CHRONIC AIRWAYS OBSTRUCTION IN PULMONARY SARCOIDOSIS: ITS POOR RESPONSE TO BRONCHODILATORS

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Emphysema, chronic bronchitis, asthma, and cystic fibrosis are often cited as examples of chronic airways obstruction, while sarcoidosis is typically restrictive. Approximately 15 percent of sarcoidosis patients, however, have airways obstruction clinically characterized by wheezing with granulomatous involvement of airways. Since the majority have Stage IV disease by chest radiograph, their lungs usually have honey-combining with pulmonary fibrosis, adhesions, cavities, and mediastinal distortion.

Patients had a mixed ventilatory defect, but obstruction of large airways was present as shown by decreased specific airways conductances. Small airways obstruction was also present as shown by low instantaneous flows at the terminal portion of the maximum expiratory flow-volume curve and diminished helium response of this curve. The closing volume, however, was not very sensitive. Radioactive xenon washout from ventilation lung scans and N2 washout from the lungs were prolonged in patients with worse disease.

The authors conclude that the obstructive type of physiologic pattern is more frequent than recognized in sarcoidosis, which like that of cystic fibrosis has some restrictive element and is characterized by poor reversibility to bronchodilators. A trial period of beclomethasone dipropionate aerosol was not helpful in two patients. Relief of this distressing airways obstruction continues to pose a challenging problem in management.

Although pulmonary sarcoidosis is characteristically described as causing a restrictive type of ventilatory defect, until recently, very little attention has been given to airways obstruction which is seen in as many as 15 percent of patients. The spirographic pattern of this obstruction is actually a combination of obstruction and restriction which co-exist, being more common in chronic radiologic stage IV disease. Pathologically, the obstructive component is caused by enlarged lymph nodes impinging on large central airways, traction emphysema caused by contracting scar tissue, granulomata in walls of larger central airways and small peripheral airways distorting them, and secretions within. The symptoms these patients manifest are apt to be more distressing than those found in pure restriction, and relief of obstruction is an unsolved problem in management.

The purpose of this paper is to better characterize this type of patient physiologically, to determine the site(s) of obstruction, to correlate xenon lung scans with nitrogen washout, and to

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assess reversibility to bronchodilators and steroid aerosols.

SUBJECTS

Fifteen patients with chronic pulmonary sarcoidosis, intractible exertional dyspnea, and wheezing on exertion, in damp weather, or at night were selected on the basis of screening pulmonary function tests confirming airways obstruction by percent $FEV_1/FVC<72$ and percent $FEV_3/FVC<92$. Patients consisted of nine women and six men, three of whom were cigarette smokers. Their mean age was 40 years, SD ±8.6. They met diagnostic clinical criteria of sarcoidosis, in that they had a compatible clinical picture and an organ biopsy from one or more sites showing noncaseating granulomatous inflammation. Ten of 15 patients had bronchial and transbronchial lung biopsies.* Granulomas were found in larger central airways in five, and in transbronchial lung biopsy specimens in ten. In four patients, Kveim-Siltzbach tests were positive and patients who entered the study in recent years had uptake of ^{67}Gallium Citrate in tissues and elevated levels of serum angiotensin convertase, indicating disease activity.

Routine pulmonary function tests of the patients are given in mean percent predicted values ± 1 SD. All patients had an increase in the alveolar nitrogen phase III plateau on the single breath oxygen test ($\Delta N_2/L$) denoting non-uniform alveolar ventilation (327 ± 123.9 percent predicted), a decreased slow vital capacity (65.7 ± 19.6 percent predicted), and normal functional residual capacity (FRC) which shows the net effect between restriction and obstruction (86.5 ± 29.6 percent predicted). The lung clearance index for N_2 was increased (158.8 ± 43.3 percent predicted), however the overall total lung capacity (TLC) was low (73.8 ± 18.5 percent predicted). As expected, gas transfer was abnormal with low carbon monoxide diffusing capacity (DL_{CO}) (55.3 ± 13.9 percent predicted), and "lung permeability," Krogh's K was slightly decreased (70.9 ± 19.1 percent predicted). Specific lung compliance (CL_{SP}) was unchanged when compared with that of controls (0.05 ± 0.05 vs 0.06 ± 0.02 cm H_2O^{-1}), not a significant difference.

Seven healthy control subjects, four men and three women, were studied for comparison. Their combined mean ages were 24.4 years, significantly younger than the patients ($P<0.01$).

