Transhepatic Ultrasound-Guided Cardiac Catheterization in the Fetal Lamb

A New Approach for Cardiac Interventions in Fetuses

Jean-Marie Jouannic, MD; Younes Boudjemline, MD; Jean-Louis Benifla, MD; Damien Bonnet, MD, PhD

Background—Percutaneous transventricular and fetoscopic umbilical catheterization have been applied to animal and human fetuses. These methods have a high rate of failure and complications. Here, we propose an alternative route for anterograde echocardiography-guided cardiac catheterization through a transhepatic approach of the intra-abdominal vessels in the fetal lamb.

Methods and Results—After exteriorization of the uterus in 12 pregnant ewes between 118 to 122 days’ gestation, a 4F sheath mounted over a 1.2-mm needle was placed into the intra-abdominal portion of the umbilical vein (n=2) and into the subdiaphragmatic portion of the inferior vena cava via a transhepatic approach (n=10) under ultrasound guidance.

In the first 2 animals using a transumbilical approach, it was impossible to reach the heart through the ductus venosus. In the next 10 animals, using a conventional technique, echocardiography-guided catheterization of the 4 chambers was performed in all the fetuses, atrial or ventricular pacing in 6 fetuses, and ballooning of the pulmonary valve in 9 of 10 fetuses. Among the 10 fetuses catheterized through the transhepatic approach, 2 were euthanized immediately after the procedure to evaluate intraperitoneal bleeding (23 and 29 mL, respectively), and 3 died after the procedure (1 of major bleeding and 2 deaths related to balloon catheter manipulation). Finally, 5 were delivered vaginally after an uneventful pregnancy, and autopsy at day 5 did not show significant liver, vascular, or cardiac injury.

Conclusions—Echocardiography-guided fetal cardiac catheterization through a transhepatic approach is feasible and provides an interesting alternative approach for human fetal cardiac interventions. (Circulation. 2005;111:736-741.)

Key Words: catheterization • ultrasonics • heart defects, congenital

Technical advances in ultrasound technology over the past decades, together with the inclusion of a simplified form of heart scanning in prenatal ultrasound screening, have greatly increased the potential impact of fetal echocardiography.1 Fetal echocardiography has also contributed to a better knowledge of the fetal pathophysiology of various cardiac defects.2–4 Obstructive lesions of the left or right outflow tracts with intact interventricular septum are a textbook example of the deleterious consequences of increased afterload on ventricular growth and function.5,6 Indeed, the insufficient growth of the ventricle has a profound impact on postnatal treatment options, because only palliative surgical procedures may be offered in the worst cases.7 In addition, heart failure may develop during late gestation, leading to fetal loss or delivery of a premature baby who needs urgent and hazardous interventions.

For these reasons, the prenatal relief of pulmonary or aortic valve obstructions by interventional procedures has been proposed to promote functional recovery of the affected ventricle and, consequently, improve postnatal outcome. Although encouraging, the human experience is still limited, and the transventricular, percutaneous ultrasound-guided balloon valvuloplasty has been associated with several technical problems, as illustrated by the high failure rate and the fetal mortality rate after cardiac intervention.8,9

Because some problems might be related to the vascular access, some authors have investigated alternative approaches to the fetal heart. In particular, a fetoscopic approach that allows direct puncture of the umbilical arteries has been proposed, with the major aim of allowing retrograde cardiac catheterization.10 Although this technique has reproduced conditions similar to the Seldinger-derived approach commonly used for postnatal cardiac interventions, it has been associated with significant mortality, mainly because of constriction or bleeding from the umbilical puncture. To date, it has not been applied to human fetuses.

We decided to investigate the feasibility of fetal cardiac catheterization using a transhepatic ultrasound-guided punc-

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Correspondence to Damien Bonnet, MD, Service de Cardiologie Pédiatrique, Hôpital Necker-Enfants-Malades, 149, rue de Sèvres, 75015 Paris Cedex, France. E-mail damien.bonnet@nck.ap-hop-paris.fr

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ture of the intra-abdominal veins in the fetal lamb. Our hypothesis was that this technique, which allows anterograde catheterization of the fetal heart, would have important potential for cardiac interventions during fetal life.

