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Natural History of Chronic Mitral Insufficiency: Relation of Peak Systolic Pressure/End-Systolic Volume Ratio to Morbidity and Mortality

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The ratio of peak systolic pressure to end-systolic volume (PSP/ESV) is a measure of contractility that is relatively independent of loading conditions. To define the relation of this index to the natural history of chronic mitral insufficiency, follow-up studies were performed in 76 patients. All had isolated mitral insufficiency and were followed up for an average of 48 months. None underwent surgery. Cardiac volumes, ejection fraction and PSP/ESV ratio were calculated and Cox multiple regression analyses were performed to determine the relation of functional status, ejection fraction and PSP/ESV ratio to morbidity and mortality.

Twenty-three patients died during follow-up; in 70% of those who died, the PSP/ESV ratio was reduced below the 20th percentile. However, as an independent predictor of mortality, this ratio was less sensitive ($p > 0.05$) than ejection fraction ($p < 0.01$). Similarly, functional status change was predicted more accurately by ejection fraction ($p < 0.01$) than by the PSP/ESV ratio ($p > 0.05$). Thus, although a decreased PSP/ESV ratio was associated with a higher mortality rate, other clinical and laboratory variables were superior to this index for determining morbidity and mortality in patients with isolated mitral insufficiency.

Left ventricular performance as measured by ejection fraction is a good predictor of the clinical course of various forms of heart disease, including coronary, valvular and heart muscle disorders. However, ejection phase indexes, including ejection fraction, are altered by preload and afterload, and thus do not indicate the true myocardial contractile state (1). This limitation becomes particularly important in mitral valve insufficiency, as the ejection fraction tends to remain high until late in the course of the disease because of favorably altered loading conditions imposed on the heart by the incompetent valve (2,3).

With the experimental demonstration (4–6) that the ratio of end-systolic pressure to end-systolic volume is relatively independent of preload and afterload, new clinical measures of myocardial contractility became apparent. Recent studies (7–12) demonstrated that both the peak systolic pressure to end-systolic volume ratio (PSP/ESV) and the end-systolic pressure/volume ratio are sensitive clinical measures of contractility.

It is not known, however, if these ratios can be used to determine the clinical outcome in patients with heart disease with the same precision as the ejection fraction. This study was, therefore, undertaken in a group of patients with isolated mitral insufficiency who had not been operated on, to assess the prognostic value of the peak systolic pressure to end-systolic volume ratio in predicting future morbidity and mortality and to decide if these measures offer any advantage over traditional indexes, such as ejection fraction, ventricular volume and clinical status.

Methods

Study group. Between January 1972 and March 1978, 5,095 patients underwent cardiac catheterization at Baptist Memorial Hospital. From this group, 76 consecutive patients were selected who met all of the following criteria: 1) documentation of isolated mitral insufficiency without other associated valvular abnormalities and without significant (>50%) coronary artery obstruction; and 2) medical

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management without surgical intervention. The medical management and the decision not to perform surgery were at the discretion of the individual attending physicians.

Follow-up data were obtained from questionnaires sent either to the responsible attending physician or directly to the patients. Data were sought to define the clinical status of the patients using New York Heart Association functional classification guidelines or delineate the time and cause of death. The duration of the follow-up period averaged 48 months (range 0.4 to 122). Seven patients were lost to follow-up and are not included in the analyses.

Control group. A second group of 536 consecutive patients found to be free of all heart disease at cardiac catheterization during the same time period was studied as a control group. All of these patients had arterial blood pressures lower than 160/90 mm Hg at the time of study.

Hemodynamic data. Cardiac catheterization was performed with patients in the postabsorptive state. Intracardiac pressures were recorded using well flushed, fluid-filled catheters. Left ventricular angiograms were filmed in two planes (35° right anterior oblique and 55° left anterior oblique) after injection of 30 to 40 cc of Renografin-76 over 2 to 3 seconds. Left ventricular volumes were calculated from cycles early after injection to reduce the effects of the negative inotropism of the dye and not from those occurring after premature beats. All patients had technically satisfactory studies. The same methods were used throughout the study period.

Left ventricular volumes and magnification factors were calculated by standard biplane formulas. The minor axis was defined as being perpendicular to the major axis at its midpoint. End-systole was defined as the frame with the smallest volume, and end-diastole as that with the largest volume. Peak systolic pressure was the maximal left ventricular systolic pressure immediately before the angiogram.

