Prediction of Late Survival in Patients with Mitral Valve Disease from Clinical, Hemodynamic, and Quantitative Angiographic Variables

K. E. Hammermeister, M.D., Lloyd Fisher, Ph.D., J. Ward Kennedy, M.D., Steven Samuels, Ph.D., and Harold T. Dodge, M.D.

SUMMARY Late follow-up (average = 7.2 years) has been obtained in 249 patients with mitral valve disease who had quantitative angiographic assessment of left ventricular function at the time of initial catheterization in the 1960s. Surgically treated patients with mitral valve disease had significantly improved survival as compared to medically treated patients with mitral disease. The subgroup with mixed mitral stenosis and regurgitation and the subgroup with moderate impairment of ejection fraction account for this improved survival in surgically treated patients, which occurred despite greater functional and hemodynamic impairment in the surgical cohorts.

Using univariate life table survival analysis, ten variables were found to be predictive of survival in the medical cohort, and three in the surgical cohort. With multivariate Cox's regression analysis, end-diastolic volume and arteriovenous oxygen difference were significantly predictive of survival in the medical cohort; age was predictive of survival in the surgical cohort.

KNOWLEDGE OF PROGNOSIS in patients with valvular heart disease and, in particular, knowledge of how prognosis is altered by therapy are vital to making rational therapeutic decisions regarding these patients. Intuitively, left ventricular function would seem to be an important prognostic factor. Indeed, several studies have demonstrated that qualitative variables relating to ventricular performance such as radiographic heart size and/or left atrial size are predictive of late prognosis. Quantitative angiographic measurement of left ventricular volumes provides a more precise estimate of ventricular performance and may improve ability to predict survival.

Since the development of the technique of quantitative angiography at this institution over 15 years ago, measurement of left ventricular volumes and ejection fraction has been routine in most patients undergoing cardiac catheterization. This report details the analysis of potential prognostic indicators (including clinical, exercise, hemodynamic and angiographic variables) in 249 patients with mitral valve disease who had quantitative angiographic assessment of left ventricular performance between 1960 and 1970, and who have been followed for three to 14 years.

Methods

Patient Population

The medical records and catheterization files of all 831 adult patients having quantitative angiographic measure-
ment of ejection fraction at cardiac catheterization between 1960 and 1970 inclusively at the Veterans Administration and University Hospitals were retrospectively reviewed. These patients represent approximately 45% of the total number (1843) of adult heart catheterizations done during this time for diagnostic purposes. The remainder were excluded only because quantitative angiographic data were not available. The possibility that their exclusion created a biased patient population cannot be ruled out. Seven quantitative angiographic, ten hemodynamic, three exercise, six clinical and five demographic variables were recorded from the catheterization or medical record. Each patient was categorized into one of 13 diagnostic categories according to the principal diagnosis on the catheterization form. Table 1 lists distribution by diagnosis, sex, and therapy for the 249 patients who had mitral valve disease as the primary cardiac diagnosis following the cardiac catheterization and who form the basis of this report. Of the remaining 582 patients, 205 had aortic valve disease and will form the basis of a subsequent report, 109 had multivalvular disease, and 268 had other diagnoses including cardiomyopathy, congenital lesions, and coronary disease.

**Laboratory Evaluation**

Exercise testing was performed according to the Bruce protocol in 79% (146/249) of the patients. Data for other variables studied are available in 90% or more of patients except for left ventricular mass which was measured in 70% (174/249). Functional aerobic impairment (FAI = percent decrement from predicted maximal oxygen intake based on age, sex, and activity status) was estimated from published nomograms or computed. Left and right heart catheterization were performed according to standard techniques; but coronary angiography was rarely done, as was the practice during this era. For patients having more than one catheterization, the earliest study with quantitative angiographic data was used. Left heart angiograms were directly filmed in the anterior-posterior and lateral projections simultaneously at a rate of six or 12 exposures per second. Left ventricular volumes were calculated on representative supraventricular beats at least one beat removed from premature ventricular beats by the method of Dodge et al. The volume of valvular regurgitation was calculated as the difference between the angiographic left ventricular output (angiographic left ventricular stroke volume times heart rate) and the net forward output measured by the Fick technique prior to the angiocardiogram, as described by Sandler et al. Intracardiac pressures were measured with fluid-filled catheters with the mid-chest used as zero pressure. Valve orifice areas were calculated using the method of Gorlin et al. The severity index, based on the valve orifice area or volume of valvular regurgitation (table 2), was used as an estimate of the hemodynamic severity of the valve lesion. For patients with combined stenosis and regurgitation, the most abnormal of the two variables (valve area or regurgitant volume) was used to classify the patient.

**Surgery**

One hundred seventy-seven patients (71%) were selected for surgical therapy of their mitral valve disease by the responsible cardiologist and/or cardiovascular surgeon at six different hospitals; this selection process was not a randomized one. Thirty day operative mortality was 12.4% (22/177). Surgery was performed an average of 30 days after catheterization. Mitral valve replacement was performed in 43 patients with 28% (12/43) operative mortality; 128 had a reparative procedure (about equally divided between commissurotomy and annuloplasty) with an operative mortality of 7.0% (9/128).

