Sebastian Kaule*, Vera Lange, Robert Ott, Finja Borowski, Eric Bohne, Jan Oldenburg, Klaus-Peter Schmitz, Stefan Siewert, and Michael Stiehm

Pulsatile flow testing of heart valve prostheses *in vitro*

https://doi.org/10.1515/cdbme-2022-1174

Abstract: For the approval-relevant testing to prove the safety and effectiveness of newly developed heart valve prostheses, a new version of the ISO 5840-family was published in 2021. One of the major *in vitro* tests in this standard is the investigation of the hydrodynamic performance of heart valve prostheses by means of a hydrodynamic cardiovascular test bench (pulse duplicator system).

A new requirement of the ISO 5840:2021 is the validation of the pulse duplicator system used, by comparing the results obtained with the test bench with a round-robin study published by the ISO Cardiac Valves Working Group in 2019.

In this work, two pulse duplicator systems at our institute (2x BDC Laboratories, Wheat Ridge, CO, USA) were evaluated according to the new ISO standard. The results obtained were compared intra-institutionally between the different test benches and internationally with the round-robin study to validate the developed test methodology regarding the normative requirements.

For the evaluation and to assess the repeatability, one measurement series with three measurements was performed for the intra-institutional comparison, a second measurement series with eight measurements with different parameters was conducted for the inter-laboratory comparison. The test parameters were selected according to the round-robin study. A mechanical prosthetic heart valve (St. Jude Medical Master Series, diameter: 25 mm) was used as test valve. The values for the effective orifice area (EOA) and the regurgitant fraction (RF) were assessed, and the pressure and flow waveforms were analysed.

In general, the developed and applied test methods lead to reliable results according to ISO 5840:2021 and compared to the international standard in different test laboratories. Both BDC pulse duplicators have achieved reliable results in terms of repeatability in the intra-institutional and inter-laboratory comparison. The test benches are therefore suitable for the hydrodynamic performance testing of heart valve prostheses according to ISO 5840:2021.

During the experiments slightly higher EOA and RF were measured by means of one pulse duplicator system although both test benches were identical. High-speed cinematography recordings identified an asymmetric closing kinematic of the test valve. Thus, leading to a prolonged closing time and closing volume of the valve. This in turn, led to an increased EOA, due to the calculation according to the ISO standard. In conclusion, even small deviations in the closing kinematics of the test valve can lead to large differences in the results. Thus, it is considered to attach great importance to the leaflet kinematics when comparing or validating test benches or test methods.

Keywords: TAVI, hydrodynamic characterization, pulsatile flow testing

1 Introduction

The first surgical heart valve prosthesis was successfully implanted in 1952. 50 years later, in 2002, the therapeutic spectrum was significantly expanded by the first-in-man implantation of a transcatheter aortic valve prosthesis (TAVP) [1]. During the last ten years, the number of transcatheter aortic valve implantation (TAVI) has steadily increased, while the number of surgical aortic valve implantations has decreased [2]. The clinical share of TAVI in the field of aortic valve implantations has more than doubled, from 30.5% in 2011 to 66.1% in 2020 [2].

Due to the increased demand, new implants are continuously being developed, which need to be characterized in terms of both safety and effectiveness. The guidelines for the testing of aortic valve prostheses are defined in a normative standard, which has been re-evaluated and re-published in an updated version in 2021 – the ISO 5840:2021 normative family [3-5]. The ISO standard and the ISO Cardiac Valves Working Group recommend pulsatile flow testing as the

***Corresponding author: Sebastian Kaule**, Institute for Implant Technology and Biomaterials e.V., Friedrich-Barnewitz-Str. 4, 18119 Rostock, Germany, e-mail: sebastian.kaule@uni-rostock.de
Vera Lange, Robert Ott, Finja Borowski, Eric Bohne, Jan Oldenburg, Klaus-Peter Schmitz, Stefan Siewert, Michael Stiehm: Institute for ImplantTechnology and Biomaterials e.V., Friedrich-Barnewitz-Str. 4, 18119 Rostock, Germany

main benchmark for the characterization of the hydrodynamic performance of prosthetic heart valves. During pulsatile flow testing, clinically relevant flow conditions were simulated using test benches modelling flow conditions in the left heart, so called pulse duplicator systems.

