Transvenous Angioplasty of Experimental Branch Pulmonary Artery Stenosis in Newborn Lambs

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SUMMARY A dilatable form of bilateral branch pulmonary artery stenosis was created in 27 newborn lambs. Nine lambs were long-term survivors and were dilated with modified Gruntzig balloon dilation catheters. They were allowed to recover for 6–9 weeks, during which time there was no significant change in the mean systolic gradients across the narrowed sites. Thirteen arteries underwent dilation. Dilation was associated with a decrease in the systolic gradient in all cases (from 34.9 mm Hg to 8.1 mm Hg) and an increase in the diameter of the narrowed site (from 4.6 to 7.6 mm) as estimated by angiography. Flows and flow distribution were measured in four lambs before and after unilateral dilation using 15-μ radiolabeled microspheres; in each case, the fraction of total flow to the dilated lung rose after dilation (19.2 to 45.4%), as did the total flow to the dilated lung (30.0 to 69.2 ml/kg-min). Four lambs were catheterized every 2–4 weeks for an average of 16 weeks after dilation; the average gradient in these lambs remained below 10 mm Hg despite considerable growth (from 9.6 to 25.9 kg). Gross pathologic examination showed an intact vascular adventitia in all cases; there were multiple linear tears in the intima in recently (less than 7 days) dilated cases, but complete intimal healing had occurred by 2 months after dilation. No significant morbidity could be attributed to the dilation procedure. These results indicate that clinical trials are warranted.

IN 1964, Dotter and Judkins reported the development and application of a coaxial catheter dilation system for the transcutaneous treatment of peripheral vascular obstructions due to atherosclerosis. By 1977, more than 1800 such procedures had been performed. The first reports of a balloon-tipped catheter to dilate such lesions were by Porstmann in 1973 and Gruntzig and Hopff in 1974. By 1978, this technique had been extended to atherosclerotic coronary vessels and to the fibrous dysplasia of renal artery stenosis.

Despite this widespread use in acquired vascular stenoses, there are no reports of the use of balloon dilation to relieve congenital systemic or pulmonary arterial narrowings. The apparent reluctance to dilate such narrowings is understandable. Congenital stenoses have no soft intimal plaque that can be "squeezed" by the balloon; dilation must be accompanied by stretching the vessel wall itself. Congenital stenoses generally require treatment during a period of growth; if the vessel dilation results in scarring, vessel growth may be impaired and restenosis may develop. Finally, congenital vessel stenosis generally involves large vessels near the heart (i.e., branch pulmonary artery stenosis or coarctation), and the ability of an already compromised circulatory system to tolerate prolonged occlusion of such a vessel is unknown.

This study was designed to create and validate an experimental model in newborn lambs of dilatable branch pulmonary artery stenosis; determine the acute results of dilating such stenoses using both hemodynamic and angiographic criteria; estimate the natural history of both dilated and undilated areas of stenosis; observe the acute and chronic pathologic changes associated with such dilations; and identify the optimal protocol of dilation.

Materials and Methods

Creation and Validation of Experimental Model

Twenty-seven newborn lambs (1–4 weeks of age) underwent a left thoracotomy for creation of bilateral branch pulmonary artery stenosis. Anesthesia was induced with pentothal and maintained with halothane and N2O. The vagus and phrenic nerves were identified and retracted, the ductus arteriosus was ligated and divided, and the right main pulmonary artery (RPA) and left main pulmonary artery (LPA) were isolated and dissected free. Three to five interrupted 5-0 polypropylene sutures were placed circumferentially around the RPA to reduce the luminal area by 75% (fig. 1). Two to four sutures were similarly placed in the LPA. At that point, the ECG was examined for signs of bradycardia or ST-segment abnormalities. If no ECG abnormalities were observed, additional plication sutures were placed until ECG changes were seen. Both pulmonary arteries were then wrapped with a single 1-0 gut suture in a snug but nonconstrictive fashion. The left lung was reexpanded, the chest was closed and the lamb was allowed to awaken from anesthesia.

