Review

Present Status of Primary Pulmonary Hypertension

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More than a century has passed since the first description of pulmonary arteriosclerosis of unknown origin. The development of our understanding of primary pulmonary hypertension (PPH) can be divided into four periods. The first period, which extended from the introduction of the concept until about 1930, may be described as the dawn of this disease. In the second period (1930–1950) the morphological aspects of the disease were recognized and studied. In the third period (1950–1960), the advent of right heart catheterization made it possible to link pathological physiology with morphology and the disease entity as primary pulmonary hypertension was firmly established. Since 1960 (the fourth period) the etiology and therapy of this disease have been studied. This paper will review chronologically the history of PPH since the 19th century and then will discuss the etiologies, pathology, and clinical manifestation including symptoms and signs, laboratory findings, therapy, and prognosis based on the nationwide survey in Japan as well as the author's own experience.

(Key Words: pre-capillary pulmonary hypertension, vasospasm, auto-immune disease, sudden death, right heart failure)

INTRODUCTION

This review will present a chronological history of our understanding of primary pulmonary hypertension (PPH), followed by analysis of its present status based on a recent nationwide survey of PPH in Japan.

HISTORY OF PPH

More than a century has passed since the early recognition of the disease and there are numerous synonyms that seem to coincide with what we consider to be PPH (20, 22, 23, 36, 37, 41, 50, 53, 56, 59, 113, 114, 117, 129, 138, 141, 148, 157, 158, 177, 187, 206, 207, 209, 221, 232, 236, 238, 256, 260) (Table 1). We can divide our understanding of PPH into four periods.

1. The first Period (The Dawn; From recognition to 1930)

In the middle of the nineteenth century, 2 reports shed light on the new entity of pulmonary artery disease (20,236). However, it was Romberg (1891) (206) who on the basis of autopsy, was the first to describe the right ventricular hypertrophy and pulmonary artery sclerosis without apparent pathogenesis.

Ayerza (1901) reported on a patient whom he called "cardiacos negros" with heart failure and marked cyanosis (20). Autopsy revealed dilatation of the bronchi, parabronchiolitis and dilatation and hypertrophy of the right ventricle. No description was given of the pulmonary vessels. Escudero (1905) found atherosclerosis of the pulmonary arteries in a case similar to that reported by Ayerza (20). Marty (1909) gave a new term "Ayerza's disease" to this pathological state (20). In the same year, Sanders (221) reported a case characterized by marked right ventricular hypertrophy (RVH) and sclerosis of the pulmonary arteries without lesions in the pulmonary parenchyma under the title "primary pulmonary arteriosclerosis with hypertrophy of the right ventricle".

For the next 20 years the pathogenesis of Ayerza's disease was debated. Various hypotheses ascribed the condition to chronic bronchitis, bronchiectasis, chronic inflammations such as syphilis or malaria, mechanical changes due to chronic alcoholism and scleroderma.
ic changes of the pulmonary arteries (20).

Clarke (1927) (41) reported the familial occurrence of the pulmonary vascular disease, and was the first to use the nomenclature of "primary pulmonary hypertension". In this period the entity as a disease was recognized. Although the term "Ayerza's disease" has historical significance, its specific meaning is obscure and the term is rarely used.

2. The Second Period (The Period of Recognition by Pathology, 1930–1950)

From 1931 to 1947 there were a series of reports on relatively young patients in whom at autopsy was found marked hypertrophy and dilatation of the right ventricle and atrium, atherosclerosis of the main pulmonary trunk and obliteratorves lesions in the small pulmonary arteries (129, 138, 148, 207, 209). They ascribed their findings to either afterload of the right ventricle and/or direct damage to the right ventricle. Another series of reports during that same period described autopsied cases that showed only minimal lesions in the pulmonary arteries in spite of the marked RVH (20, 53, 59, 187, 238).
Brenner (20) proposed the following criteria for the diagnosis of “primary pulmonary vascular sclerosis”: (1) Severe cyanosis and edema, with comparatively little dyspnea. (2) Clinical and electrocardiographic evidence of hypertrophy of the right ventricle but not of the left. (3) An accentuated pulmonary second sound, perhaps with a pulmonary diastolic murmur, without murmurs indicative of other valvular or congenital cardiac disease. (4) No clinical or roentgenographic evidence of chronic pulmonary disease. (5) Roentgenographic evidence of enlargement of the right heart with prominence of the pulmonary artery and conus of the right ventricle, but with a normal shadow of the left atrium. (6) No evidence of syphilis.

Brill (1941) (22) reported a case of a patient who died suddenly during hospitalization. The diagnosis of “primary pulmonary vascular sclerosis” was made at autopsy when severe thickening of the media of the small pulmonary arteries and “marked isolated cor pulmonale” were demonstrated. They stressed that for this diagnosis it is important to exclude all known causes of right ventricular overload.

In this period the pathological aspects of the disease entity was fairly well established. Hypertrophy and dilatation of the right ventricle was postulated to be secondary to severely increased afterload (pulmonary arteriolar hypertension).

3. The Third Period (Period of Clinical Analysis and Refinement of the Pathology, 1950–1960)

Hemodynamic correlations with clinical and pathological findings began with the introduction of right heart catheterization in the 1950’s. From 1949 to 1952, there were 4 reports of cases where pulmonary hypertension was proven by cardiac catheterization but autopsy in many cases failed to show notable changes in the lungs (36, 158, 232, 250). Briton (1950) (23) and Whittenberg (1950) (250) used the nomenclature of PPH for the diagnosis.

Owen (1953) (177) found 12 patients with chronic cor pulmonale who died in congestive heart failure of unknown cause in 8,000 autopsies during a 2-year period at the Massachusetts General Hospital. They suggested that these cases could have had multiple “silent” pulmonary emboli but they may have had PPH.

Over the next few years, in addition to Cuthler’s paper (1954) (50) which stressed the differential diagnosis of diseases showing abnormally increased pulmonary vascular resistance, there were many excellent reviews (17, 56, 141, 157, 260). Braunstein (1955) (18) found six pulmonary hypertension cases where a Kussmaul-Mayer type of periarteritis nodosa was limited only to the pulmonary vasculature.

Dressler (1952) (57) pointed out that “effort syncope” is a characteristic symptom of PPH that is rarely encountered in secondary pulmonary hypertension. He postulated that the syncope was due to severe ventricular arrhythmias secondary to the decreased coronary flow caused by the increased end-diastolic pressure in the right ventricle. Howarth (1953) (102) ascribed the syncope to acute right ventricular failure.

