Validation of Semiautomated Quantification of Mitral Valve Regurgitation by Three-Dimensional Color Doppler Transesophageal Echocardiography

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Background: The aim of this study was to evaluate the accuracy of mitral regurgitation (MR) volume quantified on three-dimensional (3D) color Doppler transesophageal echocardiography (TEE) using new semiautomated software compared with conventional two-dimensional (2D) proximal isovelocity surface area (PISA) transthoracic echocardiography (TTE) and TEE and cardiac magnetic resonance imaging (CMR).

Methods: Fifty-one patients (mean age, 63 ± 16 years; 35 men) prospectively underwent TTE, TEE, and CMR for MR evaluation. Regurgitant volume (RVol) by 3D MR flow quantification was compared with 2D TTE, TEE, and CMR, and the accuracy of evaluation of severe MR by 3D MR flow quantification was compared against guideline criteria by TEE.

Results: Twenty-nine patients had severe MR, 16 had moderate MR, and six had mild MR. Three-dimensional MR flow quantification was feasible in all patients, including prolapse ($n = 37$), restriction ($n = 9$), functional MR ($n = 5$), and eccentric or multiple jects ($n = 41$). RVol on 3D MR flow quantification correlated well with RVol on 2D PISA TTE (interclass correlation coefficient [ICC] = 0.75, $P < .001$), quantitatively estimated RVol (ICC = 0.74, $P < .001$), and 2D PISA TEE (ICC = 0.79, $P < .001$). Three-dimensional MR flow quantification agreed better with CMR (ICC = 0.86, $P < .001$) than did RVol on 2D PISA TTE (ICC = 0.66, $P < .001$) and 2D PISA TEE (ICC = 0.69, $P < .001$), with narrower limits of agreement on Bland-Altman analysis. Three-dimensional MR flow quantification had high accuracy for diagnosing severe MR using TEE (area under the curve = 0.85, 95% CI 0.74-0.96, $P < .001$) or CMR (area under the curve = 0.95; 95% CI, 0.89–1.00; $P < .001$) as the criterion.

Conclusions: The new software enabled semiautomated 3D MR flow quantification in complex MR with multiple and eccentric jets and showed better agreement with CMR than 2D PISA TTE or TEE, suggesting that this method is more accurate than conventional 2D PISA TTE and TEE. (J Am Soc Echocardiogr 2019;■:■-■.)

Keywords: Mitral valve regurgitation, Three-dimensional, PISA, TEE, Magnetic resonance imaging

Accurate quantification of mitral regurgitation (MR) severity is important for predicting risk and guiding decisions regarding surgery. The primary clinical tool for evaluating the mechanism and severity of MR is two-dimensional (2D) Doppler transthoracic echocardiography (TTE) with the help of transesophageal echocardiography (TEE) when TTE is insufficient or when further diagnostic refinement is required. Current guidelines recommend an integrated approach for echocardiographic grading of MR severity.[1-4] The flow convergence method with calculation of regurgitant volume (RVol) using the proximal isovelocity surface area (PISA) method is

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Conflicts of Interest: None.

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Abbreviations

2D = Two-dimensional

3D = Three-dimensional

AUC = Area under the receiver operating characteristic curve

CMR = Cardiac magnetic resonance imaging

EROA = Effective regurgitant orifice area

ICC = Interclass correlation coefficient

LV = Left ventricular

MR = Mitral regurgitation

PISA = Proximal isovelocity surface area

RVol = Regurgitant volume

TEE = Transesophageal echocardiography

TTE = Transthoracic echocardiography

currently the most recommended method for quantification of MR severity for both TTE and TEE. However, prior studies have suggested that the echocardiographic parameters used with the 2D PISA method to estimate MR severity, such as PISA-derived effective regurgitant orifice area (EROA), vena contracta width, and color Doppler jet area, are only moderately reproducible.[5] This probably reflects some important limitations due to underlying assumptions for these estimations, in particular regarding multiple, eccentric, or constrained jets and in the presence of temporal changes in orifice geometry.

Three-dimensional (3D) color Doppler echocardiography might allow more accurate measures of MR severity by correcting for the intrinsic limitations of the 2D PISA method. In particular, automated algorithms have been proposed that simulate the flow convergence proximal to the regurgitant orifice as a 3D velocity vector field, which is optimized to fit the data.[6,7] It was suggested that such algorithms may allow a better estimation of MR in the presence of multiple jets or noncircular regurgitant orifices, but this has not been validated in patients.

In the present work, we used novel postprocessing software that relies on a similar field optimization approach to allow semiautomated computation of MR quantification severity from 3D color Doppler transesophageal echocardiographic images. We sought to evaluate the accuracy of 3D MR flow quantification using this new software against measurements of MR severity on conventional 2D PISA TEE and 2D PISA TTE, as well as an external reference standard, cardiac magnetic resonance imaging (CMR). Accordingly, we prospectively studied 51 consecutive patients with suspected MR using 3D and 2D TEE and TTE and CMR.

METHODS

Study Design

The study protocol was approved (2017/07MAR/123) by the institutional ethics committee of Cliniques Universitaires Saint-Luc, Université Catholique de Louvain (Brussels, Belgium). Patients were included after providing written informed consent to participating in this prospective study. Between July 2017 and November 2018, patients scheduled for TEE were screened in the echocardiography laboratory of Cliniques Universitaires Saint-Luc for consideration for study enrollment. Inclusion criteria were age >18 years, sinus rhythm, and clinically indicated TEE for evaluation of the mechanism and severity of chronic MR. Exclusion criteria were atrial fibrillation, acute MR, endocarditis, unstable hemodynamic conditions and cardiac shock, New York Heart Association functional class > III, significant aortic regurgitation or cardiac shunt, constant arrhythmia (atrial fibrillation or flutter), and contraindication to CMR (pacemaker or other CMR-incompatible implant, claustrophobia). We also excluded patients with poor tolerance of TEE and in whom 3D color images could not be acquired with sufficient image quality or frame rate (<15 frames/sec). In total, 51 patients were included in this study.

Study Protocol

Subjects underwent CMR for evaluation of the severity of MR within 7 days of TEE. All subjects also underwent clinically indicated TTE before TEE.

Transthoracic Echocardiography and Transesophageal Echocardiography

TTE and TEE were performed on EPIQ ultrasound systems (Philips Medical Systems, Andover, MA) using a 1- to 5-MHz transthoracic matrix array transducer (X5-1) and a 2- to 8-MHz transesophageal matrix array transducer (X8-2t), respectively, with both 2D and 3D capabilities.

All patients underwent complete 2D color TTE, according to guidelines, from the parasternal and apical views.[8] Images were stored in Digital Imaging and Communications in Medicine format on an Xcelera 2.1 picture archiving and communication system server (Philips Medical Systems), anonymized, and analyzed offline independently by two blinded observers (B.L.G. and S.M.). Analysis was performed according to established guidelines.[9] Measurements of left ventricular (LV) diameters were performed on 2D echocardiographic images from the parasternal long-axis view, and LV volumes were computed using the biplane Simpson method from four- and two-chamber views, as recommended. The severity of valvular regurgitation was assessed using a multiparametric approach, as recommended. For the purpose of the study, we report effective regurgitant orifice and RVol values computed using the PISA method, as described previously. We also computed RVol using the continuity equation as the difference between LV systolic stroke volume (Simpson method) and aortic stroke volume (cross-sectional area of the LV outflow tract area multiplied by the LV outflow tract velocity-time integral).

TEE was performed under light sedation (midazolam 2 mg, intravenous). Continuous-wave Doppler and zoomed color Doppler of the mitral valve from different view angles (at an average frame rate of 55–60 Hz) were acquired during breath-holds. Thereafter, a 3D color triggered full-volume image of the regurgitation was acquired during a breath-hold for four to six consecutive heartbeats, at a frame rate ranging from 20 to 40 frames/sec. The 3D acquisition was optimized by adjusting the acquisition sector (minimal lateral width and elevation height to cover the mitral valve) and the color Doppler sector (as small as possible) such that it encompassed the entire flow convergence area and the entire regurgitant jet.

