Application of the Proximal Isovelocity Surface Area Method for Estimation of the Effective Orifice Area in Aortic Stenosis

Masahiro Nakabachi
 Hokkaido University Hospital: Hokkaido Daigaku Byoin

Hiroyuki Iwano (✉ h-iwano@med.hokudai.ac.jp)
 Hokkaido University   https://orcid.org/0000-0002-1267-8260

Michito Murayama
 Hokkaido University Hospital: Hokkaido Daigaku Byoin

Hisao Nishino
 Hokkaido University Hospital: Hokkaido Daigaku Byoin

Shinobu Yokoyama
 Hokkaido University Hospital: Hokkaido Daigaku Byoin

Shingo Tsujinaga
 Hokkaido University: Hokkaido Daigaku

Yasuyuki Chiba
 Hokkaido University: Hokkaido Daigaku

Suguru Ishizaka
 Hokkaido University: Hokkaido Daigaku

Ko Motoi
 Hokkaido University: Hokkaido Daigaku

Kazunori Okada
 Hokkaido University: Hokkaido Daigaku

Sanae Kaga
 Hokkaido University: Hokkaido Daigaku

Mutsumi Nishida
 Hokkaido University Hospital: Hokkaido Daigaku Byoin

Takanori Teshima
 Hokkaido University: Hokkaido Daigaku

Toshihisa Anzai
 Hokkaido University: Hokkaido Daigaku

Research Article

Abstract

Purpose: Because existence of high flow velocity at the left ventricular outflow tract (LVOT) potentially causes an overestimation of effective orifice area (EOA) by continuity equation in aortic stenosis (AS), we tested the proximal isovelocity surface area (PISA) method as an alternative tool for AS.

Methods: EOA was calculated using the continuity equation (EOA$_{Cont}$) and PISA method (EOA$_{PISA}$), respectively, in 114 patients with at least moderate AS. The geometric orifice area (GOA) was also measured in 51 patients who also underwent three-dimensional transesophageal echocardiography (TEE). Patients were divided into two groups according to the median LVOT flow velocity.

Results: Feasibility of EOA$_{PISA}$ was 95% in the 114 patients. While there was a strong correlation between EOA$_{Cont}$ and EOA$_{PISA}$, EOA$_{Cont}$ was greater than EOA$_{PISA}$ especially in patients with high LVOT velocity. In TOE cohort, both EOA$_{Cont}$ and EOA$_{PISA}$ similarly correlated with GOA. However, a fixed bias, which is supposed to exist in AS, was observed only between EOA$_{PISA}$ and GOA with smaller EOA$_{PISA}$ than GOA. The difference between EOA$_{Cont}$ and GOA was significantly greater with a larger EOA$_{Cont}$ relative to GOA in patients with high LVOT velocity than in those without (0.16±0.25 vs -0.07±0.10 cm^2, P<0.001). In contrast, the difference between EOA$_{PISA}$ and GOA was consistent in both groups (-0.07±0.12 vs -0.07±0.15 cm^2, P = 0.936).

Conclusion: The PISA method was applied to estimate EOA of AS. EOA$_{PISA}$ could be an alternative parameter for AS severity grading in patients with high LVOT velocity in whom EOA$_{Cont}$ would overestimate the orifice area.

Introduction

Aortic stenosis (AS) is the most common valvular heart disease in developed countries and its prevalence is growing with the aging population. [1,2] In clinical practice, accurate assessment of AS severity is essential for appropriate management and therapeutic decision making. Echocardiography is a key tool in determining AS severity, and the effective orifice area (EOA) assessed by the continuity equation is one of the main variables that is recommended for assessment in the guidelines. [3] Owing to its feasibility and reproducibility, the continuity equation is widely used in the assessment of AS severity; however, some potential sources of error have been identified. Among them, increased flow velocity at the left ventricular outflow tract (LVOT) due to upper septal hypertrophy (USH) was reported to cause overestimation of the stroke volume (SV) and subsequent EOA. [4,5] Because USH is common in elderly AS patients, [6] an alternative method to quantify the EOA is expected to improve the diagnostic accuracy in these patients.

The proximal isovelocity surface area (PISA) method is widely used to quantify the effective regurgitant orifice area in valve regurgitation. [7] By applying the PISA method to AS, the EOA could be estimated in patients who are potentially unsuitable for applying continuity equation. In terms of the

application of the PISA method for the stenotic valve, it has been used for mitral stenosis; [8] however, the feasibility and diagnostic accuracy of the PISA method for AS severity has not been reported. Accordingly, the present study aimed to validate the PISA method for the estimation of EOA in AS and to test whether the PISA method could overcome the overestimation of the continuity equation caused by high flow velocity at the LVOT in patients with AS.

