Thrombotic Lesions in Primary Plexogenic Arteriopathy

Similar Pathogenesis or Complication?


In 78 patients with primary plexogenic arteriopathy (PPA), numbers of organized and recanalized thrombi were established in histologic slides of lung tissue and expressed per square centimeter of section. Three control groups of ten individuals each were used: normal, plexogenic arteriopathy secondary to ventricular septal defect, and hypoxic pulmonary hypertension. Thrombotic lesions were scarce in normal individuals but numerous in all three groups with pulmonary hypertension. There is also a positive correlation with age. Thrombotic lesions are absent or scarce in children but more common in adults, even in normal control subjects and particularly in pulmonary hypertension by whatever cause. In PPA there is likely to be a relation with the duration of illness but not with the stage of the disease. The complete pattern of plexogenic arteriopathy may develop in the absence of thrombotic lesions, which clearly are not essential for its pathogenesis. Rather than being part specifically of PPA, as sometimes suggested, thrombotic lesions complicate various types of hypertensive pulmonary vascular disease. Apparently the combination of sustained pulmonary hypertension and age, possibly through endothelial injury, may elicit thrombosis and its sequelae, which in turn may aggravate the pulmonary arterial pressure.

In primary pulmonary hypertension, which has been defined as "clinically unexplained pulmonary hypertension,"1 the underlying pathologic processes are most commonly thrombotic arteriopathy and plexogenic arteriopathy. These two forms of pulmonary vascular disease are morphologically readily recognizable.2 In large series of cases of primary pulmonary hypertension in which lung tissue was available, the ratio between thrombotic and plexogenic arteriopathy was given as 57 to 38, and 56 to 27 percent respectively.3,6

The term thrombotic arteriopathy refers to a generalized pulmonary vascular disease,7 whether this results from embolism or from primary thrombosis.8,6 As such it is uncommon and rarely associated with pulmonary hypertension. However, the lesions occurring in this pattern are exceedingly common. In consecutive hospital autopsies, histologic examination revealed at least some thrombotic lesions in 51.7 percent8 and 64 percent,10 and in our experience these percentages are rather conservative, when multiple blocks of tissue are studied.4 It is therefore not surprising that they are also found in primary pulmonary arteriopathy,11,12 sometimes in large numbers.13

Recently, it has been suggested that thrombotic lesions, occurring in primary plexogenic arteriopathy, are an essential part of this disease rather than a complicating feature.14,15 Therefore, in the present study, the prevalence of thrombi and postthrombotic changes in patients with primary plexogenic arteriopathy was assessed in relation to the patient's age and duration of illness and compared with that in other forms of pulmonary hypertension and in normal individuals.

Material and Methods

From our files, we used histologic sections of lung tissue obtained at autopsy from 78 patients with primary plexogenic arteriopathy, 20 male and 58 female patients, ranging in age from 1 to 64 years (Table 1). Infants below the age of 1 year were excluded. In all patients, pulmonary hypertension had been severe and the direct or indirect cause of death. In two cases, a fresh thromboembolus in a branch of the pulmonary artery probably contributed to the patient's death. Cases were taken only when the clinical histories mentioned the approximate time of onset of the disease so that the duration of illness could be estimated. We used the time between first symptoms and death, although less reliable than the time between diagnosis and death, because in our series of patients pulmonary hypertension was commonly diagnosed clinically in the final stage of the disease or not at all. Further criteria for the selection of cases were sufficient histologic material and a firmly established morphologic diagnosis.

Plexogenic arteriopathy was judged by the presence of unmistakable plexiform lesions or, in their absence, by the finding of severe, widespread concentric-laminar intimal fibrosis.

All available sections of lung tissue stained with elastic-von Gieson stain were used without selection. The surface area of these sections was measured by planimeter, excluding large bronchi and vessels. The combined surface area of the sections per case was minimum 2 square centimeter and on the average 7.8 cm². All thrombotic lesions in muscular pulmonary arteries that were round or oval in cross-section were counted in these sections.

Thrombotic lesions may vary considerably in form and appearance (Fig 1). By organization, recent thrombi change to intimal fibrosis, which is usually eccentric or occlusive but, even if circumferential, does not have a laminar arrangement. Recanalization, characteristic of thrombotic alterations, is often present, sometimes in the form of intravascular fibrous septa. The number of each of these various lesions was calculated per square centimeter.
FIGURE 1. Histologic pattern of plexogenic arteriopathy in muscular pulmonary arteries: Top left, a, cellular intimal proliferation; top right, b, concentric-laminar intimal fibrosis; and bottom, c, plexiform lesion (a and c, hematoxylin-eosin; b, elastic-van Gieson stain).

