Sebastian Kaule*, Michael Stiehm, Stefan Siewert, Alper Öner, Klaus-Peter Schmitz, and Finja Borowski

Comparison of steady-state and transient flow measurements for the characterization of paravalvular leakage of transcatheter-aortic valve prostheses

https://doi.org/10.1515/cdbme-2023-1126

Abstract: Severe aortic valve stenosis has been successfully treated with minimally invasive transcatheter aortic valve replacement (TAVR) for more than 20 years. The therapy is applied to an increasing cohort of patients. Nevertheless, paravalvular leakage (PVL) remains one of the main complications after TAVR implantation reducing safety and efficacy of the implant.

To improve TAVR performance, virtual patient cohorts can be used to generate a significant amount of data with biologically varying conditions comparable to clinically real-world data. For this purpose, *in silico* models need to be established which are used to evaluate the possible occurrence of PVL. When establishing *in silico* models, the question between simplification to reduce computational effort and still valid information from the model must always be clarified.

Thus, we investigated the comparability between steady-state and transient PVL measurements as an input parameter for simulations in virtual cohorts. A clinically established TAVR was implanted into different annulus models and tested in a steady-state back-flow test bench and in a pulse duplicator system. As a result, leakage rates were compared and assumptions for the *in silico* models were derived.

Although the trend of PVL is comparable in steady-state and transient conditions, absolute values differ making it difficult to extract generalized assumptions. Especially when PVL increased, e.g. in a larger implantation diameter or in an imperfect annulus, the variation also increased up to 50% of the measured value.

Keywords: TAVR, hydrodynamic characterization, pulsatile flow testing, fluid-dynamic simulation, validation

1 Introduction

Therapy of severe aortic valve stenosis with minimally invasive transcatheter aortic valve replacement (TAVR) has been used for more than 20 years and is now an established procedure applied to an increasing cohort of patients [1]. Improved generations of TAVR and the increasing experience of cardiologists led to a reduction of occurring complications in recent years [2]. Nevertheless, one of the still present complications after TAVR implantation is paravalvular leakage (PVL), which reduces the safety and efficacy of TAVR [3].

The main goal of TAVR-development is the improvement of safety and efficacy of the implant and the reduction of complications such as PVL.

One approach to evaluate complications like PVL in the development process of novel TAVR is the use of virtual patient cohorts to generate a significant amount of data with biologically varying conditions comparable to clinically real-world data. For this purpose, *in silico* models need to be established which are used to evaluate the possible occurrence of PVL [4].

When establishing virtual cohorts, a reasonable compromise between necessary information and highest possible degree of simplification must be found in order to obtain valid information but to keep computational effort as low as possible.

In the context of PVL assessment, the question rises whether leakage flow during the diastolic phase of the cardiac cycle can be estimated as a steady-state *in silico* model or whether a transient consideration of occurring leakage rates is

***Corresponding author: Sebastian Kaule:** Institute for Implant Technology and Biomaterials e.V., Friedrich-Barnewitz-Str. 4, 18119 Rostock, Germany,
e-mail: sebastian.kaule@iib-ev.de
Alper Öner, Klaus-Peter Schmitz, Stefan Siewert, Michael Stiehm, Finja Borowksi: Institute for ImplantTechnology and Biomaterials e.V., Friedrich-Barnewitz-Str. 4, 18119 Rostock, Germany
Alper Oener, Department of Cardiology, University Medical Centre, Rostock, Germany

necessary. While a transient representation of the cardiac cycle is more accurate, especially during the diastolic phase pressure and flow do not change particularly. A steady-state approach would significantly reduce the computational effort.

To investigate the comparability between steady-state and transient leakage rate, we used different *in vitro* studies of a clinically established TAVR. The TAVR was implanted into a circular annulus model and into an annulus model with imperfections representing a calcified aortic root, and tested in a steady-state back-flow test bench and in pulse duplicator system. As a result, leakage rates were compared and assumptions for the *in silico* models were derived.

2 Materials and methods

2.1 Test sample and annulus model

The comparison of steady-state back-flow measurements and pulsatile flow testing was conducted with an Evolut PRO bioprosthesis (29 mm, Medtronic, Minneapolis, MN, USA). The TAVR was implanted into different aortic annulus models, already described in [5].

The annulus model was either round without any imperfections or had three symmetrically distributed elevations of 1 mm ranging into the lumen. The models were casted from silicone (Sylgard 184 Silicone Elastomer, Dow Corning, Midland, MI, USA shore hardness 30A) according to ISO 5840-3:2021 [6]. The implantation diameter was 23 mm and 26 mm (round) or 24 mm (with imperfections), see Fig. 1. Implantation was performed according to instructions for use (IFU) of the Evolut PRO.

