Sarcoidosis*

The Value of Exercise Testing

Ann E. Medinger, MD, FCCP; Samir Khouri, MD; and Prashant K. Rohatgi, MD, FCCP

Study objectives: To evaluate exercise testing for the assessment of the extent of pulmonary disease in patients with sarcoidosis.

Design: Retrospective analysis of consecutive patients with sarcoidosis referred to the Pulmonary Physiology Laboratory between 1992 and 1997, who completed at least 6 min of progressive bicycle exercise. Resting and exercise pulmonary function measurements were compared to radiographic stage of disease.

Setting: Pulmonary Physiology Laboratory at Washington, DC, Veterans Affairs Medical Center.

Patients: Forty-eight outpatient veterans with biopsy specimen-proven sarcoidosis.

Results: Across all radiographic stages of sarcoidosis, total lung capacity, resting diffusing capacity, and exercise gas exchange measurements had a significant variance with radiographic stage. Across the early radiographic stage disease (stages 0 to 2), the change in alveolar-arterial oxygen pressure gradient between rest and exercise, normalized for oxygen uptake, was the most significant measurement in its variation with radiographic stage.

Conclusions: Changes in gas exchange with exercise may be the most sensitive physiologic measurements to assess the extent of disease in early radiographic stages of sarcoidosis.

(CHEST 2001; 120:93–101)

Key words: clinical exercise testing; extent of disease; pulmonary function testing; radiographic stage; sarcoidosis

Abbreviations: ANOVA = analysis of variance; AT = anaerobic threshold; BR = breathing reserve; COHb = carboxyhemoglobin; DLCO = diffusing capacity of the lung for carbon monoxide; ΔFEV1/FVC% = difference from predicted percentage FEV1/FVC; HRR = heart rate reserve; MDI = metered-dose inhaler; MVV = maximum voluntary ventilation; ΔP(A-a)O2 = change in alveolar-arterial oxygen pressure gradient between rest and exercise; ΔPO2 = change in oxygen tension; P(A-a)O2 = alveolar-arterial oxygen pressure gradient; SLT = symptom-limited exercise; TLC = total lung capacity; VE/VO2 AT = ventilatory equivalent for carbon dioxide at anaerobic threshold; ΔVO2 = change in oxygen consumption; VO2max = peak oxygen uptake; WR = work rate

Sarcoidosis is a condition causing a spectrum of clinical and histopathologic abnormalities, ranging from asymptomatic granulomatous infiltration of the lung with spontaneous remission to severe progressive pulmonary fibrosis and respiratory failure. Our understanding of the disease pathogenesis is limited. The etiology remains unknown. Clinical measurements to differentiate patients with newly diagnosed sarcoidosis whose conditions will resolve spontaneously from patients who will develop progressive inflammation, fibrosis, and respiratory failure are unreliable. It is desirable to initiate treatment before reversible granulomatous inflammation progresses to irreversible fibrosis, but the toxicity of drug therapy for sarcoidosis is significant. It is important to avoid unnecessary diagnostic and therapeutic risks while managing patients with this disease.

Sensitive and accurate diagnostic tools are needed to measure the extent of pulmonary parenchymal disease and to detect progressive functional impairment over the course of the disease. The plain chest radiograph is often used for surveillance because of its low cost and ready availability in the community. Pulmonary function measurements are also readily available and relatively inexpensive. In patients with early radiographic stages of sarcoidosis, resting pulmonary function studies have a better correlation with lung parenchymal histology than does the chest radiograph. Pulmonary parenchymal disease may be present without appearing on the chest radiograph. The diffusing capacity of the lung for carbon monoxide (DLCO) has been found to be the most sensitive of the resting physiologic measurements. Although resting lung function measurements have

*From the Pulmonary Physiology Laboratory, Veterans Affairs Medical Center; and Department of Medicine, George Washington University, Washington, DC.
Manuscript received March 22, 2000; revision accepted December 28, 2000.
Correspondence to: Ann E. Medinger MD, FCCP, 5605 Park St, Chevy Chase, MD 20815
Laboratory for clinical exercise testing between 1992 and 1997, sarcoidosis who were referred to the Pulmonary Physiology Laboratory at the Washington, DC, Veterans Affairs Medical Center for progressive SLE testing.

