Device Thrombogenicity Emulator (DTE) – Design optimization methodology for cardiovascular devices: A study in two bileaflet MHV designs

Michalis Xenos, Gaurav Girdhar, Yared Alemu, Jolyon Jesty, Marvin Slepian, Shmuel Einava, Danny Bluestein

Abstract

Patients who receive prosthetic heart valve (PHV) implants require mandatory anticoagulation medication after implantation due to the thrombogenic potential of the valve. Optimization of PHV designs may facilitate reduction of flow-induced thrombogenicity and reduce or eliminate the need for post-implant anticoagulants. We present a methodology entitled Device Thrombogenicity Emulator (DTE) for optimizing the thrombo-resistance performance of PHV by combining numerical and experimental approaches. Two bileaflet mechanical heart valves (MHV) designs, St. Jude Medical (SJM) and ATS, were investigated by studying the effect of distinct flow phases on platelet activation. Transient turbulent and direct numerical simulations (DNS) were conducted, and stress loading histories experienced by the platelets were calculated along flow trajectories. The numerical simulations indicated distinct design dependent differences between the two valves. The stress loading waveforms extracted from the numerical simulations were programmed into a hemodynamic shearing device (HSD), emulating the flow conditions past the valves in distinct 'hot-spot' flow regions that are implicated in MHV thrombogenicity. The resultant platelet activity was measured with a modified prothrombinase assay, and was found to be significantly higher in the SJM valve, mostly during the regurgitation phase. The experimental results were in excellent agreement with the calculated platelet activation potential. This establishes the utility of the DTE methodology for serving as a test bed for evaluating design modifications for achieving better thrombogenic performance for such devices.

Introduction

Over 5.3 million patients suffered from heart failure in 2000, with their number expected to grow by 50% over the next 15 years (Lloyd-Jones et al., 2009). Of those, a significant proportion will become candidates for longer-term mechanical circulatory support (MCS), e.g., ventricular assist devices (VAD), total artificial heart (TAH), and prosthetic heart valves. As such, a major unmet need is the ability to dramatically reduce the thrombogenic potential of these devices. Mechanical heart valves (MHV) alone correspond to over 170,000 implants worldwide each year (Yoganathan et al., 2005). While hemodynamic performance of current generation of MHVs are greatly improved over their predecessors (DeWall et al., 2000; Bluestein, 2006), flow-induced thrombogenicity is still their major persistent problem (Butchart et al., 2003). To overcome this problem, patients are administered lifelong anti-thrombotic medication, reducing the risk of thrombogenic complications, however increasing hemorrhagic risk.

Blood clotting involves platelet activation and can be initiated by various mechanical and chemical agonists. The non-physiological flow conditions in MHV (Shandas et al., 2000) have been implicated in activating platelets in the absence of chemical agonists (Hellums et al., 1987) at an approximate threshold shear stress of 100–300 dyne/cm² over a few milliseconds (Hung et al., 1976; Ramstack et al., 1979). The Hellums criterion (Hellums et al., 1987; Hellums, 1994) has established a stress-exposure time threshold for hemolysis and platelet activation based on constant shear stress experiments. However, under physiological flow conditions of flow through MHVs, platelets are exposed to varying shear stress levels (Bodnar, 1996; Bluestein et al., 1997) and turbulent stresses (Bluestein et al., 2004), as well as repeated passages through the valve that may precipitate activation...
(Yeleswarapu et al., 1995; Alemu, Bluestein, 2007). The size of the smallest turbulent eddies (Kolmogorov scales) is in the range of 20–70 µm (Ellis et al., 1996; Liu et al., 2000; Travis et al., 2004) and can result in platelet activation (Liu et al., 2000) and initiate thrombosis (Bluestein et al., 2002; Travis et al., 2002; Leytin et al., 2004). Activated platelets with long residence time in these flow regions may aggregate, leading to free emboli formation (Bluestein et al., 2002).