All images were saved in Digital Imaging and Communications in Medicine format with an additional proprietary tag containing the 3D color data in raw format, transferred to an Xcelera 2.1 picture archiving and communication system server, and anonymized and analyzed offline independently by two observers blinded to 3D MR flow quantification and CMR. RVol was calculated using the PISA method. In multijet MR, major PISA was chosen for the measurement. Angle correction for eccentric jets was applied. The average measurement of both observers was taken as a reference, and MR severity was classified according to guideline criteria.

The type of MR mechanism is defined per the Carpentier classification: type 1, due to annular dilation (functional); type 2, due to

HIGHLIGHTS

- We analyzed semi-automated 3D TEE mitral regurgitation flow quantification software
- Unlike 2D PISA, using Navier Stokes equations no geometry of flow was assumed
- The software allowed quantification of multiple and eccentric regurgitant jets
  - The approach had higher inter- and intraobserver reliability than 2D PISA
  - It better correlated with cMR quantification of mitral regurgitation than 2D PISA

prolapse of one or both leaflets; and type 3, due to restriction of only one leaflet.

Cardiac Magnetic Resonance Imaging

CMR was performed using a 3-T system (Ingenia; Philips Medical Systems, Best, the Netherlands). Briefly, after locating the heart using axial and oblique locators, 12 consecutive short-axis images and two-, three-, and four-chamber long-axis image of the left ventricle were acquired, using an electrocardiographically gated, breath-hold, cine, steady-state free precession sequence. Imaging parameters were as follows: field of view, 340 mm; slice thickness, 8 mm; spacing, 2 mm; flip angle, 45°; repetition time, 3.0 msec; echo time, 1.5 msec; matrix size, 196 × 160 pixels (resulting in resolution of 1.7 × 2 mm); sense factor, 2; and temporal resolution, 25 frames/sec. A quantitative, through-plane measurement of ascending aorta flow at the level of the sinotubular junction was performed using an electrocardiographically gated, phase-contrast, velocity-gradient echo sequence. Imaging parameters were as follows: field of view, 350 mm; slice thickness, 8 mm; flip angle, 40°; repetition time, 5.1 msec; echo time, 3.1 msec; and matrix size, 140 × 140 pixels (resulting in resolution of 2.5 × 2.5 mm).

Cardiac magnetic resonance images were anonymized and analyzed by two observers (B.L.G., with 20 years of CMR experience and level 3 EuroCMR certification, and S.M., with 3 years of CMR experience) blinded to clinical data, using the freely automated software Segment version 2.2 (Medviso, Lund, Sweden). The endocardium and epicardium of the left ventricle were automatically contoured on all phases of the left ventricle, with manual adjustments as needed. LV end-diastolic volume and end-systolic volume were calculated using the Simpson method. The first image of the cardiac cycle was considered end-diastole, and the smallest volume of the LV curve was considered the end-systolic volume. LV volumes and mass were indexed to body surface area. LV ejection fraction was computed as (LV end-diastolic volume − LV end-systolic volume)/LV end-diastolic volume. Aortic stroke volume was computed from phase-contrast images in systole. Mitral RVol was calculated as the difference between LV stroke volume (determined by endocardial segmentation) and aortic forward volume on phase-contrast imaging. The average of the two observers (B.L.G. and S.M.) was taken for measurements.

Three-Dimensional MR Flow Quantification with Semiautomated Software

Three-dimensional color transesophageal echocardiographic images were stored in Philips Digital Imaging and Communications in Medicine format, exported, and analyzed offline using novel 3D MR flow quantification prototype software (Philips Research, Medisys, Suresnes, France). Three-dimensional MR flow quantification enabled the semiautomated estimation of the RVol in eccentric and multiple regurgitant jets, as well as in more classical central jets, by 3D analysis of the flow convergence proximal to the regurgitant orifice. The principles of 3D MR flow quantification and their differences compared with the standard PISA method are illustrated in Figure 1. As opposed to the standard PISA method, 3D MR flow quantification does not rely on a simple hemispheric fluid dynamics model but on a more generic fluid dynamics model described by the Navier-Stokes equations (an expression of Newton's second law for fluids), under the simplifying assumption of a steady inviscid flow.[10] The simplified Navier-Stokes model makes no geometric assumptions and hence is suitable for all valve and orifice geometries, including multiple-hole orifices.[11] To perform the analysis, the user was required to (1) tag the two frames that marked the start and end of the regurgitation and (2) click in the frame with the largest jet to roughly indicate the position of the vena contracta in the 3D volume.

After this initialization, the 3D automated analysis was run. The main principles are as follows.

- First, the ultrasound sequence is stabilized to compensate for the motion of the mitral annulus and ensure robust detection of the valve position and morphology.
- Then, for each frame of the sequence, color Doppler data localized on the surface model of the valve provide a first definition of the orifice, whether single or multiple orifices. The converging 3D flow in the ventricle is modeled accordingly and compared with the 3D color Doppler data. The extension and shape of the orifice is then refined until the best fit between the modeled flow field and the 3D color data is obtained.
- Velocity vectors are then used to obtain the instantaneous volume flow for each frame. Note that this identification process takes into account all the velocity values available in the Doppler volume (so there is no need for aliasing velocity analysis) and considers any orifice shape, including multiple orifices distributed on the surface of the valve. Thus, the algorithm is not a PISA procedure but a more complex modeling based on fluid dynamics equations.
- Finally, the instantaneous flow previously calculated for each frame is then integrated in time providing the total RVol.

Statistical Analysis

Statistical analyses were performed using SPSS version 21.0 (SPSS, Chicago, IL). P values $< .05$ were considered to indicate statistical significance. Continuous variables are presented as mean ± SD and categorical variables as counts and percentages. The primary end point of our study was feasibility and evaluation of the accuracy of 3D MR flow quantification to detect severe MR on TTE according to established guidelines or by CMR. Secondary end points were (1) comparison of agreement of RVol by 3D MR flow quantification versus TEE and 2D TTE and CMR and (2) comparison of inter- and intraobserver reproducibility of 3D MR flow quantification versus TEE, 2D PISA TTE, and CMR.

Our study had 80% power at $P < .05$ to demonstrate that 3D MR flow quantification would have ≥0.75 accuracy (defined by area under the receiver operating characteristic curve [AUC]) to diagnose severe MR by reference methods. Intertechnique comparisons between CMR and 2D PISA TTE, 2D PISA TEE, and 3D MR flow quantification were performed using two-way mixed-effects interclass correlation coefficients (ICCs) and Bland-Altman analysis. Inter- and intraobserver variability was determined using the Bland-Altman method, two-way mixed-effects ICCs, and coefficients of variation. Furthermore, we defined severe MR for all four methods separately

