Balloon Dilation Angioplasty of Peripheral Pulmonary Stenosis Associated With Williams Syndrome

Robert L. Geggel, MD; Kimberlee Gauvreau, ScD; James E. Lock, MD

Background—Experience of balloon dilation of peripheral pulmonary stenosis (PPS) in Williams syndrome (WS) is limited.

Methods and Results—Catheterizations in all patients with WS undergoing therapy for PPS from 1984 to 1999 were reviewed. Criteria for successful dilation included an increase >50% in predilation diameter and a decrease >20% in ratio of right ventricular (RV) to aortic (Ao) systolic pressure. Median age and weight were 1.5 years and 9.5 kg. There were 134 dilations during 39 procedures in 25 patients. The success rate for initial dilations was 51%. In multivariate analysis, successful dilation was more likely (1) in distal than in central pulmonary arteries (P=0.02), (2) if the balloon waist resolved with inflation (P=0.001), and (3) with larger balloon/stenosis ratio (P<0.001). RV pressure was unchanged after dilation (96±30 versus 97±31 mm Hg), primarily because of failure to enlarge central pulmonary arteries. The Ao pressure increased (102±14 versus 109±19 mm Hg, P=0.03), and the RV/Ao pressure ratio decreased (0.97±0.34 versus 0.91±0.30, P=0.05). Aneurysms developed after 24 dilations (18%) and were not related to balloon/stenosis ratio. Balloon rupture in 12 dilations produced an aneurysm in all 7 cases when rupture was in a hypoplastic segment. Three patients died, none from pulmonary artery trauma, and all before 1994.

Conclusions—Mortality occurred early in our experience. Despite successful dilation of distal pulmonary arteries, there was modest initial hemodynamic improvement, mainly because of persistent central pulmonary artery obstruction. A serial approach of distal dilations followed by surgical repair of proximal obstruction may be a rational and successful therapy. (Circulation. 2001;103:2165-2170.)

Key Words: Williams syndrome ■ catheterization ■ balloon ■ pediatrics ■ stenosis

Williams syndrome is a multisystem disorder affecting 1 in 20 000 live births and is associated with congenital cardiovascular malformations in 60% to 80% of patients.1,2 Supravalvar aortic stenosis is the most common cardiac defect, and peripheral pulmonary stenosis (PPS) is the second most commonly identified lesion.3 PPS can be multiple and bilateral and can be associated with hypoplasia of the pulmonary arterial bed.

Experience of balloon dilation of PPS associated with Williams syndrome has been limited. Previous series have either considered patients with isolated congenital PPS as a group without distinguishing those with Williams syndrome4–9 or included results from ≤4 vessels in patients with Williams syndrome.10–14

To more fully assess the effect of balloon dilation of PPS associated with Williams syndrome, we reviewed our experience with this patient group. We evaluated the change in vessel diameter as well as hemodynamic effects and complications.

Methods

Study Group
From 1984 to 1999, 25 patients with Williams syndrome underwent balloon dilation of PPS and had cineangiograms available for review.

The diagnosis of Williams syndrome was based on clinical features1 or genetic analysis.15 Thirty-nine catheterizations involved balloon dilation of PPS, and 5 were follow-up studies. No patient had >3 procedures involving balloon dilation of PPS. For patients having >1 dilation procedure, the median time interval between the first and second catheterization was 3.8 months (range 0.2 to 30 months, n=9) and between the second and third intervention, 3.9 months (range 2.3 to 55 months, n=5).

The study group included 12 female and 13 male patients. Patient age ranged from 1 month to 26 years (median 1.5 year). Patient weight ranged from 2.8 to 57 kg (median 9.5 kg). Coexisting heart defects were present in 23 patients. Seven patients had valvar and supravalvar main pulmonary artery stenosis, 18 had supravalvar aortic stenosis, 4 had coarctation, 2 had large membranous ventricular septal defect, 6 had atrial septal defect, and 1 had severe right ventricular (RV) dysfunction.

Indications
In general, the indications for balloon angioplasty were more restrictive for patients with Williams syndrome than for those with isolated or postoperative PPS.3 For the 39 interventional procedures, 32 were performed because of near systemic or suprasystemic RV pressure. One of these patients had markedly reduced flow to 1 lung, and another had syncope. The other 7 procedures were performed because of markedly reduced flow to 1 lung.

