Pulmonary Hypertension and Risk of Death in Cardiomyopathy
Patients With Myocarditis Are at Higher Risk

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Background—Pulmonary hypertension is a clinically useful predictor of death in patients with heart failure. Whether pulmonary hypertension has the same prognostic value among specific underlying causes of cardiomyopathy is unknown. Using a diverse cohort of cardiomyopathy patients, we tested the hypotheses that (1) elevated mean pulmonary arterial pressure is the most important hemodynamic predictor of death and (2) the prognostic value of mean pulmonary pressure varies among different cardiomyopathies.

Methods and Results—Patients (n=1134) with new cardiomyopathy were prospectively assigned a specific diagnosis on the basis of clinical evaluation and endomyocardial biopsy. All patients underwent right heart catheterization at baseline and were followed for an average of 4.4 years. In multivariate Cox models that allowed for nonlinear relations between hemodynamics and death, mean systemic pressure (mSP) and mean pulmonary arterial pressure (mPA) emerged as the most important hemodynamic predictors of death. Moreover, there was a statistically significant positive interaction between mPA and the diagnosis of myocarditis. For each 5-mm Hg increase in baseline mSP, mortality rates decreased with relative hazard (RH) of 0.89 (0.86 to 0.92). For a 5-mm Hg increase in baseline mPA, mortality rates increased in patients who did not carry the diagnosis of myocarditis with RH 1.23 (1.17 to 1.29); among patients with myocarditis, mortality rates increased substantially with RH of 1.85 (1.50 to 2.29; P<0.001 for interaction).

Conclusions—Baseline mPA is particularly important for stratifying risk in myocarditis. These findings suggest that secondary pulmonary hypertension may have different biological features in myocarditis and that patients with pulmonary hypertension and myocarditis should be targeted for aggressive medical therapy. (Circulation. 2002;105:1663-1668.)

Key Words: heart failure ■ hypertension, pulmonary ■ myocarditis ■ epidemiology

Elevated pulmonary arterial pressure has been established as a predictor of death in patients with heart failure with both ischemic and nonischemic cardiomyopathy.1 However, nonischemic cardiomyopathy comprises a heterogeneous group of patients with multiple causes of ventricular dysfunction. We have shown that the long-term survival of patients with nonischemic cardiomyopathy varies greatly, depending on the underlying cause.2 Whether pulmonary hypertension has the same prognostic value among the different types of nonischemic cardiomyopathy is unknown.

We examined the relation between baseline hemodynamic parameters and death in a diverse cohort of 1134 patients with newly diagnosed cardiomyopathy followed by the Johns Hopkins Cardiomyopathy Service to identify the hemodynamic abnormalities that were the best predictors of death. We tested the hypotheses that (1) mean pulmonary arterial pressure (mPA) is the most important baseline hemodynamic predictor of death and (2) the prognostic value of mPA varies among specific causes of cardiomyopathy.

Methods

Patients

Patients were selected and evaluated as previously described.2 Between December 1982 and December 1997, 1236 patients were referred to the Johns Hopkins Cardiomyopathy Service for evaluation of heart failure caused by unexplained cardiomyopathy. All patients underwent an exhaustive evaluation to define the underlying cause of cardiomyopathy including endomyocardial biopsy and, if the history suggested ischemic heart disease or if at least two standard risk factors for atherosclerosis were present, coronary angiography. All patients were prospectively assigned a specific cause of cardiomyopathy on the basis of recommendations of the World Health Organization–International Society and Federation of Cardiology Task Force for the classification of cardiomyopathy.3 For the purpose of analysis, underlying causes were categorized as follows: idiopathic, peripartum, ischemic, infiltrative (amyloidosis,
hemochromatosis, or sarcoidosis), myocarditis, substance abuse (cocaine or alcohol abuse), connective disease, HIV, hypertension, doxorubicin, or other causes. The Dallas histological criteria were used to establish the diagnosis of myocarditis. Patients with fulminating myocarditis were excluded because they have been shown to be a distinct group with excellent long-term prognosis. The study cohort was limited to the 1134 patients for whom complete hemodynamic data were available. Age, race (black, white, other), height, and weight were recorded at the time of evaluation. This study was approved by the Joint Committee on Clinical Investigation at Johns Hopkins Hospital. All patients provided informed consent to use their data in the investigation.