The *in vitro* tests are performed using various parameters, including heart rate (HR), cardiac output (CO), (relative) systolic duration (SD), and pressure conditions, e.g. main aortic pressure (MAP). The ISO 5840:2021 defines specific conditions to be used for pulsatile flow testing. Particularly, testing at nominal/standard conditions (HR: 70 BPM, SD: 35%, CO: 5.0 l/min, MAP: 100 mmHg) is linked to minimum performance criteria for prosthetic heart valves. These criteria are obligatory for all heart valve prostheses aiming for an approval.

Furthermore, the ISO standard prescribes a validation of the test bench and test method used for pulsatile flow testing by comparing both to results of a round-robin study published by the ISO Cardiac Valve Working Group [6]. 13 parties took part in this round-robin study to examine the current state-of-the-art in measuring prosthetic heart valves pulsatile flow performance. The study included three testing service providers, eight heart valve manufacturers, one academic test laboratory, and the US Food and Drug Administration.

Within the last years, we established different testing methods for heart valve prostheses, mostly in the field of pulsatile flow testing [7-11]. Therefore, the aim of this work was to evaluate and validate the used test benches and developed test methods according to the newly published ISO standard. The two different test benches were compared intra-institutionally and internationally with the inter-laboratory round-robin study [6].

2 Materials and Methods

For the intra-institutional comparison two pulse duplicator systems (2x BDC Laboratories, Wheat Ridge, CO, USA) were used. A series of three identical measurements in standard conditions according to ISO 5840:2021-2 was performed on every test bench: HR: 70 BPM, CO: 5 l/min ± 0.5 l/min, SD: 35%, MAP: 100 mmHg ± 2 mmHg [4]. For each measurement $n = 10$ cycles were recorded leading to a total cycle number of $n = 30$ for every measurement in one test bench.

A mechanical prosthetic heart valve (St. Jude Medical Master Series, diameter: 25 mm) was used as test valve. The effective orifice area (EOA) and the regurgitant fraction (RF) were used as hydrodynamic performance criteria for the evaluation according to ISO 5840-1:2021 [3].

According to the ISO standard, the EOA is calculated by means of the Gorlin equation (1) [3]. Wherein q_{vrms} represents the root mean square forward flow during the positive differential pressure period, Δp the mean pressure difference (measured during the positive differential pressure period) and ρ the density of the test fluid.

$$EOA = \frac{q_{vrms}}{51.6 \cdot \sqrt{\frac{\Delta p}{\rho}}} \qquad (1)$$

The valve q_{vrms} furthermore is defined by equation 2.

$$q_{vrms} = \sqrt{\frac{\int_{t_1}^{t_2} q_v(t)^2 dt}{t_2 - t_1}} \qquad (2)$$

Wherein $q_v(t)$ represents the instantaneous flow at time (t), t_1 the time at the start of the positive differential pressure period and t_2 the time at the end of the positive differential pressure period. In fact, the EOA strongly depends on the positive pressure period and therefore from the opening and closing kinematics of the valve.

In addition, the RF is defined as fluid volume [% of forward flow volume] that flows through the heart valve prosthesis in the reverse direction during one cycle, see equation 3.

$$RF = CV + LV \qquad (3)$$

Wherein CV represents the part of the regurgitant volume associated with the dynamics of the valve closure and LV the part associated with leakage during the closed phase of a valve in one cycle. LV furthermore is the sum of the transvalvular and the paravalvular leakage volume [3].

For the international validation of the test method used at our institute a series of eight measurements was performed with the St. Jude Medical Master Series mechanical heart valve prosthesis (25 mm) in both pulse duplicator systems. The test parameters were based on the round-robin study and presented in Table 1 [6]. A tolerance of ± 0.5 l/min for the CO and ± 2 mmHg for the MAP was accepted during the tests.

Table 1: Test parameter used for the international interlaboratory comparison according to [6].

Parameter set	Heart rate [BPM]	Systolic duration [%]	Cardiac output [l/min]	Mean aortic pressure [mmHg]
1	70	35	5	100
2	45	30	5	100
3	70	35	2	100
4	70	35	3.5	100
5	70	35	5	100
6	70	35	7	100
7	120	50	5	100
8	70	35	5	100

3 Results and Discussion

The two pulse duplicator systems showed a reasonable intra-institutional repeatability, as demonstrated by the pressure and flow waveforms (Figure 1) and the deviations of the measurements in standard conditions (parameter set 1, 5, 8, Table 1).

