Quantification of mitral-valve regurgitation in a paediatric population by real-time three-dimensional echocardiography

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Summary
Background. — Evaluation of mitral-regurgitation (MR) severity in infants is challenging. Real-time three-dimensional echocardiography (RT3DE) allows accurate left-ventricular volumetric measurements in adults.
Aims. — To validate RT3DE by measuring stroke volume in a normal paediatric population, then to use this new method to calculate regurgitant volume in paediatric patients with MR.
Methods. — Fifty-four patients, aged one week to 19 years, (29 without and 25 with MR) had two-dimensional echocardiography coupled with RT3DE left-ventricular volumetric acquisition. Stroke volume was calculated by the Doppler method at the aortic annulus (SVD). End-systolic and end-diastolic left-ventricular volumes were measured using the QLab semi-automated method; three-dimensional stroke volume (SV3D) was calculated as their difference. In the MR group, regurgitant volume was calculated by the PISA method (RVPISA) and as the difference between SV3D and SVD (RV3D). Regurgitant fraction was also evaluated by these methods (RFPISA and RF3D).

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Results. — Measurement feasibility was 88%. In the normal group, $SV_{3D}$ (27.9 ± 18.1 ml) was highly correlated with $SV_D$ (30.7 ± 19.6 ml; $r = 0.98; p < 0.000$). In the MR group, $RV_{PISA}$ (15.7 ± 14.4 ml) and $RV_{3D}$ (11.0 ± 10.2 ml) were well correlated ($r = 0.83; p < 0.001$). Regurgitant fractions were also well correlated ($RF_{PISA} = 30.4 ± 17.0\%; RF_{3D} = 24.3 ± 15.9\%; r = 0.79, p = 0.006$).

Conclusion. — RT3DE is a simple, rapid and reliable method for evaluating stroke volume in children and may, therefore, be useful for evaluating regurgitant volume and fraction in paediatric patients with MR.

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Abbreviations

LV Left ventricular
MR Mitral regurgitation
PIA Proximal isovelocity surface area
RF Regurgitant fraction
ROA Regurgitant orifice area
RT3DE Real-time three-dimensional echocardiography
RV Regurgitant volume
SV Stroke volume

Background

MR is now the second most frequently occurring heart-valve disease after aortic stenosis [1]. MR may be caused by abnormalities of any component of the mitral valve apparatus: mitral leaflets, chordae tendineae, papillary muscles or mitral annulus [2]. Major causes of MR include mitral valve prolapse (prevalence up to 2.5% [3]), rheumatic heart disease, infective endocarditis, annular calcification, cardiomyopathy and ischaemic heart disease [4]. In the paediatric population, specific congenital causes are also encountered, such as mitral valve cleft (isolated or associated with atrioventricular septal defects), anomalous papillary muscles or chordae tendineae responsible for restrictive MR.

Management of MR includes surgery — preferably conservative [5,6] — the timing of which is particularly difficult in children and is determined by the symptoms and severity of MR [7,8]. Evaluation of the severity of MR in infants is still a challenge, despite advances in echocardiography. The echocardiographic method used most frequently in adults is PISA [9]. This method can be used in the paediatric population, but there are no validated values for ROA and RV for children, given the variation in body size from neonates to adults. Hence, the only reliable measurement for evaluating MR severity that is not dependent on body size is RF. However, the PISA method has several technical limitations, which are often encountered in children [10,11].
RT3DE is now available commercially [12] and allows accurate LV volumetric measurements to be made in adult patients without any geometric assumptions [13]. RT3DE measurements correlate very well with magnetic resonance measurements of LV volumes and ejection fraction [14,15]. In paediatric patients, three-dimensional LV volume measurement was validated initially by an offline-reconstruction technique [16] and more recently by RT3DE [17—19]. The measurement of SV by a reconstruction three-dimensional technique was validated versus the Doppler method [20,21] in patients without valve heart disease [22].