Methods

Study Population

We prospectively enrolled 160 consecutive patients who had been diagnosed with at least moderate AS (peak velocity across the aortic valve >3.0 m/s or EOA <1.5 cm^2) referred for transthoracic echocardiography from May 2018 to March 2019 at Hokkaido University Hospital. After the exclusion of patients with irregular heart rhythm due to arrhythmias (N = 38) and those with poor echocardiographic images (N = 8) in whom EOA by continuous equation could not be obtained, 114 patients were included in the final analysis. In 51 of the 114 patients who also underwent transesophageal echocardiography (TEE) after transthoracic echocardiographic examination (median distance: 27 days: TEE cohort), the geometric orifice area (GOA) of the aortic valve was used as the reference for the valve area. Study approval was obtained from the institutional review board of Hokkaido University Hospital (No. 018-0179) and an opportunity to opt-out was given to each participant through a published disclosure document on the web site of the institute.

Two-Dimensional and Doppler Echocardiography

Comprehensive transthoracic echocardiography was performed in the left decubitus position using a commercially available ultrasound equipment system (Vivid E9, GE Healthcare, Horton, Norway; iE33, Philips Medical Systems, Andover, Massachusetts; Acuson SC2000 prime, Siemens Healthineers, Erlangen, Germany; Aplio Artida, Canon Medical Systems, Otawara, Japan) according to the guidelines. [9] Left ventricular (LV) mass was determined using the Devereux formula. LV ejection fraction (EF) was calculated by using the biplane method of disks. USH was defined as a ratio of upper septal wall thickness to mid-septal wall thickness ³1.3. The maximal aortic valve velocity (Vmax) was measured using continuous-wave Doppler imaging in the view that showed the highest flow velocity, and the mean transvalvular gradient was estimated based on the simplified Bernoulli equation. The LVOT diameter was measured in the parasternal long-axis view. Flow velocity at the LVOT was measured using pulsed-wave Doppler imaging in the apical long-axis view, in which the sample volume was placed just proximal to the region of flow acceleration, and the time velocity integral (TVI_{LVOT}) was measured. SV was then calculated as SV_{Cont} = (LVOT diameter / 2)^2 ´ P ´ TVI_{LVOT}. EOA of the aortic valve was calculated using the continuity equation: EOA_{Cont} = SV / TVI_{AV}, where TVI_{AV} was the time velocity integral of the maximal aortic valve flow. [3] Measurements of EOA_{Cont} were performed by blinded certified sonographers (M.M., S.Y., H.N., M.N., and S.K.) and verified by a board certified reader (H.I.).

PISA Method for Estimation of EOA

Measurements of EOA by PISA methods were performed by the sonographers (M.M. or M.N) who were blinded to the results of clinical and echocardiographic parameters. To obtain a clear visualization of the proximal convergence of the aortic stenotic jet, a cut plane was selected in each patient from the apical long-axis, apical four-chamber, right parasternal long-axis, and suprasternal long-axis views (**Figure 1A**). Care was taken to minimize the angle between the centerline of the flow convergence and ultrasound beam. Using a magnified image, the appearance of PISA was optimized by shifting the baseline of the color Doppler scale to forward direction to adjust for aliasing velocity around 50 to 70 cm/s as appropriate. The radius of PISA (r) was then measured, and the instantaneous flow rate was calculated as $2\Pi r^2 \acute{} $ aliasing velocity (mL/s). EOA was then calculated using the PISA method: EOA_{PISA} =flow rate/Vmax (cm^2) based on the principle of conservation of mass (**Figure 1**). The SV was also calculated by $EOA_{PISA} \acute{} TVI_{AV}$ (SV_{PISA}).

Measurement of GOA

Transesophageal echocardiographic images were obtained using an iE33 (Philips Medical Systems, Andover, Massachusetts) with X7-2t probe or an Acuson SC2000 prime (Siemens Healthineers, Erlangen, Germany) with Z6Ms probe. At first, the two-dimensional images were clearly obtained in the midesophageal long-axis and short-axis views. Then volume data sets were obtained using four-beat full-volume mode (N =38, median volume rate: 27 Hz) or the live three-dimensional zoom mode (N = 13, median volume rate: 21 Hz) focused on the aortic valve complex. During acquisition of full volume images, gain and compression settings were optimized to display a magnified image of the aortic valve. After choosing the mid-systolic frame, in which maximal aortic valve excursion was observed, fine adjustments of the short-axis plane were performed to obtain the smallest aortic valve orifice and the GOA was measured (**Figure 1B**). All the measurements of GOA were performed by trained cardiovascular physicians (S.I, Y.C., and S.T.) and designated by a certified reader (H.I.).