During this decade there were many papers that warned physicians that sudden death could be precipitated in patients with PPH by invasive procedures such as cardiac catheterization, pulmonary angiography and pulmonary scintigraphy. Even the administration of barbiturates was considered hazardous (11, 26, 37, 58, 106, 231, 240). Jewtt (1956) (109) reported on a patient who died suddenly two weeks after delivery and stressed that in patients with PPH pregnancy and delivery were contraindicated. However, Braunwald (19) and Blount (12) denied that cardiac catheterization was dangerous for patients with suspected PPH.

Dresdale (1951) (55) noted that RVH could be due to pulmonary hypertension on cardiac catheterization in the absence of pulmonary arteriosclerosis and that the autonomic nervous system might play some role in the development of the pulmonary hypertension. This was based on an experiment in which intravenous priscoline caused a decrease in the pulmonary vascular resistance.

It was near the end of this decade that Heath (1958) (91) classified structural changes in the pulmonary arteries in pulmonary hypertension into six grades. This classification has been used as a standard to grade the degree of hypertensive pulmonary vascular disease histologically.

Goodale (1954) (76) reported on two boys, aged 6 months and 10 years, with PPH in whom autopsy revealed a marked thickening of the media of the pulmonary arterioles. Considering this change to be the cause of right ventric-
ular hypertrophy, they proposed the term "primary pulmonary arterial disease." A similar opinion had been put forward by Heath (90) in 1957.

In this period the pathological and clinical findings were correlated, and the RVH was proved to be the result of severely increased pulmonary vascular resistance due to the medial hypertrophy and/or intimal proliferation of the small pulmonary arteries. The diagnostic term "PPH" had been used since the 1950s.

4. The fourth Period (Period of Studying Pathogenesis and Therapy: 1957 till the present)

Wade (1957)(242) made a chronological review of papers on pathogenesis and diagnostic criteria. In their report of 10 cases of "unexplained pulmonary hypertension" and postulated three possible mechanisms: (1) functional contraction of the terminal muscular pulmonary arteries, (2) abnormal broncho-pulmonary anastomoses, and (3) pulmonary arterioles. They also showed an association of pulmonary hypertension and Raynaud's phenomenon, as did several other authors (33, 189, 230). A hyperactive neurohumoral vasomotor mechanism was postulated as a possible cause. Rawson (1960) (189) reported two cases of PPH accompanied by arthritis and Raynaud's phenomenon and surmised that there is some correlation with collagen diseases pathologically.

According to McGuire (1957) (157) the diagnosis of PPH can be established when the following criteria are satisfied: (1) Right ventricular hypertrophy without any predisposing heart disease, (2) Normal pulmonary arterial wedge pressure in the presence of pulmonary hypertension, and (3) Absence of obstructive changes in the pulmonary arteries or veins. Evans (1957) (62) suggested that hypoplasia or aplasia of the media is the possible genesis of "Solitary pulmonary hypertension". Shepherd (1957) (224) speculated on the etiological influence of amniotic embolism or increased coagulability of the blood associated with menstruation based on the fact that 9 of their 10 patients were women of child bearing age.

Yu (1958) (260) conducted a statistical observation on 55 cases, and noted that PPH was most probable when the following findings were obtained: (1) History of progressive exertional dyspnea, fatigue, and repeated syncopal attacks, (2) Physical signs of pulmonary hypertension (right ventricular heave, and loud, often split, and palpable second sound), with nonspecific cardiac murmurs, (3) Electrocardiographic changes consistent with RVH, (4) Roentgenologic evidence of enlargement of the right ventricle and pulmonary artery with normal left atrium and clear peripheral lung fields, (5) Normal or only slightly altered pulmonary function, (6) Marked pulmonary hypertension with normal pulmonary "capillary" pressure by right heart catheterization and absence of intracardiac shunt.

Edwards (1957) (60) espoused a congenital etiology; that it was the result of persistence of fetal vessels. Health (196) (92) agreed that some cases may be congenital in origin. Obstructive lesions in pulmonary veins as well as in muscular pulmonary arteries were found in an autopsied case by Brewer (1960) (21).

Naeye (1960) (162) reported six cases of pulmonary hypertension accompanying portal hypertension and postulated pulmonary thromboembolism from a source in the portal system. Kerbel (1962) (133) reported a similar case. Senior (1968) (223) described a patient whose pulmonary hypertension developed after a porto-caval shunt operation. Freilich (1961) (70) reported a case diagnosed clinically as PPH where autopsy revealed pulmonary emboli from thrombi in the pelvic vein and stressed the importance of long-term anticoagulant therapy.

Nielsen (1961) (172) published a paper concerning the prognosis of PPH. James (1962) (108) noted lesions in both sinoatrial node and atrioventricular node (nodal arterio-pathy) in three autopsied cases and conjectured atrial arrhythmias or complete A-V block as a possible mechanism for the sudden death occasionally seen in patients with PPH.

Khoury (1963) (134) described PPH in children living at high altitude. Naeye (1965) (164) showed that people living at an altitude of over 10,000 feet do not undergo the normal regression of the media of the muscular pulmonary arteries. Reeves (1975) (190) showed that pulmonary artery pressures correlate negatively with partial pressure of oxygen. Grover (1966) (80) showed that high altitude pulmonary hypertension is reversible when the external en-
vironment of hypoxia is removed.

Goodwin (1963) (78) and Fowler (1966) (69) expounded on the difficulty of differentiating obliterative pulmonary hypertension from thrombo-embolism.

Many papers were published about the coexistence of collagen diseases with pulmonary hypertension: dermatomyositis by Coldwell (1956) (31), progressive systemic sclerosis in CPC of the Massachusetts General Hospital (1960, 1964) (30, 31), Naeye (1963) (163) and Sacker (1964) (216) and systemic lupus erythematos (SLE) by Slama (1967) (226).

In a CPC of MGH (1973) (32), a case clinically diagnosed as SLE with pulmonary hypertension did not demonstrate the histological findings of SLE and was diagnosed as PPH with Raynaud's phenomenon. Kanemoto (1974) (112–115) also discussed the collagen disease-PPH connection (1971, 1973, 1974). Cohen (1965) (47) reported a 19-year-old girl with PPH and systemic symptoms who showed a remarkable recovery with steroid therapy. Clausen and Geer (1969) (42) found necrotizing arterities in the pulmonary arteries in post-mortem examinations of two children with PPH. Based on this observation they proposed the term "hypertensive pulmonary arteritis".

