Eur Respir J
1990, 3, 403–407

Effects of corticosteroid treatment on pulmonary haemodynamics in patients with sarcoidosis

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Effects of corticosteroid treatment on pulmonary haemodynamics in patients with sarcoidosis. J. Gluskowski, I. Hawrylkiewicz, D. Zych, J. Zieliński.
ABSTRACT: Effects of 12 months steroid treatment on pulmonary haemodynamics in 24 patients with pulmonary sarcoidosis, stage II and III, were investigated. All patients had a chest radiograph, lung function tests, and pulmonary haemodynamics (measured at rest and during submaximal exercise) prior to the treatment. Resting pulmonary hypertension was found in 3 patients. In 18 an abnormal increase in pulmonary arterial mean pressure (PAP) on exercise was observed. All investigations were repeated after a year of treatment. In almost all patients (22) a regression of radiological changes in the lungs and improvement of pulmonary function were observed. The changes in pulmonary circulation were less uniform. In only half of the patients studied was regression of the disease seen on chest X-ray and improvement in lung function accompanied by improvement in pulmonary haemodynamics.
Eur Respir J., 1990, 3, 403–407.

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Keywords: Pulmonary haemodynamics; pulmonary sarcoidosis; steroid treatment.

Received: May, 1989; accepted after revision October 6, 1989.

In only 10–20% of patients with sarcoid the disease progresses to diffuse pulmonary fibrosis leading to pulmonary hypertension and respiratory failure, despite treatment with steroids. Recently, we documented 25 yrs experience with 960 patients followed-up for pulmonary sarcoidosis. In 214 patients treated pulmonary lesions resolved partially or totally in 81% of cases, but in the remainder the disease progressed to diffuse pulmonary fibrosis [1].

The effects of steroid therapy on pulmonary function are well known [2, 3]. Much less is written about its effects on the pulmonary circulation and prevention of cor pulmonale. RIZZATO *et al.* [4] reported that patients with stage II and III disease may present with pulmonary hypertension. This, however, was a cross-sectional study with no analysis of the reaction to treatment. BATTESTI *et al.* [5] reported some fatalities due to cor pulmonale in patients with severe pulmonary fibrosis consequent to sarcoidosis.

Previously, we have shown that pulmonary hypertension is common in patients with stage III sarcoidosis [6]. In some patients with stage II sarcoidosis we observed pulmonary hypertension at rest. Those with a normal resting pulmonary arterial pressure reacted to exercise with an abnormal increase in pulmonary arterial pressure. The aim of this study was to assess the effect of 12 months corticosteroid treatment on pulmonary haemodynamics in patients with stages II and III sarcoidosis.

Patients and methods

We studied 24 patients with stage II and III sarcoidosis [7]. Diagnosis was based on the typical clinical and radiographic picture and, in all patients, was histologically confirmed by biopsy of either lymph node, bronchial mucous membrane or lung parenchyma. There were 19 males and 5 females aged from 24–48 yrs (mean age 37 yrs) in the group studied. The signs of the disease were present between 12–24 months prior to the study. None of patients had systemic hypertension, abnormal electrocardiogram (ECG) or any other disease that may cause pulmonary hypertension. The patients qualified for corticosteroids because of the lack of spontaneous regression during at least 6 months of close follow-up, altered lung function and high lymphocyte count in bronchoalveolar lavage (BAL). We included all patients admitted to the department who qualified for treatment when the investigations were carried out.

The study was approved by the Ethical Committee for Human Research of the Institute of Tuberculosis and Lung Diseases. All subjects gave their informed consent. All patients had a chest radiograph and pulmonary function tests comprising measurements of vital capacity (VC), forced expiratory volume in one second (FEV_1), static and dynamic compliance (Cst and Cdyn) and static elastic recoil pressure (Pst_{max}). Spirography was performed using a dry spirometer (Vitalograph). Normal values were those of BERGLUND *et al.* [8]. Pulmonary mechanics were

measured in a constant-volume body plethysmograph (Body-test, Jaeger).

