Patency of the ductus arteriosus after balloon dilation: an experimental study

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ABSTRACT  Balloon dilatation of the ductus arteriosus was carried out in vivo in newborn pigs and on postmortem specimens from humans and piglets. The ductus was functionally closed in all newborn animals but patency resulted in all animals after balloon dilatation. Left-to-right shunts of 50% to 70% were found with anatomic lumen sizes of 3 to 5 mm. Patency was demonstrated up to 6 weeks after dilatation. Histologic examination showed splitting of the internal elastic layer and media, areas of hemorrhage confined to the media, and preservation of the adventitia. Mediastinal hemorrhage did not occur. This new technique is useful as an animal model of patent ductus arteriosus and could theoretically be used for palliative treatment of ductus-dependent congenital heart disease. Circulation 68, No. 3, 621–627, 1983.

SPONTANEOUS closure of the ductus arteriosus causes deterioration of the clinical condition in newborn patients with cyanotic heart disease and decreased pulmonary blood flow. Adequate pulmonary perfusion can be temporarily maintained by prostaglandin infusion or by a surgically created systemic shunt.

Very recently balloon dilatation has been applied to congenital heart disease for nonsurgical treatment of peripheral pulmonary artery stenosis and coarctation. A logical step therefore was to attempt balloon dilatation of the ductus arteriosus as a nonsurgical technique to keep the ductus patent. Such a technique could theoretically be used for long-term palliation of ductus-dependent congenital heart disease.

It is the purpose of this article to report our experience with this new technique in experimental animals.

Materials and methods

Postmortem dilatation. This study was undertaken to determine the tolerance of the ductus to balloon dilatation. Balloon size, dilating pressures, and times are summarized in table 1.

The ductus arteriosus of 16 piglets (ages 3 to 15 days) were dilated postmortem either as specimens or in situ.

Two specimens of human ductus arteriosus were dilated. Both patients had died from noncardiac causes 20 days after birth.

In vivo dilatation. Fifteen piglets (ages 2 to 13 days) weighing 1 to 2.5 kg were studied in vivo. Animals were sedated with 5 mg im acepromazine and anesthetized with 25 mg im ketamine HCl (Ketalar). After endotracheal intubation the animals were ventilated on oxygen-enriched room air (Harvard respirator) and paralyzed with periodic intravenous injections of succinylcholine chloride (Anectine).

A No. 4F tapered end-hole polyethylene catheter was reshaped, forming a 10 mm right-angled curve, and was introduced via femoral artery cutdown. Under fluoroscopic observation, the aortic opening of the ductus arteriosus was engaged with the catheter tip. To traverse the ductus, gentle forward pressure was applied to the catheter. Successful passage into the pulmonary artery was confirmed by a test injection of contrast agent.

The catheter was then exchanged over a guidewire for a No. 5F angioplasty catheter, (Cook Inc. and Meditech Inc.), and the balloon was inflated with dilute contrast agent (figure 1, B). A mechanical inflation device with a pressure gauge was used, allowing exact pressure adjustments.

Angiograms were obtained before and after dilatation with the catheter tip high in the descending thoracic aorta. Successful dilatation and shunt flow were also confirmed by the appearance of a typical murmur.

In four animals a flow-directed balloon catheter was introduced via the femoral vein. In these animals, aortic, pulmonary artery, and right ventricular pressures were obtained by a Statham P23Db strain gauge transducer and a Honeywell (Model 1858) multichannel recorder. Blood samples from the aorta, pulmonary artery, and right ventricle were analyzed for pH, PCO₂, PO₂, oxygen saturation (Instrumentation Laboratory Model 113 analyzer), and hematocrit. The postdilatation left-to-right shunt was calculated.

After animals were killed or died naturally, the ductus arteriosus, pulmonary artery, and thoracic aorta were removed. Specimens were examined grossly and by light microscopy.

Results

The ductus arteriosus was functionally closed as determined by angiography (figure 1, A) in all animals.
TABLE I

<table>
<thead>
<tr>
<th>Inflated balloon diameters and dilatation times</th>
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<tr>
<td>Postmortem Piglets (n = 16, 3-15 days old)</td>
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<td>Postmortem Humans (n = 2, 20 days old)</td>
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<tr>
<td>In vivo Piglets (n = 13, 2-13 days old)</td>
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*Dilating pressure 5 to 6 Atm.

