Valvular Heart Disease

Doppler Estimation of Left Ventricular Filling Pressures in Patients With Mitral Valve Disease

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Background—Conventional Doppler measurements have limitations in the prediction of left atrial pressure (LAP) in patients with mitral valve disease (MVD), given the confounding effect of valve area, left ventricular (LV) relaxation, and stiffness. However, the time interval between the onset of early diastolic mitral inflow velocity (E) and annular early diastolic velocity (Ea) by tissue Doppler imaging (TDI), T_E-Ea, which is well related to the time constant of LV relaxation (τ) in canine and clinical studies, is not subject to these variables. We therefore undertook this study to test its usefulness in a patient population.

Methods and Results—Two-dimensional Doppler and TDI echocardiography were performed simultaneously with right-heart catheterization in 51 consecutive patients (mean±SD age, 64±11 years) with MVD: 35 with moderately severe to severe mitral regurgitation (MR) and 16 with moderate to severe mitral stenosis (MS). Among several Doppler measurements, only the mitral E/A ratio, isovolumetric relaxation time (IVRT), and pulmonary venous Ar duration had significant relations with mean pulmonary capillary wedge pressure (PCWP). The ratio of IVRT to T_E-Ea (for MR, r=-0.92; for MS, r=-0.88; both P<0.001) and the ratio of IVRT to τ (for MR, r=-0.74; for MS, r=-0.85; both P<0.001) had the best correlations with PCWP. In 54 repeat studies, including those performed after MV repair or replacement, these ratios tracked well the changes in PCWP and readily identified changes in mean PCWP by ≥5 mm Hg. A similar correlation was noted in 13 patients with atrial fibrillation (r=-0.92, P<0.01) and in a prospective group of 14 patients with MR (r=-0.93, P<0.001).

Conclusions—The ratio of IVRT to T_E-Ea or to τ can be readily applied for estimating mean PCWP in patients with MVD and can track changes in PCWP after valve surgery. (Circulation. 2005;111:3281-3289.)

Key Words: diastole ■ echocardiography ■ mitral valve ■ regurgitation ■ stenosis

Doppler echocardiography plays a critical role in the management of patients with mitral valve disease (MVD) with respect to both diagnosis and prognosis. However, in a number of patients with either mitral regurgitation (MR) or stenosis (MS), questions arise about the impact of MVD on the presenting symptoms. For example, patients with both significant MS and increased left ventricular (LV) stiffness can have a lower LV gradient (because of increased LV diastolic pressures) and a shorter pressure half-time (because of increased LV stiffness). Accordingly, both measurements can result in an underestimation of the severity of MS. Similarly, patients with pulmonary disease and significant chronic MR but with cardiac compensation may have dyspnea because of a pulmonary rather than a cardiac cause. It is therefore advantageous to assess LV filling pressures in these cases in an attempt to prove or refute a cardiac cause for the shortness of breath. These points are relevant not only for native valves but also for prosthetic or repaired MVs, in which the implications of MVD can be more problematic, given the potential need for repeat surgery.

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In that regard, existing Doppler and 2-dimensional methods have several limitations when applied to the estimation of LV filling pressures in this patient population. For example, left atrial (LA) volumes are frequently increased to compensate for the increase in LA pressure (LAP) and also because of atrial dysrhythmia. Therefore, an enlarged LA can be associated with a normal or only slightly increased LAP. Likewise, there are concerns with the mitral inflow pattern. The mitral inflow peak early diastolic velocity (E) is highly dependent on LAP and LV diastolic function. Therefore, patients with severe MR can have an increased peak E velocity because of the increased stroke volume, despite a normal LAP. Pulmonary venous (PV) flow may also have a limited role, because both MR and MS per se can alter the venous flow pattern, independent of LAP (blunt/absent/reversal of systolic flow in MR or prolonged diastolic flow and its deceleration time [DT] in MS).
As for mitral annular diastolic velocities by tissue Doppler imaging (TDI), there is a paucity of data on their accuracy in this population. However, in the presence of MS, one would expect the peak early diastolic velocity (Ea) to be reduced (owing to decreased LV stroke volume). On the other hand, in patients with MR and normal LV function, Ea would be increased, given the increased LV stroke volume.