**Right Heart Catheterization**

Patients underwent right heart catheterization at the time of endomyocardial biopsy with a balloon-tipped, flow-directed catheter placed into the right internal jugular vein. Hemodynamics were measured at the time of presentation before optimizing medical therapy and without holding current medications. Cardiac output (CO) was determined as the mean of 3 to 5 separate measurements with the thermodilution method. Systemic arterial pressure was measured noninvasively. Mean right atrial pressure, pulmonary artery systolic (PAS) and pulmonary artery diastolic pressures, mPA, mean pulmonary capillary wedge pressure (PCW), systolic blood pressure, diastolic blood pressure, and mean systemic pressure (mSP) were recorded. CO, cardiac index (CI), and systemic vascular resistance indexed to body surface area (SVRI) were calculated by means of standard formulas. Pulmonary vascular resistance (PVR) was calculated in Wood units as the difference between mPA and PCW divided by CO.

**Follow-Up**

Patients entered the study cohort at the time of right heart catheterization and were followed until death, cardiac transplantation, or the end of the study period was reached. Vital status was obtained from clinical records and through a search of the Nation Death Index. This approach for obtaining vital status is well validated, with a negative predictive value >99%.

**Statistical Analysis**

For the purpose of analysis, variables were chosen that measure different aspects of hemodynamic derangement in cardiomyopathy. Left ventricular preload was assessed as PCW; afterload was assessed as SVRI; perfusion was assessed as CI and mSP; and secondary pulmonary hypertension was assessed as mPA and PVR. Comparison of baseline hemodynamics among types of cardiomyopathy was performed with a 1-way ANOVA. Post hoc comparisons were done for the best predictors of death. The parameters and covariates that were statistically significant in univariate analysis were entered together into a stepwise regression model. Forward and backward selection was performed by means of the likelihood ratio test, with a value of $P<0.05$ as the criterion to remain in the model. Interaction terms between mPA and underlying cause were tested with the use of nested models and the likelihood ratio test.

Kaplan-Meier survival curves were compared by means of the log-rank test. Receiver operator characteristic (ROC) curves were constructed by means of logistic regression. A 2-sided probability value of $<0.05$ was considered to indicate statistical significance in all models. All analyses were performed with the use of STATA statistical software.

**Results**

**Characteristics of the Study Population**

Among the 1134 patients studied, 371 (33%) died and 50 (4.4%) underwent heart transplantation during a mean follow-up of 4.4 years. A total of 658 (58%) underwent coronary angiography. The cohort consisted of 455 (40%) women and 679 (60%) men; 718 (63%) were white, 396 (35%) were black, and 20 (2%) were of other race. The mean±SD age was 48±15 years, and the mean BMI was 27±7 kg/m². Table 1 summarizes the baseline hemodynamics of the cohort. Patients had the characteristic hemodynamic abnormalities of heart failure, including elevated mPA and PCW, elevated PVR, low CI, and elevated SVRI. Compared with idiopathic cardiomyopathy, patients with another underlying cause had slightly different baseline hemodynamics. Patients with infiltrative cardiomyopathy had higher PVR; patients with HIV cardiomyopathy had higher CI and lower PCW; and patients with hypertensive cardiomyopathy had higher mSP (all $P<0.05$).

**Relation Between Hemodynamics and Mortality Rate**

Figure 1 displays the mortality rate within strata of each hemodynamic variable. We used these results to determine whether to model each parameter by using linear or nonlinear methods in subsequent analyses. As shown in Figure 1, mPA and PCW had positive linear relations with death. In contrast, PVR had a negative linear relation with death. Nonlinear relations were apparent for the remaining parameters. The mortality rate associated with PVR remained constant until a threshold of 3.0 Wood Units was reached. Above this threshold, the mortality rate nearly doubled. CI had a U-shaped relation with death, with relatively high rates at extremely low and high values and the lowest mortality rate at 3.0 to 3.49 L/min per square meter. There was no obvious relation between SVRI and mortality rate.

