Transcutaneous Angioplasty of Experimental Aortic Coarctation

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SUMMARY A dilatable form of juxtaductal aortic coarctation was surgically created in 29 newborn lambs. Of the 17 long-term survivors, four lambs served as controls and 13 underwent transcutaneous balloon dilation angioplasty with either polyvinylchloride or polyethylene catheters after 7–10 weeks of recovery. During growth before dilation, there was little change in the systolic gradient across the coarctation (36.6–35.3 mm Hg) despite an increase in animal weight from 3.8 to 19.3 kg. This systolic gradient remained constant in undilated lambs throughout a 6-month follow-up. Dilation produced an immediate 65% increase in the diameter of the coarctation and a 68% decrease in the systolic gradient across the coarctation site. Successful dilation required very high (6–8 atmospheres) dilating pressures. This gradient relief persisted throughout a follow-up of up to 1 year. Although no late sequelae could be attributed to the angioplasty, one lamb suffered an anterior aortic tear (associated with a difficult postdilation wire passage across the dilation site), which resulted in fatal intrathoracic hemorrhage. Gross pathologic inspection demonstrated intimal and medial tears in successfully dilated lambs in the first 3 days after dilation; on late pathologic examination, the intima appeared completely healed, without evidence of aneurysm or accelerated atheroma formation, within 2 months. These results, in conjunction with previous human in vitro studies, support the hypothesis that human aortic coarctation may be a dilatable lesion, although the safe limits and optimal protocols for dilating human coarctations are not known.

THE OPTIMAL medical and surgical management of infants and children with aortic coarctation is controversial. Early surgery seems to prevent the development of sustained, lifelong hypertension,1 but may result in a significant gradient later in life.2,3 Late surgery results in excellent long-term technical success,3,4 but may leave the child with lifelong arterial hypertension.4,5 A two-stage surgical approach (operating when necessary on recoarcted aortas) is not optimal because reoperation for recoarctation is, despite recently improved results,5 a difficult and hazardous procedure.6,7 The advent of a successful balloon dilation catheter for the treatment of peripheral atherosclerotic lesions,8,9 appears to offer a fourth alternative: One could initially dilate the coarctation transcutaneously (thus eliminating the gradient) and still allow a clean and safe operative field for subsequent definitive repair at an optimal age.

The feasibility of such an approach was first suggested by the successful dilation of a postmortem human coarctation by Sos et al.10 in 1979. That study was confirmed and extended in excised human specimens;11 in the latter study, however, native human coarctations required high dilating pressures (8 atmospheres), suggesting that the technique for successful dilation of coarcted aortas might differ from that of acquired arterial lesions.

Despite the encouraging results obtained from in vitro studies, several important questions can only be addressed by in vivo investigations: Will dilation weaken the aortic wall to the point of rupture? Will the intimal and medial injury (known to occur with balloon angioplasty12,13) result in accelerated atheroma or aneurysm formation? Will the dilated segment restenose with time, or will it grow along with the growing child?

To address these and similar questions, we developed a dilatable form of aortic coarctation in growing lambs. In this report we outline our preparation and its “unnatural” history using hemodynamic, angiographic and pathologic techniques; determine the safe-
ty and efficacy of balloon dilation angioplasty both acutely and chronically; and describe the lesion produced in a growing aorta by balloon dilation, both early and late.

Materials and Methods

Since Halsted's first description of an experimentally produced aortic coarctation in 1905, more than 70 descriptions of similar procedures can be found in the English literature in this century. Nearly all reports have, like Halsted's, described wrapping the aorta with nonabsorbable (and nondilatable) sutures. The largest gradients have developed when this technique was used in growing animals. The few previously described forms of dilatable experimental coarctation have either resulted in minimal gradients or gradients that diminished with time. Preliminary work in our laboratory indicates that a transvascular scar is difficult or impossible to dilate, even when interrupted sutures are used. Currently, we use a posterior wedge resection with additional constriction from absorbable suture wrapped around the resected site (fig. 1).

Experimental Model

Twenty-nine newborn lambs underwent left thoracotomy under halothane and nitrous oxide anesthesia. The ductus arteriosus was ligated and divided, and the juxta ductal descending aorta was dissected free for 3–5 cm. The aortic circumference was measured with knotted suture, and two 5-0 prolene sutures were placed on the aortic surface to mark two points separated by half the measured aortic circumference. Both sutures were excluded from the aortic lumen by a side-biting Potts clamp, and a 1-cm-long lengthwise incision was made in the posterior, excluded aortic wall. A wedge of aorta was then resected using the prolene sutures as limit markers and the diamond-shaped aortic opening was closed with two running 5-0 prolene sutures. The cross clamp was removed, hemostasis achieved, and the pressure gradient was measured by direct puncture of the aorta above and below the coarctation. Preliminary work indicated that systolic gradients in excess of 60 mm Hg resulted in acute renal failure and early death; therefore, we sought to produce an intraoperative systolic gradient of 40–50 mm Hg. After resection, the area was wrapped with two to four 2-0 catgut sutures, the chest was closed after measuring a final gradient, and the lamb was allowed to recover.

