Effect of Steroid Therapy on Gas Exchange Abnormalities in Patients with Diffuse Interstitial Lung Disease*

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The etiology of sarcoidosis, and other diffuse interstitial lung diseases, has been elusive. Definitive treatment has, therefore, not been available.

In 1952, Siltzbach1 documented that sarcoidosis, a diffuse interstitial lung disease, had been treated with the following medications: calcium salts, gold, arsenicals, potassium iodide, chaulmoogra oil, antileprol, tuberculin, penicillin, streptomycin, promin, diosone, aureomycin, radiation therapy, nitrogen mustard, and calciferol. In the dauntless, empirical nature of medical science it was inevitable that shortly after their availability, adrenal corticosteroids would be utilized in the treatment of sarcoidosis. When a case of sarcoidosis with severe uveitis was successfully treated with cortisone, it prompted Siltzbach1 to use cortisone in 13 patients with sarcoidosis. He found that all 13 improved either subjectively or radiologically with treatment. He thought that fresh lesions appeared to be more responsive than older and more established disease, although he never defined a "fresh" lesion.

Israel and associates2 also used clinical and roentgenographic assessment to gauge the effects of steroids on patients with sarcoidosis. They noted a variable response, depending on the extent of the disease and whether an initial or long term improvement was considered. However, the physiologic evidence of this improvement has been contradictory.3-10 Serial studies of pulmonary function tests in relation to steroid therapy have demonstrated improvement in vital capacity and flow rates, and in diffusing capacity for carbon monoxide (Dss) using either the single breath (DSSB), or exercise steady-state (DSSS) technique. A recent controlled study4 failed to demonstrate significant difference in DSSS and resting and exercise arterial oxygen tension (PaO2) between steroid-treated and untreated patients with sarcoidosis.

Since the evidence for physiologic improvement with steroid therapy has been quite contradictory, several questions must be raised about our ability to assess changes in response to therapy in diffuse interstitial disease. First, is there a variable course with spontaneous waxing and waning of the disease process? We cannot answer this question on the basis of our study which was relatively short term and so was designed to minimize the effects of spontaneous changes which tend to occur over longer time periods.

Second, to what extent is the magnitude and/or severity of the disease a factor in the amount of response? The best that can be said is that steroids are not expected to produce dissolution of fibrotic tissue. If there is active tissue injury with edema and cellular proliferative activity, then steroid therapy may affect that process and perhaps could prevent the production of fibrosis.

Third, what is the sensitivity of the measurement used to gauge response to therapy? Increased sensitivity to changes in the function of the lung may be achieved at the price of using tests which are not readily available on a widespread basis. It follows that we should consider what is necessary and sufficient to prove that an actual change has occurred in response to therapy.

Adrenal corticosteroids presumably affect diffuse interstitial lung disease through their anti-inflammatory effect, their effect on fibroblast growth and function, their effect on granulomas when present, and perhaps by other presently undefined mechanisms. We concentrated on the in vitro effect of these medications on lungs in patients with interstitial lung disease and specifically on transpulmonary gas transport. Since a sensitive evaluation of pulmonary gas exchange abnormalities is achieved by measuring alveolar-arterial oxygen differences P(A-a)O2 at different levels of oxygenation, we evaluated the effect of corticosteroid therapy on these parameters in a group of patients with diffuse interstitial lung disease.

