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ORIGINAL ARTICLE

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Incomplete expansion of transcatheter aortic valves is associated with propensity for valve thrombosis

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ADULT CARDIAC

Key question

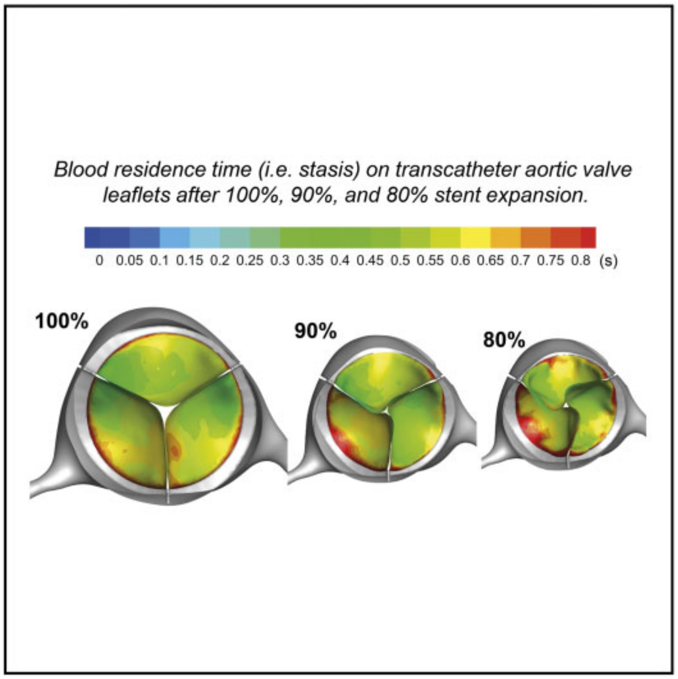
Does transcatheter aortic valve (TAV) underexpansion increase the risk of leaflet thrombosis?

Key finding(s)

The results of this study indicated that incomplete expansion of TAVs increases blood stasis on the surface of leaflets.

Take-home message

TAV underexpansion can potentially increase the risk of leaflet thrombosis in patients undergoing TAV replacement.



Abstract

OBJECTIVES: Clinical and subclinical leaflet thromboses are increasingly recognized complications following transcatheter aortic valve replacement. Identification of the risk factors is important to mitigate the occurrence of leaflet thrombosis in transcatheter aortic valves (TAVs) and ensure their long-term function. The goal of this study was to determine the effect of incomplete expansion of TAVs on the likelihood of leaflet thrombosis following transcatheter aortic valve replacement.

METHODS: Using experimental and computational methods, 3-dimensional unsteady flow fields of 26-mm SAPIEN 3 valves expanded to 3 different diameters (i.e. 26.0 mm, 23.4 mm and 20.8 mm) were determined in patient-specific geometries. The diameters corresponded to 100%, 90% and 80% stent expansion, respectively. To address the potential difference in the likelihood of leaflet thrombosis, blood residence time (i.e. stasis) and viscous shear stress on the surface of TAV leaflets were quantified and compared.

RESULTS: The results indicated that TAV underexpansion increased blood stasis on the TAV leaflets. Blood residence time on the surface of the leaflets after 80% and 90% TAV expansion on average was 9.4% and 4.1% more than that of the fully expanded TAV, respectively.

In addition, areas of blood stasis time of more than 0.5 s, which are highly prone to platelet activation, increased linearly as the degree of TAV underexpansion increased.

CONCLUSIONS: Incomplete expansion of TAVs increases blood stasis on the surface of TAV leaflets. Regions of blood stasis promote platelet activation and thrombotic events. TAV underexpansion can therefore increase the risk of leaflet thrombosis in patients with transcatheter aortic valve replacement.

Keywords: Transcatheter heart valve replacement • Leaflet thrombosis • Neosinus region • Blood residence time

INTRODUCTION

Transcatheter aortic valve replacement (TAVR) is a safe and effective treatment in patients with severe aortic valve stenosis. Despite excellent clinical outcomes, clinical and subclinical leaflet thromboses with reduced leaflet mobility have been observed following TAVR [1]. Reports indicate that the rate of leaflet thrombosis is higher in TAVR than in surgical aortic valve replacement [2]. Patients with leaflet thrombosis showed a significantly higher rate of strokes and transient ischaemic attacks [1, 2]. Therapeutic anticoagulation as compared with dual antiplatelet therapy was associated with a decrease in the incidence of reduced leaflet motion in the patients [1, 2]. However, bleeding is a complication of anticoagulation therapy, and recurrence of reduced leaflet motion has been observed following discontinuation of the therapy [2–4]. Therefore, determining the risk factors affecting leaflet thrombosis in transcatheter aortic valves (TAVs) is essential to mitigate the occurrence of leaflet thrombosis and ensure long-term function of the bioprostheses.