STUDIES

Studies were performed on an Automated Pulmonary Function Laboratory,** the heart of which is a hot wire anemometer flow sensor. Calibration was done daily with an internal Severinghaus 1L syringe and was accurate to ±3 percent in accordance with the American Thoracic Society Snowbird Workshop† standards for spirometric accuracy. Volumes were obtained from electronic integration of the flow signal. Microprocessors automatically computed measured values and percent predicted normal from standard prediction equations. Digital displays, printed outputs, and curves were recorded for each test. Forced vital capacity, its subdivisions, and peak flow were computed from maximum expiratory flow-volume curves. Small airways function was assessed by the closing volume test using the resident gas technique and expressed as percent closing volume/vital capacity (%CV/VC). Maximum expiratory flow volume curves (MEFV) were drawn automatically with an X,Y,T plotter from microprocessor memory at one quarter actual speed in order to avoid the inertial artifact, at first using room air, and then using a low density gas (20% oxygen-80% helium) mixture. An SRL medical M10B isolator (bag in box) was attached to the automated PF machine in

*Forceps biopsies were performed through the Olympus BFB2 flexible fiberoptic bronchoscope.

**M100B Automated Pulmonary Function Laboratory. Available from SRL Medical, Inc, Dayton, Ohio.

†American Thoracic Society, Snowbird Conference Workshop, Snowbird, Utah, January 1977.

order to avoid the flow artifact created by helium, which also has a high thermal conductivity. Helium and air curves were then superimposed upon each other, as described by Dosman and associates,[1] and the difference in maximal flow at 50 percent forced vital capacity between helium and air curve (helium response), expressed as a percentage of the air curve ($\Delta\dot{V}max_{50}$), and the iso-flow volume portion of the curves ($Viso\dot{V}$) expressed as percentage of FVC were calculated.

Large airways function was assessed directly by measurement of airways resistance and thoracic gas volume at FRC in a variable pressure body plethysmograph.* Resistance was expressed as its reciprocal, conductance per liter of lung volume (SG_{AW}). Lung compliance was measured as dynamic lung compliance using the esophageal balloon technique, at low respiratory frequencies.**

Ventilation lung scans were obtained by administration of 4mCi of Xenon 133 (Xe^{133}) gas into a Radx Venil-Con 200A closed spirometer system with a unit-dose dispenser with the subject in the sitting position. The inspiration of Xe^{133} was from a face mask while gamma camera imaging was carried out with the large field of view camera with a parallel hole Collimator during washin to equilibrium or to 400k counts and then each minute during washout of Xe^{133} from the lungs until there was no retention, or up to ten minutes.

An entire clinical assessment was made of each patient, complete with history, physical examination, and chest radiographs.

DATA ANALYSIS

Compilation of data was carried out by coding of data on Fortran Coding Forms which were key punched on cards and fed into a computer which used the SPSS program package of Nie et al.[2] Elementary statistics, student t test for unequal samples, Pearsons correlation for paired samples, and linear regression with tests of significance were performed. Cross tabulation was performed on one set of data.

Investigators followed the National Institutes of Health guidelines for experimentation on human subjects.

RESULTS

The quadrant diagram (Figure 1, left) shows the combined ventilatory defect. Both airways obstruction and restrictive defect were seen in this group of patients. Note that most of the controls had "normal" function. Fisher's exact test was highly significant ($P<0.01$). Dysfunction of large airways in sarcoidosis is shown in Figure 1, right. Mean specific airways conductance (SG_{AW}) of patients was significantly less than that of control subjects ($P<0.05$), while post-bronchodilator SG_{AW} failed to improve significantly in five patients studied. Patients who were cigarette smokers had very low SG_{AW}.

Dysfunction in small airways is shown in Table 1 which presents percent predicted maximal expiratory flow volume (MEFV) curve parameters in sarcoidosis patients with airways obstruction before and after inhalation of isoproterenol. Poor reversibility was demonstrated. Parameters which showed a significant decrement following the bronchodilator were on the early effort-dependent portion of the MEFV curve suggesting that patient fatigue was a factor.

Instantaneous flows at 50 and 75 percent FVC, taken from the MEFV curve, are shown in Figure 2, left. They are expressed as FEF_{50}/FVC and FEF_{75}/FVC and were significantly lower in patients with airways obstruction when compared with controls, $P<0.01$ and $P<0.05$, respectively. Expressed in this manner, these parameters would have been greater than those of controls had the ventilatory defect been a pure restrictive one.

