The pathophysiology of primary pulmonary hypertension

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Abstract

Primary pulmonary hypertension (PPH) is a progressive disease with a poor prognosis. It is characterised by an elevated pulmonary artery pressure and pulmonary vascular resistance that ultimately lead to right ventricular failure and death. PPH is a relatively rare and neglected disease which, until recently, had been poorly understood and had no effective form of therapy. This, however, is changing with the rapid accumulation of knowledge relating to the disease and its management. In this article, we review the possible mechanisms that may have a pivotal role in the development of the disease.

Key words: Primary pulmonary hypertension, WHO classification, pathophysiology

Introduction

The incidence of PPH is estimated to be one to two cases per million people in the general population.[1,2] In the National Institutes of Health (NIH) Registry on PPH, 6% of cases were familial.[1] The mean age was 36 years, with the ratio of female to male cases varying between 1.7 and 3.5:1.[1-4]

Definition and classification

Pulmonary hypertension is defined as an increase in mean pulmonary arterial pressure > 25 mmHg at rest or > 30 mmHg with exercise. Three histological types of PPH were defined by the World Health Organization in 1973: plexogenic pulmonary arteriopathy, recurrent pulmonary thromboembolism and pulmonary veno-occlusive disease.[5]

Twenty five years later, in 1998, a further committee co-spon-

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Table 1. Diagnostic classification of pulmonary hypertension

1. Pulmonary arterial hypertension
- 1.1 Primary pulmonary hypertension
  - (a) Sporadic
  - (b) Familial
- 1.2 Related to:
  - (a) Collagen vascular disease
  - (b) Congenital systemic to pulmonary shunts
  - (c) Portal hypertension
  - (d) HIV infection
  - (e) Drugs/toxins
    - (1) Anorexigens
    - (2) Other
  - (f) Persistent pulmonary hypertension of the newborn
  - (g) Other

2. Pulmonary venous hypertension
- 2.1 Left-sided atrial or ventricular heart disease
- 2.2 Left-sided valvular heart disease
- 2.3 Extrinsic compression of central pulmonary veins
  - (a) Fibrosing mediastinitis
  - (b) Adenopathy/tumours
- 2.4 Pulmonary veno-occlusive disease
- 2.5 Other

3. Pulmonary hypertension associated with disorders of the respiratory system and/or hypoxia
- 3.1 Chronic obstructive pulmonary disease
- 3.2 Interstitial lung disease
- 3.3 Sleep disordered breathing
- 3.4 Alveolar hypoventilation disorders
- 3.5 Chronic exposure to high altitude
- 3.6 Neonatal lung disease
- 3.7 Alveolar-capillary dysplasia
- 3.8 Other

4. Pulmonary hypertension due to chronic thrombotic and/or embolic disease
- 4.1 Thromboembolic obstruction of proximal pulmonary arteries
- 4.2 Obstruction of distal pulmonary arteries
  - (a) Pulmonary embolism (thrombus, tumour, ova and/or parasites, foreign material)
  - (b) *In situ* thrombosis
  - (c) Sickle cell disease

5. Pulmonary hypertension due to disorders directly affecting the pulmonary vasculature
- 5.1 Inflammatory
  - (a) Schistosomiasis
  - (b) Sarcoidosis
  - (c) Other
- 5.2 Pulmonary capillary hemangiomatosis

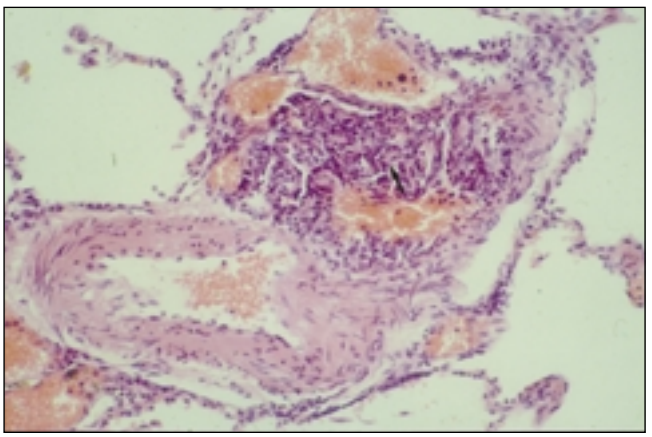
From: Rich S[6]

