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Assessment of Thrombogenic Potential of Prosthetic Heart Valves based on Particle Image Velocimetry Measurements

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Abstract
Due to the promising clinical results obtained in the last decade, transcatheter aortic valve replacement (TAVR) is a broadly recognized alternative to surgical procedures in the treatment of severe aortic valve stenosis. However, due to the implantation procedure, in which the TAVR is placed inside the stenosed native valve and the aortic root, the implant modifies the post-procedural blood flow in comparison to the physiological blood flow of the native valve. These hemodynamic alterations caused by TAVR are associated with hypo-attenuated thickening of the prosthetic leaflets resulting in reduced leaflet motion. This, furthermore, can lead to sub-clinical leaflet thrombosis (SLT), which as a result may reduce the durability of TAVR. The current assessment of SLT risk of TAVR is based, among other things, on computing discrete particle trajectories from experimental measured velocity fields to evaluate the washout of TAVR (Lagrangian approach), a parameter associated with the formation of SLT. Other groups presented a continuum-based approach to quantify washout of TAVR by using an Eulerian transport equation in numerical simulations. The scalar value of the Eulerian transport equation should be understood as the duration of time that the blood remains in a defined environment and is affected by convective and diffusive transport. Accordingly, the result of the Eulerian transport equations is defined as blood residence time. From our point of view, this approach is promising to quantify the risk of thrombosis based on experimental data. To calculate the convection term of the transport equation, information about the velocities in the vicinity of the TAVR is necessary. For this purpose, we measured flow velocities in the vicinity of a TAVR by means of particle image velocimetry (PIV). Fluid dynamic conditions were generated using a circulation loop model that mimics blood flow in the left heart. Phase-averaged velocity fields were measured at 70 bpm for 150 cycles with a time resolution of 5 ms. Based on the dataset, the particle trajectories and the solution of the Eulerian transport equation were calculated using a numerical solver. The comparison of both methods has shown that the washout assessment with the Lagrangian approach is dependent on the spatial and temporal distribution of the particle. With the continuum-based Eulerian approach, on the other hand, information about the washout behavior is available at every time and any spatial location in the native sinus and neo sinus region.

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Introduction

Transcatheter aortic valve replacements (TAVR) are implanted in high-risk patients to treat pathological blood flow of a stenosed aortic valve. Due to promising clinical results obtained in the last decade, TAVR are broadly applied as an alternative to surgical procedures in the treatment of severe aortic valve stenosis. The good results led to an application of the therapy to patient cohorts with lower surgical risk, such as younger patients who also have higher life expectancy (Arsalan et al. 2016). Accordingly, the durability of the TAVR is becoming increasingly relevant, to ensure a high quality of life until old age for these patients.

The implantation procedure, in which the TAVR is placed within the stenotic native valve and aortic root, treats patients' acute symptoms. Nevertheless, the resulting, post-procedural, blood flow does not match the physiological flow conditions of a healthy aortic valve, because the native leaflets remain in the aortic root during TAVR implantation and are radially pressed outward by the implant. As a result, the native leaflets form a boundary, separating the sinus into two regions. The so-called neo sinus is formed by the leaflets of the TAVR and the remaining native leaflets, whereas the native sinus consists only of the native leaflets and the cavities of the aortic root (Kapadia et al. 2017).

Due to the geometrical configuration, blood ejected from the ventricle during each heart cycle can't reach the two sinus regions properly because of the remaining native leaflets, thus limiting the necessary washout in this region. A low washout has been frequently associated with thrombus formation (Salmonsmith et al. 2019).

The development of a thrombus layer on the prosthetic leaflets may lead to hypoattenuating thickening of the leaflets (HALT), which has already been reported by Makkar et al. (2015) in a relevant number of TAVR patients. If HALT reaches a critical extend, the movement of the prosthetic leaflets will be reduced and the durability of the TAVR may be severely limited. At the stage of an asymptomatic subclinical leaflet thrombosis (SLT), it is difficult to identify the clinical relevance of SLT. Nevertheless, the FDA recommends (Laschinger et al. 2015) to further investigate the development of SLT with its predictors, to identify a pathological threshold at an early stage.