Unlike velocities, certain time intervals can be less prone to the confounding effect of the aforementioned hemodynamic variables. In that regard, we and others have previously reported on a novel time interval for the assessment of LV relaxation, namely, the interval between the onset of mitral E and annular Ea, TE\textsubscript{E-Ea}, which is well related to the time constant of LV relaxation (τ) in canine and clinical studies.3,4 Another time interval that has been used clinically is isovolumetric relaxation time (IVRT). IVRT can be acquired with high feasibility and is dependent on both LAP and LV relaxation,5 such that IVRT≈τLAP and TE\textsubscript{E-Ea}≈τ; therefore, IVRT≈TE\textsubscript{E-Ea}/LAP. For the prediction of LAP, LVEFP≈TE\textsubscript{E-Ea}/IVRT or IVRT/TE\textsubscript{E-Ea}×1/LAP.

Because LV end-systolic pressure (LVEFP) also determines LV diastolic pressure at the time of MV opening, a more complete characterization of the relation could be described as LAP=LVEFP×e\textsuperscript{IVRT/T\textsubscript{E-Ea}}.5 LVEFP in turn can be determined noninvasively as LVEFP=0.9×aortic systolic pressure.6

These ratios are particularly appealing for the assessment of LV filling pressures and offer a single approach for the evaluation of MR and MS, because they are not subject to the aforementioned limitations of other Doppler measurements. We therefore undertook this study to test this hypothesis in patients with MV disorders.

Methods

The Institutional Review Board of Baylor College of Medicine approved the protocol, and patients provided written, informed consent. The group comprised 51 consecutive patients (mean±SD age, 64±11 years; 24 women) with MVD (MR or MS) who were undergoing right-heart catheterization. Patients had simultaneous echocardiographic and hemodynamic measurements taken.

Echocardiographic Studies

Patients were imaged in a supine position with an ultrasound system equipped with harmonic imaging, a multifrequency transducer, and TDI capability. After acquiring parasternal and apical views, pulse-Doppler was used to record transmitial and PV flow in the apical 4-chamber view, as previously described.1 TDI was performed in the PW mode to record mitral annular velocities at the septal, lateral, inferior, and anterior areas.7–9 Studies were recorded for later analysis.

Echocardiographic Analysis

The analysis was performed offline without knowledge of hemodynamic data. LV end-diastolic volume (LVEDV), ejection fraction (EF), and LA maximum volume were assessed as recommended by the American Society of Echocardiography.10 In patients with MS, the mean diastolic transmitial pressure gradient and MV area were calculated.11 For those with MR, the regurgitant volume was calculated as the difference between antegrade mitral inflow and LV outflow volumes by using 2-dimensional measurements of LV outflow tract (LVOT) and mitral annulus diameters and PW (pulse wave) Doppler of mitral inflow at the level of the mitral annulus and LVOT outflow. Both PW signals were acquired in apical views.

All Doppler values represent the average of 3 beats. Mitral inflow was analyzed for peak E (early diastolic) and peak A (late diastolic) velocities, E/A ratio, DT of E velocity, and IVRT (interobserver variability, 4±2%). From the PV flow velocities (feasible in 36 of 51, or 71%), systolic filling fraction was computed,13 and the difference between Ar (flow from the LA into the PV with atrial contraction) and transmitial A velocity duration was calculated.14–16 Systolic filling fraction was calculated only in those patients without systolic reversal in PV flow. Ea and late-diastolic mitral annulus velocities at the 4 areas of the mitral annulus were measured, and the dimensionless ratio E/Ea7–9 was computed.

In addition, the time intervals between the peak of the R wave and the onset of mitral E velocity, as well as the time interval between the peak of the R wave and the onset of Ea at the 4 areas of the mitral annulus, were measured. The time required to perform these measurements was, on average, 5 minutes. Several precautions were taken in acquiring TDI signals and performing time interval measurements. First, we used pulse and not color TDI, because temporal resolution is lower with color TDI owing to a lower frame rate needed for longer processing time. Second, low gain and filter settings were applied so the onset of Ea could be reliably identified. This is particularly important, because higher filter settings (that may be adequate for measuring peak Ea velocity but cut the origin of Ea from the baseline) and higher gain settings (that result in a wider spectral envelop of Ea) can preclude accurate timing of the onset of Ea. Third, the scale was adjusted as needed to range from −15 to 20 to +15 to 20 cm/s, and the sweep speed was set at 100 mm/s to achieve the optimal spectral display of myocardial velocities. Finally, identical R–R intervals (≤5 ms) were chosen for timing the onset of mitral E and the onset of mitral annulus Ea, because there can be large differences in diastolic time intervals at slightly different R–R cycle lengths. The difference between the time intervals (TE\textsubscript{E-Ea}; interobserver variability, 5±2%) was computed at the 4 areas, and an average value was derived. τ was derived from TE\textsubscript{E-Ea} by using a previously validated equation:7 →τ=32.0×(TE\textsubscript{E-Ea}).