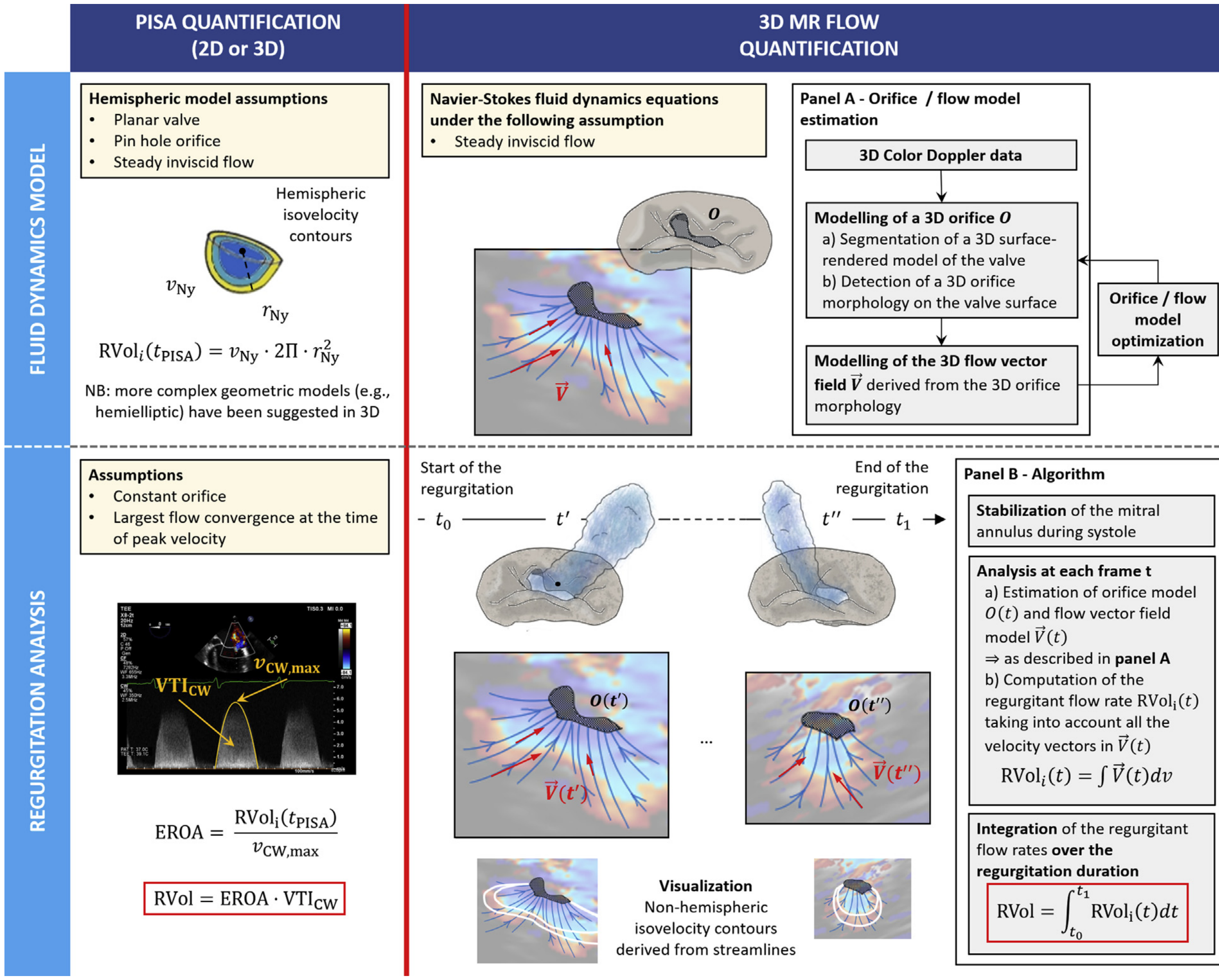

Figure 1 Comparison of the fluid dynamics models (*top row*) and computation principles (*bottom row*) used in standard PISA and 3D MR flow quantification. The standard PISA approach (*left*) is based on a hemispheric model assumption with a planar valve, a pinhole orifice, and steady inviscid flow, assuming a constant orifice with the largest flow convergence at the time of peak velocity. The equation is shown. $r_{Nyquist}$, radius of the PISA hemisphere associated with the MR jet using 2D color Doppler; *RVol*, regurgitant volume at the frame at which PISA was computed; $v_{2DCF,\ Nyquist}$, aliasing velocity on the 2D color Doppler acquisition; $v_{CW,\ max}$, maximum velocity of blood at the mitral regurgitant orifice using continuous-wave (CW) Doppler of the MR jet; VTI_{CW}, velocity-time integral of the MR jet on the CW acquisition. Three-dimensional MR flow quantification (*right*). The model is based on a simplified Navier-Stokes (NS) model of steady inviscid flow. No geometric assumptions are made. From 3D color Doppler data, first a 3D orifice is detected at the largest jet, then a 3D surface-rendered model of the valve surface is created and optimized from these streamlines. Thereafter, for each frame the regurgitant flow rate is integrated from the velocities along the modeled 3D streamlines over the surface and over time. O, 3D orifice morphology; O(t), orifice at time *t*; t_0 and t_1, start and end of MR regurgitation; *RVol*(t), instantaneous regurgitant volume at time *t*; t′ and t″, two different times during MR regurgitation; V, 3D blood flow vector field derived from the orifice morphology using the fluid dynamics equations of Navier-Stokes; $v_{si'}$ and $v_{si''}$, velocity vector at a given voxel in the 3D color Doppler acquisition.

by using 60 mL as a threshold, and we used Cohen's κ statistic to evaluate agreement between severe MR and severe MR by the other three methods. Area under ROC curves of different tests was computed using either 2D TEE or cMR as reference and compared pairwise using DeLong test.

RESULTS

Patient Population

Patient characteristics are described in Table 1. The mean age was 63 ± 16 years, and 35 patients (69%) were male. The mechanism of MR was prolapse in 37 patients (72%), restriction in nine (18%), and functional in five (10%). Eccentric regurgitant jets were present in 37 (72%), while 14 (28%) had multiple regurgitant jets. Either eccentric or multiple jets were present in 41 (80%). According to 2D TEE using guideline criteria, 29 patients had severe MR, 16 had moderate MR, and six had mild MR. The median delay between CMR and TEE or TTE was 1 day, and there was no significant difference in hemodynamic conditions (blood pressure or heart rate) between CMR and echocardiography.

Feasibility of MR Volume by 3D MR Flow Quantification and Comparison with 2D TTE, TEE, and CMR

An example of MR quantification by different methods is shown in Figures 2 and 3 and Supplemental Videos 1-4 (available at www.

Table 1 Patient characteristics (N = 51)

Characteristics	Value
Demographics	
Age, y	63 ± 16
Sex, male	36 (70.6)
BMI, kg/m^2	25 ± 4
BSA, m^2	1.88 ± 0.21
BP on TEE, mm Hg	128/72
BP on CMR, mm Hg	125/72
NYHA functional class	
1	23 (45.1)
2	21 (41.2)
3	7 (13.7)
Ischemic	
CAD	14 (28.0)
MI	5 (10.0)
PTCA	9 (18.0)
CABG	3 (6.0)
CV risk factors	
Hypertension	22 (44.0)
Dyslipidemia	26 (52.0)
Diabetes	3 (6.0)
Stroke/TIA	3 (6.0)
Current smoking	11 (22.0)
Laboratory workup	
Hb, g/dL	14 ± 2
Creatinine, mg/dL	1.08 ± 0.40
GFR (Cockroft), mL/min 1.73 m^2	74 ± 23
NT-proBNP, pg/mL	315 ± 309
MR severity (TEE)	
Mild	6 (12)
Moderate	16 (31)
Severe	29 (57)
MR mechanism	
Type 1 (functional)	5 (9.8)
Type 2 (prolapse)	37 (72.5)
Type 3 (restriction)	9 (17.6)
Prolapsed leaflet	
Flail	23 (62.2)
Anterior	2 (5.3)
Posterior	25 (65.8)
Both	11 (28.9)
Jet	
Eccentric	37 (72.5)
Multiple	14 (27.5)

BMI, Body mass index; *BP*, blood pressure; *BSA*, body surface area; *CABG*, coronary artery bypass graft; *CAD*, coronary artery disease; *CV*, cardiovascular; *GFR*, glomerular filtration rate; *Hb*, hemoglobin; *MI*, myocardial infarct; *NT-proBNP*, N-terminal pro–brain natriuretic peptide; *PTCA*, percutaneous transluminal coronary angioplasty; *TIA*, transient ischemic attack.
Data are expressed as mean ± SD or as number (percentage).

