Primary pulmonary hypertension: natural history and the importance of thrombosis

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ABSTRACT A long-term retrospective follow-up study was made of 120 patients (33 male, 87 female patients) with primary pulmonary hypertension — diagnosed by strict clinical and hemodynamic criteria — to obtain a better understanding of the natural history and possible pathogenetic mechanisms of the disease. The mean age at diagnosis was 34 (3 to 64) years, but only 24 patients (21%) remained alive 5 years later. Lung tissue obtained at autopsy from 56 patients revealed two major pathologic types: thromboembolic pulmonary hypertension in 32 patients (57%) and plexogenic pulmonary arteriopathy in 18 (32%). Thus, in more than half the patients undergoing autopsy the major histologic feature was thrombi without any evidence of plexiform lesions. The two groups were similar with respect to their clinical and hemodynamic features and short survival. Of the variables tested for prognostic importance by stepwise multivariate analysis, only two were significant: pulmonary arterial oxygen saturation (p < .00001) and anticoagulant therapy (p = .01). Anticoagulant therapy is recommended for patients with primary pulmonary hypertension.


PRIMARY pulmonary hypertension has been defined by the World Health Organization (WHO) as “pulmonary arterial hypertension of unknown cause.” Although the entity was first recognized in the late 1800s and early 1900s, publication of the first clinical description (together with cardiac catheterization data) awaited the work of Dresdale et al. in 1951. After a detailed pathologic description was published by Wagenvoort and Wagenvoort in 1970, a WHO report described three major different pathologic types of the disease.

Primary pulmonary hypertension is not common, but it poses a formidable challenge: its cause or causes are obscure, its natural history is ill-defined, and in almost all cases it is rapidly lethal. As yet, no medical therapeutic modality has been shown to affect the long-term prognosis. Identification of the patients most likely to benefit from newer therapeutic advances requires an understanding of the natural history of the disease and of the possible pathologic and pathogenetic mechanisms. Accordingly, we undertook a large long-term retrospective follow-up study that included analysis of lung material obtained at autopsy.

Methods

Patients. The study series comprised patients in whom primary pulmonary hypertension was diagnosed — by strict clinical and hemodynamic criteria to be detailed below — at the Mayo Clinic between January 1955 and April 1977 and who were followed up to 1983. Required in each case were thorough work-up (including chest roentgenography, electrocardiography, and cardiac catheterization), absence of indications for other diseases (clinical evidence or suspicion of single or recurrent thromboembolic episodes, deep venous thrombosis, chronic obstructive pulmonary disease, valvular heart disease, primary intracardiac shunts, or connective tissue disease), and thorough follow-up.

Of the 149 patients initially accepted into the study, 29 were later excluded, 11 because associated connective tissue disease was discovered at follow-up, 10 because of clinical suspicion of recurrent pulmonary emboli at diagnosis or follow-up, and eight because complete follow-up information was not obtained. There remained 120 patients constituting our study group.

Follow-up. All patients were followed for at least 5 years, or until death if that came sooner. The median follow-up period was 14 years and the longest 27 years. All patients resided in the United States and follow-up information was obtained by repeat examinations at the Mayo Clinic and from responses to letters and telephone calls to the patients or relatives and to the referring physicians.

Clinical features. Each of the initial clinical histories of the
120 patients were recorded by at least two physicians, and the clinical records were reviewed carefully by two of us for this study. Noted particularly were (1) interval from initial clinical manifestation to clinical and hemodynamic diagnosis, (2) roentgenographic evidence, including prominence of main pulmonary and hilar arteries and signs of cardiomegaly, and (3) electrocardiographic abnormalities, including right ventricular hypertrophy (R/S wave in lead V₁ > 1 mm, R wave in lead V₁ plus S in lead V₆ > 10 mm), right axis deviation (QRS axis ≥ 90 degrees), and large P wave (≥ 2.5 mm in lead II).