Ejection fraction was defined by the equation:

$$\text{Ejection fraction} = \frac{(\text{End-diastolic volume}) - (\text{End-systolic volume})}{\text{End-diastolic volume}},$$

and the pressure/volume ratio (PSP/ESV) in mm Hg/ml per m^2 (hereafter referred to as "units") by:

$$\frac{\text{Peak systolic pressure}}{\text{End-systolic volume index}}.$$

End-systolic volume index, rather than end-systolic volume, was used to provide better comparison among the study groups by correcting for body size. The variance in the control group was reduced from 67.6 to 20.6 units^2 by using the index rather than the unnormalized form.

Data analysis. Patients were selected and data analyzed in a retrospective manner. Statistical analysis (13–15) to correlate PSP/ESV ratio and mortality was based on chi-square and Cox's regression models. The latter is an analog of multiple linear regression analysis applied to censored survival data. A stepwise approach (variable inclusion, alpha = 0.10 and variable removal, alpha = 0.15) identified significant study variables affecting survivorship. The significant probabilities were based on large sample partial likelihood ratio tests (Biomedical Data Processing program BMDP2L).

Morbidity was defined as a change in the New York Heart Association functional class (16) from the time of catheterization to the time of analysis. Change in functional class was calculated by subtracting the follow-up functional class (I to V, where V equaled death) from that at the time of cardiac catheterization (range I to IV). A positive value or morbidity score thus identified an improvement and a negative score a worsening in clinical status. Stepwise regression analysis then correlated morbidity with PSP/ESV ratio, ejection fraction, diastolic volume, age and initial functional class.

Results

Clinical features. Patients ranged in age from 23 to 77 years (mean 55); 49 patients (74.5%) were women and 27 (25.5%) were men. Functional classifications of the 76 patients at the time of cardiac catheterization and of the 69 with follow-up data are tabulated in Table 1. Changes in class or morbidity during the follow-up period are summarized in Table 2. Of the 69 patients, 46 were alive at the time of follow-up; clinical status was improved in 14 of the 46, stable in 20 and worse in 12. Overall mortality rate was 35 ± 6% (mean ± standard error) (Fig. 1); 21 of the 23 who died did so from cardiovascular causes and 2 died from unrelated noncardiac conditions.

Relation of PSP/ESV ratio to mortality. The median ratio of peak systolic pressure to end-systolic volume (PSP/ESV) was 5.30 (range 1.50 to 13.37) in the 536 normal subjects and 3.40 in the 76 study patients. Table 3 shows the relation of the 50th percentile of this ratio to survival in the patients with mitral regurgitation. Patients in the lower

Table 1. Functional Class* at Beginning and End of Follow-Up Period in 69 Patients With Chronic Mitral Regurgitation

Functional Class At Follow-Up	Functional Class at Catheterization: I	II	III	IV	Total No. (%)
I	5	6	1	1	13 (19%)
II	3	10	3	0	16 (23%)
III	2	4	4	3	13 (19%)
IV	1	1	1	1	4 (6%)
V (death)	4	5	10	4	23 (33%)
Total	15	26	19	9	
(%)	(22%)	(38%)	(27%)	(13%)	

*New York Heart Association criteria. Numbers tabulated indicate the number of patients in each functional class.

Table 2. Morbidity Scores for 69 Patients With Chronic Mitral Regurgitation

Morbidity Score*	Patients No.	Patients %
−4	4	5.8
−3	6	8.7
−2	13	18.9
−1	12	17.4
0	20	29.0
1	12	17.4
2	1	1.4
3	1	1.4

*Computed as described in the text.

50th percentile of the PSP/ESV ratio at entry into study had a significantly greater mortality rate than did those with values above the median. Seventy percent of all deaths occurred in patients with ratio values below the 30th percentile (Fig. 2).

Cox regression analysis with stepwise selection was used to adjust for other factors (that is, ejection fraction, diastolic volume, age and initial functional class) that may determine mortality. In the model, only ejection fraction had significant, independent predictive value (chi-square = 27.8, probability [p] < 0.01). Thus, the PSP/ESV ratio had predictive value when used as an individual factor, but it was of less value than ejection fraction used alone and did not add to the predictive accuracy of ejection fraction when combined with it.

Ejection fraction and PSP/ESV ratio were correlated with each other. This relation was curvilinear (Fig. 3), with little difference in ejection fraction for low values of the PSP/ESV index.

Figure 1. Proportion of original 76 patients with chronic mitral regurgitation surviving at 2 month intervals during the follow-up period. Mean values are plotted, and those lost to follow-up are excluded. Limits for ± 1 standard error of the mean (SEM) for 5 year survival are marked.