Table 2. Functional assessment of patients with PHH

A. Class I. Patients with pulmonary hypertension but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnoea or fatigue, chest pain or near-syncope.
B. Class II. Patients with pulmonary hypertension resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnoea or fatigue, chest pain or near-syncope.
C. Class III. Patients with pulmonary hypertension resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnoea or fatigue, chest pain or near-syncope.
D. Class IV. Patients with pulmonary hypertension with inability to carry out any physical activity without symptoms. These patients manifest signs of right heart failure. Dyspnoea and/or fatigue may even be present at rest. Discomfort is increased by any physical activity.

Modified from the New York Heart Association (NYHA) Functional Classification

Figure 1. A plexiform lesion arising from a small muscular artery and showing a complex cellular proliferation to form tiny vascular channels (arrow). Dilated thin-walled vessels are noted around both the parent vessel and the vessel containing the plexiform lesion. (Haematoxylin-Eosinstain, x100)



sored by the World Health Organization met in Evian, France, to create a new and clinically useful classification for pulmonary hypertension (tables 1 and 2).[6]

Pathology and pathobiology

Plexogenic pulmonary arteriopathy is characterised by medial hypertrophy, intimal proliferation, concentric laminar intimal fibrosis (the latter usually arranged in a characteristic 'onion-skin' configuration), dilatation lesions, fibrinoid necrosis and plexiform lesions (figure 1). The exact pathogenesis of these unusual structures remains undefined. They are composed mainly of endothelial cells. Plexiform lesions also consist of smooth muscle cells, myofibroblasts and macrophages. They represent a mass of disorganised vessels that arise from pre-existing pulmonary arteries.

The hypothesis has been put forward that the development of such lesions may represent a form of 'misguided angiogenesis'.[7] It has been shown that the plexiform lesions in PPH[8] and in anorexigen-associated pulmonary hypertension[9] could occur as a result of monoclonal cell expansion, and this could represent somatic mutation.

As well as the theory of 'misguided angiogenesis' and endothelial monoclonal cell proliferation in the pathogenesis of plexiform lesions, other cells have been implicated in the pathological mechanisms of pulmonary hypertension. Smooth muscle cells and fibroblasts have been shown to exist in a heterogeneous population: there appear to be different smooth muscle cell types in different layers of the cell wall and these could contribute to the remodelling process that occurs in the media and adventitia.[10]

Changes in the extracellular matrix play a pivotal role in the function of vascular smooth muscle cells. Proteolytic activity in the vessel wall, such as elastase and matrix metalloproteinases, can lead to the release of mitogenic growth factors from the extracellular matrix.[11] Furthermore, upregulation of the matrix glycoprotein tenascin has been associated with the proliferation of smooth muscle cells.[12]

Hypercoagulability and thrombosis *in situ* is commonly found in patients with pulmonary arterial hypertension. It is unclear, however, whether hypercoagulability initiates pulmonary hypertension or whether it occurs in response to the disease. In patients with PPH, platelet activity is increased; levels of serotonin, fibrinopeptide A and plasminogen activator inhibitor are elevated and thrombomodulin levels are reduced.[13,14]

Aetiology of PPH

Although the exact aetiology of PPH remains undefined, genetic susceptibility is thought to play an important role. The sporadic form of the disease may be caused by interaction between a genetic factor, possibly related to the gene encoding the familial form, and one or more triggering factors. These factors include diet and drugs, hormonal factors, autoimmunity, infection and inflammation. An imbalance of vasoactive mediators, dysregulation of potassium channels and haemodynamic shear stress have also been implicated in the pathophysiology of pulmonary hypertension. The interaction between genetic and triggering factors could result in a final common pathway involving endothelial injury, vasospastic and mitogenic factors. This might lead to vascular remodelling and a change in the phenotype of a variety of cells in the pulmonary arterial wall, producing the functional and structural components of the disease (figure 2).

