Impact of Atrioventricular Compliance on Pulmonary Artery Pressure in Mitral Stenosis
An Exercise Echocardiographic Study
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Background—The decay of the pressure gradient across a stenotic mitral valve is determined by the size of the orifice and net AV compliance ($C_n$). We have observed a group of symptomatic patients, usually in sinus rhythm, characterized by pulmonary hypertension (particularly during exercise) despite a relatively large mitral valve area by pressure half-time. We speculated that this discrepancy was due to low atrial compliance causing both pulmonary hypertension and a steep decay of the transmitral pressure gradient despite significant stenosis. We therefore tested the hypothesis that $C_n$ is an important physiological determinant of pulmonary artery pressure at rest and during exercise in mitral stenosis.

Methods and Results—Twenty patients with mitral stenosis were examined by Doppler echocardiography. $C_n$, calculated from the ratio of effective mitral valve area (continuity equation) and the E-wave downslope, ranged from 1.7 to 8.1 mL/mm Hg. Systolic pulmonary artery pressure (PAP) increased from 43±12 mm Hg at rest to 71±23 mm Hg (range, 40 to 110 mm Hg) during exercise. There was a particularly close correlation between $C_n$ and exercise PAP ($r=0.85$). Patients with a low compliance were more symptomatic ($P=0.025$). Catheter- and Doppler-derived values for $C_n$, determined in 10 cases, correlated well ($r=0.79$).

Conclusions—$C_n$, which can be noninvasively assessed, is an important physiological determinant of PAP in mitral stenosis. Patients with low $C_n$ represent an important clinical entity, with symptoms corresponding to severe increases in PAP during stress echocardiography. (Circulation. 2000;102:2378-2384.)

Key Words: mitral valve ■ echocardiography ■ exercise ■ hemodynamics

Calculation of mitral valve area (MVA) by the pressure half-time method is one of the most frequently performed diagnostic assessments in patients with mitral stenosis. It has been found to be a simple, useful, and reproducible tool to grade the severity of mitral stenosis.1–3 Its physical basis is the dependence of the pressure decay across a stenotic mitral valve on orifice size.4 Nevertheless, in a series of systematic investigations, ranging from theoretical analysis of the physical determinants of the pressure half-time and computational models5,6 to in vitro and clinical studies,7–9 Thomas and coworkers5–9 have demonstrated that the pressure decay across a stenotic mitral valve is also directly dependent on atrial or net AV compliance ($C_a$). They have shown that this becomes clinically important whenever abrupt changes of atrial pressure and compliance occur, such as in the first days after percutaneous balloon valvotomy, when calculations of MVA based on pressure half-time become inaccurate.9

We have recently observed a group of symptomatic patients with mitral stenosis who are characterized by significant pulmonary hypertension, particularly during exercise, despite a relatively large MVA by pressure half-time. We speculated that this discrepancy was due to low atrial compliance causing both high pulmonary artery pressure (PAP) and a steep decay of the pressure gradient across the mitral valve despite significant stenosis.

The purpose of this study was therefore to systematically address the following hypotheses: (1) $C_a$, which can be noninvasively assessed from the slope of the transmitral velocity decay and effective MVA (calculated by the continuity equation), is an important physiological determinant of PAP at rest and during exercise in mitral stenosis; and (2) patients with low atrial compliance, characterized by a steep decay of the pressure gradient despite a significantly reduced MVA, represent an important clinical entity, with symptoms corresponding to severe increases in PAP during stress echocardiography.

Methods

Patients

Thirty-five patients with mitral valve disease were consecutively referred to exercise Doppler echocardiography for hemodynamic evaluation during a period of 1 year. Of those, 20 patients had pure, isolated mitral stenosis. These patients made up the study group.
There were 15 women and 5 men, 42 to 71 years of age (mean, 54±10 years). Four were in functional class I, 9 were in functional class II, and 7 were in functional class III. Seventeen were in sinus rhythm, and 3 were in atrial fibrillation.

**Echocardiographic and Doppler Examinations**

All patients underwent a complete standard echocardiographic examination. Doppler velocity tracings were recorded at a speed of 100 mm/s.

