-EOA, magnetic resonance imaging-derived-effective orifice area; VENC, velocity encoding.
velocity distribution in the through-plane direction. The pixel-by-pixel pickup in these discontinuous inverted phase images and phase correction, according to the equation below, were performed (Fig. 2b).

\[
\text{Phase}_{\text{corrected}} = \text{Phase}_{\text{measured}} + 2\pi
\]

Thus, the corrected flow velocity becomes

\[
\text{Velocity}_{\text{corrected}} = \text{Velocity}_{\text{measured}} + V\text{ENC}(4m/s)
\]

In the present study, since AS patients with a moderately accelerated flow were focused on, the VENC was set at 4.0 m/s.

Quantitative images of 10 cross-sectional slices of the aortic root, from 2 cm below the aortic annulus to 6 cm above the annulus in the ascending aorta, were obtained. These 10 short-axis slices were acquired towards the LVOT (Fig. 3a). Breath-holds were not performed during this process. The median MR examination time, which was the time when the patient was on the MR scanner table, was 27.0 min, with interquartile range: 24.3 to 30.8 min.

**MRI postprocessing**

Structural 2D cine True FISP images and 2D cine PC at the same cross-sectional area with 3D phase-velocity images were acquired, which were positioned at precise landmarks along the thoracic aorta, as schematically illustrated in Fig. 3b, for analysis using 4D flow MRI postprocessing software iTFlow, version 1.8.5. Trajectory blood streamlines in the Valsalva sinus were visually created in the peak systolic when the aortic valve leaflets were maximally open (Fig. 3c). The aliased flow velocity over VENC (above 4.0 m/s) was corrected semi-manually with a pixel-by-pixel phase shift using the software. The cross-sectional area at the level of the vena contracta of the reconstructed 3D streamline was defined (yellow line in Fig. 3c). Then, the velocity vector map on the cross-sectional plane was three-dimensionally reconstructed to identify the accelerated area of the flow streams, which consisted of high and accelerated flows within a functional orifice (Fig. 3d). Next, the image was reverted to a 2D fused image (Fig. 3e). A contour of the area of the vena contracta cross-section was detected after masking. Following semimanual truncation, pixels inside the area were counted and calculated as MRI-EOAs (Fig. 3f).

**Statistical analysis**

Continuous data are expressed as mean ± standard deviation, while categorical data are expressed as counts and percentages for normally distributed data. For comparison between two groups, continuous variables were assessed using the unpaired t-test or Mann–Whitney U-test. Categorical variables were compared using the Chi-squared test. Continuous agreement between TTE-EOAs and MRI-EOAs was analyzed using the Bland-Altman method. Linear regression analyses and Pearson’s correlation analysis were used to investigate the relationship between TTE-EOAs and MRI-EOAs. Severe AS was defined as an AVA ≤ 1.00 cm². Receiver operating characteristic (ROC) curve analysis was used to evaluate AS severity by MRI-EOAs using an AVA of ≤ 1.00 cm² as the reference standard. A P-value of < 0.05 was considered statistically significant. All statistical analyses were carried out using SPSS 26.0 (IBM, Armonk, NY, USA).

**Results**

**MRI-EOA in the healthy volunteers**

MRI-EOAs were obtained in two healthy volunteers with ages of 28 and 30 years MRI-EOAs were 2.84 cm² and 3.28 cm² corresponding to TTE-EOA of 2.93 cm² and 3.40 cm².

**Patient characteristics**

The moderately accelerated AS group and the highly accelerated AS group were comprised of 21 and 19 patients, respectively. The patient characteristics showed no statistically significant differences between the two groups (Table 1). Echocardiographic data are shown in Table 2. The moderately accelerated AS group had a significantly lower SVI than the highly accelerated AS group (P = 0.02). In both groups, LVEF was preserved (moderately accelerated AS; 65.9 ± 13.4% vs. highly accelerated AS; 62.6 ± 10.5%, P = 0.40). Although all the patients in the highly accelerated AS group had a TTE-EOA of < 1.00 cm², 11 patients from the moderately accelerated AS group had a TTE-EOA of < 1.00 cm² with discordance between Vmax and TTE-EOA (Fig 1). All patients in the highly accelerated AS group underwent aortic valve replacement (AVR) compared to 13 out of 21 patients in the moderately accelerated group.

