

Pulmonary Hypertension in Sarcoidosis

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Abstract. *Background:* Pulmonary hypertension has been notreported in some patients with sarcoidosis. *Methods:* We retrospectively studied 53 sarcoidosis patients with persistent dyspnea despite systemic therapy for their sarcoidosis. All patients underwent cardiac catheterization to determine pulmonary artery (PA) pressure. *Results:* Of the 53 patients, six were found to have left ventricle (LV) dysfunction, including four cases of diastolic dysfunction. Of the remaining 47 patients, 26 had a systolic PA pressure ≥ 40 Torr and 25 had a mean PA pressure ≥ 25 Torr. Using univariate analysis of those patients with normal LV function, echocardiography, vital capacity, and diffusion lung of carbon monoxide (D_{LCO}) correlated with systolic and/or mean pulmonary artery pressure. For the PA systolic, only the echocardiographic estimated PA pressure and D_{LCO} % predicted remained in the multiple regression model (Coefficient of determination = 0.76, $p < 0.005$ for both). For the PA mean pressure, the only independent variable was the echocardiographic estimate of the PA pressure (Coefficient of determination = 0.70, $p < 0.005$). While echocardiography was useful in many cases, in nine cases PA pressure could not be estimated because there was no tricuspid regurgitation seen. Seven of these patients had a measured PA pressure of ≥ 40 Torr. Seven patients with moderate to severe pulmonary hypertension were treated with pulmonary vasodilator therapy. Five patients experienced good clinical response. *Conclusion:* Pulmonary hypertension was commonly found in sarcoidosis patients with persistent dyspnea. For some of these patients, treatment of the pulmonary hypertension was associated with improved clinical status. (*Sarcoidosis Vasc Diffuse Lung Dis* 2006; 23: 108-116)

Key Words. Pulmonary hypertension. Bosanten. Epoprostenol. Cardiac catheterization.

Pulmonary hypertension has been noted to occur in sarcoidosis [1-5]. For sarcoidosis patients awaiting lung transplant, over 70% of the patients will have significant pulmonary hypertension [5-8]. This is considerably higher than the incidence noted for idiopathic pulmonary fibrosis, where less than half of patients listed for transplant will have

pulmonary hypertension [9;10]. Pulmonary hypertension has also been noted in patients with less severe disease [3, 4, 11].

Exercise studies have revealed that over 80% of patients with pulmonary sarcoidosis can experience a drop in right ventricular ejection fraction with exercise [12]. Others have demonstrated pulmonary hypertension with exercise in sarcoidosis patients with parenchymal lung disease [3, 4].

Elevation of pulmonary artery pressure is defined as a mean pulmonary artery pressure of greater than 25 Torr. It is caused by several conditions including vascular disease, such as idiopathic pul-

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monary hypertension, elevated venous pressure, such as diastolic dysfunction, and congenital heart disease. The new clinical classification for pulmonary hypertension includes these as separate categories [13]. Sarcoidosis associated pulmonary hypertension is placed in the miscellaneous category [13]. This is in part because the mechanism of pulmonary hypertension in sarcoidosis patients is multi-factorial [14]. In addition to left ventricular dysfunction, inflammatory changes of the interstitium can destroy the blood vessels and lead to pulmonary hypertension [4, 11]. Hilar adenopathy from the sarcoidosis may compress the pulmonary vasculature and lead to pulmonary hypertension [15, 16]. It may also be due to vasculitis from the sarcoidosis itself [2]. In some cases, the pulmonary hypertension will respond to systemic therapy for the sarcoidosis, such as corticosteroids [17].

Several features have been correlated with pulmonary hypertension in sarcoidosis. These include changes in spirometry [11]. However, others have failed to demonstrate a correlation between spirometry and pulmonary hypertension [5, 14]. The finding of pulmonary fibrosis is more common in patients with pulmonary fibrosis [4, 11, 14], but significant pulmonary hypertension can be found in patients with minimal parenchymal disease on chest roentgenogram [4, 14].

We were interested in determining the frequency of pulmonary hypertension in sarcoidosis patients with persistent dyspnea despite systemic therapy for their sarcoidosis. In addition, we wished to identify the best method to detect pulmonary hypertension.

