Quantitative assessment of primary mitral regurgitation using left ventricular volumes: a three-dimensional transthoracic echocardiographic pilot study

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Aims
To investigate the value of assessment of mitral regurgitant fraction (RF) using left ventricular (LV) volumes obtained by three-dimensional echocardiography (3DE) to quantify primary mitral regurgitation (MR).

Methods and results
Sixty patients with primary MR in sinus rhythm were prospectively enrolled. RF was calculated using either 2DE or 3DE LV volumes obtained as follows: (LV total stroke volume – LV forward stroke volume by Doppler)/LV total stroke volume. Severity of MR was graded independently by two cardiologists blinded to LV volumetric data using an integrative approach, as recommended by current guidelines. Sixty patients with LV ejection fraction >50% and no MR were also studied. In patients without MR, 3D total LV stroke volume was more strongly correlated with LV forward stroke volume than 2D total LV stroke volume (r = 0.75, P < 0.0001 vs. r = 0.62, P < 0.0001, respectively). The 3D method had a feasibility of 90% in patients with MR. Inter-reader concordance for MR grading (four grades) was excellent with a Kappa-value of 0.90, P < 0.0001. A significant correlation was observed between grade of MR severity and 3D RF (r = 0.83, P < 0.0001) and 2D RF (r = 0.74, P < 0.0001). Comparisons between individual grades for 3D RF were significant (P < 0.05) except for 3+ vs. 4+ MR (P = 0.213). All patients with 3D RF ≥40% had ≥3+ or 4+ MR and those with 3D RF ≤30% had 1+ or 2+ MR with a ‘grey’ overlap zone between 30 and 40%.

Conclusions
RF can be routinely determined using 3D LV volumes with a high feasibility in patients with primary MR and is reliable for identification of Grade 3+ or Grade 4+ MR. The incorporation of this parameter into the currently recommended multi-parametric integrative approach might be helpful to discriminate significant MR.

Keywords
Three-dimensional echocardiography • three-dimensional left ventricular volumes • primary mitral regurgitation • valvular heart disease

Introduction
Mitral regurgitation (MR) is the most prevalent cause of valvular heart disease in western countries.1 In the Euro Heart Survey on valvular heart disease, MR was the second most common heart valve disease requiring surgery.2 In clinical practice, mitral valve repair/replacement is considered in patients with severe primary MR. Accurate quantification of MR is, therefore, essential for decisions regarding surgery.2 Due to its relatively low cost and extensive availability, echocardiography is a key imaging method for the diagnosis of MR severity.3 Current guidelines propose integration of qualitative, semi-quantitative, and quantitative criteria for grading the severity
of MR. The Proximal Isovelocity Surface Area (PISA) method is currently the main quantitative method for MR grading. However, concerns have been raised regarding the reproducibility of the PISA method. There is, therefore, a need for other quantitative tools to refine the multi-parametric integrative assessment of MR severity.

Mitral regurgitant fraction (RF) can be calculated as the difference between total left ventricular (LV) stroke volume obtained by echocardiography and Doppler LV forward flow normalized by total LV stroke volume. Despite promising landmark reports using two-dimensional echocardiography (2DE), this method has not received wide acceptance in clinical practice, as quantification of LV volumes by 2DE is frequently flawed by significant inter-operator variability, foreshortening views and reliance upon geometric models likely to be inaccurate in hypertrophied, dilated, or remodelled LV. New semi-automated algorithms of LV endocardial border detection based on three-dimensional echocardiography (3DE) full-volume datasets allow accurate quantification of LV volumes and function with values closer to those obtained by cardiac magnetic resonance (CMR) imaging and with better reproducibility than 2DE. The use of 3D determination of LV volumes has been proposed for the calculation of mitral RF. However, the accuracy of this 3DE method has not yet been investigated. The present study was, therefore, designed to test the hypothesis that RF obtained by 3DE can be used for MR quantification in patients with primary MR.

Methods

Consecutive patients referred to our echocardiography laboratory for assessment of primary MR were prospectively screened. Clinical and demographic data were obtained prospectively at the time of echocardiography.

