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Original Research

PULMONARY HYPERTENSION

Survival in Sarcoidosis-Associated Pulmonary Hypertension

The Importance of Hemodynamic Evaluation

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Objective: **Pulmonary hypertension (PH) has been associated with increased mortality in patients with advanced pulmonary sarcoidosis. Sarcoidosis-associated PH may be the result of left ventricular dysfunction (LVD) or isolated pulmonary vasculature abnormality. Our objective was to determine if the cause of PH affects survival in patients with sarcoidosis with persistent dyspnea.**

Methods: **Patients with sarcoidosis with persistent dyspnea despite immunosuppressive therapy underwent right-sided heart catheterization. Patients with a pulmonary artery occluding pressure (PAO) $\geq$ 15 mm Hg were defined as having LVD. Patients were classified based on hemodynamics as no PH (pulmonary artery mean pressure [PAmean] $<$ 25 mm Hg), PH without LVD (PAmean $\geq$ 25 mm Hg and PAO $<$ 15 mm Hg), and PH with LVD (PH/LVD) (PAmean $\geq$ 25 mm Hg and PAO $\geq$ 15 mm Hg).**

Results: **One hundred thirty patients were studied at one institution: 50 (38.5%) patients had PH without LVD, whereas 20 (15.4%) had PH/LVD. All patients had their diagnostic procedure at least 18 months prior to analysis. The hazard ratio (HR) for death in PH without LVD vs no PH was 10.39 (95% CI, 2.99-13.78; $P < .0001$). The HR for dying for PH without LVD vs PH/LVD was 3.14 (95% CI, 1.01-5.62; $P < .05$). The presence of stage 4 chest roentgenograms and the need for supplemental oxygen were different between the groups. In a Cox proportional hazards model, independent predictors for survival were stage 4 chest roentgenogram ($P < .005$) and hemodynamic group ($P < .02$).**

Conclusion: **PH without LVD was associated with increased mortality. Proper characterization of patients required hemodynamic evaluation, as 29% of sarcoidosis-associated PH was due to LVD.**

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Abbreviations: DLCO = diffusion capacity of the lung for carbon monoxide; HR = hazard ratio; LVD = left ventricular dysfunction; LVEF = left ventricular ejection fraction; PAmean = pulmonary artery mean pressure; PAO = pulmonary artery occluding pressure; PAsys = pulmonary artery systolic pressure; PH = pulmonary hypertension; PVR = pulmonary vascular resistance

Several investigators have identified pulmonary hypertension (PH) in patients with sarcoidosis.[1-5] Based on World Health Organization classification, PH can be divided into five groups, including group 1 pulmonary arterial hypertension and group 2 PH due to left ventricular disease. Group 1 encompasses conditions such as idiopathic pulmonary arterial hypertension and scleroderma-associated pulmonary

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arterial hypertension. Because PH due to sarcoidosis can be caused by several factors, including vascular changes, fibrotic destruction of the blood vessels, and direct compression of the vessels by adenopathy,[6] sarcoidosis-associated PH is included in group 5.

Studies of patients with sarcoidosis awaiting lung transplant confirm that the presence of PH is associated with a worse prognosis[7,8] with the overall mortality of this group 27.4%.[9] However, these studies identified PH on the pulmonary artery mean pressure (PAmean) only without assessing for left ventricular dysfunction (LVD). The granulomas of sarcoidosis can also cause left ventricular disease with or without systolic dysfunction.[10-13] This can lead to congestive heart failure with clinical manifestations that mimic many other conditions.

Left ventricular disease can be caused by myocardial dysfunction leading to a reduced left ventricular ejection fraction (LVEF). However, isolated left ventricular diastolic dysfunction can occur in the setting of normal left ventricular function, as assessed by a normal LVEF.[14] In patients with left ventricular failure due to nonrheumatic disease, some authors have found a reduced LVEF is associated with poorer outcomes,[15] while others found that survival was essentially the same whether LVEF is reduced.[16]

Because we and others have noted that PH occurs in more than one-half of persistently dyspneic patients with sarcoidosis,[1,2,4] our institution routinely performed right-sided heart catheterizations on these patients. Two groups of patients with sarcoidosis with PH were identified: those with PH alone and those with PH and LVD. This report evaluates factors that influence survival in patients with sarcoidosis with persistent dyspnea.

Materials and Methods

Patients at the University of Cincinnati Sarcoidosis and Interstitial Lung Disease Clinic were eligible for this study. All patients in this clinic are entered into a database and information regarding right-sided heart catheterization has been collected prospectively for the past 7 years. All patients eligible for this study were diagnosed with sarcoidosis based on standard criteria,[17] and they underwent right-sided heart catheterization for persistent moderate-to-severe dyspnea and at least 6 months of systemic anti-inflammatory therapy prior to analysis. This study was approved by the University of Cincinnati Institutional Review Board.

