Mitral valve areas determined by Doppler pressure half-time were compared with areas obtained by planimetry in two groups of patients with mitral stenosis: 24 patients without aortic regurgitation and 32 patients with more than grade 1 aortic regurgitation. The severity of aortic regurgitation was assessed by color flow mapping; 17 patients had grade 2, 10 had grade 3 and 5 had grade 4 aortic regurgitation. Regression equations for pressure half-time area versus planimetry mitral valve area were calculated separately for the aortic regurgitation ($r = 0.88$) and the noaortic regurgitation group ($r = 0.86$); analysis of covariance revealed a significant ($p < 0.001$) difference between the two groups leading to overestimation of planimetry area by the pressure half-time method in the aortic regurgitation group. The mitral valve areas in the group without regurgitation were best calculated with the expression $239TV\sqrt{s}$ ($r = 0.77$) as compared with a best fit of $195TV\sqrt{s}$ ($r = 0.85$) for the aortic regurgitation group.

The noninvasive assessment of mitral stenosis was one of the earliest accomplishments of echocardiography (1). Mitral planimetry by two-dimensional echocardiography became a standard method for estimating mitral valve area (2). Doppler ultrasound (3) permitted direct conversion from transmural velocity into atrioventricular (AV) pressure gradient by use of the simplified Bernoulli equation. Thus, it became possible to determine noninvasively the mitral pressure half-time, the time required for the transvalvular pressure gradient to decay to half of its maximal value, a measure originally developed from cardiac catheterization data (4). It was noted that the half-time varied approximately inversely to the valve area. An empiric relation was derived (5) and gained wide acceptance for native (6,7) and prosthetic mitral valves (8,9):

$$MVA = \frac{220}{TV\sqrt{s}},$$

where MVA is mitral valve area ($cm^2$) and $TV\sqrt{s}$ is pressure half-time (ms).

Although the half-time method has been widely accepted, only recently has the physical basis for this empiric relation been examined and potential sources of error identified. For example, the pressure half-time has been shown to depend
on factors other than mitral valve area such as chamber compliance and pressure gradient (10), which render it less reliable in the acute setting of percutaneous mitral valvotomy (11). In an earlier report (12) we suggested that concomitant aortic regurgitation affects the accuracy of the preceding equation. However, this is a controversial issue with other investigators reporting that aortic regurgitation shortens (13), lengthens (14) or has little effect (15) on pressure half-time.

To clarify the effect of aortic regurgitation, we studied a second patient group to confirm our original observations. Then, recognizing the limitations of the clinically acquired data, we further analyzed this problem in vitro and in a mathematical model to understand the underlying physical principles and thus to explain and validate the clinical observations.

Methods

Clinical Study

Clinical data were obtained by reviewing the echocardiograms recorded in the years 1987 to 1988 of consecutive patients with mitral stenosis and aortic regurgitation who had 1) adequate two-dimensional images in the parasternal long- and short-axis views to perform mitral valve area planimetry; 2) suitable continuous wave Doppler recordings of transmitial flow from the apical position; and 3) Doppler color flow recordings of aortic regurgitation in parasternal long- and short-axis views, as well as apical five chamber and apical long-axis views.

The echocardiograms were obtained using a commercially available instrument (Hewlett-Packard 77090) equipped with a 2.5 MHz transducer for two-dimensional echocardiography with integrated pulsed wave and color Doppler recording and a separate continuous wave Doppler transducer. Mitral valve planimetry was performed on short-axis views of the mitral valve. Linear dimensions of the left atrium, left ventricle and interventricular septum were obtained as recommended (16).

Continuous wave Doppler tracings of transmitial flow in the apical four chamber view were recorded on hard copy using a strip chart recorder. Pressure half-time was measured (averaging five beats in sinus rhythm, seven in atrial fibrillation) manually. Only beats with more than a 300 ms diastolic filling period were analyzed because the pressure half-time often could not be reliably measured in shorter beats. The presence and severity of aortic regurgitation (grades 0 to 4) was judged based on the ratio of the cross sections of the regurgitant color jet and the left ventricular outflow tract, as previously described (17). Mitral regurgitation (grades 0 to 4) was graded by Doppler color jet area (16).

