Elevated Pulmonary Artery Pressure: An Independent Predictor of Mortality

Richard Cooper, M.D.; Jalal Chali, M.D., F.C.C.P.; Brian E. Simmons, M.D., F.C.C.P.; and Angel Castaner, M.D.

Analyses in this study were based on hemodynamic and angiographic data obtained in a cohort of 1,371 predominantly black patients during right and left heart catheterization. All patients were followed up prospectively for a mean of 117 weeks, and 103 fatal events were recorded. In Cox survival analysis, three variables were found to be independently related to survival: pulmonary artery mean pressure (PAMP), number of stenosed vessels, and left ventricular (LV) ejection fraction (p<0.01); in multivariate stepwise analysis, PAMP entered the model first with the largest x^2 value of the three prognostic variables (x^2 = 33.4; p<0.0001). The PAMP was 32 percent higher in decedents compared with survivors (25 ± 11 mm Hg vs 19 ± 8 mm Hg, p<0.01 [mean, SD]) and a 10 mm Hg increase in PAMP was associated with a more than fourfold increase in the relative risk of dying; this finding was independent of pulmonary vascular resistance and therefore could not be attributed to primary pulmonary vascular or parenchymal disease. In both the subgroup of 1,118 patients with a normal LV ejection fraction (>50 percent) and the 253 patients with a reduced ejection fraction (<50 percent), PAMP emerged as an independent predictor of mortality (p<0.0001 and 0.01, respectively), and is therefore a marker of cardiac disease beyond impairment of systolic contractile function. Among patients without obstructive coronary artery disease, PAMP alone provided prognostic information in the multivariate survival analysis.

(Chest 1991; 99:112-20)

PAMP = pulmonary artery mean pressure; LV = left ventricular; LVH = left ventricular hypertrophy; CAD = coronary artery disease; PA = pulmonary artery; MPAP = mean pulmonary artery pressure

The prognostic value of hemodynamic studies of the pulmonary circulation has been recognized for a number of years in patients with mitral valve dysfunction and chronic lung disease. Little information is available, however, on the relationship between abnormalities in pulmonary hemodynamics and prognosis in patients with coronary artery disease (CAD), and virtually no data exist (to our knowledge) on the prognostic importance of pulmonary hypertension in individuals with normal coronary arteries and normal systolic function. The presence of systemic hypertension is well known to increase the risk of cardiac death among patients with and without obstructive CAD, and much of this increased risk has been ascribed to left ventricular hypertrophy (LVH).

The mechanism of this increased mortality risk remains unknown, however. Although decreased left ventricular (LV) compliance, as demonstrated by reduced diastolic filling rates, left atrial enlargement, and direct measurement of pressure-volume relationships, has been demonstrated in hypertension with associated LVH, the prognostic significance of these findings has never been evaluated. Control for the impact of left-sided cardiac failure due to loss of systolic function is obviously necessary to evaluate the potential independent predictive importance of decreased compliance. Left ventricular hypertrophy itself can result in heart failure with normal LV systolic function, and the relative contribution of increased myocardial thickness to loss of compliance must likewise be considered.

In the course of the analysis of the impact of LVH on survival in a cohort of predominantly black patients with a high prevalence of systemic hypertension, we noted the independent increased risk associated with pulmonary hypertension. The present study was therefore undertaken to assess more fully the predictive significance of increased pulmonary pressures. Clinical and hemodynamic data were recorded on 1,371 patients who were then followed up prospectively for mortality. The degree of pulmonary hypertension that persists after control for loss of systolic function has been taken as a proxy indicator of diastolic dysfunction of the left ventricle. The purpose of this report is to provide a descriptive analysis of the statistical relationship between the hemodynamics of the pulmonary circulation and prognosis in patients with and without CAD, and, in particular, to examine the relevance of increased pulmonary artery mean pressure (PAMP) as a predictor of survival.