Information recorded from the cardiac catheterization included the pulmonary artery systolic pressure (PAsys), PAmean, pulmonary artery occluding pressure (PAO), and cardiac output. If the PAO could not be accurately measured, the left ventricular end-diastolic pressure was recorded (two cases). Cardiac output was determined by the Fick method. The pulmonary vascular resistance (PVR) was calculated using the formula (PAmean − PAO)/cardiac output and reported in Wood units.

Using the definition of PH as a PAmean $\geq$ 25 mm Hg,[18] patients were classified with PH with or without LVD. Based on catheterization findings, patients were divided into three groups: PAmean $<$ 25 mm Hg (no PH); PAmean $\geq$ 25 mm Hg and PAO $<$ 15 mm Hg (PH without LVD); and PAmean $\geq$ 25 mm Hg and PAO $\geq$ 15 mm Hg (PH/LVD) (World Health Organization group 2).

In addition to right-sided heart catheterization data, we also collected FVC, echocardiography measurements, and chest roentgenogram staging using the Scadding classification system.[19] Spirometry was done within 6 months of catheterization. Normal values for spirometry were calculated using a standard algorithm that is race specific.[20] Diffusion capacity of the lung for carbon monoxide (Dlco) was performed using the single breath technique, and normal values were calculated using a standard algorithm.[21] Survival was calculated based on last visit or date of death. In some cases, date of death was determined using the Social Security Death Index.

Statistics

Comparisons between groups were made using nonparametric testing, including Mann Whitney *U* test. Survival was compared between groups using Kaplan-Meier survival curve. Comparison between survival rates were performed by a log rank test with a calculated χ^2 and *P* value. In some cases, a hazard ratio (HR) and 95% CI were reported comparing two groups. Patients still alive at the time of analysis were censored as alive for further analysis, regardless of the length of time of follow-up. HRs for increased mortality were calculated for individual features that may be associated with increased mortality. A Cox proportional hazards regression analysis with stepwise selection was performed on those factors with a *P* value $<$ .10. For factors with a high degree of collinearity, only the most robust factor was considered. This included the absolute FVC over the FVC percent predicted and the FEV_1. Variables were included in the model if their *P* value was $<$ .10. A *P* value of $<$ .05 was considered significant. Statistics were calculated using Medcalc statistical software (Frank Schoonjans; Mariakerke, Belgium).

Results

One hundred thirty patients with sarcoidosis underwent right-sided heart catheterization, revealing 50 (38.5%) patients with PH without LVD and 20 (15.4%) patients with PH/LVD. Figure 1 summarizes the outcome of the catheterizations, including the survival of patients. At the end of the study, all patients were either accounted for by clinic visits or had died.

Table 1 summarizes the characteristics of the three groups studied. No race, age, or gender differences were identified among the three groups. In contrast, a significant difference was noted in the proportion of patients with different chest roentgenogram stage, with one-half of patients with PH without LVD having stage 4 disease ($\chi^2 = 17.195$; $P < .05$). Table 1 also reports the percent predicted for the FVC and Dlco for the three groups. Although patients with no PH experienced significantly better FVC and Dlco percent predicted than either PH group, no significant difference was measured between the two PH groups for either pulmonary function test. Also shown is the number of patients routinely using supplemental oxygen at the time of the catheterization. There was a significant difference between the groups, with the

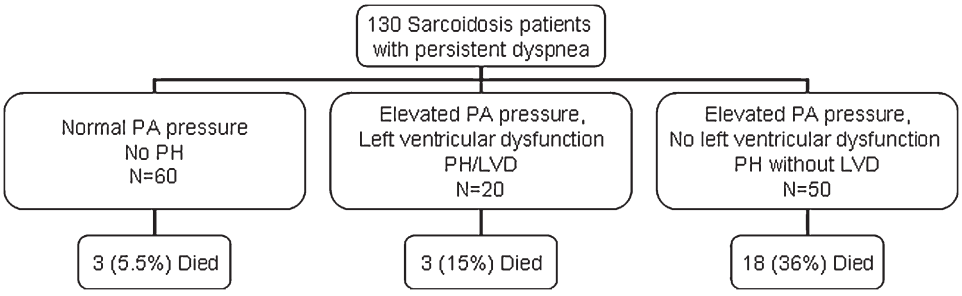

FIGURE 1. Flow diagram showing the outcome of patients enrolled in the study. LVD = left ventricular dysfunction; PA = pulmonary artery; PH = pulmonary hypertension.

no-PH group much less likely to be using supplemental oxygen than the other two groups ($\chi^2 = 27.44$; $P < .0001$). Patients in the PH/LVD group were the most likely to use supplemental oxygen (14 of 20 patients).

Table 2 summarizes the time from the right-sided heart catheterization until the time of analysis. On average, patients with no PH were studied more recently than those with PH without LVD, but there was considerable overlap. Patients with PH/LVD were not different from either of the two groups.

