Diagnostic Value of Vena Contracta Area in the Quantification of Mitral Regurgitation Severity by Color Doppler 3D Echocardiography

Hung et al: Vena Contracta Area for Quantification of Mitral Regurgitation Severity

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Echocardiography
Abstract

Background—Accurate quantification of mitral regurgitation (MR) is important for patient management and prognosis. Three-dimensional (3D) echocardiography allows for the direct measure of the regurgitant orifice area (ROA) by 3D guided planimetry of vena contracta area (VCA). We aimed to 1) establish 3D VCA ranges and cut-off values for MR grading, using the ASE recommended two dimensional (2D) integrative method as a reference; 2) Compare 2D and 3D methods of ROA to establish a common calibration for MR grading.

Methods and Results—83 patients with at least mild MR underwent 2D and 3D echocardiography. Direct planimetry of VCA was performed by 3D echocardiography. 2D quantification of MR included 2D ROA by proximal isovelocity surface area (PISA) method, vena contracta width and ratio of jet area to left atrial area. There were significant differences in 3D VCA among patients with different MR grades. As assessed by receiver operating characteristic analysis, 3D VCA at a best cut-off value of 0.41 cm\(^2\) yielded 97% of sensitivity and 82% of specificity to differentiate moderate from severe MR. There was significant difference between 2D ROA and 3D VCA in patients with functional MR, resulting in an underestimation of ROA by 2D PISA method by 27% as compared with 3D VCA. Multivariable regression analysis showed functional MR as etiology was the only predictor of underestimation of ROA by 2D PISA method.

Conclusions—3D VCA provides a single, directly visualized and reliable measurement of ROA, which classifies MR severity comparable to current clinical practice using the ASE recommended 2D integrative method. 3D VCA method improves accuracy of MR grading compared with 2D PISA method by eliminating geometric and flow assumptions, allowing for uniform clinical grading cutoffs and ranges that apply regardless of etiology and orifice shape.

Key Words: mitral regurgitation, diagnosis, 3D echocardiography, doppler echocardiography
Accurate assessment of mitral regurgitation (MR) is important for clinical decision making and outcome prediction. The calculation of an effective regurgitant orifice area by the proximal isovelocity surface area method (PISA) is a main method for quantification of mitral regurgitation. However, it requires flow and geometric (hemisphere) assumptions which has limited its clinical application. Recently, three-dimensional (3D) echocardiography allowed for the direct measurement of effective regurgitant orifice area by 3D guided planimetry of vena contracta area (VCA). This single measure is not dependent on geometric and flow assumptions, therefore it can provide direct and more accurate quantification of MR than two-dimensional (2D) measurements. In vitro validation and clinical studies showed that direct planimetry of vena contracta area was highly feasible, and this measurement correlated well with ROA derived by the volumetric Doppler approach \(^1,2\). Currently, however, there is no data on the ranges and cut-off values of 3D VCA for MR grading, compared to standard reference grading criteria using the 2D integrative method proposed by the American Society of Echocardiography, which is method of MR grading employed by most clinical echocardiography laboratories. We aimed to 1) Establish 3D VCA ranges and cut-off values for differentiation of MR grades, using the 2D integrative method as a reference; and 2) Compare color Doppler 2D and 3D vena contracta area for MR grading.

**Methods**

**Patient population**

From September 2008 to Aug 2010, 102 patients with at least mild MR who underwent color Doppler 2D and 3D echocardiography were initially enrolled in this study.
Exclusion criteria included significant mitral stenosis (area <2.0 cm²), cleft mitral valve, mitral prosthesis or annuloplasty, infective endocarditis, irregular rhythm, poor 2D or 3D image quality, and those unable to determine the etiology of MR.

The echocardiographic protocol and data were approved by the committee of Massachusetts General Hospital Institutional Review Board.

**Echocardiographic examination**

2D and 3D color Doppler echocardiographic examination were performed by using iE33 ultrasound system (Philips Medical Systems, Andover, Massachusetts).

**3D color Doppler acquisition and data analysis**

A full volume 3D Color Doppler acquisition was obtained during using the X3-1(1-3MHz) matrix array transducer from the apical window over 7 to 14 consecutive cardiac cycles with electrocardiographic gating, the narrowest sector possible to maximize the frame rate and Nyquist velocities of 50 to 80 cm/s. Patients were asked to hold respiration during acquisition if possible or breathe quietly.

