Percutaneous Fetal Cardiac Catheterization Technique for Stenting the Foramen Ovale in a Midgestation Lamb Model

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Background—Intact or highly restricted intra-atrial septum can be reliably diagnosed in the human fetus as early as 22 to 24 weeks of gestation. Fetal interventions targeting the atrial septum have used a direct approach through the atrial wall. Here, we report stenting of the foramen ovale with a large, open-cell stent via percutaneous access through the fetal hepatic vein in a sheep model.

Methods and Results—In 5 fetal sheep of 109 to 111 days of gestation (term, 147 days), the fetal hepatic vein was punctured percutaneously under ultrasound guidance and a 13.3-cm 14-gauge intravenous catheter was inserted. After catheterization of the inferior vena cava, right atrium, foramen ovale, and left atrium with a guidewire and 1.8F to 2.6F tapered catheter, a self-expandable, 8x12-mm flexible open-cell stent was positioned in an unrestricted foramen ovale. Flow and fetal well-being were documented for 45 minutes after the procedure. Access to the left atrium was achieved in all 5 animals and all survived. In 4 animals, the stent was successfully positioned in the foramen ovale. One fetus was born at term and euthanized on day 3: postmortem examination confirmed the patency of the stent. The other 3 fetuses were well after being monitored by ultrasound for 45 minutes. In 1 animal, the stent dislodged immediately after release obstructing the mitral valve. This fetus developed ascites and was euthanized after 4 days.

Conclusions—It is feasible to safely advance a large diameter, self-expandable, open-cell design stent via a percutaneous access route through the fetal hepatic vein. (Circ Cardiovasc Interv. 2015;8:e001967. DOI: 10.1161/CIRCINTERVENTIONS.114.001967.)

Key Words: atrial septum ■ cardiac catheterization ■ fetal heart ■ foramen ovale ■ hypoplastic left heart syndrome ■ stent

There are potentially several indications to open the atrial septum in a human fetus. The most common is established hypoplastic left heart syndrome (HLHS) with an intact or highly restricted intra-atrial septum (IAS), preventing sufficient left to right flow, which in turn might lead to clinically significant changes in the lung parenchyma and pulmonary vasculature.1 Others include primary premature closure or restriction of the foramen ovale (FO) restricting the normal right to left flow, which commonly results in right to left ventricle discrepancy and mild to moderate hypoplasia of the mitral and aortic valves, as well as the aortic arch, and the well-described constellation of mitral regurgitation, aortic stenosis, IAS, and severe left atrial (LA) dilation.2

Although being a rare condition that accounts for <4% of congenital heart defects, HLHS still carries a significant mortality and is responsible for 23% of all deaths caused by congenital heart disease in the first year of life. Among patients with HLHS, those with a restricted FO and restricted intra-atrial communication, and those with an intact IAS with no intra-atrial communication, have a particularly poor outcome and an in-hospital mortality rate exceeding 65%.1,3

Restricted intra-atrial communication or an intact atrial septum can be reliably diagnosed as early as 22 to 24 weeks of gestation, either by direct visualization on prenatal ultrasound or by analysis of prenatal pulmonary vein flow patterns, which is predictive for postnatal LA hypertension.4 Consequently, fetal intervention with the goal of decompressing the LA by direct transcatheter puncture of the atrial septum followed by balloon dilatation of the FO has been performed and reported, mostly as a single-center experience.5–7 Despite these fetal interventions, outcomes have not improved significantly, and

Circ Cardiovasc Interv is available at http://circinterventions.ahajournals.org

DOI: 10.1161/CIRCINTERVENTIONS.114.001967

Received September 3, 2014; accepted January 22, 2015.
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WHAT IS KNOWN

• In human fetuses with hypoplastic left heart syndrome, an intact or highly restrictive intra-atrial septum is one of the most important risk factors for poor outcome after birth and can be reliably diagnosed with ultrasound as early as 22 to 24 weeks of gestation.

• Prenatal opening of the atrial septum has been proposed as a means of preventing these complications by avoiding critical neonatal hypoxemia and potentially preventing the pulmonary lymphangiectasia and pulmonary vein muscularization that result from prolonged left atrial hypertension in utero.