Thrombus formation consists of various biomechanical and biochemical sub processes. Hemodynamic processes such as washout or high shear stress are incorporated into surrogate models to assess the thrombogenic potential of TAVR. Several experimental approaches but also simulations have been published addressing the quantification of thrombogenic potential of TAVR, e.g. Ducci et al. (2016) or Vahidkhah et al. (2017). Recently, Raghav et al. (2021) published a review of thrombosis mechanisms in context of TAVR and reported the use of Lagrangian particle tracing to analyze their thrombogenic potential. Here, the individual virtually seeded particle-trajectories are calculated and the number of particles remaining in the sinus region is counted after one cardiac cycle. The corresponding results depend on the location and number of initially defined particles in the region of interest (ROI).

To circumvent this dependence, we applied an alternative approach to compute the washout of TAVR with an Eulerian transport equation. This approach has already been used in numerical studies, as published by Vahidkhah et al. (2017) or Menichini et al. (2016) in context of aortic dissection, and provides an advantage to the Lagrangian approach by considering a continuum. Plitman Mayo et al. (2020) already published a comparison of five different surrogate parameters for the assessment of thrombogenic potential of TAVR, including the Lagrangian und Eulerian transport approach, based on numerical simulation data.

In this study, we present an approach in which a Eulerian transport equation is solved based on experimental data of the velocity field in the vicinity of a TAVR obtained by PIV. We compared this approach with the Lagrangian approach applied to the same velocity field in terms of efficacy and reliability to estimate the risk of SLT. To the authors knowledge, the application of the Eulerian approach on a PIV measured velocity field was not published yet. The

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approaches are used to calculate a surrogate parameter that identifies the localization and extent of stagnation areas in the native sinus and neo sinus of the aortic root after TAVR. Thus, the washout behavior and accordingly the thrombogenic potential of TAVR can be determined qualitatively and quantitatively.

Material and Methods

Experimental test setup to measure the velocity field

The velocity field in the vicinity of a TAVR was measured using PIV (2D2C setup, Dantec Dynamics, Skovlunde, Denmark). A detailed description of the measurement setup was previously published in Borowski et al. (2020). The results were measured phase-averaged (n = 150) with a time resolution of Δt = 5 ms. A physiological flow condition was generated using a piston pump-driven cardiovascular circulation loop (ViVitro Labs Inc., Victoria, BC, Canada) representing the blood flow of the left heart, see Table 1.

Table 1: Physiological parameters used as input parameter set of the cardiovascular circulation loop.

Clinical parameter		**Standard deviation**
Heart rate	70 bpm	± 0 bpm
Mean aortic pressure	100.84 mmHg	± 0.18 mmHg
Systolic duration	36.88 %	± 0.38%
Fluid temperature	37°C	± 2°C
Cardiac Output	5.00 l/min	± 0.10 l/min

For the anatomical implantation environment, we applied a generic aortic root model based on retrospectively analyzed clinical CT data from TAVR patients, for details see Borowski et al. (2020). The 2D measurement plane was located at the center of the non-coronary TAVR leaflet, see Fig. 1.

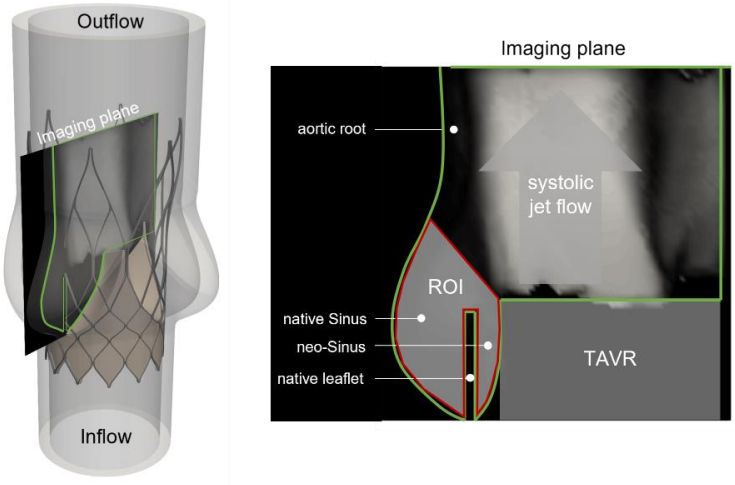

Fig. 1: Location of the laser imaging plane in the center of the non-coronary TAVR leaflet and illustration of the anatomical components at an exemplary velocity field from the PIV data.

