Relationship between haemodynamics and morphology in pulmonary hypertension

A quantitative intravascular ultrasound study*

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Background
Intravascular ultrasound imaging of the pulmonary arteries has been demonstrated to be a reliable method of quantifying vessel diameter, luminal area and pulsatility. Simultaneous measurement of flow velocity and its response to vasodilators allows the relationship between morphology and functional compromise to be studied, especially endothelial dysfunction.

Methods
In 51 patients (mean age=49.8 ± 12.6 years, 17 female) we performed right heart catheterization and simultaneous intravascular ultrasound of pulmonary artery branches. The patients were divided in two groups: group 1 with normal pulmonary artery pressure and pulmonary vascular resistance, and group 2 with pulmonary hypertension (peak pulmonary artery pressure ≥30 mmHg and/or mean pulmonary artery pressure ≥20 mmHg). Vessel wall and lumen were studied using a 2.9 F intravascular ultrasound catheter with a 30 MHz phased array transducer. Measurement of blood flow velocity was accomplished by a Doppler flow wire (0.018 inch). The maximal flow change during acetylcholine infusion (adjusted to 10⁻⁶, 10⁻⁵, and 10⁻⁴ M concentration in the blood vessel) was measured.

Results
There were no significant differences between groups 1 and 2 with respect to age (48.5 ± 14.3 years vs 50.3 ± 12.3 years; P=ns), gender (4 female/8 male vs 13 female/26 male; P=ns), luminal area of the vessel segment in which the intravascular ultrasound measurements were obtained (11.8 ± 6.1 mm² vs 16.7 ± 14.3 mm²; P=ns), internal diameter (3.9 ± 1.2 mm vs 4.2 ± 1.7 mm; P=ns), and external diameter (6.1 ± 1.3 mm vs 6.9 ± 2.1 mm; P=ns). Cross-sectional images of the pulmonary artery wall demonstrated a single ring with high echodensity with a thin inner layer regarded as intima in group 1. In contrast, the majority of patients (n=35/39) in group 2 demonstrated a thickening of the intimal layer and/or a disturbance of layering of the echogenic arterial wall. The relative wall thickness was higher in group 2 than in group 1 (22.5 ± 10.4% vs 15.3 ± 6.5%; P<0.05). There were no significant correlations between pulmonary artery pressure and area change in the cardiac cycle, acetylcholine-dependent increase in pulmonary flow and morphological changes in the vessel wall.

Conclusion
We conclude that intravascular ultrasound is capable of detecting morphological changes in the pulmonary vessel wall in pulmonary hypertension and that vessel wall hypertrophy of small pulmonary segment arteries, as detected by intravascular ultrasound, is not predictive of functional vasodilatory response of resistance vessels of the same vessel area.


Key Words: Pulmonary hypertension, endothelial dysfunction, heart failure, intravascular ultrasound imaging, acetylcholine.

Introduction
Histological studies have documented pulmonary artery abnormalities in primary and secondary pulmonary hypertension. High-frequency, intravascular ultrasound imaging has been shown to yield circumferential images of peripheral and coronary arteries, demonstrating atherosclerotic lesions, intimal tears, dissections and intravascular thrombi. It can directly monitor changes in the cross-sectional area of the vessel and demonstrate abnormalities in the vessel wall.

Intravascular ultrasound of pulmonary arteries provides useful information for assessing the degree of vascular disease. Imaging of proximal and distal pulmonary arteries in both animals and normal...
human subjects has been performed using different intravascular ultrasound transducers\(^2\). Recently, intravascular ultrasound of the pulmonary arteries has been validated as a reliable method of quantifying luminal area, pulsatility, and in describing vessel wall characteristics\(^3,4\). Several investigations delineated the potential value of intravascular ultrasound in pulmonary vessels in determining morphology in chronic thromboembolic disease\(^5,6\), peripheral pulmonary stenosis\(^7\), primary pulmonary hypertension\(^8\), and in chronic heart failure\(^9,10\).

The aim of this study was to correlate morphological changes in pulmonary conductance vessels assessed by intravascular ultrasound with reversibility of pulmonary vascular resistance in patients with pulmonary hypertension.

