Histopathology of Primary Pulmonary Hypertension

A Qualitative and Quantitative Study of Pulmonary Blood Vessels From 58 Patients in the National Heart, Lung, and Blood Institute, Primary Pulmonary Hypertension Registry

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Qualitative and quantitative studies were performed on pulmonary blood vessels in lung tissue obtained by biopsy, pneumonectomy, or autopsy from 58 patients in the Registry of Primary Pulmonary Hypertension sponsored by the Heart, Lung, and Blood Institute of the National Institutes of Health. In 49 patients (84%), the hypertensive vascular disease involved predominantly or exclusively muscular pulmonary arteries and arterioles. In each of these 49 patients, pulmonary artery medial hypertrophy was observed, and in 48 patients, it was also associated with intimal or luminal lesions. On the basis of the predominant histopathologic features, 25 of the 48 patients were classified as having pulmonary arteriopathy with plexiform lesions characterized by a combination of concentric laminar intimal fibrosis, eccentric intimal fibrosis, and plexiform lesions; in nine of these 25, recanalized thrombi were also present. Pulmonary arteriopathy with thrombotic lesions, defined by the presence of both eccentric intimal fibrosis and recanalized thrombi but without plexiform lesions, was observed in 19 patients. Intimal fibrosis, either concentric or eccentric, without plexiform or thrombotic lesions was found in four patients. Among the remaining nine patients in the Registry, pulmonary veno-occlusive disease was present in seven and chronic pulmonary venous hypertension in one. Pulmonary blood vessels were microscopically normal in a lung biopsy specimen from another patient. In general, patients with plexiform lesions and those with veno-occlusive disease had a much poorer prognosis than patients with thrombotic lesions. The present study shows the existence of several distinct histopathologic patterns of pulmonary vascular disease in individuals with primary pulmonary hypertension diagnosed by standardized clinical and laboratory criteria. (Circulation 1989;80:1198-1206)

Primary, or idiopathic, pulmonary hypertension is a rare condition that is considered in the clinical setting only after the exclusion of all heart and lung diseases known to cause elevation of pulmonary artery pressure and vaso-

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Methods

General Features

The organization of the Registry and the criteria for entry of patients have been previously reported in detail. Briefly, pulmonary hypertension was defined as a mean pulmonary arterial pressure greater than 25 mm Hg at rest or 30 mm Hg during exercise. Patients were enrolled in the Registry only after any congenital or acquired cause for pulmonary hypertension was excluded by the Data and Coordinating Center (University of Illinois, Chicago). In excluding any secondary form of pulmonary hypertensive disease, the Center did not rely on the pathology findings but on demographic, clinical, and laboratory data. These included baseline chest roentgenograms, pulmonary function studies with blood gases, cardiac catheterization, lung scan, and angiogram. The purpose of the histopathologic studies was to document the spectrum of vascular lesions in patients in whom diagnosis was made by standardized clinical investigations.

From the 195 patients in the Registry, the pathology laboratory received 66 lung samples from 58 patients (30%). The tissue samples were obtained from 37 autopsies, 23 open lung biopsies, and six pneumonectomies performed during heart-lung transplantation. In eight patients, tissues from both biopsies and autopsies or pneumonectomies were available for study. Most autopsies included examination of the thoracic and abdominal cavities. In only two patients, the examination was restricted to heart and lungs.

Owing to the voluntary nature of the Registry, the material sent to the pathology laboratory was heterogeneous. In a few instances, the entire formalin-fixed content of the chest cavity was received. More often, the available tissue consisted of generous samples of lung tissue fixed in formalin or multiple paraffin blocks. From four patients, only a few representative histologic slides were made available for review.

Handling of the pulmonary specimens at autopsy, biopsy, or pneumonectomy varied according to local customs of pathology practice, and only 48 (73%) of the 66 specimens had been fixed in a distended state.

Available for study were 284 slides stained with hematoxylin and eosin (median, 5 slides per patient; range, 2–25). Companion slides, stained with Verhoeff–van Gieson stain, Masson’s trichrome, or potassium ferrocyanide for hemosiderin, were also available for examination in 46 patients (70%).