Inclusion criteria were at least mild grade (1+) isolated primary MR as determined by standard colour Doppler imaging. Exclusion criteria were unstable cardiac rhythm (atrial fibrillation and frequent extrasystoles), inability to maintain breath-hold for at least 6 s, inability to measure LV forward stroke volume, unstable clinical condition, poor echocardiographic windows, presence of more than traces of secondary MR including ischaemic MR (valvular incompetence with regional LV wall motion abnormalities associated with mitral valve tenting owing to retracted chordae tendineae tethering normal valve leaflets), presence of aortic valvular disease, ventricular septal defects, and unwillingness to provide informed consent as required by our institutional review board.

In addition to patients with MR, 60 patients without valvular heart disease [31 (52%) male; 54 ± 15 years] and preserved LV ejection fraction (LV EF >50%) were assessed by both Doppler echocardiographic and 3DE measurements of LV total stroke volume. Exclusion criteria were the same as those for patients with MR.

Echocardiography

Echocardiograms were performed on a Vivid E9 ultrasound scanner (BT11, General Electric Healthcare, Horten, Norway) equipped with both 2D (M5S-D) and 3D (4V-D) probes. Echocardiographic data were acquired by a single cardiologist expert in echocardiography and valvular heart disease. All echocardiograms were stored on a PACS network linked to a dedicated EchoPAC workstation (BT11, General Electric Healthcare).

Assessment of MR

Two cardiologists (C.T. and S.M.), experts in echocardiography and valvular heart diseases, blinded to all aspects of patient history and without access to 3D datasets independently performed grading of MR using an integrative approach according to the European Association for Cardio-Vascular Imaging (EACVI) recommendations. If there was disagreement between the two readers, a final consensus between the two readers was obtained to give the final grading. Another investigator (C.L.G.) blinded to MR grading computed off-line LV volumes without prior knowledge of the Doppler forward stroke volume results.

Grading of MR severity using the integrative approach

The severity of MR was graded by using an integrative approach as recommended by the EACVI. Echocardiographic data for MR grading were acquired according to a standardized protocol with multiple 2D incidences and the use of different Doppler modes without access to previously stored measurements. Effective regurgitant orifice area (EROA) by the PISA was used as a quantitative parameter. Semi-quantitative parameters were vena contracta width, pulmonary vein flow, E-wave mitral velocity, and mitral-to-aortic time-velocity integral (TVI) ratio. Qualitative parameters included mitral valve morphology, characteristics of the colour flow MR jet, size of the convergence zone, and aspect of the continuous wave signal of MR jet. MR severity was graded as 1+ (mild), 2+ (mild-to-moderate), 3+ (moderately severe), and 4+ (severe) MR.

Quantitative volumetric assessment of MR

Two-dimensional data were acquired according to current recommendations for chamber quantification. LV end-diastolic and -systolic volumes were obtained on recorded datasets by the Simpson biplane method on apical four- and two-chamber views with exclusion of trabeculae and papillary muscles. Care was taken to avoid apical foreshortening and to optimize endocardial definition by using harmonic imaging and adjustment of other instrument settings.

Three-dimensional echocardiography full-volume datasets of the LV were obtained in an adjustable volume divided into six sub-volumes. Each contiguous sub-volume was acquired during one cardiac cycle and the final volume was obtained as the combination of all sub-volumes. Acquisition was triggered at the R-wave of the ECG on consecutive heart beats. High-volume rate acquisition at the apex of the LV was performed during a 6- to 8-s inspiratory breath-hold. A representation of 12 short-axis slices of the LV from base to apex was used to ensure the absence of stitching artefacts or dropouts. The size of the sector was adjusted to cover the entire LV cavity and myocardium. Three-dimensional datasets were stored in raw data format. Semi-automated endocardial surface detection was then performed off-line. First, orientation of apical views and transverse plane was performed automatically. One point was placed on the middle of the mitral annulus and at the apex of the LV, first at end-diastole and then at end-systole. Manual adjustments of the automatic trace were performed as necessary. Secondly, the adequacy of endocardial tracking was checked throughout the cardiac cycle to obtain LV end-diastolic and -systolic volumes, LV EF, and LV total stroke volume (Figure 1). Measurement of 3D LV total stroke volume was repeated independently by another observer in 20 randomly selected patients (10 patients without MR and 10 with MR).