Numerical simulations of MHV flows showed the effects of transient flow and wake dynamics on platelet activation (King et al., 1997; Kraftczyk et al., 1998; Kelly et al., 1999; Grigioni et al., 2005a). Many of these simulations assumed laminar flow or neglected intermittent turbulent flow stresses that may become critical in activating the hemostatic system (Bluestein et al., 1997). Valvular flows are dominated by intermittent turbulence in the transition range, which are based on isotropic turbulence assumption rendering most turbulence models limited (Yin et al., 2004). Bluestein et al. (2000, 2002) performed Unsteady Reynolds-averaged Navier–Stokes (URANS) simulations employing the Wilcox k–ω turbulent model, capable of handling transient turbulence and further compared the activation potentials of various MHVs (Yin et al., 2004) by studying the dynamics of shed vortices in the valve wake and quantifying the stress histories of platelets along pertinent trajectories. Recently, Large Eddy Simulation (LES) (Ge et al., 2008) were employed, as well as fluid structure interaction (FSI) approaches (Redaelli et al., 2004; Ge et al., 2008). Our group compared the thrombogenic performance of ATS and SJM MHVs using FSI simulations (Dumont et al., 2007).

Mathematical models have been developed to describe the resulting blood damage, mostly focusing at red blood cell (RBC) damage (hemolysis) as opposed to platelet damage (activation), which is more pertinent for thromboembolic complications characterizing MHV (Bludszuweit, 1995; Yeleswarapu et al., 1995; Grigioni et al., 2005b; Farinas et al., 2006). Those correlate hemoglobin release due to hemolysis, shear stress and exposure time (Pinotti and Rosa, 1995; Arora et al., 2004). Similar platelet activation models are based on percent release of lactate dehydrogenase (LDH) (Arora et al., 2004). These models satisfy limited experimental observations and may significantly underestimate cell damage (Pinotti and Rosa, 1995; Goubeargits and Affeld, 2004).

Previous studies by our group and others have focused on an overall thrombogenic potential measurement in MCS devices (Bluestein et al., 2004; Yin et al., 2004). A limitation of these studies is the lack of specific information regarding the source of elevated platelet activation. It was recently reported that varying the hinge gap in SJM MHVs (Leo et al., 2006) or constriction diameters (Fallon et al., 2008) significantly impact thrombogenicity. These studies reinforce the concept of high shear stress induced platelet activation in constricted geometries.

In the present study we utilize a novel hemodynamic shearing device (HSD) with the capability of accurately reproducing and exposing platelets to rapidly changing dynamic shear stress loading waveforms extracted from detailed numerical simulations. The MHV design specific accentuated effects of such shear stress patterns on platelets is then measured with a modified prothrombinase assay developed by our group for measuring real time thrombin generation due to platelet activation in devices (Jesty and Bluestein, 1999). We have established that the rate of thrombin formation – a universal thrombogenic marker, is directly coupled to the platelet activation level and aggregation that is induced by the flow past valves and devices (Yin et al., 2004, 2005, 2006; Nobili et al., 2008b) and the cardiovascular and mechanical circulatory support device community has long recognized that device thrombogenicity is initiated by platelet activation.

Methods

Numerical simulations

Two MHV designs were compared: a 22 mm AP ATS and a 22 mm SJM ‘Regent’ valve. Being the most implanted MHV in the world, the SJM is considered as the gold standard (Butany et al., 2003). While their leaflets design closely match, and their inner diameter and nominal orifice sizes are similar (Table 1), they significantly differ in their hinges design, and in the B-datum and valve-housing gap clearances (Dumont et al., 2007). The ATS open pivot design minimizes cavities and recesses in the pivot area of the hinges that may provide locations for platelet aggregation, departing from the St. Jude ‘ear’ type hinge mechanism (Dumont et al., 2007) (Fig. 1). The modeling geometry of the valves consisted of straight tubes upstream and downstream with corresponding lengths of 5 valve diameters. The valves are depicted in closed position, with details of the hinges, housing, and the leaflets (Fig. 1). Recent clinical studies have shown that the ATS valve has lower mortality rates and fewer complications as compared to SJM, although there is not currently enough evidence to compare thromboembolic complications rates in the two valves (Bernet et al., 2007; Sezai et al., 2009).

