Commentary: Bacterial infiltration in structural heart valve disease—Do these new insights have profound consequences?

Syed Sadeque, MBBS, FRCS(CTh), and Clifford William Barlow, FRCS(CTh), DPhil

From the Department of Cardiothoracic Surgery, University Hospital Southampton, Southampton, United Kingdom.

Disclosures: Authors have nothing to disclose with regard to commercial support.

Received for publication Feb 18, 2019; accepted for publication Feb 18, 2019; available ahead of print April 5, 2019.

Address for reprints: Clifford William Barlow, FRCS(CTh), DPhil, University Hospital Southampton, Cardiothoracic Surgery, Southampton, United Kingdom (E-mail: cliffbarlow@hotmail.com).

J Thorac Cardiovasc Surg 2020;159:127-8

0022-5223/\$36.00

Crown Copyright © 2019 Published by Elsevier Inc. on behalf of The American Association for Thoracic Surgery

<https://doi.org/10.1016/j.jtcvs.2019.02.074>

There is growing evidence that microbes have a role in noninfectious diseases, such as certain cancers¹ and even coronary artery disease.² In the case of structural heart valve disease (sVHD), classic risks such as hyperlipidemia, diabetes, hypertension, and deranged calcium metabolism are fairly well understood. Various investigators, however, have both detected bacteria in degenerated heart valve tissue³ and have proposed mechanisms whereby bacteria promote tissue calcification⁴ and therefore could have a role in the pathogenesis of sVHD. Nevertheless, the degree of polymicrobial infiltration discerned by these studies is limited, and the detection of bacteria has even been considered by some to represent contamination.⁵

In this edition of the *Journal*, Oberbach and colleagues⁶ aimed to assess which pathogen spectrum is associated with calcified heart valve tissue by using an improved protocol, including microbiologic, immunohistologic, and intricate whole-genome molecular biologic analyses, in heart valve tissue from 25 patients with sVHD. They also sought to determine whether the pathogen spectrum is polymicrobial and comparable with the pathogen spectrum of endocarditis. The study clearly and understandably describes both the complex microbiologic methods, including the use of sonication, and the molecular biologic methods involved. The findings are intriguing, considering no patient had any preoperative evidence of infection. When using standard microbiologic protocols, no bacteria were identified in the heart valves. After using sonication pretreatment, however, bacteria were isolated in 4 patients from the explanted calcified valve tissue. More interestingly, Oberbach and colleagues⁶ identified bacterial DNA infiltration in 13 patients (52%) through metagenome analysis, including both gram-positive and gram-negative bacteria, 36% of which were common endocarditis pathogens.

In the article of Oberbach and colleagues,⁶ the subsequent discussion is considered and concise. Oberbach and colleagues⁶ explore 3 major areas of clinical relevance.

Syed Sadeque, MBBS, FRCS(CTh) (left) and Clifford William Barlow, FRCS(CTh), DPhil (right)

Central Message

Microbiologic and molecular biologic investigations may detect a polymicrobial spectrum of bacteria in apparently uninfected calcified heart valve tissue, including some endocarditis pathogens.

See Article page 116.

The first relates to how subacute bacterial infiltration and subsequent inflammation might trigger or accelerate sVHD. The potential future role of antibiotic treatment in possibly preventing or slowing the process of calcification is most interesting. Second, they postulate how more comprehensive molecular biologic and microbiologic investigations of excised heart valve tissue may allow improved perioperative or postoperative antibiotic recommendations, thereby reducing the risk of postoperative prosthetic valve endocarditis. Third, in the era of rapidly increasing transcatheter aortic valve implantation (TAVI) procedures, where the calcified heart valve remains in situ, Oberbach and colleagues⁶ hypothesize that TAVI may rupture calcified valve tissue and lead to repopulation of intramurally localized bacteria. Their reference,⁷ that patients undergoing TAVI are particularly susceptible to prosthetic endocarditis, has been supported by others⁸ more recently in a meta-analysis that suggested a slightly increased incidence of prosthetic valve endocarditis in TAVI (2.3%) versus surgical aortic valve replacement (1.2%). Oberbach and colleagues⁶ postulate that improved methods of understanding bacterial infiltration in individual patients may serve not only to reduce TAVI valve endocarditis but even to assist in the choice of whether open valve replacement, with removal of the valve tissue, is appropriate versus TAVI in some patients.

There are important limitations to the study. With only 25 patients, the numbers are small. Second, their protocol, however sophisticated, requires valve tissue for analysis. Finally, these preliminary findings cannot yet be extrapolated to the individual patient. Regardless, their recommendations are meaningful. First, they recommend a multicenter collaboration, to better identify the pathogen spectrum with molecular biologic and microbiologic assessments, ultimately for the development of antibiotic strategies. Second, they recommend clinical studies to explore an association between bacterial infiltration of heart valves, as detected by their methods, both with the progression of sVHD and in the context of prosthetic valve endocarditis.

In current practice, the most common indication for valve replacement is sVHD, one of the most feared complications of valve replacement is prosthetic valve endocarditis, and TAVI is one of the most rapidly expanding and highly researched fields of cardiac surgical therapy. The study of Oberbach and colleagues⁶ has potential clinical implications in all 3 of these areas. The insights they present are

by no means complete, but the consequences may, indeed, be profound.

References

1. Meng C, Bai C, Brown TD, Hood LE, Tian Q. Human gut microbiota and gastrointestinal cancer. *Genomics Proteomics Bioinformatics*. 2018;16:33-49.
2. Pedicino D, Giglio AF, Galiffa VA, Cialdella P, Trotta F, Graziani F, et al. Infections, immunity and atherosclerosis: pathogenic mechanisms and unsolved questions. *Int J Cardiol*. 2013;166:572-83.
3. Chalupova M, Skalova A, Hajek T, Geigerova L, Kralova D, Liska P, et al. Bacterial DNA detected on pathologically changed heart valves using 16S rRNA gene amplification. *Folia Microbiol (Praha)*. 2018;63:707-11.
4. Dennis A, Carson. An infectious origin of extraskeletal calcification. *Proc Natl Acad Sci U S A*. 1998;95:7846-7.
5. Giladi M, Szold O, Elami A, Bruckner D, Johnson BL Jr. Microbiological cultures of heart valves and valve tags are not valuable for patients without infective endocarditis who are undergoing valve replacement. *Clin Infect Dis*. 1997;24:884-8.
6. Oberbach A, Friedrich M, Lehmann S, Schlichting N, Kullnick Y, Gräber S, et al. Bacterial infiltration in structural heart valve disease. *J Thorac Cardiovasc Surg*. 2020;159:116-24.e4.
7. 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.
8. Ando T, Ashraf S, Villablanca PA, Telila TA, Takagi H, Grines CL, et al. Meta-analysis comparing the incidence of infective endocarditis following transcatheter aortic valve implantation versus surgical aortic valve replacement. *Am J Cardiol*. 2019;123:827-32.