Pulmonary hypertension due to obstruction only of small pulmonary veins was presented as pulmonary veno-occlusive disease by Stovin (1965) (171), and Nasser (1967) (233).

Storstein (1966) (188) published a review dealing with etiology and treatment. Rao (1969) (252) discussed therapy and showed that acetylcholine, tolazoline and isoproterenol can all decrease pulmonary artery pressure in children with PPH. Williams (1969) (206) used pulmonary function tests as an aid in the differential diagnosis of pulmonary hypertension.

Several authors described PPH cases of unusually long duration (90, 160, 238). Inglesby (1973) (105) reported on the familial occurrence of PPH with abnormal fibrinolysis in which recurrent pulmonary micro-thromboembolism is presumed to be pathogenic. A similar pathogenesis was suggested by two interesting case records in JAMA (1973) (43) and Chest (1974) (44).

Since 1960 many reports were published suggesting sensitivity to specific drugs and parasites as etiologic agents. Gurtner (1969) (83, 84) and Gahl (1970) (73) noted that, although the mechanism of action remained unknown aminorex fumarate (Menocil), an appetite depressant, was closely related to the development of changes in the pulmonary vessels. They noted a temporal and geographical relationship with the commercial availability of aminorex. The drug is an alpha type of sympathomimetic drug with a chemical structure similar to amphetamine and epinephrine. Similar observations were made by von Smekal (1970) (241) and Fellath (1971) (65). Taking a serious view of this problem, a committee was established in West Germany (4). The survey conducted by the committee revealed that there existed a definite dose dependent correlation between the development of PPH and the use of aminorex fumarate.

Obeyesekere and Soysa (1970) (174, 175) presented 30 cases of pulmonary hypertension of unknown origin accompanied by a striking eosinophilia not due to enteric parasites and remarked that filariasis might have played some role in the occurrence of the pulmonary hypertension in these cases, since their patients were inhabitants of endemic areas and it was known that filaria caused pulmonary hypertension in animals. According to these authors, the relatively high incidence of PPH in Ceylon could be explained by the prevalence of filariasis. In 1970 two excellent reviews on PPH were published by Walcott (246) and Wagenvoort (243).

An experimental model of PPH was successfully accomplished by Lalich (1961) (142), Kay (1967) (190), and Hayashi (1967) (89) using crotalaria spectabilis (monocot), and also by Kay (1971) (131) using crotalaria fulva (fulvine) and by Burn (1972) (25) using Senecio jacobae. These substances were pyrrolizidine alkaloids. Health (1975) (95) published a case report of a 19-year-old Tanzanian boy who developed pulmonary hypertension in connection with a herbal remedy (crotalaria laburnoides) and autopsy revealed a plexogenic pulmonary arteriopathy.

The use of birth control pills gave rise to warning about the possibility of pulmonary hypertension by several authors (107, 136, 150, 202). Fahlen (1973) (64) reported two cases who developed pulmonary hypertension after taking phenformin.

Noninvasive methods for the diagnosis of pul-
monary artery pressure are urgently needed for the early diagnosis of this disease. In 1974 several papers showed that echocardiography is useful for the quantitative evaluation of pulmonary artery pressures (77, 168, 220, 249).

A WHO meeting report on PPH published in 1975 (257) divided the clinical picture of PPH into three distinct pathological entities: (1) primary plexogenic pulmonary arteriopathy, (2) pulmonary veno-occlusive disease, and (3) recurrent pulmonary thromboembolism.

Bessinger (1976) (10) raised a question about whether to consider the marked pulmonary hypertension of infants with PDA primary or secondary since they showed severe hypertensive pulmonary vascular lesions, and infants with septal defects or PDA less than 3 years of age rarely develop obstructive pulmonary lesions.

Beginning in 1976 regression of PPH was reported by several authors (15, 35, 71, 128). Since around 1980, light has been shed on the use of vasodilator therapy which will discussed later. Reitz (1982) (192) introduced heart-lung transplantation for patients with pulmonary vascular disease.

In Japan, a Research Committee on PPH was established in 1975, with the assistance of the Ministry of Health and Welfare, and a nation-wide survey has been done in hospitals with over 100 beds from 1975 to 1978 (1). Many papers were published based upon those data.

Naslund (1981) (170) and Fahey (1984) (63) demonstrated by a cold presser test that digital vasospasm in patients with primary Raynaud's phenomenon is part of a systemic vascular response that includes a decrease in the size of the pulmonary capillary bed.

Because Fuster (1984) (72) revealed a significant beneficial effect of anticoagulant therapy on overall survival in both major pathologic groups (thromboembolic arteriopathy), they recommended anticoagulant therapy for all patients with PPH.

Yamaki (1985) (257) indicated that vasodilator therapy is effective in children because arterial changes may be reversible, i.e., there may be medial hypertrophy and/or reversible cellular intimal proliferation. In adults, however, no regression can be expected as the intimal fibrosis will probably be too severe.

Beginning in 1984 several papers dealing with prognosis were published (125, 197, 210). Dawkins et al (1986) (51) showed that PPH appeared to be related to pregnancy as they noted in 6 of their 73 female patients.

Rich et al (1986) (199) reported that 40% of PPH patients have positive antinuclear antibodies with a titer of 1:80. They speculated that in some patients PPH may represent a collagen vascular disease confined to the lungs. In 1986 and 1987 several excellent reviews were published (103, 180, 200).

II. DIAGNOSTIC CRITERIA

Several papers on diagnostic criterion have already been mentioned (20, 126). In Japan a special committee for research on PPH presented proposed guidelines for the diagnosis of PPH (1986) (1) (Table 2). Its diagnosis is made by first excluding known diseases which produce pulmonary hypertension. The disease itself is not homogeneous and includes such a wide spectrum that PPH is sometimes thought to be a waste basket diagnosis.

III. AGE, SEX, AND INCIDENCE

The age and sex distribution of 189 patients with PPH in Japan are shown in Figure 1. These patients were evenly distributed all over Japan. The age distribution was highest in the third decade for males and in the fourth decade for females.

Concerning incidence, Mac Callum in 1951 (148) found only a single case among 12,000 autopsy records at the Johns Hopkins Hospital, while Kilgworth in 1939 (138) detected only one case from 2,707 autopsy records at the Children's Memorial Hospital in Chicago. In 1954, Goodale (76) reported that only 2 cases out of the 10,000 autopsied cases satisfied the criteria for primary pulmonary arterial disease in the survey carried out at the Massachusetts General Hospital.

