



# Acute Pulmonary Vasodilator Testing and Long-Term Clinical Course in Segmental Pulmonary Vascular Disease

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Received: 11 July 2017 / Accepted: 21 November 2017 / Published online: 1 December 2017  
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## Abstract

Results of acute pulmonary vasodilator testing (AVT) and the outcome of medical therapy have not been described in patients with segmental pulmonary vascular disease (SPVD). We sought to compare the pulmonary vasodilatory effects of oxygen, oxygen with nitric oxide, and diltiazem, and to describe the clinical course of patients with SPVD and pulmonary hypertension. A retrospective review of 16 patients with pulmonary hypertension and SPVD involving 2–3 major lung segments who underwent AVT between January 2000 and December 2015 was performed. Baseline hemodynamic measurements were obtained with patients breathing  $\leq 30\%$  oxygen. AVT was performed using 100% oxygen, 100% oxygen with 20 ppm nitric oxide, 21–35% oxygen, and 21–35% oxygen with intravenous diltiazem. The events associated with their long-term care were described. Nine of 16 patients were acutely responsive during AVT using the Sitbon criteria. The change in mean pulmonary artery pressure with oxygen or oxygen with nitric oxide ( $19 \pm 12$  mmHg) was significantly greater than the change with diltiazem ( $7 \pm 5$  mmHg). Pulmonary vasodilator therapy was initiated or escalated after AVT in 12 patients. Five patients subsequently experienced a decrease in mean pulmonary artery pressure or normalization in B-type natriuretic peptide. Three patients experienced adverse events associated with therapy. The actuarial survival was 94% over a period of 1–20 years. This study suggests that AVT can be used to identify patients with SPVD who are reactive to oxygen, oxygen with nitric oxide, and diltiazem. Clinical improvement was temporally associated with pulmonary vasodilator therapy in some patients with few adverse effects.

**Keywords** Segmental pulmonary vascular disease · Pulmonary hypertension · Pulmonary artery stenosis · Pulmonary vein stenosis · Acute pulmonary vasodilator testing

## Abbreviations

AVT Acute pulmonary vasodilator testing  
MPAP Mean pulmonary arterial pressure  
SPVD Segmental pulmonary vascular disease

## Introduction

In patients with segments of lung affected by peripheral pulmonary artery stenosis or pulmonary vein stenosis, blood flows primarily through the remaining segments of lung with normal vessels. Many of these patients develop an increase in pulmonary arterial pressure and progressive

pulmonary vascular disease. Right heart failure may occur in severe cases. The hemodynamic profile of this form of pulmonary hypertension is distinct from other forms of pulmonary hypertension. Segmental pulmonary hypertension or pulmonary vascular disease (SPVD) has been classified as a disease process with unclear multifactorial mechanisms [1]. Patients with SPVD are typically not included in registries of pulmonary vascular disease or studies evaluating the safety and efficacy of therapeutic agents. It is also difficult to interpret the results of acute pulmonary vasodilator testing (AVT) during heart catheterization in this setting. Thus, little is known about the safety and efficacy of medical therapy for patients with SPVD. We sought to determine whether patients with SPVD are reactive during AVT, and to describe their long-term clinical course. We hypothesize that some individuals with SPVD are acutely reactive to pulmonary vasodilators, and that targeted-therapy can be used safely in this setting long-term.

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## Methods

The Institutional Review Board of the University of Utah approved this retrospective, longitudinal single institution cohort study. The records of all patients with pulmonary hypertension and SPVD who underwent AVT with supplemental oxygen from January 2000 to December 2015 were reviewed. Patients were followed from the diagnosis of SPVD through December 2016.

### Inclusion Criteria

Patients who underwent AVT during heart catheterization with the following criteria were included in this study:

- Atrisia, obstruction, or severe stenosis of pulmonary arteries in two to three major lung segments with a mean pulmonary arterial pressure (MPAP)  $\geq 25$  mm Hg and a mean pulmonary arterial wedge pressure in the unaffected lung segments or a left atrial pressure  $< 15$  mm Hg
- Obstruction or severe stenosis of pulmonary veins in at least two major lung segments with a MPAP  $\geq 25$  mm Hg and a mean pulmonary arterial wedge pressure in the unaffected lung segments or a left atrial pressure  $< 15$  mm Hg.

