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EDITORIAL

Bioprosthetic Valve Dysfunction: A Complex Biological Process

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Life is a perpetual instruction in cause and effect.
—Ralph Waldo Emerson

Valvular heart disease remains a significant economic and societal health issue.[1] Fortunately, the advent of bioprosthetic heart valves (BPHVs) has served as a revolutionary treatment option first with surgical valve replacement and then with the advent of transcatheter valve replacement, which continues to evolve. Despite the general success of BPHVs, valve dysfunction and deterioration remain key problems to address that are often complicated by determining cause and effect in a complex biological system.[2–4]

In this issue of *Structural Heart*, Ramana and colleagues[5] propose thrombus and calcification as the primary mediators in the dysfunction of BPHV. The role of calcium and thrombus causing dysfunction as the authors propose is highly supported by both clinical imaging studies and analysis of explanted valves; thrombus and calcium are noted on dysfunctional and failed BPHVs and in the setting of increased trans-valvular gradients.[2] How the pathways associated with thrombus formation and calcification play out in BPHVs and potentially interact still requires further study; while calcification has been proposed as a platform for thrombus in other settings including the coronary arteries and on mitral annular calcification,[6,7] thrombus prior to calcification seems consistent with many imaging studies of BPHVs. Early valve thrombosis in the absence of calcification is detectable by current clinical imaging and is also a feature of valves studied on explant; thrombus has been incidentally noted on routine post procedural CT imaging within 30 days of SAVR and TAVR, well before calcification is evident on imaging. Calcification is also a histopathological feature of valves implanted for longer durations than those with thrombus alone with recent analysis of explanted TAVR valves showing calcification in TAVR explants after 4 years.[8–13] On a cellular basis, thrombus as a mediator of calcium also seems more likely. Calcification following thrombosis is a well-documented entity and calcific processes can be a long-term outcome associated with inflammation which has been shown at early time-points following BPHV implantation.[11,14]

Overall, calcification and thrombus are undoubtedly a part of BPHV dysfunction but perhaps our focus should not be solely on two entities, but take a wider view of the complex system that leads to valve dysfunction within a diverse patient population. BPHV deterioration is complicated by the fact that SAVR and TAVR valves are not homogeneous in design or tissue composition.[2,15] Moreover, BPHV implanted in different anatomical locations (e.g. mitral versus aortic position) may be subject to very different variables including flow patterns and sheer stresses. By design, implant position, or make, valves may have a varying extent of washout as well as proprietary fixation and pre-implant treatment regimens that can potentially affect leaflet degeneration.[13,16,17] Awareness and transparency regarding these differences is essential in designing the necessary experiments and studies to help advance our understanding of the mechanisms of structural valve degeneration and ultimately to advance the science in a meaningful way so as to prevent its occurrence.

Understanding BPHV degeneration is also complicated by the complex cellular nature of the process. We commend Ramana and colleagues for bringing forth these important questions as they relate to calcification and thrombus as well as highlighting the interplay of dyslipidemic, metabolic, and cardiovascular risk factors. How do we now build on this to fill in the many blanks in the wider view of the complex system that leads to valve dysfunction? There is much to be done to advance our understanding as to how to prevent early valve thrombus. Can we intercede on the pro-thrombotic flow dynamics and binding affinity of fibrinogen for the collagen that composes the majority BPHV leaflets? Although glutaraldehyde fixation of BPHVs is to improve valve durability, can we build on this pre-implant treatment to provide more protection against thrombosis?[16,18,19] In doing so, this may aid in endothelialization of BPHVs and prevent thrombus. To this end, determining the role of dysfunction of endothelial cells (ECs) on BPHVS has potential; peripheral endothelial dysfunction has been associated with BPHV thrombosis, but little is known of the state of ECs that populate implanted valves.[20] EC dysfunction, through factors such as reduced nitric oxide production and generation of reactive oxygen species and inflammatory cytokines would inevitably contribute to valve fibrosis and inflammation.[21,22] Thus, would improving endothelial function, potentially through addressing cardiovascular risk factors as the authors suggest, help? Reduction of inflammation would certainly be helpful. Inflammatory cells are a source of chemokines and cytokines that can be pro-fibrotic. Fibrosis/pannus remains a problem with BPHV and can be an outcome of organizing thrombus. Moreover, inflammatory and fibroblast signalling may drive

