Michael Stiehm*, Christoph Brandt-Wunderlich, Stefan Siewert, Eric K.W. Poon, Andrew Ooi, Peter Barlis, Titus Kühne, Leonid Goubergrits, Niels Grabow and Klaus-Peter Schmitz

Sensitivity analysis of FDA´s benchmark nozzle regarding *in vitro* imperfections - Do we need asymmetric CFD benchmarks?

Abstract: Modern technologies and methods such as computer simulation, so-called *in silico* methods, foster the development of medical devices. For accelerating the uptake of computer simulations and to increase credibility and reliability the U.S. Food and Drug Administration organized an inter-laboratory round robin study of a generic nozzle geometry. In preparation of own bench testing experiment using Particle Image Velocimetry, a custom made silicone nozzle was manufactured. By using *in silico* computational fluid dynamics method the influence of *in vitro* imperfections, such as inflow variations and geometrical deviations, on the flow field were evaluated. Based on literature the throat Reynolds number was varied Re_{throat} = 500 ± 50. It could be shown that the flow field errors resulted from variations of inlet conditions can be largely eliminated by normalizing if the Reynolds number is known. Furthermore, a symmetric imperfection of the silicone model within manufacturing tolerance does not affect the flow as much as an asymmetric failure such as an unintended curvature of the nozzle. In brief, we can conclude that geometrical imperfection of the reference experiment should be considered accordingly to *in silico* modelling. The question arises, if an asymmetric benchmark for biofluid analysis needs to be established. An eccentric nozzle benchmark could be a suitable case and will be further investigated.

Keywords: Computational fluid dynamics (CFD), FDA nozzle, geometrical imperfection, asymmetry

https://doi.org/10.1515/cdbme-2020-3020

***Corresponding author: Michael Stiehm:** Institute for ImplantTechnology and Biomaterials e.V., Friedrich-Barnewitz-Str. 4, 18119 Rostock-Warnemünde, Germany, michael.stiehm@uni-rostock.de,
Christoph Brandt-Wunderlich, Stefan Siewert, Klaus-Peter Schmitz: Institute for ImplantTechnology and Biomaterials e.V., 18119 Rostock-Warnemünde, Germany,
Niels Grabow, Klaus-Peter Schmitz: Institute for Biomedical Engineering, Rostock University Medical Center, 18119 Rostock-Warnemünde, Germany
Leonid Goubergrits, Titus Kühne: Institute for Imaging Science and Computational Modelling in Cardiovascular Medicine, Charité - Universitätsmedizin Berlin, Berlin, Germany
Titus Kühne: Department of Congenital Heart Disease and Paediatric Cardiology, German Heart Center Berlin, Berlin, Germany
Eric K. W. Poon, Andrew Ooi, Peter Barlis: Department of Mechanical Engineering, Melbourne School of Engineering, The University of Melbourne, Melbourne, VIC 3010, Australia
Peter Barlis: Department of Medicine, Melbourne Medical School, Faculty of Medicine, Dentistry & Health Sciences, The University of Melbourne, Melbourne, VIC 3010, Australia

1 Introduction

Although the age-standardized overall premature mortality rate for the four major non-communicable diseases (cardiovascular diseases, cancer, diabetes mellitus and chronic respiratory diseases) is continuously decreasing, cardiovascular diseases still have the highest mortality rate in the World Health Organization-European Region [1].

Modern technologies and approaches such as computer simulation, so-called *in silico* methods, foster the development of medical devices [2]. For accelerating the uptake of computer simulations for developing and testing medicines and medical devices international frameworks and programs have been established. The U.S. Food and Drug Administration (FDA) organized an inter-laboratory round robin study to increase credibility and reliability of a particular *in silico* method – computational fluid dynamics (CFD) simulations. They provide a database for validation, which is based on experimental (by means of particle image velocimetry, PIV) as well as numerical simulation (CFD). Data is available on https://fdacfd.nci.nih.gov/.