**Methods**

In patients \((n=51; 17 \text{ female}; \text{ mean age } 49.8 \pm 12.6 \text{ years})\) undergoing cardiac catheterization, intravascular ultrasound images of the pulmonary arterial circulation were obtained. The patients were divided in two groups: group 1 with normal pulmonary artery pressure and pulmonary vascular resistance, and group 2 with pulmonary hypertension (peak pulmonary artery pressure $>30 \text{ mmHg}$ and/or mean pulmonary artery pressure $>20 \text{ mmHg}$).

Group 1 \((n=12; \text{ mean age } 48.5 \pm 14.3 \text{ years}; 4 \text{ female})\) included eight patients without any objective evidence of cardiovascular disease or metabolic or systemic disorders affecting the cardiovascular system. They had been catheterized because of atypical chest pain, and four patients had coronary artery disease with normal systolic and diastolic left ventricular function.

Group 2 \((n=39; 13 \text{ female}; \text{ mean age } 50.3 \pm 12.3 \text{ years})\) included patients with primary pulmonary hypertension \((n=3)\), secondary pulmonary hypertension due to dilative cardiomyopathy \((n=16)\), heart failure due to coronary artery disease \((n=12)\), pulmonary embolism \((n=3)\), ventricular septal defect \((n=2)\), atrial septal defect \((n=1)\), chronic heart failure due to aortic regurgitation \((n=1)\) and systemic arterial hypertension \((n=1)\).

**Cardiac catheterization**

All catheter procedures were performed via right femoral arterial and venous access sites. Right and left heart pressures were measured with standard catheters via femoral access and pulmonary vascular resistance was calculated.

**Intravascular ultrasound imaging**

The ultrasound probe and flow wire were advanced through an 8F multipurpose guiding catheter into a pulmonary segment artery using fluoroscopic guidance. Ultrasound and Doppler probes were alternately advanced to the tip of the catheter. We used a 2.9 F/30 MHz phased array intravascular ultrasound probe (CVIS, Cardiovascular Imaging Systems, Inc.). Intravascular ultrasound imaging was performed before exposure to contrast medium. Blood flow velocity was measured by a Doppler flow wire \((0.018 \text{ inch}, \text{ Cardiometrics Inc.})\). Real-time, dynamic, cross-sectional images of the pulmonary artery branches could be obtained in all patients. All images were recorded on videotape, from which quantitative analyses were performed. The analysis and measurements of the intravascular ultrasound recordings were obtained by two independent observers, who were blinded to the haemodynamic results.

The following parameters were analysed and compared with haemodynamic findings: appearance of vessel wall layering, thickening of the intimal layer, internal and external diameter, wall thickness, end-diastolic and end-systolic external and internal vessel luminal areas. The vessel pulsatility was calculated as: end-diastolic minus end-systolic vessel area divided by end-systolic area; and the relative wall thickness was defined as the thickness of the wall divided by the internal vascular diameter in percent.

Acetylcholine infusion was adjusted to the local blood flow, as calculated from vessel area and blood flow velocity, in order to achieve $10^{-6} \text{ M}$, $10^{-5} \text{ M}$, and $10^{-4} \text{ M}$ concentrations of acetylcholine in the vessel investigated. Acetylcholine was infused through the ultrasound catheter flush lumen for a minimum of 3 min intervals. The internal vessel area was measured before and during acetylcholine infusion and remained unchanged. The maximal change in flow velocity during acetylcholine infusion as a percentage of baseline flow velocity was used for the comparison between vasodilator capacity and morphology.

Arterial and pulmonary arterial pressures were recorded continuously during the procedure. Pulmonary capillary wedge pressure was measured only prior to intravascular ultrasound measurements. Flow velocity was determined by averaging the average peak velocity of 10 consecutive cardiac cycles.

**Statistical analysis**

All values were expressed as mean ± standard deviation; a $P$ value less than 0.05 was considered significant. For nominally scaled parameters, independence and homogeneity of distribution were tested by the chi-square test with Yates' correction. For comparison of the groups the paired Student's $t$-test was used; if normality test failed, we used the Mann-Whitney sum test. Baseline flow and flow in response to acetylcholine were analysed using the Wilcoxon matched pairs test.

