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EDITORIAL COMMENT

Evaluation of Bioprosthetic Valve Deterioration

Is Tissue Analysis Sufficient?*

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In clinical practice, bioprosthetic aortic valves are the most common type of surgical valve being implanted. Many different xenograft materials have been used in these bioprosthetic valves, including porcine and bovine pericardium or valvular tissue. Tremendous effort has been invested to improve the longevity of these valves, which has been the disadvantage of these valves relative to mechanical valves. The focus has been on developing anticalcification treatments to prevent or slow leaflet calcification and modification of methods of leaflet suspension to improve hemodynamics and minimize mechanical stress. Many different methods of tissue preservation and anticalcification treatments have been applied to prolong the functional longevity of these bioprosthetic aortic valves.[1] Glutaraldehyde fixation results in collagen cross-linking, protecting the tissue from proteolytic degradation when implanted and lowering its antigenicity. Often, additional treatments of the fixed tissues are employed to reduce calcification.

Investigators recently interrogated the Swedish Cardiac Surgery Registry, which prospectively collects preoperative, perioperative, and postoperative data on all patients undergoing cardiac surgery in Sweden, in assessment of outcomes in those patients undergoing aortic valve replacement.[2] Of 16,983 patients who underwent bioprosthetic aortic valve replacement over a 15-year period, they defined which valves performed the best over a mean follow up period of 7.1 years. The PERIMOUNT valve (Edwards Lifesciences) was associated with the lowest incidence of reintervention, all-cause mortality, and heart failure hospitalizations in comparison with the other valves. The PERIMOUNT valve is a bovine pericardial valve that undergoes a process of gluteraldehyde fixation and has been shown to demonstrate no directional difference in leaflet stiffness under ex vivo biaxial testing.[3] This may not be true of glutaraldehyde-treated porcine aortic valves. However, the valves that performed the worst in the Swedish registry were also bovine pericardial valves but that underwent different postfixation treatments.

In this issue of *JACC: Basic to Translational Science*, Sakaue et al[4] evaluated the molecular and cellular mechanisms underlying degeneration of bioprosthetic aortic valves. The study involves histological analysis of explanted human bioprosthetic valves and native valves from autopsies, along with a chronic goat study that involves the long-term evaluation of porcine and bovine-derived bioprosthetic valves.

They observed critical differences in histological features, including collagen contents, localization, and the number of vimentin-positive cells, between the bioprosthetic and native valves. CD34/vimentin double-positive cells were widely located in the interstitium and on the surface of the normal valves but not in the explanted bioprosthetic valves. Accumulation of CD68-positive macrophages was specifically observed in degenerated bioprostheses. To clarify the differences in protein profiling between native valves and bioprosthetic valves, they conducted 2-dimensional gel electrophoresis and

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compared the protein profiles of the tissue lysates from the explanted, normal, and stenotic aortic valves.

Based on clinical observations, they hypothesized that pericardium-derived bioprosthetic valves might structurally allow the infiltration of circulating components, such as fibrinogen and activated macrophages, due to looser collagen density. To test this hypothesis, they implanted glutaraldehyde-treated autologous pericardium in the aortic position in goats and histologically analyzed the temporal changes in valve structures. They replaced the native aortic leaflets in goats with in-body tissue architecture (IBTA) leaflets in the aortic position and analyzed the histological features of explanted IBTA valves at 3 and 12 months after implantation. These studies confirmed that the pericardium-derived bioprosthetic valves easily allow the infiltration of circulating components, and strengthening the collagen fibers of the bioprosthesis effectively prevents structural valve degeneration.

To explore the potential mechanism underlying the calcification of implanted tissue valves, they evaluated porcine and bovine valves for Von Kossa staining in evaluation of calcification and performed proteomics-based protein analyses using 2-dimensional gel electrophoresis. The combination of proteomic analyses and histological investigations demonstrated excessive accumulations of CD68-positive macrophages and their activators, such as fibrinogen, in the interstitial space of implanted bioprosthetic valves, as well as the absence of CD34-positive fibroblastic interstitial cells, which were observed in the native valves. They suggest that the molecular mechanisms of bioprosthetic valve calcification were different from those of native valves, involving a transition of valve interstitial cells into osteoblasts.

