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Approach to determine paravalvular leakage occuring of transcatheter aortic valve prostheses implanted in a calcified annulus model using particle image velocimetry

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Particle Image Velocimetry, TAVR, paravalvular leakage

Summary

Implantation of transcatheter aortic valve replacement (TAVR) for the treatment of severe aortic valve stenosis has been shown to be a trustworthy alternative to the surgical procedure with promising clinical results. Although the first TAVP implantation was performed in 2002, third-generation TAVR is already available, and acute complications such as paravalvular leakage (PVL) have been reduced. PVL, defined as leakage between TAVR and aortic annulus, leads to a pathological backflow of blood from the aorta into the left ventricle. The occurrence of is still commonly associated with increased short- and long-term mortality.
A quantification approach using stereo particle image velocimetry (PIV) was used to improve understanding of the occurrence and impacts of PVL. With a cardiovascular circulation loop, only total leakage can be determined as a system parameter. However, the total leakage of a TAVR is composed of PVL, transvalvular leakage, and closure volume. Accordingly, to localize and quantify only PVL, the velocity field of the flow proximal to the TAVR needs to be determined.
For this purpose, a test chamber for stereo PIV recordings was developed and mounted on the cardiovascular circulation loop. A silicone mock vessel was used to mimic the aortic root, and pathophysiological modifications in annulus geometry were considered according to ISO 5840:2021. A mixture of glycerol and saline solution was used as test fluid. The test fluid has the following advantages: distortions are avoided by adapting the refractive index, and the rheological properties of blood can be modeled with a representative kinematic viscosity of 3.5 cSt. For comparison, PIV measurements of self-expanding TAVR were performed in aortic roots with physiological and pathological anatomy. Acquisition time points were chosen during the diastolic (filling) phase of the entire cardiac cycle. Furthermore, the measurements were phase-resolved.
Under pathophysiological conditions, jet flow (up to 0.5 m/s) proximal to the aortic annulus could be measured. In comparison, almost no flow was detected under physiological conditions. The presence of jet flow back into the ventricular model is also shown by in-creased total leakage of the cardiovascular circulation loop under pathophysiological conditions. Stereo PIV setup in combination with cardiovascular circulation loop can be used for precise quantification of PVL to improve the understanding of PVL occurrence and effects after TAVR deployment.

Introduction

Implantation of transcatheter aortic valve replacement (TAVR) to treat severe aortic valve stenosis has become a reliable alternative to surgery with promising clinical outcomes. Since the first TAVR implantation was performed in 2002 (Cribier et al. 2002), third-generation TAVRs have become commercially available (Rogers et al. 2017). Acute complications such as the need for a permanent pacemaker, stroke, and paravalvular leakage (PVL) were reduced while expanding the indications from high to moderate risk patients (Leon et al. 2016). Nevertheless, PVL is still associated with increased short-term and long-term mortality (Giordano et al. 2019).

PVL, defined as leakage between the TAVR and the aortic annulus, results in pathological retrograde flow of blood from the aorta into the left ventricle. This retrograde flow is often caused by calcifications in the aortic annulus, creating a gap between the TAVR and the aortic root.

Clinical studies demonstrate the influence of TAVR design on the occurrence of PVL (Costa et al. 2020). Therefore, one of the essential goals for TAVR developers is to design a minimally invasive artificial valve that covers the calcification and seals the gap between TAVR and the aortic annulus.

In vitro testing of heart valve prosthesis utilizing pulse duplicator systems are not only common for investigating leakage behavior (Wu et al. 2019) but also required by ISO 5840 for device approval. Nevertheless, commercially available pulse duplicator systems only measure the flow rate of the so-called regurgitation volume (RV). The RV consists of three fractions: PVL, transvalvular leakage, and reflux during TAVR occlusion.

The velocity field of the flow proximal to the TAVR must be determined to distinguish, localize and quantify PVL. Flow field assessment by Particle Image Velocimetry (PIV) distal the aortic valve prosthesis is recommended by ISO 5840, and several researchers (such as Lim et al. 1994, Ducci et al. 2013 / 2016, Gunning et al. 2014, Hatoum et al. 2018) as well as the US Food and Drug Administration demonstrated the potential of PIV and provided guidelines to obtain credible measurements (Raghav et al. 2018).

