Pulmonary Hypertension in Systemic Lupus Erythematosus


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Pulmonary and cardiac manifestations (**Table 1**) are common in systemic lupus erythematosus (SLE). They occur in the vast majority of patients, and as a result, patients with SLE have a marked decrease in exercise compared with controls.[1,2] Although pulmonary hypertension (PH) is less frequently reported, exercise hemodynamics are abnormal in patients with SLE, with higher pulmonary artery pressures at rest and for each stage of exercise when compared with controls.[2] This occurs in the setting of similar cardiac indexes, which suggests that the mechanism for exercise intolerance is an increase in pulmonary vascular resistance. In addition to cardiopulmonary complications, exercise intolerance in SLE may be caused by overwhelming fatigue, physical deconditioning, peripheral neuropathy, arthralgias/arthritis, and muscle weakness, which further complicates the evaluation of dyspnea in patients with SLE.

All 5 World Health Organization (WHO) categories (**Figure 1**) of PH can be found in patients with SLE. The whole spectrum of pulmonary arterial hypertension (PAH) in SLE has also been reported, including pulmonary veno-occlusive disease and pulmonary capillary hemangiomatosis.[3,4] Pulmonary arterial hypertension as a consequence of noncirrhotic portal hypertension has also been reported.[5,6] Pulmonary venous hypertension is often seen as a result of left ventricular dysfunction from diastolic dysfunction, myocarditis, ischemic heart disease, or left ventricular valvular dysfunction secondary to Libman Sachs endocarditis. Pulmonary hypertension in SLE may be a consequence of interstitial lung disease, diaphragmatic dysfunction, and chronic thromboembolic disease. Pulmonary hypertension has also been associated with pulmonary vasculitis with or without alveolar hemorrhage.[7-9]

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Table 1. Cardiopulmonary Manifestations of Systemic Lupus Erythematosus

Acute lupus pneumonitis	Obstructive lung disease
Acute reversible hypoxemia	Pericardial disease
Alveolar hemorrhage	Pleural effusion
Atelectasis	Pleurisy
Coronary artery disease	Pneumothorax
Diaphragmatic dysfunction	Pulmonary embolism
Diastolic dysfunction	Pulmonary hypertension
Interstitial lung disease	Uremic pulmonary edema
Myocarditis	Valvular lesions

Prevalence, Demographics, and Risk Factors

Studies of patients with SLE have found a prevalence of PH ranging from 0.5% to 43%, although the degree of PH is typically modest.[10-16] The prevalence varied based on the method used for detection, and many patients in these reports either had significant restrictive lung disease or data reported were inadequate to determine the etiology of the PH. The prevalence of comorbid SLE and PH (SLE-PH) has been shown to increase over time. In a serial study of 28 patients with SLE, the prevalence of PH measured by echocardiogram increased from 14% to 43% with 5 years of follow-up.[16] In an autopsy series of 20 patients with SLE, 8 (40%) patients had evidence of pulmonary vascular involvement; although clinically overt PH was present in only 1 patient.[17]

Clinical manifestations (**Table 2**) of SLE-PH are variable, but the predominant features include the insidious onset of shortness of breath, fatigue, and chest pain. Unfortunately, the disease process is usually far advanced with irreversible changes of the pulmonary vasculature by the time symptoms or signs develop. An isolated diffusion defect may be predictive of PH in patients with SLE.[18]

The characteristics of patients with SLE-PH are similar to those of patients with idiopathic pulmonary arterial hyper-

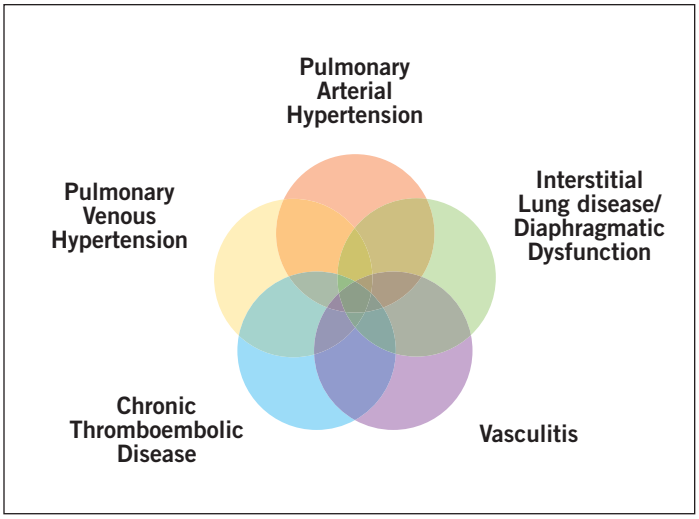

Figure 1. Etiology of pulmonary hypertension in systemic lupus erythematosus.