**Follow-up**

Follow-up was obtained by search of the medical record; questionnaire to the patient, referring physician, or next-of-kin; or by search of death certificate files in state of last residence. Current follow-up to June 30, 1973, was obtained in 88% (220/249). Mean duration of follow-up in the 133 patients known to be alive was 7.2 years (2.9 - 14.1 years), and 2.4 years (0-10.8 years) in the 87 patients known to have died.

**Statistical Analysis**

Survival curves using the life table technique were constructed for diagnostic subgroups defined by mitral valvular lesion, medical or surgical therapy, and left ventricular ejection fraction beginning with the date of catheterization. The significance of the difference between survival curves was tested by a modification of the Mantel-Haenzel-Cox statistic. Where survival of medically and surgically treated subgroups was compared, the mean and standard deviation or distribution of 14 baseline descriptor variables (table 3) were calculated. The significance of the difference of means for continuous variables was tested using Student's t-test. The chi-square test was used to test the significance of the difference in distribution of discontinuous variables.

The 14 variables listed in table 3 were tested for prediction of survival using life table survival curves. The patient population was divided into medically and surgically treated cohorts. Each of these cohorts was then divided into several subgroups according to no, moderate, and severe deviation from the normal value of the continuous variable being

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**Table 1. Distribution of Patients by Diagnosis, Therapy, and Sex**

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Surgically treated</td>
</tr>
<tr>
<td>Mitral stenosis</td>
<td>71</td>
</tr>
<tr>
<td>Mitral regurgitation</td>
<td>61</td>
</tr>
<tr>
<td>MS-MR</td>
<td>45</td>
</tr>
<tr>
<td>Sex distribution</td>
<td>82 M</td>
</tr>
<tr>
<td></td>
<td>95 F</td>
</tr>
</tbody>
</table>

| Abbreviations: MS-MR = mixed mitral stenosis and regurgitation; M = male; F = female. |

**Table 2. Definition of Severity Index**

<table>
<thead>
<tr>
<th></th>
<th>Severity index</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Aortic valve</td>
<td></td>
</tr>
<tr>
<td>Valve area (cm²)</td>
<td>≥ 1.3</td>
</tr>
<tr>
<td>Regurgitant volume (L/min)</td>
<td>≤ 3.0</td>
</tr>
<tr>
<td>Mitral valve</td>
<td></td>
</tr>
<tr>
<td>Valve area (cm²)</td>
<td>≥ 1.3</td>
</tr>
<tr>
<td>Regurgitant volume (L/min)</td>
<td>≤ 2.0</td>
</tr>
</tbody>
</table>
tested or into two to four subgroups according to the discontinuous variable being tested. Table 3 lists the variables screened by this technique, the levels at which the subgroups were divided, and the number of patients in each subgroup. Those variables which significantly predicted survival as tested by the Mantel-Haenzel-Cox statistica were further analyzed for multivariate prediction of survival using Cox’s technique,* which is an analogue of multiple linear regression analysis applied to survival data. Using the variables found to be predictive of survival when tested multivariately in Cox’s model and parameter estimates from Cox’s model, the estimated probability of survival (Pr,.) to a specified time interval after diagnosis and for specified values of the predictive variables (X1, X2 . . . , Xp) were calculated from the following equation:

$$P_r = \hat{F}_0(t) \left[ \beta_0 + \beta X_1 + \beta_2 X_2 + \ldots + \beta_p X_p \right]$$  

(1)

where F0 (t) is the probability of survival to time t with all variables set equal to their mean, and $\beta$ is a measure of the predictive value of the independent variables.