Methods

Patients were selected from those seen in an Interstitial Lung Disease and Sarcoidosis Clinic at the University of Cincinnati. Patients were seen by one of two physicians (RPB, EEL) and treated using the guidelines of the ATS/ERS/WASOG Statement of on Sarcoidosis [18]. Patients studied included those with persistent dyspnea despite medical management for their pulmonary sarcoidosis that underwent right heart catheterization. This was a retrospective review of patient records, approved by the Institutional Review Board of the University of Cincinnati.

In addition to the values from the right heart catheterization, the results of pulmonary function studies, chest roentgenogram, and echocardiogram were recorded when available.

Within the six months of the right heart catheterization, spirometry was available only in 39 patients, D_{LCO} only in 23, and echocardiography only in 30 (in 9 of which PA estimate was not available). Where possible, the echocardiogram was reviewed by one cardiologist (PE), who reevaluated the pulmonary artery pressure estimate.

Right heart catheterization was performed in a cardiac catheterization laboratory with supplemental oxygen to keep the arterial saturation (as measured by an oximeter) at $> 92\%$. The right atrial, ventricle, and pulmonary artery pressures were recorded using a continuous wave tracing. The mean pulmonary artery pressure (PAm_{ean}) was calculated. The pulmonary artery occlusion pressure (PAO) was also determined. Cardiac output (CO) was determined using the thermodilution technique. The pulmonary vascular resistance (PRV) was calculated using the formula: $PVR = 80 \times (PAm_{ean} - PAO) / CO$ (dyne*sec)/cm⁵. The normal range of PVR is 155-255 (dyne*sec)/cm⁵. If the patient had pulmonary hypertension, increasing concentrations of nitric oxide were given via a nasal cannula and the patient was considered to have a favorable acute response to vasodilator if there was a fall in mean pulmonary artery pressure of at least 10 mm Hg to 40 mm Hg, with an increase or unchanged cardiac output [19].

High resolution computed tomography within a year of the right heart catheterization was available in some patients. These scans were performed for the evaluation of interstitial lung disease and thus were obtained using 1 mm collimation at 10mm increments in end inspiration. Each scan was reviewed in mediastinal windows by one radiologist (CM). The ascending aorta and main pulmonary artery diameters were measured on a single defined axial scan level. This level was defined as the axial image that best demonstrated the transverse portion of the right pulmonary artery in continuity with the main pulmonary artery. The main pulmonary artery diameter was then measured as the maximum dimension of the pulmonary artery perpendicular to the long axis of the main pulmonary artery [20]. Short axis measurements of the ascending aorta were obtained at the same level. In addition measurements of the descending right and left pulmonary artery were performed. A main pulmonary artery to ascending aorta ratio (rPA) was calculated as described by Ng *et al* [20].

Patients with significant pulmonary hypertension were considered for vasodilator therapy. For patients treated with specific pulmonary vasodilators, a repeat catheterization was planned six months after starting therapy. When available, clinical outcome and results of catheterization were noted. Treatment decisions were based on patient preference and severity of the pulmonary hypertension. In general, patients with elevated right atrial pressures and low cardiac indexes were considered for epoprostenol, those with moderate pressures were treated with bosentan. One patient with an acute vasodilatory response was treated with a calcium channel blocker.

Comparisons were made between pulmonary artery pressure and various factors using correlation coefficient. For parameters with a significant relationship, a multiple regression model was developed to determine which parameters were independent predictors of pulmonary hypertension.

Results

During the time of the study, 1223 patients with sarcoidosis were seen in the clinic: 471 Caucasian females, 382 African American females, 220 Caucasian males, 150 African American males. A total of 53 sarcoidosis patients were identified who had undergone right heart catheterization. Six patients had a pulmonary artery occluding pressure of ≥ 15 Torr or elevated left ventricular diastolic pressure at the time of catheterization. All six had a PAO of > 20 Torr. These patients were felt to have pulmonary hypertension on the basis of left ventricular dysfunction. This includes two patients with cardiomyopathy due sarcoidosis, one patient with ischemic heart disease, and three patients with diastolic dysfunction.

