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Intravascular Stents in Congenital Heart Disease: Short- and Long-Term Results From a Large Single-Center Experience

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Objectives. **This report describes the results of the Food and Drug Administration's phase 1 and 2 clinical trials of intravascular stents at Texas Children's Hospital.**

Background. **Since the late 1980s, intravascular stent implantation for the treatment of arterial and venous stenoses in congenital heart disease has been highly successful.**

Methods. **Stents were placed in postoperative pulmonary artery (PA) stenoses, congenital PA stenoses or stenoses of systemic veins/venous anastomoses. Prospective collection of data according to protocol was done before intervention, after stent implantation and at follow-up catheterization.**

Results. **At stent implantation, pressure gradients decreased significantly in all three groups (mean ± SD): from 46 ± 25 to 10 ± 13 mm Hg in postoperative PA stenoses ($p < 0.001$); from 71 ± 45 to 15 ± 21 mm Hg in congenital PA stenoses ($p < 0.001$); and from 7 ± 6 to 1 ± 2 mm Hg in stenoses of systemic veins/venous anastomoses stenoses ($p < 0.001$). Vessel diameters markedly increased: from 6 ± 3 to 12 ± 3 mm in postoperative PA stenoses ($p < 0.001$); from 3 ± 1 to 9 ± 1 mm in congenital PA stenoses ($p < 0.001$); and from 3 ± 4 to 12 ± 4 mm in stenoses of systemic veins/venous anastomoses ($p < 0.001$). In the postoperative and congenital PA stenoses groups, right ventricular pressure decreased (right ventricular pressure indexed to femoral artery pressure ratio): from 0.63 ± 0.2 to 0.41 ± 0.02 ($p < 0.001$) and from 0.71 ± 0.3 to 0.55 ± 0.35 ($p = 0.04$), respectively. Perfusion to a single affected lung increased from 31 ± 17% to 46 ± 14% ($p < 0.001$). On recatheterization (mean 14 months), results varied minimally. Repeat angioplasty of residual stent stenoses was safe and effective. Complications included four early patients with stent migration, three with stent thrombosis and two deaths. There were no late complications. Significant restenosis occurred in only three patients.**

Conclusions. **Intravascular stents for the treatment of vascular stenoses in congenital heart disease provide excellent immediate and long-term results.**

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Vascular stenoses in patients with congenital heart disease can be the cause of significant morbidity and mortality. In patients with either congenital or postoperative branch pulmonary artery (PA) stenoses, elevated right ventricular (RV) pressure is associated with RV failure, arrhythmias and sudden death (1,2). Within the venous system, hemodynamically significant stenoses, including cavopulmonary anastomoses, can contribute to superior vena cava syndrome, poor passive flow with poor cardiac output and atrial arrhythmias. Elevated central venous pressures in these patients is a risk factor associated with higher mortality (3). To our knowledge, no Food and Drug Administration (FDA)-approved treatment for vascular stenoses in patients with congenital heart disease has previously been described.

Mullins et al. (4) first studied the use of balloon-expandable intravascular stents in pulmonary arteries and systemic veins in the late 1980s. The purposes of stent implantation were to dilate areas of stenoses using angioplasty balloons matched to the appropriate size of the adjacent vessel and to provide a support structure at the area of stenosis to prevent recoil. These stents could be delivered to distal branches not accessible surgically or within previously scarred areas of stenosis "from the inside," obviating the need for a repeat operation and its associated complications. After the initial animal studies, the investigators proceeded to the FDA clinical trials under an Investigational Device Exemption (IDE). These data are the basis of this report. There have been early serial reports about the gratifying immediate results in the phase one and two clinical trials of intravascular stents in congenital heart disease (5–7). Likewise, other investigators have reported successful treatment of vascular stenoses with this procedure

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Abbreviations and Acronyms

ANOVA = analysis of variance
FA = femoral artery
FDA = Food and Drug Administration
IDE = investigational device exemption
PA = pulmonary artery
RV = right ventricle, right ventricular
RV/FA = right ventricular pressure indexed to femoral artery pressure ratio

(8). The purpose of this study was to illustrate the safety and efficacy of intravascular stents in the treatment of vascular stenoses in patients with congenital heart disease. This report summarizes the results of the only FDA-approved IDE study of balloon-expandable stents in patients with congenital heart disease and contains both early data previously reported and new data on more recent cases, including the long-term follow-up data on all patients.

