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**Pulmonary Arterial Wall Distensibility Assessed by Intravascular Ultrasound  
in Children With Congenital Heart Disease \* : An Indicator for Pulmonary  
Vascular Disease?**

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A M E R I C A N C O L L E G E O F  
 C H E S T  
P H Y S I C I A N S

# Pulmonary Arterial Wall Distensibility Assessed by Intravascular Ultrasound in Children With Congenital Heart Disease\*

## An Indicator for Pulmonary Vascular Disease?

Rolf M. F. Berger, MD, PhD; Adri H. Cromme-Dijkhuis, MD, PhD;  
Wim C. J. Hop, MSc, PhD; Marco N. Kruit; and John Hess, MD, PhD

**Background:** Both pulmonary hypertension and pulmonary overflow are associated with functional and structural changes of the pulmonary arterial wall. Current techniques to evaluate the pulmonary vasculature neglect the pulsatile nature of pulmonary flow.

**Study objectives:** To determine whether the dynamic properties of the pulmonary arterial wall are altered in patients with abnormal pulmonary hemodynamics due to congenital heart defects, and whether these changes are associated with the progression of pulmonary vascular disease (PVD).

**Patients and methods:** In 43 children with PVD due to congenital heart defects and 12 control subjects, pulmonary arterial pulsatility (the relative increase in vessel area during the cardiac cycle) and distensibility (the inverse of the stress/strain elastic modulus) were determined with intravascular ultrasound. Results were correlated with clinical and hemodynamic parameters.

**Results:** Pulsatility correlated with pulmonary pulse pressure ( $p < 0.001$ ), pulmonary-to-systemic vascular resistance ratio (PVR/SVR) [ $p = 0.001$ ], and hemoglobin concentration ( $p = 0.01$ ). However, when corrected for these variables, pulsatility did not differ between patients and control subjects. In contrast, arterial wall distensibility decreased with the severity of PVD and correlated independently with pulmonary-to-systemic arterial pressure ratio ( $p < 0.001$ ) and PVR/SVR ( $p = 0.03$ ), and with hemoglobin concentration ( $p < 0.01$ ). Adjusted for hemodynamic variables, distensibility was still decreased in patients with PVD compared to control subjects.

**Conclusions:** These results demonstrate that pulmonary arterial wall distensibility is progressively decreased in PVD; moreover, this decreased distensibility is, in part, related to increased distending pressure as a result of pulmonary hypertension but also, in part, to stiffening of the arterial wall during the disease process. Arterial wall distensibility may be of additional value in the evaluation of pulmonary vasculature and ventricular workload. (CHEST 2002; 122:549–557)

**Key words:** dynamics, vascular; heart defects, congenital; hypertension, pulmonary; pulmonary vascular disease; ultrasound, intravascular

**Abbreviations:** CI = confidence interval; EDA = end-diastolic area; EDD = end-diastolic dimension; IVUS = intravascular ultrasound; PAP/SAP = pulmonary-to-systemic mean arterial pressure ratio; PVD = pulmonary vascular disease; PVR = pulmonary vascular resistance; PVR/SVR = pulmonary-to-systemic vascular resistance ratio; WU = Wood unit

\*From the Department of Pediatrics (Drs. Berger and Cromme-Dijkhuis, and Mr. Kruit), Division of Pediatric Cardiology, Sophia Children's Hospital/University Hospital Rotterdam, Rotterdam, The Netherlands; the Department of Epidemiology and Biostatistics (Dr. Hop), Erasmus University Rotterdam, Rotterdam, The Netherlands; and the Department of Pediatric Cardiology (Dr. Hess), German Heart Center, Technical University of Munich, Munich, Germany.

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Correspondence to: Rolf M. F. Berger, MD, PhD, Department of Pediatrics, Division of Pediatric Cardiology, Sophia Children's Hospital/University Hospital Rotterdam, PO Box 2060, 3000 CB, Rotterdam, The Netherlands; e-mail: berger@alkg.azr.nl

In children with congenital heart disease, both pulmonary hypertension and increased pulmonary blood flow lead to functional and structural changes of the pulmonary vasculature from the start of their occurrence.<sup>1–4</sup> Progression of these vascular changes, referred to as pulmonary vascular disease (PVD), largely determines the management and prognosis of these patients.<sup>1,2</sup> Pulmonary vascular remodeling, and thus PVD, starts from the very onset of abnormal pulmonary hemodynamics and eventually leads to increased pulmonary vascular resistance (PVR) due to luminal narrowing in small pulmonary arteries. This remodeling process, which includes arterial wall thick-

ening and extracellular matrix modulation, may also result in stiffening of the pulmonary arterial walls.<sup>5-8</sup> The latter will cause an increase in the pulsatile load of the right ventricle, which normally constitutes approximately 30% of the total workload of the right ventricle.<sup>9,10</sup> In the clinical setting, the state of the pulmonary vasculature is commonly evaluated at cardiac catheterization by calculating PVR and its response to vasodilators. Although these hemodynamic data provide valuable information, they are restricted to the resistance of the pulmonary vasculature to continuous flow and, consequently, neglect the essentials of a pulsatile circulation.<sup>11,12</sup> However, with increasing recognition of the importance of the pulsatile component of BP in the pathogenesis of cardiovascular diseases, this aspect of pulmonary blood flow has become of major interest.<sup>9,13,14</sup>