Lagrangian particle tracing

The Lagrangian particle tracing consisted of four steps, see Fig. 2. After the PIV measurements, we first defined the ROI including the native sinus and neo sinus, both represent sensitive areas for thrombus formation in step 1.

At step 2, particles were virtually seeded within the ROI. The minimum number of required particles to obtain a valid solution was determined by conducting a sensitivity analysis. An interaction between different particles and between particles and flow is not considered. The diameter and mass of the particles were neglected, as well as gravitational and buoyancy forces.

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Within step 3, we defined boundary conditions for the particles. The particles could leave the ROI according to the velocity field through the upper boundary of the ROI (outflow, see Figure 2). Based on the assumption of linear motion between two timesteps, the trajectories were calculated for each particle using the streamlines derived from the flow field (step 4). The particle trajectories are defined by:

$$\dot{x}(t) = \vec{u}(\vec{x}, t) \tag{1}$$

Accordingly, the time derivative of the local movement of a particle is equal to the velocity vector $\vec{u}$ of the flow field at the location $\vec{x}$ of the particle at each time step t.
This permits the calculation of the residence time of a blood component and the quantification of the washout by analyzing the number of particles remaining in the ROI after a cardiac cycle.

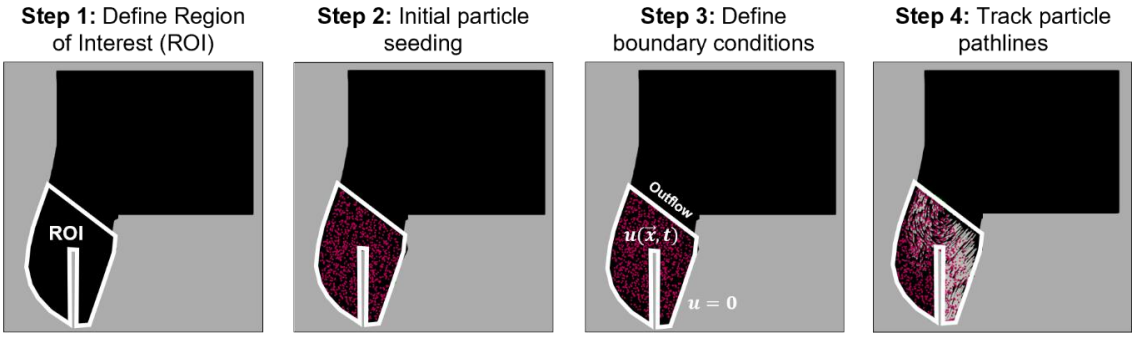

Fig. 2: Workflow of Lagrangian particle tracing based on the time-resolved measured PIV data of the velocity field during the flow through a TAVR.

Eulerian transport equation for residence time

Fig. 3 shows the workflow of the four steps to assess the washout behavior of a TAVR by means of an Eulerian transport equation for RT. In step 1 we defined the geometric environment in which the measured PIV velocity data was located and considered an unchangeable geometry over time. Step 2 implied the meshing of the 2D geometry. In step 3, we defined a concentration of $RT = 0$ at the inlet, an outflow condition at the upper boundary and a convective flux condition $-\boldsymbol{n} \cdot (D\nabla RT) = 0$ at the other boundaries.
The Eulerian approach to assess the washout of TAVR is based on the calculation of RT, which is assumed to be a continuous scalar:

$$\frac{\partial RT(\vec{x},t)}{\partial t} + \nabla\big(\vec{u}(\vec{x}, t) \cdot RT(\vec{x}, t)\big) = \nabla\big(D \cdot \nabla RT(\vec{x}, t)\big) + S(\vec{x}, t) \tag{2}$$

The alteration of RT as a function of position and time is thus dependent on the general spatial- and time-dependent velocity field $\vec{u}(\vec{x}, t)$, the diffusion coefficient *D*, and a source term $S(\vec{x}, t) = 1$.