Hemodynamic Measurements

Hemodynamic data were collected at end-expiration by an investigator unaware of the echocardiographic measurements and represent the average of 5 cycles. Cardiac output was derived by the thermodilution technique (average of 3 cardiac cycles with <10% variation). All pressures, including pulmonary capillary wedge pressure (PCWP; verified by fluoroscopy, phasic changes in pressure waveforms, and oxygen saturation), were determined with balanced transducers (0 level at the midaxillary line). In MS patients undergoing percutaneous commissurotomy, LAP was also recorded (both the v wave and mean LAP were determined).

Repeat Studies

Forty-two patients underwent a total of 54 repeat studies (31 patients with a single repeat study, 10 patients with 2 repeat studies, and 1 patient with 3 repeat studies) after MV surgery (repair in 25 and replacement in 13) or percutaneous commissurotomy (n=4). Echocardiographic imaging was simultaneously acquired with invasive measurements. Hemodynamic and echocardiographic measurements were repeated as described earlier.

Prospective MR Group

The accuracy of the Doppler-derived ratios was tested in a prospective group of 14 patients with MR. Patients had simultaneous Doppler and hemodynamic measurements taken.

Statistical Analysis

Continuous data are presented as mean±SD. Regression analysis was used to relate PCWP to the echocardiographic measurements. Receiver operating characteristic curves were used to determine the threshold Doppler values that separated patients with PCWP >15 mm Hg from those with PCWP ≤15 mm Hg. Multiple linear regression analysis was performed to determine the predictors of increased PCWP, including Doppler ratios, type of MVD (MR or...
TABLE 1. Summary of Hemodynamic and Echocardiographic Measurements in Initial Studies

<table>
<thead>
<tr>
<th></th>
<th>Total Group (n=51)</th>
<th>MR (n=35)</th>
<th>MS (n=16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate, bpm</td>
<td>78± 16</td>
<td>77± 17</td>
<td>78± 14</td>
</tr>
<tr>
<td>Mean arterial pressure, mm Hg</td>
<td>84±12</td>
<td>85±11</td>
<td>81±13</td>
</tr>
<tr>
<td>Mean pulmonary pressure, mm Hg</td>
<td>32±10</td>
<td>30±9</td>
<td>36±13</td>
</tr>
<tr>
<td>Mean right atrial pressure, mm Hg</td>
<td>13±6</td>
<td>12±4</td>
<td>15±7</td>
</tr>
<tr>
<td>Mean PCWP, mm Hg</td>
<td>22±8</td>
<td>20±7</td>
<td>25±8</td>
</tr>
<tr>
<td>LVEDV, mL</td>
<td>138±39</td>
<td>151±37</td>
<td>111±29</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>62±17</td>
<td>61±20</td>
<td>65±8</td>
</tr>
<tr>
<td>Left atrial volume, mL</td>
<td>102±49</td>
<td>106±40</td>
<td>103±19</td>
</tr>
<tr>
<td>Mitral E/A</td>
<td>2.2±1.3</td>
<td>2.46±1.4</td>
<td>1.5±0.5</td>
</tr>
<tr>
<td>IVRT, ms</td>
<td>71±23</td>
<td>73±23</td>
<td>61±16</td>
</tr>
<tr>
<td>Average annular Ea, cm/s</td>
<td>7.5±2.5</td>
<td>8.5±2.2</td>
<td>5.3±1.4</td>
</tr>
<tr>
<td>Average annular Aa, cm/s</td>
<td>6±2.4</td>
<td>6±2.2</td>
<td>4.7±2.1</td>
</tr>
<tr>
<td>Average E/Ea</td>
<td>21±15</td>
<td>12.8±4.62</td>
<td>38±16</td>
</tr>
<tr>
<td>Average T_E-Ea ms</td>
<td>28±22</td>
<td>23±20</td>
<td>39±21</td>
</tr>
</tbody>
</table>