Eighty patients had an echocardiogram available for review. Of these, only 56 (70%) had sufficient tricuspid regurgitant jet identified so that PAsys could be estimated. Of these 56 cases, there was a significant correlation between the PAsys as estimated by echocardiogram and the measured PAsys ($r = 0.62$; $P < .0001$). There was a higher estimated PAsys for 13 patients who died (median [range], 50 [27-70] mm Hg) than for those who survived (43 [9-74] mm Hg, $P < .05$), but there was considerable overlap. For the 14 patients with an estimated PAsys ≥ 50 mm Hg, there was a significantly higher mortality (HR = 4.4; 95% CI, 1.92-22.95; $P < .005$). Two of these fourteen had PH/LVD. All patients had their LVEF estimated by echocardiography. This included all 20 patients who were in the PH/LVD group.

By definition, both groups with PH had a significantly higher PAmean than the no-PH group ($P < .0001$), and Figure 2 demonstrates histograms of the PAmean for the two PH groups. There was no significant difference between the PH without LVD (median [range], 33 [25-75] mm Hg) group and the PH/LVD (37 [26-53] mm Hg) group.

Figure 3 demonstrates the PVR for the three groups. Patients with PH without LVD displayed a significantly higher PVR (median [range], 4.3 [0.9-21.2] Wood units) than either the patients with no PH (1.6 [0.3-4.4] Wood units, $P < .0001$) or those with PH/LVD (1.8 [0.6-2.8] Wood units, $P < .0001$).

Table 1—*Demographic Features of Patients*

	No PH		PH Without LVD		PH/LVD	
Feature	No.	%	No.	%	No.	%
Total	60	…	50		20	
Women	45	75.0	33	66.0	13	65.0
White	37	61.7	20	40.0	9	45.0
Age,[a] y	52 (27-81)	…	52 (24-76)	…	57 (43-76)	…
Chest roentgenogram stage (Scadding[19])[b]						
0	3	5.0	1	2.0	0	0.0
1	16	26.7	7	14.0	10	50.0
2	11	18.3	10	20.0	3	15.0
3	14	23.3	7	14.0	4	20.0
4	16	26.7	25	50.0	3	15.0
FVC,[a] % predicted	80 (33-126)	…	59 (30-85)[c]	…	66 (37-91)[d]	…
DLCO,[a] % predicted	80.5 (48-117)	…	45 (20-82)[c]	…	52 (35-94)[e]	…
Require supplemental oxygen[f]	7	12	22	44	14	70

DLCO = diffusion capacity of the lung for carbon monoxide; LVD = left ventricular dysfunction; PH = pulmonary hypertension.

[a]Median (range).

[b]Significant difference in radiologic pattern between groups: $\chi^2 = 17.195$; $P < .05$.

[c]Differs from no PH, $P < .0001$.

[d]Differs from no PH, $P < .02$.

[e]Differs from no PH, $P < .005$.

[f]Difference between groups: $\chi^2 = 27.44$, $P < .0001$.

Table 2—*Time From Catheterization Until Analysis for This Study, y*

Group	Median	Minimum	Maximum	25th Percentile	75th Percentile
No PH	3.05	1.50	6.99	2.25	4.95
PH without LVD	4.45[a]	1.50	9.00	2.90	5.40
PH/LVD	4.30	2.00	7.10	2.95	4.90

See Table 1 legend for expansion of abbreviations.
[a]Differs from no PH, $P < .05$.

There was no significant difference in the PVR between those with no PH and those with PH/LVD.

During the follow-up period, 31 (23.8%) patients died: three (5%) in the no-PH group, 24 (48%) in the PA-without-LVD group, and four (20%) in the PH/LVD group. We compared the survival of patients in the three groups. Figure 4A demonstrates a significant difference in the survival probability for those patients with PH without LVD vs those with no PH or PH/LVD ($\chi^2 = 24.16$; $P < .0001$). The median survival was 4.2 years for patients with PH without LVD. Too few deaths occurred in the other two groups to calculate median survival. The HR for death in PH without LVD vs no PH was 10.39 (95% CI, 2.99-13.78; $P < .0001$). The HR for death in PH without LVD vs PH/LVD was 3.14 (95% CI, 1.01-5.62; $P < .05$). When we examined those with more severe PAH (PAmean > 35 mm Hg), the HR was not significantly different from the less severe PH-without-LVD group (HR = 1.05; 95% CI, 0.47-2.36; $P > .05$). Thirteen of 27 patients with an initial PAmean of 25-35 mm Hg died during the observation period.

