Left Atrial Filling Volume Can Be Used to Reliably Estimate the Regurgitant Volume in Mitral Regurgitation

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Objectives. The objective was to analyze the accuracy and diagnostic value of the estimated regurgitant volume of mitral regurgitation using 1) left atrial volume variation during ventricular systole (left atrial filling volume) and 2) the percent of systolic pulmonary vein velocity integral compared with its total.

Background. Left atrial filling volume (LAfill), which represents the atrial volume variation during ventricular systole, has been used for the assessment of mitral regurgitation severity. A good correlation with invasive semiquantitative evaluation was found, but with an unacceptable overlapping among grades. The reason could be the absence of information concerning the contribution of blood entering into the left atrium from the pulmonary veins.

Methods. Doppler regurgitant volume (Dpl-RVol) (mitral stroke volume – aortic stroke volume) was measured in 30 patients with varying degrees and etiological causes of mitral regurgitation. In each patient atrial volumes were measured from the apical view, using the biplane area-length method. The systolic time-velocity integral of pulmonary vein flow was expressed as a percentage of the total (systolic-diastolic) time-velocity integral (PVs%). These parameters were used in this group of patients to obtain an equation whose reliability in estimating Dpl-RVol was tested in a second group of patients.

Results. In the initial study group, with linear regression analysis the following parameters correlated with Dpl-RVol: end-diastolic left atrial volume (R² = 0.37, p = 0.0004); LAfill (R² = 0.45, p < 0.0001); PVs% (R² = 0.56, p < 0.0001). In multiple regression analysis the combination of LAfill and the percent of the systolic pulmonary vein velocity integral (PVs%) provided a more accurate estimate of regurgitant volume (R² = 0.88; SEE 10.6; p < 0.0001; Dpl-RV = 6.18 + (1.01 × LAfill) – (0.783 × PVs%). The equation was subsequently tested in 54 additional patients with mitral regurgitation with a mean Dpl-RVol 27 ± 37 ml. Estimated regurgitant volume and Dpl-RVol correlated well with each other (R² = 0.90; SEE 12.1; p < 0.0001). In the test population, the equation was 100% sensitive and 98% specific in detecting a regurgitant volume higher than 55 ml.

Conclusions. Left atrial filling volume and pulmonary vein flow give a reliable estimate of regurgitant volume in mitral regurgitation.

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Finding the best timing for surgery in mitral regurgitation is still a challenge. Left ventricular (LV) dysfunction may affect even asymptomatic patients, leading to a poor long-term prognosis even after a successful mitral valve repair or replacement (1). The lack of simple parameters that could consistently predict this serious complication means that surgery cannot safely be postponed (2). Early surgery for severe mitral regurgitation has been suggested in asymptomatic patients with normal LV ejection fraction (3) to minimize the risk of postoperative ventricular failure. Therefore, the safest indication for surgery should not be based on symptoms or LV function but on an accurate estimation of the severity of mitral regurgitation.

The widely used semiquantitative methods of regurgitation grading have important limitations that lead to frequent and significant clinical discrepancies (4,5). A quantitative evaluation of left cardiac chamber overload is available from different and well-validated methods (6). Some of these methods (Doppler and two-dimensional echocardiography) have been extensively used in academic centers for both clinical and research purposes, but they are time-consuming and strongly dependent on operator experience (7). The proximal isovelocity surface area (PISA) method has recently been introduced and has been proved to be accurate (8,9), but it has important limitations, especially in mitral valve prolapse patients with nonoptimal flow convergence area (10). Thus, there is a need for another simple quantitative method to validate the results and improve their accuracy.

Because the drawing of atrial boundaries is very simple, it was thought that left atrial volume variation during ventricular systole (left atrial filling volume) could be used to assess the severity of mitral regurgitation, given that systolic regurgitant...
volume is its fundamental determinant. Ren et al. (11) observed an excellent correlation with invasive semiquantitative grading of mitral regurgitation; but the reliability of this method is still uncertain because of the lack of information about the amount of blood concomitantly filling the left atrium from the pulmonary veins.

The hypothesis of this study is that combining systolic pulmonary vein flow and left atrial filling volume might represent a reliable alternative method for estimating the regurgitant volume.