onlinejase.com). Three-dimensional MR flow quantification was feasible in all patients irrespective of the mechanism of MR (Figures 4 and 5). Quantitative measurements from all four imaging methods are summarized in Table 2. Mean RVol was lower by TTE (54 ± 24 mL) and 3D MR flow quantification (53 ± 32 mL) than by TEE (63 ± 29 mL) or CMR (60 ± 31 mL). RVol by 3D MR flow quantification correlated well with RVol by 2D PISA TTE (ICC = 0.75, P < .001), quantitatively estimated RVol (ICC = 0.74, P < .001), and RVol by 2D PISA TEE (ICC = 0.79, P < .001). The bias of 3D flow versus 2D PISA TTE was small and nonsignificant (−2 ± 25 mL; 95% CI, −9 to 5 mL; P = .64), while there was underestimation compared with 2D PISA TEE (−10 ± 22 mL; 95% CI, −16 to 4 mL; P < .001). Correlation and Bland-Altman plots for comparison of mean RVol among TTE, TEE, 3D MR flow quantification, and CMR are shown in Figure 6. Although all echocardiographic measurements correlated well with CMR, correlation between 3D MR flow quantification and CMR was better (ICC = 0.86; 95% CI, 0.77 to 0.92; P < .001) than that of RVol by 2D PISA TTE (ICC = 0.66; 95% CI, 0.47 to 0.79; P < .001) and by 2D PISA TEE (ICC = 0.69; 95% CI, 0.52 to 0.81; P < .001). Bland-Altman analysis demonstrated narrower limits of agreement between RVol on 3D MR flow quantification and CMR than between 2D TEE and 2D TTE and CMR. However, there was significant underestimation by −8 ± 17 mL (95% CI, −12 to −3 mL; P = .002), whereas transthoracic echocardiographic (−6 ± 23 mL; 95% CI, −12 to 1 mL; P = .07) and 2D PISA transesophageal echocardiographic measurements (mean bias, 2 ± 23 mL; 95% CI, −4 to 9 mL) were nonsignificantly different from CMR.

Accuracy for Diagnosing MR Severity

The accuracy of 3D MR flow quantification to detect severe MR compared with 2D TEE and CMR is shown in Figures 7A and 7B.

Figure 7A shows the diagnostic accuracy of 3D flow quantification versus CMR for the diagnosis of severe MR defined by guideline criteria using 2D TEE as the reference. Three-dimensional MR flow quantification showed similarly high (P = .75) agreement for diagnosing severe MR (AUC = 0.85; 95% CI, 0.74–0.96; P < .001) than CMR (AUC = 0.86; 95% CI, 0.76–0.97; P < .001) with transesophageal conventional criteria as the reference.

Figure 7B shows the accuracy of RVol by 3D flow quantification, TTE, and TEE for the diagnosis of severe MR considering CMR using a threshold of RVol > 60 mL as the reference. Three-dimensional MR flow quantification had higher diagnostic accuracy (AUC = 0.95; 95% CI, 0.89–1.00; P < .001) than both TTE (AUC = 0.85; 95% CI, 0.74–0.96; P < .001, P = .11 vs 3D flow) and TEE (AUC = 0.84; 95% CI, 0.74–0.95; P < .001, P = .04 vs 3D flow) for detecting severe MR (RVol > 60 mL) by CMR.

Table 3 shows the number of patients with mild, moderate, and severe MR by each of the four methods. For diagnosing severe versus nonsevere MR, 3D flow quantification had higher agreement with CMR (κ = 0.80, P < .001) than TTE (κ = 0.50, P < .001) and TEE (κ = 0.51, P < .001).

Inter- and Intraobserver Reproducibility

Inter- and intraobserver reproducibility of measurements of RVol by different methods is shown in Table 4, and correlation and Bland-Altman graphs for interobserver reproducibility are shown in Figure 8. Three-dimensional MR flow quantification had better inter-

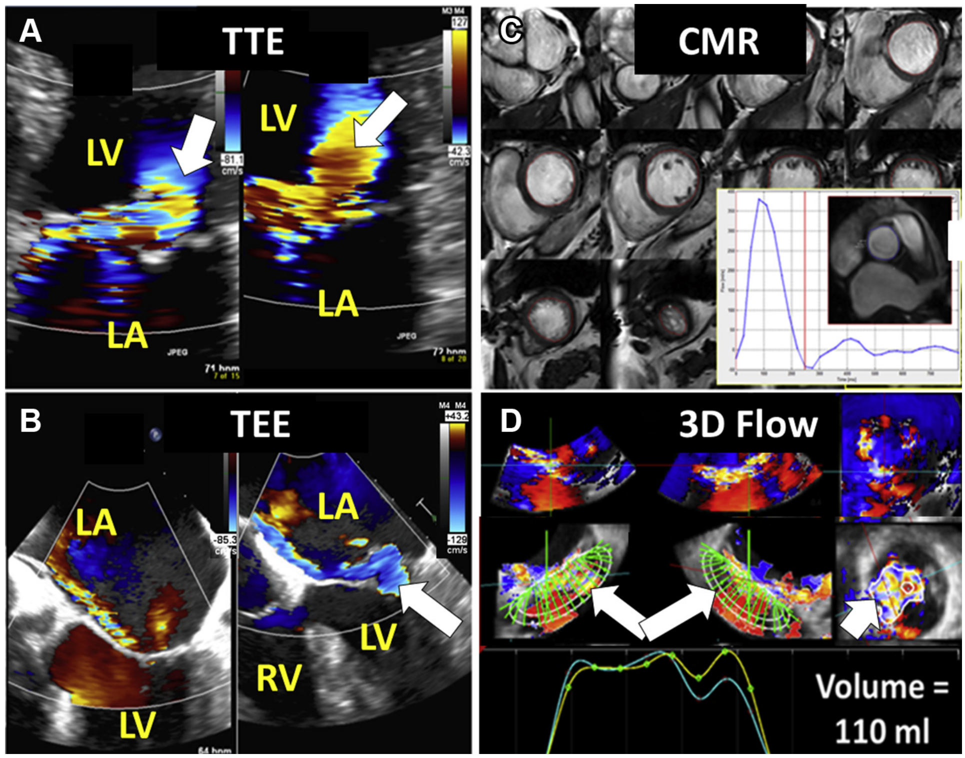

Figure 2 Illustration of methods used to compute MR severity. **(A)** Transthoracic echocardiographic PISA and **(B)** transesophageal echocardiographic PISA (see Supplemental Video 1). On Color Doppler images with baseline color velocity shifted opposite to jet direction, PISA radius was measured on the frame with the largest PISA hemisphere with corrections for angle, when PISA was constrained. Maximum velocity (Vmax) and velocity-time integral (VTI) were measured on mitral continuous Doppler images. PISA is indicated by *white arrows*. **(C)** CMR volumetric method (see Supplemental Video 3). LV endocardial contours (*red lines*) were traced through the cardiac cycle to compute LV stroke volume using the Simpson method. Aortic stroke volume (*blue, inset*) was computed from aortic phase-contrast images. Mitral RVol was computed as LV stroke volume − aortic stroke volume. **(D)** Three-dimensional MR flow quantification (see Supplemental Video 3). The vena contracta was identified manually on the area of largest jet. The number of frames with MR was introduced manually. Then the software stabilized the ultrasound sequence and identified the mitral annular plane (*blue and red lines*) and the direction of the jet (*long green line*) and fitted MR flow through as a fluid dynamics model. *White lines* illustrate fitted isovelocity surfaces, and *curved green lines* indicate flow streamlines. *Inset* shows volume-time curve (*yellow*). Isovelocity area rendering is indicated by *white arrows*. *LA*, Left atrium; *LV*, left ventricle; *RA*, right atrium; *RV*, right ventricle.

