Valvular Heart Disease

Differential Effect of 3-Dimensional Color Doppler Echocardiography for the Quantification of Mitral Regurgitation According to the Severity and Characteristics

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Background—The aim of this study is to explore the differential effect of 3-dimensional color Doppler echocardiography for the quantification of mitral regurgitation (MR). Two-dimensional color Doppler echocardiography–based MR quantification has well-documented limitations.

Methods and Results—We consecutively enrolled 221 patients with MR. Adequate image quality was obtained by 2D- and 3D-color Doppler echocardiography in 211 (95.5%) patients. The quantitative differences between the MR volumes obtained by 2D- and 3D-proximal isovelocity surface area (PISA) were analyzed in various MR subgroups. In the validation cohort (n=52), MR volume obtained by 3D-PISA showed a better agreement with phase-contrast cardiac MRI than 2D-PISA (r=0.97 versus 0.84). In all 211 patients, 2D-PISA underestimated the MR volume when compared with 3D-PISA (52.4±19.6 versus 59.5±25.6 mL; P=0.005). A total of 33.3% with severe MR based on 3D-PISA were incorrectly assessed by 2D-PISA as having nonsevere MR. In the subgroup analysis, the MR severity (odds ratio, 6.96; 95% confidence interval, 3.04–15.94; P<0.001) and having an asymmetrical orifice (odds ratio, 11.48; 95% confidence interval, 3.72–35.4; P<0.001), and an eccentric jet (odds ratio, 3.82; 95% confidence interval, 1.27–11.48; P=0.017) were predictors of significant difference in MR volume (>15 mL) between 2D- and 3D-PISA methods.

Conclusions—Quantification of MR by 3D-PISA method is clinically feasible and more accurate than the current 2D-PISA method. MR quantification by 2D-PISA significantly underestimated MR volume with severe, eccentric MR with an asymmetrical orifice. This article demonstrates that 3D-color Doppler echocardiography could be used as a valuable tool to confirm treatment strategy in patients with significant MR. (Circ Cardiovasc Imaging. 2014;7:535-544.)

Key Words: echocardiography • mitral valve insufficiency

Mitral regurgitation (MR) is the most prevalent phenotype of valvular heart diseases. Significant MR is estimated to affect ≥6 million Americans and Europeans, and its prevalence is anticipated to increase even further.1 Quantifying the severity of MR is crucial for proper clinical decision making and determining the timing of surgery.2–5

Clinical Perspective on p 544

For quantifying MR, an integrative approach of 2-dimensional (2D) and Doppler parameters that describe the amount of MR includes vena contracta width, regurgitant volume (RV) calculated by proximal isovelocity surface area (PISA), or quantitative pulsed Doppler is recommended to achieve an accurate evaluation of the severity of the lesion and its clinical significance.6 However, 2D-based MR quantification by the PISA method has some limitations on its geometric assumptions, such as hemispheric PISA shapes, circular orifices, and centralized regurgitant jets, which can lead to errors in the quantification of the MR.7–10 Notably, if the shape of the PISA is rounder, it minimizes the risk of underestimating the effective regurgitant orifice area (EROA).11 However, in cases of hemielliptic regurgitant orifices (when the shape of the flow convergence zone is not a hemisphere), the PISA method using 2D-color Doppler echocardiography (2D-CDE) may underestimate the degree of MR.11

Although the flow quantification using 3D-CDE has been proposed to overcome the inherent limitations of 2D-CDE,9,12–15 its technical limitations, such as multiple gated acquisition and time-consuming manual processing, prevent it from becoming widely adopted into daily clinical practice.

Recently, advances in technology of 3D-CDE provide the option of semiautomated MR quantification based on the 3D-PISA method, and its results could be potentially more accurate than 2D-PISA method in quantifying MR.16
Therefore, the purpose of this study is to explore the differential effect of 3D-CDE in a wide spectrum of MR phenotypes, as well as to test the accuracy and feasibility of 3D-CDE for the quantification of MR volume.

