Outcomes After Primary Transcatheter Therapy in Infants and Young Children With Severe Bilateral Peripheral Pulmonary Artery Stenosis

Jonathan W. Cunningham, BA; Doff B. McElhinney, MD; Kimberlee Gauvreau, DSc; Lisa Bergersen, MD; Ronald V. Lacro, MD; Audrey C. Marshall, MD; Leslie Smoot, MD; James E. Lock, MD

Background—Angioplasty and stent implantation have become accepted therapies for isolated peripheral pulmonary stenosis, and have been shown to increase vessel diameter and reduce right ventricular (RV) pressure acutely in patients with pulmonary artery (PA) stenosis. The purpose of this study was to assess long-term outcomes after primary transcatheter therapy for peripheral pulmonary stenosis.

Methods and Results—We studied 69 patients who underwent primary transcatheter intervention for severe isolated peripheral pulmonary stenosis at ≤5 years of age. Genetic/syndromic diagnoses included Williams syndrome (n=23), non-Williams familial arteriopathy (n=12), and Alagille syndrome (n=3). At the initial PA intervention, median RV:aortic pressure ratio decreased from 1.00 to 0.88 (median decrease, 0.18; P<0.001). Patients with a higher preintervention RV:aortic pressure ratio had a greater reduction (P<0.001). During follow-up (median, 8.5 years), 10 patients died, 5 from complications of PA catheterization (all before 1998). Thirteen patients underwent surgical PA intervention, most within 1 year and along with repair of supravalvar aortic stenosis. Freedom from any PA reintervention was 38±6% at 1 year and 22±6% at 5 years. The median RV:aortic pressure ratio decreased from 1.0 at baseline to 0.53 at the most recent catheterization (P<0.001), and 82% of patients with available clinical follow-up were asymptomatic.

Conclusions—Transcatheter therapy for infants with severe peripheral pulmonary stenosis has become safer, regardless of genetic condition. Coupled with reintervention and surgical relief in selected cases, RV:aortic pressure ratios decrease substantially and most patients are asymptomatic at late follow-up. (Circ Cardiovasc Interv. 2013;6:460-467.)

Key Words: cardiac catheterization ■ pulmonary artery ■ stenosis ■ Williams Syndrome

Isolated peripheral pulmonary stenosis (PPS)—narrowing of the branch pulmonary arteries (PAs) without major associated heart disease—can cause elevated right ventricular (RV) pressure, RV hypertrophy, and cardiac failure. PPS is often associated with Williams syndrome or other elastin deficiencies, and with Alagille syndrome.1-3 Reports of single cases or small series have suggested that PPS may improve over time without intervention, but these studies included few patients with severe disease, which may limit their applicability to patients who are generally considered for PA intervention.4-8 As with branch PA stenosis associated with other conditions, transcatheter intervention has become an accepted mode of therapy for patients with hemodynamically important PPS. Angioplasty and stent implantation have been shown to increase vessel diameter and decrease RV pressure in patients with PA stenosis in various clinical circumstances.9-14 Although several studies have focused on acute outcomes of catheterization in patients with Williams syndrome,12,13 little is known about long-term outcomes in patients who underwent transcatheter intervention for severe PPS early in life. Characterizing long-term outcomes in this population and identifying genetic, procedural, and hemodynamic factors associated with outcomes may help inform decision-making and prognosis.

Methods

Patients

Patients with bilateral PPS, who underwent transcatheter intervention at Children’s Hospital Boston at ≤5 years of age from July 1984 through July 2009, were ascertained from the computer database of the Department of Cardiology. This series does not include patients with PA stenosis in the context of other anomalies, such as tetralogy of Fallot, truncus arteriosus, transposition of the great arteries, single ventricle heart disease, congenitally discontiguous PAs, or patients with congenital rubella. Patients with isolated atrial or ventricular septal defects, or systemic arterial disease (eg, supravalvar aortic
WHAT IS KNOWN

- Infants and young children with severe isolated peripheral pulmonary stenosis are at risk for right ventricular hypertrophy and sudden cardiac death.
- Angioplasty and stent placement acutely reduce right ventricular pressures in this population.

WHAT THE STUDY ADDS

- This study reviews the long-term cardiovascular outcomes of 69 consecutive children who underwent transcatheter therapy for severe peripheral pulmonary stenosis.
- At long-term follow-up, most patients were asymptomatic, with median right ventricular pressure of approximately half-systemic.

Catheterization and Transcatheter PA Intervention

Patients generally underwent right and left heart hemodynamic catheterization, angiography, and interventions on the PAs including standard angioplasty, high-pressure angioplasty, cutting balloon angioplasty, and stent implantation, at the discretion of the operator.9–13,17 Standard angioplasty, high-pressure angioplasty, cutting balloon angioplasty, and stent implantation, at the discretion of the operator, were also performed. Patients who underwent open heart surgery before the first interventional catheterization, had a prior intervention elsewhere, or had unilateral PA stenosis were excluded. Only patients with severe PPS, defined as a preintervention RV-to-aortic pressure ratio ≥50%, were included. The Children’s Hospital Committee on Clinical Investigation approved the protocol.