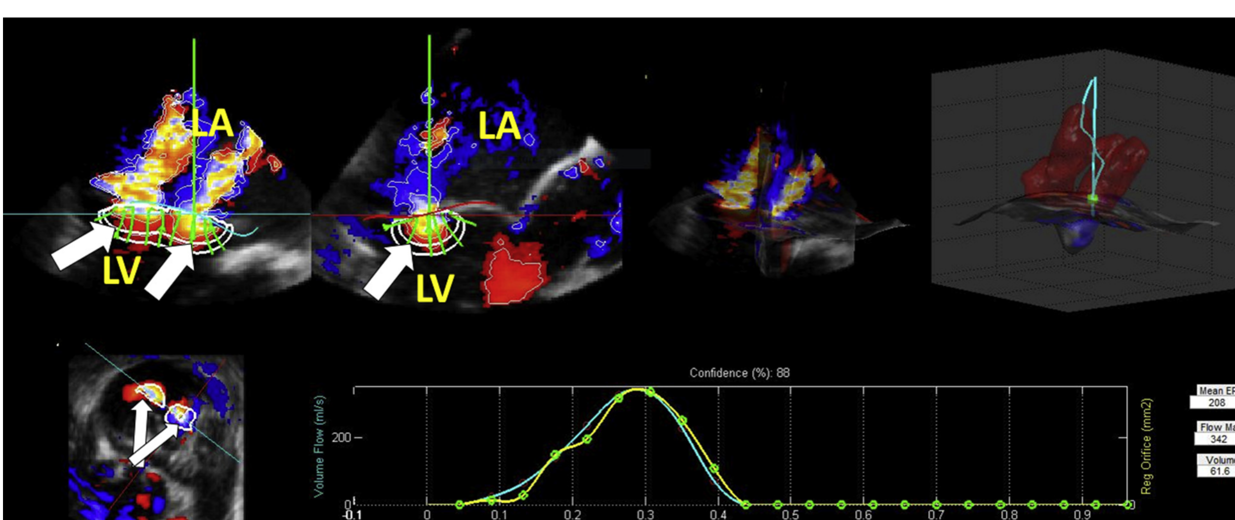

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Figure 3 Illustration of detection of multiple regurgitant jets by 3D flow quantification algorithm (see Supplemental Video 4). After stabilization and identification of the valve surface, extended or multiple orifices found at the level of the valve surfaces are integrated in the flow computation. The software identified the mitral annular plane (*blue and red lines*) and the direction of the jet (*long green line*) and fitted MR flow through as a fluid dynamics model. *White lines* illustrate fitted isovelocity surfaces, and *curved green lines* indicate flow streamlines. *Inset* shows volume-time curve (*yellow*). Isovelocity area rendering is indicated by *white arrows*. *LA*, Left atrium; *LV*, left ventricle.

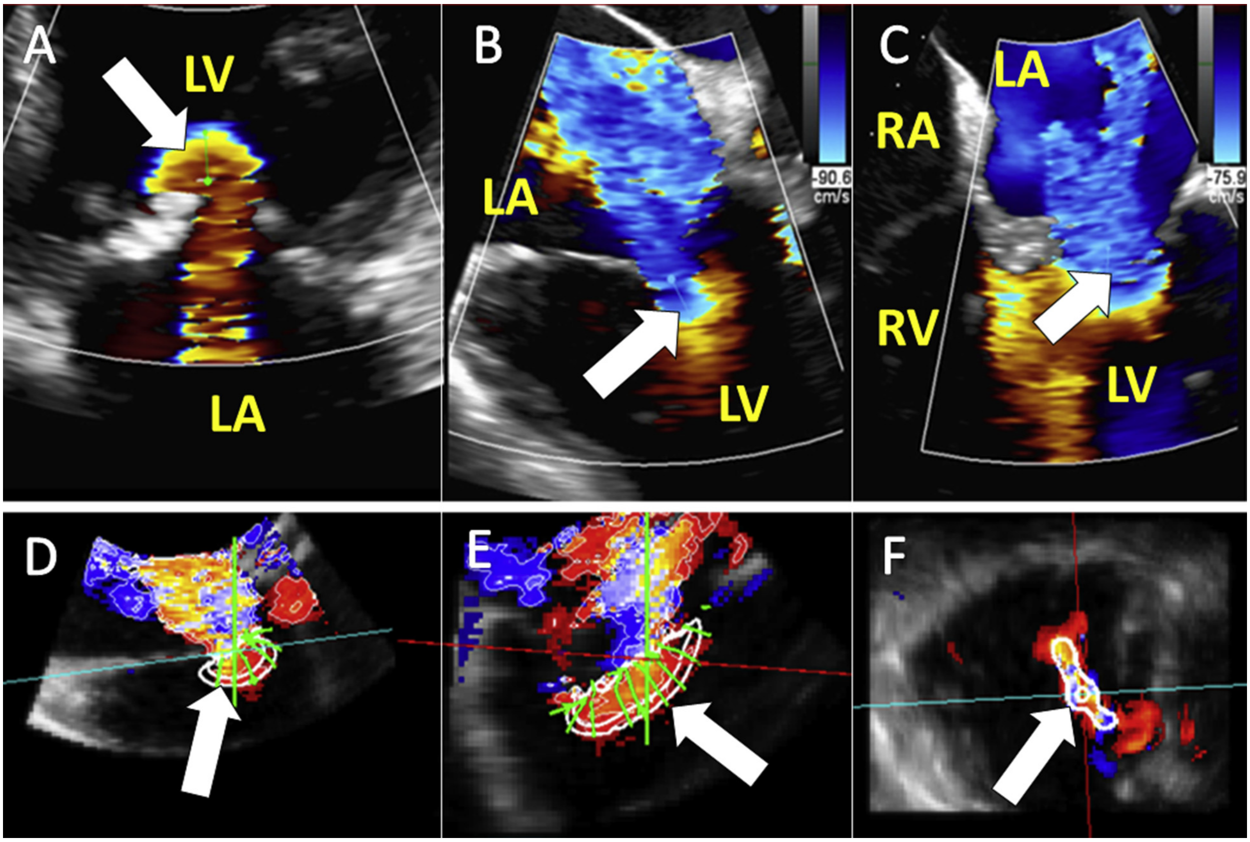

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Figure 4 Example of type 1 MR with central jet and asymmetric orifice. **(A)** Two-dimensional PISA TTE. **(B, C)** Two-dimensional PISA TEE from different angles with different sizes. **(D–F)** Images of the PISA volume seen from three different planes, illustrating the asymmetric shape of the convergent flow. Two-dimensional PISA and isovelocity area rendering by 3D flow quantification are indicated by *white arrows*. *LA*, Left atrium; *LV*, left ventricle; *RA*, right atrium; *RV*, right ventricle.

and intraobserver variability, narrower limits of agreement, and a lower coefficient of variation than 2D transthoracic and transesophageal echocardiographic PISA measurements.

DISCUSSION

We evaluated the accuracy of novel semiautomated software for 3D MR flow quantification. The prominent findings of our study were as follows.

1. Three-dimensional MR flow quantification allowed semiautomated quantification of MR from 3D color Doppler transesophageal echocardiographic images and was feasible for all types of MR, including prolapse, restrictive etiology, and eccentric and multiple jets.
2. Three-dimensional MR flow quantification had high accuracy for detecting severe MR by conventional 2D transesophageal echocardiographic guidelines.
3. Three-dimensional MR flow quantification correlated better with CMR than TTE and TEE and had lower bias and higher accuracy for the detection of severe MR defined by CMR than 2D TTE and TEE.
4. Finally, inter- and intraobserver reproducibility of 3D MR flow quantification was higher than that of the 2D counterparts.