Material and Methods

Twenty-five patients with diffuse interstitial lung disease were included in the study. Sixteen had sarcoidosis, five had usual interstitial pneumonitis (UIP) and four had granulomatous interstitial pneumonitis. The steroid treated group included 14 patients, nine with sarcoidosis, three UIP, and two granulomatous interstitial pneumonitis. The comparable untreated group included 11 patients of whom seven had sarcoidosis, two UIP, and two granulomatous interstitial pneumonitis. The mean ages of the untreated group was 41.4 (±11.4). In the treated group the mean age was 37.9 (±13.3). There was no statistically significant difference between the groups. Lung function was assessed by spirometry, lung volume measurements, and airway resistance measurements in the total body plethysmograph. Pulmonary gas exchange was evaluated by measuring arterial PaO2, resting steady-state DSSS, and alveolar arterial oxygen differences breathing FIO2 of 21 percent, 14 percent, and 100 percent at rest, and 21 percent during exercise. The studies were repeated after an average of three months (±2.3, range 1-8) of steroid therapy consisting of 30-60 mg of prednisone daily in the treated group. In the untreated group, the studies were repeated after an average of 5.6 months (±3.3, range 1-12 after the initial studies).

Results

Initially, the spirometry and flow rates were similar for the treated and untreated groups. This includes the forced vital capacity, FEV1, FEF200-1200, FEF25-75%. Ten of the 25 total patients had a reduced FEF25-75% indicating abnormal airway function. Of these ten subjects, five had an increased specific airway resistance (SRaw) while five were normal. At follow-up, the untreated group showed some worsening of all four measurements with borderline significant deterioration (P < 0.05) for the
FEV₁ and FEF₂₅₋₇₅. The treated group showed no significant difference between initial and follow-up values.

In keeping with the general concept of interstitial lung disease as restrictive, initially there was an overall decrease of vital capacity, total lung capacity, functional residual capacity and residual volume for both groups. Although the residual volume and functional residual capacity (FRC) were essentially identical for both groups of subjects, it was apparent that the treated group had a lower vital capacity and therefore a lower TLC. On subsequent observation, the untreated group had not significantly changed either residual volume or FRC. However, both the vital capacity and total lung capacity were substantially decreased, and were consistent with a continued worsening of the process. On the other hand, the treated group showed that although it started from lower values of both vital capacity and total lung capacity (TLC), there was a significant improvement (P < 0.05).

Studies in the total body plethysmograph were rather unrevealing. The volume of thoracic gas on average was the same for both groups as was the airway resistance and specific resistance. There was no change after treatment or nontreatment in any of the body plethysmography values for volume of thoracic gas, airway resistance, and specific resistance.

We were rather intrigued by the question of the effects of interstitial disease on airways function. We reviewed results on 91 of our patients with diffuse interstitial lung disease studied in the plethysmograph. Fifty-five of these patients had sarcoidosis, 36 had interstitial fibrosis. Twenty-two of 91 (24 percent) had SRaw greater than 5.5. Since, as the lung volume decreases, the resistance rises and conductance drops, we plotted the data as the conductance (Gaw) versus the volume of interstitial lung disease studied in the plethysmograph. Fifty-two of 91 (72 percent) of the cases. The mechanisms of increased or decreased airway conductance (Gaw) in interstitial lung disease merits further studies.

The initial values for the diffusing capacity of the lung for carbon monoxide, D₅₅, were a mean of 15.1 ml/min/mm Hg untreated and 11.5 ml/min/mm Hg in the treated (Fig 1). Similarly, the resting arterial oxygen (PaO₂) and the exercise arterial oxygen (PaO₂) were all worse in the treated group than in the untreated group. However, these differences were not large enough to be statistically significant.

After a period of treatment or simple observation there was obviously no change in either the rest or the exercise arterial oxygen (PaO₂) in the untreated group (Fig 1). However, in the treated group, there was a significant improvement, (P < 0.01) for both rest and exercise arterial oxygen. Although the diffusing capacity (D₅₅) improved in the treated group, this was not statistically significant, while at the same time there was a decrease in the diffusing capacity (D₅₅) for the untreated group, which was also not significant. This can be considered as evidence for the greater sensitivity of arterial blood gases to examine gas transport than the conventional method of steady-state end tidal diffusing capacity.¹²

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<tr>
<th>Diffusing Capacity (D₅₅)</th>
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<td>Untreated</td>
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<td>Treated</td>
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Figure 1. Initial and follow-up values for steady state carbon monoxide diffusion capacity (D₅₅) and arterial oxygen tension (PaO₂) at rest and during exercise in untreated (○-○) and steroid-treated (■-■) patients with diffuse interstitial lung disease. Values, represented by the vertical bars, are expressed as the mean and one standard deviation. *NS = No significance. The P value is given if the difference is statistically significant.

