Intravascular Ultrasound Assessment of Pulmonary Vascular Disease in Patients With Pulmonary Hypertension*

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Background: Measurements of pulmonary pressure and resistance are still considered to be the “gold standard” in the evaluation of pulmonary hypertension (PH), despite their limitations in predicting irreversible disease. Hemodynamic assessment also only provides a global evaluation of the pulmonary vascular bed, whereas PH is an inhomogeneous disease of the vessel wall.

Methods and results: We assessed the value of intravascular ultrasound (IVUS) in 30 patients with suspected PH and correlated the structural changes in distal pulmonary arteries found on IVUS with conventional hemodynamic data. Plasma endothelin (ET)-1 levels and pulmonary ET-1 extraction also were measured as markers of the severity of PH. The anatomic abnormalities revealed by IVUS were more severe in the lower lobes than in the upper lobes, as evidenced by the greater percentage of wall thickness (WT), the smaller lumen diameter/WT and lumen area/total vessel area (p < 0.05 for each). IVUS anatomic indexes correlated directly with hemodynamic data (eg, with pulmonary arterial systolic pressure; r = 0.56; p < 0.001) and ET-1 levels but inversely with pulmonary ET-1 extraction.

Conclusion: Patients with PH have greater pulmonary arterial WT that is more severe in the lower lobes than in the upper lobes. The severity of structural abnormalities found on IVUS is directly correlated with hemodynamic findings and ET-1 levels. IVUS may provide useful additional information in the assessment of patients with PH.

CHEST 2001; 120:809–815

Key words: endothelin-1; intravascular ultrasound; pulmonary hypertension; pulmonary vascular disease

Abbreviations: CO = cardiac output; ET = endothelin; IVUS = intravascular ultrasound; LA = lumen area; MLD = minimal lumen diameter; MWT = mean wall thickness; PA = pulmonary artery, arterial; PASP = systolic pulmonary arterial pressure; PH = pulmonary hypertension; PVR = pulmonary vascular resistance; TVA = total vessel area; TVD = total vessel diameter; WA = wall area; WT = wall thickness; WU = Wood units

Pulmonary hypertension (PH) may result from a variety of conditions, including severe left ventricular dysfunction, mitral valve disease, and congenital heart disease. Although measurements of pulmonary pressure and resistance remain the “gold standard” for the evaluation of PH, they are limited by their weak correlation with histologic findings and their imperfect prognostic value.1 Intravascular ultrasound (IVUS) is a catheter-based imaging modality that could assist in the evaluation of pulmonary vascular disease by providing additional structural information. To assess the value of IVUS in patients with PH, we first evaluated its ability to identify regional differences in structural vascular abnormalities that previously have been described with histopathology (ie, greater vascular wall hypertrophy in the lower lobes).2 Previous studies using IVUS3–10 have indeed not taken into account these regional differences in pulmonary vascular disease. Because of the limitations of hemodynamic findings in the evaluation of pulmonary vascular disease, we expected a weak correlation between IVUS and hemodynamic results. We therefore also correlated IVUS with another known marker of pulmonary vascular disease, plasma endothelin (ET)-1 levels. ET-1 is a potent vasoconstrictor and mitogenic peptide that is activated in all forms of PH.11 Because ET-1 is removed from the pulmonary circulation by the endothelial ET-B receptor,12 reduced pulmonary clearance of ET-1 may reflect pulmonary endothelial...
dysfunction. The purpose of this study was therefore to assess the value of IVUS in detecting structural abnormalities in distal pulmonary arteries and to correlate these findings with the hemodynamic data and ET-1 levels and clearance rates. Since about half of the patients studied had mitral stenosis, we also compared this subgroup of patients to the others to evaluate potential differences that could be revealed by IVUS.

MATERIALS AND METHODS

Study Population

The study population consisted of 30 patients (10 men and 20 women) ranging in age from 33 to 73 years (mean, 54 years) who had suspected primary or secondary PH and were undergoing cardiac catheterization. The causes for PH were the following: severe left ventricular dysfunction (8 patients); mitral valve stenosis (16 patients); mitroaortic valvular disease (3 patients); Eisenmenger syndrome (1 patient); CREST (ie, calcinosis, Raynaud’s phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia) syndrome (1 patient); and primary PH (1 patient). Our institutional review committee approved the study, and the subjects gave informed consent.