Patients were divided into three groups: PA sys ≥ 40 Torr, no LV dysfunction (Pulm HTN), PA ≥ 40 Torr, LV dysfunction (LV Dysfunction), PA < 40 Torr (Normal PA pressure). *Table I* demonstrates the demographics, FVC percent predicted, $D_L\text{co}$, and chest roentgenogram stage of the three groups. For patients with pulmonary hypertension

Table I
Characteristics of Patients Studied

Categories*	PA systolic ≥ 40 Torr, normal LV function	LV Dysfunction	Normal PA pressure	Total
Total Number	26	6	21	53
Age (years)	52 (24-76) †	47 (43-65)	52 (27-64)	51 (24-76)
Male:Female	10:16	3:3	6:15	19:34
Caucasian:African American	13:13	3:3	13:8	29:24
FVC, L ††	1.86 (1.19-3.67)	2.52 (1.26-3.87)	2.31 (1.13-4.99)	2.21 (1.13-4.99)
FVC% percent predicted	64% ‡ (30-85%)	70% (43-84%)	79% (34-112%)	66% (30-112%)
$D_L\text{co}$ percent predicted ††	59% (20-82%)	20% (5-35%)	80 (48-105%)	59% (5-105%)
Chest X ray stage (50)				
Zero	0	0	1	1
One	2	4	5	11
Two	6	1	2	9
Three	9	0	9	18
Four	9	1	4	14

* Patients were divided into three groups: PA sys > 40 Torr, no LV dysfunction (Pulm HTN), PA > 40 Torr, LV dysfunction (LV Dysfunction), PA < 40 Torr (Normal PA pressure). PA=pulmonary artery, LV=left ventricle
† Median (range)

‡ Significantly differs from Normal PA pressure, $p < 0.05$ (Mann Whitney U test).

†† FVC results available only in 39 patients and $D_L\text{co}$ only in 23 patients

Table II
Patients with Elevated Right Side Pressure Measurements

Parameter	Normal LV function Number positive/ Number studied † (%)	Abnormal LV function Number positive/ Number studied (%)
PA systolic > 40 mm Hg	26/53 (49%)	6/53 (11%)
PA mean > 25 mm Hg	25/53 (47%)	5/53 (9%)
PVR > 255 dynes*sec/cm ⁵ †	15/48 (31%)	0/48 (0%)

† Total number studied includes 6 patients with abnormal LV function. Only 48 total patients had PVR determined

PA=pulmonary artery, LV=left ventricle, PVR=pulmonary vascular resistance

and normal LV function, the FVC % predicted was lower than the normal pressure group ($p < 0.05$), but there was considerable overlap.

Table II demonstrates the frequency of elevated PA systolic or mean pressure for the 47 patients with normal LV function as well as the six patients with LV dysfunction. Also shown is the pulmonary vascular resistance of the 48 patients who had cardiac outputs recorded at the time of the catheterization. Patients with LV dysfunction could have elevated PA pressures, but none had elevated pulmonary vascular resistance.

The results of the right heart catheterization for the 47 patients with normal LV function are shown in *Fig. 1*. In *Fig. 1A*, we demonstrate the PA systolic pressure. In *Fig. 1B*, we demonstrate the mean PA pressure. In *Fig. 1C* we demonstrate the pulmonary vascular resistance in the 42 patients with normal LV function, in whom cardiac output was measured at the time of the catheterization.

Twelve patients had a CT scan in temporal proximity to the right heart catheterization. There was no difference in the ratio of pulmonary artery to ascending aorta for the four patients with normal PA pressure (Median = 0.88 range 0.71-1.07) versus the eight patients with pulmonary hypertension (Median = 0.99, range = 0.73-1.19).

We then compared the pulmonary hypertension patients to those with normal pressure. We excluded from this analysis those with LV dysfunction. In *Table III*, we show the correlation coefficient of PA systolic and PA mean pressure with several features. Only four variables were significantly associated with the PA systolic pressure: echocardiographic estimate of PA pressure, and the $D_L\text{co}$ either absolute value or percent predicted. The PA mean pressure also correlated with these

