Noninvasive Assessment of Left Atrial Maximum dP/dt by a Combination of Transmitral and Pulmonary Venous Flow

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The left atrium (LA) actively contracts against left ventricular (LV) diastolic pressure and expels blood to the left ventricle. It has been noted that LA contraction makes a significant contribution to maintaining cardiac output, especially in patients with LV dysfunction (1–3). Thus, the clinical assessment of LA systolic function has been an important subject. However, characterization of LA systolic function is clinically difficult because it requires simultaneous measurements of LA volume and pressure. Therefore, in part by a Grant-in-Aid from the American Heart Association Northeast Ohio Affiliate.

OBJECTIVES
The study assessed whether hemodynamic parameters of left atrial (LA) systolic function could be estimated noninvasively using Doppler echocardiography.

BACKGROUND
Left atrial systolic function is an important aspect of cardiac function. Doppler echocardiography can measure changes in LA volume, but has not been shown to relate to hemodynamic parameters such as the maximal value of the first derivative of the pressure (LA dP/dtmax).

METHODS
Eighteen patients in sinus rhythm were studied immediately before and after open heart surgery using simultaneous LA pressure measurements and intraoperative transesophageal echocardiography. Left atrial pressure was measured with a micromanometer catheter, and LA dP/dtmax during atrial contraction was obtained. Transmitral and pulmonary venous flow were recorded by pulsed Doppler echocardiography. Peak velocity, and mean acceleration and deceleration, and the time-velocity integral of each flow during atrial contraction was measured. The initial eight patients served as the study group to derive a multilinear regression equation to estimate LA dP/dtmax from Doppler parameters, and the latter 10 patients served as the test group to validate the equation. A previously validated numeric model was used to confirm these results.

RESULTS
In the study group, LA dP/dt max showed a linear relation with LA pressure before atrial contraction (r = 0.80, p < 0.005), confirming the presence of the Frank-Starling mechanism in the LA. Among transmitral flow parameters, mean acceleration showed the strongest correlation with LA dP/dtmax (r = 0.78, p < 0.001). Among pulmonary venous flow parameters, no single parameter was sufficient to estimate LA dP/dtmax with an r² > 0.30. By stepwise and multiple linear regression analysis, LA dP/dt max was best described as follows: LA dP/dt max = 0.1 M-AC + 1.8 P-V - 4.1; r = 0.88, p < 0.0001, where M-AC is the mean acceleration of transmitral flow and P-V is the peak velocity of pulmonary venous flow during atrial contraction. This equation was tested in the latter 10 patients of the test group. Predicted and measured LA dP/dtmax correlated well (r = 0.90, p < 0.0001). Numerical simulation verified that this relationship held across a wide range of atrial elastance, ventricular relaxation and systolic function, with LA dP/dtmax predicted by the above equation with r = 0.94.

CONCLUSIONS
A combination of transmitral and pulmonary venous flow parameters can provide a hemodynamic assessment of LA systolic function. (J Am Coll Cardiol 1999;34:795–801) © 1999 by the American College of Cardiology
We studied (intraoperatively) 18 patients with sinus rhythm undergoing open-heart surgery. There were 14 men and 4 women, aged 38 to 77 (mean 62 ± 12 years). Fourteen patients underwent coronary artery bypass grafting surgery, two patients had mitral valve replacement for mitral regurgitation, one of whom had concomitant coronary artery bypass grafting surgery, one patient had the maze procedure for intractable paroxysmal atrial fibrillation and one patient underwent an insertion of an implantable LV assist device for endstage heart failure. None had mitral stenosis. Patients were separated into two groups. The data obtained from the first eight patients were used to assess the relationship between LA dP/dt max and Doppler parameters and to generate an equation for estimation of LA dP/dt max. The equation was subsequently tested in the latter 10 patients. The study protocol was approved by the Institutional Review Board of the Cleveland Clinic Foundation and informed consent was obtained from all patients.