Intravascular ultrasound (IVUS) of the pulmonary vasculature allows one to characterize the arterial wall and to visualize *in vivo* the dynamics of elastic pulmonary arteries. It is feasible in infants and children and can document changes in arterial wall properties in pulmonary hypertension.<sup>15-18</sup> The *in vitro* appearance of the elastic pulmonary arterial wall, as determined by IVUS in patients with congenital heart disease and PVD, has been reported to correlate with histopathologic grade.<sup>19</sup> However, real-time vascular dynamics and mechanical properties of the pulmonary arterial wall and their relation to hemodynamic variables have not been reported earlier in patients at different stages of PVD. The purpose of this study was to assess pulmonary arterial wall dynamics in children with congenital heart disease and PVD, at very early or advanced stage, and to compare the findings with those in children with a normal pulmonary circulation. And, moreover, to establish the correlation between these findings and hemodynamic data and progression of the vascular disease.

## MATERIALS AND METHODS

### Patients

Patients who required diagnostic or therapeutic cardiac catheterization and had increased pulmonary blood flow (pulmonary-to-systemic blood flow ratio > 1.2) and/or pulmonary hypertension (mean pulmonary artery pressure > 20 mm Hg) [ $n = 43$ ] were prospectively enrolled in the study, after written informed consent of their parents. Children with normal pulmonary circulation who underwent cardiac catheterization ( $n = 12$ ) served as control subjects. This latter group consisted of nine patients with left-sided obstructive lesions, normal left ventricular end-diastolic pressure, and normal pulmonary wedge pressure who underwent a catheter intervention, and three children with echocardiographic suspicion of either a shunt at atrial level ( $n = 2$ ) or a coronary fistula ( $n = 1$ ) that could not be confirmed

during cardiac catheterization. Patients with hemoglobinopathies, interstitial pulmonary disease, liver or renal dysfunction, or unstable conditions were excluded. The study was approved by the Medical Ethical Committee of the University Hospital Rotterdam.

### Catheterization and IVUS Procedure

All procedures were performed under standardized general anesthesia.<sup>20</sup> Hemodynamic evaluation and IVUS imaging of the pulmonary arteries were performed in the same procedure according to a protocol previously reported.<sup>15</sup> Briefly, all patients underwent complete hemodynamic evaluation of the pulmonary and systemic vascular beds, including vasodilator response to inhalation of 100% oxygen, as a powerful pulmonary vasodilator. Pulmonary blood flow was determined using the dye dilution technique, and shunt size was determined by oximetry. Before, during, and after the procedure, blood gas analyses were performed to maintain metabolic stability. A Sonos Intravascular Imaging System (Hewlett Packard; Andover, MA) and Sonicath 3.5F or Spy 3.0F ultrasound catheters with a 30-MHz transducer at the tip (Boston Scientific; Watertown, MA) were used. The ultrasound catheter was directed through a 6F sheath along the pulmonary branch at consecutive sites in, successively, the proximal, segment, and peripheral arteries identified and defined by fluoroscopy.<sup>15,21</sup> IVUS images were obtained and recorded on videotape simultaneously with the ECG. IVUS imaging of the pulmonary arteries was performed at baseline and during 100% oxygen inhalation. The images were independently analyzed off-line by two observers blinded for clinical and hemodynamic data (A.H.C., R.M.F.B.). Pulmonary arterial luminal diameter and area were measured at end-diastolic dimension (minimal) and peak systolic dimension (maximal) [Fig 1]. The values of three cardiac cycles were averaged for each observer, and the mean of both averages was used for further analyses. Vascular pulsatility was defined as the difference between planimetry values for peak systolic area and end-diastolic area (EDA), divided by  $EDA \times 100\%$ .<sup>16</sup> Arterial wall distensibility (the inverse of the stress/strain elastic modulus) was calculated by dividing pulsatility by pulmonary pulse pressure (pulsatility/systolic minus diastolic pulmonary artery pressure).<sup>14,22</sup> Because adequate measurement of wall dynamics was not feasible in arteries with an end-diastolic diameter (EDD) < 2.0 mm, these arteries were excluded from pulsatility and distensibility analyses.

### Patient Classification

Enrolled patients were assigned to three groups: control subjects (group 1), children with mild-to-moderate PVD (group 2), and children with advanced PVD (group 3). Children with a normal pulmonary circulation formed the control group. Those with increased pulmonary blood flow and/or pulmonary hypertension were defined as having mild-to-moderate PVD based on criteria commonly used in clinical practice:  $PVR < 4$  Wood units (WU)/m<sup>2</sup> at baseline or a PVR responsive to 100% oxygen inhalation ( $PVR$  at 100% oxygen inhalation < 4 WU/m<sup>2</sup> or vasodilator response  $\geq 50\%$ ). Patients were defined as having advanced PVD if they had a baseline  $PVR \geq 4$  WU/m<sup>2</sup>, not responsive to 100% oxygen ( $PVR$  at 100% oxygen inhalation  $\geq 4$  WU/m<sup>2</sup> and vasodilator response < 50%). Vasodilator response was defined as  $100 \times (PVR \text{ baseline} - PVR \text{ at } 100\% \text{ oxygen inhalation})/PVR \text{ baseline}$ .

