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iVIEW

EDITOR'S PAGE

TAVR-Related Complications

Why Did We Forget the Design of a Normal Aortic Valve?

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The aortic valve leaflets are remarkable pieces of biomechanical engineering. They are just 0.15 mm thick and open and shut over 100,000× a day across a pressure difference of 100 mm of mercury. The tissue valves used for transcatheter aortic valve replacement (TAVR) are derived from either bovine or porcine pericardium and exhibit natural opening and closing characteristics and hemodynamic profiles similar to the native heart valve. However, the leaflets have altered mechanical properties due to physical and chemical treatment such as glutaraldehyde cross-linking to prevent immunogenicity. Moreover, TAVR leaflets (~0.25 mm) need to be thinner than surgical bioprosthesis (~0.4 mm) to permit transcatheter delivery. In addition, TAVR stent distortion after implantation results in varying degrees of stress and strain on leaflets (1). The durability of TAVR valves is therefore under strict scrutiny. A report from the PARTNER I (Placement of Aortic Transcatheter Valves) trial in this issue of *iJACC* reports favorable hemodynamic performance of balloon-expandable prosthesis at 5 years, although this data was based on just 16% of the original PARTNER I cohort (2).

Whereas the global uptake of TAVR has been exponential, recent investigations have presented concerns over the potential development of early prosthetic valve leaflet thickening and thrombosis (3-6). Several studies and imaging vignettes presented in this issue of *iJACC* highlight findings that range from subclinical prosthetic valve leaflet immobility, with or without thrombus, detected using either 4-dimensional (4D) computed tomography or transesophageal echocardiography, with further corroborative histopathological evidence from surgical explanted aortic valve or at autopsy that confirm thrombus formation as a true entity (7-9). Although reduction in leaflet mobility is expected to increase the transvalvular gradients, studies in this issue of *iJACC* question the accuracy of monitoring just transvalvular gradients for detecting leaflet thrombosis. Newer observations such as 2D color paucity on echocardiography or hypoattenuated leaflet thickening on computed tomography may have better diagnostic value for detecting early leaflet thrombosis (7,8). The exact mechanism of leaflet thrombosis detected in the absence of increased gradients, however, remains debated. Thrombi may result from abnormal blood flow patterns that initiate thrombus formation by imposing high shear stress on the tissue surface causing platelet activation and flow stagnation that might promote further growth of thrombus.

The quest to image the blood flow pattern across the aortic valve has continued over centuries. Leonardo da Vinci carried out a detailed hemodynamic study of the aortic valve motion (10). He described vortex formation in the sinus of Valsalva and accurately correlated the formation of vortices in perfect harmony with the curved geometry of aortic sinuses as a mechanism for the valve closure. Modern experimental studies have used in vitro models to confirm the mechanism of aortic leaflet closure with formation of vortices (11,12). The vortices in the sinus of Valsalva allow the cusps to open and close while exerting a fluid dynamic control mechanism that positions the cusps away from the wall

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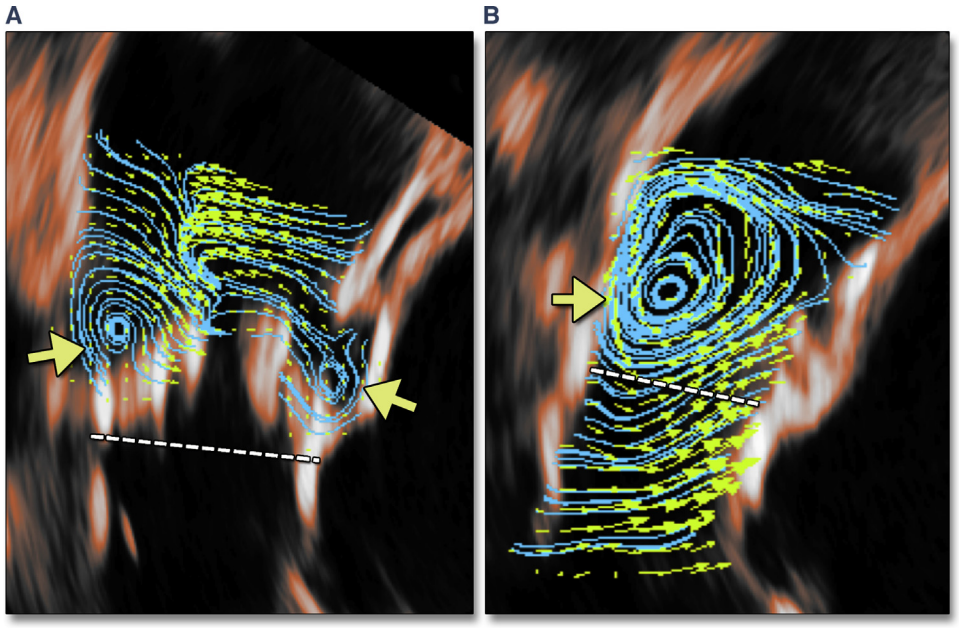
FIGURE 1 Blood Flow Patterns in Sinus of Valsalva