Percent closing volume expressed as percent of vital capacity (%CV/VC) corrected for age for both patients and controls is shown in Figure 2, right. Our data were superimposed over regression and confidence limits of McCarthy and associ-

*Body Plethysmograph from Warren E. Collins, Inc, Braintree, MA, Recorder from Electronics for Medicine, White Plains, NY

**Godart Compliance Test, Instrumentation-Associates, NY, NY

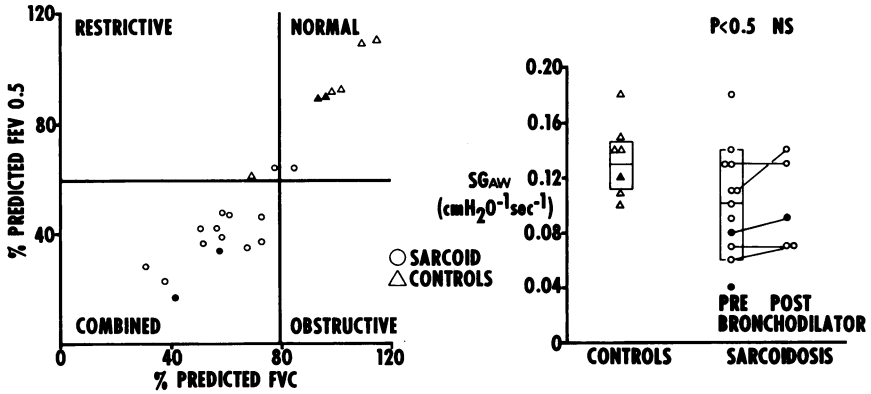

Figure 1. Quadrant diagram of percent predicted $FEV_{0.5}$ vs percent predicted FVC in control subjects (triangles) and sarcoidosis patients (circles). Darkened triangles and circles indicate smokers. Sarcoidosis patients with COPD actually have a combined ventilatory defect (left). Specific airways conductance (SG_{AW}) in sarcoidosis patients with COPD compared with that of control subjects. Mean and ±1 SD are shown. Circles connected with lines indicate patients given isoproterenol by aerosol. Mean SG_{AW} after bronchodilator did not increase significantly (right)

TABLE 1. PERCENT PREDICTED MEFV CURVE PARAMETERS* IN SARCOIDOSIS PATIENTS WITH AIRWAYS OBSTRUCTION

	Pre Bronchodilator			Post Bronchodilator			Significance
	Mean	SD	SE	Mean	SD	SE	
FVC	59	15	3.8	50	15	4.2	P<0.02
$FEV_{0.5}$	40	14	3.5	35	12	3.6	P<0.01
% $FEV_{0.5}$	68	14	3.6	70	16	4.6	NS
FEV_1	41	14	3.5	36	12	3.3	P<0.02
% $FEV_{1.0}$	69	12	3.1	70	13	3.8	NS
% $FEV_{3.0}$	85	10	2.6	85	11	3.2	NS
FEF_{25-75}	24	12	3.2	21	10	2.9	NS
MET	286	95	24.6	271	106	30.5	NS
FEF_{75-85}	24	11	2.9	20	7.0	2.1	NS
PF	63	22	5.7	51	19	5.5	P<0.005

*All mean values are expressed as percent of predicted normal

FVC=forced vital capacity

$FEV_{0.5}$=forced expiratory volume in 0.5 second

% $FEV_{0.5}$=FVC×100

FEV_1=forced expiratory volume in 1 second

% FEV_1=FEV_1/FVC×100

% FEV_3=FEV_3/FVC×100

FEF_{25-75}=forced expiratory flow between 25 and 75 percent of the forced vital capacity, sometimes known as the maximal mid-expiratory flow