The FDA nozzle, which consists of a conical diffusor and a sudden expansion, is one of the published benchmark cases [3-5]. Even before FDA introduced the nozzle benchmark preliminary studies analyzed similar geometries, representing a stenosed vessel [6,7]. Various *in vitro* and *in silico* studies used the FDA nozzle benchmark for further investigations and for validation [8-10]. Mostly, numerical studies used CFD results, which were calculated from ideal nozzle geometry and fully developed inlet flow conditions, for comparison with experimental measurements. Bergersen et al. stated that from a physical point of view, it is difficult to completely exclude imperfections in *in vitro* experiments [11].

For analysing the impact of imperfections, Hariharan et al. described a positive control PIV experiment, in which different aspects of the derived standard protocol were violated simultaneously (e.g. inlet flow conditions and PIV parameters) [3]. The used nozzle models were fabricated from cast acrylic using a CNC milling machine and were extensively post-treated to ensure high optical quality and geometrically accuracy [3]. Besides the use of acrylic models PIV community often use silicone models in combination with test fluids, which matches the refractive index [12].

In preparation for PIV measurements using a custom-made silicone nozzle we performed a sensitivity analysis of geometrical imperfections of the nozzle geometry (conical nozzle throat and curvature) by means of CFD. The backward and forward flow was calculated for three different inlet velocities. The aim of this study was the identification of sensitive parameters in order to concentrate on future nozzle manufacturing by using 3D printing technology and silicone casting.

2 Materials and methods

2.1 Nozzle model

The nozzle geometry used (Figure 1) refers to previously published work [3-5]. The unsteady generalized Navier-Stokes equations were solved by using a finite volume CFD package OpenFOAM® (OpenCFD Ltd., ESI Group, Bracknell, UK) assuming laminar flow due to our own preliminary studies.

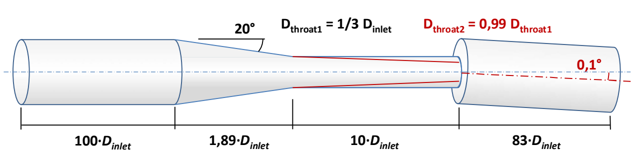

Figure 1: Schematic illustration of the nozzle geometry.

A block-structured mesh in an O-grid configuration was used for discretization. Mesh independency was achieved by comparing the numerical flow results (**U**, p) of two CFD studies at different mesh resolutions (coarsest mesh 470,000 cells; fine mesh: ~4 million cells) and was considered adequate with discrepancy in both **U** and p < 1% [13]. Furthermore, comprehensive round robin studies were performed with the co-workers at the Department of Mechanical Engineering (The University of Melbourne) and IIB to ensure inter-observer agreement on the calculated flow results. The imperfection study was conducted by IIB. In preparation of PIV measurements a nozzle model made of silicone (Sylgard 170 Silicone Elastomer, Dow Corning, Midland, MI, USA) was manufactured and measured by using the measuring machine QVI® SprintMVP™ 200 (OGP Messtechnik GmbH, Germany). A slightly conical shape of the nozzle throat and a bend of 0.1° could be detected (indicated by annotations in red), which lead to the nozzle geometry used, see Figure 1. Furthermore, shrinkage of approx. 0.5% was measured.

2.2 Initial and boundary condition

Based on the reduced orifice area due to shrinkage and on the error analysis published by Hariharan et al. an inlet velocity variation of 10% was used, leading to throat Reynolds numbers $Re_{throat} = 500 \pm 50$ (see formula 1) [3].

$$Re_{throat} = U \cdot D_{throat}/\nu \tag{1}$$

Here **U** is the average throat velocity, $\mathbf{D}_{throat}$ is the throat diameter and $\boldsymbol{\nu}$ is the kinematic viscosity of the fluid. The fluid was assumed to be Newtonian, with a fluid density and dynamic viscosity of 1,056 kg/m^3 and 0.0035 N s/m^2, respectively. No-slip conditions were defined on the walls. Zero-gradient and 0 Pa were specified as pressure condition on the inlet and outlet, respectively.