tension (IPAH), which raises the possibility of shared etiologies. Patients are predominantly women of child-bearing potential: aged from 18 to 40 years with a 10 to 1 ratio of female over male.[19,20] In a study that compared 20 patients with SLE-PH with 34 patients with IPAH, those with SLE-PH had a significantly shorter time from symptom onset to diagnosis and were more likely to have Raynaud phenomenon and the presence of autoantibodies.[21] Patients with SLE-PH were also more likely to have a pericardial effusion and were less likely to be vasoresponsive to nitric oxide during right heart catheterization. In addition, SLE-PH patients had less hypoxemia and better hemodynamics, but a significantly increased mortality risk.

Extrapulmonic manifestations can be found with IPAH including Raynaud phenomenon (30%), arthralgias, and arthritis.[22-24] Serologic abnormalities such as hypergammaglobulinemia, positive antinuclear antibody (ANA), rheumatoid factor, and biological false-tests for syphilis have also been reported, which suggests that some patients with IPAH may have an autoimmune disease confined to the pulmonary vasculature.[22-25] Alternatively, these patients may be at risk for developing an underlying connective tissue disease (CTD), such as SLE, later on in the disease course.

Study findings indicate that the duration of SLE does not correlate with the development of PH, although many patients with SLE develop PH within the first 5 years. Pulmonary hypertension may be a presenting manifestation of SLE that necessitates close follow-up of all patients newly diagnosed with IPAH.[26] The occurrence of PH also appears unrelated to the severity or activity of SLE such as high anti-double stranded (ds)DNA and/or grossly elevated erythrocyte sedimentation rate (ESR) and can occur when nonpulmonary disease activity is quiescent.[19,20,26,27] This is in contrast to a study by Simonson and colleagues[13] that showed that the duration of SLE and the duration of steroid therapy tended to be shorter in SLE patients with PH, although the use of anti-inflammatory agents was more common when compared to a population of SLE patients without PH. An additional study showed that PH, as recognized by right ventricular echocardiography, occurred during 288 acute flares of SLE, which suggests that a reversible increase in pulmonary vasoconstrictor tone may be the first hemodynamic disturbance, with fixed PH developing later.[28]

As many as 75% of patients with SLE-PH have Raynaud phenomenon, which is higher than the expected rate of 25% among all patients with SLE.[13,19,20,25,29,30] Asherson and colleagues[19,20] have reported that 63% of patients in their study had renal disease and approximately one-third had evidence of peripheral cutaneous vasculitis, livedo reticularis, and digital gangrene.

Table 2. Possible Risk Factors for the Development of Pulmonary Hypertension in Systemic Lupus Erythematosus

Female sex
Isolated reduction in diffusion
Raynaud phenomenon
Renal disease
Digital gangrene
Cutaneous vasculitis/livedo reticularis
Rheumatoid factor
Antiribonuclear protein
Antiphospholipid antibodies
Antiendothelial antibodies

Autoantibodies

Patients with SLE-PH are universally positive for ANA. Antibodies to ribonuclear protein (RNP) and rheumatoid factor (RF) are often present in SLE-PH, although no pathogenic role has been postulated. Frequently, patients have antiphospholipid antibodies (aPL) and antiendothelial antibodies (aECA).[10,19,20,30,31] The prevalence of RNP in SLE-PH is reported in a majority of patients, which is greater than the reported prevalence of 25%, which occurs in all patients with SLE.[30] The prevalence of RF has been reported to be as high as 50% to 80% in SLE-PH.[10,19] The frequency of PH in patients with SLE and a positive aPL is considerably higher than in patients with SLE and negative aPL (83% versus 25%).[30]

Pathology

Autopsy findings suggest that SLE-PH may be multifactorial in origin.[25,30-32] Findings include acute fibrinoid necrosis and vasculitis, as well as chronic intimal fibrosis, medial hypertrophy, alteration of elastic laminae, periadventitial fibrosis, aneurysmal dilation, and plexiform lesions, which are virtually identical to the alterations seen in patients with IPAH.[9,17,29] These changes occurred in arteries, arterioles, and veins. Occasional cases with thrombotic arteriopathy have also been reported and were found to correlate with a hypercoagulable status, including positive lupus anticoagulant and anticardiolipin antibodies.[6,33]