**Exercise Protocol**

The patients performed supine bicycle ergometry in a mild left lateral position with an initial workload of 25 W, which was increased by 25 W after 3 minutes, depending on the patient’s capability. Exercise was continued until a heart rate of at least 70% of the maximal predicted heart rate was reached; this level was maintained as a plateau for 3 to 5 minutes to allow Doppler interrogation at a stable heart rate.

**Measurements at Rest and During Exercise**

The duration of the diastolic filling period and maximal and mean transmural pressure gradients (Bernoulli equation) were obtained from the continuous-wave Doppler signal of mitral flow velocity. Stroke volume was calculated as left ventricular outflow tract area multiplied by the time integral of the outflow tract velocity (pulsed-wave Doppler). Outflow tract area was determined as D^2/4, where D is its diameter measured from a zoomed systolic freeze-frame in the parasternal long-axis view. With the continuity equation, MVA was calculated as stroke volume divided by mitral time-velocity integral.°–12 Because left ventricular outflow tract area has been shown to remain constant during exercise both in normal subjects and in patients with mitral stenosis,13 the resting value of left ventricular outflow tract area was used to calculate both rest and exercise stroke volume. Systolic PAP was derived from the tricuspid regurgitant jet velocity (v) with the modified Bernoulli equation (4v^2) and assuming a right atrial pressure of 10 mm Hg. For the 3 patients who were in atrial fibrillation, measurements during ≥5 cardiac cycles representing the mean heart rate were averaged and used for further calculations.

**Calculation of Net AV Compliance**

Cn can be calculated from the deceleration rate (dV/dt) of the mitral velocity profile (E-wave downslope) and effective MVA, determined by the continuity equation, as demonstrated by Flachskampf et al (see the Appendix):

\[ C_n = 1270(MVA/E\text{-wave downslope}) \]

where Cn is obtained in cm^3/mm Hg (mL/mm Hg) if MVA is expressed in cm^2 and the E-wave downslope in cm/s. Cn was assessed only from the resting measurements, and the E-wave downslope (curvilinear in 2 cases) was determined by the average slope method.

Interobserver variability was evaluated as the SD of the differences in Cn calculated by 2 independent observers for 10 different patients expressed as the percent of mean Cn (coefficient of variation) and was 7% of the mean. Intraobserver variability derived from repeated calculations 1 month apart was 6%.

**Comparison Between Invasively and Noninvasively Determined Compliance Calculations**

In 10 patients with pure mitral stenosis who underwent cardiac catheterization during the study period within 72 hours of the Doppler echocardiographic examination, noninvasively and invasively determined Cn were compared. Invasive assessment of Cn was performed as described by Thomas et al: mean left atrial compliance (Cn) was obtained by dividing the systolic rise in pulmonary wedge pressure into the cardiac stroke volume, which was calculated with the Fick method. Similarly, mean left ventricular compliance (Cv) was estimated as the diastolic rise in left ventricular pressure divided into the stroke volume. Cn was then calculated as \((1/C_v + 1/C_n)^{-1}\).

**Statistical Analysis**

Differences between rest and exercise values were tested for significance by use of a paired 2-sample t test. Linear regression analysis was used to compare invasively and noninvasively performed assessments of Cn and to determine the correlation between net AV compliance and PAP. One-way ANOVA was used to examine the relationship between functional class and Cn.

**Results**

**Valvular Hemodynamics at Rest and During Exercise**

The exercise-induced changes in valvular hemodynamics are displayed in Figure 1. With the increase in heart rate during exercise, the diastolic filling period was shortened from 420±118 to 256±67 ms (P<0.0005). Mean transmural pressure gradient increased from 8.3±4.0 to 18±7.1 mm Hg (P<0.0005), with substantial differences in the magnitude of increase in patients with comparable resting values. Stroke volume did not change significantly on average (60±13 and 62±18 mL at rest and during exercise, respectively). However, behavior was nonuniform, with individual patients substantially raising stroke volume during exercise and others showing no change or even a decline. Effective MVA mildly but significantly (P<0.05) increased on average from

![Figure 1. Exercise-induced changes in diastolic filling period, mean transmural pressure gradient, stroke volume and MVA in 20 patients with mitral stenosis at rest (R) and during exercise (E).](http://circ.ahajournals.org/content/78/1/2379.figure1)

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1.19±0.36 to 1.31±0.4 cm², again with substantial differences between individual patients. There was a significant correlation between the percent increase in stroke volume and the percent increase in MVA during exercise (r=0.54, P<0.025).

