The Relationship Between Pulmonary Hemodynamics, Arterial Blood Gases and Ventilatory Tests in Scleroderma

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SUMMARY

Scleroderma is a disorder characterized by skin, gastrointestinal tractus, cardiac, pulmonary, renal and muscular involvement with unknown etiology. Raynaud's phenomenon is a frequent finding in the early stages. Pulmonary hypertension may be observed in 33-60% of the patients. Derangement of pulmonary functions and arterial desaturation is common during the course of the disease. The aim of this study was to investigate the relationship between pulmonary hemodynamics, pulmonary function tests and arterial blood gases in 13 patients with scleroderma. All patients were female with age ranging between 27-64 years. Except for two patients, all had Raynaud's phenomenon. The analysis of mean pulmonary artery pressure showed mild pulmonary hypertension. There was a significant negative correlation between the mean pulmonary artery pressure and the PaO_2 ($p< 0.05$). Restrictive ventilatory impairment with decreased DLCO was observed. In conclusion, pulmonary hypertension which is a feature related with poor prognosis is a frequent complication of scleroderma and is correlated strongly with hypoxemia and pulmonary fibrosis.

Key Words: *Scleroderma, pulmonary hypertension, pulmonary function tests.*

ÖZET

Sklerodermada Pulmoner Hemodinami, Arteryel Kan Gazları ve Solunum Testleri Arasındaki İlişki

Skleroderma etyolojisi bilinmeyen, cilt, gastrointestinal sistem, kalp, akciğerler, böbrek ve kasları tutan bir hastalıktır. Raynaud's fenomeni erken evrelerde sık görülen bir bulgudur. Pulmoner hipertansiyon olguların %33-60'ında görülmektedir. Hastalığın seyrinde solunum fonksiyonlarında azalma ve arteryel desatürasyon sık görülür. Bu çalışmadaki amacımız; sklerodermalı 13 olguda pulmoner hemodinami, solunum fonksiyonları ve arter kan gazları arasındaki ilişkiyi araştırmaktı. Bütün olgular kadındı ve yaşları 27-64 arasında değişiyordu. İki olgu dışında hepsinde Raynaud's fenomeni bulunuyordu. Ortalama pulmoner arter basınç değerine göre hafif şiddetli pulmoner hipertansiyon tespit edildi. Ortalama pulmoner arter basıncı ile PaO_2 arasında anlamlı negatif korelasyon vardı ($p< 0.05$). Olgularımızda difüzyon kapasitesinde azalma ile birlikte restriktif ventilatuvar defekt gözlendi. Sonuç olarak; kötü prognoz göstergesi olan pulmoner hipertansiyon, sklerodermanın sıklıkla görülen bir komplikasyonudur. Hipoksemi ve pulmoner fibrozis ile koreledir.

Anahtar Kelimeler: *Skleroderma, pulmoner hipertansiyon, solunum fonksiyon testleri.*

Scleroderma is a multisystem connective tissue disorder with unknown etiology, characterized by inflammatory, fibrotic and degenerative changes and accompanied by vascular abnormalities in the skin and in a variety of internal organs, such as gastrointestinal tractus, heart, pulmonary, renal and muscles (1,2).

Pulmonary involvement may occur in the early stages of scleroderma pulmonary involvement as a restrictive lung disease and an impaired diffusing capacity for carbonmonoxide has been recognized in scleroderma since Baldwin et al first described these findings in 1949 (3). In addition, obstructive pulmonary involvement including both small and large airways has been identified (2,3). Functional impairment may not be present in the early stages of the disease. Pulmonary function test parameters, such as lung volumes and carbonmonoxide diffusing capacity (DLCO), are reduced significantly with the development of pulmonary fibrosis.

Arterial abnormalities were also identified in early studies of scleroderma. Changes in the pulmonary arterial system and pulmonary fibrosis may cause progressive pulmonary hypertension (PH), which results in pulmonary insufficiency and the development of chronic cor pulmonale (2,4,5). The incidence of PH is particularly high in the CREST variant of scleroderma.

Scleroderma is associated with a significant reduction in survival rates. Death ensues due to respiratory failure, PH or involvement of extrapulmonary organs such as heart, kidneys or gastrointestinal tract (1,6-8). A review of 11 studies, totalling over 2000 patients, revealed 5-year cumulative survival rates ranging from 34-73 percent, with a mean value of 68 percent. PH is the major cause of mortality (7).