3D color MR jet dataset was analyzed at the Xcelera workstation using Philips Qlab 2.0 software. Two orthogonal image planes parallel to the regurgitant jet direction were manually cropped across the regurgitant jet, then a third cropping plane which was perpendicularly oriented to the jet direction was moved along the jet direction until the cross-sectional area at the level of the vena contracta was visualized. The frame with the largest VCA in systole was
magnified and VCA was measured by directly planimetry of the color Doppler flow signal (refer to the online tutorial at Supplemental Video). To analyze the circularity of the regurgitant orifice, the ratio of the long axis to the short axis of VCA (L/S ratio) was calculated.

**2D echocardiography and measurements**

2D echocardiography was performed using a S5-1 probe. LV end diastolic and end systolic diameter (LVEDD and LVESD) were measured by 2D method from parasternal long axis view. LV end-diastolic volume (EDV) and LV end-systolic volume (ESV) were measured using the Simpson’s biplane method and LVEF was calculated as (EDV-ESV) × 100/EDV. 2D quantification of MR included proximal isovelocity surface area method, vena contracta width and ratio of jet area to left atrial area. A narrow color flow sector width and the least depth were chosen to maximize image resolution.

**PISA** Proximal flow convergence was acquired from magnified apical 4-chamber, 2-chamber and long axis view, with baseline shift of the Nyquist limit (30~40cm/s) to optimize visualization of flow convergence. ROA was calculated using the formula: ROA=2 × R_PISA × V_aliasing/V_max, where R_PISA was the maximal PISA radius (cm), V_aliasing was aliasing velocity of the proximal flow convergence (cm/s), and V_max was maximal velocity of continuous wave Doppler MR signal (cm/s). MR volume was calculated as (ROA × regurgitant time-velocity integral). The severity of MR was graded based on the current ASE recommendations as mild (<0.2cm²), moderate (0.2-0.39 cm²), and severe (≥0.40 cm²)⁴.

**Vena contracta width** Vena contracta was acquired from a magnified parasternal long axis view with the central beam through the leaflet tips. VCW was defined as the narrowest width of the proximal jet measured at or in the immediate vicinity of the MR orifice at the leaflet tips. The
severity of MR was graded based on current recommendations as mild (<0.3 cm), moderate (0.3-0.69 cm), and severe (≥0.7 cm) 4-6.

**JA/LAA** The color flow Doppler image of the mitral regurgitant jet was acquired from the apical 4- and 2-chamber views at a Nyquist limit of 50 to 60 cm/s. The ratio of mitral regurgitant jet area to left atrial area was calculated from the average of both views. The severity of MR was graded based on current recommendations as mild (<20%), moderate (20%-39%), and severe (≥40%) 4.

**2D integrative method** The 2D integrative method recommended by ASE as follows 4 was used as the reference standard for MR grading as this method does not rely on just one color Doppler method and is used widely in clinical laboratories 7. In order to categorize MR within a certain grade, at least 2 out of 3 color Doppler methods listed above were assessed within the same grade with at least 1 supportive data (pulmonary vein flow; mitral inflow; density of continuous wave Doppler MR jet; left atrial enlargement). The integrative grading and 3D VCA measurement were done independently and the results were blinded to each other.

**Statistical Analysis**

Results were expressed as mean ± standard deviation (SD) for continuous variables and as percentages for categorical variables. Differences between groups were analyzed with the unpaired or paired t-test. Differences among more than two groups were assessed by one way ANOVA test with the Bonferroni correction. The linear association between continuous variables was made with the Pearson’s correlation coefficient. Spearman’s rank correlation method was used to assess the associations between grading of MR by the 2D integrative method and by each quantitative method. The diagnostic values of echocardiographic parameters for MR quantification were analyzed by receiver operating characteristic (ROC) curve. The optimal
cutoff value was defined as the value for which the sum of sensitivity and specificity was maximized. Area under the curve, sensitivity, specificity, positive and negative likelihood ratio were reported. Agreement between methods was tested by using Bland-Altman analysis and plotted with lines representing mean ± 2SD. The degree of the underestimation of ROA by 2D PISA method was calculated as the ratio of 2D ROA to 3D VCA (2D ROA/3D VCA). Single predictor and multivariable linear regression with a stepwise approach were performed to identify the predictors associated with underestimation of ROA by 2D PISA method. A $P$ value <0.01 was considered statistically significant for all analyses. SPSS 13.0 software was used for statistical analysis (SPSS Inc., Chicago, Illinois).