We studied veterans with sarcoidosis who were referred to the Pulmonary Physiology Laboratory for clinical exercise testing between 1992 and 1997, who successfully completed 6 min of a progressive SLE test and had resting pulmonary function, exercise testing, and posteroanterior and lateral chest radiographs performed within a 2-month period. Each pair of chest radiographs was examined and classified by two pulmonologists: stage 0, no radiographic abnormalities; stage 1, bilateral hilar adenopathy without parenchymal abnormalities; stage 2, bilateral hilar adenopathy with interstitial parenchymal infiltrates; stage 3, interstitial parenchymal infiltrates without hilar adenopathy; and stage 4, cicatricial changes.

Prior to exercise, each patient underwent the following resting pulmonary function measurements: air flow (FEV1/FVC), plethysmographic lung volume (total lung capacity [TLC]), single-breath DLCO, and maximum voluntary ventilation (MVV) (6200 Autobox; SensorMedics; Yorba Linda, CA). Measurements were made according to American Thoracic Society standards for equipment and patient performance. MVV was performed by coaching the individual to hyperventilate as vigorously as possible for 10 s, aiming for a minimum frequency of 80 breaths/min and measuring ventilatory output as liters per minute. Each individual then completed a minimum of 6 min of exercise, pedaling a bicycle ergometer (Ergoline 800; SensorMedics) with progressively increasing work rate (WR), pedaled at 60 revolutions per minute plus or minus 5 revolutions per minute. The WR increment for each ramped exercise test was individualized on the basis of each patient’s prettest activity level (range, 10 to 25 W/min), with the objective of achieving 6 to 12 min of progressive exercise before stopping. Serial exercise measurements included 12-lead ECG (Marquette Max I; Marquette Electronics; Milwaukee, WI), BP (Hewlett Packard 7000; Hewlett Packard; Andover, MA), WR (Ergoline 800; SensorMedics), tidal oxygen and carbon dioxide tensions, tidal airflow, and respiratory rate (2900C; SensorMedics).

Arterial blood gas levels were measured at rest, at peak performance, and at 2 min postexercise, from an indwelling radial arterial line; initial hemoglobin and carboxyhemoglobin (COHb) were recorded (analysis on Radiometer 520 Radiometer Medical; Brunsbjørn, Denmark). The change in oxygen consumption (ΔVO2) was calculated as the difference in oxygen uptake between peak exercise and resting measurements of oxygen consumption. ΔPO2 was calculated as the difference in arterial oxygen tension between peak exercise and resting measurements. To normalize ΔPO2 for work performed during exercise, we also calculated ΔPO2 as a ratio of the ΔVO2 (ΔPO2/ΔVO2). An alveolar-arterial oxygen pressure gradient (P[A-a]O2) was calculated for each arterial blood sample using measured respiratory quotients; they were expressed as the difference between peak exercise and resting measurements (ΔP[A-a]O2) and normalized for ΔVO2 achieved during exercise (ΔP[A-a]O2/ΔVO2).