Classifications of the Patients

To test the influence of LVOT flow velocity and LV morphology on the accuracy of measuring the EOA, we divided the patients by the median value of LVOT flow velocity and the presence or absence of USH and compared the differences in EOA_{Cont} to aortic valve area-related variables between the groups.

Statistical Analysis

Continuous variables are expressed as mean ± standard deviation and compared by paired or unpaired t test. Categorical data are presented as number (percentage). Agreements between aortic valve areas assessed using different methods were evaluated using Pearson's correlation coefficient and Bland-Altman plot analysis. The Bland-Altman procedure for comparing two methods was also used to determine the bias (95% confidential interval: CI). A two-sided *P* value <0.05 was considered statistically

significant. All statistical analyses were performed using JMP version 14.0 (SAS Institute Inc., Cary, North Carolina).

Results

Patient Characteristics

The clinical and echocardiographic characteristics of the studied patients are summarized in **Table 1**. In the overall cohort, relatively young patients with AS who were predominantly female were enrolled. More than half of the patients had experienced some symptoms of heart failure. While 69% of the patients were diagnosed as hypertension, the blood pressure was well controlled at <140 mmHg during the echocardiographic examination[10] in the majority of these patients. LV hypertrophy defined as an increased LV mass index was observed in 57% and USH was found in 46% of patients. Since the most common reason for TEE was to decide on surgical or transcatheter aortic valve replacement, the 51 patients in the TEE cohort consisted of elderly patients with a high frequency of heart failure symptoms and more advanced AS severity, whereas the LV geometry was similar to that in the overall cohort.

Comparisons of EOA_{Cont} and EOA_{PISA}

According to EOA_{Cont}, 79 patients were classified as severe AS and remaining 35 patients as moderate AS. In the 114 patients in whom the severity of AS was assessed based on EOA_{Cont}, estimation of EOA_{PISA} was possible in 108 patients (95%) and impossible due to inadequate image quality of PISA radius in 6 patients (5%). Although there was a strong correlation between EOA_{Cont} and EOA_{PISA} (**Figure 2A**), EOA_{PISA} was statistically significantly smaller than EOA_{Cont} (**Figure 2B**). Accordingly, 14 of 33 patients (42%) who were diagnosed with moderate AS based on EOA_{Cont} was classified with severe based on EOA_{PISA}. Interestingly, the difference between EOA_{Cont} and EOA_{PISA} was greater in patients with USH (**Figure 2C**). Further, the difference was also greater in patients with high LVOT flow velocity than in those without (**Figure 2D**).

TEE Cohort

In the 51 patients who underwent TEE, both EOA_{Cont} and EOA_{PISA} similarly correlated with GOA (r = 0.70, P <0.001 and r = 0.77, P <0.001, respectively) (**Figure 3A, C**). However, a negative fixed bias, which is hydrodynamically supposed to exist between effective and geometric orifice areas, was not observed between EOA_{Cont} and GOA (95% CI -0.03 to 0.08; **Figure 3B**). In contrast, there was a negative fixed bias between EOA_{PISA} and GOA, with smaller EOA_{PISA} than GOA (95% CI -0.11 to -0.03; **Figure 3D**). Importantly, the difference between EOA_{Cont} and GOA was significantly greater with a larger EOA_{Cont} than GOA in patients with high LVOT flow velocity than in those without (**Figure 4A**). In contrast, the difference between EOA_{PISA} and GOA was consistent regardless of the LVOT flow velocity (**Figure 4B**). Similar results were observed in the comparison between patients with and without USH (**Figure 4C, D**). In a typical case with severe AS (GOA: 0.70 cm^2) complicated by mid-ventricular obstruction, a clear

difference was observed between EOA_{Cont} and EOA_{PISA} (1.46 cm^2 vs 0.55 cm^2), suggesting an overestimation of EOA_{Cont} caused by high flow velocity at the LVOT (**Figure 5**).

Reproducibility Analysis

The reproducibility for EOA_{PISA} was assessed in 30 randomly selected patients. Two independent observers (M.N. and M.M.) analyzed the same cine loops of zoomed color Doppler images and one blinded observer (M.N.) repeated the analysis on a separate day. The intra- and interobserver intraclass correlation coefficients of EOA_{PISA} were 0.98 and 0.95, respectively.