In the previously published studies investigating the flow field in aortic valves with PIV, the focus was primarily on non-physiological flow changes to determine thrombogenic and hemolytic potential distal to the aortic valve. For example, Ducci et al. (2013 / 2016) used PIV to assess the flow field distal to the TAVR in the Valsalva sinuses and measured lower flow velocities after TAVR implantation to estimate thrombotic potential. In Gunning et al. (2014) the influence of a circular and an eccentric TAVR after implantation on the flow field distal to the valve was determined.

Nevertheless, the assessment of the retrograde flow by PIV for PVL characterization of TAVR is not known to be reported yet. Therefore, we have developed an approach to investigate the retrograde flow of commercially available prosthesis CoreValve Evolut R (Medtronic Inc., Santa Ana, CA, USA) in a phantom aortic root model.

Materials and Methods

<u>Cardiovascular circulation loop</u>

A commercially available pulse duplicator system (Vivitro Inc., Victoria, Canada) was used to simulate the physiological flow conditions of the left heart. The hydrodynamic circulation loop is driven by a digitally controlled piston pump, which compresses a silicon left ventricle model (see Fig. 1). As a result, pulsatile flow through the aortic valve is enabled. A Windkessel model allows consideration of aortic compliance. Circulation is enabled by returning fluid to the atrial chamber through peripheral flow resistance. A mitral valve replacement guarantees unidirectional flow between the atrial chamber and left ventricle.

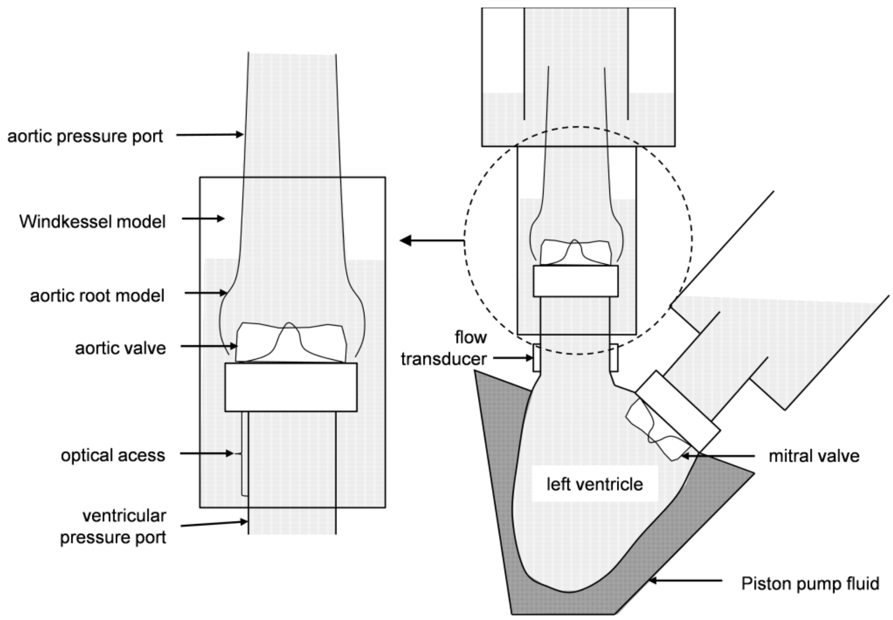

Fig. 1: Setup of the cardiovascular circulation loop to replicate pulsatile flow conditions of the left heart with detailed view of the TAVR test chamber with optical access proximal to the TAVR (Illustration based on Azadani et al. 2009).

The test setup includes transducers to measure flow rate and fluid pressure on the ventricular and aortal sides of the aortic valve. Physiological parameters such as mean aortic pressure, stroke volume, and systolic duration can be adjusted. The ejection volume, closure volume, and total leakage volume can be determined using the flow rate curve over time (see Fig. 2). A mean aortic pressure of 100 mmHg, a stroke volume of 97 ml, and a systolic duration of 35% were defined for these measurements. Furthermore, the test fluid had a physiological temperature of 37°C according to ISO 5840.

