Valvular Heart Disease

Impact of Net Atrioventricular Compliance on Clinical Outcome in Mitral Stenosis

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Background—Net atrioventricular compliance (C_n) has been reported to be an important determinant of pulmonary hypertension in mitral stenosis (MS). We hypothesized that it may be useful in assessing prognosis because C_n reflects hemodynamic consequences of MS. To date, limited data with an assumed C_n cutoff have indicated the need for larger prospective studies. This prospective study was designed to determine the impact of C_n on clinical outcome and its contribution to pulmonary pressure in MS. In addition, we aimed to identify a cutoff value of C_n for outcome prediction in this setting.

Methods and Results—A total of 128 patients with rheumatic MS without other significant valve disease were prospectively enrolled. Comprehensive echocardiography was performed and Doppler-derived C_n estimated using a previously validated equation. The end point was either mitral valve intervention or death. C_n was an important predictor of pulmonary pressure, regardless of classic measures of MS severity. During a median follow-up of 22 months, the end point was reached in 45 patients (35%). Baseline C_n predicted outcome, adding prognostic information beyond that provided by mitral valve area and functional status. C_n ≤4 mL/mmHg best predicted unfavorable outcome in derivation and validation sets. A subgroup analysis including only initially asymptomatic patients with moderate to severe MS without initial indication for intervention (40.6% of total) demonstrated that baseline C_n predicted subsequent adverse outcome even after adjustment for classic measures of hemodynamic MS severity (hazard ratio, 0.33; 95% confidence interval, 0.14–0.79; P=0.013).

Conclusions—C_n contributes to pulmonary hypertension beyond stenosis severity itself. In a wide spectrum of MS severity, C_n is a powerful predictor of adverse outcome, adding prognostic value to clinical data and mitral valve area. Importantly, baseline C_n predicts a progressive course with subsequent need for intervention in initially asymptomatic patients. C_n assessment therefore has potential value for clinical risk stratification and monitoring in MS patients. (Circ Cardiovasc Imaging. 2013;6:1001-1008.)

Key Words: compliance ■ hypertension, pulmonary ■ mitral valve stenosis ■ outcome assessment (health care)

The presence of pulmonary hypertension is fundamental in the clinical decision-making process for mitral stenosis (MS).1,2 It strongly expresses valve disease severity and conveys adverse effects on functional status, exercise tolerance, and prognosis.3–5 However, pulmonary pressure may not be uniquely determined by the stenotic lesion itself but by a combination of hemodynamic parameters.6,7

Clinical Perspective on p 1008

Several factors may contribute to clinical presentation and outcome in MS. Left-heart compliance plays a crucial role in the occurrence of pulmonary hypertension and symptoms.8–15 Net atrioventricular compliance (C_n) has been reported to be a major determinant of elevated pulmonary artery pressure in patients with MS9,10 independently of mitral valve (MV) area and transvalvular pressure gradients. Li et al10 found that C_n was the only Doppler echocardiographic variable that independently predicted pulmonary artery pressure.

C_n can be readily calculated by Doppler echocardiography. C_n was originally used for analysis of transmural flow by Thomas and Weyman,16 demonstrating that the pressure halftime to estimate MV area varies inversely with orifice area but also directly with net left atrial and ventricular compliance and the square root of the peak transmural gradient.

Flachskampf et al17 presented analytic and numeric evidence supporting the quantitative assessment of C_n from transmural velocity profiles, deriving a simple equation that relates it to effective MV area and E-wave downslope. This equation has been validated in vitro and accurately predicts C_n. Subsequently, Schwammenthal et al18 showed that C_n can be calculated noninvasively and reproducibly in the clinical setting and correlates well with invasively determined values.
Although Cn seems to be an important determinant of cardiovascular performance in MS, few data are available on its prognostic implications. To date, only 1 study has evaluated the relation between Cn and clinical events; that study was limited by the small number of patients enrolled and by an assumed cutoff value for Cn. The authors acknowledged the need for further prospective studies in more patients and the limitation of an assumed cutoff used for Cn in the analysis.

We hypothesized that Cn, which reflects the hemodynamic consequences of MS, will be a useful predictor of outcome, adding value to other well-established indices of stenosis severity. The present prospective study was designed to determine the incremental prognostic value of Cn and its independent contribution to pulmonary artery pressure in a substantial population of patients with MS. In addition, we aimed to identify an optimal cutoff value of Cn predictive of adverse outcomes for use in the clinical setting.