IVUS Instrumentation

The mechanical system used in our study consisted of 3.5F, 30-MHz monorail ultrasound catheters (Boston Scientific Corp; Watertown, MA) and an intravascular imaging console (Hewlett-Packard; Andover, MA). The distal end of the catheter has a tract that allows for use with a 0.014-inch guidewire. The transducer is held at 1,800 revolutions per minute in the ultrasound catheter. The system provides 30 images per second. Axial and lateral resolutions are 0.1 and 0.3 mm, respectively.

Cardiac Catheterization and IVUS Examination

Right and left heart catheterization and hemodynamic measurements were performed with standard catheters. Cardiac output (CO) was calculated using the Fick method, and pulmonary resistance was calculated using the following formula:

\[
\text{(MPAP-WP)/CO}
\]

where MPAP is mean pulmonary arterial pressure and WP is wedge pressure. Following these procedures, a 0.014-inch guidewire was advanced through the distal lumen of a Mullins sheath or a right coronary artery guiding catheter. The IVUS catheter was advanced over the guidewire in the distal pulmonary arterial tree (ie, as far as it was technically feasible to advance it) and was held stable for at least 15 cardiac cycles. The largest possible number of lobes in both the right and left lungs was assessed sequentially in each patient. A running detailed audio comment was performed during the entire examination to document sites of interest. A simultaneous high-resolution fluoroscopic image was continuously incorporated on the monitor through a display processor (model PK2350; Perkins; Dallas, TX). IVUS images were recorded on 0.5-inch super VHS videotape for later review.

IVUS Measurements

Recordings were reviewed offline by an experienced observer for measurements. IVUS images were analyzed with the observer blinded to hemodynamic data. Measurements were performed in the most distal vessels imaged in each lobe. Minimal lumen diameter (MLD), wall thickness (WT) in four quadrants, lumen area (LA), and area circumscribed by the external elastic membrane (the total vessel area [TVA]) were measured at end-diastole and end-systole. From these measurements, wall area (WA = TVA - LA), mean WT (MWT), total vessel diameter (TVD = MLD + 2 × MWT), and percent WT (% WT = [2 × MWT/TVD] × 100) were derived. Pulmonary artery (PA) distensibility was calculated using the following formula:

\[
\left(\frac{LAd - LAs}{LAd}\right) \times 100
\]

where LAs and LAd represent LA at end-systole and end-diastole, respectively. Elastic strain also was derived

\[
\left(\frac{[PASP - PADP]}{[LAs - LAd]}\right) \times LAd
\]

where PASP and PADP are systolic and diastolic pulmonary arterial pressures, respectively.

ET Assay and Assessment of Pulmonary Extraction of Labeled ET

Pulmonary extraction and the kinetics of ET-1 were measured in 15 patients using the indicator dilution technique, as previously described. Immunoreactive ET-1 levels were measured in paired aortic and PA samples in 16 patients and in the PA in only 4 patients.

Statistical Analysis

Hemodynamic and metabolic measurements were compared with IVUS results using least-squares linear regression analysis and Pearson’s correlation coefficients. IVUS results in different lobes were compared with analysis of variance. Values were considered to be significant if the two-tailed p < 0.05.

RESULTS

Hemodynamic Data

The baseline values for PASP and mean PA pressure ranged from 21 to 136 mm Hg (mean [± SD], 49 ± 22) and from 13 to 85 mm Hg (33 ± 14), respectively. Pulmonary vascular resistance (PVR) and indexed PVR were 3.4 ± 3.3 Wood units (WU) (range, 0.4 to 16.3 WU) and 5.5 ± 4.7 WU × m² (range, 0.8 to 22.4 WU × m²), respectively.

IVUS Measurements

We were able to perform the IVUS examination in all patients without complication (Fig 1). An average of two lobes were assessed per patient. The upper and lower lobes both were evaluated in 23 of the 30 patients. In others, only one lobe or the same lobe (upper or lower) in both lungs was assessed. Total vessel dimensions were similar between left and right lungs, indicating that the generation of the artery that was assessed was similar. Total vessel...
dimensions were also similar between the upper and lower lobes. The TVD ranged from 1.7 to 6.5 mm, and the MLD ranged from 1.4 to 6 mm. The percent WT was 16 ± 6% (range, 6 to 29%).

There were no differences between the left and right lungs for all IVUS measurements. In contrast, anatomic abnormalities were more severe in the lower lobes than in the upper lobes, as evidenced by differences in the percent WT, and by the ratios of lumen diameter to WT and of LA to TVA (p < 0.05 for each) (Table 1).

