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A Novel Method to Maintain Ductus Arteriosus Patency

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Survival of patients with certain ductal-dependent congenital heart diseases depends on continued patency of the ductus arteriosus or the surgical creation of an aortopulmonary shunt. The latter may be difficult in the presence of hypoplastic pulmonary arteries. Long-term prostaglandin therapy may be used to maintain ductal patency but is not without limitation and side effects.

This experimental study describes a novel approach to maintain ductal patency with a stainless steel stent. Six newborn lambs ≤48-h old had a ductal stent placed during right heart catheterization. Two lambs <36-h old had a stent delivered by the arterial route. The stent was delivered and released at the target with relative ease and no incidence of embolization. Continued ductal patency up to 3 months was demonstrated by repeat cardiac catheterization and angiography, two-dimensional color Doppler echocardiography and postmortem examination.

The experimental model provides a left to right shunt model in which the size may be increased as the animal grows. More important, a ductal stent could be used to maintain ductal blood flow in neonates and infants with ductal-dependent cardiac malformations, thereby avoiding a thoracotomy.

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Interventional cardiac catheterization is a rapidly advancing field offering a shorter hospital stay, rare need for blood transfusion, lower cost and the absence of scarring (1). Balloon angioplasty, first described for pulmonary valve stenosis in 1982 (2), is now the treatment of choice for this lesion. Such transcatheter therapy has been extended to the treatment of aortic valve stenosis, coarctation of the aorta, mitral stenosis and peripheral pulmonary artery stenosis.

Survival of neonates with ductal-dependent pulmonary or systemic blood flow depends on continued patency of the ductus arteriosus or the surgical creation of an aortopulmonary shunt. Furthermore, in babies whose pulmonary arteries are too small to undergo an operative shunt, patency of the ductus arteriosus may be maintained with long-term intravascular (3) or oral (4,5) prostaglandin. However, the latter therapy has practical limitations as well as side effects (3,6–10).

Transcatheter manipulation of the ductus arteriosus includes occlusion (11,12) and balloon dilation (13) to maintain patency. We describe a new method to maintain ductal patency without pharmacologic manipulation or thoracotomy by using a stainless steel stent placed in the lumen of the ductus of the newborn lamb.

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Methods

The care and treatment of all animals in this study conform to the "Position of the American Heart Association on Research Animal Use," adopted November 11, 1984. The E series of prostaglandins was not used in the study.

Experimental preparation and stent placement by the venous route. Six newborn lambs 6- to 48-h old (mean 23) and weighing 3.4 to 6.3 kg (mean 4.4) had the stent delivered by the venous route. General anesthesia was induced and maintained with halothane in nitrous oxide (4 liters/min) and oxygen (4 liters/min). A 2% solution of halothane was used during induction and a 1% solution was used for maintenance. A Puritan Bennett (model PR-1) respirator and an inflation pressure of 18 to 20 cm H_2O was used to ventilate the lambs. After a cutdown in the neck, vascular sheaths (6 to 8F) were placed in the right external jugular vein and carotid artery as described previously (14). These allowed the repeated introduction of venous and arterial catheters. A balloon end-hole catheter was introduced into the venous sheath and manipulated under fluoroscopy through the right side of the heart and across the ductus arteriosus into the descending aorta. This procedure allowed a guide wire to be placed across the ductus arteriosus, and the balloon catheter was removed leaving the guide wire in place.

A 3.5F coronary angioplasty catheter (3.5 or 4 mm diameter, 20 mm length balloon) with a Palmaz-Schatz stainless steel stent mounted securely on the balloon was then placed over the guide wire. The balloon was carefully placed into the ductus arteriosus. The position of the ductus was determined previously by angiography. The balloon was inflated with diluted angiographic contrast medium, releasing the stent in the ductus arteriosus. The stent was delivered with a 3.5-mm diameter balloon catheter in five lambs

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and with a 4-mm balloon in one lamb. Two stent sizes were used. The coronary artery stent used in five lambs had an unexpanded length of 15 mm and an external diameter of 1.65 mm; the renal artery stent used in one lamb had an unexpanded length of 20 mm and a 2.5 mm diameter. These stents consisted of two segments connected by an articulation. An aortogram shortly after stent placement was performed to demonstrate ductal stent patency. The cutdown incision was closed. Between catheterizations, the arterial and venous catheters were replaced with 3.5F polyvinyl umbilical vascular catheters filled with heparin. The tips of these catheters were placed at the level of the second rib under fluoroscopic guidance. After recovery, the lambs were returned to the pen with the ewes.

