

# Left atrial function assessed by real-time 3-dimensional echocardiography is related to right ventricular systolic pressure in chronic mitral regurgitation

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**Background** Left atrial (LA) volume is a prognostic index in chronic mitral regurgitation (MR). However, little is known about LA function in this setting. We hypothesized that LA dysfunction is related to pulmonary hypertension in chronic MR.

**Methods** Seventy-one patients with organic chronic MR who underwent real-time 3-dimensional transthoracic echocardiography (RT3DE) were studied. Left atrial volumes and peak passive and active LA emptying rates were obtained. Total LA emptying fraction was calculated as follows: [(maximum – minimum LA volume)/maximum LA volume] × 100. Similarly, active and passive LA emptying fractions were calculated. From transmitral flow, the peak early (E) and late (A) diastolic filling velocities and E/A ratio were obtained. The early (E') and late (A') diastolic myocardial velocities were obtained by tissue Doppler interrogation of mitral annulus.

**Results** Effective regurgitant orifice area (EROA) was  $0.57 \pm 0.29$  cm<sup>2</sup>. Right ventricular systolic pressure (RVSP) was measured in 57 patients and averaged  $37 \pm 13$  mm Hg. Patients with MR and high RVSP displayed higher minimum LA volume, E/A ratio, E/E' ratio, EROA, and MR volume, and lower A' velocity, peak active LA emptying rate, active LA emptying fraction, and total LA emptying fraction than patients with MR and normal RVSP. Multiple regression analysis revealed that EROA ( $r = 0.51$ ,  $P = .01$ ) active LA emptying fraction ( $r = -0.53$ ,  $P = .02$ ), E/E' ratio ( $r = 0.50$ ;  $P = .04$ ), and the lateral A' velocity ( $r = -0.46$ ;  $P = .003$ ) were independently correlated with RVSP.

**Conclusions** Left atrial function determined by RT3DE had significant correlation with RVSP in chronic MR, irrespective of MR severity. Thus, pulmonary hypertension in chronic MR may depend not only on MR severity but also on LA function. (*Am Heart J* 2009;158:309-16.)

Left atrial (LA) volume has been recognized as an independent prognostic index in diverse conditions, such as heart failure,<sup>1</sup> myocardial infarction,<sup>2,3</sup> and lone atrial fibrillation.<sup>4</sup> Moreover, LA enlargement has important prognostic implications in mitral regurgitation (MR). Left atrial dimension predicts atrial fibrillation occurrence both before<sup>5</sup> and after surgery<sup>6</sup> and survival after surgery.<sup>7</sup> As LA enlargement was identified as a prognostic index in MR, further studies used more accurate measurements of LA size. The LA volume measured by 2-dimensional echocardiography could predict the occurrence of atrial

fibrillation<sup>8</sup> and the combined end point of death or mitral surgery in MR.<sup>8</sup> However, LA function has not been addressed in such studies. Real-time 3-dimensional echocardiography (RT3DE) provides both reliable measurements of LA volume, when compared to magnetic resonance,<sup>9,10</sup> and LA time-volume curves, which can be used to estimate LA function.<sup>11,12</sup> The LA volume measured by RT3DE has been recently recognized as a predictor of clinical outcomes in heart failure.<sup>13</sup>

Pulmonary hypertension is a current criterion for mitral valve repair in asymptomatic patients with severe MR.<sup>14</sup> Furthermore, mitral valve repair is becoming more frequent in asymptomatic patients well before symptoms or left ventricular (LV) dysfunction may develop.<sup>15</sup> Therefore, it is critical to understand the factors involved in the hemodynamic deterioration in patients with chronic MR. The development of pulmonary hypertension in chronic MR is not entirely understood, and LA function may be an important contributor to this process. Therefore, we hypothesized that LA function may be related to pulmonary hypertension in chronic MR.