Fifteen of the lambs developed signs of right ventricular dilation and low cardiac output and died at surgery or during the subsequent 72 hours. One lamb died late from diarrhea and dehydration; two died at catheterization just before dilation, one from severe bradycardia during dissection of the right carotid artery and one after angiography at the time of in-
tended dilation. In the latter lamb, the guide wire was being positioned in the pulmonary artery in preparation for an attempt at dilation. The lamb suffered an ill-defined episode of bradycardia; clear fluid was aspirated from a suspected hemothorax. The fluid became bloody, and the lamb ultimately died from shock. Postmortem examination revealed an intact pulmonary endothelium; however, a 2-mm hole was seen in the right coronary artery. Of the remaining nine lambs, who form the subject of this report, five underwent unilateral and four bilateral dilation of pulmonary artery stenosis.

Acute Results of Dilation

Three methods were used to determine the results of dilation: pressure measurements, flow distribution and angiography. Pulmonary arteriograms were performed in the posteroanterior projection with the shoulders elevated 30–45° above the hips. One to 2 ml/kg of meglumine diatrizoate (Renografin-60, Squibb) were injected over 1 second. The angiogram was recorded on cutfilms at three exposures per second. The diameter of the stenotic areas was measured directly from the film, and the magnification factor was calculated by comparing the known diameter of the catheter (#5–7F) with its angiographic diameter within the pulmonary artery.

Pressure gradients were obtained from fluid-filled side-hole catheters attached to Statham P23Db transducers and recorded on an Electronics for Medicine DR 12 optical recorder.

Flow distribution was determined in lambs 5, 6, 7 and 9 (table 1) by injecting radionuclide-labeled 15-μm microspheres (3M Company) in the superior vena cava, with a reference sample obtained in the main pulmonary artery. One arterial catheter was used to monitor systemic arterial pressure during microsphere injection while blood was continuously withdrawn from a second aortic line during injection; the blood obtained from this line was counted to estimate intrapulmonary shunting. Sphere injections were made before (< 1 hour) and 30 minutes after dilation. Three isotopes were used: 141-cerium, 85-strontium, and 46-scandium. In all, 0.77 x 10⁶ to 1.54 x 10⁶ microspheres were injected. Cardiac output was determined using the reference sample technique, and flow distribution was determined by counting the lungs after sacrifice.

Natural History

Four lambs (table 1) underwent repeated right-heart catheterizations before (6 ± 1 catheterizations per lamb) and after (4 ± 1 catheterizations per lamb) dilation. Only one pulmonary artery was dilated in each of these four lambs. The catheterizations were 1–2 weeks apart before dilation and 1–4 weeks apart after dilation. The LPA-to-MPA gradient was measured in each case, and the RPA-to-MPA gradient was measured at 31 of 43 catheterizations. Pulmonary arteriograms (as described above) were performed at the first catheterization, less than 1 hour before dilation, just after dilation, and just before sacrifice.

Pathologic Changes

The lambs were sacrificed by sedative overdose at intervals of 1 hour, 2 hours, 1 day, 2 days, 7 days, 92 days, 106 days, 108 days and 137 days after dilation. The right ventricular free walls and left ventricles were weighed in each lamb and in the two lambs who died at catheterization just before dilation, and the hearts were fixed in formalin.

The pulmonary artery specimens consisted of main pulmonary artery with 2–3 cm each of attached right and left pulmonary arteries fixed in 10% buffered formalin. The specimens were opened anteriorly, photographed, and sections of the right and left pulmonary arteries were taken to include, in one block, the entire circumference at the point of maximal narrowing. These slices were prepared using standard methods and paraffin embedding, and were sectioned at superficial, midpoint and deep levels. Tissue from each level was stained with hematoxylin-eosin and Lawson elastic stains. Occasional sections were stained with Masson trichrome.

Protocol for Dilation

The techniques of dilating peripheral atherosclerotic lesions may not apply to central congenital lesions. The technical details that could influence the success or failure of a dilation procedure may include (1) fabrication material of the catheter and balloon, (2) diameter and length of the balloon, (3) fluid used to inflate the balloon, (4) pressure to which the balloon is inflated, (5) duration of inflation, (6) method for centering the balloon under the stenosis and (7) number of times a vessel is dilated. We used the Grünzig dilation catheters (Cook, Inc.). While not enough dilations were performed to allow statistical evaluation of each of these technical details, we attempted to record these details and correlate them with the apparent success or failure of the procedure.