Existing data suggest that the haemodynamic environment in the vicinity of the TAVs is crucial in the initiation and formation of leaflet thrombosis. We previously investigated the underlying flow-mediated mechanism that facilitates thrombus formation on TAV leaflets using computational modelling and simulations [5, 6]. In contrast to surgical aortic valve replacement, in which native calcified leaflets are removed from the annulus during open heart surgery, TAVs are implanted within native calcified valves in TAVR procedures or within degenerated bioprostheses in transcatheter aortic valve-in-valve (ViV) implantation. As a result, the aortic portion of the TAV frame is circumferentially surrounded by calcified native valves in TAVR or by degenerated bioprostheses in ViV procedures. This configuration is more pronounced in TAV devices that tend to operate inside the annulus than in supra-annular devices. Our previous studies have shown that the geometric confinement of TAVs, also lately called formation of a neosinus region [7], increases blood residence time (BRT) (blood stasis) on the TAV leaflets and consequently increases the likelihood of thrombogenesis [5, 6, 8]. Regions of blood stasis provide an opportunity for activated platelets and coagulation factors to accumulate to critical concentrations that in time can lead to thrombosis [9].

The native anatomy of a patient's aortic root and the geometry and relative position of the TAV after deployment together create a unique anatomical configuration that can alter the location and severity of blood stasis on the TAV and in the sinus region. Current clinical data show that leaflet thrombosis originates primarily on the aortic side of the TAV leaflets [1, 10, 11]. Furthermore, the data suggest that possible risk factors include lack of anticoagulation therapy [2, 11–14]; a ViV procedure [6, 12, 15]; larger body mass index [12, 15]; type, size and implantation depth of TAVs [1, 2, 14–19]; and patient-specific anatomical and haemodynamic features [20, 21]. Moreover, the currently available clinical data suggest that leaflet thrombosis may be associated with overall and regional underexpansion of the TAVs [17, 22]. Previous studies also suggested that alterations in the degree of stent expansion leads to distorted leaflet coaptation, which affects valve haemodynamics, puts the patients at higher risk of patient–prosthesis mismatch and over time can negatively influence long-term valve durability [23]. However, the role of TAV underexpansion in the risk of leaflet thrombosis has not been fully investigated and comprehensive data are lacking. The objective of this study was to determine the impact of incomplete TAV expansion on blood stasis on the TAV leaflets. High degrees of incomplete expansion of the TAV frame from excessive valve oversizing distort TAV leaflets, impair leaflet kinematics and can potentially increase blood stasis on the TAV leaflets. Regions of blood stasis on the surface of TAV leaflets can consequently increase the risk of leaflet thrombosis following TAVR and ViV procedures.

MATERIALS AND METHODS

Making detailed flow measurements close to the TAV leaflets is a challenge in real-world clinical settings because the currently available imaging modalities have limited temporal and spatial resolution. Therefore, in this study, both experimental testing and computational modelling were utilized to investigate the flow field nearby fully expanded and underexpanded TAVs. We focused our study on TAVR procedures with TAV devices with an intra-annular design that represents the worst-case scenario in terms of blood stasis on the leaflets [8]. A 26-mm Edwards SAPIEN 3 (Edwards Lifesciences, Irvine, CA, USA) was expanded to 3 different diameters: 26.0 mm, 23.4 mm and 20.8 mm. The degree of TAV expansion was computed using the following equation:

$$\%\ \text{TAV expansion}: \left[1 - \frac{D_i - D_t}{D_i}\right] \times 100 \qquad (1)$$

where D_i and D_t are the intended (i.e. 26 mm) and true annular diameters of the TAV, respectively. The 3 diameters (26.0 mm, 23.4 mm and 20.8 mm) correspond to 100%, 90% and 80% expansion, respectively. This range of valve underexpansion has been observed previously in clinical studies [7]. TAV underexpansion resulted in leaflet distortion as shown in Fig. 1. The valves were examined under physiological loading conditions in a custom-built pulse duplicator system (BDC Labs, Wheat Ridge, CO, USA). Transvalvular pressure waveforms and the flow rate of the valves were obtained from the *in vitro* tests. Methodological details of the tests are provided in the Supplementary Material [24].

Subsequently, a fluid–solid interaction computational method was used to simulate the 3-dimensional (3D) unsteady flow field