The purpose of this prospective study was to investigate the changes in pulmonary hemodynamic parameters, arterial blood gases and ventilatory parameters in patients with scleroderma.

MATERIALS and METHODS

The study group consisted of 13 female patients who were diagnosed as scleroderma in the department of immunology. The diagnosis of scleroderma was based on the history of Raynaud's phenomenon, physical examination and skin biopsy histopathology. Posteroanterior chest radiography (X-Ray), pulmonary function tests (PFTs), arterial blood gases (ABG) and right heart catheterization was performed in all patients in the department of pulmonary diseases. The presence of sclerodactyly, arthralgia/arthritis, dysphagia Raynaud's phenomenon and exertional dyspnea were recorded. Because of economical and technical limitations, computerized tomography was not available.

Pulmonary Function Tests (PFT)

PFT including airflow rates, lung volumes, diffusing capacity was performed by System 2400 (SensorMedics, Bilthoven, The Netherlands) at rest, on sitting position. DLCO was measured by single breath method. Tests were repeated three times and the best was accepted. Kory-Polgar nomograms were used for the calculation of the predicted (9).

Arterial Blood Gases (ABG)

Arterial blood gas samples were obtained while breathing room air, at rest. Analysis of arterial blood gas parameters was performed by ABL 330 (Radiometer, Copenhagen-Denmark).

Pulmonary Hemodynamics

Right heart catheterization based on Grandjean method was performed in supine position, at rest. 3F catheter was inserted via basilic vein and mean, diastolic and systolic pulmonary artery pressures (PAP) were recorded. Unitrans TM disposable pressure transducer was used to record the pressure tracings. In supine position the zero reference level for pressure measurements was accepted as 7.5 cm below the sternal angle. All PAP measurements were averaged over 3 consecutive respiratory cycles (10). Mean PAP > 20 mmHg was accepted as pulmonary hypertension.

Statistical Evaluation

Statistical Package for Social Sciences (SPSS) software version 6.0 (SPSS, Inc., Chicago, IL, USA) was used for statistical analysis. Mean values of demographic features and functional parameters were evaluated by descriptive statistics. The correlation between hemodynamics

and PFT and ABG parameters were evaluated by linear correlation. The significance was evaluated by Pearson test. Significance was accepted as $p < 0.05$.

RESULTS

In this study, the mean age was 45 ± 5, ranging from 27 to 67 years. Eleven patients were nonsmokers. We observed that 5 patients had exertional dyspnea, 3 patients had arthralgia/arthritis, 4 patients had skin thickness on palm fingers, 11 patients had Raynaud's phenomenon and 2 patients had dysphagia (Table 1).

The results of pulmonary hemodynamic parameters and ABG gases were shown in Table 2. Seven (54%) patients were hypoxemic. In 10 cases (76.9%) resting the mean PAP was greater than 20 mmHg. The overall mean PAP value was 22.85 ± 6.08 mmHg. The mean PaO_2 was 75.68 ± 17.98 mmHg. All hypoxemic patients had elevated mean PAP.

Table 1. Demographic characteristic and clinical findings of patients.

	Number of patients
Smoking	2 (15%)
Exertional dyspnea	5 (38%)
Arthralgia/arthritis	3 (23%)
Skin thickness	4 (31%)
Raynaud's phenomenon	11 (85%)
Dysphagia	2 (15%)

Table 2. The mean values of hemodynamic and arterial blood gases parameters.

Parameters	Number of patients	Mean ± SD
Age (years)	13	46.82 ± 13.74
Systolic PAP (mmHg)	13	29.38 ± 7.21
Diastolic PAP (mmHg)	13	14.80 ± 5.29
Mean PAP (mmHg)	13	22.85 ± 6.08
PaO_2 (mmHg)	13	75.68 ± 17.98
SaO_2 (%)	13	93.13 ± 5.98

The mean values of lung volumes, airflow rates and diffusing capacity parameters were summarized in Table 3. Nine patients (70%) had restrictive ventilatory defects (FVC < 70%) with a normal FEV_1/FVC ratio. DLCO was decreased in 7 out of 10 patients (70%).