**Relationship Between IVUS and Hemodynamic Abnormalities**

Several IVUS anatomic indexes correlated with hemodynamic data (Table 2). Lower lobe MWT, WA, percent WT, and the ratio of lumen diameter to WT correlated significantly with PASP (r = 0.56 for MWT; p < 0.05 for all). MWT also correlated with PVR and indexed PVR. Thus, greater vascular hypertrophy was associated with more severe PH. However, only the correlations between PASP and both MWT (r = 0.43; p = 0.01) (Fig 2) and the MLD/MWT ratio (r = 0.39; p = 0.03) remained significant after excluding the patient with Eisenmenger syndrome and a PASP of 136 mm Hg. There was no significant correlation between ultrasound measurements in the upper lobes and hemodynamic data.

**Relationship Between IVUS Abnormalities and ET Levels and Extraction**

ET levels correlated significantly with upper lobe WA, TVA and diameter, and LA and diameter (Table 3; Fig 3, top, A, and middle, B). The inverse relationship between upper-lobe TVA and ET-1 extraction was of borderline significance (r = –0.59; p = 0.058). There was no significant correlation between ET-1 plasma levels or extraction and lower-lobe IVUS indexes.

PA ET-1 levels were higher in patients with PASP levels of >35 mm Hg than in those patients with PASP levels of <35 mm Hg (1.52 ± 0.84 pg/mL vs 0.53 ± 0.41 pg/mL, respectively; p = 0.02). ET-1 levels correlated with PASP (r = 0.48; p = 0.06) and PVR (r = 0.53; p = 0.016). The pulmonary extraction of labeled ET-1 correlated inversely with PASP (r = −0.73; p = 0.003) and PVR (r = −0.48; p = 0.08).

**Differences Between PH Secondary to Mitral Stenosis and Other Causes**

The total vessel dimensions of the vessels studied in patients with mitral stenosis and in those with PH of other etiologies were not significantly different. The WA and MWT in the upper lobes were, however, significantly smaller in patients with mitral stenosis, despite a trend for higher PA pressure and resistance (p < 0.1 for both PASP and PVR; p < 0.05 for indexed PVR). Plasma levels of ET-1 were significantly lower and pulmonary extraction was significantly greater in patients with mitral ste-

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**Table 1—IVUS Measurements Upper Vs Lower Lobes**

<table>
<thead>
<tr>
<th>Measurements</th>
<th>Upper (n = 23)</th>
<th>Lower (n = 23)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TVA, mm²</td>
<td>9.79 ± 4.05</td>
<td>9.98 ± 4.63</td>
<td>0.85</td>
</tr>
<tr>
<td>LA, mm²</td>
<td>7.58 ± 3.55</td>
<td>7.16 ± 3.90</td>
<td>0.67</td>
</tr>
<tr>
<td>WA, mm²</td>
<td>2.21 ± 1.32</td>
<td>2.82 ± 1.40</td>
<td>0.11</td>
</tr>
<tr>
<td>MWT, mm</td>
<td>0.24 ± 0.11</td>
<td>0.29 ± 0.10</td>
<td>0.057</td>
</tr>
<tr>
<td>WT, %</td>
<td>14.3 ± 6.10</td>
<td>17.1 ± 5.70</td>
<td>0.91</td>
</tr>
<tr>
<td>MLD, mm</td>
<td>2.88 ± 0.64</td>
<td>2.90 ± 0.90</td>
<td>0.94</td>
</tr>
<tr>
<td>MLD/MWT</td>
<td>14.5 ± 6.90</td>
<td>11.4 ± 5.90</td>
<td>0.006</td>
</tr>
<tr>
<td>TVD, mm</td>
<td>3.36 ± 0.67</td>
<td>3.48 ± 0.93</td>
<td>0.61</td>
</tr>
<tr>
<td>LA/wall area</td>
<td>4.1 ± 2.10</td>
<td>3.1 ± 2.0</td>
<td>0.06</td>
</tr>
<tr>
<td>LA/TVA</td>
<td>0.77 ± 0.10</td>
<td>0.71 ± 0.11</td>
<td>0.03</td>
</tr>
<tr>
<td>PA distensibility, %</td>
<td>15.6 ± 8.7</td>
<td>13.7 ± 9.1</td>
<td>0.40</td>
</tr>
<tr>
<td>Elastic strain, mm Hg</td>
<td>676 ± 1495</td>
<td>401 ± 397</td>
<td>0.42</td>
</tr>
</tbody>
</table>

*Values given as mean ± SD, unless otherwise indicated.
nosis (aortic levels, $p = 0.03$; PA levels, $p < 0.01$; and extraction of labeled ET-1, $p = 0.02$) (Table 4).