MS), and sex. A Kruskal-Wallis 1-way ANOVA on ranks was performed to compare mean PCWP and the IVRT/TE among 3 groups of patients: those with MR and PCWP >15 mm Hg, those with MR and PCWP ≤15 mm Hg, and normal subjects without MR and with a normal mean PCWP. Pairwise multiple comparisons were performed by Dunn’s method. P≤0.05 was considered significant.

Results

Table 1 presents the hemodynamic and echocardiographic measurements at the time of the initial studies for all patients, divided according to whether they had MR or MS. There were 35 patients with MR and 16 patients with MS (2 patients with MS also had moderate MR). Mean PCWP for the 51 patients was 22±8 mm Hg and ranged from 11 to 37 mm Hg. Figures 1 and 2 show examples of pressure and Doppler recordings from 2 patients.

Prediction of Mean PCWP in Patients With MR

The 35 patients with MR had a mean PCWP of 20±7 mm Hg (Table 1). Both LVEDV and LAESV were increased. Twenty patients had hypertension and 4 had diabetes mellitus. The cause of MR was myxomatous MVD in 22 patients, incomplete mitral leaflet closure with LV dilatation and depressed LVEF in 10 patients, endocarditis in 2 cases, and hypertrophic obstructive cardiomyopathy in 1. Recording of PV flow was feasible in 24 of 35 (69%) patients. The mean regurgitant volume was 48±16 mL, with a mean regurgitant fraction of 49±10%, signifying moderately severe to severe MR lesions.

Table 2 shows the correlations between mean PCWP and several echocardiographic measurements. Although significant relations between mean PCWP and mitral peak E velocity, Ar-A duration, and E/Ea were noted, stronger correlations were present with IVRT (r=−0.59, P<0.001), ratio of IVRT to TE (r=−0.92, P<0.001; Figure 3), and τ (r=−0.74, P<0.001; Figure 3).

The mean difference between Doppler and catheter PCWP by IVRT/TE was 0.0±2.7 mm Hg; with the use of IVRT/τ, the mean difference was 0.0±4.6 mm Hg, whereas with LVEVP and IVRT/τ, the mean difference was 0.0±4.3 mm Hg.

For prediction of a mean PCWP >15 mm Hg and with the use of receiver operating characteristic curves, an IVRT/TE <5.59 (Figure 5) had a sensitivity of 100% (95% confidence interval [CI], 73.5% to 100%) and a specificity of 100% (95% CI, 85% to 100%). The area under the receiver operating characteristic curve was 1 (P<0.001). An IVRT/τ <1.73 had a similar performance, with an area under the curve of 0.9 (P=0.001).

Prediction of Mean PCWP in Patients With MR and Normal EF

There were 25 patients (10 women) with normal EF (defined as >50%) and MR. Mean PCWP was 20±7 mm Hg (range,
11 to 37), and mean EF was 72±7%. Mean arterial pressure was 86±12 mm Hg, whereas mean pulmonary artery pressure was 30±9.5 mm Hg. Similar to the overall group with MR, the best correlations were noted with the time intervals or their ratios \((r \text{ ranging from } 0.56 \text{ to } 0.78, \ P < 0.01)\). Significant but weak correlations were present with mitral inflow E/A \((r = 0.51, \ P = 0.018)\) and Ar-A duration \((r = 0.56, \ P = 0.02)\). However, no significant correlations were noted with peak E velocity \((r = 0.29, \ P = 0.17)\) or E/Ea \((r = 0.13, \ P = 0.55)\).

For prediction of a mean PCWP >15 mm Hg, an IVRT/TE \(\leq 3\) had a sensitivity of 71\% (12 of 17 patients correctly identified) and a specificity of 88\%.