**Cox Proportional Hazard Models**

Table 2 summarizes the results of several Cox models in which each of the hemodynamic parameters was entered separately as the sole hemodynamic explanatory variable. With the exception of SVRI, each parameter was a statistically significant predictor of death, even after adjustment for underlying cause, age, sex, race, BMI, and 5-year interval of calendar time. The nonlinear relations between PVR, CI, and death that were identified in exploratory analysis were also apparent in the Cox models. The risk of death associated with increased PVR was not significant below 3.0 Wood units but increased by ≈86% above this threshold. Similarly, the risk
of death associated with CI was not significantly changed for CI between 2.0 and 4.0 L/min per square meter but increased by \( \approx 94\% \) for CI < 2.0 or > 4.0 L/min per square meter.

We used stepwise regression to compare the predictive value of the hemodynamic parameters that were identified as individually significant in Table 2: mPA, PVR, PCW, CI, mSP, and covariates were entered into Cox regressions, with a value of \( P < 0.05 \) by the likelihood ratio test as the criterion to remain in the model. Using either forward or backward selection, mPA and mSP were the only hemodynamic variables that remained in the model and emerged as the most important predictors. As shown in Table 3, the hazard of death decreased by 11% for each 5-mm Hg increase in mSP and increased by 25% for each 5-mm Hg increase in mPA.

### Association Between mPA and Death by Cause of Cardiomyopathy

To determine whether increased mPA confers different degrees of risk among different types of cardiomyopathy, we constructed nested models by adding interaction terms between mPA and underlying cause to our Cox model. Taken as a whole, these interaction terms were statistically significant by the likelihood ratio test, with a value of \( P = 0.049 \). We used forward and backward stepwise regression to select the interaction terms that were most important and found a statistically significant interaction between mPA and the diagnosis of myocarditis in predicting death (Table 3). Among patients without myocarditis, an increase in mPA of 5 mm Hg increased the hazard of death by 23%, whereas the same increase in patients with myocarditis increased the hazard of death by 85%.

Figure 2A displays the interaction between mPA and myocarditis by means of Kaplan-Meier survival curves. The entire cohort was split into tertiles of mPA and further stratified by the presence or absence of myocarditis. Patients with low mPA and myocarditis had the lowest mortality rates, with transplant-free survival of 100%, 100%, and 98% at 6, 12, and 18 months, respectively. In contrast, patients with the combination of high mPA and myocarditis had the highest mortality rates, with transplant-free survival of 79%, 63%, and 53% at equivalent follow-up times. mPA was not as effective at stratifying risk among other cardiomyopathies, as indicated by the poorer separation of the survival functions in patients without myocarditis. Figure 2B compares the prognostic ability of mPA to predict death 1 year after presentation by means of ROC curves. The area under the ROC curve is substantially higher among patients with myocarditis, indicating better separation of high- and low-risk patients.

### Discussion

The principal findings of this investigation are (1) that mPA and mSP are the most important baseline hemodynamic predictors of death in a large, diverse cohort of cardiomyopathy patients and (2) that mPA is a more powerful predictor of death among patients with myocarditis than among patients with other underlying causes of cardiomyopathy. For each 5-mm Hg increase in baseline mSP, mortality rates decreased with relative hazard (RH) of 0.89 (0.86 to 0.92). For an equivalent increase in baseline mPA, mortality rates increased with RH 1.23 (1.17 to 1.29) in patients who did not carry the diagnosis of myocarditis; among patients with myocarditis, mortality rates increased substantially, with RH of 1.85 (1.50 to 2.29; \( P < 0.001 \) for interaction). To our knowledge, this investigation is the largest systematic analysis of hemodynamic data in patients with cardiomyopathy and congestive heart failure.