**PAP and Net AV Compliance**

Systolic PAP at rest was 43±12 mm Hg (range, 26 to 74 mm Hg) and increased to 71±23 mm Hg during exercise (P<0.0005), with values ranging from 40 to 110 mm Hg (Figure 2, left). Again, substantial differences in the magnitude of increase during exercise were observed in patients with comparable resting values. Cₚ ranged from 1.7 to 8.1 mL/mm Hg (4.7±1.7 mL/mm Hg on average). There was a significant inverse correlation between Cₚ and PAP at rest (r=0.73, P<0.05) and an even closer correlation to exercise PAP (r=0.88, P<0.0001; Figure 2, right). No correlation was found between MVA and the response of PAP to exercise. No significant correlation was found between left atrial size (systolic left atrial area measured in the apical 4-chamber view) and Cₚ.

With a cutoff value of ≤4 mL/mm Hg (lower third of values), patients with low Cₚ were more symptomatic: 71% were in functional class III compared with 29% in the range of 4 to 6 mL/mm Hg and 0% with values ≥6 mL/mm Hg (P<0.025). The only 2 patients who had suffered a short episode of pulmonary edema were in the group of very low Cₚ. Five patients in this group were referred to interventional therapy (3 patients underwent mitral valve replacement; 2 patients, percutaneous mitral valvotomy) compared with 1 patient in the range of 4 to 6 mL/mm Hg and 0 patients with values ≥6 mL/mm Hg.

Figure 3 demonstrates a typical example of a symptomatic patient with pure, isolated mitral stenosis, a sizeable mean pressure gradient across the mitral valve, and steep E-wave downslope, leading to a calculated MVA of 1.7 cm² by the pressure half-time method. Using the continuity equation reveals an effective MVA of 0.7 cm². The steep E-wave deceleration is due to a low Cₚ (2 mL/mm Hg) corresponding to high systolic PAP at rest (74 mm Hg) and during exercise (105 mm Hg). Other patients with a low Cₚ showed only a moderate elevation of PAP at rest but comparably high values during exercise (Figure 2, right). The same constellation is demonstrated by cardiac catheterization in Figure 4 (left) in 2 patients with remarkably high V waves in the pulmonary wedge pressure tracing resulting from low atrial compliance. The steep pressure decay (y descent), corresponding to a steep velocity decay of the mitral E-wave Doppler signal, would lead to overestimation of the MVA (0.9 cm² by the Gorlin formula) when the pressure half-time method is applied to the catheterization data. PAP was 80/40 and 85/45 mm Hg, respectively.
Overestimation of MVA by Pressure Half-Time as a Function of Net AV Compliance

Figure 5 plots the percent difference between the MVA calculated by the pressure half-time method and the continuity equation against C_n. As C_n dropped to <4 mL/mm Hg, overestimation increased dramatically. The Table details the individual results of MVA assessment by the 3 different methods, as well as AV compliance in all 20 study subjects.

Comparison Between Invasively and Noninvasively Determined Net AV Compliance

In the 10 patients who underwent cardiac catheterization, catheter- and Doppler-derived values for C_n correlated reasonably well (r=0.79, P<0.007, SEE=±0.57 mL/mm Hg; Figure 6).

Discussion

The decay of the pressure gradient across a stenotic mitral orifice is determined by the size of the orifice and C_n. Therefore, the attempt of the pressure half-time method to estimate MVA empirically by assessing only 1 of the other variables (pressure decay) necessarily introduces an error of unknown magnitude, which is the result of the variation in C_n observed in mitral stenosis. This limitation of the pressure half-time method is well recognized in the setting of percutaneous mitral valvotomy, which induces substantial changes in chamber compliance within a short period of time.9 However, the magnitude of variation in C_n observed in this consecutive group of patients with mitral stenosis (>400%) suggests that the half-time method may be inaccurate in many cases even without outside intervention. This is consistent with the findings of Smith et al,16 who showed that although a pressure half-time of >250 ms predicted a MVA of <1.0 cm² in 95% of the patients, a half-time of <200 ms identified a valve area >1.0 cm² in only 78% of the patients, and a range of valve areas between 0.5 and 1.5 cm² was observed for half-times between 200 and 250 ms.