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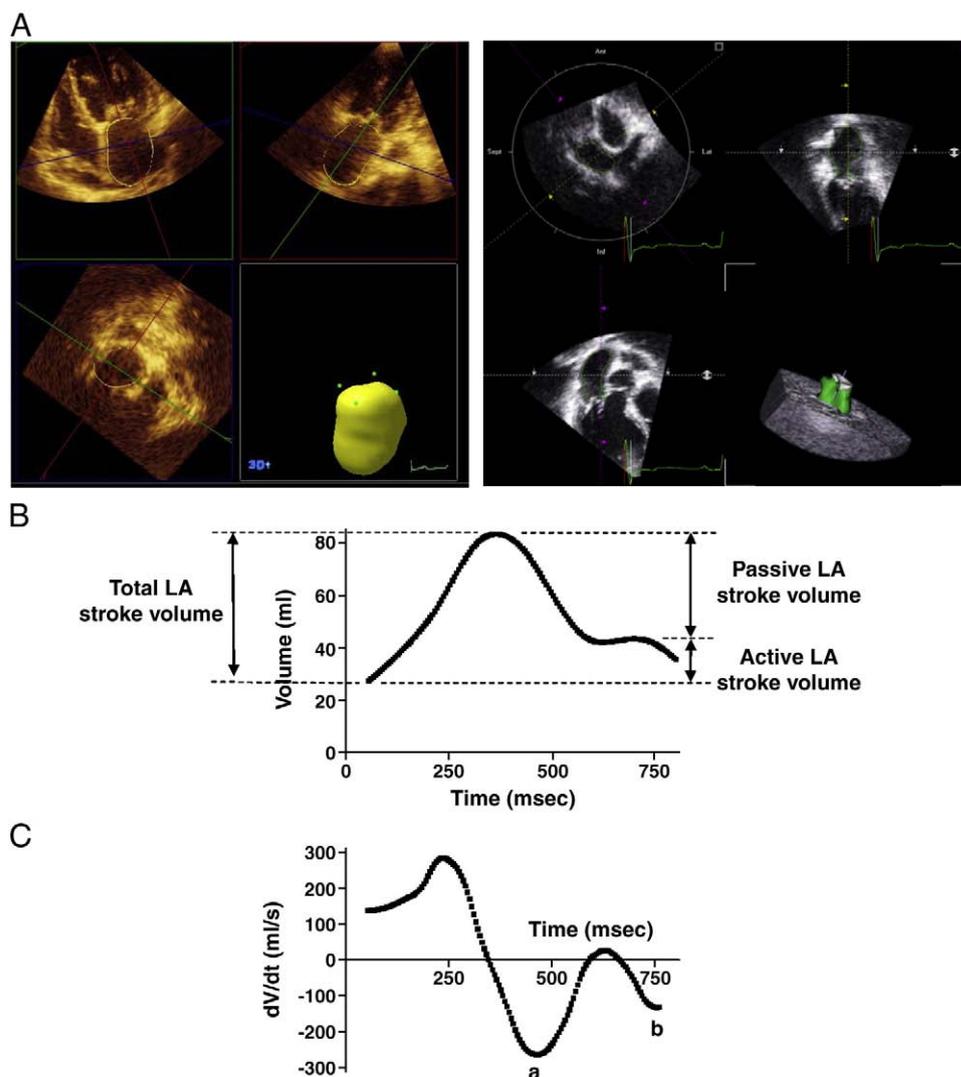
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Figure 1



RT3DE LA volume measurement. **A**, Quad screen display of the Q-Lab analysis software (left panel) and TomTec software (right panel) showing semiautomatic tracing of LA endocardial border for LA volume calculation. **B**, Representative example of LA time-volume curve derived from RT3DE. Note the definitions of total, passive, and active LA stroke volumes. **C**, Graph obtained by deriving the time-volume curve in **B**. The peak passive (**a**) and active (**b**) LA emptying rates represent the maximal slopes of time-volume curve of respective phases.

## Methods

### Patients

We retrospectively examined data from all consecutive adult patients with chronic isolated MR due to organic mitral valve disease who underwent RT3DE in our echocardiographic laboratory between January 2007 and December 2008. Within the study period, 104 patients who met eligibility criteria underwent RT3DE imaging. Of these, patients with any of previous valvular surgery ( $n = 2$ ), LV hypertrophy ( $n = 2$ ), atrial fibrillation ( $n = 4$ ), inadequate mitral inflow or tissue Doppler interrogation ( $n = 10$ ), concomitant aortic

regurgitation ( $n = 3$ ), or inadequate apical RT3DE imaging ( $n = 12$ ) were excluded from analysis. The data presented were abstracted from our echocardiography database that is approved by the Institutional Review Board for clinical research at Cleveland Clinic (Cleveland, OH).

### Echocardiography

Studies were performed through phased-array, commercially available, ultrasound systems (iE33, Philips, Andover, MA, or Vivid7, GE Medical Systems, Milwaukee, WI), equipped with 2.5 MHz phased-array and 2- to 4-MHz 4

matrix-array transducers. Cardiac dimensions were measured in accordance with the American Society of Echocardiography recommendations.<sup>16</sup> M-mode echocardiography was used to measure LA diameter and LV end-diastolic and end-systolic diameters. The LV ejection fraction was determined by modified Simpson's rule with images obtained from apical 4- and 2-chamber views. Pulsed wave Doppler was obtained in apical 4-chamber view, positioned at the mitral leaflet tips. From transmitral recordings, the peak early (E) and late (A) diastolic filling velocities, E/A ratio, and E-wave deceleration time were obtained. Right ventricular systolic pressure (RVSP) was derived from continuous wave Doppler interrogation of tricuspid regurgitation. Right atrial pressure was estimated on the basis of inferior vena cava size and inspiratory collapse, in accordance with the American Society of Echocardiography recommendations<sup>16</sup> and previous works of the literature.<sup>17,18</sup>

*Mitral valve prolapse* was defined as displacement of one or both leaflets into the LA beyond the mitral annulus level during systole. The severity of MR was assessed by quantitative Doppler by the proximal isovelocity surface area method.<sup>19</sup> Mitral regurgitation severity was also semiquantitatively assessed and classified into I to IV according to American Society of Echocardiography criteria.<sup>20</sup>

Tissue Doppler imaging of the mitral annulus level was obtained at the septal and lateral positions. Maximal early (E') and late (A') diastolic myocardial velocities were obtained. Echocardiograms were stored digitally and reviewed off-line with software (Prosolv Cardiovascular Analyzer, Problem Solving Concepts, Indianapolis, IN).