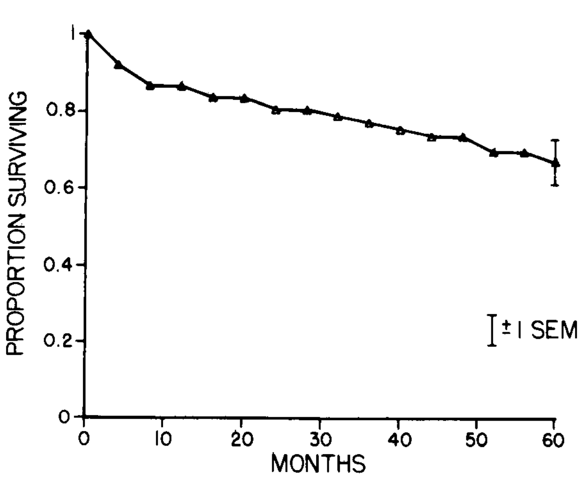


Table 3. Mortality Rates in 76 Patients With Chronic Mitral Regurgitation With Values For Ratio of Peak Systolic Pressure to End-Systolic Volume (PSP/ESV) Above and Below 50th Percentile

PSP/ESV (units)	No. Patients	No. Deaths
≥3.4*	38 (50%)	18 (78.3%)
<3.4	38 (50%)	5 (21.7%)

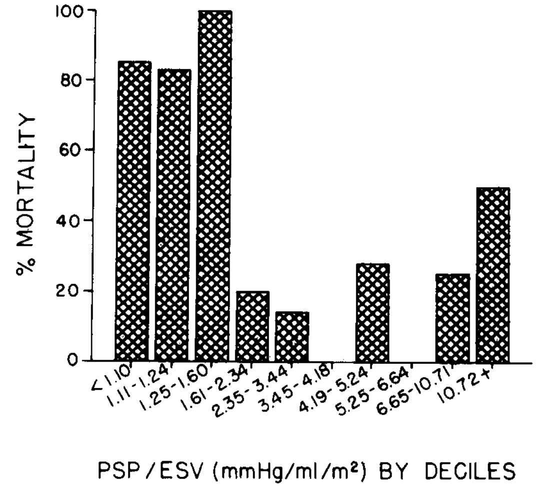
*Median value of PSP/ESV in patients with mitral regurgitation.

Relation of PSP/ESV ratio to morbidity. Morbidity was quantitated by the change in morbidity score (Table 2). Analysis of the relation of the PSP/ESV ratio to morbidity in conjunction with ejection fraction, age, diastolic volume and functional class at the time of catheterization revealed that this ratio was not a significant predictor of morbidity. Both ejection fraction, with a parameter estimate of 0.03 ($p < 0.01$), and initial functional class, with a value of 0.71 ($p < 0.01$), were better indicators of morbidity than was the PSP/ESV ratio, which did not achieve statistical significance (Table 4).

Discussion

Methods to assess ventricular function in patients with mitral insufficiency. The natural history of chronic mitral insufficiency is significantly affected by the state of left ventricular function (17). Ventricular dysfunction in this disease, however, may be difficult to detect because most commonly employed indexes of ventricular performance are sensitive to loading conditions as well as to contractility. In mitral insufficiency, the left ventricle empties into the low pressure left atrium, reducing overall afterload (2). Thus,

Figure 2. Survival of patients classified by decile of peak systolic pressure/end-systolic volume (PSP/ESV) ratio. Decile values are based on values in patients with mitral regurgitation. **Ordinate** values represent percent of patients in each decile dying during the follow-up period.



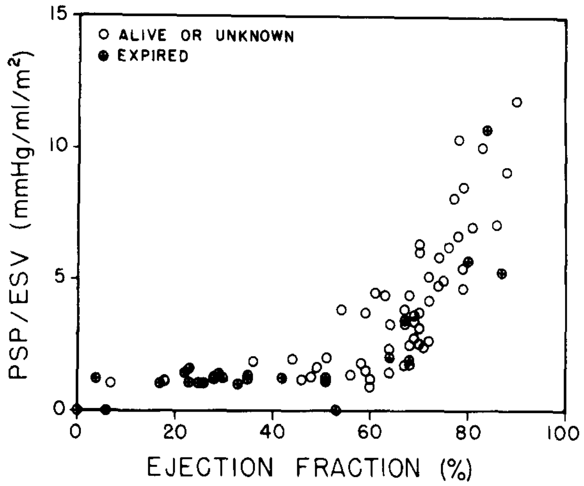


Figure 3. Relation between ejection fraction **(abscissa)** and the ratio of peak systolic pressure to end-systolic volume (PSP/ESV) **(ordinate).**

ejection phase indexes tend to remain normal, although significant left ventricular dysfunction may exist (3).