With the introduction of cardiac catheterization, cases with PPH have been more frequent. In 1951 Dresdale (56) found 4 cases over a period of two year at a 500-bed general hospital, and Wood found that the incidence of PPH was 0.17% among all his patients with heart disease. The Japanese survey revealed an incidence of 2.1% in patients with chronic cor pulmonale. (1). According to a 1987 National
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Table 2 Proposed guidelines for the diagnosis of PPH

PPH is the clinical diagnostic term for pulmonary hypertension of unknown cause. The definition is required to confirm pulmonary arterial (precapillary) hypertension or right ventricular hypertrophy caused by pulmonary hypertension and to ascertain that the pulmonary hypertension is to be primary.

Symptoms and signs that suggest pulmonary arterial hypertension or right ventricular hypertrophy:

Cardinal symptoms and signs

- Dyspnea
- Easy fatigability
- Retrosternal pain (pulmonary hypertensive pain) or syncope on exertion
- Right ventricular heave
- Accentuation of P₂ and S₃, diastolic murmur at pulmonic area, systolic regurgitant murmur at tricuspid area

Laboratory data

- Prominence of the central pulmonary artery trunk and decreased peripheral pulmonary vasculature on chest roentgenograms
- Right ventricular hypertrophy on ECG
- Normal or slightly disturbed restrictive ventilatory function (almost normal SaO₂)
- Right heart catheterization
  - Increased pulmonary arterial pressure (mean pressure of 25 mm Hg or more)
  - Normal pulmonary capillary wedge pressure (12 mm Hg or less)
  - Increased "a" wave in jugular venous pressure

Procedure suggesting that pulmonary hypertension is primary

There are some cases of PPH that show increased erythrocyte sedimentation rate, increased value of γ-globulin, immunologic disorders, rarely arthritis, Raynaud's phenomenon, and splenomegaly. After finding no existing primary or congenital cardiopulmonary disease, and complicating liver cirrhosis, the following histologic changes should be watched for:

Histologic findings

- Pulmonary vascular lesions that show medial hypertrophy, concentric intimal fibrosis, necrotizing arteritis, and plexiform lesions

Diseases to be excluded

- Since the following diseases may cause pulmonary hypertension succeeded by right ventricular hypertrophy, it is necessary to exclude

- Diseases primarily affecting air passage of the lung and alveoli
  - Chronic bronchitis, bronchial asthma, emphysema, pulmonary fibrosis and pneumonitis of various origins, pulmonary granulomatosis (e.g., sarcoidosis, berylliosis, histiocytosis, and tuberculosis), collagen diseases, infectious diseases of the lung, malignant tumors of the lung, alveolar microlithiasis, congenital cystic disease of the lung, pulmonary resection, hypoxia of severe degree (e.g., mountain sickness and chronic obstructive disease of upper respiratory airway)

- Diseases primarily affecting the movements of the thoracic cage
  - Kyphoscoliosis and other thoracic deformities, thoracoplasty, pleural fibrosis, chronic neuromuscular weakness (e.g., poliomyelitis), obesity with alveolar hypoventilation, idiopathic alveolar hypoventilation

- Diseases affecting primarily the pulmonary vasculature
  - Pulmonary thromboembolism, collagen diseases and other arteritis, schistosomiasis, sickle cell anemia, pressure on main pulmonary arteries and veins by mediastinal tumors, aneurysm, granuloma, or fibrosis and pulmonary veno-occlusive disease

- Diseases affecting primarily the left ventricle
  - Valvular heart diseases (especially mitral stenosis) and left heart failure

- Congenital heart diseases
  - Atrial septal defect, ventricular septal defect, patent ductus arteriosus, and others

Criteria for the diagnosis

Definite case

- Must meet criteria of more than half of symptoms and signs and laboratory data and conditions of histologic findings excluded diseases

Probable case

- Must meet criteria of more than half of symptoms and signs and laboratory data and conditions of histologic findings excluded diseases but without histologic examination

Prospective Study in the USA, which included 32 medical centers between 1981 and 1985, 187 patients were gathered (200), the disease is most prevalent from the third to the fifth decade. The average age was reported to be 23 years (110 cases, Wagenvoort, 1970) (243) 28 years (141 cases, Kanemoto, 1976) (116), and 36 years (187 cases, Rich, 1987) (200).


Although the familial occurrence of this disease is rare, 53 patients in 23 families have been reported in the world literature (122, 146). Most of them were parent and child, or brothers and sisters.

IV. CLINICAL MANIFESTATIONS

1. Symptoms

Initial and chronic symptoms in Japanese cases are shown in Figure 2 (A, B) (1). Dyspnea on exertion is the commonest early symptom, with fatigue being the second most common. Chest pain and syncope are less common.

Dyspnea is considered to coincide with the progression of the obstructive changes in the small pulmonary vessels. Angina-like chest pain is postulated to result from (1) the disturbance in coronary flow due to a marked increase in the end-diastolic pressure of the right ventricle, (2) functional coronary insufficiency resulting from low cardiac output, (3) subendocardial ischemia and necrosis of the right ventricle due to the relative ischemia developing in the hypertrophied right ventricle, and (4) dilatation of the pulmonary artery with exertion.

Syncope was noted to have an incidence of 55% (Yu, 1957) (260), and 56% (Rich, 1987) (200), but less in Japan where it is only 17% (1). The mechanism of syncope has been ascribed to (1) a vagovagal reflex via the pressure receptors in the walls of the pulmonary arteries, (2) fixed cardiac output and (3) arrhythmias and/or complete A-V block (108, 242, 260).

2. Physical Findings

The physical findings of the Japanese patients are shown in Figure 2 (1). Characteristically there is a high jugular venous pressure, a parasternal systolic heave (thrust), hepatomegaly, and peripheral edema, suggesting RVH and right heart failure. Raynaud's phenomenon is
seen in 14% (Japan), 30% (Walcott) (246), and 6% (Wagenvoort) (243). Cyanosis develops in 38% of the cases, which is usually peripheral but according to Berthrong (1955) (9) all of the cases accompanied by central cyanosis had a patent foramen ovale, low cardiac output and polycythemia. However, intrapulmonary shunts may also occasionally cause central cyanosis. On auscultation there is a tachycardia with an accentuation of the pulmonic component of the second heart sound, right-sided third and fourth heart sounds, and the murmurs of pulmonic and tricuspid regurgitation.