• Despite the use of current transatrial fetal intervention techniques, outcomes have not improved significantly, and there is an ongoing discussion about how best to create a persistent and adequately sized atrial septal defect.

WHAT THE STUDY ADDS

• Percutaneous transhepatic access to the fetal heart in this animal model was associated with low procedure-related mortality and high technical success, largely independent of fetal positioning, and enabled safe delivery of 4F devices through a 14-gauge access.

• The open-cell, self-expandable stent design allowed advancement of stents with diameters of 7 to 10 mm and lengths of 12 to 24 mm through a 4F delivery system, substantially larger than the current transatrial approach, in which the stent diameter is limited to 2 to 3 mm.

Methods

Ethics Statement

All procedures in this study were performed using sterile surgical techniques and in accordance with the guidelines of the Australian Code of Practice for the Care and Use of Animals for Scientific Purposes, established by the National Health and Medical Research Council of Australia. The Monash University/Monash Medical Center Animal Ethics Committee approved this study.

Subjects and Preparation

Five fetal lambs at 109 to 111 days of gestation (Merino/Border-Leicester cross; term, 147 days) were used: 4 were singletons and 1 was a twin. All ewes were brought into the animal house 1 week before the procedure for acclimatization. The ewes were initially anaesthetized with an intravenous bolus injection of sodium thiopentone (20 mg/kg; Pentothal); once anesthesia was established, the ewes were placed supine, intubated, and ventilated; anesthesia was subsequently maintained using 2% isoflurane in O2. The ewe received infusion (300 mL/h) of 0.18% saline+4%glucose for the duration of anesthesia. Antibiotics (ampicillin 500 mg and gentamicin 80 mg) were administered during the procedure and repeated daily for 3 days. Ultrasound (Voluson 730 Expert; GE Healthcare) was used to determine the fetal number and position and optimal access point. When required, suboptimal fetal position was managed by external manipulation of the fetus to improve access. No fetus was excluded or suspended from the procedure because of a suboptimal position. Ultrasound was used to measure the distance from the skin to the right hepatic vein (RHV) or left hepatic vein (LHV), the diameters of the RHV, LHV, inferior vena cava (IVC), FO, and the length of IVC between the insertion of the RHV or LHV and the right atrium (RA).

Foramen Ovale Stent Procedure

Access to the fetal venous system was obtained using a percutaneous puncture through the maternal abdominal and uterine wall and into the fetal abdomen; all under continuous ultrasound guidance. Depending on the position of the fetus and the ease of access, the RHV or LHV was selected for puncture and sheath insertion. In all fetuses, hepatic access and sheath insertion were achieved using a 13.3-cm 14-gauge intravenous catheter (BD Angiocath; Becton Dickinson, North Ryde, Australia) inserted into the fetal RHV or LHV with the 1.4-cm needle in situ as previously described.10 Once venous access was achieved, and the catheter sheath was positioned close to the junction of the hepatic vein and IVC, the needle was removed leaving the catheter sheath in situ. The internal diameter of the sheath allows 4F access. Under ultrasound guidance, a 1.8F to 2.6F tapered catheter (FineCross MG; Terumo, Macquarie Park, Australia) was inserted into the sheath, over a 0.014-inch guidewire, which was curled at the tip (Hi Torque Balance Middelweight Universal; Abbott Vascular, Santa Clara, CA), and catheterization of the RA, FO, and LA was performed. Once the coronary catheter tip and guidewire were visible in the LA, the Balance Middelweight-wire was exchanged for a stiffer 0.014-inch guidewire (Hi Torque Extra S’tor; Abbott Vascular, Santa Clara, CA). The FineCross catheter was then removed, leaving the guidewire in the LA, and a 4F delivery system for a self-expandable, open-cell-design, flexible stent (8×12-mm Superflex DS; OptiMed, Ettlingen, Germany) was advanced through the FO. The distal portion of the stent was then opened in the LA, and the delivery system was carefully withdrawn to allow opening of the proximal portion of the stent in the RA (Figure 1). The delivery catheter and guidewire were then withdrawn completely, and flow through the stent was documented with color Doppler ultrasound. On removal of the sheath, the intrahepatic portion of the 14-gauge intravenous catheter entry canal was embolized to reduce the risk of intra-abdominal hemorrhage in the fetus (Gelfoam; Pharmacia & Upjohn Company, MI). Movie 1 in the Data Supplement.