Finally, we have developed equations and computer programs (appendix) for estimating the standard error of Pr, so that differences in survival of surgical and medical cohorts with specified values of the predictive independent variables (X1, X2, . . . , Xp) can be tested for significance.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Level</th>
<th>Number of medical patients</th>
<th>Number of surgical patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>≤40</td>
<td>19 (26%)</td>
<td>55 (31%)</td>
</tr>
<tr>
<td></td>
<td>41-60</td>
<td>39 (54%)</td>
<td>107 (60%)</td>
</tr>
<tr>
<td></td>
<td>≥61</td>
<td>14 (19%)</td>
<td>15 (8%)</td>
</tr>
<tr>
<td>Arterio-venous oxygen difference (ml/100 ml)</td>
<td>≤5.3</td>
<td>36 (55%)</td>
<td>52 (32%)</td>
</tr>
<tr>
<td></td>
<td>5.4-6.5</td>
<td>15 (23%)</td>
<td>64 (39%)</td>
</tr>
<tr>
<td></td>
<td>≥6.6</td>
<td>15 (23%)</td>
<td>49 (30%)</td>
</tr>
<tr>
<td>End-diastolic volume (ml/m²)</td>
<td>≤102</td>
<td>39 (55%)</td>
<td>94 (53%)</td>
</tr>
<tr>
<td></td>
<td>103-200</td>
<td>27 (38%)</td>
<td>75 (45%)</td>
</tr>
<tr>
<td></td>
<td>≥201</td>
<td>5 (7%)</td>
<td>7 (4%)</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>&gt;50</td>
<td>49 (68%)</td>
<td>132 (75%)</td>
</tr>
<tr>
<td></td>
<td>31-50</td>
<td>20 (28%)</td>
<td>40 (23%)</td>
</tr>
<tr>
<td></td>
<td>≤30</td>
<td>3 (4%)</td>
<td>5 (3%)</td>
</tr>
<tr>
<td>Exertional ST response</td>
<td>ST depression &lt;1 mm</td>
<td>2 (5%)</td>
<td>8 (8%)</td>
</tr>
<tr>
<td></td>
<td>ST depression ≥1 mm</td>
<td>12 (28%)</td>
<td>14 (14%)</td>
</tr>
<tr>
<td></td>
<td>Digitalis effect</td>
<td>29 (67%)</td>
<td>78 (75%)</td>
</tr>
<tr>
<td>Functional aerobic impairment (%)</td>
<td>≤26</td>
<td>22 (51%)</td>
<td>23 (22%)</td>
</tr>
<tr>
<td></td>
<td>27-50</td>
<td>15 (35%)</td>
<td>40 (30%)</td>
</tr>
<tr>
<td></td>
<td>≥51</td>
<td>6 (14%)</td>
<td>40 (30%)</td>
</tr>
<tr>
<td>Fick cardiac output (L/min/m²)</td>
<td>≥3.0</td>
<td>25 (35%)</td>
<td>40 (23%)</td>
</tr>
<tr>
<td></td>
<td>2.5-2.9</td>
<td>17 (24%)</td>
<td>41 (23%)</td>
</tr>
<tr>
<td></td>
<td>≤2.4</td>
<td>29 (41%)</td>
<td>96 (54%)</td>
</tr>
<tr>
<td>Functional class</td>
<td>I</td>
<td>5 (7%)</td>
<td>9 (5%)</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>28 (39%)</td>
<td>35 (20%)</td>
</tr>
<tr>
<td></td>
<td>III</td>
<td>32 (44%)</td>
<td>111 (63%)</td>
</tr>
<tr>
<td></td>
<td>IV</td>
<td>7 (10%)</td>
<td>21 (12%)</td>
</tr>
<tr>
<td>LVEDP (mm Hg)</td>
<td>≤12</td>
<td>44 (68%)</td>
<td>122 (77%)</td>
</tr>
<tr>
<td></td>
<td>13-18</td>
<td>11 (17%)</td>
<td>26 (10%)</td>
</tr>
<tr>
<td></td>
<td>≥19</td>
<td>10 (15%)</td>
<td>10 (6%)</td>
</tr>
<tr>
<td>LV mass (g/m²)</td>
<td>≤124</td>
<td>31 (63%)</td>
<td>88 (70%)</td>
</tr>
<tr>
<td></td>
<td>125-200</td>
<td>16 (33%)</td>
<td>34 (27%)</td>
</tr>
<tr>
<td></td>
<td>≥201</td>
<td>2 (4%)</td>
<td>3 (2%)</td>
</tr>
<tr>
<td>Mean pulmonary artery pressure (mm Hg)</td>
<td>≤20</td>
<td>27 (41%)</td>
<td>34 (22%)</td>
</tr>
<tr>
<td></td>
<td>21-40</td>
<td>33 (50%)</td>
<td>88 (56%)</td>
</tr>
<tr>
<td></td>
<td>≥40</td>
<td>6 (9%)</td>
<td>34 (22%)</td>
</tr>
<tr>
<td>Mean pulmonary capillary wedge pressure (mm Hg)</td>
<td>≤12</td>
<td>27 (39%)</td>
<td>30 (17%)</td>
</tr>
<tr>
<td></td>
<td>13-18</td>
<td>24 (35%)</td>
<td>48 (28%)</td>
</tr>
<tr>
<td></td>
<td>≥19</td>
<td>18 (26%)</td>
<td>95 (55%)</td>
</tr>
<tr>
<td>Severity index</td>
<td>1</td>
<td>24 (35%)</td>
<td>20 (11%)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>28 (41%)</td>
<td>84 (48%)</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>17 (25%)</td>
<td>71 (41%)</td>
</tr>
<tr>
<td>Sex</td>
<td>Female</td>
<td>27 (37%)</td>
<td>95 (54%)</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>45 (63%)</td>
<td>82 (46%)</td>
</tr>
</tbody>
</table>

Abbreviations: LVEDP = left ventricular end-diastolic pressure.
Results

Comparison of Survival of Medical and Surgical Cohorts

Figure 1 shows the survival curves for 177 surgically treated patients and 72 medically treated patients with mitral valve disease demonstrating significantly improved survival in the surgical cohort \( (P = 0.009) \). We then examined the comparability of these two cohorts for variables possibly predictive of survival. Table 4 lists the values of the six baseline variables in which differences \( (P < 0.05) \) were observed between the two cohorts. Note that in each instance (except sex), the surgical cohort is more severely impaired. No significant difference was observed between the two cohorts in age, end-diastolic volume, angiographic stroke volume, total angiographically measured left ventricular output, ejection fraction, left ventricular mass, net forward cardiac output, arterio-venous oxygen differences, and left ventricular end-diastolic pressure.