Methods

The patients were enrolled after parental (and, when applicable, patient) written informed consent was obtained. Data were collected under a U.S. FDA-IDE protocol for phase one and two clinical trials. The Institutional Review Boards of Baylor College of Medicine and Texas Children's Hospital approved the protocol, and procedures followed were in accordance with institutional guidelines.

All patients enrolled in the study had vascular stenoses that required balloon angioplasty or surgical repair—specifically, significant stenoses in branch PAs, stenoses in RV to PA conduits and stenoses in systemic veins (including cavopulmonary anastomoses) or other postoperative venous channels. Between September 1989 and June 1995, 200 patients underwent cardiac catheterization with placement of a total of 347 stents. To provide uniformity of initial and follow-up data, this report does not include initial phase one data on 30 additional patients treated at Children's Hospital in Boston. The Palmaz stent (Johnson and Johnson Interventional Systems) was used in all patients; most stents were model P-308 (3 cm long, 3.4 mm nominal diameter, expandable to 12 to 18 mm). Later in the study, model P-204 stents (2.0 cm long, 2.5 mm nominal diameter, expandable to 8 to 10 mm) were used to treat stenoses in smaller, more distal vessels.

The technique for stent delivery and implantation has been extensively described previously (4–8). In brief, most patients have diagnostic catheterization under conscious sedation. Rare, higher risk patients require general anesthesia. Standard venous sheaths are then replaced with a larger diameter, long ("transseptal") sheath over a stiff, exchange-length wire previously anchored across the stenosis. Patients are anticoagulated with 50 to 100 U/kg body weight after the initial activated clotting time is measured. Heparin was not reversed routinely, unless the activated clotting time was >350 s at the end of the procedure.

Stents are mounted on low pressure angioplasty balloons sized not to exceed the diameter of the vessel adjacent to the stenosis. The long sheath is advanced through the area of stenosis, and the balloon–stent assembly is advanced within the sheath to the level of stenosis. The sheath is withdrawn, exposing the balloon and stent. Confirmatory angiography documents the position of the stent before inflation of the balloon. After the initial inflation and stent deployment, subsequent dilation with both low and high pressure balloons optimizes results.

When awake and taking oral fluids, all patients were begun on aspirin and dipyridamole. This therapy was continued for 6 months, after which all antithrombotic therapy was discontinued. If an additional stent was implanted at repeat catheterization, aspirin and dipyridamole were restarted for an additional 6 months.

In accordance with the FDA protocol, all patients had a full outpatient evaluation, including a chest X-ray film, an electrocardiogram and, when applicable, an echocardiogram. In addition, patients with precatheterization evidence of unilateral PA stenosis underwent a radionuclide lung perfusion study. After the procedure, the patients were hospitalized overnight to observe vascular access sites, to receive 4 doses of intravenous cefazolin and to monitor cardiopulmonary stability. The morning after catheterization, a chest X-ray film, an echocardiogram and, if applicable, a follow-up lung perfusion study were obtained (only in patients with unilateral stenoses). Intially, follow-up in all patients consisted of an outpatient evaluation, a chest X-ray film and an electrocardiogram. Later in the study, the 3- and 6-month post-stent evaluations were tailored according to the clinical status of the patient. Cardiac catheterization and, when applicable, lung perfusion studies were scheduled 12 months after stent implantation. Data collection points were defined as pre-implantation, postimplantation and follow-up catheterization.