**Prediction of Mean PCWP in Patients With MR and Depressed EF**

There were 10 patients (4 women) with depressed EF and MR. Mean PCWP was 21±8 mm Hg (range, 12 to 36), and mean EF was 29±13\%. The mean arterial pressure was 83±11 mm Hg, whereas mean pulmonary artery pressure was 30±9 mm Hg. Similar to the overall group with MR, the best correlations were noted with the time intervals or their ratios \((r \text{ ranging from } -0.65 \text{ to } -0.86, \ P < 0.01)\), but good correlations were also observed between mean PCWP and mitral inflow peak E velocity \((r = 0.73, \ P = 0.017)\) and E/Ea \((r = 0.72, \ P = 0.018)\). For prediction of a mean PCWP >15 mm Hg, an IVRT/TE \(\leq 3\) had a sensitivity of 80\% (4 of 5 patients correctly identified) and a specificity of 100\%. However, caution should be exercised with regard to the calculated accuracy, given that only 10 patients were in this subgroup.

**Prediction of Mean PCWP in Patients With MS**

These 16 patients (mean±SD age, 67±11 years; 10 women) had a mean PCWP of 25±8 mm Hg (range, 12 to 34). Mean LVEF was 65±8\%, with a mean LA volume of 103±19 mL. Ten patients had hypertension and 2 had diabetes mellitus.
For patients with MS, the mean gradient across the MV was 7.8 ± 3.3 mm Hg, with a valve area of 1.29 ± 0.3 cm², signifying moderate to severe MS. Recording of PV flow was feasible in 9 of 16 patients (56%).

Table 2 presents the correlation between several Doppler measurements and mean PCWP. The only significant relations were noted with IVRT (r = -0.62, P = 0.01), IVRT/T_E-Ea (r = -0.88, P < 0.001), and IVRT/τ (r = -0.85, P < 0.001; Figure 4). The mean difference between Doppler and catheter PCWP from IVRT/T_E-Ea was 0.2 ± 3.6 mm Hg; from IVRT/τ, the mean difference was 0.0 ± 4.1 mm Hg; whereas with LVESP and IVRT/τ, the mean difference was 0.0 ± 3.8 mm Hg.

For prediction of a mean PCWP >15 mm Hg, an IVRT/T_E-Ea <4.16 (Figure 5) had a sensitivity of 100% (95% CI, 70% to 100%) and a specificity of 100% (95% CI, 78% to 100%). The area under the receiver operating characteristic curve was 1 (P = 0.008). An IVRT/τ <1.42 had a similar performance, with an area under the curve of 0.93 (P = 0.02).

Relation Between Mean PCWP and IVRT/T_E-Ea in Patients With and Without MVD

To address the effect of MR on our hypothesis (ie, IVRT/T_E-Ea ×1/LAP), IVRT/T_E-Ea was compared among 3 groups: patients with MR and a PCWP >15 mm Hg (group 1), patients with MR and a PCWP ≤15 mm Hg (group 2), and subjects without cardiovascular disease and with normal cardiac function (group 3; 15 healthy individuals with no cardiac symptoms; no history of heart failure, hypertension, or coronary artery disease; normal LV volumes; an EF of 65%; lack of regional wall motion abnormalities; absence of valvular disease; normal filling pressures with a mean PCWP of 12 ± 3 mm Hg; and τ = 34 ± 4.8 ms). These patients were in the intensive care unit because of medical problems: pneumonia in 6, sepsis in 6, and bleeding in 3). The normal group was included in a previous report.4

Mean PCWP was significantly different among the 3 groups (P < 0.001 by Kruskal-Wallis test): PCWP for group 1 was 24 mm Hg (25th to 75th percentile, 20 to 28) versus 12 mm Hg (25th to 75th percentile, 11 to 13.5) for group 2 and 11 mm Hg (25th to 75th percentile, 10 to 12) for group 3. Pairwise multiple comparisons revealed that mean PCWP was significantly higher in patients in group 1 than in the other 2 groups (P < 0.05), with no significant difference in mean PCWP between groups 2 and 3.