Figure 4B demonstrates the 95% CIs for the survival curves for all three groups. It also shows the number of patients who were at risk at the various time points shown. These are patients who are still alive at the denoted years after the catheterization. All patients had undergone catheterization at least 18 months before (Table 2). There was no significant difference between the survival 1 year after catheterization for the no-PH group (one of 60 had died) vs the PH-without-LVD group (six of 50 had died; $\chi^2 = 3.31$; $P > .05$). Of those patients evaluated 2 years after catheterization, three of 53 (6%) in the no-PH group had died, whereas 12 of 35 (34%) in the PH-without-LVD group had died ($\chi^2 = 10.28$; $P < .002$). Of the PH/LVD group evaluated after catheterization, three of 20 (15%) had died, which was not significantly different from either of the two groups. For those patients who could be evaluated 3 years after catheterization, only two of

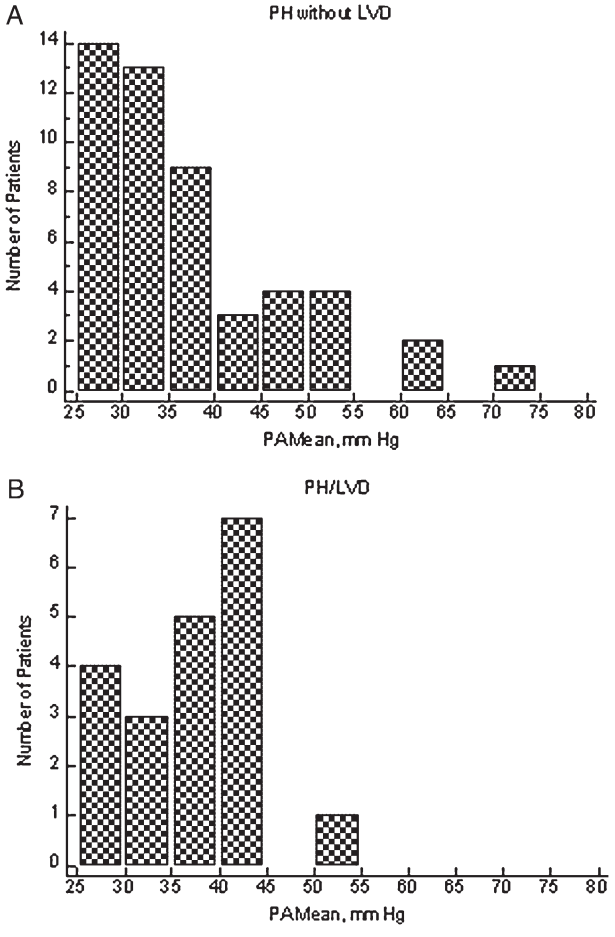

FIGURE 2. The histograms of the PAmean for: A, the PH-without-LVD group; B, the PH/LVD group. There was no significant difference between the two groups. See Figure 1 legend for expansion of abbreviations.

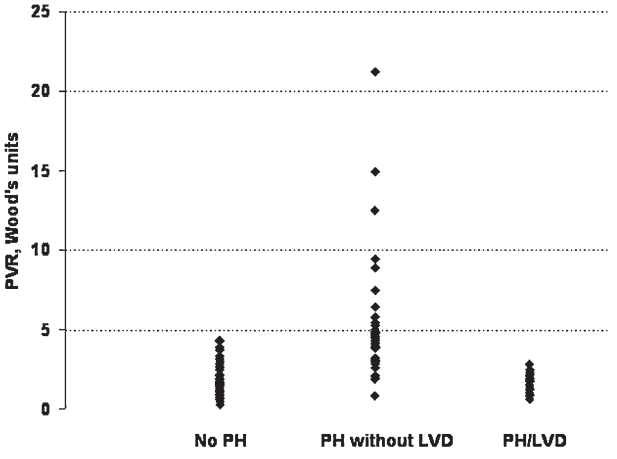

FIGURE 3. The calculated PVR values of the three groups. The PH-without-LVD group had significantly higher PVR values than either the no-PH or PH/LVD groups ($P < .0001$ for both comparisons). There was no difference in the PVR values between the no-PH and PH/LVD groups. PVR = pulmonary vascular resistance. See Figure 1 legend for expansion of other abbreviations.