Methods

Study Population and Protocols
We consecutively enrolled 221 patients with mild to severe degrees of MR, who were referred to Severance Cardiovascular Hospital for transthoracic echocardiography from December 2011 to October 2013. The severity of MR was defined by the MR volume obtained by the 2D-PISA method, as described in the 2013 European Society of Cardiology recommendations.11 Patients with any of the following criteria were excluded: the presence of other significant valvular heart diseases, tachycardia with a heart rate ≥100 bpm, decompensated heart failure with an ejection fraction ≤30%, intracardiac shunts, and patients contraindicated for MRI.

Ten (4.5%) patients were further excluded because of inadequate image acquisitions of 3D-CDE. A total of 211 patients with MR, quantified by 2D- and 3D-PISA methods with a dedicated software system, were included into the final analysis. For the purpose of validation, 52 patients underwent concurrent phase-contrast cardiac magnetic resonance (PC-CMR) imaging as a reference (validation cohort). MR volumes by 2D- and 3D-PISA methods were compared with the volumes obtained by PC-CMR.

The differences in MR volume between the 3D- and 2D-PISA methods were analyzed in 211 patients overall, and in the subgroups according to the severity, the characteristics of MR (pathogenesis, orifice shape, jet direction, and number of jets), and ECG rhythms, respectively.

MR severity was defined based on the 2D-PISA method: mild or grade I if the MR volume was <30 mL; mild-to-moderate or grade II if the MR volume was 30 to 44 mL; moderate-to-severe or grade III if the MR volume was 45 to 59 mL; severe or grade IV if the MR volume was ≥60 mL.12 The cause of MR was classified as either organic or functional.13,14 The orifice shape was classified by the ratio of vena contracta from apical 2-chamber view/apical 4-chamber view, as either symmetrical or asymmetrical; symmetrical if the ratio was <1.5 and asymmetrical if the ratio was ≥1.5. The cutoff value of 1.5 was revealed by receiver operating characteristic curve analysis for the prediction of significant difference in MR volume (>15 mL) between the 2D- and 3D-PISA methods. Area under the curve was 0.742. Sensitivity and specificity were 78.8% and 67.2%, respectively. The jet direction and number of jets were classified as central versus eccentric and single versus multiple.6 The ECG was classified as either in sinus rhythm or atrial fibrillation (AF).

All of these data sets were obtained within 24 hours of the index transthoracic echocardiography. The study protocol was approved by the Institutional Review Board of Severance Cardiovascular Hospital, and written informed consent was obtained from all study participants.

Image Acquisition and Analysis

Two-Dimensional Color Doppler Echocardiography
Two-dimensional echocardiographic data sets were obtained with ACUSON SC2000 (Siemens Medical Solutions Inc, Mountain View, CA) with a 4V1c phased-array transducer at a frequency of H4.3-4.0 MHz. In all patients, the standard 2D echocardiography and Doppler data sets were obtained in the left lateral decubitus position.12 The area of interest was optimized by lowering the depth and reducing the Color Doppler Nyquist limit to 31 to 42 cm/s (mean, 36.2±7.1 cm/s). The radius of the 2D-PISA was measured at midsystole using the largest aliasing radius from the apical view, where the hemispheric morphology of the flow convergence could be best visualized and the continuous Doppler signal could be well aligned with the regurgitant jet flow convergence. The PISA radius was defined as the largest distance between the aliasing border and the regurgitant orifice measured parallel to the direction of the Doppler beam. If there were multiple MR jets, the continuous Doppler signal was aligned with the major regurgitant jet. The EROA was calculated by the PISA method as follows: EROA=2π×r×Vr/Vstr, where r is the isovelocity radius, Vr is the aliasing velocity, and Vstr is the maximal velocity of the regurgitant jet. MR volume by 2D-PISA was calculated as EROA by 2D-PISA multiplied by the MR time-velocity integral. The regurgitant time-velocity integral was determined by tracing the contour of the regurgitant jet obtained by continuous-wave Doppler. Maximal velocity and time-velocity integral were averaged 25 beats in patients with AF.15 A representative case of quantification of MR by the 2D-PISA method is demonstrated in Figures 1A and 1B and 2A–2C.