Mitral Stenosis

For patients with MS, the mean gradient across the MV was 7.8 ± 3.3 mm Hg, with a valve area of 1.29 ± 0.3 cm², signifying moderate to severe MS. Recording of PV flow was feasible in 9 of 16 patients (56%).
Likewise, IVRT/Tₑₑₑₐₑₑ was significantly different among the 3 groups ($P<0.001$ by Kruskal-Wallis test): 2.6 for group 1 (25th to 75th percentile, 1.43 to 2.98) versus 11.2 (25th to 75th percentile, 8.1 to 27) for group 2 versus 11.2 (25th to 75th percentile, 8.13 to 15) for group 3. Pairwise multiple comparisons revealed that IVRT/Tₑₑₑₐₑₑ was significantly lower in patients in group 1 than in the other 2 groups ($P<0.05$), with no significant difference in IVRT/Tₑₑₑₐₑₑ between groups 2 and 3 (patients with normal PCWP, irrespective of MR).

To evaluate the relation between mean PCWP and IVRT/Tₑₑₑₐₑₑ in patients with and without MR but with a similar wide range of PCWP, regression (inverse first order, where $y=y₀+a/x$) analysis was applied. Figure 6 shows the regression plots between mean PCWP and IVRT/Tₑₑₑₐₑₑ in age- and sex-matched patients (included in previous reports$^4,7$) without (n=51, closed circles, continuous line, $r^2=0.92$, $P<0.0001$) and with (n=51, open squares, dashed line, $r^2=0.79$, $P<0.0001$) MVD. In both groups, a significant inverse correlation was present.

Repeat Studies
On repeat studies, the change in mean PCWP ranged from $-11$ to $+20$ mm Hg. The changes in mean PCWP had significant correlations ($P<0.01$) with IVRT ($r=-0.66$), IVRT/Tₑₑₑₐₑₑ ($r=-0.75$), and IVRT/Tₑₑₑₑₑ ($r=-0.81$), with the last variable having the best correlation (Figure 7). There were 22 repeat measurements, with a decrease in mean PCWP by $\geq 5$ mm Hg. An increase in IVRT/Tₑₑₑₐₑₑ by $\geq 1.5$ readily identified 21 of these 22 (95%) occasions. Seven of the 9 instances (78%) with a decrease in PCWP by $<5$ mm Hg had an increase in IVRT/Tₑₑₑₐₑₑ of $<1.5$.

There were 6 patients who had an increase in mean PCWP of $\geq 5$ mm Hg on repeat studies. A decrease in IVRT/Tₑₑₑₐₑₑ of $\geq 3$ readily identified all of them. Twelve of the 16 patients (75%) with an increase in PCWP of $<5$ mm Hg had a decrease in IVRT/Tₑₑₑₐₑₑ of $<3$.

Prospective MR Group
The prospective MR group (n=14) had a mean regurgitant volume of 45$±$13 mL and a mean regurgitant fraction of 46$±$8%. The cause of MR was myxomatous MVD in 6 patients, incomplete mitral leaflet closure with LV dilatation and depressed LVEF in 5 patients, and hypertrophic obstructive cardiomyopathy in 3 patients. The mean PCWP of the group was 21$±$8 mm Hg (range, 9 to 35). The relation of mean PCWP to IVRT/Tₑₑₑₐₑₑ (Figure 8) was highly significant ($r=-0.93$, $P<0.001$). An IVRT/Tₑₑₑₐₑₑ <5.59 readily identified the 9 patients with a mean PCWP >15 mm Hg from the 5 patients with a mean PCWP of $\leq 15$ mm Hg (sensitivity and specificity of 100%).

Application of Doppler Ratios in Patients With Atrial Fibrillation
To evaluate the Doppler ratios in the presence of atrial fibrillation, IVRT, mitral inflow, and TDI (by PW) recordings were acquired in patients with MVD and atrial fibrillation. To ensure an adequate number of cycles for analysis, 20 cardiac cycles were recorded at each of the mentioned sites. Because all diastolic time intervals can change widely and to varying degrees, identical R-R cycle lengths were chosen from mitral

$\text{Figure 6. Relation between mean PCWP and IVRT/Tₑₑₑₐₑₑ in patients without (solid circles and continuous line, n=51; y=7.5±25.5/x, r=-0.96, P<0.0001) and with (open squares and dashed line, n=51; y=14±14.66/x, r=-0.89, P<0.0001) MVD.}$

$\text{Figure 5. Receiver operating characteristic curve for accuracy of IVRT/Tₑₑₑₐₑₑ in predicting mean PCWP >15 mm Hg in patients with MR (left) and MS (right).}$
inflow and annular TDI signals to measure IVRT and \( T_{E-E_a} \). This analysis was feasible in all 13 patients in this subgroup. We noticed that with an adequate number of cardiac cycles recorded, it is feasible to identify matching R-R intervals for the aforementioned Doppler measurements in patients with atrial fibrillation (all patients with atrial fibrillation and not limited to only those with MV pathology) in 90% of cases.