### Statistical Analysis

Interobserver agreement was determined by calculating intraclass correlation coefficients. Pulsatility and distensibility out-

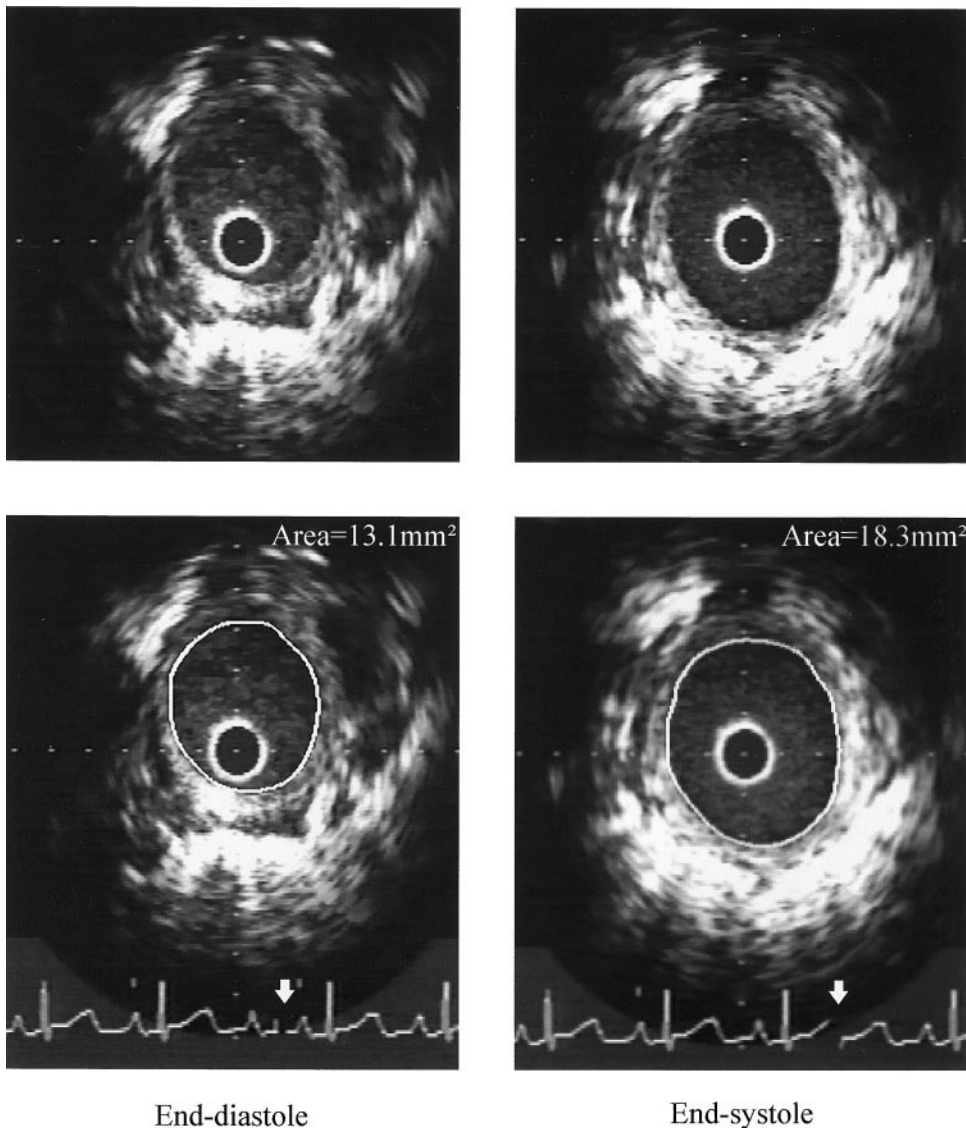


FIGURE 1. IVUS imaging of a segmental, elastic pulmonary artery during the cardiac cycle. Arterial luminal area was measured at end-diastolic dimension (minimal, *left*) and peak systolic dimension (maximal, *right*). The arrows denote the timing in the cardiac cycle.

comes, taking account of differences between and within patients, were evaluated using regression analysis for repeated measurements using the BMDP statistical software package (SPSS; Chicago, IL).<sup>23</sup> Both outcomes were logarithmically transformed to obtain approximate normal distributions. Univariate comparison of IVUS data between patient groups was done using mixed-model analysis of variance. Using backward elimination, the clinical and hemodynamic variables most predictive for pulsatility and distensibility were determined. To allow comparison between results at baseline and at 100% oxygen inhalation, however, regression coefficients are given for both conditions if one of them proved to be significant. In the multivariate analysis, we have chosen the pulmonary-to-systemic mean arterial pressure ratio (PAP/SAP) and the pulmonary-to-systemic vascular resistance ratio (PVR/SVR) to represent measures for pulmonary arterial pressure and resistance, respectively. The limit of significance was set at  $p = 0.05$  (two sided).

## RESULTS

### *Clinical and Hemodynamic Data*

A total of 55 patients were enrolled in the study: 31 patients with mild-to-moderate PVD, 12 patients with advanced PVD, and 12 control subjects. Tables 1, 2 present the clinical diagnoses and patient characteristics.