**METHODS**

**Study population.** We studied (intraoperatively) 18 patients with sinus rhythm undergoing open-heart surgery. There were 14 men and 4 women, aged 38 to 77 (mean 62 ± 12 years). Fourteen patients underwent coronary artery bypass grafting surgery, two patients had mitral valve replacement for mitral regurgitation, one of whom had concomitant coronary artery bypass grafting surgery, one patient had the maze procedure for intractable paroxysmal atrial fibrillation and one patient underwent an insertion of an implantable LV assist device for endstage heart failure. None had mitral stenosis. Patients were separated into two groups. The data obtained from the first eight patients were used to assess the relationship between LA dP/dt max and Doppler parameters and to generate an equation for estimation of LA dP/dt max. The equation was subsequently tested in the latter 10 patients. The study protocol was approved by the Institutional Review Board of the Cleveland Clinic Foundation and informed consent was obtained from all patients.

**Measurements.** We measured high-fidelity LA pressure using a micromanometer-tipped catheter (Millar MicroTip model SPC-751, Millar Instruments, Houston, Texas) in the operating room. After calibrating relative to atmospheric pressure, the catheter was inserted from the right upper pulmonary vein into the LA and LA pressure was obtained. Pressure waveforms were digitized at 1,000 Hz and transferred to a personal computer (Macintosh Quadra 950, Apple Computer, Cupertino, California) for off-line analysis. Intraoperative transesophageal echocardiography was performed with a commercially available echocardiographic system (Hewlett-Packard SONOS OR and SONOS 1500 [Hewlett-Packard, Andover, Massachusetts] or ACUSON 128XP [Acuson, Mountain View, California]) and a 5-MHz phased-array transducer. Transmitral and left upper pulmonary venous flow velocities were recorded using pulsed Doppler echocardiography with simultaneous pressure measurements and stored to optical disk in TIFF-based format. The Doppler sample volume was positioned at the tips of the mitral leaflets for recording transmitral flow velocity and at 1 cm beyond the pulmonary vein orifice to the LA for recording pulmonary venous flow velocity. A timing signal was generated and stored simultaneously with pressure and Doppler recordings to insure temporal alignment of pressure waveforms and Doppler velocity spectra. Pressure and ultrasound measurements were obtained under different loading conditions induced by partial cardiopulmonary bypass, resulting in a total of 17 data sets from the initial 8 patients and a total of 25 data sets from the latter 10 patients of the test group. Secondary to hemodynamic instability and concern for patient safety, a single measurement was performed in one patient in the test group. All measurements were done at end-expiration with ventilation suspended after pericardiectomy (within a pericardial cradle).

**Analysis.** Left atrial pressure just before atrial contraction was measured as a substitute for a preload index of LA contraction. Left atrial pressure was differentiated and the maximal value of its first derivative was obtained as an index of LA systolic function (LA dP/dt max) (Fig. 1). Peak velocity, mean acceleration and deceleration and time-velocity integral of the flow during atrial contraction were obtained from both transmitral flow (A wave) and pulmonary venous flow (AR wave). Discrimination of transmitral early wave and A wave was possible in all measurements. An average of five consecutive beats in each loading condition was used for analysis. Data were analyzed in a blinded fashion.

**Mathematical modeling.** Using a previously described and clinically verified mathematical model of the cardiovascular system (8), the relationship between pulmonary venous and transmitral flow characteristics and left atrial contractility was also examined to verify experimental results. In brief, our model used 24 first-order differential equations to simulate pressure, volume and flow throughout the heart.
and vessels, implemented in the LabView programming environment (National Instruments, Austin, Texas) on a 200-MHz MMX Pentium based computer. For 126 different conditions of LA systolic elastance (0.3–0.5 mm Hg/ml), diastolic elastance (0.12–0.2 mm Hg/ml), ventricular t (35–90 msec) and ventricular systolic elastance (2–8 mm Hg/ml), instantaneous pulmonary venous, LA and LV pressures, volumes and flows were derived in 5 msec intervals for analysis. Left atrial pressure, LA dP/dtmax and pulmonary venous and transmitral velocity waveform characteristics were determined in methods similar to those obtained in the patients previously described.