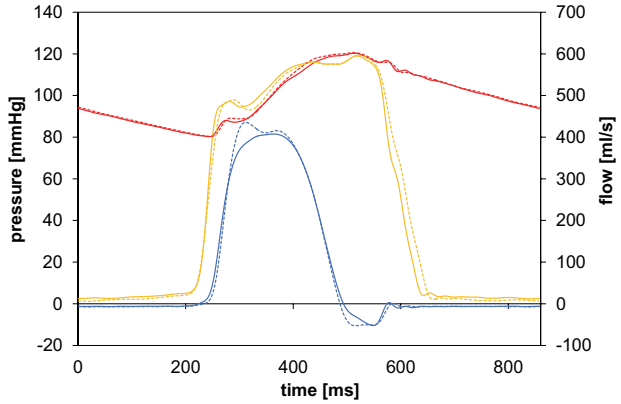

Figure 1: Pressure and flow waveforms of a pulsatile flow test of a mechanical heart valve prosthesis (25 mm) in two pulse duplicator systems of the same type at standard test parameters (mean curves of n = 30), standard test parameters: HR: 70 BPM, SD: 35%, CO: 5 l/min, MAP: 100 mmHg.

The EOA was 2.9 cm² ± 0.05 cm² for the BDC 1 and 3.6 cm² ± 0.03 cm² for the BDC 2. The RF for the BDC 1 was 8.2% ± 0.60% and 9.5% ± 0.80% for the BDC 2, see Figure 2.

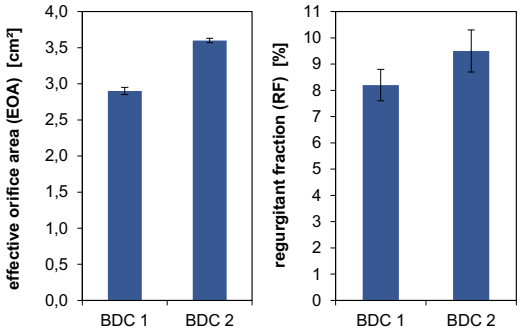

Figure 2: Effective orifice area (EOA) and regurgitant fraction (RF) of a mechanical heart valve prosthesis (25 mm) tested in two pulse duplicator systems of the same type (n = 30), standard test parameters: HR: 70 BPM, SD: 35%, CO: 5 l/min, MAP: 100 mmHg.

The inter-laboratory standard deviation for the n = 60 measurements (three measurements of 10 cycles each, per test bench) at our institute was ± 0.2 cm² for the EOA and ± 1.0% for the RF. In comparison, Wu et al. reported an inter-laboratory maximum standard deviation for the EOA of 1.1 cm² and 1.6% for the RF in the round-robin study [6].

In general, the experiments presented show a good repeatability for both test benches, since the standard deviations are smaller compared to the round-robin study [6].

Figure 3 and Table 2 show the comparison between the results obtained with the two test benches at the institute and the 13 different test laboratories which participated in the round-robin study of the ISO Cardiac Valve Working Group [6].

While the measured RF is in the same range as in the different test laboratories, the values for the EOA are slightly larger. Additionally, Table 2 shows a comparison to a round-robin study from 2005 also published from Wu et al. [6]. These results are in good agreement with the results obtained within the presented study at our institute.

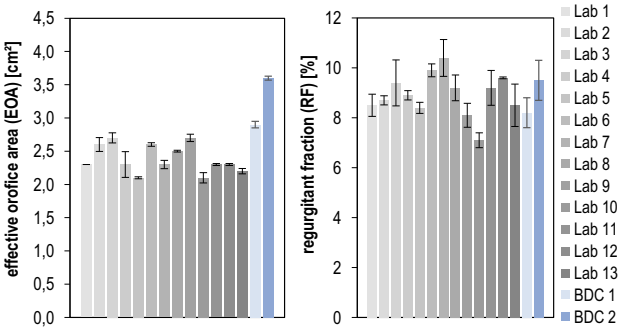

Figure 3: Effective orifice area (EOA) and regurgitant fraction (RF) of a mechanical heart valve prosthesis (25 mm) tested in two pulse duplicator systems of the same type (n = 30) compared to a round-robin study of the ISO Working Group [6], standard test parameters: HR: 70 BPM, SD: 35%, CO: 5 l/min, MAP: 100 mmHg

Table 2: Comparison of Effective orifice area (EOA) and regurgitant fraction (RF) of a mechanical heart valve prostheses (25 mm) in standard conditions (parameter set 1, 5, 8, Table 1) between our own studies and the two round-robin studies of the ISO Working Group from 2005 and 2019 [6].

