Impairment of Endothelium-Dependent Pulmonary Artery Relaxation in Children With Congenital Heart Disease and Abnormal Pulmonary Hemodynamics

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Background. Endothelial injury may be an important event in the pathophysiology of pulmonary hypertension. We therefore investigated whether endothelial dysfunction occurs early in children with congenital heart defects who are at risk of developing pulmonary vascular disease.

Methods and Results. In 25 children aged 3–16 years, we studied the response of the pulmonary circulation to graded infusions of acetylcholine (an endothelium-dependent vasodilator) and nitroprusside (a dilator not dependent on endothelial function). Diameter of a bronchopulmonary segment artery and pulmonary blood flow velocity were measured using quantitative angiography and intra-arterial Doppler catheters in 10 children aged 4–16 years with normal pulmonary hemodynamics (controls), seven children aged 3–12 years with left-to-right shunt lesions resulting in increased pulmonary flow, and eight children aged 3–14 years with established pulmonary vascular disease. In the controls, there was a dose-dependent increase in flow velocity in response to acetylcholine (maximal increase, 93±7%) and in response to nitroprusside (51±8%). In contrast, in patients with pulmonary vascular disease, the response of flow velocity to similar doses of acetylcholine (33±7%, p<0.01) and nitroprusside (7±13%, p<0.01) were impaired. In the patients with high pulmonary flow, there was an impaired response to acetylcholine (46±9%, p<0.01), but response to nitroprusside was preserved (42±8%, p>0.10), consistent with endothelial dysfunction. Arterial diameter was unchanged during acetylcholine infusion in all subjects and increased only modestly in response to nitroprusside (±10%), indicating that the major site of action of each agent is distal to the segmental pulmonary arteries.

Conclusions. Endothelium-dependent pulmonary artery relaxation can be demonstrated in vivo and is impaired in young patients with increased pulmonary flow secondary to congenital heart disease. This impairment may be an important early event in the pathogenesis of pulmonary vascular disease.

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Key Words • endothelium • pulmonary hypertension • children/infants • pulmonary vascular disease

Pulmonary vascular disease (PVD) is one of the most serious complications of congenital heart disease. Once established, it is progressive and irreversible, despite correction of the underlying defect or medical treatment, and leads to premature death. Although clinical risk factors for the development and progression of PVD are recognized, the pathogenesis remains poorly understood. Many studies have been based on histological examination of lung tissue, often in advanced disease. Newer data have indicated a potential role for endothelial dysfunction as an early event in the pathophysiology of PVD, preceding morphological changes. Healthy vascular endothelium is known to produce endothelium-derived relaxing factor (EDRF), and failure of secretion of EDRF by damaged pulmonary endothelium may lead to vasoconstriction. Endothelial dysfunction may also predispose to thrombosis and abnormal cellular interactions with neutrophils and macrophages and thereby lead to more extensive vascular damage.

Structural abnormalities of the endothelial cells have been demonstrated in the first years of life in children with congenital heart disease and pulmonary hypertension, and recent in vitro physiological research has revealed impairment of endothelium-dependent vasorelaxation in small to medium-sized pulmonary arteries from the explanted human adult lung in patients with Eisenmenger's syndrome or severe chronic obstructive lung disease.

Despite these extensive in vitro observations, endothelium-dependent pulmonary artery relaxation has not been investigated systematically in vivo. We have therefore examined pulmonary endothelial and smooth muscle functions in children with normal and abnormal
pulmonary hemodynamics. Our aim was to demonstrate endothelium-dependent relaxation in control subjects and to determine whether endothelium-dependent vasorelaxation is impaired in young patients with congenital heart disease and increased pulmonary flow and/or resistance.

