Review Article on Novel Concepts in Cardiopulmonary and Structural Heart Disease

Are the dynamic changes of the aortic root determinant for thrombosis or leaflet degeneration after transcatheter aortic valve replacement?

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Abstract: The role of the aortic root is to convert the accumulated elastic energy during systole into kinetic flow energy during diastole, in order to improve blood distribution in the coronary tree. Therefore, the sinuses of Valsalva of the aortic root are not predisposed to accept any bulky material, especially in case of uncrushed solid calcific agglomerates. This concept underlines the differences between surgical aortic valve replacement, in which decalcification is a main part of the procedure, and transcatheter aortic valve replacement (TAVR). Cyclic changes in shape and size of the aortic root influence blood flow in the Valsalva sinuses. Recent papers have been investigating the dynamic changes of the aortic root and whether those differences might be correlated with clinical effects, and this paper aims to summarize part of this flourishing literature. Post-TAVR aortic root remodeling, dynamic flow and TAVR complications might have a fluidodynamic background, and clinically observed side effects such as thrombosis or leaflet degeneration should be further investigated in basic researches. Also, aortic root changes could impact valve type and size selection, affecting the decision of over-sizing or under-sizing in order to prevent valve embolization or coronary ostia obstruction.

Keywords: Aortic root; dynamic; leaflet thrombosis; leaflet degeneration; structural valve degeneration; transcatheter aortic valve replacement (TAVR)

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Introduction

The idea of a valve implanted by a transcatheter approach was born in 2000 at the Necker University Hospital. It was designed by Bonhoeffer *et al.* (1) to circumvent the problem of reoperation in patients who received pulmonary valvectomy or transannular pulmonary patches and who developed pulmonary insufficiency leading to severe right ventricular failure (2,3). The device was arranged using a vein segment incorporating a native biological valve. It was harvested using a bovine jugular vein that was assembled and sutured into a platinum stent. Subsequently, this unitary tubular structure was smothered in profile and positioned on a balloon catheter. Thus, the new transcatheter device was inserted with a percutaneous approach similarly to coronary catheterization. Finally, the valved stent was deployed and fixed in the position of the native pulmonary valve (1). In subsequent years, this technology was improved and reached the clinical scenario in the treatment of aortic valve disease, with transcatheter aortic valve replacement (TAVR) that is now being evaluated even in the setting of low risk patients (4).

Besides the results of the clinical studies, the percutaneous concept of adding a new functional valve over a calcified diseased valve is strikingly different from the surgical concept of aortic valve replacement. The structures of the aortic root are not removed in percutaneous procedures and seem to have crucial role in early and late outcomes of TAVR. This article intends to summarize the dynamic changes of the aortic root and their role in thrombosis or leaflet degeneration after TAVR.

Dynamic changes of the aortic root

The principles of transcatheter valvular therapy have to deal with the different mechanical stress at the level of the different vascular structures: the pulmonary root, where it was conceived, and the aortic root, where it was applied. The living aortic and pulmonary roots are two sophisticated structure including four major elements: annulus, leaflets, sinuses of Valsalva, and ascending vascular segment. Also, the sinotubular junction of the aortic root functionally guarantees the continence of the valve. The aortic and pulmonary valves used to be thought as passive structures, limited to opening and closure subjected to transvalvular pressure gradients and blood flow through sinuses of Valsalva; however, evidences from pre-clinical and clinical studies have shown that each component of the aortic and pulmonary root is a dynamic structure that works with other components to form a single cohesive functional structure (5).

To date the enormous progress related to the advancement in technology and design probably continues to clash with this primitive concept that transcatheter valvular therapy was initially designed as a prosthesis for use in the pulmonary artery, which has a higher degree of extensibility and distortion compared to the aortic root (1,6). Aortic and pulmonary root respond differently to mechanical stresses due to the pressure load. Biomechanical experiments have shown that the aortic root undergoes various 3-dimensional cyclic changes in systole and diastole; those changes are not present in the native pulmonary artery but appears in case of external reinforcement, resulting in a similar behavior to the aortic root (7-11). The stress shielding due to expansile and contractile mechanical deformations, occurring at the level of the annulus, sinuses of Valsalva, and sinotubular junction in aortic root, plays a pivotal role reducing leaflets stress and promoting laminar flow at each systole. In the aortic root, those functions optimize the coronary flow reserve in both systole and diastole (7,12).

The role of the sinuses of Valsalva is to convert the accumulated elastic energy during systole into kinetic flow energy during diastole, in order to improve blood distribution in the coronary tree. Therefore, the sinuses of Valsalva of the aortic root are not predisposed to accept any bulky material, especially in case of uncrushed solid calcific agglomerates. This delicate action of the sinuses of Valsalva in TAVR is not preserved by the presence of stent [more deformable in nitinol (13,14) *vs.* less deformable in chrome-cobalt (14,15)], with uncrushed calcifications potentially leading to paravalvular leakage. Secondly, refractory calcific blocks may impact on procedure outcomes such as suboptimal deployment, stent deformation and paravalvular leak which may favors the dislodgment of the device with complications involving the coronary arteries (13-15). Therefore, the bioprosthetic constituents of the self- and balloon-expandable TAVR that normally do not require antiplatelet medicaments or anticoagulants may develop thrombosis (4,16,17). The mechanisms by which preoperative aortic root measurements can interfere with devices functionality, especially in the presence of bulky calcific blocks, should be further investigated. Although the role of calcification is more clear, the effects of aortic root dynamic have scarce evidence of data in the literature in the development of thrombosis (14,18).

