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Review Article

Fetal Surgery for Congenital Heart Disease

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Certain congenital heart defects, which present at birth as complex morphologic defects, are actually the result of a relatively simple primary lesion and the subsequent acquired development of a complex secondary lesion during gestation. Moreover, fetal heart approach during gestation can prevent simple cardiac lesions from such development. Specific structural lesions can be diagnosed before 12 weeks of gestation by transvaginal fetal echocardiography, and animal experiments have shown that direct or indirect fetal cardiac approach and fetal cardiac bypass are technically feasible. A number of fetal bypass models have resulted in long-term survivors, with for example, the delivery of normal lambs at full-term gestation. Also, successful full-term delivery has been obtained after fetal cardiac intervention. The success of fetal cardiac bypass was accomplished by the use of total spinal anesthesia and the administration of indomethacin. Moreover, a 42 % long-term survival after fetal cardiopulmonary bypass in a fetal lamb model has been reported. Maternal risk related to fetal bypass should be considered carefully alongside fetal risks and benefits. Most fetal malformations do not directly threaten maternal health, yet the procedures required to address fetal malformations can produce significant maternal risk and discomfort and subsequent pregnancies may be jeopardized. Further investigation of maternal outcome is required. Deep exploration of fetal and maternal pathophysiologic responses to intervention and comprehensive investigation is required to overcome current limitations, and should precede clinical trials as many problems remain to be solved before these techniques can be applied to human beings.

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INTRODUCTION

With the great advancements being made on the understanding of the morphogenesis and pathophysiology of congenital defects, early correction in fetal life can be achieved with better results and defect progression prevented. Moreover, precise fetal diagnosis makes such intervention easier. Actually, human fetal interventions were successfully performed for posturethral obstruction and congenital diaphragmatic hernia.

Since the first fetal intervention with Liley's successful blood transfusion into the peritoneal cavity of a fetus affected with erythroblastosis fetalis,[1] big advances have been made on researches into fetal cardiovascular physiology,[2,3] extracorporeal circulatory support,[4-9] and the pathophysiologic responses of the fetomaternal unit to an extracorporeal circuit.[10-14] Anesthetic management of the fetus during fetal surgery has also been rigorously studied, to avoid detrimental effects on fetal cardiac function and placental blood flow.[15-17] In 1994, Fenton and associates[18] reported the first long term success involving fetal cardiac bypass. Total spinal anesthesia and indomethacin administration were used to inhibit fetal stress and block placental vasoconstriction. Moreover, a long-term survival of 42% after fetal cardiopulmonary bypass was shown in a fetal lamb model. Reddy and associates[19] raised the long term survival rate to 89% using a bypass circuit incorporating an in-line axial flow pump, and successfully made a fetal sheep model of single ventricle physiology by creating Damus-Kaye-Stansel aortopulmonary anastomosis, and achieved live birth rate of 90%.[20] The cumulative knowledge gained has permitted the application

of techniques of inhibiting fetal stress and blocking placental dysfunction,[21] and has resulted in a high degree of recovery and long-term survival after fetal cardiac bypass in lambs.[18,19]

RATIONALE

Although primary cardiac morphogenesis is completed after 8 weeks of intrauterine life, further development of the heart is substantially influenced by fetal blood flow patterns.[22] A structural abnormality that develops during primary morphogenesis can alter intracardiac blood flow patterns, and cause important secondary morphologic consequences. After birth, these secondary structural lesions may pose more serious management problems than the primary lesion itself. With recent advances in ultrasonic imaging, it is now possible to accurately diagnose structural heart defects after as little as 12 weeks of gestation. Theoretically, if the primary lesion is corrected in utero, the secondary morphologic consequences can be avoided.[23-25] Examples of the type of lesion that might be approached in this way include, critical aortic stenosis with a dysfunctional left ventricle, pulmonary atresia with an intact ventricular septum, Tetralogy of Fallot with absent pulmonic valve syndrome, and some forms of hypoplastic left heart syndrome.