Genetic/Syndromic Diagnosis

Patients were grouped into 6 categories according to genetic or syndromic diagnosis: (1) Williams syndrome diagnosed genetically (usually by fluorescence in situ hybridization testing); (2) Williams syndrome diagnosed clinically based on documented noncardiovascular stigmata but without genetic testing; (3) Alagille syndrome diagnosed clinically and genetically; (4) non-Williams familial arteriopathy (family history of at least 1 first or second degree relative with SVAS or PPS, but no syndromic diagnosis); (5) nonsyndromic and nonfamilial arteriopathy (ruled out for Williams syndrome on the basis of negative genetic testing or absence of noncardiac syndromic features on clinical evaluation at ≥5 years of age, and no diagnosis of Alagille syndrome); and (6) indeterminate genetic/syndromic diagnosis (no genetic testing, no clinical signs of Alagille syndrome, no family history of SVAS or PPS, and no or inconclusive evaluation for noncardiac stigmata of Williams syndrome at ≥5 years of age). A subset of patients with familial arteriopathy but genetically confirmed absence of Williams syndrome were tested for mutations in the ELN gene, according to previously reported methods.16

Follow-up

Cross-sectional follow-up was obtained on the basis of medical record review or physician correspondence through June 15, 2011. Hemodynamic data recorded during subsequent catheterizations and echocardiograms were collected, as were data about surgical or transcatheter interventions. Cardiac symptoms at most recent follow-up were categorized using the New York Heart Association classification. Survival data were also collected from the National Death Index through December 2009 for the 36 patients from the United States for whom clinical follow-up was not available past this date. Among this group, patients not identified as deceased in the National Death Index database were censored event-free as of December 2009 for survival analyses. National Death Index data were applied only to the survival outcome.

Data Analysis

The primary outcome was survival over time. Secondary outcomes included freedom from PA reintervention, RV/aortic pressure ratio, and cardiac symptoms at most recent follow-up. For time-to-event analyses, Kaplan–Meier analysis, log-rank testing, and Cox regression were performed. Patients lost to follow-up were censored event-free at the date of most recent follow-up. For analysis of freedom from reintervention, patients who died without reintervention were censored event-free. Patients who underwent surgical PA reintervention were not censored from subsequent analysis of transcatheter reintervention because surgical reintervention relieved proximal stenosis, whereas transcatheter intervention generally addressed more distal stenosis. For paired continuous data, paired t test or Wilcoxon signed-rank test was performed, and for comparison of continuous data between groups, independent samples t test, Wilcoxon rank-sum test, or analysis of variance was used, as appropriate. For categorical outcomes, χ² or Fisher exact test was performed. Data are presented as mean±SD, median (minimum–maximum), or frequency (%).

Results

Patients

Demographics and Associated Anomalies

From 1983 to 2009, 69 patients underwent transcatheter intervention for PPS at ≤5 years of age and met study criteria (Figure 1). Of these 69, 41 (59%) were referred from

Figure 1. Age at first intervention and genetic/syndromic diagnosis of the study cohort (as defined in methods section). PA indicates pulmonary artery.
outside our geographic catchment area of Massachusetts, New Hampshire, Vermont, and Rhode Island. The median age at intervention was 16 months, and 81% of patients were <3 years of age; 32 patients (46%) were male. At the time of catheterization, 41 patients (59%) also had SVAS (Table 1). SVAS was more common in patients with either Williams syndrome or non-Williams familial arteriopathy \((P=0.003)\) than those in other diagnostic subgroups, and was also associated with younger age at the first catheterization \((1.3±1.1 \text{ versus } 2.3±1.5 \text{ years}; \; P=0.002)\). Other than systemic arterial obstruction, the only significant- associated cardiovascular anomalies were a moderate or large ventricular septal defect in 3 patients and a right aortic arch in 2 patients.

**Genetic/Syndromic Diagnosis**

Thirty-eight patients had genetic or syndromic diagnoses, which included Williams syndrome in 23 patients, non-Williams familial arteriopathy in 13 patients, and Alagille syndrome in 3 patients. Ten patients with Williams syndrome were diagnosed with a chromosome 7q11.23 deletion by fluorescence in situ hybridization testing, and the other 13 had documented noncardiac physical examination findings consistent with Williams syndrome at ≥5 years of age but no reported genetic testing (see Materials in the online-only Data Supplement for further detail).