Genetics

In the familial form of PPH, the age of onset is variable and the penetrance is incomplete. The familial form of PPH is inherited as an autosomal dominant and is associated with a pattern of genetic anticipation. The gene for familial PPH has been localised to a 27-centimorgan region on chromosome 2q31–32.[15,16] Recently, both familial and sporadic PPH have been associated with muta-

Figure 2. A diagrammatic illustration of the aetiology and pathophysiology of pulmonary hypertension

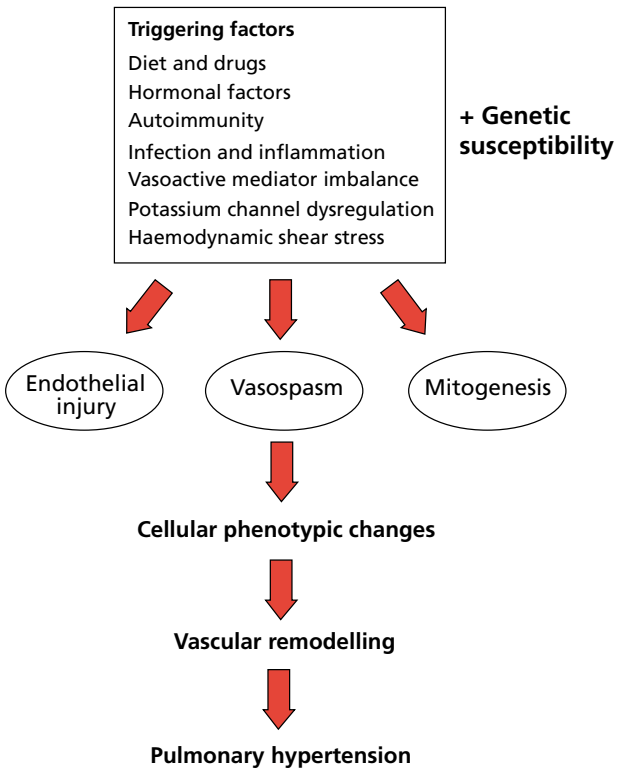
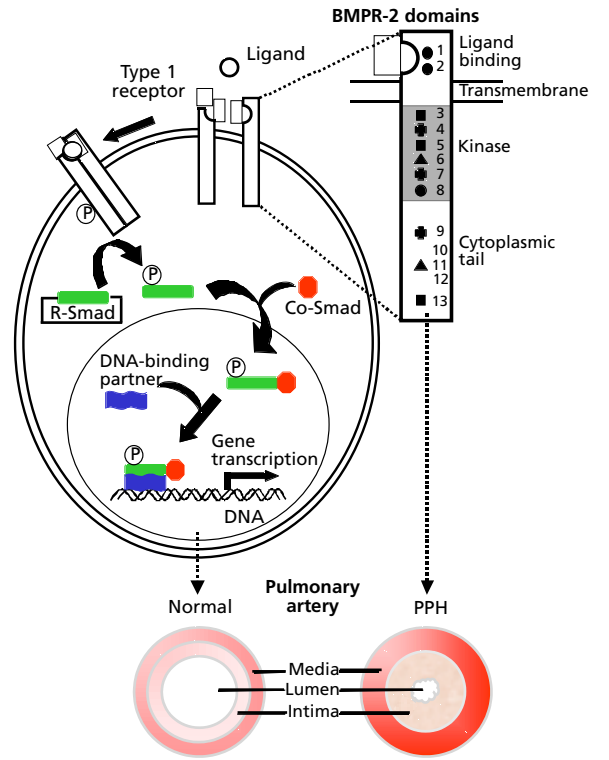


Figure 3. Diagram illustrating the TGF-β signalling pathway and position of BMPR-2 mutations. Following ligand binding, BMPR-2 forms a heterometric complex with a type 1 receptor which results in activation of the type 1 receptor kinase domain. This leads to phosphorylation of cytoplasmic signalling proteins (Smads) and signal transduction. The BMPR-2 mutations (upper right) are likely to disturb the normal cellular effects of pathway activation, leading to the characteristic histological features seen in PPH



From: Thomson JR, Machado RD, Pauciulo MW *et al.*[18]

tions of the bone morphogenetic protein receptor type II gene (BMPR-2) (figure 3).[17,18] The latter is a component of the transforming growth factor beta (TGF-β) family, which plays a pivotal role in cell growth. Furthermore, the heterogeneity of BMPR-2 mutations has been demonstrated,[19] supporting the theory that additional triggering factors combined with genetic susceptibility are responsible for the development of PPH.