Inspection of the specimens before dilatation showed that the pulmonary artery opening of the ductus was pinhole sized and frequently covered by endothelium, whereas the aortic opening appeared larger. Because of the oblique entry of the ductus into the aorta, the aortic opening appeared partially covered by a flap on the superior aspect.

The catheter easily and consistently engaged the aortic opening of the ductus. Minimal pressure with the catheter resulted in passage through the ductus. Early experience with in situ catheterization in the dead animals indicated that forcing the catheter against resistance or probing with a guidewire invariably resulted in a false passage. This occurred in two attempted in vivo dilations, and the ductus could not be catheterized in these animals. In one animal the tip of the balloon catheter perforated the anterior wall of the pulmonary artery just above the pulmonary valve. Al-

FIGURE 1. A, Angiogram before dilatation. Ductus closed. B, Angioplasty catheter sitting across ductus. Balloon diameter 4 mm. C, Ductus size 1 to 2 mm after dilatation for 30 sec repeated three times (arrow). D, Ductus size 3 to 4 mm after dilatation for 5 min repeated twice. E, Follow-up angiogram after 7 days. The pulmonary end of ductus is slightly narrowed (arrow). F, Follow-up pulmonary angiogram after 6 weeks. The aortic end is slightly narrowed (arrow), while the pulmonary end is widely patent.
though the ductus was successfully dilated, the animal died later from cardiac tamponade. This was avoided in the subsequent experiments by a more careful positioning of the angioplasty catheter.

Successful dilatation was achieved in all animals and was confirmed by aortography and the appearance of a murmur. The size of the ductus varied according to dilatation time (table 2). Dilatation for 30 sec repeated three times resulted in a ductus lumen measuring 1 to 2 mm in all animals (figure 1, C). Dilatation for 5 min repeated two or three times resulted in a lumen measuring 3 to 5 mm in five animals (figure 1, D) and 1 to 2 mm in one animal. Dilatation for 5 min only yielded a ductus size of 1 to 2 mm in two animals and 3 mm in one animal.

The age of the animals did not influence postdilatation diameter of the ductus. Angiographically, the ductus wall appeared smooth (figure 1, C and D); however, prominent intimal flaps were occasionally seen.

Five animals were killed 60 min after dilatation. Follow-up angiograms taken before the animals died showed the ductus to be patent and of the same size as immediately after dilatation in four animals. In one animal the lumen was narrowed. The ductus in this animal had been dilated with a 5 mm balloon for 30 sec repeated three times. One animal was killed after 7 days, and an angiogram showed the ductus to be patent (figure 1, E). One animal was killed 6 weeks after dilatation, and the ductus was patent with some narrowing at the aortic opening. The pulmonary opening was larger than immediately after dilatation (figure 1, F).

The other animals died spontaneously at 4, 6, 24, and 48 hr. Follow-up angiograms were therefore not obtained. All of these animals had murmurs up to the time of death.

Estimation of the left-to-right shunt based on blood gas analysis showed 68% and 62% left-to-right shunts in two animals dilated with 5 mm balloon catheters for 5 min repeated twice and for 5 min, respectively. In these animals, the ductus lumen measured 4 mm and 3 to 4 mm. Another animal followed up for 6 weeks had a 25% left-to-right shunt when it was killed.

The differences in oxygen saturation between the right ventricle and pulmonary artery in these three cases were 13%, 17%, and 5%. The differences in Po2 were 42, 25, and 16 mm Hg.

The left-to-right shunt in another animal could not be calculated because of technical problems.

Pathologic findings. There was no evidence of mediastinal hemorrhage at autopsy in the 13 animals that underwent in vivo dilatation.

Small areas of discoloration of the ductus wall and around the pulmonary orifice of the ductus were seen in 10 of the 13 animals. Figures 2A and 2B show the specimen with the most marked changes. Histologically the hemorrhage was confined to the media, with the adventitial layer intact (figure 2C).