Pulmonary artery catheterization was carried out with a Swan-Ganz catheter using a Seldinger method in the supine position. Pulmonary arterial mean pressure (PAP), pulmonary wedge pressure (Pw) and inspiratory to expiratory swings of pulmonary arterial diastolic pressure (ΔP_{APD}) were measured with a 746 Siemens-Elema pressure transducer averaging beat by beat values over 3 respiratory cycles and recorded simultaneously with an ECG lead on a Mingograph 34 recorder. The hydrostatic zero level was at 5 cm below the sternal angle. Arterial and mixed venous blood samples were taken for oxygen, carbon dioxide tensions and pH measurements by Radiometer microelectrodes. Cardiac output was measured in triplicate using a thermodilution method with the aid of a cardiac output computer COC 5000 (Universal Medical Instrument Inc). Cardiac index (CI), and pulmonary vascular resistance (PVR) were calculated according to generally accepted principles [9]. After blood gases, pressures and flow measurements at rest were completed subjects performed steady-state submaximal exercise [10] on a mechanically-braked cycle ergometer (Mijnhardt). Workload was individually chosen for each patient the day before catheterization. All measurements were repeated between the 5th and 7th minute of exercise. Seven patients, all 5 with stage III and 2 with stage II disease, presented with exertional dyspnoea grade I (MRC).

After the initial investigations patients started treatment. Prednisolone was started at 60 mg daily decreasing to 30 mg·day^{-1} at the end of the sixth month. During the last six months the dose of prednisolone was 25 mg·day^{-1}. Chest X-ray, pulmonary function tests and pulmonary haemodynamics at rest and during steady-state exercise using the workload as before treatment were repeated at the end of the year of treatment. Initial and final results were analysed statistically using Student's test for paired data.

Results

Lung function data before and after steroid treatment are presented in table 1. Vital capacity before treatment was slightly reduced. The same applied to the FEV_1. After treatment lung volumes increased. Static and dynamic pulmonary compliances before treatment were slightly to moderately reduced. After treatment both significantly improved. Static elastic recoil pressure fell.

Pulmonary haemodynamics and blood gas data at rest and on exercise, before and after treatment are presented in table 2. Arterial oxygen tension (Pao_2) at rest and during exercise before treatment was at the lower limit of normal. After treatment Pao_2 rose significantly at rest and on exercise. Mixed venous oxygen tension ($P\bar{v}o_2$) measured at rest was higher after treatment than before. On exercise we observed a similar decrease in $P\bar{v}o_2$ before and after treatment. Arterial carbon dioxide tension ($Paco_2$) remained unchanged at rest and on exercise before and after treatment.

Table 1. – Lung function before and after one year of steroid treatment in 24 patients with sarcoidosis (mean±SD)

Variable	Before treatment	After treatment
VC *l*	4.1±0.98	4.33±0.98
VC % N	82±17	87±15*
FEV_1 *l*	3.1±0.71	3.3±0.80
FEV_1 % N	80±19	84±18
Cdyn ml·cmH_2O^{-1}	154±62	185±54**
Cst ml·cmH_2O^{-1}	185±64	211±649*
Pst_{max} cmH_2O	44±17	37±13**

VC: Vital capacity; % N: % normal values FEV_1: forced expiratory volume in one second; Cdyn: dynamic compliance; Cst: static compliance; Pst_{max}: static elastic recoil pressure; *: $p<0.05$; **: $p<0.01$.