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METHODS

Database

Information describing the clinical history, resting electrocardiogram, hemodynamics, and coronary arteriograms was prospectively collected in the Cook County Hospital (Chicago) Heart Disease Registry on 1,749 patients undergoing cardiac catheterization for presumed CAD between June 1982 and December 1987. All patients with valvular and congenital heart disease were excluded from the present analysis. A total of 378 patients were eliminated because of missing information on either pulmonary artery pressures (n = 323), ejection fraction (n = 49), or coronary arteriograms (n = 6). A sample of 1,371 patients with complete data on left-sided cardiac function as well as pulmonary artery pressures were thus available for survival analysis. The subsample of patients with right atrial pressure and pulmonary wedge pressure—and therefore estimates of pulmonary vascular resistance—was somewhat smaller (n = 1,027), and analyses requiring these variables were performed on a sample reduced by 344 persons. Diagnostic procedures were performed based on routine clinical indications and no attempt was made to standardize the clinical care provided. The performance of an echocardiogram and the right heart catheterization were considered standard procedures at our institution during the period of this study. It is possible, however, that some selection for more severe cases did occur. It was not possible in retrospect to identify potential selection biases, however. All prospective analyses were based on the cohort as defined at baseline, so the risk factor–outcome relationships themselves should not be biased.

Left ventricular hypertrophy on the electrocardiogram was considered to be present when it met the criteria for LVH (voltage included) according to the computer programs from Marquette Electronics, Inc (Marquette Analysis Program 1984, pp 18-19).

Cardiac Catheterization

Hemodynamic data were collected from both the right and left heart catheterization. Pressure tracings were recorded on a recorder (Hewlett-Packard 4568C) with fluid-filled catheters. Left ventricular angiograms were obtained in the standard 30° right anterior oblique projection and the ejection fraction was calculated using the single plane method of Dodge.11 Significant CAD was defined as a 70 percent or greater luminal diameter narrowing of at least one of the following major vessels: the left anterior descending, the left circumflex (or large marginal branch), and the right coronary artery. Left main coronary disease was considered to be present when a 50 percent or greater narrowing was visualized, and these patients were assigned triple-vessel disease for the overall statistical analysis. All other vessels were considered “normal.” The angiograms were read as part of the clinical practice of the institution and not under controlled conditions. Pulmonary vascular resistance was calculated as pulmonary artery mean pressure minus pulmonary capillary wedge pressure divided by cardiac output times 80.

Echocardiography

Ultrasound imaging was performed in 715 patients. Two-dimensionally targeted M-mode echocardiographic recordings of the LV activity were performed using the parasternal view in a 30° left lateral position. The “leading edge to leading edge” convention was employed for estimates of cardiac dimensions according to standards of the American Society of Echocardiography.12-13 Wall thickness was measured to the nearest 0.1 mm. Left ventricular mass was estimated by a modification of the Penn formula, as proposed by Devereux et al14: LV mass = 1.05 ([LVDD + IVS + LVFW]3 – [LVDD]3) where LIDD = left ventricular internal diastolic dimension (cm), IVS = interventricular septum, and LVFW = diastolic posterior wall. This value was made comparable to anatomic findings by multiplying the LV mass calculation by 0.80 and adding 0.6 g.14 Because of the correlation between height and LV mass (LV mass vs height, r = 0.3 in our data set),14 the principal variable used to estimate the degree of LVH was LV mass indexed to height (g/m).

Follow-up Procedures

An attempt was made to contact all patients during an outpatient visit, by telephone, or by review of medical records of clinic attendance. When patients were unavailable for follow-up by these procedures, the records of the Illinois Department of Health were searched for death certificates. Finally, the database provided by the National Death Index was searched for all members of the original cohort.15 Patients who were not contacted and confirmed to be alive and who were not matched to a death certificate were considered alive as of the last date included in the National Death Index file, namely, December 31, 1986. Copies of death certificates were obtained for decedents and served as the sole source of information for assigning primary cause of death. The mean follow-up interval for all patients was 117 weeks. A total of 103 deaths were recorded, 80 percent of which were coded as due to a primary cardiac cause.

Statistical Analysis

Data were coded and entered into a computerized database and analyses were performed with programs available on SPSS – PC+ (SPSS, Inc, Chicago, Illinois) and BMDP (University of California Press, Berkeley, California). For analyses comparing two groups, χ² tests were used for dichotomous variables and two-tailed t tests were applied to continuous variables. Multivariate survival analyses were carried out with the Cox regression model using the maximum partial likelihood ratio method available through programs included in BMDP. Covariates included in this model that had no predictive value were excluded from the analyses presented herein, including sex, age, and smoking status. Survival curves for the comparison of two groups were constructed using the Kaplan-Meier product limit function and differences in the probability of survival tested with the generalized Wilcoxon statistic. In these analyses, “improvement χ²” refers to the improved prediction of the model when the associated term was added.