Gross rupture of the ductus wall was seen only in the two postmortem specimens dilated with very large balloons, 8 and 9 mm in diameter.

Technically satisfactory sections were available from 26 of the 29 dilated animal ductus and from both human specimens. A lumen was seen in all cases. Because the specimens were not fixed under pressure no attempt was made to evaluate the size of the lumen.

All cases showed splitting of the internal elastic membrane and radial tears of the media in one or two segments of the circumference (figure 3, A). The tear of the media involved the inner third in one case, the inner two-thirds in 12 cases, and all of the media in 13 cases. The extent of medial disruption did not differ between cases dilated in vivo and postmortem. No correlation was found between balloon size or inflation time and the extent of medial splitting, and the degree of medial tears did not correlate with the postdilatation size of the ductus visualized angiographically. The adventitia was intact in all in vivo dilatations and there was no extravasation of blood.

The ductus of the animal killed 1 week after dilatation showed fibroblastic proliferation in the areas of medial disruption (figure 3, B). Six weeks after dilatation, collagen tissue was demonstrated in the wall (figure 3, C and D).

In the two human specimens, the findings after dilatation were similar to those described in the animals (figure 4).

Discussion

The ductus arteriosus was found to be functionally closed by aortography in all animals and could be catheterized in all but two cases. This is in agreement with the experience of Evans et al., who found the piglet ductus to contract within 24 hr after birth and to be probe-patent for up to 14 days. The size of the aortic

| TABLE 2 |
| Size of the ductus arteriosus after dilatation |
| Dilation time | 30 sec × 3 | 5 min | 5 min × 2/ |
| Lumen size | 5 min | 5 min × 3 |
| 1-2 mm | 4* | 2 | 1 |
| 3-5 mm | — | 1 | 5 |

*Data expressed as number of cases.

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orifice and the oblique origin of the ductus from the aorta explain the ease of engagement by curved catheters.

The size of the lumen after dilatation appears primarily related to the inflation time (table 2). It is possible that postdilatation size of the ductus is influenced by age. In this study, the majority of animals were of the same age and such a relationship did not appear. A lumen of 3 to 5 mm resulted from 4 and 5 mm balloons inflated for a total of 10 min or longer.

Patency was shown in this study up to 6 weeks. The case followed up to 7 days showed slight narrowing at the pulmonary end (figure 1, E). The case followed up for 6 weeks had a narrowing at the aortic end (figure 1, F). This may have been caused by insufficient dilating force at the extremes of the ductus. Dilatation could be repeated if such narrow areas are detected on follow-up examination.

The complications encountered in this study were minor and are probably avoidable in the future. Perforation of the pulmonary artery by the tip of the dilating catheter can be avoided by proper placement, leaving a soft guide in place or use of catheter with a shorter distance between the tip and the balloon.

Six animals died spontaneously of unknown causes. Hemorrhage was excluded with certainty in all cases. Ill effects of anesthesia in these small animals may have contributed, since some animals did not regain consciousness before death. Sudden large left-to-right shunts may not be well tolerated in piglets, which are known to be prone to arrhythmias. All animals had tachycardia after dilatation. Electrocardiograms were not available at the time of death. Collateral circulation in swine is poorly developed, and occlusion of the femoral artery may lead to gangrene with superimposed infection and to venous stasis, thrombosis, and possible pulmonary embolism.

We found considerable elasticity of the porcine ductus. Balloons of 8 or 9 mm in diameter were required to cause rupture of all layers of the wall. Balloons of 4 and 5 mm did not cause gross rupture either in the piglet or human ductus.

Small areas of discoloration (figures 2A to 2C) seen in the majority of in vivo dilatations were caused by hemorrhage confined to the media. Because the adventitial layer was intact, no permanent ill effect is to be expected. It is interesting that intimal disruption and hemorrhage in the media has been described by Gittenberger-de Groot et al.\(^5\) in the ductus from patients treated with prostaglandin infusion. Similar findings were noted by Silver et al.\(^6\) in both the untreated ductus that remains open after birth and in the ductus of prostaglandin-treated patients.