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a pro-osteogenic environment and remodelling process prone to the development of dystrophic calcification. This may also relate to the deposition of oxidized low-density lipoprotein and glycosaminoglycans as well as expression of proteinases with the potential to degrade BPHV leaflets.[14,23–25]

Collectively, the underlying composition of BPHV would seem to have potential to serve as a biological scaffold for factors that contribute to SVD. As Ramana and colleagues detail, thrombus and calcification are major components of this SVD process. Clinically, we evaluate the outcomes of these processes through imaging and evaluation of pressures and patient symptoms. On the bench, we have made strides to understand the more granular cellular aspects. Creating links between these two views of BPHV degeneration and understanding more about valve thrombosis and calcification as Ramana and colleagues encourage us to do seems a timely goal (Figure 1).

Disclosure statement

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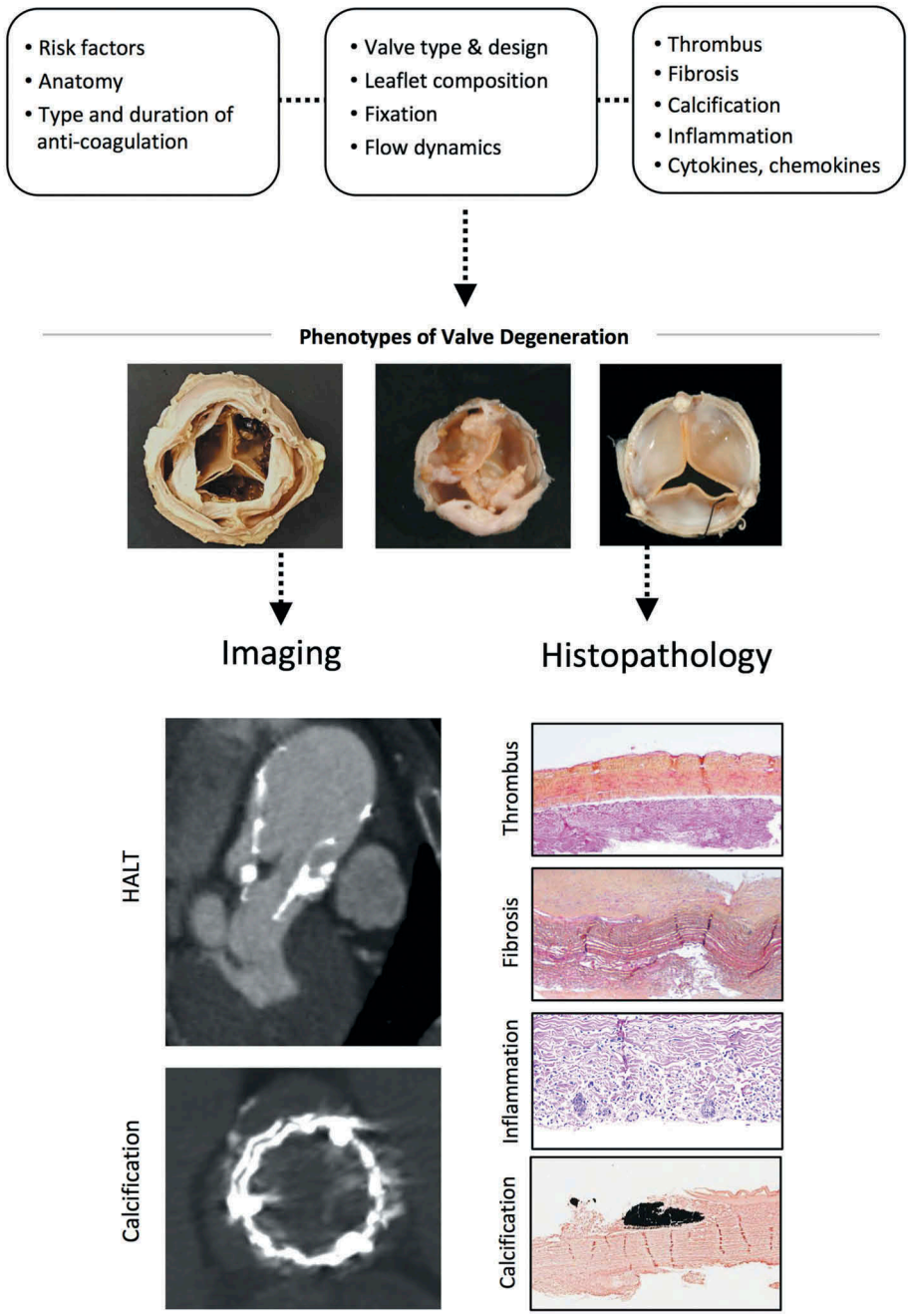