Acute inflammation of small pulmonary arteries and arterioles has also been found on autopsy in patients with SLE.[30] Deposition of circulating immune complexes (IgG and C1q) with antinuclear and anti-dsDNA activity has been

described. The presence of diffuse interstitial fibrosis in affected vessels further supports the likelihood of chronic inflammation that occurs as a result of the deposition of such complexes and/or direct injury to the vessel wall.[10,34]

Pathogenesis

The causal relationship between SLE and PH has never been established. However, multiple small vessel inflammation and/or vasculitis as well as sustained vasoconstriction, in situ thrombosis, and/or thromboembolism and interstitial pulmonary fibrosis, all features of SLE, may damage and reduce the pulmonary vascular bed and lead to PH.[20,35]

There is an imbalance between vasoconstrictors and vasodilators in SLE-PH. Higher serum endothelin levels were found in patients with SLE-PH compared with non-PH patients with SLE and healthy controls.[36] There is also an imbalance of thromboxane and prostacyclin that results in endothelial dysfunction, vascular damage, and remodeling that is felt to be pathophysiologically important.[37] The inhibition of prostacyclin production by endothelial cells is possibly related to the action of aPL on the endothelial surface.[38,39] In addition, when antiphospholipid antibodies bind to the phospholipids on the endothelial surface, there is resultant in-situ thrombosis and the release of soluble mediators and subsequent vascular injury.[9,37]

Antiendothelial cell antibodies may also play a key pathogenic role in the development of SLE-PH. Systemic lupus erythematosus is an autoimmune disease characterized by polyclonal B cell activation. One factor that stimulates B cells to produce immunoglobulin is interleukin 6 (IL-6), and endothelial cells are an important source of IL-6. Serum titers of aECA are elevated in patients with active SLE, particularly in patients with PH, digital vasculitis, Raynaud phenomenon, or serositis. Binding of antiendothelial cell antibodies or immune complexes to endothelial cells may augment the release of IL-6 and result in vascular injury and ensuing intimal and medial proliferation and in situ thrombosis.[40]

The striking correlation between the occurrence of Raynaud phenomenon and SLE-PH suggests that pulmonary arterial vasospasm may also be involved in the pathogenesis of SLE-PH. Raynaud phenomenon is part of a systemic vascular response that includes a decrease in size of the pulmonary capillary bed, which may in turn result in muscular necrosis and secondary inflammation.[41,42] However, since the vast majority of patients with Raynaud phenomenon do not develop PH, this would suggest that other factors are operative in those who are prone to develop PH. Alternatively, in conjunction with the high prevalence of RNP found in SLE-PH, this subset of SLE patients may actually belong to the scleroderma spectrum of disease where PH is more common.

Treatment

There are no independent consensus guidelines for the treatment of SLE-PH; instead, treatment recommendations are generalized for PAH from all causes. There are no reports of the efficacy of calcium channel blockers in patients with SLE-PH and vasoreactivity is rare.

Endothelin receptor antagonists. Endothelin is a key pathogenic mediator of PAH secondary to CTD.[43] A post-hoc analysis of the CTD subgroup from the pivotal studies of bosentan and their open-label extensions included 8 patients (12%) with SLE.[43] Patients with PAH secondary to CTD who were treated with bosentan were stable during the 6-minute walking distance test (+19.5 m, 95% confidence interval [CI] –3.2 to 42.2), whereas patients treated with placebo deteriorated (–2.6 m, 95% CI –54.0 to 48.7). In a second small uncontrolled study composed of patients with scleroderma and SLE, long-term treatment with bosentan was effective in improving exercise capacity and pulmonary hemodynamics in patients with CTD-associated PAH.[44] Patients with SLE were also included in the pivotal trials for ambrisentan and sitaxsentan; the CTD subgroup analyses in these trials have yet to be published.

Phosphodiesterase type-5 inhibitors. Case reports have shown that sildenafil improved quality of life in patients with SLE-PH and a minority of patients with SLE was included in the pivotal trial leading to the regulatory approval of sildenafil.[45,46]

Prostanoid therapy. Treatment of PAH with intravenous epoprostenol has been shown to improve hemodynamics, exercise tolerance, functional status, and quality of life in patients with IPAH and PAH related to the scleroderma spectrum of disease and is felt to be of significant benefit in other forms of CTD. There are multiple case reports describing a benefit from epoprostenol in patients with SLE-PAH. The largest case series (n = 6) of patients with SLE showed that epoprostenol improved functional class in all patients with a dose ranging from 4 to 46 ng/kg/min.[26] Four of the 6 patients underwent repeat hemodynamic evaluation (9 to 16 months after starting epoprostenol) and had a 38 ± 21% improvement in their mean pulmonary artery pressure and a 58 ± 12% improvement in their pulmonary vascular resistance.