Statistical analysis. Data are expressed as mean ± SD. All statistical analyses were done using statistical analysis software available for a Macintosh personal computer (StatView 4.0, Abacus Concepts Inc., Berkeley, California or SPSS 4.0, SPSS Inc., Chicago, Illinois). Comparison of Doppler parameters and LA pressure parameters was done using linear regression analysis. Similar regression analysis was performed on the results of numerical modeling to correlate different parameters of transmitral and pulmonary venous flow to LA dP/dtmax. Stepwise and multivariate regression analyses were used to identify the best determinants of LA dP/dtmax among all ultrasound parameters. The validity of estimated LA dP/dtmax was assessed with a linear regression analysis and analysis of agreement method by Bland and Altman (9). We considered results significant when the probability value (p) was less than 0.05. To assess the effects of between-patient and within-patient effects in the analysis, we performed analysis of variance (ANOVA). The error in LA dP/dtmax estimation (estimated LA dP/dtmax – measured LA dP/dtmax) was taken as the dependent variable, with the patient number as the grouping variable. A between-group effect at p < 0.05 was taken as evidence of significant interpatient differences in the prediction equation.

RESULTS

Relationship between LA pressure and LA dP/dtmax. In 17 data sets obtained from the initial eight patients of the study group, LA pressure just before atrial contraction ranged from 2 to 15 mm Hg with the mean of 9.8 mm Hg. Left atrial dP/dtmax mmHg ranged from 47 to 158 mm Hg/s with the mean of 97 mm Hg/s. A strong linear relationship was noted between LA pressure and LA dP/dtmax with mild scattering (r = 0.80, SEE = 21.5) (Fig. 2).

Correlation between LA dP/dtmax and Doppler parameters in the study group. Relationships between LA dP/dtmax and Doppler parameters are shown in Table 1. Among transmitral flow parameters, mean acceleration of A wave showed the strongest correlation with LA dP/dtmax (r = 0.78, p < 0.001) (Fig. 3). Peak velocity and mean deceleration showed fair correlations (r = 0.53, p < 0.05 and r = 0.52, p < 0.05, respectively). Among pulmonary venous flow parameters, only peak velocity and time-velocity integral of AR wave showed significant but rough correlation with LA dP/dtmax (r = 0.52, p < 0.05 and r = 0.54, p < 0.05, respectively). Because no single Doppler parameter was satisfactory to predict LA dP/dtmax, we

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean Value (range)</th>
<th>R</th>
<th>p</th>
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<tbody>
<tr>
<td>M-V (cm/s)</td>
<td>59 ± 16 (29–87)</td>
<td>0.53</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>M-AC (cm/s²)</td>
<td>661 ± 225 (349–1013)</td>
<td>0.78</td>
<td>&lt; 0.001</td>
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<tr>
<td>M-DC (cm/s²)</td>
<td>957 ± 260 (555–1459)</td>
<td>0.52</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>M-I (cm)</td>
<td>4.5 ± 1.2 (1.9–6.9)</td>
<td>0.27</td>
<td>ns</td>
</tr>
<tr>
<td>P-V (cm/s)</td>
<td>16 ± 8 (4–35)</td>
<td>0.52</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>P-AC (cm/s²)</td>
<td>411 ± 210 (114–1054)</td>
<td>0.10</td>
<td>ns</td>
</tr>
<tr>
<td>P-DC (cm/s²)</td>
<td>475 ± 233 (100–965)</td>
<td>0.06</td>
<td>ns</td>
</tr>
<tr>
<td>P-I (cm)</td>
<td>0.8 ± 0.8 (0.2–3.0)</td>
<td>0.54</td>
<td>&lt; 0.05</td>
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AC = mean acceleration; DC = mean deceleration; I = time-velocity integral; M = transmitral flow; P = pulmonary venous flow; V = peak velocity.
combined transmitral and pulmonary venous Doppler parameters to find a better predictor. By stepwise and multiple linear regression analysis, the best predictors of LA \( \frac{dP}{dt_{max}} \) were found to be the mean acceleration of transmitral A wave and the peak velocity of pulmonary AR wave. The following equation best described LA \( \frac{dP}{dt_{max}} \): 

\[
LA \frac{dP}{dt_{max}} = 0.1 M-AC + 1.8 P-V - 4.1 \quad (Equation \ 1; \ r = 0.88, p < 0.0001),
\]

where M-AC was the mean acceleration of transmitral A wave and P-V was the peak velocity of pulmonary AR wave.