Standard exercise calculations included VO2max, peak exercise expired minute ventilation, AT, and ventilatory equivalent for carbon dioxide at AT (Ve/VD0 EAT). AT was determined by V-slope method, and reported as percentage of predicted VO2max. Breathing reserve (BR) was calculated as the difference between measured resting MVV and the peak exercise ventilation, expressed as a percentage of MVV and normalized for the achieved oxygen uptake. Heart rate reserve (HRR) was calculated as the difference between peak and resting heart rate, normalized for achieved oxygen uptake. The age-, gender-, and weight-dependent normal predicted VO2max was derived from Hansen et al. and reported as percentage of predicted VO2max. Normal ranges for ΔP[A-a]O2/ΔVO2 and ΔPO2/ΔVO2 were not available to us. Predicted values for resting pulmonary function were derived as follows: TLC from Goldman and Becklake, FEV1/FVC from Crapo et al., and single-breath DLCO from Miller et al. Predicted resting lung volume reference values were adjusted for African American individuals. Measured single-breath DLCO was adjusted for abnormal hemoglobin and COHb concentra-
inflammatory drugs, cisapride, hydrochlorothiazide, colchicine, diphenylhydantoin, and guaifenesin. One patient (stage 2) was receiving propranolol, and one patient (stage 0) was receiving felodipine. Nine of the patients were receiving prednisone at the time of testing (one stage 0 patient with uveitis, six stage 2 patients, and two stage 4 patients). No patient was tested twice in this study; when two sets of data were available for one patient, the complete data set was entered. Six patients were unable to perform the breathing maneuver required for measuring DLco. Eleven patients had no peak exercise blood gas measurement because of technical problems with arterial access. Thirty patients had complete data sets (5 patients with stage 0, 4 patients with stage 1, 12 patients with stage 2, 2 patients with stage 3, and 7 patients with stage 4). Table 1 gives results of resting and exercise measurements by radiographic stage. There was no significant association between radiographic stage and \( \Delta \text{FEV1}/\text{FVC} \), \( \text{Vo2max} \), AT, HRR, BR, or \( \text{Ve}/\text{Vo2} \). A significant association was found between all radiographic stages and TLC, DLco, \( \Delta \text{P(A-a)O2} \), and \( \Delta \text{PO2} \). Across all radiographic stages of sarcoidosis, the most significant association was found between radiographic stage and the \( \Delta \text{PO2} \) with exercise (Table 1). For patients with radiographic stage 0 to 2 disease, the physiologic measurements most significantly associated with radiographic stage were the \( \Delta \text{P(A-a)O2} \) and \( \Delta \text{P(A-a)O2}/\text{Vo2} \) as dependent variable, stage as a factor, and percent of predicted single-breath DLco as covariate).

Exercise gas exchange measurements were also correlated with resting DLco in patients with complete data sets, using simple linear regression calculations. The statistical package employed was the Microsoft Excel 5.0 Analysis Toolpak program (Gray Matter International; Cambridge, MA) and SAS version 6.12 (SAS Institute; Cary, NC).

### Results

Forty-eight individuals completed a minimum of 6 min of exercise testing. The mean age of the subjects was 41 years, 17 were white, 24 were African American, 8 were smokers, and 4 of the smokers had initial COHb measurements > 3%. No patient had clinical evidence of heart disease. Seventeen patients were receiving treatment with one or more of the following medications: clonidine, \( H_2 \)-receptor antagonists, ipratropium via metered-dose inhaler (MDI), albuterol via MDI, triamcinolone via MDI, insulin, oral hypoglycemics, amitriptyline, haloperidol, angiotensin-converting enzyme inhibitors, nonsteroidal anti-inflammatory drugs, cisapride, hydrochlorothiazide, colchicine, diphenylhydantoin, and guaifenesin. One patient (stage 2) was receiving propranolol, and one patient (stage 0) was receiving felodipine. Nine of the patients were receiving prednisone at the time of testing (one stage 0 patient with uveitis, six stage 2 patients, and two stage 4 patients). No patient was tested twice in this study; when two sets of data were available for one patient, the complete data set was entered. Six patients were unable to perform the breathing maneuver required for measuring DLco. Eleven patients had no peak exercise blood gas measurement because of technical problems with arterial access. Thirty patients had complete data sets (5 patients with stage 0, 4 patients with stage 1, 12 patients with stage 2, 2 patients with stage 3, and 7 patients with stage 4). Table 1 gives results of resting and exercise measurements by radiographic stage. There was no significant association between radiographic stage and \( \Delta \text{FEV1}/\text{FVC} \), \( \text{Vo2max} \), AT, HRR, BR, or \( \text{Ve}/\text{Vo2} \). A significant association was found between all radiographic stages and TLC, DLco, \( \Delta \text{P(A-a)O2} \), and \( \Delta \text{PO2} \). Across all radiographic stages of sarcoidosis, the most significant association was found between radiographic stage and the \( \Delta \text{PO2} \) with exercise (Table 1). For patients with radiographic stage 0 to 2 disease, the physiologic measurements most significantly associated with radiographic stage were the \( \Delta \text{P(A-a)O2} \) and \( \Delta \text{P(A-a)O2}/\text{Vo2} \) as dependent variable, stage as a factor, and percent of predicted single-breath DLco as covariate).