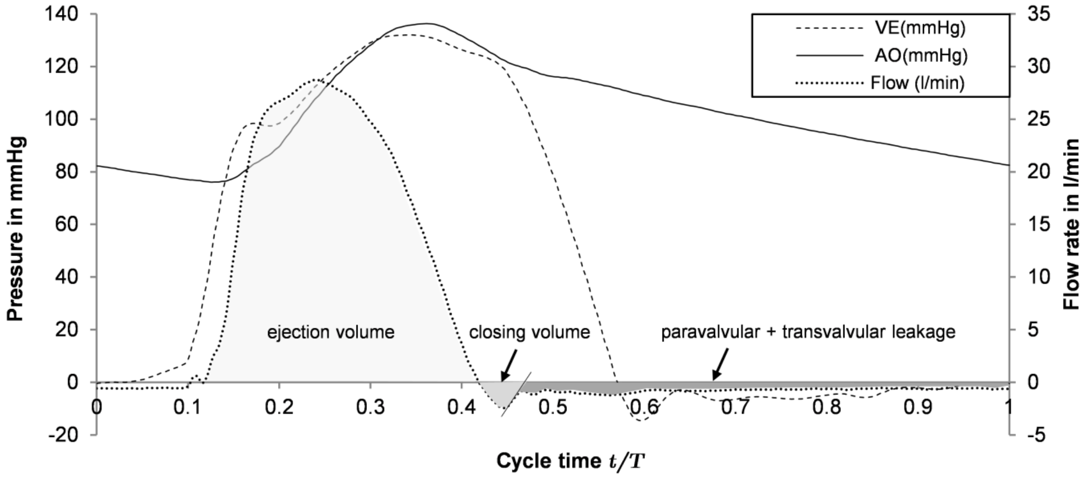

Fig. 2: Volume flow and pressure curves of the aortic (AO) and ventricular (VE) pressure in the cardiac cycle with identification of the components of the regurgitation volume (closing volume, paravalvular and transvalvular leakage) and the ejection volume

The original configuration of the pulse duplicator system allows optical access distal to the aortic valve. However, optical access to observe paravalvular leak flow proximal to the aortic valve is not provided. For this reason, a new test chamber was designed and manufactured that allows optical access from different camera perspectives to perform stereoscopic or even tomographic PIV measurements.

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Annulus models and used transcatheter aortic valve replacements

The aortic root model was used to model a physiological and pathological implantation environment based on anatomical data from patients with severe aortic valve stenosis. The model geometry consists of a tubular entrance proximal of the valve, an annulus region with adjacent native leaflets (ISO 5840), and the aortic root with sinus Valsalva (previously published in Borowski et al. (2020) and based on Reul et al. (1990)) a tubular outflow distal to the TAVR.

The model was manufactured by casting a two-component, optically clear elastomer (Sylgard 184 Silicone Elastomer, The Dow Chemical Company, Midland, MI, USA) as used by several research groups (Fernandes et al. 2019, Gülan et al. 2019).

The pathological modification utilizing calcification nodules was added to the model according to ISO 5840-3:2021. The calcification nodule has a radial protrusion of 2.0 mm into the vessel lumen, a circumferential extension of 4 mm. It was made of a rigid polymer.

Currently, self-expandable TAVR platforms of the CoreValve family are most commonly used in clinical practice in Western Europe with the Evolut R or the Evolut Pro (Medtronic Inc., Santa Ana, CA, USA) (Bibamedtech, 2019). Both valves use a self-expandable nickel-titanium alloy frame with three leaflets and a pericardial sealing skirt. In this study, we used the Evolut R (size 29) to investigate paravalvular leakage.

Particle image velocimetry test setup

For experimental flow investigation of PVL, a stereo PIV set up from DantecDynamics (Dantec Dynamics, Ulm, GER) was used. The PIV system includes two CMOS cameras (EoSens 12CXP+, Mikrotron, DE) with Scheimpflug adapters positioned 45° to the laser light sheet (see Fig. 3). A double pulsed Nd:YAG dual-cavity laser performed the illumination (532 nm, max. energy 145 mJ, 15 Hz, Litron Laser Ltd., UK), which induces a laser light sheet of approximately 1 mm thickness.

The PIV system was synchronized with the pump of the pulse duplicator system to trigger the cameras at selected times in the cardiac cycle. Each time point was phase-averaged over 200 instantaneous velocity fields. For comparison, PIV measurements of TAVR prototypes were performed in aortic roots with physiological and pathological anatomy. Acquisition time points were chosen during the diastolic (filling) phase of the entire cardiac cycle.