The key challenge faced in the analysis of these data was the application of statistical procedures to demonstrate the independent prognostic information provided by the measurement of pulmonary artery pressure. Given the high degree of collinearity observed among the various physiologic measures of cardiac function performed as part of this study, multivariate techniques were required. As others have noted, however, statistical “control” in multivariate models often does not provide adequate tests of independence, especially when the degree of precision of measurement of the variables in the model is unequal or unknown.15-16 To address this problem, two basic analytic strategies were applied. First, the standard multivariate regression models were employed and interaction terms were generated based on the outcomes of the analyses that used first-order terms. Second, the sample was stratified on one variable (eg, ejection fraction) while outcome analysis was performed with a second variable (eg, pulmonary artery pressure). Only when the outcome was concordant for all analyses were the results presented. While use of these multiple analytic approaches add complexity to the presentation of the results, this procedure increases the degree of confidence that can be ascribed to the conclusions.

RESULTS

The descriptive characteristics of the entire cohort of 1,371 patients, survivors compared with decedents, are presented in Table 1. Most of the patients were blacks while the proportion of male sex was higher

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Table 1—Descriptive Characteristics of Study Cohort:
Survivors vs Decedents

<table>
<thead>
<tr>
<th>Variable</th>
<th>Survivors (N = 1268)</th>
<th>Decedents (N = 103)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>55.2 ± 8.8</td>
<td>55.9 ± 9.2</td>
</tr>
<tr>
<td>Sex, No. %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>606 (48)</td>
<td>621 (60)</td>
</tr>
<tr>
<td>Female</td>
<td>664 (52)</td>
<td>41 (40)</td>
</tr>
<tr>
<td>Race, No. %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>965 (76)</td>
<td>877 (84)</td>
</tr>
<tr>
<td>White</td>
<td>118 (9)</td>
<td>8 (8)</td>
</tr>
<tr>
<td>Other</td>
<td>187 (15)</td>
<td>8 (8)</td>
</tr>
<tr>
<td>Medical history, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior MI</td>
<td>27</td>
<td>52‡</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>27</td>
<td>35</td>
</tr>
<tr>
<td>Hypertension</td>
<td>76</td>
<td>79</td>
</tr>
<tr>
<td>Ever smoked</td>
<td>56</td>
<td>65</td>
</tr>
<tr>
<td>Electrophysiological LVH, %</td>
<td>25</td>
<td>35†</td>
</tr>
<tr>
<td>Angiographic findings:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. (%) of vessels stenosed:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>606 (47)</td>
<td>23 (22)</td>
</tr>
<tr>
<td>1</td>
<td>243 (19)</td>
<td>16 (16)</td>
</tr>
<tr>
<td>2</td>
<td>185 (14)</td>
<td>28 (27)</td>
</tr>
<tr>
<td>3</td>
<td>236 (20)</td>
<td>36 (35)</td>
</tr>
<tr>
<td>Hemodynamic findings, mean ± SD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aortic mean pressure, mm Hg</td>
<td>103.7 ± 16.2</td>
<td>103.7 ± 15.8</td>
</tr>
<tr>
<td>LVEDP, mm Hg</td>
<td>12.8 ± 5.8</td>
<td>16.5 ± 9.2‡</td>
</tr>
<tr>
<td>LV ejection fraction, %</td>
<td>64.2 ± 15.1</td>
<td>54.9 ± 16.4‡</td>
</tr>
<tr>
<td>PAMP, mm Hg</td>
<td>19.2 ± 7.6</td>
<td>24.7 ± 11.0‡</td>
</tr>
<tr>
<td>Pulmonary wedge pressure, mm Hg</td>
<td>10.0 ± 5.9</td>
<td>14.5 ± 7.8‡</td>
</tr>
<tr>
<td>PVR, dyne/cm²·s</td>
<td>141.8 ± 96.3</td>
<td>184.9 ± 106.1‡</td>
</tr>
<tr>
<td>Right atrial pressure, mm Hg</td>
<td>5.8 ± 3.0</td>
<td>7.5 ± 4.7‡</td>
</tr>
</tbody>
</table>

*significant at p<0.05;
‡significant at p<0.01.

among patients who died. Hypertension was common in both groups and electrocardiographic (ECG) evidence of LVH was present in almost one third of each group. Among the medical history variables, only a history of myocardial infarction was more prevalent in the decedents.