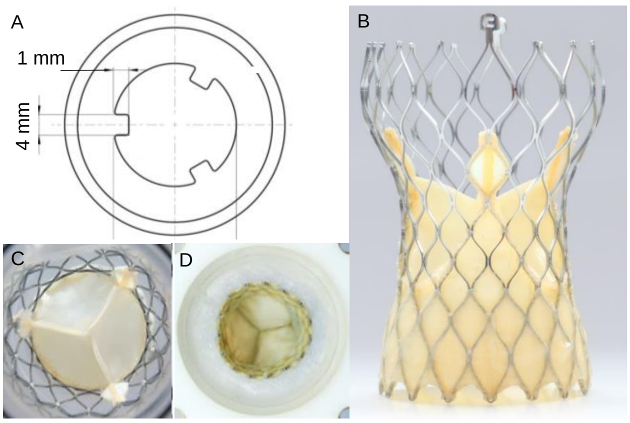

Figure 1: Silicone annulus model of a calcified aortic annulus with three elevations protruding into the lumen for 1 mm, symmetrically distributed around the circumference (A), Evolut PRO bioprosthesis used for the experiments (B); valve implanted into the annulus models (C-view on the closed valve, D-view on the inflow side of the valve).

2.2 Steady-state back-flow measurements

To characterize PVL in different aortic annulus models as a function of increasing pressure on the closed TAVR (blood pressure represented by the pressure difference of aortic and ventricular pressure) in steady-state retrograde flow, we used a test method and test bench developed in earlier studies [7].

In short, the test bench represents a hydrodynamic circuit model for measuring the leakage volume in steady-state flow conditions. Within the test-bench, the fluid is pumped into a reservoir and further into the test chamber. The pressure in the test chamber as a pressure difference across the closed TAVR is controlled by means of a variable flow resistor.

The occurring regurgitation as a function of increased pressure in the TAVR was measured in a blood pressure range of 0 – 110 mmHg in 10 mmHg increments. Distilled water with a temperature of 37°C± 2°C, a density of 993.32 kg/m³ and a viscosity of 0.705 mPa s was used as test fluid.

2.3 Pulsatile flow testing

For the pulsatile flow testing we used a commercial pulse duplicator system (ViVitro Labs, Inc., Victoria, BC, Canada). Testing was conducted at a heart rate of 70 bpm, a systolic duration of 35% ± 3% and a cardiac output of 5 l/min. The test fluid was 0.9% saline and the test temperature was 37 °C± 2°C.

According to ISO 5840-3:2021 $n = 10$ cycles were recorded for the measurement. To characterize opening and closing behavior of the Evolut PRO, high-speed videos were performed using a frame rate of 500 fps (CR600x2, Optronis, Kehl, Germany). For the comparison, leakage was measured at different mean aortic pressures (100 mmHg, 120 mmHg, 160 mmHg) to generate increasing pressure on the closed valve resulting in different mean diastolic pressure differences Δp corresponding to the pressure on the closed valve in the steady-state back-flow measurements. Fig. 2 shows exemplary pressure and flow curves derived from a pulse duplicator measurement.

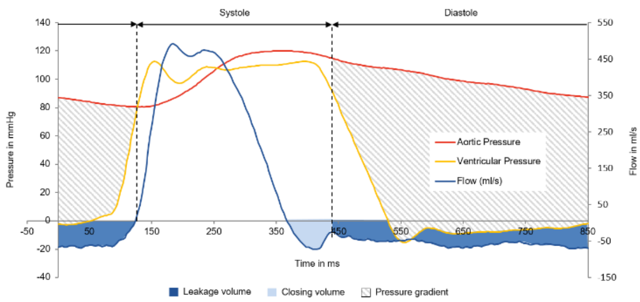

Figure 2: Illustration of pressure and flow curves derived from transient measurements in a pulse duplicator system; blue area underneath the flow curve represents the leakage of the TAVR during the diastolic phase of the cycle.

3 Results and Discussion

An increasing pressure on the closed Evolut PRO TAVR in different annuls models during the steady flow measurements resulted in an increased flow, see Fig. 3. Additionally, the results show an increased leakage in the larger implantation diameter of 26 mm.

The maximum leakage of 28.86 ml/s ± 0.20 ml/s was measured in the annulus model with 1 mm elevated imperfections. Furthermore, the variation of the leakage flow in the imperfect annulus model was higher compared to the round annulus model, resulting in slightly higher standard deviations.

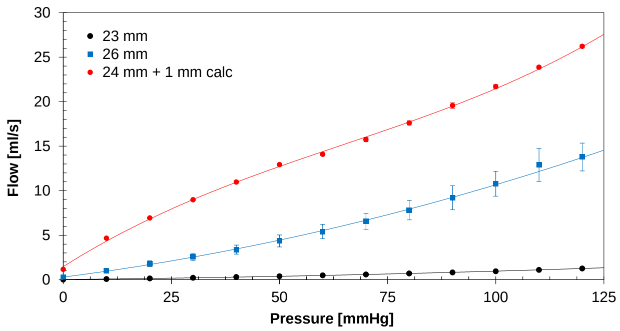

Figure 3: Steady-state back-flow measurements of a TAVR implanted into different annulus models, curves show mean values and standard deviations of $n = 3$ measurements.