Histopathologic Classification

Pulmonary arteries were evaluated for medial hypertrophy (Figure 1A), muscularization of arterioles, concentric laminar intimal proliferation and fibrosis (Figure 1B), eccentric intimal proliferation and fibrosis (Figure 1C), plexiform (Figure 1D) and dilatation lesions, active and healed arteritis, and fresh and recanalized thrombi (Figures 1E and 1F). Although intimal fibrotic lesions, including eccentric plaques and occlusive plugs, could also have represented histopathologic forms of organized thrombi, they could also have corresponded to primary intimal proliferative processes of nonthrombotic origin. Therefore, in the present study, these lesions were categorized as eccentric intimal proliferation rather than as thrombotic lesions. Only lesions that contained blood elements or recanalization channels were considered thrombotic in origin.

Pulmonary veins were examined for medial hypertrophy, arteriolarization, fresh and organized thrombi, and eccentric intimal fibrosis.

The classification of the hypertensive pulmonary disease adopted in this study included not only previously described categories, but also isolated pulmonary arteritis and pulmonary capillary hemangiomatosis, which have been recognized as causes of primary pulmonary hypertension. In the present classification (Table 1), primary pulmonary arteriopathy was divided into five subsets according to the dominant structural abnormalities involving the arterial wall and lumen.

The patients were identified by a registry number assigned by the Data and Coordinating Center, and coded slides were circulated among three pathologists (G.G.P., W.D.E., and J.M.K.) for classification, without knowledge of clinical or laboratory data. Discrepancies in diagnosis were resolved in joint sessions at the microscope. By convention, patients with both plexiform lesions and recanalized thrombi were included in the subset of primary pulmonary arteriopathy with plexiform lesions. Also, the term “primary pulmonary arteriopathy” with “thrombotic” lesions rather than “thrombo-embolic” lesions was preferred because the predominant involvement of peripheral muscular arteries and arterioles in these patients suggested in situ thrombosis rather than embolism.

After all the patients had been classified with the criteria described above, the distribution of arterial lesions was analyzed in the two largest subsets of pulmonary arteriopathy (i.e., those with plexiform lesions and with thrombotic lesions). A secretary was instructed to select three slides stained with Verhoeff–van Gieson’s stain from six biopsies and 20 autopsies of arteriopathy with either plexiform or thrombotic lesions. Coded slides were circulated among three pathologists (G.G.P., W.D.E., and J.M.K.) who scanned the slides microscopically and categorized the first 10 preacinar arteries and the first 10 intra-acinar arterioles observed. Each pathologist examined one slide per patient. The slides were cut at different levels from the same tissue block, but did not necessarily contain the same vessels. At the completion of the study, the code was broken, and the frequency of different vascular lesions for the two groups was calculated.

Because the distribution of lesions in both preacinar and intra-acinar arteries was found to be similar, the
FIGURE 1. Photomicrographs of pulmonary arterial lesions in primary pulmonary hypertension. Panel a: Medial hypertrophy. Muscular pulmonary artery with moderate increase in medial thickness of the media. In intra-acinar arteries, medial hypertrophy is characterized by a complete muscular coat in vessels usually only partially muscularized. Medial hypertrophy could be an isolated abnormality, as shown, or could be associated with intimal lesions (c, below). Panel b: Concentric laminar intimal fibrosis. Concentric layers of myofibroblasts, collagen, and elastic fibers narrow the lumen of a muscular artery. Severe concentric laminar intimal fibrosis is frequently associated with atrophy of the adjacent media. Panel c: Eccentric intimal fibrosis. Muscular artery with medial hypertrophy and a crescent-like fibrous intimal cushion that causes luminal narrowing. Eccentric fibrosis could become so extensive that it produces complete luminal occlusion. Panel d: Plexiform lesion. This lesion characteristically involves muscular arteries, 50–300 μm in diameter, at their origin from larger parent vessels. The lesion is composed of a complex network of small blood vessels and proliferation of myofibroblasts within a dilated arterial segment with partially disrupted media. Proximally, the lumen of the parent vessel is markedly narrowed by laminar intimal fibroelastosis, and distally, the plexiform lesion feeds into dilated thin-walled vessels. Panel e: Recanalized thrombus. The arterial lumen is partially obstructed by thick bands of cellular connective tissue lined by endothelial cells. Panel f: Recanalized thrombus (collanderlike lesion). Several endothelial cell-lined channels are present within the lumen of a muscular artery. Note the intact internal elastic lamina and medial coat. Verhoeff-van Gieson stain; Panels a–c, f, ×400; Panel e, ×180.
The histopathologic classification of primary pulmonary vascular disease is presented in Table 1. This classification includes cases of primary pulmonary arteriopathy with various types of lesions, such as plexiform lesions with or without thrombotic lesions, thrombotic lesions, isolated medial hypertrophy, intimal fibrosis and medial hypertrophy, isolated arteritis, pulmonary veno-occlusive disease, and pulmonary capillary hemangiomatosis.