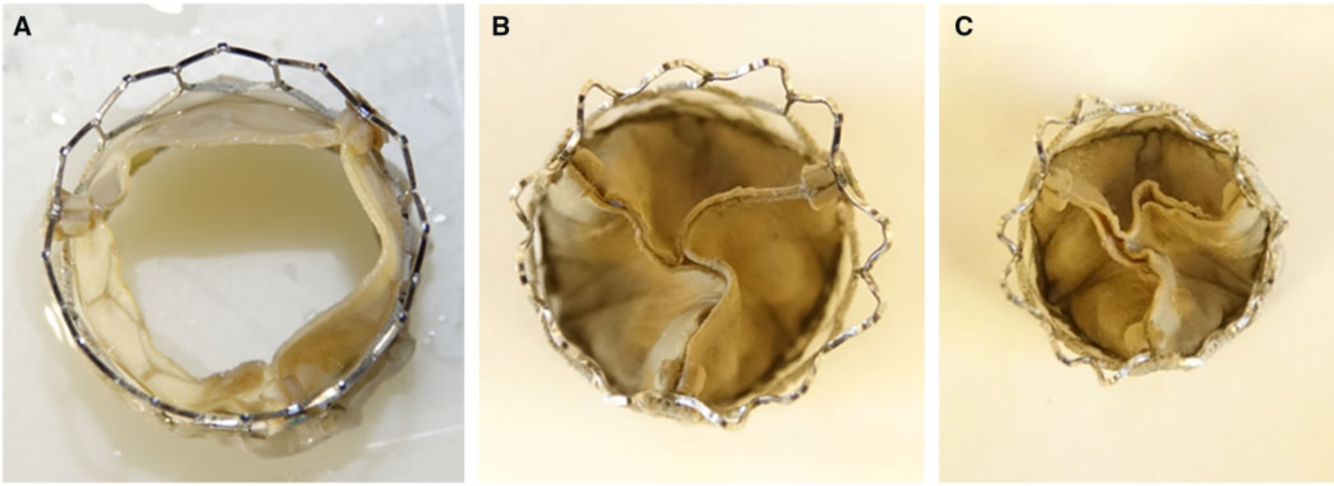


Figure 1: The 26-mm SAPIEN 3 valves with different degrees of expansion: (**A**) fully expanded, (**B**) 90% expanded and (**C**) 80% expanded.

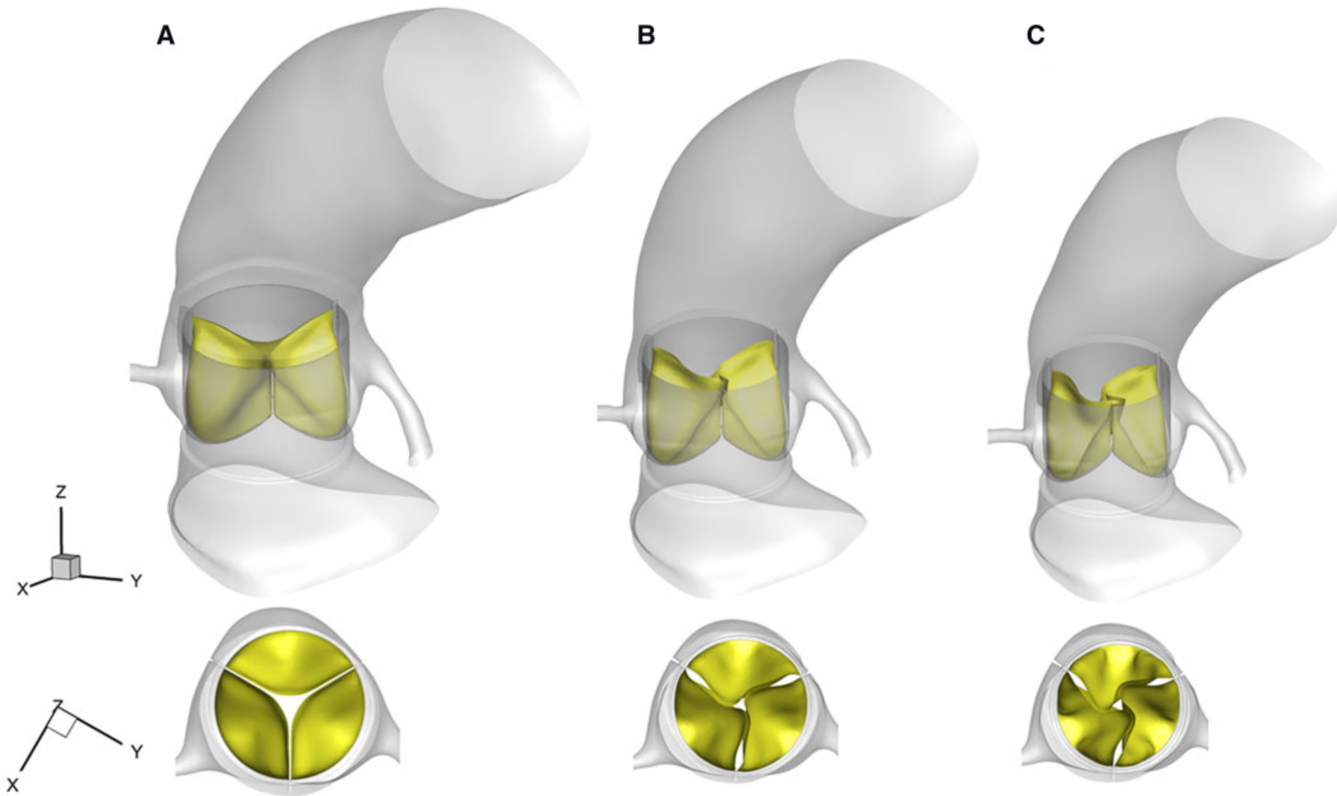


Figure 2: Computational 3-dimentional models for the transcatheter aortic valve replacement model for (**A**) fully expanded transcatheter aortic valve (TAV), (**B**) 90% TAV model and (**C**) 80% TAV model.

of the TAVs in patient-specific geometries (Fig. 2). An advantage of the computational modelling approach is that it can overcome the inherent limitations of *in vitro* experimental testing to obtain 3D flow patterns adjacent to the TAV leaflets (e.g. lack of optical access to the entire 3D neosinus region and difficulties in simulating physiological coronary flow in the *in vitro* systems). Methodological details of the computational approach are also available in the Supplementary Material. To address the potential difference in blood stasis, and in turn, thrombus formation in the models, blood washout from the leaflets was visualized and quantified. To visualize the washout of blood from the leaflets, a Lagrangian approach was used. Randomly distributed imaginary massless particles in the volume between the aortic surface of each leaflet and the inner surface of the confining geometry were individually tracked during 1 cardiac cycle. It should be noted that this is not a particle-tracking approach and that particles were created for visualization only and were imaginary to show the flow pattern over leaflets. Then, a Eulerian approach was implemented to quantify BRT (stasis) on the leaflets. BRT was represented by a scalar quantity