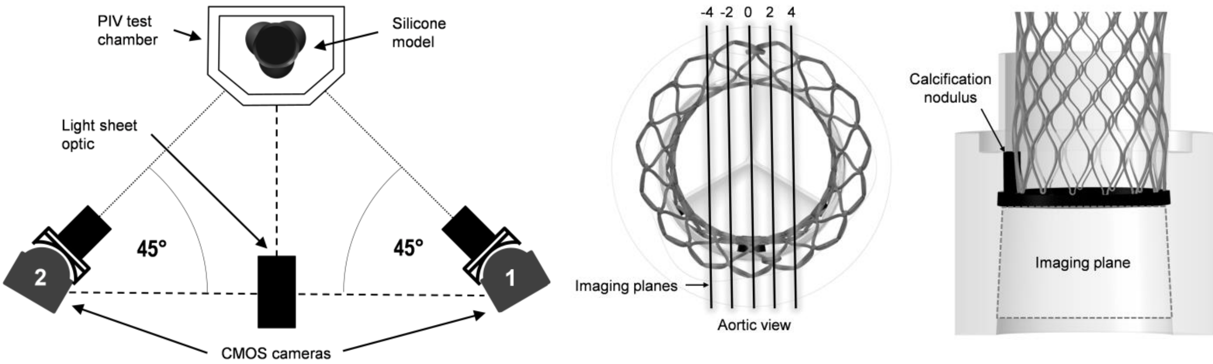

Fig. 3: PIV set up: Camera arrangement of the two cameras with Scheimpflug adapter at a 45° angle to the light sheet with the light sheet optic aligned with the silicon model in the PIV test chamber (left), TAVR in the pathological annulus model from the aortic view with the with imaging planes (middle); lateral view of the silicone model with TAVR and calcification and the outlined imaging plane (right).

Measurements were performed measuring five laser light-section positions at a distance of 2 mm to record the spatial extension of the leakage flow (see fig. 3). Due to the expected range of velocity magnitudes (leakage jet: up to 1.0 m/s vs. proximal flow with closed TAVR: under 0.5 m/s), different time intervals (Δt = 200 µs *and* 2000 µs) were chosen between the double images for realistic detection of all velocities.

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Several pure liquids and liquid solutions have already been used to define a blood substitute fluid, including a saline solution (Ducci et al. 2013), a water (or saline)-glycerol mixture (such as Azadani et al. 2009), or other multi-component mixtures (Leo et al. 2006, Quosdorf et al. 2011). Due to optical accessibility and rheological properties, different mixtures composed of glycerol and 0.9% saline solution were investigated. The refractive index and the kinematic viscosity were determined for nine different mixing ratios with a refractometer (ABBE refractometer AR4, A. KRÜSS Optronic GmbH, DE) and a rheometer (HAAKE RheoStress 1, Thermo Fisher Scientific, DE), respectively (see Fig. 4).