Methods

Patients

We studied 25 children who were undergoing routine diagnostic catheterization for evaluation of congenital heart disease. They were classified into three groups on the basis of their hemodynamic findings. Group 1 consisted of 10 control patients aged 4–16 years with normal pulmonary arterial pressure, blood flow, and resistance (≤1.5 units · m⁻², using oxygen saturations, assumed oxygen consumption, and the Fick principle). Because normal people do not undergo cardiac catheterization, we selected as our control subjects those with congenital heart lesions that did not alter pulmonary hemodynamics; six subjects had left heart obstructive lesions such as aortic stenosis or coarctation but a normal left ventricular diastolic pressure, three subjects had tiny intracardiac defects with no detectable left-to-right shunt, and one child had a fistula from the left coronary artery to the left atrium. Group 2 consisted of seven children aged 3–12 years with a left-to-right shunt and a pulmonary-to-systemic flow ratio of >1.5 (range, 1.7–5.0); three of these subjects had an atrial septal defect, three had a restrictive ventricular septal defect, and one had a persistent ductus arteriosus. Group 3 consisted of eight children aged 3–14 years with a pulmonary vascular resistance of ≥6 units · m⁻² before and after administration of 100% oxygen; six had congenital heart disease (ventricular septal defect in five cases, two of whom also had transposition of the great arteries, and persistent ductus arteriosus in one), and two had primary pulmonary hypertension.

Study Design

All medications other than diuretics were discontinued at least 24 hours before the study. Diagnostic cardiac catheterization was performed under local anesthesia and benzodiazepine sedation via a percutaneous femoral approach, and hemodynamic data were obtained. Heparin (50 units/kg) and diazepam (0.1–0.3 mg/kg) were administered intravenously before the vascular study began. Studies were performed before diagnostic angiography. Arterial blood gases were taken at the beginning of, during, and at the end of each study to exclude carbon dioxide retention and to document respiratory stability throughout the infusion protocol. Depending on patient size, a 5F, 6F, or 7F long biopsy sheath (Cordis, UK; Cook, UK) was inserted into the left or right lower lobe pulmonary artery. A 20-MHz pulsed Doppler crystal side-mounted on a 3F catheter (Wessex Medical, Midhurst, UK) was positioned through the biopsy sheath into a straight segment of the medial or posterior branch of the lower lobe pulmonary artery. If neither of these branches had a straight segment, the Doppler catheter was positioned in the distal lower lobe artery (Figure 1). Position in the center of this vessel was confirmed by “sighting” angiography and a stable flow–velocity signal with minimal noise. The Doppler catheter was connected via a flow–velocimeter box (Millar Instruments Inc., Houston, Tex.) to a multichannel recorder, which displayed ECG, pulmonary arterial pressure, and mean or phasic Doppler flow velocity. Measurement of flow velocity using intra-arterial Doppler catheters has been previously validated; the catheters are nonobstructing, steerable, safe, and accurate. Side-mounted catheters may be less accurate at very low-flow rates but have high accuracy and reproducibility for the measurement of flow ratios (i.e., relative changes in flow velocity in a given subject during different interventions).

Serial infusions were made at a rate of 0.8 ml/min via the Doppler catheter into the segmental pulmonary artery in the following sequence using an infusion pump (Harvard Apparatus, Edenbridge, UK): 1) a 4-minute control infusion (5% dextrose), 2) three 4-minute acetylcholine infusions each with final estimated concentrations of 10⁻⁵, 10⁻⁴, and 10⁻³ M, respectively, 3) an 8-minute repeat control infusion, and 4) a 4-minute infusion of sodium nitroprusside at a rate of 0.1 μg/kg/min. If the systemic arterial pressure was stable, the nitroprusside infusion was continued at twice the above rate for an additional 2 minutes. In the group of patients with increased pulmonary flow, the infusion rate was adjusted to account for the degree of flow increase so that the vasculature was exposed to similar concentrations of vasodilators in each patient (e.g., if there was a
pulmonary-to-systemic flow ratio of 2.0, the infusion rate was doubled to 1.6 ml/min). Furthermore, a 100-fold dose range of acetylcholine was used in each subject (10^{-4} to 10^{-6} M). Throughout the protocol, the heart rate, systemic and pulmonary arterial pressures, and ECG were monitored continuously. Thirty seconds before the end of each infusion, Doppler flow velocities were recorded. Values for mean and phasic flow velocities were calculated automatically and read directly from the chart recorder. Flow velocity during each infusion was expressed as a percentage relative to the velocity during the first control infusion. The study protocol was approved by the institution's committee on ethical practice, and informed written consent was obtained from the parents of all subjects.