Table 2. – Blood gases and pulmonary haemodynamics at rest and on exercise in 24 patients with sarcoidosis before (B) and after (A) one year of treatment (Mean±SD are shown)

	Rest		Exercise	
	B	A	B	A
Heart rate beats·min^{-1}	81±12	78±12	135±20	138±22
Pao_2 kPa	10.5±2.1	11.7±1.6*	10.6±2.5	12.5±1.6**
$Paco_2$ kPa	4.9±0.7	4.7±0.5	5.0±0.8	4.7±0.5
$P\bar{v}o_2$ kPa	4.9±0.7	5.7±0.9	4.1±0.4	4.8±0.7
PAP kPa	2.4±0.8	2.1±0.7	4.3±1.6	3.9±1.2
Pw kPa	1.1±0.4	0.9±0.5	1.9±0.8	1.6±0.8
ΔP_{APD} kPa	0.8±0.4	0.8±0.3	2.4±0.9	2.3±0.8
CI *l*·min^{-1}·m^{-2}	3.6±1.6	3.0±1.0	7.6±4.2	5.3±2.0*
PVR kPa·*l*$^{-1}$·s	12.0±7.9	11.1±5.7	13.9±8.4	11.0±4.3

Pao_2: arterial oxygen tension; $Paco_2$: arterial carbon dioxide tension; $P\bar{v}o_2$: mixed venous oxygen tension: PAP: pulmonary arterial mean pressure; Pw: pulmonary wedge pressure; ΔP_{APD}: inspiratory to expiratory swing of pulmonary arterial diastolic pressure; CI: cardiac index; PVR: pulmonary vascular resistance; *: $p<0.05$; **: $p<0.01$.

Resting heart rate before and after treatment was normal. Resting mean pulmonary arterial pressure for the group before and after treatment was normal. An abnormal increase in PAP on exercise (by more than 10 mmHg) was seen in 18 patients before and in 12 patients after treatment. Mean pulmonary wedge pressure was normal both at rest and on exercise, before and after treatment. Inspiratory to expiratory swings of pulmonary arterial diastolic pressure at rest, before and after treatment were slightly elevated. Normally ΔP_{APD} does not exceed 4 mmHg [11]. During exercise ΔP_{APD} increased before treatment to 18 mmHg and after to 17 mmHg. Cardiac index at rest, before and after treatment, was normal. Pulmonary vascular resistance was slightly elevated before treatment with no significant change on exercise.

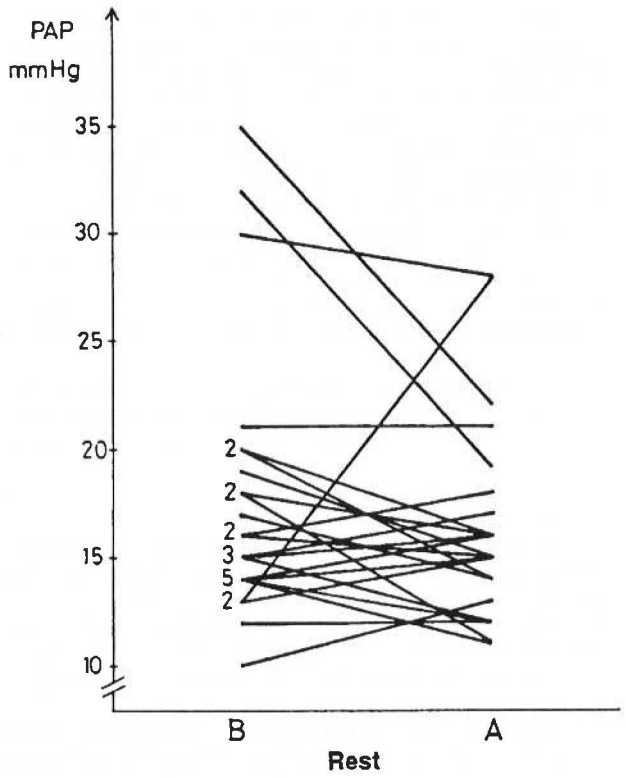

Fig. 1. – Pulmonary arterial mean pressure (PAP) at rest before (B) and after (A) a year's treatment with steroids in 24 patients studied. Numbers on the left side of lines signify number of patients with the same pressure value.