3 Results and discussion

3.1 Round robin study

Reliability and credibility of the used CFD method was formerly proved by comprehensive round robin studies of both steady and pulsatile flow at Re_{throat} = 500. Figure 2 demonstrates the excellent agreement of the shear rate distribution between both teams at the University of Melbourne and IIB.

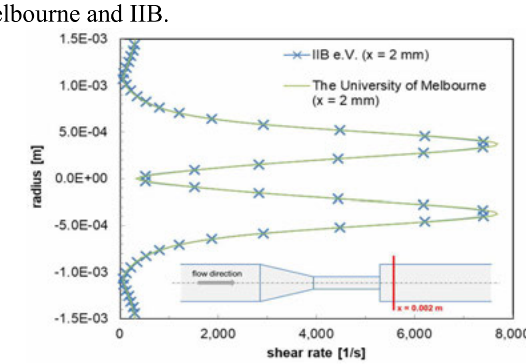

Figure 2: Numerically calculated shear rate obtained by IIB e.V. and The University of Melbourne downstream of the coronary nozzle model (at x = 2mm) under steady flow conditions Re_{throat} = 500.

3.2 Variation of inlet condition

The velocity and shear rate distribution within the nozzle throat (x = -2 mm) and upstream of the sudden expansion (x = 15 mm) for Re_{throat} = 500 ± 50 (forward flow) is depicted in Figure 3. Additionally, the velocity is normalized by the mean inflow velocity (0.184 m/s ± 10%). Based on the normalized velocity distribution the normalized shear rate was calculated.

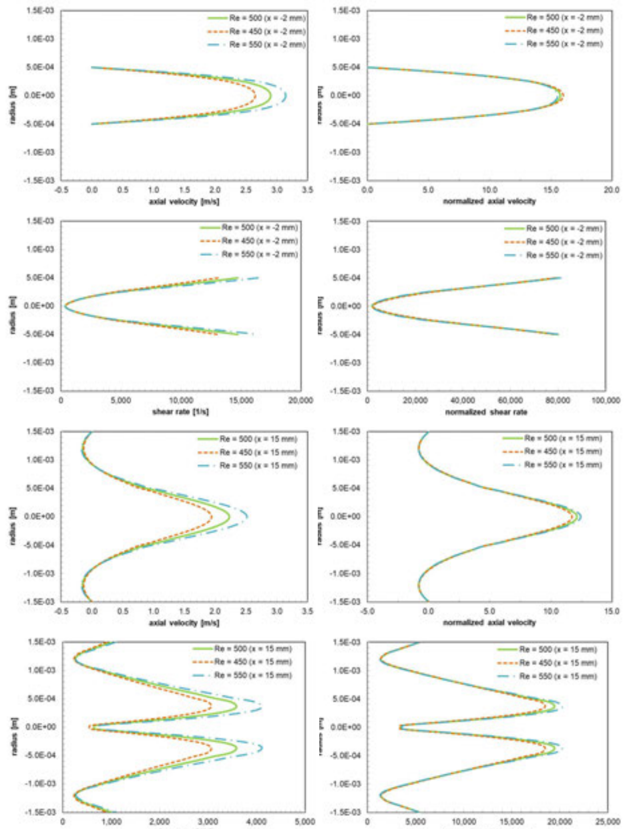

Figure 3: Numerically calculated velocity and shear rate distribution (x = -2 mm and 15 mm) for Re_{throat} = 500 ± 50 (forward flow) of the ideal nozzle geometry.

The normalized velocity distribution for x = 15 mm (x = $5D_{inlet}$) matches very well with published data (compare Hariharan et al. at x = $5D_{inlet}$) [3].

By normalizing the velocity field the error derived from variations of inlet conditions can be largely eliminated if the Reynolds number is known. For example, at x = 15 mm the highest differences in axial (dimensional) velocity and shear rate are ~13% and up to ~15%, respectively, when comparing with the mean Re_{throat} at 500. However, the differences in the normalized velocity and shear rate are <3% and <5%, respectively. Same results could be obtained for backward flow. In addition to velocity and shear rate, FDA also mandates compulsory measurements of the viscosity of test fluid, accurate temperature control and average flow rate for further validation using FDA´s published data. Geometrical imperfections such as alterations of the cross-sectional area due to shrinkage have an impact on the Reynolds number and therefore should be reported as well. Nevertheless, the varied inlet condition is only marginally different by ~10% and hence flow is neither turbulent nor transitional for the Reynolds number considered.