We were able to identify three diagnostic subgroups of the mitral valve disease population in which the surgical cohort appeared to have improved survival: 1) patients with mixed mitral stenosis and regurgitation, 2) patients with mitral regurgitation, and 3) mitral valve disease patients with moderate reduction in ejection fraction.

Figure 2 illustrates the survival curve for patients with mixed mitral stenosis and regurgitation demonstrating improved survival \( (P = 0.006) \) for the 45 surgically treated patients compared to the 22 medically treated patients. Table 4 lists the four variables which were significantly different

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**TABLE 4. Baseline Variables which are Significantly Different between Medically and Surgically Treated Cohorts**

<table>
<thead>
<tr>
<th>Patient population variable</th>
<th>Surgically-treated patients</th>
<th>Medically-treated patients</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>All mitral valve disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>177 95 (54%) F</td>
<td>72 27 (38%) F</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Functional class</td>
<td>176 2.82 ± 0.70</td>
<td>72 2.57 ± 0.77</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>FAI (%)</td>
<td>103 41.8 ± 24.6</td>
<td>43 24.0 ± 29.8</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>PA (mm Hg)</td>
<td>156 31.9 ± 13.8</td>
<td>66 24.3 ± 10.9</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>PC (mm Hg)</td>
<td>173 20.0 ± 7.6</td>
<td>69 15.4 ± 7.4</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Severity index</td>
<td>175 2.29 ± 0.66</td>
<td>69 1.90 ± 0.77</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Mixed mitral stenosis and regurgitation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FAI (%)</td>
<td>25 50.4 ± 23.0</td>
<td>13 22.8 ± 30.4</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>PA (mm Hg)</td>
<td>40 35.7 ± 16.5</td>
<td>17 24.9 ± 7.9</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>PC (mm Hg)</td>
<td>44 21.2 ± 7.3</td>
<td>21 15.4 ± 4.8</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Severity index</td>
<td>45 2.11 ± 0.65</td>
<td>22 1.77 ± 0.61</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Mitral regurgitation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regurgitant volume (L/min)</td>
<td>60 7.3 ± 4.5</td>
<td>34 4.7 ± 3.3</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Stroke volume (mL/m²)</td>
<td>60 8.2 ± 2.5</td>
<td>36 6.7 ± 2.0</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Total left ventricular output (L/min/m²)</td>
<td>60 6.7 ± 2.5</td>
<td>36 5.2 ± 1.5</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Severity index</td>
<td>60 2.5 ± 0.6</td>
<td>34 2.2 ± 0.6</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Ejection fraction = 31-50%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FAI (%)</td>
<td>27 48.6 ± 18.0</td>
<td>9 32.0 ± 24.3</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>EDV (mL/m²)</td>
<td>40 109 ± 40.4</td>
<td>19 141 ± 50.9</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>40 44.8 ± 4.1</td>
<td>20 42.2 ± 5.3</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Abbreviations: N = number of patients in whom variable was measured; SD = standard deviation; \( P = \) Significance of difference between means or distribution; FAI = functional aerobic impairment; PA = mean pulmonary artery pressure; PC = mean pulmonary capillary wedge pressure; EDV = end-diastolic volume.
Only those variables of regurgitation demonstrating improved survival of borderline significance in the surgical cohort.

(P < 0.05) between the surgical and medical cohorts. For each of these four variables, the surgical cohort is more severely impaired. The remaining ten of the 14 baseline variables listed above were not significantly different between the two cohorts.

Figure 3 demonstrates the survival curves for the patients with mitral regurgitation showing improved survival of borderline significance (P = 0.07) in the surgically treated patients. Only those variables directly reflecting the volume of regurgitation were significantly different between the medically and surgically treated cohorts, and demonstrated more severe regurgitation in the surgically treated cohort (table 4).

Surgically-treated patients with mitral valve disease and moderate reduction in ejection fraction (31-50%) also have improved survival (P = 0.004) as shown in figure 4. Table 4 shows those variables which were significantly different between the medically and surgically treated cohorts.