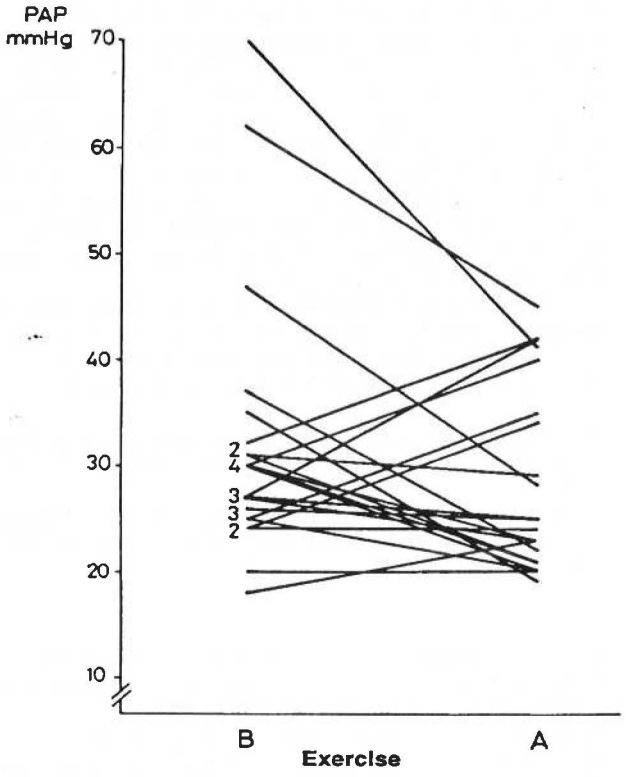

Fig. 2. – Pulmonary arterial mean pressure (PAP) at the end of steady-state exercise before (B) and after (A) a year's treatment with steroids.

Comparison of individual data of pulmonary haemodynamics before and after treatment (fig. 1) showed that resting PAP in 2 patients remained the same. In 14 patients resting PAP decreased and in 8 patients it increased. In 7 patients the increase was small and within the normal range of pressures. In one patient PAP increased from 13 mmHg to 27 mmHg. In this patient disease progressed radiologically together with deterioration of the lung function parameters despite treatment.

The rise in pulmonary arterial pressure in response to exercise was the same in 5 patients. In 12 patients the increase in PAP was lower during the same workload than before treatment. In 7 patients PAP on exercise increased more after treatment than before (fig. 2). In 5 of the 7 patients reporting exercise dyspnoea grade 1 before treatment, symptoms disappeared. In 2 dyspnoea remained. One of these 2 patients was the one in whom there was a significant increase in PAP despite treatment.

Discussion

The patients in this study qualified for corticosteroid treatment because of lack of spontaneous regression of the disease, altered lung function and signs of active disease. We recruited all patients admitted to the Department to start treatment during the time the investigations were carried out. We have assumed that they represent an average cross-section of cases of sarcoidosis.

The majority of patients had stage II pulmonary sarcoidosis. Only 5 patients were stage III according to the accepted diagnostic principles [12]. In this study and in our former work [6] there was no definite correlation between radiological changes and altered lung function. Similar observations have been previously reported [13, 14].

One year of steroid treatment resulted in significant improvement of pulmonary function. Lung volumes increased and the pulmonary elasticity decreased. The most important changes were improvements in static and dynamic pulmonary compliance. Pulmonary gas exchange at rest and during exercise increased in most patients after treatment. The assessment of the chest radiographs showed regression of sarcoid in all but 2 patients in whom radiological changes progressed despite treatment. Resting pulmonary arterial pressure before treatment was normal (<20 mmHg) in all but one case with stage II of the disease. Resting pulmonary hypertension was found in 3 out of 5 patients with stage III. An abnormally high increase in PAP during submaximal exercise was observed in 75% of patients. These findings confirmed both our [6] and other author's [15, 16] observations of restriction of the pulmonary vascular bed in patients with stages II and III sarcoidosis.

