Fourteen patients with restrictive pulmonary disease due to sarcoidosis were studied with radionuclide angiocardiography in order to define the incidence and significance of right and left ventricular dysfunction. Right and left ventricular ejection fractions were determined by an equilibrium technique at both rest and exercise. All patients had a normal left ventricular ejection fraction with rest and 12 of 14 had the normal 5 percent or greater rise in ejection fraction with exercise. The right ventricular ejection fraction was abnormal in three patients at rest and only two patients had a 5 percent or greater rise in ejection fraction with exercise. A correlation was found between the right ventricular ejection fraction with exercise and the total lung capacity (r = 0.73, p < 0.01) and the arterial PaO2 during exercise (r = 0.74, p < 0.01).

Understanding the pathogenesis and natural history of cardiovascular dysfunction in restrictive lung disease has been hindered by the lack of a noninvasive quantitative technique for assessing right and left ventricular function. Recent studies using radionuclide angiocardiography in obstructive lung disease have added insight into the ventricular performance in this disease.1-4 There have been few studies using this technique in the evaluation of cardiac function in restrictive lung disease.

We chose to study patients with sarcoidosis. Though sarcoidosis is known to involve the heart, the incidence of clinically significant cardiac sarcoidosis is presumed to be low.5-7 We studied patients having sarcoidosis with resultant restrictive pulmonary disease in order to define the incidence and significance of isometrically measured right and left ventricular dysfunction with various levels of lung involvement.

**Methods**

**Patient Population**

The study population consisted of 14 patients with biopsy-proven sarcoidosis and pulmonary involvement. The patients were recruited from the outpatient pulmonary clinic at the University of Cincinnati. Biopsy specimens were taken from the lung or hilar region and revealed noncaseating granuloma in all cases. Cultures for tuberculosis and fungal disease were negative. Approximately 50 percent of patients eligible for study agreed to participate. There were six black men and eight black women with a mean age of 39 ± 9.2 (X ± SD, range 24 to 59). None had evidence of obstructive airway disease as determined by pulmonary function tests. Seven of the patients were receiving diuretics at the time of the study for salt and fluid retention secondary to steroid therapy. All patients had been treated with steroids for their sarcoidosis, and nine were receiving prednisone at the time of the exercise study. We excluded from study any patient with longstanding hypertension or diabetes. Most patients suffered from mild hypertension while receiving steroid therapy for their sarcoidosis, but all were normotensive at the time of study. Patients with other cardiac disease were excluded to avoid other possible causes of myocardial disease. No patient had electrocardiographic evidence of right or left ventricular hypertrophy or of myocardial necrosis.

A group of six, healthy, untrained subjects served as controls. Mean age of this group was 31 ± 3.1 years, and five of the six subjects were men.

**Study Protocol**

Each subject gave informed written consent at the time of exercise testing.

All patients underwent a progressive supine bicycle stress test. Control and sarcoid patients were exercised to limiting fatigue and/or dyspnea. The control patients achieved a double product (heart rate × systolic blood pressure) of 33,000 ± 4,800, while the sarcoid patients achieved a double product of 24,000 ± 4,900. In ten of the sarcoid patients, an indwelling Pott's-Cournand needle was used to obtain arterial blood gas levels at rest and at maximal exercise.

Electrocardiographic leads 1, 2, and 3 were used to monitor cardiac rate and rhythm during exercise and for gating purposes. In ten sarcoid patients and all six control patients, a gated right ventricular first-pass radionuclide study containing five to ten cardiac cycles was performed at maximal exercise in the 30 degree right anterior oblique projection. Twenty to 25 mCi of techne-
tium-99m pertechnetate was given as a bolus injection through a free
flowing intravenous catheter. The bolus was flushed by 10 to 15 ml of
normal saline solution. The scintigraphic data were acquired using a
portable gamma camera (Ohio Nuclear Series 120) equipped with an
all-purpose technetium collimator and interfaced to a dedicated
minicomputer system.