Real-time 3-dimensional echocardiography was performed in apical views. Three-dimensional LA images were taken by wide-angled acquisition (full-volume method) during end expiration. Off-line softwares (Q-lab system, Philips; 4D LV Cardio-view, TomTec, Munich, Germany) were used for displaying and quantifying 3-dimensional images. The LA volume was measured using a semiautomatic tracing of endocardial border at each frame during one cardiac cycle (Figure 1, A).<sup>21</sup> Automatic tracings were manually modified if correction was needed. Left atrial appendage and pulmonary vein entrance were excluded from LA volume calculations. Time-volume curves were obtained (Figure 1, B), and the maximal slope during passive and active LA emptying were expressed as peak passive and peak active LA emptying rates, respectively (Figure 1, C). From LA time-volume curves, maximum LA volume, minimum LA volume, and LA volume before LA contraction were determined. The following indexes of LA function were calculated according to previous studies.<sup>12,21</sup> Total LA emptying fraction was calculated as follows: [(maximum LA volume – minimum LA volume)/maximum LA volume] × 100. Active LA emptying fraction was calculated as follows: [(precontraction LA volume – minimum LA

**Table 1.** Clinical characteristics of study patients

	<b>Total (n = 71)</b>
Age (y)	56.5 ± 11.5
Body mass index (kg/m <sup>2</sup> )	24.5 ± 3.9
Male	51 (71.8%)
Etiologies:	
Mitral valve prolapse	64/71 (90%)
Anterior leaflet	4/64 (6.3%)
Posterior leaflet	29/64 (45.3%)
Bileaflet	31/64 (48.4%)
Flail	33/64 (51.6%)
Anterior leaflet	1/33 (3%)
Posterior leaflet	32/33 (97%)
Rheumatic disease	2/71 (3%)
Healed infective endocarditis	3/71 (4%)
Occlusive vasculopathy	1/71 (1.5%)
Fen-phen related valvular disease	1/71 (1.5%)

volume)/precontraction LA volume] × 100. Passive LA emptying fraction was calculated as follows: [(maximum LA volume – precontraction LA volume)/maximum LA volume] × 100.

### Statistical analysis

Calculations were done using commercially available statistical software (GraphPad Prism 3.02, GraphPad Software, La Jolla, CA, and MedCalc 9.2.0.2, MedCalc Software, Mariakerke, Belgium). Continuous variables were expressed as mean ± SD, and discrete variables were presented as percentages. All echocardiographic variables passed standard tests of normality (Kolmogorov-Smirnov test) allowing the use of parametric tests. Comparisons between patients with and without elevated RVSP were performed by unpaired Student *t* test. Each variable was tested for correlation with RVSP by simple linear regression analysis (Pearson's correlation). All variables with significant univariate association with RVSP were entered in a multivariate stepwise regression analysis with RVSP as the dependent variable. Intraobserver and interobserver variabilities were carried out by Bland-Altman analysis and concordance correlation coefficient analysis. The null hypothesis was rejected at *P* < .05. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper, and its final contents.

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## Results

### Patient characteristics

Population characteristics are summarized in Table 1. The population studied consisted of 71 patients, mostly male and middle-aged. Most patients presented with mitral valve prolapse involving the posterior leaflet or both anterior and

**Table II.** Two-dimensional echocardiographic characteristics of study patients

	Total (n = 71)	Normal RVSP (n = 32)	High RVSP (n = 25)
LA diameter (cm)	4.70 ± 0.67	4.57 ± 0.77	4.89 ± 0.59
LA area (cm <sup>2</sup> )	29.2 ± 6.4	28.4 ± 6.8	30.5 ± 6.0
LV end-diastolic diameter (cm)	5.79 ± 0.63	5.75 ± 0.61	5.72 ± 0.67
LV end-systolic diameter (cm)	3.25 ± 0.61	3.24 ± 0.63	3.23 ± 0.64
LV end-diastolic volume (mL/m <sup>2</sup> )	78.3 ± 19.0	75.4 ± 17.8	83.3 ± 20.9
LV end-systolic volume (mL/m <sup>2</sup> )	18.5 ± 7.1	18.7 ± 7.1	17.9 ± 7.1
LV ejection fraction (%)	76.2 ± 7.1	75.0 ± 7.3	78.4 ± 6.7
E (cm/s)	122.0 ± 33.2	107.7 ± 29.8	140.0 ± 31.9*
A (cm/s)	74.3 ± 22.4	70.5 ± 18.5	78.9 ± 26.5
E/A ratio	1.77 ± 0.72	1.55 ± 0.49	2.07 ± 0.92†
E-wave deceleration time (ms)	198.4 ± 56.9	191.0 ± 58.2	208.7 ± 55.9
E' average (cm/s)	10.4 ± 2.9	10.1 ± 2.6	10.2 ± 2.9
E/E' ratio	12.5 ± 5.0	11.1 ± 3.4	14.6 ± 5.9†
Septal A' (cm/s)	9.7 ± 2.9	10.6 ± 2.8	8.2 ± 2.6†
Lateral A' (cm/s)	10.5 ± 3.3	11.7 ± 2.9	8.8 ± 3.2*
EROA (cm <sup>2</sup> )	0.57 ± 0.29	0.45 ± 0.22	0.79 ± 0.28*
MR volume (mL)	79.5 ± 38.9	66.7 ± 36.8	106.7 ± 31.7†

\*  $P < .001$  versus normal RVSP.†  $P < .01$  versus normal RVSP.

posterior leaflets. In almost half of the patients, a flail of at least one of the scallops of the posterior leaflet was present (Table D).