**Table 1. Selected Demographic and Diagnostic Data in 69 Patients ≤5 Years of Age Undergoing Primary Transcatheter Therapy for PPS**

<table>
<thead>
<tr>
<th>Associated Cardiovascular Anomalies</th>
<th>n=69</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supravalvular aortic stenosis</td>
<td>41 (59%)</td>
</tr>
<tr>
<td>Mild (10–30 mm Hg gradient)</td>
<td>19 (28%)</td>
</tr>
<tr>
<td>Moderate (30–50 mm Hg gradient)</td>
<td>11 (16%)</td>
</tr>
<tr>
<td>Severe (&gt;50 mm Hg gradient)</td>
<td>11 (16%)</td>
</tr>
<tr>
<td>Coarctation of the aorta/transverse arch obstruction</td>
<td>7 (10%)</td>
</tr>
<tr>
<td>Mild/moderate (10–50 mm Hg gradient)</td>
<td>5 (7%)</td>
</tr>
<tr>
<td>Severe (&gt;50 mm Hg gradient)</td>
<td>2 (3%)</td>
</tr>
</tbody>
</table>

**Preintervention systolic pressure (mm Hg)**

- **Right ventricle (RV)**: 90 (54–180)
- **Aorta**: 86 (50–160)
- **Left ventricle (LV), n=57**: 110 (72–220)

**Preintervention RV:aortic pressure ratio**

- **0.5–0.74**: 9 (13%)
- **0.75–0.99**: 23 (33%)
- **≥1.0**: 37 (54%)

**Interventions at the first catheterization**

- Number of PA branches dilated: 3 (0–6)
- Bilateral intervention: 59 (86%)
- Stent implantation: 10 (13%)
- Lobar/segmental PA intervention: 40 (58%)
- Cutting balloon angioplasty: 4 (6%)

Data are presented as mean±SD, median (minimum–maximum), or frequency (%), n=69 unless otherwise specified. PA indicates pulmonary artery; PPS, peripheral pulmonary stenosis.

*Peak-to-peak systolic pressure measured directly in the catheterization laboratory.

**Initial PA Hemodynamics**

Initial PA hemodynamics are described in Table 1. Patients who underwent catheterization in the first year of life had higher preintervention RV:aortic pressure ratios than those first catheterized at an older age (median 1.19 versus 0.97; \(P=0.04)\). Hemodynamic data are shown by genetic/syndromic diagnosis in the Materials in the online-only Data Supplement.

**Interventions**

**PA Intervention**

At the first catheterization, all but 2 patients (both of whom had adverse events before planned intervention) underwent intervention on the PAs (Table 1). Ten patients (13%) had stents implanted at the first catheterization. 9 in the proximal right PA, and 1 in the proximal left PA, despite all patients having bilateral PA stenosis; 8 of these patients had either Williams syndrome or non-Williams familial arteriopathy (23% of patients with these diagnoses received a stent versus 6% of patients in other subgroups; \(P<0.001)\). In 10 of the 18 patients who had a stent implanted at the first or second catheterization (7 with Williams syndrome), the indication for the stent was an obstructive or potentially obstructive intimal flap after angioplasty. An atrial septal defect was created before PA intervention in 11 patients, beginning in 1994.

**Acute Outcomes**

The RV:aortic pressure ratio decreased from a median of 1.00 (0.52–2.16) before treatment to a median of 0.88 (0.40–1.40) after the first intervention (pairwise median decrease of 0.18; \(P<0.001)\). The RV:aortic pressure ratio decreased by ≥0.3 in 20 patients (31%), and either increased or decreased by ≤0.1 in 24 patients (38%). Higher preintervention RV:aortic pressure ratio was associated with a greater decrease in the RV:aortic pressure ratio after intervention \((P<0.001; \; \text{Figure 2})\). Syndrome diagnosis, stent implantation, age at intervention, and the number of vessels dilated were not associated with differences in the magnitude of change in the RV:aortic pressure ratio.

**Adverse Events**

There were 4 deaths from complications of the first catheterization; the most recent occurred in 1997 in the 38th patient in the series. All 4 of these patients had suprasystemic RV pressure. Three of these deaths that occurred after hemodynamic instability during catheterization in patients with concomitant SVAS were summarized in a prior report. 12 The fourth patient died of pulmonary hemorrhage after rupture of a PA aneurysm that developed during catheterization 5 days earlier. Embolization coils had been deployed in the aneurysm at catheterization. The patient had a large unrestricted ventricular septal defect, but did not have SVAS. A fifth patient with suprasystemic RV pressure and mild SVAS developed bradycardia and asystole as the catheter was being passed across the RV outflow tract, and recovered after resuscitation in the catheterization laboratory with the aid of extracorporeal membrane oxygenation.
Follow-up

Survival

At a median cross-sectional follow-up of 8.5 years (1 day–23 years), 10 patients (14%) were known to be dead, including the 4 procedural deaths described above. One patient died of cardiac arrest during a second catheterization at 9 months of age. Two patients with severe biventricular hypertrophy died after other transcatheter or surgical procedures (at 2 and 14 months of age). Three patients died in the community 8 days, 16 months, and 12 years after the first catheterization: 1 because of PA disease that was much severe to be treated further, 1 of suspected acute endocarditis, and 1 of an unknown cause. Survival was 88±4% at 1 year after the initial intervention and 87±4% at 10 years (Figure 3A). Patients with lower initial RV:aortic pressure ratio tended to survive longer, although this was not statistically significant (Figure 3B).