In an attempt to determine possible specific risk factors that might unmask the underlying pulmonary hypertensive disease or contribute to its development, we determined and analyzed (1) sex and age, (2) 52 professional and possible environmental factors (Hollingshead Occupational and Educational Scales Code, U.S. Government, 1958), (3) history of one or more previous pregnancies, (4) oral contraceptive use, (5) history of Raynaud’s phenomenon, (6) history of liver disease, (7) history of thrombophlebitis, (8) family history, defined as documented primary pulmonary hypertension in at least one first-degree relative, and (9) long-term use of amphetamines or other vasoactive drugs.

The majority of patients received anticoagulant therapy of the oral warfarin type at some stage during their illness. To assess the benefit of such treatment and to minimize bias, we defined “anticoagulated” patients as those whose anticoagulant therapy had been started within the first 12 months after diagnosis.

**Hemodynamic features.** At the cardiac catheterization required for acceptance into the study, the following procedures were performed: (1) measurement of pulmonary arterial pressure (Pap), (2) measurement of pulmonary capillary wedge or left atrial pressure, (3) estimation of pulmonary index (PI) with the use of the oxymetric principle of Fick, (4) estimation of the total pulmonary resistance (RP, in U/m²), according to the formula RP = mean Pap/PI, (5) calculation of right ventricular end-diastolic pressure (RVEDP) and right ventricular work index (RVWI), according to the formula RVWI = PI × (mean Pap – RVEDP) × 0.0136 kg/min/m², (6) determination of oxygen saturation in the systemic, pulmonary, and venous circulations as well as in the right cardiac chambers, and (7) assessment of intracardiac shunts in 102 patients according to the indicator-dilution technique with indocyanine green. Pulmonary angiography was also performed in 36 patients.

The 120 patients in this study are those who had pulmonary hypertension (mean pulmonary arterial pressure of at least 30 mm Hg) without discernible cause at cardiac catheterization.

**Pathologic evaluation.** Among the 112 patients who died, autopsy material was obtained in 56 (18 from the Mayo Clinic Tissue Registry and 38 from other institutions). Histologic slides were prepared with hematoxylin and eosin stain and with elastic-van Gieson stain; when necessary, additional sections for study were prepared from available paraffin tissue blocks. Each case was reviewed and diagnosed by one of us (W. D. E.) without prior knowledge of the patient’s age, sex, or clinical history. Three previously described major histologic types of primary pulmonary hypertension were identified (thromboembolic pulmonary hypertension, primary pulmonary arteriopathy, and pulmonary venoocclusive disease) and several subcategories were observed.

**Statistical analysis.** Significance of univariate analysis of prognostic factors was tested with Student’s t test or the chi-square test. Multivariate analysis of prognostic factors was done with use of the Cox stepwise proportional-hazards general linear model. Actuarial analysis of survivors was done with the Kaplan-Meier method. Differences in survival curves were tested by the log-rank procedure.

**Results**

**Clinical and laboratory features**

**Clinical features.** The patient group consisted of 33 men (27%) and 87 women (73%). At entry into the study, the mean age was 34 years. The age distribution, by sex, is illustrated in figure 1. The median interval from the initial clinical manifestation of disease to the clinical and hemodynamic diagnosis of primary hypertension was 1.9 years. At the time of diagnosis the four most frequent clinical features were exertional dyspnea (75%), loud second heart sound (98%), roentgenographic abnormalities (95%) in the form of cardiomegaly or prominent central pulmonary arteries, and electrocardiographic abnormalities (95%) in the form of right ventricular hypertrophy, right axis deviation, or large P wave. All patients had either dyspnea or a loud second heart sound, and all had at least one of the roentgenographic or electrocardiographic abnormalities described. Less frequent clinical features were exertional dizziness or syncope (30%), exertional chest pain (8%), and ankle swelling (8%).

Among the defined possible specific risk factors, none of the 52 professional and environmental factors correlated significantly with the incidence of primary pulmonary hypertension, apart from the fact that 53 (44%) of the patients were housewives. Of the 82 postpubertal female patients, 65 (79%) had had at least one previous pregnancy; in 14 (17%) the initial symptoms appeared shortly after pregnancy. Of these 82 women, 17 (21%) had been long-term users of oral contraceptives, but this is not significantly different from the frequency of use among adult women in the general population. The records showed that 12 patients (10% of all) had Raynaud’s phenomenon, seven (6%) had chronic liver disease, and five (4%) had a history of superficial thrombophlebitis. Again, this is probably not different from the frequency in the general population. In two families primary pulmonary hypertension affected two brothers; that is, four patients (3%) had a family history of the disease. Two patients (3%) were long-term users of amphetamines.

