Quantification of Chronic Functional Mitral Regurgitation by Automated 3-Dimensional Peak and Integrated Proximal Isovelocity Surface Area and Stroke Volume Techniques Using Real-Time 3-Dimensional Volume Color Doppler Echocardiography

In Vitro and Clinical Validation

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Background—The aim of this study was to test the accuracy of an automated 3-dimensional (3D) proximal isovelocity surface area (PISA) (in vitro and patients) and stroke volume technique (patients) to assess mitral regurgitation (MR) severity using real-time volume color flow Doppler transthoracic echocardiography.

Methods and Results—Using an in vitro model of MR, the effective regurgitant orifice area and regurgitant volume (RVol) were measured by the PISA technique using 2-dimensional (2D) and 3D (automated true 3D PISA) transthoracic echocardiography. The mean anatomic regurgitant orifice area (0.35±0.10 cm²) was underestimated to a greater degree by the 2D (0.12±0.05 cm²) than the 3D method (0.25±0.10 cm²; P<0.001 for both). Compared with the flowmeter (40±14 mL), the RVol by 2D PISA (20±19 mL) was underestimated (P<0.001), but the 3D peak (43±16 mL) and integrated PISA-based (38±14 mL) RVol were comparable (P>0.05 for both). In patients (n=30, functional MR), 3D effective regurgitant orifice area correlated well with cardiac magnetic resonance imaging RVol r=0.84 and regurgitant fraction r=0.80. Compared with cardiac magnetic resonance imaging RVol (33±22 mL), the integrated PISA RVol (34±26 mL; P=0.42) was not significantly different; however, the peak PISA RVol was higher (48±27 mL; P<0.001). In addition, RVol calculated as the difference in automated mitral and aortic stroke volumes by real-time 3D volume color flow Doppler echocardiography was not significantly different from cardiac magnetic resonance imaging (34±21 versus 33±22 mL; P=0.33).

Conclusions—Automated real-time 3D volume color flow Doppler based 3D PISA is more accurate than the 2D PISA method to quantify MR. In patients with functional MR, the 3D RVol by integrated PISA is more accurate than a peak PISA technique. Automated 3D stroke volume measurement can also be used as an adjunctive method to quantify MR severity. (Circ Cardiovasc Imaging. 2013;6:125-133.)

Key Words: 3D integrated PISA ■ 3D peak PISA ■ automated 3D stroke volume ■ cardiac MR imaging ■ mitral regurgitation ■ real-time 3D volume color flow Doppler echocardiography

Current recommendations underscore the use of qualitative and quantitative echocardiographic methods to grade severity of chronic mitral regurgitation (MR).1,2 A commonly used quantitative method is the proximal isovelocity surface area (PISA) technique that has several limitations when performed by 2-dimensional (2D) echocardiography.3,4 Although 3-dimensional (3D) echocardiography-based PISA techniques have been shown to be more accurate,5-9 it is not widely used because of limitations of gated acquisitions, the need for time-consuming manual interaction with the data, and ongoing need for shape assumptions. Also, current 3D PISA techniques do not account for the dynamic nature of the regurgitant orifice, which is especially important in functional MR.10,11

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The use of an automated 3D method to quantify the true 3D peak PISA using nongated real-time 3D volume color flow Doppler (RT-VCFD) transthoracic echocardiography in mostly degenerative MR was recently illustrated \(^\text{12}\) in comparison with echocardiographic reference standards. However, this method has not been validated in an in vitro model of MR under controlled hemodynamic conditions or tested against an external reference standard, such as cardiac magnetic resonance (CMR) imaging. Furthermore, a single peak PISA measurement does not account for the dynamic nature of the regurgitant orifice, especially in functional MR \(^\text{10,11}\) and can result in inaccuracy in the calculation of the regurgitant volume (RVol) \(^\text{10,13}\). Also, the PISA method may be limited as in multiple MR jets and when PISA is constrained by adjacent wall.

Using RT-VCFD, the aims of this study were first to assess the feasibility and accuracy of the automated true 3D PISA technique for quantification of MR using an integrated PISA approach in comparison with the peak PISA method in an in vitro model and in patients with functional MR and second to assess the accuracy of an automated 3D color Doppler-based stroke volume (SV) quantification method \(^\text{14}\) that uses translational and aortic SVs to quantify MR severity in the same patient population. CMR imaging was used as the reference standard in patients.

Methods

In Vitro Validation of Automated 3D Surface Area Computation

The accuracy of the automated algorithm for computation of the 3D surface area (similar to PISA) was first tested using a hollow sphere submerged in a solution with consistency similar to chest wall tissue (Figure 1 in online-only Data Supplement). This sphere was imaged with the SC2000 platform (2.8 MHz frequency; 14 cm depth), and the surface area was computed for 5 separate trials of acquisition and segmentation.