As anticipated, among the hemodynamic variables, those reflecting LV function were all significantly related to mortality, including left ventricular ejection fraction (LVEF) and left ventricular end-diastolic pressure (LVEDP). In addition, PAMP, pulmonary wedge pressure, pulmonary vascular resistance, and right atrial pressure were all significantly increased among those who died during the follow-up period (p<0.01).

The interrelationships among the various measures of cardiac structure and function are presented in Table 2. As the most widely used measure of global LV systolic function, LVEF was negatively related to LVEDP, PAMP, and pulmonary wedge pressure (p<0.01). At the same time, LVEDP, PAMP, and pulmonary wedge pressure were all highly positively intercorrelated (r=0.6 to 0.7; p<0.001). Increasing echo-LV mass and septal wall thickness were associated with a lower LVEF and higher intracardiac pressures.

The major focus of this analysis was to assess the predictive value of right-sided hemodynamic measurements independent of systolic LV function and the severity of coronary atherosclerosis. For this purpose, LVEF was taken as a measure of LV systolic function and Cox regression models were constructed to estimate the relative contribution of pulmonary hemodynamics to the prediction of death. In the univariate Cox regression model, the expected predictors of survival were confirmed, namely male sex, LVEDP, LVEF, and the number of vessels stenosed. In addition, however, PAMP was highly related to survival, being associated with the largest chi² value of any of the angiographic variables (Table 3). In the stepwise regression model, three variables—PAMP, the number of stenosed vessels, and the LVEF—maintained statistical significance (Table 3). Among these variables, PAMP was associated with the greatest predictive power, entering the model first and achieving the largest standardized β-coefficient.

Additional analyses were performed using pulmonary wedge pressure, pulmonary vascular resistance, and right atrial pressure. Although these variables

Table 2—Correlation Matrix of Measures of Cardiac Structure and Function:
Hemodynamic and Echo Variables* (N = 1371)

<table>
<thead>
<tr>
<th>Ejection Fraction</th>
<th>LVEDP</th>
<th>PA Mean</th>
<th>Pulmonary Wedge</th>
<th>Aortic Mean</th>
<th>IV Septum</th>
<th>LV Mass</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ejection fraction</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>LVEDP</td>
<td>—.316†</td>
<td>—</td>
<td>—.686†</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>PAMP</td>
<td>—.317†</td>
<td>—.586†</td>
<td>—.683†</td>
<td>—.160†</td>
<td>—.057</td>
<td>—.603†</td>
</tr>
<tr>
<td>Pulmonary wedge</td>
<td>—.370†</td>
<td>—.693†</td>
<td>—.683†</td>
<td>—.160†</td>
<td>—.057</td>
<td>—.603†</td>
</tr>
<tr>
<td>Aortic mean pressure</td>
<td>.103†</td>
<td>.048</td>
<td>.160†</td>
<td>—</td>
<td>.057</td>
<td>—.142†</td>
</tr>
<tr>
<td>IV septum</td>
<td>.057</td>
<td>—.004</td>
<td>.051</td>
<td>—.003</td>
<td>.209†</td>
<td>—</td>
</tr>
<tr>
<td>LV mass</td>
<td>—.269†</td>
<td>—.145†</td>
<td>—.217†</td>
<td>—.163†</td>
<td>—.142†</td>
<td>—</td>
</tr>
</tbody>
</table>

*LVEDP = left ventricular end-diastolic pressure; PAMP = pulmonary artery mean pressure; IV septum = interventricular septal thickness; LV mass = left ventricular mass/height. N for correlations including echo variables = 661.
†p<0.001; two-sided test.