All patients received 5 to 10 mg of stannous pyrophosphate
intravenously 20 minutes before technetium-99m injection, and rest
and exercise equilibrium radionucleide ventriculograms were subse-
quently obtained by means of the in vivo red blood cell-labeling
 technique. These were also obtained on the four sarcoid patients in
whom an adequate gated first pass study could not be obtained.
Equilibrium studies were obtained in a left anterior oblique position
selected to achieve maximal separation of the left and right ventri-
cles. Ten degrees of caudal angulation was added to minimize overlap
of the left ventricle and left atrium. Two minutes of scintigraphic data
were obtained at rest during symptom-limited exercise with the
exercise work load in terms of heart rate and systolic blood pressure
equalling the level achieved during the gated first pass study. The left
ventricular time-activity (volume) curve was generated with the aid
of a semiautomatic computer algorithm. To avoid observer bias,
determinations of right ventricular ejection fraction were made in
random order with the operator (MG) blinded with respect to the
patient's name and clinical status. The gated first pass right
ventricular ejection fraction was calculated by a previously described
technique. Briefly, the end-systolic frame was identified by
drawing a region of interest around the right ventricle on the end-
diastolic gated first pass image using a joystick; a time-activity curve
was then generated, and end-systole was determined as the
frame with the minimum number of counts in the region of the right
ventricle. The right ventricular diastolic and systolic contours were
outlined with a joystick, taking care not to include activity within
the right atrium or pulmonary artery. A background region of interest
was selected adjacent to the right ventricle. Right ventricular
ejection fraction equaled the background corrected right ventricular
end-diastolic counts minus the background corrected end-systolic
counts, divided by the background corrected end-diastolic counts.

The equilibrium right ventricular ejection fraction was calculated
by a modification of the method described by Slutsky et al. The
R-R interval was divided into 16 frames. The first frame was taken as
end-diastole, and an outline was drawn around the right ventricle
using a joystick. The right ventricular end-systolic frame was taken as
the same frame as the left ventricular end-systolic frame as deter-
mined by the semi-automated left ventricular ejection fraction
determination. The right ventricular contour was outlined using the
cinematic display to guide localization of valve planes. A background
region adjacent to the right ventricular region was determined, and
the right ventricular ejection fraction determined by the above
formula.

Intraobserver variation was calculated for the rest and exercise
equilibrium right ventricular ejection fraction by having the same
observer redraw right ventricular regions of interest on two occasions
six months apart in seven sarcoid patients. The initial mean resting
right ventricular ejection fraction was 0.447 percent; and the repeat
mean resting right ventricular ejection fraction was 0.456 percent
with a standard deviation of intraobserver measurement error equal
to 0.110 percent. The initial mean exercise right ventricular ejection
fraction was 0.329 percent with a repeat measurement of 0.381
percent and a standard deviation of intraobserver measurement
error of 0.165 percent.

Arterial blood samples were drawn into 1 ml heparinized
 syringes both at rest and at peak exercise. Samples were run
immediately on a Corning automated blood gas machine, and values
for arterial pH, PaO2 and PCO2 were determined.

Pulmonary function tests were performed on a 9.0 L Collins
spirometer. Predicted normal values for lung volumes and diffusion
of carbon monoxide using the single breath technique were taken

\[ \text{Fraction} = \frac{\text{Background corrected end-diastolic counts} - \text{Background corrected end-systolic counts}}{\text{Background corrected end-diastolic counts}} \]

\[ \text{Intraobserver variation} = \frac{\text{Standard deviation of intraobserver measurement error}}{\text{Initial mean}} \]

**Statistical Methods**

All data were compared using the Student's paired t-test. Correlations were performed using the least squares method. A p
value of less than 0.05 was considered significant. All values are
expressed as the mean ± 1 standard deviation.

