Fetal cardiac surgery: Simplicity versus success in a new frontier

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See related article in 2003;125: 1276-82.

The current status of fetal cardiac surgery is similar to the field of infant heart surgery 50 years ago, when it was clear that correction of certain congenital defects would provide great benefit, but there was no safe and effective method to gain access to the heart. However, with the development of cardiopulmonary bypass (CPB) equipment and techniques, intraoperative access to the heart became possible. Moreover, surgeons developed an understanding of the pathophysiologic responses of the child to these techniques and learned how to protect the myocardium, as well as the patient, during open cardiac repair.^{1,2} This allowed postnatal cardiac surgery to be done safely and effectively. If similar "low-risk" techniques, understanding, and equipment existed for the fetus, there would be little argument that fetal cardiac surgery would be preferable for certain congenital lesions. However, little is known about the pathophysiologic effect of surgical intervention or CPB on the developing fetus. As a consequence, many of the surgical techniques developed over the past 50 years for patients with cardiac disease, including those of extracorporeal circulation and myocardial protection, must be redeveloped before application to the fetus.

Early experimental work on fetal cardiovascular interventions demonstrated it was technically possible to place the fetal lamb on and separate from CPB.^{3,4} Nevertheless, most animals died within hours as a result of placental dysfunction after a marked increase in placental vascular resistance. Moreover, even when placental dysfunction was prevented, the post-CPB fetus routinely had progressive metabolic acidosis as a result of decreased cardiac output, leading to late death.^{3,5,6} These studies clearly establish that the major limitation to successful clinical fetal cardiac surgery would not be technical but related to the pathophysiologic responses of the fetus to various forms of intervention.

Physiologic challenges to fetal cardiac surgery relate both to CPB management and optimization of protection of the fetal heart. It makes no sense to perform an intervention to alter the flow dynamics of the myocardium only to end up with heart muscle that is severely damaged and unable to support the circulation. Protection of the fetal heart is complicated by immature calcium regulation and energy use, decreased tolerance to ischemia, limited coronary vascular response, an impaired length-tension relationship, and a reduced cardiac and inotropic reserve compared with that of the mature infant.^{3,4,6-9} Moreover, the clinical fetal heart is likely to be further stressed by the structural abnormality that requires intervention, thus making it even less tolerant to ischemia than the unperturbed (morphologically normal) fetal heart used in experimental studies. This makes complete recovery of myocardial function in the experimental setting absolutely critical before fetal intervention is undertaken clinically.

As an initial step, Malhotra and associates⁶ used an isolated fetal heart preparation in an attempt to examine fetal myocardial protection without the complicating factor of the placenta because fetal death and myocardial failure can be caused by either myocardial or placental dysfunction.³⁻⁶ Although this seems like an excellent solution, an isolated heart preparation has its own inherent problems, and the results might not always be applicable to the clinical setting. For example, bronchial blood flow and noncoronary collateral flow are both absent in the isolated heart preparation. Bronchial blood flow may actively rewarm the heart, whereas noncoro-

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Received for publication Jan 7, 2003; accepted for publication March 4, 2003.

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J Thorac Cardiovasc Surg 2003;126:1254-6

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0022-5223/2003 \$30.00 + 0

doi:10.1016/S0022-5223(03)00754-2

nary collateral flow helps wash out cardioplegic solution, thereby changing the cellular environment during myocardial arrest.^{1,2,10,11} Several cardioplegic constituents (ie, calcium and glucose) that have been found to be protective or deleterious in the isolated heart have been found to have the opposite effect in the intact (in vivo) heart as a result of cardioplegic washout.^{1,2,10,11} One might also question whether the fetal heart is damaged by excision alone because baseline measurements were not taken until the heart was placed in an isolated preparation. Moreover, the authors used a crystalloid (Krebs-Henseleit) solution containing high calcium, the harbinger to damage, to perfuse their isolated heart preparation.^{2,10} This can profoundly alter the coronary vascular response and calcium loading, particularly after ischemia.^{1,2,10,12} This might be especially important during the period of ventricular fibrillation, as well as after reperfusion after ischemia in both groups. For example, is fetal subendocardial perfusion improved or worsened during ventricular fibrillation in the presence of crystalloid perfusion? A blood perfused model would have been more physiologic and alleviated some of these concerns.¹⁰⁻¹² Nevertheless, the intact (in vivo) animal is still preferable because differences will always remain, and no interventions should be applied clinically until proved successful in the intact animal.

