JACC: CASE REPORTS VOL. 4, NO. 22, 2022

EDITORIAL COMMENT

Bioprosthetic Valve Thrombosis

Not as Simple as it Looks*

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Bioprosthetic valve thrombosis (BPVT) was described soon after the introduction of biological prostheses in clinical practice. However, only over the past decade has systematic evaluation been carried out for this disease.[1-10] Several concepts have clearly emerged: 1) BPVT is not an isolated event, with ≤20% to 30% of patients having evidence of leaflet thrombosis 1 year after implantation;[3,4] 2) BPVT occurs in both surgically implanted and transcatheter valves[3,4] and in all valve positions;[1] and 3) anticoagulant therapy is successful in both preventing BPVT[5,6] and restoring prosthetic function,[7] albeit sometime after a prolonged course.[8] Several important questions remain and are pertinent to the clinical case presented by Al Abri et al[11] in this issue of *JACC: Case Reports*.

WHAT CAUSES BPVT?

The patient presented 3 years after transcatheter aortic valve replacement, which is the most common time of a clinical BPVT diagnosis.[1] It is obvious from the description that the patient had a complex clinical picture, with a history of peripheral vascular disease, prior strokes, chronic lung disease, and advanced kidney disease. None of these were previously identified as predisposing factors for BPVT; indeed, the mechanism responsible for BPVT remains unknown in most patients. The authors discuss potential causes of leaflet thrombosis, highlighting mostly hypotheses driven by the concept that transcatheter valves are more prone to BPVT than are surgically implanted ones. This misconception has been recently corrected by data from both the PARTNER 3[3] and the CoreValve Evolut low-risk[4] clinical trials, both showing that BPVT occurs to a similar extent in surgical and transcatheter valves at 1 year. Given this observation, future studies should focus more on potential common pathways leading to BPVT. The presence of a local or general low-flow state, unexplained cusp immobility immediately after implantation, subclinical prothrombotic state, and immune-mediated mechanisms are potential culprits. Certainly, more research is needed to answer this question.

IS BPVT A BENIGN CONDITION?

Clearly, most patients with evidence of BPVT on 4-dimensional computed tomography (CT) are asymptomatic, and hypoattenuated leaflet thickening (HALT) (the CT hallmark of BPVT) may spontaneously resolve without anticoagulant therapy.[3,4] Whereas the CoreValve Evolut low-risk trial showed no evidence of increased embolic events in patients with subclinical BPVT,[4] the pooled rates of stroke, transient ischemic attack, and thromboembolic complications at 30 days were higher in patients with subclinical BPVT in the PARTNER 3 trial. HALT was more often associated with clinically manifest BPVT, and patients with HALT at both 30 days and 1 year had worse prosthetic hemodynamic profiles. These seemingly conflicting results could be explained by the small number of patients whose conditions were systematically evaluated (<800 patients with available CT data in the 2 trials combined), the low incidence of the study endpoints, and the fact that data are available only for the first year after implantation. A recent meta-analysis of 25 clinical trials and 11,000 patients suggested that subclinical leaflet thrombosis

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The author attests they are in compliance with human studies committees and animal welfare regulations of the author's institution and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

ISSN 2666-0849 https://doi.org/10.1016/j.jaccas.2022.09.003

was associated with a 2.6-fold increase in the risk of stroke and transient ischemic attack at follow-up.[9] Furthermore, as shown in the clinical case, BPVT may have a very aggressive clinical course. In a retrospective matched cohort analysis we also noted that clinically manifest BPVT tends to recur and was associated with accelerated bioprosthetic failure at long-term follow-up.[10] Given these observations, it seems that BPVT is not an entirely benign condition, and it is prudent to treat even subclinical BPVT with a course of anticoagulation in patients who do not have a high risk of bleeding. As clearly demonstrated by Al Abri et al,[11] patients in cardiogenic shock should undergo emergent surgery or, if at prohibitive risk, should be considered for thrombolytic therapy.

WHAT IS THE OPTIMAL THERAPY TO PREVENT BPVT?

There is abundant evidence that anticoagulants prevent BPVT.[5,6,9] but hypothetically, lifelong anticoagulation would negate the major advantage of bioprostheses over mechanical valves. A more challenging question is whether an early course of anticoagulation after implantation would prevent late BPVT by allowing unimpeded endothelialization of the prosthetic valve. Surgical registry data show excess mortality and embolic events in patients undergoing surgical aortic valve replacement who do not take warfarin for the first 3 to 6 months.[12] By contrast, there is no evidence in clinical trials of early benefit of direct anticoagulant therapy versus standard of care for transcatheter valves.[5,6] Whether the use of warfarin rather than of direct anticoagulant therapy early on would be any different, and whether a benefit would be detected only at a longer follow-up time, remains unknown.