3. Laboratory Findings

a) Blood Examination

In the Japanese survey, the average hematocrit was 45.7 ± 6.0%. An increased erythrocyte sedimentation rate of more than 20 mm/hr was noted in 27% of the patients, increased total protein value of over 8.0 g/dl in 9%, and hypergamma-globulinemia with γ-globulin over 25% in 27% (1).

b) Chest X-rays

The chest x-ray characteristics of 59 patients with PPH and 100 healthy control subjects studied by us were summarized in Table 3 (119). The width of the main pulmonary artery
from the midline divided by half the thoracic
diameter (DPA/T/2) showed a significant
correlation with mean pulmonary artery
pressure (r = 0.31, p < 0.05). The cardiothoracic
ratio showed a significant correlation with a mean
right atrial pressure (r = 0.37, p < 0.01). These
findings were nonspecific and were brought
about by marked pulmonary hypertension,
right ventricular enlargement and/or right ven-
tricular failure.

c) Electrocardiograms

A summary of our ECG data is presented in
Table 4. These findings are the reflection of the
severe systolic overload to the right ventricle.
The ECG might even suggest prognosis because
there was a significant negative correlation be-
tween the mean frontal axis of the QRS
(r = 0.40, p < 0.01) and survival months and
there was a positive correlation between R waves
in leads V5-6 and the survival months (r = 0.40
and r = 0.44, both p < 0.01, respectively) (227).
We examined 171 routine 12-lead ECG trac-
ing of 101 patients for arrhythmias and,
although more arrhythmias were detected in
deepest patients than survivors, no major ar-
rythmias were detected (121).

d) Pulmonary Function

Fifty-five percent of patients showed normal
ventilatory functions, 30% restrictive, and 15%
obstructive dysfunction (1). Arterial blood gas
analysis showed oxygen saturations of
90.7 ± 5.8%, PO2 of 67.9 ± 17.0 mmHg, PCO2
of 32.0 ± 8.4 mmHg, and pH of 7.45 ± 0.05.
The reduced DLco and wide A-aDO2 is a common
finding. From these findings, the charac-
teristics of the lung function might be attributed
to venous admixture but not alveolar hypoventi-
lation or ventilation-perfusion inequality (1).
The mild respiratory alkalosis may be the result
of increased afferent activity from intrapulmo-

Table 3 Summary of chest roentgenographic findings

<table>
<thead>
<tr>
<th></th>
<th>Control (n = 100)</th>
<th>PPH (n = 59)</th>
<th>P value</th>
</tr>
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<tbody>
<tr>
<td>Ao/T/2 (%)</td>
<td>24.2 ± 3.4</td>
<td>24.0 ± 3.9</td>
<td>NS</td>
</tr>
<tr>
<td>DPA/T/2 (%)</td>
<td>28.1 ± 4.5</td>
<td>43.7 ± 7.7</td>
<td>P &lt; 0.001</td>
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<td>PL/T</td>
<td>33.6 ± 4.2</td>
<td>44.0 ± 5.5</td>
<td>P &lt; 0.001</td>
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<tr>
<td>dPA (mm)</td>
<td>12.1 ± 1.2</td>
<td>25.1 ± 6.4</td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td>CTR (%)</td>
<td>43.8 ± 2.7</td>
<td>55.9 ± 6.8</td>
<td>P &lt; 0.001</td>
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</tbody>
</table>

Table 4 Summary of ECG data

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
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</thead>
<tbody>
<tr>
<td>AQRS (degree)</td>
<td>+110.8 ± 25.0</td>
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<tr>
<td>AP (degree)</td>
<td>64.0 ± 15.2</td>
</tr>
<tr>
<td>Duration of P II (sec)</td>
<td>0.08 ± 0.01</td>
</tr>
<tr>
<td>Amplitude of P II (mm)</td>
<td>1.7 ± 0.7</td>
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<tr>
<td>PTFV1 (mm/sec)</td>
<td>-0.03 ± 0.04</td>
</tr>
<tr>
<td>RV1 (mm)</td>
<td>11.4 ± 6.6</td>
</tr>
<tr>
<td>AV1 (mm)</td>
<td>4.4 ± 5.4</td>
</tr>
<tr>
<td>R/SV1</td>
<td>6.2 ± 6.0</td>
</tr>
<tr>
<td>RV5 (mm)</td>
<td>11.5 ± 6.1</td>
</tr>
<tr>
<td>SV5 (mm)</td>
<td>10.3 ± 5.2</td>
</tr>
<tr>
<td>R/SV5</td>
<td>1.8 ± 2.7</td>
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<tr>
<td>RV6</td>
<td>2.4 ± 3.5</td>
</tr>
<tr>
<td>RV1 + SV5 (mm)</td>
<td>21.8 ± 8.9</td>
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<tr>
<td>RV1 + SV6 (mm)</td>
<td>17.7 ± 8.4</td>
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<td>RaVR (mm)</td>
<td>3.2 ± 2.0</td>
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<tr>
<td>VATV1 (sec)</td>
<td>0.04 ± 0.01</td>
</tr>
<tr>
<td>R/SV5 − R/SV1</td>
<td>1.17 ± 4.01</td>
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</table>

10mm = 1mV

Table 4 Continued

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
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<tr>
<td>AQRS (degree)</td>
<td>+110.8 ± 25.0</td>
</tr>
<tr>
<td>AP (degree)</td>
<td>64.0 ± 15.2</td>
</tr>
<tr>
<td>Duration of P II (sec)</td>
<td>0.08 ± 0.01</td>
</tr>
<tr>
<td>Amplitude of P II (mm)</td>
<td>1.7 ± 0.7</td>
</tr>
<tr>
<td>PTFV1 (mm/sec)</td>
<td>-0.03 ± 0.04</td>
</tr>
<tr>
<td>RV1 (mm)</td>
<td>11.4 ± 6.6</td>
</tr>
<tr>
<td>AV1 (mm)</td>
<td>4.4 ± 5.4</td>
</tr>
<tr>
<td>R/SV1</td>
<td>6.2 ± 6.0</td>
</tr>
<tr>
<td>RV5 (mm)</td>
<td>11.5 ± 6.1</td>
</tr>
<tr>
<td>SV5 (mm)</td>
<td>10.3 ± 5.2</td>
</tr>
<tr>
<td>R/SV5</td>
<td>1.8 ± 2.7</td>
</tr>
<tr>
<td>RV6</td>
<td>2.4 ± 3.5</td>
</tr>
<tr>
<td>RV1 + SV5 (mm)</td>
<td>21.8 ± 8.9</td>
</tr>
<tr>
<td>RV1 + SV6 (mm)</td>
<td>17.7 ± 8.4</td>
</tr>
<tr>
<td>RaVR (mm)</td>
<td>3.2 ± 2.0</td>
</tr>
<tr>
<td>VATV1 (sec)</td>
<td>0.04 ± 0.01</td>
</tr>
<tr>
<td>R/SV5 − R/SV1</td>
<td>1.17 ± 4.01</td>
</tr>
</tbody>
</table>