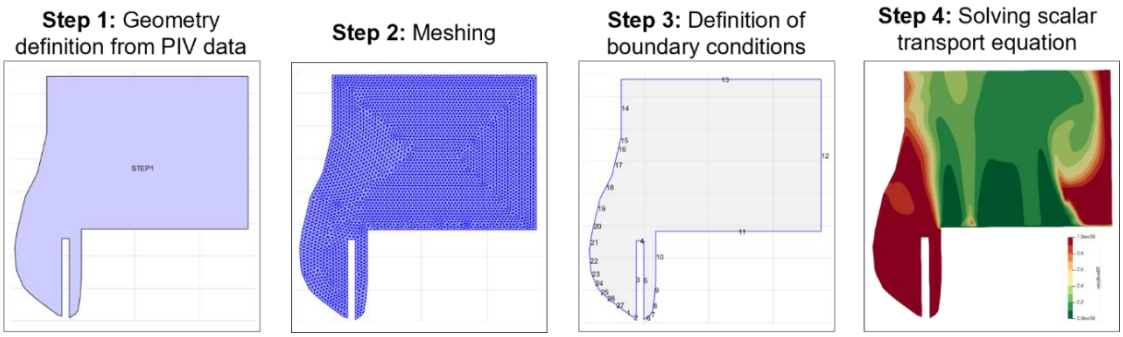

Fig. 3: Workflow of the scalar transport calculation based on the time-resolved measured PIV data of the velocity field during the flow through a TAVR.

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The FEATool Multiphysics software (Precise Simulation Limited, Hong Kong) was used to solve the Eulerian transport equation. We used a time dependent linear backslash solver with a Crank-Nicolson time stepping scheme.
To quantify the thrombosis risk, the area of high RT was calculated. For this purpose, we normalized RT due to the cardiac cycle time and evaluated the area with a relative RT above 95%.

Results and Discussion

Evaluation of the washout by means of Lagrangian particle tracing

For the Lagrangian approach, different numbers of initially distributed particles were investigated. Based on the calculated trajectories, the number of particles remaining in the ROI was obtained for one cardiac cycle. The percentage of particles remaining in the ROI as a function of time is shown in Fig. 5.
For the simulation with 10, 100 and 1,000 particles, larger deviations in the percentage of particles present in the ROI were observed. There is only minor variation between 5,000 and 10,000 particles, so we assumed that a particle count of 5,000 particles in the ROI was sufficient. It can be determined that approx. half of the particles are washed out during the systolic phase of the cardiac cycle. At the end of diastole, approx. 30% of the initially seeded particles were still in the ROI with the Lagrangian particle tracing.

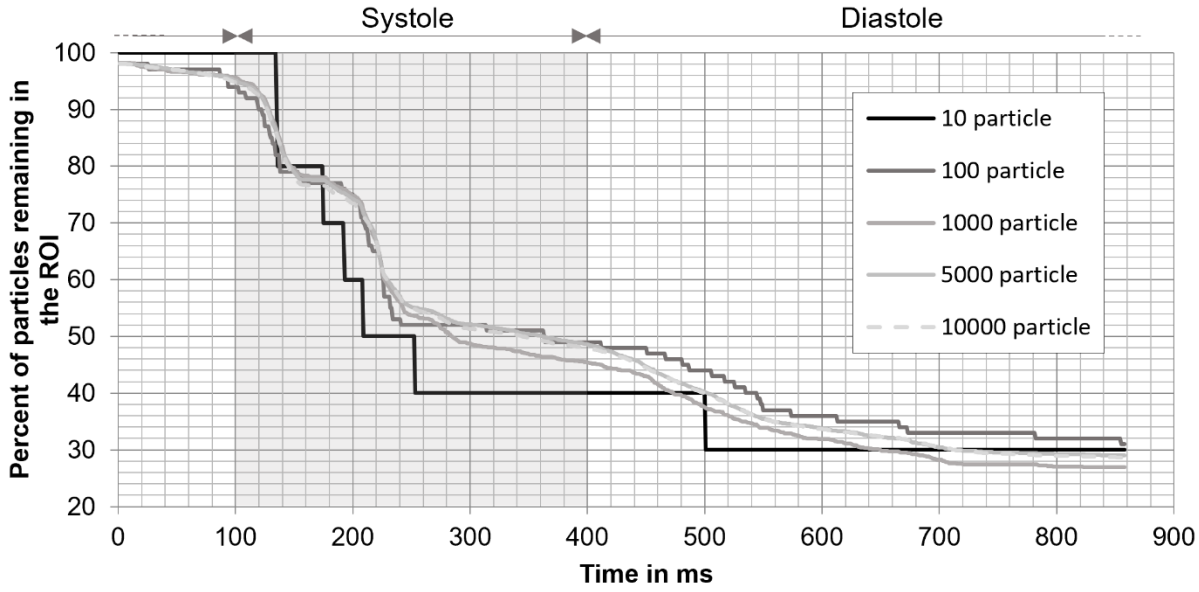

Fig. 5: Time-resolved percentage of particles remaining in the ROI for different numbers of particles initially distributed in the ROI.