**RESULTS**

In 16 cases (ten sarcoid patients and six controls), the
gated first pass and equilibrium right ventricular
ejection fractions were both performed at the same
level of exercise as assessed by work load and double
product. Figure 1 shows the relationship between
these two determinations. There was a significant
correlation of the right ventricular ejection fraction
measurements by the two methods \((r = 0.81, p<0.01)\).

For purposes of this study, we compared three
groups as follows: the control group with no pulmonary
disease; those patients with mild restrictive lung
disease related to sarcoidosis (total lung capacity [TLC]
>60 percent of predicted); and those with severe
restrictive lung disease related to sarcoidosis (TLC<60
percent). Table 1 shows the total lung capacity (TLC),
the pulmonary diffusion of carbon monoxide (DCO),
and the rest and exercise right ventricular ejection
fraction for the two patient groups. In ten patients, rest
and exercise arterial blood gas levels were obtained
and are also shown.

Figure 2 illustrates the results of right ventricular
ejection fraction at rest as determined by the equilib-
The mean resting right ventricular ejection fraction for the control group was .45±.070 (X±SD). The mild (RVEF = .57±.095) and severe (RVEF = .43±.168) groups were not significantly different from the controls. Two patients in the severe group had right ventricular ejection fractions that were two standard deviations below the control group.

Exercise equilibrium right ventricular ejection fractions for the three groups are also shown in Figure 2. Others have shown that a 5 percent or greater rise in the ejection fraction is the normal response to exercise for either ventricle. A normal response to exercise was observed in the control group for both the left and right ventricle. In the control group, the mean right ventricular ejection fraction rose to .65±.145 (p<0.01 compared to rest). In the severe group, the ejection fraction fell in all patients to a mean value of .25±.154 (p<0.01 compared to rest). In the mild group, five of the seven patients had a fall in right ventricular ejection fraction, but overall, there was an insignificant fall in the mean from .57±.095 to .54±.077. The ejection fraction calculated during exercise, determined by the equilibrium technique, showed no significant difference between the control and mild group. The change in right ventricular ejection fraction in the severe group was significantly different from both the control and mild group (p<0.01).

Similar results were found in the six control and ten sarcoid patients in whom the right ventricular ejection fraction at peak exercise was calculated using the first pass technique. The mean right ventricular ejection fraction for the control group at peak exercise (.60±.092) was similar to the group with a mild restrictive defect (.59±.106). The severe group with a gated first pass right ventricular ejection fraction of .31±.054 showed significantly greater exercise-in-
duced dysfunction than either the control or the mildly impaired group (p<0.01).

We compared the total lung capacity (TLC, percent of predicted) to the right ventricular ejection fraction at exercise determined by the equilibrium technique. There is a linear correlation (r = 0.73, p<0.01) relating decreasing TLC and decreasing right ventricular ejection fraction during exercise. There was a smaller number of patients who had first pass studies; however, there remained a significant correlation of TLC and right ventricular ejection fraction by the first pass technique (r = 0.50, p<0.01). We found a significant correlation between the Dco percent of predicted and the exercise right ventricular ejection fraction calculated by the equilibrium (r = 0.58, p<0.05) and the first pass method (r = 0.56, p<0.01). No relationship was found between the right ventricular ejection fraction at rest and any pulmonary function test.

Arterial blood gas levels were obtained on ten patients (five from the mild group and five from the severe group) at rest and with submaximal exercise. Resting hypoxemia (Po2<70 mm Hg) was seen in two patients in the severe group, but there was no significant difference in the mean level of Po2 between the groups. There was a fall in Po2 with exercise in nine of ten patients (one mild patient had a rise). There was no significant difference between the mild group (Po2 = -8±8.5 mm Hg) and the severe group (Po2 = -14±11.0 mm Hg). There was a significant relationship between the exercise Po2 and the equilibrium RVEF (r = 0.74, p<0.01). There was no correlation between the degree of fall in the arterial Po2 and fall in the RVEF.