The adverse effects from epoprostenol did not differ from those seen in patients with IPAH, and except for one patient, there was no exacerbation of SLE. All patients were treated with anticoagulation; nevertheless, one patient with aPL developed a right subclavian and jugular vein thrombosis that required removal of a Hickman catheter and subsequently severe thrombocytopenia developed. Severe refractory thrombocytopenia has been reported in a second case series of patients with SLE-PH.[47]

A subgroup analysis of 2 multicenter, randomized double-blind placebo-controlled prospective trials of treprostinil versus placebo in 470 patients with PAH included 90 patients with CTD, 25 (28%) of whom had SLE.[48] There were no statistically significant differences in pretreatment and posttreatment hemodynamic variables between patients with different CTDs. Modest statistically significant improvements were seen in cardiac index and pulmonary vascular resistance. After 12 weeks, the placebo-corrected median improvement from baseline in the 6-minute walking distance test was 25 m in treprostinil-treated patients (P = .055); this improvement appeared to be dose related. Dyspnea-fatigue scores also improved in the treprostinil group compared with the placebo group (P = .014). Adverse effects included infusion site pain and typical side effects

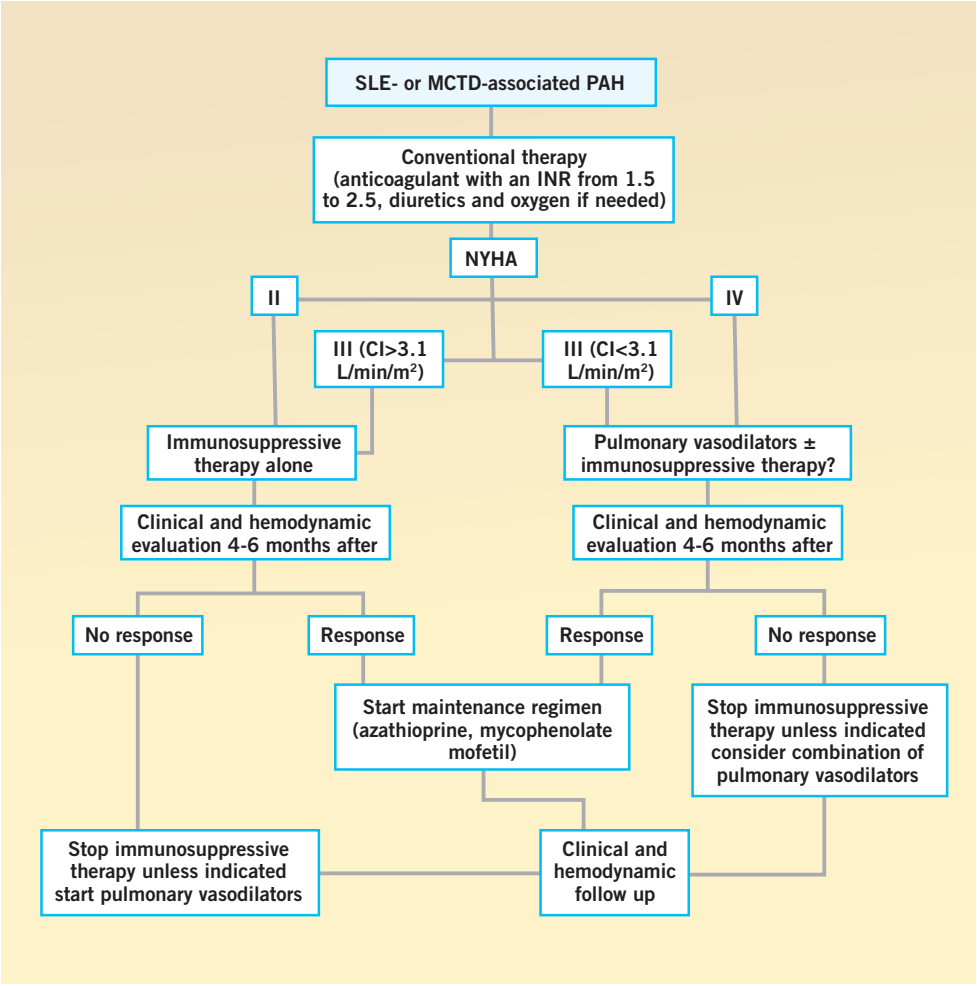

Figure 2. Proposed algorithm for treatment of patients with PAH associated with SLE or MCTD. Responders to immunosuppressive therapy were defined as patients in NYHA functional class 1 or 2 with hemodynamic improvement after the last pulse of cyclophosphamide. This algorithm must be read with caution because it relies on retrospective and open-label data and must therefore be confirmed by future randomized controlled trials. CI, cardiac index; INR, international normalized ratio; MCTD, mixed connective tissue disease; PAH, pulmonary arterial hypertension; NYHA, New York Heart Association; SLE, systemic lupus erythematosus. Copyright © 2008 American College of Rheumatology. Reprinted with permission from Jais et al.[55]

related to prostaglandins, and were tolerated by most patients.