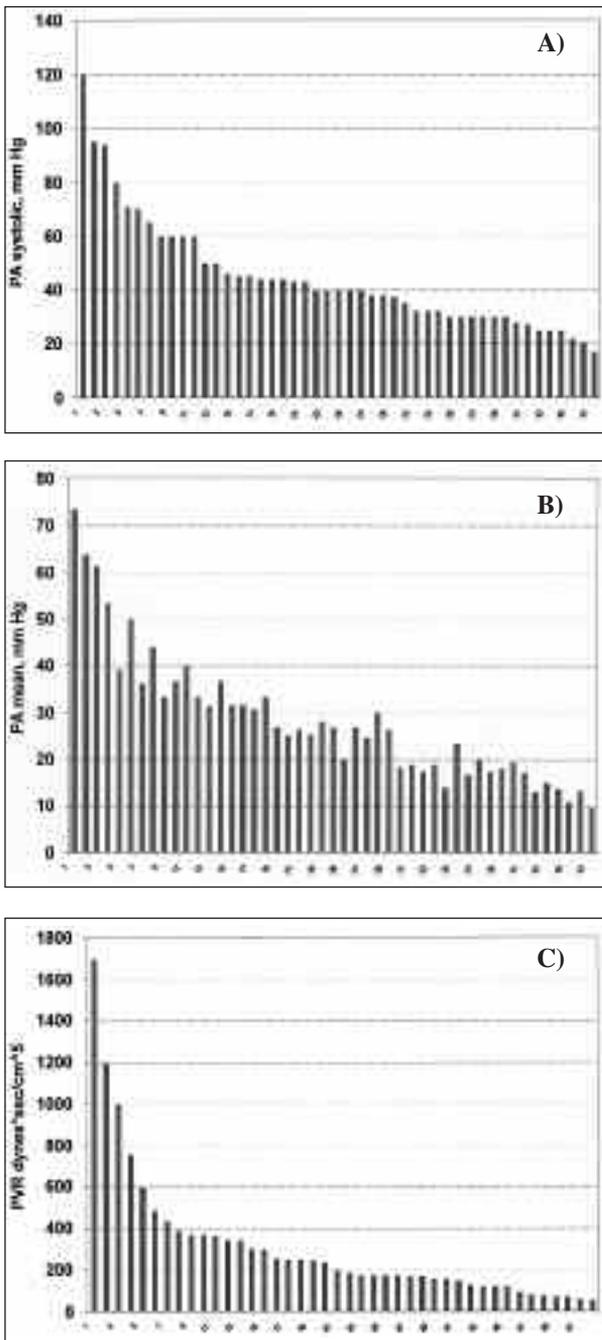


Fig. 1. Results of right heart catheterization in 47 patients with normal LV function. Figure 1 A shows the PA systolic pressure, Figure 1B shows the PA mean pressure, Figure 1C shows the pulmonary vascular resistance in the 42 patients in whom the cardiac output was recorded at the time of the catheterization

four variables. There was also a correlation between PA mean and the absolute FVC and absolute FEV-1 values.

The results of echocardiography were compared to actual PA pressure measurements. In 9 of the 30 patients, it was not possible to estimate the PA pressure by echocardiography because there was no visible tricuspid regurgitation. Two patients had LV dysfunction. For the remaining 19 patients, there was a significant correlation between the PA systolic as estimated by echocardiography and measured by catheterization ($R = 0.79, p < 0.001$). This comparison is shown in *Fig. 2*. We also show in *Fig. 2* the results of the pulmonary artery pressure for the nine patients in whom the pulmonary artery pressure could not be estimated by echocardiography (Median = 50 Torr, range 25 to 80 Torr).

The D_{LCO} was also compared to the PA systolic and mean in patients with normal LV function. Again there was a significant correlation. *Figure 3* shows the comparison of the 23 patients who had D_{LCO} and their systolic PA pressure measurements by catheterization.

We then performed a stepwise multi regression model to examine which variables were associated with pulmonary hypertension. We examined the PA systolic or PA mean pressure versus those values which had a univariate correlation p value of less than 0.1 from *Table III*. This included echocardiographic estimated PA pressure, D_{LCO} absolute

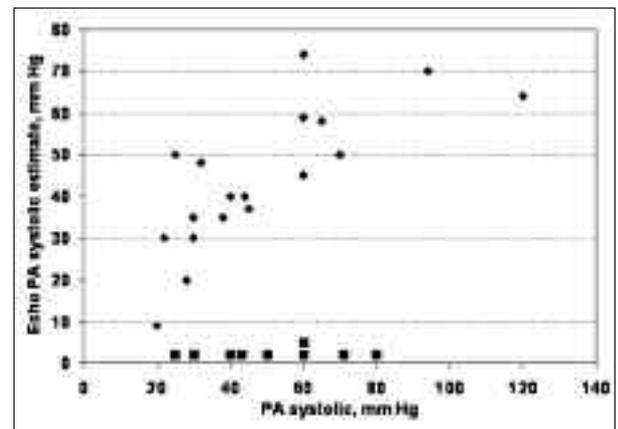


Fig. 2. The estimated PA pressure by echocardiography was compared to the measured PA systolic pressure. The diamonds represent the 19 patients in whom an echocardiographic estimate was performed of the PA pressure and there was no evidence of LV dysfunction. The squares represent the nine patients whose pulmonary artery pressure could not be estimated by echocardiography. For the 19 patients in whom echocardiography derived values were available, there was a significant positive correlation ($R = 0.74, p < 0.001$)