The left ventricular ejection fraction (LVEF) was calculated from the equilibrium studies. Figure 3 shows the rest and exercise values of the control, mildly involved, and severely involved group. The mean left ventricular ejection fraction of the sarcoid patients rose from .67 to .79. There were two sarcoid patients with severe disease who had less than a 5 percent rise of the LVEF with exercise. There was no evidence of abnormal left ventricular regional wall motion in any of the patients studied.

**DISCUSSION**

Standards for determining the left ventricular ejection fraction were developed using angiographic studies of the left ventricle. Assuming the ventricle is an ellipse, linear dimensions can be converted to volume using the appropriate mathematical formulae. The right ventricle is an irregularly shaped organ and cannot be accurately measured in this fashion. Radionuclide techniques avoid the issue of anatomic configuration and offer a method for more precise measurements of right ventricular function than were previously available.

We studied the right ventricle in our patients with two methods. The first pass study has been considered to be the most reproducible radionuclide technique for estimating right ventricular performance. The major limitation of the gated first-pass technique is the inability to perform serial studies of both ventricles in a short period of time using a peripheral injection. The gated first-pass technique requires accurate measurements of a compact bolus over only a few beats of the cardiac cycle. In our series, four of 20 patients had technically inadequate gated first-pass studies of the right ventricle due to a poor bolus injection. We chose to use the first pass technique exclusively during the exercise study, since we felt this would be the most likely time to detect right ventricular abnormalities.

The recently introduced equilibrium ejection fraction technique gives the opportunity for serial measurements of left and right heart function. Despite a less satisfactory separation of the right ventricle from surrounding structures using the equilibrium technique, we were able to show a significant correlation between the two methods, as shown in Figure 1. A similar assessment has been noted by others. The correlation tended to worsen when the results of both tests were substantially abnormal (RVEF<40 percent).
In all tests where we looked at only the exercise RVEF, there was no statistically significant difference in the results when we used either the first-pass or equilibrium technique. The normal response of either ventricle to exercise is an increase in ejection fraction of at least 5 percent. In our control group, the right ventricular ejection fraction rose with exercise as we expected, while a fall in right ventricular ejection fraction was seen in 12 of the 14 patients with sarcoidosis. Though the control group exercised to a higher double product (heart rate × blood pressure) than our sarcoid patients, the sarcoid patients accomplished a moderate level of stress as shown by a mean double product of nearly 25,000. In both control and sarcoid patients, the left ventricular ejection fraction was normal at rest and increased as expected with exercise in all but two patients.

The exercise tests were performed in the supine position. This ensured that the angulation of the single crystal camera in relation to the heart was constant during serial studies and helped to minimize motion artifact. Thus, the comparison between rest and exercise was more reproducible. Radionuclide angiography of the right ventricle has been validated both for the upright exercise position, and the supine position. Upright exercise generally produced higher heart rates but a lower blood pressure response compared to the supine exercise position.

Ejection fraction can be altered by any of three factors: (1) altered preload, (2) myocardial dysfunction, or (3) altered afterload. Our patients were clinically stable. Though some patients were receiving diuretics, no postural changes in systemic blood pressure measurements were noted. There was no evidence for volume depletion in our patients, and we believe that preload was normal. Performing the tests in the supine position minimized volume changes between rest and exercise.

Though other causes of myocardial dysfunction have to be considered, we specifically excluded any patient with known ischemic heart disease or valvular disease. We also excluded those patients with a long history (>5 years) of hypertension or diabetes mellitus to avoid silent ischemic heart disease. The normal rest and exercise left ventricular ejection fraction in most of our subjects argues against any significant ischemic heart disease.