**Diagnostic performance of PC-MRI for AS severity depending on the transvalvular flow**

The data quality for blood flow visualization and analysis was performed without physiological motion artifacts in all patients, including five patients with atrial fibrillation with good rate control, although arrhythmia rejection function was not used in this study. Aortic peak velocities derived from MRI exhibited a significant correlation with Vmax (r = 0.708, P < 0.001), showing a mean difference of 0.20 m/sec, with a limit of agreement of -0.1 m/sec to 2.1 m/sec. All of the highly accelerated AS group cases had pixels that represented velocities exceeding the VENC around the peak velocity regions, known as aliasing artifact signals, indicating that they were again defined as highly accelerated AS (peak velocity > 4.0 m/s) in PC-MRI, while none of the moderately accelerated AS group had the aliasing artifact signal (100% vs. 0%, P < 0.01). The average transvalvular peak velocity was significantly lower in the moderately accelerated AS group than in the highly accelerated AS group (3.07 ± 0.63 vs. 4.70 ± 1.44.
m/sec, \( P = 0.001 \)). The average MRI-EOAs were statistically similar between the two groups (moderately accelerated AS, 1.36 ± 0.37 cm² vs. highly accelerated AS, 1.39 ± 0.43 cm², \( P = 0.66 \)) (Table 3). The correlation and agreement between TTE-EOAs and MRI-EOAs in the moderately accelerated and the highly accelerated AS groups are depicted in Fig. 4 and Fig. 5. In the moderately accelerated AS group, MRI-EOAs showed a significant positive correlation with TTE-EOAs (\( r = 0.76, P < 0.001 \)) (Fig. 4, red dots). The Bland-Altman plot showed a mean difference of 0.42 cm² (range 0.30–0.53 cm²) with a limit of agreement of -0.07 cm² to 0.90 cm² for MRI-EOAs.

**Fig. 3** Visualization of blood flow and determination of the effective orifice area by 2D phase-contrast MRI. (a) The positioning of the image planes uses 10 slices parallel to the aortic valve, from 2 cm below the aortic annulus to 6 cm above the annulus in the ascending aorta. (b) Structural true FISP cine imaging and PC imaging at the same cross-sectional area with three orthogonal velocity axes: lateral, longitudinal, and vertical directions, are acquired for analysis. The 2D planes are oriented to the short axis of the aortic root to fully cover the sinus of Valsalva with 10 serial slices as described in (a). (c) Blood flow velocity patterns are visualized using iTFlow, where 3D streamline is created using data from the aforementioned 2D true FISP and cine PC MRI. Trajectory blood streamlines in the Valsalva sinus are created with 3D velocity vector visualizations in the peak systole. The convergence of the streamline, which corresponds to the vena contracta, is selected (yellow line). (d) 3D reconstruction of aortic blood flow during peak systole with colorized velocity vector maps at the selected cross-sectional area determined by the yellow line (c) as vena contracta. The red velocity vectors show the high and perpendicular velocity vectors to the cross-sectional area, that is, the accelerated flow (upper figure). When looking down it from the right above, the area encircled by the black line represents the cross-sectional area of the vena contract (lower figure). (e) A reverted 2D fused image is provided. The area encircled by the black line represents the area of the convergence of the streamline corresponding to the vena contracta. (f) A contour of the vena contracta cross-sectional area was detected after masking. Following semimanual truncation, pixels inside the area are counted and calculated as MRI-EOAs. FISP, fast imaging of steady-state free precession; MRI-EOA, magnetic resonance imaging-derived effective orifice area; PC-MRI, phase-contrast magnetic resonance imaging.
Table 1  Clinical characteristics of patients with moderately accelerated and highly accelerated AS