Table III
Correlation between Pulmonary Artery Pressure and Features of Patients with Normal LV function

Feature	Number studied	PA Systolic R value	P value	PA Mean R value	P value
Echo PA estimate	19	0.79	< 0.002	0.76	< 0.002
D _L co absolute	21	-0.46	< 0.05	-0.56	< 0.01
D _L co % predicted	21	-0.56	< 0.02	-0.62	< 0.001
FVC Absolute	39	-0.26	0.11	-0.31	0.06
FVC % predicted	39	-0.29	0.09	-0.34	< 0.05
FEV-1 Absolute	39	-0.34	< 0.05	-0.37	< 0.05
Ratio PA/Aorta ratio	12	0.18	0.56	0.38	0.22
Chest X-ray stage (50)	47	0.25	0.08	0.26	0.09
Age	47	0.19	0.29	0.10	0.55

* NS, not significant

LV= left ventricle, PA= pulmonary artery, DLCO= diffusion lung of carbon monoxide

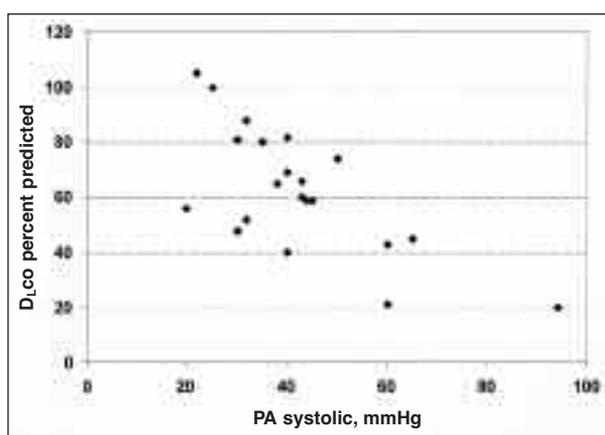


Fig. 3. The D_Lco percent predicted was compared to the PA systolic pressure. There was a significant negative correlation (R = -0.70, p < 0.0005)

te and percent predicted and absolute value of the FVC and FEV-1. Only 11 patients had all these determinations performed. For the PA systolic, only the echo estimated PA pressure and D_Lco % predicted remained in the multiple regression model (Coefficient of determination = 0.76, p < 0.005 for

both). For the PA mean pressure, the only independent variable was the echographic estimate of the PA pressure. Again the correlation was significant (Coefficient of determination = 0.70, p < 0.005).

Seven of the patients with significant pulmonary hypertension were treated for at least four months with pulmonary vasodilator therapy. *Table IV* details the initial and follow up mean pulmonary artery pressure as determined by right heart catheterization. It lists the vasodilator drugs used during the time between the two catheterizations. It also lists the initial and final immunosuppressive therapy used to treat the sarcoidosis. Two patients died during the period of observation. One of these patients had his first catheterization performed after 12 months of oral bosanten. He still had significant elevated pressures and epoprostenol was added. He was also referred for lung transplant. Despite an initial clinical improvement with the addition of epoprostenol, he died of pneumonia and respiratory failure two months after starting epoprostenol. No autopsy was performed

Table IV
Results of Vasodilator Therapy

Pt	Initial PA Systolic: Mean, Torr	Follow PA Systolic: Mean, Torr	Duration therapy until follow up catheterization, months	Vasodilator therapy	Initial Systemic Sarcoidosis Medications	Final Systemic Sarcoidosis Meds
1	120: 73	71: 41	6	Epo	Pred, MTX	Pred, MTX, AZA, Inflix
2 *	95: 63	75: 45	6	Bos	Pred	Pred
3 *	94:61 †	N.D. ‡	N.D.	Bos, Epo	Pred, AZA	Pre, AZA
4	80: 53	41: 23	4	Amlodipine	Pred	Pred, MTX
5	70: 50	N.D.	N.D.	Bos	Pred	Pred, CTX
6	60: 38	60: 36	6	Bos	Pred, MTX	Pred, MTX, AZA
7	60: 36	42: 24	8	Bos	Pred, MTX	MTX, Inflix

* Died

† Patient studied after 12 months of bosanten therapy alone. Epoprostenol was added for an additional 2 months before he died.