**Discussion**

**Assessment of the Pulmonary Circulation Using IVUS and Correlations With Hemodynamic Abnormalities**

The use of IVUS imaging allowed for the in vivo identification of regional differences in pulmonary vascular abnormalities found in patients with PH. Greater vascular wall hypertrophy already had been demonstrated in the lower lobes by histopathology, a finding attributed to the higher hydrostatic pressure chronically present in these segments with the patient in the upright posture. In contrast, there was no difference in IVUS indexes between the right and left lungs, demonstrating the reliability of the technique. Our findings also indicate that the severity of structural PA disease, as demonstrated by IVUS, at best correlates only moderately with hemodynamic abnormalities. IVUS results, however, correlated better with ET levels and with the reduced pulmonary clearance of this peptide.

IVUS has demonstrated excellent correlations with anatomic measurements in the assessment of the pulmonary arterial lumen and wall in vitro. The ability to visualize the vessel lumen and wall in

![Figure 2. Correlation between PASP and MWT in the distal lower lobes measured with IVUS (the patient with Eisenmenger syndrome and a PASP of 136 mm Hg has been excluded).](image)

**Table 2—IVUS Indexes in the Lower Lobes vs Hemodynamic Data**

<table>
<thead>
<tr>
<th>Indexes</th>
<th>PASP</th>
<th>PVR</th>
<th>Indexed PVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>MWT</td>
<td>0.56</td>
<td>0.0005</td>
<td>0.41</td>
</tr>
<tr>
<td>Percent WT</td>
<td>0.41</td>
<td>0.01</td>
<td>0.30</td>
</tr>
<tr>
<td>MLD/MWT</td>
<td>-0.35</td>
<td>0.04</td>
<td>-0.24</td>
</tr>
<tr>
<td>WA</td>
<td>0.35</td>
<td>0.04</td>
<td>0.22</td>
</tr>
</tbody>
</table>

*MLD = minimal lumen diameter.*

**Table 3—ET Levels and IVUS Indexes for Upper Lobe**

<table>
<thead>
<tr>
<th>Indexes</th>
<th>Aorta</th>
<th>Pulmonary Artery</th>
</tr>
</thead>
<tbody>
<tr>
<td>WA</td>
<td>0.58</td>
<td>0.05</td>
</tr>
<tr>
<td>TVA</td>
<td>0.51</td>
<td>0.001</td>
</tr>
<tr>
<td>TVD</td>
<td>0.73</td>
<td>0.007</td>
</tr>
<tr>
<td>LA</td>
<td>0.67</td>
<td>0.02</td>
</tr>
<tr>
<td>MLD</td>
<td>0.56</td>
<td>0.058</td>
</tr>
</tbody>
</table>

In *vivo* has led to the rapid growth of the use of IVUS in the coronary circulation in the past few years. Although this technique also has been safely performed in PAs in humans, thus providing dynamic two-dimensional images, its clinical use in this vascular tree has been more limited. Nevertheless, IVUS has shown diagnostic applications in acute and chronic pulmonary thromboembolic disease. In addition, it has been utilized in the evaluation of surgical and mechanical interventions such as PA angioplasty or lung transplantation.
the patient with Eisenmenger syndrome and a PASP of 136 mm Hg were excluded. These weak correlations were expected, considering those observed between hemodynamics and histology in previous studies. The value of pulmonary hemodynamics as a "gold standard" is, therefore, relatively limited, and this created the impetus for comparing IVUS findings with another marker of pulmonary vascular disease.

**Relationship Between IVUS Findings and ET Levels and Extraction**

ET levels correlated directly with the severity of arterial wall hypertrophy on IVUS. This further supports the value of ET as a marker of vascular abnormalities in PH. Giaid et al previously demonstrated that the expression of ET-1 was increased in PA endothelial cells in patients with PH. Furthermore, plasma ET-1 levels have been shown to correlate with PA pressure and PVR in patients with congestive heart failure and other causes of secondary PH.

The pulmonary extraction of ET was correlated inversely with upper-lobe arterial WA on IVUS. Pulmonary ET-1 clearance is mediated by the endothelial ET-B receptor. Pulmonary clearance of ET-1 is reduced in secondary PH induced by monocrotaline in rats as well as in the rat myocardial infarction model. A reduction in pulmonary ET-1 clearance may therefore suggest pulmonary vascular endothelial dysfunction. Taken together with previous reports and with the rest of our data, the significant correlations between wall hypertrophy and ET extraction and levels found in our study further support the validity of IVUS in the assessment of pulmonary vascular disease.