Patients with grade I aortic regurgitation were excluded from study because, although they cannot be considered normal, the hemodynamic significance of the lesions appears negligible. Also excluded were patients with previous mitral valve surgery or valvuloplasty.

The control group consisted of 24 consecutive patients with mitral stenosis but no aortic regurgitation who were examined in our laboratory during the same period with the same examination protocol.

In Vitro and Mathematic Analysis

Because variation in clinical measurement might account for some of the variability in the previously reported results, we also studied the physical effects of aortic regurgitation on the pressure half-time using mathematical and in vitro modeling to more precisely define the governing relations. From previous analytic and experimental work, it was anticipated that changes in ventricular compliance might also significantly affect the impact of aortic regurgitation on the pressure half-time and this issue was addressed in vitro and with a mathematic model of ventricular filling.

In vitro model. Our in vitro model of transmitial flow has been described previously (19). In short, it consisted of two rectangular Plexiglas boxes modeling an atrium and a ventricle connected through an orifice that could be varied in size and shape. It was filled with 25% (by weight) glycerol and saline solution, a mixture similar to blood in density and viscosity. To operate the model the ventricular chamber was sealed and air pumped in, forcing fluid backward through the orifice. Chamber pressure and valvular flow rate were digitized at 20 to 100 Hz from valve opening to pressure...
Aortic regurgitation was simulated by simultaneous manual injection of fluid into the ventricle during transmural flow. Our data were generated with 200 ml of transmural flow and a regurgitant volume between 30 and 90 ml, injected gradually by hand during transmural filling, yielding regurgitant fractions between 10% and 45%. Chamber compliance was adjusted by inserting vertical Plexiglas blocks into the atrial or ventricular sides of the model. These decreased the cross-sectional area of the chamber so that less fluid was required to raise pressure by 1 mm Hg (20).

Computer model. We have previously described (19,20) a lumped variable mathematic model of mitral filling that uses descriptions of atrial and ventricular compliance and mitral impedance to predict the time course of transmural blood velocity and atrial and ventricular pressure. For the current simulation we incorporated two additional equations to model diastolic pressure-velocity relations in the presence of aortic regurgitation. This extended model had five variables: atrial (pA), ventricular (pV) and aortic pressure (pA0); and the velocity across the mitral valve (vMV) and the regurgitant velocity across the aortic valve (vAV). Several additional variables were also specified. The relation between changes in chamber volume and pressure was given by compliance in the atrium (CA), ventricle (CV) and aorta (AA). Also specified were the effective area of the mitral valve (AM) and the regurgitant orifice of the aortic valve (AR); when multiplied by the corresponding velocity, these yielded the forward and regurgitant flow rate, respectively. The blood passing through each valve also had associated with it an inertial term (MM and MV) in large part determined by the distance over which blood accelerates approaching the valve. Blood density was given by \( \rho \) (1.05 g/ml). Finally, because blood in the aorta could exit through the arterioles, we also specified the systemic vascular resistance (SVR).

The temporal derivatives of the chamber pressures and valvular velocities were given by five coupled nonlinear differential equations:

\[
\begin{align*}
\frac{dv_{MV}}{dt} &= (pA - pV - \gamma pV^2) / MMV \\
\frac{dv_{AV}}{dt} &= (pA0 - pV - \gamma pV^2) / MAV \\
\frac{dpA}{dt} &= -AMVvMV / CA \\
\frac{dpV}{dt} &= (AMVvMV + MAVvAV) / CV \\
\frac{dpA0}{dt} &= (-AMVvMV / CA) - pA0(CA / SVR) 
\end{align*}
\]

The first two equations are representations of Newton’s second law of motion: Acceleration (dv/dt) = Force + Mass. The final three equations simply use the definition of compliance to couple flow into or out of the three chambers to pressure change in those chambers.

Because these five equations were not solvable analytically, they were integrated numerically with the fourth order Runge-Kutta method (20) at 1 ms intervals until mitral flow velocity fell to zero. Pressure half-time was calculated from the computed AV pressure gradient and related to changes in mitral valve area, ventricular compliance and aortic regurgitant area. With other variables held constant, pressure half-time was related to ventricular compliance and aortic regurgitant fraction (produced by changes in aortic regurgitant area).