Three-Dimensional Color Doppler Echocardiography
After the completion of 2D-CDE, we sequentially performed 3D-CDE using the Siemens ACUSON SC2000 and 4Z1c real-time nonstitched volume imaging transducer (H2.8-2.8 MHz). Software specifically developed for 3D-PISA determination (eSie PISA Volume Analysis; Siemens Medical Solutions Inc) was adopted. Real-time nonstitched 3D apical full-volume images and 3D-color Doppler images of the MR were acquired. Color Doppler aliasing velocities were set in the same manner as during 2D-CDE data acquisition (37±3 cm/s; range, 31–42 cm/s). The volume PISA acquisitions were obtained with the depth and sector optimized for color Doppler resolution. To minimize the potential effects of low temporal resolution of 3D color Doppler imaging, 3 consecutive nonstitched real-time 3D color Doppler volumes from consecutive cardiac cycles were acquired in each patient for optimal estimation of the largest volume PISA. All 3D image data sets were analyzed by independent and blinded observer using an offline, dedicated SC2000 workplace system (Siemens Medical Solutions Inc).

The software performed an automated quantification of 3D-PISA and visualized as green overlay on 3D color Doppler images. After the selection of an appropriate volume, the software allows the user to select an aliasing velocity and initial seed point for 3D-PISA analysis. The seed point is an approximate location in 3D space that the software needs as an input to find the 3D flow convergence. Then, the software performs the 3D segmentation with the volume data, applying an optimized segmentation algorithm.16 The segmented mask is used to generate a mesh in 3D space, and PISA is computed and displayed free of any geometric assumptions. The eSie PISA segmentation results are also displayed on the X/Y/Z reference planes, as well as in the volume-rendered image for clinical confirmation of accurate flow convergence quantification by the user. Three-dimensional-PISA was used to derive EROA as (3D-PISA×Vr/Vstr), MR volume by 3D-PISA was calculated as EROA by 3D-PISA multiplied by the MR time-velocity integral.17 A representative case of quantification of MR by 3D-PISA method is demonstrated in Figures 1C and 2D and E.

PC-CMR Imaging
PC-CMR data acquisition was performed with a 1.5-T MR scanner (Philips), using a 12-channel phased-array surface coil. The volume of the left ventricle (LV) was determined by planimetry from a series of short-axis acquisitions covering the LV completely from the apex to the base. Quantifications of LV end-systolic volume, end-diastolic volumes, and ejection fraction were performed on the short-axis series with manual contour segmentation of the endocardial borders. The total LV stroke volume (SV) was obtained by subtracting the LV end-systolic volume from the LV end-diastolic volume (typical echo time, 1.5 ms; repetition time, 3.1 ms; slice thickness, 10 mm; 25 phase). Aortic forward flow volume was obtained from 2 to 3 cm above the aortic valve in an orthogonal orientation to the aortic root (typical echo time, 2.8 ms; repetition time, 4.7 ms; slice thickness, 8 mm; 50 frames/cardiac cycle; aliasing velocity, 200 cm/s; number of excitations, 2). MR volume was calculated by subtracting the aortic forward flow volume from the total LVSV.18 A representative case of quantification of MR by PC-CMR is demonstrated in Figure 1D–1F.

Reproducibility
The interobserver variability of the MR volume measurements was obtained by 2 independent and double-blinded observers using 20 randomly selected cases (mean difference of MR volume by observer 1–observer 2). Intraobserver variability was assessed by comparing the measurements by the same observer after an interval of 1 week between making measurements (mean difference of MR volume by first test–second test).
Statistical Analysis
Continuous data are expressed as means± SD. Categorical data are expressed as an absolute number (percentage). Linear regression analysis, Pearson correlation coefficient were used to evaluate the correlation, and Bland–Altman plots were used to compare the agreement between the measurements. The $\kappa$ statistic was used to assess agreement in categorizing MR severity. The $t$ test was used to evaluate the differences in MR volume between the measurements. Logistic regression models were used to identify univariate predictors for the prediction of significant difference in MR volume (>15 mL) between 2D- and 3D-PISA methods. These predictors were then added to a multivariate model to assess independent predictors. A $P$ value <0.05 was considered to be statistically significant. PAWS statistic version 18.0 (SPSS Inc, Chicago, IL) and MedCalc version 12.3 (MedCalc Software, Mariakerke, Belgium) were used for the statistical analysis.