**FIGURE 1.** Age distribution of 33 male and 87 female patients at diagnosis of primary pulmonary hypertension.
TABLE 1
Hemodynamic features at diagnosis

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary arterial pressure (mm Hg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak</td>
<td>98</td>
<td>53-208</td>
</tr>
<tr>
<td>Mean</td>
<td>64</td>
<td>36-120</td>
</tr>
<tr>
<td>Pulmonary index, (l/min/m²)</td>
<td>2.2</td>
<td>0.7-5.0</td>
</tr>
<tr>
<td>Total pulmonary resistance (Um²)</td>
<td>33</td>
<td>11-95</td>
</tr>
<tr>
<td>Right ventricular end-diastolic pressure (mm Hg)</td>
<td>13</td>
<td>2-30</td>
</tr>
<tr>
<td>Right ventricular work index (kg/min/m²)</td>
<td>1.6</td>
<td>0.4-5.8</td>
</tr>
<tr>
<td>Systemic arterial oxygen saturation (%)</td>
<td>91</td>
<td>42-99</td>
</tr>
<tr>
<td>Pulmonary arterial oxygen saturation (%)</td>
<td>60</td>
<td>20-80</td>
</tr>
</tbody>
</table>

Hemodynamic and angiographic features (table 1). Hemodynamic evaluation at the time of diagnosis revealed peak systolic pulmonary arterial pressures higher than 50 mm Hg in all patients (100%), a pulmonary index less than 2.5 liters/min/m² in 85 patients (71%), total pulmonary resistance greater than 15 Um² in 113 patients (94%), and pulmonary capillary wedge or left atrial pressures within normal limits in all patients. Systemic arterial oxygen saturation of less than 90% was observed in 32 patients (27%). Indicator-dilution studies in 102 cases disclosed right-to-left shunting in 19 (19%), which is slightly less than the incidence of patent foramen ovale in the general population. Pulmonary angiographic examination, performed in 36 patients, showed abnormalities in 30 (83%). Typically (in 78% of the patients), the main pulmonary arteries and their primary branches were enlarged, but the distal branches quickly narrowed in 83% and became quite tortuous in 28%. No occlusion was demonstrated angiographically. In all 36 cases the levo phase was normal, but the pulmonary transit time was frequently very slow.

Clinical course. At the time the latest follow-up information was obtained, 112 patients (93%) had died (figure 2). In this group the median interval from diagnosis to death was 1.9 (range 0 to 16) years, and more than three-fourths of the deaths occurred within the first 5 years after diagnosis. The contributing factors, causes, or kinds of deaths identified were right cardiac failure in 71 (63%), pneumonia in eight (7%), sudden death in eight (7%), death related to cardiac catheterization in five (5%), pulmonary arterial dissection with tamponade in one (1%), and death during a minor operation in one (1%). In 18 instances (16%) the contributing factors or cause of death could not be determined.

Prognostic factors. A number of clinical and hemodynamic variables were tested for prognostic importance by univariate and stepwise multivariate analysis. With univariate analysis (table 2) several hemodynamic variables were found to be strongly predictive of early death. Pulmonary arterial oxygen saturation (SO₂) appeared to be a good predictor: taking the median for the total group (63%) as the discriminating value, 3 year survival was 55% among patients in whom SO₂ was that high or higher and 17% among those in whom SO₂ was lower (p = .0001). In 35 patients, the hemodynamic response to oxygen or tolazoline was not prognostically significant. Age was not prognostically important, but the children in this study seemed to do very badly: of the 11 patients 14 years old or younger, seven (64%) died in the first year of follow-up. Because of the small number of patients in this group, their survivorship did not differ significantly from that of patients older than 14 years.