We used the paired t test to determine whether dilat-
tion influenced either hemodynamic or angiographic variables, using the Bonferroni modification to correct for multiple comparisons. The unpaired t test was used to determine any statistical difference between the right ventricular/left ventricular + septum weight ratio in recently dilated lambs when compared with normal controls. The significance of gradient changes in the four lambs that underwent multiple catheterizations was determined by an analysis of variance, on a random block design. Pairwise comparisons of the means used Tukey's distribution. In those lambs, we analyzed the gradients at each of five predilation catheterizations obtained the same number of weeks (± 1 week) before dilation. All results are expressed as the mean ± SD.

### Results

#### Experimental Model

In the nine surviving lambs, surgery was performed at 7–27 days of age (mean 11.6 days) and at an average weight of 6.0 ± 2.4 kg. A significant stenosis, as measured by pressures and angiography, was created in both pulmonary arteries in each of the lambs. The mean systolic main pulmonary artery pressure was 66 mm Hg 1 week after surgery, and was 60 mm Hg just before dilation (table 1). Thus, the main pulmonary artery pressure remained unchanged before dilation even though the mean weight of the lambs increased from 6.8 ± 2.6 to 14.6 ± 6.5 kg over 48.5 ± 8.0 days. Pulmonary artery obstruction resulted in right ventricular muscle hypertrophy; the right ventricular free wall/left ventricular + septum weight ratio in the five lambs sacrificed less than 1 week after dilation (0.40–0.74) was more than that of normal lambs (p < 0.05).

Finally, to determine whether dilation produced vessel stretching or suture rupturing, we determined that 5-0 polypropylene sutures could not be broken by any of our dilation catheters in vitro, although 6-0 and 7-0 sutures could be ruptured by these catheters.

#### Acute Results of Dilation

Thirteen dilations were performed in the nine lambs. After dilation of the first branch pulmonary artery, there was a substantial decrease in the gradient across not only the dilated side (from 41.6 ± 6.4 mm Hg to 8.3 ± 2.9 mm Hg; p < 0.01), but also across the undilated side (33.6 ± 5.8 mm Hg to 16.9 ± 4.1 mm Hg; p < 0.05) (table 1) in the seven lambs in which it was measured. Consequently, in the four lambs that underwent dilation of both pulmonary arteries, the change in gradient after the second dilation was unimpressive (19.8 ± 4.4 mm Hg to 7.5 ± 2.7 mm Hg; p < 0.05).

The decrease in pressure gradient induced by dilation was associated with an increase in flow to the dilated lung. The percentage of cardiac output directed to the dilated lung increased after dilation (from 19.2% to 45.4%) in each of four lambs, while total cardiac output was unchanged after dilation (150 ml/kg-min to 152 ml/kg-min). Thus, there is a simultaneous increase in flow (p < 0.05) and a decrease in pressure gradient across a branch pulmonary artery stenosis after balloon-induced dilation (fig. 2). This increase in flow to the dilated lung did not alter the intrapulmonary shunting of micro-
spheres, which was less than 0.5% before and after dilation.

Angiography in the 13 dilated pulmonary arteries also demonstrated an increase in pulmonary artery diameter after dilation (figs. 3 and 4). The diameter of the narrowest segment rose after dilation in every case, from 12-210% (mean 63%) \( p < 0.001 \). The main pulmonary artery diameter decreased an average of 24% \( p < 0.01 \) immediately after dilation.

Natural History

Four lambs underwent right-heart catheterization at 7-12-day intervals before dilation; the mean gradient across both the RPA and LPA stenoses are shown in figure 5. Although those gradients vary considerably, there is no statistically significant change in the predilation gradient despite considerable animal growth, implying concomitant growth in the area of stenosis. An increase in the size of the narrowed segment was observed on the angiogram (fig. 6).

