JACC: BASIC TO TRANSLATIONAL SCIENCE VOL. 7, NO. 3, 2022

EDITORIAL COMMENT

In Vivo Imaging of Tissue-Engineered Grafts Within Pulmonary Artery of a Growing Large Animal Model*

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Treatment of complex congenital heart defects often requires the total replacement of the right ventricular outflow tract (RVOT) using a valved conduit to replace the pulmonary valve and the main pulmonary artery (MPA). Standard timing for RVOT reconstruction has shifted to earlier time points for severe cases, with most patients undergoing surgical treatment within the first year of life. However, currently used graft materials have issues of early degeneration, calcification, and lack of somatic growth potential. These issues force pediatric patients to undergo one or more replacement procedures.[1] Because RVOT reconstruction lacks an ideal conduit, tissue engineering efforts for a biocompatible, readily available, nonimmunogenic material with synchronous growth potential are ongoing to address this large clinical need.

Importantly, clinical management of RVOT reconstruction is reliant on imaging modalities to monitor conduit function after implantation. Currently, echocardiography and cardiac magnetic resonance are two noninvasive imaging modalities that are frequently used in patient treatment. Although echocardiography is the primary imaging modality for RVOT reconstruction patients, cardiac magnetic resonance is considered the gold standard because of its ability to both assess volume and flow and accurately quantify ventricular size and function. However, the lack of availability and the high costs of these imaging modalities limit their use in preclinical large animal studies.

In this issue of *JACC: Basic to Translational Science*, Rapetto et al[2] use porcine small intestinal submucosa (SIS) grafts with and without seeding of allogeneic mesenchymal stem cells derived from Wharton's jelly (WJ-MSCs) for reconstruction of the MPA in a growing swine model.[2] The beating hearts of 4-week-old piglets in this model were accessed via median sternotomy followed by the excision of an 8-mm segment of the MPA and replacement with the tissue-engineered SIS interposition grafts. All 11 animals that underwent surgery survived, although 2 animals died before the first follow-up, which the investigators attribute to causes unrelated to the graft implantation. Six months after implantation, with significant growth of the animal, WJ-MSC SIS conduits showed significant host cell invasion and protein presence, including newly synthesized elastic fibers, while no calcification was observed. The investigators assessed their WJ-MSC SIS in vivo using imaging techniques commonly used in the clinic, including transthoracic echocardiography and cardiac magnetic resonance with Doppler flow measurements. Cardiac magnetic resonance imaging showed an increase of about 200% in average cross-sectional area of WJ-MSC SIS grafts, which was not observed in the unseeded SIS control material. Overall, the WJ-MSC-seeded SIS conduits showed successful integration into the tissue of the growing piglets after 6 months. Although the replacement grafts lacked valves, the host integration and increase in physical parameters with the growth of the animal are promising advances in the use of tissue-engineering approaches for cardiovascular tissue repair.

*Editorials published in *JACC: Basic to Translational Science* reflect the views of the authors and do not necessarily represent the views of *JACC: Basic to Translational Science* or the American College of Cardiology.

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ISSN 2452-302X https://doi.org/10.1016/j.jacbts.2022.01.006

A significant hurdle for RVOT repairs has been the requirement of the biomaterial to physically grow with the patient. To achieve a graft capable of growing in situ, the biomaterial must be capable of being recellularized and remodeled. Porcine-derived SIS is a native acellular collagen-based extracellular matrix (ECM) that is commonly used as a biomaterial in the reconstruction and repair of a variety of tissues. SIS is among the most studied ECM-based materials for clinical applications, and its use has been approved by the U.S. Food and Drug Administration for many different tissue repair applications. The use of a biologically derived material for tissue repair has many advantages, including maintaining the native mechanical properties, biochemical composition, and the microarchitecture of the tissue, as well as the ability to be remodeled and therefore grow with the recipient. SIS is composed primarily of various collagen types, functional growth factors, proteoglycans, glycosaminoglycans, and, importantly, cell adhesion molecules. The presence of these bioactive molecules allows exogenous and endogenous cellularization of SIS, which is important for host integration. In this study, Rapetto et al[2] demonstrate the use of allogenic WJ-MSCs as an effective cell source to reconstruct the MPA. Wharton's jelly is the mucous proteoglycan-rich matrix surrounding the vessels within the umbilical cord and has been identified as a region with a large, unique cell population of MSCs. Compared with adult-derived MSCs, WJ-MSCs are more proliferative and immunoprivileged.[3] Importantly, the use of WJ-MSCs has the potential for clinical translation to autologous or allogenic implantation, as the cells can easily be isolated and stored. The addition of WJ-MSCs to acellular SIS was shown to be crucial for the neovascularization, growth, and remodeling of the graft, as well as reintegration with the host tissue. Of note, the study demonstrated that the WJ-MSC conduit had an increased concentration of elastin fibers, complete endothelialization, recruitment of smooth muscle cells, and clearance of the donor MSCs in the host body by the study endpoint. By using allogenic WJ-MSCs, the investigators show the advantages of this cell source and its translation potential to the clinic, although more studies are warranted to assess both longer term implantation and the fate of the donor cells within the host body.

Assessment of tissue-engineered reconstructions in growing animal models is a long-standing challenge in vascular graft research. Rapetto et al[2] used transthoracic echocardiography and cardiac magnetic resonance imaging to follow the in vivo progression of their pulmonary artery replacement graft in a growing porcine model. The porcine model of pulmonary artery replacement in a piglet weighing about 20 kg included the excision of 8 mm of native pulmonary artery while the animal was on cardiopulmonary bypass, as previously established.[4] Transthoracic echocardiography and cardiac magnetic resonance imaging enabled assessments of the flow (peak velocities across the MPA and RVOT) and physical graft parameters (laterolateral and superoinferior diameters and cross-sectional areas of the MPA) at both implantation and 6-month follow-up, when the pigs' average weight was about 116 kg. These imaging modalities are standard in clinical assessments but rarely used in preclinical testing. Recent use of angiography and intravascular ultrasound in an ovine model of tissue-engineered vascular graft replacement of the inferior vena cava suggested spontaneous reversal of stenosis due to vessel wall remodeling after 6 months.[5] Yet the invasive nature of angiography and intravascular ultrasound can both affect the remodeling process and limit the number of follow-up assessments. Although transthoracic echocardiography and cardiac magnetic resonance imaging are more expensive, their noninvasive nature facilitates the sequential assessment of tissue-engineered vascular grafts, particularly during the recruitment of endogenous cells to the graft in a growing animal model.

The limitations of the work by Rapetto et al include the single-time point assessment at 6 months, the short length of the implanted graft, the lack of a pulmonary valve, and the limited number of animals. Yet the successful remodeling and growth, as measured by in vivo imaging of the tissue-engineered graft in the MPA within the growing animal, presents a promising direction for RVOT repairs. The investigators describe the assessment of an SIS tissue-engineered graft with and without WJ-MSC preseeding in a growing animal model to demonstrate the remodeling potential of ECM-based vascular grafts.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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JACC: BASIC TO TRANSLATIONAL SCIENCE VOL. 7, NO. 3, 2022
MARCH 2022:220–222

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KEY WORDS growing swine model, right ventricular outflow tract reconstruction, small intestinal submucosa, tissue engineering