<table>
<thead>
<tr>
<th>Present classification</th>
<th>Previous classification (References 2-8)</th>
<th>Characteristic histopathologic features*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary pulmonary arteriopathy with</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plexiform lesions with or without thrombotic lesions</td>
<td>Plexogenic pulmonary arteriopathy</td>
<td>Plexiform lesions. Medial hypertrophy, eccentric or concentric-laminar intimal proliferation and fibrosis, fibrinoid degeneration, arteritis, dilatation lesions, and thrombotic lesions.</td>
</tr>
<tr>
<td>Thrombotic lesions</td>
<td>Thromboembolic pulmonary arteriopathy</td>
<td>Thrombi (fresh, organizing, or organized, and recanalized-collander lesions). Varying degrees of medial hypertrophy; no plexiform lesions.</td>
</tr>
<tr>
<td>Isolated medial hypertrophy</td>
<td>Plexogenic pulmonary arteriopathy</td>
<td>Medial hypertrophy. Increase of medial muscle, muscular arteries, muscularization of nonmuscularized intra-acinar arteries; no appreciable intimal or luminal obstructive lesions.</td>
</tr>
<tr>
<td>Intimal fibrosis and medial hypertrophy</td>
<td>Plexogenic pulmonary arteriopathy</td>
<td>Eccentric or concentric-laminar proliferation and fibrosis. Varying degrees of medial hypertrophy; no thrombotic or plexiform lesions.</td>
</tr>
<tr>
<td>Isolated arteritis</td>
<td>Plexogenic pulmonary arteriopathy</td>
<td>Active or healed arteritis. Limited to pulmonary arteries; varying degrees of medial hypertrophy intimal fibrosis, and thrombotic lesions; no plexiform lesions.</td>
</tr>
<tr>
<td>Pulmonary veno-occlusive disease</td>
<td>Pulmonary veno-occlusive disease</td>
<td>Intimal fibrosis and recanalized thrombi (collander lesions). Pulmonary veins and venules; arterialized veins, capillary congestion, alveolar edema and siderophages, dilated lymphatics, pleural and septal edema and arterial medial hypertrophy, intimal fibrosis, and thrombotic lesions.</td>
</tr>
<tr>
<td>Pulmonary capillary hemangiomatosis</td>
<td>—</td>
<td>Infiltrating thin-walled blood vessels. Widespread throughout pulmonary parenchyma, pleura, bronchi, and walls of pulmonary veins and arteries.</td>
</tr>
</tbody>
</table>

*Medial hypertrophy may be accompanied by muscularization of arterioles.

Data from these two types of vessels were pooled. The distribution of arterial lesions was compared in biopsies and autopsies in the two subsets of pulmonary arteriopathy and in both groups combined.

**Morphometric Measurements**

To obtain a quantitative assessment of the severity of medial and intimal lesions, we measured (G.G.P. and B.S.) by computer-aided planimetry the fractional areas occupied by the media and intima in arteries 100–300 μm in diameter. Twenty-seven patients were studied (13 biopsies and 14 autopsies), and in each, the lungs had been fixed in the distended state. The profiles of the intima and media of arteries, stained with Verhoeff–van Gieson stain, were projected onto a digitizing tablet and traced with a stylus connected to an Apple II computer (Apple Computer, Cupertino, California). The computer was programmed to classify arteries according to their external diameter and to calculate the percent cross-sectional areas occupied by the lumen, media, and intima. To correct for artifact caused by vascular contraction, the program contained algorithms to normalize the measurements to that of distended vessels with smooth elastic laminae. On average, 10 arteries (range, 4–19) were measured in each patient.

**Clinicopathologic Correlations**

Relations were tested between the different histologic subtypes and clinical variables reported on the baseline report forms at the time patients were enrolled into the Registry and between histologic subtypes and patient survival.