10mm = 1mV
### Table 5: Summary of hemodynamic data

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>RA (mean)</td>
<td>7.8 ± 5.6</td>
</tr>
<tr>
<td>RV (systolic)</td>
<td>98.1 ± 25.9</td>
</tr>
<tr>
<td>(end-diastolic)</td>
<td>9.9 ± 6.3</td>
</tr>
<tr>
<td>PA (systolic)</td>
<td>97.0 ± 26.7</td>
</tr>
<tr>
<td>(diastolic)</td>
<td>42.5 ± 15.5</td>
</tr>
<tr>
<td>(mean)</td>
<td>61.0 ± 17.2</td>
</tr>
<tr>
<td>PC (mean)</td>
<td>7.3 ± 3.9</td>
</tr>
<tr>
<td>BA (systolic)</td>
<td>112.6 ± 18.8</td>
</tr>
<tr>
<td>(diastolic)</td>
<td>74.4 ± 12.2</td>
</tr>
<tr>
<td>(mean)</td>
<td>87.1 ± 13.3</td>
</tr>
<tr>
<td>Ps (P/A)</td>
<td>0.85 ± 0.21</td>
</tr>
<tr>
<td>CI (L/min/m²)</td>
<td>2.81 ± 0.93</td>
</tr>
<tr>
<td>RVWI (kg m/min/m²)</td>
<td>1.98 ± 0.96</td>
</tr>
<tr>
<td>TPVR (dyne sec cm⁻²)</td>
<td>1342 ± 683</td>
</tr>
<tr>
<td>TSVR (dyne sec cm⁻²)</td>
<td>1891 ± 763</td>
</tr>
<tr>
<td>R (P/A)</td>
<td>0.69 ± 0.14</td>
</tr>
</tbody>
</table>

**Abbreviations:**
- RA: right atrial, RV = right ventricular, PA = pulmonary artery, PC = pulmonary capillary,
- BA = brachial artery, Ps(P/A) = systolic pulmonary to brachial artery pressure ratio, CI = cardiac index, TPVR = total pulmonary vascular resistance, TSVR = total systemic vascular resistance, R(P/A) = total pulmonary to systemic vascular resistance ratio

![Fig. 3 Presenting symptoms](image-url)
should be used. Pulmonary angiography should be done right and left separately. Right sided hemodynamics showed mean right atrial pressures of -2 to 23 mmHg, mean pulmonary artery pressures 46-116 mmHg, mean pulmonary capillary wedge pressures 2-12 mmHg, cardiac indexes 0.74-3.37, total pulmonary vascular resistance 909-6,390 dyne sec cm⁻⁵ (11-80 Wood units) and right ventricular work indexes 0.56-4.25 kg m/min/m² (120, 126, 141, 172, 227, 246).

In our study (120), there were no relationship between pulmonary artery pressure and right atrial pressure, suggesting that patients with the higher pulmonary artery pressure did not always suffer from right ventricular failure. This was confirmed by the fact that pulmonary artery pressure did not correlate with the number of survival months from the time of right heart catheterization.

Hemodynamic variables affecting prognosis were pulmonary artery diastolic pressure, cardiac index, pulmonary vascular resistance, right ventricular work index, systolic pulmonary artery/systemic pressure ratio, and pulmonary/systemic vascular resistance ratio (125, 197). The cardiac index was the best variable to determine prognosis correlating significantly with the survival months from the time of measurement (Figure 4) (125).

g) Electrocardiographic and Hemodynamic Correlation

We (127) evaluated these correlations and demonstrated the following: (1) The sensitivity of RV₁ > 1.2 mV suggesting a pulmonary artery systolic pressure > 90 mmHg was 94% and the specificity was 47%.(2) But the sensitivity and specificity of AQRS ≥ 100°, RV₆ < 1 mV, SV₆ ≥ 0.7 mV, and R/SV₆ ≥ 2 for suggesting a CI of < 2.8 l/min/m² were good enough to be clinically useful, (3) A combination of criteria using an AQRS ≥ 100° plus an SV₆ ≥ 0.7 mV increases the sensitivity and specificity for the identification of a CI of < 2.8 l/min/m².

V. THERAPY

1. General consideration for pulmonary hypertension

a) restriction of exercise and emotional excitement
b) prevention of infection
c) contraindication of pregnancy and use of contraceptive pill
d) catheterization should be done using a self-guiding catheter

2. Therapy for right heart failure

a) bed rest
b) low salt diet
c) digitalis and diuretics

![Graph showing relationship of cardiac index to survival months from the time of measurement](image-url)
3. Anticoagulants (56, 63, 78, 90, 141, 227, 233)

4. Vasodilator therapy
   a) oxygen (2 L/min during asleep) (165, 166)
   b) β-stimulating agents (144, 147, 156, 181, 183, 185, 194)
      isoproterenol (10–20 mg, g 2hr)
      terbutaline (5 mg, qid)
   c) α-blocking agents
      tolazoline (50 mg, tid/qid)
      phenolamine (50 mg, tid/qid)
      phenoxybenzamine (10 mg, tid) (135)
      prazosin (0.5–3 mg, tid/qid) (124)
   d) hydralazine (20–200 mg, tid/qid)
      (140, 154, 178, 195, 212)
   e) diazoxide (50–150 mg, tid/qid)
      (85, 137, 213, 247)
   f) nitrates
      nitroglycerine (ointment 1–3 cm:
      5 mg/cm) (99, 110, 184)
      isosorbide dinitrate (5 mg, tid/qid) (124)
   g) Ca-blocking agents
      nifedipine (52, 66, 68, 87, 99, 198, 218, 248, 254, 259)
      diltiazem (30–60 mg, tid) (111, 198)
      verapamil (40–120 mg, tid) (143, 149, 179, 198)
   h) captopril (12.5–100 mg, tid)
      (101, 104, 139, 145, 186, 191, 193)
   i) prostaglandins
      PGI₂ (prostacyclin), PGE₁ (7, 81, 82, 87, 97, 235, 248)
   j) indomethacin (50 mg, tid/qid) (185)
   k) amrinone (155, 156, 213)
   l) thromboxane synthetase inhibitors (200 mg, qid)
      (96, 201)

5. Serotonergic blockers
   a) ketanserin (20 mg, tid) (155, 156)

   Vasodilator therapy has been indicated for
   this illness with the hope of improving prognosis.
   There are still no guidelines that help you to
   choose an adequate drug for each patient. Moreover, the results are controversial and
   there are even some reports of deleterious effects.