### Exclusion Criteria

Patients with the following criteria were excluded from this study:

- A MPAP  $< 25$  mm Hg
- A mean pulmonary arterial wedge pressure in the unaffected lung segments or a left atrial pressure  $\geq 15$  mm Hg
- Atrisia, obstruction, or severe stenosis of pulmonary arteries in less than two major lung segments
- Atrisia, obstruction, or severe stenosis of pulmonary arteries in all major lung segments
- Obstruction or severe stenosis of pulmonary veins in less than two major lung segments
- Obstruction or severe stenosis of pulmonary veins in all major lung segments
- A functional single ventricle
- A post-tricuspid valve shunt.

### Acute Pulmonary Vasodilator Testing

Medications were not given on the day of heart catheterization if patients were already being treated with medications

for pulmonary hypertension. Hemodynamic measurements were performed during the following phases for 10- to 15-min intervals to evaluate pulmonary vascular reactivity:

- Baseline 1: room air or enough supplemental oxygen ( $\leq 30\%$  oxygen) to achieve oxygen saturation measurements  $> 87\%$
- 100% Oxygen: 8–12 L/min oxygen through a non-rebreathing mask or approximately 100% oxygen through an endotracheal tube
- 100% Oxygen with Nitric Oxide: 8–10 L/min oxygen through a non-rebreathing mask or approximately 100% oxygen through an endotracheal tube with 20 parts per million (ppm) nitric oxide
- Baseline 2: room air or enough supplemental oxygen ( $\leq 35\%$  oxygen) to achieve an oxygen saturation measurement  $> 87\%$
- Diltiazem: the same amount of supplemental oxygen that was used during Baseline 2 and intravenous diltiazem at a dose of 30–60 mcg/kg/min.

The dose of nitric oxide was 20 ppm because a previous study demonstrated similar pulmonary vasodilatory effects with 12 and 60 ppm nitric oxide [2]. Nitric oxide was administered with oxygen due to the potential additive vasodilatory effects of these agents [2]. Some of the patients were also tested with diltiazem because we have seen a discrepancy between the response to oxygen or inhaled nitric oxide during vasodilator testing and the response to a calcium channel blocker [3]. Diltiazem was started at a dose of 10–20 mcg/kg/min and gradually increased over a period of 10–15 min until a decrease in mean systemic blood pressure of approximately 10% was observed or to a maximum dose of 60 mcg/kg/min. Using the Sitbon criteria, reactive patients were identified by a decrease in MPAP  $\geq 10$  mm Hg to a value  $< 40$  mm Hg [4].

### Statistical Analysis

Numerical data are presented as mean  $\pm$  standard deviation. A paired *t* test was used to identify significant differences ( $P < 0.05$ ) between the MPAP during paired phases of heart catheterization. An unpaired *t* test was used to compare the change in MPAP with oxygen or oxygen with nitric oxide to the change in MPAP with diltiazem.

### Long-Term Therapy

The long-term clinical course of patients was reported descriptively without a statistical analysis since this was a retrospective study with no predefined criteria for the safety and efficacy of medical therapy. However, the number of potential adverse effects of medical therapy and the

number of serious complications associated with SPVD were reported.

## Results

### Demographic Information

Sixteen patients were included in the study. The median age of the patients was 11.5 months with a range of 1 month to 20 years at the time of diagnosis, and 6.4 years with a range of 3 months to 27 years at the time of acute vasodilator testing. The gender, anatomical features, and the factors associated with SPVD and pulmonary hypertension are summarized in Table 1. Patients 1–12 had severe stenosis or obstruction of 2–3 major pulmonary veins. Patients 13 and 14 had severe stenosis or obstruction of the right pulmonary artery and its branches. Patients 15 and 16 had a combination of branch pulmonary artery stenosis and pulmonary vein stenosis. Factors associated with SPVD are also listed in Table 1, including congenital heart disease, chromosome abnormalities, premature birth, lung or airway disease, infection or inflammation, and thrombophilia. Six of the 13 patients who were tested for variants in factor V Leiden, prothrombin 20210, and methylenetetrahydrofolate reductase were heterozygous for the factor V Leiden variant ( $n=1$ ), or homozygous or compound heterozygous for the methylenetetrahydrofolate reductase c.665CT or c.1286AC variants ( $n=6$  or 46.2%, expected genotype frequency of 40.6) [5].