|                          | Moderately accelerated AS | Highly accelerated AS | p    |
|--------------------------|---------------------------|-----------------------|------|
| Age (years)              | 80.4 ± 6.8                | 77.0 ± 8.7            | 0.20 |
| Gender (male, %)         | 13 (61.9)                 | 7 (36.8%)             | 0.20 |
| Body mass index          | 22.6 ± 2.2                | 23.5 ± 3.5            | 0.54 |
| Body surface area (m²)   | 1.58 ± 0.18               | 1.53 ± 0.15           | 0.42 |
| NYHA III/IV (n, %)       | 8 (38.1)                  | 10 (52.6)             | 0.53 |
| Hypertension (n, %)      | 14 (66.7)                 | 16 (84.2)             | 0.40 |
| Dyslipidemia (n, %)      | 8 (38.1)                  | 11 (57.9)             | 0.50 |
| Diabetes (n, %)          | 7 (33.3)                  | 5 (26.3)              | 0.47 |
| CKD (n, %)               | 14 (66.7)                 | 9 (47.4)              | 1.00 |
| IHD (n, %)               | 10 (47.6)                 | 4 (21.1)              | 0.31 |

AS, aortic stenosis; BMI, body mass index; BSA, body surface area; CKD, chronic kidney disease; IHD, ischemic heart disease; NYHA, New York Heart Association.

Table 2  Transthoracic echocardiography examination with moderately accelerated and highly accelerated AS

|                                          | Moderately accelerated AS | Highly accelerated AS | p    |
|------------------------------------------|---------------------------|-----------------------|------|
| LV end-diastolic diameter (mm)           | 41.2 ± 7.4                | 46.8 ± 7.2            | 0.03 |
| LV end-systolic diameter (mm)            | 24.9 ± 8.9                | 30.2 ± 7.6            | 0.05 |
| Interventricular septum (mm)             | 12.3 ± 2.2                | 13.0 ± 1.8            | 0.43 |
| Posterior wall thickness (mm)            | 11.0 ± 1.7                | 12.0 ± 1.6            | 0.02 |
| LV end-diastolic volume (ml)             | 66.1 ± 23.0               | 82.6 ± 35.8           | 0.16 |
| LV end-systolic volume (ml)              | 25.2 ± 17.3               | 33.8 ± 25.2           | 0.30 |
| Relative wall thickness                  | 0.62 ± 0.23               | 0.55 ± 0.11           | 0.23 |
| Stroke volume index (ml/m²)              | 26.2 ± 7.0                | 33.1 ± 8.1            | 0.02 |
| LV ejection fraction (%)                 | 65.9 ± 13.4               | 62.6 ± 10.5           | 0.30 |
| Peak transaortic velocity (m/sec)        | 3.46 ± 0.33               | 4.69 ± 0.65           | < 0.01|
| Mean pressure gradient (mmHg)            | 26.1 ± 6.1                | 53.9 ± 18.5           | < 0.01|
| Effective orifice area (cm²)             | 0.95 ± 0.33               | 0.58 ± 0.18           | < 0.01|

AS, aortic stenosis; LV, left ventricle.

Table 3  Parameters of magnetic resonance image of patients with moderately accelerated and highly accelerated AS

|                                         | Moderately accelerated AS | Highly accelerated AS | p    |
|-----------------------------------------|---------------------------|-----------------------|------|
| Peak velocity (m/sec)                   | 3.07 ± 0.63               | 4.70 ± 1.44           | 0.001|
| MRI-EOA (cm²)                           | 1.36 ± 0.37               | 1.39 ± 0.43           | 0.66 |