Results
Baseline Characteristics
The baseline characteristics of the 211 patients are summarized in Table 1. The mean age was 58.6±14.9 years, and 111 (52.6%) patients were men. The mean systolic blood pressure and diastolic blood pressure were 118.3±21.4 and 75.5±12.5 mm Hg, respectively. The mean heart rate was 75.9±18.9 bpm. The cause of MR was organic in 111 (52.6%) patients and functional in 100 (47.4%) patients. The orifice shape of MR was symmetrical in 127 (60.2%) patients and asymmetrical in 84 (39.8%) patients. The jet direction of MR was central in 122 (57.8%) patients and eccentric in 89 (42.2%) patients. The number of jets was single in 145 (68.7%) patients and multiple in 66 (31.3%) patients and 77 (36.5%) patients had AF. On the basis of 2D-PISA method, we categorize the severity of MR as mild (grade I) in 28 (13.3%) patients, mild-to-moderate (grade II) in 62 (29.4%) patients, moderate-to-severe (grade III) in 73 (34.6%) patients, and severe (grade IV) in 48 (22.7%) patients. Five patients had nonholosystolic MR and all of them revealed as organic mild MR by both 2D- and 3D-PISA methods.

Comparison of 2D- and 3D-PISA Methods With PC-CMR as a Reference
The comparison of the 2D- and 3D-PISA methods was performed in the validation cohort (n=52), who underwent concurrent PC-CMR within 24 hours of transthoracic echocardiography image acquisitions. The baseline characteristics of the validation cohort are summarized in Table 1.

Two-dimensional-PISA underestimated the MR volume when compared with the volumes obtained by 3D-PISA and PC-CMR (55.3±19.6 mL by 2D-PISA versus 64.3±28.6 mL by PC-CMR; $P=0.018$; 67.4±29.1 mL by 3D-PISA versus...
The MR volume by 3D-PISA showed a better correlation and agreement ($r=0.97$; $P<0.001$; 2 SD, 13.4 mL) than MR volume by 2D-PISA ($r=0.84$; $P<0.001$; 2 SD, 26.9 mL) with PC-CMR (Figure 3).

**Comparison of MR Quantification by 2D- and 3D-PISA Methods**

MR quantification by 3D-PISA was successfully performed in 211 of the 221 (95.5%) patients. Ten patients were excluded because of poor image quality. The mean time required for the 3D-PISA image acquisitions was 4.6±2.0 minutes (range, 2.8–7.0 minutes).

The inter- and intraobserver variability (mean difference of MR volume±2 SD and intraclass correlation coefficient) of 3D-PISA for the quantification of MR volume is excellent and comparable with that of 2D-PISA (interobserver variability, 0.8±7.5 mL in 3D-PISA versus 2.1±13.7 mL in 2D-PISA; 0.97 versus 0.95 and intraobserver variability, 0.5±5.6 versus 0.6±6.2 mL; 0.98 versus 0.98).

Two-dimensional-PISA underestimated MR volume when compared with 3D-PISA (52.4±19.6 versus 59.5±25.6 mL; $P=0.005$; Figure 4A). Furthermore, the differences in MR volumes obtained by 3D- and 2D-PISA (RV by 3D-PISA–RV by 2D-PISA) were more remarkable in severe MR when compared with mild MR (–2.5±5.5 mL in mild MR versus 14.9±10.7 mL in severe MR; $P=0.003$; Figure 4B). For the 2D-PISA method, there was moderate agreement with 3D-PISA method ($k=0.56$; $P<0.001$). Among the patients who were classified as having severe MR (grade IV) by 3D-PISA, 24 (33.3%) patients were misclassified as having nonsevere MR by 2D-PISA (Table 2).

**Subgroup Analysis According to the Characteristics of MR**

When we classified the patients into individual subgroups according to MR pathogenesis, the RV of organic MR (n=111) by 2D- and 3D-PISA (mean±SD, 53.2±19.0 and 58.4±24.9 mL, respectively) showed an excellent correlation ($r=0.91$; $P<0.001$). However, the correlation between 2D- and 3D-PISA was weaker in functional MR (n=100; 47.0±16.2 mL in 2D-PISA and 55.2±21.2 mL in 3D-PISA; $r=0.79$; $P<0.001$).