In Vitro Flow Model and Echocardiographic Acquisition

The in vitro validation was performed using a pulsatile cardiac flow model previously described \(^\text{13}\). The model consisted of a circulatory loop, regurgitant circuit, a flowmeter, and an ultrasound imaging chamber. Pulsatile flow was driven through the regurgitant loop incorporating a divider plate containing a modifiable orifice. Orifices evaluated included 0.15 and 0.4 cm\(^2\), circle, 0.4 cm\(^2\), arc, and 0.39 cm\(^2\) rectangle (Figure 1). Regurgitant flow through the orifices ranged between 12 and 57 mL/beat at a heart rate of 60 beats/min.

Using 2D transthoracic echocardiography (Siemens ACUSON SC2000 with 4 v1 2D, 2.25–4.25 MHz transducer), color and continuous wave (CW) Doppler data were acquired for every orifice/flow condition (total of 11 conditions; Figure 1) with the transducer aligned parallel to the regurgitant flow using an apical window. The Nyquist limit was adjusted to achieve a clear PISA. The 2D color Doppler frame rate was 14 to 24 Hz at a Doppler scan depth of 12 to 16 cm. For each of the 11 orifice/flow conditions, 5 different PISA measurements were made resulting in 55 measurements. For each condition, 3 CW Doppler signals and the corresponding flowmeter measurements of the RVol (reference standard for RVol) were also recorded for a total of 33 measurements.

With the same flow conditions and imaging window, RT-VCFD acquisitions were made immediately after the 2D acquisition with acquisition of 3 consecutive nonstitched 3D volumes. The depth and color Doppler sector size were optimized, resulting in an acquisition volume rate between 12 and 43 volumes per second (VPS). As for the 2D data, the visualization of the 3D PISA was optimized during acquisition. Similar to the 2D acquisition, 55 PISA, 33 CW, and flowmeter recordings were made.

RT-VCFD Acquisition (Patients)

Consecutive patients aged >18 years, referred to the CMR laboratory with incidental finding of at least mild functional MR, were recruited to participate in an institutional review board (The Ohio State University)-approved study. Exclusion criteria included atrial fibrillation, intracardiac shunts, concomitant aortic valve disease, and poor echocardiographic windows (inability to visualize 2 myocardial segments or to image the entire ventricle without dropouts or artifacts). RT-VFCD of MR in the apical 4-chamber view optimized for PISA was acquired (Figure 2) with 3D B-mode and color Doppler volume sector adjusted for the left ventricle and mitral valve (Movie 1 in online-only Data Supplement). Three 3D volumes were recorded from 3 consecutive cardiac cycles (nonstitched). Postacquisition, offline analysis was performed using custom software (described below) for quantification of the effective regurgitant orifice area (EROA) and RVol.

Subsequently, a second set of 3D volumes was acquired from 3 consecutive cycles (nonstitched) in the apical 3- or 5-chamber view incorporating the left ventricular outflow tract and mitral valve in a single volume (Movie II in online-only Data Supplement; Figure 3B and 3D). The color Doppler box was placed to cover both the mitral and aortic valves simultaneously. The depth and space-time settings were optimized, and the highest possible color Doppler velocity scale was used to minimize aliasing. The total acquisition time for each data set was 3 to 5 seconds. Using this technique, the mitral RVol and regurgitant fraction (RF) were quantified using previously validated custom software \(^\text{14,16}\) described below.

Automated Measurement of 3D PISA

The algorithm that is used to recognize, segment, and quantify 3D PISA has been previously described \(^\text{13}\). The essential steps are summarized in Figure 2 and Movie I in online-only Data Supplement. The user first selects the aliasing velocity and identifies the PISA on the appropriate systolic frames (Figure 2B). Then the direction of the MR jet is identified in the same frame (Figure 2B). The algorithm generates an isovelocity segmentation in the voxel-based 3D space representing the 3D geometry (free of specific geometric assumptions) of the PISA (Figure 2C–2G) using an optimized random walker method with a directed graph approach. The segmentation results were automatically smoothed by 3D Gaussian kernel, and an isovelocity surface mesh was computed using a marching cube algorithm. No modifications were made to the automatically
generated surface areas. The mesh vertexes were transformed from acoustic to Cartesian space for computation of 3D PISA.