Results

Characteristics of the study population

102 patients were initially enrolled in the study, 19 patients were excluded due to poor 3D image quality which was technically inadequate or suboptimal for 3D cropping or direct planimetry of 3D VCA. The majority (68%) of the excluded patients with poor image quality were patients with mild MR. The final study group consisted of a total 83 patients (mean age, 67±19 years; 41 men). The etiology of MR was functional in 39 patients (47%) and degenerative in 44 patients. Eccentric MR jet was present in 39 (47%) patients, while central MR jet in 44 patients. Mean LVEDD was 52.1±8.8 mm, mean LVESD was 38.8±11.8 mm, and a mean LVEF of 50.3±19.2%. All patients were in sinus rhythm with the mean heart rate of 71±17 beats/min.
Assessment of VCA by 3D color Doppler echocardiography

MR severity was graded as mild, moderate or severe according to the 2D integrative method as a reference standard. The 2D and 3D echocardiographic quantitative variables in various grades are summarized in the Table 1. There were significant differences in 3D VCA among mild, moderate and severe MR groups as assessed by the 2D integrative criteria, as well as the 2D ROA, VCW and JA/LAA (all \( P < 0.001 \)).

Diagnostic values of 3D VCA to differentiate between moderate and severe MR

Spearman’s rank correlation showed that 3D VCA had the best correlation with the 2D integrative method (\( r = 0.88 \)). The correlation coefficient between 2D ROA, MR volume, VCW, JA/LAA and the 2D integrative method was 0.86, 0.77, 0.83 and 0.65 respectively. As assessed by receiver operating characteristic analysis, the area under the curve (AUC) was 0.96, 0.95, 0.94 and 0.78 for 3D VCA, 2D ROA, VCW and JA/LAA respectively to differentiate moderate from severe MR. 3D VCA at an optimal cut-off value of 0.41 cm\(^2\) yielded a sensitivity of 97% and a specificity of 82% to differentiate moderate from severe MR (Figure 1). The best cut-off value for 2D ROA was 0.32 cm\(^2\), lower than 3D VCA. The diagnostic and cut-off value of these variables are demonstrated in Table 2.

Correlations and differences between 2D and 3D methods

The ranges of 3D VCA and 2D ROA in different MR grades are demonstrated in Figure 2A. 3D VCA correlated well with 2D ROA (\( r = 0.88, P < 0.001 \), Figure 2B) in all patient sample. Correlations were strong for both central and eccentric MR jets, although patients with central MR jet showed a significantly better agreement than patients with eccentric MR jets (\( r = 0.93 \) vs. ...
The correlation between 3D VCA and 2D ROA demonstrated a significantly better agreement in patients with degenerative MR than functional MR ($r=0.91$ vs. $r=0.78$, $P<0.001$, Figure 3A & 3B). Paired $t$ test showed 3D VCA was significantly higher than 2D ROA in the entire patient sample ($0.43\pm0.25$ cm$^2$ vs. $0.36\pm0.24$ cm$^2$, mean difference was $0.08$ cm$^2$, $P<0.001$). Bland-Altman analysis showed 3D VCA was slightly higher than 2D ROA in patients with degenerative MR ($0.47\pm0.30$ cm$^2$ vs. $0.44\pm0.30$ cm$^2$, mean difference was $0.04$ cm$^2$, $P=0.05$, Figure 4C), however, the difference was more statistically significant in patients with functional MR ($0.39\pm0.17$ cm$^2$ vs. $0.27\pm0.11$ cm$^2$, with a mean difference of $0.12$ cm$^2$, $P<0.001$, Figure 4D), resulting in an underestimation of ROA by 2D PISA method by a mean of 27% when compared to 3D VCA. This is demonstrated in Figure 4D with an overall positive slope of overestimation by 3D VCA in patients with functional MR. If the currently recommended ranges and cut off values of <0.2 cm$^2$, 0.2~0.39 cm$^2$ and $\geq0.4$ cm$^2$ were applied for grading MR severity as mild, moderate and severe respectively for both 2D ROA and 3D VCA, compared to 2D ROA, 31.3% of the patients would be upgraded to a more severe grade based on the measurement of 3D VCA, among which 69% were the patients with functional MR. 2D ROA was in accordance with 3D VCA in MR grading in 67% of the patients. Similarly, when compared to 2D ROA, 19.3% of the patients would be upgraded one grade of MR severity by 2D integrative method, among which 75% were patients with functional MR.