The histologic findings in the dilated ductus are identical to those described in other muscular arteries after angioplasty.\(^7\) A controlled rupture of the internal elastic layer and muscular media is produced, and only with extreme dilatation is the strong adventitia ruptured. Repair of the disruption in the wall can be expected as shown by appearance of fibroblasts and collagen tissue (figures 3, B and D).

For this technique to be useful in clinical practice,
the following basic conditions must be fulfilled: Catheterization of the ductus must be technically possible and the patient must tolerate cessation of flow through the ductus for the duration of balloon inflation.

It is well known from results of cardiac catheterization that, although functionally closed, the ductus is commonly traversed by the catheter. In patients with pulmonary outflow obstruction, the course of the ductus is frequently altered and it may be more difficult to enter.

Patients with true ductus-dependent lesions are unlikely to tolerate inflation times as long as those used in

FIGURE 3. A, Transverse section immediately after dilatation. Splitting of intima and media (arrows) can be seen. The outer elastic layer is intact (arrowheads). (Verhoeff–van Gieson elastic stain; ×30.) B, Section of ductus wall 7 days after dilation. Early fibroblastic changes are in the area of medial tear (arrows). (H&E; ×48.) C and D, Transverse section of the pulmonary end (C) and aortic end (D) at 6 weeks. Reparative changes can be seen (arrows). (Verhoeff–van Gieson elastic stain; ×11.)
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FIGURE 4. Transverse sections from two human ductus arteriosus; 4 mm balloon inflated 5 min (A) and 5 min repeated three times (B). There is rupture of internal elastic membrane and media (arrows). The outer elastic layers are intact (arrowheads). (Verhoeff–van Gieson elastic stain; × 30.)

this study. However, use of relatively larger balloons or balloons that tolerate higher inflation pressure may allow reduction in inflation time. Multiple inflations of short duration may also be effective.

Corwin et al.⁹ have reported a case of interrupted aortic arch and ventricular septal defect treated palliatively on a short-term basis by dilatation with an expandable balloon catheter (Berman). This type of latex balloon does not allow control of the balloon size and was not found to be useful in peripheral angioplasty, which requires nonexpandable balloons.⁹

Treatment with either prostaglandin infusions or surgical shunt procedures has vastly improved the prognosis of patients with ductus-dependent congenital heart disease. Although prostaglandin infusion is effective, results of a multicenter study indicate that the response varies depending on the type of lesion, status of the ductus, and age and weight of the patient at the time therapy begins.¹⁰ Prostaglandin therapy also requires intravenous or intra-arterial infusions, and side effects occur frequently.¹¹ Surgical creation of a systemic shunt is effective but has significant mortality and morbidity. Furthermore, late complications are not uncommon, related to stenosis or to high or unevenly distributed flow.

The concept of balloon dilatation of the ductus arteriosus is presented as an alternative and an addition to the management of ductus-dependent congenital heart disease.

Further experimental work is required before the technique is used in humans. Long-term patency rates and the effects of prostaglandin therapy on the dilated ductus need to be established. Furthermore, postmortem dilatation of the human ductus from patients with pulmonary outflow obstruction should be performed.

Conclusions

(1) The functionally closed porcine ductus arteriosus can be safely catheterized and dilated by angioplasty techniques.

(2) Dilatation results in a lumen size of 3 to 5 mm and a significant left-to-right shunt. Long-term patency can be expected.

(3) Histologically, a controlled rupture of the intima and media is produced; the adventitia is preserved. Two human ductus specimens showed the same changes after dilatation.

(4) The technique may serve as an animal model to study the effects of patency of the ductus arteriosus and left-to-right shunts.

(5) The new technique should be further investigated before it is used clinically.

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Addendum

Since preparation of this manuscript we have undertaken a long-term study. The following changes in procedure have contributed to elimination of early mortality:

(1) Use of animals with minimum weight of 5 kg.

(2) Use of intravenous ketamine, allowing easy control of anaesthesia and spontaneous respiration.

(3) Repair of the femoral artery to preserve circulation in the leg, avoiding infection and the possibility of venous stasis, thrombosis, and pulmonary embolism.

References


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