Diet and drugs

Aminorex fumarate (Menocil®) is an appetite suppressant that was introduced in Switzerland in November 1965, in West Germany in April 1966 and in Austria in August 1969. A few months after introduction of this agent, the epidemic of PPH began in those three countries.[20,21] More recently, there has been a clear association between another appetite suppressant, fenfluramine, and PPH.[22] Fenfluramine is a sympathomimetic protein that mediates its anorectic actions by activating serotoninergic pathways in the central nervous system. It thus leads to the rapid release of serotonin and inhibits its reuptake. It may also have receptor agonist activity.[23]

Anorexigenic agents such as aminorex, fenfluramine and dexfenfluramine have been shown to inhibit potassium channels, resulting in membrane depolarisation and calcium entry through voltage-gated calcium channels.[24,25] This leads to pulmonary vasoconstriction, smooth muscle cell proliferation and vascular remodelling. Aminorex, fenfluramine and chlorphentermine have also been shown to be serotonin transporter substrates.[26] They become translocated into pulmonary cells; here they accumulate and can exert their toxic effects, with subsequent development of PPH in susceptible individuals.[26]

The use of rapeseed oil for cooking in Spain, through its illegal sale, resulted in an epidemic of pulmonary hypertension.[27,28] The use of rapeseed oil led to an acute toxic syndrome consisting of skin, gastric, neurological and pulmonary symptoms. Examination of the contaminated oil showed that the pathogenic products included fatty acid oleyl anilides and the monoester and diester of 3-phenylamino-1,2-propanediol.[29,30]

Circulatory hormones and vasoactive mediators

The regulation of pulmonary artery tone relies upon a balance between constrictor and dilator mechanisms, with the endothe-

Key messages

- Primary pulmonary hypertension (PPH) remains a progressive, fatal disease with a poor prognosis
- A new classification, set out by the WHO in 1998, has been developed
- The exact pathogenesis of the disease remains undefined
- Familial PPH has been localised to chromosome 2q31–32
- Both familial and sporadic PPH have been associated with mutations in BMPR-2, a component of the TGF-β family which has a pivotal role in cell growth. This finding could for the first time provide rational exciting possibilities for understanding and treating PPH
- Various triggering factors on the background of genetic susceptibility may play a pivotal part in the pathophysiology of PPH

lium playing an important role. Thus, an imbalance of vasoactive mediators could lead to the development of pulmonary hypertension.

In 1992, a study by Christman *et al*.[31] demonstrated that in pulmonary hypertensive patients there was an increase in the urinary excretion of the vasoconstrictor 11-dehydro-thromboxane B_2 and a reduction in the urinary excretion of the potent vasodilator 2,3-dinor-6-ketoprostaglandin F_{1a}. In 1993, Giaid *et al*.[32] demonstrated increased expression of endothelin-1, a potent vasoconstrictor, in vascular endothelial cells in the lungs of patients with pulmonary hypertension. We have also shown reduced circulating levels of endothelin-1 in patients with primary and secondary pulmonary hypertension.[33] In 1995, Giaid and Saleh showed that patients with pulmonary hypertension have reduced expression of endothelial nitric oxide synthase.[34] Two recent studies have also shown that patients with PPH and secondary pulmonary hypertension have reduced expression of the prostacyclin receptor protein[35] and the enzyme prostacyclin synthase[36] in their lung tissue. This deficiency could explain the lack of prostacyclin-induced pulmonary vasodilation in patients with severe pulmonary hypertension.

The role of serotonin in patients with PPH remains unclear. Patients with PPH have abnormal storage of serotonin by platelets, leading to an increase in plasma serotonin.[37] Furthermore, patients who use anorexigens have increased plasma serotonin levels.[38]

Because of the higher incidence of PPH in females, it is thought that sex hormones may play a part in the aetiology of this disease. In 1976 Kleiger *et al*.[39] reported six women who developed pulmonary hypertension after taking the oral contraceptive pill for between six months and five years. Similar observations were made by Oakley and Somerville in 1968.[40]