   The author (125) found that patients whose
   right ventricular function was compensated at
   the time of catheterization might be expected to live \( \geq 48 \) months regardless of the level of pulmonary hypertension. The pulmonary vasculature of these patients is thought to be in a
   state of reversible vasoconstriction, and hence may respond to vasodilator drugs.

   However, the pulmonary vasculature of pa-
   tients with severe pulmonary vascular resistance may have fixed obstruction. Consequently no
   favorable effects with vasodilators may be expected and only adverse effects may ensue.

6. Surgical procedures
   a) atrial septostomy (2, 3, 174, 196)

   Obeyesekere (1970) (174) noted that the pa-
   tients with a patent foramen ovale had a more
   favorable clinical outcome than those without
   patency because patency allows right ventricu-
   lar unloading. Although the surgical creation of a shunt by atrial septostomy may reduce right ventricular systolic loading and lead to a longer
   survival, one such trial (196) did not succeed because of the sudden demand put on the left
   ventricle in the immediate postoperative period.

   b) banding of pulmonary artery plus (a)

   c) thoracic sympathectomy and stellate ganglionic blockade (56, 86, 90)

7. Immunosuppressive therapy
   a) adrenocortical steroids (42, 90, 189, 199, 227)

   b) azathioprine

8. Heart-lung transplantation (75, 192)

VI. CLINICAL COURSE

   The disease is characterized by a progressive course and the prognosis is unfavorable when
   symptoms develop and the diagnosis is estab-
   lished. Bedford (1951) (76) observed that cardia
   c failure developed within 6 to 12 months after
Fig. 5 Prominent concentric intimal proliferation and medial hypertrophy

Fig. 6 Plexiform lesion
the onset of symptoms, and Evans (1957) (62) stated that death occurred 5 months to 7 years (average 2.5 years) after the development of symptoms. The prognosis in young patients was found by Wood (1968) (255) to be an average of 3.2 years (in 20 cases from a month to 10 years), by Rosenberg (1964) (208) to be 2 years (in 5 cases from 5 months to 6 years), and by Walcott (1970) (246) to be 5 years (in 21 cases, 6 months to 17 years). Noteworthy is Walcott's observation that a mean survival of only 2 years was obtained for those patients characterized by the association of Raynaud's phenomenon, arthritis, and abnormal serologic reactions, while it was 6.6 years for those without any of these symptoms and signs.

In Japan the average survival after the diagnosis was 2.8 years (2 months—19 years), and it shortened to 1.5 years (7 months—5 years) after developing right heart failure. The cause of death in 70 patients included right heart failure in 37 patients (53%) and sudden death in 16 patients (37%), these two causes accounting for 90% of the deaths (1).

Sudden deaths were reported to occur during cardiac catheterization, pulmonary angiography, minor surgical procedure, induction of anesthesia, and perfusion lung scans. Jewett (1956) (109) reported deterioration and death after pregnancy and subsequent delivery. Similar cases have been noted in Japan. Pregnancy must be avoided in PPH patients. However, Rozkovec et al (1986) (210) reported that those patients whose onset is associated with pregnancy had a favorable prognosis. It should be stressed that pregnancy tends to aggravate pulmonary vascular disease in general, irrespective of its nature (51, 62, 113, 114).

Melmon (1963) (160) reported three familial cases where death occurred at the ages of 45, 65, and 35 years, respectively, 10, 12, and 18 years after the development of the initial symptoms. A patient reported by Charters (1970) (39) died at the age of 25 years after a clinical course extending over a period of 19 years. However, those affected by PPH cannot achieve a normal life span even if they survive for considerable periods of time. However, with the advent of vasodilator therapy, some patients showing regression have had their deterioration halted.

VII. PATHOLOGIC FINDINGS

1. Macroscopic Findings

All of our patients revealed enlargement and hypertrophy of both the right atrium and right ventricle. In Japan, the thickness of the right ventricle ranged from 4.5 to 15 mm (average 9 mm), while thickness of the left ventricle was normal (ranging from 10 to 15 mm with an average of 11.3 mm). The ratio of the left-to-right ventricular wall thickness was less than 2.6 (average 1.7) in all cases. A patent foramen ovale was only occasionally demonstrated. Main pulmonary trunks were markedly dilated and showed atherosclerosis.

Right ventricular wall thickness and heart weight correlated significantly with mean pulmonary artery pressure (r = 0.676, p < 0.01 and r = 0.501, p < 0.05, respectively) (Figure 7).

2. Microscopic Findings

The histopathological features of plexogenic pulmonary arteriopathy are summarized as follows: (1) Increased medial thickness of "muscular pulmonary arteries" between 100 and 1,000 μm in external diameter, (2) The appearance of small muscular vessels less than 80 μm in diameter with a distinct media of circular muscle bounded by internal and external elastic laminae, (3) The development of intimal fibrosis and fibroelastosis arranged in a characteristic "onion-skin" configuration, (4) The development of localized "dilatation lesions" such as plexiform or angiomatoid lesions in the side branches of muscular pulmonary arteries proximal to sites of occlusion by intimal fibroelastosis, (5) Occasional necrotizing arteritis in the walls of muscular pulmonary arteries. All these features are characteristic but except for the plexiform lesions, are not pathognomonic (256).

Clinical differentiation of PPH from "silent" recurrent micro-thromboembolism is extremely difficult. However, thrombotic or thromboembolic lesions are characterized as follows: (1) Recent thrombi, thrombi in the process of organization, and other lesions in the form of cushion-like patches of intimal fibrosis, usually causing eccentric narrowing of the lumen but sometimes causing complete occlusion, (2) Recanalization sometimes so prominent that it results in the formation of intra-arterial fibrous
Fig. 7 Upper panel showing relationship between thickness of right ventricular wall and mean pulmonary artery pressure. Lower panel showing relation between heart weight and mean pulmonary artery pressure.

septa, (3) No plexiform lesions or fibrinoid necrosis (243, 244). Typical histologic features are shown in Figure 4 and 5.