‡ N.D. = Not done; Epo=Epoprostenol; Bos = Bosanten; Pred = Prednisone; MTX = Methotrexate; AZA = Azathioprine; Inflix=Infliximab; CTX = cyclophosphamide

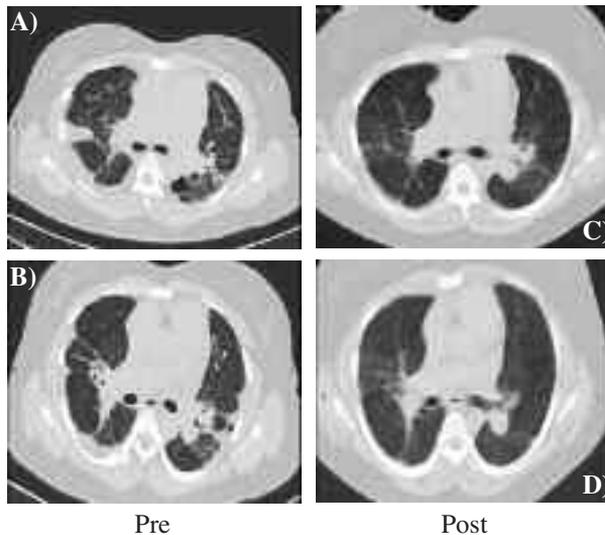


Fig. 4. Representative HRCT slices from a patient with sarcoidosis. Fig. 4 A and 4 B are on only 10 mg prednisone and with increasing respiratory symptoms, while Fig. 4C and 4D are at similar views after treatment with infliximab. See text for further details

on either patient who died. A second patient refused a repeat catheterization but continues to do well clinically a year after starting bosentan. In four of the five cases where a repeat catheterization was performed, there was a significant drop in the pulmonary artery pressure. Two cases responded to bosentan and one each to epoprostenol and amlodipine. The amlodipine patient was the only patient who demonstrated an acute response to vasodilators.

For the treated patients, it became clear that systemic therapy for the pulmonary sarcoidosis was needed to maintain the patient. In most cases, an increase in immunosuppressive therapy was felt to be necessary. For example, patient 1 had a significant improvement in her pulmonary artery pressure with epoprostenol therapy. However, as her corticosteroids were decreased, she developed a worsening of lung function and chest CT scan. Fig. 4A and B are representative CT slices obtained at the time of clinical worsening. Her cardiac catheterization at that time demonstrated her PA pressure was decreased by 40% from her pre-epoprostenol study. She was begun on infliximab therapy. Follow-up HRCT is shown in Fig. 4C and D and demonstrates improved lung parenchyma. In addition, there was a 20% improvement in the FVC.

Discussion

Pulmonary hypertension is a significant health problem. It can occur because of increase in the left ventricular filling pressure, pulmonary vasculature changes, or be the result of loss of lung tissue [14, 21]. Sarcoidosis has been a well recognized cause of pulmonary hypertension [3-5, 11, 22, 23]. While hypoxia could be a contributing factor to pulmonary hypertension in sarcoidosis, patients remained hypertensive on supplemental oxygen to keep saturation > 92% during the catheterization.

The frequency of pulmonary hypertension in sarcoidosis is unclear. In our study, half of the patients with persistent dyspnea had pulmonary hypertension. This high frequency has been observed by others. Sarcoidosis patients awaiting lung transplant usually have pulmonary hypertension [5, 6]. It has been found that elevated pressures, especially elevated right atrial pressure, is the best predictor of mortality in these end stage patients [6-8]. In our study, less than 5% of the patients seen in our clinic were referred for right heart catheterization. The prevalence of significant pulmonary hypertension in all patients with sarcoidosis remains unclear.

In studying patients who are not being considered for transplant, pulmonary hypertension has been noted. Gluckowski *et al* noted pulmonary hypertension at rest in patients with stage 3 disease by chest roentgenogram [3]. Rizzato *et al* also found pulmonary hypertension in many of their patients with stage 2 or 3 chest roentgenographic changes [4]. Sulica *et al* recently reported that 54 of 106 sarcoidosis patients studied at their institution had echocardiographic evidence of pulmonary hypertension. They only used echocardiography to assess for pulmonary hypertension. They also found pulmonary hypertension was more common with advanced parenchymal disease by chest roentgenogram, with two third of their patients with stage 4 disease having pulmonary hypertension [11]. Nunes *et al* reviewed the records of 22 sarcoidosis patients with pulmonary hypertension seen at two centers in France [14]. In this study, seven had no evidence of pulmonary fibrosis on chest roentgenogram, including 2 patients with no parenchymal lung disease. Histology was available from five patients who underwent lung transplant. Granuloma-

tous disease was predominantly in the veins in four cases. All five cases were stage four at time of transplant and histology confirmed fibrosis [14].