The 13 patients (mean \( \pm SD \) age, 66 \( \pm 10 \) years; 6 women) had a mean PCWP pressure of 24 \( \pm 6 \) mm Hg (range, 9 to 33). Mean LVEF was 54 \( \pm 11 \)%, with a mean LA volume of 116 \( \pm 25 \) mL. Mean MR regurgitant volume was 47 \( \pm 19 \) mL, with a mean regurgitant fraction of 50 \( \pm 15 \)%.

A good correlation was noted between mean PCWP and the ratio of IVRT to \( T_{E-E_a} \) \( (r=-0.92, \ P<0.001; \text{Figure 9}) \). An IVRT/\( T_{E-E_a} \) \( \leq 5.59 \) readily identified the 8 patients with PCWP \( >15 \) mm Hg from the 5 patients with a PCWP \( \leq 15 \) mm Hg. Although the results in this subset are promising, caution should be used when extrapolating from these data because there were only 13 patients in this subgroup.

### Predictors of Mean PCWP

In the multiple regression model, including the novel Doppler ratios, sex, and MV pathology, only the Doppler ratios (IVRT/\( T_{E-E_a} \) or IVRT/\( \tau \), both \( P<0.001 \)) accounted for the ability to predict mean PCWP. MV pathology (MR or MS) did not determine whether PCWP was increased or not \( (P=0.38) \), and likewise, sex was not a predictor of elevated PCWP \( (P=0.91) \). Similarly, in patients with repeat measurements and in the prospective group (model including sex and Doppler ratios only), the only significant variables predictive of mean PCWP were the Doppler ratios.

### Discussion

The present study supports the use of the ratio of IVRT to \( T_{E-E_a} \) or \( \tau \) for the estimation of LAP in patients with MVD. In addition, IVRT/\( T_{E-E_a} \) or IVRT/\( \tau \) successfully tracks changes in mean PCWP after MV repair or replacement. On the contrary, conventional parameters of LV diastolic function are of limited value. Interestingly, a number of patients with significant MR had a mean PCWP \( <15 \) mm Hg, emphasizing the importance of assessment of PCWP in this patient population.

### Mitral Inflow for Prediction of LV Filling Pressures in Patients With MVD

Previous studies have reported on the estimation of mean PCWP by using mitral inflow in patients with MR\(^{17,18}\) and in
patients with atrial fibrillation. In one study, only patients in advanced heart failure (New York Heart Association class III–IV) and with a severely depressed EF were included, and MR severity was assessed by regurgitant jet area. In that report, several measurements derived from mitral inflow related well to PCWP, including IVRT, E/A, and DT. However, the best correlations between Doppler measurements and PCWP were observed in patients without significant MR. In the other report, which included patients with normal and depressed EF and who had varying severity of MR, E/A and DT had only modest relations with LVEDP and were significantly related to MR volume. For patients with atrial fibrillation and no significant MVD, DT was useful only in the group with depressed but not normal EF.

In our study in patients with MVD (with and without atrial fibrillation), there were weak relations between PCWP and mitral inflow velocities. The finding of weak relations between mean PCWP and mitral inflow velocities is expected, given the confounding effects of LV relaxation, LV stiffness, LAP, and MV area on these measurements. Patients with severe but compensated chronic MR usually have an increased transmitral flow with an increased E velocity and E/A, despite a mean PCWP that falls within the normal range. In fact, a previous study has shown that peak E velocity can be used as a marker of MR severity. Likewise, patients with MS have a prolonged DT despite an elevated LAPs due to valvular stenosis, and DT (or pressure half-time) itself can be used to grade the severity of MS. It is therefore not surprising that estimation of PCWP from mitral peak diastolic velocities and DT in patients with MVD was inaccurate in our study.

