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

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Profile (A) and inflow surface (B) of an explanted TAVR bioprosthesis with structural degeneration and endocarditis (reprinted with permission¹).

Central Message

The isolation of bacterial DNA from bioprosthetic heart valves (BHVs) is hypothesis-generating; however, there is inadequate evidence to conclude that bacterial infiltration contributes to BHV failure.

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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.² In their recent publication, Oberbach and colleagues³ 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 and chronic inflammation as a causative mechanism contributing to SVD.^{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 colleagues⁶ 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.⁶ Also in 2004, Shapira and colleagues⁷ 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.⁸

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.^{9,10} 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 bacteremia may be from local or systemic infections. Following bacterial adherence, additional development of vegetations essentially walls off the infection but may also provide protection to proliferating bacteria, thereby complicating antibacterial penetration.^{11,12} 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,¹³ 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 thickening¹⁴) in transcatheter valves is greater than that of surgical valves, with an estimated incidence up to 40%.^{15,16} 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.¹⁷ 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.¹⁸ 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,^{19–22} and valve durability at 5 years between TAVR and surgery in high-risk patients appears similar at this early stage.²³ 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

1. Seeburger J, Weiss G, Borger MA, Mohr FW. Structural valve deterioration of a Corevalve prosthesis 9 months after implantation. *Eur Heart J*. 2013;34:1607.
2. Côté N, Pibarot P, Clavel MA. Incidence, risk factors, clinical impact, and management of bioprosthesis structural valve degeneration. *Curr Opin Cardiol*. 2017;32:123-9.
3. Oberbach A, Friedrich M, Lehmann S, Schlichting N, Kullnick Y, Gräber S, et al; CardiOmics group; Clinical Microbiology group; Bioinformatics group. Bacterial infiltration in structural heart valve disease. *J Thorac Cardiovasc Surg*. February 19, 2019 [Epub ahead of print].
4. Dvir D, Bourguignon T, Otto CM, Hahn RT, Rosenhek R, Webb JG, et al; VIVID (Valve in Valve International Data) Investigators. Standardized definition of structural valve degeneration for surgical and transcatheter bioprosthetic aortic valves. *Circulation*. 2018;137:388-99.
5. Ghazy T, Dittfeld C, Jannasch A, Haase M, Galli R, Plötze K, et al. Subclinical endocarditis might be a hidden trigger of early prosthetic valve calcification: a histological study. *Heart Surg Forum*. 2018;21:E300-4.
6. Lang S, Watkin RW, Lambert PA, Littler WA, Elliott TS. Detection of bacterial DNA in cardiac vegetations by PCR after the completion of antimicrobial treatment for endocarditis. *Clin Microbiol Infect*. 2004;10:579-81.
7. Shapira N, Merin O, Rosenmann E, Dzigivker I, Bitran D, Yinnon AM, et al. Latent infective endocarditis: epidemiology and clinical characteristics of patients with unsuspected endocarditis detected after elective valve replacement. *Ann Thorac Surg*. 2004;78:1623-9.
8. Morris AJ, Drinkovic D, Pottumarthy S, Strickett MG, MacCulloch D, Lambie N, et al. Gram stain, culture, and histopathological examination findings for heart valves removed because of infective endocarditis. *Clin Infect Dis*. 2003;36:697-704.
9. Thiene G, Basso C. Pathology and pathogenesis of infective endocarditis in native heart valves. *Cardiovasc Pathol*. 2006;15:256-63.
10. Galar A, Weil AA, Dudzinski DM, Muñoz P, Siedner MJ. Methicillin-resistant *Staphylococcus aureus* prosthetic valve endocarditis: pathophysiology, epidemiology, clinical presentation, diagnosis, and management. *Clin Microbiol Rev*. 2019;32:e00041-18.
11. Holland TL, Baddour LM, Bayer AS, Hoen B, Miro JM, Fowler VG Jr. Infective endocarditis. *Nat Rev Dis Primers*. 2016;1:16059.
12. Werdan K, Dietz S, Löffler B, Niemann S, Bushnaq H, Silber RE, et al. Mechanisms of infective endocarditis: pathogen-host interaction and risk states. *Nat Rev Cardiol*. 2014;11:35.
13. Zareian R, Tseng JC, Fraser R, Meganck J, Kilduff M, Sarraf M, et al. Effect of stent crimping on calcification of transcatheter aortic valves. *Interact Cardiovasc Thorac Surg*. 2019;29:64-73.
14. Yanagawa B, Mazina A, Bhatt DL, Clavel MA, Côté N, Cheema AN, et al. Subclinical bioprosthetic aortic valve thrombosis: clinical and translational implications. *Curr Opin Cardiol*. 2017;32:137-46.
15. Kanjanathai S, Pirelli L, Nalluri N, Kliger CA. Subclinical leaflet thrombosis following transcatheter aortic valve replacement. *J Interv Cardiol*. 2018;31:640-7.
16. Sachdev S, Bardia N, Nguyen L, Omar B. Bioprosthetic valve thrombosis. *Cardiol Res*. 2018;9:335-42.
17. Rosseel L, De Backer O, Søndergaard L. Clinical valve thrombosis and subclinical leaflet thrombosis following transcatheter aortic valve replacement: is there a