For some sarcoidosis patients, the pulmonary pressure may be normal with rest, but rise with exercise [3]. In a study using multiple uptake gated acquisition (MUGA) to measure right ventricular ejection fraction, a drop in right ventricular ejection fraction (RVEF) occurred with exercise in 12 of 14 pulmonary sarcoidosis patients [12]. The drop in RVEF was presumed to be the result of pulmonary hypertension. In the current study, we only studied patients at rest. One would expect a higher rate of pulmonary hypertension if we studied patients with exercise.

In this study, we used right heart catheterization to directly measure the pulmonary artery pressure. This direct measurement is the standard for the diagnosis of pulmonary hypertension [21]. Six patients were found to have left ventricular dysfunction as the cause of the elevated pressures. This included two cases of cardiomyopathy due to sarcoidosis. There were four cases of diastolic dysfunction. These cases may be related to the underlying sarcoidosis [24, 25]. The patients with diastolic dysfunction would have been misclassified as isolated pulmonary hypertension if using echocardiography alone.

The most commonly used noninvasive method for screening for pulmonary hypertension has been echocardiography. In the large study by Sulica *et al*, that was the only method used to assess for pulmonary hypertension [11]. In this study, we found the echocardiographic estimate of the PA systolic pressure was in good agreement with the direct PA measurement (*Fig. 2*). This has been noted in prior studies of sarcoidosis patients [4]. However, there were several limitations to using echocardiography alone to assess pulmonary hypertension. There were some patients with high PA estimates and normal PA pressures by catheterization. Thus, although the echocardiogram may prove a good screening test for pulmonary hypertension, there is still a need for catheterization to determine the absolute pressure. Other authors have found that the echocardiogram can be misleading in estimating PA pressure, especially in lung disease [26-28].

The method chosen to estimate pulmonary pressure in this study was to perform Doppler

analysis of tricuspid regurgitant velocity spectrum [29;30]. Unfortunately, one can not always find a tricuspid regurgitant flow to analyze. In this study, nine of thirty patients (30%) of the sarcoidosis patients undergoing echocardiography did not have visible tricuspid regurg and therefore did not have a PA estimate made. As shown in *Fig. 2*, several of these patients still had significant pulmonary hypertension. There are other methods of estimating PA pressure by echocardiogram. Most of these rely on changes of the right ventricle either at rest or during contraction [31]. This has been shown to have benefit in detecting pulmonary hypertension in sarcoidosis patients [4, 32]. The estimates, however, still have false positive and false negatives. In a study comparing echocardiography to direct PA measurement in 33 patients, Rizzato *et al* used the right ventricular anterior wall thickness determined by echocardiography to estimate pulmonary artery pressure. While there was a significant correlation between the echocardiography and right heart catheterization values, the R value was 0.68 [4]. There were several patients who would have been misclassified using echocardiography alone. This is similar to a prospective study of patients with scleroderma [33]. In that study, as well as our current study, patients with unexplained dyspnea should be considered for right heart catheterization even if the echocardiogram is considered normal.

Radiologists often suggest pulmonary hypertension on the basis of increased pulmonary artery size [34]. However, this is the beginning, not the end, of the evaluation. In sarcoidosis, the hilum may also be enlarged by increased lymph nodes. The use of CT scan to estimate pulmonary hypertension has been successful in studies on non sarcoidosis diseases [20, 35]. The current study did not find any correlation between the estimated PA pressure by CT scan versus actual PA pressure.

We were interested in what non invasive measures could predict pulmonary hypertension. We performed a univariate analysis of several possible features associated with pulmonary hypertension. Prior studies had suggested that parenchymal lung disease (stage 2, 3, and 4) was associated with pulmonary hypertension [3, 4, 11]. In this study, six of eleven with stage 1 chest roentgenograms had PA pressures of > 40 mm, including two patients with normal LV function.