Procedure
Venous access was obtained from the femoral vein (n=38) or the subclavian vein (n=1). Beginning in 1991, if there was either RV
pressure >90% of systemic level or left-sided obstruction of >30 mm Hg, and if a septal communication was not present, an atrial septal defect was created by transseptal puncture followed by balloon dilation with a 6- or 8-mm balloon. For pulmonary artery dilations, balloon dilation catheters were manufactured by Meditech, ACS, or B. Braun. The angioplasty technique has been described previously.13 Predilation and postdilation arterial diameters were determined from biplane cineangiograms. Magnification errors were corrected by relating vessel size to the known diameter of a fully inflated balloon on the dilation catheter. An aneurysm was defined according to previous criteria as a sacular formation that tapered abruptly and measured at least twice the diameter of the adjacent pulmonary artery.17 Pulmonary perfusion scans were performed by established techniques.16

Criteria for Success
A successful dilation was defined by parameters proposed previously.17 These included an increase of >50% of predilation diameter, a decrease of >20% in the ratio of systolic RV to aortic pressure (RV/Ao), or an increase of >20% in flow to a lung.

Statistical Analysis
Arterial diameters and hemodynamic parameters were compared before and after dilation by the paired t test. Fisher’s exact test was used for the comparison of proportions. Generalized estimating equation (GEE) models were used to evaluate factors associated with successful vessel dilation.19 Unlike logistic regression, the GEE technique adjusts for the correlation among multiple vessels within the same patient. To examine the simultaneous effects of all factors on outcome status, variables significant at the 0.20 level in univariate analysis were considered for inclusion in a multivariate GEE model. A significance level of 0.05 was required for retention in the final model.

Results

Procedure
In the 39 interventional procedures, initial management involved intravenous sedation in 22 procedures and general anesthesia in 17 procedures. Three patients receiving sedation required subsequent intubation, 1 for management of hemoptysis and 2 for cardiopulmonary resuscitation. After 1992, all patients with RV systolic pressure >90% of systemic level alone (5 patients) or in combination with left-sided obstruction of >30 mm Hg (7 patients) had general anesthesia at the start of the case. From 1984 through 1992, only 2 of 14 patients fulfilling these criteria had general anesthesia (14% versus 100%, P<0.001).

A total of 134 dilations were performed. The median number of arteries dilated in each procedure was 3, ranging from 0 to 9. There was no effect of year of procedure on the number of vessels dilated (P=0.62). One patient had 2 vessels that were not imaged after dilation because of hemodynamic instability. Stents were dilated in 3 mediastinal arteries. Of the remaining 129 dilations, 111 were initial, 14 were second, and 4 were third attempts. Twenty-nine dilations involved the mediastinal portion of the pulmonary artery, and 100 involved the intraparenchymal segments. Fluoroscopy time ranged from 29 to 264 minutes (median 71 minutes, n=29). The contrast used ranged from 1.7 to 8.9 mL/kg (median 4.1 mL/kg). The balloon inflating pressure was recorded in 42 dilations (31%) and ranged from 5 to 28 atm (median 14 atm).

Atrial Septal Defect Creation
An atrial septoplasty was performed in 7 procedures. In 6 procedures, left-sided obstruction of >30 mm Hg alone (1 patient) or in combination with RV systolic pressure >90% of systemic level (5 patients) was present. In 1 patient, antegrade entry into the left ventricle was required for angiography. Twenty-one other procedures were performed in which RV systolic pressure was >90% of systemic level alone (n=7) or in combination with left-sided obstruction of >30 mm Hg (n=14). In 2 of these procedures, no septal defect was present or created; 1 of these patients had a catheterization-related death.

Arterial Diameter
Biplane pulmonary angiography was mandatory to adequately define pulmonary artery anatomy and direct wire and catheter placement (Figure 1). Because multiple dilations of the same vessel are unlikely to be independent, the change in arterial diameter was analyzed for initial dilations only. For the 111 initial dilations, the average increase in diameter was 68±67%. The mean arterial diameter increased from 2.4±1.2 to 3.6±1.7 mm (P<0.001). In 51% of vessels, the angiographic diameter increased by ≥50%. For successful dilations, the diameter increased 112±65%, with the mean diameter increasing from 2.0±1.0 to 4.0±1.9 mm (P<0.001). For failed dilations, the diameter increased 20±20%, with the mean diameter changing from 2.7±1.3 to 3.3±1.4 mm (P<0.001).