LV forward stroke volume was calculated as the product of LV outflow tract (OT) velocity-time integral (VTI) by LVOT cross-sectional area (CSA). To obtain CSA, LVOT diameter was measured from inner edge to inner edge using a magnified image with depth and focus set to optimize visualization of the LV OT perpendicular to the ultrasound beam and allowing clear visualization of the basal insertion points of the aortic leaflets. The LVOT VTI was classically obtained on an apical five-chamber
view using pulse-wave Doppler. Mitral 2D and 3D RF were obtained off-line by measuring the difference in LV total stroke volume (obtained from either 2D or 3D acquisition) and aortic forward stroke volume divided by 2D or 3D total stroke volume (Figure 1).

**Statistical analysis**

Continuous variables were expressed as mean ± standard deviation (SD). Categorical variables were expressed as absolute numbers and percentages. Comparisons between two groups were performed using Student’s t-test. Categorical variables were compared using the χ² test or Fisher’s exact test as appropriate. The relations between severity of MR and 2D or 3D RF were examined by the Spearman rank-order correlation. Comparisons between three or more groups were performed using the Kruskal–Wallis test. Thus, post hoc comparisons between groups were performed using the Mann–Whitney U-test. Linear correlations were studied using Pearson’s correlation test. Bland–Altman plots were used to study the agreement between two methods. Inter-reader variability of MR grading was assessed using the weighted Kappa statistic as MR grading categories are ordered. Statistical analyses and figures were obtained using PASW 18.0 (IBM, Inc., Bois-Colombes, France), GraphPad Prism (GraphPad Software, La Jolla, CA, USA), and MedCalc for Windows version 12.5.0 (MedCalc Software, Mariakerke, Belgium).

**Results**

**Consistency of measurements in patients without MR**

The clinical characteristics of the 60 patients without MR are depicted in Table 1. Three-dimensional total LV stroke volume was strongly correlated with LV forward stroke volume (r = 0.75, P < 0.0001, Figure 2A), with an absolute difference between 3D total LV stroke volume and Doppler forward stroke volumes of −0.5 mL with no

![Figure 1: Quantification of mitral RF by subtracting Doppler forward stroke volume from LV total stroke volume obtained by 3DE full-volume dataset in a patient with severe MR (4+). LVOT, left ventricular outflow tract; VTI, velocity-time integral; SV, stroke volume; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume.](image-url)

**Table 1  Clinical and echocardiographic characteristics of the study population**

<table>
<thead>
<tr>
<th></th>
<th>MR (−) (n = 60)</th>
<th>MR (+) (n = 60)</th>
</tr>
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<tbody>
<tr>
<td>Age (years)</td>
<td>54 ± 15</td>
<td>61 ± 14</td>
</tr>
<tr>
<td>Male sex (n, %)</td>
<td>31 (52)</td>
<td>40 (67)</td>
</tr>
<tr>
<td>Diabetes (n, %)</td>
<td>11 (18)</td>
<td>5 (8)</td>
</tr>
<tr>
<td>Hypertension (n, %)</td>
<td>17 (28)</td>
<td>17 (28)</td>
</tr>
<tr>
<td>Hyperlipidaemia (n, %)</td>
<td>10 (17)</td>
<td>17 (28)</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>28 ± 6</td>
<td>26 ± 5</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>133 ± 21</td>
<td>137 ± 19</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>68 ± 11</td>
<td>69 ± 13</td>
</tr>
<tr>
<td>3D LVEDV (mL)</td>
<td>113 ± 28</td>
<td>154 ± 39</td>
</tr>
<tr>
<td>3D LVESV (mL)</td>
<td>47 ± 13</td>
<td>61 ± 22</td>
</tr>
<tr>
<td>3D total SV (mL)</td>
<td>66 ± 16</td>
<td>93 ± 24</td>
</tr>
<tr>
<td>3D LV ejection fraction (%)</td>
<td>59 ± 5</td>
<td>61 ± 8</td>
</tr>
<tr>
<td>Doppler forward SV (mL)</td>
<td>67 ± 16</td>
<td>59 ± 16</td>
</tr>
</tbody>
</table>

MR, mitral regurgitation; LV, left ventricle; EDV, end-diastolic volume; ESV, end-systolic volume; SV, stroke volume.
systematic bias, as demonstrated by the Bland–Altman plots (Figure 2B); 2D total LV stroke volume was correlated with Doppler forward stroke volume ($r = 0.62$, $P < 0.0001$, Figure 2C), with an absolute difference of $-3.6$ mL (Figure 2D). However, wider limits of agreements on Bland–Altman plots were observed between 2DE and Doppler data than for 3DE, indicating poorer agreement for 2DE (Figure 2C and D).