**EROA and RVol Calculations**

Two-dimensional PISA (in vitro) was calculated using the hemispheric assumption. EROA was derived as \( \text{PISA} \times \text{aliasing velocity} / \text{peak MR velocity} \), and RVol was derived as \( \text{EROA} \times \text{VTI}_\text{avg} \), where VTI is the velocity-time integral of the transorifice CW Doppler. The 3D EROA was calculated using the largest systolic 3D PISA (Figure 3A). With RT-VCFD, for the in vitro and patient study the RVol was calculated in 2 ways. First, the EROA was multiplied by the \( \text{VTI}_\text{avg} \), and we refer to this as the peak PISA RVol. Second, RVol was calculated for each systolic frame as (3D PISA from that frame) \( \times \) (color Doppler aliasing velocity from that frame)/(frame rate)\(^{10} \) and summed for the entire systolic period to obtain an integrated PISA RVol (Figures 2G and 3A; Movie I in online-only Supplement Data). EROA and RVol were obtained from 3 separate but consecutive 3D volumes and averaged for each patient.

**Automated Quantification of Aortic and Mitral SV (Patients)**

A detailed mathematical basis of the automated SV quantification algorithm for the measurement of mitral inflow and aortic outflow SV was previously described and validated.\(^{14,16} \) Briefly, the algorithm incorporated the color Doppler velocities and the sampling region (mitral valve or left ventricular outflow tract) to calculate SV without assumptions of geometry or uniformity of flow velocities (Figure 3B–3D). Automated dealiasing algorithm was applied as necessary as described previously.\(^{14,17} \) The difference between mitral inflow and left ventricular outflow tract SV was the mitral RVol, whereas the RF was the RVol divided by the LVSV.

**CMR Data Acquisition and Analysis**

CMR data acquisition and analysis is described in the online-only Data Supplement.\(^{18} \) Briefly, the aortic SV determined by phase contrast imaging was subtracted from left ventricular SV (LVSV) obtained by planimetry of short axis cines to obtain mitral RVol, and RF was obtained by dividing RVol by the LVSV.

**Grading Severity of MR and Eccentricity**

The CMR RF was used to categorize the patients into mild, mild-to-moderate, moderate-to-severe, and severe MR (grades 1–4 MR) based on RF thresholds from American Society of Echocardiography (ASE) guidelines.\(^{7} \) The MR jets were also categorized as central or eccentric with eccentric jets defined as the majority of the MR jet not being parallel to the long axis of the left atrium in standard views.

**Reproducibility**

The interobserver variability for the PISA technique was assessed for all patients, whereas the intraobserver variability was performed in 50%. The inter- and intraobserver variability for the SV technique was also tested in all patients. In 10 patients, test–retest reproducibility was assessed for the PISA and SV techniques by first obtaining a 3D acquisition, followed by repositioning the patient and the transducer and obtaining a second data set by a different sonographer.

**Statistical Analysis**

Continuous data are expressed as mean±SD, whereas categorical data as frequency or percentage. The in vitro EROA was skewed and hence Spearman rho and Wilcoxon tests were used. Linear regression analysis, the Pearson correlation coefficient, the Lin concordance correlation coefficient (CCC), and ANOVA with Bonferroni post hoc analyses were used for RVol comparisons. ANCOVA was used to assess the impact of regurgitant orifice or MR eccentricity on EROA or RVol measurements.

All patient data were normally distributed as determined by Kolmogorov–Smirnov test and visual inspection of the data using normal plots. We assessed for the presence of outliers in our data using the outlier labeling rule;\(^{20} \) however, none were identified. Linear regression analysis and Pearson correlation coefficient were used to test the strength of relationships. For the linear regression analysis, P-P plots of the residuals were used to assess for normality. Paired \( t \) test was used to test the difference between measurements. Agreement between methods and reproducibility was examined using Bland–Altman analysis and CCC. The \( \kappa \) statistic was used to assess agreement in categorizing MR severity. Receiver operating characteristic curve was used to identify the 3D EROA to differentiate severe from nonsevere MR.\(^{20} \) MedCalc (11.4.2.0, Mariakerke, Belgium) was used for statistical analyses.
Belgium) and SPSS (ver 19.0.0, IBM Corporation, Chicago, IL) were used for statistical analysis.

Results

In Vitro Validation of Automated 3D Surface Area Computation

No statistically significant difference was observed between the caliper-measured mean±SD surface area and that obtained by automated 3D segmentation (49.1±0.2 versus 49.9±2.1 cm²; \(P=0.31\); Figure I in online-only Data Supplement), illustrating the accuracy of the 3D segmentation algorithm with gray-scale images.

In Vitro 2D and 3D PISA-based EROA

Three-dimensional PISA was successfully quantified for all orifice/flow conditions with typical quantification time of <20 seconds for the peak PISA technique and 60 seconds for the integrated PISA technique for an average of 8±2 systolic frames.