Methods

Study Population
Patients were recruited prospectively and consecutively from a tertiary center for heart valve disease among those routinely referred for management of rheumatic valve disease.

The study enrolled 140 patients (124 women and 16 men) with rheumatic MS from 2007 to 2011. Exclusion criteria were pregnancy, other hemodynamically significant valve disease, and congenital or myopathic lesions that could independently affect pulmonary artery pressure. On the basis of these criteria, 12 patients were excluded for pregnancy (n=1), moderate to severe aortic regurgitation (n=3), moderate mitral regurgitation (n=2), interatrial communication (n=1), aortic prosthesis (n=1), Schistosomiasis mansoni with pulmonary hypertension (n=1), AIDS (n=1), Chagas heart disease (n=1), and intestinal neoplasia with chemotherapy treatment (n=1). The study was approved by the Federal University of Minas Gerais in Brazil, and the subjects gave informed consent.

Clinical Data
At entry, a complete clinical evaluation was performed on all patients. Only clinically stable patients were included, and functional status was determined using the New York Heart Association (NYHA) classification based on functional capacity and dyspnea.

Echocardiographic Evaluation
At the time of enrollment, 2-dimensional and Doppler echocardiographic imaging was performed and analyzed according to the recommendations of the American Society of Echocardiography using a commercially available echocardiograph (GE Vivid 7, Horten, Norway or Philips ie33, Andover, MA). Left atrial (LA) volume was assessed by the biplane area-length method from apical 2- and 4-chamber views.

MV morphology was evaluated using the score of Wilkins et al by grading valvular leaflet thickness, mobility, calcification, and subvalvular thickening. MV area was measured using planimetry and concurrently calculated using the pressure half-time method. Peak and mean transmural diastolic pressure gradients were measured from Doppler profiles recorded in the apical 4-chamber view. The continuous-wave Doppler tricuspid regurgitant velocity was used to determine systolic pulmonary artery pressure (SPAP) using the simplified Bernoulli equation. Mean right atrial pressure was estimated based on the diameter of the inferior vena cava and its respiratory change.

Global right ventricular (RV) function was quantitatively assessed using the RV myocardial performance index, peak systolic velocity at the tricuspid annulus using tissue Doppler imaging, and the tricuspid annular plane systolic excursion at the RV free wall obtained from 2-dimensionally guided M-mode recordings. Each echocardiographic parameter was averaged from 3 consecutive cardiac cycles for patients in sinus rhythm or 5 consecutive cycles for patients in atrial fibrillation. The echocardiographic measurements were performed by 2 independent observers who were blinded to the clinical information.

Assessment of Cn
Cn was determined noninvasively by means of Doppler echocardiography as previously described: Cn (mL/mm Hg)=1270x (planimetric MV area [cm²]/E-wave downslope [cm/s²]). In those patients with nonlinear diastolic flow, the mid-diastolic flow was used, which is felt to best represent the valve stenosis as opposed to early LA depressurization, and the slope was extrapolated back to obtain the initial maximal velocity.

Cn was also calculated invasively in 25 patients with pure MS in sinus rhythm who underwent percutaneous valvuloplasty to compare with its noninvasive value. As described by Thomas et al, mean LA compliance (Cn) was obtained by dividing the cardiac stroke volume by the systolic rise in LA pressure. The cardiac stroke volume was calculated using the Fick method. Similarly, mean left ventricular compliance (Cn) was estimated as the stroke volume divided by the diastolic rise in left ventricular pressure. Ventricular compliance was calculated using a left ventricular catheter passed retrograde through the aortic valve. Fluid-filled catheters were used to measure the pressures. Cn was then calculated as (1/Cn+1/Cn)y⁻¹.

End Point Definition
The primary outcome was composite end points of either MV intervention (percutaneous or surgical) or death related to MS. Follow-up data were obtained during clinical follow-up appointment or telephone interviews.

To satisfy the assumption of the independence of events, hospitalization for progressive dyspnea or overt pulmonary edema, during which valve intervention was recommended, was not defined as a separate end point.