Stepwise multivariate analysis of the variables listed in table 2 identified only two variables of prognostic

TABLE 2
Univariate analysis of prognostic factors

<table>
<thead>
<tr>
<th>Factor</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary arterial oxygen saturation</td>
<td>&lt;.00001</td>
</tr>
<tr>
<td>Systemic arterial oxygen saturation</td>
<td>&lt;.00001</td>
</tr>
<tr>
<td>Total pulmonary resistance</td>
<td>&lt;.00001</td>
</tr>
<tr>
<td>Right ventricular end-diastolic pressure</td>
<td>.004</td>
</tr>
<tr>
<td>Pulmonary artery pressure, mean</td>
<td>.006</td>
</tr>
<tr>
<td>Pulmonary index</td>
<td>.009</td>
</tr>
<tr>
<td>Anticoagulant therapy</td>
<td>.02</td>
</tr>
<tr>
<td>Cardiomegaly</td>
<td>.03</td>
</tr>
<tr>
<td>Age</td>
<td>.2</td>
</tr>
<tr>
<td>Right ventricular work index</td>
<td>.3</td>
</tr>
<tr>
<td>Sex</td>
<td>.9</td>
</tr>
</tbody>
</table>

Data were obtained at entry into study from the 115 patients who survived diagnostic heart catheterization.
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significance: \( \text{SO}_2 (p < .00001) \) and anticoagulant therapy \((p = .01)\). This confirms the fact that the hemodynamic variables were highly correlated.

To further evaluate the effect of anticoagulant therapy, we compared the survivorship of the 78 anticoagulated patients (as defined previously) with that of the 37 who received no anticoagulants (figure 3). The treated group had more favorable survivorship \((p = .02)\), even though there were no significant differences between the groups with respect to clinical or hemodynamic variables.

Pathologic types (table 3). Examination of material obtained at autopsy from 56 patients revealed that, in 32 \((57\%)\), the major histologic feature was thrombus, the entity of so-called thromboembolic pulmonary hypertension. Thus, the muscular pulmonary arteries alone (in 22 patients) or the muscular and elastic pulmonary arteries (in 10 patients) showed organized thrombi, with or without recanalization or partial lysis. Fresh thrombi were identified less frequently and were composed either primarily of red blood cells or primarily of platelets and fibrin. No plexiform lesions were identified and no foci of active necrotizing arteritis were observed. All muscular pulmonary arteries were involved by various degrees of medial hypertrophy.

Primary pulmonary arteriopathy was histologically evident in 21 patients \((38\%)\). In 18 of these it was plexogenic — the muscular pulmonary arteries were characterized focally by classic plexiform lesions and by noninflammatory necrotizing arteritis, and were clearly different from thromboembolic pulmonary hypertension. Such focal lesions not infrequently also contained fresh platelet-fibrin thrombi, and organized arterial thrombi, presumably occurring as a late complication, were also identified in some cases. Dilatation lesions were rare. All muscular arteries were diffusely involved by medial hypertrophy and were focally involved by intimal cellular proliferation and concentric intimal fibroelastosis. Most arterioles were muscularized.

In two other patients with primary pulmonary arteriopathy, both middle-aged females, the disease was characterized only by medial hypertrophy of muscular and elastic pulmonary arteries, without plexiform lesions, necrotizing arteritis, thromboemboli, or veno-capillary lesions. It is unclear whether this disease, designated as primary nonplexogenic pulmonary arteriopathy, represents the early stages of rapidly fatal forms of the plexogenic type or is a unique histologic type of pulmonary hypertension.

In patient No. 21, who at clinical presentation appeared to have severe pulmonary hypertension, histologic study disclosed a necrotizing and inflammatory panarteritis that involved only the pulmonary circulation and was accompanied by secondary obstructive thrombosis.

The remaining three patients had pulmonary veno-occlusive disease, which was characterized by organized or, rarely, fresh thrombi within the pulmonary venules and veins. Secondary lesions included engorgement of the microcirculation, intra-alveolar clusters of hemosiderin-laden macrophages, edema or fibrosis of pleura or interlobular septa, dilated lymphatics, dilated bronchial circulation, and medial hypertrophy of pulmonary arteries. No plexiform lesion, necrotizing arteritis, or active pulmonary phlebitis was observed.