As was the case for arterial WA, upper-lobe TVA correlated inversely with ET extraction and directly with ET levels. Two mechanisms could account for these particular correlations. Progressive vascular hypertrophy and lumen narrowing as pulmonary vascular disease becomes more severe may have prevented catheter passage distally and may have resulted in a systematic difference in the generation of distal PAs that was assessed. Alternatively, vascular remodeling may have occurred, causing the external elastic membrane to enlarge as wall hypertrophy became more severe.

There was no correlation in our study between

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**Table 4—Influence of the Etiology of PH on IVUS, Hemodynamic, and ET-1 Results**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Mitral Stenosis (n = 16)</th>
<th>Other Etiologies (n = 14)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IVUS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper lobe WA, mm²</td>
<td>1.67 ± 0.44</td>
<td>2.79 ± 1.64</td>
<td>0.03</td>
</tr>
<tr>
<td>Upper lobe MWT, mm</td>
<td>0.20 ± 0.07</td>
<td>0.30 ± 0.13</td>
<td>0.03</td>
</tr>
<tr>
<td>Hemodynamics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indexed PVR, WU × m²</td>
<td>7.00 ± 5.70</td>
<td>3.56 ± 3.05</td>
<td>0.02</td>
</tr>
<tr>
<td>ET-1 Extraction, %</td>
<td>47 ± 17.8</td>
<td>26 ± 10.5</td>
<td>0.02</td>
</tr>
<tr>
<td>Aorta, pg/mL</td>
<td>1.31 ± 0.66</td>
<td>1.68 ± 0.75</td>
<td>0.03</td>
</tr>
<tr>
<td>PA, pg/mL</td>
<td>0.85 ± 0.47</td>
<td>1.80 ± 0.98</td>
<td>&lt; 0.01</td>
</tr>
</tbody>
</table>

*Values given as mean ± SD, unless otherwise indicated.
IVUS indexes in the lower lobes and both ET levels and extraction. The reasons for these findings are not entirely clear. Considering that we have shown that structural abnormalities were significantly more severe in the lower lobes, it is possible that the pulmonary abnormalities process associated with PH begins in this region because of the higher hydrostatic pressure. The presence of pulmonary vascular disease would be more uniformly present across patients in the lower lobes than in the upper lobes, as exemplified by the ratios of the percent WT and MLD/MWT. Extension of the process to the upper lobes then would follow to a variable degree that would represent a better discriminator of the severity of pulmonary vascular disease. This may explain the better correlations observed between IVUS abnormalities in the upper lobes and both ET-1 levels and extraction.

**Influence of the Etiology of PH**

Since more than half the patients studied had mitral stenosis, we tried to see whether IVUS could bring additional insight into the evaluation of this subgroup of patients. PH in mitral stenosis is remarkably reversible, even if it is hemodynamically severe prior to intervention. Thus, it is possible that this subgroup could present less severe structural abnormalities for the same degree of PH. This indeed has been previously demonstrated by histologic studies. We found that wall hypertrophy on IVUS was significantly less pronounced in patients with mitral stenosis despite a trend for higher pulmonary pressures compared to other patients in our study. Additionally, the pulmonary extraction of labeled ET was greater and plasma levels of ET-1 were significantly lower in patients with mitral stenosis. Our group without mitral stenosis, however, contained patients with PH of various etiologies, and this represents a limitation of this subanalysis. This analysis nevertheless suggests that IVUS-derived indexes may provide additional information and could be a better predictor for the reversibility of PH, but this conclusion remains speculative and will require future studies.

**Conclusion**

IVUS brings additional useful information to the evaluation of patients with PH. IVUS confirms *in vivo* the *in vitro* observation of greater vascular hypertrophy in the more dependent regions of the lungs. IVUS-derived indexes correlate with classic hemodynamic indexes of PH and with two biochemical markers of PH, plasma ET-1 levels and reduced ET-1 clearance. Additional studies are necessary to determine whether the structural information derived from IVUS may help in the evaluation of the different etiologies of PH and the prediction of their reversibility.

**ACKNOWLEDGMENTS:** The authors thank Joanne Vincent and Nathalie Ruel for their technical assistance, and Suzanne Taillefer for her help in the preparation of the manuscript.

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