Statistics

Clinical study. Statistical analysis of the clinical data was done in three ways:

1. Analysis of covariance was performed with pressure half-time area as the dependent variable, presence of aortic regurgitation as the grouping variable and valve area obtained by planimetry as the covariate.

2. To investigate other possible factors affecting the mitral half-time, a multinomial regression model was constructed with pressure half-time area as the dependent variable. Planimetry-determined mitral valve area, presence and severity of aortic regurgitation, age, gender, left ventricular end-diastolic diameter, left atrial diameter, interventricular septal thickness, presence of aortic stenosis (indicated by a mean systolic gradient >10 mm Hg) and severity of mitral regurgitation were entered as independent variables in a stepwise fashion. An independent variable was considered significant if its inclusion improved the multiple linear regression model at a p < 0.05 level.

3. Finally, we used nonlinear least squares regression to obtain the optimal parameter K in the expression: \( TV = K / MAV_{\text{planimetry}} \) for patients with and those without aortic regurgitation. The standard error of the estimate was used to determine if the values of K differed significantly in the two groups and if each differed from the commonly applied constant of 220.

In vitro study. Linear regression analysis was performed on the in vitro data from multiple runs with different orifice areas and regurgitant fractions. To normalize for different mitral orifice areas and initial pressure gradients, we used the ratio of measured pressure half-time to baseline pressure half-time (without regurgitation) as the dependent variable. Regurgitant fraction was used as the independent variable and the effect of alterations in compliance on the absolute pressure half-time was analyzed.

Results

Clinical Study

Study patients. Thirty-two patients with mitral stenosis and more than grade I aortic regurgitation met the entry...
requirements and were analyzed; 17 patients were judged to have grade 2, 10 grade 3 and 5 grade 4 aortic regurgitation. Table 1 displays clinical and echocardiographic data from these patients with data from 24 control patients with mitral stenosis but without aortic regurgitation.

Figure 2 compares planimetry- with half-time-derived mitral valve area for one patient without concomitant aortic regurgitation (Fig. 2, top; both planimetry- and Doppler pressure half-time derived area are 1.4 cm²). Bottom, Patient with mitral stenosis and grade 3 aortic regurgitation. Note overestimation of mitral valve area by the pressure half-time formula (right, 1.3 cm²) as compared with planimetry (left, 0.9 cm²).

Predictors of pressure half-time mitral valve area. Multiple regression analysis demonstrated that presence of aortic regurgitation (p < 0.001) and planimetry-derived mitral valve area (p < 0.0001) were the only significant predictors of T½-derived mitral valve area: T½-MVA = 0.87P-MVA + 0.22AR + 0.39, where T½-MVA is pressure half-time-derived area (cm²), P-MVA is planimetry-determined area (cm²) and AR is aortic regurgitation in values from 0 (absence) to 1 (presence). This indicates that on average the presence of aortic regurgitation added approximately 0.22 cm² to the half-time area. Age, gender, severity of mitral regurgitation, left atrial dimension, left ventricular end-diastolic diameter and presence of aortic stenosis did not significantly predict the T½ area. Severity of aortic regurgitation did not significantly improve the prediction compared with presence or absence of aortic regurgitation alone.

Finally, we obtained the best fit for the empiric constant (corresponding to the currently used 220) in the pressure half-time formula separately for both groups (Fig. 4). The planimetry-determined areas in the group without regurgitation were best calculated by 2391/2 (r = 0.77) and in the regurgitation group 1951/2 yielded the best estimate (r = 0.85). These constants were significantly different from each other (p < 0.001) and from the commonly applied 220.

These results are virtually identical with those we have previously reported for an earlier study group of patients (12).
Figure 3. Relation between planimetry-derived and pressure half-time mitral valve areas (MVA). The line of identity is shown; note that most of the data points of the aortic regurgitation (AR) group (n = 32) (squares) are located above the line of identity, indicating overestimation of planimetry-determined area by pressure half-time in the presence of aortic regurgitation. Some data points overlap. Most data points of the group without regurgitation (n = 24) (circles) lie under the line of identity, representing underestimation of planimetry-determined area by the pressure half-time method. Regression lines for each group are also displayed. The regression equation (where x denotes planimetry-determined area and y denotes Doppler-derived area) is y = 0.99x + 0.14 (n = 32, r = 0.91, p < 0.0001, SD = 0.20) for the group with regurgitation and y = 0.76x + 0.14 (n = 24, r = 0.86, p < 0.0001, SD = 0.22) for the group without regurgitation.