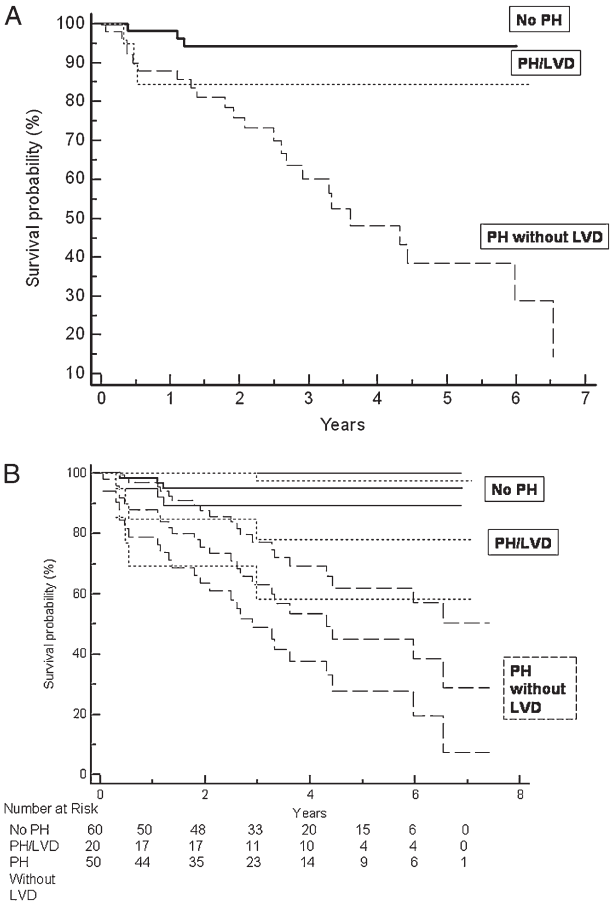

FIGURE 4. A, The survival curves of three groups based on right-sided heart catheterization: no PH, PH/LVD, and PH without LVD. There was a significant difference in survival based on Kaplan Meier analysis ($\chi^2 = 24.16$; $P < .0001$). B, The same figure with the 95% CIs for the three survival curves, as well as the number of patients at risk at each of the time points. See Figure 1 legend for expansion of abbreviations.

35 (6%) patients with no PH had died. For the PH-without-LVD group, 17 of 40 (42%) had died, which was significantly higher than the no-PH group ($\chi^2 = 11.48$; $P < .001$). Once again, the PH/LVD group fell between these two groups, with four of 15 (27%) patients having died. There was no significant difference between the other two groups.

Of the 20 patients with PH/LVD, seven patients displayed echocardiographic evidence of a reduced LVEF with a median of 25%, range 20% to 45%. There was no difference between the clinical features of these seven patients with systolic dysfunction compared with those patients with isolated diastolic dysfunction. During the follow-up period, two of seven patients (28.6%) with reduced LVEF died, whereas only one of 13 (7.7%) of PH/LVD patients with normal LVEF died. There was no significant difference in survival between these two groups, but the numbers were relatively small.

Patients were also evaluated based on PVR, with 49 patients demonstrating a PVR ≥ 3 Wood units. This included seven patients from the no-PH group. Six of these seven patients had a PAmean between 20 and 25 mm Hg. Eight patients who were classified with PH without LVD displayed a PVR of < 3 Wood units, and these patients had high cardiac outputs (median = 9.0; range, 5.3-16.4 L/min). None of the patients who were classified as PH/LVD had a PVR of ≥ 3 Wood units. Figure 5 demonstrates the survival curves of the 49 patients with increased PVR compared with the 81 patients with normal PVR. There was a significant difference in survival between these two groups ($\chi^2 = 10.1921$; $P < .002$). For those with a PVR ≥ 3 Wood units, the HR for mortality was 3.60, with a 95% CI of 1.70-9.14.

Survival was also analyzed for patients based on age, self-declared race and sex, FVC ≤ 1.5 L, need for supplemental oxygen, and chest roentgenogram stage 4. Age was analyzed as a continuous variable and was not a predictor of mortality. Approximately one-third of patients had stage 4 chest roentgenograms, and these patients experienced significantly higher mortality during the study period (HR = 2.68; 95% CI, 1.45-7.03; $P < .005$). In contrast, a reduced FVC, sex, or race was not associated with increased risk for death. One-third of patients required supplemental oxygen, and this was associated with a borderline worse survival (HR = 1.83; 95% CI, 0.91-4.17; $P = .09$).

A Cox proportional hazards regression analysis with stepwise selection was performed on factors that on univariate analysis were associated with a P value $< .10$. These were presence or absence of chest roentgenogram stage 4, need for supplemental oxygen, and hemodynamics. To calculate HRs, patients were classified based on whether they did or did not have PH. There were two independent predictors of

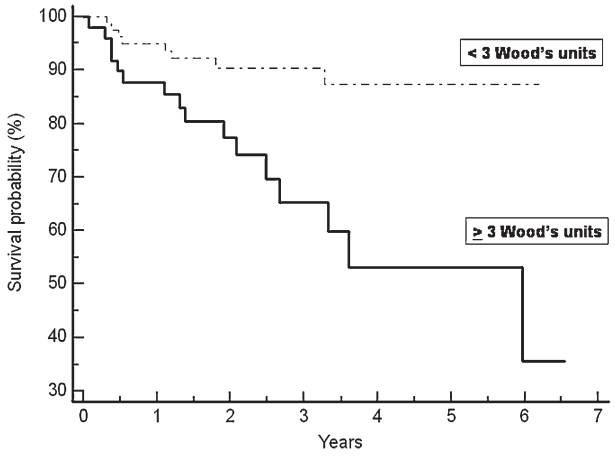

FIGURE 5. The survival curves of patients with PVR < 3 Wood units vs those with PVR ≥ 3 Wood units. There was a significant difference in survival curves based on Kaplan Meier analysis ($\chi^2 = 10.1921$; $P < .002$). See Figure 1 legend for expansion of abbreviations.

mortality: chest roentgenogram stage 4 (HR = 2.21; 95% CI, 1.08-4.51) and presence of PH (HR = 7.43; 95% CI, 2.26-24.45).