Clinical management of the patients and decisions about valve intervention were handled by their respective physicians who were independent of the study and unaware of the results of the Cn measurement. Indications for valve intervention were according to the 2008 American College of Cardiology/American Heart Association guidelines based on a combination of functional limitation, severity of obstruction, and pulmonary hypertension: NYHA functional class III or IV; NYHA class II with moderate or severe MV area reduction and valve morphology favorable for percutaneous mitral valvuloplasty; or asymptomatic patients with pulmonary hypertension, moderate or severe stenosis, and valve morphology favorable for percutaneous intervention. The purpose of this study, therefore, was to determine which baseline measures best predicted this outcome.

Statistical Analysis
Baseline demographic features and echocardiographic variables are presented as mean±SD. All data have been tested for normality, and transformation has been performed when necessary. A multivariable regression analysis was performed to identify the factors associated with pulmonary artery pressure, including all MV parameters and measures of right-sided function described above. The associated increase of R² was assessed to identify the respective contribution of each variable to the variance of the pulmonary pressure in the multivariable model. Model fit was assessed by residual analysis. Residual plots were examined for relationship between residual and predicted values. The Shapiro-Wilk test was used to assess the normality of residuals for the overall and the final model.

Multivariable Cox proportional hazards analysis was used to identify risk factors for MS-related intervention. The potential predictive variables of outcome included in the Cox analysis were age, symptoms, atrial fibrillation, MV area, transvalvular gradients, RV myocardial performance index, LA volume, SPAP, and Cn. The variables were checked for collinearity, and obviously interdependent covariates were not used simultaneously in any of the analyses. The
interaction between $C_n$ and MV area (product term) was also included in the multivariable analysis. The predictors of outcome by multivariable analysis were then tested for their incremental contribution to the model prediction of outcome using the likelihood ratio statistic, which follows a $\chi^2$ distribution.

Receiver-operating characteristic curve analysis was performed to determine the cutoff values of $C_n$ that best predict binary outcome. Applying a randomized splitting technique, the cutoff value was compared in derivation and validation sets. Intervention-free survival rates were estimated by the Kaplan-Meier method and compared by the log-rank test. Reproducibility of $C_n$ was assessed by the intraclass correlation coefficients for repeated measures in a random sample of 10 patients. Intermethod agreement (noninvasive versus invasive) was evaluated using the Bland-Altman method. A value of $P<0.05$ was regarded as statistically significant. Statistical analysis was performed using the Statistical Package for Social Sciences for Windows, version 18.0 (SPSS Inc, Chicago, IL).

Results

Baseline Clinical Characteristics

The mean age was 42.6±11.2 years, and 116 patients were women (90.6%). The baseline clinical characteristics of the study population are summarized in Table 1. Sixty-eight patients (53%) were asymptomatic at the time of recruitment into the study, whereas the remaining 60 patients (47%) had exertional dyspnea. Fifty-three patients (41%) had associated mild aortic valve rheumatic disease, and 6 patients (5%) had rheumatic tricuspid valve disease.

Mitral valvuloplasty had previously been performed in 35 patients (27%), including either percutaneous or surgical intervention. At the time of enrollment, 5 patients (4%) had had ≥2 valvuloplasties. The mean time between the last valve intervention and enrollment in the study was 5 years (range, 1–14 years).

Atrial fibrillation was present in 18 patients (14%) at enrollment. The medications most frequently used were β-blockers (20 patients (16%) were taking anticoagulants. Patients with atrial fibrillation or previous embolic events had a higher incidence of cardiovascular score of 7 (range, 4–12). There was no difference in transmitral gradients, pulmonary artery pressure, or $C_n$ between patients with atrial fibrillation and sinus rhythm. There was a weak negative correlation between LA volume index and $C_n$ ($r=-0.3; P=0.002$). $C_n$ decreased with worsening NYHA functional class, with a mean $C_n$ of 5.1±1.1 mL/mm Hg in asymptomatic patients and 4.1±1.1 mL/mm Hg in symptomatic patients ($P=0.001$).