Our aim in this study was twofold: firstly, to validate the measurement of SV by RT3DE in a normal paediatric population; secondly, to test the correlation of RV and RF measurements made by RT3DE and by the PISA method in patients with MR.

Methods

Study population

Fifty-four consecutive paediatric patients referred for echocardiography at our laboratory were included. Twenty-nine patients had normal mitral valves (normal group) and 25 patients had MR (MR group). All patients had normal LV outflow tracts, no ventricular septal defects and no aortic regurgitation. We performed two-dimensional echocardiography (IE33 or Sonos 7500, with S3 or S8 transducers; Philips® Medical Systems) and RT3DE acquisition of the left ventricle (X3-1, X4-2 or X7-2 matrix probes; Philips® Medical Systems) on each patient.

Two-dimensional echocardiography

For two-dimensional measurements, SV was calculated by the Doppler method at the aortic annulus (SVDoppler) [20,21]. Care was taken to measure LV outflow tract in mid systole as precisely as possible (parasternal long-axis view with zoom) at the insertion of the aortic valve leaflets. Pulsed Doppler was used in apical five-chamber view to measure the LV outflow tract flow with the best alignment possible (recording of sole closing aortic valve artefact). SVDoppler was calculated by multiplying the LV outflow cross area by the LV outflow. In the MR group, the PISA method [9] (Fig. 1A) was used to evaluate ROA and RV PISA. RF PISA (percentage) was calculated by dividing RV PISA by the sum of RV PISA and SV Doppler (with the total multiplied by 100). Convergence zone diameter was measured in mid systole, notably for mitral valve prolapse.

Three-dimensional echocardiography

For three-dimensional measurements, full-volume acquisition was used from apex to analyse the entire left ventricle. For acquisition of a full-volume data set, four smaller real-time volumes, acquired from consecutive cardiac cycles (during a breath hold when possible), were combined to provide a large pyramidal volume. To optimize the frame rate of acquisition, depth was minimized; care was taken to ensure that the entire LV cavity would be in the acquired volume. A second generation matrix array transducer (X4-2 – 2 to 4 MHz or X3-1 – 1 to 3 MHz) was used for most patients. The recently developed X7-2 matrix probe (2–7 MHz) was used for 12 patients without MR and for three patients with MR. End-systolic and end-diastolic volumes were measured by a semiautomated method (QLab 3D Advanced software, version 4.2; Philips Medical Systems); the three-dimensional stroke volume (SV3D) was calculated as their difference (Fig. 1B). The mean time for measuring SV3D was less than 1 min in patients with good endocardial detection and up to 3 min when manual corrections were needed. In the MR group, RV3D was calculated as the difference between SV3D and SVDoppler. RF3D (percentage) was calculated by dividing RV3D by SV3D (with the total multiplied by 100).
### Statistical analysis

Continuous variables are expressed as mean plus or minus standard deviation; normal distribution was tested by Shapiro-Wilk and skewness/kurtosis tests. Nominal variables are expressed as percentages. Continuous variables were assessed with the unpaired Student’s t test and one-way analysis of variance, as appropriate. Nominal variables were compared with the Chi-square test or Fisher’s exact test, as appropriate. Correlations were performed with linear regression (Pearson’s coefficient or nonparametric Spearman coefficient, as appropriate). Interobserver and intraobserver agreement were assessed using linear regression and the Bland-Altman method, with the average difference between readings corrected for their mean. A p value less than 0.05 was considered significant.