Fig. 4 shows flow and pressure curves of the transient measurements in the pulse duplicator system at different mean aortic pressures. These mean aortic pressures of 100 mmHg, 120 mmHg and 160 mmHg resulted in different mean diastolic pressure differences Δp which furthermore correspond to the pressure on the closed valve in the steady-state back-flow measurements.

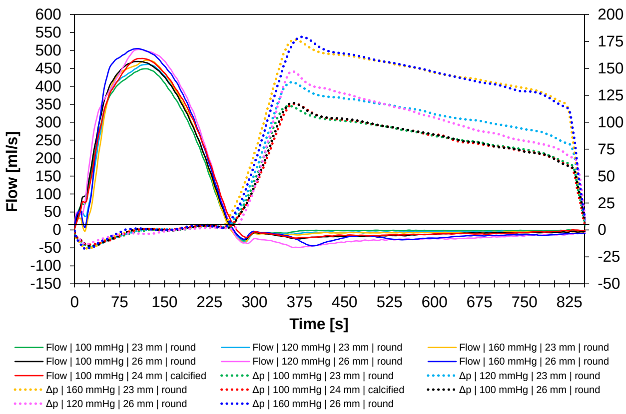

Figure 4: Pressure and flow curves of transient measurement of a TAVR implanted into different annulus models, curves show mean values of $n = 10$ measured cycles.

In general, transient flow measurements show the same trends compared with the steady-state measurements. The leakage rate increased with increasing implantation diameter and was highest in the annulus model with 1 mm imperfections protruding into the lumen.

Due to technical limitations of the pulse duplicator system not the whole pressure range measured in the steady-state experiments was investigated. Nevertheless, Tab. 1 summarizes the different measurements. It must be stated that although the trend of PVL is comparable in steady-state and in pulsatile conditions, absolute values differ. Particularly in a larger implantation diameter transient PVL flow is increased compared to PVL flow in steady state. Additionally, the variation within the $n = 10$ transient measurement cycles is high resulting in standard deviations of about 50% of the measured value.

Table 1: Comparison of steady state and transient flow measurements for the characterization of PVL of TAVR; measurements show mean values and standard deviations of $n = 3$ (steady) and $n = 10$ (transient) measurements in different annulus diameter.

	Flow [ml/s]											
	23 mm				26 mm				24 mm + 1 mm calc			
***Δp* Dia**	**steady**		**transient**		**steady**		**transient**		**steady**		**transient**	
[mmHg]	mean	SD	mean	SD	mean	SD	mean	SD	mean	SD	mean	SD
60	0,49	0,04	-	-	5,41	0,80	12,60	5,60	14,08	0,13	11,6	5,3
70	0,59	0,05	2,30	2,20	6,55	0,88	-	-	15,74	0,23	-	-
80	0,70	0,08	5,39	2,10	7,81	1,09	26,10	10,10	17,61	0,23	-	-
100	0,95	0,10	-	-	10,78	1,39	19,10	5,30	21,70	0,22	-	-
110	1,10	0,10	7,80	2,40	12,89	1,85	-	-	23,87	0,15	-	-

As a result, the simplification of PVL measurements from transient to steady-state conditions was not fully demonstrated. Although the trend of PVL is comparable in steady-state and transient conditions, absolute values differ, making it difficult to extract generalized assumptions. The compromise between simplification and computational effort must be investigated carefully to obtain valid information.

Author Statement

Research funding: This project has received funding from the European Union's Horizon 2020 research and innovation program under grant agreement No 101017578. The EU is not responsible for any use that may be made of the results shown in this publication or any information contained therein.
Conflict of interest: Authors state no conflict of interest.

References

[1] Sektorenübergreifende Versorgungsanalyse zur Kardiologie, Herzchirurgie und Kinderherzmedizin in Deutschland, Deutscher Herzbericht 2021, Deutsche Herzstiftung e.V., Frankfurt am Main, 09/2022.

[2] Scatter Y; Prakash P; Almas T, et al., Cardiovascular Outcomes of Older versus Newer Generation Transcatheter Aortic Valve Replacement Recipients: A Systematic Review & Meta-analysis. Current Problems in Cardiology. 101467.

[3] Bhushan S; Huang X, Li Y; et al., Paravalvular leak after transcatheter aortic valve implantation its incidence, diagnosis, clinical implications, prevention, management, and future perspectives: a review article. Current Problems in Cardiology. 47(10) 2022, 100957.

[4] Bianchi M; Marom G; Ghosh R; et al., Patient-specific simulation of transcatheter aortic valve replacement: impact of deployment options on paravalvular leakage. Biomechanics and Modeling in Mechanobiology. 2019 18, pp. 435-451.

[5] Kaule S, Oener A, Grabow N, Schmitz K-P, Siewert S, Stiehm Mel. "Paravalvular leakage of transcatheter aortic valve replacements depending on aortic annulus calcification" Current Directions in Biomedical Engineering, vol. 7, no. 2, 2021, pp. 609-612. https://doi.org/10.1515/cdbme-2021-2155

[6] ISO 5840-3:2021, Cardiovascular implants — Cardiac valve prostheses, Part 3: Heart valve substitutes implanted by transcatheter techniques.

[7] 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.