**Statistical Analysis**

Comparison of variables between groups was made using the χ² test for the incidence of histopathologic lesions and the Mann-Whitney U tests for morphometric data. Differences in hemodynamic variables and clinical presentations among histopathologic subsets were tested by Tukey’s Studentized Range test after an F test indicated an overall significant difference. In all comparisons a p value less than 0.05 was considered statistically significant.

**Results**

**Histopathologic Classification**

Among the 58 patients, 49 (84%) were classified as having pulmonary arteriopathy and seven (12%) as having pulmonary veno-occlusive disease. The classification of two patients (3%) remained uncertain.

In the 49 examples of pulmonary arteriopathy, pulmonary artery medial hypertrophy was a constant
finding, and in most patients, it was associated with other lesions involving the intima, lumen, or entire vascular wall. In the autopsy or pneumonectomy material, there were 22 patients that had arteriopathy with plexiform lesions and 13 with thrombotic lesions (Tables 2 and 3). In the biopsy material, however, thrombotic lesions occurred more frequently than did plexiform lesions. Among the 25 patients in the overall study in whom plexiform lesions were observed (Table 4), recanalized thrombi were also found in nine. It was unclear, however, whether the thrombi were primary or secondary lesions. In the remaining 24 patients, 19 showed thrombotic lesions, four showed intimal fibrosis with plexiform or thrombotic lesions, and one showed isolated pulmonary artery medial hypertrophy. No examples of primary pulmonary arteritis or pulmonary capillary hemangiomatosis were found in our material.

The three pathologists agreed on the initial classification in 56 (96%) of the 58 patients. The two discrep-

**Table 2. Patterns of Hypertensive Pulmonary Vascular Disease in Lung Tissues Obtained From 37 Autopsies and Six Pneumonectomies**

<table>
<thead>
<tr>
<th>Histopathologic type</th>
<th>Patients (n)</th>
<th>(%)</th>
<th>Sex ratio (M/F)</th>
<th>Age (yr) Mean Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary arteriopathy with</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plexiform lesions</td>
<td>22*</td>
<td>51</td>
<td>6/16</td>
<td>30 10–57</td>
</tr>
<tr>
<td>Thrombotic lesions</td>
<td>13*</td>
<td>30</td>
<td>7/6</td>
<td>35 22–55</td>
</tr>
<tr>
<td>Intimal fibrosis and medial hypertrophy</td>
<td>3 7</td>
<td>1/2</td>
<td>44 6–66</td>
<td></td>
</tr>
<tr>
<td>Medial hypertrophy</td>
<td>—</td>
<td>0</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Veno-occlusive disease</td>
<td>5</td>
<td>12</td>
<td>3/2</td>
<td>28 11–43</td>
</tr>
</tbody>
</table>

*These differences are not statistically significant.

**Table 3. Patterns of Hypertensive Pulmonary Vascular Disease in 23 Biopsy Specimens*”

<table>
<thead>
<tr>
<th>Histopathologic type</th>
<th>Patients (n)</th>
<th>(%)</th>
<th>Sex ratio (M/F)</th>
<th>Age (yr) Mean Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary arteriopathy with</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombotic lesions</td>
<td>8†</td>
<td>35</td>
<td>3/5</td>
<td>39 39–57</td>
</tr>
<tr>
<td>Plexiform lesions</td>
<td>5†</td>
<td>22</td>
<td>1/4</td>
<td>31 17–53</td>
</tr>
<tr>
<td>Medial hypertrophy</td>
<td>1</td>
<td>5</td>
<td>0/1</td>
<td>60 —</td>
</tr>
<tr>
<td>Intimal fibrosis and medial hypertrophy</td>
<td>1 5</td>
<td>1/0</td>
<td>33 —</td>
<td></td>
</tr>
<tr>
<td>Veno-occlusive disease</td>
<td>4</td>
<td>17</td>
<td>2/2</td>
<td>41 29–50</td>
</tr>
<tr>
<td>Venous hypertension</td>
<td>2</td>
<td>9</td>
<td>2/0</td>
<td>47 32–62</td>
</tr>
<tr>
<td>Normal</td>
<td>1</td>
<td>4</td>
<td>1/0</td>
<td>37 —</td>
</tr>
<tr>
<td>Nondiagnostic</td>
<td>1</td>
<td>4</td>
<td>1/0</td>
<td>22 —</td>
</tr>
</tbody>
</table>

*Eight patients from whom biopsy and autopsy or pneumonectomy lung samples were available are included also in Table 2. Among these eight patients, two had plexiform lesions, two thrombotic lesions, two veno-occlusive disease, one venous hypertension, and one was nondiagnostic.