At the initial catheterization and at all follow-up catheterizations or interventions, the data collected included the stenosis location and diameter, the adjacent vessel diameter, the pressure proximal and distal to the stenosis (gradient) and, when applicable, the ratio of RV systolic pressure indexed to a simultaneous femoral artery (FA) systolic pressure (RV/FA ratio). The development of neointima within the stent was assessed at follow-up catheterization by the separation of the column of contrast from the stent wall during vessel imaging.

The patients were classified into three groups based on the type and location of the stenoses. The first group had PA stenoses after previous surgical palliation or repair. The second group included patients with congenital PA stenoses. The third group included patients with systemic vein stenoses, including stenoses of postsurgical venous anastomoses (Table 1).

Statistical analysis. Statistical analysis was used to validate the sample size but should not suggest clinical success or failure of the procedure. Success in this patient group can

Table 1. Diagnoses and Previous Surgical Interventions

Postoperative branch PA stenoses	
Tetralogy of Fallot	
s/p RVOT augmentaton	55
s/p systemic to PA shunt	17
s/p RV to PA conduit	9
With absent right or left PA	6
Pulmonary atresia	
s/p RV to PA conduit	17
s/p systemic to PA shunt	8
s/p RVOT augmentation	8
Transposition of the great arteries	
s/p arterial switch operation	7
With VSD, s/p RV to PA conduit	3
Truncus arteriosus s/p RV to PA conduit	8
VSD s/p PA band	6
Other diagnoses, s/p systemic to PA shunt	13
Congenital branch PA stenosis	15
Venous stenoses	
s/p Fontan and Fontan variants for tricuspid atresia, previous shunts	10
s/p Fontan and Fontan variants (various diagnoses)	12
s/p Glenn/bidirectional Glenn (various diagnoses)	9
Atrial switch for transposition of the great arteries	7
Superior vena cava stenosis (various diagnoses)	5
Systemic venous stenoses	5

Data are presented as number of patients. PA = pulmonary artery; RV = right ventricle; RVOT = right ventricular outflow tract; s/p = status post; VSD = ventricular septal defect.

further be defined by pressure gradients <10 mm Hg in the postoperative and congenital PA anastomoses groups. In the systemic vein stenoses/venous anastomoses group, where initial pressure gradients were small to absent, success was defined by a significant increase in the diameter of the vessel. Statistical significance across the study period was evaluated by analysis of variance (ANOVA). On selected comparisons, the paired two-tailed Student *t* test was used. Because of the large number of patients, statistical significance was defined at $p < 0.001$. Data are expressed as the mean value ± SD. Graphic representation of data is presented as the mean value ± SEM.

Results

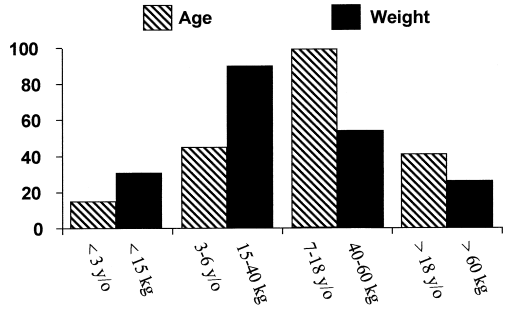
Demographic data. The study group consisted of 116 males and 84 females. The geographic distribution of patients included 38% from Houston, 33% from other institutions within Texas, 25% from outside Texas and 4% from outside the United States. The patients' median age at stent implantation was 10.5 years (range 6 months to 43 years), and the median weight was 28 kg (range 5.3 to 83) (Fig. 1). Diagnoses and previous surgical procedures are described in Table 1. The longest follow-up was 62 months after stent implantation, with a mean follow-up of 19 ± 15 months. Of the patients who were at least 1 year status post-stent implantation, follow-up catheterization was performed at a mean of 14 months after implantation.