Fetal cardiac intervention offers several advantages. First, correction of the primary lesion can normalize flow patterns in the abnormally developing fetal heart. This restores normal cardiac flow patterns, which result in less secondary maldevelopment. Second, the remainder of the gestation period in uterus provides the fetal heart with the time and the environment it needs to recover and resume normal development. The placenta of the fetal circulation can be regarded as a natural extracorporeal oxygenating membrane, which aids heart recovery without stress to the overall fetus caused by a struggling heart.[26]

FETAL CARDIAC SURGERY

The technical feasibility of fetal cardiac surgery have been investigated from the early 1980s.[27] Most of the animal experiments have been performed using sheep. Basic fetal physiologic data on sheep is available and this provides an excellent background for evaluating the pathologic responses that occur on instituting fetal extracorporeal circulation. Additionally, because the fetal sheep is about the size of the human fetus, critical technical issues can be appropriately assessed. For these reasons, the sheep is an excellent model for studying fetal extracorporeal techniques.

Many surgical interventions of the fetal heart need extracorporeal bypass, and the feasibility of cardiopulmonary bypass has been technically proven by animal experiments upon 1000-1500 g fetal lambs.[6] However, the fetal lambs were eventually died, because physiologic changes, such as hypoxemia and acidosis could not be overcome, which has since been attributed to placental dysfunction and fetal low cardiac output after surgery.[6,7,10]

PLACENTAL RESPONSE TO FETAL CARDIOPULMONARY BYPASS

Placental dysfunction

The most immediate cause of fetal demise after fetal cardiopulmonary bypass is placental dysfunction, which is characterized by the elevation of fetal Pco_2, respiratory acidosis, and terminal ventricular fibrillation. In a mechanistic investigation of placental dysfunction it was found that increased placental vascular resistance was a direct cause.[27,28] The stimulus for the vasoconstrictive response of the placenta to bypass is not completely understood, but it is known to be partly related to fetal stress[16,17] and to the exposure of blood to the extracorporeal circuit.[3,5,10] A number of mechanisms are involved in placental dysfunction. Prostaglandin and other eicosanoid products, for example, are major mediators of placental vasoconstriction.[29-32]

Sabik and associates demonstrated that indomethacin,[12] which blocks the arachidonic acid cascade at the cyclooxygenase step, and corticosteroids[13] cause a marked reduction in the unwanted placental response to fetal bypass. Corticosteroids were found to block the arachidonic

acid cascade at the phospholipase step[33] and the use of corticosteroid was more specifically associated with thromboxane or prostaglandin E_2, as the important mediator,[13] and both of these are known to be potent placental vasoconstrictors that are locally produced in placental tissue.[31,32]

Endothelial factors, such as nitric oxide and endothelin-1 are also known to have a role in placental dysfunction during and after fetal cardiac bypass. Reddy and associates[34] compared the vasoactive effects of acetylcholine (endothelium-dependent), nitroprusside (endothelium-independent) and endothelin-1 before and after fetal bypass, to evaluate the ability of the endothelium to produce nitric oxide. They observed that endothelium-dependent vasodilatation after fetal bypass was impaired and that the rise in placental resistance during fetal bypass was limited, after the injection of a nonspecific endothelin-1 receptor blocker (PD 145065). They further suggested that the endothelium plays an important role in placental dysfunction, and that nitric oxide and endothelin-1 are the mediators of placental vascular tone. Nitric oxide is an endothelium- derived relaxing factor and an important regulator of placental vascular tone, and endothelin-1 is one of the most potent vasoconstricting peptides and known to be another important regulator of placental vascular tone. Moreover, physiologic antagonism between nitric oxide and endothelin-1 has been demonstrated in many regional circulations.[35]

Recently it has been proved that fetal cardiac bypass activates many inflammatory reactions, for example, the complement cascade, and the white cell activation and rennin-angiotensin pathways. These are regarded as other mediators of placental response to fetal bypass.[36-38]

To optimize fetal outcome after intrauterine extracorporeal bypass, interventions to reduce postbypass placental dysfunction are needed. Highly selective inhibition of the mediator is desirable, because less specific inhibitors, such as indomethacin, may lead to unwanted effects, such as the constriction of the ductus arteriosus.

Fetal response to fetal cardiac intervention and extracorporeal circulation

A number of observations have shown progressive metabolic acidosis and fetal hemodynamic instability after weaning from cardiopulmonary bypass.[21,26] It is believed that this detrimental outcome is due to a depressed fetal cardiac output.[26]

A massive catecholamine-mediated response to surgical stress is known to develop in the fetus,[39,40] which elevates total fetal vascular resistance. Fetal stress also leads to the release of prostaglandins[41-43] and activation of the rennin-angiotensin pathway, which are known to affect placental and systemic vascular resistance. The immature fetal myocardium is not able to compensate for the increased afterload and induces a substantial drop in cardiac output, which is associated with a redistribution of blood flow in various peripheral beds.[26]