Reintervention

Freedom from transcatheter reintervention was 47±7% at 1 year after the initial intervention and 24±6% at 5 years (Figures 3 and 4). Higher RV:aortic pressure ratio at the end of the first catheterization was associated with shorter freedom from reintervention (hazard ratio 1.18 per 0.1 increase in RV:aortic pressure ratio; P=0.01). Details of the second and third interventional catheterizations are summarized in Table 2 and in the Materials in the online-only Data Supplement. RV:aortic pressure ratio decreased from a median of 0.90 (0.41–1.74) to a median of 0.70 (0.37–1.46), with a median pairwise decrease of 0.17 (P<0.001) during the second catheterization, and again at the third catheterization (median pairwise decrease 0.07; P=0.05; n=24; Figure 5).

Between the end of the first catheterization and the beginning of the second in patients who underwent reintervention, there was no significant change in RV:aortic pressure ratio (median change, −0.02; range, −0.38 to 0.88); RV:aortic pressure ratio was higher in 22 patients and lower in 21 (in 4 patients, RV:aortic pressure ratio was not available at 1 of the 2 time points). The patients whose RV:aortic pressure ratio decreased had fewer branches dilated at the first catheterization (mean 2.5±1.3 versus 3.9±1.6; P=0.002) and were less likely to have had lobar or segmental branch dilations (33% versus 64%; P=0.02). Patients with a larger decrease in the RV:aortic pressure ratio during the first catheterization tended to have a larger increase or a smaller decrease between the...
first and second catheterizations \(P=0.002\). There was no significant change in RV:aortic pressure ratio between the end of the first reintervention and the beginning of the second reintervention (median pairwise increase 0.02; \(P=0.4; n=23\)).

Surgical PA augmentation arterioplasty was performed in 12 patients, 8 within 1 year of the initial catheter intervention and 6 after at least 1 transcatheter reintervention (Table 3). One additional patient underwent bilateral lung transplant after there was persistent severe RV hypertension and progressive peripheral pulmonary arterial disease after repeated transcatheter intervention. Freedom from surgical PA reintervention was 82±5% at 1 year and 78±6% at 5 years (Figure 3A). Aortoplasty for SVAS was also performed in 10 of these patients, as well as 8 additional patients who did not undergo surgical intervention on the PAs (see Materials in the online-only Data Supplement). Two patients underwent surgical PA augmentation arterioplasty without SVAS repair: 1 underwent atrial septal defect closure during the procedure and 1 had removal of a stent that fractured in situ in the main PA. Only 1 patient underwent a second PA surgery, in which a retained stent and catheterization balloon that had broken off the catheter shaft were removed. None of the 3 patients with Alagille syndrome underwent surgical PA augmentation.

Overall, freedom from death or any PA reintervention was 33±6% at 1 year and 19±5% at 5 years. Factors associated with shorter freedom from reintervention or death in univariate Cox regression were age <1 year at the first catheterization (hazard ratio 1.9; \(P=0.02\)), and higher preintervention RV:aortic pressure ratio (hazard ratio 1.1 per increase of 0.10 in RV:aortic pressure ratio; \(P=0.02\)).

### Table 2. Procedural and Diagnostic Data at the Second Catheterization (n=47)

<table>
<thead>
<tr>
<th>Number of branches dilated</th>
<th>3 (1–11)</th>
<th>1</th>
<th>7 (14%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2</td>
<td>12 (26%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>9 (19%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>7 (14%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥5</td>
<td>12 (26%)</td>
<td></td>
</tr>
<tr>
<td>Bilateral PA angioplasty</td>
<td>37 (79%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stent implantation</td>
<td>10 (21%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LPA branches</td>
<td>6 (13%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RPA branches</td>
<td>7 (15%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cutting balloon angioplasty</td>
<td>9 (20%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lobar/segmental PA angioplasty</td>
<td>40 (85%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change in RV:aortic pressure ratio (n=49)*</td>
<td>−0.17 (−1.17 to 0.14)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Peak-to-peak systolic pressures measured directly in the catheterization laboratory.