To avoid confusion with other arterial changes, clots of fibrin and/or platelets were not counted as thrombi, since they are often associated with fibrinoid necrosis or plexiform lesions and then part of plexogenic arteriopathy.

Intimal thickening due to cellular proliferation or with a laminar arrangement was not counted to avoid confusion with the pattern of plexogenic arteriopathy, while we excluded intimal fibrosis comprising less than one third of the shortest luminal diameter of the arterial cross-section. Obliterated arteries with prominent shrinkage were not included because then the original type of intimal fibrosis is no longer recognizable. Also excluded was intimal thickening resulting from vasculitis or cotton wool embolism.

Of the various lesions of plexogenic arteriopathy (Fig 2), concentric-laminar intimal fibrosis and plexiform lesions were assessed semiquantitatively and graded as absent (0), mild to moderate (+), and severe (++) (Table 1).

Three different control groups were used. Each group consisted of ten patients, respectively, without cardiac or pulmonary disease (Table 2), with plexogenic arteriopathy secondary to a ventricular septal defect (Table 3), and with hypoxic pulmonary hypertension resulting from chronic bronchitis, kyphoscoliosis, or pickwickian syndrome (Table 4). In selecting these cases from our autopsy files, we attempted to include patients of various ages for better compar-

![Table 1 - Thrombotic Lesions in Primary Plexogenic Arteriopathy*](https://example.com/table1)

<table>
<thead>
<tr>
<th>Characteristic (n = 78)</th>
<th>Mean ± SD</th>
<th>Age, yr</th>
<th>39.5 ± 22.7</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1; 39.5; 78</td>
<td></td>
</tr>
<tr>
<td>Duration of illness, mo</td>
<td>49.0 ± 65.6</td>
<td>1; 24; 348</td>
<td></td>
</tr>
<tr>
<td>Thrombotic lesions</td>
<td>3.27 ± 4.85</td>
<td>0; 1.2; 24</td>
<td></td>
</tr>
<tr>
<td>Sex, M/F</td>
<td>0/14/64</td>
<td>20/58</td>
<td></td>
</tr>
<tr>
<td>CLIF, −/+/++</td>
<td>0/1/4/34</td>
<td>11/33/34</td>
<td></td>
</tr>
</tbody>
</table>

*SD = standard deviation; min = minimum; med = median; max = maximum; CLIF = concentric-laminar intimal fibrosis; Plex = plexiform lesions; − = absent; + = mild; ++ = severe.
shown in Table 1. In all but 11 instances, plexiform lesions were found, usually in fairly large numbers. In their absence, there was always pronounced concentric-laminar intimal fibrosis (Fig 1).

In primary plexogenic arteriopathy, thrombotic lesions were very common, in adults significantly more than in adults from the control group (Mann-Whitney: p = 0.003). A total of 1,340 was counted in 78 patients. They were absent in 11 patients, mild (less than 1/cm²) in 25, moderate (1 to <5/cm²) in 25, and numerous (>5/cm²) in 17. In a few cases their numbers were excessive, up to 24/cm². Recent thrombi, with no more than early organization and therefore easily recognizable as such, were exceedingly scarce: in nine patients, a single such thrombus was found and two other patients each had two.

Organized thrombi in the form of eccentric, fibrotic, intimal patches or as obliterator changes without recanalization were numerous with a total count of 985 and up to 19/cm² in individual cases. In 44 patients, there was an additional number of 342 lesions with recanalization, with a maximum of 6/cm² in a single case. In 126 of these, recanalization channels had become so wide that the intimal fibrosis had been converted to intravascular septa (Fig 2).

The frequency of all thrombotic lesions together did not significantly differ between the sexes (Mann-Whitney: p = 0.426). There is, however, a correlation of the lesions with age (rank correlation = 0.5; p = 0.000). These lesions were absent or scarce in children, but common in adults. There is also a correlation with the duration of the patient's illness. In a multiple regression analysis, age and duration of illness, included simultaneously in the model, were both found to be significantly related to the logarithm of thrombotic lesions (p = 0.002 for age; p = 0.007 for duration of illness). While thrombotic changes in adults vary greatly in numbers, their presence does not correlate with the severity of concentric-laminar intimal fibrosis (Mann-Whitney test: p = 0.629), while there is a marginally significant positive correlation with the frequency of plexiform lesions (Kruskal-Wallis test: p = 0.0473).