Figure 1. Phenotypes of structural valve degeneration including thrombus, calcification, and fibrosis arise as a result of factors including patient risk factors, valve type, and cellular response. The outcomes of this complex system can be observed with imaging and histopathological analysis.

References

1. Moore M, Chen J, Mallow PJ, Rizzo JA. The direct health-care burden of valvular heart disease: evidence from US national survey data. *Clinicoecon Outcomes Res*. 2016;8:613–627. doi:10.2147/CEOR.S112691.
2. Rodriguez-Gabella T, Voisine P, Puri R, Pibarot P, Rodes-Cabau J. Aortic bioprosthetic valve durability: incidence, mechanisms, predictors, and management of surgical and transcatheter valve degeneration. *J Am Coll Cardiol*. 2017;70(8):1013–1028. doi:10.1016/j.jacc.2017.07.715.
3. Del Trigo M, Munoz-Garcia AJ, Wijeysundera HC, et al. Incidence, timing, and predictors of valve hemodynamic deterioration after transcatheter aortic valve replacement: multicenter registry. *J Am Coll Cardiol*. 2016;67(6):644–655. doi:10.1016/j.jacc.2015.10.097.
4. Salaun E, Mahjoub H, Dahou A, et al. Hemodynamic deterioration of surgically implanted bioprosthetic aortic valves. *J Am Coll Cardiol*. 2018;72(3):241–251. doi:10.1016/j.jacc.2018.04.064.
5. Ramana R, Morreale C, Burke M, Rajamannan N. Calcification and thrombosis as mediators of bioprosthetic valve deterioration. *Struct Heart*. 2018;3:this issue. doi:10.1080/24748706.2018.1562265.
6. Sia YT, Dulay D, Burwash IG, Beauchesne LM, Ascah K, Chan KL. Mobile ventricular thrombus arising from the mitral annulus in patients with dense mitral annular calcification. *Eur J Echocardiogr*. 2010;11(2):198–201. doi:10.1093/ejechocard/jep181.
7. Karanasos A, Ligthart JM, Witberg KT, Regar E. Calcified nodules: an underrated mechanism of coronary thrombosis? *JACC Cardiovasc Imaging*. 2012;5(10):1071–1072. doi:10.1016/j.jcmg.2012.04.010.
8. Leetmaa T, Hansson NC, Leipsic J, et al. Early aortic transcatheter heart valve thrombosis: diagnostic value of contrast-enhanced multidetector computed tomography. *Circ Cardiovasc Interv*. 2015;8(4). doi:10.1161/CIRCINTERVENTIONS.114.001596.
9. Pache G, Blanke P, Zeh W, Jander N. Cusp thrombosis after transcatheter aortic valve replacement detected by computed tomography and echocardiography. *Eur Heart J*. 2013;34(46):3546. doi:10.1093/eurheartj/eht316.
10. Chakravarty T, Sondergaard L, Friedman J, et al. Subclinical leaflet thrombosis in surgical and transcatheter bioprosthetic aortic valves: an observational study. *Lancet*. 2017;389(10087):2383–2392. doi:10.1016/S0140-6736(17)30757-2.