Successful dilation was more likely to occur in intraparenchymal than mediastinal arteries, in arteries in which an aneurysm developed, in arteries with a smaller initial diameter, and with use of a larger balloon/stenosis ratio (Table 1). For a balloon/stenosis ratio ≥3, 66% of dilations were successful, whereas for a ratio <3, 32% were successful (P=0.001). Successful dilations were also somewhat more likely to occur in procedures performed in 1992 or later and with disappearance of the balloon waist. In multivariate analysis (Table 2), successful dilations were more likely to occur in distal rather than central pulmonary arteries, when the balloon waist resolved with inflation, and with use of larger balloon/stenosis ratios.

Serial Angiography
Follow-up angiograms were available for 49 arteries. Ten of these vessels were dilated a second time and 4 a third time. Twenty-eight of these initial dilations were successful (7 of
TABLE 1. Factors Associated With Success for Initial Vessel Dilation: Univariate Analysis

<table>
<thead>
<tr>
<th>Factor</th>
<th>Success (n=57)</th>
<th>Failure (n=54)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Balloon/stenosis ratio</td>
<td>3.8±1.5</td>
<td>3.0±0.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Initial diameter, mm</td>
<td>2.0±1.0</td>
<td>2.7±1.3</td>
<td>0.002</td>
</tr>
<tr>
<td>Vessel type intraparenchymal</td>
<td>50 (88)</td>
<td>37 (69)</td>
<td>0.01</td>
</tr>
<tr>
<td>Aneurysm</td>
<td>16 (28)</td>
<td>6 (11)</td>
<td>0.02</td>
</tr>
<tr>
<td>Year of catheterization</td>
<td>16 (28)</td>
<td>26 (48)</td>
<td>0.06</td>
</tr>
<tr>
<td>Age &lt;2 y</td>
<td>24 (42)</td>
<td>25 (46)</td>
<td>0.48</td>
</tr>
<tr>
<td>Intimal tear</td>
<td>18 (32)</td>
<td>11 (20)</td>
<td>0.25</td>
</tr>
<tr>
<td>Balloon rupture</td>
<td>6 (11)</td>
<td>6 (11)</td>
<td>0.64</td>
</tr>
</tbody>
</table>

Data are No. of patients (%) or mean±SD.

TABLE 2. Factors Associated With Success for Initial Vessel Dilation: Multivariate Analysis

<table>
<thead>
<tr>
<th>Factor</th>
<th>OR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intraparenchymal vessels</td>
<td>3.5</td>
<td>1.3–9.9</td>
<td>0.02</td>
</tr>
<tr>
<td>Disappearance of balloon waist</td>
<td>6.2</td>
<td>2.1–18</td>
<td>0.001</td>
</tr>
<tr>
<td>Larger balloon/stenosis ratio</td>
<td>2.7</td>
<td>1.5–4.8</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Associated with each 1-unit increase in balloon/stenosis ratio.

13 mediastinal and 21 of 36 intraparenchymal arteries). Of these dilations, restenosis to a diameter similar to the baseline value occurred in 9 arteries (32%), 1 mediastinal (14%) and 8 intraparenchymal (38%) (P=0.37). Two distal vessels that restenosed were redilated, 1 of which was successful and maintained its diameter when imaged 4 months later. Redilations in 8 arteries that had been failures were successful in 1. Redilations in 4 arteries that were successful increased the diameter by >50% from the new baseline in 1.

Hemodynamics

For initial dilations, baseline and postdilation values for systolic pulmonary artery pressure distal to a stenosis were measured in 20 vessels (18%) and a systolic pressure gradient across the segment was measured in 12 vessels (11%). For 8 successful dilations, the initial distal pressure was 20±10 mm Hg, postdilation pressure 47±29 mm Hg (P=0.03), initial gradient (available for 5 dilations) 76±37 mm Hg, and postdilation gradient 56±37 mm Hg (P=0.09). For 12 failed dilations, baseline pulmonary pressure was 22±7 mm Hg, postdilation pressure 29±12 mm Hg (P=0.02), initial gradient (available for 7 dilations) 42±18 mm Hg, and postdilation gradient 39±18 mm Hg (P=0.25).

Baseline and postdilation measurements of RV and aortic systolic pressures were available for 25 interventional procedures. Comparisons were not made in 14 procedures because of death (3 patients), presence of a nonrestrictive ventricular septal defect (2 patients), or an unavailable pressure value (9 procedures). Mean RV pressure was unchanged (96±30 versus 97±31 mm Hg, P=0.72), aortic pressure increased (102±14 versus 109±19 mm Hg, P=0.03), and the RV/Ao ratio decreased (0.97±0.34 versus 0.91±0.30, P=0.05).