### Pulmonary Vascular Reactivity

The results of AVT during heart catheterization are shown in Fig. 1. The mean pulmonary artery pressures were significantly lower during testing with oxygen and oxygen with nitric oxide in comparison to baseline 1, and during testing with diltiazem in comparison to baseline 2. For eight patients, the change in MPAP with oxygen or oxygen with nitric oxide ( $19 \pm 12$  mmHg) was significantly greater than the change in MPAP with diltiazem ( $7 \pm 5$  mmHg) ( $p < 0.05$ ). For all paired observations, there were no significant differences in the pH of arterial blood samples, the pulmonary arterial wedge pressures in normal lung segments, and the cardiac indices estimated by the Fick principle.

Nine of the sixteen patients were acutely reactive to oxygen or oxygen with nitric oxide using the Sitbon criteria for acute pulmonary vasoreactivity. Eight of the sixteen patients had a MPAP  $\leq 35$  mmHg during baseline 1. Seven of these eight patients did not meet the Sitbon criteria during AVT. However, three of these seven patients experienced a decrease in MPAP  $\geq 20\%$  with oxygen or oxygen and nitric oxide [6, 7]. Six of the nine patients who were reactive,

and two of the three patients with a MPAP  $\leq 35$  mmHg who experienced a decrease in MPAP  $\geq 20\%$  were also evaluated with intravenous diltiazem (30–60 mcg/kg/min). Only two of the six patients who were reactive to oxygen or oxygen with nitric oxide were also reactive to diltiazem using the Sitbon criteria. No patients with a MPAP  $\leq 35$  mmHg experienced a decrease in MPAP  $\geq 20\%$  with diltiazem.

### Long-Term Pulmonary Vasodilator Therapy

All 16 patients were treated with one or more of the following agents long-term: supplemental oxygen, a calcium channel blocker, a phosphodiesterase V inhibitor, an endothelin receptor antagonist, and a prostacyclin analog. Medical treatment was initiated or escalated after AVT in twelve patients. The number of patients treated with each agent is shown in Table 1. Patients were treated with nighttime oxygen unless they were unwilling to use it consistently. Two patients with lung disease need supplemental oxygen to maintain saturation measurements greater than 92% while resting and awake. No patient required an increase in supplemental oxygen after being treated with medications for pulmonary hypertension. Amlodipine was typically used if patients were responsive to oxygen or oxygen with nitric oxide, or showed some improvement in pulmonary arterial pressure with intravenous diltiazem during acute vasodilator testing. An oral phosphodiesterase V inhibitor was used to treat patients who failed to acutely respond to intravenous diltiazem or failed to improve with long-term nighttime oxygen or amlodipine. Combination therapy with endothelin receptor antagonists and prostacyclin analogs were used in patients with high baseline pulmonary arterial pressures, limited improvement in pulmonary arterial pressure during acute vasodilator testing, or failure to improve with other oral agents.