3.3 Geometrical imperfections

The shear rate as well as normalized shear rate distribution for Re = 450, 500 and 550 (forward flow) at x = 15 mm calculated for both deformed nozzle geometries are depicted in Figure 4. Additionally, the values for the ideal nozzle geometry is plotted as reference for Re_{throat} = 500.

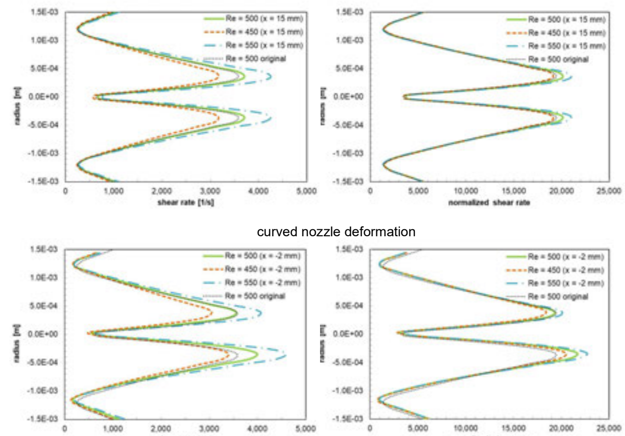

Figure 4: Numerically calculated shear rate distribution (x = 15 mm) for Re_{throat} = 500 ± 50 (forward flow) of the imperfect nozzle geometry.

The conical throat leads to slightly increase in centerline velocity (approx. 2.5% at x = 15 mm and Re_{throat} = 500) compared to the ideal geometry, resulting in higher shear rate magnitudes (shear rate maximum: 3,690 s^{-1} vs. 3,570 s^{-1}). However, the conical shape does not affect the flow situation due to inflow variations in an over-proportional manner.

On the other hand, the curved nozzle leads to a highly asymmetrical velocity and shear rate distribution. The maximum shear rate differs ~12% comparing to the ideal nozzle (3,990 s^{-1} vs. 3,570 s^{-1}). In other words, a minor asymmetric imperfection could lead to a major altered flow field.

4 Conclusion

In preparation for PIV measurements using a silicon nozzle model numerical simulations were performed in order to study the effect of inflow variations and geometrical imperfection on the flow field. Based on the obtained results it is suggested that normalized and not absolute fluid dynamic values were used for validation. Therefore, it is mandatory that the correct Reynolds number is known by measuring the flow rate, the viscosity of the fluid and the exact geometry.

The numerical modeling of *in vitro*-imperfections has further advantages. Several studies showed significant discrepancies in the flow situation by comparing numerical and experimental results for axisymmetric geometries at moderate Reynolds numbers. These discrepancies were manifested in errors regarding flow break down and reattachment due to transition from laminar to turbulent flow. Numerical simulations of symmetric geometries and fully developed flow condition tend to underestimate the turbulent situation, which can be found in experimental flow and is caused by *in vitro*-imperfections. A good overview of this topic can be found in Pedrón, 2016 [14].

Therefore, Verghase et al. studied stenosis model with a geometric perturbation in the form of an eccentricity at the stenosis throat. This case not only models the vessel in more physiological way but also showed higher accuracy in comparing *in silico* and *in vitro* data [6,7]. Bergersen et al. summarized that one way to numerically mimic experimental noise is to perturb the numerical simulation with a finite level of noise or imperfection in order to transit the otherwise stable flow simulation (due to geometry symmetry) to turbulence [11].

The question arises, if an asymmetric benchmark for biofluid analysis needs to be established. The level of asymmetry should be chosen to effect the flow situation more than unintended imperfections. An eccentric stenosis benchmark could be a suitable case [6,7,15,16] and will be further investigated.