The geometry of VCA in the majority of patients was elliptical rather than circular, even in patients with degenerative MR. Patients with functional MR had more elongated and elliptical shape of VCA (as assessed by L/S ratio of VCA) compared with patients with degenerative MR ($2.25\pm0.85$ vs. $1.62\pm0.48$ cm, $P<0.01$; Figure 5A&5B).
By single predictor regression analysis, variables including LVESV, LVEF, eccentricity of MR jet, L/S ratio and functional MR as etiology were statistically significant predictors for the underestimation of ROA by 2D PISA method (Table 3). Six variables with a $P$ value <0.1 by single predictor regression analysis were entered as covariates in the multivariable model, including LVESV, LVEF, eccentricity of MR jet, L/S ratio, functional MR as etiology and heart rate. Multivariable analysis showed functional MR as etiology was the only independent predictor of the underestimation of ROA by 2D PISA method ($P<0.001$).

**Reproducibility of 3D VCA measurement**

To evaluate interobserver variability, two independent observers (X.Z and L.H) measured the 3D VCA in 15 patients using the same 3D datasets. To test the intraobserver variability, measurement of 3D VCA was repeated by the same observer (X.Z) 3 months later. Bland-Altman analysis and interclass correlation coefficient (ICC) were used to assess the observer variability. There was good interobserver variability for 3D VCA (ICC: 0.92; 95% confidence interval: 0.79-0.97; mean difference: 0.03 cm$^2$) as well as intraobserver variability (ICC: 0.95; 95% confidence interval: 0.85-0.98; mean difference: 0.04 cm$^2$). The Bland-Altman plot for observer variability is provided in the online Supplemental Figure.

**Discussion**

The results of the present study showed that 3D vena contracta area correlated well with the 2D integrative method of assessing mitral regurgitation severity. In addition, 3D VCA showed high diagnostic value for separating moderate from severe MR in all etiologies. The etiology of MR was the only factor independently affected the accuracy of ROA derived by 2D PISA method.
The 2D PISA method underestimated the ROA in patients with functional MR because of the hemispherical assumption when the PISA zone was more often hemielliptical. 3D VCA which allows for direct planimetry of the regurgitant orifice area, circumvents this inherent limitation of the 2D PISA method and provides uniform clinical grading cutoffs and ranges that apply regardless of etiology and orifice shape.

**Quantification of MR by Color Doppler 2D and 3D echocardiography**

Accurate assessment of MR is important but still challenging in daily clinical practice. Currently, various color Doppler 2D methods are used for MR quantification; however, each method has its limitations based on technical issues or inaccurate geometric assumption. For example, JA/LAA method is limited by instrument settings, hemodynamics, jet eccentricity, left atrial compliance et al. The 2D PISA method provides an indirect measurement of ROA, and the limitations arise from geometric assumption of a hemispherical regular shape which appears in fact to be less frequent than a hemielliptical one. Similarly, one dimensional measurement of vena contracta width is used as a surrogate of an often irregular ROA which limits its correlation. In individual cases, the results of different methods may be discordant. Even among experienced echocardiographers, intraobserver variability for these common parameters is high⁸. Therefore, integrating different parameters would be more reliable for MR grading by minimizing the limitations of each method.

Besides the above 2D methods, recent studies showed that planimetry of VCA was highly feasible by using color Doppler 3D echocardiography, which provided a new approach for MR quantification by direct measurement of ROA. As there are no geometric and flow assumptions involved in 3D method, direct planimetry of VCA might be more accurate than conventional 2D calculations of EROA. A recent study by Marsan reported that 3D VCA was highly accurate
compared with MR volume measured by velocity-encoded cardiac magnetic resonance in patients with functional MR\(^9\). However, without the information of ranges and cut-off values for MR grading, it is hard to apply 3D VCA in daily clinical practice. In the present study, our results showed that 3D VCA was a powerful method for accurate quantification of MR severity, and had the best correlation with the 2D integrative method compared to other color Doppler methods. Moreover, the ability to accurately distinguish severe from non severe MR is of particular clinical importance, because severe MR is associated with significant LV remodeling, morbidity and mortality\(^{10,11}\) and is often the grade at which clinical decision making is based. Severity of MR has a significant influence on the decision toward timing of surgical intervention or watchful waiting as well, as a result, current ACC/ AHA guidelines recommend surgery for asymptomatic severe MR\(^{12}\). By using ROC curve analysis, we found 3D VCA at a cut-off value of 0.41 cm\(^2\) had high sensitivity and specificity to identify severe MR for all etiologies. The current study establishes the ranges of 3D VCA in different MR grades and proposes a reliable cut-off value for differentiating severe from non severe MR, which would facilitate this new method in clinical use.