The benefits of corticosteroid treatment on the pulmonary circulation were not as effective as on lung function and radiological changes. Pulmonary haemodynamics at rest were the same before and after treatment in 2 patients. In 14 patients the pulmonary arterial pressure was lower after treatment and in 8 patients resting

PAP increased, but in 6 it remained in the normal range. Of four patients with resting pulmonary hypertension before treatment, the PAP in one became normal and in one pulmonary hypertension was markedly reduced. Improvement in pulmonary haemodynamics during exercise was observed in half of the cases. Performing the same work resulted, after treatment, in a smaller increase in PAP than before treatment in 12 patients.

In 7 patients we noted a larger increase in PAP on exercise. All of these patients had reacted with an abnormally large increase in pulmonary arterial pressure on exercise before treatment. Interestingly, in all but one of these patients, we observed improvement in both the lung function variables and the radiological picture.

Inspiratory to expiratory fluctuations of pulmonary arterial diastolic pressure remained unchanged after treatment. It was shown that ΔP_{APD} closely follows fluctuations in pleural pressure necessary for maintaining adequate pulmonary ventilation and indirectly reflects disturbances in pulmonary mechanics [17]. It might be expected that improvement in pulmonary compliance observed after steroid therapy would cause a decrease in respiratory swings of intravascular pressure, but this was not the case. Small decreases in respiratory fluctuations of pulmonary arterial pressure during exercise were not statistically significant.

Depending on the localization of sarcoid lesions in relation to the structures responsible for the efficiency of alveolar ventilation and perfusion, differences in the impairment of pulmonary function and circulation may result. This may explain the lack of correlation between alterations in pulmonary function and pulmonary blood pressure. Our study showed that in the majority of patients both pulmonary function and circulation were impaired before treatment. Restriction of pulmonary volumes, increased lung recoil pressure and limitation of the pulmonary vascular bed was found in most cases.

After steroids, pulmonary function improved in almost all patients but a corresponding change in pulmonary haemodynamics was only found in half. It is possible that sarcoid granulomas in the walls of pulmonary vessels disappear more slowly with steroids than those in the interstitium. The study showed that despite a similar radiological picture in some patients with stage II disease the level of pulmonary arterial pressure varied between cases. The improvement in the chest radiograph correlated with the lowering of the pulmonary blood pressure only in some cases. The same applies to the discrepancy between the improvement in pulmonary function and PAP. These differences probably depend on the localization of sarcoid granulomas in relation to pulmonary arteries [18, 19]. Investigation of pulmonary haemodynamics could be a valuable complement in the assessment of functional derangements caused by the disease.