Potassium channels

Patients with PPH have recently been shown to have abnormalities of potassium channels which result in depolarisation of the membrane of pulmonary vascular smooth muscle cells. This leads to an increase in intracellular calcium and vasoconstriction.[41-44] In this study, there was attenuation of the potassium channel gene transcription and reduction in the mRNA stability of the potassium channel α subunit, resulting in a reduction in the potassium current in pulmonary arterial smooth muscle cells.[44]

Autoimmunity

PPH has been associated with Raynaud's phenomenon,[45,46] scleroderma,[47] the CREST syndrome,[48,49] dermatomyositis,[50] rheumatoid arthritis,[51,52] systemic lupus erythematosus[46,53] and hypothyroidism.[54] In 1986, a study demonstrated that 40% of patients with PPH had positive antinuclear antibodies at titres of 1:80 dilutions or greater. In patients with secondary pulmonary hypertension, there was a 6% incidence rate of antinuclear factors, a similar level to that of the general population. These results suggest that some forms of pulmonary arterial hypertension may represent a collagen vascular disease confined to the lung.[55]

Infection

There is an association between human immunodeficiency virus (HIV) and the development of PPH.[56] It is thought that HIV may have an indirect role in the production of cytokines and growth factors by activated lymphocytes and macrophages.[57,58] Direct infection of the pulmonary vasculature by HIV, however, has not been demonstrated.[58,59]

Inflammation

Mediators of inflammation can cause vasoconstriction and cell growth. Inflammatory cells have been shown to be present in the vicinity of pulmonary vessels and may play a part in vascular remodelling. In 1994 Tuder *et al.*[60] and in 1997 Cool *et al.*[61] demonstrated the presence of macrophages, as well as T and B cells, in the vicinity of remodelled pulmonary arteries. These cells release cytokines and growth factors such as transforming growth factor (TGF)-β,[62] platelet-derived growth factor (PDGF)[58] and vascular endothelial growth factor (VEGF).[63]

Other workers have demonstrated increased serum concentrations of interleukin 1 and interleukin 6[64] and of the chemokine MIP-1α in lung tissue[65] in patients with PPH. Overexpression of 5-lipoxygenase and 5-lipoxygenase activating protein (FLAP) in small pulmonary arteries in patients with PPH has been demonstrated by Wright *et al.* 1998,[66] and these may play a role in cell proliferation.

Conclusions

Pulmonary hypertension continues to offer a challenge to the physician in terms of both diagnosis and treatment. Over recent years, the various aetiological mechanisms have come to light. The recent genetic findings provide a means for diagnosing and understanding the basis of the disease and possibly for providing novel avenues for its treatment. Many exciting lines of research

need to be pursued to optimise the management of this condition.

Editors' note

The second part of this article on the management of primary pulmonary hypertension will appear in next month's issue.