Anesthesia

Various methods have been investigated to block fetal stress response. Experimental surgical studies in the fetal lamb model have typically been performed using halothane anesthesia, which has some advantages. First, it crosses the placenta after maternal administration, and therefore, direct fetal anesthesia is unnecessary. Second, it allows improved fetal exposure because it is a potent uterine muscle relaxant. However, halothane has a myocardial depressive effect, it affects placental perfusion, and cannot block the stress response elicited by pain or surgery.[15]

Total spinal anesthesia has been attempted to block all afferent neural signals to the brain by applying tetracaine to the spinal fluid via the cisterna magna. It is a reliable method of blocking the fetal stress response to painful stimuli. Fenton and associates[16] also demonstrated that total spinal anesthesia led to a markedly increased fetal cardiac output and placental blood flow compared with other anesthetic techniques.

Recently, experiments using a combination of indomethacin, to block the specific placental response to bypass, and total spinal anesthesia, to block the stress response and preserve fetal myocardial function in the standardized fetal lamb bypass model, have shown that placental and myocardial function are conserved with excellent gas exchange and cardiac output.[18]

Ideal fetal cardiopulmonary bypass

At the present time, the ideal circuitry for fetal bypass has not been determined with certainty. Because the fetus has a unique cardiovascular physiology, standard techniques of neonatal cardiopulmonary bypass need to be modified to preserve the milieu of the fetal-placental -maternal unit.

Fetal bypass circuitry and the placenta

Because the placenta function is a critical factor for the survival of the fetus, it must be preserved after bypass. The ideal way of handling the placenta during bypass remains undetermined. Inclusion of placenta in the bypass circuit has the advantage of eliminating an extracorporeal oxygenator from the bypass circuit, as the placenta will act as the gas exchange unit. However, this circuit has some disadvantages. First, the perfusion of the placenta may continuously stimulate the production of vasoactive substances, which will tend to cause placental vasoconstriction. Second, the placenta normally requires a large blood flow rate, and perfusion rates using bypass with the placenta are approximately 400 ml/kg/min. These high flow rates can be difficult to achieve in small fetuses because of limitations in the cannula size.

Excluding the placenta from the bypass circuit would potentially decrease the stimulation of vasoactive substances and reduce the required blood flow rates by about 50%. However, an extracorporeal oxygenator is necessary, and the effects of arresting placenta flow, for a substantial time during the period of bypass, are not yet well understood.[21]

Experiments with isolated placental models and on the effects of placental circulatory arrest in intact animal models, have shown that the placenta will tolerate a 30-minute period of normothermic umbilical and placental circulatory arrest, and will resume normal gas exchange after reperfusion. These experiments suggest a beneficial effect of arrested placental flow on postbypass placental vasoconstriction.[3,4,21,44]

Axial pump

Placental dysfunction is an inevitable result of fetal extracorporeal bypass using a conventional bypass circuit. Stimuli responsible for placental dysfunction are extracorporeal surfaces, priming substances, flow characteristics, and fetal stress. The surfaces of extracorporeal bypass circuit are nonphysiologic and activate a number of humoral pathways.[24,26,45,46] Large volumes of priming substances cause fetal hemodilution, and adult blood is not ideal because adult hemoglobin shows a lower affinity for oxygen than fetal hemoglobin. For this reason, improvements in the extracorporeal circuitry should significantly minimize fetal placental-uterine milieu perturbation after fetal cardiac bypass.

To minimize the extracorporeal surface and avoid priming volume, a new bypass circuit incorporating an in-line axial pump was designed. This miniaturized bypass circuit was filled with fetal blood (14 to 16 mL) at the time of cannulation. The amount of extracorporeal surface was markedly reduced, and no external priming solution was required. When compared with a conventional roller-pump circuit, this circuit resulted in significantly better fetal and placental hemodynamics, and fetal arterial blood gases during and after bypass.[47]

Pulsatile flow

Flow characteristic is another factor influencing fetal and placental response to fetal extracorporeal bypass. In some experiments it has been observed that pulsatile flow may overcome the progressive rise in peripheral and vascular placental resistance observed during steady-flow fetal bypass.[9,48] It was also shown that the use of pulsatile flow bypass for 30 minutes may assist in preventing the onset of fetal hypoxia.[9]

Champsaur and associates[48] showed that improved placental and fetal responses to pulsatile flow are mediated by the release of endothelium-derived relaxing factor. Recently Vedrinne and associates[37] measured the release of endothelial vasoactive substances during a 60-minute experimental fetal bypass in utero, and proved that the use of pulsatile flow resulted in a better preservation of endothelial function and reduced activation of the fetal renin-angiotensin system, which might be the major mechanism behind the superior results of pulsatile flow.