Seventeen percent of subjects had CTD-associated PAH in the pivotal trial for inhaled iloprost, including a minority of patients with SLE-PAH.[49]

Immunosuppressive therapy. It is currently accepted that immune and/or inflammatory mechanisms contribute to PAH genesis or progression, especially in patients with CTD. Inflammatory cell infiltrates composed of macrophages and lymphocytes have been detected in plexiform lesions from patients with CTD-associated PAH. In addition, ANA, rheumatoid factor, IgG, and complement have been identified in the pulmonary vessel walls of the patients.[50] There are anecdotal reports of improvement in SLE-PH with corticosteroids, although corticosteroids alone are rarely sufficient.[51-53] There are also multiple case-reports and small case series of improvement in SLE-PH with immunosuppressive therapy, which suggests that a small subset of patients have more of a vasculitic as opposed to a vasculopathic phenotype.[54-56] Although most studies have shown no benefit in SLE-PAH without the addition of PAH specific therapy, these case-reports support aggressive control of the underlying SLE in addition to treatment of the PAH.

In the largest case series, 23 consecutive patients with SLE or mixed connective tissue disease-associated PH were treated with first-line immunosuppressive therapy (600 mg/ m^2 cyclophosphamide intravenously monthly for 6 months and oral prednisone 0.5-1 mg/kg/d for 4 weeks) either alone (n = 16) or in combination with vasodilators (n = 7).[55] Fifty percent of the patients in the first line immunosuppressive therapy alone group had a significantly improved WHO functional class, 6-minute walking distance test, and mean pulmonary artery pressure. Patients in WHO functional class I or II and/or with a cardiac index greater than 3.1 L/m^2 at baseline and a pulmonary vascular resistance less than 6.6 mmHg/L/min were more likely to respond to immunosuppressive therapy. There was also a trend for responders to have anti-dsDNA and anti-Sm antibodies. Although this was not significant, SLE activity was higher in the responders than in the nonresponders. Among the 8 patients who responded to the immunosuppressive therapy alone, 5 had a stable clinical and hemodynamic status and were alive after a mean follow-up of 47 ± 30 months after the last pulse of cyclophosphamide. Three patients had a relapse after the last pulse of cyclophosphamide and required further immunosuppressive therapy.

This relatively high frequency of relapses raises the issue of the need for an immunosuppressive maintenance regimen similar to that recommended for other serious visceral involvement such as nephritis. For patients with more severe disease, combination therapy with immunosuppressants and PAH-specific therapy was more effective, although the exact role of immunosuppressive therapy in this combination is not known (**Figure 2**). It remains to be demonstrated, in a large randomized placebo-controlled trial, whether adding immunosuppressive therapy to vasodilators at diagnosis would provide additional benefits to patients with SLE-PH.

Pregnancy. It is dangerous for women with active SLE to be pregnant. Pregnancy can exacerbate underlying SLE and is an absolute contraindication in patients with PAH.[57] Experts suggest that consideration should be given to screening all pregnant women with SLE and women with SLE who are planning on conceiving, given the seriousness

of SLE-PH.[58,59] The maternal mortality secondary to SLE-PH has been reported to be 66%, which is higher than the 56% mortality that has been reported in a systematic review of pulmonary vascular disease in pregnancy.[60,61]

Transplantation. Patients with multisystem involvement from CTD are generally excluded from consideration from heart-lung and lung transplantation because of profound donor organ shortages and complications of comorbidities as a result of systemic disease. However, heart-lung and lung transplantation for PAH has resulted in long-term survival in patients with SLE.[62,63] This is consistent with the favorable outcomes that can be expected after renal transplantation, an organ that is frequently transplanted in patients with SLE.[62]

Survival

Death due to PH is rare in several western series of SLE patients, accounting for less than 1% to 15.7% of the total, and PH is often unrecognized for a long period of time in those patients who eventually die from it. This is in contrast to SLE patients in Korea, where PH is the third leading cause of death in SLE patients.[64] The overall mortality rate of SLE-PH is 25% to 50% at 2 years after PH is diagnosed, although these studies are largely from the pretreatment era.[11,13,14,35,36,56,65] Even with improved mortality in today's treatment era, SLE-PH has a worse prognosis than IPAH.