### Results

#### Patient characteristics

The 54 patients were aged between 1 week and 19 years (mean: 85 ± 60 months; median: 79 months), with a mean height of 116 ± 33 cm, a mean weight of 23 ± 14 kg and a mean calculated body surface area of 0.85 ± 0.39 m². Overall measurement feasibility was 88% (impossible or poor quality three-dimensional acquisition due to agitation). Twenty-five patients from the normal group and 23 from the MR group were included in the final analysis. MR aetiology was mitral valve prolapse in nine patients (39%; 6 isolated prolapses, 1 of rheumatic origin, 1 arising in Marfan syndrome and 1 in a mixoide mitral valve), congenital MR in nine patients (39%; 7 cases of mitral valve cleft — 6 nonoperated and one postoperative residual MR — and 2 cases of mitral valve restriction), ischaemia in two patients (9%; by anomalous left coronary artery originating in the pulmonary artery) and mitral annulus dilatation in three patients (13%; functional MR).

#### Normal group

In the normal group, mean SV 3D was 27.9 ± 18.1 ml and mean SV Doppler was 30.7 ± 19.6 ml. SV 3D was highly correlated with SV Doppler (normally distributed values, \( r_{Pearson} = 0.98; p < 0.0001; y = 0.90x + 0.08 \); Fig. 2). The mean difference was −2.8 ± 3.8 ml (underestimated values for SV 3D compared with SV Doppler; Fig. 3). The correlation was highly significant in the subgroup of patients with good endocardial detection (12 patients) and in those needing manual correction (13 patients), but tended to be slightly better when no endocardial contour correction was needed (\( r_{Pearson} = 0.97 \) and 0.94, respectively).

#### MR group

In the MR group, the severity of MR, measured by the PISA method and classified by RF PISA was found to be severe in five patients (22%), moderate in six patients (26%) and mild in 12 patients (52%). The aetiology of severe MR was cleft in three patients (20%), whereas the aetiology of mild MR was dominated by prolapse in six patients (67%; \( p_{\text{exact}} = 0.04 \)). Thus, architectural abnormalities of the mitral valve are responsible for higher-grade MR than mitral valve dysfunction (prolapse). The MR grade was less often severe when classified by RF 3D (one patient, 4%) than by RF PISA (five patients, 22%; \( p_{\text{exact}} < 0.001 \)).

RF PISA (15.8 ± 14.4 ml, median: 11.3 ml) and RV 3D (11.0 ± 10.2 ml, median: 6.5 ml) were well correlated (normally distributed values, \( r_{Pearson} = 0.83; p < 0.0001 \); Fig. 4). The mean difference between RV 3D and RF PISA was −4.8 ± 8.2 ml (Fig. 5). RF values measured by the two methods were also correlated (RF PISA = 30.4 ± 17.0%, median: 27.0%; RF 3D = 24.3 ± 15.9%, median: 18.4%; \( r_{Pearson} = 0.79; p < 0.0001 \); Fig. 6). The mean difference between RF 3D and RF PISA was −6.1 ± 10.5% (Fig. 7). In almost all patients (86%) in the MR group, manual corrections were needed for calculating end-diastolic and end-systolic volumes by the QLab semiautomated method. Acquisition artefacts of the three-dimensional volume were present in six patients (26%), but measurements were still possible.

![Figure 2. Relation between SV 3D and SV Doppler in the normal group: \( r = 0.98; p < 0.0001, y = 0.90x + 0.08 \).](image)

![Figure 3. Agreement between SV 3D and SV Doppler in the normal group: mean difference: −2.8 ± 3.8 ml.](image)
Reproducibility

The reproducibility of the SV3D measurement was evaluated. Seventeen patients (9 from the normal group and 8 from the MR group) were selected for analysis of reliability between two observers. On the same full volume acquisition of the LV, each observer measured the end-diastolic volume and the end-systolic volume of the LV using the described method. There was excellent correlation between the SV3D measurements calculated by the two observers (r_Pearson = 0.98; p < 0.0001); the mean difference was 0.17 ± 4.76 ml. The correlation was excellent in both normal and MR groups (r_Spearman = 0.96 and 1.0, respectively).