Methods
We studied 12 pregnant Pre-Alp ewes between 118 to 122 days' gestation (term, 145 to 150 days; mean weight \( \sim 1500 \) g). The first 4 animals were included in a feasibility study to assess the best vascular access and the amount of abdominal bleeding (group 1). The subsequent 8 ewes were kept alive and received conventional care until spontaneous vaginal delivery (group 2). Lambs were kept with their mothers until they were euthanized at day 5. This study was approved by the ethics committee of our institution, and animals received care in accordance with the “Principles of Laboratory Animal Care” and the “Guide for the Care and Use of Laboratory Animals.” Pregnant ewes were fasted 48 hours before surgery. Ewes were sedated with intravenous injection of pentothal (10 mg/kg body weight), placed in supine position, intubated, and ventilated with 100% oxygen and 1% halothane. The uterus was exteriorized through a maternal midline laparotomy.

Intra-abdominal vessels and heart structures were first located with ultrasound guidance and high-resolution color Doppler ultrasound equipment with sterile-packed 3- to 5-MHz broadband transducers. We aimed to place a 1.2-mm trocar (Karl Stroz) either into the intra-abdominal portion of the umbilical vein or in underneath the diaphragmatic portion of the inferior vena cava using a fetal transthoracic approach (Figures 1 and 2). Mean diameter of the right hepatic vein was \( 3.2 \pm 1 \) mm; the diameter of the inferior vena cava was \( 6.4 \pm 1.5 \) mm. After vascular access was obtained, the mandrel was retrieved; a wire was inserted through the lumen of the needle, advanced into the vessel, and pushed into the heart (Figure 3). A 4F sheath previously mounted onto the trocar was then advanced in the vessel over the trocar and the wire. Using a conventional technique and under echocardiography, we aimed to perform a cardiac catheterization (Figure 4). For each lamb, we tested the feasibility of a right atrial or ventricular pacing using a bipolar catheter connected to an external pacemaker and/or the feasibility of a pulmonary valve dilation using an 8- or 10-mm balloon catheter (Tyshak, Numed Inc) over a 0.014-in guidewire (Figure 5). At the end of the procedure, the sheath was removed under ultrasound guidance. The occurrence of intraperitoneal bleeding was evaluated by ultrasound. Antibiotics (1 g of ampicillin and 50 mg of gentamicin sulfate) were administered to the ewe during the surgery and repeated daily for 4 days.

According to grouping, postmortem examination of included fetuses was performed acutely or 5 days after delivery. The abdominal cavity was inspected to search and evaluate the amount of intraperitoneal bleeding. The liver was removed for macroscopic examination. The heart was dissected and examined for any significant lesions of the intracardiac structures.

Results
Site of Insertion of the Sheath and Assessment of Blood Loss
In the first 2 lambs, we inserted the sheath into the intra-abdominal portion of the umbilical vein; however, progres-

Figure 1. Postmortem angiographies through umbilical vein showing 2 sites of vascular access. A, Intra-abdominal portion of umbilical vein. Note restriction of ductus venosus. B, Inferior vena cava in its intrahepatic segment.

Figure 2. A, Exteriorization of uterus through midline laparotomy. B, 4F sheath is mounted over trocar. C, Trocar has been retrieved, and sheath is sutured on uterus to prevent migration.
sion of a guidewire from this site through the ductus venosus into the fetal heart was impossible because of the angles and/or constriction of the ductus. We then chose a direct puncture of the infradiaphragmatic portion of the inferior vena cava using a transhepatic approach. The vessel that was reached was the right hepatic vein. The distance between the uterine surface and the abdominal wall was <1 cm, and the total distance from the uterine surface to the inferior vena cava was 6 to 8 cm. The puncture site was 1 cm under the ribs, and the angle of entry was ≈45°. This access was granted in 10 of 10 fetuses in which we decided to puncture this vessel. One to 3 attempts were necessary to puncture the right hepatic vein. In one animal, accidental retrieval of the sheath occurred before the end of the procedure. In this animal, the inferior vena cava was repunctured to complete the procedure. The sheath was subsequently fixed to the uterus with a thread (n=6). According to the protocol, lambs from group 1 (feasibility study) were euthanized at the end of the procedure to allow a precise evaluation of blood loss. In the 2 fetuses in which the transhepatic approach was performed, intraperitoneal bleeding was 23 and 29 mL, respectively.