Conclusion

Pulmonary and cardiac manifestations are common in SLE, and all 5 WHO categories of PH can be found in patients with SLE. Since there is no relationship between the severity or duration of SLE and the development of pulmonary hypertension, the association of these 2 conditions should be kept in mind by all clinicians who treat these patients. PAH can be a presenting manifestation of SLE, so patients with newly diagnosed IPAH need to be carefully evaluated for the development SLE. Consideration should be given to screening SLE patients with Raynaud phenomenon, positive aPL, RNP, RF, aECA, or those considering pregnancy. In patients with SLE-PH, experts suggest that the underlying SLE should be aggressively treated with immunosuppressive therapy in addition to PAH-specific therapies. ■

References

1. Gladman DD, Sternberg L. Pulmonary hypertension in systemic lupus erythematosus. *J Rheumatol*. 1985;12:365-367.
2. Winslow TM, Ossipov M, Redbert RF, et al. Exercise capacity and hemodynamics in systemic lupus erythematosus: a Doppler echocardiographic exercise study. *Am Heart J*. 1993;126:410-414.
3. Corrin B, Spencer H, Turner-Warwick M, et al. Pulmonary venoocclusion—an immune-complex disease? *Virchows Arch Pathol Anat*. 1974;364:81-91
4. Fernández-Alonso J, Zulueta T, Reyes-Ramirez JR, et al. Pulmonary capillary hemangiomatosis as cause of pulmonary hypertension in a young woman with systemic lupus erythematosus. *J Rheumatol*. 1999; 26:231-233.
5. Woolf D, Voigt MD, Jaskiewicz K, Kalla AA. Pulmonary hypertension associated with non-cirrhotic portal hypertension in systemic lupus erythematosus. *Postgrad Med J*. 1994;70:41-43.
6. DeClerck LS, Michielsen PP, Ramael MR, et al. Portal and pulmonary vessel thrombosis associated with systemic lupus erythematosus and anticardiolipin antibodies. *J Rheumatol*. 1991;18:1919-1921.
7. Hübscher O, Ermon A, Elmer B, Arana RM. Fatal postpartum pulmonary vasculitis in systemic lupus erythematosus. *Clin Rheumatol*. 1984;3:547-50
8. Haupt H, Moore GW, Hutchins GH. The lung in SLE. *Am J Med*. 1981;71:791-98
9. Rubin LA, Geran A, Rose TH, Cohen H. A fatal pulmonary complication of lupus in pregnancy. *Arthritis Rheum*. 1995;38:710-714.
10. Quismorio FP, Sharma O, Koss M, et al. Immuno-pathologic and clinical studies in pulmonary hypertension associated with systemic lupus erythematosus. *Semin Arthritis Rheum*. 1984;13:349-359.
11. Badui E, Garcia-Rubi D, Robles E, et al. Cardiovascular manifestations in systemic lupus erythematosus: prospective review of 100 patients. *Angiology*. 1985;36:431-441.
12. Perez HD, Kramer N, Pulmonary hypertension in systemic lupus erythematosus: report of four cases and review of the literature. *Semin Arthritis Rheum*. 1981;11:177-181.