Hemodynamic and Clinical Status

Among the 41 patients who were alive and had a diagnostic or interventional catheterization at least 1 year after the initial catheterization, the median RV:aortic pressure ratio had decreased from 1.0 (0.52–2.17) at the first catheterization to 0.53 (0.2–1.1) at the most recent (median pairwise decrease 0.34; \(P<0.001\)) over a median duration of 5.1 years (13 months–19 years). When the most recent RV:aortic pressure

![Figure 4. Frequency, time course, and outcomes of transcatheter reinterventions. FU indicates follow-up; and RV:Ao, right ventricular to aortic systolic pressure ratio.](http://circinterventions.ahajournals.org/)

![Figure 5. Sample angiograms from 1 study patient (A) at the beginning of the first intervention (right ventricular [RV]:aortic pressure ratio of 1.46) and (B) at the beginning of the third intervention 7 years later (RV:aortic pressure ratio of 0.52). There is a clear increase in the diameter of the pulmonary arteries.](http://circinterventions.ahajournals.org/)

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n=47 unless otherwise specified. LPA indicates left pulmonary artery; PA, pulmonary artery; RPA, right pulmonary artery; and RV, right ventricle.
In this long-term observational study, we followed 69 patients with severe PPS at ≤5 years of age, with a focus on acute outcome, reinterventions, survival, and RV pressures over time. Mortality was concentrated early in our experience and in the acute period because of complications surrounding PA interventions and other cardiac procedures. Reinterventions on the branch PAs were common, but RV:aortic pressure ratios were significantly lower at follow-up than before intervention, and no patients are known to have died from long-term progressive RV cardiac failure.

### Discussion

#### Survival

In this long-term observational study, we followed 69 patients who underwent primary transcatheter intervention for severe PPS at ≤5 years of age, with a focus on acute outcome, reinterventions, survival, and RV pressures over time. Mortality was concentrated early in our experience and in the acute period because of complications surrounding PA interventions and other cardiac procedures. Reinterventions on the branch PAs were common, but RV:aortic pressure ratios were significantly lower at follow-up than before intervention, and no patients are known to have died from long-term progressive RV cardiac failure.

#### Acute Outcomes

Little is known about outcomes in infants and young children undergoing primary transcatheter intervention with severe PPS. Many studies have shown acute improvement from transcatheter intervention in patients with PA stenosis, but those typically included patients with tetralogy of Fallot and surgical anastomoses, among other conditions.\(^3\)–\(^11\),\(^13\)

Geggel et al,\(^12\) reporting on a cohort of 25 patients of various ages with Williams syndrome and PPS, found a modest acute decrease in the RV:aortic pressure ratio. In contrast, in this series, which included a larger and more diverse cohort of exclusively young patients, more recent results, and greater statistical power, there was clear and significant acute hemodynamic improvement after the initial intervention. RV:aortic pressure ratio was used to adjust for changes in systemic pressure related to changes in physiological conditions. In particular, depression of RV and systemic pressures after induction of anesthesia confounds analysis of absolute RV pressure change. Geggel et al\(^12\) also reported an acute increase in vessel diameter after angioplasty, although in our experience, the relationship between central PA diameter increase and hemodynamic improvement is variable. This variability is likely attributable to the presence of diffuse, distal stenosis, and to abnormalities in the mechanical behavior of these patients’ PAs.

Acute mortality was an important problem early in this experience, and occurred most often because of asystole and ventricular failure in the catheterization laboratory, as previously reported.\(^12\) In response, it became common practice at our institution to create a small atrial septal defect before PA dilation in patients with severe biventricular obstruction if one was not present, to allow preserved left ventricle filling and output during PA angioplasty. No patients have died in this manner since the adoption of this strategy. No other severe adverse events occurred more than once.

#### PA Reintervention

PA reintervention was performed during the follow-up period in more than two thirds of the patients, and usually consisted of additional transcatheter therapy. Similar to the initial intervention, transcatheter reinterventions were generally successful in reducing the RV:aortic pressure ratio. Surgical PA reintervention was uncommon, and usually occurred in patients with concomitant SVAS requiring repair. Our results suggest that serial transcatheter treatment of proximal PA stenosis is sufficiently effective that surgical PA augmentation is rarely indicated in the absence of other anomalies.

#### Long-term Hemodynamics and Clinical Course

Aside from survival, one of the most important outcomes in this patient population is RV:aortic pressure ratio over time. Hemodynamics improved over time after intervention; at most recent catheterization follow-up, the median RV pressure was ≤50% of systemic blood pressure. Most patients with clinical
follow-up status were New York Heart Association class I, although many of these nevertheless had modestly elevated RV pressure. Chronic RV pressure overload causes sarcomere synthesis and increased myocyte size; if this adaptation fails to compensate for greater wall strain, the patient can progress to chamber dilation and cardiac failure. Although it is not known whether mildly or moderately high RV pressure increases the risk of adverse outcomes in humans, or whether there is a threshold pressure or RV:aortic pressure ratio above which risk increases, modestly elevated RV pressure is relatively common in patients with congenital and acquired heart disease and is generally well-tolerated. In dogs, severe but not mild RV afterload elevation causes loss of RV function.