†These differences are not statistically significant.

**Table 4. Relative Frequency of Histopathologic Types of Hypertensive Pulmonary Vascular Disease in Three Published Series and the Present Study**

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n) (%) Mean age (yr) M/F</td>
<td>(n) (%) Mean age (yr) M/F</td>
<td>(n) (%) Mean age (yr) M/F</td>
<td>(n) (%) Mean age (yr) M/F</td>
</tr>
<tr>
<td>Plexiform</td>
<td>110 71 23 36/74 14 35 21 4/10 22 28 30 7/15 25 43 30 6/19</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombotic</td>
<td>31 20 44 9/22 12 30 40 6/6 45 56 41 15/30 19 33 36 9/10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intimal fibrosis and medial hypertrophy</td>
<td>—</td>
<td>—</td>
<td>3 4 34 1/2 1 2 39 0/1</td>
<td></td>
</tr>
<tr>
<td>Medial hypertrophy</td>
<td>—</td>
<td>—</td>
<td>2 5 7 2/0 5 6 21 4/1 7 12 33 4/3</td>
<td></td>
</tr>
<tr>
<td>Veno-occlusive disease</td>
<td>5 3 16 2/3 2 5 7 2/0 5 6 21 4/1 7 12 33 4/3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary venous hypertension</td>
<td>5 3 35 2/3 10 25 44 6/4 2 3 45 2/0 1 2 62 1/0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Others*</td>
<td>5 3 — — 2 5 — — 3 4 — — 1 2 37 1/0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>156 — — 40 80 58</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Includes primary pulmonary arteritis, sarcoidosis, schistosomiasis, hypoxic arteriopathy, and normal blood vessels.
was not
was no
patient,
contributing
records
between
concordance
resolved
at a
specific
Two
biopsy
chronic
parenchyma
suggesting
lesions.
Because
lesions.
The
other
six
patients,
other
family
members,
other
diseases
had
lung
tissue
from
available
from
one
patient,
the
pathologist
and
the
lesions.
Because
lung
was
not
available
from
other
family
members,
it
remains
unclear
whether
specific
histopathologic
subtypes
are
transmitted
within
specific
families.
In
seven
patients,
both
biopsy
and
autopsy
specimens
were
available.
The
interval
between
biopsy
and
autopsy
varied
(Table
5).
One
patient
died
4
days
after
biopsy,
and
no
discrepancies
in
diagnosis
between
biopsy
and
autopsy
tissues
were
observed.
The
other
six
patients
had
a
mean
survival
of
30
months
(range,
10–56
months)
after
biopsy;
in
two
patients,
the
autopsy
findings
allowed
a
more
precise
characterization
of
the
pulmonary
vascular
disease
(Table
5).

Quantitative Measurements

The
mean±SEM
percent
distribution
of
vascular
lesions
was
calculated
in
1,031
muscular
pulmonary
arteries
and
arterioles
from
26
patients
that
had
arteriopathy
with
erithromel lesions
or
thrombotic
lesions
(Figure
2).
There
were
no
statistically
significant
differences
between
the
groups
in
the
mean
frequency
of
isolated
pulmonary
artery
medial
hypertrophy
in
either
the
biopsy
or
autopsy
tissues
(Figures
2A
and
2B).
Concentric
laminar
fibrosis
was
nearly
confined
to
the
group
with
plexiform
lesions.
Eccentric
inimal
fibrosis
was
present
in
both
plexiform
and
thrombotic
lesions,
but
it
was
significantly
(p<0.02)
more
frequent
in
the
thrombotic
subset
(Figure
2A
and
2B).
In
the
plexiform
subset,
lesions
were
uncommon,
and
only
involved
3.9%
and
7%
of
the
vessels
in
biopsy
and
autopsy
tissues,
respectively.
By
definition,
they
were
not
a
feature
of
the
thrombotic
group.
Although
recanalized
thrombi
were
present
in
both
groups,
they
were
more
frequent
in
pulmonary
arteriopathy
with
thrombotic
lesions
(p<0.01).
When
the
data
from
all
arteries
in
the
plexiform
and
thrombotic
groups
were
combined,
no
statistically
significant
differences
were
found
in
the
distribution
of
histopathologic
lesions
between
autopsies
and
biopsies
(Figure
2C).