Groups

The lambs in whom a coarctation was successfully created were separated into three groups. Control lambs were catheterized sequentially to determine the effect of growth on the undilated coarctation; lambs that underwent acute dilation were killed within 2 days of dilation; and lambs that underwent chronic dilation were catheterized sequentially for as long as 1 year after dilation to determine the late effects of the procedure.

Dilation Technique

All but five lambs underwent repeated femoral catheterization from the groin using the Seldinger percutaneous technique. The lambs were anticoagulated with 100 U/kg of heparin. Pressure gradients across the coarcted site were measured with fluid-filled catheters connected to Statham P23Db strain gauges, and recorded on an Electronics for Medicine DR12 optical recorder. At each catheterization, single-plane cutfilm (3 films/sec for 2 seconds) aortograms were performed in the lateral position, injecting meglumine diatrizoate (Renografin-76, Squibb) at a dose of 1–1.5 ml/kg over 1–2 seconds.

After determining the pressure gradient and lateral angiographic diameter of the coarctation, a 0.038-inch guidewire was advanced across the coarctation under fluoroscopic control. In the first five lambs, a Cook polyvinylchloride catheter was used for dilation; for the rest of the lambs, we used either Cook or Medi-Tech polyethylene dilation catheters. In the first few lambs, we attempted to use 4 atmospheres of dilating pressure; but 4 atmospheres was insufficient to eliminate the "waist" in the balloon caused by the coarctation. We have since used 6–8 atmospheres. Balloons were 6–12 mm in diameter and 2–4 cm long. In each

**Figure 1.** Coarctation surgery. The resected wedge is intended to constrict the aorta by 50%, and is closed with 5-0 polypropylene suture. As. Ao. = ascending aorta; Des. Ao. = descending aorta; PDA = patent ductus arteriosus.
case, the balloon diameter chosen was 1.5–3.0 times the narrowest diameter of the coarctation, but smaller than the aortic diameter proximal to the constriction (15.3 ± 3.0 mm). Coarctation diameters were estimated directly from the angiograms, using the known catheter diameter to correct for magnification.

Pathologic Studies

The lambs were killed by sedative overdose 1 hour to 365 days after dilation. In the acutely dilated lambs, blood pressures were normal at the time of sacrifice; in the others, blood pressures were not measured at sacrifice. Right and left ventricular free walls were weighed in each lamb. The aortic specimens consisted of the coarctation site and 3 cm of aorta both proximally and distally, fixed in 10% buffered formalin in a nondistended state. The specimens were opened posteriorly (through the surgically resected wedge), inspected grossly, and sectioned transversely through the area of coarctation. Tissues from three different sections (proximal, midpoint and distal) were stained with hematoxylin-eosin and Lawson elastic stains. Occasional sections were stained with Masson trichrome.

We used the two-tailed paired t test to determine whether dilation influenced the pressure gradients and angiographic diameters of the coarctations, using the Bonferroni modification to correct for multiple inferences. The unpaired two-tailed t test was used to determine the differences between hemodynamic and anatomic variables in dilated lambs when compared to normal controls. All results are expressed as the mean ± SD.

Results

Experimental Model

In the 17 surviving lambs, coarctations were created at 5–13 days of life (mean 6.9 ± 2.1 days) at an average weight of 3.8 ± 0.9 kg. In these lambs, the intraoperative systolic gradient was 36.6 ± 13.1 mm Hg. Of the 12 lambs that died, six died of immediate congestive heart failure associated with intraoperative gradients of 50–70 mm Hg. Three other lambs died late, two from infection and one from accidental soap ingestion. The other three, catheterized early in the study, died of a presumed arrhythmia during carotid artery dissection for line placement. Because of this experience, all subsequent lambs were catheterized percutaneously from the groin.

The lesion produced by this procedure is illustrated in figure 2. Although all of the narrowing was produced in the posterior aorta, the coarctation “shelf” extended around the entire circumference of the aorta. The anterior area of coarctation was composed, at least in part, of intimal thickening. Large collateral arteries were visible, coursing from the ascending aorta to the posterior wall of the descending aorta, just distal to the coarctation. All predilation angiograms demonstrated varying degrees of poststenotic dilatation.