Discussion

For patients with sarcoidosis, the rate of PH has been reported to be between 5% and 15%.[3,5] In studies of patients with dyspnea, the percentage of patients with PH has been reported as >50%.[2,4] The current study evaluated right-sided heart catheterization findings in 130 patients with sarcoidosis with persistent moderate to severe dyspnea despite antiinflammatory therapy for sarcoidosis. We did not have a standard protocol for referring patients for right-sided heart catheterization. We did not collect specific information for those patients who refused right-sided heart catheterization. Previous studies have suggested that reduced 6-min walk distance, desaturation with 6-min walk, stage 4 chest roentgenogram, and reduced Dlco may be useful in identifying patients with an increased risk for PH.[2-5,22]

In 28% of these patients with sarcoidosis with PH, LVD was the cause of PH. The noncaseating granulomas of sarcoidosis can infiltrate the myocardium, leading to a reduced LVEF. Left ventricular cardiomyopathy was identified in seven (35%) of our patients with PH/LVD.

Isolated left ventricular diastolic dysfunction has been identified in patients with sarcoidosis.[10,12] It has been postulated that granulomatous involvement can lead to isolated left ventricular diastolic dysfunction.[12] We did not perform either MRI or PET scan on our patients. Those techniques may have identified granulomatous involvement in our patients.[23]

In patients with sarcoidosis who were awaiting lung transplant, PH was an independent predictor for increased mortality.[9] In a subsequent analysis of these patients, there was a positive correlation between the pulmonary artery pressure and PAO.[8] This is not surprising, since left ventricular disease is a common cause of PH.[18] However, it is unclear how many of these patients had left ventricular diastolic dysfunction that caused PH.

In the current study, the clinical outcome of patients with PH associated with left ventricular disease was significantly better compared with those with PH without LVD. At the time of catheterization, no clinical features could distinguish between PH/LVD and PH without LVD. This emphasizes the importance of performing hemodynamic measurements to fully characterize patients with sarcoidosis with PH.

All patients with PH and LVD had a PVR <3 Wood units. An increase in PVR would suggest pulmonary vascular disease, which has been reported in patients with sarcoidosis with PH.[6] In the current study, an elevated PVR was also associated with a reduced survival. This has been reported in patients with idiopathic pulmonary fibrosis.[24]

In a prior study of unselected patients with sarcoidosis, we reported that patients with FVC <1.5 L had increased risk for mortality from sarcoidosis.[25] In the current study, a reduced FVC was not associated with increased mortality. However, because this study evaluated only patients with persistent dyspnea despite antiinflammatory therapy, it included patients with lower FVC values. Shorr et al[9] also detected no difference in the FVC for survivors vs nonsurvivors in their orthotopic lung transplant candidates.

As noted in previous observations, this study found that patients with sarcoidosis with fibrotic chest roentgenograms (stage 4 disease) had an increased mortality.[25] Multivariate analysis confirmed chest roentgenogram staging as an independent predictor for mortality. The association between pulmonary fibrosis and PH in sarcoidosis has been previously noted.[1,2] However, using chest roentgenogram staging in sarcoidosis may not be sufficiently sensitive or specific to identify fibrosis.[26] We did not have CT scans at the time of catheterization on enough patients to do that analysis.

Fibrotic lung disease is also associated with hypoxia. In other lung diseases, hypoxia is associated with PH.[27,28] The need for supplemental oxygen has been associated with PH in sarcoidosis in some studies[8] but not all.[4] We did not find that need for supplemental oxygen was predictive of PH without LVD. This may have been because of the large percentage of PH/LVD patients on supplemental oxygen. In sarcoidosis, vascular changes have also been noted to lead to PH.[6]

In an analysis of patients with sarcoidosis who were awaiting lung transplant,[9] African-American race, but not sex, was a significant predictor of increased mortality.[9] We did not find either race or sex associated with worse survival. These differences may reflect the diverse populations studied. None of the patients in the current study was listed for lung transplant at the time of study initiation, although one patient underwent transplant during follow-up and unfortunately died 2 months later. In our analysis, we chose to use time of death rather than time of transplant.