**Patients with MR**
Measurement of both 3D LV total stroke volume and Doppler forward stroke volume was attempted in 67 patients with primary organic MR, and these parameters were adequately obtained in 60 patients (90%). Baseline clinical and echocardiographic characteristics of the 60 patients of the study population are depicted in Table 1. The cause of MR was mitral valve prolapse in 57 patients (95%), related to drug toxicity in 2 (3%) and rheumatic heart disease in 1 (2%). MR was Grade 3+ in 12 patients (20%) and Grade 4+ in 21 (35%). Twenty-six patients with 3+ or 4+ MR (79%) underwent surgery during follow-up, but none with 1+ or 2+ MR. The mean values of vena contracta width, mitral-to-aortic TVI ratio, E-wave velocity, mitral EROA, and the frequency of systolic flow reversal according to the grading of MR are summarized in Table 2. The Kappa coefficients for the inter-reader concordance in four grades (1+/2+/3+/4+) or in two categories (1+/2+ vs. 3+/4+ patients) were 0.90 and 0.93, respectively.

**Comparison between RF obtained by the volumetric method and MR grade**
Mean values for 3D RF and 2D RF for each grade are detailed in Table 3 and demonstrate significant differences between grades (overall $P < 0.001$). A significant correlation was observed between MR grading and 3D RF ($r = 0.83$, $P < 0.0001$, Figure 3) and 2D RF ($r = 0.74$, $P < 0.0001$). Comparisons between individual grades for 3D RF were significant ($P < 0.05$) except for 3+ vs. 4+ MR ($P = 0.213$, Table 3).
Table 2  Mean ± SD and/or frequency of variables of MR quantification according to the MR grade

<table>
<thead>
<tr>
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<th>MR severity</th>
<th>Overall</th>
<th>P-value</th>
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<tr>
<td></td>
<td>1+ (n = 10)</td>
<td>2+ (n = 17)</td>
<td>3+ (n = 12)</td>
</tr>
<tr>
<td>Vena contracta width (mm)</td>
<td>2.9 ± 1.6</td>
<td>4.0 ± 1.2</td>
<td>5.7 ± 1.0</td>
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<tr>
<td>Mitral to aortic TVI ratio</td>
<td>1.07 ± 0.45</td>
<td>1.24 ± 0.35</td>
<td>1.55 ± 0.35</td>
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<tr>
<td>E-wave (m/s)</td>
<td>0.68 ± 0.18</td>
<td>0.80 ± 0.19</td>
<td>1.10 ± 0.25</td>
</tr>
<tr>
<td>PISA EROA (mm²)</td>
<td>8 ± 6</td>
<td>15 ± 7</td>
<td>35 ± 8</td>
</tr>
<tr>
<td>Systolic pulmonary flow reversal (n,%)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>5 (42)</td>
</tr>
</tbody>
</table>

Table 3  Mean ± SD for RF obtained from 2D and 3D volumes corresponding to each MR severity grade

<table>
<thead>
<tr>
<th></th>
<th>Overall population (n = 60)</th>
<th>MR severity</th>
<th>Overall</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1+ (n = 10)</td>
<td>2+ (n = 17)</td>
<td>3+ (n = 12)</td>
</tr>
<tr>
<td>2D RF (%)</td>
<td>32 ± 26</td>
<td>12 ± 14</td>
<td>12 ± 27</td>
<td>43 ± 16</td>
</tr>
<tr>
<td>3D RF (%)</td>
<td>34 ± 18</td>
<td>12 ± 9</td>
<td>20 ± 10</td>
<td>45 ± 8</td>
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</table>

Discussion

This study shows that mitral RF may be obtained by using 3DE full-volume datasets of the LV in 90% of cases. Three-dimensional RF >40% is highly specific for Grade 3+ and Grade 4+ MR. 3D RF could therefore be used clinically as part of a comprehensive Doppler assessment of primary MR and appears to be superior to 2DE determination of RF.