The results of the correlation between hemodynamic, PFTs and ABG parameters were shown in Table 4. There were statistically significant negative correlation between mean PAP and PaO_2 (r: -0.56, $p < 0.05$); mean PAP and SaO_2% (r: -0.56, $p < 0.05$) (Figure 1,2). There was a significant positive correlation between MVV% and DLCO% (r: 0.71, $p < 0.05$) (Figure 3).

Roentgenographic findings revealed bilateral, diffuse, scattered infiltration and honeycombing at the lower two-thirds of the lungs. Two patients had cardiomegalia.

DISCUSSION

High prevalence of pulmonary involvement up to 70% was found at autopsy in scleroderma

Table 3. The mean values of airflow rates, diffusing capacity parameters.

Parameters	Number of patients	Mean ± SD
FVC (L)	13	2.02 ± 0.75
FVC (%)	13	71.08 ± 23.60
FEV_1 (L)	13	1.72 ± 0.67
FEV_1 (%)	13	73.54 ± 22.95
FEV_1/FVC (%)	13	87.69 ± 5.34
FEF_{25-75} (L/sec)	13	2.45 ± 0.88
FEF_{25-75} (%)	13	86.23 ± 28.02
FEF_{50} (L/sec)	13	3.04 ± 0.93
FEF_{50} (%)	13	83.77 ± 30.67
FEF_{75} (L/sec)	13	1.13 ± 0.65
FEF_{75} (%)	13	83.00 ± 40.64
MVV (L/min)	12	71.33 ± 22.22
MVV (%)	12	72.42 ± 21.25
DLCO (mL/min/mmHg)	10	13.57 ± 7.89
DLCO (%)	10	63.50 ± 32.33
DLCO/VA (1/min/mmHg)	10	4.21 ± 1.12
DLCO/VA (%)	10	110.90 ± 33.51

Table 4. The correlation between hemodynamic, PFT and ABG parameters.

	PAP sys	PAP dias	PAP mean
PaO_2 (mmHg)	-0.54	-0.60*	-0.56*
SaO_2 (mmHg)	-0.51	-0.60*	-0.56*
FVC (%)	-0.37	0.07	-0.23
FEV_1 (%)	-0.41	0.09	-0.23
FEV_1/FVC (%)	-0.54	-0.55*	-0.47
FEF_{25-75} (%)	-0.33	0.03	-0.19
FEF_{50} (%)	-0.05	0.36	0.16
FEF_{75} (%)	-0.37	-0.24	-0.36
MVV (%)	0.04	0.44	0.25
DLCO (%)	-0.60	-0.36	-0.62
DLCO/VA %	-0.10	0.03	-0.20

* $p< 0.05$

(11). Pulmonary involvement is characterized pathologically by diffuse interstitial fibrosis and vascular lesions such as medial hypertrophy and intimal proliferation in pulmonary arterioles. In the later stage of the disease, pulmonary abnormalities may be associated with ventilatory restriction, severe impairment of diffusion, the development of PH, corpulmonale, and respiratory failure (5).

Isolated pulmonary vascular injury is the most common histopathologic feature, occuring in 50% of autopsy and surgical pathologic specimens of patients with CREST syndrome (11). The prevalence of PH in scleroderma has been estimated to be as high as 33-60% (5,11-14).

The evidence of PH in cases with scleroderma is a valuable finding in the determination of prognosis and degree of disability. PH is the result of progressive reduction of pulmonary arterial bed and increased pulmonary vascular resistance in the sclerodermic patients with pulmonary fibrosis. Pulmonary arteriopathy is the probable cause of PH in patients with scleroderma. Pulmonary arterial changes expressed as medial hypertrophy and concentric intimal proliferation in smaller muscular arteries and in the arterioles are common in scleroderma. Chronic hypoxia leads to hypoxic pulmonary vasoconstriction