Quantitative Angiography

Before the end of each infusion, a single-plane digital subtraction angiogram (Digitron 2 System, Siemens) was performed in the anteroposterior projection or with a few degrees of left anterior oblique angulation if the Doppler catheter overlay the left cardiac border. Contrast was injected via the long biopsy sheath; one-third-strength nonionic contrast material (Ultravist, Schering, UK) in normal saline (0.3–0.5 ml/kg) was administered at a rate of 0.3–0.5 ml/kg/sec via a power injector (Angiomat, Phillips, UK) to optimize the quality and reproducibility of the opacification. After each angiogram (biplane system, Siemens, UK), fluoroscopy was performed in anteroposterior and lateral projections to confirm the stability of the Doppler catheter position.

For each angiogram, the first four diastolic frames with good, even opacification of the lower lobe artery were selected. Analysis was performed by an observer blinded to the patient's diagnosis. Each frame was magnified at a power of ×16, and the diameter of a segment of straight artery just below the tip of the Doppler catheter was measured. The same arterial segment was analyzed for each infusion, and a computerized measurement of diameter was obtained using the “percent stenosis” software package (Siemens). Automated quantitative angiography has been validated as an accurate and reproducible method for the measurement of vessel size, especially in vessels >1 mm in diameter.21–23 This technique has been used by others24,25 to detect changes as small as 0.1 mm in coronary artery diameter. Arterial diameter was calculated in pixels on a 512×512 matrix and expressed as percentage relative to the diameter of the vessel in the first control infusion.

Statistical Analysis

All data are expressed as mean±SEM. Results for each experimental condition were expressed as a percentage relative to the first control value. The t test for unpaired values was used for comparisons of pulmonary blood flow velocities and arterial diameters between the control group and each of the groups with abnormal hemodynamics. The relations between percent flow-velocity increase and vessel diameter were assessed by linear regression analysis. Statistical significance was inferred at a value of p<0.05.

Results

Hemodynamic and Respiratory Monitoring

In 24 of 25 patients, heart rate, arterial blood gas measurements, and systemic arterial and pulmonary arterial pressures remained constant throughout the infusion protocol. In one control patient, all parameters were stable until minute 3 of the nitroprusside infusion, when systemic hypotension and tachycardia were noted; these values returned promptly to normal on cessation of the drug infusion. All subjects tolerated the procedure well.

Control Subjects

Pulmonary hemodynamics were normal in all subjects, with a mean pulmonary artery pressure of 11±1 mm Hg and resistance of 1.0±0.1 units · m⁻² (Table 1 and Figures 2 and 3). A dose-dependent increase in flow velocity occurred in response to acetylcholine; during infusions of 10⁻⁴, 10⁻⁷, and 10⁻⁶ M acetylcholine, flow velocity increased by 16±7%, 60±10%, and 93±7%, respectively (Figure 2). Flow velocity also increased in response to the nitroprusside infusion (51±8%). The diameter of arteries measured was 5.3±0.8 mm, with a wide range of values (2.1–10.5 mm), reflecting the wide range of age and size of the children. Diameter was not significantly changed during the acetylcholine infusions (1±1%) and increased modestly in response to nitroprusside infusion (5±1%, p<0.05 compared with baseline diameter). There was no relation between the size of the vessel measured and the increase in flow velocity to acetylcholine or nitroprusside for either the control subjects (r=0.40 and 0.43, respectively; p=NS) or the entire group of 25 subjects (r=0.33 and 0.10, respectively; p=NS).

Increased Pulmonary Flow Subjects

In subjects with increased pulmonary flow, pulmonary arterial pressure (mean, 12±1 mm Hg) and resistance (0.9±0.1 units · m⁻²) were normal in these patients, and the average pulmonary-to-systemic flow ratio was 2.4 (range, 1.7–5.0) (Table 1). A dose-dependent increase in flow velocity in response to acetylcholine also occurred but was significantly less than in control subjects (flow velocity increase after acetylcholine, 10⁻⁶ M; 46±9%; p<0.01 compared with controls). The two subjects with the highest increases in flow velocity (75% and 80%) had pulmonary-to-systemic flow ratios of 2.3 and 2.1, respectively (mid range for this group). Endothelium-independent dilation, as reflected by the flow-velocity increase in response to nitroprusside, was similar to that in control subjects (42±8%, p>0.10). Vessel diameter was not significantly different from that of the control children (6.8±1.2 mm; range, 2.4–11.5 mm). Diameter was unchanged in response to acetylcholine (2±1%) and increased slightly in response to nitroprusside (6±2%, p<0.05 compared with baseline).