AS, aortic stenosis; MRI-EOA, MRI-derived effective orifice area.
and TTE-EOAs (Fig. 5a). Meanwhile, in the highly accelerated AS group, MRI-EOAs demonstrated significant positivity but a moderate correlation with TTE-EOAs ($r = 0.63$, $P = 0.004$) (Fig. 4, blue dots). The Bland-Altman analysis also demonstrated a mean difference of 0.82 cm$^2$ (range 0.65–0.98 cm$^2$) with a limit of agreement of 0.13 cm$^2$ to 1.45 cm$^2$ for MRI-EOAs and TTE-EOAs (Fig. 5b). Furthermore, MRI-EOAs demonstrated a similar correlation with other parameters of AS severity ($V_{\text{max}}$: $r = -0.642$, $P = 0.002$; MG: $r = -0.624$, $P = 0.003$) and TTE-EOAs ($V_{\text{max}}$: $r = -0.625$, $P = 0.002$; MG: $r = -0.535$, $P = 0.015$).

Feasibility and clinical impact of MRI-EOA in patients with moderately accelerated AS
In moderately accelerated AS, ROC curves were calculated using a TTE-EOA of < 1.00 cm$^2$ as the reference standard. The ROC was found to have an area under the curve (AUC) of 87% (95% confidence interval [CI]: 0.72–1.00, $P = 0.004$), suggesting a high accuracy of TTE-EOAs as a diagnostic test, and the optimal binary cut-off for MRI-EOAs was 1.23 cm$^2$ (sensitivity of 82% and specificity of 90%) in predicting severe AS in the moderately accelerated AS group. Next, we analyzed the impact of MRI-EOAs on clinical features in patients with moderately accelerated AS. The cut-off value of MRI-EOA < 1.23 cm$^2$ significantly discriminated the New York Heart Association (NYHA) classification of III or IV ($P = 0.015$): sensitivity, 87.5%; specificity, 76.9%; meanwhile, TTE-EOA of < 1.00 cm$^2$ did not ($P = 0.30$): sensitivity, 75%; specificity, 61.5%.

Discussion
The main findings of the present study are as follows: 1) MRI-EOAs were successfully achieved with blood-flow imaging using the reconstruction method of multislice 2D PC-MRI; 2) in highly accelerated AS, exceeded VENC velocity (peak velocity derived from MRI > 4.0 m/s) was obtained in all cases; 3) in moderately accelerated AS, MRI-EOAs could be an alternative to TTE-EOAs for evaluating the severity of AS because MRI-EOAs had a good correlation and acceptable agreement with TTE-EOAs and equivalent correlation with any other echocardiographic data ($V_{\text{max}}$ and MG); however, in highly accelerated AS, MRI-EOAs only moderately correlated with TTE-EOAs.
Motivations and utility of the PC-MRI method for assessment of moderately accelerated AS

When calculated using the continuity equation, TTE-EOA, which is a component for determining the severity of AS, requires three parameters: the velocity-time integral of the LVOT, the maximum velocity-time integral across the valve, and the diameter of the LVOT. TTE-EOA = (CSA_{LVOT} \times TVI_{LVOT})/TVI_{AS}, where CSA_{LVOT} is the LV outflow tract cross-sectional area, TVI_{LVOT} is the time-velocity integral of the LV outflow tract flow, and TVI_{AS} is the time-velocity integral of the aortic flow. In TTE-EOA estimations, AS severity is sometimes reported to be disturbed by the underestimation of the LVOT dimension because of the hypertrophied septum and protruding calcification into the LVOT, which disturbs the identification of the inner edge of the septal endocardium and anterior mitral leaflet, and because of the circular assumption of LVOT using the anteroposterior diameter in actually elliptical outflow. Even when using transesophageal echocardiography (TEE), the measurement of the LVOT dimension is affected by these anatomical properties, as previous studies have reported that TEE sometimes underestimates the aortic annulus size and LVOT diameter. Hence, TEE and TEE may underestimate the LVOT area and subsequently cause discordant echocardiographic parameters and misclassification in the grading of AS severity. Therefore, the LVOT diameter measurement is considered the weakest link in the AVA estimation.