Access and Positioning of the Stent

Access to the fetal circulation was achieved in 5/5 cases, and all fetuses survived the intervention. In 3 cases, access to the IVC was achieved via the RHV: the RHV diameters were 5.3, 5.4, and 6.5 mm, and the distances along the IVC from the RHV to the RA were 27, 30, and 31 mm. In 2 cases, access to the IVC was achieved via the LHV: the LHV diameters were 4.2 and 5.0 mm, and the distance along the IVC from the LHV to the RA was 32 mm in both cases. The IVC (n=5) and FO (n=5) had median (range) diameters of 7.4 (6.3–7.7) mm and 7.0 (6.3–8.0) mm, respectively. Ultrasound scanning, the sole form of imaging used in all cases, provided adequate imaging of the fetal heart, catheter,
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The stent was positioned by direct ultrasound visualization within the sonographic landmarks of the FO. The stent was successfully positioned in the FO in 4 of the 5 animals (Figure 1). The unsuccessful case was in the first animal, in which the stent became dislodged immediately after being advanced out of the delivery catheter and became caught in the mitral valve, resulting in partial obstruction of LV inflow and moderate to severe mitral regurgitation. Although the fetus showed no signs of acute deterioration or injury to the heart, the animal developed increasing ascites over the next few days and was euthanized 4 days post procedure. In the 4 successful cases, the stable stent position and Doppler flow were observed over a period of 45 minutes after insertion of the stent. After careful exclusion of procedure-related complications such as hemopericardium or ascites, 3 of the 4 successful animals underwent an additional experimental protocol.11 One of these animals died acutely because of a complication arising during the additional protocol: immediate postmortem examination revealing bodyweight of 1920 g and the stent positioned in the FO. The other 2 were euthanized 3 weeks later according to the additional experimental protocol: bodyweights of 4570 and 4660 g, both stents fixed within the FO on postmortem examination. One of the 4 animals was returned to the animal housing facility and delivered spontaneously at term without any complications (birth weight 5310 g). Postmortem examination after euthanasia of the lamb on day 3 of life showed the stent securely positioned in the atrial septum with a patent lumen (Figure 2).

Flow Through the Stent
Unrestricted flow through the stent was demonstrated in all animals using color Doppler immediately after the procedure, and also on day 3 after stent insertion in the animal that was allowed to proceed to term delivery (Figure 3).

Discussion
Postnatal management and prognosis of infants with HLHS have improved significantly over recent decades.12,13 Advances in interventional and hybrid therapy for congenital heart disease are raising expectations in regard to the efficacy and safety of in utero interventions and their ability to provide a positive risk–benefit ratio when compared with postnatal interventions.14 Because the almost uniformly fatal prognosis of children with HLHS-IAS, this group is an ideal population

Figure 1. Ultrasound and color Doppler image sequence of positioning the self-expandable, open-cell-design, flexible 8×12-mm stent in the foramen ovale (FO) of the fetal heart. A, Curled tip of the 0.014-inch guidewire (red arrow) in left atrium (LA), 4F delivery system advanced through the FO, distal portion of the stent opening in the LA (orange arrow). B, Opening of the distal portion of the stent and the delivery system is partially withdrawn. C, Opening of the proximal portion of the stent in the right atrium (RA; red arrow). D, Stent positioned in FO, delivery system completely withdrawn.