Elevated Pulmonary Artery Pressure (Cooper, Ghali, Simmons)
were predictive of a fatal event in the univariate model ($\chi^2$ to enter = 12.4 for pulmonary wedge pressure, 9.7 for pulmonary vascular resistance, and 10.9 for right atrial pressure), only right atrial pressure was retained in the stepwise multivariate model, including LVEF and number of stenosed vessels. Thus, despite the high degree of intercorrelation, PAMP was a more powerful predictor of mortality than right atrial or pulmonary wedge pressure. These findings further demonstrate that pulmonary vascular resistance was not a key contributing factor in the prediction of mortality. Given the low predictive value of these variables, and their elimination from the stepwise model, they were not included in subsequent analyses.

Inclusion of LV mass in a multivariate regression model yielded independent significance for PAMP, LV mass, and number of vessels, with respective $p$ values of <0.01, 0.03, and 0.05. The standardized $\beta$-coefficients in this analysis were 3.9 for PAMP and 2.2 for LV mass. The mortality risk associated with PAMP was thus entirely independent of the effect of increasing severity of LVH.

To assess further the relative contribution of PAMP in relation to the level of LV systolic function, Cox regression analysis was performed separately in patients with and without depressed LV function (Table 4). In patients with normal LV function (ie, LVEF $>50$), PAMP was confirmed as a powerful predictor of outcome along with ejection fraction, followed by number of stenosed vessels. Similarly, in patients with a reduced ejection fraction, PAMP provided the most explanatory information regarding outcome, followed by the number of stenosed vessels; the contribution of ejection fraction did not reach statistical significance in this subgroup.

To determine whether the predictive value of PAMP was relevant in patients with normal coronary arteriograms, further Cox regression analyses were carried out in this subgroup. (At baseline, 629 patients had normal coronary arteries and 23 fatal events were recorded during the follow-up period.) Pulmonary artery mean pressure was found to be the only hemodynamic variable among those described above that retained its predictive value ($p = 0.016$) in these patients. In this analysis, number of vessels was not included in the model, of course, while LVEDP, LVEF, and right atrial pressure contributed no statistically significant information regarding prognosis.

To estimate the magnitude of the effect of increased pulmonary pressure on survival, Kaplan-Meir product limit survival curves were constructed to compare patients with and without pulmonary pressures above 20 mm Hg (Fig 1). Survival differences for these two groups appeared early in the course of the follow-up and were highly significant ($p < 0.01$). Survival at an interval of four years was 91 percent (95 percent confidence interval [CI] = $\pm 2$) among patients with normal pulmonary pressures, and 82 percent

### Table 3—Cox Stepwise Regression Analysis of Determinants of Survival after Cardiac Catheterization ($N = 1371$)

<table>
<thead>
<tr>
<th>Variable</th>
<th>$\chi^2$ to enter</th>
<th>$p$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAMP</td>
<td>47.4</td>
<td>0.000</td>
</tr>
<tr>
<td>Ejection fraction</td>
<td>39.3</td>
<td>0.000</td>
</tr>
<tr>
<td>No. of vessels†</td>
<td>26.8</td>
<td>0.000</td>
</tr>
</tbody>
</table>

**A. Univariate Model**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Improvement</th>
<th>Standardized $\beta$-Coefficient</th>
<th>$p$ value</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAMP*</td>
<td>33.4</td>
<td>4.0</td>
<td>0.000</td>
<td>4.2†</td>
</tr>
<tr>
<td>No. of vessels†</td>
<td>10.1</td>
<td>−3.2</td>
<td>0.000</td>
<td>9.8§</td>
</tr>
<tr>
<td>Ejection fraction</td>
<td>9.8</td>
<td>−3.4</td>
<td>0.002</td>
<td>1.3§</td>
</tr>
</tbody>
</table>

*PAMP = pulmonary artery mean pressure.
†Number of coronary vessels with $>70$ percent stenosis.
‡Associated with 10 mm Hg increase.
§Associated with 1 unit increase.
¶Associated with 10 percent decrease.