13. Simonson JS, Schiller NB, Petri M, Hellmann DB. Pulmonary hypertension in systemic lupus erythematosus. *J Rheumatol*. 1989;16: 918-925.
14. Shen JY, Chen SL, Wu YX et al. Pulmonary hypertension in systemic lupus erythematosus. *Rheumatol Int*. 1999;18:147-151.
15. Pan TL, Thumboo J, Boey ML. Primary and secondary pulmonary hypertension in systemic lupus erythematosus. *Lupus*. 2000;9:338-342.
16. Winslow TM, Ossipov MA, Fazio GP, et al. Five-year follow-up study of the prevalence and progression of pulmonary hypertension in systemic lupus erythematosus. *Am Heart J*. 1995;129:510-515.
17. Fayemi AO. Pulmonary vascular disease in systemic lupus erythematosus. *Am J Clin Pathol*. 1976;65:284-290.
18. Hodson P, Klemp P, Meyers OL. Pulmonary hypertension in systemic lupus erythematosus: a report of four cases. *Clin Exper Rheumatol*. 1983;1:241-245.
19. Asherson RA, Higenbottam TW, Xuan ATD, et al. Pulmonary hypertension in a lupus clinic. Experience with twenty-four patients. *J Rheumatol*. 1990;17:1792-1798.
20. Asherson RA, Mackworth-young CG, Boey ML et al. Pulmonary hypertension in systemic lupus erythematosus. *Brit Med J*. 1983;287: 1024-1025.
21. Chung S, Lee C, Lee E, et al. Clinical aspects of pulmonary hypertension in patients with systemic lupus erythematosus and in patients with idiopathic pulmonary arterial hypertension. *Clin Rheumatol*. 2006;25:866-872.
22. Walcott G, Burchell HB, Brown AL. Primary pulmonary hypertension. *Am J Med*. 1970;49:70-79.
23. Winters WL, Joseph RR, Learner N. Primary pulmonary hypertension and Raynaud's phenomenon. *Arch Intern Med*. 1964;114:821-829.
24. Rawson AJ, Woske HM. A study of etiologic factors in so-called primary pulmonary hypertension. *Arch Intern Med*. 1960;105:233-243.
25. Kanemoto N, Gonda N, Katsu M, et al. Case report: Two cases of pulmonary hypertension with Raynaud's phenomenon: primary pulmonary hypertension and systemic lupus erythematosus. *Jpn Heart J*. 1975;16:354-360.
26. Robbins IM, Gaine SP, Schilz R, et al. Epoprostenol for treatment of pulmonary hypertension in patients with systemic lupus erythematosus. *Chest*. 2000;117:14-18.
27. Boumpas DT, Austin HA III, Fessler BJ, et al. Systemic lupus erythematosus: emerging concepts. Part 1: renal, neuropsychiatric, cardiovascular, pulmonary, and hematologic disease. *Ann Intern Med*. 1995;122:940-950.
28. Ito M, Kagiyama Y, Omura I, et al. Cardiovascular manifestations in systemic lupus erythematosus. *Jpn Cir J*. 1979;43:985-994.
29. Sivaramkrishnan S, Nair MD, Askari MD et al. Pulmonary hypertension and systemic lupus erythematosus. *Arch Intern Med*. 1980; 140:109-111.
30. Asherson RA, Oakley CM. Pulmonary hypertension and systemic lupus erythematosus. *J Rheumatol*. 1986;13:1-6.
31. Wilson L, Tomita T, Braniecki M. Fatal pulmonary hypertension in identical twins with systemic lupus erythematosus. *Hum Pathol*. 1991;22:295-297.