References

1. Zych D, Krychniak W, Pawlicka L, Zieliński J. – Sarcoidosis of the lung. Natural history and effects of treatment. *Sarcoidosis*, 1987, 4, 64–67.
2. Johns CJ, MacGregor MI, Zachary JB, Ball WC. – Extended experience in the long term corticosteroid treatment of pulmonary sarcoidosis. *Ann NY Acad Sci*, 1976, 278, 722–731.
3. Scano G, Monechi GC, Gigliotti F, Stendardi L, Espositolacenna V, Tarduecci G, Schiaffini P. – Effects of steroid therapy on pulmonary involvement in sarcoidosis. *Int J Clin Pharmacol Ther Toxicol*, 1983, 21, 468–475.
4. Rizzato G, Pezzano A, Sala G, Merlini R, Ladelli L, Tausini G, Montanari G, Bertoli L. – Right heart impairment in sarcoidosis: haemodynamic and echocardiographic study. *Eur J Respir Dis*, 1983, 64, 121–128.
5. Battesti JP, Georges R, Basset F, Saumon G. – Chronic cor pulmonale in pulmonary sarcoidosis. *Thorax*, 1978, 33, 76–84.
6. Gluskowski J, Hawrylkiewicz I, Zych D, Wojtczak A, Zieliński J. – Pulmonary haemodynamics at rest and during exercise in patients with sarcoidosis. *Respiration*, 1984, 46, 26–32.
7. Crofton J, Douglas A. – *In:* Respiratory Diseases, 3rd edn. Blackwell, Oxford, 1982, pp. 458–462.
8. Berglund E, Birath G, Bjure J, Grimby G, Kjellmer I, Sandqvist L, Söderholm B. – Spirometric studies in normal subjects. *Acta Med Scand*, 1963, 173, 185–192.
9. Harris P, Heath D. – *In:* The human pulmonary circulation, 3rd edn. Churchill, Livingstone, 1986, pp. 97–134.
10. Astrand PO, Rodahl K. – *In:* Manuel de physiologie de l'exercise musculaire. Masson, Paris, 1973.
11. Rodbard S, Kariv I, Herman DF. – The diagnostic significance of the respiratory fluctuations of the pulmonary arterial pressure in man. *Am Heart J*, 1956, 52, 182–192.
12. Sharma OP. – *In:* Sarcoidosis: clinical management. Butterworths, London, 1984, pp. 29–40.
13. Miller A, Teirstein AS, Jackler I, Chuang M, Siltzbach LE. – Airway function in chronic pulmonary sarcoidosis with fibrosis. *Am Rev Respir Dis*, 1974, 109, 179–189.
14. Huang CT, Henrich AE, Rosen Y, Moon S, Lyons HA. – Pulmonary sarcoidosis: roentgenographic, functional and pathologic correlations. *Respiration*, 1979, 37, 337–345.
15. Emirgil C, Sobol BJ, Herbert WM, Trout K. – The lesser circulation in pulmonary fibrosis secondary to sarcoidosis and its relationship to respiratory function. *Chest*, 1971, 60, 371–378.
16. Rizzato G, Brambilla I, Bertoli L, Conti F, Merlini R, Mantero O. – Impaired airway function and pulmonary haemodynamics in sarcoidosis. *In:* Eighth international conference on sarcoidosis and other granulomatous diseases. Alpha Omega Publ, Cardiff, UK, 1978, pp. 349–360.
17. Weitzenblum E, Pauli G, Roeslin N, Vandevenne A, Bohner C, Oudet P. – Les données hemodynamiques pulmonaires au cours de la crise d'asthme: incidence des conditions mecaniques endothoraciques. *J Fr Med Chir Thorac*, 1971, 25, 487–509.
18. Vogt P, Ruttner JR. – Das Cor pulmonale aus pathologisch-anatomischer sicht, *Schwei Med Wschr*, 1977, 107, 549–553.
19. Smith LJ, Lawrence JB, Katzenstein ALA. – Vascular sarcoidosis: a rare cause of pulmonary hypertension. *Am J Med*, 1983, 285, 38–44.

Effets des traitements aux corticostéroïdes sur l'hémodynamique pulmonaire des patients sarcoïdosiques. J. Gluskowski, I. Hawrylkiewicz, D. Zych, J. Zieliński.

RÉSUMÉ: Nous avons investigué les effets d'un traitement de 12 mois aux stéroïdes sur l'hémodynamique pulmonaire chez 24 patients atteints de stade II ou III de sarcoïdose pulmonaire. Avant traitement, tous les patients ont subi un cliché thoracique, des épreuves fonctionnelles pulmonaires et une

hémodynamique pulmonaire mesurée au repos et au cours d'un effort submaximal. L'on a trouvé une hypertension pulmonaire de repos chez 3 patients, et observé une augmentation anormale de la PAP à l'effort chez 18 patients. Toutes les investigations ont été répétées après un an de traitement. Chez presque tous les patients (22), l'on a noté une régression des modifications radiologiques pulmonaires et une amélioration de la fonction pulmonaire. Les modifications de la circulation pulmonaire furent moins homogènes. Chez seulement la moitié des patients étudiés, la régression de la maladie observée sur les clichés thoraciques et l'amélioration de la fonction pulmonaire se sont accompagnées d'une amélioration de l'hémodynamique pulmonaire.
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