Pulmonary Vascular Disease Subjects

In subjects with PVD, mean pulmonary artery pressure was markedly elevated (63±3 mm Hg) and pulmonary resistance was 6.4±16.0 units · m⁻² (mean, 9.6 units · m⁻²) (p<0.01 compared with controls). There was a right-to-left shunt in one patient, no shunt in two patients, and a
small left-to-right shunt in five patients. The responses to acetylcholine and nitroprusside were similar in the six patients with congenital heart disease and the two patients with primary pulmonary hypertension. The increases in flow velocity to both acetylcholine (maximal response, 33±7%) and nitroprusside (7±13%) were significantly lower than those in control subjects (p<0.01 for both). Arterial diameter was similar to that of controls (5.5±1.0 mm; range, 2.0–11.0 mm) and changed little during the acetylcholine (−3±2%) and nitroprusside infusions (−1±1%).

Discussion

The present study demonstrates that endothelium-dependent vasodilation occurs in the lungs of children with normal pulmonary hemodynamics. Given that there was almost no change in segmental artery diameter in response to acetylcholine but a large increase in flow velocity, the major site of endothelium-dependent vasorelaxation must occur distal to the level of the large arteries.

The vascular responses of patients with established PVD are grossly abnormal, with impaired responses to both endothelium-dependent and -independent agents. Furthermore, impaired endothelium-dependent vasorelaxation is evident in some children with congenital heart disease with increased pulmonary flow but without established PVD, suggesting that physiologically important endothelial dysfunction is an early event in such patients.

Most studies of the pathogenesis of PVD complicating congenital heart disease have involved histological study of lung tissue, often from subjects with late stages of the disease. Conclusions from these studies are limited because of imperfect correlation between structural and hemodynamic findings and a lack of information about the early stages of the disease. Emphasis has now shifted from morphology to the functional and metabolic state of the endothelium; thus, effective ways

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**TABLE 1. Vascular Responses of Pulmonary Arteries to Vasodilators**

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (controls) (n=10)</th>
<th>Group 2 († Qp) (n=7)</th>
<th>Group 3 (PVD) (n=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) (range)</td>
<td>9±1 (4–16)</td>
<td>7±1 (3–12)</td>
<td>8±1 (3–14)</td>
</tr>
<tr>
<td>Qp/Qs</td>
<td>1.0</td>
<td>2.4 ±0.4§</td>
<td>1.2 ±0.1</td>
</tr>
<tr>
<td>PAP (mean, mm Hg)</td>
<td>11±1</td>
<td>12±1</td>
<td>63±3§</td>
</tr>
<tr>
<td>PAR (units · m⁻²)</td>
<td>1.0±0.1</td>
<td>0.9±0.1</td>
<td>9.6±1.2§</td>
</tr>
<tr>
<td>Diameter (mm) (range)*</td>
<td>5.3±0.8 (2.1–10.5)</td>
<td>6.8±1.2 (2.4–11.5)</td>
<td>5.5±1.0 (2.0–11.0)</td>
</tr>
<tr>
<td>Maximum increase in FV (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACh†</td>
<td>93±7</td>
<td>46±9§</td>
<td>33±7§</td>
</tr>
<tr>
<td>NP</td>
<td>51±8</td>
<td>42±8</td>
<td>7±13§</td>
</tr>
<tr>
<td>Maximum increase in diameter (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACh</td>
<td>1±1</td>
<td>2±1</td>
<td>−3±2</td>
</tr>
<tr>
<td>NP</td>
<td>5±1§</td>
<td>6±2†</td>
<td>−1±1§</td>
</tr>
</tbody>
</table>

Qp, pulmonary blood flow; PVD, pulmonary vascular disease; Qs, systemic blood flow; PAP, pulmonary artery pressure; PAR, pulmonary arteriolar resistance; FV, flow velocity; ACh, acetylcholine; NP, nitroprusside.