The intra-observer reproducibility of the two-dimensional measurements was assessed by one
There were no significant differences with respect to age, gender, external and internal vessel diameter, and internal vessel area (Table 1). The relative wall thickness was higher in group 2 than in group 1 ($P<0.05$), and the appearance of layering of the vessel wall in group 2 was abnormal. Abnormal layering of the vessel wall was defined as follows: (1) intimal thickening (>0.2 mm) and/or (2) increased relative vessel wall thickness (>15%) and/or (3) changes in layering (>2 layers and/or disturbances of clear delineation of the layers).

**Intravascular ultrasound in patients with normal pulmonary artery pressure**

In patients with normal pulmonary haemodynamics, the wall of the pulmonary arteries demonstrated a single ring with high echogeneity, differentiation of a small inner layer of lower echogeneity with maximal 0.1 up to 0.2 mm thickness (Fig. 1). The relative wall thickness was 15.3±6.5% and ranged from 10 to 32% (other parameters see Table 1).

**Intravascular ultrasound in patients with pulmonary hypertension**

Only four of 39 patients with pulmonary hypertension had a vessel wall architecture similar to those with normal pulmonary artery pressures. In the majority of patients there was thickening of the intimal layer (n=35; thickness of the internal layer >0.2 mm) and disturbance of the vessel wall architecture (n=32; Fig. 2). The relative vessel wall thickness was 22.5±10.4% and ranged from 10 to 42% (for other parameters see Table 1). There were no differences between pre- and post-capillary hypertension forms.

**Relationship between haemodynamics and morphology**

There is a clear relationship between morphology of the pulmonary artery vessel wall and haemodynamics in patients with secondary pulmonary hypertension. We demonstrated a significant difference regarding pulmonary artery pressure mean and pulmonary vascular resistance in patients with normal and pathological intravascular ultrasound findings (Fig. 3), but no differences in acetylcholine dependent flow change between patients with normal and pathological intravascular ultrasound findings (Fig. 4). In patients with primary pulmonary hypertension, the number of patients and the range of abnormalities was too small (mean pulmonary artery pressure of 45/54/53 mmHg corresponding to higher values of relative wall thickness of 22/28/36% and acetylcholine-dependent flow increase ranging from 32 to 89%) to draw definitive conclusions. There were no significant correlations between mean pulmonary artery pressure and wall thickness, mean pulmonary artery pressure and vessel area change, acetylcholine dependent increase in pulmonary flow velocity and wall thickness. Furthermore, in patients with secondary pulmonary hypertension, there were no significant differences with respect to age, gender, external and internal vessel diameter, and internal vessel area (Table 1). The relative wall thickness was higher in group 2 than in group 1 ($P<0.05$), and the appearance of layering of the vessel wall in group 2 was abnormal. Abnormal layering of the vessel wall was defined as follows: (1) intimal thickening (>0.2 mm) and/or (2) increased relative vessel wall thickness (>15%) and/or (3) changes in layering (>2 layers and/or disturbances of clear delineation of the layers).

**Results**

The patients' characteristics and haemodynamic findings of the two groups are given in Table 1. Intravascular ultrasound imaging was successful in all 51 patients. Cross-sectional images obtained from different branches displayed similar shapes, which were generally circular except for bifurcation or branching sites. Pulsation of the artery could be recognised in the images. Luminal area and internal diameter could be delineated clearly. The signals caused by adjacent air-filled alveolar structures made it difficult to determine the external diameter and the vessel wall thickness at distal and small branches. A clear delineation of the external wall structure was possible only in 45/51 cases. In the other patients the definition of vessel wall thickness was suboptimal. These data were not included in the calculations.

There were no significant differences with respect to age, gender, external and internal vessel diameter, and internal vessel area (Table 1). The relative wall thickness was higher in group 2 than in group 1 ($P<0.05$), and the appearance of layering of the vessel wall in group 2 was abnormal. Abnormal layering of the vessel wall was defined as follows: (1) intimal thickening (>0.2 mm) and/or (2) increased relative vessel wall thickness (>15%) and/or (3) changes in layering (>2 layers and/or disturbances of clear delineation of the layers).