The RV/Ao ratio decreased ≥20% in 4 procedures. Three procedures included dilations of the pulmonary valve or main pulmonary artery; in 1 procedure without dilation in this region, the RV pressure did not change (80 mm Hg). Four patients with serial catheterizations had reduction in RV systolic pressure from systemic or suprasystemic values at the initial catheterization to <80% of systemic levels at the second study. Three of these patients had intervening surgery, including closure of a large ventricular septal defect (1 patient), repair of central pulmonary artery stenosis by pericardial patch augmentation (1 patient) (Figure 2), or placement of a RV–pulmonary artery homograft (1 patient). The fourth patient had unchanged RV pressure (90 mm Hg).

Endovascular Stents

Three stents were dilated in the proximal portion of mediastinal vessels. The diameter increased in each artery (3.3 to 5.7, 3.9 to 7.5, and 2.3 to 5.9 mm). Because of hemodynamic instability, reliable pressures were not available in 1 patient. In the other 2 patients, RV pressure remained suprasystemic.

Pulmonary Perfusion Scans

Baseline and postdilation scans were obtained for 7 of the 39 dilation procedures. In 5 of these, the percentage change in percent perfusion to a lung was <20%. Two procedures included dilations of intraparenchymal arteries that were equally distributed between the 2 lungs. Three procedures had dilations of only the proximal right pulmonary artery, 2 of
which were unsuccessful. These 5 patients also had distal obstructions that masked the effects of proximal dilations. In 2 procedures, the percent change in perfusion was >20%. The percent perfusion to the right lung in 1 patient increased from 17% to 33% (94% increase) and in the other from 32% to 45% (41% increase).

Aneurysms

Twenty-five aneurysms developed after 24 dilations (18%). Twelve occurred distal to the stenosis (Figure 3), 9 at the stenotic site, and 4 proximal to the stenosis. The balloon/stenosis ratio for first dilations associated with aneurysm formation was 3.5±1.2 and without this complication, 3.4±1.3 (P=0.81). Serial measurements were available for 13 aneurysms. Eight aneurysms increased in size (Figure 2), 4 persisted with similar size, and 1 resolved. One distal aneurysm produced occlusion of its proximal arterial segment.

Balloon Rupture

The balloon ruptured in 12 dilations (9%). An aneurysm formed in all 7 procedures in which the balloon ruptured in a hypoplastic portion of the pulmonary artery. An aneurysm did not form in the 5 procedures in which the balloon ruptured in an enlarged segment (P=0.001). In 1 instance, balloon rupture produced a transmural tear that required placement of Gianturco coils to achieve hemostasis (Figure 4).

Complications

Complications occurred in 19 of 39 interventional procedures (49%). Hypotension occurred in 11 procedures (28%) and was treated with transfusion alone (2 procedures) or in combination with inotropic agents (9 procedures). Transient pulmonary edema developed after 6 procedures (15%). Arrhythmia occurred in 5 procedures (13%) and consisted of ventricular premature beats, ventricular tachycardia, or supraventricular tachycardia. Pulmonary artery perforation occurred in 3 vessels in 2 procedures because of overdistention of segments distal to the stenosis. Each vessel was occluded with Gianturco coils (Figure 4). One of these patients developed hemoptysis that was treated with intubation, and the other required pleurocentesis. Transient hemoptysis occurred in another patient who developed aneurysmal dilation.

There were 3 deaths, each occurring before 1994, and none associated with pulmonary artery trauma. The first occurred in the initial patient and has been reported previously. The patient had suprasystemic RV pressure, had an intact atrial septum, and developed hypotension as the dilating catheter was being passed into the left pulmonary artery. The second death occurred when hypotension developed after a pigtail catheter was placed retrogradely into the left ventricle, documenting a 60 mm Hg gradient. An autopsy demonstrated preostial obstruction to coronary flow created by a thickened shelf of aortic wall at the sinotubular junction and dysplastic aortic valve leaflets. In addition, there was severe biventricular hypertrophy. The third death occurred in a child with severe RV dysfunction and suprasystemic RV pressure. He was hemodynamically unstable during multiple dilations. An autopsy showed moderate left main coronary ostial stenosis and severe RV hypertrophy.