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to benefit from novel in utero therapies. Decompression of the LA in utero, close to delivery, might enable improved postnatal adaptation and greatly reduce immediate postnatal mortality. However, the long-term outcome of these late in utero interventions close to delivery, despite initial success, remains disappointing. Ideally, by decompressing the LA earlier in gestation, the presence of pulmonary lymphangiectasia and pulmonary vein muscularization at birth could be avoided. This injury to the pulmonary vasculature and lymphatic system limits the successful transition, in many patients, toward a univentricular circulation in later life. The timing of the development of the pulmonary vascular and lymphatic changes, and its ability to normalize once the causative insult, LA hypertension, and pulmonary venous congestion secondary to IAS is removed, is not clearly determined. In 1 study in which 4 fetuses with HLHS-IAS underwent atrial decompression at 28 to 35 weeks of gestation, all had histological evidence of pulmonary lymphangiectasia and pulmonary vein muscularization at birth. There are 2 explanations for the persistence of these changes at birth, despite apparent atrial decompression: either the damage occurred before the intervention and did not reverse or the atrial decompression was insufficient, possibly because of the relatively small stent size, which was limited to 2.75 or 3.0 mm, or because of the restenosis of the interatrial communication which was noted in some cases. We are hoping that with the much larger stent used in our techniques that full and prolonged atrial decompression will result in better pulmonary vasculature at birth.

The current transcardiac approach to create a sufficient interatrial communication by accessing the heart with a relatively large introducer/sheath (18 gauge) through the paper-thin wall of the atria has 3 major drawbacks:

1. High risk of bleeding, cardiac tamponade, and the need for in utero resuscitation.
2. High rate of stent dislocation. Although a balloon-mounted stent prevents septal recoil and reclosure of the interatrial communication, this is frequently hampered by stent dislocation, especially because of the need to retrieve the balloon after delivery of the stent.

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**Figure 2.** Postmortem photograph taken of the heart of the 3-day-old lamb born at term. A, Frontal view of the stent from the left atrium showing it being patent and positioned in the foramen ovale. B, Lateral view of the stent showing its fixation with surrounding atrial tissue. Note open-cell design of stent.

**Figure 3.** Ultrasound and color Doppler imaging of the fetal heart 3 days after stent implantation demonstrating position, patency, and unobstructed flow through the stent.
We propose that an alternative access route and novel stent materials may have the potential to reduce the risk of in utero LA decompression and may, if applied early enough, prevent damage to the pulmonary vasculature and the lymphatic system. Our transhepatic access to the fetal heart has shown a low procedure-related mortality rate, a high technical success rate, is largely independent of fetal positioning, and enables safe delivery of 4F devices through a 14-gauge access. To demonstrate the feasibility of FO access in an animal model equivalent in size to a 31- to 32-week human fetus, which has a weight of 1900 to 2000 g, we used the fetal lamb at 110 days of gestation. At this stage, the fetal sheep FO is wide open with little to no septum primum for perforation and the anchorage of an adequately sized stent. Therefore, the procedures simulating perforation and stenting of the FO as performed in humans were performed in 2 separate steps. First, in a previous publication, we have shown that diathermy of the fetal cardiac tissue using the percutaneous transhepatic approach under ultrasound guidance is a feasible method to create perforations. Second, because IAS has been reported as showing recoil of the septum after balloon dilation alone, we have addressed that by stent insertion, which is necessary to ensure sustained patency of the created intra-atrial communication.

In this study, we used self-expandable sinus-superflex-DS (Optimed) stents with a length of 12 mm and a diameter of 8 mm. The size was chosen based on the measurement of the FO and the distance between the posterior LA wall and the anterior RA wall. The unrestricted and significant atrial communication in these nondiseased fetal lambs make stent placement extremely challenging and resulted in dislocation of the stent in the first animal. Nonetheless, we expect the risk for this complication to be minimal when stenting a restrictive or restricted FO of 5 to 7 mm were successfully stented.