Author Statement

Research funding: Financial support by European Regional Development Fund (ERDF) and by the European Social Fund (ESF) with the excellence research program of the state Mecklenburg-Vorpommern Card-ii-Omics. Conflict of interest: Authors state no conflict of interest. Informed consent: Informed consent is not applicable. Ethical approval: The conducted research is not related to either human or animal use.

References

[1] World Health Organization – Regional Office for Europe. European Health Report 2018 – More than numbers – evidence for all. 2018.

[2] Morrison TM, Pathmanathan P, Adwan M and E Margerrison. Advancing Regulatory Science With Computational Modeling for Medical Devices at the FDA's Office of Science and Engineering Laboratories. Front. Med. 2018,5(241):1-11.

[3] Hariharan P, Giarra M, Reddy V et al. Multilaboratory Particle Image Velocimetry Analysis of the FDA Benchmark Nozzle Model to Support Validation of Computational Fluid Dynamics Simulations. J. Biomech. Eng. 2011;133: 041002-1 - 14.

[4] Stewart SFC, Hariharan P, Paterson EG et al. Results of FDA´s First Interlaboratory Computational Study of a Nozzle with a Sudden Contraction and Conical Diffusor. Cardiovasc. Eng. Techn. 2013; 4(4): 374–391.

[5] Stewart SFC, Paterson EG, Burgreen GW et al. Assessment of CFD Performance in Simulations of an Idealized Medical Device: Results of FDA's First Computational Interlaboratory Study. Cardiovasc. Eng. Techn. 2012; 3(2):139-160.

[6] Varghese SS, Frankel SH and PF Fischer. Direct numerical simulation of stenotic flows. Part 1. steady flow. J. Fluid Mech., 2007;582:253-280.

[7] Varghese SS, Frankel SH and PF Fischer. Direct numerical simulation of stenotic flows. Part 2. pulsatile flow. J. Fluid Mech., 2007, 582:281-318.

[8] Stiehm M, Wüstenhagen C, Siewert S, Grabow N and KP Schmitz. Numerical simulation of pulsatile flow through a coronary nozzle model based on FDA´s benchmark geometry. Current Directions in Biomedical Engineering. 2017;3(2):1-2.

[9] Konnigk L, Torner B, Hallier S, Witte M and FH Wurm. Grid-Induced Numerical Errors for Shear Stresses and Essential Flow Variables in a Ventricular Assist Device: Crucial for Blood Damage Prediction? J. Verif. Valid. Uncert. 2018,3(4): 041002-1 - 10.

[10] Gao H, Zhu X and JX Wang. A Bi-fidelity Surrogate Modeling Approach for Uncertainty Propagation in Three-Dimensional Hemodynamic Simulations. 2019. preprint

[11] Bergersen AW, Mortensen M and K Valen-Sendstad. The FDA nozzle benchmark: "In theory there is no difference between theory and practice, but in practice there is". Int. J. Numer. Meth. Biomed. Engng. 2019;35:1-10.

[12] Raghav V, Sastry S and N Saikrishnan. Experimental Assessment of Flow Fields Associated with Heart Valve Prostheses Using Particle Image Velocimetry (PIV): Recommendations for Best Practices. Cardiovasc Eng. Techn. 2018;9(3):273-287.

[13] Gijsen F, Katagiri Y, Barlis P et al. Expert recommendations on the assessment of wall shear stress in human coronary arteries: existing methodologies, technical considerations, and clinical applications. Eur. Heart J. 2019;40(41):3421-3433.

[14] Pedrón FAS. Study of Symmetry Breaking Instabilities in Axissymmetric geometries. Université de Montréal. Phd thesis. 2016.

[15] Fearn RM, Mullin T and KA Cliffe. Nonlinear flow phenomena in a symmetric sudden expansion. J. Fluid Mech., 1990;211: 595-608.

[16] Griffith MD, Leweke T, Thompson MC and K Hourigan. Effect of small asymmetries on axisymmetric stenotic flow. J. Fluid Mech. 2017;721:R1-1 - 11.