A recent study from Madukauwa-David *et al.* (19)

characterized the geometry of the aortic root before and after TAVR using a contrast-enhanced 4D-multi-detector-CT evaluation. In each cardiac cycle, comparing systolic with diastolic measurements, aortic annulus diameter decreased by 4%, as well as left coronary artery height (11%), right coronary artery height (14%), and sinotubular junction height (13%). Conversely, LVOT diameter increased by 4%, as well as ascending aorta diameter (7%), and Valsalva sinus diameter (14%). Annulus diameter, sinotubular junction diameter, and LVOT ellipticity were not different before or after TAVR procedure. However, TAVR resulted in several geometric modifications: LVOT diameter increased (15%), left coronary artery height decreased (22%), right coronary artery height increased (7.3%), ascending aorta diameter decreased (7.9%), mean sinus diameter decreased (4%), and sinotubular junction height decreased (9%). Annular ellipticity decreased by 53%, while ascending aorta ellipticity and sinotubular junction ellipticity increased (54% and 56%). Geometric changes occurring after TAVR suggest a radial bulging and axial shortening of the aortic root during diastole due to retrograde pressure. Also, the lowest point of the native aortic cusps may be displaced by TAVR prosthesis, resulting in differences in measured distances. In line with these results (20), aortic annulus deformation during the cardiac cycle was not influenced by the amount of aortic calcification, which play a role only in the incidence of paravalvular leaks (20,21). However, some reports lead to different conclusion (22), leaving an open debate. The systolic effective diameter represents an appropriate parameter for sizing the aortic annulus and ECG-gated CT is the gold standard technique (20). Aortic root dimensions change after TAVR and systolic-diastolic variations should also be taken into account in the design of future valves.

Mechanisms of thrombosis

The flow direction and the geometric axis of the expanded valve are not adequately investigated and compared with the axis of the LVOT, anulus and Valsalva sinus. Ribeiro *et al.* warned that a significant mismatch between TAVR prosthesis and Valsalva sinus diameter should alert for malposition and migration of TAVR that may ultimately lead to obstruction of coronary ostia (23,24). The relationship between different anatomical components in which the valve is placed and the mechanical stresses on leaflet and stent, as well as their fluid-dynamic effects, warrant an adequate investigation (14,18,23-25).

Considering the mechanisms of thrombosis, literature rarely focuses on specific pre-operative measures of LVOT, annulus, Valsalva sinus and sinotubular junction in the setting of valve thrombosis (23,24). However, a recent report found that TAVR thrombosis at level of coronary ostia might be related to asymmetric measurements of left ventricular outflow tract (LVOT), annulus and sinotubular junction, and thrombosis might be a consequence of the "Bernoulli effect" (25). This phenomenon was potentiated by the 26 mm CoreValve implanted. In fact, in this case there was a clear mismatch between LVOT, that measured 20 mm, and the valve that sized 26 mm, favoring a funnel condition in which fluid dynamic is compromised. The finding of thrombus in inner zone of valve, corresponding to the ventricular side, and a circumferential involvement of the entire valve was due to the significant disturbance of kinematic viscosity features (fluid dynamic component). We observed at CT scan the same unfavorable situation with the creation of a second funnel in the upper part of the implant where mismatch is determined by the lower dimensions of the STJ, measuring 20×18 mm compared to the valve measuring 26 mm. In this way, the valve was between two hinge zones. This condition of precarious geometry and hemodynamics could not prevent thrombus formation despite the patient had dual antiplatelet treatment and the size of TAVR was large (25).

This hypothesis is in line with the flow dynamic aspect of TAVR compared to surgical aortic valve replacement, as a longer blood residence time was observed on the TAVR leaflets compared with the surgical leaflets (26). Most importantly, in tele-diastole the areas of high blood resistance time (greater than 1.2 seconds) were four times larger in TAVR than in surgical model, with a similar distribution among the leaflet compared with a predominance for the non-coronary leaflet in survival valves. Geometric boundaries by the leaflet and the frame increase the likelihood of blood stasis in TAVR leaflet, thus contributing to thrombosis (26,27).

Sirois *et al.* (28) found that slight ellipticity does not translate into hydrodynamic poor performance, reinforcing previous studies (29). However, large ellipticity increases the transvalvular pressure gradients (28). TAVR hemodynamic is more negatively influenced by an under-expanded prosthesis than by elliptical deployment. Despite not being high enough to cause hemolysis, this can cause platelet activation in under-expanded valves that might contribute to TAVR thrombosis. These data support the finding of Hatoum *et al.* (30) with peak maximal Reynold shear stress values that exceeds platelet activation limit, although another study found conflicting results (31).