- need for a patient-tailored antithrombotic therapy? *Front Cardiovasc Med*. 2019; 6:44.
18. Butt JH, Ihlemann N, De Backer O, Søndergaard L, Havers-Borgersen E, Gislason GH, et al. Long-term risk of infective endocarditis after transcatheter aortic valve replacement. *J Am Coll Cardiol*. 2019;73: 1646-55.
 19. Mack MJ, Leon MB, Smith CR, Miller DC, Moses JW, Tuzcu EM, et al; PARTNER 1 trial investigators. 5-year outcomes of transcatheter aortic valve replacement or surgical aortic valve replacement for high surgical risk patients with aortic stenosis (PARTNER 1): a randomised controlled trial. *Lancet*. 2015;385:2477-84.
 20. Baron SJ, Arnold SV, Wang K, Magnuson EA, Chinnakondapali K, Makkar R, et al; PARTNER 2 Investigators. Health status benefits of transcatheter vs surgical aortic valve replacement in patients with severe aortic stenosis at intermediate surgical risk: results from the PARTNER 2 randomized clinical trial. *JAMA Cardiol*. 2017;2:837-45.
 21. Reardon MJ, Kleiman NS, Adams DH, Yakubov SJ, Coselli JS, Deeb GM, et al. Outcomes in the Randomized CoreValve US pivotal high risk trial in patients with a society of thoracic surgeons risk score of 7% or less. *JAMA Cardiol*. 2016;1:945-9.
 22. Reardon MJ, Van Mieghem NM, Popma JJ, Kleiman NS, Søndergaard L, Mumtaz M, et al; SURTAVI Investigators. Surgical or transcatheter aortic-valve replacement in intermediate-risk patients. *N Engl J Med*. 2017;376:1321-31.
 23. Daubert MA, Weissman NJ, Hahn RT, Pibarot P, Parvataneni R, Mack MJ, et al. Long-term valve performance of TAVR and SAVR: a report from the PARTNER I trial. *JACC Cardiovasc Imaging*. 2017;10:15-25.
 24. Pollock J, Glendinning L, Wisedchanwet T, Watson M. The madness of microbiome: attempting to find consensus "best practice" for 16S microbiome studies. *Appl Environ Microbiol*. 2018;84:e02627-17.
 25. Frickmann H, Zautner AR, Moter A, Kikhney J, Hagen RM, Stender H, et al. Fluorescence in situ hybridization (FISH) in the microbiological diagnostic routine laboratory: a review. *Crit Rev Microbiol*. 2017;43: 263-93.
 26. Jeng EIH, Hall DJ, Matthews C, Manning EW III, Beaver TM. Infective endocarditis: a review of the past and present, and a look into the future. *Cardiovasc Innov Appl*. 2017;2:365-72.
 27. Regueiro A, Linke A, Latib A, Ihlemann N, Urena M, Walther T, et al. Association between transcatheter aortic valve replacement and subsequent infective endocarditis and in-hospital death. *JAMA*. 2016;316:1083-92.