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EDITORIAL COMMENT

Large Animal Models for Transcatheter Heart Valve Prosthesis Development

Making Sheep's Eyes at Supra-Annular Banding*

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Transcatheter aortic valve replacement (TAVR) has become the standard of care for symptomatic severe aortic valve stenosis in patients deemed at high or intermediate surgical risk and is currently a valuable option in low-risk patients >65 years of age.[1] Technical development, increased operator experience, and optimal patient selection have led to clinical and safety outcome improvements of TAVR for aortic valve stenosis treatment. To further extend the TAVR indication to more complex cases, several technical challenges persist and are related to both the patient's anatomy and prosthesis design. The largest follow-up data come mostly from 2 widely implanted worldwide prostheses: 1 self-expandable and the other balloon-expandable. Since the first in-human implantation in 2002, an increasing number of companies with transcatheter heart valve development projects have emerged. Validation of new TAVR platforms by the different national and international quality-control agencies relies on strict safety and efficacity criteria. Before in-human implantation, prosthesis platform design adaptation and optimization are performed during bench testing. Even though validation test protocols are prone to variability, durability concerns are verified by accelerated wear testing to 200 million cycles (equivalent to 5 years), according to the International Organization for Standardization Standard 5840-3:2013 guidelines.[2] However, although bench testing targets the mechanical causes of valve failure, biological conditions may prevent adequate prosthesis deployment and expansion, and they certainly affect hemodynamic performances. Similarly, bench testing also lacks prosthesis degeneration related to progressive leaflet calcifications. Overall, bench testing accuracy is undoubtedly limited by the complexity of static and hydrodynamic forces applied to in vivo heart valve prostheses.

As an alternative or in a complementary way to in vitro platforms, research regarding heart valve therapies has targeted large animals for novel device development. Indeed, animal models using ovine, bovine, or porcine hearts closely replicate human anatomy and have already long been used for research purposes in the surgical field. In this issue of *JACC: Basic to Translational Science*, Buszman et al[3] reported the 6-month evaluation of a transcatheter balloon-expandable valve implantation in a novel ovine model. A surgical supra-annular banding was performed in blackface crossbreed sheep at an equidistance between the sinotubular junction and the innominate trunk to achieve a 10% stenosis. After a recovery period of at least 10 days, 20- and 23-mm Myval valves (Meril Life Sciences) were implanted in 11 sheep at the level of the annular banding through the left carotid artery. Buszman et al[3] reported 2 procedure-related deaths, respectively caused by high banding and consequent aortic cross sub-occlusion after valve deployment and severe bleeding secondary to sheath insertion. Two supplementary early deaths occurred between the 30-day and

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6-month follow-up because of prosthetic septic thrombosis and severe prosthesis regurgitation related to fibrous pannus development on the leaflets. At 6 months, there were no cases of severe prosthesis stenosis, regurgitation, or paravalvular regurgitation among the remaining 7 living sheep. Mean transvalvular mean gradient at the end of follow-up was 21.9 ± 11.5 mm Hg, and the gradient remained similar between 30 days and 6 months. At the end of the follow-up, all sheep were sacrificed. Pathologic analysis revealed neointimal leaflet endothelization with thick pannus formation limiting leaflet mobility.

Ovine hearts are considered as the most appropriate large animal models for heart valve research, mainly because of their similar physiologic parameters (hear rate, blood pressure) and aorta size. This novel ovine model using a supra-annular banding overcame anchoring concerns regarding the transcatheter heart valve in the absence of aortic annulus calcifications and might be the target of aortic regurgitation–specific device development. Creating a large animal model is particularly challenging because it requires precise surgical skills and is costly and time-consuming. Other models with prosthesis implantation at the annular level have been reported but required very complex modified aortic annuloplasty and cardiopulmonary bypass and led to high procedural mortality.[4] Supra-annular banding as proposed by Buszman et al[3] avoids challenges related to low coronary ostia in sheep. Moreover, aortic banding is less complex than the modified aortic annuloplasty and requires a short recovery period of 10 days for the animals before valve implantation.

However, a major limitation of the presented model is the stenosis provided by the banding, which led to prosthesis incomplete expansion and alarming hemodynamic consequences. High transvalvular mean gradients were already reported at 30 days. Interestingly, although an important fibrocellular reaction leading to thick pannus formation has been shown, the mean gradient did not change significantly with time. To better characterize the prosthesis degeneration process, this study misses a detailed comparison between animals with high and low transvalvular gradients, namely, with regard to pathologic analysis, including the degree of pannus deposition, excessive neointimal proliferation, and leaflet mobility. Indeed, an elevated postprocedural mean gradient is associated with valve failure, and anatomopathologic investigations are mandatory for further prosthesis durability understanding. With respect to the high transvalvular gradient, Buszman et al[3] performed looser banding while the study progressed. However, they did not report valve migration or embolization attributable to the reduced prosthesis anchoring. Whether greater valve oversizing was necessary would have been important information when considering prosthesis injury related to excessive oversizing.[5] Finally, it is noteworthy to highlight the fact that no thrombus was reported at 6 months despite leaflet hypomobility or immobility secondary to pannus formation.

In conclusion, models using large animals are of particular interest for transcatheter heart valve research because of their similarities with the human anatomy and cardiovascular system. A supra-annular banding sheep model allowed adequate balloon-expandable prosthesis anchoring, but the consequent stenosis led to prosthesis underexpansion with suboptimal hemodynamic performance and durability concerns. Large animal models may help the development of TAVR platforms specifically designed to overcome challenges related to complex anatomies.

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