Table 1 shows the complications associated with SPVD that occurred in 6 patients. Patient 5 developed respiratory failure from aspiration pneumonia and died when the family withdrew life-sustaining medical treatment. All other patients are alive. The actuarial survival for our patients at 1, 5, 10, 15, and 20 years was 94% (95% CI 0.75–0.95). Three patients had evidence of right heart failure. Two patients were hospitalized after developing pulmonary edema in lung segments with normal pulmonary vessels while traveling to elevations  $> 3000$  m. Both episodes occurred while patients were not using oxygen or medications consistently. Patient 2 who resides at an altitude of 800 m and patient 13 who resides at an altitude of 1700 m have been able to travel to elevations greater than 2000 and 3000 m, respectively, several times without symptoms since being treated consistently with medications. Three patients have experienced hemoptysis. Patient 1 intermittently experiences hemoptysis, particularly when he has respiratory infections. Patient 3

**Table 1** Demographic information, complications, and long-term therapy

Patient	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Age: diagnosis of vascular obstruction, years	4	2	1	<1	1	2	<1	20	<1	<1	1	1	<1	<1	1	13
Age: acute vasodilator testing, years	4	2	15	7	1	2	3	27	<1	9	1	14	16	4	8	13
Age: study closure 12/31/16, years	14	7	18	16	1	14	19	30	1	19	5	24	22	11	14	18
Gender, female		•		•	•	•									•	•
Anatomical sites of obstruction																
Left upper pulmonary vein	•	•	•	•	•	•	•	•		•	•	•				•
Left lower pulmonary vein	•	•	•	•	•	•		•	•	•	•	•				•
Right upper pulmonary vein		•		•	•		•	•	•						•	•
Right lower pulmonary vein							•									
Left pulmonary artery															•	•
Right pulmonary artery													•	•		
Associated factors																
Congenital heart disease	•	•	•	•	•	•	•	•	•	•	•	•				
Anomalous pulmonary venous return							•									
Down syndrome		•	•		•			•	•							
Premature birth with chronic lung disease				•	•	•					•					
Obstructive or restrictive lung disease								•	•		•		•	•		
Airway obstruction	•	•	•		•	•		•	•				•	•		
Prior pulmonary infection	•	•			•			•			•					•
Lung hypoplasia													•	•		
Bowel ischemia or perforation																
Necrotizing enterocolitis				•												
Hirschsprung disease			•													
Iatrogenic															•	
Inflammatory disease																
Sarcoidosis								•								
Hypersensitivity pneumonitis																•
Thrombophilia																
Factor V Leiden													•			
MTHFR	•	•	•		•				•				•		•	
Complications associated with segmental pulmonary vascular disease																
Death					•											
Right heart failure					•			•	•							
Segmental high altitude pulmonary edema		•											•			
Resolution with therapy		•											•			
Hemoptysis	•		•													•
Persistence with medical therapy	•		•													
Resolution with medical therapy																•
Long-term pulmonary vasodilator therapy																
Oxygen	•	•	•	•	•	•	○	•	•		•		•	•	○	○
Calcium channel blocker	•	•	•			•		•		○	○	•				
Phosphodiesterase V inhibitor		•	•	•	•	•		•	•		•		•	•		○
Endothelin receptor antagonist	•		•					○	•				•			
Prostacyclin analog								○	•							
Complications associated with therapy																
Calcium channel blocker																
Gingival hyperplasia											•					
Phosphodiesterase V inhibitor																
Aspiration pneumonia					•											
Prostacyclin analog																

**Table 1** (continued)

Patient	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Cause or exacerbation of arthritis								●								
Surgical interventions																
Residual vascular obstruction								○								
Catheter-mediated interventions																
Residual vascular obstruction	●		●							●						○

MTHFR—homozygous or compound heterozygous for the methylenetetrahydrofolate reductase c.665CT and c.1286AC variants

● Presence of a characteristic; pulmonary vasodilator therapy: ongoing; surgical or catheter-mediated interventions: with residual vascular obstruction

○ Pulmonary vasodilator therapy: discontinued; surgical or catheter-mediated interventions: without residual vascular obstruction

has experienced no hemoptysis following occlusion of his left lower pulmonary artery with a vascular plug. Patient 16 experienced no hemoptysis after being treated with tadalafil. Her pulmonary arterial pressure improved, her tadalafil was discontinued, and her hemoptysis has not recurred.