Predictors of Pulmonary Artery Systolic Pressure

The predictors of pulmonary pressure in MS are shown in Table 2. There was a correlation between SPAP and measures of MS severity, including MV area and transvalvular pressure gradients. As expected, several measures of RV function also correlated with SPAP. Of note, although there was an inverse correlation between MS severity (valve area) and SPAP, there was a wide spectrum of SPAP in a subgroup of patients with severe MS, with a median of 50.5 mm Hg (interquartile range, 37.8–65.8 mm Hg; range, 25–110 mm Hg), indicating that additional variation in SPAP must be accounted for by other factors. Specifically, $C_n$ inversely correlated with SPAP and directly correlated with net stiffness ($y=170x3.3; R^2=0.39; P<0.001$; Figure 1). By multivariable analysis, mean transvalvular gradient, MV area, and $C_n$ were identified as the most significant predictors of increased SPAP (Table 2). $C_n$ was therefore a powerful predictor of pulmonary hypertension, which contributes beyond MS severity itself.

Predictors of Outcome

During a median follow-up of 22 months (limits, 3–49 months), the end point was reached in 45 patients (35%): 1 patient died, 41 underwent percutaneous mitral valvuloplasty, and 3 underwent MV replacement. The baseline clinical and echocardiographic variables associated with patient outcome are compared in Table 3. As expected, patients who reached the end point presented with more advanced functional class and more severe MS by echocardiography than medically treated patients. Of note, however, only 24% of patients who reached the end point had NYHA class III to IV functional status at baseline. By multivariable analysis, the baseline determinants predicting valve intervention were $C_n$, MV area, and NYHA functional class (Table 4). There was a significant interaction between MV area by planimetry and $C_n$ ($P=0.007$), demonstrating that the prognostic impact of MV area is modulated by $C_n$. Therefore, patients with larger valve areas have worse prognosis if their $C_n$ is lower.

Although the classic markers of hemodynamic severity, particularly mean transvalvular pressure gradient and SPAP, were significant determinants on individual analysis, they were not predictors of outcome in a model including MV area and $C_n$. (59% of cases). Thirty-three patients (28%) were using penicillin benzathine for secondary prevention of rheumatic fever. Patients with atrial fibrillation or previous embolic events were taking anticoagulants.

MV area was 1.2±0.4 cm$^2$ (range, 0.6–2.0 cm$^2$) with mild MS (area >1.5 cm$^2$) found in 34 patients, moderate (area, 1–1.5 cm$^2$) in 52 patients, and severe (area <1 cm$^2$) in 42 patients based on MV area by pressure half-time (PHT). The MV morphology was suitable for percutaneous valvuloplasty in the majority of the patients, with a median Wilkins echocardiographic score of 7 (range, 4–12). There was no difference in transmural gradients, pulmonary artery pressure, or $C_n$ between patients with atrial fibrillation and sinus rhythm.

Data are expressed as mean±SD or number (percentage) of patients.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Value</th>
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<tbody>
<tr>
<td>Age, y</td>
<td>43±11</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>69±13</td>
</tr>
<tr>
<td>Systolic/diastolic blood pressures, mm Hg</td>
<td>118±14/76±10</td>
</tr>
<tr>
<td>Left ventricular ejection fraction, %</td>
<td>58±5</td>
</tr>
<tr>
<td>Left atrial diameter, mm</td>
<td>49±6</td>
</tr>
<tr>
<td>Left atrial volume index, mL/m$^2$</td>
<td>52±16</td>
</tr>
<tr>
<td>Transvalvular mitral peak/mean gradients, mm Hg</td>
<td>18±8/10±6</td>
</tr>
<tr>
<td>Mitral valve area by planimetry, cm$^2$</td>
<td>1.2±0.4</td>
</tr>
<tr>
<td>Mitral valve area by pressure half-time, cm$^2$</td>
<td>1.3±0.3</td>
</tr>
<tr>
<td>Pulmonary artery systolic pressure, mm Hg*</td>
<td>44±19</td>
</tr>
<tr>
<td>Peak systolic velocity at the tricuspid annulus, cm/s</td>
<td>11±2</td>
</tr>
<tr>
<td>Tricuspid annular motion, mm</td>
<td>19±4</td>
</tr>
<tr>
<td>Right ventricular myocardial performance index</td>
<td>0.3±0.1</td>
</tr>
<tr>
<td>Moderate to severe tricuspid regurgitation, n (%)</td>
<td>17 (13)</td>
</tr>
<tr>
<td>Net atrioventricular compliance, mL/mm Hg†</td>
<td>4.7±1.3</td>
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</tbody>
</table>