**Comparisons of 2D and 3D methods for MR grading**

2D PISA method is widely and frequently used for MR grading, which is based on the assumption of hemispheric symmetry of proximal flow convergence region\(^{13}\). In our study, overall, 2D PISA method correlated with both the 2D integrative method and 3D VCA. However, the correlation between 2D PISA method and 3D VCA was significantly worse in patients with eccentric MR than central MR. It is well known that PISA method has limitations in assessing eccentric jets due to the theoretical, technical, or measurement errors\(^{8,14}\), while 3D
VCA might be more accurate, because it is derived by subsequent cropping, which is exactly perpendicular to the laminar vena contracta flow. Although no gold standard is available for comparison, this result supports the previous finding of the advantages of 3D VCA in assessing eccentric MR jets compared with 2D methods.  

2D PISA method can under- or overestimate the ROA when geometric assumptions do not fit. The geometry of PISA is often not hemispheric but hemielliptic and the shape of ROA may be noncircular. Earlier studies showed that 2D PISA method ignoring the horizontal length of PISA could systematically underestimate the actual ROA in cases with a hemielliptic shaped orifice. Furthermore, recent color Doppler 3D studies revealed that different geometry of PISA and shape of ROA might be associated with the etiology of MR. Matsumura et al demonstrated an elongated and slightly curved PISA geometry along the leaflet coaptation in functional MR, whereas the shape was rounder in mitral valve prolapse. Kahlert et al found significant asymmetry of ROA in functional MR compared with organic MR. Our results are consistent with these previous findings. We observed elliptical shaped VCA in most cases, even in degenerative MR. In addition, patients with functional MR had significantly more elliptical shape of VCA than degenerative MR. By multivariable regression analysis, functional MR as etiology was the only predictor of underestimation of ROA by 2D PISA method.

Our results support re-evaluating the cut-off value for severe MR based on etiologies if the 2D PISA method is applied. The recommended cut-off value of ROA according to ASE recommendation and Dujardin’s study for severe MR is 0.4 cm$^2$. However Grigioni et al proposed a different cut-off value in patients with ischemic MR. ROA $\geq$ 0.2 cm$^2$ by either 2D PISA or volumetric Doppler approach which might otherwise be qualified as moderate MR was independently associated with severe clinical consequences in post-myocardial infarction.
patients. Thus, such patients should be considered to have clinically severe MR. Our results are in agreement with these clinical findings. As 2D PISA method systematically underestimates the ROA in patients with functional MR, a lower cut-off value (less than 0.4 cm²) might be considered for severe in such patient sample. With the study population of all etiologies, our results showed although 2D PISA method had high accuracy in separating severe from non severe MR, the best cut-off value was 0.32cm², lower than the value recommended by ASE and the cut-off value of 3D VCA. Since the best cut-off point is subject to specific study population, further studies with a larger population may be required to determine the cut-off value for severe functional MR by using 2D PISA method. Current 2D ROA methods thus appear to require different grading scales for functional versus degenerative MR. Quantitative 3D VCA can be used to potentially establish unified normative ranges for MR grading that would apply to all MR etiologies.