In Vitro Study

Pressure half-time versus regurgitant fraction. Figure 5 displays the pressure half-times measured from four experiments with the same initial gradient, orifice area and compliance but with increasing regurgitant fraction. Analysis of the relation between pressure half-time and regurgitant fraction in 18 model runs yielded the following regression equation: y = -0.48x + 99.41 (r = 0.91, p < 0.0001), where y is the pressure half-time expressed as percent of baseline (no regurgitation) pressure half-time to normalize for different orifice areas and initial pressure gradients; x is aortic regurgitant fraction in percent.

Role of ventricular compliance. Figure 6 demonstrates how changes in ventricular compliance confound the effects of aortic regurgitation on pressure half-time. Shown are four runs of the in vitro model displaying the time course of the transvalvular pressure gradient with and without 60 ml of aortic regurgitation and in the presence of high and low ventricular compliance. Regurgitation caused half-time to decrease considerably at both compliance settings. However, an increase in ventricular compliance largely counteracts the effect of aortic regurgitation on TV1/2. Thus, the high compliance curve with regurgitation has a longer half-time than the low compliance curve without regurgitation. This indicates that, if chronic aortic regurgitation is accompanied by a significant increase in ventricular compliance, the net effect on TV1/2 is unpredictable.

Computer Simulation

Figure 7 shows a computer simulation of the time course of transmitral velocity both with and without different degrees of aortic regurgitation generated by increasing regurgitant orifice areas with afterload and preload held constant. The augmented ventricular filling from the aorta raises

Figure 4. Relation between pressure half-time and planimetry-determined mitral valve area. With use of the function TV1/2 = K/MVA, the aortic regurgitation (AR) group (n = 32) and the group without regurgitation (n = 24) were fitted separately. The best value for K for each group is shown (r = 0.77 for the group without regurgitation, r = 0.85 for the group with regurgitation). Some data points overlap.
Figure 6. Effect of aortic regurgitation (AR) and compliance on pressure half-time in the in vitro model. The two top curves are generated with high ventricular compliance, the two lower curves with low ventricular compliance (all with a 0.3 cm² mitral orifice). Addition of aortic regurgitation (60 ml) shortens pressure half-time in each compliance setting. However, pressure half-time for high compliance with aortic regurgitation is the same as in the setting of low compliance with no regurgitation. Thus, the reduction of pressure half-time by aortic regurgitation can be counteracted by a concomitant increase in compliance.

ventricular pressure prematurely and clearly shortens the mitral pressure half-time. However, consistent with the in vitro observations, note that if ventricular compliance is sufficiently increased, pressure half-time returns to baseline because the same regurgitant volume causes less ventricular pressure rise (curve indicated in Fig. 7). The competing effects of regurgitant fraction and ventricular compliance on TV½ are shown in Figure 8. At any given level of compliance regurgitation always shortens TV½.

**Discussion**

Clinical observations. In our analysis of patient data we observed a moderate but significant overestimation of mitral valve area by the pressure half-time method in the presence of aortic regurgitation. On average, the presence of aortic regurgitation shortened the pressure half-time sufficiently to add about 0.2 cm² to the calculated valve area. Although random measurement error of the same magnitude affects all current methods to calculate mitral valve area, this finding represents a systematic error; it might be particularly worrisome in settings where accurate valve area evaluation is critical, as in assessment of the short- and long-term results of mitral valvuloplasty.

However, more than the clinical implications of these empiric observations, this study provides important theoretic and experimental evidence regarding the conflicting effects of ventricular compliance and aortic regurgitation on the mitral pressure half-time.