Pulmonary artery stenoses. The 136 patients in the postoperative PA stenoses group accounted for the largest number of stents (237) placed in the PAs. In this group, the systolic pressure gradient decreased from 46 ± 25 to 10 ± 12.8 mm Hg after stent implantation and dilation ($p < 0.001$). There were 152 stenotic lesions with postimplant gradients <10 mm Hg. Data on 75 patients (112 stents) illustrated a slight pressure gradient increase at follow-up catheterization to 13 ± 14.2 mm Hg ($p = 0.006$). The decrease in gradient from the prestent measurement to the gradient at follow-up was statistically significant ($p < 0.001$ by ANOVA). In the patients with higher pressure gradients at follow-up, further dilation of the stent decreased the mean gradient from 19 ± 15.7 to 6 ± 7.3 mm Hg ($p < 0.001$) (Fig. 2A).

In the 15 patients with congenital PA stenoses, there was a similar immediate decrease in the pressure gradient (from 71 ± 45 to 15 ± 20 mm Hg, $p < 0.001$) (Fig. 2D). At follow-up catheterization of seven patients, data on 14 stents revealed an increase in the gradient compared with the post-stent measurement (21 ± 17 mm Hg), but this was not statistically significant ($p = 0.2$). In patients with higher gradients at follow-up, further dilation of the stent resulted in a statistically significant decrease in the gradient (from 34 ± 9.8 to 19 ± 14.6 mm Hg, $p < 0.001$).

In both the postoperative and congenital PA stenoses groups, vessel diameters increased markedly: the initial increase was statistically significant in both groups (from 5.6 ± 2.6 to 12.1 ± 3.0 mm, $p < 0.001$ and from 3.3 ± 1.2 to 8.9 ± 1.2 mm, $p < 0.001$, respectively). Alternatively, this was a >100% increase in diameter in 65% of the procedures in the postoperative and 88% in the congenital PA stenoses groups. There was a >200% increase in diameter in >50% of the congenital PA stenoses group. At follow-up there was a small decrease in diameter in both groups (postoperative PA stenoses group: 11.0 ± 2.8 mm, $p = 0.0007$; congenital PA stenoses group: 7.9 ± 2.1 mm, $p = 0.12$). Although the 1-mm decrease in diameter seen in both groups at follow-up did reach statistical significance in the larger postoperative PA stenoses group, it had no significant effect on the gradient. In both groups, those stents/vessels which were further dilated had an increase in diameter that did not reach our defined level of statistical significance (postoperative PA stenoses group: from 9.6 ± 2.8 to 12.3 ± 3.4 mm, $p = 0.01$; congenital PA stenoses group: from 6.7 ± 0.8 to 8.8 ± 1.0 mm, $p = 0.006$) (Fig. 2, B and E).

Figure 1. Age and weight distributions of patients. y/o = years old.