![FIGURE 3](http://circ.ahajournals.org/)

**FIGURE 3.** Observed survival with and without anticoagulant treatment in patients with primary pulmonary hypertension (those who survived diagnostic catheterization). Survival rate was better among 78 patients who received oral anticoagulants (solid line) than among 37 who did not (dashed line) \((p = .02, \log\text{-rank test})\). Parentheses enclose numbers of patients living and under observation at end of each year.

<table>
<thead>
<tr>
<th>Pathologic types of clinical primary pulmonary hypertension in 56 patients from whom autopsy material was obtained</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
</tr>
<tr>
<td>----------</td>
</tr>
<tr>
<td>Mean</td>
</tr>
<tr>
<td>Thromboembolic pulmonary hypertension</td>
</tr>
<tr>
<td>Muscular and elastic</td>
</tr>
<tr>
<td>Muscular only</td>
</tr>
<tr>
<td>Primary pulmonary arteriopathy</td>
</tr>
<tr>
<td>Plexogenic</td>
</tr>
<tr>
<td>Nonplexogenic</td>
</tr>
<tr>
<td>Arteritis</td>
</tr>
<tr>
<td>Pulmonary venoocclusive disease</td>
</tr>
</tbody>
</table>
Comparisons of pathologic groups. We compared the two main pathologic groups, the 32 patients with thromboembolic pulmonary hypertension and the 18 with plexogenic pulmonary arteriopathy. There were no significant differences between the groups with respect to any of the clinical or hemodynamic variables except age, which at diagnosis averaged 39 years in the group with thromboembolic pulmonary hypertension and 25 years in the group with plexogenic pulmonary arteriopathy (p = .002). The three with pulmonary venoocclusive disease were male patients who were 7, 17, and 18 years old. There were no specific clinical, hemodynamic, or angiographic features of this group and the pulmonary wedge pressures were at the upper limits of normal (12, 13, and 17 mm Hg).

For the 56 patients whose lung tissue was examined, univariate and multivariate analyses of prognostic factors were performed as before but with the addition of pathologic type as a separate factor. The results were essentially the same as when data from the entire patient population were analyzed (as shown in table 2), and the pathologic type was of no prognostic significance (p = .2). This conclusion was supported by the fact that survivorship of the 32 patients with thromboembolic pulmonary hypertension was not significantly different from that of the 18 with plexogenic pulmonary arteriopathy (p = .2).

In all 56 patients undergoing autopsy, univariate analysis demonstrated a beneficial effect of anticoagulant therapy (p = .04). Of the 32 patients with thromboembolic pulmonary hypertension, 17 (53%) had received anticoagulant therapy, as did nine (50%) of the 18 patients with plexogenic pulmonary arteriopathy. In both of these groups there was a trend toward improved short-term survival among patients who received anticoagulant therapy, but the patient numbers were not sufficient to allow statistical significance to be reached.

Discussion

This is a large clinical series of patients with primary pulmonary hypertension who received this diagnosis based on rigid clinical and hemodynamic criteria and whose cases were reviewed at one institution. Previously reported large series have been obtained by pooling of cases from many centers without uniform criteria for diagnosis or for inclusion of patients in the study.\(^5\)\(^6\) In addition, there have been no previous reports of long-term follow-up of large numbers of patients. Thus, this study provides a unique opportunity to evaluate the natural history of primary pulmonary hypertension. In addition, examination of lung tissue obtained at autopsy from 56 patients has enabled us to make observations about the pathogenesis of this ill-understood entity. A number of points require further discussion.

Etiologic considerations. The well-established predominance of women with this condition, confirmed in our study, has given rise to hypotheses concerning pregnancy\(^5\)\(^11\) and oral contraceptives\(^12\) as potential initiating factors. As reported above, however, the percentage of women in this study using oral contraceptives was 21%, which is not significantly different from that in the general population.\(^8\) Similarly, despite the fact that 79% of the sexually mature women in this study had had a prior pregnancy, it is likely that a similar percentage may be noted in a normal female population in the same age range. In 17% of these women, the initial symptoms of the disease began shortly after pregnancy, an observation that supports the idea that pregnancy may aggravate or initiate pulmonary vascular disease.\(^13\)

The preponderance of young female patients, therefore, cannot be explained easily by pregnancy or use of oral contraceptives. The events surrounding menstruation may initiate the insidious process, as suggested by Shepherd et al.\(^11\) in 1957. Perhaps pelvic microthrombi are formed at this time and embolize to the lung, but the normal phenomenon of thrombolysis does not occur in these women. Alternatively, in some women with hyperreactive muscular pulmonary arteries, the hormonal environment associated with menstruation may produce prolonged vasoconstriction. But although either, or both, mechanisms may be involved in the pathogenesis of pulmonary hypertension in women, the disease process in men and young children is more difficult to explain. Perhaps the common basis is a hyperreactive pulmonary vasculature that vasoconstricts in response to any one of a number of stimuli.