Figure 7. Computer simulation showing flow curves with different aortic regurgitant orifices. Flow decays faster and pressure half-time shortens (perpendicular arrows) with increasing regurgitation (regurgitant orifice areas [AoA] 0, 0.1 and 0.3 cm², corresponding to regurgitant fractions of 0%, 27% and 51%, respectively). The other variables are held constant at values that are in the order of magnitude observed in vivo: mitral valve area = 1 cm², atrial compliance = ventricular compliance (Cv) = 8.5 ml/mm Hg, aortic compliance = 5 ml/mm Hg, systemic vascular resistance = 700 dynes/cm³, initial atrial pressure = 20 mm Hg, initial ventricular pressure = 0 mm Hg and initial aortic pressure = 100 mm Hg. However, if in the presence of a 0.1 cm² aortic regurgitant orifice ventricular compliance is increased to 20 ml/mm Hg (dashed line), flow curve and pressure half-time are similar to the run with 8.5 ml/mm Hg compliance and no aortic regurgitation.

Theoretic and in vitro observations. As used clinically, the mitral pressure half-time is assumed to be inversely related to the mitral valve area. Recent theoretic analysis, in vitro simulation and observations in patients immediately
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after percutaneous mitral valvotomy (10,11,21) have confirmed this inverse relation but have also shown that TVr is directly influenced by AV compliance and the maximal pressure gradient:

\[ TVr = \frac{11.6C_v \sqrt{\Delta p_0}}{MVA_{\text{eff}}} \]

where \( C_v \) is the net chamber compliance (ml/mm Hg), \( \Delta p_0 \) the initial pressure gradient (mm Hg) and \( MVA_{\text{eff}} \) the effective mitral valve area (cm²) (the anatomic area multiplied by the coefficient of discharge) (10). Note that the numerator of this equation is analogous to the constant 220 in the equation \( MVA = 220/TVr \). It has been shown (10) that rapid shifts in pressure and compliance render TVr unreliable immediately after valvuloplasty. Similar changes may also explain the variation in TVr with heart rate (22,23) and exercise (5).

In the current in vitro and computer simulation we showed that increasing aortic regurgitation (with other variables held constant) predictably shortens the pressure half-time. This is not surprising because aortic regurgitation is a second source of blood into the ventricle causing ventricular pressure to rise more rapidly. However, it was also demonstrated that changes in ventricular compliance considerably modify the effect of aortic regurgitation on the pressure half-time. In particular, a significant increase in compliance may completely offset the reduction in half-time induced by aortic regurgitation. This observation has important clinical implications and may in part explain the relatively modest reductions in half-time observed in our patients despite significant regurgitation.

Changes in ventricular compliance with aortic regurgitation. All of the patients in the current study had rheumatic valve disease and presumed long-standing aortic regurgitation. Previous work (24) has demonstrated that ventricular chamber compliance is increased in chronic aortic regurgitation. Thus, patients with chronic aortic regurgitation might be expected to have increased compliance, which would partially offset the half-time shortening. In contrast, patients with acute aortic regurgitation (secondary to endocarditis or dissection, for example) do not show significant remodeling of the ventricle and pericardium; the additional volume therefore causes a shift to steeper (less compliant) portions of the ventricular pressure-volume curve. Thus, this decreased compliance might be expected to exacerbate further the shortening in pressure half-time induced by aortic regurgitation. Indeed, a recent study (25) confirmed such a dramatic shortening in mitral deceleration time with acute severe aortic regurgitation; the observations were based on normal rather than stenotic mitral valves but the results appear analogous.

Previous studies. Most previous studies (12,13) have also observed an increase in half-time area with aortic regurgitation. One study (15) found no significant difference in pressure half-time area compared with hemodynamic data in the presence of aortic regurgitation. However, nearly half of the patients had only trace or mild aortic regurgitation, which may have diluted the observations in patients with more significant aortic regurgitation. Another study (14) reported prolongation of pressure half-time by aortic regurgitation; however, those patients had a normal mitral valve and the regurgitant jet may have partially depressed the anterior mitral leaflet, causing some degree of obstruction. This finding is known from two-dimensional echocardiography as the smile sign, a depression of the midportion of the anterior mitral leaflet in the parasternal short-axis view. However, in the stenotic valves of the present study this distortion was not observed in the two-dimensional images presumably because of the persisting AV gradient, which kept the stenotic orifice maximally open.

Study limitations. A number of limitations must be recognized in interpreting the results of this study.