Discussion

Vessel Diameter

Balloon dilation of PPS has been the subject of numerous reports, principally of postoperative conditions. The success rate with low-pressure balloons has ranged from 34% to 71%. Hypotension occurred in 11 procedures (28%) and was treated with transfusion alone (2 procedures) or in combination with inotropic agents (9 procedures). Transient pulmonary edema developed after 6 procedures (15%). Arrhythmia occurred in 5 procedures (13%) and consisted of ventricular premature beats, ventricular tachycardia, or supraventricular tachycardia. Pulmonary artery perforation occurred in 3 vessels in 2 procedures because of overdistention of segments distal to the stenosis. Each vessel was occluded with Gianturco coils (Figure 4). One of these patients developed hemoptysis that was treated with intubation, and the other required pleurocentesis. Transient hemoptysis occurred in another patient who developed aneurysmal dilation.

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This structure has been considered the basis for less success of dilation in this group. The success rate in our study was similar to that reported in patients with PPS associated with other conditions. Disappearance of the waist on the inflated balloon has been considered the sine qua non of successful dilation and was a predictive feature in our experience. Vessels in which dilation attempts failed generally were unsuccessfully dilated at later catheterizations, indicating that balloon dilation in subsequent interventions should be directed to different arteries.

Hemodynamic Changes
Despite the success in improving vessel diameter, there was no change in RV pressure and only a modest decrease in the RV/Ao ratio. The persistently elevated RV pressure was produced by stenoses distal to the dilated region and hypoplasia of the pulmonary vascular bed; these issues contributed to doubling of distal pressure after successful dilations. An additional factor was the difficulty in dilating the proximal portions of pulmonary arteries. Reduction of the RV/Ao ratio of >20% occurred principally in procedures involving successful dilation of the pulmonary valve and main pulmonary artery or in serial studies with intervening surgical enlargement of the proximal pulmonary arteries.

Restenosis
Successfully dilated pulmonary arteries have been reported to restenose to near their baseline diameter in 10% to 44% of cases. Aneurysms occurred after 18% of dilations in our patients, a value 2 to 4.5 times higher than in previous series of PPS associated with other conditions. The aneurysms in our series occurred most often distal to the obstruction, a pattern reported in other studies. The presence of elevated pulmonary pressure and overdistension of small distal segments contributed to the higher incidence. Aneurysms can resolve, become smaller, persist without change in dimension, or increase in size.

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Effect of Balloon Rupture
The relative sizes of the balloon and vessel determine the degree of vessel wall injury after balloon rupture. In vitro studies of infant aortas have demonstrated that balloon rupture produces vessel rupture if the balloon is oversized, intimal-medial tears if the aortic and balloon sizes are similar, and no injury if the balloon is undersized. If the balloon size is similar to or larger than that of the vessel, rupture of the balloon can concentrate pressure release at 1 adherent site and produce injury. Our experience was consistent with these experimental results and documented that balloon rupture in hypoplastic segments produces aneurysms. The thickened vessel wall present in Williams syndrome may provide a “cushioning” effect, because only 1 of 7 balloon ruptures in a hypoplastic segment was complicated by vessel rupture.

Complications
Unilateral pulmonary edema, arrhythmias, and hypertension were more common than, whereas the incidence of vessel perforation was similar to, that reported in other series of PPS. Our mortality rate of 7.7% (3 of 39 procedures) was more than twice that of other series. Patients with Williams syndrome have increased mortality associated with cardiac catheterization caused by coronary artery stenosis or subendocardial ischemia arising from hemodynamic perturbations in the setting of ventricular hypertrophy. Both of these factors accounted for the 3 deaths in our series. There were no deaths after 1993 in the final 14 patients. During this period, there was greater use of general anesthesia as well as creation of an atrial communication if no septal defect was present in patients with severe obstruction. Statistical analysis of the effects of these 2 procedural issues was not possible.

Intervention Versus Observation
In Williams syndrome, the obstruction associated with PPS may improve spontaneously, especially in patients with milder, more proximal obstructions. Although mortality improved in the second half of this series, the incidence of complications remains significant. This finding, coupled with the possibility of spontaneous improvement has caused us to recommend frequent noninvasive observation in the asymptomatic infant or young patient with systemic RV pressure who does not have significant left-sided involvement. In the patient with persistent systemic levels of RV pressure or significant biventricular obstruction, balloon dilation is effective in the majority of distal vessels. Because of a lower success rate in proximal vessels, however, the hemodynamic benefit is modest in most patients. Because patients having surgical enlargement of central pulmonary artery obstruction resistant to balloon dilation had reduction in RV pressure, a serial approach of distal dilation followed by proximal surgical repair may be a rational and successful therapy for this difficult group of patients.

References
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