In contrast to other clinical measurements, the ratio of end-systolic pressure to end-systolic volume is largely independent of loading conditions. As demonstrated in cross-circulated and intact, chronic dog experiments (4), peak values of end-systolic pressure/end-systolic volume ratios vary by less than 10% with changes in peload or afterload, or both, but increase by 200 to 300% with inotropic augmentation. Theoretic advantages of this method include its independence of preload, its lack of dependence on any conceptual muscle model and the inclusion of an estimate of afterload in the formula, so that changes may more closely assess only contractility rather than a mixture of both contractility and afterload (7).

Clinical studies (7–12) have supported the validity of this ratio as a contractility index. First, in any one patient, end-systolic pressure/volume relations are linear during interventions that alter loading but not contractility (8). Second, interventions that alter inotropism reliably alter the slope of the relation in a concordant direction. Third, patients with cardiac dysfunction documented by independent methods have a slope less steep than do normal subjects.

Table 4. Final Morbidity Model Computed Using Peak Systolic Pressure/End-Systolic Volume (PSP/ESV) Ratio, Ejection Fraction, Initial Functional Status, Diastolic Volume and Age as Independent Variables

Variable	Parameter Estimate
Constant	−3.94
Ejection fraction	0.03*
Functional class at catheterization	0.71*
PSP/ESV	†
Diastolic volume	†
Age	†

*$p < 0.01$; †$p < 0.05$.

Inclusion of peak rather than end-systolic pressure has also been studied. The former, which is easier to measure and generally equals the latter (18), functioned well in previous invasive studies (5,8); however, when pressures and volumes are measured noninvasively, peak pressure ratios may not be reliable indicators of inotropic status (12).

Values and limitations of PSP/ESV ratio and ejection fraction. This study was undertaken to determine the efficacy of the peak systolic pressure/end-systolic volume ratio as a measure of prognosis in patients with medically managed chronic mitral regurgitation. Results did demonstrate that a single value of PSP/ESV ratio determined during routine cardiac catheterization did significantly relate to mortality rate; mortality rate increased as the PSP/ESV ratio decreased (Table 3, Fig. 2).

Analogous data have been reported in studies (19,20) utilizing stress/volume ratios and volumes, respectively, in predicting operative outcome in patients with mitral regurgitation. Carabello et al. (19) demonstrated that the ratio of end-systolic wall stress to end-systolic volume index was a good predictor of postoperative functional class. Borow et al. (20) reported that preoperative end-systolic volume correlated well with postoperative cardiac function. Although Carabello et al. (19) found significant differences in the ratio of PSP/ESV in patients with better and worse postoperative cardiac status, significant overlap in values between the two groups occurred. This reduced accuracy as compared with that from use of wall stress may reflect the better approximation of afterload by the latter, which incorporates wall thickness.

Ejection fraction, however, remained a more accurate predictor of survival than did the PSP/ESV ratio by stepwise discriminant analysis. This may be partly explained by the relation between these two variables, as shown in Figure 2 and in other studies (8,10). The PSP/ESV ratio in our study remained relatively constant over a wide range of low ejection fraction levels. In contrast, Carabello et al. (19) observed that ejection fraction was inferior to wall stress/pressure ratios, and Borow et al. (20) concluded that end-systolic volume was superior to ejection fraction in predicting postoperative function. These discrepancies may well reflect methodologic variables (for example, use of wall stress rather than peak pressure, use of end-systolic volume rather than PSP/ESV ratio and use of slopes rather than single point values) or differences in outcome variables (for example, postoperative function versus mortality).

In contrast to predicting survival, the PSP/ESV ratio was not a significant predictor of morbidity. Ejection fraction and preoperative clinical status were significant variables. This result also differs from that of Carabello et al. (19)

using wall stress, but is in agreement with the results of that study using peak systolic pressure.

Clinical implications. This study therefore identified both the values and limitations of the peak systolic pressure/end-systolic volume ratio when applied to patients with chronic mitral insufficiency. Whereas it is a significant predictor of mortality, the commonly employed measure of ejection fraction was still superior in this regard. It did not significantly predict morbidity, whereas other hemodynamic and clinical variables did.

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