### Table 4—Cox Stepwise Regression Analysis of Determinants of Survival after Cardiac Catheterization: By Level of Left Ventricular Function

<table>
<thead>
<tr>
<th>Patients with Normal Ejection Fraction $&gt;50%$ ($N = 1118$; 64 fatal events)</th>
<th>Improvement</th>
<th>$p$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variable</td>
<td>$\chi^2$</td>
<td></td>
</tr>
<tr>
<td>PAMP*</td>
<td>15.6</td>
<td>0.000</td>
</tr>
<tr>
<td>Ejection fraction</td>
<td>12.7</td>
<td>0.000</td>
</tr>
<tr>
<td>No. of vessels†</td>
<td>5.2</td>
<td>0.023</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patients with Reduced Ejection Fraction $&lt;50%$ ($N = 253$; 39 fatal events)</th>
<th>Improvement</th>
<th>$p$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variable</td>
<td>$\chi^2$</td>
<td></td>
</tr>
<tr>
<td>PAMP*</td>
<td>6.70</td>
<td>0.010</td>
</tr>
<tr>
<td>No. of vessels†</td>
<td>5.21</td>
<td>0.023</td>
</tr>
</tbody>
</table>

*PAMP = pulmonary artery mean pressure.
†Number of coronary vessels with $>70$ percent stenosis.
As noted, an important challenge of the analysis procedures applied to these data was to parcel out the separate impact of the various physiologic measures. Given the multicollinearity observed among the measures of cardiac structure and function demonstrated in Table 3, a series of subanalyses were undertaken to define the independent effect of each factor.

First, to control for the effect of the association between worsening severity of pulmonary hypertension and the degree of coronary atherosclerosis, the cohort was stratified by the number of stenosed vessels and univariate comparisons made in PAMP between survivors and decedents (Fig 2). At each level of coronary disease, PAMP was significantly increased among those dying during the follow-up period (p<0.01), and the magnitude of the difference was consistent in each subgroup (approximately 30 percent). Minor increases in PAMP were noted with increasing severity of CAD among the survivors.

Second, since it is likely that increased pulmonary pressure correlates with diastolic dysfunction, we were interested to know if a possible interactive effect on survival existed between LVH—itself a major determinant of LV compliance—and increased PAMP. As shown in Table 5, it is evident that increases in pulmonary artery (PA) pressure and LV mass are independently and at least additively related to the risk of dying. The coexistence of both high LV mass and high PAMP carried a fivefold increase in mortality.

**Figure 1.** Survival among patients with normal and elevated pulmonary artery (PA) pressures (Kaplan-Meir product limit curves).

**Figure 2.** Mean pulmonary artery pressure in survivors and decedents by severity of coronary artery disease (mean and standard deviation).
risk. The interaction between elevated pulmonary pressure and LVH was further examined by introducing a cross-product term (PA mean x LV mass) into the Cox regression model (Table 6). This term was highly significant in the univariate and multivariate models, and it eliminated the predictive value of both PAMP and LV mass entered separately.

Third, in an additional analysis, the sample was successively divided into (1) subjects with high and low PAMP at baseline, and the predictive value of LV mass was examined, and (2) subjects with high and low LV mass, and the predictive value of PAMP was tested (Table 6). An increased PAMP was strongly associated with the risk of dying in patients with high LV mass, but not in those with moderately increased or normal LV mass. Contrariwise, increases in LV mass were associated with a greater chance of dying in patients with mean pulmonary pressures equal to or greater than 20 mm Hg, but not in those with lower pressures. No interaction was noted between PAMP and LV mass.

Table 5—Percentage of Patients Dying during Follow-up Observation Stratified for the Presence of Pulmonary Hypertension and Left Ventricular Hypertrophy

<table>
<thead>
<tr>
<th>Pulmonary artery mean pressure</th>
<th>Low</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>PA mean</td>
<td>2.6% (6/231)</td>
<td>5.1% (9/157)</td>
</tr>
<tr>
<td>LV mass</td>
<td>8.6% (12/140)</td>
<td>10.7% (20/187)</td>
</tr>
</tbody>
</table>

Table 6—The Interactive Effect of Increases in Pulmonary Artery Pressure and Left Ventricular Mass on Survival