11. Yahagi K, Ladich E, Kutys R, et al. Pathology of balloon-expandable transcatheter aortic valves. *Catheter Cardiovasc Interv*. 2017;90:1048–1057. doi:10.1002/ccd.v90.6.
12. Yahagi K, Torii S, Ladich E, et al. Pathology of self-expanding transcatheter aortic valves: findings from the CoreValve US pivotal trials. *Catheter Cardiovasc Interv*. 2018;91(5):947–955. doi:10.1002/ccd.27314.
13. Dangas GD, Weitz JI, Giustino G, Makkar R, Mehran R. Prosthetic heart valve thrombosis. *J Am Coll Cardiol*. 2016;68(24):2670–2689. doi:10.1016/j.jacc.2016.09.958.
14. Demer LL, Tintut Y. Inflammatory, metabolic, and genetic mechanisms of vascular calcification. *Arterioscler Thromb Vasc Biol*. 2014;34(4):715–723. doi:10.1161/ATVBAHA.113.302070.
15. Vesely I. The evolution of bioprosthetic heart valve design and its impact on durability. *Cardiovasc Pathol*. 2003;12:277–286.
16. Schoen FJ, Levy RJ. Calcification of tissue heart valve substitutes: progress toward understanding and prevention. *Ann Thorac Surg*. 2005;79(3):1072–1080. doi:10.1016/j.athoracsur.2004.06.033.
17. Simionescu DT. Prevention of calcification in bioprosthetic heart valves: challenges and perspectives. *Expert Opin Biol Ther*. 2004;4(12):1971–1985. doi:10.1517/14712598.4.12.1971.
18. Manji RA, Ekser B, Menkis AH, Cooper DK. Bioprosthetic heart valves of the future. *Xenotransplantation*. 2014;21(1):1–10. doi:10.1111/xen.12080.
19. Schoen FJ, Tsao JW, Levy RJ. Calcification of bovine pericardium used in cardiac valve bioprostheses. Implications for the mechanisms of bioprosthetic tissue mineralization. *Am J Pathol*. 1986;123:134–145.
20. Kaya H, Ozkan M, Yildiz M. Relationship between endothelial dysfunction and prosthetic heart valve thrombosis: a preliminary investigation. *Eur Rev Med Pharmacol Sci*. 2013;17:1594–1598.
21. Forstermann U, Sessa WC. Nitric oxide synthases: regulation and function. *Eur Heart J*. 2012;33(7):829–837, 837a–837d. doi:10.1093/eurheartj/ehr304.
22. Li H, Forstermann U. Nitric oxide in the pathogenesis of vascular disease. *J Pathol*. 2000;190(3):244–254. doi:10.1002/(SICI)1096-9896(200002)190:3<244::AID-PATH575>3.0.CO;2-8.
23. Mahmut A, Mahjoub H, Boulanger MC, et al. Lp-PLA2 is associated with structural valve degeneration of bioprostheses. *Eur J Clin Invest*. 2014;44(2):136–145. doi:10.1111/eci.12199.
24. Vattikuti R, Towler DA. Osteogenic regulation of vascular calcification: an early perspective. *Am J Physiol Endocrinol Metab*. 2004;286(5):E686–696. doi:10.1152/ajpendo.00552.2003.
25. Nissinen L, Kahari VM. Matrix metalloproteinases in inflammation. *Biochim Biophys Acta*. 2014;1840(8):2571–2580. doi:10.1016/j.bbagen.2014.03.007.