The current study extends our previous one (Dumont et al., 2007) to turbulent and direct numerical simulations (DNS), utilizing highly resolved computational grids in order to capture the smallest scales of the flow. Simulation were carried out during the deceleration phase up to 350 ms from peak systole, before leaflet closure, with the leaflets fixed at the fully open position (Bluestein et al., 2002; Alemu and Bluestein, 2007), corresponding to the phase of the cardiac cycle in which the elevated turbulent stresses and the shed vortices formed in the valve’s wake contribute the most to platelet activation and aggregation (Bluestein et al., 2000). Another set of simulations was conducted during the diastolic regurgitant flow phase, which is implicated in thrombus and thromboemboli formation – especially through the hinges region, with the valve fully closed and a constant velocity of \(v_{\text{ref}}=0.05\text{ m/s}\) (Dumont et al., 2007). Blood was assumed to be two-phase Newtonian fluid consisting of fluid carrier phase and neutrally buoyant solid particles (Morsi and Alexander, 1972, see Appendix A) representing platelets, as previously described (Bluestein et al., 2002). The stress loading history along flow trajectories experienced by the platelets seeded into the flow field was computed by a summation of the combined effect of the total stress acting on the platelets (a scalar representation of the various components of the stress tensor) and exposure time – as previously described (Alemu and Bluestein, 2007) (Apel et al., 2001, see Appendix A), following the well-established shear induced platelet activation (SIPA) concept (Hellums, 1994).

URANS simulations were conducted using the Wilcox k–ω turbulent model (Wilcox, 1994; Dhindsa et al., 2005) previously validated by our group experimentally (Bluestein et al., 2000) and applied by us in numerous MHV flow simulations studies (Bluestein et al., 2000, 2002, 2004; Yin et al., 2004; Alemu and Bluestein, 2007). We have employed a progressive density highly resolved numerical meshes approach (Alemu and Bluestein, 2007) (9 \(\times\) 10\(^6\) and 10 \(\times\) 10\(^6\) finite volumes for the SJM and ATS valves, respectively) to capture various hydrodynamic effects in the small confines of MHV complex geometries. Table 1 summarizes valve specifications, diameters and gap clearance for the two designs. The mesh was further refined for the DNS, resulting in over 17 \(\times\) 10\(^6\) finite volumes – within the range of previously reported Kolmogorov scales in MHV flows (Ellis et al., 1996; Liu et al., 2000; Travis et al., 2004; Ge et al., 2008). A Typical mesh is shown in Fig. 2 in two orthogonal sectional planes. Insets in the figure reveal the boundary layers close to the walls. Grid independence was established and results were compared to experimental measurements (Table 2) (see Appendix A).

Table 1

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<th>Valve diameters and gap clearance.</th>
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<td>Valve diameter (tissue annulus diameter)</td>
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<td>Valve inner diameter</td>
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<tr>
<td>B-datum gap, closed position</td>
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<tr>
<td>Gap clearance between hinge and leaflet</td>
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<td>Gap clearance, closed position, leaflet and housing</td>
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quantitative measure based on computing the probability density function (PDF) of the stress accumulation values of all the trajectories. The PDF is used as a surrogate for the overall thrombogenic potential of each valve, e.g., the MHV thrombogenic ‘footprint’. For comparing PDFs of different platelet populations in the various simulations (varying from 15,000 to 50,000), while guaranteeing that the percentage activation is independent of number of seeded particles and spatiotemporal variations, we have used bootstrapping statistics (Dumont et al., 2007) to interpolate between smaller and larger populations. This approach guarantees that the statistical distributions extracted from the different population sizes are compatible and comparable.

Experimental methodology

Platelet trajectories and their corresponding loading shear stress waveforms were extracted from the numerical simulations during the systolic deceleration and regurgitation phases for both MHVs, to be used in the platelet experiments. As only a fraction of the numerous trajectories could possibly be tested experimentally, we have concentrated on ‘hot-spot’ trajectories that are expected to contribute the most to platelet activation. An in-house code was developed that sorted all the trajectories based on specific locations of interest (i.e., gap between valve and housing, B-datum, hinges, etc.). The localized particle distribution was identified with a sphere of interest, $SOI$, that captured all particle trajectories passing through it. After choosing these ‘hot-spot’ trajectories, their corresponding loading waveforms were programmed into the hemodynamic shearing device (HSD), described below.