Dilatation
lesions,
recent
thrombi,
and
arteritis
were
so
rarely
seen
that
no
meaningful
conclusions
on
their
relative
prediction
for
one
or
the
other
subtype
of
pulmonary
arteriopathy
could
be
reached.

Morphometric
measurements
of
arterial
media
and
intima
failed
to
detect
statistically
significant
differences
in
arterial
wall
thickness
between
the
thrombotic
and
plexiform
groups.
In
three
patients
in
whom
both
biopsy
and
autopsy
specimens
were
available
from
the
same
patient,
the
relative
contribution
of
the
intima
and
media
to
the
arterial
wall
thickness
did
not
change
significantly
between
biopsy
and
autopsy
data
not
shown).

Clinicopathologic Correlations

No
differences
were
found
between
the
histologic
subtypes
and
symptoms
at
the
time
pulmonary
hypertension
was
diagnosed,
or
were
there
any
differences
with
respect
to
functional
class,
anti-
uclear
antibody
titre,
smoking
history,
family
history,
or
any
measure
of
pulmonary
function.

The
only
statistically
significant
differences
were
observed
between
the
groups
of
arteriopathy
with
plexiform
lesions
and
arteriopathy
with
thrombotic
lesions
and
between
the
thrombotic
and
veno-
occlusive
groups
in
the
levels
of
pulmonary
vascular
resistance
(corrected
for
body
surface
area)
and
pulmonary
artery
pressures
at
the
time
the
patients
underwent
baseline
catheterization.
Patients
having

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age at biopsy (yr)</th>
<th>Sex</th>
<th>Time*</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>25</td>
<td>F</td>
<td>4 day</td>
<td>PAPLX</td>
</tr>
<tr>
<td>2</td>
<td>32</td>
<td>M</td>
<td>10 mo</td>
<td>PVH</td>
</tr>
<tr>
<td>3</td>
<td>36</td>
<td>F</td>
<td>24 mo</td>
<td>PATHR</td>
</tr>
<tr>
<td>4</td>
<td>26</td>
<td>M</td>
<td>26 mo</td>
<td>PVOD</td>
</tr>
<tr>
<td>5</td>
<td>29</td>
<td>F</td>
<td>32 mo</td>
<td>PVOD</td>
</tr>
<tr>
<td>6</td>
<td>22</td>
<td>M</td>
<td>33 mo</td>
<td>PAPLX</td>
</tr>
<tr>
<td>7</td>
<td>39</td>
<td>M</td>
<td>56 mo</td>
<td>PATHR</td>
</tr>
</tbody>
</table>

*Between biopsy and autopsy.
PAPLX, pulmonary arteriopathy with plexiform lesions; PATHR, pulmonary arteriopathy with thrombotic lesions; PVH, chronic pulmonary venous hypertension; PVOD, pulmonary veno-occlusive disease.
arteriopathy with plexiform lesions had a mean pulmonary vascular resistance of 44.5±22.4 units (mean±SD) (n=20) compared with 28.9±13.1 (p<0.05; n=10) for the group with thrombotic lesions, and 28.7±8.3 (p<0.05; n=5) for the group with pulmonary veno-occlusive disease. The higher pulmonary vascular resistance was manifested by both higher pulmonary artery pressures (mean pulmonary artery pressure 76.4±22.2 mm Hg) and lower cardiac indexes (1.7±0.4 l/min/m²) in the group having arteriopathy with plexiform lesions. The mean pulmonary artery pressure in the groups with pulmonary veno-occlusive disease and thrombotic lesions was 59.6±14.6 and 61.3±10.9 mm Hg, respectively. The cardiac index in pulmonary veno-occlusive disease group was 1.8±0.1, whereas that in group with thrombotic lesions was 2.4±1.7 l/min/m².