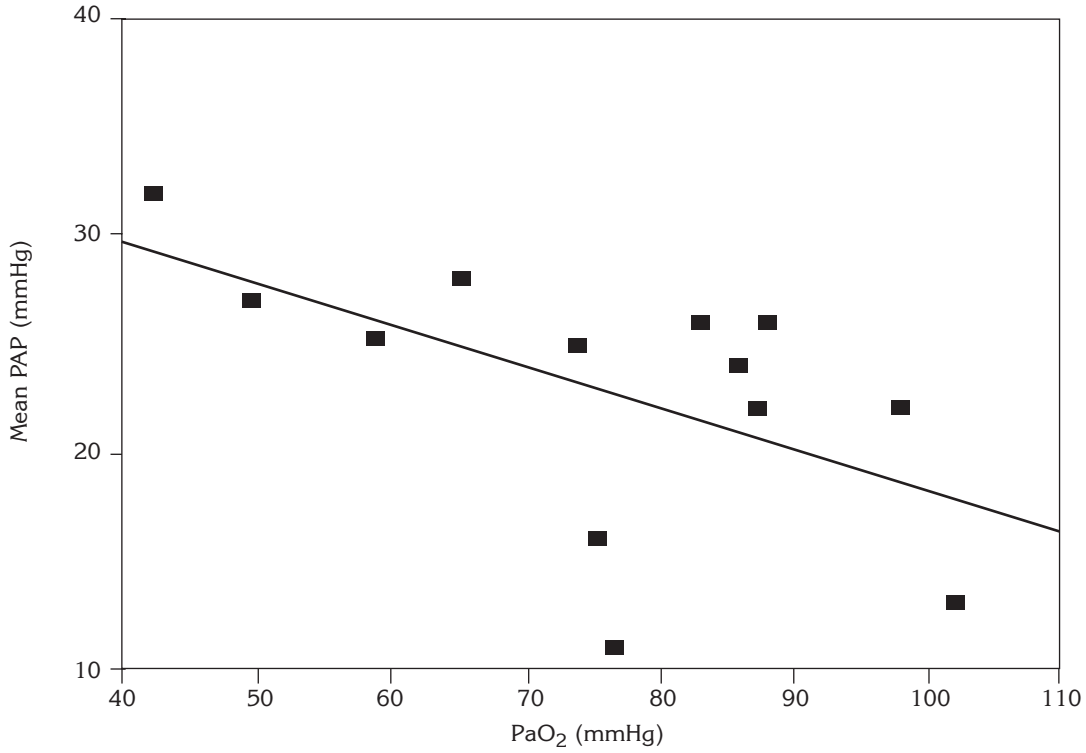

Figure 1. The correlation between PaO_2 and mean PAP (r: -0.56, $p< 0.05$).