MET=mid-expiratory time

FEF_{75-85}=forced expiratory flow between 75 and 85 percent of FVC

PF=peak flow rate

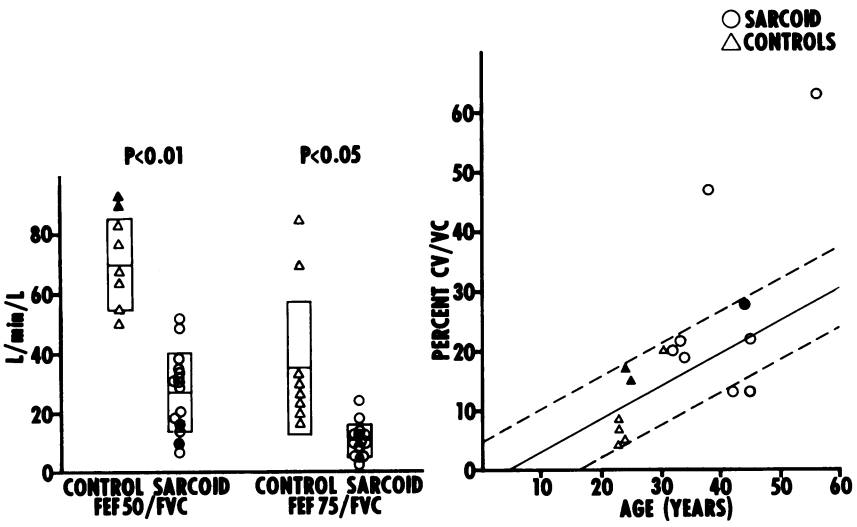

Figure 2. Instantaneous flow at 50 and 75 percent of FVC, (FEF_{50}/FVC and FEF_{75}/FVC respectively) in sarcoidosis patients with COPD is compared with that of controls. Mean and ±1 SD are shown. When displayed in this manner, persons with pure restrictive lung disease have values greater than control values (right). Closing volume as percent of vital capacity (percent CV/VC) vs age in sarcoidosis patients with COPD (circles) compared with that of controls (triangles). Our data was superimposed over regression (solid line) and confidence limits (dashed line) of McCarthy and associates.[3] Only two patients had increased percent CV/VC for their age, and they were non-smokers (left)

ates.[3] Note that only two patients had elevated (%CV/VC) for their ages, and they were non-smokers.

Comparison of helium response in eight non-smoking sarcoidosis patients is shown in Figure 3. Normal limits for healthy non-smoking ethnically matched control subjects are shown by the two crosshatched areas.* With the exception of one unexplained very high value, the majority of values for $\Delta\dot{V}max_{max}$ were decreased, while the majority of values for Viso$\dot{V}$ were increased.

Xenon[133] washin and washout from the lungs was both non-uniform regionally as well as generally prolonged. This was especially true for patients with radiographic stage IV cavitary sarcoidosis, in which washin was regionally delayed and washout was delayed further, beyond the general delay. Figure 4, left shows the relationship of general Xenon 133 washout by the "eye ball method" to N_2 washout from the lungs of six patients and three controls at separate times. The regression equation for this line is:

$$Xe^{133}\ \text{washout(min)} = 0.51 \times N_2\ \text{washout(min)} + 1.58 \pm 0.79$$

$$r = 0.81;\ P<0.01$$

One patient, a cigarette smoker, had a markedly prolonged washout time. By comparison, that of controls was within four minutes for Xe^{133}, and within three minutes for N_2.

The typical MEFV curve of a patient is shown in Figure 4, right before and after administration of isoproterenol by aerosol, and following therapy with beclomethasone dipropionate aerosol for a one-month period. Neither bronchodilator nor aerosol steroid provided relief of airways obstruction in this patient.

DISCUSSION

Although the older literature has mentioned airways obstruction in sarcoidosis, real interest in

*Previously unpublished data from this laboratory indicate helium response in healthy non-smokers shows $\Delta Vmax_{50}$ $\bar{x}$ = 47, SD ±3.9, while Viso$\dot{V}$ $\bar{x}$=17, SD ±2.1 percent.