We developed a high-torque hemodynamic shearing device (HSD – Fig. 3), which combines features of cone and plate and Couette viscometers, to dynamically expose platelets to uniform shear stress field of rapidly varying levels (Girdhar and Bluestein, 2008). The electrical components of the HSD comprise of a high-torque servo motor-controller system (Baldor Electric Company, AR) with a programmable interface. The shear stress can be changed instantaneously (3 ms resolution), with peak shear stresses up to 900 dyne/cm$^2$. The motor is mounted onto a mortiser support attached to the cone (Delta, TN and R & W America, IL). The base supports an aluminum block with water recirculation ports, maintaining a physiologic temperature of 37 °C. Precise positioning of the cone height above the base-plate is achieved with a dual-bearing-support and the Couette gap between the cone and the ring is controlled with X–Y positioning micrometers. The platelet sample occupies the Couette and the conical spaces. A sample volume of up to 3.5 ml may be used. Platelet activation was measured by sampling from the suspension inside the device before and after the experiment. The HSD was utilized to expose platelets repeatedly (600 times, 10 min) to each dynamic shear stress loading waveforms $\tau (t)$ obtained from numerical simulations. During each successive cycle, platelets were exposed to variable shear stress for 0.21–0.35 s, followed by a constant baseline shear stress of 1 dyne/cm$^2$ for 0.65–0.89 s, to keep the platelets in equivalent circulation conditions while not passing through the device. This shear stress level does not activate the platelets and has been used in our previous studies (Nobili et al., 2008b).

![Fig. 1. Geometric details of the hinges regions of a 22 mm AP ATS open pivot valve and a 22 mm SJM Regent valve (both in closed position) – left. Geometric details of the bileaflet SJM MHV – right.](image)

![Fig. 2. (A) A horizontal cross-sectional plane showing the computational mesh near the open leaflets of the MHV. Inset shows the details of the computational grid near the hinges. (B) A vertical cross-sectional plane showing the computational mesh at the leaflets. The insets depict the boundary layers mesh near the wall (left) and the grid at the vicinity of the leaflet (right).](image)

<table>
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<th>Table 2 Wilcox $k$–$\omega$ constants.</th>
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<tr>
<td>$\omega_w = 1$, $\omega_o = 0.52$, $\omega_p = \frac{1}{3}$, $\beta_w = 0.09$, $\beta_i = 0.072$</td>
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<td>$R_p = 8$, $R_k = 6$, $R_o = 2.95$, $\zeta = 1.5$, $M_b = 0.25$, $\sigma_k = \sigma_o = 2.0$</td>
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30 ml of citrated whole blood was collected from adult human volunteers (n=10 unique donors) after informed consent, in accordance with Stony Brook University Institutional Review Board guidelines. Purified platelets (2 x 10^9/ml) were prepared by gel-filtration of platelet-rich-plasma (PRP) with a Sepharose-2B column, as previously described (Jesty and Bluestein, 1999). In order to achieve high peak shear stresses in our study, we used Dextran (MW 200,000–500,000; Sigma-Aldrich) to increase viscosity of the suspension to either 3.5 cp (peak stress up to 350 dyne/cm²) or 10 cp (peak stress up to 900 dyne/cm²). Platelet activation measurements were performed in the HSD by exposing platelets (2 x 10^10/ml) to the loading shear stress waveforms. The activation was measured with a Platelet Activity State (PAS) assay developed by our group (Jesty and Bluestein, 1999), which is based on a modified prothrombinase assay. Since platelets from different donors may exhibit high variability in their response to shear stress exposure, the platelet activation measured for any given experimental run was normalized to a maximum value of platelet activation from the same batch by sonication of the platelet suspension at 10 W for 10 s (Yin et al., 2004, 2005, 2006).