Potential complications of medical therapy that resulted in a serious adverse event or a change in therapy for three patients are listed in Table 1. Patient 11 developed significant gingival hyperplasia while being treated with amlodipine and was treated instead with a phosphodiesterase V inhibitor. Patient 5 developed aspiration pneumonia while being treated with sildenafil. Patient 8 developed clinical evidence of sarcoidosis while being treated with inhaled treprostinil. A right supraclavicular lymph node biopsy demonstrated granulomatous lymphadenitis. His arthritis improved when inhaled treprostinil was stopped, worsened during a second trial of treatment, and improved again when the medication was permanently stopped.

Four patients underwent repeat AVT after the initiation or escalation of medical therapy. Three patients who were reactive during initial AVT developed a decrease in MPAP, and one patient who was not reactive during initial AVT developed an increase in MPAP. Two patients had B-type natriuretic peptide levels > 100 pg/mL, which normalized after the initiation or escalation of medical therapy.

### Surgical and Catheter-Mediated Interventions

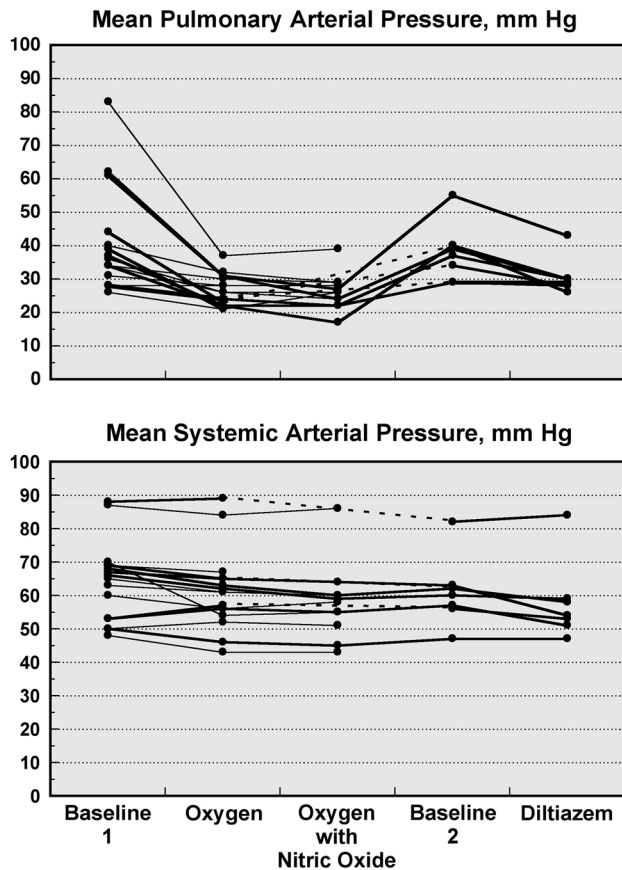
Five patients underwent additional interventions after vasodilator testing including surgical repair of pulmonary vein stenosis, balloon dilation of peripheral branch pulmonary arteries, balloon dilation of pulmonary vein stenosis, placement of a bare metal stent in a stenotic pulmonary vein, and placement of a drug eluting stent in a stenotic pulmonary vein. After surgical repair of pulmonary vein stenosis and balloon dilation of peripheral pulmonary artery stenosis, patient 7 and patient 15 had a MPAP < 25 mmHg during repeat AVT. Their care providers have not subsequently treated them with oxygen or medications for pulmonary

hypertension. Patient 1, patient 3, and patient 10 underwent catheter-mediated interventions long after AVT. They subsequently developed evidence of recurrent pulmonary vein stenosis. Patient 1 and patient 3 have increased pulmonary arterial pressures and remain on oxygen and medications targeted for pulmonary hypertension. Patient 10 had a MPAP < 25 mmHg during repeat heart catheterization. His care providers are treating him with lisinopril for systemic hypertension.