The orifice shape was classified as symmetrical or asymmetrical by the ratio of vena contracta from apical 2-chamber view/apical 4-chamber view. Asymmetrical orifice was significantly associated with difference in MR volume between the 3D- and 2D-PISA methods ($P<0.001$; Figure 5). When we compared the MR volume obtained by 2D- and 3D-PISA...
LVESD, mm 42.0±10.5 43.1±11.4
LAVI, mL/m² 78.4±53.9 82.5±52.3
LVEF, % 56.7±17.5 57.5±18.4
LVEDD, mm 59.0±9.6 60.7±8.8

Severity of MR by 2D-PISA, %

<table>
<thead>
<tr>
<th>Rhythm</th>
<th>No. of jets</th>
<th>Jet direction</th>
<th>Orifice shape</th>
<th>Diastolic BP, mm Hg</th>
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Data are expressed as number (%) or mean±SD. 2D-PISA indicates 2-dimensional proximal isovelocity surface area; AF, atrial fibrillation; BP, blood pressure; BSA, body surface area; LAVI, left atrial volume index; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; and MR, mitral regurgitation.

methods according to the orifice shape, the MR volume of symmetrical orifice (n=127) by 2D- and 3D-PISA (48.4±15.3 and 51.4±17.7 mL) showed an excellent correlation (r=0.94; P<0.001). However, the correlation between 2D- and 3D-PISA was weaker in asymmetrical orifice (n=84; 52.9±21.3 mL in 2D-PISA and 51.4±17.7 mL in 3D-PISA; r=0.87) than 2D-PISA (r=0.97) as a reference method and agreement with PC-CMR (r=0.97; P<0.001). In this study, MR volume by 3D-PISA had better correlations and agreement with PC-CMR (r=0.97) as a reference method than 2D-PISA (r=0.84; P<0.001). Cardiac MRI is often used as a reference method for MR quantification because it is the most accurate noninvasive technique for quantifying the LVSV.23 In addition, its phase-contrast velocity flow mapping of the aortic forward SV is also accurate and reproducible; therefore, it can be a more objective and consistent method for quantifying eccentric and multiple MR jets.

Comparison of 2D- and 3D-PISA Methods With PC-CMR as a Reference

In this study, MR volume by 3D-PISA had better correlations and agreement with PC-CMR (r=0.97) as a reference method than 2D-PISA (r=0.84). Cardiac MRI is often used as a reference method for MR quantification because it is the most accurate noninvasive technique for quantifying the LVSV.23 In addition, its phase-contrast velocity flow mapping of the aortic forward SV is also accurate and reproducible; therefore, it can be a more objective and consistent method for quantifying eccentric and multiple MR jets.

Comparison of MR Quantification by 2D- and 3D-PISA Methods

Our data showed that 2D-PISA underestimated MR volume when compared with 3D-PISA (52.4±25.6 mL versus 59.5±25.6 mL; P=0.005). The differences in MR volume between 2D- and 3D-PISA were more remarkable in severe MR than mild MR (~25±5.5 mL in mild MR versus 14.9±10.7 mL in severe
Current treatment guidelines for MR recommend surgery for severe MR (RV, ≥60 mL) with symptoms and overt LV dysfunction, LV enlargement, pulmonary hypertension, or AF. In this study, 24 (33.3%) patients with identified as having severe MR by 3D-PISA were undergraded as having nonsevere MR by 2D-PISA. Considering the importance of quantifying the severity of MR for proper clinical decision making and determining the timing of surgical intervention, the 2D-based quantification of severe MR has significant limitations.

Figure 3. Correlation and agreement between tests. Linear regression analysis for comparison of mitral regurgitation (MR) volume assessments between (A) 2-dimensional proximal isovelocity surface area (2D-PISA) and phase-contrast cardiac magnetic resonance (PC-CMR); (B) 3D-PISA and PC-CMR. Bland–Altman plots for comparison of MR volume assessments between (C) 2D-PISA and PC-CMR; (D) 3D-PISA and PC-CMR. The MR volume by 3D-PISA showed a better correlation and agreement ($r=0.97; P<0.001$; 2 SD, 13.4 mL) than 2D-PISA ($r=0.84; P<0.001$; 2 SD, 26.9 mL) with PC-CMR. RV indicates regurgitant volume.