On examination, all lambs had diminished or absent femoral pulses, but otherwise appeared healthy, except for one that developed a progressive lower-limb neuropathy; this lamb had marked poststenotic dilatation of the aorta. By 2 months after surgery, he could not stand and was dilated and killed.

The systolic gradient remained constant in all groups of lambs (36.6 vs 35.3 mm Hg) during the first 2½ months of life despite an increase in weight from 3.8 to 19.3 kg (fig. 3). Thirteen lambs underwent dilation at an average age of 82.2 days. The four remaining lambs were followed, undilated, for an average of 180 days; during that time, the systolic gradient remained constant between 24.5 and 33.2 mm Hg (fig. 3).

These gradients also produced mild left ventricular hypertrophy. The ratio of right ventricular free wall to left ventricular weight was lower in the undilated lambs (0.22) than in a group of four sham-operated lambs (0.30) (p < 0.01).

Pathologic examination of the undilated coarctation demonstrated intimal hyperplasia at the site of coarctation. There was also marked medial thickening, composed of normal-appearing elastic and smooth muscle tissue.

Results of Balloon Angioplasty

Thirteen lambs underwent angioplasty of their coarctations with balloon dilation catheters. In every case, balloon dilation (fig. 2) increased the angiographic diameter of the coarctation (from 4.8 ± 2.0 to 7.9 ± 1.6 mm, p < 0.01) (fig. 4) and decreased the systolic gradient (from 37.0 ± 16.2 to 11.7 ± 5.8 mm Hg, p < 0.01). The gradient relief was entirely due to a decrease in the arterial pressure above the coarctation from 136/98 to 103/81 mm Hg (p < 0.01).

High dilating pressures (8 atmospheres) and polyethylene catheters (rather than polyvinylchloride catheters) may have given the best results. We also determined that the lambs would tolerate dilation with balloon diameters as large as 2½ times the size of the coarctation diameter. These modifications in the tech-

Figure 2. Lateral angiogram of the descending aorta before (PRE) and 15 minutes after (POST) balloon dilation angioplasty. Although resection involved only the posterior aspect (left side of figure) of the descending aorta, a “curtain” of endothelial thickening involves the entire circumference of the coarctation site. Before dilation, the large collateral vessels, originating from the ascending aorta, enter the dilated poststenotic descending aorta.
nique we had previously used in pulmonary arteries seemed to result in progressively better gradient relief during the course of the study: The decrease in systolic gradient produced by angioplasty was larger in the last four lambs (86%) than in either the first four (46%) or the middle five (63%) lambs.

Twelve of the 13 lambs tolerated balloon dilation without apparent difficulty. One lamb with a tight (3-mm) coarctation underwent dilation with a 9-mm balloon. After dilation, we had difficulty in passing the guidewire across the previously dilated site. At angiography, a faint collection of extravascular contrast was seen anterior to the coarctation site (fig. 5). The lamb developed progressive hypotension; no attempt was made to maintain blood pressure with transfusion, and he died 4 hours after dilation. At postmortem examination, we found a tear in the anterior aortic wall that resulted in extensive mediastinal hemorrhage.

Seven of the dilated lambs were killed within 48 hours of dilation; in each case but one, there was evidence of intimal tears, 1–3 mm long, extending varying distances into the media. These tears were always on the anterior, or nonoperated, aortic wall, and produced intramedial hemorrhage with separation of the medial muscle fibers (fig. 6).

Six of the dilated lambs were allowed to recover and were serially catheterized for 6–12 months after dilation (fig. 7). In each, the gradient remained low after dilation despite an increase in animal weight from 20.4 ± 3.6 to 46.3 ± 6.2 kg. Similarly, left ventricular hypertrophy was less obvious in these lambs at the time of sacrifice (RV/LV + S = 0.25). Pathologic examination of specimens more than 8 weeks after dilation revealed an intact and normal appearing intima. Two lambs had evidence of medial thinning grossly, but no evidence of aneurysm or atheroma formation. Microscopically, the areas of prior dilation showed evidence of spreading of the medial elastic fibers. We saw no evidence of acute or chronic inflammation.

Discussion

A surgically created cardiac defect as a model for human congenital heart disease is, at best, imperfect. Important differences between the human and ovine lesions, including the presence of foreign suture material or surgically induced scar tissue, make comparisons hazardous and uncertain. Nonetheless, the use of a posterior wedge resection and absorbable suture to create a coarctation results in a preparation that, in several important ways, mimics human coarctation. Gradients remained constant as the lambs grew, despite the development of extensive collaterals. Poststenotic dilatation is observed within 2 months of age. Intimal hyperplasia develops not only on the operated, posterior side of the aorta but also on the opposite side, suggesting that the obstruction itself may injure the intimal surface, worsening the obstruction. As in human coarctation, the lambs are hypertensive about the coarctation and pulseless below, but otherwise healthy. The absence of an in utero lesion in the lambs

![Figure 3](http://circ.ahajournals.org/lookup/figure-pdf/10.1161/CIRCULATIONAHA.107.181128.1283/Figure3.pdf)

FIGURE 3. Changes with time in the mean systolic pressure gradient in three groups of lambs. Gradients in undilated lambs (closed squares) remain relatively constant despite considerable animal growth. The fall in gradient produced by dilation (open squares) remained at late follow-up (dot).