*Pulmonary artery systolic pressure could not be assessed in 4 patients (3%). †Compliance could not be calculated in 3 patients (2%) because of extensive calcification of mitral valve leaflets; hence, there was an inability to planimeter MV area accurately.
To assess the additional value of low Cn in predicting adverse outcome, we selected a subgroup of patients with moderate to severe anatomic mitral stenosis without indication for MV intervention at the time of recruitment into the study, which included asymptomatic patients with pulmonary artery systolic pressure at rest <50 mmHg. Of the 52 patients in this group (40.6% of the entire study population), 17 subsequently achieved criteria that warranted MV intervention. In this subset of initially asymptomatic patients, multivariable analysis demonstrated that Cn predicted subsequent MV intervention (hazard ratio, 0.33; 95% confidence interval, 0.14–0.79; P=0.013) after adjustment for classic measures of hemodynamic MS severity. Baseline Cn therefore had an additional and incremental effect for predicting adverse outcome even after adjustment for valve area, pressure gradient, and pulmonary artery pressure.

The cutoff level for Cn was set according to the receiver-operating characteristic curve analysis. To validate this cutoff point, our population was split randomly into 2 portions. The first 65 patients were analyzed as the derivation set and the next 63 as the validation set, without significant differences in key measures between the 2 sets. In the overall population, different cutoff values of Cn to predict binary outcome were obtained (Figure 2). The best cutoff value of Cn for outcome prediction was 4 mL/mmHg, with a sensitivity of 82% and a specificity of 68%.

Of the patients with baseline values of Cn >4 mL/mmHg, only 18% of patients were referred for interventional therapy compared with 82% of patients with values of Cn ≤4 mL/mmHg. Of note, although not an end point because it determined intervention, all 4 patients who developed acute pulmonary edema had Cn <4 mL/mmHg.

In the Kaplan-Meier analysis (Figure 3), the event-free survival rate was significantly higher in patients with Cn >4 mL/mmHg than in patients with Cn ≤4 mL/mmHg (P<0.001). Furthermore, in the initially asymptomatic subgroup, of the patients with Cn >4 mL/mmHg, 30% later underwent MV intervention compared with 69% of those with Cn ≤4 mL/mmHg (P=0.001). The Kaplan-Meier curve (Figure 4) showed that the event-free survival rate was significantly higher in the patients with Cn >4 mL/mmHg than in those with Cn ≤4 mL/mmHg (P<0.001), although patients in this analysis did not have indication for a procedure at baseline.

In 25 patients who underwent percutaneous valvuloplasty and in whom Cn was also measured by catheterization before the procedure, the catheter- and Doppler-derived values for Cn showed reasonable correlation (r=0.60; P=0.002). There was also a good intermethod agreement (noninvasive versus invasive) calculation of Cn as shown by Bland-Altman plot (Figure 5).

**Reproducibility**

For the Cn measurement, 2 independent observers achieved a high level of agreement, with intraobserver correlation coefficients of 0.93 for interobserver variability and 0.97 for intraobserver variability.

**Discussion**

MS is a progressive disease, usually after a stable early course with subsequent progressive clinical evolution. Its prognosis depends mainly on symptoms at presentation, and once limiting symptoms develop, survival is dismal. However, the
clinical presentation of MS varies widely, and symptoms may be inconsistent with the standard measurements of MS severity.28 MS is best described as a disease continuum, with no single value that can define its severity. More specifically, a wide variation in pulmonary pressures for the same range of mitral obstruction emphasizes the need to identify key factors implicated in the development of pulmonary hypertension and functional limitation in MS.5

This study addresses the value of Cn as a predictor of pulmonary artery pressure in rheumatic MS and evaluates the impact of baseline Cn on clinical outcome. The results show that Cn not only contributes to pulmonary hypertension, a basic determinant of functional capacity, but also adds incremental value in predicting clinical outcome beyond that provided by MV area and NYHA functional class.

Cn does not merely reflect severity of symptoms but identifies patients at high risk of ultimately requiring intervention within an intermediate follow-up period. Cn assessed in patients who at baseline were mostly asymptomatic or had mild exercise intolerance (NYHA class I or II) had prognostic importance, highlighting that there are pathophysiologic predictors of adverse outcome apart from symptoms and reduction in valve area.

