Bacterial infiltration and bioprosthetic valve failure: Emerging diagnostics for emerging therapies

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Increasing life expectancy, the emergence of transcatheter aortic valve replacement (TAVR) therapy in intermediate- and high-risk surgical patients with aortic stenosis, and more frequent use of biologic surgical prostheses has resulted in increasingly large populations facing bioprosthetic structural valve degeneration (SVD). Greater understanding of the risk factors and pathogenic mechanisms underlying SVD is critical to improving the durability of any individual prosthesis. Despite the increasing incidence of both native and bioprosthetic heart valve disease, however, there remains a paucity of knowledge regarding the precise mechanisms contributing to SVD and strategies for disease mitigation.1 In their recent publication, Oberbach and colleagues2 used a novel technique for identification of bacterial infiltration, in contrast to standard histopathologic analysis, in explanted native aortic valves from patients with aortic valvulopathy without preoperative clinical signs or symptoms of infective endocarditis; these patients lacked macro- and microscopic evidence of bacterial infiltration or infection during surgical or histological evaluation by standard protocols. The explanted valves instead were largely characterized by increased mineralization, collagen content, and fibrosis, all of which represent classical endpoints of SVD. The authors suggest the possibility of subclinical or latent valvular bacterial infiltration into valvular tissue, which may facilitate a chronic inflammatory state and ultimately contribute to accelerated SVD.

A comprehensive, standardized definition of SVD has eluded clinicians and researchers for several decades due largely to a combination of heterogeneous clinical presentations, differences in valve materials and fabrication particularly in the context of failed bioprostheses, and an overall lack of understanding regarding the pathophysiology underlying the condition. Most definitions of SVD purposefully exclude prosthetic valve infection and thrombosis as underlying etiologies, as these 2 conditions are more readily considered complications than risk factors.4 The VIVID (Valve in Valve International Data) Investigators recently defined bioprosthetic SVD as, “An acquired intrinsic bioprosthetic valve abnormality defined as deterioration of the leaflets or supporting structures resulting in thickening, calcification, tearing, or disruption of the prosthetic valve materials with eventual associated valve hemodynamic dysfunction, manifested as stenosis or regurgitation,” and thus the isolation of potentially virulent bacteria from culture-negative patients with clinically and histologically uninfected valves is particularly interesting, as it presents a possibility of latent endocarditis as a causative mechanism contributing to BHV failure.5,6 Given the rapidly increasing popularity of TAVR and the resultant increase in bioprosthetic valve use, these findings warrant further consideration of a putative role for latent endocarditis in bioprosthetic heart valve degeneration, specifically with regards to the durability of surgical and, more significantly, transcatheter bioprostheses.
Of note, this is not the first reported account of inflammation or infection in valvular tissue excised from patients without clinical or laboratory evidence of infective endocarditis. In a study from 2004, Lang and colleagues evaluated valvular tissue from patients undergoing valve replacement for noninfective valvulopathy but with previous episodes of successfully treated infective endocarditis. Polymerase chain reaction was used to identify bacterial DNA in these explanted valves up to 18 months following successful antibiotic treatment for endocarditis; however, the inability to culture any bacteria from these samples cast doubt on the presence of any truly viable bacteria. Also in 2004, Shapiro and colleagues described their experience with histologic identification of inflammatory infiltrates in explanted valves from patients undergoing valve replacement, 98.7% of whom lacked any clinical or laboratory evidence of infective endocarditis. Bacterial debris and DNA may persist for weeks or months within sterile vegetations following successful medical treatment of infective endocarditis, and therefore the significance of bacterial DNA isolation from clinically uninfected valves in this study must be considered.

To put these findings into the context of bioprosthetic valve failure, particularly in the case of TAVR, our current understanding of the pathogenesis underlying infective endocarditis is reviewed here. To summarize, infective endocarditis generally requires 2 major predisposing events: insult to native valve endocardium and bacterial inoculation. Aside from more aggressive strains of bacteria that possess virulence factors capable of promoting adherence and direct destruction of intact cardiac endothelial cells such as Staphylococcus aureus, animal models of infective endocarditis have established that endothelial damage must occur before bacterial adherence and proliferation. Mechanisms of endothelial damage include but are not limited to turbulent blood flow, congenital defects, and immunogenic or iatrogenic injury. Such endothelial damage facilitates the formation of sterile platelet–fibrin vegetations resulting in non-bacterial thrombotic endocarditis, which confers susceptibility to secondary infection. Animal models have also confirmed that platelet–fibrin complex formation on damaged endothelium and subsequent establishment of non-bacterial thrombotic endocarditis is an essential component of bacterial adherence and eventual infiltration. Sources of transient or prolonged bacteraemia may be from local or systemic infections. Following bacterial adherence, additional development of vegetations essentially wall off the infection but may also provide protection to proliferating bacteria, thereby complicating antibacterial penetration. Vegetations may calcify over time and may persist even following successful antibiotic-mediated eradication of infection.