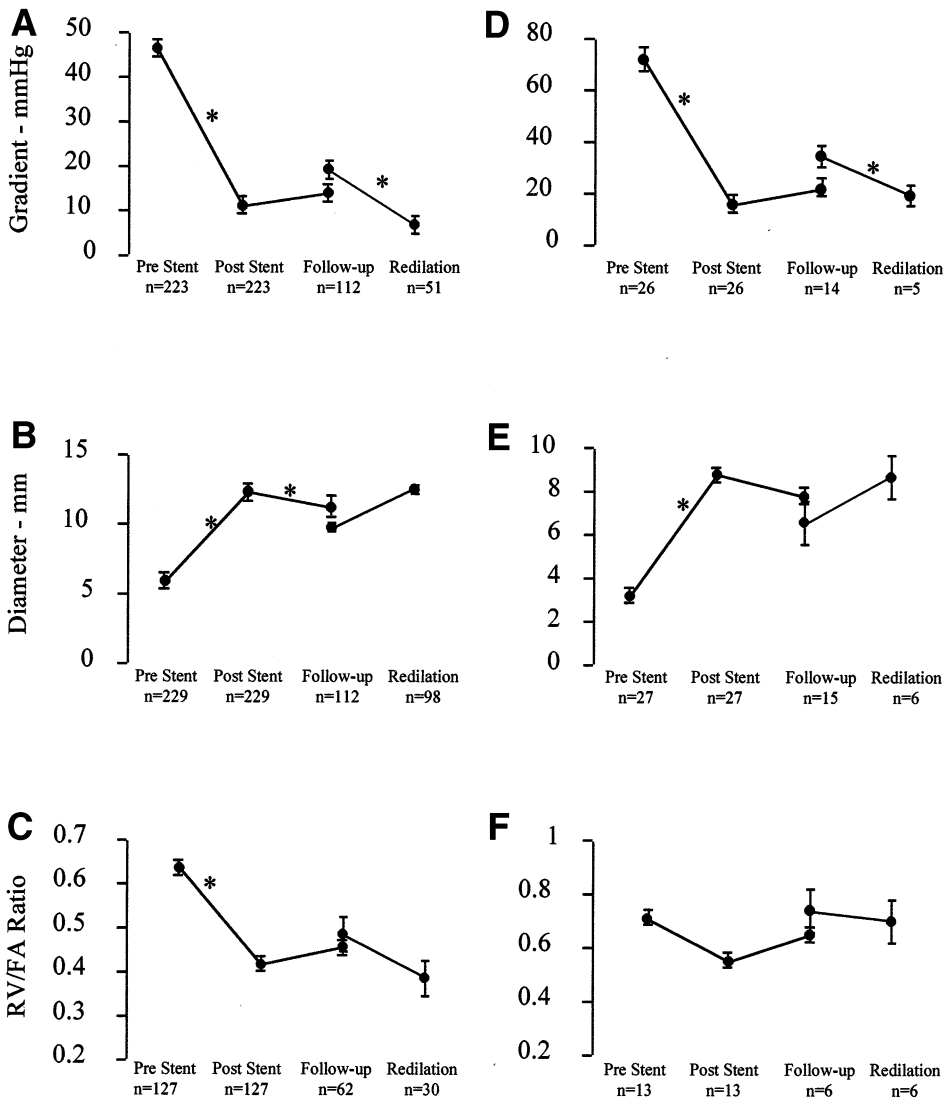


Figure 2. A series of plots illustrating changes in pressure gradients, diameters and RV/FA ratios. **A to C** show plots for patients with postoperative PA stenoses; **D to F** show plots for patients with congenital PA stenoses. The use of "n" in the gradient and diameter plots reflects measurements available for individual stents, whereas "n" in the RV/FA ratio plots refers to patients (mean ± SEM, *$p < 0.001$).

The RV/FA systolic pressure ratio improved in both groups. The RV systolic pressure in the postoperative PA stenoses group decreased to less than half systemic (RV/FA: from 0.63 ± 0.2 to 0.41 ± 0.02, $p < 0.001$). This decrease persisted at follow-up catheterization (0.45 ± 0.01, $p = 0.002$). In patients who required further stent dilation, the RV/FA pressure ratio decreased again (from 0.48 ± 0.14 to 0.38 ± 0.09, $p = 0.2$). (Fig. 2C). In the congenital PA stenoses group, a drop in the RV/FA pressure ratio also occurred, although this change was not statistically significant (from 0.71 ± 0.3 to 0.55 ± 0.35, $p = 0.04$) (Fig. 2F). At follow-up catheterization, the RV/FA pressure ratio in the congenital PA stenoses group increased to 0.65 ± 0.3 ($p = 0.8$). Further dilation of stents in a limited number of the patients with congenital PA stenoses decreased the ratio from 0.74 ± 0.15 to 0.70 ± 0.14 ($p = 0.2$), which was not statistically significant.