The flow model had anatomic regurgitant orifice area (AROA) ranging from 0.15 to 0.4 cm² (mean±SD, 0.35±0.10 cm²). Modest correlation was observed between the 2D PISA EROA and AROA (\(\rho=0.74; P<0.001\)); the values were, however, underestimated (mean±SD, 0.12±0.05 cm²; range, 0.04–0.25 cm²; \(P<0.001\)). The 3D EROA had a good correlation with the AROA (\(\rho=0.83; P<0.001\)), but although larger than 2D PISA EROA (mean±SD, 0.25±0.10 cm²; range 0.07–0.38 cm²; \(P<0.001\)), it was smaller than the AROA (\(P<0.001\)). The mean EROA for each orifice was underestimated by both techniques (Figure II in online-only Data Supplement). When the large circle versus arc and rectangle (noncircular) orifices were compared, a significant difference was observed in the measurement of EROA by 2D transthoracic echocardiography (TTE) (\(P=0.01\); ANCOVA) but not with RT-VCFD (\(P=0.43\); ANCOVA).

In Vitro 2D and 3D PISA-based RVol

A good correlation was observed between the flowmeter and 2D TTE measurements of RVol (\(r=0.73; P<0.001\); CCC=0.26), and integrated (\(r=0.93; P<0.001\); CCC=0.92) and peak PISA (\(r=0.91; P<0.001\); CCC=0.88) measurements of RVol (Figure 4). Significant differences were observed in the RVol between the techniques (\(P<0.001\); ANOVA). On post hoc analysis, compared with the flowmeter RVol (40±14 mL [range, 12–58 mL]), there was no statistically significant difference in RVol determined by 3D peak PISA (43±16 mL [range, 12–72 mL]) or integrated PISA (38±14 mL [range, 9–57 mL]) methods (\(P>0.05\) for both); however, the 2D PISA-based RVol (20±9 mL [range, 5–33 mL]) was underestimated (\(P<0.001\)). When regurgitant orifice shapes were compared (large circle, arc, and rectangle), a significant difference was observed in the measurement of RVol by 2D TTE (\(P=0.02\)) but not with RT-VCFD integrated or peak PISA RVol (\(P=0.73\) and 0.11, respectively).

Figure 3. Illustration of the proximal isovelocity surface area (PISA) and stroke volume (SV) technique and cardiac magnetic resonance (CMR) regurgitant volume (RVol) for the same patient. A, PISA technique: the 3D surface area for each frame is illustrated above the PISA and RVol at the bottom. The first frame was the peak PISA. B to D, SV technique mitral inflow (B), left ventricular outflow tract flow (C), and flow volume curves (D) for 3 consecutive cardiac cycles. E to G, CMR end-diastolic (E) and systolic (F) volumes by planimetry and aortic stroke volume by phase contrast imaging (G). There was good agreement in RVol.
Patient Population
Among the 35 patients evaluated, 30 (Table) had adequate RT-VCFD studies for analysis (n=2 for dropouts of ≥2 segments; n=3 for artifacts). The mean RT-VCFD volume rate was 22±6 VPS (range, 13–38 VPS). MR was functional in all patients, 11 had eccentric MR, whereas 19 had central MR. Using CMR RF, 9 patients had grade 1 MR, 8 grade 2, 6 grade 3, and 7 grade 4 MR. All RT-VCFD studies were completed within 30 minutes of the CMR study. Heart rate and blood pressure were not different between studies (80±18 versus 83±17 beats/min; 124±18/74±11 versus 127±17/74±11 mm Hg).

Automated 3D Peak PISA-based EROA (Patients)
Quantification of EROA using automated 3D peak PISA was feasible in all included patients. A good correlation was observed between 3D EROA and the CMR MR severity grade (ρ=0.86; P<0.001), RVol (r=0.87; P=0.001), and RF (r=0.89; P<0.001) (Figure 5).

Automated 3D Peak and Integrated PISA-based RVol (Patients)
The time duration for the peak PISA calculation for 1 cardiac cycle was 15±4 seconds, whereas for the integrated PISA technique it was 1.7±0.7 minutes. The mean number of systolic frames used for integrated PISA was 7±4. CMR quantification took 6 to 8 minutes. A good correlation was observed between RVol obtained by CMR and peak (r=0.87; P<0.001; Figure 6; CCC=0.71) and integrated PISA (r=0.92; P<0.001; Figure 6; CCC=0.92) methods. Compared with CMR RVol (33±22 mL), the mean peak PISA RVol (48±27 mL) was higher (P<0.001); however, the integrated PISA RVol (34±26 mL) was not significantly different (P=0.42). Also, the RVol quantification in comparison with CMR was not affected by the eccentricity of the MR for both peak (P=0.89) and integrated PISA (P=0.09).