### Discussion

Our study, which is the largest in the literature, describes acute pulmonary vasodilator testing in a subset of patients with SPVD and pulmonary hypertension. Collectively, patients experienced a significant decrease in MPAP while breathing oxygen, breathing a combination of oxygen with nitric oxide, or receiving intravenous diltiazem. This suggests that there is a component of immediately reversible pulmonary hypertension in some patients with SPVD. However, the responses of individual patients were quite variable. Patients were acutely more responsive to oxygen and nitric oxide than intravenous diltiazem. Cardiac catheterization and AVT may help determine the severity of pulmonary hypertension in lung segments without SPVD, the immediate pulmonary vasodilatory reserve, and a strategy for long-term medical therapy.

In our study, long-term medical therapy was temporally associated with a decrease in MPAP and normalization of B-type natriuretic peptide in some patients. This suggests that some patients may benefit from therapy with medications that decrease pulmonary vascular resistance. Supplemental oxygen may be an appropriate long-term therapy for some patients. Oral calcium channel blockers may be beneficial for a small subset of patients. However, it is not uncommon for even reactive patients to fail calcium channel blocker therapy long-term [4, 8]. Thus, additional medications for pulmonary hypertension may have a role in the



**Fig. 1** Acute pulmonary vasodilator testing. In comparison to Baseline 1, mean pulmonary arterial pressure decreased when patients were evaluated with oxygen ( $40 \pm 16$  vs.  $27 \pm 5$  mmHg,  $n=16$ ,  $p < 0.001$ ) and oxygen with nitric oxide ( $43 \pm 18$  vs.  $26 \pm 6$  mmHg,  $n=11$ ,  $p < 0.001$ ). In comparison to Baseline 2, mean pulmonary arterial pressure decreased when patients were evaluated with diltiazem ( $38 \pm 8$  vs.  $31 \pm 5$  mmHg,  $n=8$ ,  $p < 0.005$ ). The change in mean pulmonary arterial pressure was greater with oxygen or oxygen with nitric oxide than with diltiazem ( $19 \pm 12$  vs.  $7 \pm 5$  mmHg,  $n=8$ ,  $p < 0.01$ ). Baseline 1: 21–30% oxygen. Oxygen: 8 to 12 L/min oxygen with a non-rebreathing facemask or nearly 100% oxygen through an endotracheal tube. Oxygen with Nitric Oxide: 8 to 10 L/min oxygen with a non-rebreathing facemask or nearly 100% oxygen through an endotracheal tube with 20 ppm nitric oxide. Baseline 2: 21–35% oxygen. Diltiazem: 21–35% oxygen with 20–60 mcg/kg/min intravenous diltiazem. Thin lines (baseline 1 and oxygen alone; or baseline 1, oxygen and oxygen with nitric oxide). Thick lines (baseline 1, oxygen, baseline 2 and diltiazem; or baseline 1, oxygen, oxygen with nitric oxide, baseline 2 and diltiazem). Dotted lines (transition from oxygen to baseline 2 without an intervening test with oxygen and nitric oxide)

treatment of patients with SPVD. Schuurin and associates recently reported a case series of adults with congenital heart disease and segmental pulmonary artery hypertension who experienced a significant improvement of functional class and exercise capacity after treatment with bosentan [9].

We believe patients with stenotic branch pulmonary arteries or pulmonary veins should be treated with any

surgical or catheter-mediated intervention that has a reasonable probability of success. Medical options to treat or prevent pulmonary venous obstruction may also merit consideration [10–12]. However, some forms of SPVD are simply not amenable to repair and no medication has demonstrated efficacy in the reversal of established vascular stenosis or occlusion. Pulmonary vasodilators may at least limit some of the consequences of SPVD.

Pulmonary venous obstruction induces pulmonary vascular changes and pulmonary arterial hypertension [13, 14]. Roman and colleagues described the distribution of pulmonary artery blood flow in patients with pulmonary vein stenosis using phase contrast magnetic resonance imaging [15]. An increased proportion of flow was distributed to lung regions without SPVD. Branch pulmonary artery stenosis results in a similar increase in the proportion of flow to lung regions without SPVD. This may lead to hypertensive vascular changes in patent segments and pulmonary arterial hypertension [16, 17]. Some of our patients were not acutely reactive during AVT. It is possible that pulmonary vascular disease progresses in lung regions without SPVD over time. If so, early treatment strategies may help prevent a progressive increase in pulmonary arterial pressure and eventual right heart failure.