Other investigations have examined the prognostic value of hemodynamic data within hospital-based cohorts of patients with cardiomyopathy and have noted higher baseline PCW than in our cohort.\(^9,10\) This difference may be due to the broader range of patients in our cohort, which included inpatients admitted for treatment of severe heart failure as well as minimally symptomatic outpatients referred for evaluation of new left ventricular dysfunction.\(^3\) In addition, prior analyses have implicated nearly every hemodynamic parameter as the most important predictor of death, including mean right atrial pressure,\(^10\) PAS,\(^1\) pulmonary artery diastolic pressure,\(^11\) PCW,\(^12\) and systolic blood pressure.\(^13\) This seems-
ingly contradictory literature can be explained by the smaller sample size of these studies and the highly integrated nature of the cardiovascular system. Hemodynamic parameters are highly interdependent, as demonstrated by the strong correlation between PAS and PCW in patients with heart failure observed by Drazner et al. As a result, the prognostic information buried within hemodynamic data are highly redundant, and it is no surprise that among a series of smaller studies that used different statistical approaches, each parameter has at one time been implicated, whereas the others were excluded.

In addition to the large size of our cohort, our study design has several strengths that limit the impact of redundant information and enhance the validity of our findings. Rather than analyzing all 11 of the measured hemodynamic parameters, we chose 6 parameters a priori that represent the characteristic hemodynamic derangements of cardiomyopathy. Unlike prior investigations, we did not assume that these 6 parameters had linear relations with death, and, in fact, we found nonlinear relations for PVR and CI. The sharp increase in the hazard of death above a PVR of 3.0 Wood units (200 dyne · s⁻¹ · cm⁻⁵) suggests that the right ventricle can

![Figure 1. Mortality rates within strata of different hemodynamic variables for all causes of cardiomyopathy combined. Data are displayed as deaths per person-year of follow-up time within each stratum. Error bars indicate 95% confidence intervals. Number of patients in each stratum is indicated in italics. Probability values for linear and nonlinear relations were calculated from nested log-linear models.](image-url)
compensate for elevated PVR until a threshold of 3.0 Wood units is reached. Above this threshold, right ventricular failure may occur. This observation is consistent with noninvasive studies that demonstrate associations between right ventricular ejection fraction and survival in patients with advanced heart failure.15

The increased mortality rates associated with extremely high CI is counterintuitive and prompted further analysis. Among patients with CI >4.0 L/min per square meter, there was a high proportion of HIV cardiomyopathy compared with patients with CI <4.0 (26.7% versus 3.3%). This is consistent with Table 1, which shows that patients with HIV cardiomyopathy have elevated CI, perhaps the result of anemia or occult infection. Thus, it is unlikely that high CI per se caused increased mortality rates in our cohort. Rather, elevated CI was a marker for HIV cardiomyopathy, which has a particularly poor prognosis.2

Because patients in our cohort were classified through the use of endomyocardial biopsy, we were able to explore the relative importance of mPA among specific types of cardiomyopathy. The finding that pulmonary hypertension is a more potent predictor of death in patients with myocarditis has not been reported previously and suggests that right heart catheterization is especially useful when myocarditis is suspected. We offer two hypotheses to explain the increased sensitivity

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**TABLE 2. Association Between Hemodynamic Variables and Survival**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Unadjusted Analysis</th>
<th>Multivariate Analysis*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hazard Ratio for Death (95% CI)</td>
<td>P</td>
</tr>
<tr>
<td>mA (5 mm Hg)</td>
<td>1.19 (1.14–1.24)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PCW (5 mm Hg)</td>
<td>1.19 (1.13–1.25)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>mSP (5 mm Hg)</td>
<td>0.94 (0.91–0.97)</td>
<td>0.001</td>
</tr>
<tr>
<td>PVR, Wood units</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;2.5</td>
<td>1.00 (reference)</td>
<td>...</td>
</tr>
<tr>
<td>2.5–3.0</td>
<td>1.41 (1.07–2.05)</td>
<td>0.08</td>
</tr>
<tr>
<td>3.0–3.5</td>
<td>2.32 (1.65–3.28)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>3.5–4.0</td>
<td>2.10 (1.35–3.26)</td>
<td>0.001</td>
</tr>
<tr>
<td>&gt;4.0</td>
<td>2.55 (1.93–3.38)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CI, L/min per square meter</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;2.0</td>
<td>2.02 (1.36–3.00)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2.0–3.0</td>
<td>1.33 (0.90–1.96)</td>
<td>0.15</td>
</tr>
<tr>
<td>3.0–4.0</td>
<td>1.00 (reference)</td>
<td>...</td>
</tr>
<tr>
<td>&gt;4.0</td>
<td>2.36 (1.25–4.46)</td>
<td>0.008</td>
</tr>
<tr>
<td>SVRI (100 dyne · s−1 · cm−5 per square meter)</td>
<td>1.00 (0.99–1.01)</td>
<td>0.67</td>
</tr>
</tbody>
</table>