The myocardium may be infiltrated with granuloma in as many as 30 percent of unselected patients with sarcoidosis, though in less than 10 percent it is massive enough to be seen grossly at autopsy. Gross cardiac involvement is highly associated with sudden death, but even microscopic involvement is associated with a higher than normal incidence of arrhythmias and conduction defects. Sarcoid granulomata may be seen diffusely but are more frequent in the left than the right ventricle. If sarcoidosis has involved the heart directly, we would have expected to have detected left ventricular abnormalities in the majority of the patients. However, only two of 14 patients had any evidence of left ventricular dysfunction, while 12 of the 14 had abnormal right ventricular function. Since our patients had a disproportionate involvement of the right ventricle and none had conduction defects, we believe that diffuse myocardial damage secondary to granulomatous infiltration is an unlikely explanation for our findings. The possibility of hypoxemia causing selective right ventricular dysfunction cannot be ruled out; however, at least two patients had abnormal right ventricular ejection fractions with exercise with no evidence of hypoxemia.

The decreased right ventricular ejection fraction is probably related to an increased afterload. Increased afterload is due to increased pulmonary vascular resistance. Others have documented an inverse relationship between right ventricular ejection fraction and mean pulmonary artery pressure in a variety of clinical conditions. It is well known that end-stage sarcoidosis may be associated with massive pulmonary fibrosis and right sided heart failure.

The mechanism for pulmonary hypertension in sarcoidosis has been a matter of debate. Hypoxemia may cause active vasoconstriction and pulmonary hypertension. It is well known that in interstitial lung disease, hypoxemia is often found with exercise. In our study, nine of ten patients studied had a fall in Po2 with exercise. We also found a correlation between arterial oxygenation with exercise and the right ventricular ejection fraction with exercise. However, hypoxemia alone cannot explain all of our findings. Though there was a clear separation between the ejection fraction of the mild and severe group, we found no significant difference between the oxygen saturation of arterial blood in our mild or severe group. We also had two patients with a right ventricular ejection fraction of less than 30 who had an arterial Po2 with exercise of 60 mm Hg or greater. A lack of correlation between hypoxemia and pulmonary artery pressure in interstitial lung disease has been reported using direct measurements of the pulmonary artery pressure.

Severe restriction of the pulmonary capillary bed may also cause pulmonary hypertension. In sarcoidosis, the inflammatory process may impinge upon and finally obliterate pulmonary capillaries. Our finding of increased right ventricular dysfunction with decreasing total lung capacity or Dco suggests that this may be an important mechanism in the etiology of pulmonary hypertension in this disease. The normal findings at rest imply that the mean pulmonary artery pressure is not greatly elevated at rest. During exercise, as flow increases, the restricted vascular bed is
not capable of dilating to accept the increased flow and pulmonary artery pressures rise. Thus, exercise brings out an abnormality which was not apparent at rest. In a hemodynamic study of patients with interstitial lung disease, Enson et al. clearly demonstrated an increase in pulmonary vascular resistance and decrease in pulmonary blood volume even in mildly affected patients, some of whom had sarcoidosis. The significance of an abnormal response of the right ventricle to exercise is not yet known in interstitial lung disease. In patients with chronic pulmonary disease, Matthay et al. reported that a fall in right ventricular ejection fraction was seen in patients who had clinical evidence of right sided heart failure or later developed it, though not all patients with an abnormal right ventricular ejection fraction developed cor pulmonale. We studied only one patient with clinical evidence of right-sided heart failure, and she was in the severe group with a rest right ventricular ejection fraction of .14 which fell with exercise to .09. Since chronic obstructive lung disease is a progressive disease, the prognosis of an abnormal right ventricular ejection fraction may be different in sarcoidosis, especially in the patient who appears to have no further pulmonary inflammation.

In conclusion, right ventricular dysfunction was documented by radionuclide angiocardiography in patients with moderate-to-severe sarcoidosis. This dysfunction did not appear to be due to myocardial dysfunction or volume depletion. The right ventricular dysfunction appeared to be due to pulmonary hypertension. A linear relationship existed between decreasing lung volumes and an increasing right ventricular dysfunction. Right ventricular dysfunction at exercise occurred in all patients with a total lung capacity of less than 60 percent of predicted.

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