If complex intracardiac repairs require hypo-

thermic bypass, cardioplegia, and circulatory arrest, the specific effects of these factors on the fetus need to be studied carefully. Further research is needed to preserve normal placental flow, to optimize uterine perfusion, and to apply these techniques to a primate model.

MATERNAL RESPONSE

Preterm labor

In the majority of animal experiments, the most serious problem of maternal response was caused by hysterotomy. Hysterotomy inevitably provokes uterine contractions and results in preterm labor. Moreover, the benefit of fetal surgery is lost if the fetus is delivered prematurely, because preterm labor is the leading cause of perinatal morbidity and mortality, and remains a great challenge of fetal intervention.

Human beings are not exceptions. Harrison and associates[45] reported upon the maternal outcome of 50 cases of open fetal surgery in human beings, including various non-cardiac procedures. No maternal deaths and few postoperative maternal complications occurred, but considerable morbidity resulting primarily from preterm labor and its treatment were observed. All patients experienced labor after hysterotomy, and the treatment of preterm labor accounted for most of the morbidity. Therefore, the prevention of preterm labor by effective tocolytic therapy represents an important area of investigation.

Tocolytic therapy

In spite of technical advances, preterm labor is still a major obstacle of fetal therapy. Several regimens, such as, indomethacin, deep halogenated inhalation anesthesia, and combined treatment with magnesium sulfate and β-sympathomimetics, have proven effective in monkeys.[49-51] However, these are inadequate for humans. Halogenated inhalation agents at the depth of anesthesia necessary to achieve intraoperative uterine relaxation can produce fetal and maternal myocardial depression and affect placental perfusion.[15] Indomethacin can constrict the fetal ductus arteriosus, and the combination of magnesium sulfate and β-sympathomimetics can produce maternal pulmonary edema. Currently intravenous nitroglycerin is used intraoperatively and postoperatively because nitric oxide is known to be a potent tocolytic in animal experiments using monkeys,[49] but it requires careful control to avoid serious complications. More investigation is needed in this field.

Artificial placenta

Because tocolytic therapy has been distressingly unsuccessful, the development of the artificial placenta was initiated in the late 1950s. Zapol and colleagues[52] reported 2 days of total extrauterine support of an isolated immature lamb fetus. In 1993 Unno and colleagues[53] reported 3 weeks of total extrauterine support using a roller pump. In 1998, Sakata and associates[54] developed a new artificial placenta with a centrifugal pump to support immature fetuses and achieved long-term extrauterine support of goat fetuses for up to 237 hours. They achived near normal umbilical blood flow, maintained near physiologic fetal oxygen saturation levels and minimized circuit prime volume to 95 ml. In spite of their achievement, much room is left for further improvement, as the artificial placenta should be capable of providing the fetus with nutrition and of allowing subsequent maturation, before it can be used as a fetal extrauterine support system or as a backup system for fetal operations.

FETOSCOPIC CARDIAC INTERVENTION

The minimally invasive fetal cardiac approach has been investigated to minimize maternal and fetal damage. In 1997 Kohl and associates[55] reported successful fetoscopic transumbilical fetal cardiac catheterization without hysterotomy and fetal exteriorization in sheep.

The feasibility of direct fetal cardiac access by operative fetoscopy was also shown in pregnant ewes.[56] Under fetoscopic visualization, the diaphragmatic surface of the heart was exposed through a skin incision above the fetal xiphoid process, and the left or right ventricle punctured

and a guide-wire and balloon catheter placed across the aortic and pulmonary valves. This method permits direct fetal cardiac access in sheep fetuses weighing as little as 350 g, and may permit cardiac interventions in similarly sized human fetuses at less than 20 weeks of gestation. Fetuses with severe semilunar valvular obstruction may benefit from this technique. Pacemaker insertion for refractory congenital complete heart block or tumor resection for large pericardial tumors may be other indications of this intervention (Fig. 1).

Although open fetal cardiac surgery for valvotomy has not yet been achieved, fetal cardiac catheterization and balloon valvuloplasty have been performed in selected human fetuses.[57-60] Cardiac access for this procedure has been obtained by ultrasound-guided direct puncture of the obstructed ventricle.