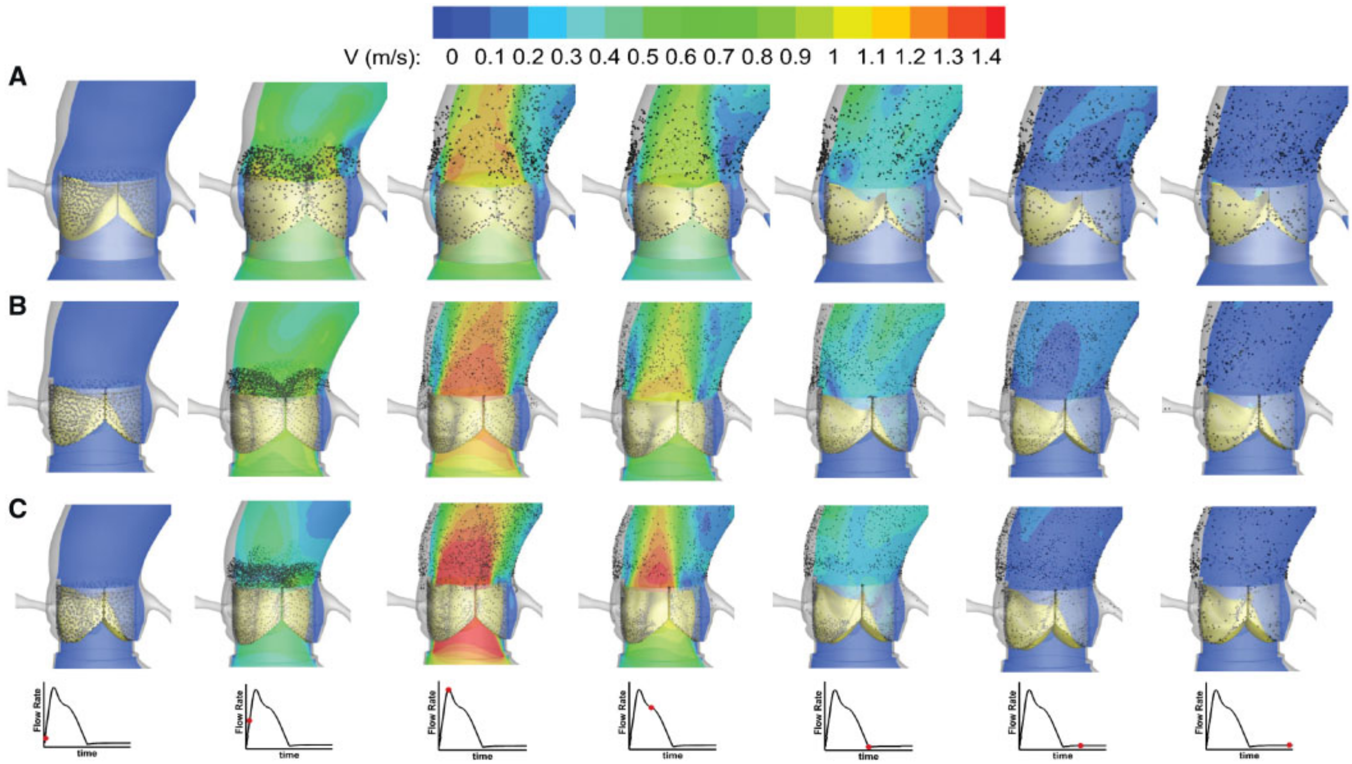


Figure 3: Snapshots showing the configuration of the flow field and the particles released on the leaflets at different time instances in a cardiac cycle for (**A**) fully expanded transcatheter aortic valve (TAV), (**B**) 90% expanded TAV and (**C**) 80% expanded TAV. The contours of the velocity magnitude are shown in the mid-plane longitudinally cutting through the computational domain.

defined as residence time (T_R). T_R is governed by the following equation:

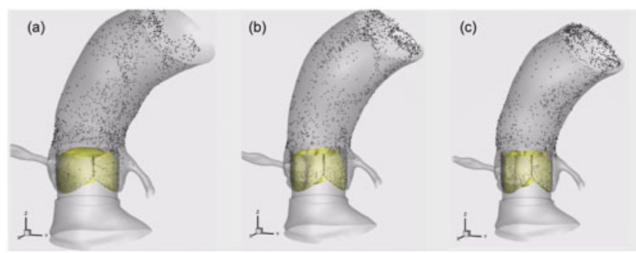
$$\frac{\partial T_R}{\partial t} + \mathbf{v}.\nabla \mathrm{T_R} = 1 \qquad (2)$$

where $\boldsymbol{v}$ is the flow velocity vector. Equation 2 and the mass and momentum conservation equations were solved simultaneously.