*Diameter of the arterial segment measured by quantitative angiography.
†Maximum increase in the flow velocity in response to acetylcholine was not significantly different between groups 2 and 3 (p>0.10).
§p<0.05 compared with baseline (control) diameter.
††p<0.05 compared with control subjects.

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**FIGURE 2. Plot of change in pulmonary arterial flow velocity in response to three doses of acetylcholine (ACh1, ACh2, and ACh3 are equal to estimated local concentrations of 10⁻⁸, 10⁻⁷, and 10⁻⁶ M, respectively) and to nitroprusside (NP) (0.1–0.2 μg/kg/min) in control subjects, those with high pulmonary flow († Qp) and normal resistance, and those with established pulmonary vascular disease (PVD).**

**FIGURE 3. Scatterplots of maximal increase in flow velocity in pulmonary arteries in response to acetylcholine and nitroprusside in each control patient, each patient with increased pulmonary flow († Qp), and each with pulmonary vascular disease (PVD). Each horizontal line indicates the group mean. Solid circles represent the two subjects with primary pulmonary hypertension.**
of studying endothelial function in vivo have been sought. In systemic arteries, this has been accomplished successfully by studying changes in vascular diameter and flow velocity in response to infused vasodilator substances.27-29 We have now applied these principles to the in vivo study of the pulmonary circulation, using acetylcholine as an endothelium-dependent vasodilator and comparing its effects with those of an endothelium-independent vasodilator, sodium nitroprusside. These vasodilator agents were infused into a subsegmental pulmonary artery and caused no systemic hypotension or tachycardia, thus excluding a pulmonary pressor response related to a reflex rise in cardiac output as the cause of the observed increases in pulmonary flow.

All subjects were catheterized under local anesthetic to avoid any potential influence of anesthesia agents on pulmonary endothelial function, and relatively long infusion times were chosen to ensure that any transient effect of contrast material on the endothelium would have worn off; use of diluted contrast at normal osmolality minimized these effects, and in our pilot studies, contrast injection caused a reversible rise in flow velocity that returned to baseline values within 60 seconds. In our calculations of diameter and flow velocity, relative changes rather than absolute values have been used; with children of different ages and sizes, we have used each child as their own control and normalized each observation to the first control result for each case. Changes in relative rather than absolute flow velocity have also been used extensively by investigators of the coronary circulation.29,30 Calculation of vascular resistance was based on assumed rather than measured oxygen consumption; the potential error thereby introduced is likely to be of a much smaller magnitude than the large differences between the groups.

In 1957, Fritts et al11 reported that an infusion of acetylcholine into the lungs of normal subjects produced a decrease in pulmonary arterial pressure and that this effect was exaggerated if the pulmonary circulation was preconstricted by hypotension. In the intact lungs of cats and rabbits, acetylcholine produces vasoconstriction; only in preconstricted arteries does acetylcholine induce vasodilation.32-35 However, numerous studies on intact humans have shown that acetylcholine lowers pulmonary pressure and vascular resistance31,36-39; this response is now thought to be due to the release of relaxing factors from the endothelium that act on underlying smooth muscle in vessels with basal vasoconstrictor tone. This hypothesis has been supported by in vitro studies46,17 and is confirmed by our findings in children.

In our subjects, the dilation of the conduit arteries was less than has been found during in vitro studies of medium-sized pulmonary arteries of animals35,40 and humans.16,17,41,42 Lack of dilation of large pulmonary arteries in response to vasodilators has recently been found in vivo in normal adult subjects.43,44 The discrepancy between the in vitro and in vivo results may be due to the fact that in the in vitro studies, the pulmonary artery segments were preconstricted, usually with phenylephrine, whereas in our in vivo study this was not done. Other contributing factors include lower doses of vasodilators that are used in vivo, smaller arteries being studied in vitro, and/or insensitivity of the angiographic technique to very small changes in diameter. Despite this, our study and the research of others43 suggest that the major site of endothelium-dependent pulmonary artery relaxation in control subjects studied in vivo occurs distal to the bronchopulmonary segment arteries.