Exercise gas exchange measurements were also correlated with resting DLco in patients with complete data sets, using simple linear regression calculations. The statistical package employed was the Microsoft Excel 5.0 Analysis Toolpak program (Gray Matter International; Cambridge, MA) and SAS version 6.12 (SAS Institute; Cary, NC).

### Table 1—Rest and Exercise Physiology in Sarcoidosis: Correlation With Radiographic Stage*

<table>
<thead>
<tr>
<th>Variables</th>
<th>Radiographic Stage</th>
<th>ANOVA for Stages 0 to 4</th>
<th>ANOVA for Stages 0 to 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 1 2 3 4</td>
<td>p Value</td>
<td>p Value</td>
</tr>
<tr>
<td>Patients, No.</td>
<td>8 8 18 2 12</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Age, yr</td>
<td>42 (9.9) 38 (9.1) 38 (9.7) 48 (7.8) 46 (8.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resting function</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TLC percent of predicted</td>
<td>86 (8.6) 87 (11.6) 75 (15.7) 71 (9.9) 69 (17.3)</td>
<td>0.036</td>
<td>NS</td>
</tr>
<tr>
<td>( \Delta \text{FEV1}/\text{FVC} %</td>
<td>6 (6.1) 4 (7.5) 6 (6.1) 6 (16.2) 12 (12.2)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>DLco percent of predicted</td>
<td>71 (9.8) 78 (15.7) 60 (15.2) 62 (10.6) 45 (12.6)</td>
<td>0.0002</td>
<td>0.039</td>
</tr>
<tr>
<td>( \text{P(A-a)O2} )</td>
<td>4.5 (6.5) 5.25 (4.2) 11.4 (8.2) 7.3 (8.1) 6.5 (6.2)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Exercise function</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( \text{Vo2max} ) percent of</td>
<td>76 (18.1) 80 (16.1) 73 (16.2) 92 (13.5) 66 (23.6)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>predicted</td>
<td>45 (7.0) 51 (15.0) 48 (15.1) 70 (4.2) 47 (11.6)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>AT percent of predicted ( \text{Vo2max} )</td>
<td>46 (9.8) 44 (10.7) 51 (23.1) 65 (18.4) 68 (39.9)</td>
<td>NS</td>
<td>0.034</td>
</tr>
<tr>
<td>HRR</td>
<td>42 (22.2) 32 (28.2) 24 (15.7) 38 (27.6) 24 (28.6)</td>
<td>NS</td>
<td>0.046</td>
</tr>
<tr>
<td>BR. percent of MVV</td>
<td>39 (18.8) 29 (14.0) 19 (16.3) 27 (24) 32 (48)</td>
<td>NS</td>
<td>0.033</td>
</tr>
<tr>
<td>BR. percent of MVV/( \text{Vo2max} )</td>
<td>30.25 (4.2) 26.2 (4.1) 30.6 (4.1) 31.5 (3.5) 31.3 (5.6)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>( \text{Ve}/\text{Vo2} ) AT</td>
<td>2.82 (6.2) 15.52 (6.0) 23.59 (9.8) 30.70 (5.5) 30.73 (17.1)</td>
<td>0.0016</td>
<td>0.0005</td>
</tr>
<tr>
<td>( \Delta \text{P(A-a)O2} )</td>
<td>1.37 (3.2) 2.30 (7.8) 17.54 (7.2) 19.85 (5.2) 23.59 (15.7)</td>
<td>0.00057</td>
<td>0.00000493</td>
</tr>
<tr>
<td>( \Delta \text{PO2} )</td>
<td>9.6 (10.2) 6.8 (7.3) 9.1 (10.5) 20.5 (9.2) 23.3 (17.9)</td>
<td>0.00016</td>
<td>0.023</td>
</tr>
<tr>
<td>( \Delta \text{PO2}/\text{Vo2} )</td>
<td>−5.74 (6.2) 3.46 (3.7) 2.27 (8.6) 13.4 (7.0) 19.2 (18.2)</td>
<td>0.0014</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Data are presented as mean ± SD; NS = not significant.
\( \Delta V_{O_2} \) (Table 1). In this group with less extensive disease by chest radiographic criteria, TLC did not vary significantly with radiographic stage and the DLCO had a weaker association than it had across all radiographic stages. Excluding from analysis the patients with COHb evidence of antecedent smoking did not significantly alter these findings, nor did elimination of the patient receiving calcium channel-blocking medication. The 30 individuals who had complete data sets of both resting and exercise measurements had the same highly significant association of \( \Delta P(A-a)O_2/\Delta V_{O_2} \) with radiographic stage as did the whole group (\( p < 0.000331 \) for stages 0 to 2; \( p < 0.000067 \) for stages 0 to 4). For this group of 30 patients, the \( R^2 \) coefficient of determination for single-breath DLCO and \( \Delta P(O_2) \) was 0.52 for all stages and 0.33 for those with stage 0 to 2 disease (Fig 1). The \( R^2 \) coefficient for single-breath DLCO and \( \Delta P(A-a)O_2 \) was 0.58 for all radiographic stages and 0.47 for stages 0 to 2 (Fig 2). The best correlation of exercise measurements with DLCO was \( \Delta P(A-a)O_2/\Delta V_{O_2} \), where \( R^2 \) was 0.78 for all radiographic stages and 0.66 for stages 0 to 2 (Fig 3). Further analysis of the 30 patients with matched data across all stages, considering \( \Delta P(A-a)O_2/\Delta V_{O_2} \) as dependent variable, radiographic stage as a factor and percentage of predicted single-breath DLCO as covariate also gave a statistically significant model (\( p = 0.0001 \)). Both variables together accounted for 71.7% of the variation in \( \Delta P(A-a)O_2/\Delta V_{O_2} \). There was no improvement in prediction of exercise gas exchange gained by factoring in the radiographic stage to the percent of DLCO.