*Adjusted for age, sex, race, body mass index, cause, and 5-year interval of calendar time.

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**TABLE 3. Association Between Hemodynamics and Survival After Stepwise Regression***

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard Ratio for Death (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>mA (5 mm Hg)</td>
<td>0.89 (0.86–0.92)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>mPA (5 mm Hg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>1.25 (1.19–1.31)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Nonmyocarditis</td>
<td>1.23 (1.17–1.29)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Myocarditis</td>
<td>1.85 (1.50–2.29)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Statistically significant variables after stepwise regression also include age, sex, race, body mass index, and cause.

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Figure 2. A, Kaplan-Meier survival curves comparing highest and lowest tertiles of mPA stratified by presence or absence of myocarditis. Patients with myocarditis and high mPA have particularly poor prognosis. *P<0.001 for trend by log-rank test. B, ROC for mPA as a predictor of death 1 year after presentation. Among patients with myocarditis, mPA is particularly good at predicting death at 1 year, whereas its prognostic value is much less among other cardiomyopathies. *P<0.0001 vs other causes.
to pulmonary hypertension in this subgroup. Patients with myocarditis become ill over the course of weeks or months, as opposed to the more chronic course in patients with idiopathic left ventricular dysfunction.5,16 Pulmonary hypertension may therefore develop more acutely, overwhelming compensatory mechanisms such as right ventricular hypertrophy. As a result, elevated pulmonary pressures may be less well tolerated and patients may die sooner because of early right heart failure. Alternatively, there may be a common pathobiological process responsible both for myocardial inflammation and for pulmonary vascular damage. Further investigation is required to address this question, which may involve molecules that have been shown to trigger pulmonary hypertension in model systems, such as angiogenic growth factors17 or matrix metalloproteinases.18 We were unable to detect different sensitivities to pulmonary hypertension among subtypes of cardiomyopathy other than myocarditis; however, our ability to do so was limited by the smaller sizes of these subgroups.

Our study has several limitations. Like all hospital-based cohorts, this is a selected population of patients that depends on referral patterns. Even so, the patients represent a broad spectrum of cardiomyopathy, and there is likely to be little misclassification regarding underlying cause, because all patients underwent detailed evaluation including endomyocardial biopsy. As with many studies of chronic disease, the time of disease onset is not precisely known, and there may be variation in the length of the preclinical phase that influences the relations between hemodynamics and death. Our data did not allow us to assess the impact of medical therapy on the relation between hemodynamics and outcome. Because all patients were cared for by a single team of physicians, it is unlikely that large differences in therapy explain the associations that we observed. In addition, we adjusted for secular trends in heart failure therapy by including calendar time in our analyses. We did not have data on the number of covariates that are known predictors of death in patients with cardiomyopathy, such as left ventricular ejection fraction, peak exercise oxygen uptake, and levels of circulating neurohormones. However, whether or not the observed associations between hemodynamics and risk of death are causal or are confounded by other known factors does not detract from their ability to predict outcome.

In conclusion, mean pulmonary arterial pressure and mean systemic pressure are the most important baseline hemodynamic prognosticators in patients with cardiomyopathy caused by both ischemic and a wide range of nonischemic causes. Furthermore, patients with myocarditis and pulmonary hypertension are a particularly high-risk group. These findings should aid the interpretation of hemodynamic data and suggest that patients with pulmonary hypertension and myocarditis should be targeted for aggressive medical therapy.

Acknowledgments
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References
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