### Table 1 Haemodynamic and intravascular ultrasound data

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group 1</th>
<th>Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>12</td>
<td>39</td>
</tr>
<tr>
<td>Age</td>
<td>48.5±14.3</td>
<td>50.3±12.3</td>
</tr>
<tr>
<td>Gender</td>
<td>f=m</td>
<td>f=m</td>
</tr>
<tr>
<td>PAP peak (mmHg)</td>
<td>19.7±3.9</td>
<td>58.3±26.5**</td>
</tr>
<tr>
<td>PAP mean (mmHg)</td>
<td>11.7±2.9</td>
<td>37.8±16.1**</td>
</tr>
<tr>
<td>PVR (wu)</td>
<td>1.1±0.2</td>
<td>47.7±3.9**</td>
</tr>
<tr>
<td>Ach (%)</td>
<td>36.6±52.4</td>
<td>40.5±41.3</td>
</tr>
<tr>
<td>Wth (%)</td>
<td>15.3±6.5</td>
<td>22.5±10.4*</td>
</tr>
<tr>
<td>Internal area (mm²)</td>
<td>11.8±6.1</td>
<td>16.7±14.3</td>
</tr>
<tr>
<td>Internal area change (%)</td>
<td>7.5±4.6</td>
<td>12.3±10.9</td>
</tr>
<tr>
<td>Internal diameter (mm)</td>
<td>3.9±1.2</td>
<td>4.2±1.7</td>
</tr>
<tr>
<td>External diameter (mm)</td>
<td>6.1±1.3</td>
<td>6.9±2.1</td>
</tr>
</tbody>
</table>

PAP=pulmonary artery pressure; PVR=pulmonary vascular resistance; Wth=relative wall thickness; Ach=flow increase after acetylcholine-application; f=m=female; n=m=male; †the internal area change was defined as the change of the internal vessel wall during the cardiac cycle (see Methods).

*P<0.05; **P<0.01.
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Figure 1 Real-time cross-sectional ultrasound image from a patient with normal pulmonary arterial pressure. The pulmonary arterial wall appears as a single echogenic ring with no differentiation of separate layers.

Figure 2 Cross-sectional ultrasound image from a patient with severe pulmonary hypertension with intimal thickening and disturbance of the vessel wall architecture.

hypertension due to heart failure (n = 30) there were no significant correlations between haemodynamic (mean pulmonary artery pressure, pulmonary artery pressure peak and pulmonary vascular resistance and morphological parameters (wall thickness, internal vessel area, pulsatility).
Intravascular ultrasound measurement variability

Inter-observer variability ranged from 9.2 to 11%; intra-observer variability ranged from 4.2 to 6.3%. There was a concordant semi-quantitative characterization of the vessel wall architecture in 93% of the analysis of the two observers.

Discussion

In normal subjects, the walls of pulmonary lobar and segmental arteries (diameter more than 2 mm) are comprised of regular, parallel elastic laminae separated by occasional smooth muscle cells and a small amount of collagen. These vessels have a medial layer of circular-orientated smooth muscle cells between the internal and external elastic laminae. The ultrasound catheter can visualize the wall structure of pulmonary arteries with a diameter of more than 2 mm and in normal subjects two layers are seen: an echogenic layer, and a thin internal layer (<0.2 mm) which can be seen using lower echodensity. Previous studies suggested that there is a relationship but no close correlation between pressure and histopathological changes in secondary pulmonary hypertension. However, in primary pulmonary hypertension there appears to be a correlation between mean pulmonary artery pressure, pulmonary vascular resistance and morphology.

The morphological changes may have important implications. When cardiac transplantation is being considered for patients with severe left ventricular dysfunction, the presence of irreversible pulmonary vascular changes is usually regarded as a contraindication and indicates the need for combined heart and lung transplantation. Therefore it is important to establish the severity and reversibility of pulmonary vascular changes. So far, morphological changes in the pulmonary vascular bed can definitively be diagnosed only by lung biopsy. A high complication rate in pulmonary hypertension renders this approach unhelpful. Therefore, it would be advantageous to obtain such structural information in vivo, at the time of cardiac catheterization.