### *IVUS Data*

For each patient, IVUS studies were performed in two to seven consecutive sites along the pulmonary arterial tree. A total of 199 artery segments were studied, of which 196 segments had sufficient delin-



**Table 1—Diagnoses of the Study Patients**

Diagnoses	No.
Left-to-right shunt	
Ventricular septal defect with or without atrial septal defect or persistent arterial duct	19
With pulmonary arterial banding	2
Atrial septal defect	6
Persistent arterial duct	2
Complete atrioventricular septal defect	1
Truncus arteriosus	1
No left-to-right shunt	
Persistent pulmonary hypertension after corrected heart defect	2
Unexplained pulmonary hypertension	1
Left-sided obstructive lesions with pulmonary venous congestion	9
Control subjects	12
Total	55

ation between blood and the inner vessel wall to allow reproducible measurement of vessel dimensions during the cardiac cycle. Three recordings were excluded because of poor image quality. EDD of the investigated vessels ranged from 1.4 to 10.4 mm; 148 of these vessels were  $\geq 2$  mm in diameter and were included in wall dynamics analysis. Measurements included 33 cross-sections of proximal arteries (EDD,  $6.1 \pm 2.1$  mm [mean  $\pm$  SD]; range, 2.1 to 10.4 mm), 85 cross-sections of segment arteries (mean,  $3.6 \pm 1.2$  mm; range, 1.8 to 7.0 mm), and 78 cross-sections of peripheral arteries (mean,  $2.1 \pm 0.7$  mm; range, 1.4 to 4.9 mm). The size of the studied arteries was similar in the three patient groups ( $p = 0.20$ ). There was a high level of agreement between both observers. The intraclass correlation coefficients for the measurement of EDD, end-systolic dimension, EDA, and peak systolic area were 0.997, 0.998, 0.998, and 0.998, respectively.

### Vascular Pulsatility

In a univariate analysis, pulsatility at baseline correlated with hemoglobin concentration ( $p < 0.01$ ), dia-

stolic pulmonary artery pressure ( $p = 0.03$ ), pulmonary pulse pressure ( $p = 0.08$ ), shunt size ( $p = 0.08$ ), and PVR/SVR ( $p = 0.10$ ) [Fig 2]. Pulmonary blood flow, pulmonary wedge pressure, and pulmonary vasodilator response to 100% oxygen inhalation were not correlated with pulsatility. Pulsatility did not differ significantly ( $p = 0.29$ ) between patients with mild-to-moderate PVD (geometric mean, 23%; 95% confidence interval [CI], 20 to 26%), patients with advanced PVD (geometric mean, 18%; 95% CI, 14 to 24%), and control subjects (geometric mean, 21%; 95% CI, 16 to 27%) [Fig 3, top, a]. Pulsatility at baseline and adjusted for patient group correlated independently with pulmonary pulse pressure and PVR/SVR and, in addition, with hemoglobin concentration (multivariate regression, Table 3). Adjusted for these variables, no difference in pulsatility between patient groups and control subjects was demonstrated ( $p = 0.58$ ). At 100% oxygen inhalation, pulsatility was independently correlated with pulse pressure and EDA of the vessel, without significant differences between patient groups (Table 3).

### Arterial Wall Distensibility

Arterial wall distensibility at baseline correlated univariately with age ( $p = 0.05$ ), hemoglobin concentration ( $p = 0.08$ ), mean pulmonary artery pressure ( $p < 0.001$ ), shunt size ( $p = 0.06$ ), PVR ( $p < 0.001$ ), PAP/SAP ( $p < 0.001$ ), and PVR/SVR ( $p < 0.001$ ) [Fig 2]. Pulmonary blood flow, pulmonary wedge pressure, and pulmonary vasodilator response to 100% oxygen inhalation were not correlated with distensibility. Distensibility was decreased ( $p < 0.001$ ) in patients with mild-to-moderate PVD (geometric mean, 1.22; 95% CI, 1.04 to 1.42) compared to control subjects (geometric mean, 2.15; 95% CI, 1.67 to 2.77). Wall distensibility in patients with advanced PVD (geometric mean, 0.55; 95% CI, 0.42 to 0.71) was decreased compared to patients with mild-to-moderate PVD and to control subjects (both  $p < 0.001$ ; Fig 3, bottom, b). Distensibility was independently associated with PAP/SAP, PVR/SVR,

**Table 2—Patient Characteristics\***

Characteristics	Control Subjects	Mild-to-Moderate PVD	Advanced PVD
Patients, No.	12	31	12
Age (range), yr	5.6 (0.5–16.9)	3.7 (0.2–30.7)	2.6 (0.2–15.8)
Weight (range), kg	21.0 (8.2–51.9)	13.0 (3.0–76)	11.4 (4.3–44)
Hemodynamics			
Mean PAP, mm Hg	$13 \pm 3$	$22 \pm 9$	$50 \pm 12$
PWP, mm Hg	$8 \pm 3$	$9 \pm 4$	$11 \pm 7$
Shunt size, Qp:Qs	$1.0 \pm 0.0$	$2.6 \pm 1.5$	$1.2 \pm 0.4$
PVR, WU/m <sup>2</sup>	$1.2 \pm 0.6$	$1.9 \pm 1.2$	$10.2 \pm 3.5$

\*Data are presented as mean  $\pm$  SD unless otherwise indicated. PAP = pulmonary artery pressure; PWP = pulmonary wedge pressure; Qp: Qs = pulmonary-to-systemic blood flow ratio.