The possibility that the number of thrombotic lesions may have changed over the years as a result of differences in treatment or prolongation of life was

### Table 2 — Thrombotic Lesions in Normal Control Subjects*

<table>
<thead>
<tr>
<th>Characteristic (n = 10)</th>
<th>Mean ± SD (min; med; max)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>30.1 ± 22.6 (1; 30; 60)</td>
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<tr>
<td>Thrombotic lesions</td>
<td>0.33 ± 0.35 (0; 0.3; 0.9)</td>
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<tr>
<td>Sex, M/F</td>
<td>4/6</td>
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</table>

*For abbreviations, see Table 1.

### Table 3 — Thrombotic Lesions in Ventricular Septal Defect With Pulmonary Hypertension*

<table>
<thead>
<tr>
<th>Characteristic (n = 10)</th>
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<tr>
<td>Age, yr</td>
<td>21.6 ± 18.3 (2; 13.5; 47)</td>
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<tr>
<td>Thrombotic lesions</td>
<td>0.98 ± 1.28 (0; 0.25; 3.73)</td>
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<td>Sex, M/F</td>
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<tr>
<td>CLlF, +/+/+ +</td>
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<tr>
<td>Plex, +/+/+ +</td>
<td>0/7/3</td>
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</table>

*For abbreviations, see Table 1.

### Table 4 — Thrombotic Lesions in Hypoxic Pulmonary Hypertension*

<table>
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<th>Characteristic (n = 10)</th>
<th>Mean ± SD (min; med; max)</th>
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</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>57.1 ± 24.7 (5; 67.5; 83)</td>
</tr>
<tr>
<td>Thrombotic lesions</td>
<td>3.29 ± 4.18 (0; 1.64; 13.14)</td>
</tr>
<tr>
<td>Sex, M/F</td>
<td>4/6</td>
</tr>
</tbody>
</table>

*For abbreviations, see Table 1.

### Statistical Analysis

Spearman’s rank correlation coefficient was used to test for a monotonic relationship between two at least ordinally scaled variables. Mean differences of a continuous variable between groups (Kruskal-Wallis) only after logarithmic transformation as follows: In (thrombotic lesions + 1), in order to symmetrize its distribution.

### Results

**Primary Plexogenic Arteriopathy**

The results of the counting of thrombotic lesions in the 78 cases of primary plexogenic arteriopathy are shown in Table 1. In all cases, intimal fibrosis of the concentric-laminar type was present in at least a number of pulmonary arteries and was usually severe. In all but 11 instances, plexiform lesions were found, usually in fairly large numbers. In their absence, there was always pronounced concentric-laminar intimal fibrosis (Fig 1).

In primary plexogenic arteriopathy, thrombotic lesions were very common, in adults significantly more than in adults from the control group (Mann-Whitney: p = 0.003). A total of 1,340 was counted in 78 patients. They were absent in 11 patients, mild (less than 1/cm²) in 25, moderate (1 to <5/cm²) in 25, and numerous (>5/cm²) in 17. In a few cases their numbers were excessive, up to 24/cm². Recent thrombi, with no more than early organization and therefore easily recognizable as such, were exceedingly scarce: in nine patients, a single such thrombus was found and two other patients each had two.

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The frequency of all thrombotic lesions together did not significantly differ between the sexes (Mann-Whitney test: p = 0.426). There is, however, a correlation of the lesions with age (rank correlation = 0.5; p = 0.000). These lesions were absent or scarce in children, but common in adults. There is also a correlation with the duration of the patient's illness. In a multiple regression analysis, age and duration of illness, included simultaneously in the model, were both found to be significantly related to the logarithm of thrombotic lesions (p = 0.002 for age; p = 0.007 for duration of illness). While thrombotic changes in adults vary greatly in numbers, their presence does not correlate with the severity of concentric-laminar intimal fibrosis (Mann-Whitney test: p = 0.629), while there is a marginally significant positive correlation with the frequency of plexiform lesions (Kruskal-Wallis test: p = 0.0473).