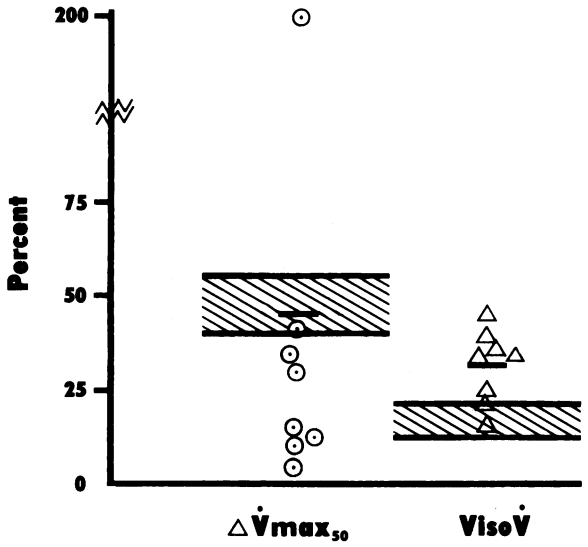

Figure 3. Diminished helium response of maximum expiratory flow-volume (MEFV) curves are shown in eight sarcoidosis patients who are non-smokers, indicative of disease of small peripheral airways. Differences between helium and air curve at 50 percent FVC, expressed as percent of the air curve ($\Delta \dot{V}max_{50}$), are shown as open circles, while the iso volume, iso flow portion of the curves are expressed as percent of FVC ($Viso\dot{V}$) and shown as triangles. Mean values for each are indicated by heavy horizontal lines. Crosshatched areas indicate normal values from this laboratory. Note the majority of values for $\Delta \dot{V}max_{50}$ are decreased, while the majority of values for $Viso\dot{V}$ are increased. One patient had an unexplained very high $\Delta \dot{V}max_{50}$ value

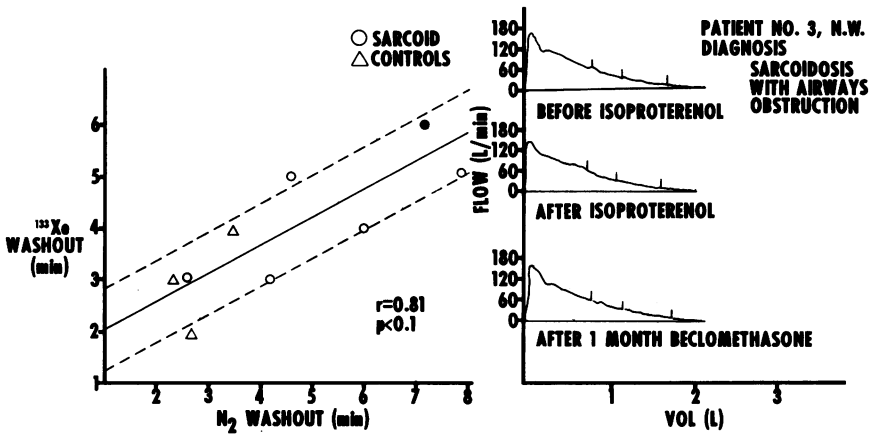

Figure 4. Xe^{133} washout of the lung measured by gamma camera imaging vs nitrogen washout time in lungs of sarcoidosis patients with COPD (circles) and controls (triangles). Darkened circle indicates a smoker. Note washout time of patients is prolonged. Regression line (solid line) and confidence limits (dashed line) are shown (left). Maximum expiratory flow volume curves of patient 3, with expiratory slowing. Half, one, and three second time marks are on each curve. Airways obstruction failed to respond to isoproterenol or beclomethasone dipropionate aerosol (right)

obstruction in this disease is just beginning to emerge.

In an early study of pulmonary function among ten patients with sarcoidosis, Coates and Comroe[4] found five had an increase in residual volume. The following year, McClement and associates[5] included one of the clinical presentations of sarcoidosis in a pattern of emphysema which responded to steroids. A detailed clinical summary of one patient was presented and, in findings similar to those of clinicians since, reported clinical improvement with two courses of cortisone therapy; however, the emphysematous lesions were irreversible. In a study of 22 patients with sarcoidosis, Stone and associates[6] reported three patients with functional patterns of "emphysema," including one with spirographic evidence of airways obstruction of the right middle lobe bronchus due to lymph node compression who was treated surgically with lobectomy five years prior to the study. This uncommon form of obstruction has been since described in the literature, as has endobronchial disease. In an early attempt at a functional classification of sarcoidosis from this laboratory, Harden and associates[7] described a group of six patients with "obstructive pneumonopathy" consisting of prolonged expiration and evidence of air-trapping. These workers suggested the pattern resulted from bronchial and bronchiolar lesions. They cited clear evidence given earlier by Spain (1950) of development of bullae and emphysema in a patient whose lung revealed, after pneumonectomy, diffuse infiltration of broncholar walls with granulomatous lesions of Boeck sarcoid.