Assessment of MR severity is clinically important because severity predicts outcomes, not only in organic mitral valve disease[12] but also in cardiomyopathies associated with functional, secondary MR.[13-16] Accurate grading of MR severity is crucial for treatment decisions, as both European Society of Cardiology[4] and American College of Cardiology/American Heart Association[3] guidelines recommend surgery only in patients with severe MR. Although echocardiography is the main method for the evaluation of MR severity, in clinical practice, the grading of MR severity using echocardiography can often be difficult. Indeed, the guidelines recommend an integrated approach, which combines quantitative, semiquantitative and qualitative methods,[1,17,18] which allow a wide range of interpretation (discretionary leeway or margin of discretion) of MR severity. Although quantitative parameters for MR severity, which include the calculation of RVol and EROA using PISA, are preferred, PISA has intrinsic limitations. Indeed, the PISA approach assumes the uniform hemispheric shape of the convergent isovelocity area and performs the EROA and RVol calculation according to the maximum size of the PISA radius. This radius is usually obtained from a single frame loop and is later squared in the PISA formula.[19] However, there are several situations in which PISA assumptions are violated. Indeed, the PISA geometry may vary, depending on the geometry of the orifice and mitral valve leaflets surrounding the orifice. This variability is particularly observed in functional MR, in which the PISA shell presents elongated hemielliptic shapes,[20] leading to underestimation of the true RVol. Conversely, the presence of a constraining wall, notably in flail mitral leaflets, distorts the converging flow field and the assumptions of hemispheric symmetry of the PISA, leading to overestimation of calculated flow rates.[21] Although this can be corrected by a correction factor based on the observed geometry surrounding the regurgitant

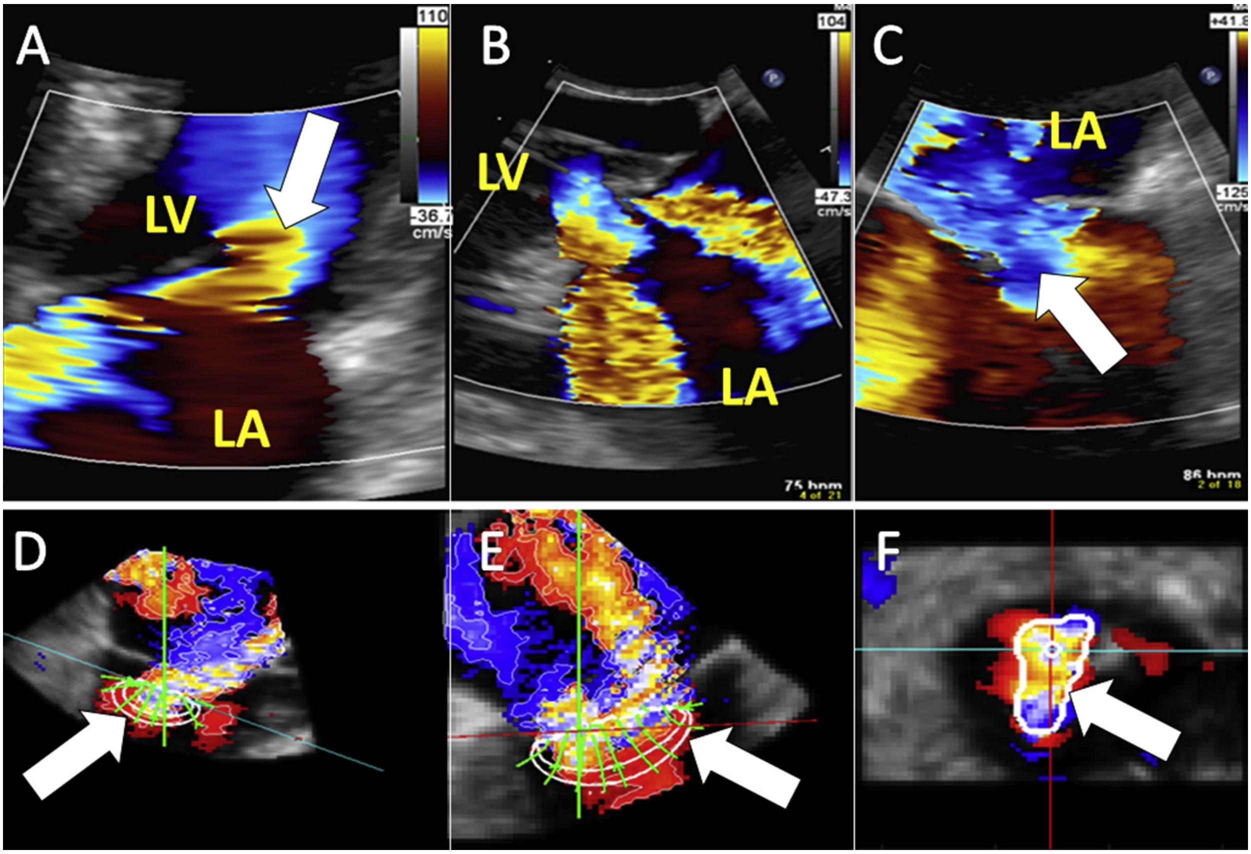

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Figure 5 Example of type 3 MR with eccentric and multiple jets. **(A, B)** Two-dimensional transesophageal echocardiographic images showing constrained PISA and multiple jets. **(C)** Two-dimensional transesophageal echocardiographic constrained PISA. **(D–F)** Images of the PISA volume seen from three different planes, illustrating the asymmetric shape of the convergent flow. Two-dimensional PISA and isovelocity area rendering by 3D flow quantification are indicated by *white arrows*.

orifice, the measurement of this correction angle adds another variable influencing the accuracy and reproducibility of the PISA measurement.[22] Additional errors in the measurement of PISA regurgitant flow result from the assumption that the convergent area will have a hemispheric aspect. In reality, however, because of the inability to visualize flow perpendicular to the incident Doppler signal, the shell of the isovelocity surface appears with urchinoid rather than hemispheric geometry,[23] which can distort the resulting PISA estimation. Further error in MR measurements by PISA can be caused by frame-to-frame variability of PISA distance, which can result in errors upward of 25% and beat-to beat variability, which can result in errors upward of 15%.[23] Additional difficulties may arise in the presence of temporal flow changes of MR, such as protosystolic or mid- and telesystolic jets, which occur frequently in the presence of mitral valve prolapse. Finally, there is currently no validated approach for quantification of MR in the presence of multiple jets, such as with Barlow's disease. These factors explain why MR quantification by echocardiography,[24] and even by the PISA approach,[5] has been shown to have suboptimal interobserver agreement. Moreover, intermodality agreement between echocardiographic assessment of MR and other methods, such as CMR, was also relatively poor,[25,26] even though the agreement of PISA EROA and RVol was better than that of other parameters such as vena contracta width and color Doppler jet area.[27]

CMR has indeed recently emerged as an alternative technique for quantification of MR severity.[28] The use of CMR has been shown to provide better interobserver variability,[26,29] and to better predict reverse remodeling after mitral surgery.[25] It has also been shown to better predict patient response to surgery compared with using echocardiographic grading of MR.[30] Also, CMR shows better 5-year all-cause mortality or indication for mitral valve surgery compared with TTE.[31] CMR also has the advantage of being less invasive and better tolerated than TEE, therefore not requiring sedation. However TEE still allows better evaluation of mechanism of MR required for preoperative planning of repair.

Some of the intrinsic limitations of the 2D PISA method could be overcome using 3D color imaging. Indeed, 3D echocardiography better accounts for the 3D shape of the anatomic regurgitant orifice in noncircular nonplanar orifices,[6,32] as well as in multiple jets. Quantification of MR using the 3D PISA method was shown to allow more accurate measurement of MR than the 2D PISA method, particularly in eccentric MR with asymmetric orifice.[33] Three-dimensional assessment of MR using different methods was shown to compare more accurately with CMR than the 2D PISA method[34] and allowed the assessment of multiple jets.[34,35] Recently, the feasibility of automated 3D PISA detection on TTE was demonstrated.[36] The automated 3D PISA method described was validated in vitro against a flow meter and validated in 30 patients against CMR, but this was done only in patients with functional MR. As opposed to the previously described methods, one of the key benefits of the new 3D MR flow quantification approach described in our article is that it does not rely on the simple hemispheric model used in the PISA

Table 2 Imaging measurements of MR severity

Measurements	Value
2D TTE	
LAESV, mL	112 ± 39
LVEDV, mL	184 ± 44
LVESV, mL	80 ± 29
Vena contracta, mm	5.9 ± 2.1
ERO, mm^2	42 ± 24
PISA RVol, mL	54 ± 24
Regurgitant fraction, %	63 ± 31
2D TEE	
Vena contracta, mm	6.0 ± 2.0
ERO, mm^2	50 ± 32
PISA RVol, mL	63 ± 29
3D MR flow quantification	
RVol, mL	53 ± 32
CMR	
LVEDV, mL	226 ± 69
LVESV, mL	100 ± 61
SV, mL	125 ± 35
LVEF, %	58 ± 12
RVol, mL	60 ± 31
Regurgitant fraction, %	45 ± 17