Previous studies have also indicated that Cn contributes to determining pulmonary hypertension in MS,3,12-14,17,25,29 but these studies had several limitations. Li et al10 could not find any relation between parameters of MS severity and pulmonary pressure from the small number of patients studied. The rate of pressure decay across the MV, which ultimately determines the mean LA pressure that is transmitted to the lungs, also depends on MV area and flow, yielding transmitial gradient.30 Kim et al12 demonstrated the potential value of Cn in predicting MV intervention but with relatively few patients and events, which limited analysis and indicated the need for confirmation by larger studies. Finally, the cutoff value of Cn used for clinical correlation in previous studies9,10 was selected on the basis of an assumed proportion of the statistical distribution of Cn in patients with MS. This cutoff, which might be used to guide patient management, required prospective determination without assumption based on the ability of Cn to predict outcomes.

The present study assessing the role of Cn in patients with MS overcomes these previous limitations. It is prospective and includes a larger number of MS patients with a wide

<table>
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<th>Table 3. Predictors of Adverse Outcome</th>
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<tr>
<td><strong>Baselines Values</strong></td>
</tr>
<tr>
<td>Age, y</td>
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<tr>
<td>NYHA class III–IV, n (%)</td>
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<tr>
<td>Loud P2, n (%)</td>
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<tr>
<td>Atrial fibrillation, n (%)</td>
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<tr>
<td>LAV index, mL/m²</td>
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<tr>
<td>RV MPI</td>
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<tr>
<td>Peak gradient, mmHg</td>
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<td>Mean gradient, mmHg</td>
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<td>MV area, cm²</td>
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<tr>
<td>SPAP, mm Hg</td>
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<td>Cn, mL/mm Hg</td>
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Data are expressed as mean±SD or number (percentage) of patients. Cn indicates net atrioventricular compliance; CI, confidence interval; LAV, left atrial volume; MV, mitral valve; NYHA, New York Heart Association; P2, pulmonic valve closure sound; RV MPI, right ventricular myocardial performance index; and SPAP, systolic pulmonary artery pressure.

*Hazard ratio per 1-SD increase.

<table>
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<tr>
<th>Table 4. Multivariable Cox Proportional Hazards Analysis for Predicting Adverse Outcome</th>
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<tr>
<td>Variables</td>
</tr>
<tr>
<td>NYHA class III–IV</td>
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<tr>
<td>MV area, cm²</td>
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<tr>
<td>Cn, mL/mm Hg</td>
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<tr>
<td>MV area and Cn †</td>
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</tbody>
</table>

Cn indicates net atrioventricular compliance; CI, confidence interval; MV, mitral valve; and NYHA, New York Heart Association.

*Hazard ratio per 1-SD increase.
†Interaction between MV area by planimetry and Cn.
spectrum of severity to address current gaps in the field. The results of this study verify the important contribution of Cn to pulmonary pressure, establishes the prognostic value of Cn, and supports the use of a cutoff value for predicting outcomes, which have also been confirmed by comparing derivation and validation sets.

**Rationale for Prognostic Significance of Net Atrioventricular Compliance**

The decay rate of the atrioventricular pressure gradient is determined by orifice size and left-sided chamber pressures, which in turn are determined by flow and chamber compliance. For a given planimetered MV area, more rapid mitral deceleration (and consequent low Cn) indicates that the atrium is filling on a steeper portion of its pressure-volume curve and is more likely to have higher mean pressure, regardless of the transmural gradient. Therefore, Cn contributes to the overall severity of the disease beyond anatomic valve obstruction itself.

The prognostic value of Cn in general and in asymptomatic patients can be understood in several ways. First, baseline Cn can predict pulmonary hypertension not only at rest but also during exercise or in situations of increased cardiac output in a way that would influence prognosis. Second, for a given orifice area, Cn determines LA pressure, which in turn influences pulmonary artery pressure. Compensatory mechanisms, however, including adjustments of heart rate, cardiac output, and pulmonary vasoreactivity, can delay the onset of symptoms. The ability of baseline Cn to predict subsequent need for intervention, even in initially asymptomatic patients, is consistent with the possibility that Cn can predict progressive deterioration of functional capacity otherwise masked by initial compensation. Third, it is conceivable that low Cn may also induce progressive worsening of function through repeated exertional elevation of left-sided filling pressures, promoting reactive pulmonary vasoconstriction and arteriolar obliteration, which ultimately lead to indications for intervention. Additionally, low Cn can reflect atrial myocardial fibrosis and stiffening, which may be progressive and lead to adverse outcomes in initially asymptomatic patients.