Discussion

In the present study, we tested the feasibility and reliability of EOA_{PISA} in AS patients and found that 1) estimation of EOA using the PISA method was possible in up to 95% of AS patients, in whom EOA_{Cont} could be obtained, with acceptable consistency with EOA_{Cont}, 2) EOA_{PISA} was as well corelated with GOA as EOA_{Cont} was, and importantly, 3) the concordance between EOA_{PISA} and GOA was consistent in patients with high LVOT flow velocity and those with USH in whom EOA_{Cont} potentially overestimated the valve orifice area. Although the PISA method has been applied for other valvular heart diseases, [11-14] this is the first study to demonstrate the feasibility and reliability of this method in AS.

PISA Method for Assessment of AS Severity

In the same manner as the continuity equation, the PISA method is based on the principle of conservation of mass, where flow rate during the ejection period through the proximal isovelocity surface is equal to that through effective orifice area of the narrowing orifice. The physical basis of this method is quite solid, and use of the PISA method to quantify the severity of mitral regurgitation, mitral stenosis, and aortic regurgitation is recommended by the guidelines. [15,16] However, the use of PISA method for AS has not been mentioned probably because of the spread and retention of EOA_{Cont}. In the present study, we demonstrated an acceptable feasibility and reproducibility of EOA_{PISA} in clinical AS patients.

EOA_{Cont} for Assessment of AS Severity

Transvalvular gradients and EOA_{Cont} are the principal measures for the echocardiographic grading of severity in AS. [3] Among them, estimation of EOA is important because transvalvular gradients vary depending on the flow conditions. [17] An accurate estimation of EOA_{Cont} is thus mandatory for managing patients with AS; however, sources of errors have been noted in the measurement of its components. [18,19] As the LVOT cross-sectional area is calculated based on the anterior to posterior diameter assuming a circular shape, it can underestimate the area, which has an elliptical shape in most patients. [20-24] At the same time, a study showed that TVI_{LVOT} was overestimated using pulsed-wave Doppler, resulting in compensation for the underestimation of the LVOT area with subsequent good concordance between EOA_{Cont} and cardiac magnetic resonance-derived EOA. [5] This overestimation of

TVI_{LVOT} was thought to be due to the alteration of the flow velocity profile from flat to skewed in the presence of high flow velocity at the LVOT, as seen in USH. [5,25] Koto et al. [4] demonstrated that AS patients with USH had greater SV and EOA calculated using the Doppler method than those without. Consistent with these previous findings, when SV was compared between patients with and without USH or those with and without high LVOT flow velocity, apparent differences were observed only in SV_{Cont} but not in SV_{PISA} between groups (**Table 3**). Therefore, the significant differences in EOA_{Cont} and EOA_{PISA} (**Figure 2 C and D**) and those in EOA_{Cont} and GOA (**Figure 4 A and C**) between patients with and without USH or those with and without high LVOT flow velocity, along with the absence of a negative fixed bias between EOA_{Cont} and GOA, suggests overestimation of EOA_{Cont} in patients with high LVOT flow velocity.

Clinical Implication

Owing to the increasing elderly population with AS, a substantial population of the patients could show a narrowing LV cavity with USH, resulting in increased LVOT flow velocity. [26,27] As observed in a previous study[4] and ours, the continuity equation would overestimate SV and subsequent EOA in these patients. In typical cases with USH or LVOT obstruction, it is generally impossible to avoid sampling high flow speed by placing the sample volume at anywhere of the proximal site of the aortic valve annulus due to the turbulent flow. In that case, EOA_{PISA} could be an alternative parameter to determine AS severity. EOA_{PISA} is expected to be particularly effective in patients showing EOA_{Cont} that is larger than expected from the transvalvular flow velocity as shown in **Figure 5**. As the diagnosis of severity is critical in AS,[3] many reliable and feasible variables are needed for its assessment. EOA_{PISA} is in line with other recently proposed markers of AS severity. [4,27,28]

Study Limitations

This study had several limitations. First, the relatively small number of studied patients limits the strength of our findings; thus, the results of our study should be confirmed in a larger study. Second, test-retest reproducibility between the two examinations was not assessed, although the consistency of the EOA_{PISA} obtained from the same cine loops was acceptable. Third, while the PISA method assumes the shape of the proximal isovelocity area to be hemispherical, we could not confirm its exact geometry in AS. As noted in a recent computational simulation, [15] an ellipsoidal PISA geometry results in substantial underestimation. In addition, based on the funnel shape geometry of the stenotic orifice, PISA might require correction based on an angle such as the PISA method in mitral stenosis. However, shape of stenotic orifice in AS, especially in sclerotic degenerative valves, is symmetrical and far from funnel shape compared to that of mitral stenosis, which might have reduced the alteration of PISA geometry in AS. In fact, the EOA_{PISA} was 10−30% smaller than GOA in our study, which was within the previously reported difference ranges between EOA and GOA (10% to 30%),[29] and can justify the application of PISA method without angle correction for AS.