In the present study, we have identified low C_n as a clinically relevant cause for significant overestimation of
MVA precisely in a distinct group of symptomatic patients characterized by high PAP during exercise as a consequence of low Ca. We have demonstrated that Ca can be reliably and noninvasively assessed in the clinical setting and that it represents an important physiological parameter in mitral stenosis.

Net AV Compliance: A Physiological Modulator of PAP

Flachskampf et al. have presented analytic and numeric evidence supporting the quantitative assessment of Ca through analysis of transmitral velocity profiles, deducing a simple equation that relates effective MVA and E-wave downslope; this equation was then validated in vitro, accurately predicting true net compliance. The present study shows that Ca can be calculated noninvasively with good reproducibility in the clinical setting, correlating well with invasively determined values. Not surprisingly, given the variability of the reference method (in addition to that tested) and the nonsimultaneous assessment, the correlation coefficient was lower than in the ideal in vitro comparison against a true gold standard.

Stress echocardiography offered the ideal instrument to test the hypotheses stated in the introduction, because it allows us to relate Ca to an independent parameter of disease severity such as PAP and its response to exercise. We found that Ca was closely related to PAP, particularly during exercise. The primary reason for this finding is that low atrial compliance will become evident first during exercise, as left atrial pressure and PAP rise significantly in response to increases in heart rate and flow. At a later stage, particularly when pulmonary vascular resistance increases, pulmonary hypertension may be present even at rest (Figure 3).

No correlation was found between left atrial size and Ca. The reason for this finding is that Ca is defined operationally, expressing the actually observed pressure-volume relationship during left atrial discharge, regardless of its cause: It does not distinguish whether the patient operates on a steep left atrial pressure-volume curve or on the steep portion of a normal left atrial pressure-volume curve. In both cases, left atrial pressure and PAP are expected to rise significantly in response to increases in heart rate and flow. At a later stage, particularly when pulmonary vascular resistance increases, pulmonary hypertension may be present even at rest. The reason for this finding is that Ca is defined operationally, expressing the actually observed pressure-volume relationship during left atrial discharge, regardless of its cause: It does not distinguish whether the patient operates on a steep left atrial pressure-volume curve or on the steep portion of a normal left atrial pressure-volume curve. In both cases, left atrial pressure and PAP are expected to rise significantly in response to increases in heart rate and flow. At a later stage, particularly when pulmonary vascular resistance increases, pulmonary hypertension may be present even at rest (Figure 3).

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Net AV Compliance and MVA Assessed by Continuity Equation, Pressure Half-Time Method, and Planimetry in 20 Patients With Mitral Stenosis Referred to Exercise Echocardiography

<table>
<thead>
<tr>
<th>Patient</th>
<th>Net Compliance, mL/mm Hg</th>
<th>MVA by Continuity, cm²</th>
<th>MVA by T₁/₂, cm²</th>
<th>MVA by Planimetry, cm²</th>
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Mean±SD 4.7±1.7 1.19±0.36 1.49±0.34

Figure 6. Correlation between invasively (Ca Cath) and noninvasively (Ca Doppler) determined net AV compliance in 10 patients with mitral stenosis.
Cn. This would even expand the pathophysiological concept of Cn (pulmonary hypertension begetting pulmonary hypertension by affecting left ventricular compliance). In fact, a shortening of E-wave deceleration time with pulmonary hypertension has been reported. However, others have found a prolongation, and recently, a lack of ventricular interdependence has been reported in chronic severe pulmonary hypertension explained by pericardial adaptation. We therefore believe that low atrial compliance is the dominant factor in most patients with mitral stenosis.

The Syndrome of Short Pressure Half-Time in Severe Mitral Stenosis: Mistaking Low Atrial Compliance for Mild Mitral Stenosis

The clinical importance of our findings is emphasized by the fact that patients characterized by a low Cn and a dramatic response of PAP to exercise who would benefit most from surgery or percutaneous mitral valvotomy were at the highest risk of underestimation of disease severity (Figure 2, right, and Figure 5). Several patients were indeed referred to our laboratory after they were misdiagnosed as having mitral stenosis of a milder degree, because their relatively short pressure half-time led to significant overestimation of MVA.