Venous stenoses. The systemic vein stenoses/venous anastomoses group included patients with stents placed in low pressure–low velocity flow locations. These locations included clinically and/or hemodynamically significant stenoses in systemic veins, in atrial baffles or conduits or in the branch PAs and veno-pulmonary artery anastomoses of the patient with a postoperative cavopulmonary anastomosis. Eighty stents were placed in 49 patients. Although initial pressure gradients in the venous stenoses were much lower than those in both the postoperative and congenital stenoses, after stent implantation there was still a statistically significant decrease in the pressure gradient (from 7 ± 6.4 to 1 ± 1.9 mm Hg, $p < 0.001$). At follow-up catheterization of 13 patients (22 stents), there was no statistically significant difference in the gradient (1 ± 2.2 mm Hg, $p = 0.9$). Five stents were further dilated; the gradient decreased (from 4 ± 3.3 to 1 ± 0.8 mm Hg), but this change did not reach statistical significance ($p = 0.06$) (Fig. 3A).

The diameter of the stenotic segment increased dramatically after venous stent implantation (from 2.8 ± 3.6 to 12.5 ± 3.9 mm, $p < 0.001$). Twelve of the venous stenoses (18%) were totally occluded vessels before stent implantation. Stent im-

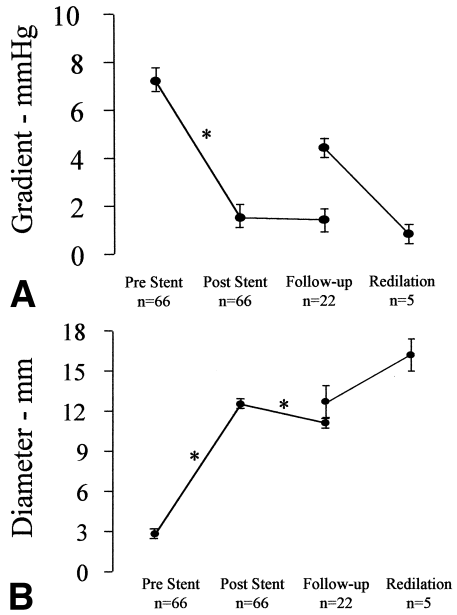


Figure 3. Pressure gradients and diameter changes in patients who had stents implanted in low pressure systems—that is, systemic vein stenoses/venous anastomoses (mean ± SEM, *$p < 0.001$).

plantation resulted in a >100% increase in diameter in 80% of the procedures (55% of procedures had a >200% increase in diameter). At follow-up catheterization there was a small decrease in diameter (11.1 ± 3.8 mm), which did reach statistical significance ($p = 0.001$), although there was no apparent change in flow through the stents (Fig. 3B).

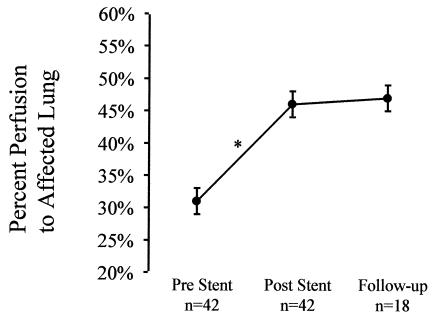
Lung perfusion studies. Improvement in perfusion to an affected area after stent implantation was best quantitated in patients with unilateral PA stenoses. There were 42 patients who met this criterion. In these patients, the percentage of perfusion to the affected lung increased from 31 ± 17% to 46 ± 14% after stent implantation ($p < 0.001$). This increase remained unchanged on the follow-up perfusion scan (47 ± 17%, $p = 0.2$) (Fig. 4).

Complications. *Morbidity.* Early in our experience, there were four instances of stent migration. Two of these stents were surgically removed, and the other two were "captured" and expanded in a benign position other than the original, intended site. Three patients developed thrombosis of the PA within the stent. All three of these patients had postoperative cavopulmonary anastomoses. Two of the three patients had significant pulmonary vein stenosis on the side of the thrombosis that was noted only after stent implantation. The third patient had a previously diagnosed right atrial thrombus that extended into the stent after implantation in spite of anticoagulation. There were no episodes of systemic embolization or thrombosis.