Methods

Patients. Patients were included in the study prospectively. Inclusion criteria were 1) mitral regurgitation of any degree (some of them had no mitral regurgitation at all) as determined by standard Doppler color flow imaging; 2) complete two-dimensional (2-D) and Doppler measurements, allowing quantitation of mitral regurgitation; 3) availability of pulmonary vein flow velocity from transthoracic echocardiography. The only exclusion criterion was the presence of more than trivial aortic regurgitation. The initial study group consisted of 30 patients (20 male and 10 female; mean age 58.8 ± 13.1 years) with varying degrees and etiological causes of mitral regurgitation; 7 of them had no mitral regurgitation as determined by standard Doppler color flow imaging. Data obtained in the initial study group were used to derive a regression equation for the estimation of mitral regurgitant volume. The equation was subsequently tested in a separate group (test group) of 54 patients (36 male and 18 female; mean age 56.0 ± 13.8 years) with varying degrees and etiological causes of mitral regurgitation (Table 1).

Measured Doppler regurgitant volume. All patients had a complete Doppler and echocardiographic examination using multiple windows. The mitral and aortic stroke volumes were calculated as the product of the annulus areas and the mitral and aortic time-velocity integral. The regurgitant volume (Dpl-RVol) was then calculated by subtracting the aortic stroke volume from the mitral stroke volume (6). This well-validated method was regarded in the present study as the gold standard for quantifying mitral regurgitation.

Left atrial volume. The technical basis for obtaining this parameter has previously been described by Ren (11). Left atrial areas were measured at end-systole (the largest dimension or the end of the T wave) and end-diastole (the smallest dimension or the onset of QRS complex), from apical four-chamber and apical two-chamber views (Fig. 1), using the highest frame rate. The left atrial outlines at both end-systole and end-diastole were traced off-line for three consecutive beats (six beats for patients with atrial fibrillation), then averaged. Atrial area variation (end-systole − end diastole) was subsequently measured in four-chamber view (ΔA4) and two-chamber view (ΔA2). The end-diastolic (LAmin) and end-systolic (LAmmax) atrial volumes were calculated according to Dodge’s method using a biplane area-length formula: $V = \frac{A1 A2}{3 \pi L}$, where $A1$ and $A2$ represent the enclosed area of the atrial chamber from two orthogonal views, respectively, and $L$ is the shared axis running from the apex to the base. Left atrial filling (LAfill) volume is the volumetric change from end-systole to the end-diastole.

Pulmonary vein flow velocity. Pulmonary vein flow velocities were obtained by placing the sampling volume 0.5 to 1 cm into the orifice of the right upper pulmonary vein during the transthoracic examination. The time-velocity integral of the systolic and diastolic phase was subsequently measured, and the systolic component was expressed as a percentage of the total (systolic-diastolic) velocity time integral (PVs%). If a systolic reversal flow in the pulmonary vein was present, the percentage of the systolic time-velocity integral compared with the total was considered zero by definition. Seven patients (7.6%) were excluded because of unsatisfactory pulmonary vein tracings.

Interobserver variability. In 20 subjects atrial volumes and Dpl-RVol were measured by two observers independently.

Table 1. Characteristics of the Study Populations

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Study population (n = 30)</th>
<th>Test population (n = 54)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>59 ± 13</td>
<td>56 ± 14</td>
</tr>
<tr>
<td>AF</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Dpl-RVol (ml)</td>
<td>27 ± 30</td>
<td>27 ± 37</td>
</tr>
<tr>
<td>Etiology of MR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Organic</td>
<td>8</td>
<td>26</td>
</tr>
<tr>
<td>Ischemic</td>
<td>10</td>
<td>14</td>
</tr>
<tr>
<td>Functional</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>No MR</td>
<td>7</td>
<td>10</td>
</tr>
<tr>
<td>ΔA4 (cm²)</td>
<td>9.1 ± 3.3</td>
<td>9.3 ± 3.3</td>
</tr>
<tr>
<td>ΔA2 (cm²)</td>
<td>9.6 ± 2.5</td>
<td>9.9 ± 2.9</td>
</tr>
<tr>
<td>LAmin (ml)</td>
<td>46.6 ± 29.4</td>
<td>47.5 ± 33.0</td>
</tr>
<tr>
<td>LAmmax (ml)</td>
<td>98 ± 32</td>
<td>98 ± 43</td>
</tr>
<tr>
<td>LAfill (ml)</td>
<td>51 ± 17</td>
<td>50 ± 21</td>
</tr>
<tr>
<td>PVs%</td>
<td>39 ± 25</td>
<td>43 ± 21</td>
</tr>
<tr>
<td>Estimated RV (ml)</td>
<td>23 ± 30</td>
<td>23 ± 30</td>
</tr>
</tbody>
</table>