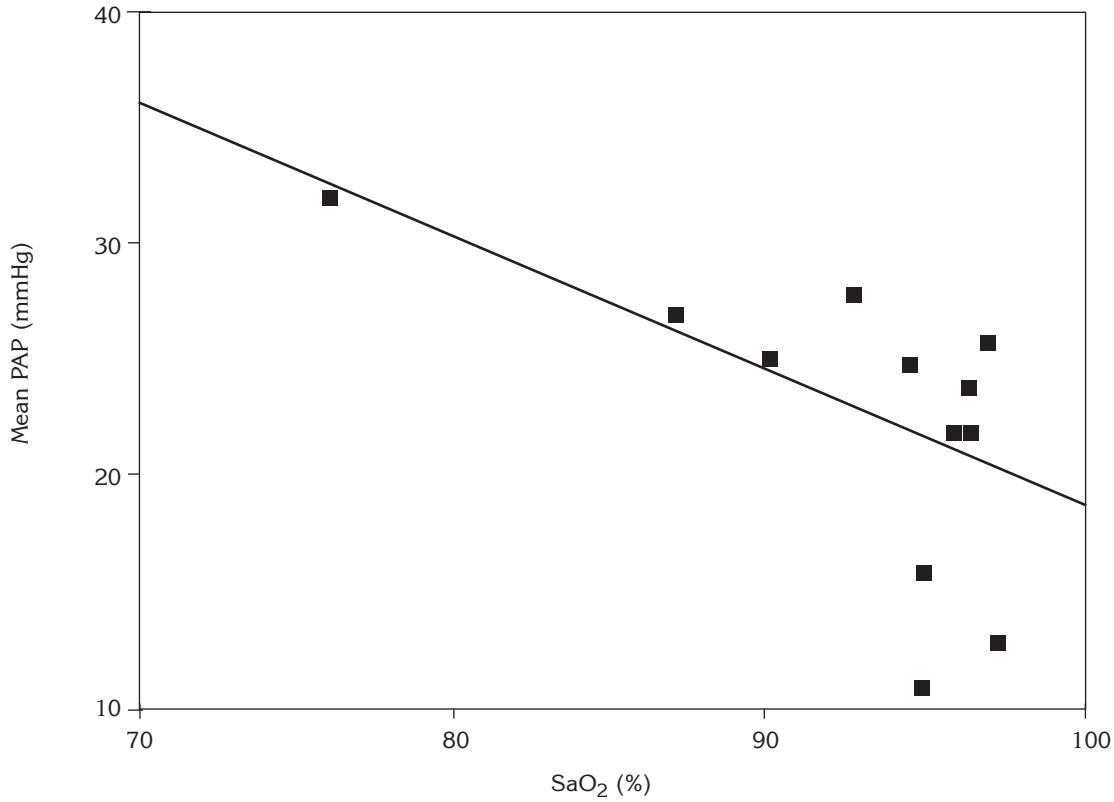

Figure 2. The correlation between SaO_2 and mean PAP (r: -0.56, p< 0.05).

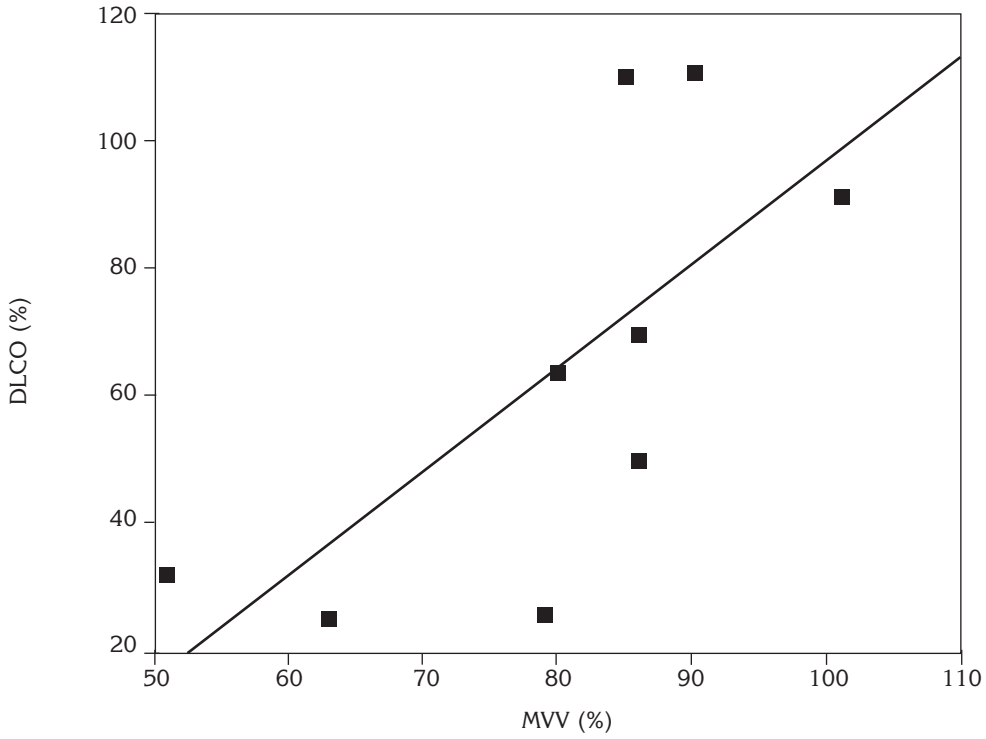

Figure 3. The correlation between MVV (%) and DLCO (%) (r: 0.71, p< 0.05).

and pulmonary hypertension in patients with scleroderma (4,5,13-15). Murata et al, showed that 59% patients with scleroderma had pulmonary hypertension. According to these researchers pulmonary fibrosis and pulmonary arteriopathy are 2 significant factors for the development of PH (13).

In our study, we demostrated a marked increase in mean PAP in 10 out of 13 patients with scleroderma. All patients with PH had various degress of fibrosis in X-Ray. In 5 patients with PH, PaO_2 and SaO_2 were also decreased. We found a significant correlation between the mean PAP and PaO_2, SaO_2 % at rest.