BEWARE OF BPVT MIMICKERS

Transcatheter valve endocarditis is a challenging diagnosis, and not infrequently transcatheter aortic valve replacement patients may present with obstructive symptoms before an overt infectious syndrome.[13] We screen for possible infection with blood cultures and inflammatory markers before committing to anticoagulant therapy in all patients with tentative diagnoses of BPVT. Similarly, reduced leaflet motion can exist in isolation and is not necessarily related to valve thrombosis. Indeed, careful echocardiographic inspection of a bioprosthetic valve at the time of implantation can reveal abnormal cusp motion.[14] This phenomenon seems to occur more in larger valve sizes and in patients with low cardiac output. One could hypothesize that immobile cusps may be more prone to thrombosis during follow-up care.

In conclusion, BPVT is a clinical entity still incompletely characterized. To advance our understanding, we must start by increasing the awareness of clinical practitioners. To that end, I would like to congratulate the authors and this journal for bringing this BPVT clinical case to the attention of the medical community.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

The author has reported that he has no relationships relevant to the contents of this paper to disclose.

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REFERENCES

1. Egbe AC, Pislaru SV, Pellikka PA, et al. Bioprosthetic valve thrombosis versus structural failure: Clinical and echocardiographic predictors. *J Am Coll Cardiol*. 2015;66:2285–2294.

2. Makkar RR, Fontana G, Jilaihawi H, et al. Possible subclinical leaflet thrombosis in bioprosthetic aortic valves. *N Engl J Med*. 2015;373:2015–2024.

3. Makkar RR, Blanke P, Leipsic J, et al. Subclinical leaflet thrombosis in transcatheter and surgical bioprosthetic valves: PARTNER 3 cardiac computed tomography substudy. *J Am Coll Cardiol*. 2020;75:3003–3015.

4. Blanke P, Leipsic JA, Popma JJ, et al. Bioprosthetic aortic valve leaflet thickening in the Evolut low risk sub-study. *J Am Coll Cardiol*. 2020;75:2430–2442.

5. De Backer O, Dangas GD, Jilaihawi H, et al. Reduced leaflet motion after transcatheter aortic-valve replacement. *N Engl J Med*. 2020;382:130–139.

6. Collet JP, Van Belle E, Thiele H, et al. Apixaban vs. standard of care after transcatheter aortic valve implantation: The ATLANTIS trial. *Eur Heart J*. 2022;43:2783–2797.

7. Egbe AC, Connolly HM, Pellikka PA, et al. Outcomes of warfarin therapy for bioprosthetic valve thrombosis of surgically implanted valves: A prospective study. *J Am Coll Cardiol Intv*. 2017;10:379–387.

8. Naser JA, Petrescu I, Ionescu F, et al. Gradient changes in bioprosthetic valve thrombosis: Duration of anticoagulation and strategies to improve detection. *Open Heart*. 2021;8:e001608.

9. Bogyi M, Schernthaner RE, Loewe C, et al. Subclinical leaflet thrombosis after transcatheter aortic valve replacement: A meta-analysis. *J Am Coll Cardiol Intv*. 2021;14:2643–2656.

10. Petrescu I, Egbe AC, Ionescu F, et al. Long-term outcomes of anticoagulation for bioprosthetic valve thrombosis. *J Am Coll Cardiol*. 2020;75:857–866.

11. Al Abri Q, El Nihum LI, Hinohara T, et al. Late transcatheter aortic valve thrombosis leading to

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NOVEMBER 16, 2022:1464–1466

cardiogenic shock. *J Am Coll Cardiol Case Rep*. 2022;4(22):1459–1463.

12. Mérie C, Køber L, Skov Olsen P, et al. Association of warfarin therapy duration after bioprosthetic aortic valve replacement with risk of mortality, thromboembolic complications, and bleeding. *JAMA*. 2012;308:2118–2125.

13. Miranda WR, Connolly HM, Baddour LM, et al. Infective endocarditis following transcatheter aortic valve replacement: Diagnostic yield of echocardiography and associated echo-Doppler findings. *Int J Cardiol*. 2018;271:392–395.

14. Naser JA, Crestanello JA, Nkomo VT, et al. Immobile leaflets at time of bioprosthetic valve implantation: A novel risk factor for early bioprosthetic failure. *Heart Lung Circ*. 2022;31:1166–1175.

KEY WORDS aortic valve, echocardiography, thrombosis