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OPINION

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Calcification and Thrombosis as Mediators of Bioprosthetic Valve Deterioration

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Calcific aortic valve disease is the most common indication for surgical aortic valve replacement (SAVR) and transcatheter aortic valve replacement (TAVR) of diseased valves worldwide.[1] For years, the mechanisms of bioprosthetic valve deterioration were thought to be due to passive degeneration of the valve leading to structural valve failure. However, in the last decade, studies have emerged which have demonstrated the phenotypic characteristics of bioprosthetic valve calcification, identification of risk factors for valve deterioration including risk of thrombosis, and the possibility of medical therapies to slow the progression of disease. With the advent of TAVR, possible mechanisms of bioprosthetic heart valve deterioration in patients with calcific aortic valve disease have been rapidly emerging in the field. Risk factors, *ex vivo* studies, and retrospective databases have provided clues to the mechanistic causes of bioprosthetic valve deterioration.[2] The role of lipids in the development of calcification and the timing of thrombosis have been the leading discoveries in the field of bioprosthetic valve calcification. This opinion paper will discuss the role of risk factors in the initiation of calcification, and eventual discovery of thrombosis in the progression of valve deterioration, and the potential role of therapeutic agents to slow progression, preserve, and maintain bioprosthetic valve function long term.

Calcification in valvular heart disease

Calcific aortic stenosis is the most common indication for surgical valve replacement in the United States and Europe.[3] Currently, mechanical and bioprosthetic heart valves (SAVR and TAVR) are the two options for valve replacement.[2] The choice of valve depends on patient characteristics and preference at the time of surgery.[4] In the past, bioprosthetic heart valves have been thought to have a decreased risk of thrombosis leading to a decreased need for anticoagulation. Therefore, despite their limited long-term durability,[2] bioprosthetic valves have remained the treatment of choice in patients who are older than 75 years of age or who have contraindications to long-term anticoagulation.[5,6] It is estimated that 20–30% of implanted bioprosthetic heart valves will have some degree of hemodynamic dysfunction at 10 years, but more recent studies indicate improved outcomes for this patient population.[2,7]

For decades, the mechanism of native valvular calcification was thought to be due to a passive degeneration. However, in 2009, the National Heart, Lung, and Blood Institute established the first working group in biology to study heart valves, confirming the established hypothesis from scientists across North America that calcification in the heart valve is an osteogenic process.[3,8–10] Additionally, recent studies have demonstrated risk factors for bioprosthetic valve calcification similar to those of vascular atherosclerosis.[11–14] An inflammatory reaction involving lipid deposition, inflammatory cell infiltration, and bone matrix protein expression in calcifying bioprosthesis have been clearly shown in pathology studies.[15–19] These findings parallel the histopathology[3] found in native calcific aortic valve disease.[8–10,20–25] The role of calcification in the heart-osteocardiology[26] may reveal a parallel mechanism of calcification in the bioprosthesis as more animal models emerge to define the cellular mechanisms.

Cardiovascular risk factors in bioprosthetic valve calcification

Already established in the literature are parallel risk factors for native valve calcification as well as bioprosthetic calcification including hyperlipidemia, smoking, hypertension, and male gender.[3] Recently, a seminal discovery in the field of bioprosthetic valve calcification determined that hemodynamic deterioration of bioprosthetic heart valves is secondary to specific lipid risk factors including elevated plasma Lp-PLA2, PCSK9, and HOMA index.[1] The authors concluded that hemodynamic valve deterioration is associated with adverse outcomes and the presence of leaflet calcification on computed tomography (CT) is strongly associated with hemodynamic valve deterioration (HVD) and subsequent adverse clinical outcomes including re-intervention and death.[1]

Thrombosis in bioprosthetic valve deterioration

In 2015, during an ongoing clinical trial, the discovery of reduced aortic valve leaflet motion was noted on computed

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tomography angiography (CTA) in a patient who had suffered a cerebrovascular event following TAVR. This finding raised concern of the possibility of subclinical leaflet thrombosis in this patient population.[25] The investigators discovered reduced leaflet motion which was noted on CTA in 22 of 55 patients (40%) in the clinical trial and in 17 of 132 patients (13%) in the two registries; the SAVORY registry, NCT02426307; and RESOLVE registry, NCT02318342.

Notably, reduced leaflet motion was detected among two different patient populations with multiple bioprosthesis types, including transcatheter and surgical bioprosthesis. Finally, the investigators discovered in these databases, that therapeutic anticoagulation with warfarin, as compared with dual antiplatelet therapy, was associated with a decreased incidence of reduced leaflet motion (0% and 55%, respectively, $p = 0.01$ in the clinical trial; and 0% and 29%, respectively, $p = 0.04$ in the pooled registries). In patients who were re-evaluated with follow-up CTA, restoration of leaflet motion was noted in all 11 patients who were receiving anticoagulation and in 1 of 10 patients who were not receiving anticoagulation ($p < 0.001$).