In former studies the frequency of pulmonary function abnormalities has varied widely from 60% to 100%. Restrictive ventilatory defects are present in the late stages of the disease. A markedly decreased DLCO is an important predictor of mortality. Several studies have demonstrated that a diminished DLCO is the earliest abnormality. Moreover the reduction in DLCO proved to be an important criterion for disability in cases with normal X-Ray and PFT (3,8,16-20). We observed reduction in FVC and DLCO% which resulted from the restriction due to the fibrosis.

When various connective tissue diseases (SLE, scleroderma, RA) were compared, it has been shown that the impairment of respiratory function was greater in scleroderma (17). Steen et al, showed that the pulmonary function indices were not significantly different between patients with diffuse scleroderma and those with CREST syndrome. The overall mean FVC percent predicted was significantly lower in diffuse scleroderma. The patients with pulmonary fibrosis and restrictive disease had a marked decrease in FVC (3).

Fibrosing alveolitis consists of a mixture of inflammatory cell infiltration and interstitial fibrosis. Inflammation leads to fibrosis (21). According to some investigators, fibrosis causes restriction and PH. Wells et al, showed a close relationship between the extent of fibrosing alveolitis determined by CT findings and percent predicted FVC and DLCO (19). The reduction of DLCO may be the result of either reduced alveolar capillary surface area available for gas transfer because of interstitial fibrosis or the presence of a primary vascular lesion, unrelated to fibrosis, obliterating many of the small pulmonary vessels and capillaries (16).

We observed small airways obstruction characterized by decreased FEF_{50} and FEF_{75} in 4 patients (30%). Positive correlation ($p< 0.05$) was found between FEF_{50}, FEF_{75} and FVC, FEV_1 (Table 3). Small airways obstruction, due to mainly peribronchial inflammation and fibrosis, is sensitive finding for the detection of obstructive disease in the early stages. Kostopoulos et al, observed that 22.6 percent of all patients had evidence of small airways dysfunction (22).

Ungerer et al suggested that the patients with definite PH had a significantly lower mean single breath diffusing capacity for carbonmonoxide than those with normal mean pulmonary artery pressure. Nearly all patients with progressive systemic sclerosis have some abnormality in pulmonary function, most commonly a reduction in single breath diffusing capacity for carbonmonoxide. However, studies have shown that an abnormal result of lung function testing is unlikely to correlate well with pulmonary arterial hypertension (5). In our study, there was no significant correlation between mean PAP and pulmonary function test parameters. On the other hand, the negative correlation between the mean PAP and PaO_2, also the mean PAP and SaO_2% were statistically significant. All hypoxemic patients had elevated mean PAP. It is known that hypoxic pulmonary vasoconstriction contributes to elevated pulmonary vascular resistance in patients with scleroderma. Morgan et al, showed that there was a significant correlation between the fall in pulmonary vascular resistance and baseline PaO_2 in patients with scleroderma. In these patients, PaO_2 and PAP were predictive of pulmonary vascular response to oxygen therapy (15). Furthermore, pulmonary fibrosis in patients with scleroderma contributes to the development of PH (4,5,13). In our study, all sclerodermic patients with PH had bilateral, diffuse scattered infiltration at the lower two-thirds of the lung on X-Ray. The advent of computerized

tomography has been more important clinical advance in the management of diffuse lung disease in the last decade. The prevalence of lung fibrosis found on computerized tomography ranges from 60-70% in the studies (23). Unfortunately, because of economical and technical limitations, computerized tomography was not available in our study.

In conclusion, pulmonary vascular system is often affected by scleroderma. The development of PH is an indicator of poor prognosis and degree of disability. Pulmonary hypertension was accompanied with arterial hypoxemia and pulmonary fibrosis in these patients. There fore, the evaluation of pulmonary hemodynamics has an important role in the follow up and the determination of proper mode of therapy and prognosis in patients with scleroderma.