**Prediction of Prognosis**

Table 5 lists P values derived from the Mantel-Haenszel-Cox statistic for each of the 14 variables when survival curves are constructed for patients subgrouped according to the several levels of each variable as tabulated in table 3. Ten variables (age, arterio-venous oxygen difference, end-diastolic volume, ejection fraction, functional class, left ventricular mass, mean pulmonary artery pressure, mean pulmonary capillary pressure, severity index, and sex) are univariately predictive of survival (P < 0.05) in the medical cohort. Three of these variables (age, end-diastolic volume, and ejection fraction) were also predictive of survival in the surgical cohort. These ten variables were then examined for multivariate prediction of survival using Cox's regression analysis. In the medical cohort arterio-venous oxygen difference and end-diastolic volume were significantly predictive of survival. In the surgical cohort only age was significantly predictive of survival. Figures 5 and 6 illustrate survival curves for medically treated patients categorized by three levels of arterio-venous oxygen difference and end-diastolic volume respectively, while figure 7 illustrates survival curves for the surgical cohort categorized by age.

Finally, using parameter estimates from Cox's regression analysis, five year survival for the medical (table 6) and surgical (table 7) cohorts was estimated according to equation (1) for three discrete values of age, arterio-venous oxygen difference, and end-diastolic volume. Improved probability of survival (\(P_r\)) at five years of 0.15 or more was predicted in surgically-treated patients with end-diastolic volume equal to 180 ml and at all age and arterio-venous oxygen difference levels except for normal arterio-venous oxygen difference at ages 50 and 60. Similarly, improved survival probability (\(P_r\) ≥ 0.15) was seen in patients with end-diastolic volume equal to 130 ml/M² and arterio-venous oxygen difference.
equal to 7.0 ml/100 ml at all three age levels. However, in these cells the standard error of the survival probability (P) is large. Statistically significant differences between comparable medical and surgical cells were not seen.

**Discussion**

**Comparison of Survival of Medical and Surgical Cohorts**

Carefully controlled trials comparing survival of medically and surgically treated patients with mitral valve disease have never been done. Two recent reports\(^{10,11}\) indicate improved survival in mitral stenosis patients treated by commissurotomy versus medical therapy, but there was less apparent difference in survival of medically treated and surgically treated patients undergoing single valve replacement.\(^{11}\) Roy and Gopinath\(^{10}\) reviewed several of the earlier reports of survival following mitral commissurotomy in which comparison was usually made with medically managed patients from a different time span, again showing improved survival in the more severely affected surgically treated patients. However, none of these studies presented hemodynamic data or left ventricular function data.

The present study examines the survival of patients with mitral valve disease who have been carefully characterized both by hemodynamic measurements and by quantitative angiographic analysis of left ventricular function. As in any nonrandomized comparison of medical versus surgical therapy, it is possible that differences in survival between the two treatment groups are due to patient selection rather than the therapy. The more carefully characterized the patient populations are with respect to prognostic variables, the more likely it is that patient selection can be excluded (or included) as the cause of observed differences in survival. In the present study we have analyzed survival in relation to a number of important prognostic variables; an important exception is the presence or absence of coronary disease (vide infra).

The patient population reported is restricted by the requirement of technically adequate quantitative angiography. We feel that this selection of the study population is unlikely

**Figure 5.** Actuarial survival curve of medically treated mitral valve disease patients, demonstrating significantly different (P = 0.001) survival when they are grouped according to arteriovenous oxygen (A-VO\(_2\)) difference.

**Figure 6.** Actuarial survival curves of medically treated mitral valve disease patients demonstrating significantly different (P = 0.003) survival when they are grouped according to end-diastolic volume (EDV).

**Figure 7.** Actuarial survival curves of surgically treated mitral valve disease patients demonstrating significantly different (P = 0.0003) survival when they are grouped according to age.

**Table 6.** Five Year Survival Estimated from Parameter Estimates of Cox's Regression Analysis for Three Discrete Values of Age, Arteriovenous Oxygen Difference (A-VO\(_2\)), and End-diastolic Volume for Patients with Medically Treated Mitral Valve Disease

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>A-VO(_2) (ml/100 ml)</th>
<th>80</th>
<th>130</th>
<th>180</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>0.88 ± 0.04</td>
<td>0.89 ± 0.09</td>
<td>0.64 ± 0.27</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>0.82 ± 0.06</td>
<td>0.69 ± 0.11</td>
<td>0.48 ± 0.35</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>0.73 ± 0.13</td>
<td>0.57 ± 0.22</td>
<td>0.36 ± 0.49</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>0.84 ± 0.07</td>
<td>0.73 ± 0.11</td>
<td>0.57 ± 0.30</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>0.77 ± 0.07</td>
<td>0.62 ± 0.08</td>
<td>0.42 ± 0.33</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>0.67 ± 0.14</td>
<td>0.48 ± 0.17</td>
<td>0.26 ± 0.43</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>0.90 ± 0.16</td>
<td>0.67 ± 0.23</td>
<td>0.48 ± 0.43</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>0.71 ± 0.19</td>
<td>0.54 ± 0.25</td>
<td>0.32 ± 0.46</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>0.60 ± 0.27</td>
<td>0.39 ± 0.33</td>
<td>0.18 ± 0.51</td>
<td></td>
</tr>
</tbody>
</table>
to introduce bias into the results, since technically inadequate quantitative angiography was most commonly due to randomly occurring events such as injection-induced arrhythmia and inadequate opacification of the ventricle.