Intra-observer variability was assessed by having a single observer making two measurements in 19 patients (11 from the normal group and eight from the MR group), with an interval of more than 1 week between the two measurements. The correlation between the two measurements made by the same observer was excellent (r_Pearson = 0.97; p < 0.0001); the mean difference was 0.92 ± 5.74 ml. The correlation was excellent in both normal and MR groups (r_Spearman = 0.97 and 0.95, respectively).

Discussion

The purpose of this study was twofold. Firstly, we validated SV measurement by RT3DE in a normal paediatric population; RT3DE had an excellent correlation with the Doppler method. We then proposed a method for evaluating MR severity in children, based on RF evaluation by RT3DE. Our study has illustrated that RF3D measurement is simple in concept, feasible and reproducible and correlates well with the echocardiographic method (PISA) used most frequently.

RF allows classification of MR severity as mild (< 30%), moderate (30—49%) or severe (≥ 50%) [7], and may be obtained by the PISA method [1,9]. However, the PISA method has several technical limitations, which are encountered largely in the paediatric population due to specific aetiologies (cleft and prolapse): irregular ROA, confinement of the convergence zone [11], variation of ROA throughout
systole in prolapse [10] and multiple regurgitation jets. RT3DE has already been proposed for evaluating MR severity by measuring ROA using three-dimensional colour Doppler [23, 24]. RV has also been evaluated by colour Doppler RT3DE in an in vitro model of MR [25], which yielded better results than two-dimensional PISA. These variables were not evaluated in our series. Three-dimensional echocardiography also brings valuable insights into the mechanism of MR [26].

The values for RV and RF, measured by RT3DE, were slightly lower than the values obtained by the PISA method. As a consequence, MR was classified as severe less often by RT3DE (1 patient) than by the PISA method (5 patients). In most of these cases, RF values were borderline around a value of 50%, with small differences between the two methods. Two factors most probably contributed to the difference. The most important factor is the overestimation of MR severity by the PISA method, due to its nonhemispheric shape and its variation throughout systole, especially during prolapse [27]; there was a high incidence of prolapse in our MR group (39%). The second factor is the slight underestimation of MR severity by RT3DE. In our normal group, SV\textsubscript{1D} was underestimated slightly compared with the SV\textsubscript{Doppler} and this underestimation may have further contributed to the underestimation of RV measured by RT3DE. Furthermore, end-diastolic and end-systolic volumes have been underestimated slightly in studies comparing volume measurements by RT3DE with gold standard volumetric evaluation (magnetic resonance imaging [14, 15], or ventriculography [17]). This underestimation is explained partially by the possibility of including the LV apex in the acquired volume — a technical limitation that was encountered in some of our patients, despite the smaller LV size in children compared with adults. In effect, significant MR is associated with a remodelled LV, which may be dilated with a laterally-deviated apex. Moreover, modified LV geometry, reflex tachycardia and, sometimes, dyspnoea influenced the quality of the three-dimensional acquisition volume; manual corrections were therefore needed for volume semiautomated measurements in the majority of the MR group. One last limitation of our study was the monocentric evaluation of this new technique. Nevertheless, the volume of literature is growing and largely supports the advantages of RT3DE.

The next step in the clinical evaluation of RT3DE in quantification of MR is three-dimensional PISA (ROA and RV measurement by colour Doppler-RT3DE); ROA by colour Doppler-RT3DE has already been validated in adults [23] but RV measurement by colour Doppler-RT3DE has only been assessed in an in vitro model of MR [25]. Upcoming matrix probes (including a first transesophageal matrix probe) have better spatial and temporal resolution and should allow accurate three-dimensional PISA measurements to be made. These variables (ROA and RV by colour Doppler-RT3DE) are currently under study in our centre.

**Conclusion**

Volumetric RT3DE is a simple, rapid and reliable method for evaluating SV in children and may, therefore, be of particular use in evaluating RV and RF in paediatric patients with MR.

**Conflicts of interest**

None.

**References**