Validation of the estimated LA \( \frac{dP}{dt_{max}} \) in the test group. The validity of the above equation was tested in 25 data sets obtained from 10 patients in the test group. There was a good linear relationship between the estimated and measured LA \( \frac{dP}{dt_{max}} \) \( (y = 1.09 x - 13.3, \ r = 0.90, p < 0.0001, \text{Fig. 4}) \). The error in the estimation was small enough without systematic overestimation nor underestimation, demonstrating validity of this equation (Fig. 4). For all 42 data sets (combining the study data and the test data), the correlation coefficient between the estimated and measured LA \( \frac{dP}{dt_{max}} \) was 0.90 (Fig. 5).

Between-patient and within-patient effects. Mean error in LA \( \frac{dP}{dt_{max}} \) estimation (estimated LA \( \frac{dP}{dt_{max}} \) – measured LA \( \frac{dP}{dt_{max}} \)) for the initial 17 data sets ranged from 32 mm Hg/s to 30 mm Hg/s (mean 0 ± 17 mm Hg/s), but ANOVA demonstrated no statistically significant difference among patients. In Figure 5, data obtained from the same individual were connected with a line, showing neither significant between-patient nor within-patient effects.

Model results. For the 126 conditions simulated, mean LA pressure ranged from 2.6 to 16.4 mm Hg with LA \( \frac{dP}{dt_{max}} \) ranging from 32.2 to 256.1 mm Hg/s. Left atrial \( \frac{dP}{dt_{max}} \) was strongly correlated with the mean acceleration of the A wave \( (r = 0.906, \text{Fig. 6A}) \) and the peak velocity of the AR wave \( (r = 0.935, \text{Fig. 6B}) \). Consistent with experimental results, when the mean acceleration of the A wave and the peak velocity of the AR wave were combined to predict LA \( \frac{dP}{dt_{max}} \) (using Equation 1), a linear relation was also observed \( (\text{measured} = 0.88 \times \text{predicted} - 13.3; \ r = 0.94) \). No single atrial or ventricular systolic or diastolic functional parameter, when adjusted, resulted in a stronger...
correlation with actual patient data for the range of loading conditions tested.

DISCUSSION

Index of LA systolic function. Some indexes have been proposed to characterize LA contractility, ranging from a simple index of A wave velocity or atrial ejection force determined by noninvasive ultrasound technique (4,5,10) to a highly invasive index, such as LA elastance requiring simultaneous measurements of LA pressure and volume under different loading conditions (11–14). Among them, the instantaneous pressure–volume relation of the LA would provide a most accurate measurement of LA contractility (13,14). However, the measurement of this index is technically difficult and too invasive to perform in beating human hearts in routine clinical practice.

The dP/dt max of the LV has been commonly used to assess LV contractility, although this index is sensitive to loading conditions (15). The present study extends the use of dP/dt max to the LA to assess its systolic function. Ideally, dP/dt max should be assessed in the isovolumic phase as in the LV. However, the mitral valve opens immediately after LA contraction and the pulmonary veins are always available for flow out of the atrium, essentially eliminating any isovolumic phase of the LA. It has been reported that LA dP/dt max increases with contractility of the LA myocardium, suggesting it as an index for assessing LA contractility (16). We found a linear correlation between LA dP/dt max and LA pressure just before atrial contraction. This suggested the existence of the Frank-Starling mechanism in these data sets and supported the feasibility of LA dP/dt max as an overall index of systolic function or load dependent index of LA contractility.