RVol Measurements by Automated 3D SV Technique
The time required to obtain 3D mitral and aortic SV for 3 to 5 cardiac cycles was 30 to 60 seconds. The RVol computed by

![Figure 4. Linear regression and Bland–Altman analysis for comparison of 2-dimensional (2D) transthoracic echocardiography, 3-dimensional (3D) integrated and peak proximal isovelocity surface area regurgitant volumes (RVol), and flowmeter measured RVol.](http://circimaging.ahajournals.org/)

### Table. Patient Demographic and Hemodynamic Data

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean±SD*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>52±19</td>
</tr>
<tr>
<td>Men/women, %</td>
<td>37/63</td>
</tr>
<tr>
<td>MR severity by CMR</td>
<td></td>
</tr>
<tr>
<td>Mild or mild-to-moderate MR, n</td>
<td>17</td>
</tr>
<tr>
<td>Moderate-to-severe or severe, n</td>
<td>13</td>
</tr>
<tr>
<td>Cardiac MRI</td>
<td></td>
</tr>
<tr>
<td>LV end-diastolic volume, mL</td>
<td>247±116</td>
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<tr>
<td>LV end-systolic volume, mL</td>
<td>158±104</td>
</tr>
<tr>
<td>LV total stroke volume, mL</td>
<td>88±23</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>40±14</td>
</tr>
<tr>
<td>Aortic SV by phase contrast, mL</td>
<td>54±21</td>
</tr>
<tr>
<td>RVol, mL</td>
<td>33±22</td>
</tr>
<tr>
<td>RF, %</td>
<td>36±19</td>
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<tr>
<td>RT-VCFD</td>
<td></td>
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<tr>
<td>EROA, cm²</td>
<td>0.36±0.21</td>
</tr>
<tr>
<td>RVol by integrated PISA, mL</td>
<td>34±26</td>
</tr>
<tr>
<td>RVol by peak PISA, mL</td>
<td>48±27</td>
</tr>
<tr>
<td>RVol by stroke volume technique, mL</td>
<td>34±21</td>
</tr>
<tr>
<td>RF by stroke volume technique, %</td>
<td>37±17</td>
</tr>
</tbody>
</table>

CMR indicates cardiac magnetic resonance; EF, ejection fraction; EROA, effective regurgitant orifice area; LV, left ventricle; MRI, magnetic resonance imaging; MR, mitral regurgitation; PISA, proximal isovelocity surface area; RVol, regurgitant volume; RF, regurgitant fraction; RT-VCFD, real-time volume color flow Doppler; SV, stroke volume.

*Applies to all parameters except for the number of patients with the various MR severity categories.
the automated SV technique correlated significantly with those obtained by CMR ($r$=0.91; $P<0.001$; Figure 7; CCC=0.91). No significant difference was observed in the mean RV ol by RT-VCFD and CMR (34±21 versus 33±22 mL; $P=0.33$). Similarly, the RF by RT-VCFD and CMR had good correlation ($r$=0.92; $P<0.001$; Figure 7; CCC=0.91) with no significant difference (37±17 versus 36±19%; $P=0.81$).

**Classification of MR Severity**

The agreement between the integrated PISA or SV technique and CMR classification of MR (grades 1–2 versus 3–4) was compared. For the PISA technique using the integrated RVol, there was substantial agreement with CMR severity categories ($\kappa=0.79$; $P<0.001$). When MR grades 1 to 4 were examined individually, the integrated PISA RVol method categorized 5 patients into lower and 3 into higher MR grades when compared with CMR RVol. However, none were reclassified from clinically insignificant (grades 1–2) to clinically significant (grades 3–4) MR or vice versa. If the peak PISA RVol was used, in comparison with the integrated PISA method, 50% of the patients would have been classified into higher MR severity by at least 1 grade. Using receiver operating characteristic curves, the 3D PISA EROA that best differentiated severe (grade 4) from nonsevere (grades 1–3) MR was 0.51 cm² with a sensitivity and specificity of 86% (95% CI, 42%–100%) and 96% (95% CI, 78%–100%), respectively, and an area under the curve of 0.91 (95% CI, 0.75–0.98). This cutoff had a sensitivity and specificity of 100% (95% CI, 83%–100%) and 86% (95% CI, 52%–86%), respectively, to differentiate severe MR (grade 4) from moderate MR (grades 2 and 3). For the SV technique using RF, there was substantial agreement with CMR MR severity (grades 1–2 versus 3–4) categories ($\kappa=0.73$; $P<0.001$). For MR grades 1 to 4, compared with CMR, the SV technique categorized 3 patients into higher and 1 into lower MR grade. Among these patients one was reclassified from grade 2 to 3 MR, whereas the other from 3 to 2 MR.