<table>
<thead>
<tr>
<th>Variable</th>
<th>Improvement</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PA mean</td>
<td>28.1</td>
<td>.000</td>
</tr>
<tr>
<td>LV mass</td>
<td>8.0</td>
<td>.003</td>
</tr>
<tr>
<td>Ejection fraction</td>
<td>6.4</td>
<td>.012</td>
</tr>
<tr>
<td>No. of vessels</td>
<td>6.3</td>
<td>.012</td>
</tr>
<tr>
<td>PA mean x LV mass</td>
<td>37.0</td>
<td>.000</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Variable</th>
<th>Standardized Improvement</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PA mean x LV mass</td>
<td>5.47</td>
<td>22.7</td>
</tr>
<tr>
<td>No. of vessels</td>
<td>1.89</td>
<td>3.5</td>
</tr>
</tbody>
</table>

Multivariate Cox Regression Models in High and Low Bivariate Distribution of PA Mean Pressure and LV Mass

<table>
<thead>
<tr>
<th>Variable</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>High or low PA mean pressure*</td>
<td></td>
</tr>
<tr>
<td>High PA mean (≥20 mm Hg)</td>
<td>LV mass</td>
</tr>
<tr>
<td>Low PA mean (≤19 mm Hg)</td>
<td>Ejection fraction</td>
</tr>
<tr>
<td>High or low LV mass†</td>
<td></td>
</tr>
<tr>
<td>High LV mass (≥140 g/m)</td>
<td>PA mean</td>
</tr>
<tr>
<td>Low LV mass (&lt;140 g/m)</td>
<td>(No variables)</td>
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</tbody>
</table>

*Variables in the model include LV mass, ejection fraction, and number of vessels.
†Variables in the model include PAMP, EF, and number of vessels.

In summary, these last three analyses demonstrate the following: (1) the predictive value of increased PAMP is independent of the degree of CAD; (2) PAMP provides prognostic information independent of increases in LV mass and exhibits a strong positive interaction with worsening LVH; and (3) the interaction of PAMP and LV mass is independent of the effect of more severe CAD and LV dysfunction.

**DISCUSSION**

The data presented herein demonstrate that among a cohort of patients with a high prevalence of hypertension and LVH, important prognostic information was contained in the measurement of the hemodynamics of the pulmonary circulation. Across a wide spectrum of functional and structural cardiac abnormalities, pulmonary pressure appeared as the strongest predictor of mortality, entirely independent of the severity of coronary atherosclerosis, level of LVEF, and the degree of LVH. This predictive power was apparent among patients with both a normal and depressed LVEF, and patients with increased as well as normal LV mass, as determined by echocardiography. At each level of coronary disease, from patients without obstructive lesions to those with multivessel disease, higher pulmonary pressures were found among patients who died during follow-up. Based on relative risk estimates from multivariate regression analysis, an increase in PAMP of 10 mm Hg resulted in more than a fourfold increase in mortality.

Early studies of the survival determinants after cardiac catheterization demonstrated that global systolic LV function, as measured by ejection fraction, was highly predictive of survival. It has subsequently been recognized, however, that the information captured by the level of ejection fraction is essentially dichotomous; knowledge of LVEF has little prognostic value in patients with normal LV function (ie, LVEF>50 percent), likewise within the group of patients with a severely reduced LVEF, the absolute level of ejection fraction does not consistently contribute additional predictive power. The weak predictive power of LVEF within the normal range is perhaps not surprising; however, its insensitivity among patients with significant disease raises a series of interesting and important questions. It would appear that the loss of cardiac pump function that generates the risk of dying is not linearly related to systolic function and reflects a more complex interaction with other aspects of myocardial damage.

Several previous reports in patients with a reduced ejection fraction have proposed a prognostic role for the severity of hemodynamic abnormalities. In these studies, patients with a markedly depressed cardiac output and stroke work index, associated with
an elevated LV filling pressure and high systemic vascular resistance, experienced a significantly worse prognosis than patients with near normal values for these hemodynamic variables. The significance of pulmonary pressures, however, has not been adequately assessed previously. The absence of a wide range of PAMP values and the limited sample size included in these previous studies may explain why the predictive value of PAMP was not identified.