Stent implantation is subject to the same complications as balloon angioplasty. Three patients developed retroperitoneal hemorrhage, presumably due to multiple, large sheaths, catheters and/or balloons in the iliac vessels. One patient required laparoscopic evacuation of the hematoma. Self-limited hemoptysis occurred in four patients. This was thought to be secondary to tiny vascular ruptures not appreciated on angiography or an acute increase of perfusion to the affected segment after stent deployment (with rupture of a small distal vessel into the alveoli). In one patient during repeat stent dilation, the balloon within the stent "milked" distally and a PA laceration occurred distal to the stent. A pedunculated aneurysm with a stenotic mouth developed and has remained contained by the lung parenchyma without treatment. Follow-up magnetic resonance imaging approximately 6 months after the catheterization revealed a decrease in aneurysm size.

Mortality. There were two deaths directly attributed to the stent procedure. In one patient with unusual familial congenital PA branch stenosis and suprasystemic PA pressure, dilation and stent implantation into two small distal pulmonary segments were successful. After the procedure, the increase in flow to the stented lung segments became so great that severe segmental pulmonary edema developed with a progressive and lethal ventilation-perfusion mismatch. The second death was in a small child 7 weeks status post tetralogy of Fallot repair with severe residual bilateral branch PA stenosis. He had intractable right heart failure and was not considered a candidate for reoperation. During stent dilation, there was a main PA tear resulting in a massive hemothorax and the patient died. There have been no late deaths related to the stents.

Figure 4. In postoperative and congenital PA stenoses, radionuclide lung perfusion scan results are plotted across the study period (mean ± SEM, *$p < 0.001$).



Discussion

As reported in earlier reports on this series and in several other smaller series, the results of intravascular stents for patients with congenital heart disease have been superb (4–8). This report summarizes this single institution's 6 years of experience during the FDA phase one and two clinical trials of the Palmaz stent in congenital heart disease. In our experience, excellent results occur immediately after stent implantation and at follow-up catheterization; neither the vessel stenoses nor the pressure gradients return. Furthermore, in those patients with residual pressure gradients or initial suboptimal vessel diameters, further dilation of the stents can be safely and effectively accomplished.

Technical limitations of intravascular stents. The majority of our patients with stents are older children and young adults. A relative patient size (age and weight) limitation exists, mainly because of the use of the 11F sheath needed for the smooth delivery of model P-308 "iliac" stent. With improved balloon technology, smaller sheaths may be used for stent delivery, allowing smaller patients to undergo this procedure. We have used 8F sheaths for the delivery of model P-204 "renal" stents into more distal, smaller vessels. We have avoided using these smaller stents in proximal or central vessels, even in infants or small children, because these stents, limited to 8 to 10 mm maximal diameter, would themselves create a fixed, nondilatable stenosis that would require surgical opening or removal as the patient grows.

Further dilation of implanted stents. Previously published reports have discussed the redilation of intravascular "iliac" stents on a portion of this patient group (9,10). As the younger patient grows, further dilation of the stent will be required until the PA is of adequate size for an adult. Before this current study, there was excellent animal data on further dilation of implanted stents. Grifka et al. (11) reported success in further dilation of stents in the aorta of growing mini-pigs whose weights had increased by 400%. We report data on patients who had successful further dilation of previously implanted stents in a variety of locations and lesions. This was well tolerated, without complications, and resulted in a favorable anatomic and hemodynamic response.