The next day, under light inhalation anesthesia, a Doppler echocardiographic examination was performed and repeated periodically thereafter, usually in conjunction with another cardiac catheterization or balloon dilation of the ductal stent, or both. In three lambs with the smaller stent, the ductus was further expanded to 4 mm at subsequent catheterization. After the lambs died or were killed (within 3 months), the thoracic viscera were removed as a block for further examination.

Stent placement by the arterial route. Two additional lambs 24- and 18-h-old and weighing 3.4 and 7 kg, respectively, had their stent placed by the arterial route under general anesthesia as described earlier. Long-term implantation of vascular sheaths in the neck vessels was not performed. A 5F vascular sheath was placed percutaneously in the left femoral artery. An end-hole catheter was manipulated retrograde up the aorta, across the ductus arteriosus into the main pulmonary artery. This procedure allowed a guide wire to be placed across the ductus arteriosus. Similar to the transvenous delivery of a ductal stent, the end-hole catheter was replaced with the stent delivery catheter. The stent was released in the ductus arteriosus, whose position was previously determined by angiography. A coronary artery stent was used in both of these lambs. The femoral artery sheath was removed after ductal stent patency was demonstrated on aortography. After hemostasis over the puncture site was secured, the lambs were returned to the ewes.

Results

Stent placement. The outcome of transcatheter placement of a ductal stent in six newborn lambs is summarized in Table 1. The ductus arteriosus was anatomically open in all lambs at the time of initial cardiac catheterization and stent placement. After angiographic location of the ductus arteriosus, the stent was delivered and released with little difficulty. The delivery catheter balloon was deflated and withdrawn through the right side of the heart with ease in all but one lamb. In this lamb, the stent was partially pulled back into the pulmonary artery when the delivery catheter was withdrawn. Presumably, the folds of the deflated balloon were caught in the stent. Embolization did not occur in any lamb and an aortogram shortly after stent placement demonstrated patency in all.

Table 1. Ductal Stent Placement in Six Newborn Lambs

Lamb No.	Body Weight (kg)	Age Stent Inserted (h)	Complications	Postmortem Findings
1	3.4	26.5	None	Age 10 weeks; stent in place
2	4.9	6.0	Stent protruding in pulmonary artery	Died at age 4 weeks, stent in place; pneumonia
3	4.8	27.5	None	Died at age 3 weeks; stent in place; no obvious findings
4	3.75	28	None	Age 4 weeks; stent in place
5	6.3	35	None	Age 3 weeks; stent in place; small thrombus
6	3.6	48	None	Age 8 weeks; stent in place

Chest radiography demonstrated that the stent was readily visible (Fig. 1). Repeat aortograms up to 3 months after stent placement showed rapid opacification of the pulmonary arteries through the ductal stents in all lambs. The stent allowed passage of a 6 to 8F catheter without difficulty. Similarly, Doppler echocardiography demonstrated patency of all ductal stents (Fig. 2 and 3).

In the two stents placed transarterially, locating the aortic orifice of the ductus and passing a guide wire into the pulmonary artery were easily accomplished. Stent embolization did not occur. When the lambs were studied at 6 weeks of age, both stents were patent by angiography and Doppler echocardiography.

Pathologic examination. Two of the lambs died spontaneously, one from pneumonia and the other from unknown cause 4 weeks and 3 weeks, respectively, after stent placement. Pathologic examination of the second lamb did not reveal any obvious gross abnormality in any area, including the lungs. The other four lambs were killed 4 to 12 weeks after stent placement (Fig. 4). A small thrombus was seen in one of the stents, but the ductus was patent on angiography and by Doppler echocardiography during life.

Discussion

The concept of percutaneous stenting of vascular stenosis was introduced by Dotter (15) in 1969. Simple nonexpanding stainless steel coils were placed in canine femoral arteries. The device kept the vessels open by scaffolding the inner surface with a tubular metal structure. Since then, several stent designs have been studied in animal and human vessels (16–22), primarily in adults. These vessels included the aorta and major branch arteries with peripheral vascular disease

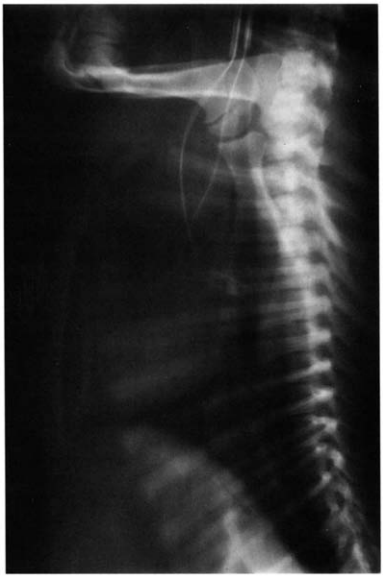

Figure 1. Lateral chest radiograph 3 weeks after implantation of a ductal stent. The arterial (posterior) and venous catheters in their corresponding vascular sheaths are shown.

and coronary and renal artery stenosis. Many of the stents were placed after balloon angioplasty to provide intravascular support to maintain patency. Studies (17) with pediatric implications were carried out in adult dogs, with the stent maintaining patency in stenotic pulmonary arteries and various systemic venous sites for up to 1 year.