There were also differences with respect to survival when the patients were stratified by their pathology type (Figure 3). Patients having arterio-

![Figure 2](image_url) **Figure 2.** Bar graphs illustrating the distribution (mean±SEM %) of lesions in 243 arteries from six biopsies (Panel a) and 788 arteries from 20 autopsies (Panel b) of patients with primary pulmonary arteriopathy with either plexiform or thrombotic lesions. In both biopsy and autopsy tissues, concentric laminar intimal fibrosis was confined to the plexiform group. Eccentric intimal fibrosis and recanalized thrombi were present in both groups but were significantly more frequent in the thrombotic group. By definition, plexiform lesions were absent in the thrombotic group. (p values shown over bars). Distribution of histopathologic lesions in 1,031 arteries from autopsy and biopsy specimens (Panel c) from the 26 patients with pulmonary arteriopathy shown above. Data from both plexiform and thrombotic groups were pooled. Although the mean frequency of recanalized thrombi is greater in the biopsies than in the autopsies, the differences between the means of the two groups are not statistically significant for any of the histologic features. BX, biopsies; AX, autopsies; BX-PLX, biopsies of arteriopathy with plexiform lesions; AX-PLX, autopsies of arteriopathy with plexiform lesions; BX-THR, biopsies of arteriopathy with thrombotic lesions; AX-THR, autopsies of arteriopathy with thrombotic lesions; NL, normal vessels; IMH, isolated pulmonary artery medial hypertrophy; CLIF, concentric laminar intimal fibrosis; EIF, eccentric intimal fibrosis; PLX, plexiform lesions; THR, thrombotic lesions.

![Figure 3](image_url) **Figure 3.** Plot of survival of patients in the Registry by pathologic classification. Mortality was higher during the first 6 months after diagnosis among patients with pulmonary veno-occlusive disease and the plexiform type of pulmonary arteriopathy than for those with thrombotic pulmonary arteriopathy (p<0.02).
pathy with thrombotic lesions had the best survival (mean, 1,070 days; median, 858 days) compared with those having arteriopathy and plexiform lesions (mean, 297 days; median, 102 days), and pulmonary veno-occlusive disease (mean, 289 days; median, 84 days). These differences in survival between thrombotic and plexiform arteriopathies and between the thrombotic arteriopathy and veno-occlusive disease were statistically significant ($p<0.02$). The differences were most apparent when survival during the first 6 months was compared in the three groups (Figure 3). In the first 6 months after entering into the Registry, 71% of patients having pulmonary veno-occlusive disease, and 52% of those having plexiform arteriopathy were dead compared with 30% mortality in patients with thrombotic arteriopathy.

Among the 23 patients in whom open lung biopsy was performed, one patient died 4 days after the procedure (Table 5), and his death was attributed to the biopsy. Of the remaining 22 patients, four had no complications associated with the operation, and information was unavailable in 18. In one patient, the biopsy tissue included only a narrow strip of subpleural tissue and was considered inadequate for diagnosis because of the paucity of blood vessels.

**Discussion**

The unique features of the present study are its prospective nature and the selection of patients by standardized clinical and hemodynamic criteria. To our knowledge, only three other large series on the vascular pathology of primary pulmonary hypertension have been published.\(^2,3,10\) One series\(^3\) reported findings from 156 autopsies performed at 51 centers in 14 different countries. This was a retrospective study, and the criteria for clinical diagnosis of primary pulmonary hypertension were heterogeneous. In another series,\(^10\) 40 open-lung biopsies obtained from patients with unexplained pulmonary hypertension were analyzed. Included among the patients were 10 patients with pulmonary hypertension and abnormal chest roentgenograms. These patients would have been excluded from the Registry.\(^1\) The third series\(^2\) was a retrospective study of 80 patients diagnosed at Mayo Clinic between 1930 and 1983. Because the study spanned several decades, the clinical criteria for the diagnosis of the disease were not as standardized or complete as in the present study. Despite the heterogeneous diagnostic approaches in all of the series, pulmonary arteriopathy was the most common form of hypertensive pulmonary vascular disease (Table 4). Differences among the series existed, however, in the relative proportion of the various subsets of pulmonary arteriopathy. Thus, the frequency of “plexogenic arteriopathy” was highest in the study by Wagenvoort and Wagenvoort,\(^3\) and lowest in the Mayo Clinic series\(^2\) (Table 4). However, the former study’s patient group of “plexogenic pulmonary arteriopathy” included patients without plexiform lesions, which we would have classified as pulmo-

nary arteriopathy with intimal fibrosis, by the criteria proposed by Bjornsson and Edwards.\(^2\) Conversely, the high incidence of thrombotic pulmonary arteriopathy reported by Bjornsson and Edwards\(^3\) could have been related to the inclusion of patients in whom the clinical diagnosis of primary pulmonary hypertension was established without the benefit of pulmonary angiograms or lung scans.