These investigators suggests that infiltration of fibrinogen might directly induce the activation of macrophages and their transformation into cathepsin-positive foam cells, followed by their apoptosis via caspase-3 activation and degradation of collagen fibers of an implanted bioprosthesis via induction of proteases production, such as cathepsin and matrix metalloproteinases.[4]

Their implantation of an autologous pericardium-derived bioprosthesis in goats reproduced human pathologies, which involve the infiltration of macrophages and erythrocytes and circulating protein accumulation, suggesting that the degeneration of bioprostheses may be mainly induced by disruptions in pericardial tissues. Their IBTA technology-enabled tissue regeneration with the invasion of endothelial cells, mesenchymal cells, and strengthened collagen fibers resulted in the avoidance of calcification, indicating that these technologies may enable the development of durable bioprostheses. The novelty of the study rests in the long-term goat study, which involves comparison of histological and molecular analysis of normal aortic valves (n = 4) with IBTA valves implanted in 5 goats and pericardial valves implanted in 5 goats. While the number of animals was small some interesting observations were made. Normal valves demonstrated an inverse relationship between CD34 expression and α smooth muscle actin expression due to fibroblast and osteoblast differentiation. They found increased CD68 cells in explanted bioprosthetic valves associated with valve calcifications, and an associated role of fibrin and fibrinogen. Fibrinogen β-chain accumulations were significantly decreased in IBTA valves compared with explanted bioprosthetic valves. They observed increased cell death in cathepsin-positive activated macrophages in association with increased calcium deposition as defined by Von Kossa staining. They suggest that there is an advantage of valvular structure of the IBTA valve over the pericardial-derived valve due to increased collagen density and leaflet strength, which prevents infiltration of inflammatory cells. However, no information is provided regarding the structural differences in the valves or in vivo performance or mobility of the IBTA valves relative to conventional valves. An important component of the evaluation of a prosthetic valve involves assessment of the mechanical performance. This type of functional analysis was absent in the current study, and therefore their conclusions are somewhat speculative.

Imaging of both the structure and function of a bioprosthetic valve is critical in the assessment of valvular dysfunction.[5] Transthoracic echocardiography is the primary clinical modality that is used for evaluation of valvular function. It would have been valuable to perform either serial echocardiography or more invasive hemodynamic evaluation of the functional status of the valvular implants in the goats and to relate their histological observations and molecular analyses with functional performance. Computed tomography can provide additional information about valvular morphology, thrombosis, and valvular calcifications. Targeted molecular imaging probes are also available and could have been used to serially evaluate local inflammation, thrombosis, or microcalcifications in the valves in vivo using either hybrid single-photon emission computed tomography-computed tomography or positron emission tomography-computed tomography imaging. For example, positron emission tomography imaging

with ^{18}F-fluorodeoxyglucose could have been used to detect early valve inflammation; ^{18}F-glycoprotein 1, which targets the glycoprotein IIb/IIIa receptor and is expressed on activated platelets, could identify thrombosis; or alternatively, ^{18}F-sodium fluoride imaging could be employed to evaluate microcalcification. These targeted molecular imaging approaches could define critical early molecular events in vivo that are associated with subsequent valve dysfunction.

The other contributor to valvular degeneration and failure relates to configuration of the valve and mechanical stresses and flow dynamics that are imposed on the tissue leaflets. The potential impact of mechanical forces on valvular leaflet degeneration and calcification would also need to be addressed in future long-term animal or clinical studies. The evaluation of regional mechanical stresses could be determined by computational modeling of the prosthetic valves using high-resolution dynamic computed tomography imaging or magnetic resonance 4-dimensional flow mapping around the aortic valve prosthesis.

In summary, while interesting histological and molecular changes were observed in their analysis of conventional and novel prosthetic aortic valvular constructs, the study is primarily observational and does not definitively define a true functional advantage of the IBTA valves. The clinical study population was small and could be complicated by many confounding clinical conditions like renal failure and dialysis or adjunctive pharmacological therapy present in these patients that could have contributed to the degeneration and calcification of leaflets observed in their histological analyses. The animal studies were also limited in number, and information regarding in vivo valve performance was not performed and is critical for putting their histological and molecular findings in the context of predicting valvular longevity and clinical relevance. Although the results from their preclinical and clinical studies are promising, the true advantage of the IBTA valve would be better defined by additional demonstration of improved mechanical performance and serial evaluation of molecular changes within and around the valve leaflets. This could be accomplished in the animal model and patients using serial high-resolution hybrid multimodality functional and targeted molecular imaging with computational modeling of tissue stress and flow dynamics and quantification of noninvasive markers of tissue inflammation, thrombosis, and microcalcifications.

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