There are several unique advantages that differentiate our technique from an approach using a balloon-mounted stent:

- The open-cell, self-expandable stent design allows advancement of stents with diameters of 7 to 10 mm and lengths of 12 to 24 mm through a 4F delivery system. This is a significantly larger diameter than the current transatrial approach with a balloon-mounted stent delivered through 18-gauge needles, in which the stent diameter is limited to 2 to 3 mm.
- The open-cell design (Figure 2) prevents the stent from slipping and improves fixation within the atrial septum, as demonstrated in the present study, in which large non-restricted FO of 5 to 7 mm were successfully stented.
- A high opening pressure is achieved by the self-expandable stent without the need for balloon inflation. If further dilatation of the restrictive FO is required, balloon dilation within the open-cell, self-expandable stent followed by balloon retrieval is expected to be feasible without risk of stent dislodgement, as both ends of the stent would have expanded to be much wider than its midportion at the atrial septum. In contrast, retrieval of the deflated balloon in balloon-mounted stents induces a high risk of stent slipping and dislodgement because the fixation in the thin atrial septum is relatively weak, because of minimal contact area between the stent and the thin atrial septum, and uniform diameter of the stent.
- Sonographic views of the fetal heart structures are not obscured by our intravascular and intracardiac approach, whereas the needles used in the transatrial approach may impede views or cause ultrasound artifacts resulting in loss of imaging detail.

The size of the atrial septal defect created and the stent type used are critical for patency and postnatal outcome in HLHS-IAS. Because embolization of the intrahepatic section of the sheath entry tract is feasible in our transhepatic approach to minimize the risk of hemorrhage once the sheath is removed, the capability to deliver large, open-cell designed stents through a 4F sheath may improve the efficacy (most interventions could be completed within 45 minutes, including access to the fetal circulation) and safety of the procedure when compared with the use of small, balloon-mounted coronary stents, which are at an increased risk of early stent occlusion and stent embolization.

Even with timely postnatal treatment of HLHS-IAS after birth to decompress the LA, mortality before and after surgical reconstruction is still double that of HLHS infants with naturally open FO. Death is typically related to ongoing hypoxemia, which may be because of the development of pulmonary vascular and parenchymal changes in utero, as a result of the long-standing elevated pulmonary venous pressure and reduced forward flow into the pulmonary arteries. As such, creating an atrial septal communication after birth is probably too late to mitigate the pulmonary pathological process, and an alternative such as noninvasive creation of atrial septal defect by histotripsy is still not clinically available yet.
this study. The sinus-superflex-DS stent expands with a radial force of 4.4 to 5 atmospheres, but if that is not sufficient, ballooning of the implanted stent by catheter should be possible. To our knowledge, there are no published data on the diameter of the human fetal hepatic vein for comparison with the fetal sheep, but limited evidence suggests that the diameters of nearby vessels, namely the ductus venosus and intrahepatic umbilical vein, are of similar caliber in the human and sheep fetus.\(^{25-26}\) The 14-gauge intravenous catheter that we used in the experiments reported here to access the fetal hepatic vein could be comfortably positioned with some safety margin allowing for the potentially narrower diameter of the hepatic vein in the human fetus. Alternatively, direct access to the intrahepatic section of the IVC could be an option.

To conclude, transhepatic percutaneous delivery of large open-cell stents is a potential treatment for HLHS-IAS and other conditions with an intact or restrictive atrial septum. This approach is a potentially effective alternative to transcatheter manipulations of the atrial septum using balloon-expandable stents. Our experience with this large animal model supports moving forward toward potential clinical application.

Acknowledgments
We acknowledge the technical support provided by Dalibor Stanojkovic and Grace Davies for the animal studies.

Sources of Funding
The study received funding support from The Monash Faculty Strategic Grant Scheme, The ANZ Trustee - William Buckland Foundation, The Heartkids Grant-in-aid Program and the Victorian Government’s Operational Infrastructure Support Program. Dr Wong was supported by the National Health and Medical Research Council Health Professional Research Fellowship. The Superflex DS Stents were provided free of charge by Optimed, Ettlingen, Germany.

Disclosures
None.

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Circ Cardiovasc Interv. 2015;8:
doi: 10.1161/CIRCINTERVENTIONS.114.001967
Circulation: Cardiovascular Interventions is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1941-7640. Online ISSN: 1941-7632

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http://circinterventions.ahajournals.org/content/8/3/e001967

Data Supplement (unedited) at:
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