32. Yokoi T, Tomita Y, Fukaya M, et al. Pulmonary hypertension associated with systemic lupus erythematosus. *Arch Pathol Lab Med*. 1998;122:467-470.
33. Yutani C, Imakita M, Ishibashi-Ueda H, et al. Pulmonary thromboembolic hypertension in systemic lupus erythematosus with lupus anticoagulant: histopatholical analysis of localization and distribution of thromboemboli in pulmonary vasculature. *Intern Med*. 1995;34: 1030-1034.
34. Brentjens J, Ossi E, Albini B, et al. Disseminated immune deposits in lupus erythematosus. *Arthritis Rheum*. 1977;20:962-968.
35. Orens JB, Martinez FJ, Lynch JP III. Pleuropulmonary manifestations of systemic lupus erythematosus. *Rheum Dis Clin North Am*. 1994;20:159-193.
36. Fagan KA, Badesch DB. Pulmonary hypertension associated with connective tissue disease. *Prog Cardiovasc Dis*. 2002;45:225-234.
37. Yoshio T, Masuyama J, Kohda N. Association of interleukin 6 release from endothelial cells and pulmonary hypertension in SLE. *J Rheumatol*. 1997;24:489-495.
38. Roncoroni AJ, Alvarez C, Molinas F. Plexogenic arteriopathy associated with pulmonary vasculitis in systemic lupus erythematosus. *Respiration*. 1992;59:52-56.
39. Rustin MHA, Bull HA, Machin SJ, et al. Effects of the lupus anticoagulant in patients with systemic lupus erythematosus on endometrial cell prostacyclin release and procoagulant activity. *J Invest Dermatol*. 1988;90:744-748.
40. Yoshida T, Kameda H, Akizuki M, et al. Abnormal prostanoid metabolism in systemic lupus erythematosus with pulmonary hypertension. *J Rheumatol*. 1994;2393-2394.
41. Naslund MJ, Pearson TA, Ruitter JM. A documented episode of pulmonary vasoconstriction in systemic sclerosis. *Johns Hopkins Med J*. 1981;148:78-80.
42. Fahey PJ, Utell MJ, Condemi JJ, et al. Raynaud's phenomenon of the lung. *Am J Med*. 1984;76:263-269.
43. Denton CP, Humbert M, Rubin L et al. Bosentan treatment for pulmonary arterial hypertension related to connective tissue disease: a subgroup analysis of the pivotal clinical trials and their open-label extensions. *Ann Rheum Dis*. 2006;65:1336-1340.
44. Cozzi F, Montisci R, Marotta H, et al. Bosentan therapy of pulmonary arterial hypertension in connective tissue diseases. *Eur J Clin Invest*. 2006;36 (Suppl 3): 49-53.
45. Watanebe H, Ohashi K, Takeuchi. Sildenafil for primary and secondary pulmonary hypertension. *Clin Pharmacol Ther*. 2002;71:398-402.
46. Molina J, Lucero E, Luluaga S. Systemic lupus erythematosus-associated pulmonary hypertension: good outcome following sildenafil therapy. *Lupus*. 2003;12:321-323.
47. Horn EM, Barst RJ, Poon M,. Epoprostenol for treatment of pulmonary hypertension in patients with systemic lupus erythematosus. *Chest*. 2000;118:1229-1230.
48. Oudiz RJ, Schilz RJ, Barst RJ, et al. Treprostinil, a prostacyclin analogue, in pulmonary arterial hypertension associated with connective tissue disease. *Chest*. 2004;126:420-427.
49. Olschewski H, Simonneau G, Galie N, et al. Inhaled iloprost for severe pulmonary hypertension. *N Engl J Med*. 2002;347:322-329.
50. Yeo PP, Sinniah R. Lupus cor pulmonale with electron microscope and immunofluorescent antibody studies. *Ann Rheum Dis*. 1975;34:457-460.
51. Cummings P. Primary pulmonary hypertension and SLE. *N Engl J Med*. 1973;88:1078-1079.
52. Schwartzberg M, Lieberman DH, Getzoff B, et al. Systemic lupus erythematosus and pulmonary vascular hypertension. *Arch Intern Med*. 1984;144:605-607.
53. Pines A, Kaplinsky N, Olchovsky D, et al. Pleuro-pulmonary manifestations of systemic lupus erythematosus; clinical features of its subgroups, prognostic and therapeutic implications. *Chest*. 1985;88:129-135.
54. Sanchez O, Sitbon O, Jais X, et al. Immunosuppressive therapy in connective tissue diseases-associated pulmonary arterial hypertension. *Chest*. 2006;130:182-189.
55. Jais X, Launy D, Yaici A, et al. Immunosuppressive therapy in lupus- and mixed connective tissue disease- associated pulmonary arterial hypertension. *Arthritis Rheum*. 2008;58:521-531.
56. Tanaka E, Harigai M, Tanaka M, et al. Pulmonary hypertension in systemic lupus erythematosus. Evaluation of clinical characteristics and response to immunosuppressive treatment. *J Rheumatol*. 2002; 29:282-287.
57. Schwarz EB, Manzi S. Risk of unintended pregnancy among women with systemic lupus erythematosus. *Arthritis Care Res*. 2008;59:863-866.
58. Greenstone MA. Delayed diagnosis of systemic lupus erythematosus associated pulmonary hypertension. *Brit J Rheumatol*. 1991; 1991:390-396.
59. Ray J, Sermer M. Systemic lupus erythematosus and pulmonary hypertension during pregnancy: report of a case fatality. *Can J Cardiol*. 1996;12:753-756.
60. Martin WL, Gordon C, Kilby MD. Systemic lupus erythematosus. *Lancet*. 2001;358:586.
61. Weiss BM, Zemp L, Seifert B, Hess OM. Outcome of pulmonary vascular disease in pregnancy: a systematic overview from 1978 through 1996. *J Am Coll Cardiol*. 1998;31:1650-1657.
62. Levy RD, Guerraty AJ, Yacoub MH, Loertscher. Prolonged survival after heart-lung transplantation in systemic lupus erythematosus. *Chest*. 1993;104:1903-1905.
63. Hutter JA, Despins P, Higenbottam T, et al. Heartlung transplantation: better use of resources. *Am J Med*. 1988;85:4-11.
64. Kim WU, Min JK, Lee SH, et al. Causes of death in Korean patients with systemic lupus erythematosus: a single center retrospective study. *Clin Exper Rheumatol*. 1999;17:539-545.
65. Li EK, Tam LS. Pulmonary hypertension in systemic lupus erythematosus. Clinical association and survival in 18 patients. *J Rheumatol*. 1999;26:1923-1929.