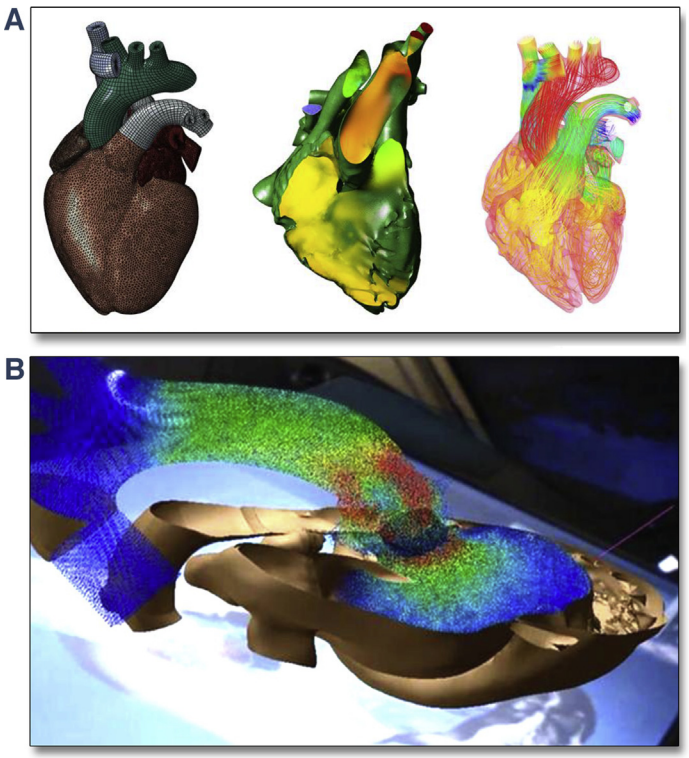
Two-dimensional blood flow patterns have been delineated using vector flow mapping (Hitachi Aloka Medical America Inc., Wallingford, Connecticut). Presence of vortices **(yellow arrow)** are noted on the side of the aortic valve leaflets in the sinus of Valsalva in patient with aortic stenosis **(A)**. In contrast, a single vortex formation is seen in a patient with Sapien 3 valve (Edward Lifesciences Ltd., Irvine, California). The vortex is displaced upward into the ascending aorta above the sinotubular junction. The **dotted line** shows the plane of native aortic valve **(A)** and bioprosthetic aortic leaflet attachment **(B)**.

of the aorta so that the slightest reversed flow in the ascending aorta will close the valve. It has also been demonstrated that the aortic valve remains open for a longer time and closes with rapid closing velocity in the absence of an aortic sinus (11). This increases hemodynamic stress and causes increased bending of the valve. On the other hand, presence of sinuses of Valsalva facilitates the smooth closure of the aortic valve, thereby avoiding the building up of abnormal stress in the leaflet.

In vitro studies and computational modeling have also investigated the flow across prosthetic tissue valve (13). Quite like a normal aortic valve, a jet-like flow emerges from the open leaflets of a bioprosthesis during the ejection phase. The jet is characterized by a vena contracta immediately downstream of the valve followed by an expansion region. The forward flow jet is surrounded by counter-rotating recirculation regions. Although the general flow characteristics of all bioprosthetic valves are the same, differences do exist on a valve-to-valve basis because of subtle differences in valve design, such as the height of the valve, the material (porcine, pericardial, etc.) and stent characteristics (stented vs. stentless valves) (13). Aortic valve bioprosthesis in general do not conserve the flow characteristics seen with a normal aortic valve. Studies have reported asymmetric distribution of flow and wall stress, suggesting that flow characteristics in the ascending aorta after aortic valve replacement are different from native aortic valves. Furthermore, the flow characteristics differ by the type of valve and for different types of aortic valves. For instance, the flow across a balloon-expandable transcatheter valve can vary in relation to the height of implantation. In the event of high implantation, the physical spacing between the leaflet's free edge and sinotubular junction is considerably reduced and that causes a weaker sinus vortex and a lower washout (14). These regions in the sinus with low velocity may create areas of hemodynamic stasis associated with thrombus formation (14,15).