### Two-dimensional echocardiographic characteristics

All patients had LV ejection fraction >50%. Mitral regurgitation was graded as follows: II, 4; II to III, 3; III, 16; III to IV, 16; and IV, 32. Effective regurgitant orifice area (EROA) was  $0.57 \pm 0.29$  cm<sup>2</sup>. Right ventricular systolic pressure was measurable from adequate tricuspid regurgitation spectra in 57 patients and averaged  $37.3 \pm 12.9$  mm Hg. There were 25 patients with elevated RVSP (>35 mm Hg) according to current criteria.<sup>18</sup> There was no significant difference in gender proportion between patients with elevated RVSP (18 males/7 females) and normal RVSP (22 males/10 females,  $P = .79$ ). Patients with elevated RVSP had greater EROA and MR volume than patients with normal RVSP. They also had larger E/A ratio, E-wave velocity, and E/E' ratio and lower lateral and septal A' than patients with normal RVSP (Table II). There was no significant difference regarding age ( $57.4 \pm 11.8$  vs  $58.5 \pm 10.8$  years) or body mass index ( $24.0 \pm 4.6$  vs  $24.2 \pm 3.2$  kg/m<sup>2</sup>) between patients with and without elevated RVSP.

### Left atrial function by RT3DE

**Left atrial volume.** Minimum LA volume was larger in patients with elevated RVSP than in patients with normal RVSP (Table III, Figure 2).

**Table III.** RT3DE characteristics of study patients

	Total (n = 71)	Normal RVSP (n = 32)	High RVSP (n = 25)
Maximum LA volume (mL/m <sup>2</sup> )	49.9 ± 15.8	47.5 ± 15.1	53.4 ± 17.2
Minimum LA volume (mL/m <sup>2</sup> )	26.7 ± 11.9	23.2 ± 10.4	31.9 ± 12.7*
Precontraction LA volume (mL/m <sup>2</sup> )	35.4 ± 12.7	32.8 ± 12.5	38.6 ± 13.6
Peak passive LA emptying rate (mL/s)	-224 ± 99	-234 ± 87	-215 ± 102
Peak active LA emptying rate (mL/s)	-169 ± 80	-177 ± 77	-134 ± 67†
Total LA emptying fraction (%)	47.8 ± 12.5	52.7 ± 11.0	41.1 ± 10.9‡
Active LA emptying fraction (%)	27.0 ± 11.0	30.7 ± 10.2	20.3 ± 9.7‡
Passive LA emptying fraction (%)	29.4 ± 9.8	31.9 ± 9.9	27.3 ± 8.1

\*  $P < .01$  versus normal RVSP.†  $P < .05$  versus normal RVSP.‡  $P < .001$  versus normal RVSP.

The LA volumes showed significant correlations with LV size, diastolic parameters, and MR degree. Maximum LA volume presented positive correlations with LV end-diastolic volume ( $r = 0.56$ ,  $P < .0001$ ), E-wave velocity ( $r = 0.37$ ,  $P = .001$ ), E/A ratio ( $r = 0.34$ ,  $P = .004$ ), EROA ( $r = 0.41$ ,  $P = .0006$ ), and MR volume ( $r = 0.42$ ,  $P = .0004$ ).

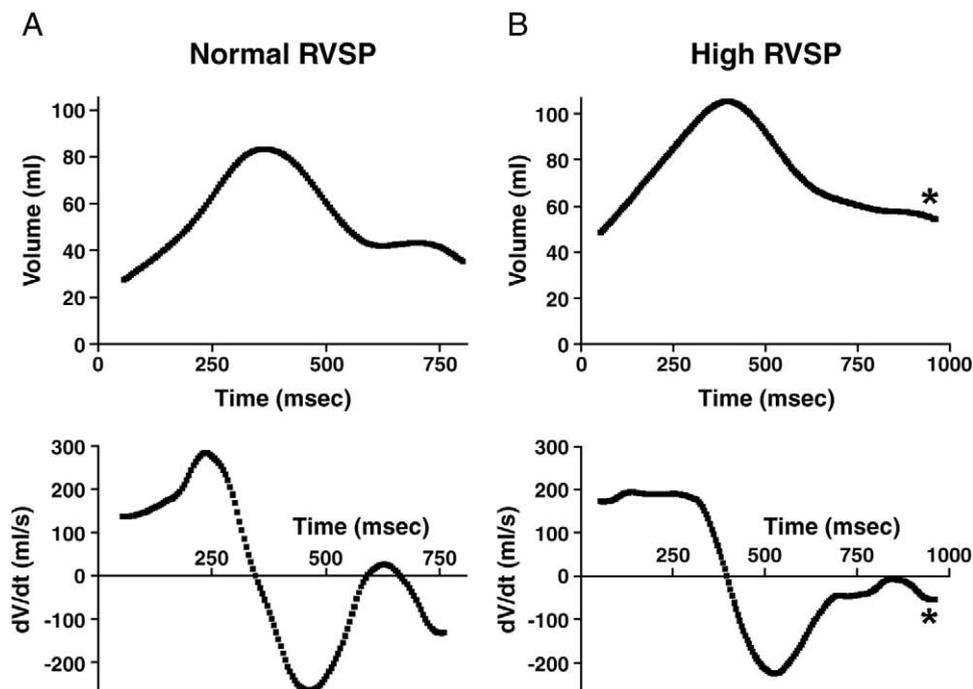
**Left atrial booster pump function.** The LA emptying indexes (active LA emptying fraction and peak active LA emptying rate) were decreased in patients with elevated RVSP compared with patients with normal RVSP (Table III, Figure 2).