After dilation, the gradients remained low on multiple postdilation studies despite animal growth. The angiograms supported the hypothesis that the dilated segments grew as the lambs grew. (fig. 6).

Pathologic Observations

Neither the fresh nor the formalin-fixed pulmonary artery specimens had evidence of adventitial rupture or false aneurysm formation. On gross examination, the intima showed no evidence of suture rupture. In each recently (less than 3 days) dilated segment there was evidence of linear tears in the intima which ranged from minimal tears (lamb 7, LPA) to rather extensive tears. The tears were always at or near the area of greatest narrowing; the orientation of the tears appeared circumferential and ranged from 1 mm to
several millimeters long. Seven days after dilation, the tears were still visible, but were covered with a yellowish neointima. By 90 days, the intima of dilated vessels were, except for the presence of sutures, indistinguishable from normal. Intimal tears were not seen in any undilated pulmonary artery.

Microscopic sections of the stenotic areas of all vessels showed variably thick walls due to fibrous intimal plaques, fibrosis of the media with disruption of the elastic fibers and interposition of smooth muscle bundles, and a thick fibrotic adventitia. Vasa vormarum were prominent and often extended through the entire vessel wall. Sutures and foreign body granulomas were visible in all specimens, and lamb 8 had multiple small infected mural thrombi in both pulmonary arteries.

Recently dilated arteries showed tears of the vessel wall, often overlying a suture but found in other areas as well. The tears were accompanied by fresh hemorrhage, which produced collections of blood in the media (fig. 7). Dissection of blood between the media and adventitia, and into the adventitia, was occasionally noted. Tears through the entire thickness of media were seen in all recently dilated arteries, but these never extended through the adventitia. We saw acute inflammation in the adventitia adjacent to one deep tear in one lamb.

Sections through healed dilation sites (> 7 days) showed intact intima, media and adventitia. Areas of old medial hemorrhage continued to show separation of medial elastic fibers, although the blood had been replaced by smooth muscle cells.

Protocol for Dilation

For the first four lambs, we used a short balloon (1.5 cm long) with a diameter 1.7–2.0 times larger than the narrowed segment to be dilated. In each case (and in all subsequent cases), the postdilation angiographic diameter of the narrowed pulmonary artery was within 1 mm of the balloon diameter. In each case, 4 atmospheres or more were used for a dilating pressure.

We initially used full-strength contrast (Renografin-60) as the dilating fluid and left the balloon inflated for a full 30–40 seconds. The contrast material was difficult to withdraw rapidly from the balloon, and periods of more than 1 minute of occlusion resulted. Two lambs developed acute bradycardia, presumably from subtotal right ventricular outflow obstruction, after 45 seconds of obstruction. When half-strength contrast material (diluted with normal saline) was used, and the duration of dilation was confined to 30 seconds or less, the occlusion time was kept under 45 seconds and bradycardia did not occur. Using this approach, balloon visualization was excellent, and dilation appeared to be just as effective.

In three lambs, we tried to rupture the pulmonary artery by selecting balloons 2.5–3.5 times larger in diameter than the narrowed segment. The balloons were then inflated slowly until balloon rupture occurred, between 6 and 8 atmospheres of pressure. The diameter of these vessels increased an average of 2.7-fold, no vascular rupture occurred, and the procedure was well tolerated.

The most difficult part of the procedure was centering the balloon directly under the stenosis. As the in-
flated balloon is oval-shaped, and the narrowed segment is very short, the force of inflation tended to push the balloon forward or backward away from the stenosis. Thus, the balloon needed to be positioned within approximately 1-2 mm of the center of the narrowing for the balloon to remain stable during the entire 30 seconds needed for dilation. The problem was alleviated by using slightly longer (2.0-cm) balloons in the later lambs, and by incorporating a single radiopaque line into the catheter at the center of the balloon. No attempt is made to fully inflate the balloon unless the “notch” made by the narrowed segment on the balloon’s surface is within 1 mm of that center line. Because of the appearance of intimal and, occasionally, transmedial tears after dilation, we were reluctant to pass guide wires or unguided catheters through a previously dilated site.

Using these measures, no more than three unsuccessful dilations were attempted before a successful dilation. Our protocol is summarized in table 2.