Figure 4. Comparison of mitral regurgitation (MR) quantification by 2-dimensional proximal isovelocity surface area (2D-PISA) and 3D-PISA methods in overall patients. (A) The mean MR volume by 2D-PISA method and 3D-PISA method. (B) Difference in MR volume by 2D- and 3D-PISA methods according to the MR severity. Two-dimensional-PISA method underestimated MR volume when compared with 3D-PISA method. The differences in MR volume obtained by 3D- and 2D-PISA (regurgitant volume [RV] by 3D-PISA–RV by 2D-PISA) were more remarkable in severe MR when compared with mild MR.
of PISA is ignored, then the 2D-PISA method may underestimate the degree of functional MR. In our study, 33 patients with functional MR (33%) had a symmetrical orifice shape. This might be the reason why functional MR did not demonstrate a statistical significant difference in these 2 subgroups (Table 5). In case of multiple MR jets, the respective radius of PISA was not additive, which could be the reason why multiple MR jets also did not show statistical differences. Furthermore, there was a relatively large number of patients with AF included in this study. AF is more common in patients with MR and can reduce the accuracy of flow measurements by echocardiography and PC-CMR. However, we only included patients with AF, who also had low heart rate variability (beat-to-beat variability, <30 bpm). This could be the reason why AF did not show a statistical significance as a predictor of significant difference in MR volume obtained by the 2D- and 3D-PISA methods.

Limitations of 2D-PISA Method

Quantifying the severity of MR is crucial because it is related to the prognosis and guidance for the management of patients. The current standard for MR quantification are the PISA method and vena contracta using 2D-CDE. Although 2D methods are well validated for MR quantification, these methods have many innate limitations and assumptions. For example, the PISA method assumes the hemispheric shape of the PISA. However, the orifice shape of MR is often elliptical rather than circular, and this can affect the accuracy of PISA calculations. The dynamic nature of the orifice shape of MR can also lead to errors. Furthermore, the calculation of RV by PISA assumes that the PISA radius is measured at the same point in the cardiac cycle at which the peak MR velocity occurs. This assumption is not necessarily correct and might lead to underestimation of EROA. This error can be overcome if RV is computed by integrating 3D-PISA over the entire cardiac cycle. However, this process is time-consuming and requires multiple measurements. For determination of EROA, it is essential that the CW Doppler signal is well aligned with the regurgitant jet. Poor alignment with an eccentric jet will lead to an underestimation of velocity and an overestimation of EROA by PISA.

**Advantage of MR Quantification Using 3D-PISA Method**

The direct measurement of the PISA using 3D-CDE can overcome these limitations of the 2D-PISA method.

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**Table 2. Difference of MR Severity Classification Between 2D- and 3D-PISA Methods**

<table>
<thead>
<tr>
<th>MR Severity by 2D-PISA</th>
<th>MR Severity by 3D-PISA</th>
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<tbody>
<tr>
<td>Mild (Grade I)</td>
<td>Mild-to-Moderate (Grade II)</td>
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<tr>
<td>18</td>
<td>10</td>
</tr>
<tr>
<td>Mild-to-moderate (grade II)</td>
<td>Moderate-to-severe (Grade III)</td>
</tr>
<tr>
<td>6</td>
<td>33</td>
</tr>
<tr>
<td>Moderate-to-severe (grade III)</td>
<td>Severe (Grade IV)</td>
</tr>
<tr>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>Severe (grade IV)</td>
<td>0</td>
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Data are expressed as number (%). \( \kappa = 0.56; P < 0.001 \). 2D indicates 2-dimensional; 3D, 3-dimensional; MR, mitral regurgitation; and PISA, proximal isovelocity surface area.