	IIB	ISO Group 2005	Wu et al. 2019
EOA [cm²]	3.2 ± 0.2	2.7 ± 0.3	2.4 ± 0.2
RF [%]	9.6 ± 1.0	9.0 ± 3.0	8.9 ± 0.9

This trend is also recognizable in all the other measurements according to Table 1 and Wu et al, see Figure 4 and Figure 5 [6]. The discussion of the results is difficult because the reasons for the variations are multifactorial.

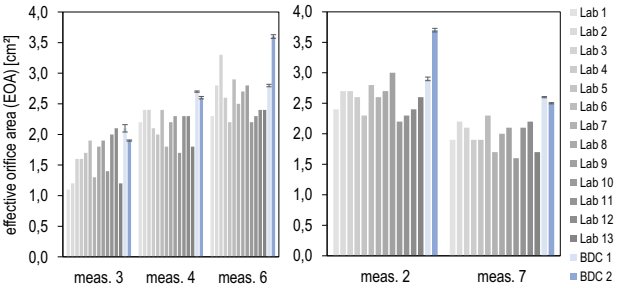

Figure 4: Effective orifice area (EOA) of a mechanical heart valve prostheses (25 mm) tested in two pulse duplicator systems of the same type (n = 30) compared to round-robin study of the ISO Working Group [6], test parameters: according to Table 1.

The asymmetric closing kinematics of the test valve, recognized by means of high-speed cinematography recordings during the measurements, is thought to be a possible cause of the minor deviations. This asymmetric closing of one tilting disc of the mechanical valve led to a prolonged closing time of the valve and an increased positive differential pressure period. This in turn, led to an increased EOA, see equations (1) and (2). In some measurements, the prolonged closing time also led to an increased closing volume of the valve, which in turn, led to an increased RF, see equation (3).

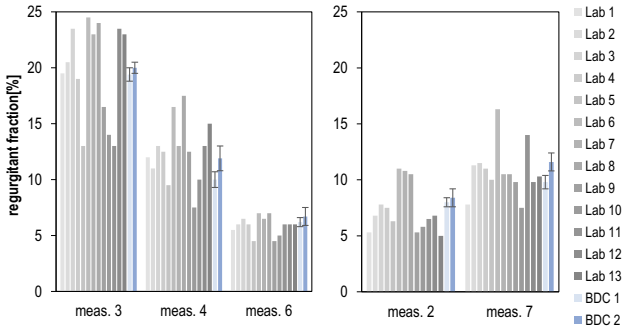

Figure 5: Regurgitant fraction (RF) of a mechanical heart valve prosthesis (25 mm) tested in two pulse duplicator systems of the same type (n = 30) compared to round-robin study of the ISO Working Group [6], test parameters: according to Table 1.

Additionally, Wu et al. identified significant variations among the investigated pulse duplicator systems, which might be caused by the varying positioning and mounting of the pressure sensors and flow meters relative to the heart valve specimens. Further possible explanations for the varying results are differences in the applied aortic root models and compliances of the heart valve chambers, as well as varying pump characteristics and data filter parameters [6].

Nevertheless, in this study the global valve performance measures EOA and RF met the minimum performance criteria of the ISO 5840-2:2021, leading to the summary, that the results presented here show that the different test benches and the test methods used are in accordance with the ISO 5840:2021 standard [4]. Since EOA and RF are strongly dependent on the valve opening and closing kinematics, the evaluation of a test bench and a test method by means of these parameters should be scrutinised in further investigations.