![Figure 4](http://circ.ahajournals.org/lookup/figure-pdf/10.1161/CIRCULATIONAHA.107.181128.1283/Figure4.pdf)

FIGURE 4. Immediate impact of dilation on coarctation diameter as estimated by lateral angiography.
may be important; however, the small amount of blood flow across the aortic isthmus in utero suggests that the hemodynamic load of a coarctation in utero is relatively small.

Although the experimental preparation we describe is apparently adequate for the study of the hemodynamic impact of coarctation in a growing lamb, the primary purpose of these experiments was to study, indirectly, the structural properties of aortic coarctation. One method of validating the adequacy of the experimental preparation is to compare its histologic appearance with the histology of human coarctation. Other than intimal hyperplasia encircling the site, we observed no differences between normal and coarctation-associated aortic wall. Most workers have also described circumferential aortic intimal hyperplasia in human specimens. Descriptions of medial histology have, however, varied. Hutchins found no medial abnormal histology; Dunnill described increased acid mucopolysaccharides in medial tissue distal to the coarctation; and Ho and Anderson described pale-staining ductal media encroaching into the aortic wall. These disparate reports make comparison of human disease to experimental preparations difficult.

Perhaps more importantly, the "dilational" properties of these lamb coarctations are similar to those found in excised human coarctations: the inflation pressures required for dilation are similar and the changes in diameter are similar, as are the observations of intimal and medial tears. While in vitro coarctation...
may well differ from in vivo lesions, we would conclude that observations made in our lambs should, at least tentatively, be used in designing clinical trials.

Recognizing that these surgically created coarctations are imperfect estimates of human coarctations, we found them to be dilatable lesions. Dilation succeeds at the expense of intimal and medial tears, which are largely healed within 2 months. Although small areas of medial thinning were seen in occasional late specimens, we observed neither aneurysms nor atheroma formation as late as 1 year after dilation. The absence of atheroma formation in these lambs is not, however, entirely reassuring; high cholesterol diets may be required before sheep will develop atheroma even under adverse circumstances.25

Of more concern is the observation that one can rupture the aortic wall during the process of a dilation procedure. It is not clear whether that lamb's aorta ruptured because of an overlarge dilating balloon diameter, or whether a small intimal tear was enlarged after dilation by the extravascular passage of a guidewire. Extravascular wire passage is possible; we will no longer pass an unguided wire or nonballoon catheter across a recently (less than 1 month) dilated site. Since adopting this approach, we have had no complications in four animals in whom it was used (including one whose diameter was almost tripled by the balloon diameter).

The success of balloon dilation angioplasty appears heavily dependent on technical considerations. Our approach evolved during the course of this study, and the current protocol is the result largely of trial and error (table 1). Dilating balloons of polyethylene26 appeared superior to those of polyvinylchloride, largely because they retained their cylindrical shape during inflation, even at the high pressures required for dilating coarctation. Lambs tolerated without difficulty the 75–90 seconds of aortic occlusion required for inflation, dilation and deflation, presumably because of collateral flow. We found no evidence that more than one dilation was helpful or necessary, nor did longer dilation durations appear useful. Although using a balloon twice the diameter of the coarctation appears to be quite safe, best hemodynamic results were achieved when we used slightly larger balloons (2½ to 3 times the diameter). The upper limit of safety in experimental coarctations cannot be defined from our data; moreover, even if it could be defined, it may not apply to human coarctation.

The data derived from these animal studies, in conjunction with prior in vitro data, suggest that balloon dilation angioplasty of the infant aortic coarctation, although potentially hazardous, may be a feasible and relatively safe procedure. Angioplasty is only partially successful, and seems to be a palliative rather than a definitive procedure. This conclusion is at least partially supported by the recent, apparently safe dilation of a postoperative coarctation in an infant.27 The margin of safety does not appear to be quite as large as was found with experimental branch pulmonary artery stenosis,28 although the safety may be enhanced by scrupulous catheter and guidewire techniques. The absence of long-term sequelae is encouraging. If a safe upper limit of balloon diameters can be defined, we believe that clinical trials may be warranted.

### References
APPENDIX. Experimental Animal Data

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<th>Coarct. gradient (mm Hg)</th>
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