Balloon-dilatable stent in the ductus arteriosus. In this report, we describe the first successful delivery and placement of a balloon-dilatable stent in the ductus arteriosus. Although a ductal stent placed by the venous route will be useful in ductal-dependent systemic circulation, a retrograde arterial approach is necessary in babies with ductal-dependent pulmonary circulation. Both procedures are relatively straightforward, with no incidence of embolization. One stent (venous approach) was partially pulled back into the pulmonary artery as the delivery catheter was retrieved. This might have been avoided by rotating the catheter counterclockwise during the pullback procedure as the unexpanded balloon on the catheter was folded clockwise. In the lambs studied, irritation of the ductus arteriosus by catheter and guide wire did not hinder the delivery and placement of a ductal stent. In the clinical setting, prostaglandin E_1 or E_2 may be used to lessen the possibility of irritating the ductal tissue, thereby hampering the procedure. However, a widely patent ductus arteriosus resulting from prostaglandin administration may increase the risk of embolization if careful sizing of the ductus arteriosus is not done before the ductal stent is released. An assumption is made that the human and the lamb ductus respond similarly in view of the dilative response to prostaglandin E in both species. The ductal stents were observed for up to 3 months and all remained patent. Despite a small thrombus in situ in one stent, the stent was patent angiographically and echocardiographically.

Stent designs. Several stent designs are currently available (23). Heat-expandable stents or nitinol stents are made of a biologic inert alloy of nickel and titanium that has shape-memory properties related to temperature (24). Significant technical expertise is required to prevent rewarming and inadvertent expansion of these stents during introduction into the body. Preimplantation sizing is necessary and the diameter of the stent cannot be increased by balloon dilation. Because the ductus arteriosus is a dynamic structure, its size may change during the manipulation associated with stent delivery. This heat-expandable stent is therefore not suitable for placement in the ductus. The self-expanding multifilament stainless steel stent is a pliable elastic device such that its diameter can be reduced by elongation (25). On its release at the target by the delivery catheter, the stent expands until a balance is reached between the circumferential elastic resistance of the arterial wall and the dilating force of the prosthesis. However, questions concerning the biocompatibility of this device and acute thrombosis related to the amount of metal and movement of the cross struts have been raised. The continued expanding force may stimulate smooth muscle proliferation.

Available stent models. Two models of balloon-expandable stents are currently available. They allow expansion to the limit of the delivery balloon. Furthermore, they permit repeated expansion of ductal stents to increase the left to right shunt in the growing animal. The serpentine stainless steel coil, originally developed by Wright et al. (26), consists of surgical wires (0.006 in. [0.015 cm]) wrapped cylindrically, with bends adopting a sequential U and inverted U configuration every 360°. In addition to being balloon expandable, the coil stent does not shorten during expansion. It contains less metal than other stents, covering <10% of the endothelial surface. Although this design allows rapid endothelialization, it does not create the smooth luminal outline produced by more tubular designs (23), perhaps making thrombosis more likely.

The second balloon-expandable tubular stainless steel stent, originally designed by Palmaz et al. (20), relies on plastic deformation of metal beyond its elastic limit. Once stretched beyond a certain limit, it cannot collapse. It is easy to deliver, with an expansion ratio of 6:1. The profile is streamlined (0.0003 in. [0.0008 cm]) covering 10% of the surface area when expanded. Although the expansion of the

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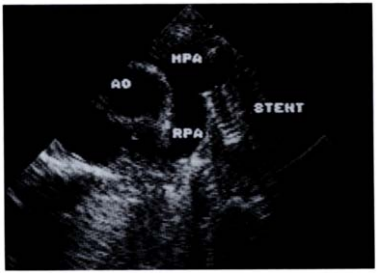

Figure 2. Two-dimensional echocardiogram (short-axis view) demonstrating the ductal stent. The left pulmonary artery is out of view in this section. AO = aorta; MPA = main pulmonary artery; RPA = right pulmonary artery.