4 Conclusion

The purpose of this study was to examine the intra-institutional variability of different test benches and to compare the developed test methods at our institute to the state-of-the-art in prosthetic heart valve hydrodynamic performance measurements. The test benches showed a high reproducibility, also in comparison to the round-robin study. Nevertheless, variability among different test systems still exists. Therefore, it is important to develop resilient standard operating procedures and exercise care in the testing itself and the training of test engineers to minimize variations and obtain valid and repeatable measurements. Additionally, an investigation of the functionality of the test valve with respect to leaflet kinematics should be required for the validation of test methods and test benches. A testing of at least three samples of the test valve may also be a suggestion as it is required for newly developed heart valve prostheses.

Author Statement

Research funding: Financial support by the European Regional Development Fund (ERDF) and the European Social Fund (ESF) within the collaborative research between economy and science of the state Mecklenburg-Vorpommern, by the Federal Ministry of Education and Research (BMBF) within RESPONSE "Partnership for Innovation in Implant Technology" is gratefully acknowledged. Conflict of interest: Authors state no conflict of interest.

References

[1] Cribier A, Eltchaninoff H, Bash A, et al. Percutaneous transcatheter implantation of an aortic valve prosthesis for calcific aortic stenosis: first human case description. Circulation 2002; 106: 3006–3008, doi:10.1161/01.cir.0000047200. 36165.b8.

[2] Beckmann A, Meyer R, Lewandowski J, et al. German Heart Surgery Report 2020: The Annual Updated Registry of the German Society for Thoracic and Cardiovascular Surgery. The Thoracic and cardiovascular surgeon 2021; 69: 294–307, doi:10.1055/s-0041-1730374.

[3] ISO 5840-1:2021: Cardiovascular implants - cardiac valve prostheses - Part 1: General requirements. International Organization for Standardization, Geneva, Switzerland.; 2021.

[4] ISO 5840-2:2021: Cardiovascular implants - cardiac valve prostheses - Part 2: Surgically implanted heart valve substitutes. International Organization for Standardization, Geneva, Switzerland.; 2021.

[5] ISO 5840-3:2021: Cardiovascular implants - cardiac valve prostheses - Part 3: Heart valve substitutes implanted by transcatheter techniques. International Organization for Standardization, Geneva, Switzerland.; 2021.

[6] Wu C, Saikrishnan N, Chalekian AJ, Fraser R, Ieropoli O, Retta SM et al., In-Vitro Pulsatile Flow Testing of Prosthetic Heart Valves: A Round-Robin Study by the ISO Cardiac Valves Working Group. Cardiovascular Engineering and Technology, 2019: 10, No. 3: 397–422, https://doi.org/ 10.1007 /s13239-019-00422-5.

[7] Oldenburg J, Kaule S, Siewert S, Grabow N, Schmitz KP, Stiehm M, Impact of aortic annulus geometry according to ISO 5840:2019 (draft) on hydrodynamic performance of transcatheter aortic valve prostheses, Current Directions in Biomedical Engineering 2020;6(3): 20203117, https://doi.org /10.1515/cdbme-2020-3117.

[8] Borowski F, Kaule S, Oldenburg J, Oener A, Schmitz KP, Stiehm M, Quantification of noncircular stent expansion after TAVR into a pathological annulus and its impact on paravalvular leakage, Current Directions in Biomedical Engineering 2021;5(1):1-3, https://doi.org/10. 1515/cdbme-2021-2152.

[9] Ott R, Öner A, Bellé PH, Borowski F, Schmitz KP, Stiehm M, Validation of a Fluid-Structure Interaction Model for the Characterization of Transcatheter Mitral Valve Repair Devices. Current Directions in Biomedical Engineering 7.2 (2021), S. 605–608, https://doi.org/10.1515/ cdbme-2021-2154.

[10] Borowski F, Höing S, Kaule S, Schmitz KP, Oener A, Stiehm M, Approach to determine paravalvular leakage occuring of trans-catheter aortic valve prostheses implanted in a calcified annulus model using particle image velocimetry, German Association for Laser Anemometry, GALA e.V., Karlsruhe, Germany, ISBN 978-3-9816764-7-1.

[11] Borowski F, Kaule S, Oldenburg J, Schmitz KP, Oener A, Stiehm M, Particle image velocimetry for flow analysis of the thrombogenic potential of transcatheter aortic valve prostheses, tm – Technisches Messen 2022; aop, https://doi.org /10.1515/teme-2021-0124.