**DISCUSSION**

We do not have a true noninvasive "gold standard" for measuring the extent of disease in patients with pulmonary sarcoidosis. The American Thoracic Society, European Thoracic Society, and the World Association of Sarcoidosis and other Granulomatous Disorders have issued a joint statement\(^\text{19}\) of recommendations for following patients with pulmonary sarcoidosis. They recommend that system review, physical examination, chest radiograph, and spirometry be performed regularly. These will suffice for most patients; however, management of some patients will require lung CT scans and further physiologic measurements, including single-breath DLCO and exercise testing.\(^\text{19}\) No one measurement is adequate to assess disease extent and activity. Although the chest radiograph is known to be an insensitive marker of disease extent, activity, and progression in sarcoidosis, it has been the least expensive, least invasive, and most accessible histologic correlate we have had. In this study, we have used the chest radiograph as the indicator of extent of sarcoidosis in the lung.

At high levels of exercise performance, the normal individual experiences a fall in mixed venous oxygen tension, decrease in pulmonary capillary transit time, and rise in \( P(A-a)O_2 \). However, overall ventilation/
perfusion matching improves so that both the physiologic shunt fraction and dead space to tidal volume ratio improve. This is achieved through recruitment of normally closed pulmonary vascular channels, increasing pulmonary capillary surface area, increasing the rate of gas exchange commensurate with increased blood flow through the lung, and increased ventilation. Hence, while oxygen consumption rises dramatically during exercise in normal individuals, arterial oxygen tension remains relatively unchanged.