AF = atrial fibrillation; Dpl-RVol = mitral regurgitant volume measured by Doppler methods; Estimated RV = mitral regurgitant volume estimated using the equation derived from multilinear regression analysis; LAfill = left atrial filling volume; LAmmax = end-systolic left atrial volume; LAmin = end-diastolic left atrial volume; MR = mitral regurgitation; PVs% = percentage systolic component of the total pulmonary time-velocity integral; ΔA4 = variation of left atrial area measured in four-chamber view; ΔA2 = variation of left atrial area measured in two-chamber view.
Intraobserver differences were calculated as the difference between the values obtained by the two observers divided by the mean.

Statistical analysis. In the initial study group, atrial volumes, areas and systolic pulmonary vein velocities were correlated with Dpl-RVol by linear regression analysis. In addition, measurements were analyzed by forward stepwise multiple linear regression analysis, and an equation was derived to estimate mitral regurgitant volume. In the test group the relation between actual Dpl-RVol and estimated (by the equation) regurgitant volume was analyzed with linear regression analysis and the Bland and Altman method, plotting and regressing the method difference against the method mean value. Significance was established at a level of \( p < 0.05 \).

Results

Study group. The clinical and echocardiographic characteristics of the 30 patients forming the study group are reported in Table 1. Echocardiographic variables were correlated with Dpl-RVol by linear regression analysis (Table 2). The PVs% had the highest correlation (\( R^2 = 0.56; p < 0.0001 \)) (Fig. 2) with Dpl-RVol, followed by LAfill (\( R^2 = 0.48; p < 0.0001 \)), Lmax (\( R^2 = 0.37; p < 0.0004 \)). Hemodynamic and anatomical variables with a significant univariate correlation were introduced as candidate independent variables in multivariate analysis performed using stepwise forward multiple linear regression model (Table 3). The only independent predictors of Dpl-RVol were LAfill and PVs%. Therefore Dpl-RVol can be predicted from a linear combination of the two, which gives a high correlation coefficient (\( R^2 = 0.88; \text{SEE} 10.6; p < 0.0001 \)) according to the equation

\[
\text{Dpl-RVol} = 6.18 + (1.01 \times \text{LAfill}) - (0.783 \times \text{PVs%}).
\]

To simplify the method, a second model of forward stepwise regression analysis was constructed by eliminating as a candidate independent variable the strongly predictive but more time-consuming LAfill. The Dpl-RVol can be predicted from a linear combination of \( \Delta A4 \) and PVs% with a lower but still quite consistent correlation coefficient (\( R^2 = 0.74; \text{SEE} 14.5; p < 0.0001 \)) according to the second equation: 

\[
\text{Dpl-RVol} = 20 - (0.969 \times \text{PVs%}) - (4.99 \times \Delta A4).
\]

Table 2. Simple Linear Regression Correlation Matrix Between Dpl-RVol and Echocardiographic Left Atrial and Doppler Variables in the Study Population

<table>
<thead>
<tr>
<th>Single Regression Analysis</th>
<th>( R^2 ) Value</th>
<th>( p ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \Delta A4 ) (cm²)</td>
<td>0.17</td>
<td>0.02</td>
</tr>
<tr>
<td>( \Delta A2 ) (cm²)</td>
<td>0.25</td>
<td>0.005</td>
</tr>
<tr>
<td>Lmax (ml)</td>
<td>0.37</td>
<td>0.0004</td>
</tr>
<tr>
<td>Lmin (ml)</td>
<td>0.06</td>
<td>0.17</td>
</tr>
<tr>
<td>LAfill (ml)</td>
<td>0.48</td>
<td>0.0001</td>
</tr>
<tr>
<td>PVs%</td>
<td>0.56</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

Abbreviations as in Table 1.

Reproducibility of measurements. The mean percent interobserver variability for measurement of LAfill was 4.4%; for measurement of \( \Delta A4 \) variation it was 2.0%.