Fig. 6 shows the initial particle distribution as well as the particle distribution at selected time points within the cardiac cycle. Additionally, the flow velocities from the PIV data at the same time points are shown. Based on the particle distribution, the particles in the neo sinus were washed out rapidly during systole and only fewer particles above the native leaflets exit the outflow. After one cardiac cycle (t = 850 ms), the concentration of locally remained particle was very high, whereas almost no particles remained in the neo sinus region.

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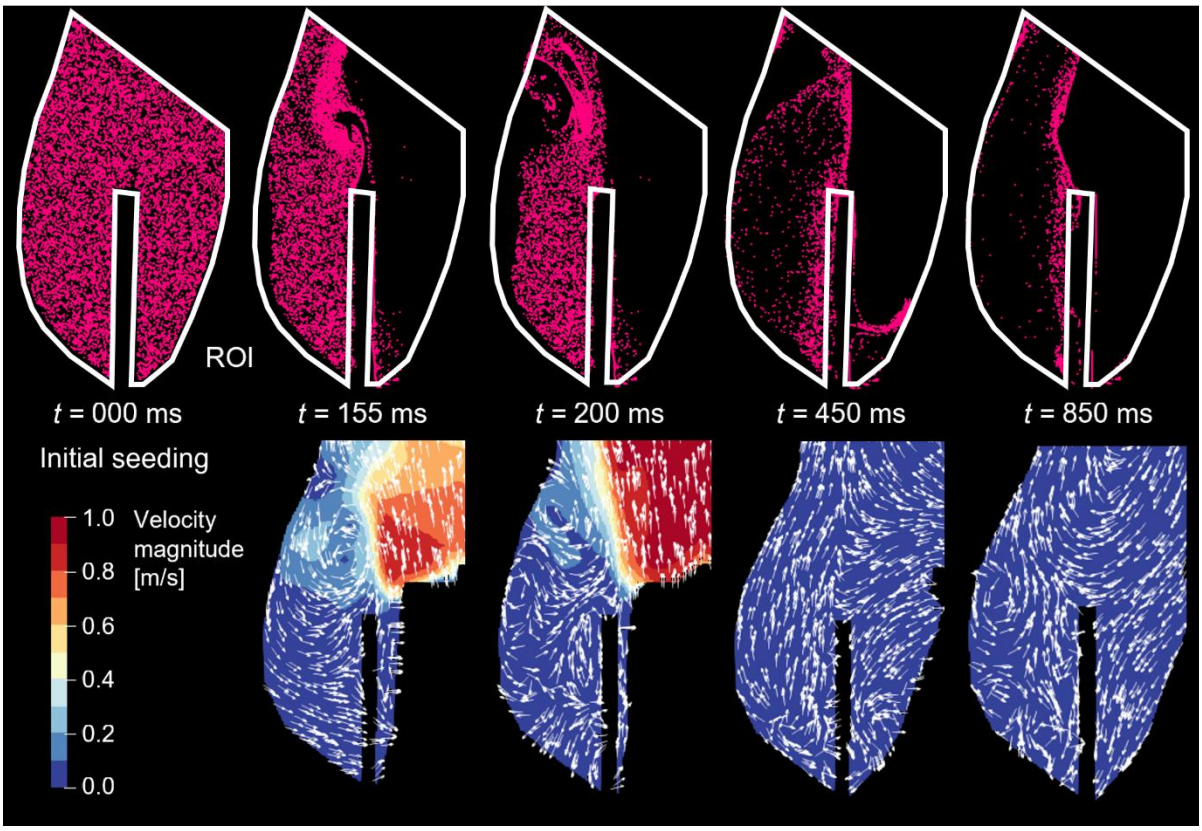

Fig 6: Plot of virtually seeded particles (top) and velocities from PIV data (bottom) at several times.