**Reproducibility**

The inter- and intraobserver variability (mean±2SD) for the EROA in the clinical study was 0.02±0.14 and 0.01±0.08 cm² (respective CCC were 0.93 and 0.98) and for the
RVol by integrated PISA was 2.2±15.0 and 0.7±6.7 mL (CCC=0.95 and 0.99). With the SV technique, interobserver variability (mean±2SD) for RVol and RF was 0.9±11.5 mL and 0.2±10.9%, respectively (CCC=0.96 and 0.93), whereas the intraobserver variability was 0.6±7.6 mL and 0.5±6.9% (CCC=0.98 and 0.97).

On test–retest analysis, the mean±2SD absolute difference in EROA and integrated PISA RVol was 0.0±0.13 cm² and 2.1±13.7 mL (CCC=0.91 and 0.94), respectively. With the volumetric technique the difference in RVol and RF was 1.2±8.8 mL and 1.6±9.7%, respectively (CCC=0.97 and 0.95).

**Discussion**

This study illustrates the accuracy and reproducibility of real-time (nonstitched) 3D transthoracic echocardiography acquisition by 2 automated methods to quantify MR. In an in vitro model, an automated 3D PISA method (without geometric assumptions) was more accurate than the 2D PISA method for the quantification of EROA and RVol. The estimation of RVol by the 3D peak or integrated PISA method was not significantly different. In patients with functional MR, the 3D PISA determined EROA had good correlation with CMR MR severity. However, because of the dynamic nature of the regurgitant orifice, the integrated PISA method was more accurate than the peak PISA method for RVol quantification. An additional approach using automated mitral and aortic SVs calculated using a 3D color Doppler-based technique was accurate for quantification of MR RVol and RF. In patients, both techniques had substantial agreement with CMR for differentiating moderate-to-severe versus less severe MR and had good inter, intra, and test–retest reproducibility. The feasibility of 86% (similar to 2D PISA) and advantages of automation may further promote the clinical adoption of these techniques.

**Automated 3D PISA-based EROA and RVol**

Among other factors, the need for shape assumptions and the inability to account for the dynamic regurgitant orifices are technical limitations to 2D and 3D PISA-based EROA and RVol measurements. The latter is specifically important in patients with functional MR where the regurgitant orifice is thought to be largest at the beginning and end of systole and smallest in the middle. Although previous studies have shown that 3D methods are more accurate than 2D PISA methods for MR quantification, these studies either required significant manual interaction with the data or ongoing geometric assumptions and were unable to account for the dynamic nature of the regurgitant orifice.

In this study, the 3D PISA was measured in an automated method without making any specific geometric assumptions. Using this technique, in the in vitro model, there was smaller underestimation of the AROA by the 3D method compared with the 2D PISA method. An important reason for underestimation by both techniques is the boundary effects of pulsatile flow through a rigid sharp-edged orifice resulting in flow contraction at the EROA by up to 40% compared with the AROA. In addition, for the 3D method the velocity component of the 3D PISA that is not radial to the transducer cannot be detected with color Doppler and can cause underestimation of the true 3D PISA. However, the latter is a limitation of ultrasound technology as opposed to the 3D technique. The 3D underestimation is unlikely related to the segmentation algorithm, which was accurate in the gray-scale images of a hollow sphere where Doppler velocities were not an issue. The relatively smaller EROA by 2D compared with 3D method is likely because of greater underestimation of EROA for 2 large asymmetrical orifices by 2D PISA and the errors in 2D PISA radius measurements because of the challenges in identifying the center of the regurgitant orifices particularly in the in vitro model.

Also similar to previous 2D studies but different from all previous 3D PISA publications, this study compared the use of 3D peak and integrated PISA methods to quantify MR RVol. In the in vitro model, the RVol by the 3D peak and integrated PISA methods was accurate, whereas the 2D RVol was underestimated by 50%. The degree of underestimation of
RVol by 2D TTE is similar to previous studies,\textsuperscript{5,12,22,23} including a study with the same in vitro model.\textsuperscript{21} However, unlike the 50% and 16% underestimation of EROA and RVol, respectively, seen in this latter study\textsuperscript{23} using gated 3D acquisition, our study with RT-VFCFD showed less underestimation. The difference between flowmeter and both 2D and 3D methods for RVol calculation was smaller than that seen for the EROA versus AROA comparison because the CW Doppler measures velocities at the EROA and not at the AROA. The comparable RVol measurements by the 3D integrated and peak PISA methods in the in vitro model illustrate that when the regurgitant orifice is static both methods are accurate. Also, the measurements of both the EROA and the RVol using automated 3D PISA were not affected by orifice geometry.