Leaflet stress and leaflet degeneration

The innovative use of Finite Element Analysis (FEA) can help research in cardiovascular science and may shed light on structural changes in biological systems, such as describing the role of stress condition on the dynamic of aortic root after TAVR or elucidating the mechanism to avoid the degeneration of leaflets due to higher stress condition (32,33). The geometry of stented porcine and bovine pericardium xenografts have been studied and measurements of biomechanical stress have revealed interesting findings regarding leaflet stresses (4,13-18). Eccentric distortion of a TAVR stent might have detrimental effects on the dynamic of leaflet deformation, inducing bending of the leaflet and increased commissural strain, and thus enhancing leaflet structural failure, compared with a circular deployed valve (29,34,35).

One study of Xuan *et al.* evaluated the features of TAVR in the aortic root and performed measurements of different component: the leaflets, stent, and sutures (36). Maximum leaflet stress was registered at commissural tips, where leaflets connected to the stent, with a maximum stress on leaflet of 1.31 MPa. Principal stresses for the stent were 188.91 MPa and located at stent tips. Authors concluded that due to this mechanism, these regions are prone to leaflet degeneration, although the causal relationship is not conclusive.

Another report (37), using a quasi-static simulation at 120 mmHg, analyzed leaflet stresses in 22 mm-diameter self-expandable bovine and porcine valves. The authors investigated the calculated geometry of leaflets and changes in thickness to deduce the stress exerted. The results showed that the bovine and porcine pericardial leaflets had maximum principal stress of 915.62 and 1,565.80 kPa, respectively, in the completely loaded position (36,37). The measurement of leaflet stresses revealed higher deformation and peak stresses along the leaflet-stent attachment along the commissures.

Recently, using FEA research combined with 3D CT reconstruction, predictive models can be developed on the potential risk of thrombosis and structural degeneration after TAVR implantation. For example, several reports have provided various explanations for the biomechanical performance of second generation of SAPIEN™ or Corevalve TAVR, and evaluated the relationship between the geometry of the aortic root and the location of the self- and balloon-expandable valves (13-15,18,25). The results of these studies reinforce the idea that a bulky calcific agglomerates in aortic valve and root are associated with a higher risk of coronary obstruction, reduced leaflet motion and paravalvular leakage (13-15,18,25).

However, leaflet degeneration might also be related to intrinsic limitations of the materials currently used for TAVR, as structural degeneration is not a mere consequence of leaflet stress. In the search for alternative leaflet material, novel polymeric TAVR device (e.g., Polynova) are being shown to outperform clinically used tissue valves in terms of thrombogenicity and hemodynamic, although those results should be further validated (38). Also, variations in the thickness of leaflet should be balanced between pros and cons. An increasing leaflet thickness results in increased regurgitation, by means of configuration deformation. On the other hand, a thinner leaflets is able to adapt more to deformation but has a higher risk of deterioration (39).

Future directions

Aortic root rupture may be predicted with the determination of higher level of stress located in particularly zone of aortic wall (13-15) and Morganti and co-workers studied the correlations among stresses in the aortic root and leaflet asymmetry to estimate the rate of root rupture (13,15). Wang *et al.* (40) retrospectively revised some cases, finding that a large calcified spot on the left coronary sinus was pushed by the stent, resulting in aortic rupture. However, these studies were limited by the scarce number of patients and lack of precise measurement concerning the influences of asymmetry on TAVR leaflet stresses. Prevention of aortic rupture remains a significant field of research and would provide interesting results in the next years.

Patient-specific computer simulation is a promising technique to optimize TAVR design through FEA and fluid dynamics simulation (41,42). In a recent analysis of Rocatello *et al.* (43), two geometrical issues of the frame were investigated: the diameter of the ventricular inflow and the height of the first row of cells. Comparing optimal (simulated) patients with implanted devices, the optimal device had a three-fold lower predicted contact pressure and minimal paravalvular aortic regurgitation. Larger diameters and higher cells favor a higher anchoring of the TAVR device within the aortic root with a better apposition to the aortic root. Those results were also replicated by Bianchi *et al.* (44) and Mao *et al.* (45), with a 50% reduction in postoperative occurrence of paravalvular leak and a 70% reduction in the regurgitant volume. Those features were also considered in the setting of bicuspid aortic valve (46), generally characterized by the presence of an asymmetrical structure that might even complicate the dynamics of the aortic root. Paravalvular regurgitation and conduction abnormalities might be reduced by tailored TAVR sizing and positioning (46,47). Patient-specific modelling would help in the evaluation of device performance before patient implantation and might translate to improved devices and outcomes (48).

Conclusions

Cyclic changes in shape and size of the aortic root influence blood flow in the Valsalva sinuses. This might indicate a connection between post-TAVR aortic root remodeling, dynamic flow and TAVR complications such as thrombosis or leaflet degeneration and should be adequately explored in future researches. Also, aortic root changes could impact valve type and size selection, affecting the decision of over- or under-sizing in order to prevent valve embolization or coronary ostia obstruction.

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