In the present series surgically-treated patients with mitral valve disease had significantly improved survival \((P = 0.009)\) over medically treated patients (fig. 1), even though the surgical cohort was more severely impaired as measured by functional class, functional aerobic impairment, pulmonary artery pressure, mean pulmonary capillary pressure, and hemodynamic severity of valve lesion (table 4). The remaining five variables found to be predictive of survival (table 5) were not significantly different between the two cohorts, except sex distribution.

Subgroup analyses have demonstrated that statistically significantly improved survival in the surgical cohort occurs primarily in patients with mixed mitral stenosis and regurgitation (fig. 2; \(P = 0.006\)) and mitral valve disease patients with moderate impairment of ejection fraction (fig. 4; \(P = 0.004\)), while surgically treated patients with mitral regurgitation had improved survival of borderline significance (fig. 3; \(P = 0.07\)). Again, the ten variables predictive of survival (table 5) were either similar or more severely impaired in the Surgically treated cohorts (table 4), except for medically treated patients with moderately reduced ejection fraction where the end-diastolic volume was larger and the ejection fraction minimally reduced compared to the surgically treated subgroup.

Before making a definitive statement that surgical therapy prolongs survival in patients with mitral valve disease, the comparability of surgically and medically treated cohorts with regard to variables known to affect survival must be ascertained. We have examined many of these variables, but have no data on the presence or absence of coronary disease, since coronary arteriography was rarely done during this era. None of these patients carried a principal diagnosis of coronary disease. Furthermore, the survival of our medical cohort is virtually identical to that of other cohorts of medically treated mitral stenosis patients,\(^10\)\(^-\)\(^13\) suggesting that these were representative patients. On the other hand, the increased proportion of males in the medical cohort may increase the likelihood of coronary artery disease in this group. Male sex is associated with decreased survival in the medical cohort (table 5). While occult coronary disease was undoubtedly present in some of these patients, both medically and surgically treated, we believe it is unlikely to account for the large differences in survival between medically and surgically treated patients.

In the surgical cohort, valve replacement was performed in 25\% (43/171), the remainder having a reparative procedure. Current surgical practice is to perform valve replacement in most patients undergoing surgery for mitral valve disease. However, the late survival curve for patients undergoing valve replacement was parallel to that for patients undergoing reparative procedures. The only difference was the rather high operative mortality rate (28\%) in patients undergoing mitral valve replacement. With currently improved surgical mortality (5-10\%) for mitral valve replacement, the surgical survival curves might be moved upward magnifying further the improved survival with surgery. We believe the data confirm that surgical therapy prolongs life in patients with mitral valve disease, particularly those with mixed stenosis and regurgitation and those with moderate reduction in ejection fraction. The data also indicate reasonable probability that surgery improves survival in patients with mitral regurgitation. The survival curves for surgically treated and medically treated mitral stenosis patients were similar, but the surgically treated patients had more hemodynamic impairment. Thus, with current low operative mortality it is likely that patients with mitral stenosis experience improved survival with surgical therapy as well.

### Prediction of Prognosis

Our univariate analysis demonstrated ten variables predictive of survival in the medical cohort (table 5); but only three of these were predictive in patients with surgically treated mitral valve disease. Previous univariate studies of medically treated mitral valve disease patients have demonstrated clinical status or functional class, sex, age, atrial fibrillation, right axis deviation on electrocardiogram, and increased hilar markings to be related to survival.\(^13\)\(^-\)\(^14\) Our data are consistent with these findings. In addition, we have found that four hemodynamic variables (arterio-venous oxygen difference, mean pulmonary artery pressure, mean pulmonary capillary pressure and severity index) and three quantitative angiographic variables (end-diastolic volume, ejection fraction and left ventricular mass) are also significantly predictive of survival. We are not aware of other studies relating late survival of medically treated mitral valve disease patients to hemodynamic or left ventricular function variables.

When these ten variables were examined multivariately using Cox's regression analysis, only three were found to be predictive of survival. These were arterio-venous oxygen difference and end-diastolic volume in the medical cohort, and age in the surgical cohort. The other eight variables in the medical cohort and two variables in the surgical cohort, which are predictive of survival on univariate analysis, presumably carry similar prognostic information to that given by these three variables.