Estimation of LA dP/dt max by Doppler parameters. During LA contraction, the blood in the LA flows into both the LV and the pulmonary vein system (17). Therefore, parameters derived from each flow should reflect LA systolic function. First, we tried to assess LA systolic function by a single parameter that was obtained from either transmitral or pulmonary venous flow. Although several Doppler parameters showed modest to fair correlation with LA dP/dt max as expected, none was an excellent indicator of LA systolic function. One explanation for why transmitral flow parameters alone are not sufficient to assess LA systolic function is that the transmitral A wave is affected not only by LA function but also by LV function: transmitral flow is determined by the pressure difference between the LA and the ventricle (7,18). Matsuda et al. (19) have reported that LA pressure waveform is altered with changes in LV end-diastolic pressure. Stoddard et al. (20) have demonstrated that transmitral A wave velocity decreases with an impairment of LV compliance. Rossvoll and Hatle (21) have showed that the duration of transmitral A wave is affected not only by LA function but also by LV function: transmitral flow is determined by the pressure difference between the LA and the ventricle (7,18). Matsuda et al. (19) have reported that LA pressure waveform is altered with changes in LV end-diastolic pressure. Stoddard et al. (20) have demonstrated that transmitral A wave velocity decreases with an impairment of LV compliance. Rossvoll and Hatle (21) have showed that the duration of transmitral A wave is affected not only by LA function but also by LV function: transmitral flow is determined by the pressure difference between the LA and the ventricle (7,18). Matsuda et al. (19) have reported that LA pressure waveform is altered with changes in LV end-diastolic pressure. Stoddard et al. (20) have demonstrated that transmitral A wave velocity decreases with an impairment of LV compliance. Rossvoll and Hatle (21) have showed that the duration of transmitral A wave is affected not only by LA function but also by LV function: transmitral flow is determined by the pressure difference between the LA and the ventricle (7,18). Matsuda et al. (19) have reported that LA pressure waveform is altered with changes in LV end-diastolic pressure. Stoddard et al. (20) have demonstrated that transmitral A wave velocity decreases with an impairment of LV compliance. Rossvoll and Hatle (21) have showed that the duration of transmitral A wave is affected not only by LA function but also by LV function: transmitral flow is determined by the pressure difference between the LA and the ventricle (7,18). Matsuda et al. (19) have reported that LA pressure waveform is altered with changes in LV end-diastolic pressure. Stoddard et al. (20) have demonstrated that transmitral A wave velocity decreases with an impairment of LV compliance. Rossvoll and Hatle (21) have showed that the duration of transmitral A wave is affected not only by LA function but also by LV function: transmitral flow is determined by the pressure difference between the LA and the ventricle (7,18). Matsuda et al. (19) have reported that LA pressure waveform is altered with changes in LV end-diastolic pressure. Stoddard et al. (20) have demonstrated that transmitral A wave velocity decreases with an impairment of LV compliance. Rossvoll and Hatle (21) have showed that the duration of transmitral A wave is affected not only by LA function but also by LV function: transmitral flow is determined by the pressure difference between the LA and the ventricle (7,18). Matsuda et al. (19) have reported that LA pressure waveform is altered with changes in LV end-diastolic pressure. Stoddard et al. (20) have demonstrated that transmitral A wave velocity decreases with an impairment of LV compliance. Rossvoll and Hatle (21) have showed that the duration of transmitral A wave is affected not only by LA function but also by LV function: transmitral flow is determined by the pressure difference between the LA and

![Figure 6. Results of mathematical modeling demonstrating the relationship between LA dP/dt max and the acceleration of the transmitral A wave (A) and the peak velocity of the pulmonary AR wave (B).](image-url)
and pulmonary venous flow A wave parameters is theoretically sound. For example, a reduced transmitial A wave caused by increased LV stiffness in the presence of preserved LA systolic function will be accompanied by a prominent pulmonary venous atrial reversal flow velocity.

Further validation of our experimental results was obtained through the use of numerical modeling. By applying the results of our mathematical model under a wide range on simulated physiologic conditions to the experimental observations, we have confirmed the linear relationship between the mean acceleration of the transmitial A wave and the peak velocity of the pulmonary AR wave. At higher values for LA dP/dt max the predicted actual slope for the experimental results diverge slightly from the model derived slope. The clinical significance of this observation is minimal since the patients with poor LA systolic function would be more likely to benefit from accurate determination of atrial function. Nevertheless, the overall strong linear correlation for both the observed and model LA dP/dt max and pulmonary venous flow and transmitial indexes demonstrates the integrity of the relationship. In addition, by modeling a wide range of LA and ventricular function under a spectrum of loading conditions, we have shown that the observed results can be applied to the vast spectrum of hemodynamic and pathophysiologic conditions in which accurate determination of LA systolic function is important.