Factors in the clinical presentation, which contributed to an underestimation of disease severity, included that these patients were periodically relatively free of symptoms during everyday activity despite significant disease. There was also a high incidence of sinus rhythm, usually associated with a milder degree of stenosis. In fact, a distinct group of patients with mitral stenosis, usually young women, who present with paroxysmal dyspnea and recurrent pulmonary edema has been described.

These patients have tight mitral stenosis and left atrial hypertension but a noncompliant left atrium and generally remain in sinus rhythm.

They may be relatively free from symptoms during everyday activity but respond to stress, exertion, emotion, fever, tachycardia, or occasionally premenstrual fluid retention with episodes of pulmonary edema. The present article provides a reliable tool to detect this potentially undiagnosed pathophysiologic mechanism.

Overestimation of MVA by misinterpretation of a short pressure half-time can be avoided by calculating MVA using alternative methods (the Table), particularly when mitral pressure gradients are higher than expected for the observed half-time. Cn should be calculated and PAP assessed during stress echocardiography.

Comparison With Other Studies

The ability to assess the response of PAP to exercise in a physiological setting is one of the most important aspects of stress echocardiography in mitral stenosis. In the present study, substantial differences in the magnitude of increase in PAP during exercise were observed in patients with comparable resting values, clearly demonstrating the incremental value of stress echocardiography in the hemodynamic assessment of mitral stenosis. Tunick et al found that patients with mitral valve disease who are limited by dyspnea show a significantly greater increase in PAP during exercise, as well as a significantly shorter exercise capacity, than those who are limited by fatigue. This is in keeping with results of the present study, which demonstrates that patients with a low Cn show substantial increases in PAP during exercise and predominantly present with signs or symptoms of pulmonary congestion. In accordance with the findings of Dahan et al, we also observed a nonuniform behavior of stroke volume during exercise in mitral stenosis, in which the ability to raise stroke volume depends on an increase in MVA during exercise.

Study Limitations

Although the determination of the E-wave downslope is usually straightforward, because it is linear in most cases, the downslope can be curved concave upward if Cn decreases during atrial discharge. E-wave deceleration should then be assessed with the average rather than the instantaneous slope method. Determination of effective MVA with the continuity equation, although accurate and subject to fewer limitations than alternative methods, is more complex. The basic message of this article remains unaffected by the limitations: Even in a case in which Cn cannot be calculated precisely, the combination of a high mean transmitral gradient and a steep pressure decay suggests the presence of a low Cn and a substantial increase of PAP during stress echocardiography is expected.

Appendix

Following are the definition of net AV compliance and its derivation for noninvasive calculation as demonstrated by Flachskampf et al. Because the atrium and ventricle can be regarded as 2 capacitors in series, Cn is given by the sum of the reciprocal value of Cn and Cn,

\[ C_n = \frac{1}{C_a} + \frac{1}{C_v} \]

Net compliance is also the change in volume shift between atrium and ventricle during diastole divided by the change in transmural pressure difference:

\[ C_n = \frac{dV}{d\Delta p} \]

The ratio of volume to pressure change, which defines compliance, can also be expressed using the first derivatives with respect to time:

\[ C_n = \frac{(dV/dt)}{(d\Delta p/dt)} \]

Note that dV/dt is simply flow rate, Q, through the mitral valve, ie, effective MVA times the mitral velocity, v. Also, for restrictive orifices, the Bernoulli equation applies, so d\Delta p/dt can be substituted by \( \rho(v^2/dt) \):

\[ C_n = \frac{(dV/dt)}{(d\Delta p/dt)} = \frac{Q(d\Delta p/dt)}{MVA\rho v (dv/dt)} = \frac{MVA\rho (dv/dt)}{\rho v (dv/dt)} \]

where Cn is measured in cm³/dynes/cm², \( \rho \) is blood density (1.05 g/cm³), and \( dv/dt \) (cm/s²) is the deceleration rate of the mitral velocity profile (or E-wave downslope). To express Cn in cm³/ml/mm Hg, the right side of the equation is multiplied by 1333
(dynes/cm²)/mm Hg, and incorporating ρ (which is constant) yields this simple expression:

\[ C_n = 1270(MVA/E-wave \text{ downslope}) \]

where \( C_n \) is obtained in cm³/mm Hg (mL/mm Hg) if MVA is expressed in cm² and the E-wave downslope in cm/s².

Acknowledgments

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References

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