**PV Flow for Prediction of LV Filling Pressures**
We analyzed several parameters derived from PV flow velocities. Only the duration of the Ar signal reached the level of statistical significance in patients with MR. Nevertheless, it was less accurate than the ratio of IVRT to T_{E-Ea} or T_{E-a}. Previous studies have shown that the velocity, duration, and time-velocity integral of Ar are correlated best with late LV diastolic pressures (LVEDP and A rise in LV diastolic pressure). Because MVD primarily influences early LV filling and pressures, late diastolic Doppler measurements (including Ar) are expectedly less affected by the altered LV filling in these patients. However, because Ar relates best to late diastolic LV pressures, we observed only modest correlations of Ar with mean PCWP.

Unlike the higher accuracy of systolic filling fraction in other patient groups, it was not useful for predicting PCWP in this group of patients with predominantly normal EF and significant MVD. Similarly, DT of the PV flow diastolic velocity was not accurate in predicting mean PCWP, given the presence of significant MV pathology. The lack of a significant correlation with mean PCWP was noted in both MR and MS patient groups.

**TDI Velocities**
With regard to TDI velocities, we made a number of important observations. Ea velocity was reduced in patients with MS, despite a normal EF (Table 1) and was positively correlated with regurgitant volume in patients with MR (r=0.5, P<0.05). Given the observed relations between Ea and MR volume, E/Ea did not improve the predictive role of mitral E velocity alone, underscoring an important limitation in using E/Ea for the prediction of LAP in patients with significant MVD. Similar observations were recently reported in which E/Ea was not predictive of LVEDP in patients with MR due to myxomatous MVD.

**Time Intervals**
Unlike Doppler velocities, we noted a good correlation between IVRT and mean PCWP. This time interval has been used for decades in the clinical evaluation of patients with MS, being shorter in patients with more severe MS.

However, LV relaxation also influences IVRT. We therefore attempted to correct for the effect of LV relaxation on IVRT by using the T_{E-Ea} time interval, given previous observations in canine studies and patients, showing a strong correlation between T_{E-Ea} and T_{E-Ea}. Expectedly, the ratio of IVRT to T_{E-Ea} and the ratio of IVRT to Doppler-derived T_{E-Ea} were more accurate than IVRT alone. Importantly, it was clinically applicable, irrespective of the cause of MVD, be it MR or MS.

**Limitations**
Although we included patients with MR and MS, there were more cases with MR than MS. However, we were still able to test the clinical usefulness of the ratio of IVRT to T_{E-Ea} and to Doppler-derived T_{E-Ea} in both patient groups. There were fewer patients with MR due to LV systolic dysfunction and a depressed EF. Therefore, we are limited in extrapolating conclusions to this particular subgroup. However, a previous study showed that the ratio of mitral E to annular Ea is clinically useful in these patients. More important, the same investigators showed the absence of a significant correlation between this ratio and LVEDP in patients with primary MV pathology, a group that constituted the majority of our patient cohort. Additional studies are warranted in patients with prosthetic MVs.

We used mean PCWP in lieu of LAP. This was done because most patients (excluding MS patients being evaluated for percutaneous commissurotomy) underwent right-heart catheterization to measure mean PCWP in place of transseptal puncture (with its extra costs and risks) for estimation of mean LAP. It was therefore not ethically possible to proceed with transseptal puncture for the sole purpose of this investigation in most of the patients in this study.

The Doppler-derived time intervals may not be accurate if acquired and performed by inexperienced operators, and careful attention to gain, filter settings, scale, sweep speed, and R-R cycle length is needed for reliable measurements. In subjects with normal diastolic function and simultaneous onset of mitral E and annular Ea, the ratio of IVRT to T_{E-Ea} cannot be applied to predict LAP. The complete separation of patients with MVD into 2 subgroups according to PCWP (≤15 or >15 mm Hg) according to the ratio of IVRT to T_{E-Ea} was noted in relatively few cases with MR and normal EF or with MS and is unlikely to occur in a larger
sample. Given the curvilinear relation between mean PCWP and the ratio of IVRT to $T_E-E_A$, as well as the CIs, this Doppler ratio is most reliable in identifying patients with PCWP $>$ 15 mm Hg. Notwithstanding these considerations, our application of this time interval in this and other studies was highly reproducible, and increasing experience with its measurement will likely enhance its clinical usefulness for the assessment of LAP.

References
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