Compared with surgical bioprosthetic valves, transcatheter bioprostheses possess several unique characteristics that may contribute to both thrombosis and infective endocarditis, and thus theoretically to accelerated SVD. First, transcatheter valves utilize calcifications on the pre-existing valve for anchoring which, as suggested by Oberbach and colleagues, allows for a potential nidus of infection for the newly implanted valve upon implantation. Calcified vegetations may persist even after apparently successful medical treatment of infective endocarditis, which could harbor bacteria that would not be easily detectable by conventional means. As mentioned previously, endothelial damage is necessary for infective endocarditis pathogenesis. Aside from a lack of functional endothelial cells in biomaterials used for bioprosthetic valve fabrication, transcatheter bioprostheses undergo mechanical damage from crimping, which may serve as a nidus for calcification and, perhaps more significantly, thrombosis. In a recent publication from Zareian and colleagues, an ex vivo–accelerated wear-and-tear system was used to demonstrate that transcatheter valves are more susceptible to both mechanical damage and passive calcification than non-stented valves, most significantly adjacent to the valvular stent struts. As mentioned previously, insult to valvular tissue results in platelet adherence and aggregation, and may predispose to vegetation formation and infection. In fact, the incidence of hypoattenuated leaflet thrombosis (HALT; subclinical valve thrombosis resulting in more than a 50% reduction in the motion of at least one bioprosthetic valve leaflet, which may manifest radiologically on computed tomography imaging as hypoattenuated leaflet thickening) in transcatheter valves is greater than that of surgical valves, with an estimated incidence up to 40% HALT generally resolves following initiation of anticoagulant therapy; however, the functional, clinical consequences of HALT with regard to bioprosthetic valve durability remain to be elucidated, and the precise relationship between HALT and SVD remains contested. As the pathogenesis of infective endocarditis generally requires some element of valvular thrombosis, HALT may constitute a substrate for secondary infection. Despite this theoretical risk factor for postimplantation complications, however, the 5-year incidence of infective endocarditis following TAVR was recently estimated at 5.8%, which is comparable with that of surgical aortic valve replacement. Moreover, the rates of endocarditis between patients treated with TAVR versus surgical valve replacement have been consistently equivalent in high-risk and intermediate surgical risk randomized trials and valve durability at 5 years between TAVR and surgery in high-risk patients appears similar at this early stage. It is therefore somewhat less likely that the DNA detected in the protocol described by Oberbach and colleagues represents the presence of viable bacteria and rather may be related to bacterial debris.

Oberbach and colleagues described several methods employed to avoid bacterial contamination in their study;
however, the possibility remains, especially considering that the researchers were unable to culture the identified bacteria. Whole-genome analysis identified a mix of typical and atypical gram-positive and gram-negative bacteria, including species of Clostridium, Staphylococcus, Enterococcus, Streptococcus, Enterobacter, Acinetobacter, Pseudomonas, Burkholderia, and Cupriavidus, some of which are exceptionally rare causes of infective endocarditis and typically only cause infections in immunocompromised patients. Staphylococcus, Enterococcus, and Streptococcus are common causes of endocarditis and are also constituents of skin flora and/or otherwise commensal; Staphylococcus is not fastidious and thus likely should have been amenable bacterial culture if viable. Furthermore, the consistent yield of polymicrobial results, in conjunction with the discordant results between samples and the overall limited number of samples, calls the specificity of the presented technique into question. As advanced, high-throughput techniques for antimicrobial analyses like whole-genome sequencing, 16S rRNA gene metabarcoding, and fluorescence in situ hybridization continue to increase in both sophistication and implementation, it is essential to consider the clinical implications of novel findings and to determine whether, for example, the presence or infiltration of bacteria in tissue necessarily constitutes pathology.24,25

Long-term TAVR outcomes do not yet exist, and thus their long-term durability is still in question. Consequently, the respective roles of thrombosis and bacterial infiltration in transcatheter bioprosthetic SVD remain incompletely understood, and the findings presented by Oberbach and colleagues warrant further consideration. Presently, there is no universal indication for systemic antibiotics in patients undergoing surgical or percutaneous valve replacement beyond perioperative prophylaxis. The identification of bacterial DNA from native valves creates a hypothetical scenario in which preservation of the native valve apparatus for TAVR procedures may leave infected tissue in the surgical field, thus predisposing to bioprosthetic infective endocarditis. Considering that the methods presented by Oberbach and colleagues require valvular tissue, clinical analysis after TAVR will be challenging, and it would be exceptionally difficult to identify patients who might benefit from prolonged perioperative antibiotics. In the case of surgical valve replacement, however, this novel identification technique may provide a powerful tool to direct postoperative antibiotic therapy, particularly in endocarditis. It is essential to note, however, that the technique reported by Oberbach and colleagues identifies bacterial genomes and not necessarily viable bacteria, and thus the clinical applicability of these findings must be carefully considered. Infective endocarditis remains a relatively uncommon but lethal complication of both surgical and transcatheter valve replacement.26,27

The findings presented by Oberbach and colleagues offer valuable insights into latent infection and chronic valvular inflammation, which may or may not have significant implications for bioprosthetic valve durability and degeneration.

Conflict of Interest Statement

Dr George is a consultant and speaker for Edwards Lifesciences and Medtronic and a consultant for Boston Scientific, Abbott SJM, and W. L. Gore & Associates, Inc. All other authors have nothing to disclose with regard to commercial support.

References

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