It is possible that the powerful independent predictive contribution of pulmonary hypertension to the survival analysis that we observed reflects primarily abnormalities of diastolic dysfunction and reduced LV compliance.13,20 Several important caveats apply, however. First, pulmonary pressure during routine cardiac catheterization is a crude physiologic measure of LV compliance.38 A number of conditions, including, among others, the geometry of the left ventricle,13,30 loading conditions,40 and myocardial ischemia,41 influence diastolic function and make it difficult to obtain accurate estimates of compliance. Second, increases in pulmonary pressures are also an important consequence of loss of LV systolic function, as demonstrated in our data by the significant correlation between LVEF and mean pulmonary pressure (r = -0.32, p<0.001). It is also possible that increases in mean pulmonary artery pressure (MPAP) reflect primarily the presence of pulmonary disease.

The presence of LVH has long been recognized to predict future cardiac events.5-8,20 Recent data with echocardiographic measurements have now supplemented the ECG studies.8,20,42,44 Since hypertension is a potent risk factor for CAD, and the presence of CAD alone is associated with an increase in LV size,20,44-46 significant confounding of the CAD-LVH risk relationship must exist. In support of this content ion is the recent Framingham analysis that demonstrates that the standard coronary risk factors, namely hypercholesterolemia and cigarette smoking, are predictive of the presence of LVH.8 Any analysis that attempts to quantify the risk associated with LVH must therefore control for coexisting CAD. With coronary arteriography on all participants, our data provide the first direct examination of this question, and confirm the interaction between CAD and LVH.

In the present analysis, it is apparent that the presence of LVH and increased PAMP have both an independent and an interactive effect on mortality. The interactive effect of LVH and elevated PAMP is best illustrated by the estimated fivefold increase in mortality when these two conditions coexist. Although the nature of this interaction is undoubtedly complex, it is possible that myocardial thickness is not a very accurate measure of compliance under the conditions of this study. Some individuals may respond to the pressure overload of hypertension with hypertrophy, while others will not. It is also now well known that echo-LV mass is not highly correlated with blood pressure, at least as measured short term.47 None of these cardiac abnormalities therefore can be reliably ascribed in quantitative terms to the lifetime effect of hypertension.

Beyond these methodologic limitations, it is clear that the state of the myocardium of our patients is determined by a complex mixture of the effects of ischemic and hypertensive heart disease. Many patients will have experienced periods of sustained hypertension in the past, along with intermittent blood pressure control. Myocardial hypertrophy and subsequent regression probably occurred in most patients and may have resulted in an increase in myocardial collagen content that contributed to loss of compliance.48-49 A recent clinical trial among mildly hypertensive patients demonstrated that despite regression of LV mass with blood pressure control, diastolic filling rates did not return to normal.49 These findings suggest that the diastolic abnormalities of hypertensive heart disease may persist after reduction in protein mass. Similar loss of compliance may have occurred among the third of patients who had experienced a prior myocardial infarction.51 However, since the relative risk associated with high pulmonary pressures was virtually identical in patients with 0-, 1-, 2-, and 3-vessel coronary disease, we assume that whatever the cause for the loss of compliance, the pathophysiologic outcome remained the same.

An additional potential explanation of the significance of an increased PAMP may be its role as a marker for the effect of hypertension on the pulmonary vascular bed. It is well known, for example, that there is marked variability in pulmonary vascular reactivity to various stimuli, including hypoxia and chronic increases in pulmonary venous pressure.44-46 The elevation of PAMP may reflect changes in the pulmonary circulation related to hormonal or other systemic abnormalities associated with essential hypertension that contribute to an increased risk of cardiac death. The finding that PAMP correlates positively with aortic mean pressure and LV mass suggests that a stimulus raising vascular tone affects both the pulmonary circulation and the systemic circulation. Overresponsiveness of pressures in both vascular beds has been shown to occur with both adrenergic stimuli and exercise in hypertensive patients,54,55 and there is evidence that in systemic hypertension with LVH, there is an elevation of MPAP whose degree is proportional to the severity of hypertension.56

In summary, our data indicate a strong association between PAMP and mortality in patients followed up after cardiac catheterization. This relationship is independent of LV systolic function, the status of the
coronary arteries, and the severity of LVH. It also points to the powerful interaction between increased pulmonary pressure and LVH. These data strongly suggest that measures of pulmonary artery pressure are reflecting LV diastolic dysfunction and provide for the first time prospective data on the mortality risk associated with this form of myocardial abnormality.

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