In patients who have had repeat catheterization, our redilation protocol has been somewhat patient specific. If a high gradient is present, we routinely attempt further dilation of the stent. This can sometimes be accomplished with lower pressure angioplasty balloons but often requires higher pressure balloons. In some patients with severe pulmonary insufficiency that may be aggravated by even minimal stenoses or in patients with discrete stenoses within the stent, we have been more aggressive at attempting further dilation in the presence of minimal gradients. Finally, as follow-up catheterizations occurred per protocol, there have been patients with minimal clinically or echocardiographically evident restenosis. When minimal gradients were confirmed during catheterization, we attempted to optimize stent diameters for future growth of the patient.

In several patients, "redilation" data reflect additional stents placed inside previously implanted stents for additional support or further dilation of the initial stent. This is particularly useful in right PA stents that are positioned directly posterior to the aorta. Anteroposterior compression of the stent in this position has occasionally occurred, resulting in an oval distortion of the stent. The additional stent helps to "round out" the original stent. In addition, this technique has been helpful in stented vessels made oval after using two high pressure angioplasty balloons to dilate a persistent stenosis. The additional stent on a larger diameter balloon can "round out" the vessel.

One group of patients where further dilation of existing stents is particularly important includes those with congenital PA stenosis. The response to the initial dilation of these vessels is unpredictable and the vessels are not "protected" by surrounding scar from a previous operation. During implantation of the stent, it is expanded within the stenosis only to the diameter of the adjacent vessel. This vessel usually is smaller than normal for the patient's size. The ability to safely further dilate these stents at future catheterization allows a conservative approach by not having to overdilate with the initial implant. It is our impression that vascular disruption is less likely when these smaller vessels are initially stented to submaximal diameters with standard, lower pressure angioplasty balloons.

Limitations of the pediatric age range. Although gradients are not age or weight specific, the size of both PAs and systemic veins does increase as the patient grows. The stent diameters presented here represent the spectrum of mean diameters across the entire study group. Smaller patients will have smaller post-stent implant diameters. Although normative values for PA radius/diameter have been published for both angiographic and echocardiographic measures, there are sparse data on expected values for patients with congenital heart disease (12–16). No adjustment in data has been made to account for comparison with age- and weight-specific norms. However, the significant change in mean diameter demonstrated by this data is dramatic and associated with hemodynamic improvement and anecdotal improvement in the patient's clinical status.

Neointimal proliferation. At follow-up catheterization there has been a consistent 1- to 2-mm decrease in the lumen diameter within the stent. This is due to "normal" neointimal covering of the stent surface. One to two millimeters of neointimal growth is insignificant in these patients, although this same amount of neointima is a very significant problem in (much smaller) coronary artery stents. This has prompted extensive discussion in the adult cardiology data about the implications of neointimal proliferation as well as speculation about its cause (17,18). Of the entire 200 patients, there were only three (1.5%) with significant stenosis due to neointimal proliferation. Each of these three patients has some peculiarity of the vascular anatomy or the nature of the stent implant, or both, that probably explains their unusual intimal reaction to the stent. In a few of our patients, a larger amount of neointimal proliferation was noted where the native vessel diameter immediately proximal or distal to the stent was less than the stent diameter. There was increased neointimal proliferation immediately proximal and distal to any residual stenosis ("waist") within the stent. Thus, intimal build-up appears to occur so that the entire vessel will remold to a uniform diameter. Intraluminal wall irregularities that result in turbulent flow are "smoothed out" during the endothelialization process. In 12 patients who have had two or more repeat catheterizations at least 2 to 5 years after the initial stent implantation, there was no further progression of neointimal thickening once the internal diameter of the vessel had become uniform.

Modifications in thrombosis prevention. On the conclusion of the protocol, some of the investigators now use only aspirin for thrombosis prevention in patients who are not taking oral anticoagulants for other reasons.

Conclusions. The results of this data obtained during the FDA clinical trial indicate that intravascular stents are an effective and safe therapy for the treatment of vascular stenoses in patients with congenital heart disease. There appears to be no long-term morbidity associated with this device or the procedure. Follow-up will continue to provide data on any unexpected very long-term complications that may occur.

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