**Results**

**Numerical simulations**

Various flow characteristics of the SJM and ATS valve designs are presented and compared. The flow field through the valves is dominated by a triple jet structure through the major orifice (between the leaflets) and the two minor orifices (between the leaflets and the valve housing). At peak systole ATS valve has higher maximum velocity (u_{ATS}=1.73 m/s), compared to the SJM (u_{SJM}=1.59 m/s). During regurgitant flow the SJM has a higher maximum velocity of 2.99 m/s at the leaflet-housing gap clearance, while the ATS has max. velocity of 2.70 m/s at the gap between the leaflets (B-datum). The flow field at the center plane for the two valves in three time instances during the cardiac cycle is depicted in Fig. 4. In general, slightly higher velocities and more disturbed flow patterns were observed in the forward flow phase for the ATS valve. However, this was reversed during regurgitant flow phase, in which the SJM valve had stronger flow disturbances, with jets forming at the leaflet-housing gap.

The secondary flow for both valves consisted of a pair of counter-rotating vortices emanating from the jet flow that is generated in the hinges region (Fig. 5, transverse cross-section with inset zoom in). In an animation of the simulation (Appendix A – Animation 1), the spinning of these counter-rotating vortices appear to be more rapid for the ATS valve with their axis of rotation entrained towards the core flow. For the SJM valve larger and slower counter-rotating vortices were spinning much closer to the valve housing. The formation of these vortices appears to trap a significant number of platelets. The instantaneous vorticity contours at the plane of symmetry of both MHV designs are presented in Appendix A.

The statistical distribution of the stress accumulations along the multiple trajectories was used as the MHV thrombogenic ‘footprint’, as described above. Both designs have Log-Normal PDF distributions, with different means and variances. The peaks correspond to the mode(s) of each distribution – defined as the value of stress accumulation that most frequently occurs. The mean value of the SJM PDF during the deceleration phase was 4.77 ± 3.23 dyne x s/cm² while that of the ATS valve was 8.14 ± 3.57 dyne x s/cm². t-Test and parametric and non-parametric ANOVA of the two distributions indicate that in the range below 20 dyne x s/cm² the SJM valve exposed more platelets to lower stress accumulation values (dominant mode close to 20 dyne x s/cm²) as compared to 4.0 dyne x s/cm² for the ATS valve (p < 0.01), Fig. 6). However, at the higher stress accumulation range (>20 dyne x s/cm²) the ATS valve appeared to expose very few platelets to values higher than 25 dyne x s/cm² (only 0.008% of the trajectories between 25 and 35 dyne x s/cm² for ATS and insignificant 0.006% for the higher 35 dyne x s/cm² range). For the SJM valve the percentage at these ranges was significantly higher: 1% of the platelet population was exposed to 25–35 dyne x s/cm², and 0.025% to above 35 dyne x s/cm² (Fig. 6).

During the forward deceleration phase, differences in valve hinge mechanism design resulted in more particles passing through the hinge regions of the ATS, as compared to the SJM valve, 33% and 4%, respectively. The mean value of the SJM was 3.02 ± 0.75 dyne x s/cm², and 6.43 ± 2.22 dyne x s/cm² for the ATS. Specifically, while passing through the hinge area 85% of the SJM trajectories were exposed to low stress accumulation ranges (0–5 dyne x s/cm²), as compared to only 50% for the ATS. Only 14.8% of the SJM trajectories exposed platelets to higher stress accumulation range (5–25 dyne x s/cm²), whereas the ATS hinges exposed the rest 50% of the platelets to this higher range. However, for both valves during forward flow no trajectories that pass through the hinges exceeded a cumulative stress of 25 dyne x s/cm².

During the diastolic phase of the cardiac cycle, flow through the closed valve is characterized by much higher shear stress values. The two MHV PDF distributions during regurgitation indicate that the ATS valve exposes platelets to much lower stress accumulation levels as compared to the SJM (Fig. 7: mean SJM: 1.85 ± 0.4 dyne x s/cm², mean ATS 1.2 ± 0.1 dyne x s/cm², p < 0.01). The dominant mode for the ATS was slightly lower (Fig. 7, inset), with 33% of the trajectories
passing through the B-datum for the ATS, as compared to only 4% for the SJM. Localized statistics at the B-datum indicated significantly lower mean for ATS (mean ATS: 1.01 dyne \( \times \) \( \text{s/cm}^2 \); mean SJM: 1.5 dyne \( \times \) \( \text{s/cm}^2 \)).