Methods of myocardial protection must be evaluated in the fetal heart and not simply extrapolated from adult and infant studies because the immature fetal myocardium might react quite differently to various interventions. This investigation by Malhotra and associates⁶ is a very important introduction because it is one of the first attempts to address the issue of fetal myocardial protection, and therefore its simplicity seems justified. However, the myocardium must be optimally and fully preserved for fetal surgery to be successful. Myocardial dysfunction likely dooms the fetus to death before delivery because the stress of CPB alone (without myocardial ischemia) uniformly leads to fetal death from progressive metabolic acidosis caused by low cardiac output.^{3,5} An injured heart will only exacerbate this post-CPB stress. Furthermore, even if the fetus survives, when born, it will be left with a heart that is destined to fail despite its structural normality.

Malhotra and associates⁶ compared crystalloid cardioplegia with ventricular fibrillation in hearts subjected to only 30 minutes of cardiac arrest. They concluded that the 2 methods of protection are similar and that ventricular fibrillation is therefore probably preferable because it is "simpler." I am not sure this is the correct question because the goal should be avoidance of myocardial injury and not simplicity of technique, especially because longer periods of ischemia might be necessary to correct certain lesions. Moreover, further analysis of their data is concerning. De-

spite only 30 minutes of ischemic arrest, recovery of end-systolic elastance (contractility) was markedly reduced in both groups, as was diastolic compliance and overall myocardial function (preload recruitable stroke work). Furthermore, the increase in postarrest myocardial water was extensive and resembles levels seen only in neonatal and infant hearts that have sustained a severe and usually irreversible injury.^{1,2,10,11} This calls into question the efficacy of both methods of protection because the damage is quite profound for such a short period of ischemia.

Many surgeons previously used the technique of ventricular fibrillation with continuous perfusion because it was simple. However, they found, to their dismay, that hearts (especially those with hypertrophy) that were fibrillated during extracorporeal circulation frequently sustained some degree of ischemic damage, especially to the vulnerable subendocardial region.² Although a single dose of crystalloid cardioplegic solution and ventricular fibrillation might simplify fetal cardiac surgery, the ultimate goal of myocardial protection is not simplicity. As with the technical aspects of the repair, the primary objective is use of the optimal strategy. Integration of surgical techniques is usually required to perform the best possible operation. Optimal myocardial protection also requires integration of various techniques and strategies.^{1,2} Most surgeons would not abandon a complex surgical procedure that was proved superior solely because of its lack of simplicity. Likewise, we should not choose a protection strategy for its simplicity unless it provides optimal and complete myocardial protection. Optimal myocardial protection is as important as an excellent technical repair to achieve a good long-term outcome with surgical correction. Although the surgeon might desire *simplicity*, the patient is only concerned with *success*.

In conclusion, the authors are to be commended for this pioneering study in the new frontier of fetal cardiac surgery. However, one must look with caution both to their model and their results. Success must be achieved in an appropriate clinical (in vivo) model before clinical application. Moreover, no matter what the risk of subsequent repair, unless fetal surgery can be done safely with minimal myocardial injury and complete preservation of cardiac function, we have simply traded one problem for another (ie, a heart with normal structure for one with myocardial dysfunction). Hopefully, this important initial study will spur others to continue investigations in this field so that fetal cardiac surgery can become a reality in the future. Although the task seems daunting, it is probably no more daunting than infant surgery appeared to those surgeons 50 years ago. If we show the same perseverance and dedication as our predecessors, there is no reason this new frontier cannot be tamed in the same way.

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