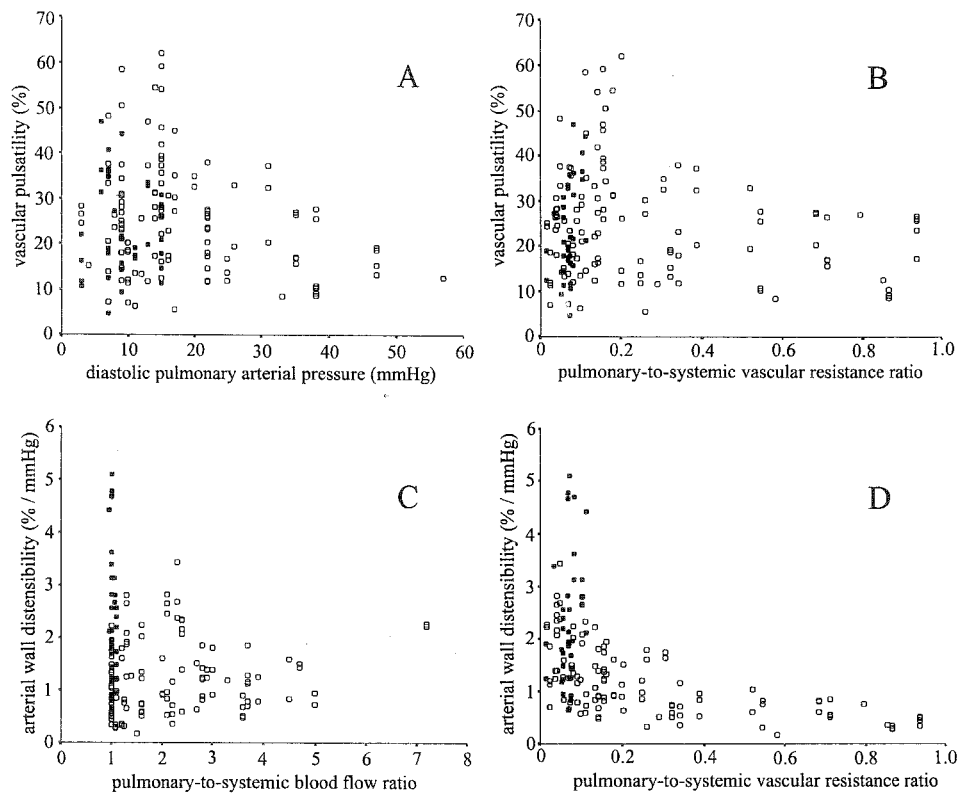


FIGURE 2. Data points illustrating the correlation between vascular pulsatility (*top left, A and top right, B*) or arterial wall distensibility (*bottom left, C and bottom right, D*) of the pulmonary arteries and various hemodynamic parameters, in control subjects (closed circles) and patients (open circles).

and hemoglobin concentration (multivariate regression; Table 4). At baseline, differences between patient groups for distensibility (adjusted for the described variables) just failed to reach significance ( $p = 0.06$ ). At 100% oxygen inhalation, PAP/SAP and the EDA of the vessel were identified as variables independently correlated with wall distensibility (Table 4). Adjusted for these variables, distensibility at 100% oxygen inhalation differed between the patient groups ( $p = 0.03$ ). Pulmonary arterial wall distensibility in a vessel with a given EDA at a given PAP/SAP showed a 26% decrease in patients with mild-to-moderate PVD compared to control subjects ( $p = 0.012$ ). In patients with advanced PVD, adjusted wall distensibility showed a 39% decrease compared to control subjects ( $p = 0.024$ ). The difference in adjusted distensibility between group 2 and group 3 (13%) was not statistically significant ( $p = 0.27$ ; Fig 4).

After 100% oxygen inhalation (as pulmonary vasodilator) the mean increase in EDA for all patients combined was 2.7% (95% CI, 0.9 to 4.5;  $p = 0.003$ ). There were no significant correlations between the increase in vessel area and vessel size, patient group, PVR/SVR, or pulmonary vasodilator response.

## DISCUSSION

In our series, pulmonary arterial wall distensibility was progressively decreased in patients with mild-to-moderate PVD and with advanced PVD compared to control subjects. This in contrast to vascular pulsatility, which did not differ between patient groups. Arterial wall distensibility correlated with vascular distending pressure (PAP/SAP). However, independent from this latter relationship, distensibility correlated with PVR/SVR and hemoglobin concentration at baseline, and with vessel area at inhalation of 100% oxygen. Furthermore, after correction for these variables, arterial wall distensibility was still substantially decreased in patients with PVD compared to control subjects. This difference was accentuated by inhalation of 100% oxygen. These findings suggest a stiffening of the pulmonary arterial wall in PVD that can be measured *in vivo* with IVUS.