Arterial blood gas levels are a good measure of gas exchange across the lung, and a normal P(A-a)O₂ reflects normal ventilation/perfusion function of the lung. Abnormalities in P(A-a)O₂ are specific for lung disease or less commonly right-to-left cardiovascular shunt. The patient with interstitial lung disease has...
fewer pulmonary vascular channels and hence a smaller reserve pulmonary vascular bed is available for recruitment to increase the lung surface area for gas exchange during exercise. Hence, with progressively increasing workload and increased peripheral oxygen uptake, both mixed venous oxygen tension and arterial oxygen tension fall. The degree of fall in arterial oxygen tension depends on both the extent of interstitial lung disease and the amount of work performed. Patients with interstitial lung disease may be found to have a normal peak exercise arterial oxygen tension when they have minimal disease or when they perform a low level of exercise during the test. Studies in patients with sarcoidosis, which have shown a poor correlation of exercise measurements with other measures of disease extent and progression, have tested the patients at low levels of exercise. Because peak WR with exercise testing is a subjective end point that can be influenced by the coach-technician and the patient’s own willpower, all measurements obtained at peak WR have a subjective element. This may confound their correlation with extent of pulmonary disease. Normalizing peak exercise cardiac and gas exchange measurements for achieved oxygen uptake helps remove this subjective bias.

In normal individuals, the $\Delta VO_2$ with exercise has a constant linear relationship to total work performed ($VO_2$/WR). This makes change in oxygen uptake between rest and exercise ($\Delta VO_2$) generally a good measurement of the level of exercise performed. However, both VO$_2$max and $\Delta VO_2$ with exercise are determined by multiple factors: gas exchange across the lung, oxygen content of blood, oxygen delivery to tissues, and oxygen uptake in the tissues, in addition to the subjective coaching and patient’s willingness to work hard during the test. The peak WR achieved is influenced by body weight in addition to the above-named factors. Impairment in oxygen flow can alter the slope of VO$_2$/WR and affect our ability to normalize the exercise blood gas measurements by using delta VO$_2$. Thus, when significant heart, peripheral vascular, or metabolic mus-

![Figure 4](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21964/ on 06/25/2017)

**Figure 4.** For each radiographic stage of sarcoidosis 0 to 2, mean resting single-breath DLCO measurements, given as percentage of the predicted value, are represented by closed diamonds. Ninety-five percent confidence intervals for each measurement at each radiographic stage are represented by vertical lines. See text for definition of radiographic stages. The number of patients with measurements at each stage is given in parentheses.
When a disease is present, use of the $\Delta Vo_2$ to normalize the $\Delta P(A-a)O_2/DVo_2$ for work achieved during testing may decrease its sensitivity and specificity for measuring extent of lung disease.

In this study, radiographic and physiologic measurements and interpretations were performed independent of each other. To achieve consistency of data analysis, chest images and physiologic measurements were interpreted by one individual or pair of individuals. Analysis of the results shows a significant association of exercise gas exchange with radiographic stage in patients with sarcoidosis who can perform at least 6 min of progressive exercise. The study has the limitations of any retrospective analysis, including the heterogeneity of medications and the antecedent cigarette smoking used by patients. Some substances taken prior to exercise testing can alter exercise test measurements and reduce their validity (such as calcium channel blockers and cigarette smoking). When we eliminated the patients with these factors from the analysis, we found no change in the significance of the associations between physiologic and radiographic measurements.

Although clinical evidence of myocardial involvement is only present in about 5% of patients with sarcoidosis, unsuspected cardiac involvement may be found in as many as 10 to 15% of patients with sarcoidosis. Sarcoidosis patients with chronic respiratory failure commonly develop cor pulmonale. Patients with radiographic stage 0 to 2 disease are less likely than stage 3 to 4 patients to have cardiac impairment from cor pulmonale. Hence, exercise measurements may be a more specific reflection of extent of pulmonary disease in the radiographic stage 0 to 2 patients with sarcoidosis.