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**Figure 5.** The linear regression analysis of difference in mitral regurgitation (MR) volume between 3-dimensional proximal isovelocity surface area (3D-PISA) and 2D-PISA methods according to the orifice shape. Asymmetrical orifice was significantly associated with difference in MR volume between the 3D- and 2D-PISA methods. A2C indicates apical 2-chamber view; A4C, apical 4-chamber view; and VC, vena contracta.
Three-dimensional imaging has the advantage of avoiding any geometric assumptions and thereby determining the actual PISA. Therefore, complete 3D visualization of the convergent flow zone is the ideal solution for the accurate calculation of EROA. Experimental in vitro studies have demonstrated that the PISA might be measured with 3D-CDE even in complex geometric flow fields.31–33 These in vitro studies also showed that visualization of the complex flow field by 3D reconstruction of color flow Doppler images is feasible and gives excellent results for flow rate calculation. Recent advances in 3D echocardiography have enabled high-frame rate acquisition of volumetric color Doppler flow images in a single heart cycle, enabling direct measurement of the PISA without geometric assumptions. In our experience, MR quantification by 3D-CDE is feasible, reproducible, and accurate in quantifying MR severity.

**Clinical Implications**

When feasible, 2D-PISA method is highly recommended to quantify the severity of MR. If MR severity is definitely mild...
or severe, then the 2D-PISA method was sufficient to quantify the severity of MR. However, if MR severity is severe, with an asymmetrical orifice, and the MR jet direction is eccentric, then the 2D-PISA method significantly underestimated MR volume when compared with 3D-PISA. These results provide the differential effect of 3D-CDE for the quantification of severe, eccentric MR with an asymmetrical orifice. Considering the fact that treatment options might need to be changed if severe MR is misclassified, 3D-CDE could be a valuable tool to quantify the clinical severity of MR.

Limitations
There were several limitations in our study. First, although all of the patients were enrolled consecutively, this study was a single-center prospective observational study. Second, PC-CMR, the reference method for MR volume quantification, also has some limitations. For example, in PC-CMR, the aortic SV is obtained from a plane above the level of the aortic valve, which differs from that of the LVOT plane. However, the PC-CMR method is well validated for quantifying MR volume and is widely used in clinical practice and research studies.22,23 Third, a relatively large number of multiple jets (66, 31.3%) were included in our study. We had expected that the 2D-PISA method might underestimate the MR volume in these patients. However, the results yielded no statistically significant differences between the 2D- and 3D-PISA–derived MR volumes in the cases of multiple jets. MR with multiple jets requires individual PISA radii to be added; however, we could not average or add multiple respective PISA radii automatically by the 3D-PISA method. This could be the reason for the observed statistically insignificant difference between the 2D- and 3D-PISA–derived MR volumes in multiple jets; hence, it cannot be assumed that the observed statistical insignificance equates to no differences between the actual values obtained by the 2D- and 3D-PISA methods in multiple jet MR. The summing of the individual PISA radii can be done manually by individual frame analysis and manual averaging of all frames to quantify and integrated holosystolic 3D-PISA results. Therefore, the scope of this study does not address comparisons between single and multiple jets on a frame by frame basis.

Conclusions
Quantification of MR by the 3D-PISA method is clinically feasible and has been found to be more accurate than the current 2D-PISA methods. MR quantification by 2D-PISA significantly underestimates MR volume versus 3D-PISA and was found to especially underestimate MR volume significantly in patients with severe, eccentric MR with asymmetrical orifice. This article demonstrates that 3D-CDE could be used as a valuable tool to confirm treatment strategy in patients with significant MR.

Acknowledgments
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Disclosures
None.

References

Table 5. Classification of Orifice Shape Within the Type of Cause of MR

<table>
<thead>
<tr>
<th>Cause of MR (n=211)</th>
<th>Mean Ratio of VC From A2C/A4C</th>
<th>Symmetrical (n=127)</th>
<th>Asymmetrical (n=84)</th>
</tr>
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<tbody>
<tr>
<td>Organic (n=111)</td>
<td>1.17</td>
<td>94</td>
<td>17</td>
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<tr>
<td>Functional (n=100)</td>
<td>1.89</td>
<td>33</td>
<td>67</td>
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</table>

A2C indicates apical 2-chamber view; A4C, apical 4-chamber view, as symmetrical if the ratio of vena contracta from A2C/A4C was <1.5 and asymmetrical if the ratio was ≥1.5; MR, mitral regurgitation; and VC, vena contracta.


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