ERO, Effective regurgitant orifice; *LAESV*, left atrial end-systolic volume; *LVEDV*, LV end-diastolic volume; *LVEF*, LV ejection fraction; *LVESV*, LV end-systolic volume; *SV*, stroke volume.
Data are expressed as mean ± SD.

method but on a more generic fluid dynamics model that makes no geometric assumptions. Hence it is suitable for all valve and orifice geometries, including multiple-hole orifices[10,11] and eccentric jets with constrained PISA geometry. The method is semiautomated, requiring as the sole user interventions tagging the start and end of the regurgitation and identification of the vena contracta on one frame by a mouse click. A minor limitation of the current 3D MR flow quantification software is slight but significant underestimation of RVol compared with 2D TEE and CMR. This could result from several factors, such a limited frame rate of 3D TEE or errors in detection of the mitral annulus plane. Therefore, optimal cutoff values for definition of severe MR were slightly lower than those of other methods. One explanation for this could be that the spatial resolution of 3D color is limited, reducing the accuracy of flow path detections. In particular in the case of prolapsing scallops, the regurgitant orifice is a tunnel, which makes fitting more difficult for this type of model (which is based on a smooth valve surface). Another current limitation is that the software currently allows measurement of RVol but no other measures of MR severity, such as effective regurgitant orifice or vena contracta. These measurements could be implemented in further versions of the software.

Clinical Implications

Our study suggests that MR flow quantification from 3D color Doppler TEE allows better evaluation of MR severity, particularly for difficult cases of MR. It might thus help better evaluate MR severity in patients with complex MR, such as flail leaflets, multiple jets, or eccentric PISA. Because 3D MR flow quantification compared favorably with CMR, it could avoid having to resort to CMR to confirm MR severity in such difficult cases. Because 3D MR flow quantification demonstrated less inter- and intraobserver variability than conventional methods for MR quantification, it might help reduce variability in MR quantification and particularly help reduce uncertainty in MR evaluation for less experienced centers or observers. Given the complexities of quantifying MR severity in functional MR, the approach might also be particularly interesting for the selection of patients for novel catheter-based repair techniques such as MitraClip implantation.[37] Finally, because the method is semiautomated, 3D MR flow quantification may allow reduction in time required to perform MR quantification during echocardiographic examinations.

Study Limitations

Our study had several limitations. This was a single-center study, performed in a relatively limited number of patients. The findings should be confirmed in a larger population and a multicenter setting. Inherent to selection criteria, our population had a disproportionate distribution of severe MR, which may have influenced some of the statistical analysis, in particular the receiver operating characteristic curve results. Also, body mass index among our patients was less than that of typical US populations, potentially biasing results in favor of TTE. An inherent limitation to the comparison of MR severity among different methods is that the different imaging modalities were not performed simultaneously, and potentially, the severity of MR could change between tests. Yet 2D TEE and 3D TEE were performed within the same examination, and most transesophageal echocardiographic and CMR studies were performed within a median of 1 day, without significant differences in medical treatment, loading, and hemodynamic conditions. As the delay between TTE and CMR was somewhat longer, this might however explain the larger variability between the transthoracic echocardiographic and CMR assessments of MR severity. Another limitation is the lack of a true reference method for MR severity. We used CMR as the reference standard for RVol quantification because it is independent of underlying functional mechanisms of MR, and it has been shown to more accurately predict reverse LV remodeling and mortality. Nevertheless, the use of CMR as the reference standard for mitral RVol has limitations because it is an indirect method that requires the use of two different approaches (i.e., LV volume quantification using Simpson techniques and aortic stroke volume measurement using phase contrast), each of which can have measurement variability ranging from 3% to 9%.[38] For TTE, 3D imaging might have allowed more accurate measurement of LV volume than the 2D Simpson method, but limited echocardiographic windows did not allow the performance of 3D TTE in all patients. Finally, 3D MR flow quantification did not calculate the effective regurgitant orifice, which may be a better predictor of outcomes than RVol in some types of MR. As we did not evaluate follow-up, we were not able to assess how the difference in threshold criteria would affect outcomes.

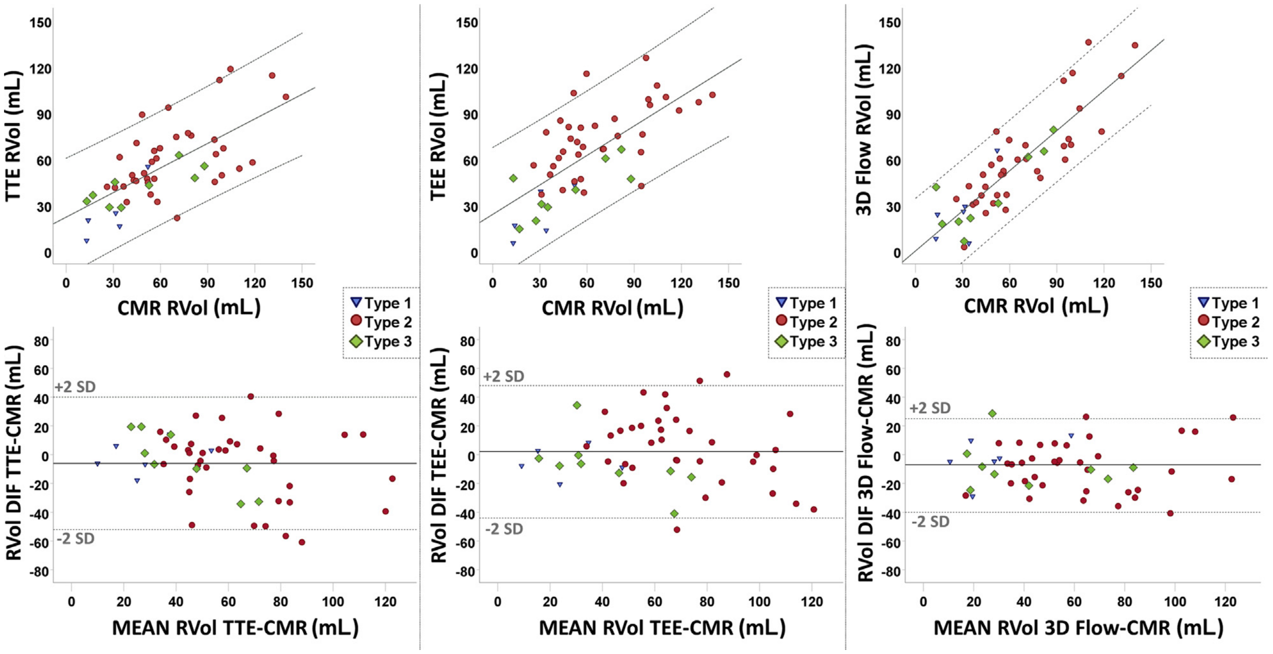

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Figure 6 Correlation and Bland-Altman graphs comparing RVol by 2D and 3D MR flow quantification with CMR RVol.