Clinical study. First, the reference standard used in the clinical study was echocardiographic planimetry. Although not always obtainable in ideal quality, it has been confirmed to be accurate by comparison with invasive and necropsy measurements (2,26) and to be feasible in 95% of patients with rheumatic mitral stenosis (26). It is not affected by mitral regurgitation, cardiac output measurement errors and other problems inherent in invasive measurements. However, recognition of the potential errors in all clinical data were the motivation for the in vitro and mathematic modeling parts of this study. Thus, while the apparent difference between planimetry and pressure half-time area formed the impetus for additional study, the results of the theoretic part of the study indicate that the clinical findings represent an obligate relation given the physics of the disorder.

Study patients with aortic regurgitation apparently had more advanced mitral stenosis with a mean planimetry-derived valve area 0.3 cm² smaller than that in patients without aortic regurgitation. However, this difference was adjusted by analysis of covariance.

An issue of concern is that in our clinical study the severity of aortic regurgitation graded by Doppler color flow mapping did not add significantly to the simple presence of regurgitation in predicting the amount of shortening of pressure half-time. There appear to be two possible explanations for this. First, Doppler color flow mapping to date is, at best, a semiquanitative means of assessing the severity of regurgitant lesions; having excluded grade 1 regurgitation from our study, the range of severity encountered may have been small compared with the inaccuracy of the method. Second, because compliance could not be directly measured in our patients, it is possible that compliance increases related to the severity of regurgitation may have countered

*Net compliance \((C_d)\) combines the atrial \((C_a)\) and ventricular \((C_v)\) compliance as \(C_d = (1/C_a + 1/C_v)^{-1}\).
any further shortening in the half-time. Furthermore, the presence of aortic stenosis (10 patients in the regurgitation group) and coronary artery disease affect ventricular distensibility and render these changes unpredictable in the individual case.

In vitro and theoretic study. For both the in vitro and mathematical simulations, we assumed constant chamber compliance based on linear pressure-volume curves. This was a deliberate simplification of the typical exponential pressure-volume curves and was designed to highlight changes in mean compliance. We have previously reported (19,27) both in vitro and computer modeling of ventricular filling with variable compliance; the findings were qualitatively similar to those observed here. Furthermore, we have shown clinically (11) that net AV compliance, the critical compliance for transmural filling, changes little during diastole and, in fact, is responsible for the linear atrial compliance curve normally observed. Another simplification used in our model was to treat the atrium and pulmonary veins as functionally one common chamber. This appears reasonable because it has been shown previously (28) that in mitral stenosis the atrium and pulmonary veins do empty as a unit.

Clinical implications. It appears that the controversy about the effect of aortic regurgitation on pressure half-time (12-15) is based on variations in the amount of regurgitation and on parallel compliance changes that have an opposite effect on pressure half-time. These changes are very difficult to predict in individual cases. Our clinical results, however, suggest that the counteracting effect of chamber compliance increase on pressure half-time was not strong enough to blunt the more rapid filling of the ventricle in chronic regurgitation, so that the net result was still a shortening of pressure half-time.

Fitting the expression Kiplanometry to the pressure half-times separately for patients with and without regurgitation, we obtained a significantly different empirical constant K for each group (Fig. 4). We do not propose to use the new constant 195 rather than 220 in patients with concomitant regurgitation or to replace 220 by 239 in patients without aortic regurgitation. Instead, the dependence of pressure half-time on factors other than orifice area should be borne in mind; such factors, as in aortic regurgitation, render the pressure half-time formula less reliable. Because the severity of regurgitation and the effect on ventricular compliance characteristics are highly variable, the individual error is unpredictable and cannot simply be accounted for by a new constant correction factor. Therefore, when technically adequate, planimetry is likely to be a more reliable method of mitral valve area quantification in the presence of significant aortic regurgitation.

Conclusions. We present clinical patient data together with in vitro and computer models confirming that the pressure half-time of stenotic mitral valves shortens in the presence of nontrivial aortic regurgitation, thus leading to an overestimation of valve area as compared with planimetry. This observation was supported by in vitro and mathematical modeling that reflected the physics of the clinical setting. Increases in ventricular or atrial compliance counteract this influence to an individually varying degree but the overall effect remains a shortening of the half-time even for chronic aortic regurgitation. This moderate but systematic and significant error has implications for the accurate assessment of mitral valve area.

References