Dietary sodium restriction and aggressive diuresis are usually successful as the initial treatment of isolated left ventricular diastolic dysfunction.[14] Those patients with reduced ejection fractions associated with sarcoidosis received afterload reduction and diuretics as well as angiotensin-converting enzyme inhibitors and β-blockers as tolerated. Antiinflammatory drugs, including corticosteroids and methotrexate,[29] were also prescribed.

A variety of agents, including prostacylines,[1,30,31] endothelin receptor antagonists,[1,31,32] and phosphodiesterase inhibitors,[32,33] have been prescribed to treat

sarcoidosis-associated PH. The patients in this study received a variety of agents; however, there was no consistent treatment protocol. The median survival was 4.2 years for our patients with PH without LVD. This is similar to survival reported in patients with idiopathic PH treated with bosentan.[34] This 60% 3-year survival rate is similar to the 74% survival rate reported by Barnett et al[32] in their series of 22 patients with sarcoidosis-associated PH.

Previous echocardiographic studies of sarcoidosis-associated PH have failed to distinguish between PH with and without LVD.[4,5] Our study found that patients who had a moderately elevated estimated PAsys of ≥ 50 mm Hg had an increased mortality. However, an echocardiographic estimate of PA pressure was not available on many of our patients. Therefore, we did not include the echocardiography results in our multiregression model.

The retrospective nature of our study leads to several limitations. The time from catheterization was longer for the PH-without-LVD group than for the no-PH group. However, the median time from catheterization for the no-PH group was >3 years. We found that the mortality for the PH-without-LVD group studied at 2 and 3 years after their catheterizations was significantly higher than the no-PH group. However, we could not demonstrate a difference in the survival at these earlier time points between PH/LVD and the other two groups. We also did not have standard criteria for referral for right-sided heart catheterization and did not follow those who did not have catheterization. Given the frequency of PH in sarcoidosis, a prospective trial of screening patients for sarcoidosis-associated PH seems warranted. During the course of the study, new agents to treat pulmonary arterial hypertension were available, but they were not consistently applied to these patients.

Our study demonstrated reduced survival for patients with sarcoidosis with PH without LVD. For patients with sarcoidosis with PH associated with left ventricular disease, the predicted survival rate fell between the PH-without-LVD group and the group without PH. Because of the difference in PVR between the two groups, it is likely that the reduced survival in patients with sarcoidosis with PH without LVD is related to pulmonary vascular disease. This prognostic difference, coupled with the dramatic difference in therapy for the two forms of PH, highlights the importance of right-sided heart catheterization when PH is suspected in patients with sarcoidosis.

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Ms Taylor: contributed to the care of patients, obtaining data on patients, and reading and approving the manuscript.
Dr Lower: contributed to the design of the study, the care of patients, obtaining data on patients, and writing, reading, and approving the manuscript.
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References

1. Baughman RP, Engel PJ, Meyer CA, Barrett AB, Lower EE. Pulmonary hypertension in sarcoidosis. *Sarcoidosis Vasc Diffuse Lung Dis*. 2006;23(2):108-116.
2. Rizzato G, Pezzano A, Sala G, et al. Right heart impairment in sarcoidosis: haemodynamic and echocardiographic study. *Eur J Respir Dis*. 1983;64(2):121-128.
3. Bourbonnais JM, Samavati L. Clinical predictors of pulmonary hypertension in sarcoidosis. *Eur Respir J*. 2008;32(2):296-302.
4. Sulica R, Teirstein AS, Kakarla S, Nemani N, Behnegar A, Padilla ML. Distinctive clinical, radiographic, and functional characteristics of patients with sarcoidosis-related pulmonary hypertension. *Chest*. 2005;128(3):1483-1489.
5. Handa T, Nagai S, Miki S, et al. Incidence of pulmonary hypertension and its clinical relevance in patients with sarcoidosis. *Chest*. 2006;129(5):1246-1252.
6. Nunes H, Humbert M, Capron F, et al. Pulmonary hypertension associated with sarcoidosis: mechanisms, haemodynamics and prognosis. *Thorax*. 2006;61(1):68-74.
7. Arcasoy SM, Christie JD, Pochettino A, et al. Characteristics and outcomes of patients with sarcoidosis listed for lung transplantation. *Chest*. 2001;120(3):873-880.
8. Shorr AF, Helman DL, Davies DB, Nathan SD. Pulmonary hypertension in advanced sarcoidosis: epidemiology and clinical characteristics. *Eur Respir J*. 2005;25(5):783-788.
9. Shorr AF, Davies DB, Nathan SD. Predicting mortality in patients with sarcoidosis awaiting lung transplantation. *Chest*. 2003;124(3):922-928.
10. Angomachalelis N, Hourzamanis A, Vamvalis C, Gavrielides A. Doppler echocardiographic evaluation of left ventricular diastolic function in patients with systemic sarcoidosis. *Postgrad Med J*. 1992;68(suppl 1):S52-S56.
11. Yazaki Y, Isobe M, Hiroe M et al. Prognostic determinants of long-term survival in Japanese patients with cardiac sarcoidosis treated with prednisone. *Am J Cardiol*. 2001;88(9):1006-1010.
12. Fahy GJ, Marwick T, McCreery CJ, Quigley PJ, Maurer BJ. Doppler echocardiographic detection of left ventricular diastolic dysfunction in patients with pulmonary sarcoidosis. *Chest*. 1996;109(1):62-66.
13. Deng JC, Baughman RP, Lynch JPI III. Cardiac involvement in sarcoidosis. *Semin Respir Crit Care Med*. 2002;23(6):513-527.
14. Aurigemma GP, Gaasch WH. Clinical practice. Diastolic heart failure. *N Engl J Med*. 2004;351(11):1097-1105.
15. Pocock SJ, Wang D, Pfeffer MA, et al. Predictors of mortality and morbidity in patients with chronic heart failure. *Eur Heart J*. 2006;27(1):65-75.
16. Miyagishima K, Hiramitsu S, Kimura H, et al. Long term prognosis of chronic heart failure: reduced vs preserved left ventricular ejection fraction. *Circ J*. 2009;73(1):92-99.