Discussion

The present study has shown that LAfill is a reliable method for obtaining a noninvasive estimation of mitral regurgitant volume, when the amount of blood filling the left atrium from
the pulmonary veins during ventricular systole is taken into consideration.

Because LV dysfunction is frequent even after successful mitral valve surgery (12,13) and is associated with poor long-term survival (1), it has been suggested that surgery should be performed early in the course of the disease, even in asymptomatic patients with normal LV function (14), provided that the degree of regurgitation is severe. Therefore, a correct estimate of mitral regurgitation is crucial for clinical decision making. Furthermore, the importance of quantitative evaluation of mitral regurgitation has been emphasized in a recent study (15) in patients with LV dysfunction. In this clinical setting, multiple intricate relations account for the limited comprehension of the variability of the functional and hemo-

dynamic consequences of LV dysfunction. Because mitral regurgitation affects important prognostic and diagnostic parameters, such as diastolic filling, pulmonary hypertension and left ventricular ejection fraction, its quantitation is essential for a complete hemodynamic assessment in individual patients.

In the majority of centers, a mitral regurgitation grading is obtained by invasive or noninvasive semiquantitative methods. Jet assessment by color flow imaging is easy and rapid, but it tends to underestimate the severity of eccentric jets (4) and to overestimate the severity of central jets (16), especially in functional mitral regurgitation. Also, LV angiography has important limitations (5), and it cannot be performed routinely or for the purpose of follow-up. Thus, a pressing need exists for noninvasive quantitation methods for mitral regurgitation.

Although quantitative methods are well validated and in some academic centers represent the gold standard for mitral regurgitation grading, there are some technical difficulties, and their reliability is strictly related to the operator’s experience (7). The Doppler quantitative method is the most commonly

![Figure 2](image.png)

**Figure 2.** Scatterplot of regurgitant volume measured by Doppler (Dpl-RVol) versus pulmonary vein systolic time-velocity integral compared to total pulmonary vein time-velocity integral (PVs%) (A) and left atrial volume variation during ventricular systole (LAfill) (B) in study-group patients.

![Figure 3](image.png)

**Figure 3.** Correlation between regurgitant volume measured by Doppler (Dpl-RVol) and the regurgitant volume estimated by the regression equation in 54 patients of the prospective group. Dotted line represents the line of identity.

| PVs% | 0.56 |
| PVs% + LAfill | 0.88 |
| Dpl-RVol = 6.18 + (1.01 × LAfill) − (783 + PVs%) | 0.88 |
| PVs% | 0.56 |
| PVs% + ΔA4 | 0.74 |
| Dpl-RVol = 20 + (0.969 × PVs%) − (4.99 × ΔA4) | 0.74 |

### Table 3. Multiple Linear Regression Analysis Relating Echocardiographic and Doppler Variables to Dpl-RV in the Study Population

*Abbreviations as in Table 1.*
used to measure mitral regurgitant volume. It involves measuring the aortic and mitral stroke volume, where the difference is the regurgitant volume. The mitral stroke volume is a difficult measurement to obtain because both mitral annulus and mitral velocity time integral are technically difficult and time-consuming (17). These measurements are consistent only if they are routinely included in everyday examinations. Using 2-D echocardiography, regurgitant volume can be calculated as the difference between LV stroke volume and aortic stroke volume. The LV stroke volume is obtained by drawing the ventricular boundaries at end-diastole and at end-systole. These measurements are extremely difficult because the endocardium is often not clearly identifiable, so that the degree of intra- and interobserver variability is often unacceptable. The newly developed PISA method is simple and provides rapid quantitation of mitral regurgitation (8). The PISA method can be performed in a large number of patients (18) and has recently been simplified to allow wider utilization (19). Nevertheless, eccentric jets due to mitral valve prolapse with a suboptimal flow convergence area are a potential source of errors (10).