**Discussion**

The feasibility of dilating certain kinds of atherosclerotic vascular narrowings is well established. However, a similar approach might not be safe or effective in the treatment of congenital vascular stenosis. The vascular wall is different in the two types of disorders, and one might expect that a soft atherosclerotic plaque would be easier to dilate than a congenital abnormality. Congenital narrowings tend to be central in the circulation; thus, the act of dilation itself, by occluding a major vessel, might alter circula-

tion enough to cause hemodynamic instability. Even if balloon dilation were initially successful, its value would be limited if the dilated area did not grow along with the child or if the vascular intima did not return to normal. Finally, the optimal protocol for, and safety of, such a procedure must be at least tentatively known before the institution of clinical studies.

We chose the bilateral branch pulmonary artery stenosis model in newborn lambs for several reasons: There is a similar lesion in children (with or without the associated tetralogy of Fallot); the availability of two vessel sites in a single lamb would allow one vessel to serve an internal control; and the relatively thin vessel wall might improve the chance of a successful dilation. Also, residual right ventricular hypertrophy from the prenatal period might allow the lamb to tolerate a more severe acute obstruction.

Previous attempts to surgically obstruct pulmonary arteries have relied on the use of a non-absorbable banding material that could be “grown into.” This approach is obviously unsuitable for subsequent dilation. We chose circumferential plication sutures. With these sutures alone, the gradient tended to decrease over time in several preliminary animals. Wrapping the vessel with gut alone (analogous to

<table>
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wrapping the aorta with fascia\textsuperscript{10}) also produced only a transient gradient. The combination of plication sutures and wrapping with gut produced a satisfactory lesion in our lambs.

Several observations suggest that this preparation represents an adequate model of congenital or surgically-related branch pulmonary artery stenosis. The amount of narrowing, relative to body size, is neither progressive nor regressive with time,\textsuperscript{13} and significant right ventricular hypertrophy develops within 2 months. The narrowed area has a substantial amount of adventitial scar tissue, although most of its circumference is composed of normal intima and media. The suture material is strong enough to resist rupture in vitro, and dilation was not achieved at the expense of a broken suture in any lamb. The gradients achieved were substantially higher than those reported previously in normal lambs.\textsuperscript{14} Finally, we waited 5–9 weeks before attempting dilation, assuming near-maximal vascular strength by that time.\textsuperscript{15}

If balloon-induced dilation were successful in relieving a stenotic branch pulmonary artery, we would anticipate a fall in pressure gradient as well as a rise in flow across the narrowed area. Similarly, the angiographic diameter should increase. In all 13 dilated pulmonary arteries, the gradient decreased (by an average of 79\%) and the diameter increased (by an average of 63\%) after dilation. The diameters were measured from single-plane angiograms; and while single-plane angiography may be inaccurate with eccentric narrowings, in all cases the narrowings appeared symmetric on postmortem examination. In all four lambs studied with microsphere injection, the percentage of flow and the absolute flow across the narrowed site increased after dilation (fig. 2). These results clearly indicate that balloon-induced dilation of these lambs resulted in a substantial hemodynamic improvement of a branch pulmonary artery stenosis.

The long-term results of dilation also appear to be favorable. Both the dilated and the undilated sides grew with the lambs, such that there was no significant change in gradient with time. Neither aneurysmal dilation nor restenosis develops in these lambs at a follow-up of 3–4 months.

Pathologically, the undilated lesions have patchy areas of intimal hyperplasia and very thick adventitia with scarring. Examination of recently diluted pulmonary arteries indicates that dilation is accomplished due to intimal tearing and medial stretching of the relatively normal sections of pulmonary artery, between the plication sutures. Similar lesions have been noted in other studies.\textsuperscript{16} In each case, the adventitia remained intact. Microscopic examination of freshly diluted specimens indicated that the intimal tears usually extended into the media. In two lambs, whose narrowed pulmonary arteries were expanded by 2 1/3-fold and 3 1/3-fold, the tears appeared to extend through the full thickness of the media. Although such tears appeared to be well tolerated, the long-term effects of such lesions remain unknown.