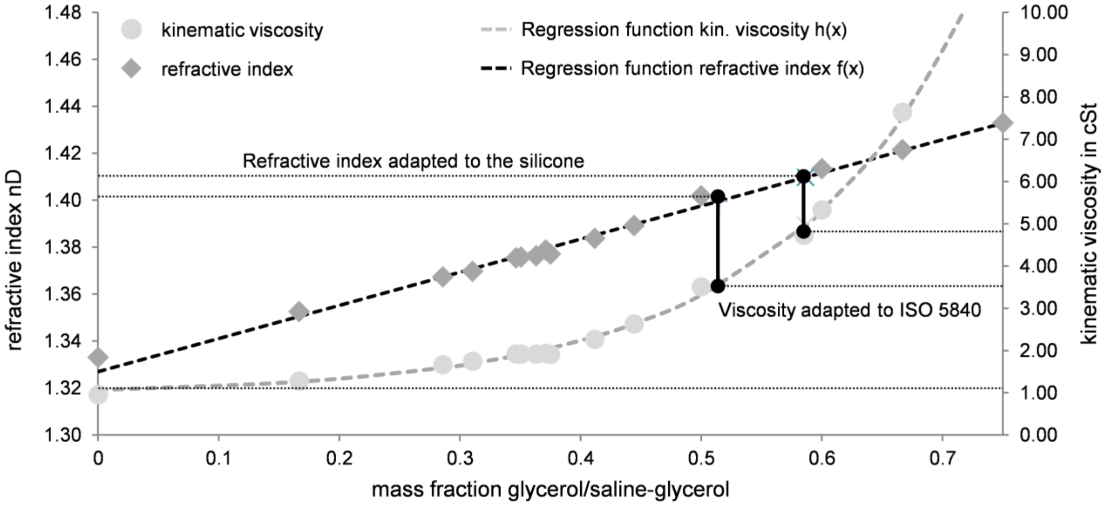

Fig. 4: Analysis of refractive index and rheological properties if different saline-glycerol-mixtures used as test fluid. Refractive index of silicone aortic model made of Sylgard 184 Silicone Elastomer and recommended kinematic viscosity of 3.5 cSt (according to ISO 5840) were marked.

As a result, the appropriate kinematic viscosity was obtained at a mixing ratio of 50.6% glycerol in the total mixture and showed negligible optical distortions.

Results

The implantation of the Evolut R into a physiological and pathological annulus model is shown in Fig. 5. Due to the calcification nodule in the pathological annulus model, the nitinol stent cannot expand into a circular state, resulting in a potential leakage area.

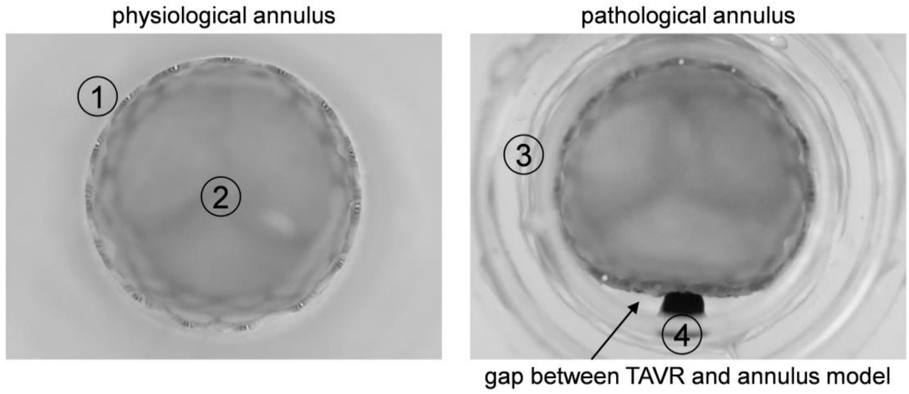

Fig. 5: Comparison of the TAVR stent (1) and leaflets (2) in the physiological and pathological annulus (3) with stent deformation due to the calcification (4) from the ventricular side.

Comparing the hydrodynamic parameters measured, an increased leakage volume can be seen for the pathological annulus model during diastole, see Fig 6. The leakage volume increased from 5.73 ± 1.17 ml (physiological) to 21.01 ± 3.19 ml (pathological) averaged over three independent measurements with ten cycles each.