Long-term outcome studies after tetralogy of Fallot repair have shown that an RV:left ventricular pressure ratio >0.5 is associated with higher mortality, although this association may be confounded by collinear risks related to reoperation, which is likely to occur more often in patients with obstructions in the pulmonary circulation and consequent elevation of RV pressure. Further study of this issue, and longer follow-up of this cohort of patients, may help determine how aggressively to pursue RV pressure relief in patients with PPS and other congenital cardiovascular conditions.

Genetic/Syndromic Diagnosis

Although we were not able to characterize the genetic/syndromic status in many patients because of the rigorous definition we applied for the clinical diagnosis of Williams syndrome, there were no dramatic differences in acute or long-term outcomes between diagnostic groups. Previous publications have speculated that transcatheter intervention might be less effective in patients with elastin arteriopathy because decreased vessel elasticity might increase the risk of vessel rupture and smooth muscle proliferation might lead to earlier restenosis. There were no cases of acute PA rupture in our series, although 1 patient of indeterminate genetic diagnosis died after rupture of an iatrogenic PA aneurysm on postprocedure day 5. Our study does not necessarily provide insight into the risk of restenosis. It has been our experience that PA stenoses in this population usually respond to conventional or cutting balloon angioplasty, but there is often considerable postangioplasty recoil. Patients with Williams syndrome seem to be prone to the development of intimal flaps, and of the 10 patients in our cohort who underwent stent implantation for an obstructive flap at the initial or follow-up catheterizations, 7 had Williams syndrome. This tendency may be related to the abnormal architecture of the arterial media in these patients, which is characterized by increased thickness and fragmented elastin lamellae. There was a tendency toward shorter freedom from reintervention in patients with Williams syndrome compared with those who had other conditions. There were too few patients with Alagille syndrome to determine whether outcomes differed from patients with other forms of arteriopathy.

Assessment of Intervention

This study does not allow definitive conclusions about the relative benefit of transcatheter intervention in this population, because there was no control cohort of similar patients who did not undergo intervention. The published literature on the natural history of PPS includes few patients with severe PPS. In the natural history study reported by Wren et al., only 7 of 35 patients had an RV pressure ≥50 mm Hg; in 5 of those 7, the RV pressure was observed to decrease spontaneously (without any interventions) by up to 40 mm Hg during the first several years of life. It is possible that some of the patients in our series would have experienced similar improvements in RV pressure without intervention. However, the fact that we observed larger decreases in RV:aortic pressure ratio immediately after intervention and that there was generally no change between interventions suggest that the long-term reduction in RV:aortic pressure ratio was at least, in part, because of or facilitated by intervention.

Even if the RV:aortic pressure ratio would have decreased over time without treatment in some or all of our patients, early intervention may be indicated to ameliorate RV hypertension acutely, particularly in young patients with systemic or suprasystemic RV pressure. As discussed above, severe RV hypertension is associated with RV hypertrophy, chamber dilation, and cardiac failure. In Williams syndrome patients, sudden death has been reported to occur about once per 1000 patient years, most commonly because of myocardial ischemia, decreased cardiac output, and arrhythmias. Patients with biventricular outflow tract obstruction and coronary artery stenosis are at particular risk. These results suggest a model in which the combination of increased RV oxygen demand because of hypertrophy and decreased oxygen supply because of coronary artery stenosis or restriction of flow into the sinuses of Valsalva related to SVAS predisposes patients with arteriopathy to sudden cardiac death. Thus, it is reasonable to infer that if severe RV hypertension were allowed to go untreated, RV myocardial oxygen demand would be greater and RV hypertrophy would be more severe, with a concomitantly higher risk of morbidity and mortality.

Primary open surgical intervention is an alternative treatment strategy. One recent case series of 16 patients reported low mortality, low rates of reintervention, and long-term RV pressures of less than half-systemic pressure.

Limitations

The study cohort is not representative of all patients with severe PPS because of our inclusion criteria, particularly the requirement for primary transcatheter therapy. The number of patients receiving primary surgical treatment for severe PPS at our institution is quite small, and is generally limited to patients with significant SVAS and other anomalies that are treated surgically. In addition, our study population may be skewed by the fact that we are a referral center for this condition (59% of patients were referred from outside our region), and as a result of survival bias, with some patients dying before receiving transcatheter intervention. Because of the retrospective nature of the study, there were no pre-established criteria for initial intervention or follow-up care, and decisions on intervention and reintervention may have varied across providers. Because many patients arefollowed elsewhere, follow-up data were incomplete for some. The National Death Index was used to determine whether patients lost to follow-up were known to be dead as of December 2009; however, this...
database may not be complete. Even, when current follow-up information was available, it may not have encompassed the patient’s full and complex longitudinal care. Because many patients underwent follow-up catheterization only within several years of the initial intervention, our ability to trace the time course of improvement in RV pressure was limited. Also, as noted above, we did not have complete information on genetic/syndromic status, which limited our ability to assess differences according to this factor.