Recently, numerous studies have reported that PC-MRI is one of the gold standards for the measurement of blood-flow velocity, and MRI flow visualization has the potential to...
reveal hemodynamic and pathophysiologic conditions in cardiovascular diseases. Moreover, recent progress in 4D flow MRI has been explosive, with a sufficiently short scan time and fine resolution, thanks to the outstanding developments in MRI equipment and post-processing software; however, the use of these novel technologies is not yet widespread in most general hospitals, which have many AS patients with complicated hemodynamics. Therefore, we introduced a far simpler method than 4D flow MRI by reconstructing multislice 2D cine PC-MRI that confined the ROI only to the aortic root, including the LVOT and Valsalva sinus, which only required slice accumulation of simple 2D PC-MRI, not full 4D PC-MRI; consequently, MRI-EOAs do not require the specification of MRI equipment, even with an old version of the equipment that does not have a 4D flow sequence, whereby MRI-EOAs are accessible and showed good reproducibility during postprocessing. However, we should note that the simplified technology which we presented here is temporary until high-resolution 4D flow MRI becomes widespread even among general hospitals.

In contrast to simple MR angiography, 3D velocity vector field reconstruction can define vena contracta, based on the visualization of flow detachment. Several studies using MRI with velocity-encoded measurements of the blood flow velocity and volume flow for measurement of EOAs have been reported in patients with AS. In these volumetric methods, EOAs were calculated by applying the continuity equation, where the LVOT area, LVOT velocity-time integrals (VTI), and aortic VTI were used for the calculation in the same way as TEE-EOAs. This means that the EOAs derived from volumetry were not directly measured as functional EOAs, such as MRI-EOAs, but were calculated using equations, which could cause inherent errors, such as the measurement of TTE-EOAs, although each parameter could be precisely measured by velocity-encoded MRI. Additionally, planimetry was mentioned, in which the measured areas are not functional, but only anatomical; it is difficult to decide the plane of the short-axis steady-state free precession (SSFP) image for direct tracing of the leaflet tips. Moreover, planimetry can be suboptimal in cases of heavily calcified aortic valves due to signal voids and stenotic jet turbulence. In contrast, in our method, MRI-EOAs are based on the concept of the cross-sectional area of the vena contracta of the accelerated jet streamline. The vena contracta is the narrowest portion of a jet that occurs at or just downstream from the orifice of the aortic valve, which is characterized by high velocity and accelerated forward flow. The separatrix of the flow separation caused by the jet flow is identified by visualized velocity vectors with oppositely directed vectors in the flow separation vortex. Regarding cardiac arrhythmia, in five patients (12.5%) with atrial fibrillation, 2D PC-MRI data were available for analysis, even though arrhythmia rejection function was not used. A previous study reported that 2D PC-MRI in patients with cardiac arrhythmia had relevant reproducibility and stability, which supports our method. As explained above, MRI-EOAs are completely independent of the flow rate and driving pressure for a fixed orifice, in addition to the anatomical properties of the patient. In fact, we revealed that MRI-EOAs could evaluate AS severity to the same extent as TTE-EOAs for cases of moderately accelerated AS. When we evaluate the severity of AS in patients with discordant grading between TTE-EOAs and VM by anatomical abnormalities, MRI-EOAs can have diagnostic advantages over TTE-EOAs and become an alternative method for evaluation of AS severity. This is due to the fact that the area of vena contracta is based on the direct measurement of the physiological orifice area of the 3D stenotic flow, unlike TTE-EOAs, which are calculated from data, using the continuity equation, and is assumed to be independent of the anatomical structure of the LVOT or the functional status of the LV. Moreover, the mean scan time was 12 min, which is mediocre, but the total examination time was 27 min, which is tolerable even for elderly patients, who account for the majority of AS patients. However, the present method has still a poor efficiency of data collection, and both temporal and spatial resolutions are inferior to 4D flow MRI, and placement of the 2D acquisition plane at the level of the aortic valve can lead to the underestimation of peak velocities if misplaced or not orthogonal to the direction of flow.