In the present material (Table 4), arteriopathy with thrombotic lesions was found in 33% of patients. Because these changes were found in the absence of clinical or pathologic evidence of pulmonary embolism, these vascular lesions probably result from in situ thrombosis as was originally proposed by Bjornsson and Edwards.\(^2\)

One interpretation of these previous studies is that different histopathologic subsets of hypertensive pulmonary vascular disease result from different causes and pathogenetic mechanisms. This view, however, has been challenged in a recently published study of the pulmonary vascular pathology of familial primary pulmonary hypertension, an autosomal dominant disease, clinically indistinguishable from the idiopathic form.\(^12\) In this retrospective analysis of 23 autopsies from affected members of 13 families, the histopathologic lesions were analyzed by an objective quantitative approach in a uniquely homogeneous patient population. Pulmonary arteriopathy was found in every patient, but plexiform and thrombotic lesions were present in affected members of the same family. Although some methodologic differences exist between this study and ours, the distribution of the arterial lesions in familial pulmonary arteriopathy is remarkably similar when our data from the thrombotic and plexiform groups are combined. Plexiform lesions were found in 3.4% of vessels in autopsies of patients with familial hypertensive disease and in 3.8% of vessels in the present population.

However, the Registry experience suggests that the classification of primary pulmonary arteriopathy into distinct subsets has prognostic implications. Histopathologic classification can be achieved accurately and reproducibly with the criteria described in Table 1, as shown by 96% interobserver agreement among the pathologists and by the good correlation between premortem and postmortem diagnosis in the limited number of patients in which biopsies and autopsies from the same individual were available. Discrepancies between biopsies and autopsies existed only in the distinction between chronic pulmonary venous hypertension and veno-occlusive disease.

The clinical presentation of patients with primary pulmonary hypertension is remarkably similar between the histologic subtypes so that there is no distinctive feature that would allow the clinician to distinguish these patients based on these clinical variables. Although pulmonary vascular resistance was significantly higher in the group having the plexiform arteriopathy, there was still enough het-
erogeneity between the hemodynamic parameters of all groups so that the value of pulmonary vascular resistance obtained at the time of catheterization would not distinguish the three classes of patients. In a recent study, however, Rich et al. found the pattern of chest radiogram and perfusion lung scans useful in the differential diagnosis of these entities. Patients with plexiform lesions or pulmonary veno-occlusive disease have a much poorer prognosis than those with thrombotic arteriopathy. Because the clinical features of the patients were similar at the time of their presentation, this is likely a reflection of the progression of the underlying disease processes. Patients with plexiform lesions were more frequently young and female. The mean age of patients with plexiform lesions at death was 29±12 years, whereas that of patients with thrombotic lesions was 37±10 years (p<0.04). The male to female ratio in this group was 1:3 compared with 1:1 in the thrombotic group (p<0.05). Similar results have been reported by others. Thus, the histopathologic distinction between plexiform and thrombotic variants of hypertensive pulmonary arteriopathy is justified by characteristic histopathologic features, differences in age of onset, sex incidence, and clinical course of the syndrome. However, it is unclear whether these different histopathologic features indicate different pathogenetic mechanisms or different progression of the same pathologic process.

To correlate vascular changes with prognosis, Robinovitch et al. and Mooi and Wagenvoort have recommended measurements of relative medial and intimal thicknesses in two perpendicular diameters of muscular pulmonary arteries. Because of the uneven pattern of intimal thickening in many of the pulmonary arteries, measurements of the arterial cross-sectional area occupied by media and intima appeared to provide a better estimate of luminal obstruction than those provided by measurements of two perpendicular diameters. Our data showed that both the plexiform and the thrombotic forms of primary pulmonary hypertension are associated with advanced and apparently irreversible arterial obstructive lesions at the time of clinical diagnosis.

The present study also confirms previous studies showing that open-lung biopsy generally provides a representative sample of hypertensive vascular alterations of the lung as a whole and is a relatively safe procedure. However, the usefulness of the biopsy in assessing the severity and nature of the vascular lesions is limited because patients with primary pulmonary hypertension commonly become symptomatic and come to clinical attention only late in the course of their disease when the vascular changes are advanced and include a mixture of primary and secondary lesions. Moreover, the diagnostic value of open-lung biopsy in patients with primary pulmonary hypertension is further limited because previous thoracotomy and associated pleural adhesions are considered by some surgical teams a contraindication to lung transplantation.

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References


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