Conclusions

After several early adverse events, transcatheter treatment has matured into a safer and more effective approach for infants and young children with severe bilateral PPS, regardless of genetic/syndromic diagnosis. During intermediate and long-term follow-up, mortality and PA surgical intervention were rare, the median RV pressure was approximately half-systemic, and young children with severe bilateral PPS, regardless of maturity, matured into a safer and more effective approach for infants. This work was funded by Department of Cardiology, Children’s Hospital Boston and Harvard Medical School Scholars in Medicine Program (J.W. Cunningham).

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Disclosures

None.

References

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Supplemental Methods
Data Analysis
Changes in RV:aortic pressure ratios over time were characterized using linear mixed-effects models, which accounted for the correlation among repeated measurements on the same subject. Individual patients were treated as random effects, while additional clinical covariates were treated as fixed effects. If changes in the ratio over time were not linear, quadratic and piecewise relationships were also explored. When statistically significant relationships between the RV:aortic pressure ratio and clinical covariates were identified, interaction terms were used to determine whether trends over time differed among subgroups of patients.

Supplemental Results
Genetic/Syndromic Diagnosis
One of the 10 patients with a genetic diagnosis of Williams syndrome was found to have a larger than typical deletion in chromosome 7; this patient has more severe and diverse symptoms than other patients with Williams syndrome, including epilepsy, tracheomalacia, and coronary artery stenosis. Of the 12 patients (17%) with non-Williams familial arteriopathy, Williams syndrome was ruled out by absence of the deletion on fluorescence in situ hybridization in 5 of these patients and by absence of non-cardiac stigmata in the remaining 7. Three of these patients were tested for mutations in the \textit{ELN} gene, and were included in a prior report. \textsuperscript{16} 1 had a CAG to TAG nonsense mutation in exon 21, 1 had a TAA to TAC nonsense mutation in exon 9, and 1 did not have any mutations. Williams syndrome was ruled out on the basis of genetic testing in 9 patients and by the absence of non-cardiac stigmata at 5 years of age or older in 9 others.

PA Intervention
Interventions on 1 or more lobar/segmental PA branches were performed at the first catheterization in 40 patients (58%). Patients who had lobar or segmental interventions tended to be younger than those who did not, though the difference was not statistically significant (1.4±1.2 vs. 1.9±1.5 years, \(p=0.13\)). The baseline RV:aortic pressure ratio did not differ between stented and non-stented patients, or between those who did and did not have lobar/segmental interventions performed.

Reintervention
Absolute RV pressure decreased from a median of 85 (44-150) mmHg after the first catheterization to a median of 80 (35-135) mmHg at the second catheterization before intervention (median pairwise decrease of 9 mmHg, \(p=0.2\)).

At the second catheterization, 36 patients (78%) underwent bilateral PA intervention. The median number of PA branches dilated at the second catheterization was 3 (1-11), and lobar or segmental vessel intervention was performed in 39 (85%) cases. Ten (15%) patients had stents implanted, 3 in the left PA only, 4 in the right PA only, and 4 bilaterally; 2 of these patients had previously had stents implanted at the first catheterization. In 4 of these cases, the indication for stent implantation was an obstructive intimal flap or tear. RV:aortic pressure ratio decreased more at the second catheterization in patients with either Williams Syndrome or non-Williams familial arteriopathy than in patients with other diagnoses (-0.30±0.30 vs -0.11±0.17, \(p=0.02\)). There was no change in absolute RV pressure (median pairwise change 0). As described above, 1 patient died during the second catheterization due to cardiac arrest.

Twenty-nine patients underwent 2 or more reinterventions. Between the end of the first reintervention and the beginning of the second reintervention, there was no significant change in RV:aortic pressure ratio (median pairwise increase of 0.02, \(p=0.4\), \(n=23\)). During the second reintervention, RV:aortic pressure ratio decreased from a median of 0.84 (0.34-1.33) prior to intervention to a median of 0.67 (0.30-1.51) following the intervention (median pairwise decrease of 0.07; \(p=0.05\), \(n=24\)).
All patients who underwent surgery for SVAS were found to have SVAS at the initial catheterization. Three patients initially had only mild SVAS; of these, 1 underwent surgery for PPS and episodes of syncope, 1 progressed to have severe SVAS (60 mmHg gradient) within 6 months, and 1 had progression to moderate SVAS (45 mmHg gradient) within 12 months.