**Fetal Cardiac Catheterization and Cardiac Interventions After Direct Puncture of the Inferior Vena Cava**

With direct insertion of the sheath into the inferior vena cava via the liver, a complete fetal cardiac catheterization was possible in all 10 fetal sheep. The mean procedure time was 38±12 minutes. With echocardiographic guidance, the 4 chambers were catheterized with a 4F Judkins right coronary catheter (Cordis) in all 10 cases. Left atrium and left ventricle were catheterized through the foramen ovale. The progression of the catheter beyond the main pulmonary artery into the pulmonary branches and through the ductus arteriosus in the descending aorta was possible in all 10 fetuses. Anterograde catheterization of the ascending aorta was not possible.

Right atrial or ventricular pacing was attempted and performed in 6 lambs. An overdrive stimulation, documented by pulsed-Doppler analysis, was possible in all 6 cases. In addition, we placed a balloon catheter through to the right ventricular outflow tract and dilated the pulmonary valve in 9 of 10 fetuses. In one case, although the guidewire was correctly placed in the descending aorta through the pulmonary valve, we failed to advance the balloon catheter beyond the right ventricle.

**Complications**

Three of 10 fetuses catheterized via the transhepatic approach died during or soon after the procedure (30%). In one case, this followed the intravascular rupture of the balloon. Another fetus exhibited sudden profound bradycardia secondary to an unusual slow balloon deflation. It died despite the attempt of atrial pacing and the intracardiac administration of atropine and adrenalin. For these 2 fetuses, postmortem examination did not reveal any significant lesions of either the fetal heart or great vessels. There was intra-abdominal bleeding of 20 and 26 mL, respectively. One additional death occurred at the end of a complete successful cardiac intervention. This procedure had been the longest one, with several attempts to correctly insert the sheath because of its accidental removal at the beginning of the procedure. At autopsy, there was a major intra-abdominal bleeding (70 mL). Excluding the 2 fetuses included in the feasibility study, 5 (62.5%) of 8 fetuses were alive at the end of procedure, for which the end of pregnancy was uneventful. They were vaginally delivered and had normal postnatal outcome until the day of euthanasia (day 5).
Postmortem Examination of Normally Delivered Fetuses

As shown in Figure 6, no scar was visible on the skin of the lambs. No hemorrhage was found at the opening of the abdominal cavity. A small fibroid scar (≈2 mm diameter) was visible on the anterior wall of the liver. Examination of the heart did not reveal any significant lesion of either atrioventricular or ventriculoarterial valves or cavities.

Discussion

Rationale of Fetus Intervention

Prenatal diagnosis of congenital heart defects enables parental counseling, monitoring of the progression of the cardiac defect, and planning of the delivery.\textsuperscript{11,12} For many structural heart defects, the progression of the lesion must be considered to provide accurate counseling regarding the prognosis. Aortic and pulmonary valve stenosis can be associated with the development of major secondary pathology, such as progressive hypoplasia of the ipsilateral ventricle or ventricular dysfunction with fetal hydrops.\textsuperscript{5–7} By preventing the pathophysiology that leads to development of ventricular hypoplasia or congestive heart failure, antenatal aortic or pulmonary balloon valvuloplasty may improve the outcome of fetuses with severe aortic or pulmonary valve stenosis.\textsuperscript{8,9} However, despite theoretical advantages, the human experience is still limited, and the results of the in utero treatment of such stenotic lesions have been disappointing, with a low rate of success and efficacy in terms of restoration of normal function and anatomy and a high rate of complications.\textsuperscript{8}