Using parameter estimates from Cox's regression analysis, we have calculated five-year survival probability \(P_5\) for the medical and surgical cohorts for three levels of these three variables (tables 6, 7). This technique has the advantage over the univariate subgroup analysis previously

### Table 7. Five Year Survival Estimated from Parameter Estimates of Cox's Regression Analysis for Three Discrete Values of Age, Arteriovenous Oxygen Difference (A-VO2), and End-diastolic Volume for Patients with Surgically Treated Mitral Valve Disease

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>A-VO2 (ml/100 ml)</th>
<th>End-diastolic Volume (ml/M2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>0.84 ± 0.06</td>
<td>0.82 ± 0.09</td>
</tr>
<tr>
<td>60</td>
<td>0.84 ± 0.08</td>
<td>0.82 ± 0.07</td>
</tr>
<tr>
<td>70</td>
<td>0.84 ± 0.10</td>
<td>0.82 ± 0.09</td>
</tr>
</tbody>
</table>

... (remaining data)
presented of utilizing all the data on all the patients. From the
standard error of survival probabilities (appendix), the
significance of difference in survival of two subgroups can be
tested. Surgical therapy appears to have the greatest benefi-
cial effect on estimated survival probability (P̂) in mitral
valve disease patients with large end-diastolic volumes and
abnormal arterio-venous oxygen difference. However, due to
the relatively large standard error, the estimated survival
probabilities (P̂) are not statistically significantly different
for medically versus surgically treated patients. Presumably,
with a larger patient population, significant differences in
survival probabilities (P̂) could be established for certain
specified values of age, arterio-venous oxygen difference,
and end-diastolic volume. A cooperative study is currently
being organized to accomplish this goal. Until data from a
prospective study are available, it is premature to recom-
 mend surgical therapy based on specified values of end-
diastolic volume and arterio-venous oxygen difference alone.

The number of variables univariate predictively of sur-
vival are fewer in the surgical cohort (3) compared to the
medical cohort (10). Also, although end-diastolic volume
and arterio-venous oxygen difference are univariately
predictive of survival in the surgical cohort, the level of
statistical significance is less than in the medical cohort.
This is an expected finding, since successful surgery would be ex-
pected to return most of these abnormal preoperative
variables toward normal. Thus, the patient who has a high
pulmonary artery pressure and impaired survival without
surgery, following surgery has a lower pulmonary artery
pressure and improved survival. In addition, valve replace-
ment adds a new set of variables which affect outcome and
which are not related to pre-operative status such as emboli,
bleeding, valve dysfunction, and valve infection.

Further prospective studies with larger numbers of pa-
tients are necessary to further define differences in survival
between specific diagnoses (e.g., mitral stenosis vs. mitral
regurgitation), the effect of coronary disease on survival, and
the effect of lowered operative mortality on survival in the
surgical cohort. Our data indicate improved survival with
surgical treatment of mitral valve disease, particularly
patients with mixed stenosis and regurgitation, mitral re-
regurgitation, moderate impairment of ejection fraction, large
end-diastolic volume and abnormal arterio-venous oxygen
difference. The survival of patients with medically-treated
mitral valve disease is poor, suggesting a need for earlier sur-
gery.

Appendix

Asymptotic Normality and Estimated Variance for Pr in the Cox Model

1. Introduction

1. The estimated probability, P̂r, of survival to a specified time t, for
fixed values of the predictive variables X0, X0, . . . , Xr is

\[ P_r = F_r(t) = \exp \left( \sum_{i=1}^{r} \beta_i (X_i - X_i) \right) \]

Here "\( \exp \)" indicates an estimated quantity. The \( \beta_i \)s are calculated as de-
scribed by Cox, and \( F_r(t) \) is calculated according to Breslow. When
the Cox model holds, the \( \beta_i \)s are approximately normal random variables with
the true \( \beta_i \)s for means for large samples. The variances can be estimated from
the data. However, there are no published results on the variances or large
sample behavior of \( F_r(t) \) and of \( P_r \).

Recent work (Samuels - unpublished data) outlined in Section 2 provides a
basis for believing that if \( P_r \) is asymptotically normal, it has an asymptotic
mean \( \mu_r \) (the true value) and a variance which can be estimated. We stress in
Sec. 2.5 that the conditions for the normality are assumed, not proved.

2. The Argument

2.1 Consider \( t \) and \( X_0, X_0, . . . , X_r \) in (1) to be specified and unchanging in
what follows. \( P_r \) is to be estimated on the basis of a sample of \( N \) patients. For
the \( i \)-th patient (\( i = 1, 2, \ldots , N \)), the following data are observed.

\[ T_i = \text{observed time on study} \]
\[ \delta_i = 1 \quad \text{if the patient died at } T_i \]
\[ \delta_i = 0 \quad \text{if the patient was alive at } T_i \]

( Failure time is "censored." )

\[ X_0, X_0, . . . , X_r = \text{values of the predictive variables} \]

We can combine this information for the \( i \)-th patient by defining a vector

\[ (T_i, \delta_i, X_0, X_0, . . . , X_r) \]

The data for the entire experiment now consists of \( N \) sample points \( Z_1, Z_2, . . . , Z_N \). We can further summarize the experiment by defining the sample

\[ G_N(x) \]

distribution as the distribution which puts mass \( 1/N \) at each of the

observed sample points \( Z_i (i = 1, 2, \ldots , N) \).