17. Hunninghake GW, Costabel U, Ando M, et al. ATS/ERS/WASOG statement on sarcoidosis. American Thoracic Society/European Respiratory Society/World Association of Sarcoidosis and other Granulomatous Disorders. *Sarcoidosis Vasc Diffuse Lung Dis*. 1999;16(2):149-173.
18. Rubin LJ, Badesch DB. Evaluation and management of the patient with pulmonary arterial hypertension. *Ann Intern Med*. 2005;143(4):282-292.
19. Scadding JG. Prognosis of intrathoracic sarcoidosis in England. *BMJ*. 1961;2(5261):1165-1172.
20. Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general U.S. population. *Am J Respir Crit Care Med*. 1999;159(1):179-187.
21. Crapo RO, Morris AH. Standardized single breath normal values for carbon monoxide diffusing capacity. *Am Rev Respir Dis*. 1981;123(2):185-189.
22. Baughman RP, Sparkman BK, Lower EE. Six-minute walk test and health status assessment in sarcoidosis. *Chest*. 2007;132(1):207-213.
23. Mehta D, Lubitz SA, Frankel Z, et al. Cardiac involvement in patients with sarcoidosis: diagnostic and prognostic value of outpatient testing. *Chest*. 2008;133(6):1426-1435.
24. Corte TJ, Wort SJ, Gatzoulis MA, Macdonald P, Hansell DM, Wells AU. Pulmonary vascular resistance predicts early mortality in patients with diffuse fibrotic lung disease and suspected pulmonary hypertension. *Thorax*. 2009;64(10):883-888.
25. Baughman RP, Winget DB, Bowen EH, et al. Predicting respiratory failure in sarcoidosis patients. *Sarcoidosis Vasc Diffuse Lung Dis*. 1997;14(2):154-158.
26. Baughman RP, Shipley R, Desai S, et al; Sarcoidosis Investigators. Changes in chest roentgenogram of sarcoidosis patients during a clinical trial of infliximab therapy: comparison of different methods of evaluation. *Chest*. 2009;136(2):526-535.
27. Chaouat A, Bugnet AS, Kadaoui N, et al. Severe pulmonary hypertension and chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2005;172(2):189-194.
28. Corte TJ, Wort SJ, Wells AU. Pulmonary hypertension in idiopathic pulmonary fibrosis: a review. *Sarcoidosis Vasc Diffuse Lung Dis*. 2009;26(1):7-19.
29. Baughman RP, Lower EE. Therapy for sarcoidosis. *European Respiratory Monograph*. 2005;32:301-315.
30. Fisher KA, Serlin DM, Wilson KC, Walter RE, Berman JS, Farber HW. Sarcoidosis-associated pulmonary hypertension: outcome with long-term epoprostenol treatment. *Chest*. 2006;130(5):1481-1488.
31. Diaz-Guzman E, Farver C, Parambil J, Culver DA. Pulmonary hypertension caused by sarcoidosis. *Clin Chest Med*. 2008;29(3):549-563., x.
32. Barnett CF, Bonura EJ, Nathan SD et al. Treatment of sarcoidosis-associated pulmonary hypertension: a two-center experience. *Chest*. 2009;135(6):1455-1461.
33. Milman N, Burton CM, Iversen M, Videbaek R, Jensen CV, Carlsen J. Pulmonary hypertension in end-stage pulmonary sarcoidosis: therapeutic effect of sildenafil? *J Heart Lung Transplant*. 2008;27(3):329-334.
34. McLaughlin VV, Sitbon O, Badesch DB, et al. Survival with first-line bosentan in patients with primary pulmonary hypertension. *Eur Respir J*. 2005;25(2):244-249.