The structural and functional changes in the pulmonary arteries of patients with congenital heart disease and flow-associated pulmonary hypertension will lead to a reduction of cross-sectional area of the vascular bed due to luminal narrowing of the smallest pulmonary arteries.<sup>1-4</sup> From a morphologic point

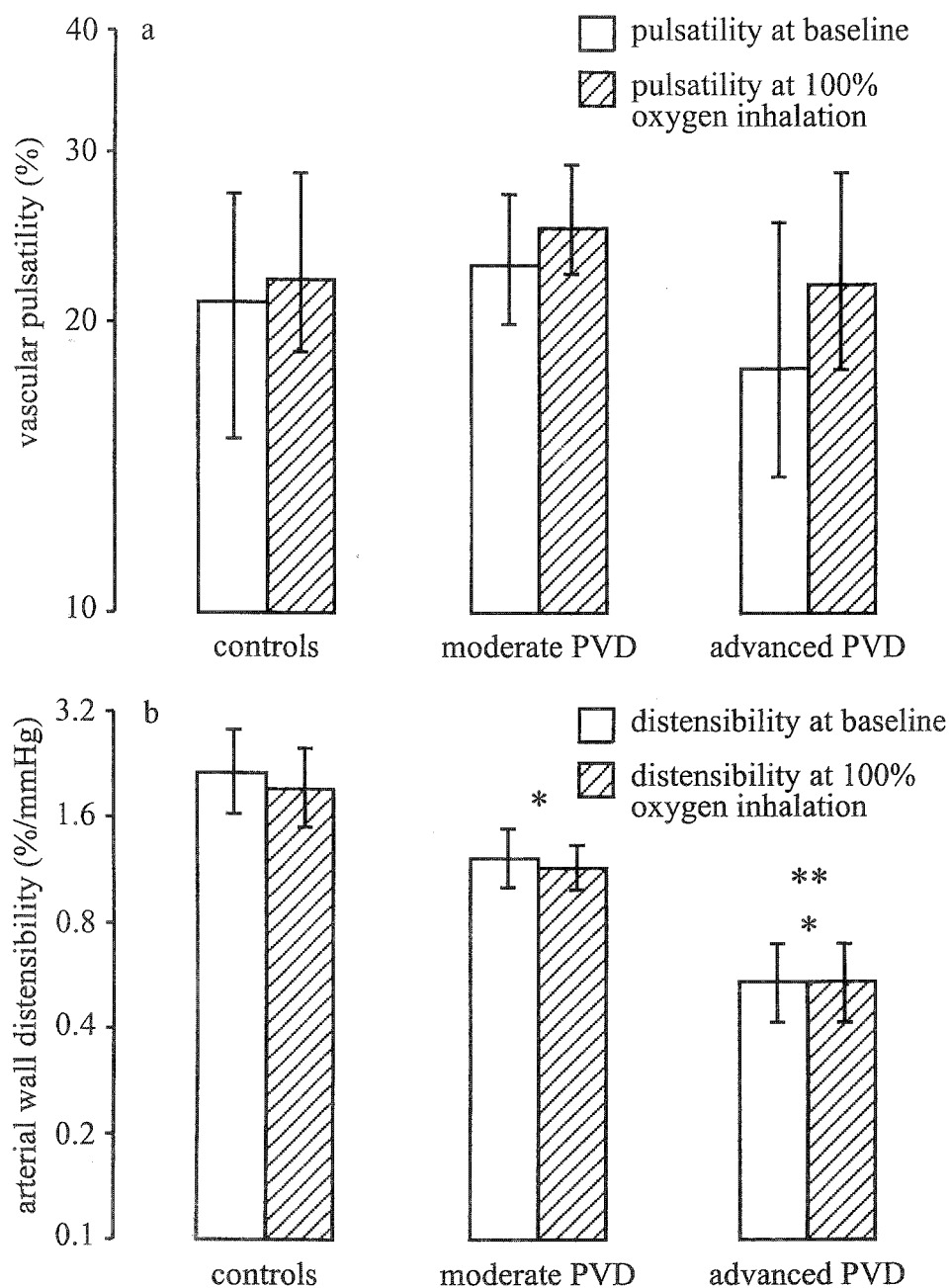


FIGURE 3. Vascular pulsatility (*top, a*) and arterial wall distensibility (*bottom, b*) of the pulmonary arteries at baseline and at 100% oxygen inhalation in the three patient groups. Data are expressed as geometric means and 95% CIs. \* $p < 0.001$  compared to control subjects; \*\* $p < 0.001$  compared to moderate PVD.

of view, the most prominent vascular changes occur in small neomuscularized pulmonary arteries that are not accessible for the ultrasound catheter. However, functional and structural alterations have also been demonstrated in the larger, elastic pulmonary arteries.<sup>4,5</sup> These alterations in tone and structure of the wall will result in a loss of its elastic properties and will be reflected in its dynamic behavior.<sup>3,6,7,24-26</sup> Different types of cardiac shunts may have different

effects on pulmonary vascular dynamics, due to different characteristics of pulmonary hemodynamics. Therefore, we correlated arterial wall dynamics primarily with pulmonary hemodynamic variables.

