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EDITORIAL COMMENT

Minimally Invasive Delivery of Tissue Engineered Heart Valves to the Pulmonary Annulus*

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Approximately 9 in 1,000 infants are born with congenital heart defects, which are a significant contributor to early mortality and long-term morbidities (1). Current treatment of these defects includes invasive reconstructive surgeries and the use of bioprosthetic valves or valved conduits that can be delivered surgically or minimally invasively. Some fetal cardiac anomalies, including pulmonary atresia with an intact or almost intact ventricular septum, can lead to single ventricle disease. However, due to the use of foreign materials in their components (including synthetic materials or grafts), these implants can cause multiple adverse effects once implanted. Among these sequelae are calcification, contracture of the implant, immune rejection, and tissue degeneration. As a result, replacement of bioprostheses is often warranted, necessitating further intervention, often within 5 years after the initial placement (2).

Tissue engineered heart valves (TEHVs) have potential to circumvent the aforementioned issues caused by the use of synthetic materials and xenografts or homografts in bioprostheses. In this paradigm, biodegradable scaffolds are used to promote the host's own cells to populate the implant and become dynamic tissue that has the capability to grow and remodel. In the fetus, regeneration and formation of new tissue are particularly effective, thus motivating fetal implantation of TEHVs as a favorable strategy for subsequent growth and adaptation.

In this issue of *JACC: Basic to Translational Science*, Zakko et al. (3), a highly interdisciplinary group of researchers have described the first transcatheter, fully biodegradable tissue engineered fetal heart valve. By using a degradable zinc-aluminum alloy for the stent frame, and electrospun polycaprolactone for the leaflets, they successfully manufactured a valve that could be crimped over a 17G trocar to ultimately allow percutaneous delivery. It is a notable feat of engineering to overcome the challenges associated with fabricating a functional biodegradable valve, and further designing it so that it can be crimped to such a small diameter and retain its functionality after percutaneous delivery. Current transcatheter technology was used to crimp the valve onto an angioplasty balloon for subsequent delivery through a catheter. Once at the valve annulus, the balloon can be inflated to expand the stent, and the polycaprolactone leaflets overtake the function of the stenotic valve.

Extensive in vitro testing was performed with the valve to validate its performance including measurements of stenosis and regurgitation, accelerated aging, cyclical mechanical testing, and dynamic flow loop evaluation. Notably, the valve showed negligible regurgitation when subjected to pulsatile flows and a peak transvalvular gradient of 20 mm Hg.

Remarkably, the researchers showed that the valve could be delivered percutaneously into the fetal pulmonary annulus in an ovine model. After

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implantation, echocardiographic imaging of the valve showed laminar flow with no stenosis or regurgitation. The fetus matured after valve implantation and was delivered at full term.

This success was not without challenges and limitations. The experiments revealed multiple challenges associated with the procedure. Overall, in 16 fetuses, only 1 fetus survived the implantation and was delivered at term. In a pilot study of 9 pregnant sheep with a total of 12 fetuses, the researchers attempted implantation of a zinc stent without any polycaprolactone leaflets to learn about the minimally invasive approach. Implantation was successful in 5 of 12, and 4 of these fetuses did not survive due to bradycardia or pericardial effusion. In the 1 successful implantation, the stent was implanted in the main pulmonary artery instead of the pulmonary annulus, and the fetus subsequently died due to a maternal strangulated bowel. The researchers identified multiple improvements in percutaneous delivery techniques from the pilot study including: 1) fluoroscopy of the abdomen in addition to ultrasound; 2) anterior right ventricular free wall puncture; 3) optimal fetal positioning; 4) a small medial Pfannenstiel incision on the contralateral side of the fetal position to allow manipulation of this position through the uterine wall; 5) administration of intracardiac epinephrine before balloon inflation; 6) careful choice of ovine breed; and 7) minimizing fetal blood loss through the introducing cannula. Guided by the new knowledge gleaned from the pilot study, subsequent implantations were more successful, but still revealed serious complications associated with this procedure including heart block, stent migration, bradycardia, and pericardial effusion. In the successful implantation, the valve demonstrated laminar flow without regurgitation but subsequently migrated to the main pulmonary artery. Still, the fetus survived to term and was alive at 18 months.

A major contribution of this paper is the development and percutaneous delivery of a fully biodegradable heart valve in the pulmonary annulus. This is the first report of transcatheter delivery of a TEHV. Previously, researchers (4) had used nitinol stent frames for stem-cell based pulmonary valves which do not grow with the child, and require a fetal thoracotomy for delivery through the right ventricle using a delivery system that is approximately 4 times larger than that described in this work. Indeed, percutaneous delivery has many advantages including obviating the need for maternal and fetal incisions and a lower incidence of iatrogenic preterm prelabor rupture of membranes (5).

Future work will be needed to investigate the cause of the many complications reported with this procedure, to optimize the design of the delivery system and the implant, and to fully characterize the degradation of the stent, and the rate of neotissue formation.

In summary, the work shows the first proof-of-concept of transcatheter fetal implantation of a TEHV which has transformative potential to alter fetal hemodynamics and prevent complex cardiac anomalies such as single ventricle disease.

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REFERENCES

1. Van Der Linde D. Birth prevalence of congenital heart disease worldwide: a systematic review and meta-analysis. J Am Coll Cardiol 2011;58:2241–7.

2. Breuer CK, Mettler BA, Anthony T, Sales VL, Schoen FJ, Mayer JE. Application of tissue-engineering principles toward the development of a semilunar heart valve substitute. Tissue Eng 2004;10:1725–36.

3. Zakko J, Blum KM, Drews JD, et al. Development of tissue engineered heart valves for percutaneous transcatheter delivery in a fetal ovine model. J Am Coll Cardiol Basic Trans Science 2020;5:815–28.

4. Weber B, Emmert MY, Behr L, et al. Prenatally engineered autologous amniotic fluid stem cell-based heart valves in the fetal circulation. Biomaterials 2012;33:4031–43.

5. Beck V, Lewi P, Gucciardo L, Devlieger R. Preterm prelabor rupture of membranes and fetal survival after minimally invasive fetal surgery: a systematic review of the literature. Fetal Diagn Ther 2012;31:1–9.

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