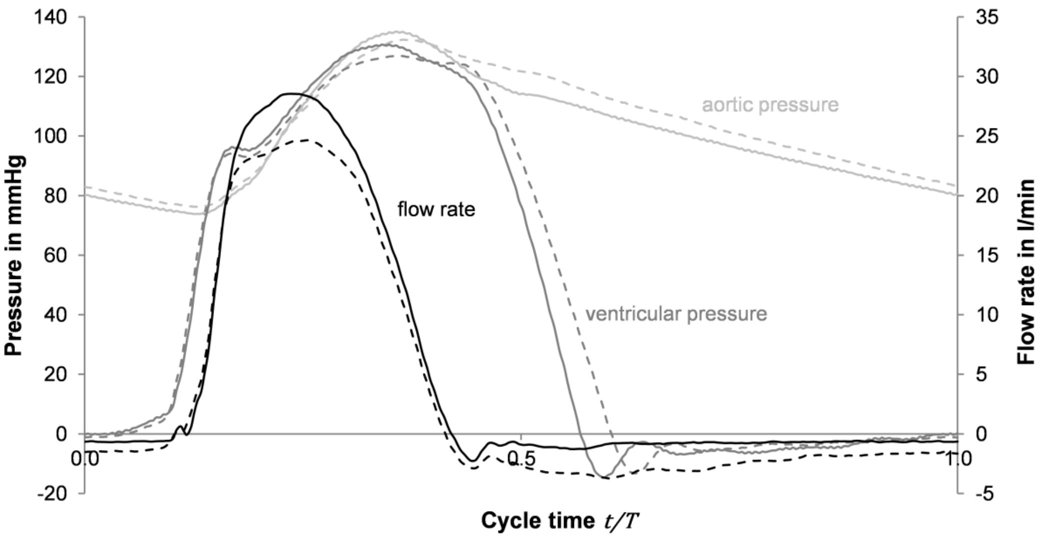

Fig. 6: Comparison of the pressure and volume flow curves of TAVI recorded in the cardiovascular circulation loop in the physiological (solid line) and pathological (dashed line) annulus at constant pump volume and mean aortic pressure.

As a result, the RF increases from 6.71 ± 1.06 % to 31.80 ± 4.51 %. At constant stroke volume and mean aortic pressure, cardiac output (ejection volume minus leakage volume and closing volume) decreases from 5.07 ± 0.07 l/min in the physiological annulus model to 4.25 ± 0.09 l/min in the pathological annulus model. However, the ejection volume remains constant.

Based on the CMR classification of PVL, which is calculated by retrograde flow volume, the pathological annulus model results in a moderate-classified PVL. Moderate PVL occurs at an RF of 21-39% (Hartlage et al. 2014).

The PIV results confirm the hydrodynamic metrics from the pulse duplicator measurements. Fig. 7 shows the two-dimensional velocity fields proximal to the TAVR in the physiological and pathological annulus models. The velocity fields were acquired during mid-diastole. While the velocity field proximal to the physiological annulus shows only small velocity magnitudes and leakage flows, a leakage jet with velocities up to 0.6 m/s can be identified below the calcification in the pathological annulus model.

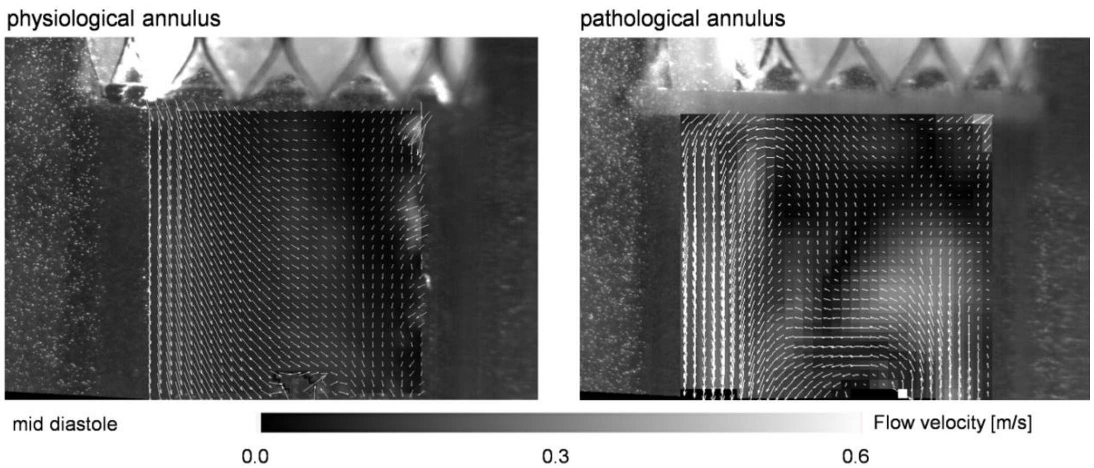

Fig. 7: Velocity magnitude and vectors proximal to the Evolut R measured during mid-diastole in the physiological (left) and pathological (right) annulus model.

The stereo PIV results of the different imaging levels are shown in Fig. 8. From the planes in the area around the center of the calcification, it can be seen that the jet flows still occur 2 mm and 4 mm around the calcification.