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References

1. Rich S, Dantzker DR, Ayres SM *et al*. Primary pulmonary hypertension. A national prospective study. *Ann Intern Med* 1987;**107**(2):216-23.
2. Rubin LJ. Primary pulmonary hypertension. *Chest* 1993;**104**:236-50.
3. Braman SS, Eby E, Kuhn C, Rounds S. Primary pulmonary hypertension in the elderly. *Arch Intern Med* 1991;**151**:2433-8.
4. Brenot F. Primary pulmonary hypertension: case series from France. *Chest* 1994;**105** (suppl):33S-6S.
5. Hatano S, Strasser T. World Health Organization – Primary Pulmonary Hypertension. Report on a WHO Meeting, Geneva, 1975.
6. Rich S. Executive summary from the World Symposium on Primary Pulmonary Hypertension 1998. http://www.who.int/ned/evd/pph.htm 1999.
7. Voelkel NF, Cool C, Lee SD, Wright L, Geraci MW, Tuder RM. Primary pulmonary hypertension between inflammation and cancer. *Chest* 1998;**114**:225S-9S.
8. Lee SD, Shroyer KR, Markham NE, Cool CD, Voelkel NF, Tuder RM. Monoclonal endothelial cell proliferation is present in primary but not secondary pulmonary hypertension. *J Clin Invest* 1998;**101**:927-34.
9. Tuder RM, Radisavljevic Z, Shroyer KP, Polak JM, Voelkel NF. Monoclonal endothelial cells in appetite suppressant-associated pulmonary hypertension. *Am J Respir Crit Care Med* 1998;**158**:1999-2001.
10. Frid MG, Moiseeva EP, Stenmark KR. Multiple phenotypically distinct smooth muscle cell populations exist in the adult and developing pulmonary arterial media *in vivo*. *Circ Res* 1994;**75**:669-81.
11. Thompson K, Rabinovitch M. Exogenous leukocyte and endogenous elastases can mediate mitogenic activity in pulmonary artery smooth muscle cells by release of extracellular matrix-bound basic fibroblast growth factor. *J Cell Physiol* 1996;**166**(3):495-505.
12. Jones PL, Rabinovitch M. Tenascin-C is induced with progressive pulmonary vascular disease in rats and is functionally related to increased smooth muscle cell proliferation. *Circ Res* 1996;**79**(6):1131-42.
13. Frank H, Mlczoch J, Huber K *et al*. The effect of anticoagulant therapy in primary and anorectic drug-induced pulmonary hypertension. *Chest* 1997;**112**:714-21.
14. Welsh C, Hassell KL, Badesch DB *et al.* Coagulation and fibrinolytic profiles in patients with severe pulmonary hypertension. *Chest* 1996;**110**:710-7.
15. Nichols WC, Koller DL, Slovis B *et al*. Localization of the gene for familial primary pulmonary hypertension to chromosome 2q31-32. *Nat Genet* 1997;**15**(3):277-80.
16. Morse JH, Jones AC, Barst RJ, Hodge SE, Wilhemsen KC, Nygaard TG. Mapping of familial primary pulmonary hypertension locus (PPH1) to chromosome 2q31-q32. *Circulation* 1997;**95**:2603-6.
17. The International PPH Consortium; Lane KB, Machado RD, Pauciulo MW *et al*. Heterozygous germline mutations in BMPR2, encoding a TGF-β receptor, cause familial primary pulmonary hypertension. *Nature Genetics* 2000;**26**:81-4.
18. Thomson JR, Machado RD, Pauciulo MW *et al*. Sporadic primary pulmonary hypertension is associated with germline mutations of the gene encoding BMPR-II, a receptor membrane of the TGF-β family. *Genetics* 2000;**37**:741-5.
19. Machado R, Pauciulo M, Thomson JR *et al*. BMPR-2 haploinsufficiency as the inherited molecular mechanism for primary pulmonary hypertension. *Am J Genet* 2001;**68**:92-102.
20. Gurtner HP. Aminorex and pulmonary hypertension. A review. *Cor Vasa* 1985;**27**(2-3):160-71.
21. Fishman AP. Aminorex to Fen/Phen. An epidemic foretold. *Circulation* 1999;**99**:156-61.
22. Abenhaim L, Moride Y, Brenot F *et al*. Appetite-suppressant drugs and the risk of primary pulmonary hypertension. International Primary Pulmonary Hypertension Study Group. *N Engl J Med* 1996;**335**(9):609-16.
23. Mitchell P, Smythe G. Hormonal responses to fenfluramine in depressed and control subjects. *J Affect Disord* 1990;**19**(1):43-51.