Twelve (10%) of the patients in our study had Raynaud’s phenomenon, the incidence of which has been reported to be as high at 30% in those with primary pulmonary hypertension.\(^14\) It seems unlikely that the Raynaud’s phenomenon observed in this study was a variant form of a connective tissue disease,\(^5\)\(^14\) since patients were rigorously excluded if there was any evidence of multisystem disease and since the autopsy results in the six patients whose diagnoses included Raynaud’s phenomenon disclosed no systemic pathology or parenchymal lung pathology characteristic of connective tissue disease. It seems possible that Raynaud’s phenomenon in these patients represents vascu-
lar hyperreactivity in a second vascular bed — the digital arteries.

Association of cirrhosis of the liver with primary pulmonary hypertension has been reported previously and recent studies have confirmed the validity of this association. Seven (6%) of the patients in our study had chronic liver disease (five had cirrhosis, one had chronic active hepatitis, and one had portal venous hypertension with minimal liver pathology as a result of neonatal umbilical vein thrombosis). Perhaps the pulmonary hypertension in these patients was initiated by a vasoconstrictor substance reaching the pulmonary circulation via portal systemic shunts.

Other investigators have reported familial cases of primary pulmonary hypertension. Our study included two sets of brothers, and autopsy material from one brother of each set was examined. The diagnosis was plexogenic pulmonary arteriography in one and pulmonary venoocclusive disease in the other.

Recurrent pulmonary embolism is frequently cited as a cause of primary pulmonary hypertension. Indeed, recurrent episodes of subclinical pulmonary embolism probably produce an identical clinical and hemodynamic picture. For this reason our study was designed to exclude all patients with a history of pulmonary embolism or deep venous thrombosis or clinical features suggestive of pulmonary embolism. Furthermore, only five patients had a history of superficial thrombophlebitis, which is not more than one would expect in the general population.

Clinical and hemodynamic features. The clinical features exhibited by the patients in this study confirm previous reports. Clearly, by the time that patients with primary pulmonary hypertension present for examination, they already have advanced disease. This is reflected in the fact that the median interval from initial clinical manifestation to diagnosis was 1.9 years, at which time the hemodynamic diagnostic indexes were typical of advanced pulmonary vascular obstructive disease: high mean pulmonary arterial pressure (mean 64 mm Hg), high total pulmonary resistance (mean 33 U/m²), and low pulmonary index (mean 2.2 liter/min/m²).

Clinical course and prognostic factors. The usual clinical course in patients with primary pulmonary hypertension is one of inexorable deterioration. In our study most patients developed right heart failure and died within 5 years after diagnosis. There were five deaths related to cardiac catheterization — confirming that this procedure carries an increased risk in patients with primary pulmonary hypertension. Interestingly, pulmonary angiography had been performed in only one of these. Despite the increased risk, we believe that almost all patients should undergo cardiac catheterization, pulmonary angiographic examination, and if possible, biopsy of the lung in an effort to find the cause of their pulmonary hypertension.

The average survival time of patients in this study group was short (figure 2). A number of hemodynamic factors, however, showed significant correlation with survival (table 2), suggesting that the more severe the underlying pulmonary disease and right ventricular dysfunction, the worse the prognosis. The most potent predictor of survival was the SO₂, presumably because it reflects the adequacy of cardiac output as well as the degree of desaturation of systemic blood resulting from the perfusion/ventilation inequalities in the lung or the presence of a right-to-left shunt. Thus, the SO₂ gives an overall assessment of the degree of decompensation of the cardiorespiratory system.