Our patients have not experienced an increased need for supplemental oxygen during long-term medical therapy. Pulmonary edema and hypoxemia may occur when patients with diffuse pulmonary veno-occlusive disease or conditions with left atrial hypertension are treated with vasodilators. We do not believe the risk of developing pulmonary edema is similar in patients with SPVD who have an alternative route for normal pulmonary venous return. We believe the severity of pulmonary edema from pulmonary vein stenosis could even decrease by lowering the afferent driving pressure into segments of lung with pulmonary venous obstruction. Two of our patients have developed pulmonary edema in patent lung segments while traveling to a moderately high altitude prior to medical therapy. Pulmonary edema has not recurred in these patients while traveling to higher elevations during medical therapy. Thus, lowering the afferent driving pressure through the pulmonary circulation with medical therapy may decrease the risk of developing edema in patent lung segments, as well.

Three of our patients experienced adverse events that could be attributed to medical therapy. However, these events might be expected with treatment in patients with other forms of pulmonary hypertension. Additional experience is needed to determine whether patients with SPVD have any unique factors that increase their risk of complications related to vasodilator therapy.

## Limitations

This study has several limitations.

- This is a retrospective observational study of a limited number of patients. SPVD is relatively rare.
- Inaccurate calculations of blood flow and vascular resistance may occur when using assumed values of oxygen consumption. Further, the resistance of different lung segments, with and without SPVD, cannot be determined unless the blood flow through corresponding lung segments is known. Thus, we relied primarily on direct measurements of pulmonary arterial pressures for this report.
- It is possible that an inadequate dose of diltiazem was used during acute vasodilator testing to compare its effect with the effects of oxygen or oxygen with nitric oxide.
- This study was performed at an altitude of 1500 m. Hemodynamic measurements and the response to vasodilators may vary at different elevations.
- A uniform strategy for the long-term treatment of pulmonary hypertension was not used in our patients. Our approach to treatment evolved as different medications became available, as insurance providers covered medications, as criteria for treatment with calcium channel blockers evolved, and as hemodynamic measurements provided guidance for personalized therapy.
- We evaluated a heterogeneous group of patients. Patients with Down syndrome frequently have additional conditions that influence the progression of pulmonary vascular disease or limit their response to treatment. Patients with chronic lung disease may respond more favorably to supplemental oxygen. There is also considerable variation in the number of involved lung segments and the severity of disease within affected segments for different patients. We tried to limit the impact of diversity by focusing on patients with SPVD in two to three major lung segments.
- We were not able to report serial estimates of pulmonary arterial pressure, right ventricular hypertrophy, or right ventricular function by echocardiography. Patients did not consistently have reliable waveforms of tricuspid valve regurgitation, reliable waveforms of pulmonary valve insufficiency, or adequate imaging to measure the right ventricular anterior wall thickness. Further, tests of right ventricular function have evolved over time and were not uniformly accepted during the course of this study.
- We have not systematically evaluated the safety and efficacy of long-term therapy for pulmonary hypertension.
- We did not evaluate the effects of medical therapy on exercise performance in this study. Some patients were

too young or too delayed to perform reliable exercise tests.

## Concluding Observations and Recommendations

This study suggests that AVT can be used to identify patients with SPVD who are acutely reactive to oxygen, oxygen combined with nitric oxide, and diltiazem, and that clinical improvement is temporally associated with pulmonary vasodilator therapy in some patients. The results of AVT and long-term therapy are similar in patients with SPVD and patients with other forms of pulmonary hypertension. Thus, we believe it is appropriate to use medical therapy in this subset of patients. We support a large collaborative effort to better define the natural course of SPVD, to determine whether the acute response to a specific vasodilator can be used to predict the outcome of long-term therapy, and to determine whether early medical therapy can prevent a progressive increase in right ventricular pressure and right heart failure.<sup>1</sup>

## Compliance with Ethical Standards

**Conflict of interest** The authors declare that they have no conflict of interest.

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