VIII. ETIOLOGY AND PATHOGENESIS

PPH is a heterogeneous disease covering a wide spectrum and making a clinical syndrome. Consequently a number of possible etiologies and pathogeneses have been postulated. The susceptibility and degree of hyperactivity of the pulmonary vasculatures in each individual plays a very important role in the development of pulmonary hypertension (243).

1. Vasconstriction

Increased vasomotor tone has been thought to precipitate the development of pulmonary hypertension from the following observations (113, 114):

a) The capability of active constriction and dilatation in the small pulmonary arteries and the ability of the cold pressor test to produce pulmonary vasoconstriction,

b) The existence of patients whose pulmonary artery pressure falls with vasodilator drugs or who show spontaneous regression,

c) The ability of pulmonary hypertension at high altitude to normalize spontaneously at sea
level.

d) The demonstration of minimal pathologic lesions in some patients with severe pulmonary hypertension.

e) The progression in most patients from only medial hypertrophy in the early stage followed only later by the development of other alterations.

f) The association with Raynaud's phenomenon. Although the direct mediators are not yet determined, a number of substances, such as norepinephrine, serotonin, histamine, prostaglandins, angiotension converting enzyme inhibitors fibrinopeptide A and B, epinephrine, T3 and T4, and female sex hormones have been suggested as mediator for the vasoconstriction (8, 38, 60, 69, 79, 204, 217, 222). Overactivity of the autonomic nervous system has also been proposed (243, 253).

2. Congenital Relationships

Although familial occurrences have been reported, the mode of inheritance has not been fully clarified (14, 41, 48, 56, 60, 62, 122, 152, 182, 203, 205, 224, 239). Some have postulated an autosomal dominant gene with variable penetrances, and others an autosomal recessive gene with incomplete male penetrance (100, 160). Other theories have been proposed, such as persistence of the fetal pulmonary vasculature, congenital hypertrophy of the small pulmonary arteries, medial hypoplasia or aplasia of the small muscular pulmonary arteries and arterioles with reactive intimal proliferation and abnormal bronchopulmonary anastomosis (60, 62, 224).

3. Pulmonary Thromboembolism

Clinical differentiation of PPH and recurrent silent micro-thromboembolism is considered to be almost impossible (256). Formerly it was thought that pulmonary microthromboembolism was always necessary for the pathogenesis (5, 56, 70, 88, 105). However, Owen (1953) (177) strongly suggested separation of the diagnosis of PPH from that of multiple embolism. It is generally clearly distinguishable histologically as described in the former section. Shepherd et al (224) proposed that either amniotic embolism during pregnancy or thrombosis in either the pulmonary or uterine vessels stimulated by the menstrual cycle may initiate

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PPH.

4. Portal hypertension

Pulmonary hypertension of unknown cause has been reported in association with liver cirrhosis and portal-caval shunts (16, 40, 46, 133, 153, 162, 215, 223). The reason for this association was speculated as resulting either from portal vein thrombosis and consequent emboli, multiple arteriovenous fistula in the lungs, dilatation of the peripheral pulmonary arteries (lung spider nevi), increased cardiac output, and a vascular toxin normally inactivated by the liver.

5. Dietary or Drug-Related

Several drugs and chemicals were thought to produce pulmonary hypertension in man. Although appetite suppressants, such as amphetamine, fenfluramine, and methamphetamine (65, 73, 83, 84, 241) were thought to be such agents, conclusive evidence has not been forthcoming. The daily administration of amphetamine to experimental animals did not cause the development of pulmonary hypertension or of any histologic changes in the pulmonary arteries (61, 94, 132, 228, 229, 244, 251). The illegal sale of tained rapeseed oil for use in cooking was reported to cause an epidemic of pulmonary hypertension in Spain (173).

Contraceptive pills may also produce pulmonary hypertension; one mechanism is via pulmonary thromboembolism and the other is presumed to be a direct effect on the pulmonary vasculature by causing medial hypertrophy and intimal fibroelastosis (107, 136). The latter mechanism is exaggerated in patients with congenital cardiac septal defects or pre-existing with congenital cardiac septal defects or pre-existing pulmonary hypertension (161, 173). Oral hypo-glycemic agents such as phenformin and drugs such as sulfonylides, penicillin, and chloramphenicol have been reported to have pulmonary hypertension (42, 64, 161).

The pyrrolizidine alkaloids in Crotalaria spectabilis, Crotalaria fulva, Crotalaria laburnoides and Senecio jacobae produce pulmonary hypertension in experimental animals (105-109). The mechanism is postulated to be the result of direct vasoconstriction and muscularization of the pulmonary vascular bed.
6. Hypoxia

Hypoxia causes a potent vasoconstriction of muscular pulmonary arteries and it is well-known that there is a strong positive relationship between partial pressure of oxygen and pulmonary artery pressure (151). However, in most of the patients with PPH, the partial pressure of oxygen is only slightly decreased. Although there are reports of PPH living at high altitudes, hypoxia itself is unlikely to be responsible for the vasoconstriction.

7. Autoimmunity

The association of Raynaud’s phenomenon, immunological abnormalities, and arthritis has occasionally been observed in patients with PPH (33, 56, 86, 112-114, 117, 141, 189, 203, 230, 242, 256). Also, there have been some patients with collagen diseases associated with pulmonary hypertension. These include systemic lupus erythematosus, progressive systemic sclerosis, rheumatoid arthritis, dermatomyositis, polymyositis, Hashimoto’s disease, polyarteritis nodosa, CRST, CREST, mixed connective tissue disease, and Sjögren’s disease (15, 27, 29, 30-32, 49, 67, 112, 115, 118, 126, 163, 167, 216, 220, 226, 245, 259). Therefore, although immunological processes may play an etiological role in some patients with PPH, the exact relationship has not been elucidated.

In Japan, there were 37 PPH patients with Raynaud’s phenomenon and/or immunological abnormalities (123). They were all women with an average age of 31 ± 12 years. Also there were 39 patients (38 women and 1 man) with a collagen disease and pulmonary hypertension not due to pulmonary fibrosis, 21 patients with SLE, 8 patients with progressive systemic sclerosis, 5 patients with mixed connective tissue disease, and 5 patients with Sjögren’s disease. Their average age was 31 ± 9 years.

Raynaud’s phenomenon was the most conspicuous feature. However, morphological studies have so far failed to find histologic features in the lungs specific to collagen diseases not only in patients with PPH associated with immunological disorders but also in patients with definite collagen disease. Consequently pulmonary Raynaud’s phenomenon is thought to be the possible mechanism in this category of patients.

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