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Paravalvular leakage of transcatheter aortic valve replacements depending on aortic annulus calcification

Abstract: Paravalvular leakage (PVL) has a crucial impact on clinical outcomes of transcatheter aortic valve replacements (TAVR), especially the mortality increases dramatically with high-grade PVL. Furthermore, the calcification of the aortic annulus has a decisive influence on the PVL of TAVR. Therefore, we developed a technical model of a calcified aortic annulus and used it for the investigation of PVL in steady-state back-flow conditions.

We investigated an Evolut PRO (Medtronic, Minneapolis, MN, USA), implanted the TAVR at different depths in the aortic annulus model ranging between 0 mm and -6 mm and characterized PVL in steady-state retrograde flow from 0 mmHg up to a maximum achievable pressure. The used test bench and detailed test method was described in previous studies. The aortic annulus model exhibits three elevations symmetrically distributed around the circumference. Depending on the degree of calcification the elevations reached 1 mm to 3 mm into the lumen.

For the Evolut PRO bioprosthesis, a decreasing PVL was measured with increasing implantation depth. At an implantation depth of 0 mm (inflow of TAVR and annulus model at same height) maximum PVL was measured. Minimum PVL was measured at a height of -6 mm. Furthermore, even a small calcification of 1 mm led to a large increase in PVL. This trend continued with increasing height of the calcification. The maximum regurgitation of $(2,025.21 \pm 12.47)$ ml ($n = 3$ measurements) was measured at a pressure of 6 mmHg in the annulus model with 3 mm calcification.

A test method to quantify PVL depending on annular calcification was successfully developed. Additionally, the influence of implantation depth on PVL was characterized. Due to the technical operating principle of the test bench, only a limited increase in pressure was possible when large PVL occurred. In this respect, the test bench must be optimized in the future.

Keywords: transcatheter aortic valve implantation, paravalvular leakage, paravalvular regurgitation

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1 Introduction

For the *in vitro* investigation of the regurgitation of TAVR in detail, a consideration under steady-state flow conditions is helpful to characterize the resulting problems, especially due to PVL, in more detail. In addition to the relationship between increased PVL and mortality, other clinical complications exist that can be more accurately analyzed in a steady-state setting other than under pulsatile flow conditions.

Clinical studies shows that particularly the implantation height of a TAVP in the aortic annulus has a crucial influence on regurgitation on the one hand and on the rate of new pacemaker implantations on the other hand [1-3].

Because of the local proximity of the aortic annulus to the AV node, disturbances may occur within the conduction system of the heart itself, due to the radial force exerted by a TAVR on the aorta. If a TAVR in the aortic annulus with high radial force and an abluminal attached skirt presses on the AV node as well as on the distally attached His-bundle, which is responsible for the forwarding of action potentials in the myocardium, the increased pressure leads to a left bundle branch block, leading to an indication for the implantation of a permanent pacemaker [1].

The degree of stimulus conduction disorder can be influenced by the interventional cardiologist's implantation technique.

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The higher the TAVR is implanted in the aortic annulus, the lower the pressure on the AV node is resulting in a lower risk for a left bundle branch block. At the same time, however, a high implantation is clinically associated with increased PVL [2, 4, 5]. Furthermore, high implantation of TAVR in the aortic annulus may result in an occlusion of the coronary arteries by the TAVR-stent or valve leaflets [6, 7].

For this reason, we investigated the influence of the implantation depth of the TAVR in the aortic annulus on PVL depending on aortic annulus calcification in steady-state retrograde flow.

2 Materials and Methods

In order to take the clinical findings into account during the development of novel TAVR, we used a method to characterize PVL at different implantation depths of the TAVR in the aortic annulus as a function of increasing pressure on the closed TAVR (blood pressure) in steady-state retrograde flow. For the investigations we used a test method and test bench developed in earlier studies [8].

The test bench represents a hydrodynamic circuit model for measuring the leakage volume under steady-state flow conditions. Via a pump with integrated thermostat (ED-2, Julabo, Seelbach, Germany), the fluid is pumped into a reservoir from which a supply line to the test chamber and a bypass lead off. The pressure in the test chamber, i.e. on the TAVR to be tested, is thereby regulated by changing the volume flow by means of two flow resistors. From the reservoir tank, the fluid flows through a flow sensor (LFS-008, LFS-08, Levitronix, Zurich, Switzerland) into the test chamber.

Since the calcification of the aortic annulus has a crucial influence on the PVL of TAVR, we developed technical models of a calcified aortic annulus and used them for the investigation of PVL under steady-state flow conditions. The annulus models exhibit three elevations symmetrically distributed around the circumference. Depending on the degree of calcification, elevations from 1 mm to 3 mm reached into the lumen, see Figure 1.