The LA emptying indexes showed significant correlations with diastolic parameters and MR degree. Active LA emptying fraction presented negative correlation with LV end-diastolic volume ( $r = -0.31$ ,  $P = .009$ ), E-wave velocity ( $r = -0.40$ ,  $P = .0007$ ), E/A ratio ( $r = -0.38$ ,  $P = .001$ ), E/E' ratio ( $r = -0.34$ ,  $P = .005$ ), EROA ( $r = -0.42$ ,  $P = .0004$ ), and MR volume ( $r = -0.36$ ,  $P = .003$ ). Peak active LA emptying rate presented positive correlations with both septal ( $r = 0.38$ ,  $P = .001$ ) and lateral A' ( $r = 0.35$ ,  $P = .004$ ).

**Left atrial conduit function.** Passive LA emptying fraction and peak passive LA emptying rate were similar between patients with and without high RVSP (Table III, Figure 2).

The LA conduit function indexes showed significant correlations with LV size, tissue Doppler, and diastolic parameters. Passive LA emptying fraction presented positive correlations with E' ( $r = 0.32$ ,  $P = .008$ ) and negative correlation with E/E' ratio ( $r = -0.35$ ,  $P = .003$ ). Peak passive LA emptying rate presented positive correlations with LV end-diastolic ( $r = 0.47$ ,  $P < .0001$ ) and end-systolic ( $r = 0.31$ ,  $P = .008$ ) volumes, E/A ratio ( $r = 0.33$ ,  $P = .005$ ), E' ( $r = 0.51$ ,  $P < .0001$ ), EROA ( $r = 0.27$ ,  $P = .03$ ), and MR volume ( $r = 0.30$ ,  $P = .01$ ), and negative correlation with E/E' ratio ( $r = -0.29$ ,  $P = .01$ ).

**Figure 2**



LA time-volume curves. Representative examples of LA time-volume curves (upper panel) and derived dV/dt curves (bottom panel) for patients with normal RVSP (A) and elevated RVSP (B). Note the flatter aspect of the terminal part (\*) of the LA time-volume curve of the patient with high RVSP indicating a lower active LA emptying fraction in this patient. This difference is also highlighted by the reduced peak active LA emptying rate shown in the bottom panel (\*).

**Left atrial reservoir function.** Total LA emptying fraction was lower in patients with elevated RVSP (Table III, Figure 2).

Total LA emptying fraction presented positive correlations with both septal ( $r = 0.34$ ,  $P = .004$ ) and lateral  $A'$  ( $r = 0.37$ ,  $P = .002$ ) and negative correlation with E-wave velocity ( $r = -0.32$ ,  $P = .007$ ), E/A ratio ( $r = -0.34$ ,  $P = .004$ ), E/E' ratio ( $r = -0.39$ ,  $P = .001$ ), and EROA ( $r = -0.29$ ,  $P = .02$ ).

#### Correlation between echocardiographic parameters and RVSP

Simple linear regression analysis revealed significant positive correlations between RVSP and EROA, MR volume, E-wave velocity, E/E' ratio, E/A ratio, end-diastolic LV volume, and LA diameter, and negative correlations between RVSP and both septal and lateral  $A'$  (Table IV, Figure 3). There was no significant relationship with age or body mass index.

#### Correlation between LA parameters measured by RT3DE and RVSP

Simple linear regression analysis revealed significant positive correlation between RVSP and LA volumes and negative correlations between RVSP and total, active, and

passive LA emptying fractions, and peak active LA emptying rate, (Table IV, Figure 3).

Multiple stepwise regression analysis including 2-dimensional echocardiographic and RT3DE parameters with significant univariate association with RVSP revealed that EROA ( $r = 0.51$ ,  $P = .01$ ), active LA emptying fraction ( $r = -0.53$ ,  $P = .02$ ), E/E' ratio ( $r = 0.50$ ,  $P = .04$ ), and lateral  $A'$  velocity ( $-0.46$ ,  $P = .003$ ) independently correlated with RVSP. Together their variance ( $R^2$ ) accounted for 56% of the variance of the RVSP.

#### Interobserver and intraobserver analysis

There were good interobserver and intraobserver agreements for LA volumes as evaluated by both concordance correlation coefficient and Bland-Altman analysis. The intraobserver correlation coefficient yielded values of 0.98, 0.98, and 0.99 for maximum LA volume, minimum LA volume, and precontraction LA volume, respectively. The interobserver correlation coefficient yielded values of 0.96, 0.99, and 0.98 for maximum LA volume, minimum LA volume, and precontraction LA volume, respectively.