The feasibility of MRI-EOA for moderately accelerated AS including paradoxical LF/LG

LF/LG severe AS, including the classical LF/LG severe AS, paradoxical LF/LG severe AS, and normal-flow LG severe AS, is reported in up to 30–40% of patients with AS, which is attributed to discordant Doppler echocardiographic findings in the presence of AVA ≤ 1.0 cm², MG < 40 mmHg, and VMax < 4.0 m/s, and has a huge clinical impact on prognosis. This is due to the fact that the prognosis of medical therapy for LF/LG severe AS was worse than that of surgical treatment, and misclassification of the severity of LF/LG AS could result in catastrophic outcomes for patients. However, it is difficult to accurately estimate the severity of LF/LG AS with or without preserved LVEF in a clinical setting. For the purpose of distinguishing true AS from pseudo-severe AS in patients with LF/LG AS, dobutamine-stress echocardiography (DSE), in which the inotropic effect of dobutamine results in an augmentation of SV, is recommended. However, it is still cumbersome and the interpretation is difficult. Meanwhile, in the present study, paradoxical LF/LG and normal-flow LG AS were found in 9 out of 21 patients (42.9%) in the moderately accelerated AS group (Fig. 1), who were more likely to have a smaller LV cavity than those in the highly accelerated AS group (Table 2). Generally, older people are considered more likely to have a small LV cavity, and the number of paradoxical LF/LG and normal-flow LG AS patients cannot be ignored in the clinical setting. However, DSE is not recommended for

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assessing the severity of AS in patients with paradoxical LF/LG and normal-flow LG AS. From the point of view of the necessity of multimodality, some studies suggested CT aortic valve calcium scoring (CT-AVC) for the diagnosis of paradoxical LF/LG AS. However, another study reported no correlation between CT-AVC and AS severity in middle-aged patients with bicuspid aortic valve, which is a limitation of this method. As a result, the present method using visualized blood flow with 2D PC-MRI could be an auxiliary to echocardiography for the assessment of surgical intervention in paradoxical LF/LG AS patients, who are more likely to be older and have protruding calcification from the aortic annulus and bulging septum into the LVOT, yielding an incorrectly small LVOT diameter. Representative cases with discordant echocardiographic parameters: moderately accelerated flow and TTE-EOA < 1.0 cm², in which MRI was both affirmatively and correctly helpful for echocardiographic assessment of AS severity, are depicted in Fig. 6. In case 1, MRI-EOA confirmed paradoxical LF/LG severe AS, which was supported by the operative findings. In case 2, moderate AS was determined based on the cut-off value of the MRI-EOAs (Fig. 6).
Conversely, assessment of AS severity using MRI-EOAs is not applicable to patients with highly accelerated AS because a high transvalvular flow velocity that exceeds the selected VENC (above 4 m/s in our study) causes aliasing artifact signals, and the phase-correction process causes overestimation of EOA (Fig. 2c-f). Velocity errors could influence 3D streamlines because they were determined by 3D velocity vectors from VENC and their interpolated values inside the voxels. MRI-EOA is defined as the area of the vena contracta, which is visually determined as the narrowest portion of the 3D streamlines, which is often located on an interpolated cross-section between the scanned cross-section. The area of the vena contracta is therefore determined using integrated and interpolated velocities. Regarding the correction of the over-VENC velocity voxels, the current technology introduces dual-VENC 4D flow MRI, which acquires high-VENC and low-VENC data, to improve the velocity signal-to-noise ratio of the aliasing artifact in PC-MRI. AS jet flow is turbulent flow with high energy, and a somewhat stochastic phenomenon regarding the velocity vector fields in the periodic cardiac cycle, the feasibility of repeated data acquisition such as dual- or triple-VENC scans for the determination of streamlines under high-energy turbulence warrants further study. Our semimanual correction of the exceeding VENC phase could help these future studies in the diseased turbulent flow.