12 patients (13 percent) had a low Gaw. A normal conductance (Gaw) for the patients’ Vtg was present in 72 percent of the cases. The mechanisms of increased or decreased airway conductance (Gaw) in interstitial lung disease merits further studies.

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Considering gas transport across the lung, let us briefly summarize the classical analysis of Riley and Cournand.¹³¹⁴ Venous admixture affects the P(A-a)O₂ especially at a high inspired oxygen level (FIO₂). Diffusion limitation is important for oxygen, especially at low inspired oxygen levels (FIO₂), while exercise will accentuate a diffusion defect and may also worsen the effects of venous admixture or a low ventilation/perfusion ratio (V/Q). The arterial alveolar CO₂ difference is due mainly to over ventilated alveoli (high V/Q) while arterial alveolar nitrogen difference results mainly from over
We examined the alveolar arterial oxygen difference, \( P(A-a)O_2 \), with the patients breathing room air (\( FIO_2 = 21 \% \)) at rest, low oxygen (\( FIO_2 = 14 \% \)), high oxygen (\( FIO_2 = 100 \% \)) breathing room air (\( FIO_2 = 21 \% \)) during exercise. Overall, these initial values were fairly comparable for the two groups; the \( P(A-a)O_2 \) was elevated for every patient studied and there were no statistical differences between the two groups (Fig 2). After the period of time of either nontreatment or treatment with 30-60 mg prednisone, daily for at least a month, the resting alveolar-arterial oxygen difference \( P(A-a)O_2 \) was not significantly changed for the untreated group while the treated group had a substantial decrease (\( P < 0.001 \)). Breathing low inspired oxygen (\( FIO_2 = 14 \% \)), the untreated groups showed a slight worsening which was not significant while the treated group showed a small but definite improvement which was statistically significant (\( P < 0.01 \)). Breathing 100 percent oxygen (\( FIO_2 = 1.0 \)) the variances were noted to be quite large. Nevertheless, the untreated group showed a decrease which was not statistically significant, while the treated group showed a much larger decrease which was significant (\( P < 0.001 \)). With exercise, the untreated group showed no change while the treated group showed a decrease in the alveolar arterial oxygen difference which was significant (\( P < 0.001 \)). Overall, this can be construed as representing improvement in the efficiency of the lung for gas transport subsequent to treatment by steroids.

**References**


**Session 6: Basic Science**

**Lung Lysyl Oxidase and Elastin Synthesis during Compensatory Lung Growth**


Lysyl oxidase is an enzyme responsible for the initial deamination of lysine and hydroxylysine leading to formation of compounds which produce the characteristic crosslinks of elastin and collagen. In our previous studies of postpneumonectomy lung growth, we noted physiologic changes consistent with synthesis of lung connective tissue. To investigate the time course and control of this process, we measured lysyl oxidase activity (LO) in the right lungs of adult hamsters that had undergone prior left pneumonectomy (PN). We found that LO was similar in central and peripheral lung tissue, so that all subsequent analyses were performed on whole lung homogenates. Lysyl oxidase activity rose within two hours of surgery, reached a peak that was 201 ± 20 percent of control values at one day and fell to control values five days after pneumonectomy. There was a suggestion of a secondary rise during the second postoperative week. Amino acid analysis of NaBH₄ reduced elastin extracted in hot alkali in five day post-PN lungs revealed a distribution of crosslink components consistent with biosynthesis of new crosslinks.

We have recently shown that inspired oxygen influences the size of the lung following PN, hyperoxia abolishing and hypoxia accentuating the post-PN increase in lung volume (Am Rev Resp Dis 109:732, 1974). Thirty percent oxygen depressed the first day