24. Weir EK, Reeve HL, Huang JMC *et al*. Anorexic agents aminorex, fenfluramine and dexfenfluramine inhibit potassium current in rat pulmonary vascular smooth muscle cells and cause pulmonary vasoconstriction. *Circulation* 1996;**94**:2216-20.
25. Wang J, Juhaszova M, Conte J, Gaine S, Rubin L, Xio-Jian Yuan J. Action of fenfluramine on voltage gated K+ channels in human pulmonary artery smooth-muscle cells. *Lancet* 1998;**352**:290.
26. Rothman R, Ayestas M, Dersch C, Bamann MH. Aminorex, fenfluramine and chlorphentermine are serotonin transporter substrates. Implications for primary pulmonary hypertension. *Circulation* 1999;**100**:869-75.
27. Garcio-Dorado D, Miller DD, Garcia EJ, Declan JL, Maroto E, Cahitam BR. An epidemic of pulmonary hypertension after toxic rapeseed oil ingestion in Spain. *J Am Coll Cardiol* 1983;**5**:1216-22.
28. Gomez Sanchez MA, Mestre de Juan MJ, Gomez Pajuelo C, Lopez JI, Diaz de Atauri MJ, Martinez Tello FJ. Pulmonary hypertension due to toxic oil syndrome. A clinicopathologic study. *Chest* 1989;**95**(2):325-31.
29. Posada de la Paz M, Philen R, Abaitua Borda I *et al*. Factors associated with pathogenicity of oils related to the toxic oil syndrome epidemic in Spain. *Epidemiology* 1994;**5**:404-9.
30. Bell S, Sander C, Kuntze I *et al*. The acute pathology of fatty acid anilides and linoleic diester of 3-phenylamino-1,2-propanediol in mice; possible implication as aetiologic agents for the toxic oil syndrome. *Archives Toxicol* 1999;**73**:493-5.
31. Christman BW, McPherson CD, Newman JH *et al*. An imbalance between the excretion of thromboxane and prostacyclin metabolites in pulmonary hypertension. *N Engl J Med* 1992;**327**(2):70-5.
32. Giaid A, Yanagisawa M, Langleben D *et al*. Expression of endothelin-1 in the lungs of patients with pulmonary hypertension. *N Engl J Med* 1993;**328**(24):1732-9.
33. Mikhail G, Chester AH, Gibbs JSR, Borland JAA, Banner NR, Yacoub MH. Role of vasoactive mediators in primary and secondary pulmonary hypertension. *Am J Cardiol* 1998;**82**:254-5.
34. Giaid A, Saleh D. Reduced expression of endothelial nitric oxide synthase in the lungs of patients with pulmonary hypertension. *N Engl J Med* 1995;**333**(4):214-21.
35. Mason NA, Bishop AE, Yacoub MH, Tuder RM, Voelkel NF, Polak JM. Reduced expression of prostacyclin receptor protein on remodelled vessels in pulmonary hypertension. *Am J Respir Crit Care Med* 1999;**159**: A166.
36. Tuder RM, Cool CD, Geraci MW *et al*. Prostacyclin synthase expression is decreased in lungs with severe pulmonary hypertension. *Am J Respir Crit Care Med* 1999;**159**(6):1925-32.
37. Herve P, Launay JM, Scrobohaci ML *et al*. Increased plasma serotonin in primary pulmonary hypertension. *Am J Med* 1995;**99**(3):249-54.
38. Michelakis D, Weir E. Anorectic drugs and pulmonary hypertension from the bedside to the bench. *Am J Med Sci* 2001;**321**:292-9.
39. Kleiger RE, Boxer M, Ingham RE, Harrison DC. Pulmonary hypertension in patients using oral contraceptives. A report of six cases. *Chest* 1976;**69**(2):143-7.
40. Oakley C, Somerville J. Oral contraceptives and progressive pulmonary vascular disease. *Lancet* 1968;**1**(548):890-3.
41. Nelson MT, Patlak JB, Worley JF, Standen NB. Calcium channels, potassium channels, and voltage dependence of arterial smooth muscle tone. *Am J Physiol* 1990;**259**:C3-18.
42. Nelson MT, Quayle JM. Physiological roles and properties of potassium channels in arterial smooth muscle. *Am J Physiol* 1995;**268**:C799-822.
43. Yuan XJ. Voltage-gated K+ currents regulate resting membrane potential and Ca 2+ in pulmonary arterial myocytes. *Circ Res* 1995;**77**:370-8.
44. Yuan XJ, Wang Y, Juhaszova M, Gaine SP, Rubin LJ. Attenuated K+ channel gene transcription in primary pulmonary hypertension. *Lancet* 1998;**351**:726-7.