Reports have confirmed the feasibility of intravascular ultrasound, using a 20 MHz transducer, in the evaluation of normal animal and human pulmonary arteries, in patients with pulmonary hypertension, with pulmonary thrombembolic disease, and in patients with heart failure. Pandian et al. demonstrated a good correlation between intravascular ultrasound-derived measurements of pulmonary artery area, diameter, and wall thickness in vivo and anatomical measurements in vitro using a 20 MHz ultrasound transducer in pulmonary artery segments of dogs.

According to these studies, intravascular ultrasound accurately measured the luminal size, but it was unable to identify the degree of intimal hyperplasia because of the homogenous echogenicity across the different layers of the artery and could not distinguish between media and intima. The thickness of the single
wall layer evident on intravascular ultrasound was, on average, twice the thickness of combined intima plus media and could therefore represent a combination of intima, media and adventitia\textsuperscript{1,11,14,15}\).

In our study there was ultrasonic evidence of some of the morphological changes associated with pulmonary hypertension and in particular of intimal thickening and proliferation. The appearance of a three layered vessel wall could be due to dilation of the small pulmonary arteries and represent disruption of the normally elastic pulmonary arterial wall architecture. We confirmed the findings of other studies, that there is no close correlation between pressure and morphological changes in secondary pulmonary hypertension\textsuperscript{11}.

This technique provides the opportunity to assess the pulsatility and vasoreactivity of the pulmonary vessels. Pulmonary vascular stiffness was assessed using intravascular ultrasound-derived pulmonary artery area changes in the cardiac cycle. Loss of normal vasoreactive response has been described in the pulmonary arteries of patients with congestive heart failure using intravascular ultrasound\textsuperscript{1,12,13}. It has been shown that the endothelial response of pulmonary arteries in patients with chronic heart failure who maintain normal pulmonary artery pressures inhibit vasoconstriction\textsuperscript{1,15,16}. The function of the endothelium in pulmonary hypertension demonstrates a major role of the pulmonary artery endothelium in preventing pulmonary hypertension via attenuating vasoconstriction\textsuperscript{16}. We demonstrated a great variance in acetylcholine response and pulmonary artery area change without any significant correlation between the extent of morphological changes in the conductive vessels and the endothelial function of the resistance vessels. The results suggest that in pulmonary hypertension there are two different pathophysiological mechanisms: the morphological changes of the conductance vessels as a secondary phenomenon on the one hand and the endothelial function of the resistance vessels on the other\textsuperscript{1,16}. It has been demonstrated that, in patients with chronic heart failure and secondary pulmonary hypertension, an endothelium-mediated flow reserve of the resistance vessels exists, independent of the extent of morphological changes in the conductance vessels. In addition, the pulsatility of the conductance vessels seems to be independent from the extent of morphological changes of the vessel wall as assessed by intravascular ultrasound. Apparently the increase in pulmonary artery pressure results in a remodelling of the conductance vessel wall independent of the cause and of the endothelium-dependent vasodilatory reserve of the resistance vessels.

These results and conclusions are in accordance with histopathological studies, which could demonstrate reversibility of morphological changes in secondary pulmonary hypertension due to mitral valve stenosis after mitral valve replacement up to the state of plexiformic lesions\textsuperscript{1,11,14}, which is probably irreversible.

Clinical implications and conclusions

Various diseases can result in histopathological changes in the pulmonary arterial vessel wall. Alterations in the vasoresponsiveness, the degree of increase in pulmonary vascular resistance, the severity of pulmonary hypertension, the state of reversibility or irreversibility of morphological changes all have important clinical, prognostic, and therapeutic implications. In addition to pulmonary contrast arteriography and haemodynamic measurements, intravascular ultrasound may provide more information with which to evaluate the severity of the structural and functional changes of the pulmonary artery wall and can demonstrate impairment of endothelium-dependent pulmonary artery relaxation. We could demonstrate the ability of intravascular ultrasound and Doppler to assess morphological and functional alterations in pulmonary hypertension, which opens new insights into the disease without the higher risk of histological assessment via lung biopsy. Morphological changes, i.e. hypertrophy and intima proliferation, and endothelial dysfunction are two independent mechanisms effective at different localizations (first of the conductive vessels, secondly of the resistance vessels).

References

[10] Porter TR, Taylor D, Pandian NG, Nixon JV, Vetrovec GW, Mohanty PK. Pulmonary arterial dynamics in congestive