**Future Investigation**

The present method will not upend echocardiographic diagnosis, which is a major quality measure that has been established by a large number of studies. We introduced a prototype of an alternative diagnostic method for AS severity using conventional and commercially available 2D-PC MRI when echocardiographic assessment is not suitable, ambiguous, or discordant with clinical findings. The daily clinical use and prevalence of 4D flow MRI can improve the disadvantage of 2D-PC MRI in terms of temporal and spatial resolution, and the diagnostic accuracy, facilitating robust management of patients with AS.

**Limitations**

Our study had several limitations. First, the study population was small, and the study was only performed at a single center. Second, in the present method, the temporal and spatial resolutions were not superior to 4D flow MRI. Third, although post-hoc analyses are not available, placement of the 2D acquisition plane at the level of the aortic valve can either be misplaced or not be orthogonal to the direction of flow. Fourth, the scan phase number of 20 in the present study, in terms of temporal resolution, was not very high but conformed to the guideline’s recommendation. Fifth, free breathing was allowed in the present study because breath holding may also prove difficult for patients with AS, who are likely to be older and have or develop dyspnea in the supine position due to heart failure. A recent study showed that there was misalignment with only a few pixels between methods with and without breath holding in the cardiac PC images when no respiratory motion compensation was performed. Sixth, the present method was not suitable for patients with transaortic flow higher than the VENC range because aliasing artifacts decrease the accuracy of flow quantification. However, when the VENC was set at a high velocity, the resolution of a moderate-flow field decreased, making discordant parameters and ambiguous or borderline judgments more probable. Seventh, the average bias between MRI-EOAs and TTE-EOAs was larger than zero, and the optimal cut-off MRI-EOA was 1.23 cm². It remains uncertain whether MRI-EOAs could be overestimated or TTE-EOAs could be underestimated. Moreover, the absolute value of MRI-EOAs is not the same as that of TTE-EOAs, as supported by many guidelines, and should be interpreted with caution. The dependency of EOA on the spatial resolution, especially slice thickness, has not been fully clarified. A higher resolution would increase the accuracy of the EOA. Finally, only one patient with LF/LG AS had a reduced LVEF in the present study. Therefore, we were unable to confirm the discriminatory performance of this method for patients with LF/LG AS with reduced LVEF.

**Conclusion**

Reconstructed multislice 2D cine PC-MRI in the aortic root can detect severe AS with a high VENC flow acceleration of 4.0 m/s. In moderately accelerated AS with peak velocity < 4.0 m/s, MRI-EOAs showed good correlation and acceptable agreement with TTE-EOAs. Additionally, MRI-EOAs demonstrated better discriminatory function for the severity of heart failure symptoms than TTE-EOAs in moderately accelerated AS patients. MRI-EOAs can be an alternative method for the assessment of hemodynamics in moderately accelerated AS cases with insufficient image quality on echocardiography. The feasibility of MRI-EOAs as a novel surgical indication for paradoxical LF/LG AS warrants further study.

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**Conflicts of Interest**

Keiichi Itatani was an endowed chair at the Kyoto Prefectural University of Medicine, founded by Medtronic.
Japan, and has a stock option of Cardio Flow Design Inc. Yoshiaki Komori is an employee of Siemens Healthcare K.K., Tokyo, Japan. Shohei Miyazaki is a chief technology officer of Cardio Flow Design Inc. Teruyasu Nishino is a chief executive officer of Cardio Flow Design Inc. and has a stock option. Yu Hohri, Akiko Matsuo, Takeshi Okamoto, Tomoyuki Goto, Takuma Kobayashi, Takeshi Hiramatsu, and Hitoshi Yaku declare that they have no conflicts of interest.

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