A now well-established use of 3DE is the evaluation of LV volumes and EF by eliminating the need for geometric modelling, which is inaccurate in the presence of aneurysms, asymmetrical ventricles, or wall motion abnormalities and the errors caused by foreshortened views in symmetrical ventricles. Accordingly, the value of 3DE imaging has consistently been demonstrated by multiple studies that compared 3DE volume measurements with reference techniques such as radionuclide ventriculography or CMR.18–24 The agreement between 3DE and the reference technique was higher than with 2DE in most studies. The reproducibility of 3DE volumes has also been reported in previous studies to be higher than those obtained by 2D echocardiography.25 Hence, EACVI/AASE guidelines for imaging and display using 3D echocardiography recommend the use of LV volumes and EF for clinical practice.10 In the present study, the finding that 3D LV stroke volume was more closely correlated with LV Doppler forward stroke volume than 2D LV stroke volume in patients without MR confirms the interest of this method.

The present study shows that quantification of MR by 3D RF (>40%) accurately discriminates patients with 3+ or 4+ MR. Accordingly, RF >40% in patients with MR is the classical invasive haemodynamic criterion for 3+ or 4+ MR.26 An echocardiographic

Reproducibility

Inter-observer coefficient of variation for measurement of 3D stroke volume in 20 patients (10 with MR and 10 without MR) was 4.9% (mean difference: −3.2 mL).

Figure 3: Three-dimensional RF (individual data and mean ± SD) according to the MR grade

As shown in Figure 4A, all patients with 3D RF >40% had 3+ or 4+ MR and those with 3D RF <30% had 1+ or 2+ MR, with a ‘grey’ overlap zone between 30 and 40%. Comparatively, all patients with 2D RF >40% had 3 or 4+ MR and those with 2D RF <12% 1+ or 2+ MR, with a larger ‘grey’ zone compared with 3DE, ranging from 12 to 40% (Figure 4B).
RF >40% with the PISA method was consistently calibrated as ≥3+ angiographic MR. Quantification of MR by 3D RF may be of interest in clinical situations when other quantitative or semi-quantitative indices are not feasible or suboptimal. Three-dimensional RF may be used, for example, in cases of a double mitral valve orifice after MitraClip procedure, after mitral valve repair, of multiple regurgitant jets or in the case of a late systolic MR.

CMR calculation of the degree of MR has been proposed using the same approach as with 3DE: forward stroke volume measured by phase contrast in the aorta and total LV stroke volume calculated from endocardial border tracings. The reproducibility of this method was shown to be excellent. However, its cost and availability may remain problematic for routine clinical evaluation.

**Limitations**

No CMR or invasive haemodynamic reference for RF was available in the present study. The reference standard was MR grading using the multi-parametric integrative approach as recommended by the EACVI. This multi-parametric grading of primary MR is subjective and highly depends on the experience of the reader. However, a close inter-reader agreement for MR grading using this approach was found in our series, hence reinforcing its value as a reference standard in clinical practice. In addition, 3D RF was calculated by a third investigator blinded from the result of MR grading using the integrative approach. Quantification of 3D RF may only be achieved in patients with isolated MR, in sinus rhythm, and with good echogenicity. In the present study including only patients in sinus rhythm, determination of RF using the 3DE method was performed in 90% of cases. 3D RF cannot differentiate patients with 3+ from 4+ MR, as showed by the overlap between 3+ and 4+ MR in patients with RF >40%. Interestingly, the same overlap has previously been reported with other parameters used for quantification of MR, such as mitral-to-aortic TVI ratio, Doppler RF, vena contracta, and with the PISA method. In clinical practice, mitral valve repair or replacement is discussed in patients with 3+ and 4+ primary MR. In these patients, the decision concerning surgery is based on feasibility of mitral valve repair, symptoms, LV enlargement and systolic function, occurrence of atrial fibrillation, pulmonary artery hypertension, and on the operative risk. A ‘grey’ zone overlap between 1+/2+ and 3+/4+ MR was observed for 3D RF values between 30 and 40%, indicating that this approach should be integrated with other methods of assessment of MR severity. The limits of agreement between Doppler and 3D stroke volume in patients without MR (±22 mL) were relatively wide and may be related to both errors in computation of Doppler SV (e.g. measurements in LVOT diameter, non-rounded LVOT) and in inaccurate endocardial border tracings by 3DE. Thus, 3D RF cannot accurately identify patients with 1+ or 2+ MR from controls without MR. We acknowledge that the sample size of this pilot study was relatively small. Further larger-scale confirmatory studies are necessary to confirm the results of this pilot study.

**Conflict of interest:** none declared.

**References**

Three-dimensional regurgitation fraction in primary MR

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