RESULTS

Figure 3 shows sample snapshots of the simulated flow fields at multiple time instants in a cardiac cycle, namely (i) early systole (ii) flow acceleration, (iii) peak of flow, (iv) flow deceleration, (v) early diastole, (vi) mid-diastole and (vii) end of diastole. The flow patterns are shown by the contours of velocity magnitude in the mid-plane cutting through the TAV. The configuration of the massless particles that were initially released on the TAV leaflets for flow visualization is shown by black dots. Each dot represents 1 massless particle. The general characteristics of the central jet were observed to be similar between the 3 models. However, the maximum jet velocity was higher in the underexpanded TAVs. At the peak of flow, the maximum jet velocity was 1.79 m/s and 1.51 m/s for 80% and 90% models, respectively, which was higher than the maximum jet velocity of 1.40 m/s for the fully expanded TAV. In addition, Video 1 clearly shows the movement of the massless particles during 1 cardiac cycle in the 100%, 90% and 80% TAV models.

Figure 4 shows viscous shear stress in the flow field in the mid-plane cutting through the TAV (top row) and wall shear stress on the TAV leaflets on the ventricular side (bottom row) at the peak



Video 1: Movement of the massless particles in the (**A**) fully-expanded transcatheter aortic valve (TAV), (**B**) the 90% expanded TAV and (**C**) the 80% expanded TAV during a cardiac cycle.

of flow in the 100%, 90% and 80% TAV models. Both viscous shear stress in the flow field and wall shear stress on the TAV leaflets increased as the degree of valve underexpansion increased. The non-physiological flow pattern after valve implantation is associated with blood damage ranging from platelet activation (to probably thrombosis) and haemolysis. Platelet activation is known to depend not only on the cell contact with foreign surfaces but also on the flow shear stress magnitude and exposure time. Several studies investigated the risk of platelet activation and set shear stress thresholds that mark the onset of platelet activation (Table 1). The results of the simulations demonstrated that the shear stress levels and exposure times were below the reported flow-induced platelet activation thresholds. Therefore, shear-induced platelet activation is unlikely in the settings.

We also observed a considerable difference in blood stasis on the leaflets in the 100%, 90% and 80% models. BRT was quantified by calculating T_R in Equation 2. Figure 5 shows the contours of the BRT during different time instants of a cardiac cycle from a

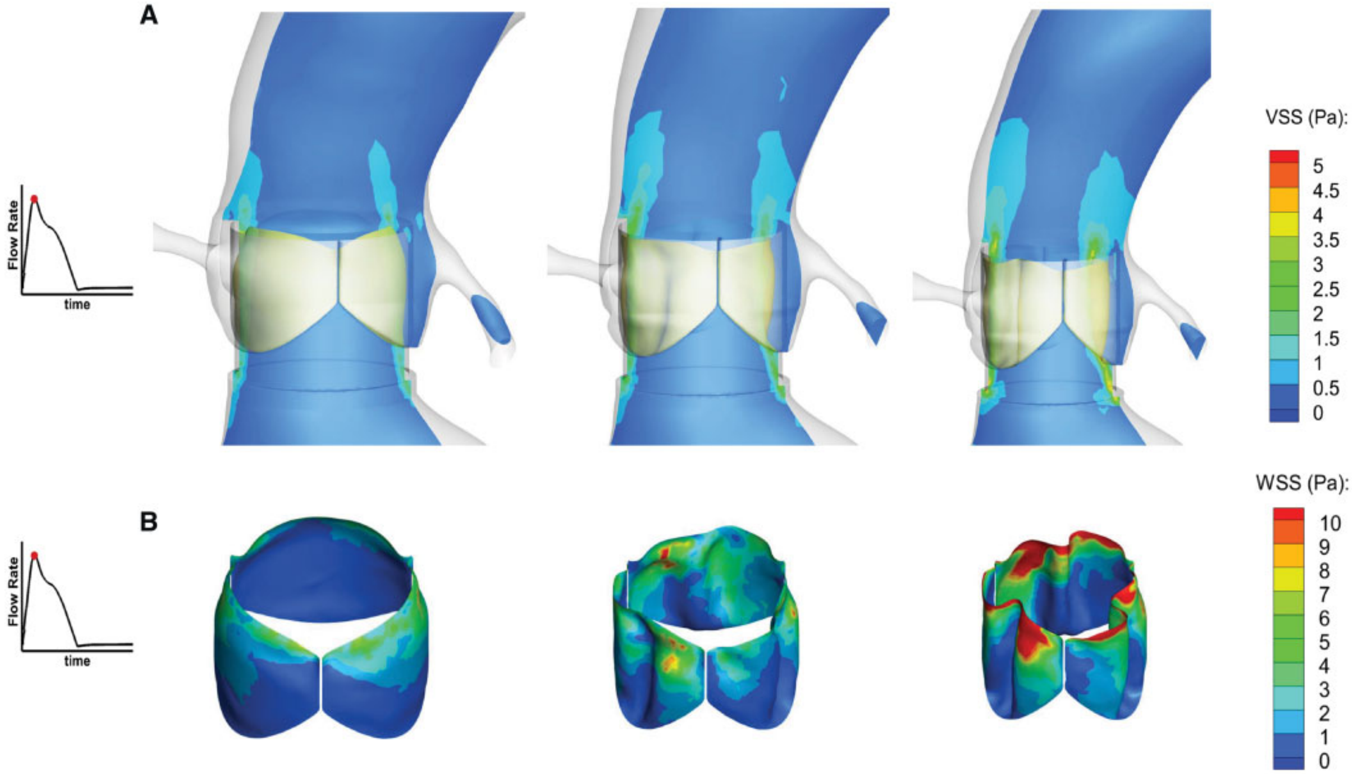
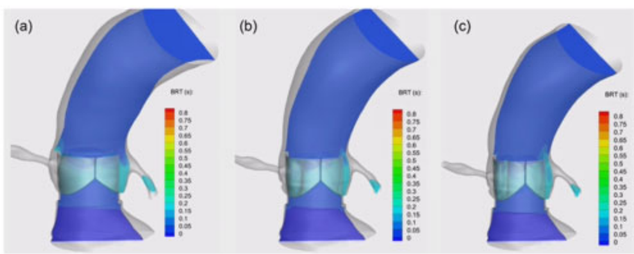