Can we image abnormal flow patterns directly in vivo? Common Doppler-related variables such as velocities and gradients may not be sensitive for detecting regions of hemodynamic stasis across the edges of the valve. Pulsed wave and continuous wave Doppler measurements are based on a priori assumptions that flow through the left ventricular outflow

FIGURE 2 Computation Modeling for Delineating Blood Flow Patterns



The electrical activation, geometry, deformation from a real-life ultrasound exam can be added into the model (The Living Heart Project, www.3ds.com) and blood flow can be determined for understanding the hemodynamic impact (**upper panel**, courtesy of Capvidia). The developed model can subsequently be displayed as a 3-dimensional holographic model **(lower panel)**. Such technology can be useful for testing and designing valves.

region and aorta is symmetric and laminar. However, flow across aortic prosthesis is highly complex with secondary flows and regions of stasis that may not be identified by merely sampling axial flow. Cardiac imaging technologies that can be specifically used for profiling spatial distributions of blood flow are not commonly used in clinical trials and may throw light on understanding the hemodynamic performance of bioprosthetic valves. These techniques include the use of 4D flow using cardiac magnetic resonance (CMR), 2D vector flow mapping using color Doppler, and echocardiographic contrast particle imaging velocimetry.

Time-resolved 3D magnetic resonance phase contrast imaging (4D flow CMR) allows for noninvasive in vivo measurement and visualization of blood flow. Currently, applications have expanded from blood flow quantification, visualization, and its parametric characterization to derivation of hemodynamic and rheological properties, including the calculation of pressure differences. Four-dimensional flow CMR has illustrated the presence of vortices in sinus of Valsalva in vivo. Furthermore, anatomically shaped surgical aortic root prostheses have been shown to exhibit hemodynamics that closely relate to those of age-matched volunteers with a tendency toward more pronounced sinus vortex formation (16). Blood flow pattern across bioprosthesis can also be evaluated using echocardiographic techniques such as echocardiographic contrast particle imaging velocimetry or 2D Doppler vector flow mapping techniques (17). **Figure 1A** shows the demonstration of vortices in sinus of Valsalva using vector flow mapping. In comparison, **Figure 1B** shows flow across balloon-expandable valve in aortic position; only a single vortex across one of the leaflet is identified. The lack of vortices in TAVR may be related to reduction in the space within the sinus due to displaced native leaflet tissue, presence of skirt and stent material, which together might hinder the blood flow circulation. Interestingly, the layer of the thrombotic material in surgically explanted and autopsy specimens of TAVR reported in this issue of *iJACC* can be seen to extend over the leaflets on the aortic side from the site of attachment toward the body of the leaflets; these areas correspond to the location of vortices formed within the sinus of Valsalva. Future studies would aim toward exploring potential association between reduced flow velocities and vorticity after valve implantation with the frequency of thrombus formation and reduced leaflet mobility seen on follow-up.

Aortic valve and root geometry differs from patient to patient. Therefore, with all the knowledge from imaging techniques, the ultimate engineering challenge would be to design a heart valve that would work optimally for a given subject. For this, firstly, we need to incorporate computational modeling to improve prediction of the fluid mechanics profile in the vicinity of heart valves (18). Conceptually, it would appeal to extract subject-specific imaging data from ultrasound and CMR and import them into a computational model that is subsequently used for designing a valve that is patient-specific and can be 3D-printed (**Figure 2**). Secondly, we need to identify the exact coagulation mechanisms that are triggered by hemodynamics in heart valves, thus opening avenues to correct the detrimental effects on platelet activation and coagulation pathways. Presence of high risk for thromboembolism as determined by elevated D-dimer levels in the presence of leaflet thickening on 4D computed tomography and increased transvalvular gradients may be a

reasonable indication to add anticoagulation therapy, with reversal of TAVR gradients after anticoagulation therapy reported in a recent observational study (19). However, more clinical information would be needed to establish the scientific validity of such a strategy. And finally, we need to step back from the concept of artificial valve toward engineering a living tissue that could be 3D printed with a design that resembles the native heart valve.