REFERENCES

1. *Bryan C, Knight C, Black CM, Silman AJ. Prediction of five-year survival following presentation with scleroderma. Arthritis & Rheumatism 1999; 42: 2660-5.*
2. *Owens GR, Follansbee WP. Cardiopulmonary manifestations of systemic sclerosis. Chest 1987; 91: 118-27.*
3. *Steen VD, Owens GR, Fino GJ, et al. Pulmonary involvement in systemic sclerosis (scleroderma). Arthritis & Rheumatism 1985; 28: 759-67.*
4. *Trell E, Lindström C. Pulmonary hypertension in systemic sclerosis. Ann Rheum Dis 1971; 30: 390-400.*
5. *Ungerer RG, Tashkin DP, Furst D, et al. Prevalence and clinical correlates of pulmonary arterial hypertension in progressive systemic sclerosis. Am J Med 1983; 75: 65-74.*
6. *Tashkin DP, Clements PJ, Wright RS, et al. Interrelationship between pulmonary and extrapulmonary involvement in systemic sclerosis. Chest 1994; 105: 489-95.*
7. *Lee P, Langevitz P, Alderdice CA, et al. Mortality in systemic sclerosis (scleroderma). Quarterly J Med 1992; 82: 139-48.*
8. *Peters-Golden M, Wise RA, Hochberg MC, et al. Carbonmonoxide diffusing capacity as predictor of outcome in systemic sclerosis. Am J Med 1984; 77: 1027-34.*
9. *Kory RC, Callahan R, Baren HG, Syner JC. The veterans administration army cooperative study of pulmonary functions I. clinical spirometry in normal man. Am J Med 1961; 30: 243-58.*
10. *Çelik G, Karabıyıkoğlu G. Local and peripheral plasma endothelin-1 in pulmonary hypertension secondary to chronic obstructive pulmonary disease. Respiration 1998; 65: 289-94.*
11. *Battle RW, Davitt MA, Cooper SM, et al. Prevalence of pulmonary hypertension in limited and diffuse scleroderma. Chest 1996; 110: 1515-9.*
12. *Stupi AM, Steen VD, Owens GR, et al. Pulmonary hypertension in the chest syndrome variant of systemic sclerosis. Arthritis & Rheumatism 1986; 29: 515-24.*
13. *Murata I, Takenaka K, Yoshinoya S, et al. Clinical evaluation of pulmonary hypertension in systemic sclerosis and related disorders. Chest 1997; 111: 36-43.*
14. *Salerni R, Rodnan GP, Leon DF, et al. Pulmonary hypertension in the CREST syndrome variant of progressive systemic sclerosis (scleroderma). Ann Inter Med 1977; 86: 394-9.*
15. *Morgan JM, Griffiths M, Bois RM, Evans TW. Hypoxic pulmonary vasoconstriction in systemic sclerosis and primary pulmonary hypertension. Chest 1991; 99: 551-6.*
16. *Sfikalis PP, Kyriakidis M, Vergos C, et al. Diffusing capacity of the lung and nifedipine in systemic sclerosis. Arthritis & Rheumatism 1990; 33: 1634-9.*
17. *Laitinen O, Salorinne Y, Poppius H. Respiratory function in systemic lupus eryhematosus, scleroderma and rheumatoid arthritis. Ann Rheum Dis 1973; 32: 531-5.*
18. *Edelson JD, Hyland RH, Ramsden M, et al. Lung inflammation in scleroderma: Clinical, radiographic, physiologic and cytopathological features. J Rheumatology 1985; 12: 957-63.*
19. *Wells AU, Hansell DM, Rubens MB, et al. Functional impairment in lone crptogenic fibrosing alveolitis and fibrosing alveolitis associated with systemic sclerosis. Am J Respir Crit Care Med 1997; 155: 1657-64.*
20. *Tager RE, Tilky M. Clinical and laboratory manifestations of systemic sclerosis (scleroderma) in Black South Africans. Rheumatology 1999; 38: 397-400.*
21. *Wells AU, Rubens MB, Bois RM, Hansell DM. Functional impairment in fibrosing alveolitis: Relationship to reversible disease on thin section computed tomography. Eur Respir J 1997; 10: 280-5.*
22. *Kostopoulos C, Rassidakis A, Sfikakis PP, et al. Small airway dysfunction in systemic sclerosis. Chest 1992; 102: 875-81.*
23. *Lynch DA. Imaging of diffuse infiltrative lung disease. In: Oliveri D, Du Bois RM (eds). Interstitial Lung Diseases. Eur Respir Monograph 14, 2000; 5: 29-54.*

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