45. Wagenvoort CA, Wagenvoort N. Primary pulmonary hypertension. A pathologic study of the lung vessels in 156 clinically diagnosed cases. *Circulation* 1970;**42**:1163-84.
46. Walcott G, Burchell HB, Brown AL Jr. Primary pulmonary hypertension. *Am J Med* 1970;**49**(1):70-9.
47. Trell E, Lindstrom C. Pulmonary hypertension in systemic sclerosis. *Ann Rheum Dis* 1971;**30**(4):390-400.
48. Salerni R, Rodnan GP, Leon DF, Shaver JA. Pulmonary hypertension in the CREST syndrome variant of progressive systemic sclerosis (scleroderma). *Ann Intern Med* 1977;**86**(4):394-9.
49. Stupi AM, Steen VD, Owens GR, Barnes EL, Rodnan GP, Medsger TAJ. Pulmonary hypertension in the CREST syndrome variant of systemic sclerosis. *Arthritis Rheum* 1986;**29**:515-24.
50. Caldwell IW, Aitchinson JD. Pulmonary hypertension in dermatomyositis. *Br Heart J* 1956;**18**:273-6.
51. Onodera S, Hill JR. Pulmonary hypertension. Report of a case in association with rheumatoid arthritis. *Ohio Med J* 1965;**61**:141-4.
52. Morikawa J, Kitamura K, Habuchi Y, Tsujimura Y, Minamikawa T, Takamatsu T. Pulmonary hypertension in a patient with rheumatoid arthritis. *Chest* 1988;**93**:876-8.
53. Asherson RA, Higenbottam TW, Dinh Xuan AT, Khamashata MA, Hughes GRV. Pulmonary hypertension in the lupus clinic: experience with twenty four patients. *J Rheumatol* 1990;**17**:1292-8.
54. Badesch DB, Wynne KM, Bonvallet S, Voelkel NF, Ridgway C, Groves BM. Hypothyroidism and primary pulmonary hypertension: an autoimmune pathogenetic link? *Ann Intern Med* 1993;**119**:44-6.
55. Rich S, Kieras K, Hart K, Groves BM, Stobo JD, Brundage BH. Antinuclear antibodies in primary pulmonary hypertension. *J Am Coll Cardiol* 1986; **8**(6):1307-11.
56. Petipretz P, Brenot F, Azarian R *et al*. Pulmonary hypertension in patients with HIV infection. *Circulation* 1994;**89**:2722-7.
57. Tuder RM, Weinberg A, Bates T *et al*. Tat-protein of HIV enhances inflammatory cell binding and PDGF levels in CMV infected endothelial cells (abstract). *Circulation* 1994;**90**:2237.
58. Humbert M, Monti G, Fartoukh M *et al*. Platelet-derived growth factor expression in primary pulmonary hypertension: comparison of HIV seropositive and HIV seronegative patients. *Eur Respir J* 1998;**11**:554-9.
59. Mette SA, Palevsky HI, Pietra GG *et al*. Primary pulmonary hypertension in association with pulmonary hypertension infection. A possible viral etiology for some forms of hypertensive pulmonary arteriopathy. *Am Rev Respir Dis* 1992;**145**:1196-200.
60. Tuder RM, Groves B, Badesch DB, Voelkel NF. Exuberant endothelial cell growth and elements of inflammation are present in plexiform lesions of pulmonary hypertension. *Am J Pathol* 1994;**144**:275-85.
61. Cool CD, Kennedy D, Voelkel NF, Tuder RM. Pathogenesis and evolution of plexiform lesions in pulmonary hypertension associated with scleroderma and human immunodeficiency virus infection. *Human Pathol* 1997;**28**:434-42.
62. Botney MD, Bahadori L, Gold LI. Vascular remodelling in primary pulmonary hypertension. *Am J Pathology* 1994;**114**(2):286-95.
63. Tuder RM, Wang J, Lee SD *et al*. Vascular endothelial growth factor (VEGF) expression in normal and remodeled pulmonary arteries in severe pulmonary hypertension (abstract). *Am J Respir Crit Care Med* 1997;**155**: (4):A627.
64. Humbert M, Monti G, Brenot F *et al*. Increased interleukin-1 and interleukin-6 serum concentrations in severe primary pulmonary hypertension. *Am J Respir Crit Care Med* 1995;**151**(5):1628-31.
65. Fartoukh M, Emilie D, LeGall C, Monti G, Simonneau G, Humbert M. Chemokine macrophage inflammatory protein-1α mRNA expression in lung biopsy specimens of primary pulmonary hypertension. *Chest* 1998;**114**:50S-1S.
66. Wright L, Tuder RM, Cool CD, Lepley RA, Voelkel NF. 5-Lipoxygenase and 5-Lipoxygenase activating protein (FLAP) immunoreactivity in lungs from patients with primary pulmonary hypertension. *Am J Respir Crit Care* Med 1998;**157**:219-29.