#### Vascular Pulsatility

Vascular dynamics can be described by pulsatility, defined as the relative increase in vessel area during

**Table 3—Multivariate Analysis of Pulsatility at Baseline and at 100% Oxygen Inhalation\***

Variables	Pulsatility at Baseline			Pulsatility at 100% Oxygen		
	Data	Change, %	p Value	Data	Change, %	p Value
Pulse pressure	0.010 ± 0.003	+ 2	< 0.001	0.009 ± 0.002	+ 2	< 0.001
PVR/SVR	- 0.05 ± 0.02	- 11	0.001	- 0.01 ± 0.01	- 2	0.20
Hemoglobin	- 0.05 ± 0.02	- 11	0.01	- 0.02 ± 0.02	- 4	0.41
EDA	0.001 ± 0.001	+ 0.2	0.30	0.003 ± 0.001	+ 0.7	0.01

\*Data given are regression coefficients with <sup>10</sup>log pulsatility as dependent variable. Change indicates the percentage change in pulsatility per millimeters of mercury change in pulse pressure, per 0.1-U change in PVR/SVR, per millimole per liter change in hemoglobin concentration, and per millimeters squared change in EDA. Data given are adjusted for patient group. Adjusted for the described variables, no differences between patient groups could be demonstrated for pulsatility (at baseline, p = 0.58; at oxygen inhalation, p = 0.23).

the cardiac cycle. In the present study, there was no difference in vascular pulsatility between patients with PVD and control subjects. This might be because pulsatility is not only determined by intrinsic properties of the wall itself, but is the net result of a complex interaction between these intrinsic properties and “extrinsic” mechanical forces acting on the vessel wall. Pulsatility correlated most strongly with the pulse pressure that (acting as a direct radial mechanical force on the arterial wall) can constitute a major determinant of vascular pulsatility.

#### Arterial Wall Distensibility

The elastic properties of a vessel wall can be characterized *in vivo* by arterial distensibility, the inverse of the stress/strain elastic modulus. Arterial distensibility reflects the relative increase in arterial area (strain) per millimeters of mercury increase in arterial BP (*ie*, pulse pressure [stress]), and represents a measure for arterial compliance.<sup>14,22,26</sup> A decreased distensibility of the systemic arteries has been demonstrated in essential hypertension, coronary artery disease, diabetes mellitus, and aging.<sup>14</sup> However, because the arterial wall exhibits a nonlinear, viscoelastic behavior, distensibility is directly affected by the distending pressure. Under these conditions, it remains debatable whether the decrease in distensibility is a consequence of elevated distending pressure and, thus, of the artery operating

on a steeper part of its pressure-volume relationship, or is a result of changes in the vessel wall itself.<sup>14</sup> We found that pulmonary arterial wall distensibility decreased progressively with the severity of PVD, and that the decreased distensibility correlated strongly with an increase in PAP/SAP, reflecting an elevated distending pressure. However, independent from this distending pressure, at baseline distensibility correlated with PVR/SVR.

These findings indicate that pulsatility and distensibility of elastic pulmonary arteries correlate with changes at the level of the pulmonary vascular bed, reflected by PVR/SVR. Moreover, this correlation proved to be independent from a concomitant rise in pulmonary artery pressure. Hemoglobin concentration (regarded as a measure for blood viscosity) will affect inertia, pulse wave propagation, and shear stress on the arterial wall and, consequently, may directly influence vascular dynamics.<sup>9,27</sup>

How can the effects of oxygen inhalation on these relations be explained? Inhaled oxygen is a powerful pulmonary vasodilator. In the pulmonary circulation, the effect of selective vasodilation is most prominent in the small muscular arteries of the vascular bed, causing a decrease in PVR.<sup>11</sup> In the present study, oxygen did not affect the distensibility of the larger pulmonary arteries, suggesting that muscular tone is not an important contributing factor in the distensibility of these elastic arteries. This agrees with data

**Table 4—Multivariate Analysis of Distensibility at Baseline and at 100% Oxygen Inhalation\***

Variables	Distensibility at Baseline			Distensibility at 100% Oxygen		
	Data	Change, %	p Value	Data	Change, %	p Value
PAP/SAP	- 0.06 ± 0.01	- 13	< 0.001	- 0.05 ± 0.01	- 11	< 0.001
PVR/SVR	- 0.04 ± 0.02	- 9	0.03	- 0.004 ± 0.011	- 1	0.71
Hemoglobin	- 0.05 ± 0.02	- 11	0.008	- 0.007 ± 0.018	- 2	0.70
EDA	0.001 ± 0.001	+ 0.2	0.22	0.003 ± 0.001	+ 0.7	0.02

\*Data given are regression coefficients with <sup>10</sup>log distensibility as dependent variable. See Table 3 for definitions. Differences between patient groups for distensibility, adjusted for the described variables, just failed to reach statistical significance at baseline (p = 0.06). Distensibility at oxygen inhalation, adjusted for the described variables, differed between patient groups (p = 0.03).