Conclusions

In conclusion, the PISA method was applied for the estimation of EOA in patients with AS. EOA_{PISA} can be used as an alternative variable when assessing the AS severity in patients with high LVOT flow velocity or USH in whom EOA_{Cont} would potentially overestimate the orifice area.

Declarations

Acknowledgements

Compliance of Ethical Standards

As mentioned above, the study protocol has been approved by the ethics committee in our hospital and therefore was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

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Tables

Table 1. Clinical and echocardiographic characteristics

	All (N = 108)	TEE cohort (N = 51)
Age, years	78 ± 12	84 ± 7
Male, N (%)	41 (38%)	20 (39%)
Systolic blood pressure, mmHg	131 ± 19	130 ± 16
Diastolic blood pressure, mmHg	67 ± 11	66 ± 10
NYHA, N (%)		
I	50 (46%)	7 (14%)
II	52 (48%)	38 (75%)
III	5 (5%)	5 (10%)
Comorbidity, N (%)		
Hypertension	74 (69%)	41 (80%)
Diabetes mellitus	28 (26%)	16 (31%)
Dyslipidemia	53 (49%)	25 (49%)
Etiology, N (%)		
Tricuspid valve	93 (86%)	50 (98%)
Bicuspid or unicuspid valve	12 (11%)	1 (2%)
Rheumatic	3 (3%)	0 (0%)
LV end-diastolic volume, mL	80 ± 36	79 ± 34
LV end-systolic volume, mL	33 ± 30	34 ± 28
LVEF, %	63 ± 12	61 ± 12
LVEF < 50%, N (%)	13 (12%)	9 (18%)
LV mass index, g/m^2	113 ± 38	124 ± 36
Relative wall thickness	0.42 ± 0.07	0.43 ± 0.07
USH, N (%)	50 (46%)	24 (22%)
Left atrial volume index, mL/m^2	46 ± 14	47 ± 12
E, cm/s	75.7 ± 26.0	75.1 ± 24.2
E/A	0.80 ± 0.33	0.76 ± 0.32
e', cm/s	5.2 ± 2.2	4.7 ± 1.5
E/e'	15.2 ± 7.4	16.4 ± 6.9

Tricuspid regurgitation pressure gradient, mmHg	28 ± 9	27 ± 8

TEE, transesophageal echocardiography; LV, left ventricular; EF, ejection fraction; USH, upper septal hypertrophy; E, LV early-diastolic inflow velocity; E/A, ratio of E to LA systolic velocity; e', early-diastolic mitral annular velocity; E/e', the ratio of E to e'.

Table 2. Echocardiographic findings

	All (N = 108)	TEE cohort (N = 51)
LVOT TVI, mm	21 ± 2	23 ± 7
LVOT velocity, m/s	1.03 ± 0.33	0.99 ± 0.33
SV_{Cont}, mL	77.2 ± 21.8	73.6 ± 23.1
SV_{PISA}, mL	66.3 ± 17.9	63.2 ± 15.5
EOA_{Cont}, cm^2	0.86 ± 0.33	0.72 ± 0.29
EOA_{PISA}, cm^2	0.75 ± 0.29	0.62 ± 0.22
GOA, cm^2		0.69 ± 0.16
Peak aortic valve velocity, m/s	4.2 ± 1.0	4.7 ± 0.8
Mean aortic valve gradient, mmHg	43.9 ± 21.4	53.3 ± 20.0

LV, left ventricular; LVOT, LV outflow tract; TVI, time velocity index; SV_{Cont}, stroke volume measured using the Doppler method; SV_{PISA}, stroke volume measured using the proximal isovelocity surface area method; EOA_{Cont}, effective orifice area calculated using the continuity equation; EOA_{PISA}, effective orifice area calculated using the PISA method; GOA, geometric orifice area.

Table 3 Comparisons of stroke volume according to LV morphology and LVOT flow velocity

	Upper septal hypertrophy			LVOT flow velocity		
	Presence (N = 50)	Absence (N = 58)	P value	>0.96 m/s (N = 53)	£0.96 m/s (N = 55)	P value
SV$_{Cont}$, mL	87.4 ± 21.3	68.5 ± 18.2	<0.001	87.7 ± 21.4	67.1 ± 16.9	<0.001
SV$_{PISA}$, mL	68.2 ± 22.1	64.6 ± 13.3	0.329	69.8 ± 20.6	62.9 ± 14.1	0.045

Abbreviations are the same as Table 2.