2.2 Next, the estimated \( P_r \) is shown to be a mathematical function \( \rho(G) \):

\[ \hat{P}_r = \rho(G_0) \]

2.3 The data points are assumed to arise from an underlying distribution \( G(z) \),
of which \( G_0 \) is a sample estimate. \( G(z) \) is defined by the following, very

general, mechanism of generating a data point \( z \):

2.3a. The predictive variables \( X_0, X_0, . . . , X_r \) are picked according to an ar-
bitrary joint distribution.

2.3b. Conditional on the \( X_0 \)’s picked in 2.3a, a survival time \( S \) is selected
according to the Cox model.

2.3c. A censoring time \( C \) is picked according to an arbitrary censoring
distribution (which represents variable entry and losses to followup). \( C \)
may depend on the \( X_0 \)’s, but conditional on the realized values \( X_0, X_0, . . . , X_r \)
\( C \) must be independent of \( S \).

2.3d. Finally the observed time on study, \( T \), is calculated as the minimum of
\( S \) and \( C \), and the censoring indicator \( \delta \) is set appropriately. This com-
pletes the generation of \( Z = (T, \delta, X_0, X_0, . . . , X_r) \).

The repetition of this random process results in the distribution \( G(z) \). The
observations are then independent and identically distributed according to \( G \). The
value, \( G \), may be called a random censorship model with covariates.

2.4 For any random censorship \( G \) as defined in 2.3, it can be proved that,

\[ \rho(G) = \hat{P}_r \]

This property of the estimator, \( \hat{P}_r = \rho(G_0) \), is known as Fisher consis-
tency.

2.5 For Fisher consistent estimates with sufficiently regular \( \rho \) and \( G \), a kind of
Taylor’s series expansion is possible.\(^{15}\)

\[ (2) \quad \rho(G) - \rho(G) = N^{-1} \sum_{i=1}^{N} IC(Z_i, p; G_0) = O(N^{-1}) \]

The function \( IC(Z_i, p; G) \) is Hampel’s influence curve of \( p \) and \( G \), evaluated
at \( Z_i \). \(^{16}\)

We assume that the expansion (2) holds. The terms \( IC(Z_i, p; G) \) (\( i = 1, \ldots , N \))
are independent and identically distributed random variables with mean
equal to zero. Therefore, \( \rho(G_0) = \hat{P}_r \) is asymptotically a normal random variable
with mean \( \rho(G) = \hat{P}_r \) and variance \( V_r(G) / N \) where

\[ V_r(G) = \int IC(Z_i, p; G) dG(Z) \]

\( V_r(G) \) is estimated by substituting \( G_0 \), \( G \) in (3). The function

\( IC(Z_i, p; G_0) \) is called the empirical influence curve; this has been derived. The
resulting variance estimator is

\[ (4) \quad V_r(G) = N^{-1} \sum_{i=1}^{N} IC(Z_i, p; G_0) \]

The properties of this estimator have not been investigated. There are con-
nections with the jackknife estimator of variance, which is known to break
down in some situations.\(^{15}\)

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**Blood Volume Prior to and Following Treatment of Acute Cardiogenic Pulmonary Edema**

**JAIME FIGUERAS, M.D., AND MAX HARRY WEIL, M.D., PH.D.**

**SUMMARY** Following onset of acute cardiogenic pulmonary edema in 21 patients, increases in hematocrit, plasma protein concentration, and colloid osmotic pressure were associated with decreases in plasma volume. Accordingly, there was a loss of hypo-osmotic fluid into the extravascular spaces. Following treatment with oxygen, furosemide, and morphine sulfate and reversal of clinical and radiographic signs of pulmonary edema, declines in hematocrit, plasma protein concentration, and colloid osmotic pressure were associated with increases in plasma volume. Hypo-osmotic edema fluid was therefore reabsorbed into the vascular compartment.

The concept that acute heart failure with pulmonary edema is associated with an increase in intravascular volume is therefore not supported. To the contrary, there is a reduction of blood volume during acute pulmonary edema. During reversal of acute pulmonary edema with diuresis, there was re-expansion rather than contraction of blood volume.

**DURING HEART FAILURE** in which there is a rise in left ventricular filling pressure and secondarily in mean left atrial and pulmonary artery pressures and pulmonary blood volume, hydrostatic forces account for increased pulmonary capillary filtration with extravasation of fluid into the interstitium and subsequently into the alveoli of the lung. At the same time, renal and endocrine mechanisms account for salt and water retention. Acute cardiogenic pulmonary edema (PE) has been attributed, at least in part, to retention of fluid, increases in plasma volume, and consequently increases in the preload on the heart. However, acute cardiogenic pulmonary edema is associated more often with decreases than increases in hematocrit and plasma protein concentration. The changes would be more consistent with a decrease rather than an increase in plasma volume. In

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