**Clinical implications**

This study proposes ranges for 3D VCA for MR grading, which is important for clinical reference and highlights the potential advantages of using 3D VCA over 2D ROA. Our study emphasizes the importance of etiology of MR in the underestimation of ROA by 2D PISA method and supports redefining the ranges of MR degree based on etiologies if 2D PISA method is applied. 3D VCA provides a reliable alternative method for MR grading that provides a unified range for all etiologies, which is likely to be more consistent in functional MR and probably when the ROA is elliptical even in degenerative MR. Therefore, its clinical use can be applied in such patient population or in cases of borderline severity.
Limitations

Some limitations should be acknowledged. First, 3D planimetry of the vena contracta has limited spatial resolution, particularly in the non-axial planes (lateral resolution). In this study, approximately 19% of patients were excluded due to technically inadequate image quality for planimetry of the VCA. In order to optimize spatial resolution, depth was adjusted for maximal resolution and 3D data acquisitions were performed using a minimum of 7 beats and preferably 14 beats whenever possible. In addition, color gain settings were set in a standardized manner by increasing gain just below level where random noise develops, allowing for uniform color gain settings. The vena contracta area was measured at aliased velocities, avoiding potential color bleeding that may occur at lower nonaliased velocities. Limited spatial resolution is more likely to affect mild MR ranges where the vena contracta area is smallest and also likely accounts for the varied results with mild MR. In this study planimetry of the VCA was inadequate or suboptimal in about 45% of patients with mild MR. However, clinical decision making is based predominantly in the moderate to severe MR ranges where spatial resolution limitations should have a lesser effect. Thus, our study primarily focused on the diagnostic value of 3D VCA for differentiating moderate from severe MR, which is also more clinically important. Second, variation in ROA during systole was not taken into account by this method. Although integrating instantaneous EROAs throughout the cardiac cycle would take into account ROA variation, this is not practical in the clinical setting. No color Doppler technique avoids this limitation. Practice guidelines have supported the use of single ROA measurements for quantification of MR. The variation in ROA has less of an impact in degenerative MR such as flail leaflet where the ROA is generally uniform throughout systole. In ischemic/functional MR, the temporal pattern of ROA during systole is bimodal with peaks early and late in systole and minimum during mid-systole.
The bimodal pattern in ischemic MR is enhanced in lower ranges of MR (mild) where driving pressure can have a greater effect at mid-systole. In larger degrees of MR (moderate or greater) where driving pressure has less of an impact due to the larger MR flows, the bimodal pattern is blunted. The impact of ROA should be minimized in the more clinically important situations involving moderate or greater MR ranges. Third, the accuracy of 3D VCA would be affected by the three cropping planes, especially the cross sectional plane. In some cases with eccentric MR, the perfect plane of 3D VCA could be difficult to determine. Inappropriate cropping would result in overestimation of VCA. Fourth, stitch artifacts which might be caused by arrhythmias, respiration, patient motion, and movements of the probe by the operator also affect the accuracy of results. Lastly, as the sample was limited, ROC analysis was likely to be optimistic, further studies in larger patient population are needed to confirm these results.

Conclusions

3D VCA provides a single, directly visualized and reliable measurement of ROA, independent of geometric and flow assumptions, which classifies MR severity comparable to current clinical practice using the ASE recommended 2D integrative method. 3D VCA method improves accuracy of MR grading compared with 2D PISA ROA method by eliminating geometric assumptions that frequently fail to describe the true flow convergence shape. This is especially pertinent for functional MR where the shape of the PISA region is mainly hemielliptical. 3D VCA method provides uniform clinical grading cutoffs and ranges that apply regardless of etiology and orifice shape.
Disclosures

None.

References


Table 1. 2D and 3D Quantitative Variables in Mild, Moderate and Severe MR as Assessed by the 2D Integrative Method

<table>
<thead>
<tr>
<th></th>
<th>Mild MR (n=15)</th>
<th>Moderate MR (n=34)</th>
<th>Severe MR (n=34)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3D VCA (cm²)</td>
<td>0.15±0.06</td>
<td>0.34±0.09</td>
<td>0.66±0.21</td>
</tr>
<tr>
<td>2D ROA (cm²)</td>
<td>0.13±0.05</td>
<td>0.25±0.08</td>
<td>0.57±0.25</td>
</tr>
<tr>
<td>MR volume (ml)</td>
<td>25±11</td>
<td>42±12</td>
<td>83±37</td>
</tr>
<tr>
<td>VCW (cm)</td>
<td>0.29±0.11</td>
<td>0.47±0.15</td>
<td>0.84±0.16</td>
</tr>
<tr>
<td>JA/LAA</td>
<td>0.17±0.06</td>
<td>0.29±0.09</td>
<td>0.40±0.12</td>
</tr>
</tbody>
</table>

One way ANOVA test is used to compare mean values for variables among different groups (all P<0.001).