In patients with established PVD, we found an impaired response to both endothelium-dependent and -independent agents. This suggests that there is a combination of endothelial dysfunction and smooth muscle dysfunction and/or that the pulmonary vessels are encased in a rigid matrix of adventitial connective tissue, which prevents vasodilation. Recent research on isolated pulmonary vessels from patients with Eisenmenger’s syndrome shows that there is endothelial dysfunction but normal smooth muscle cell relaxant ability17; therefore, adventitial thickening may be a component that is more important in vivo in the context of an intact parenchyma. Interestingly, endothelium-dependent dilation in our patients was decreased rather than abolished, a finding that is in accord with experimental studies showing that endothelium-dependent dilation may be observed even in the presence of significant widespread endothelial injury45 or if only a few endothelial cells remain after mechanical injury.7 Extensive endothelial denudation is not a feature of PVD, even when advanced.15

In our patients with high pulmonary flow but normal pressure and resistance, the vasodilation observed in response to acetylcholine was reduced but was preserved to nitroprusside. This indicates that there is endothelial dysfunction or that the diminished response to acetylcholine is due to increased background secretion of EDRF by endothelium stimulated by high flow, leading to maximal relaxation of the underlying smooth muscle. This latter explanation seems less likely, as the smooth muscle in these patients retained the ability to relax in response to nitroprusside to the extent observed in controls. If the arteries had failed to respond normally to acetylcholine because they were already maximally dilated, one might expect an inverse relation between vessel diameter and percent flow-velocity increase; in our study, no such relation was observed. Furthermore, the two patients with the greatest responses to acetylcholine were not those with the lowest pulmonary flows. Despite these considerations, the best way to distinguish between these two possible interpretations of the data would involve studying the effects of EDRF antagonists on the pulmonary circulation; such studies are currently under way.

The hypothesis that endothelial dysfunction is present in children with increased pulmonary flow is also consistent with histological studies showing structural endothelial damage as an early event in children with abnormal pulmonary hemodynamics and congenital heart disease.15 Only a minority of patients with congenital heart disease leading to increased pulmonary flow but normal pressure and resistance subsequently develop significant pulmonary hypertension, and in two of the seven patients studied endothelium-dependent relaxation appeared normal (Figure 3). However, the abnormal responses of the majority suggest that increased flow and shear stress may damage pulmonary endothelial cell function.

The maximum acetylcholine- and nitroprusside-induced increases in pulmonary blood flow in the controls
(approximately 90% and 50%, respectively) are very similar to the maximum relaxation that has been observed in response to these agents in isolated pulmonary arteries from normal subjects studied in vitro (approximately 80% and 40%). Both in vivo and in vitro, vasodilation was greater in response to acetylcholine than to nitroprusside. This may be because nitroprusside is a relatively weak stimulator of pulmonary vascular smooth muscle compared with EDRF, the endogenous nitrovasodilator, or that (at least in vivo) the dosing schedule elicited the maximal responses to acetylcholine but a submaximal response to nitroprusside; for the latter drug, the dose range is limited by its powerful systemic vasodilator effect.

The impairment of endothelial function itself may have far-reaching adverse effects in the pulmonary circulation. Reduced EDRF responsiveness may be just one manifestation of altered endothelial function. Abnormal endothelium may interact with platelets to favor thrombosis and cause leukocyte adhesion, with neutrophils and macrophages attracting and promoting growth of underlying cells, thereby altering the vessel wall. Abnormal endothelial cells may also have enhanced elastolytic activity, causing underlying tissue damage. Therefore, endothelial cell injury may be a key early event in the pathogenesis of PVD.

Endothelium-dependent pulmonary artery relaxation is impaired in young patients with increased pulmonary blood flow secondary to congenital heart disease. The availability of an in vivo method for assessment of pulmonary endothelial function enables further studies to be conducted to examine whether endothelial dysfunction is reversible at an early stage, e.g., by surgical correction of the predisposing congenital heart lesion.

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