A growing awareness of the complication of airways obstruction in sarcoidosis focused considerably more attention upon it in the 1970s as newer technology for assessment of airways obstruction became available. The development of flexible fiberoptic bronchoscopy during the late 1960s as a diagnostic tool increased accessibility to the tracheobronchial tree and brought the problems of endo and perigranulomata into clearer perspective for the clinician. In a previous study from this laboratory, Young and associates[8] demonstrated a frequency dependent C_L dyn in all eight sarcoidosis patients despite the fact that five of these were non-cigarette smokers, indicating impairment of small airways function in this group. De Remee and Anderson[9] reported on 107 sarcoidosis patients and correlated radiographic stage of disease with dyspnea. They correlated dyspnea with "distorted" chest radiologic picture with expiratory slowing from MEFV curves which highlighted the obstructive component caused by "intrinsic bronchial obstruction as well as restriction." These authors pointed out that the obstructive lesions and their clinical expression of dyspnea were rarely relieved by steroids and probably represented irreversible pulmonary disease. At the same time Renzi and Dutton studied 44 sarcoidosis patients: "evidence of diffuse airways obstruction in 13 patients who were non-smokers was assumed to be due to peribroncholar peripheral airways involvement."[10] Since none of the above mentioned patients had a history of chronic bronchitis, asthma, or repeated lower respiratory tract infections, this study presented strong evidence that sarcoidosis in the absence of co-existing disease can produce airways obstruction.

From Mt. Sinai Hospital in New York, Miller and associates[11] used maximal expiratory flow volume curves to demonstrate airways obstruction in 12 of 16 sarcoidosis patients. These workers pointed out that although fibrosis and late-stage disease could cause obstruction, granulomatous involvement of airways, prior to fibrotic change, may be responsible.

Levinson and associates,[12] in a recent study of 18 symptomatic sarcoidosis patients using a variety of newer tests of airways function (including those which measure small airways disease), demonstrated that all patients had at least one abnormal test of airways function; in most patients, nearly all were abnormal. Eleven of their patients were cigarette smokers.

Kaneko and Sharma[13] used MEFV loops and studies of elastic recoil pressures to show that 9 of 21 random sarcoidosis patients with pulmonary involvement had smaller peak flows at 50 percent FVC than could be expected from restriction alone due to low peripheral airways conductance and/or loss of elastic recoil of the lungs. These workers speculated that "non-uniform transmission of transpulmonary pressures within inhomogeneous lung tissues might play a role in obstructive sarcoidosis."[13]

In the present study, sarcoidosis patients were older than healthy control subjects, but since most tests of airways function were age and/or lung size adjusted, comparison of data is valid.

The decreased mean specific airways conductance indicates involvement of larger airways, while failure of this test to improve following inhalation of isoproterenol in 5 of 12 patients suggests that mechanical factors such as endobronchial granulomas limit reversibility. Dysfunction of smaller peripheral airways can be inferred from decreases in maximal airflow at mid forced vital capacity FEV_{50} and after 75 percent of FVC has been expired (FEF_{75}), which is decreased further than can be expected had restrictive lung disease existed alone. In fact, in pure restrictive lung disease, the ratio FEF/FVC is greater than compared with that of healthy controls.

The helium response of the MEFV curve as evaluated by the $\Delta\dot{V}max_{50}$ and $Viso\dot{V}$ has been used as a measure of small airways disease.[1] In small peripheral airways, flow is laminar and viscosity-dependent, whereas in large central airways, it is turbulent and density-dependent. "Convective acceleration," as airflow progresses from smaller to larger airways, is also density-dependent. The greater the contribution of small airways in increasing resistance to airflow, the less will be the helium response, thus decreasing $\Delta\dot{V}max_{50}$ and increasing $Viso\dot{V}$. Since $\Delta\dot{V}max_{50}$ is not influenced by loss of elastic recoil, it is thought to represent true airways narrowing. Since the sarcoidosis patients in the present study were slightly older than controls, the increased $Viso\dot{V}$ could have been due to age-related loss of elastic recoil. Thus the non-smoking sarcoidosis patients studied have a diminished helium response which is due to small airways narrowing. Other workers have reported a decreased helium response in sarcoidosis.[14,15]

Surprisingly, the closing volume test was not as sensitive an indicator of small airways dysfunction as shown by Levinson.[12] Only two of our patients had percent CV/VC significantly above the confidence limits. The fact that these patients were non-smokers confirms the beliefs of others that smoking is not a cause of obstruction in these patients. The marked hypoxemia at rest observed in these two patients is undoubtably due to non-uniform ventilation-blood flow ratios because their dependent lung zones cease to ventilate well within their tidal volume range.

It is reasonable to suspect further that airways narrowing due to secretions and/or endobronchial granulomata or fibrosis is more commonly the cause of obstruction than is emphysema, since the normal specific lung compliance suggested that a decreased elastic recoil of the lungs was not responsible for enhanced dynamic compression of airways among patients.

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