Because the regurgitant volume fills the left atrium, LAfill can be an index of mitral regurgitation, as described by Ren et al. (11). However, an overlapping among groups weakened their study. In our study, the poor, although significant, correlation between LAfill and Dpi-RVol meant that we could not consider LAfill a reliable parameter in individual patients. The underlying reason is that systolic pulmonary vein flow, which also fills the left atrium during ventricular systole, is not taken into account. Pulmonary venous flow is often used to assess the severity of mitral regurgitation (20). Under normal conditions systolic pulmonary vein velocity is higher than diastolic velocity, but it is progressively impaired with increasing degree of mitral regurgitation and it is reversed with markedly severe regurgitation. A recent experimental study emphasized a strong correlation ($r = 0.81$) between pulmonary systolic flow index (pulmonary vein systolic time-velocity integral divided by total pulmonary vein time-velocity integral) and regurgitant volume (21). A significant correlation ($r = 0.75$) was also found in the present study. Nevertheless, patterns of pulmonary venous blood flow are influenced by several factors, including regurgitant volume, left atrial pressure and compliance, left ventricular systolic and diastolic function, systolic blood pressure and peripheral vascular resistance, age and cardiac rhythm. Therefore, the complex interactions among factors governing pulmonary vein flow raise doubts about the wisdom of taking this isolated parameter as an index of mitral regurgitation.

The combination of these two parameters (LAfill and PVs%) has theoretical advantages because they integrate each other, representing two concomitant but independent phenomena occurring in the presence of mitral regurgitation. The use of an equation that included both these parameters allowed a close correlation with regurgitant volume as measured traditionally with Doppler echocardiography. The demonstration that an equation which involves the use of a single-plane atrial area instead of a biplane atrial area has comparable accuracy in estimation of the regurgitant volume is an important simplification of this method, because the time-consuming measurements, necessary for volume calculation, can be avoided. Furthermore, the accuracy of this second equation may enhance this method, because the new automatic border-detection technology can display a real-time atrial volume curve using the area variation, so that a rapid estimate of the regurgitant volume can be made.

**Study limitations.** The applicability of the method in patients with atrial fibrillation has not been evaluated, for few patients were enrolled. However, as with other quantitative methods, the presence of atrial fibrillation should not interfere with the results if multiple measurements are used. Systolic pulmonary vein flow is mainly determined by LV systolic function and by atrial relaxation. Therefore, atrial fibrillation influenced the amount of blood filling the atrium from the pulmonary veins decreasing PVs%. Nevertheless, LAfill provides a comprehensive summary of the blood filling the atrium independent of its origin (the mitral valve, if it is insufficient, or the pulmonary vein).

In this study only the right upper pulmonary vein velocity was obtained because transthoracic examination does not allow reliable detection of velocities from other pulmonary veins; therefore, the issue of the discordance between right and left pulmonary vein velocity could not be addressed. The main concern is that the different direction of the eccentric jet may determine discordant flow pattern in right and left pulmonary veins. A recent study (22) emphasized that a discordant pattern of pulmonary vein velocity is possible in mitral regurgitation, but the discordancy is not predictable from the jet direction; in fact, most of the patients with discordant pattern had central jets. For unknown reasons, when discordant right- and left-sided flow pattern existed, the right upper pulmonary vein displayed the more abnormal pattern. Furthermore, the use of different parameters in the multilinear regression equation should attenuate any error due to that discordance.

Although angiography has important limitations in grading mitral regurgitation (5), the lack of an angiographic control might be considered another limitation of our study. However, the two echocardiographic parameters (LAfill and PVs%) have already been validated separately, using angiographic correlation, in different studies (11,23).

Another limitation of this study is the underestimation in severe mitral regurgitation (Fig. 4), when systolic reversal flow is present in pulmonary veins. It is obvious because the negative velocity of the systolic reversal flow was not contemplated, and in this situation the parameter was considered zero by definition. Nevertheless, the high sensitivity of the equation in identifying severe mitral regurgitation allows us to consider this underestimation meaningless. It would probably represent a real limitation in acute severe mitral regurgitation, when the stiff atrium does not allow distension of its walls and makes the majority of the regurgitant blood move into the pulmonary veins. However, this was a pilot study to determine the feasibility and applicability of an alternative method in patients.
with chronic mitral regurgitation undergoing echocardiographic evaluation in a routine clinical setting.

**Conclusions.** A quantitation of mitral regurgitation is needed for better clinical management of patients. This study has shown that a simple and rapid quantitation of regurgitant volume in mitral regurgitation is reliably obtainable using left atrial filling volume and pulmonary vein flow velocity. This method might be enhanced by automatic atrial border-detection technology, which may provide a real-time atrial volume curve.

**References**