Evaluation of the washout by Eulerian scalar transport

For washout behavior evaluated from Eulerian transport equation, the area of blood with high RT was calculated as a quantitative metric for the two-dimensional velocity data. The time dependent area with high RT within a cardiac cycle is shown in Fig. 7.

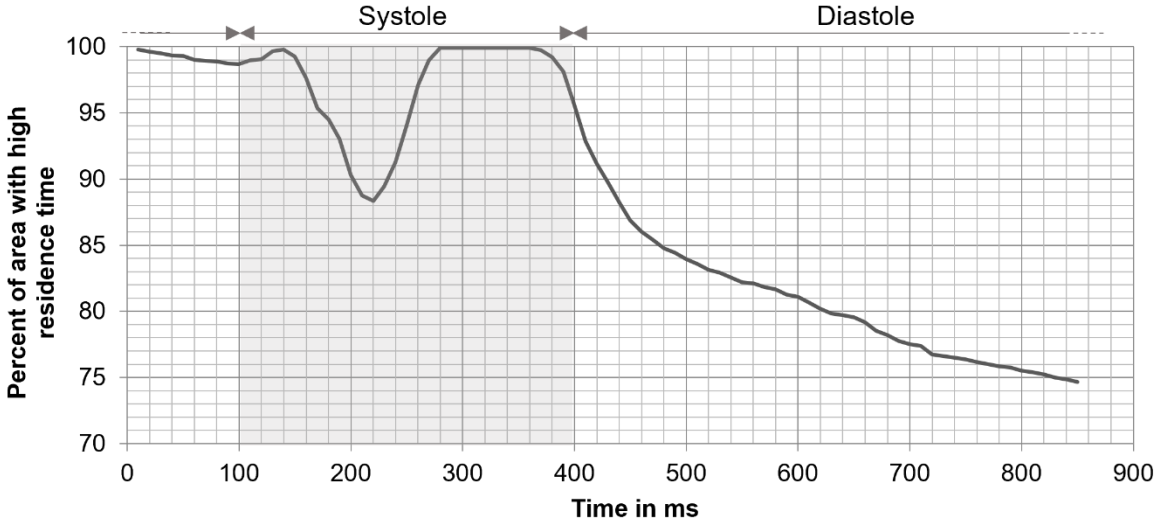

Fig. 7: Time-resolved percentage of area with high residence time (t > 95%) relative to the total cardiac cycle time.

The graph shows that during systole, the area of high RT in the ROI initially decreased, but new blood with high RT flowed in so that the percentage of high RT increased again. The percentage of the area with high RT thus reaches 100% of the ROI again at the end of systole.

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During diastole, the area with high RT decreased continuously and is approx. 75% at the end of one cardiac cycle.
Figure 8 shows the spatial distribution of blood RT, particularly in the ROI, and velocities obtained from the PIV data for different time points in the cardiac cycle. Based on the time points, the reduction in the area of high RT during systole was caused by the recirculation area above the native leaflets. After one cardiac cycle, the RT in the neo sinus was significantly lower than in the native sinus.