Pathologic types. Despite every effort to exclude patients in whom there was any evidence of pulmonary embolism, pathologic evidence of thromboembolic pulmonary hypertension was found in 32 (57%) of the 56 patients from whom autopsy material from the lungs was obtained. The cause of the thrombotic process is unknown. It seems likely to have been thromboembolic in the 10 patients (18% of 56) in whom both elastic and muscular arteries were involved, but the common form of venous thromboembolism is unlikely in the 22 patients (39% of 56) in whom only the small muscular arteries contained thrombi. The pathogenesis in these 22 patients may have been the result of microemboli, perhaps from the pelvis (as suggested above), or the thrombosis may have been in situ and due to some arterial wall–coagulation interaction abnormality.

The other major pathologic category was plexogenic pulmonary arteriopathy, which included 18 patients (36%). This entity may be the end result of sustained arterial spasm in hyperreactive pulmonary vessels.

Apart from the fact that the patients with thromboembolic pulmonary hypertension were older, there were no significant differences between the groups. Thus, despite distinctive pathologic and presumably pathogenetic differences, it is impossible to predict the pathologic type from clinical or hemodynamic variables.

Anticoagulant therapy. The effect of oral anticoagulant therapy on outcome was difficult to assess in this retrospective study because treatment was begun at varying intervals after diagnosis and because specific
reasons for initiating or withholding therapy were seldom stated. To minimize bias, we defined anticoagulated patients as all of those treated with anticoagulants, provided that therapy was started within the first year after diagnosis.

It should be realized that even among patients receiving anticoagulant therapy, the mortality rate was high. Nevertheless, univariate and multivariate analysis did show a significant beneficial effect of anticoagulant therapy on overall survival, which was confirmed by an improved short-term survival in anticoagulated patients (figure 3). This improved survival was noted in patients in both major pathologic groups (thromboembolic pulmonary hypertension and plexogenic pulmonary arteriopathy) who were treated with anticoagulants, but the numbers were small and statistical significance was not reached. To our knowledge, this is the first major study of patients with primary pulmonary hypertension to show a beneficial effect of oral anticoagulant therapy. At the present time we recommend that all patients with this condition be considered candidates for anticoagulant treatment.

Future considerations. We have shown the importance of a thrombotic mechanism in the pathogenesis of primary pulmonary hypertension. However, many questions remain unanswered. What is the basis of the thrombosis? Is it due to microemboli or does it arise in situ? What is the etiologic basis of pulmonary plexogenic arteriopathy — is it hyperreactive pulmonary arteries that sustain such prolonged spasm that the vessels undergo the pathologic changes described?

More animal preparations need to be developed to reproduce the hemodynamic and pathologic features of the disease. It would be of great value to follow prospectively patients with primary pulmonary hypertension of known pathologic type. Obviously, this necessitates open-lung biopsy, which would provide tissue for histochemical and physiologic analysis as well as for structural examination of the pulmonary vasculature. A group of patients with primary pulmonary hypertension who underwent lung biopsy without serious complications has been reported recently. A diagnosis based on biopsy results also may prove to be of therapeutic importance. For example, a patient with thromboembolic pulmonary hypertension (pathologic diagnosis) may be optimally treated with anticoagulants and possibly a platelet-inhibiting agent, whereas a patient with plexogenic pulmonary arteriopathy may be best treated with a vasodilating agent; however, the data from this study suggest that patients in the latter group may also benefit from anticoagulant therapy, probably by prevention of complicating secondary thrombi. In addition, the use of vasodilating agents in patients with pulmonary hypertension may induce potentially serious sequelae and as yet has not been shown to alter prognosis. Nevertheless, their use in certain subgroups of patients whose disease is at an early stage may prove to be beneficial. Cardiopulmonary transplantation is a new hopeful therapeutic modality, but long-term results are still unknown.

If any therapeutic modality is to be effective in treatment of patients with primary pulmonary hypertension, it must be started early in the course of the disease. We have shown that many patients in this study had symptoms for considerable periods before diagnosis, by which time the disease had progressed to an advanced stage. Perhaps a high index of suspicion and a knowledge of the clinical features described in this report will promote referral of patients with less advanced disease for diagnostic cardiac catheterization and evaluation for treatment.

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References

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