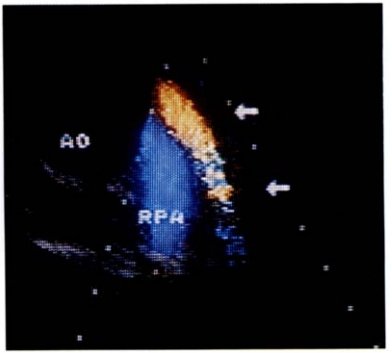

Figure 3. Doppler color flow echocardiogram of the ductal stent (same view as in Fig. 2) demonstrating flow in the ductal stent into the pulmonary artery (**arrows** indicating mosaic flow pattern.) Normal flow (**blue**) is seen in the right pulmonary artery (RPA). AO = aorta.

stent is reliable, shortening occurs when it is dilated beyond a certain diameter, depending on the stent size.

The modified Palmaz stent, consisting of short segments connected by an articulation, allows for manipulation and delivery to the target site. It is longitudinally flexible but radially noncompliant (19). The unexpanded stent is sufficiently small and pliable to be introduced and negotiated through the right side of the heart and across the valves or retrograde up the aorta and then expanded at the target site to a diameter several times its original size. Our study showed that a stent of such design allows for manipulation of the stent and release in the ductus arteriosus with little difficulty. Concern expressed about the fluoroscopic visibility in the expanded state because of the small amount of

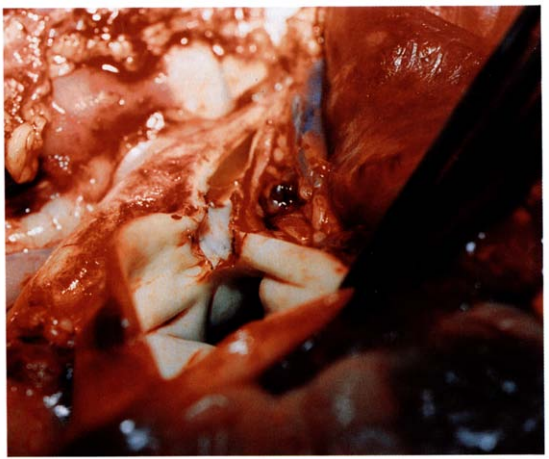

Figure 4. Left lateral view of the "ductal block" 3 months after stent placement. The main pulmonary artery (held by forceps) and the ductus arteriosus have been incised lengthwise into the descending aorta. The criss-cross struts of the ductal stent covered by neoendothelium are clearly visible.

metal may be a problem in adults, but is not likely to be a difficulty in infants. Placement of the stent at the "target" may be made with precision with use of a high resolution system, utilizing a catheter with a reference radiopaque marker near its tip. In the lambs studied, the stent was clearly visible (Fig. 1)

Thrombosis and embolization. The success of a vascular stent should depend on minimal thrombosis and rapid endothelialization (19). Occlusion by thrombosis is therefore a major concern of intravascular metallic devices. Acute occlusion from thrombosis may occur related to bioincompatibility, whereas stenosis may present later as a result of intimal proliferation with or without further thrombosis. Intimal and neointimal fibrous proliferation appears to pose a major problem in arterial reconstruction in vessels with caliber of superficial femoral and smaller arteries (27). Further studies are warranted to observe the development of such events in ductal stents.

Clinical implications. Patency of the ductus arteriosus is vital to the survival of the fetus in utero. After birth, dramatic hemodynamic alteration occurs, including the closure of the ductus arteriosus. In certain ductal-dependent congenital heart lesions, maintaining ductal flow is critical to the baby's survival. Ductal patency may be maintained or achieved pharmacologically or surgically with an aortopulmonary shunt. Although this animal study demonstrates the feasibility of maintaining such patency with an intravascular stent, the need for concurrent anticoagulant or antiplatelet therapy, or both, remains to be explored. Although surgical aortopulmonary shunts do not require antithrombotic therapy, experimental evidence (19) suggests that without anticoagulation metallic stents, regardless of design, have a thrombogenic effect.

The practical implications of using a stent to maintain ductal patency without thoracotomy or drugs are threefold. 1) The ductal stent provides an experimental model of a left to right shunt in which size may be increased as the animal grows. 2) More important, the ductal stent could be used to maintain ductal blood flow in neonates and infants with ductal-dependent cardiac malformations, thereby avoiding a thoracotomy. This may be of special advantage in low birth weight infants. 3) Finally, in patients with ductal-dependent pulmonary blood flow and underdeveloped pulmonary arteries, prolonged stent-ensured patency of the ductus arteriosus may stimulate sufficient growth to make subsequent surgery possible.

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