The mean difference for intraobserver agreement ( $\pm 1.96$  SDs) was  $-3.0$  mL ( $\pm 13.3$ ),  $0.5$  mL ( $\pm 11.8$ ), and  $-1.0$  mL ( $\pm 8.9$ ) for maximum LA volume, minimum LA

**Table IV.** Univariate regression analysis—echocardiographic parameters and RVSP

	<i>r</i>	<i>P</i>
LA	0.33	.01
LA area	0.24	NS
LV end-diastolic volume	0.39	.003
LV end-systolic volume	0.08	NS
LV ejection fraction	0.21	NS
E	0.49	.0001
A	0.06	NS
E/A ratio	0.34	.01
E-wave deceleration time	0.06	NS
E' average	-0.09	NS
E/E' ratio	0.51	<.0001
Septal A'	-0.35	.008
Lateral A'	-0.45	.0007
EROA	0.52	<.0001
MR volume	0.45	.0005
Maximum LA volume	0.29	.03
Minimum LA volume	0.45	.0005
Precontraction LA volume	0.34	.01
Peak passive LA emptying rate	-0.09	NS
Peak active LA emptying rate	-0.31	.02
Total LA emptying fraction	-0.50	<.0001
Active LA emptying fraction	-0.52	<.0001
Passive LA emptying fraction	-0.29	.03

NS, Not significant.

volume, and precontraction LA volume, respectively. The mean difference for interobserver agreement was -3.5 mL ( $\pm 19.9$ ), -1.6 mL ( $\pm 6.5$ ), and -2.0 mL ( $\pm 9.6$ ) for maximum LA volume, minimum LA volume, and precontraction LA volume, respectively.

## Discussion

In this article, we show that LA function is an important correlate of RVSP in chronic MR, along with the MR severity (reflected by EROA) and LA pressure (reflected by E/E'). Decreased LA function was correlated with elevated RVSP, irrespective of MR severity. Among all LA function parameters studied, active LA emptying fraction and lateral A' velocity had the best correlation with RVSP.

### Importance of LA volume measurement and advantages of RT3DE

Interest in investigating LA size and function has increased in recent years as LA volume has emerged as a prognostic index in conditions as diverse as heart failure,<sup>1</sup> myocardial infarction,<sup>2</sup> and lone atrial fibrillation.<sup>4</sup> The LA volume has been recognized as a more powerful predictor than LA diameter or area.<sup>22</sup> In chronic MR, LA enlargement has important prognostic implications, as it can predict atrial fibrillation occurrence,<sup>5,6,8</sup> the combined end point of death or mitral surgery,<sup>8</sup> and postoperative survival.<sup>7</sup>

In all previously mentioned studies, LA volumes were analyzed by 2-dimensional echocardiography. However,

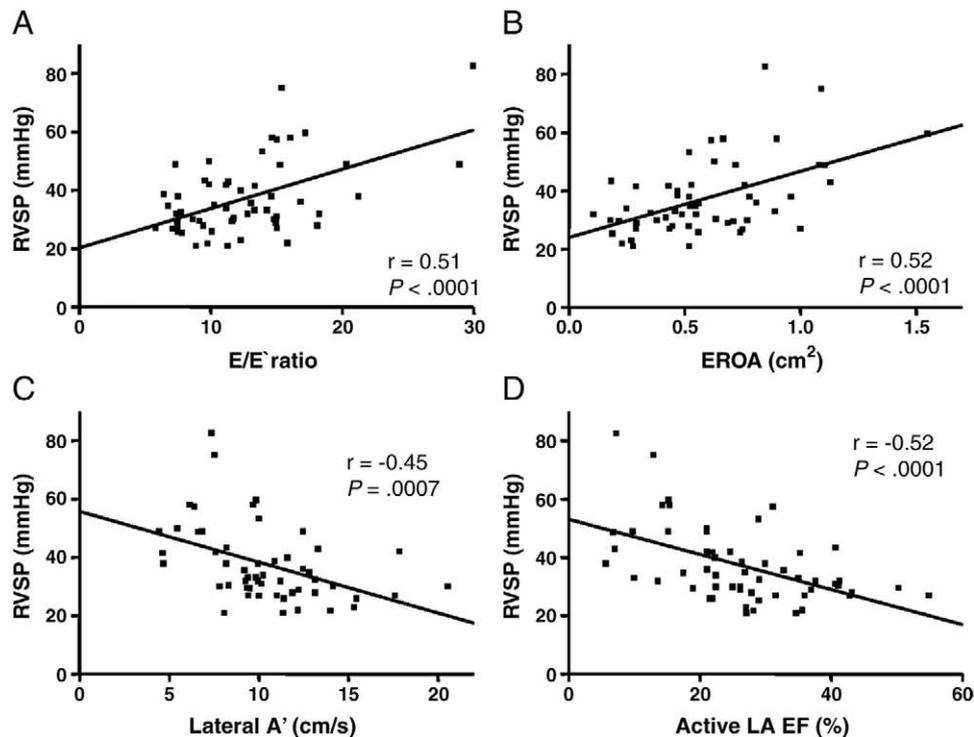
this method assumes a geometrical model and depends on mathematical calculations to determine the volume of a nonsymmetrical chamber. Furthermore, the LA can be distorted by its own dilation<sup>13</sup> or dilation of neighboring structures. Owing to this complex anatomy, LA volume may be better assessed by RT3DE than by 2-dimensional echocardiography.<sup>13,23-26</sup> The LA volume measurement by RT3DE does not require geometrical assumptions and avoids errors due to foreshortening that may occur in 2-dimensional measurements. In consequence, the correlation between LA volume measured by these 2 methods are modest,<sup>25</sup> and 2-dimensional echocardiography underestimates LA volumes.<sup>13,26</sup> In addition, 3-dimensional LA volume measurements were reliable when compared to magnetic resonance imaging<sup>9,10,24</sup> and had a better correlation with magnetic resonance than 1- or 2-dimensional LA volume estimates.<sup>24</sup> Moreover, LA volume measurement by RT3DE presents less test-retest variation<sup>23</sup> and interobserver and intraobserver variability<sup>13,23</sup> than LA volume measured by 2-dimensional echocardiography, making it more suitable for sequential analysis. We showed excellent interobserver and intraobserver agreements for LA volume measured by RT3DE. Therefore, we decided to use RT3DE to analyze LA volumes and function in our study.