Figure 1: Silicone models of a calcified aortic annulus with three elevations ranging from 1 mm to 3 mm into the lumen, symmetrical distributed around the circumference.

The annulus models were casted from silicone with a shore hardness of 30A (Sylgard 184 Silicone Elastomer, Dow Corning, Midland, MI, USA) according to ISO 5840-3:2021 [9].

To investigate the influence of implantation depth on regurgitation/PVL of the TAVR, an Evolut PRO bioprosthesis (29 mm, Medtronic, Minneapolis, MN, USA), see Figure 2, was implanted at different depths in the silicone models of the aortic annulus with a target implantation diameter of 24 mm. For the characterization the implantation depth D was varied in the range from 0 mm to - 6 mm in steps of 2 mm.

The regurgitation that occurred as a function of the implantation depth was measured in a blood pressure range of 0 – 200 mmHg in 10 mmHg increments. Distilled water with a temperature of 37°C, a density of 993.32 kg/m³ and a viscosity of 0.705 mPa s was used as test fluid.

Figure 2: Evolut PRO bioprosthesis (A), detailed view of the pericardium outer skirt for prevention of PVL of the Evolut PRO bioprosthesis (B) and top view of the implanted and deformed valve into a technical calcification model with 3 mm calcification (C).

3 Results and Discussion

For the Evolut PRO bioprosthesis, a decreasing regurgitation was measured with increasing implantation depth. At an implantation depth of 0 mm (inflow of TAVR and annulus model at same height) the PVL was greatest and at a height of -6 mm it was lowest.

Furthermore, even a small calcification of 1 mm led to a large increase in regurgitation/PVL. This trend continued with increasing height of the calcification (1 mm to 3 mm). Due to the technical operating principle of the test bench, only a limited increase in pressure was possible, depending on the amount of retrograde volume flow. In this respect, the test bench must be optimized for future experiments.

The maximum PVL of $2,025.21 \pm 12.47$ ml ($n = 3$) was measured at a pressure of 6 mmHg in the aortic annulus model with 3 mm calcification, see Figure 3.

Sherif et al. developed criteria for predicting regurgitation *in vivo* in relation to implantation depth for a previous version of the Evolut PRO bioprosthesis, the CoreValve (Medtronic, Minneapolis, MN, USA). In these studies, minimal PVL correlated with an implantation depth of - 10 mm

for an implantation diameter of 23 mm [10]. However, since the aortic annulus is difficult to identify *in vivo*, this implantation height was measured starting from the valvular plane (non-coronary cusp/left coronary cusp) and is therefore not directly comparable to the implantation height defined in this work.

Figure 3: Regurgitation of an Evolut PRO bioprosthesis at different implantation depths $-6 \text{ mm} \leq D \leq 0 \text{ mm}$ in different technical calcification models with elevations between 0 mm to 3 mm as a function of increasing pressure at steady-state flow on the closed TAVR; mean curves $\pm$ standard deviations from $n = 3$ measurements and polynomial trend lines are shown.

Based on the anatomy, the aortic annulus and the left ventricular outflow tract (LVOT) are lying in a range of approximately -10 mm to -20 mm below the valvular plane [11]. Thus, it can be assumed that the implantation depth according to Sherif et al. corresponds approximately to the implantation depth of -2 mm to -4 mm in this work.

To be able to seal sufficiently to the aortic annulus, the TAVR must be positioned with as large an area as possible in the region of the annulus as well as the LVOT, otherwise the TAVR would not endothelialize and free ends of the inflow-side could lead to an increased risk of thrombosis [12, 13].

In an *in vitro* study with an Evolut R TAVR, the direct predecessor of the Evolut PRO bioprosthesis, Azadani et al. demonstrated the dependence of the hydrodynamic properties on the implantation depth of the prosthesis in a surgically implantable heart valve prosthesis (valve-in-valve procedure) [14]. These dynamic experiments in a hydrodynamic circulation model showed that the lowest regurgitation was measured at an implantation depth between -6 mm and -8 mm. The implantation height according to Azadani et al. was measured starting from the scaffold of the surgically implantable prosthetic heart valve and is therefore not directly comparable with regard to the absolute value.

However, since additional radiographs of the valve-in-valve configuration were obtained, it can be concluded that the implantation depth according to Azadani et al. corresponds approximately to an implantation height of -4 mm in the present work.

Accordingly, these dynamic tests also show good comparability to the steady-state tests in this work.

The presented method is suitable for the investigation of PVL under steady-state flow conditions. The obtained results can be compared with clinical results as well as *in vitro* investigations of other groups and provide comparable correlations between the implantation depth of a TAVR and its PVL.