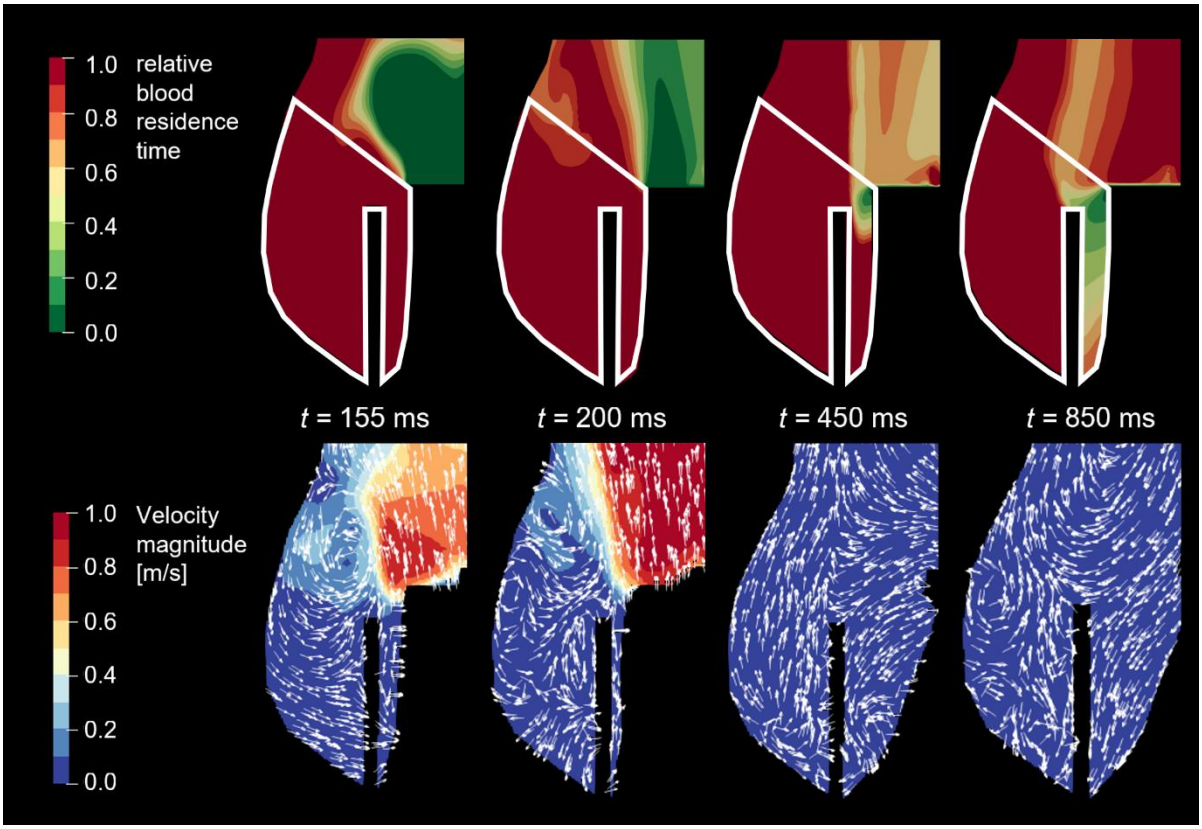

Fig. 8: Contour plot of relative blood residence time (top) and velocities from PIV data (bottom) at several times.

Lagrangian vs. Eulerian

In this study, both the Lagrangian and the Eulerian approach were used to investigate the washout behavior of TAVR. For this purpose, the same data set determined experimentally by PIV was used in both approaches. However, the surrogate parameter for the Lagrangian and the Eulerian approach as a function of cardiac cycle time show differences, compare Fig. 5 and Fig. 7. While for Lagrangian particle tracing only a decrease of particles in the ROI was allowed, with the Eulerian approach it is possible that the area of high RT increases again during the cardiac cycle.
A limitation of the discrete approach with Lagrangian particle tracing is that information about the current washout is only available at the current position of the particles. Accordingly after one cardiac cycle, information of potentially thrombogenic regions are rare due to the low particle density, see Fig. 6 (t = 850 ms). In addition, the initial position and timing of particles in the cardiac cycle could have an influence on the washout of the particles.
This dependence of local distribution and temporal onset in the cardiac cycle is not applicable for the continuum-based Eulerian transport approach. These aspects are therefore not a limitation for the Eulerian approach. With this approach, information about the blood RT is available at any time and any location, influenced only by the boundary condition $RT = 0$ at the inflow of the TAVR. Continuous seeding of particles at the inflow of the TAVR for the Lagrangian

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approach, however, would probably not increase the number of particles flushed into the sinus during the cardiac cycle. Therefore we could recommend the Eulerian transport approach for quantitative and qualitative assessment of thrombosis potential of TAVR.

Conclusion

In this study, we compared two approaches to assess the thrombotic potential of TAVR. The results show that physiological seeding of particles with the Lagrangian approach is questionable and that the continuum-based Eulerian approach is a less sensitive method with respect to initial conditions. In addition, the presented Eulerian approach provides spatial and temporal information on the washout behavior of TAVR throughout the whole cardiac cycle.
As recommended by the FDA (Laschinger et al. 2015) further investigation of the development of SLT with its predictors, to understand the SLT development process and to identify a pathological threshold should be the aim of hemodynamic analysis. The Eulerian method thus offers the potential to expand the understanding of the complex fluid mechanical processes to derive specific design modifications.

Acknowledgement

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