### Chronic MR and pulmonary hypertension

Pulmonary hypertension in isolated chronic MR is a long recognized condition, and its importance as a signal of a patient's hemodynamic deterioration is emphasized by that pulmonary hypertension is a current criterion for mitral valve repair in patients with asymptomatic MR.<sup>14</sup> In a previous study where pulmonary hypertension was evaluated by cardiac catheterization in patients with MR with preserved LV systolic function, high mean pulmonary capillary wedge pressure, and pulmonary arteriole resistance were the only variables independently differing between patients with and without elevated RVSP.<sup>27</sup> The echocardiographic parameters studied were not significantly different between the 2 groups, but only LA and LV diameters were studied in this last study.<sup>27</sup>

The LA function is important in adaptation of the heart to the volume burden caused by MR. In chronic severe MR, the LA undergoes remodeling and dilation due to volume overload. However, LA remodeling is also associated with changes in LA function, secondary to structural, functional, metabolic, and neurohormonal consequences.<sup>28</sup> Our data demonstrated that not only the MR severity but also the LA function may be important to the development of pulmonary hypertension in chronic MR. Our multiple regression analysis showed that both active LA emptying fraction and lateral A' velocity had independent influence on RVSP, irrespective of the MR severity. Patients with high RVSP presented depressed LA contractile function, as active LA emptying fraction, peak

**Figure 3**



Correlations between echocardiographic parameters and RVSP. Right ventricular systolic pressure displayed independent positive correlations with E/E' ratio (A), and EROA (B); and negative correlations with lateral A' (C), and active LA EF (D). EF, Emptying fraction.

active LA emptying rate, and A' velocity were decreased in patients with high RVSP. Interestingly, lateral A' velocity was a RVSP correlate almost as good as the active LA emptying fraction. Although A' velocity may be affected by Doppler angle, this parameter is easier to measure than any 3-dimensional variables. Patients with elevated RVSP also presented high E/E' ratio, which indicated that they likely have elevated LA pressure, as the E/E' ratio has been reported to be a reliable predictor of LV end-diastolic pressure in patients with MR.<sup>29</sup> Furthermore, the active LA emptying fraction was inversely related with the E/E' ratio. Therefore, it is speculated that the depressed contractile LA function may contribute to a further rise in the LA pressure in patients with MR that may aggravate the pulmonary venous congestion and the secondary pulmonary artery hypertension.

#### Limitations

The retrospective nature of this study and the selection criteria used limit the conclusions of this study to patients with chronic organic MR in sinus rhythm. The extrapolation of these results to populations with functional MR or in atrial fibrillation remains to be explored.

The LA tracing may be problematic owing to the LA being in the far field. However, most 3-dimensional images

analyzed in our study were clear enough to allow tracing of LA border in all planes.

In the present study, only 56% of the variation in RVSP in patients with MR was explained by the variables analyzed. This may be due not only to the known variability of echocardiographic measurements but also to other factors not included in the model, as concurrent pulmonary disease, that may influence RVSP.

#### Conclusions

The LA function determined by RT3DE is an important correlate of RVSP in chronic MR, along with the MR severity (reflected by EROA) and LA pressure (reflected by E/E'). Active LA emptying fraction and A' velocity were inversely related to RVSP, indicating that LA contractile dysfunction may contribute to pulmonary congestion and development of pulmonary hypertension. Further studies are warranted to determine the prognostic significance of LA function in chronic MR.

#### References

1. Rossi A, Ciccoira M, Zanolla L, et al. Determinants and prognostic value of left atrial volume in patients with dilated cardiomyopathy. *J Am Coll Cardiol* 2002;40:1425-30.