Depending on the TAVR type, an optimal implantation depth has to be identified individually. No general criteria for the implantation depth of a TAVR can be identified, since especially the regurgitation of the TAVR is determined by its individual design.

4 Conclusion

It was shown that the geometry of the implantation environment has a crucial influence on the PVL of TAVR. Therefore, the pathophysiology of the aortic annulus should also be considered for *in vitro* testing methods.

The developed technical calcification models in combination with the developed test method for the hydrodynamic characterization of TAVR under steady-state conditions are suitable for such investigations and provide a comprehensive *in vitro* characterization of the hydrodynamics of TAVR.

Future studies of the radial force of a TAVR, possibly even along the prosthesis height in different areas, could identify additional design parameters for the relationship between implantation height, regurgitation, and conduction system disturbance.

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References

- [1] Dumonteil N, Meredith IT, Blackman DJ, et al. Insights into the need for permanent pacemaker following implantation of the repositionable LOTUS valve for transcatheter aortic valve replacement in 250 patients: results from the REPRISE II trial with extended cohort. *EuroIntervention : journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology* 2017; 13: 796–803.

- [2] Tang GHL, Kaneko T. Assessing Implant Depth Using Aortography in Transcatheter Aortic Valve Replacement: What You See May Not Be What You Get. *JACC. Cardiovascular interventions* 2018; 11: 129–132.
- [3] Ortak J, D'Ancona G, Ince H, et al. Transcatheter aortic valve implantation with a mechanically expandable prosthesis: a learning experience for permanent pacemaker implantation rate reduction. *European journal of medical research* 2018; 23: 14
- [4] van Gils L, Wöhrle J, Hildick-Smith D, et al. Importance of Contrast Aortography With Lotus Transcatheter Aortic Valve Replacement: A Post Hoc Analysis From the RESPOND Post-Market Study. *JACC. Cardiovascular interventions* 2018; 11: 119–128.
- [5] Miyazaki Y, Abdelghani M, Boer ES de, et al. A novel synchronized diastolic injection method to reduce contrast volume during aortography for aortic regurgitation assessment: In vitro experiment of a transcatheter heart valve model. *EuroIntervention : journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology* 2017; 13: 1288–1295.
- [6] Vavuranakis M, Kariori M, Scott L, et al. Impact of "high" implantation on functionality of self-expandable bioprosthesis during the short- and long-term outcome of patients who undergo transcatheter aortic valve implantation: Is high implantation beneficial? *Cardiovascular therapeutics* 2018; 36: e12330.
- [7] Søndergaard L. Transcatheter aortic valve implantation: don't forget the coronary arteries! *Euro-Intervention : journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology* 2018; 14: 147–149.
- [8] Kaule S, Siewert S, Pfensig S, et al., Aortic regurgitation after transcatheter aortic valve replacement, *Current Directions in Biomedical Engineering*, vol. 4, no. 1, 2018, pp. 195-198. <https://doi.org/10.1515/cdbme-2018-0048>.
- [9] ISO 5840-3:2021, Cardiovascular implants — Cardiac valve prostheses, Part 3: Heart valve substitutes implanted by transcatheter techniques.
- [10] Sherif MA, Abdel-Wahab M, Stöcker B, et al. Anatomic and procedural predictors of paravalvular aortic regurgitation after implantation of the Medtronic CoreValve bioprosthesis. *Journal of the American College of Cardiology* 2010; 56: 1623–1629.
- [11] Buchner S, Debl K. Left Ventricular Outflow Tract. In: Saremi F, editor. *Cardiac CT and MR for adult congenital heart disease*. New York: Springer; 2014: 173–198.
- [12] Stiehm M, Wüstenhagen C, Siewert S et al., Impact of strut dimensions and vessel caliber on thrombosis risk of bioresorbable scaffolds using hemodynamic metrics", *Biomedical Engineering / Biomedizinische Technik*, vol. 64, no. 3, 2019, pp. 251-262. <https://doi.org/10.1515/bmt-2017-0101>
- [13] Serruys P, Piazza N, Cribier A, Webb J, Laborde J, de Jaegere P. Transcatheter Aortic Valve Implantation: Tips and Tricks to Avoid Failure. In: Ying-Fu C, editor. *Aortic Valve: InTech*; 2011.
- [14] Azadani AN, Reardon M, Simonato M, et al. Effect of transcatheter aortic valve size and position on valve-in-valve hemodynamics: An in vitro study. *The Journal of thoracic and cardiovascular surgery* 2017; 153: 1303-1315.e1.