**LA Size and Compliance**

The influence of LA size on compliance has not been established. Previous studies found no correlation between Cn and LA size.9,10,13,31 This study demonstrated a significant but weak correlation. This is reasonable because, as indicated by Schwammenthal et al,9 Cn not only reflects intrinsic compliance but also expresses the position of the left heart on its pressure-volume curve. LA compliance can also be altered as a consequence of atrial fibrillation. Kim et al29 showed higher Cn in atrial fibrillation; in contrast, in a study by Güray et al32 and the present study, Cn was similar in patients with and without atrial fibrillation. Low Cn (and by implication low C) indicates a steeper portion of the pressure-volume curve, probably a shift to the right along an exponential curve as the LA enlarges.
RV Function
Although the hemodynamic consequences of MS affect mainly the RV as mediated by pulmonary hypertension, the pathophysiological mechanisms of RV dysfunction in MS are unclear.16,35 RV dysfunction is not a simple expression of elevated pulmonary artery pressure.35 Pande et al16 showed that RV dysfunction was observed in all cases of rheumatic MS regardless of SPAP. Similarly, Sagie et al46 demonstrated that right heart disease can progress independently of MV area. In our relatively young patients, impaired ventricular SPAP determinants, Cn is the physiologically meaningful variable regardless of SPAP. Similarly, Sagie et al34 demonstrated that RV dysfunction was observed in all cases of rheumatic MS.

Limitations of the Study
Cn is not equal to atrial compliance.9,17 However, in considering SPAP determinants, Cn is the physiologically meaningful variable, not LA compliance alone, because Cn ultimately determines the transmural pressure gradient and pressure-volume curve. In our relatively young patients, impaired ventricular myocardial relaxation is unlikely to have influenced Cn.35 In addition, particularly in MS, the left ventricle fills on the flat low-volume portion at the left end of the pressure-volume curve. Although Cn is a predictor of pulmonary pressure during exercise, exercise echocardiography was not performed. However, even at rest, Cn was powerful enough to predict adverse events.

Clinical Implications
Risk stratification and decisions about valve intervention are most difficult in patients with moderate MS who have a similar anatomic severity of stenosis but varying functional status. In this subset, there may be discrepancies between symptoms and conventional echocardiographic parameters, requiring more complete evaluation of physiology. Baseline Cn may have its greatest use in this subset of patients by providing an additional indication of impaired physiology and progression to the need for intervention in those initially asymptomatic patients with moderate MS and no significant pulmonary hypertension. 40.6% of our overall study population, in whom there is the greatest need for additional decision-making guidance.

Conclusions
In a wide spectrum of severity of MS, Cn contributes to pulmonary hypertension and is a powerful predictor of adverse outcome, adding prognostic information beyond that provided by clinical evaluation and MV area. Importantly, baseline Cn may provide its greatest value by predicting a progressive course with subsequent need for intervention in initially asymptomatic patients. Cn assessment therefore has potential value for clinical risk stratification and monitoring in MS patients.

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Disclosures
None.

References
18. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise JS, Solomon SD, Spencer KT, Sutton MS, Stewart WJ. 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;18:1440–1463.


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**CLINICAL PERSPECTIVE**

Management of patients with mitral stenosis is determined by the severity of obstruction and its hemodynamic consequence expressed by pulmonary hypertension and symptoms. In a subset of patients with limited symptoms, the functional significance of a given obstruction may be difficult to establish, and their management may therefore be uncertain. Net atrioventricular compliance (Cn), a modulator of pulmonary hypertension, is an objective measure obtained noninvasively that helps clarify whether symptoms are related to an inappropriately increased pulmonary pressure at exercise. Furthermore, low Cn predicts adverse outcome, independently of the conventional hemodynamic parameters of stenosis severity. Therefore, assessment of Cn seems to offer important information not only by helping classify the underlying hemodynamic burden of obstruction but also by identifying initially asymptomatic patients who are at high risk of subsequent functional deterioration indicating the need for intervention, in whom a more aggressive monitoring and approach may be warranted.