Mechanisms in bioprosthetic valve calcification

The mechanisms of bioprosthetic heart valve dysfunction are secondary to complex mechanisms derived from the multiple risk events involved in the degeneration process. Canadian investigators, describe the role of lipids in bioprosthetic heart valves removed from patients for valve degeneration and oxidized lipoproteins and inflammatory cells in the commissural areas of macroscopic calcification and pannus formation.[27] Pannus tissue appears to be formed as the result of a neointimal response in periannular regions of prosthetic valves that consist of periannular cellular migration, myofibroblast and extracellular matrix proliferation with vascular components. This process is similar to the calcification and nodules which develop along the surface of a calcified valve leaflet. It is a chronic active process in which mediators such as TGF-β, VEGF and MMP-2 play roles in both matrix formation, atherosclerosis and future calcification mechanisms.[27]

Large multi-center registries predict risk factors for valve deterioration

The data from the large multi-center registries are critical evidence as to the timing and potential approach towards slowing the development of bioprosthetic valve calcification. A recent analysis of explanted TAVR valves[28] demonstrates calcium in TAVR explants after 4 years, but findings of thrombus at earlier time points. Del Trigo et al.,[29] has published in a large multicenter registry that elucidates key predicators and timing of TAVR valve degeneration. These predicators include: (1) absence of anticoagulation therapy at discharge; (2) valve-in-valve procedure (TAVR in a surgical valve); (3) ≤23 mm transcatheter heart valve; and (4) greater body mass index. Dvir et al., have also proposed a novel classification system for valve degeneration. Hemodynamic valve deterioration (HVD) as identified by Doppler echocardiography occurred in one third of patients and was associated with a 2.2-fold higher adjusted mortality. Diabetes mellitus and renal insufficiency were associated with early HVD, whereas female sex, warfarin use, and stented BPs (versus stentless) were associated with late HVD.[29]

Another high risk patient population are patients with renal failure on hemodialysis who receive anticoagulation, Vitamin K inhibitors may be at risk for accelerated calcification a well-known complication in this patient population in their native aortic valves, as defined by Holden et al.[30] Renal failure may pose a serious risk for bioprosthetic valve calcification and place them at higher risk for anticoagulation. Finally, the role of osteocardiology in the native mitral valve versus the aortic valve is well defined.[31] The native valve mechanisms important foundation

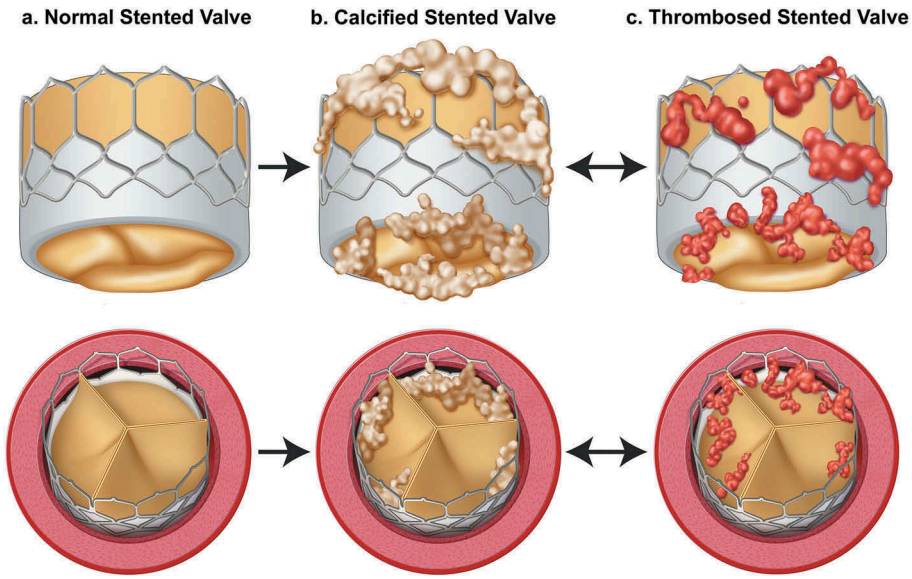

Figure 1. The phenotype of bioprosthetic valve deterioration with the development of calcification secondary to cardiovascular risk factors and subclinical thrombosis as detected by CT imaging.

for studying HVD as defined by anatomic location and hemodynamics for the mitral versus aortic valves and the role of pressure differentials across these two different valves.[26] Further prospective studies are required to determine whether a specific antithrombotic versus aggressive risk factor reduction post-TAVR will help to reduce the risk of VHD.

Conclusion

In conclusion, the role of traditional cardiovascular risk factors in the development of calcification is a critical discovery towards understanding that valve deterioration is not a passive phenomenon. Instead, this calcification process and the discovery of subclinical thrombosis leads to the understanding of a possible dual mechanism of hemodynamic valve deterioration: (1) the development of calcification along the surface of the aortic valve leaflets as defined in parallel mechanisms of osteocardiology;[24] and (2) the development of subclinical valve thrombosis with subsequent hemodynamic valve deterioration (Figure 1).

The timing of the calcification and the thrombus may be due to the timing of endothelialization of the bioprosthetic valve in vivo, various risk factors in patients and or the type of bioprosthetic valve. Future models to test the mechanisms of calcification and thrombus are necessary to understand the cellular mechanisms of this disease process. Future studies are needed to determine the extent of management of cardiovascular risk factors such as prophylactic lipid lowering, aggressive management of diabetes, and smoking cessation in patients with bioprosthetic heart valves. Finally, critical studies are needed to study targeting the timing and or the need for antithrombotic component to prevent subclinical thrombosis in this patient population and risk factor reduction to prevent osteocardiology[24] cellular mechanisms in the bioprosthesis.

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This opinion paper is dedicated to the late Dr Emile Mohler whose dedication to the field of cardiovascular calcification is the foundation for the future understanding of bioprosthetic valve calcification.

Disclosure statement

Dr Rajamannan is the inventor on a US patent for bioprosthetic valve degeneration (U.S. 6,660,260), which is owned by the Mayo Clinic and she does not receive royalties from this intellectual property. Dr Rajamannan is also an inventor on a US patent for bioprosthetic valve degeneration (U.S. 10,058,63), which is owned by ConcieValve LLC, and she does not receive royalties from this intellectual property.

All other authors report no conflicts of interest.

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