2. Beinart R, Boyko V, Schwammenthal E, et al. Long-term prognostic significance of left atrial volume in acute myocardial infarction. *J Am Coll Cardiol* 2004;44:327-34.
3. Moller JE, Hillis GS, Oh JK, et al. Left atrial volume: a powerful predictor of survival after acute myocardial infarction. *Circulation* 2003;107:2207-12.
4. Osranek M, Bursi F, Bailey KR, et al. Left atrial volume predicts cardiovascular events in patients originally diagnosed with lone atrial fibrillation: three-decade follow-up. *Eur Heart J* 2005;26:2556-61.
5. Grigioni F, Avierinos JF, Ling LH, et al. Atrial fibrillation complicating the course of degenerative mitral regurgitation: determinants and long-term outcome. *J Am Coll Cardiol* 2002;40:84-92.
6. Kernis SJ, Nkomo VT, Messika-Zeitoun D, et al. Atrial fibrillation after surgical correction of mitral regurgitation in sinus rhythm: incidence, outcome, and determinants. *Circulation* 2004;110:2320-5.
7. Reed D, Abbott RD, Smucker ML, et al. Prediction of outcome after mitral valve replacement in patients with symptomatic chronic mitral regurgitation. The importance of left atrial size. *Circulation* 1991;84:23-34.
8. Messika-Zeitoun D, Bellamy M, Avierinos JF, et al. Left atrial remodelling in mitral regurgitation-methodologic approach, physiological determinants, and outcome implications: a prospective quantitative Doppler-echocardiographic and electron beam-computed tomographic study. *Eur Heart J* 2007;28:1773-81.
9. Bauer F, Shiota T, White RD, et al. Determinant of left atrial dilation in patients with hypertrophic cardiomyopathy: a real-time 3-dimensional echocardiographic study. *J Am Soc Echocardiogr* 2004;17:968-75.
10. Li F, Wang Q, Yao GH, et al. Impact of the number of image planes of real-time three-dimensional echocardiography on the accuracy of left atrial and ventricular volume measurements. *Ultrasound Med Biol* 2008;34:40-6.
11. Shin MS, Fukuda S, Song JM, et al. Relationship between left atrial and left ventricular function in hypertrophic cardiomyopathy: a real-time 3-dimensional echocardiographic study. *J Am Soc Echocardiogr* 2006;19:796-801.
12. Poutanen T, Jokinen E, Sairanen H, et al. Left atrial and left ventricular function in healthy children and young adults assessed by three dimensional echocardiography. *Heart* 2003;89:544-9.
13. Suh IW, Song JM, Lee EY, et al. Left atrial volume measured by real-time 3-dimensional echocardiography predicts clinical outcomes in patients with severe left ventricular dysfunction and in sinus rhythm. *J Am Soc Echocardiogr* 2008;21:439-45.
14. Bonow RO, Carabello BA, Kanu C, et al. ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (writing committee to revise the 1998 Guidelines for the Management of Patients With Valvular Heart Disease): developed in collaboration with the Society of Cardiovascular Anesthesiologists: endorsed by the Society for Cardiovascular Angiography and Interventions and the Society of Thoracic Surgeons. *Circulation* 2006;114:e84-e231.
15. Enriquez-Sarano M, Avierinos JF, Messika-Zeitoun D, et al. Quantitative determinants of the outcome of asymptomatic mitral regurgitation. *N Engl J Med* 2005;352:875-83.
16. Lang RM, Bierig M, Devereux RB, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr* 2005;18:1440-63.
17. Ommen SR, Nishimura RA, Hurrell DG, et al. Assessment of right atrial pressure with 2-dimensional and Doppler echocardiography: a simultaneous catheterization and echocardiographic study. *Mayo Clin Proc* 2000;75:24-9.
18. Barst RJ, McGoon M, Torbicki A, et al. Diagnosis and differential assessment of pulmonary arterial hypertension. *J Am Coll Cardiol* 2004;43(12 Suppl S):40S-7S.
19. Enriquez-Sarano M, Miller Jr FA, Hayes SN, et al. Effective mitral regurgitant orifice area: clinical use and pitfalls of the proximal isovelocity surface area method. *J Am Coll Cardiol* 1995;25:703-9.
20. Zoghbi WA, Enriquez-Sarano M, Foster E, et al. Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography. *J Am Soc Echocardiogr* 2003;16:777-802.
21. Anwar AM, Soliman OI, Geleijnse ML, et al. Assessment of left atrial volume and function by real-time three-dimensional echocardiography. *Int J Cardiol* 2008;123:155-61.
22. Tsang TS, Abhayaratna WP, Barnes ME, et al. Prediction of cardiovascular outcomes with left atrial size: is volume superior to area or diameter. *J Am Coll Cardiol* 2006;47:1018-23.
23. Jenkins C, Bricknell K, Marwick TH. Use of real-time three-dimensional echocardiography to measure left atrial volume: comparison with other echocardiographic techniques. *J Am Soc Echocardiogr* 2005;18:991-7.
24. Keller AM, Gopal AS, King DL. Left and right atrial volume by freehand three-dimensional echocardiography: in vivo validation using magnetic resonance imaging. *Eur J Echocardiogr* 2000;1:55-65.
25. Muller H, Burri H, Shah D, et al. Evaluation of left atrial size in patients with atrial arrhythmias: comparison of standard 2D versus real time 3D echocardiography. *Echocardiography* 2007;24:960-6.
26. Maddukuri PV, Vieira ML, DeCastro S, et al. What is the best approach for the assessment of left atrial size? Comparison of various unidimensional and two-dimensional parameters with three-dimensional echocardiographically determined left atrial volume. *J Am Soc Echocardiogr* 2006;19:1026-32.
27. Alexopoulos D, Lazzam C, Borrico S, et al. Isolated chronic mitral regurgitation with preserved systolic left ventricular function and severe pulmonary hypertension. *J Am Coll Cardiol* 1989;14:319-22.
28. Casclang-Verzosa G, Gersh BJ, Tsang TS. Structural and functional remodeling of the left atrium: clinical and therapeutic implications for atrial fibrillation. *J Am Coll Cardiol* 2008;51:1-11.
29. Agricola E, Galderisi M, Oppizzi M, et al. Doppler tissue imaging: a reliable method for estimation of left ventricular filling pressure in patients with mitral regurgitation. *Am Heart J* 2005;150:610-5.