The relationship between lung volume and pulmonary artery pressure was studied. In the current study, the FVC was weakly correlated to the PA pressure. In a prior study, patients were more likely to have an abnormal RVEF if their total lung capacity was less than 60% [12]. Patients with echocardiographic criteria for pulmonary hypertension had a lower FVC [11]. For patients awaiting lung transplant and found to have pulmonary hypertension, the mean FVC was 46% [5]. However, there was no correlation between the FVC and the degree of pulmonary hypertension in patients awaiting lung transplant. These studies emphasize the potential role of pulmonary vasculopathy in sarcoidosis rather than just fibrotic lung disease as a cause of the pulmonary hypertension in sarcoidosis [14].

The fact that chest roentgenogram and vital capacity do not predict all cases of pulmonary hypertension is probably a reflection of the multiple mechanisms associated with pulmonary hypertension in sarcoidosis. The direct destruction of the lung parenchyma is seen with various fibrotic lung diseases, such as sarcoidosis and idiopathic pulmonary fibrosis. However, this is not the only mechanism. For patients awaiting lung transplant, the incidence of pulmonary hypertension is much higher for sarcoidosis versus idiopathic pulmonary fibrosis patients [6, 7, 9, 36]. Sarcoidosis can also lead to vascular changes. These changes are usually on the arterial side [2, 23, 37], but have been reported to be exclusively in the venous side [38]. Direct compression of the pulmonary arteries and subsequent pulmonary hypertension has been reported as well [16, 37]. We did not observe any patients in this study with pulmonary hypertension due to nodal constriction of the pulmonary artery outflow tract.

The two most likely causes of pulmonary hypertension, restrictive disease and vascular changes, could also lead to a reduction in the DLCO. Primary pulmonary hypertension itself has been shown to reduce the DLCO [39] and is predictive of increased mortality [40]. Studies in scleroderma have shown that a low DLCO is predictive of pulmonary hypertension [41, 42]. In a careful study of chronic infiltrative lung disease, Bonay *et al* found that pulmonary capillary blood volume was normal in patients with pulmonary hypertension [43]. The

authors found that all 24 patients with infiltrative lung disease had a reduced DLCO, but there was no significant difference between the 14 patients with pulmonary hypertension and the 10 with normal pressure. The study by Bonay *et al* included only six sarcoidosis patients. In the current study, we did find DLCO predictive of pulmonary hypertension. This goes along with the study by Sulica *et al*, who found a reduced DLCO with pulmonary hypertension in their sarcoidosis population [11].

The best treatment of pulmonary hypertension in sarcoidosis remains unclear. In some cases, treating the inflammatory reaction from the sarcoidosis is sufficient to control the disease [14, 44]. However, the patients in this study were all on therapy for their sarcoidosis and still had persistent symptoms. Half of these patients still had significant pulmonary hypertension.

It has been noted that the pulmonary hypertension in sarcoidosis may be responsive to pulmonary vasodilators [2, 22, 45]. In one study, short-term improvement was seen in seven of eight patients receiving inhaled nitrous oxide, four of six patients receiving epoprostenol, and two of five patients receiving calcium-channel blockers [22]. Most patients are not responsive to an acute vasodilation challenge [14]. In our series, only one of seven was responsive. In this study, we treated seven patients for at least four months with vasodilator therapy. In five of these seven patients, follow up catheterization studies were performed. Four patients had significant improvement in their pulmonary artery pressures and a fifth patient has had a significant clinical improvement. Six minute walk distance has been shown to be a good marker for efficacy of pulmonary vasodilator therapy [46]. However, we did not systematically collect this information on these patients.

The long term outcome of the pulmonary hypertension has been good for five of seven patients. However, these patients still required systemic therapy for their sarcoidosis. In two cases, we have added the anti-TNF therapy infliximab to control the lung disease. This drug has been shown to be useful in treating refractory sarcoidosis [47, 48]. It has been reported that anti-TNF therapy may lead to higher mortality in patients with left ventricular heart failure [49]. Both of our patients had normal left ventricular ejection fractions and have expe-

rienced no untoward cardiac effects from the infliximab after more than two years of therapy for both patients.

In conclusion, pulmonary hypertension is a significant problem in patients with sarcoidosis. In patients with persistent dyspnea despite systemic therapy for their disease, one should consider an echocardiogram to screen for pulmonary hypertension. However, direct measure of the pressure is the best method to determine the actual pressure. Catheterization will also detect left ventricular problems and will also be useful in assessing for response to vasodilator drugs, which have a role in the treatment of this disease.

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