Access to the Fetal Heart

Balloon dilation has been performed by direct puncture of the fetal heart either percutaneously or transuterinely with ultrasound-guided needles.\textsuperscript{8,9,13} Insertion of the needle directly into the fetal heart made it impossible to achieve correct alignment of the needle with the great vessels in half of the reported cases of aortic valve dilatation.\textsuperscript{8} Various factors might explain this drawback. First, fetal position is an important limitation to cardiac access and the echocardiographic window. Then, the nonstandardized aspect of the technique might also explain the relatively low rate of success reported. Finally, the presence of the needle in the cardiac chambers has been associated with diffraction of the ultrasound beam, which makes echocardiographic guidance difficult or impossible to perform. In addition, significant lesions of the fetal heart with balloon catheters have been reported. To overcome the apparent limitations of the percutaneous ultrasound–guided techniques, various authors have investigated alternative approaches, namely, direct heart or umbilical puncture using fetoscopy derived from endoscopic surgery.\textsuperscript{14,15} In this latter technique, one of the 2 umbilical arteries is dissected, which allows for the insertion of a 4F sheath. From this site, it is then possible to perform a retrograde catheterization of the fetal left heart. Unfortu-
nately, this procedure has been associated with a high fetal mortality rate after bleeding and thrombosis of the punctured umbilical artery. Although these complications have probably precluded its application to the human fetus, this procedure was the first to allow fetal retrograde heart catheterization with a Seldinger-derived technique. More recently, percutaneous ultrasound–guided fetal atrial septoplasty has been successfully performed in human fetuses with hypoplastic left heart syndrome and restrictive atrial septum.13 As mentioned by the authors in the latter study, technical limitations and small size of the defect in the atrial septum were related to the size of the material used.

Transhepatic Puncture of Intra-Abdominal Vessels

We speculated that the puncture of a fetal vessel in the umbilicoportal region would reduce the risk of bleeding because reabsorption of the red blood cells by the peritoneum would potentially attenuate the consequences of fetal blood loss. The intraperitoneal route has been proposed by others as an alternative procedure to intraumbilical vein transfusion for the treatment of severe fetal anemia.16 This approach would allow for a more standardized catheterization under conditions and with materials that do not differ from the Seldinger-derived technique commonly used for neonatal cardiac catheterizations. Finally, because the site of puncture is far from the heart, the diffraction problems would be eliminated and the echogenicity preserved.

The present study demonstrates that fetal cardiac catheterization is feasible under echocardiographic guidance in the fetal sheep when the intra-abdominal portion of the inferior vena cava is punctured. Indeed, the intrahepatic portion of the umbilical vein did not allow progression of the catheters and guidewires through the ductus venosus into the fetal heart in 2 animals. Alternatively, we successfully tested anterograde cardiac catheterization from the inferior vena cava via the liver. This access was granted in 10 of 10 fetuses. From this site, we observed that intraperitoneal bleeding represented up to 10% to 15% of the total fetal blood volume at the end of the procedure. We assumed that this fetal blood loss may be compatible with further normal fetal development, but we are aware that this tolerance may be worse in hemodynamically compromised fetuses with congenital heart disease. However, in pathological conditions, the deleterious effect of procedure-associated fetal blood loss may be counterbalanced by fetal blood transfusion at the end of the procedure via the same vascular access. The 2 other deaths could potentially have been avoided by the use of new balloon catheters for each procedure.

Study Limitations

The applicability of these results to successful fetal cardiac therapy in human fetuses is limited. First, we decided to perform the echocardiography-guided procedure after the exteriorization of the uterus because of the limited length of our devices (both the needle and the sheath). In addition, this method permitted the use of a much broader set of angles than would be available in human fetuses. Second, the procedure was performed almost at the end of gestation in fetal lambs, whereas interventions should probably be performed earlier in human fetuses of a lower weight (second trimester) to be efficient. Finally, it remains uncertain whether stenotic or atretic valves could be crossed by these methods. In this respect, the use of smaller sheaths or catheters (3F or smaller) should be considered to allow for a high rate of success and in the meantime a low rate of complications.17 Because fetal size is an important factor for the success of such a procedure, any efforts should focus on the development dedicated catheters.

Conclusions

This study in fetal sheep demonstrates that fetal cardiac catheterization through a transhepatic puncture of the infradiaphragmatic part of the inferior vena cava guided by ultrasound is feasible and provides an interesting alternative approach for human fetal cardiac interventions. Further studies and technical developments are needed to investigate the
feasibility of this approach at mid-gestation before it may be applied to the human fetus.

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