While these studies do not permit a definitive description of the optimal protocol for the dilation of branch pulmonary artery stenosis, they do provide a reference framework (table 2). Further modifications can be expected, especially in the areas of catheter design and placement procedure.

The crucial question is whether the lesion in congenital branch pulmonary artery stenosis will respond to attempted dilation in a fashion similar to that of these lambs. Microscopic findings in branch pulmonary artery stenosis\textsuperscript{17, 18} show a thicker intima than seen in our lambs, with less adventitial disease. However, whether different forms of branch pulmonary artery stenoses have similar microscopic findings is not known. Thus, the dilatability of congenital lesions will probably only be determined by clinical trials. Similarly, our ability to dilate acquired stenotic lesions in children is undocumented. Nonetheless, the absence of signs of vessel stretching in the scarred areas around the sutures in our lambs suggests that attempts to dilate an anastomotic suture line may be unsuccessful.\textsuperscript{19}

This study, indicating that balloon dilation of surgically induced branch pulmonary artery stenosis is safe and successful in lambs, does not assure a similar result in humans. Nonetheless, the consistent results of this study, as well as the apparently high margin of safety, warrants the extension of this technique to infants and children with similar lesions.

Acknowledgment

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References

SIDE EFFECTS OF PGE₁/Lewis et al.

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Side Effects of Therapy with Prostaglandin E₁ in Infants with Critical Congenital Heart Disease

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SUMMARY The case reports of 492 infants with critical congenital cardiac disease treated with prostaglandin E₁ (PGE₁) were reviewed to determine the nature and incidence of intercurrent medical events. Forty-three percent of the infants had at least one such event, but only half of these were related to PGE₁ and the majority required only minor changes in management. Cardiovascular events were the most common (18% incidence), with cutaneous vasodilation and edema occurring more frequently during intraaortic infusion than during i.v. infusion. Central nervous system events were reported in 16% of the patients. Respiratory depression was reported in 12%, and was particularly common in infants weighing less than 2.0 kg at birth (42%). Hematologic, infectious and renal events appeared for the most part to be unrelated to PGE₁. The overall mortality (excluding 19 patients with hypoplastic left-heart syndrome) was 31%; the mortality for the patients with critical coarctation or interruption of the aortic arch was nearly twice that for the cyanotic infants (50% vs 27%). No death was attributed to PGE₁ administration.

During infusion of PGE₁, arterial blood pressure and respiratory activity should be monitored carefully and appropriate supportive steps taken if hypotension or respiratory depression occurs. The development of fever or jitness may require reduction of the infusion rate and, in view of the possible increased incidence of infections, the prophylactic use of antibiotics is recommended.

AFTER Coceani and Olley¹ showed that PGE₁ and PGE₂ were potent dilators of the fetal ductus arteriosus, numerous independent reports of their efficacy in treating infants with ductus arteriosus-dependent cyanotic and acyanotic congenital cardiac defects appeared in the literature.¹⁰ However, data on the side effects of PGE₁ have been difficult to gather because so few patients were treated by each group. Therefore, we have examined the experiences of all 56 investigators in the United States who administered PGE₁ under the investigational new drug protocol of the Upjohn Company between January 1976 and June 1979.

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Patients and Methods

The case reports of 492 infants treated with PGE₁ were reviewed and all intercurrent medical events (IMEs) were recorded. An IME was defined as any unanticipated or undesirable incident that occurred during the course of treatment and might have necessitated an alteration in therapy. Several categories listed as IMEs in the original reports were deleted because they were either expected responses to the underlying cardiac anomaly, other congenital anomalies, or were undocumented. These included "cyanosis" in patients with pulmonary atresia or tetralogy of Fallot, "congestive heart failure" (CHF) in infants with left ventricular (LV) outflow obstruction, "possible sepsis" without any confirmatory clinical or laboratory evidence, and associated congenital anomalies, e.g., "hypoplastic lungs."

Each IME was counted separately to determine the total number of reactions. Patients who had more than one IME were counted only once, thereby permitting the incidence of IMEs to be calculated.

The data were analyzed using the chi-square test and the probability was obtained from a cumulative
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