Nature has evolved over 3.8 million years to perfect a design for the aortic valve. New imaging techniques are allowing us to understand the mechanistic basis of this natural design that is suited for lifetime performance. Just as animals in nature intelligently mimic shapes, colors, and behaviors to protect themselves from predators, at least mimicking the natural design could help evade threats of platelet activation and thrombus formation over a bioprosthetic surface that differs in tissue properties.

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REFERENCES

1. Martin C, Sun W. Comparison of transcatheter aortic valve and surgical bioprosthetic valve durability: a fatigue simulation study. J Biomech 2015;48:3026–34.

2. Daubert MA, Weissman NJ, Hahn RT, et al. Long-term valve performance of TAVR and SAVR: a report from the PARTNER I trial. J Am Coll Cardiol Img 2017;10:15–25.

3. Hansson NC, Grove EL, Andersen HR, et al. Transcatheter aortic valve thrombosis: incidence, predisposing factors, and clinical implications. J Am Coll Cardiol 2016;68:2059–69.

4. Tsunaki T, Yamamoto M, Shimizu K, Suzuki T. Silent massive Valsalva thrombosis identified on contrast-enhanced multislice computed tomography following transcatheter aortic valve replacement. J Am Coll Cardiol Intv 2016;9:2454–5.

5. Makkar RR, Fontana G, Jilaihawi H, et al. Possible subclinical leaflet thrombosis in bioprosthetic aortic valves. N Engl J Med 2015;373:2015–24.

6. Neylon A, Degrell P, Troussier X, et al. Very early thrombosis of Sapien 3 valve. J Am Coll Cardiol Intv 2016;9:e35–6.

7. Yanagisawa R, Hayashida K, Yamada Y, et al. Incidence, predictors, and mid-term outcomes of possible leaflet thrombosis after TAVR. J Am Coll Cardiol Img 2017;10:1–11.

8. Marcoff L, Koulogiannis KP, Aldaia L, et al. Color paucity as a marker of transcatheter valve thrombosis. J Am Coll Cardiol Img 2017;10:78–81.

9. Mangione F, Jatene T, Gonçalves A, et al. Leaflet thrombosis in surgically explanted or post-mortem TAVR valves. J Am Coll Cardiol Img 2017;10:82–5.

10. Robicsek F. Leonardo da Vinci and the sinuses of Valsalva. Ann Thorac Surg 1991;52:328–35.

11. Katayama S, Umetani N, Sugiura S, Hisada T. The sinus of Valsalva relieves abnormal stress on aortic valve leaflets by facilitating smooth closure. J Thorac Cardiovasc Surg 2008;136:1528–35, 1535.e1.

12. Bellhouse BJ, Bellhouse FH. Mechanism of closure of the aortic valve. Nature 1968;217:86–7.

13. Yoganathan AP, Woo YR, Sung HW, Williams FP, Franch RH, Jones M. In vitro hemodynamic characteristics of tissue bioprostheses in the aortic position. J Thorac Cardiovasc Surg 1986;92:198–209.

14. Kumar G, Raghav V, Lerakis S, Yoganathan AP. High transcatheter valve replacement may reduce washout in the aortic sinuses: an in-vitro study. J Heart Valve Dis 2015;24:22–9.

15. Ducci A, Pirisi F, Tzamtzis S, Burriesci G. Transcatheter aortic valves produce unphysiological flows which may contribute to thromboembolic events: an in-vitro study. J Biomech 2016 Nov 3 [E-pub ahead of print].

16. von Knobelsdorff-Brenkenhoff F, Trauzeddel RF, Barker AJ, Gruettner H, Markl M, Schulz-Menger J. Blood flow characteristics in the ascending aorta after aortic valve replacement—a pilot study using 4D-flow MRI. Int J Cardiol 2014;170:426–33.

17. Baillargeon B, Rebelo N, Fox DD, Taylor RL, Kuhl E. The Living Heart Project: a robust and integrative simulator for human heart function. Eur J Mech A Solids 2014;48:38–47.

18. Sengupta PP, Pedrizzetti G, Kilner PJ, et al. Emerging trends in CV flow visualization. J Am Coll Cardiol Img 2012;5:305–16.

19. Ruile P, Jander N, Blanke P, et al. Course of early subclinical leaflet thrombosis after transcatheter aortic valve implantation with or without oral anticoagulation. Clin Res Cardiol 2016 Nov 16 [E-pub ahead of print].