**Study limitations.** We used transesophageal echocardiography to obtain transmitial and pulmonary venous flow velocities in the operating room. Although transesophageal echocardiography offers high quality Doppler spectra of pulmonary venous flow, the disadvantages of transesophageal approach prevent its use in routine investigation. We have shown that LA dP/dt max is well predicted by the acceleration of transmitial A wave and the peak velocity of pulmonary venous flow atrial reversal. Transthoracic echocardiography can measure the peak velocity of the pulmonary venous flow atrial reversal with sufficient quality in most patients (22), >85% by a recent report (24), allowing the findings of this study to be extended to transthoracic echocardiography. The measurement of the right upper pulmonary vein flow may be more clinically relevant because transthoracic echocardiography can often obtain it. However, in the present study the right upper pulmonary vein was used to insert the pressure catheter. In addition, because of the time pressure of obtaining measurements from other pulmonary veins in the operating room, acquisition was confined to the left upper pulmonary vein. Although we do not anticipate a significantly different result from the right pulmonary vein, such observations should be the subject of future investigations.

The number of the patients was relatively small, but it is important to note that the findings of the initial 8 patients were equally applicable to a subsequent independent group of 10 patients. Most of these patients had coronary artery disease; a larger number of patients with a wide variety of disease etiology would be necessary to fully elucidate the physiologic aspects of LA contraction. In addition, despite the limited number of overall patients tested, further confirmation of our findings was obtained through the application of an existing and clinically verified numerical model.

We used LA pressure just before atrial contraction as a substitute for a preload index of LA contraction. In a strict sense, however, preload of the LA should not be LA pressure but the volume just before contraction. Because interventions that alter LA pressure may also alter the relation between LA volume and pressure just before contraction, changes in LA pressure do not always represent changes in volume. We could perhaps have obtained a stronger correlation between preload and LA dP/dt max had we used LA volume as an index of preload; such a measurement, however, would have required epicardial imaging, which was not feasible in the current study.

All patients in the present study had sinus rhythm and we assessed LA systolic function by Doppler-derived flow velocities during atrial contraction. Although it is of interest to assess atrial function during atrial fibrillation, this was beyond the scope of the current study.

**Clinical implications.** There are many occasions where evaluation of LA systolic function is desirable. In patients with profound myocardial dysfunction, the LV is sometimes mainly filled by late diastolic filling, and atrial function is thus critical in maintaining cardiac output (1,2). In this case, evaluation of LA function would have therapeutic and prognostic values. Some patients with valvular heart disease or cardiomyopathy develop acute heart failure with sudden change of cardiac rhythm from sinus rhythm to atrial fibrillation. If one could evaluate LA function at baseline, the hemodynamic risk of atrial fibrillation might be predicted. After cardioversion for atrial fibrillation, the transmitial A wave gradually increases, suggesting return of LA contractility (4). Our present study suggests that we can evaluate the return of LA function more quantitatively.

Recently, the maze procedure has been used to treat chronic or intractable paroxysmal atrial fibrillation. Sinus rhythm has been restored in most cases by this procedure, but some patients show regular rhythm without significant atrial contraction (25). The combined parameter proposed in the present study may allow serial evaluation of LA systolic function from the very early phase in the operating room to the chronic phase.

**Conclusions.** We sought noninvasive parameters obtained from transmitial and pulmonary venous flow velocities by Doppler echocardiography that best correlated with LA dP/dt_max. Left atrial dP/dt_max correlated closely with mitral flow acceleration during atrial contraction. Although no single pulmonary venous flow parameter was sufficient to estimate LA dP/dt_max, the addition of transmitial flow parameters provided a more comprehensive assessment of LA systolic function. Our study suggests methodology for the noninvasive evaluation of LA systolic function that
could be of great value, especially in treating patients with LV dysfunction. Validation of our findings with the results of a numerical model demonstrates that the relationship between LA systolic function and pulmonary venous and transmirtal flow is maintained over a wide range of conditions, further broadening the clinical application of our findings.

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REFERENCES