In patients with functional MR, although a good correlation was seen between EROA and MR severity measures as determined by CMR, the EROA measurements in the various severity categories were higher than expected by ASE guidelines. This is because of the use of the largest systolic PISA for EROA measurement in patients with functional MR,\textsuperscript{10,13} the use of the 3D surface area that results in larger proximal flow convergence region surface area than that determined using a hemispheric or hemiellipse assumption (Results and Figure III in online-only Data Supplement), and limitations of lateral resolution of the 3D acquisition at the site of the proximal flow convergence region. As a consequence, a peak PISA EROA cutoff of 0.51 cm$^2$ (compared with the traditional 2D EROA of 0.4 cm$^2$) was necessary to differentiate severe from nonsevere MR. Also because of the larger EROA, the peak PISA technique–based RVol was overestimated compared with CMR. This was overcome by using the integrated PISA method where the dynamic variation in the EROA is accounted for. This finding is in concordance with the better accuracy of 2D integrated PISA-based RVol compared with peak PISA-based RVol, especially in functional MR.\textsuperscript{10} But unlike this manual 2D TTE study, our data demonstrated overestimation (not underestimation) of peak PISA–based RVol because the 3D PISA is usually larger than 2D formulations of PISA (Results and Figure III in online-only Data Supplement). Similar to the previous 3D PISA studies, the eccentricity of the MR jet did not affect the accuracy of MR RVol quantification.\textsuperscript{5,12}

Also, the integrated PISA RVol had good agreement with CMR to differentiate patients with grade 1 to 2 versus 3 to 4 MR. This is particularly relevant because intervention may be considered in asymptomatic patients with grade 3 to 4 MR, whereas those with grade 1 to 2 may be followed clinically. Finally, the EROA and integrated RVol measurements had good inter- and intraobserver reproducibility, as well as test–retest reproducibility.

**Automated 3D SV Technique-based RVol and RF**

We previously demonstrated the accuracy (compared with CMR) and reproducibility of automated measurement of mitral and aortic SV using RT-VFCD imaging in patients without valvular heart disease.\textsuperscript{14} We extended this approach in this study to quantify RVol and RF in patients with functional MR in a rapid and accurate manner with acceptable reproducibility. The use of this 3D technique for MR quantification has not been previously demonstrated. This method is unique as compared with any previously studied 3D SV quantification\textsuperscript{24} or 2D pulsed wave Doppler method\textsuperscript{1} because the mitral inflow and aortic outflow SV are obtained from the same cardiac cycle from the same 3D volume data. Also, the velocities from the entire mitral annulus or left ventricular outflow tract are used to quantify SV as opposed to assumption of uniformity of velocities across the orifice as with 2D pulsed wave methods. This approach may be particularly useful in the presence of multiple MR jets or in cases where the PISA technique would be inaccurate and also to verify the accuracy of quantification using a second complementary method.

**Limitations**

The limitations of the in vitro model have been previously described.\textsuperscript{15,23} In the current PISA algorithm, although the peak PISA technique was automated, the integrated PISA technique required manual addition of RVol from each frame. However, this is more practical than any other integrated PISA method described in the literature.\textsuperscript{10} The number of systolic frames used in our study for integrated PISA method reflects the limitation of the 3D temporal resolution; however, it was not different from 2D studies of integrated PISA.\textsuperscript{5} Although the number of patients studied was not large, we had patients with the entire range of MR severity. Also, although we do not have an independent assessment of orifice shape in our patients, the preponderance of noncircular orifice shape in functional MR has been well described.\textsuperscript{25}

The use of CMR as the reference standard has limitations because RVol and RF quantification require the use of several measurements (LV end-diastolic volume, end-systolic volume, and aortic SV), each of which can have measurement variability ranging from 3% to 9%.\textsuperscript{14} However, other CMR techniques for MR quantification also have similar limitations. Therefore, the wider level of agreement for RVol and RF between CMR and the 3D techniques in our study is at least partially because of this limitation. This is further supported by the fact that the variability in RVol when compared with flowmeter measurements in the in vitro study was small (Figure 4) and that classification of patients into grade 1 to 2 versus 3 to 4 MR using these techniques was good. Unfortunately, good external reference standards for MR quantification are limited, and CMR measurements have been compared with invasive cardiac catheterization\textsuperscript{16} and used as reference standard in other MR studies where the variability in RVol was also as high.\textsuperscript{10} Finally, there are no societal guidelines as to the appropriate threshold criteria to grade MR severity by CMR and hence we used the ASE RF and RVol criteria.