In this study, the correlation of exercise gas exchange with radiographic stage was less significant when stage 3 to 4 patients were included in the analysis. Although we had no antecedent clinical evidence of heart disease in any of our patients, 5 of...
the 48 patients had exercise evidence of an oxygen flow problem (3 stage 2 patients; 2 stage 4 patients). These individuals were younger than average for the whole group, and showed good effort during the test; they achieved a peak heart rate within 15 beats of the maximum predicted or had a very low BR at peak performance with a peak \( \text{Vo}_2 < 84\% \) of predicted. All reached AT at an oxygen uptake < 40% of predicted \( \text{Vo}_2\text{max} \). All had a low oxygen pulse, and three patients had a low slope of \( \text{Vo}_2/\text{WR} \). No patients developed arrhythmias or ischemic ECG changes during exercise. One radiographic stage 4 patient stopped the exercise test because of leg pain. In the other stage 4 patient, \( \text{Po}_2 \) fell from 97 to 51 mm Hg at peak exercise, suggesting that cor pulmonale was likely to be present. No significant change in the peak exercise \( \text{Po}_2 \) and no leg pain was noted in the stage 2 patients with exercise evidence of oxygen flow problems. An echocardiogram was normal in one of the stage 2 patients, but no other cardiac imaging was available to further evaluate right heart function or identify myocardial sarcoidosis. When we excluded from the analysis the patients with exercise evidence of an oxygen flow problem, the significance of the association between radiographic stage and physiologic measurements did not change.

Other authors have emphasized the value of the single-breath DLCO to measure extent of disease in sarcoidosis. Our measurements confirm the value of single-breath DLCO as a measurement of resting pulmonary function that varies significantly with radiographic stage in sarcoidosis. However, in our patients with radiographic stage 0 to 2 sarcoidosis, we found the stage to be more significantly associated with exercise gas exchange measurements than with single-breath DLCO (\( p < 0.0005 \) for \( \Delta P[A-a]O_2 \) vs \( p < 0.039 \) for DLCO). The exercise gas exchange measurement was even more discriminating among radiographic stages 0 to 2 when normalized for work performed during testing (\( p < 0.0000493 \) for \( \Delta P[A-a]O_2/\Delta \text{Vo}_2 \)). Figures 4, 5 show the relative changes in percentage of predicted single-breath DLCO and \( \Delta P[A-a]O_2/\Delta \text{Vo}_2 \) across radiographic stages 0 to 2. The 95% confidence intervals of the percentage of predicted single-breath DLCO overlap for all radiographic stages. This suggests that the percentage of predicted single-breath DLCO is not able to separate patients with and without radiographic evidence of pulmonary parenchymal disease (Fig 4). The 95% confidence intervals for \( \Delta P[A-a]O_2/\Delta \text{Vo}_2 \) distinguish patients with radiographic evidence of pulmonary parenchymal disease (stage 2) from those without (stages 0 to 1; Fig 5). The clinician is most concerned to have a sensitive test for quantifying extent of disease in asymptomatic patients with sarcoidosis who have radiographic stage 0 to 2, so that progression can be detected on sequential measurements. One seeks to withhold treatment from those who are remitting spontaneously but initiate with conviction in those who are progressing. \( \Delta P[A-a]O_2/\Delta \text{Vo}_2 \) may be more sensitive than single-breath DLCO for monitoring disease extent and progression in early radiographic stages of sarcoidosis.

Further assessment of \( \Delta P[A-a]O_2/\Delta \text{Vo}_2 \) is needed. Normal ranges and reproducibility need to be established. These may enable us to use this measurement to detect and quantify lung impairment with greater sensitivity in patients with early radiographic stages of sarcoidosis. Sequential physiologic measurements are most useful in the management of patients with sarcoidosis, and additional study is needed to follow changes in \( \Delta P[A-a]O_2/\Delta \text{Vo}_2 \) over the course of the disease. We need to correlate changes in this measurement with other longitudinal markers of disease extent and activity, with and without treatment. We have found the \( \Delta P[A-a]O_2/\Delta \text{Vo}_2 \) to have a promising correlation with radiographic stage. Further investigation is needed to determine whether we can use it as a reliable marker of the extent of disease in patients with pulmonary sarcoidosis.

ACKNOWLEDGMENT: We are grateful to Heather Young for her help with statistical analysis of the data.

REFERENCES