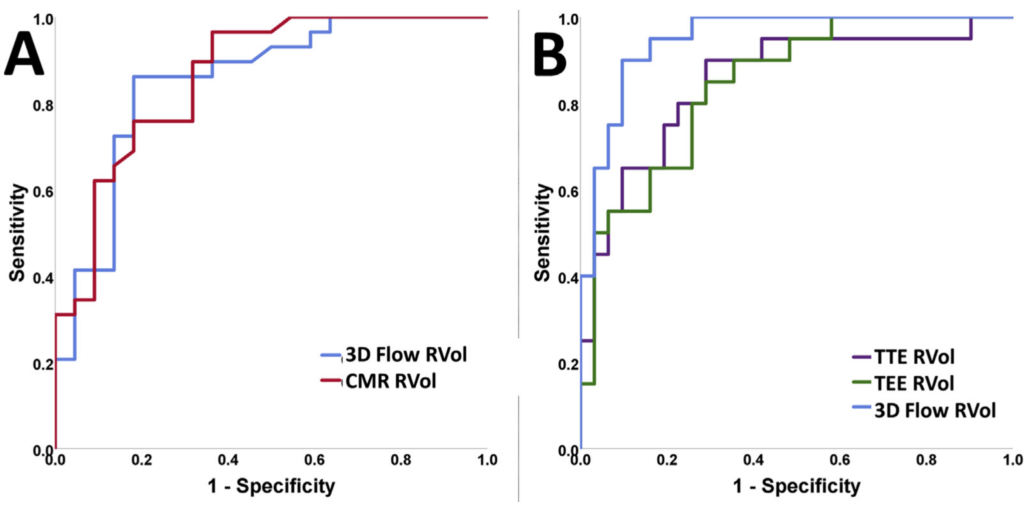

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Figure 7 Receiver operating characteristic curve of accuracy to predict severe MR of **(A)** 3D MR flow quantification and CMR vs 2D TEE and **(B)** 3D MR flow quantification, TTE, and 2D PISA TEE vs CMR.

Table 3 Distribution of patients according to MR severity by all four methods

MR Severity	RVol by TTE	RVol by TEE	RVol by 3D flow quantification	RVol by CMR
Mild MR (RVol ≤ 30 mL)	7 (14)	6 (12)	12 (24)	6 (12)
Moderate MR (RVol 31–59 mL)	26 (51)	16 (31)	18 (35)	25 (49)
Severe MR (RVol ≥ 60 mL)	18 (35)	29 (57)	21 (41)	20 (39)

Data are expressed as number (percentage).

Table 4 Inter- and intraobserver variability of different measurements of RVol severity

Variability	2D PISA TTE	2D PISA TEE	3D MR flow quantification	CMR
Intraobserver				
ICC	0.64	0.82	0.90	0.96
95% CI	0.16–0.85	0.61–0.95	0.72–0.96	0.88–0.99
P	.011	<.001	<.001	<.001
Bias ± LOA	−14 ± 50	−7 ± 38	−3 ± 26	−4 ± 17
CV, %	41	20	17	13
Interobserver				
ICC	0.65	0.73	0.92	0.94
95% CI	0.45–0.78	0.57–0.84	0.87–0.96	0.89–0.96
P	<.001	<.001	<.001	<.001
Bias ± LOA	15 ± 45	17 ± 43	2 ± 25	−1 ± 18
CV, %	43	35	17	10

CV, Coefficient of variation; *LOA*, limits of agreement.

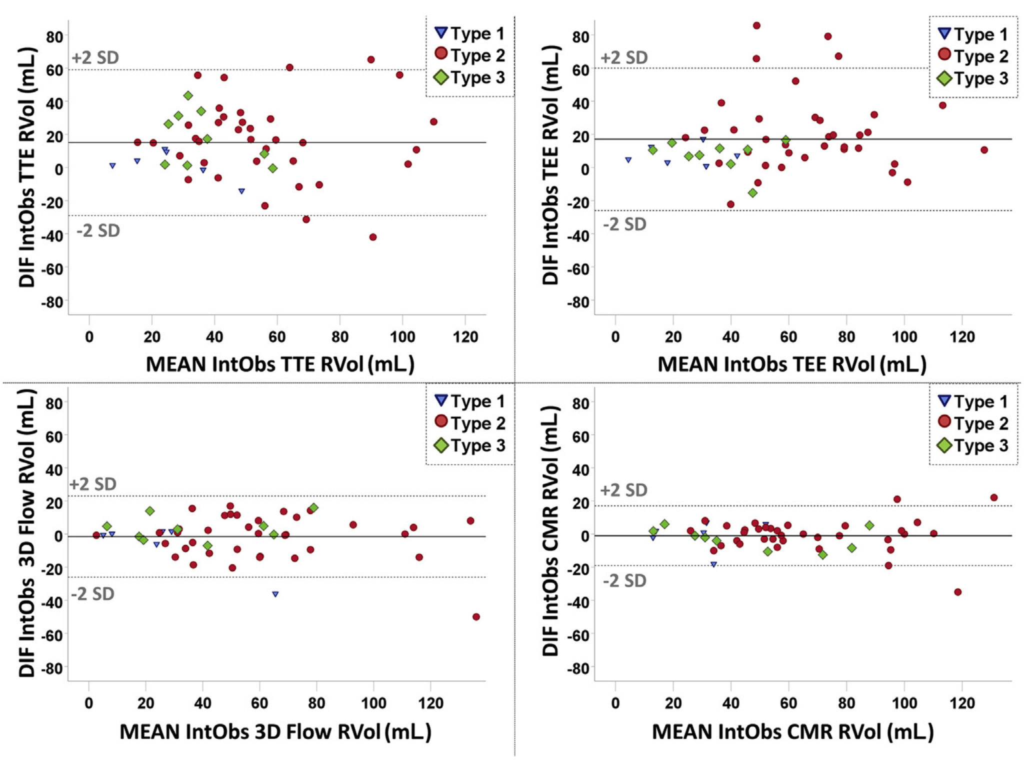

Figure 8 Interobserver reproducibility Bland-Altman graphs for measurements of RVol by 2D PISA TTE, 2D PISA TEE, 3D MR flow quantification, and CMR.

CONCLUSION

We demonstrated the feasibility of RVol measurement from 3D color TEE (3D MR flow quantification) using new semiautomated software. Three-dimensional MR flow quantification allowed MR severity quantification in all types of MR, including difficult cases for conventional PISA measurements such as functional MR, multiple jets, and constrained or incomplete jets in flail leaflets. Three-dimensional MR flow quantification was found to have higher agreement and accuracy for calculating RVol than peak 2D PISA TEE and TTE, when using CMR as the gold standard. Therefore, 3D MR flow quantification could allow more accurate quantification of MR in routine clinical echocardiography, in particular in complex morphology when the assessment of MR severity using conventional methods is difficult.

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SUPPLEMENTARY DATA

Supplementary data related to this article can be found at https://doi.org/10.1016/j.echo.2019.10.013.

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Video 1 RVol measurement using the 2D PISA method. The steps are detailed in the subtitles. (1) Diameter of hemisphere (*r*) is measured on the frame with the largest PISA hemisphere images with baseline color velocity shifted and aliasing velocity is recorded. (2) Then the correction angle is measured. (3) Finally the velocity-time integral (VTI) and maximum velocity (Vmax) are measured on continuous Doppler images of MR. Applying the PISA formula, the RVol is computed.

Video 2 RVol measurement using CMR. The steps are detailed in the subtitles. (1) On a stack of consecutive short-axis images, LV endocardial contours (*red lines*) were traced through in diastole and systole to compute LV stroke volume using the Simpson method. (2) Aortic stroke volume (*blue, inset*) is computed from aortic phase-contrast images. Then mitral RVol is computed as the difference between LV stroke volume and aortic stroke volume.

Video 3 RVol measurement using the new 3D flow algorithm. The steps are detailed in the subtitles. (1) The 3D volume is loaded in the program. (2) The range of systolic frames showing MR were determined manually. (3) The vena contracta is identified manually on the area of largest jet. (4) The number of frames with MR was introduced manually. (5) Then the software stabilizes the ultrasound sequence and identified the mitral annular plane (*blue and red lines*) and the direction of the jet (*long green line*) and fitted MR flow through as a fluid dynamics model. (6) RVol is calculated by integration over time. *White lines* illustrate fitted isovelocity surfaces, and *curved green lines* indicate flow streamlines. *Inset* shows volume-time curve (*yellow*). Isovelocity area rendering is indicated by *white arrows*.

Video 4 Illustration of detection of multiple regurgitant jets by 3D flow quantification algorithm. The video shows successive automatically stabilized time frames in a patient with two mitral regurgitant orifices. The flow in both orifices is detected and integrated in total flow computation. Fitted mitral annular plane is shown by *blue and red lines*, and the direction of the jet is shown by the *long green straight line*. *White lines* illustrate fitted isovelocity surfaces, and *curved green lines* indicate flow streamlines.