The possibility that the number of thrombotic lesions may have changed over the years as a result of differences in treatment or prolongation of life was
investigated by grouping together patients who died in the same decade. No significant differences in prevalence of these changes over the decades from the 1940s to the 1980s could be demonstrated (Kruskal-Wallis test: p = 0.209).

**Normal Control Subjects**

As could be expected, intimal fibrosis with or without recanalization, occupying at least one third of the luminal diameter, was scarce in pulmonary arteries of normal individuals (Table 2). The prevalence of the combined thrombotic alterations never exceeded 1 cm². In children, they were almost completely absent. In five of seven adults, there were occasional lesions in three of the five with recanalization.

**Secondary Plexogenic Arteriopathy**

In all ten patients with plexogenic arteriopathy secondary to a ventricular septal defect (Table 3), plexiform lesions were found. Thrombotic lesions were absent or very scarce in children. In adults, they were significantly more common than in normal adult individuals (Mann-Whitney: p = 0.042). Recanalization was found in four of five adults. No relation with lesions as concentric-laminar intimal fibrosis or plexiform lesions could be demonstrated.

**Hypoxic Arteriopathy**

In all patients with hypoxic pulmonary hypertension, the pattern of pulmonary vascular lesions characteristic for this condition was observed. It consisted of widespread muscularization of intra-acinar arterioles while in muscular pulmonary arteries associated with the bronchial tree there was no or at most mild to moderate medial hypertrophy. Moreover, in all instances, there were at least some arterioles with bundles of longitudinal smooth muscle cells located within the intima. Thrombotic arterial changes were absent in the one child included in this group. In adults, their numbers varied from scarce to numerous; on the average, they were far more common than in the adult control group (Mann-Whitney: p = 0.007) (Table 4). Recanalization of the lesions was usually present.

**Discussion**

The histologic pattern of primary plexogenic arteriopathy is often combined with thrombotic lesions.5,6,11,12,13,14 This has been confirmed in the present study. It appears that there is a significant relation with age. These lesions are absent or scarce in children with this condition but common in adults, though varying in numbers.

There is no distinct relation with the stage of the disease; all patients with primary plexogenic arteriopathy, also those without or with few thrombotic lesions, were in the final stage and had died directly or indirectly as a result of the condition. There was a significant positive correlation with the duration of the patient's illness, independent of age. As was pointed out before, this duration was anamnestic and thus certainly not always reliable. However, in view of the large group of patients, it is suggestive that thrombotic lesions may increase with a protracted course of the disease. It is unlikely that differences in treatment have a major influence, since the prevalence of thrombotic lesions in patients with primary plexogenic arteriopathy appeared not to have changed significantly over a period of 50 years.

Age of the patient could influence thrombus formation in more than one way. Organized thrombi may retract but do not disappear, so that over a lifetime, occasional primary or embolic thrombotic lesions gradually accumulate. This explains why these changes tend to increase with age, not only in the presence of pulmonary hypertension, but also, though to much lesser extent, in normal individuals, where they correspond to the age changes described in a larger series.15

Another possible factor by which age could be instrumental in producing thrombotic lesions was mentioned by Weir et al.14 The chance of endothelial damage or dysfunction with the risk of thrombosis is likely to increase with age and with the duration of illness, at least in the presence of a high pressure in the pulmonary circulation. Not only in primary plexogenic arteriopathy but also in ventricular septal defect, a positive relation between thrombotic lesions and age appears to exist since they were absent or minimal in children but common and even prominent in adults. Also in hypoxic pulmonary hypertension thrombotic changes occurred in all adult patients, varying in number but sometimes numerous. They were absent in the one child, suggesting a relation with age similar to that in the other groups, although the difficulty to obtain adequate material from the younger age group in this condition makes a reliable judgment impossible.

While age appears to be a major factor in the development of thrombotic lesions, the association of age with sustained pulmonary hypertension appears to be particularly important. In children with primary plexogenic arteriopathy sequelae of thrombosis are absent or scarce but in adults they are regularly present and occasionally very numerous. In 41 of 62 adult patients, thrombotic lesions are more common than in normal adult individuals (≥1.0 cm²) and in seven of these they were abundant (≥10.0 cm²).

The frequency of thrombotic lesions in primary plexogenic arteriopathy has led to the assumption that they are part of this morphologic pattern rather than complicating features.14,15,19 This would imply that
plexogenic and thrombotic arteriopathies cannot be reliably distinguished but should be regarded as a single morphologic entity with a broad spectrum of greatly varying lesions.