By linear mixed effects modeling, there was a progressive decrease in the RV:aortic pressure ratio over time (Figure S1). Compared with the pressure ratio immediately after the initial intervention, there was a continued decrease of 0.03 per year (p<0.001). The rate of decrease was greater in patients with suprasystemic RV pressure prior to intervention than those with systemic or subsysteicm RV pressure (0.04 vs 0.02 per year, p=0.04 for interaction of time and suprasystemic RV pressure pre-intervention), and for patients were <1 year of age at the initial intervention than those who were older (0.04 vs 0.02 per year, p=0.05 for interaction of time and age at intervention).
## Supplemental Table

### Table S1: Diagnostic and Interventional Data by Genetic/Syndromic Diagnosis

<table>
<thead>
<tr>
<th></th>
<th>Williams Syndrome</th>
<th>Non-Syndromic Familial Arteriopathy</th>
<th>Non-Syndromic &amp; Non-Familial</th>
<th>Alagille Syndrome</th>
<th>Unknown/Indeterminate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Patients</td>
<td>23</td>
<td>12</td>
<td>18</td>
<td>3</td>
<td>13</td>
</tr>
<tr>
<td><strong>Associated Cardiovascular Anomalies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supravalvar Aortic Stenosis</td>
<td>18 (78%)</td>
<td>9 (75%)</td>
<td>7 (39%)</td>
<td>0 (0%)</td>
<td>7 (54%)</td>
</tr>
<tr>
<td>Mild (10-30 mmHg gradient)</td>
<td>11 (48%)</td>
<td>3 (25%)</td>
<td>3 (17%)</td>
<td>0 (0%)</td>
<td>2 (15%)</td>
</tr>
<tr>
<td>Moderate (30-50 mmHg gradient)</td>
<td>5 (22%)</td>
<td>1 (8%)</td>
<td>3 (17%)</td>
<td>0 (0%)</td>
<td>2 (15%)</td>
</tr>
<tr>
<td>Severe (&gt;50 mmHg gradient)</td>
<td>2 (9%)</td>
<td>5 (42%)</td>
<td>1 (6%)</td>
<td>0 (0%)</td>
<td>3 (23%)</td>
</tr>
<tr>
<td>Coarctation of the Aorta / Transverse Arch Obstruction</td>
<td>3 (13%)</td>
<td>2 (17%)</td>
<td>0 (0%)</td>
<td>1 (33%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Mild/Moderate (10-50 mmHg gradient)</td>
<td>2 (9%)</td>
<td>2 (17%)</td>
<td>0 (0%)</td>
<td>1 (33%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Severe (&gt;50 mmHg gradient)</td>
<td>1 (4%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Pre-Intervention RV:aortic Pressure Ratio (^1)</td>
<td>1.16 (0.68-1.76)</td>
<td>1.08 (0.75-1.84)</td>
<td>1.01 (0.61-2.17)</td>
<td>0.78 (0.69-0.97)</td>
<td>1.0 (0.52-1.50)</td>
</tr>
<tr>
<td>&lt;0.75</td>
<td>1 (4%)</td>
<td>0 (0%)</td>
<td>5 (28%)</td>
<td>1 (33%)</td>
<td>2 (15%)</td>
</tr>
<tr>
<td>0.75-0.99</td>
<td>8 (35%)</td>
<td>6 (50%)</td>
<td>4 (22%)</td>
<td>2 (67%)</td>
<td>3 (23%)</td>
</tr>
<tr>
<td>≥1.0</td>
<td>14 (61%)</td>
<td>6 (50%)</td>
<td>9 (50%)</td>
<td>0 (0%)</td>
<td>8 (62%)</td>
</tr>
<tr>
<td><strong>Interventions at the First Catheterization</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of PA Branches Dilated</td>
<td>3 (0-7)</td>
<td>2 (2-7)</td>
<td>3 (1-6)</td>
<td>3 (2-4)</td>
<td>2 (0-5)</td>
</tr>
<tr>
<td>Bilateral Intervention</td>
<td>18 (78%)</td>
<td>11 (92%)</td>
<td>16 (89%)</td>
<td>3 (100%)</td>
<td>11 (85%)</td>
</tr>
<tr>
<td>Stent Implantation</td>
<td>4 (17%)</td>
<td>4 (33%)</td>
<td>2 (11%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Lobar/Segmental PA Intervention</td>
<td>12 (52%)</td>
<td>6 (50%)</td>
<td>11 (61%)</td>
<td>2 (67%)</td>
<td>9 (69%)</td>
</tr>
<tr>
<td>Cutting Balloon Angioplasty</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>2 (11%)</td>
<td>1 (33%)</td>
<td>1 (8%)</td>
</tr>
<tr>
<td>Acute Change in RV:aortic Pressure Ratio (^1) (n=64)</td>
<td>-0.29 (-0.66 to 0.45)</td>
<td>-0.09 (-0.48 to 0.43)</td>
<td>-0.16 (-1.37 to 0.07)</td>
<td>-0.15 (-0.17 to -0.07)</td>
<td>-0.19 (-0.45 to 0.16)</td>
</tr>
</tbody>
</table>

\(^1\)Peak to peak systolic blood pressures measured directly in the catheterization laboratory.
Figure S1 Legend:
Scatterplot depicting RV:aortic pressure ratios at the end of the first catheterization (after all interventions) and at follow-up catheterizations, after any interventions performed at those catheterization.