**Conclusions**

Automated measurement of 3D PISA-based EROA and RVol is feasible, accurate, and reproducible using RT-VFCFD. The integrated PISA method is more accurate than peak PISA method in patients with functional MR. Automated measurement of mitral and aortic SV can be used to calculate RVol/RF and provides a novel approach to assess MR severity from a single volumetric data set. Combined with the workflow advantages of automation, it may now be possible to accurately quantify MR in routine clinical echocardiography using RT-VFCFD imaging.
Disclosures
Dr Vannan is a member of Per Diem Advisory Board, speakers honorarium, and received research support from Siemens. Dr Datta has ownership interest and is an employee of Siemens Medical Solutions, USA, Inc. The other authors have no conflicts to report.

References

CLINICAL PERSPECTIVE
The current recommendations for the assessment of severity of mitral regurgitation include quantitative measures. However, these are underused because 2- and 3-dimensional quantitative measures are time consuming, require mathematical assumptions, and are subject to significant interobserver variability. This study describes the use of real-time 3-dimensional full-volume color Doppler imaging coupled with automated proximal isovelocity surface area and stroke volume methods to quantify the severity of mitral regurgitation. The feasibility, accuracy, reproducibility, and the workflow advantages of the methods described may promote wider clinical adoption of 3-dimensional echocardiography for routine quantification of mitral regurgitation.
Quantification of Chronic Functional Mitral Regurgitation by Automated 3-Dimensional Peak and Integrated Proximal Isovelocity Surface Area and Stroke Volume Techniques Using Real-Time 3-Dimensional Volume Color Doppler Echocardiography: In Vitro and Clinical Validation

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SUPPLEMENTAL MATERIAL
Supplemental Methods

CMR Data Acquisition and Analysis

CMR was performed using a 1.5T magnet (MAGNETOM Avanto, Siemens Medical Solutions) using a 12-channel phased array coil. LV short axis cines were acquired using: segmented balanced steady state free precession (bSSFP) sequence, TR/TE 3/1.3ms, bandwidth 930Hz/pixel, flip angle 65°, effective temporal resolution of 20-25 frames per cardiac cycle, 8 mm short axis slices. LV end-diastolic (LVEDV) and end-systolic volumes (LVESV) were quantified as per guidelines(1). LV SV was calculated by subtracting LVESV from LVEDV (Figure 3 E-F of main manuscript). Aortic SV was obtained using through-plane phase contrast imaging 1-2cm above the aortic valve (Figure 3G main manuscript): TR/TE =53.3ms/2.1ms, bandwidth 401Hz/pixel, flip angle 25°, 6mm slice thickness, 20 frames per cardiac cycle, with aliasing velocity set at 150cm/s. An ROI was also placed on the chest wall closest to the aortic valve and propagated through all slices and used for phase offset error correction. The aortic SV was subtracted from LV SV to obtain mitral regurgitant volume (RVol) and regurgitant fraction (RF) was RVol divided by the LV SV(2-4).
Supplemental Results

Hemisphere versus Hemi-ellipse versus 3-D PISA

In a subgroup of 10 patients (moderate MR=5, severe MR =5) using the RT-VCFD acquisition we measured PISA by 3 methods: 2-D PISA using hemispheric and hemi-ellipse assumption, and the “true” 3-D PISA method. The major and minor dimensions and radius for the 2-D PISA methods were obtained by multiplanar reformat of the 3-D data (Figure III). The hemispheric surface area was calculated using the standard formula while the hemi-ellipse area was calculated using MATLAB which generated a mesh for the hemi-ellipse by numerically solving the hemi-ellipse equation and computing the surface area by integration of the mesh elements. The mean PISA measured with the hemispheric(0.27 ± 0.11 cm²) and hemi-ellipse techniques(0.39 ± 0.20 cm²) were significantly smaller than that determined by 3-D surface area method (0.46 ± 0.22 cm²) (p=0.001 and 0.04 respectively).
Supplemental References


Movie Legends

**Movie 1.** An illustration of the quantification of mitral regurgitation using an automated 3-D PISA technique.

**Movie 2.** An illustration of the automated mitral inflow and aortic outflow stroke volume quantification for calculation of mitral regurgitant volume and fraction.
Supplemental Figures

Figure I. Validation of the automated surface area segmentation algorithm.
Figure II. *In vitro* measurements of EROA by 2-D TTE and RT-VCFD in comparison to the true orifice area for each orifice tested. The EROA was underestimated for each orifice by both techniques, however, the underestimation was much higher with 2-D TTE than RT-VCFD.
Figure III. Comparison of (B) 3-D surface area (C) hemispheric and (D) hemi-ellipse assumption based surface area to compute EROA. Based on the EROA, the patient would be categorized as having mild MR based on hemispheric PISA, moderate MR by hemi-ellipse PISA, and severe MR by 3-D. CMR severity was grade 3 (moderately severe), and CMR RVol was 56.1ml, RF 47