Fetoscopic fetal cardiac intervention may be more favorable than the open approach for human fetal cardiac interventions, because it is less invasive for the mother and fetus. Laparotomy, hysterotomy, and fetal exteriorization have been accompanied by a substantial decrease in fetoplacental blood flow and a poorer outcome in human fetuses with noncardiac lesions.[61] In addition, fetoscopic techniques do not require cesarean section for fetal delivery, because the uterus is accessed through minimal openings. Cesarean section is obligatory after open fetal surgery because of the risk of uterine rupture during normal delivery. However, fetoscopic procedures are not always favorable because it is technically far more demanding and time consuming than the open approach.[55]

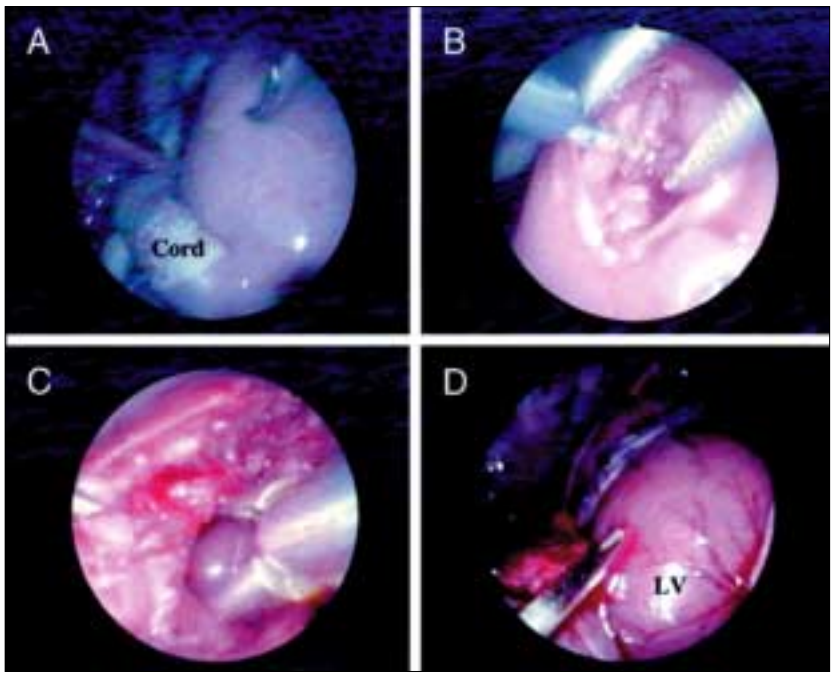

Fig. 1. Digitized video images of fetoscopic direct fetal cardiac access. A, Fetoscopic view after gaseous distension of the uterine cavity and fetal posturing. The fetoscopic grasper was positioned in the epigastrium. B. A 15-mm skin incision was made above the xiphoid process, and this was followed by resection of the xiphoid process to enter the chest cavity. C. The pericardium was incised and spread using a fetoscopic grasper. D, A 16-gauge needle shaft was inserted into the fetal left ventricle (LV). The shaft is oriented toward the fetal left ventricular outflow tract to facilitate the placement of a 0.014-inch guide-wire and a balloon catheter across the aortic valve antegrade (in this acute study, the pericardium was widely removed to obtain a fetoscopic view of the heart). (from Thomas Kohl, Danja Strumper, Ralf Witteler, Gregor Merschhoff, Rasa Alexiene, Claudia Callenbeck, Boulos Asfour, Julia Reckers, Sebastian Aryee, Christian Vahlhous, Johannes Vogt, Hugo Van Aken, and Hans Scheld, Fetoscopic Direct Fetal Cardiac Access in Sheep: An Important Experimental Milestone Along the Route to Human Fetal Cardiac Intervention. Circulation 2000;102:1602-1604, with permission)

CONCLUSION

As techniques of fetal cardiac surgery have advanced to reduce the placental, fetal and maternal responses to fetal cardiopulmonary bypass, it is now expected that the outcome of fetal cardiac surgery be as good as that of conventional therapy after birth, and that secondary consequences derived from primary cardiac lesions can be minimized. Moreover, the risk of fetal cardiac surgery is expected to be as low as that of neonatal cardiac surgery, and to be free of undue risk to maternal health or future pregnancy.

Fetal cardiac intervention and surgery will be commonly applied to human beings in near future, through comprehensive research upon fetal and maternal pathophysiologic responses.

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