MR=mitral regurgitation; VCA=vena contracta area; ROA=regurgitant orifice area; VCW=vena contracta width; JA/LAA=ratio of jet area to left atrial area
Table 2. ROC analysis of Echocardiographic Parameters for Identification of Severe MR

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Cut-off</th>
<th>Sensitivity (%)</th>
<th>95% CI</th>
<th>Sensitivity (%)</th>
<th>Specify (%)</th>
<th>+LR</th>
<th>-LR</th>
</tr>
</thead>
<tbody>
<tr>
<td>3D VCA(cm²)</td>
<td>0.41</td>
<td>97</td>
<td>0.96</td>
<td>97</td>
<td>82</td>
<td>5.50</td>
<td>0.04</td>
</tr>
<tr>
<td>2D ROA(cm²)</td>
<td>0.32</td>
<td>94</td>
<td>0.95</td>
<td>94</td>
<td>85</td>
<td>6.40</td>
<td>0.07</td>
</tr>
<tr>
<td>VCA(cm²)</td>
<td>0.62</td>
<td>91</td>
<td>0.94</td>
<td>91</td>
<td>91</td>
<td>10.33</td>
<td>0.10</td>
</tr>
<tr>
<td>VCW(cm)</td>
<td>0.39</td>
<td>65</td>
<td>0.78</td>
<td>65</td>
<td>88</td>
<td>5.50</td>
<td>0.40</td>
</tr>
</tbody>
</table>

AUC: area under the curve; +LR: Positive likelihood ratio; -LR: Negative likelihood ratio; other abbreviations as in Table 1.
Table 3. Single Predictor and Multivariable Regression Analysis of Predictors of Underestimation of ROA by 2D PISA Method Compared to 3D VCA

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Single Predictor</th>
<th>Multivariable</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>beta</td>
<td>coefficient</td>
</tr>
<tr>
<td></td>
<td>P value</td>
<td>P value</td>
</tr>
<tr>
<td>Age</td>
<td>-0.04</td>
<td>0.73</td>
</tr>
<tr>
<td>LVEDV</td>
<td>-0.11</td>
<td>0.31</td>
</tr>
<tr>
<td>LVESV</td>
<td>-0.24</td>
<td>0.03</td>
</tr>
<tr>
<td>LVEF</td>
<td>0.34</td>
<td>0.002</td>
</tr>
<tr>
<td>MR severity</td>
<td>0.08</td>
<td>0.48</td>
</tr>
<tr>
<td>Eccentricity of MR jet</td>
<td>0.27</td>
<td>0.01</td>
</tr>
<tr>
<td>L/S ratio</td>
<td>-0.29</td>
<td>0.008</td>
</tr>
<tr>
<td>Functional MR as etiology</td>
<td>-0.41</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Heart rate</td>
<td>-0.19</td>
<td>0.09</td>
</tr>
<tr>
<td>Acquisition beats (7 or 14)</td>
<td>-0.08</td>
<td>0.5</td>
</tr>
</tbody>
</table>

EDV=end diastolic volume; ESV=end systolic volume; EF=ejection fraction; MR=mitral regurgitation; L/S ratio=the ratio of the long axis to the short axis of VCA.
Figure Legends

Figure 1. Receiver operating characteristics analysis shows that 3D VCA with a cutoff value of 0.41 cm² is a highly accurate parameter for the detection of severe MR.

Figure 2. Correlation between 3D VCA and 2D ROA for the entire patient sample (A). The ranges of 3D VCA and 2D ROA in different MR grades as assessed by the 2D integrative method (B).

Figure 3. Correlations between 3D VCA and 2D ROA in patients with central MR jet (A) and patients with eccentric MR jet (B).

Figure 4. Correlations between 3D VCA and 2D ROA in patients with degenerative MR (A) and in patients with functional MR (B). The solid line represents a linear regression fit through all the points, and the dashed line in Figure 4B represents the line of identity. Bland-Altman depiction of regurgitant orifice area bias using the 2D PISA method and 3D direct planimetry method in patients with degenerative MR (C) and patients with functional MR (D).

Figure 5. Geometry of VCA is more elliptical in patients with functional MR compared with degenerative MR.
ROC curve
(moderate vs. severe MR)

Sensitivity (%)

100
80
60
40
20
0

1- Specificity (%)

0
20
40
60
80
100

3D VCA > 0.41 cm²

AUC = 0.96
SE = 0.02
P < 0.001
Functional MR

Degenerative MR