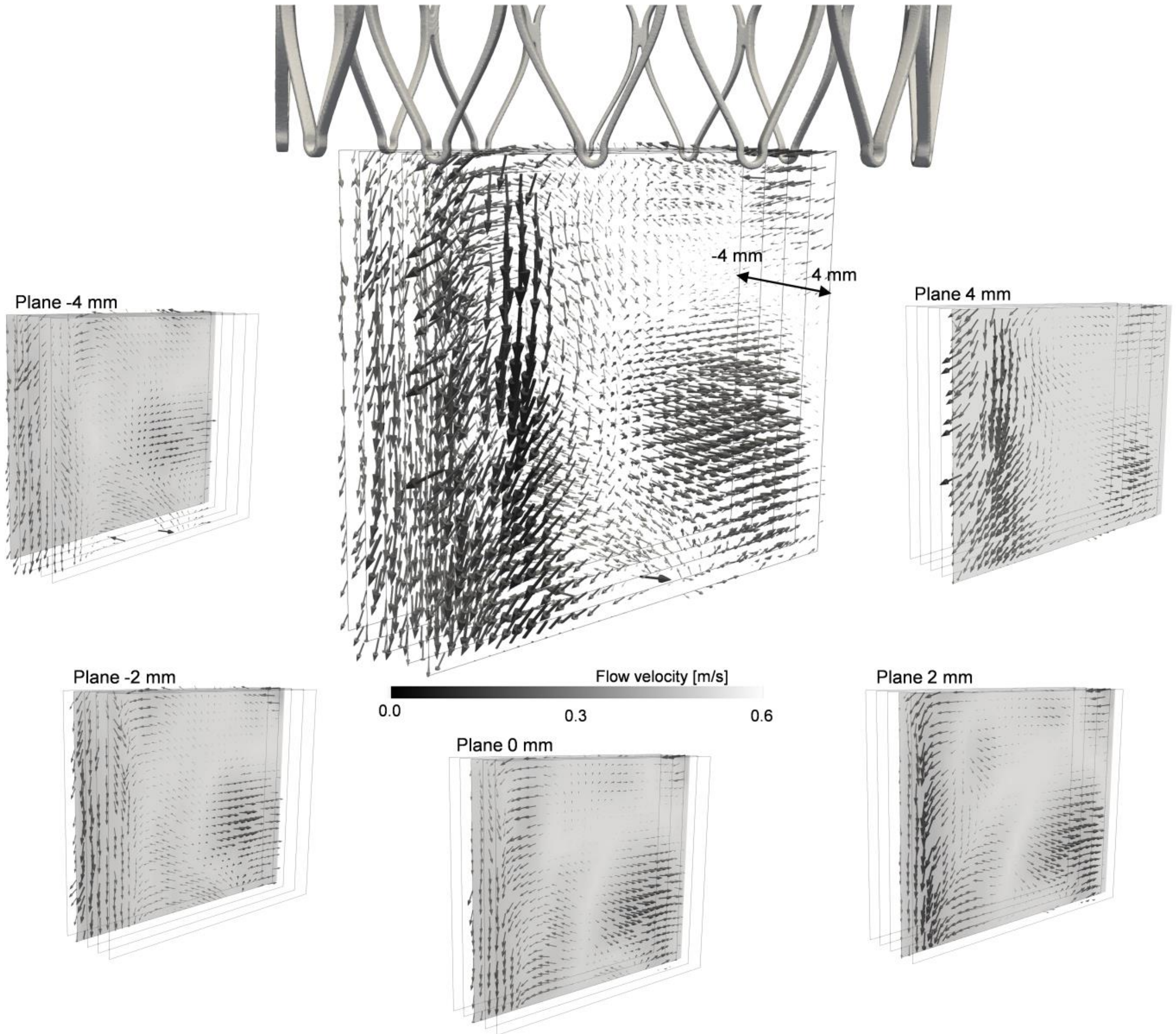

Fig. 8: Three-dimensional velocity vectors of the leakage jet, based on the stereo PIV measurements in different imaging planes.

The flow vectors in the investigated region give the impression of a leakage flow whose three-dimensional character is probably not negligible. On the contrary, the outer planes suggest that a more extensive area should be included in the measurements, as velocity magnitudes above 0.5 m/s still occur there as well. In this case, the use of a tomographic imaging strategy of PIV should be considered.

In this study, the flow visualization was presented at a point in time in diastole. However, a temporally and spatially highly resolved measurement is possible with this method.

Conclusion

Pulse duplicator system equipped with a stereo PIV setup is feasible for precise quantification of PVL, which leads to an improved understanding of the hemodynamic situation. Analysis of the PVL jet by PIV enhances the outcome of pulse duplicator measurements. Not only could TAVR developers gain necessary information for future patent-sealed devices, but cardiologists could also benefit through improved implantation strategies.

Author Statement

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