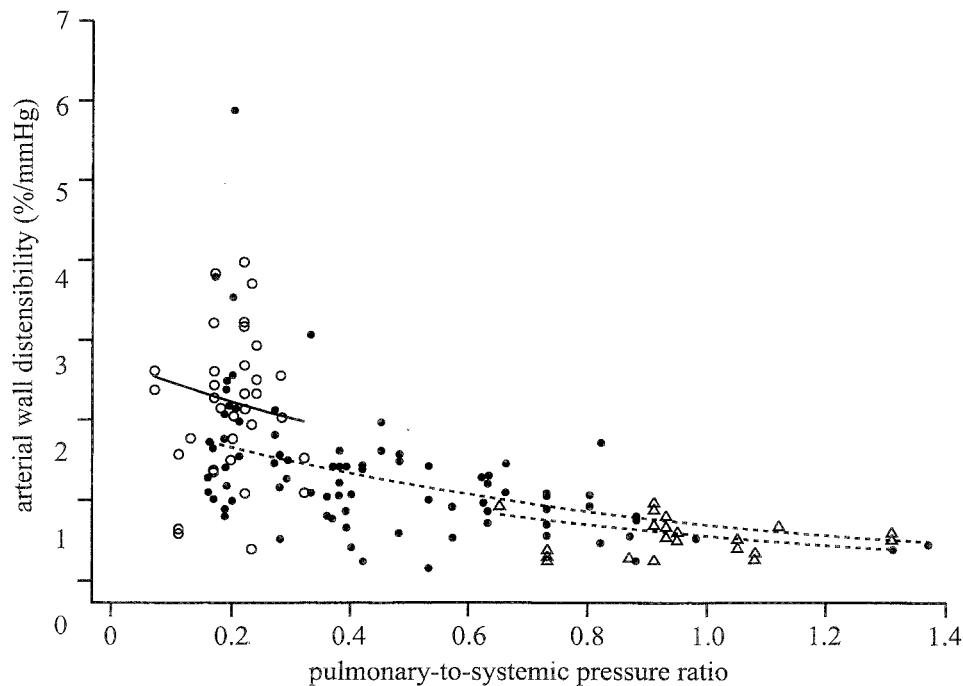


FIGURE 4. Relation between pulmonary arterial wall distensibility at 100% oxygen inhalation (adjusted for an EDA of 15 mm<sup>2</sup>) and the PAP/SAP. The solid regression line represents the relation in control subjects (open circles), the dotted regression line represents the relation in patients with mild-to-moderate PVD (closed circles), and the dashed regression line represents the relation in patients with advanced PVD (triangles).

from the rat lung that suggest that decreased distensibility in monocrotaline-induced pulmonary hypertension is due to structural changes in the vascular wall rather than to increased muscular tonus.<sup>28,29</sup> Thus, the independent correlation of pulsatility and distensibility with PVR/SVR disappears during selective pulmonary vasodilation because of the different vasodilator response of muscular and elastic pulmonary arteries. The effect of viscosity on vascular dynamics depends on the area of the vessel<sup>27</sup>; in our study, the increased EDA found on IVUS after inhalation of 100% oxygen may have diminished, or eliminated, the measurable effect of hemoglobin on vascular wall dynamics. The extent of this increase in vessel diameter did not correlate with vessel size, PVR/SVR, pulmonary vasodilator response, or patient group. This means that determination of pulmonary artery dilatation with IVUS is not interchangeable with the assessment of vasodilator response as currently practiced by assessing the response of PVR.<sup>30,31</sup>

An important finding of our study is that, after correction for all the described variables, pulmonary arterial wall distensibility was still decreased in patients with PVD compared to control subjects. After adjustment for hemodynamic variables, vessel size, and hemoglobin concentration, a mean decrease in

arterial wall distensibility of approximately 40% was seen in patients with advanced PVD. In our opinion, this decrease indicates a stiffening of the pulmonary arterial wall caused by intrinsic properties of the arterial wall, which cannot be assessed with hemodynamic variables. Arterial wall stiffness is considered to be important in both the pathogenesis and clinical course of PVD.<sup>9,14</sup> Pulmonary arterial wall distensibility is a new feature in the assessment of the pulmonary vasculature, which is easily obtained during routine cardiac catheterization. It may provide additional information on PVD and its effect on right ventricular load. Moreover, this parameter may be useful when evaluating and interpreting the effects of therapies for advanced PVD, such as high-dose calcium-channel blocking therapy or continuous infusion of epoprostenol.

#### Study Limitations

The definitions of mild-to-moderate and advanced PVD (based on hemodynamic parameters) used in our study are subjective, but are commonly used in clinical practice. Because the design of this *in vivo* study did not allow comparison with corresponding histologic sections of the arteries studied with IVUS,

decreased arterial wall distensibility could not be directly related with structural changes of the arterial wall.

In conclusion, we have demonstrated that pulmonary arterial wall distensibility is progressively decreased in PVD. Our data suggest that this decrease is, in part, related to an increased distending pressure as a result of pulmonary hypertension and, in part, to a stiffening of the arterial wall in the disease process. These changes in wall properties of elastic pulmonary arteries correlated with changes at the level of the pulmonary vascular bed. Moreover, this correlation was independent from a rise in pulmonary artery pressure. Pulmonary arterial wall distensibility may become a new variable in the *in vivo* evaluation of the pulmonary vasculature. This variable takes into account the pulsatile nature of the pulmonary circulation and thereby provides additional information on the progression of pulmonary vascular disease and its consequences for the integrated pulmonary circulation and right ventricular load.

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John Hess

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