Figure 4: Snapshots showing the (**A**) VSS in the flow field around the transcatheter aortic valve (TAV) and (**B**) WSS on the TAV leaflet at the peak of flow for different degrees of underexpansion, i.e. (left) fully expanded TAV, (centre) 90% expanded TAV and (right) 80% expanded TAV. VSS: viscous shear stress; WSS: wall shear stress.



Video 2: Distribution and magnitude of blood residence time on the surface of the transcatheter aortic valve (TAV) leaflets and in the mid-plane longitudinally cutting through the computational domain in the (**A**) fully expanded TAV, (**B**) 90% expanded TAV and (**C**) 80% expanded TAV during a cardiac cycle.

top view on the 3 leaflets of the SAPIEN 3 at the 3 degrees of valve expansion. The BRT on the TAV leaflets was considerably higher in the underexpanded valves than in the fully expanded TAV. The areas that exhibited high BRT, shown in red, were concentrated near the fixed boundary of the leaflets. Video 2 clearly shows the distribution and magnitude of BRT in the 100%, 90% and 80% models. The difference among the settings was also quantified by comparing the average value of the BRT on the surface of the TAV leaflets. The surface-averaged value of the BRT on the leaflets signifies the tendency towards blood stasis on the leaflets on an average basis. At the end of diastole, the average values of the BRT on the surface of the TAV leaflets after 80% and 90% TAV expansion were 9.4% and 4.1% more than that of the fully expanded TAV, respectively. We also observed regions of blood stasis in the base of the aortic sinuses. For more details regarding distribution and magnitude of BRT in the sinus region (Video 2).

Table 1: Shear stress threshold ranges and corresponding exposure times

Shear stress threshold (Pa)	Order of exposure time (s)	References
10–16.5	10^{2}	Hung *et al.* [25]
13	10^{-3}	Williams [26]
30–100	10^{-2} to 10^{1}	Ramstack *et al.* [27]

Acute thrombogenesis occurs on foreign surfaces of the TAV leaflets following valve implantation. The characteristic time of platelet activation is suggested to range from 0.1 s to 0.5 s [28]. In this study, areas of BRT more than 0.5 s that are highly prone to platelet activation were compared among the 3 models. The areas of the BRT on the aortic surface of the TAV leaflets with a value more than 0.5 s were found to be 93.4% and 84.4% of the total surface of the TAV leaflets after 80% and 90% TAV expansion, respectively. This value was only 70.4% in the fully expanded valve. A summary histogram of the escalation of the BRT on the surface of the TAV leaflets as a result of TAV underexpansion is shown in Fig. 6. As the degree of valve underexpansion increased, a clear shift was observed in the BRT histograms towards the right side, particularly with a higher number at the end of histogram, representing more stasis (Fig. 6A–C). In addition, as shown in Fig. 6D, the percentage of leaflet area with a BRT greater than 0.5 s increased linearly as the degree of TAV underexpansion increased. The results of the present study show that TAV underexpansion will increase considerably the areas with high BRT on the surface of TAV leaflets.