The results of our study do not support this hypothesis. First, in the pathogenesis of primary plexogenic arteriopathy, thrombotic lesions appear not to be essential. In their absence, the complete pattern, including such end-stage alterations as plexiform lesions, may develop as shown in children and some adults. It may also be pointed out that in experimental pulmonary hypertension, plexogenic arteriopathy has been produced without evidence of thrombosis.20,21

Moreover, thrombotic lesions appear to be numerous not only in adult patients with primary plexogenic arteriopathy, but also in adults with pulmonary hypertension secondary to ventricular septal defect and with hypoxic pulmonary hypertension. In ventricular septal defect, four of five, and in hypoxic pulmonary hypertension, seven of nine adult patients had thrombotic lesions in excess of 1.0 cm³, while none of the normal individuals reached that number. This strongly suggests that there is no specific relation of thrombotic lesions with primary plexogenic arteriopathy, but that there is a relation with sustained pulmonary hypertension, in general, irrespective of its type.

It has been argued that plexogenic and thrombotic arteriopathies are nonspecific conditions because a single stimulus, such as aminorex or portal hypertension, may result in their combined occurrence.14 However, while it is true that thrombotic lesions have been described in association with plexogenic arteriopathy due to aminorex22 as well as in portal hypertension,23-26 all these patients were adults and most older than 40 years of age. These cases, therefore, do not behave differently from the primary forms.

Another argument to treat thrombotic lesions and those of plexogenic arteriopathy as a single condition relates to familial pulmonary hypertension. It has been claimed that in these families, some patients had plexogenic and others had thrombotic arteriopathy.27 In 18 of 23 patients from this study, plexiform lesions were found. The other five were supposed to have pure thrombotic arteriopathy because there were no plexiform lesions. However, all five had, in addition to eccentric postthrombotic intimal lesions, the concentric-laminar type of intimal fibrosis characteristic of plexogenic arteriopathy. Thus, there is little doubt that all 23 patients suffered from primary plexogenic arteriopathy with varying numbers of thrombotic changes.

Our study shows that in adult patients, thrombotic lesions are numerous not only in primary plexogenic arteriopathy, but also in pulmonary hypertension caused by a ventricular septal defect and even in hypoxic pulmonary hypertension with its completely different vascular abnormality. This indicates that thrombosis and its sequelae are not essential in the pathogenesis of primary plexogenic arteriopathy, but complicate any form of hypertensive pulmonary vascular disease. Apparently, thrombosis is a response to endothelial injury or dysfunction,28 related to high pressure and age, and possibly to duration of illness.

The etiology of plexogenic arteriopathy is considerably varied but the pathogenesis is likely to be the same, whatever the cause, in view of its rather complicated but characteristic pattern of vascular lesions. Intense vasoconstriction is the most likely common denominator, although probably in interplay with factors as endothelial damage, shear stress and endothelial-derived vasoactive substances.29,30 An individual hyperreactivity of pulmonary arteries is likely to be an important contributing factor, particularly in the primary form.

Two pathogenetic mechanisms can be effective at the same time, resulting in simultaneous occurrence of two histopathologic patterns of lesions. There is also a common combination of plexogenic arteriopathy with the pattern of pulmonary venous hypertension whenever there is left ventricular failure or, as for instance in atrioventricular septal defect or mitral regurgitation. Of course, a complicating role of thrombotic lesions does not detract from their possible clinical significance. They are likely to aggravate pulmonary hypertension in a number of cases. Anticoagulant therapy had a favorable effect in some patients, although it was ineffective in others.5

In congenital heart disease, the lesions of plexogenic arteriopathy occur in a sequence with a reversible and an irreversible phase.30-32 It is likely that this also applies to the primary form, though this is difficult to demonstrate since regression cannot be expected as long as the cause cannot be eliminated. The lesions of plexogenic arteriopathy differ from those of thrombotic arteriopathy, not only in morphologic features and pathogenesis but also in reversibility and therapy.4,31 Therefore, these two conditions should not be lumped together as a single, nonspecific form of hypertensive pulmonary vascular disease but, if present in a lung biopsy specimen, each should be diagnosed as such. Also, if plexogenic arteriopathy appears to be complicated by thrombotic lesions, the pathologist should report this to the clinician, since it may have clinical and therapeutic consequences.

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