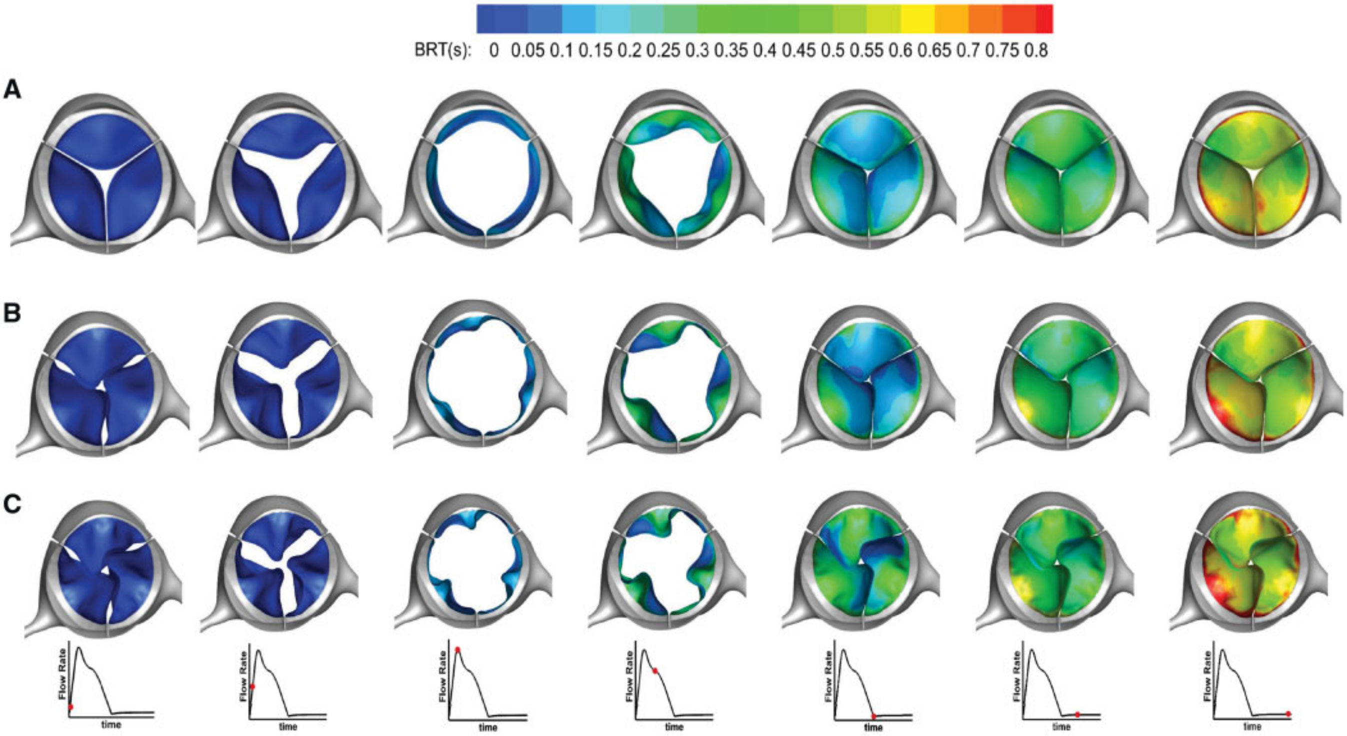


Figure 5: Snapshots showing the time evolution of the contours of the BRT on the valve leaflets from the top view during a complete cardiac cycle for the (**A**) fully expanded transcatheter aortic valve (TAV), (**B**) the 90% expanded TAV and (**C**) the 80% expanded TAV. BRT: blood residence time.

DISCUSSION

Detailed flow field measurements in the vicinity of TAV leaflets in patients who had TAVR is challenging due to the limited temporal and spatial resolution of the currently available imaging modalities. As a result, personalized computational modelling has the potential to provide a mechanistic explanation for TAV thrombosis on a case-by-case basis and fill the knowledge gap by obtaining detailed 3D flow patterns in proximity to TAVs from which metrics such as the BRT and shear stress can be derived. The results of the present study indicated that TAV underexpansion increases blood stasis on the surface of TAV leaflets. Regions of blood stasis promote thrombotic events and provide an opportunity for activated platelets and blood components to accumulate to critical concentrations, which in time can lead to leaflet thrombosis. As a result, it can be postulated that incomplete expansion of the TAV devices increases the risk of leaflet thrombosis following TAVR procedures.

Clinical and subclinical leaflet thromboses of TAVs following TAVR and ViV procedures have been characterized in different studies [15]. Variations in classifications of leaflet thrombosis and diagnostic methods have led to differences in rate of thrombosis among different studies. A number of patient-related factors such as inadequate antithrombotic therapy, poor left ventricular systolic function or aortic root morphology can be considered responsible for leaflet thrombosis of TAV devices [15, 19, 20, 29]. The available clinical data also suggest that the risk of clinical leaflet thrombosis is higher in ViV procedures than in TAVR [12, 15]. In addition to the type of procedure (TAVR vs ViV), several device-related risk factors could potentially play an important role in leaflet thrombosis. The risk factors may include TAV type, size, implantation depth and degree of overall and regional oversizing. Although limited clinical data are available, the data show that clinical valve thrombosis occurs significantly more often with balloon-expandable valves than with self-expanding devices [15]. Regions of blood stasis are also expected to be more prominent in TAVs with an intra-annular design than in TAVs with a supra-annular design due to superior blood washout on the surface of the TAV leaflets with supra-annular design [8]. Furthermore, it is well known that high degrees of incomplete expansion of TAV stents due to excessive oversizing distort TAV leaflets, impair leaflet kinematics and may impact long-term durability of the TAV devices. Postmortem analyses of TAVs have also shown that leaflet thrombosis may be associated with valve underexpansion or asymmetry [17]. Mangione *et al.* reported that 4 out of 13 patients with a prior TAVR who underwent a postmortem examination or who had a TAV device surgically explanted in an attempt to understand better the causes of TAVR failure, were diagnosed with leaflet thrombosis. Incomplete expansion or asymmetry of the TAV occurred in 3 of those cases [17].

Another recent study conducted by Midha *et al.* was designed to identify clinical risk factors that relate to the presence and severity of thrombus on TAVs [7]. Data from 72 patients, 40 of whom received a SAPIEN 3 and 32 of whom received a CoreValve family self-expanding device, were reanalysed retrospectively. The results showed that SAPIEN 3 devices with leaflet thrombosis were on average 10% further expanded (by diameter) than those without leaflet thrombosis (95.5 ± 5.2% vs 85.4 ± 3.9%; $P < 0.001$). In other words, SAPIEN 3 devices without thrombus were on average 7.3%, 10.1% and 8.8% less expanded by diameter at the inflow, waist and outflow regions, respectively, than SAPIEN 3 devices with leaflet thrombus ($p < 0.001$). This relationship was not evident with CoreValve devices. The finding

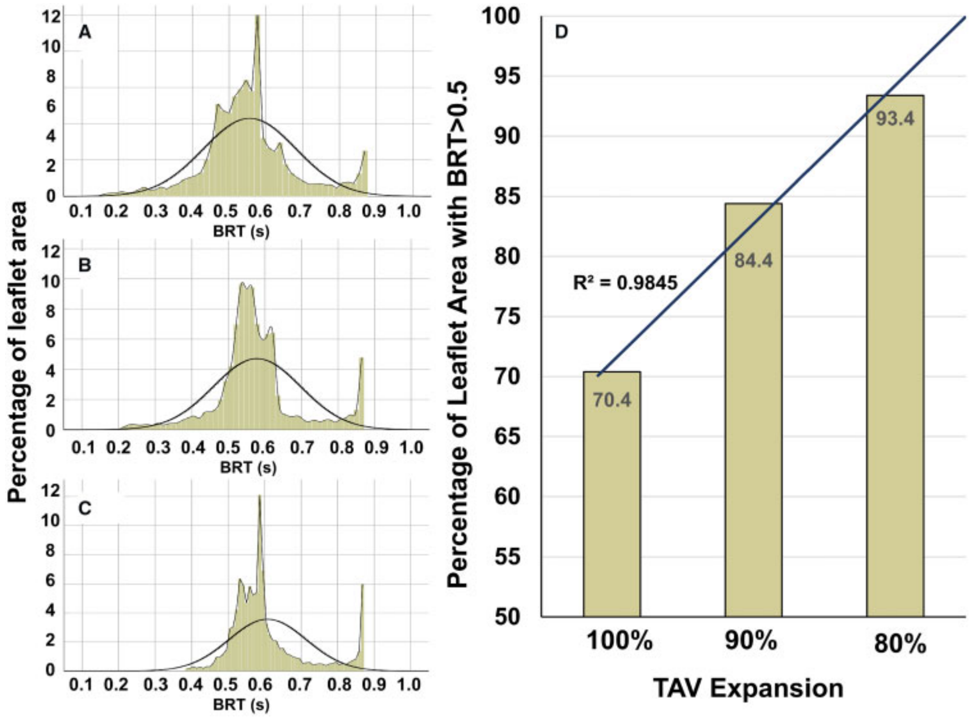


Figure 6: Histogram of the BRT over the surface of the leaflets for (**A**) fully expanded TAV, (**B**) 90% expanded TAV and (**C**) 80% expanded TAV. (**D**) Percentage of surface area with high BRT ($T_R > 0.5$ s) on all 3 leaflets of TAVs with different degrees of expansion. BRT: blood residence time; TAV: transcatheter aortic valve.

contradicted the authors' expectations, which were that underexpansion would increase the risk of thrombosis by increasing TAV leaflet folding and increasing the potential for stagnation. Several potential reasons were provided in the manuscript such as (i) further expansion of the TAV may increase endothelial injury, providing a nidus for thrombus formation; (ii) the size of the stagnation zones may be reduced through slight underexpansion; or (iii) underexpansion may yield higher jet velocities, which may affect the neosinus washout. Nevertheless, the results of the current study clearly show that TAV underexpansion increases blood stasis on the surface of the TAV leaflets. As a result, TAV underexpansion has the potential to increase the risk of leaflet thrombosis in TAVR. The present results are compatible with those of other clinical studies that showed that leaflet thrombosis can be associated with TAV underexpansion [11, 17].

Limitations

The present results and the other available data underline the fact that randomized prospective studies with more patients and longer follow-up periods are required to confirm the effects of TAV underexpansion on TAV leaflet thickening and thrombosis in patients who have TAVR and ViV. The limitations of the present study include the number of cases considered and the fact that we focused our study on SAPIEN 3 devices. TAV devices with an intra-annular design represent the worst-case scenario in terms of blood stasis on the leaflets [8]. Further studies are needed to assess the effect of TAV underexpansion in other intra-annular TAVs and supra-annular devices such as the Medtronic CoreValve. In addition, the study was solely focused on TAV underexpansion with stents with circular geometry. Further studies are also motivated to assess the effect of asymmetric and oval-expansion of the TAV stent expansion, over-expansion and the role of predilation in optimizing full expansion of the SAPIEN 3 valve. However, the study design allowed us to isolate the effects of TAV underexpansion and to quantitatively compare the BRT on the TAV leaflets with different degrees of valve expansion.

CONCLUSION

In summary, the results of the current study demonstrated that TAV underexpansion decreases blood washout on the surface of TAV leaflets and increases blood stasis on the leaflets. Regions of blood stasis promote thrombotic events and provide an opportunity for platelet activation and aggregation. Therefore, TAV underexpansion has the potential to increase the risk of leaflet thrombosis in patients who have TAVR. Further prospective studies are needed to confirm the effects of TAV underexpansion on TAV leaflet thickening and thrombosis in patients who undergo TAVR. Lastly, personalized computational modelling of TAVR procedures has the potential to provide a mechanistic explanation for leaflet thrombosis on a case-by-case basis by computing detailed blood flow characteristics. The flow simulations can also be improved by implementing multiphysics and multiscale models to simulate formation and growth of thrombosis on TAV devices.

SUPPLEMENTARY MATERIAL

Supplementary material is available at *ICVTS* online.

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