Platelet activation measurements in the HSD

We have previously measured platelet activation in LVAD mounted with bileaflet and monoleaflet MHVs (Yin et al., 2004, [Fig. 4]. Velocity flow field at the center plane for SJM and ATS MHV during the cardiac cycle. Three time instants are shown: peak systole, deceleration phase, and regurgitant flow through the closed valve during diastole. Arrows indicate the blood flow direction (valve geometry is reversed during the regurgitant flow phase to reveal the flow field behind the closed leaflets).

[Fig. 5]. A pair of counter-rotating vortices emanating from the jet flow that is generated in the hinges region of the SJM and ATS MHVs (transverse cross-section, details appear in the cross-sectional zoom-in – bottom). In an animation of the simulation (Animation 1) for the ATS valve the spinning of these counter-rotating vortices is faster and entrained towards the core flow, while for the SJM larger counter-rotating vortices are spinning slower and closer to the valve housing (the hinges are shown in the insets).
While those studies provided a measure of overall thrombogenicity of the valves, the goal of the current study was to delineate the region-specific valve design/geometry effects on platelet activation in the 'hot-spot' regions. A validation study was initially conducted to test the ability of the HSD to emulate stress loadings of region-specific trajectories and distinguish the differences in the platelet activity measured (see Appendix A).

High stress trajectories were extracted from the hinge regions during the forward flow (1–5 SJM; 6–10 ATS; Fig. 8a and b) with their corresponding stress loading waveforms programmed into the HSD and platelet activity measured (Fig. 8c: presented as normalized platelet activation values). One-way ANOVA indicated no statistical difference between the two groups of valve trajectories during the forward flow phase (mean platelet activity: 0.0169 ± 0.0011 (SJM); 0.0178 ± 0.0014 (ATS)).

High shear stress trajectories (D1–D3 SJM; D4–D6 ATS) during the regurgitant flow phase were extracted from the B-datum regions (Fig. 9). Platelet activation measurements for these trajectories emulated in the HSD show significant difference between the valves, with the SJM overall activation being more than double than the ATS (mean SJM: 0.0275 ± 0.0012; mean ATS: 0.0104 ± 0.0011, p < 0.05). Additional high shear stress trajectories from the gap between leaflets and housing regions (W1–W3 SJM; W4–W6 ATS) indicated that the SJM activation level was more than four times higher (mean SJM: 0.0665 ± 0.0038; mean ATS: 0.0153 ± 0.0013, p < 0.05).

High shear stress trajectories (H1–H3 SJM; H4–H6 ATS) during regurgitant flow were extracted from the hinges regions (Fig. 10). The platelet activation measurements for these HSD emulated trajectories show significant difference between the two valves, with the SJM overall activation approx. five times higher (mean SJM: 0.0465 ± 0.0023; mean ATS: 0.0090 ± 0.0007, p < 0.05).

### Discussion

The novel Device Thrombogenicity Emulator (DTE) methodology introduced in this work, integrates two approaches – numerical and experimental. In the first step a probability density function (PDF) provides an overall measure of the valve
thrombogenic potential (‘thrombogenic footprint’), followed by region-specific flow trajectories that are extracted from ‘hot-spot’ regions. We have demonstrated that this global ‘footprint’ facilitates a one-to-one comparison of various valve designs. In the second step ‘hot-spot’ trajectories extracted from the numerical simulations are used to program the hemodynamic shearing device (HSD) with the corresponding loading waveforms – emulating extreme flow conditions, and measuring the resultant platelet activity.

The two bileaflet MHV designs, the SJM and ATS, were chosen for illustrating the sensitivity of the methodology in investigating small thrombogenic differences between MHV designs that share many similarities, and differ mostly in their hinge design. High resolution numerical meshes were employed for capturing the smallest scales and realistic valve geometries. Further global and localized statistical analysis of the trajectories was used to quantify the overall and region-specific valve thrombogenic performance. We have specifically investigated whether small design variations can produce observable differences in the flow fields and in the resulting platelet activation.

Both MHVs have distinct advantages and disadvantages at various phases of the cardiac cycle. A complex pattern of counter-rotating helical vortices was emanating from the hinges region of both valves. Stronger jets during forward flow exposed platelets to slightly higher stresses for the ATS valve. The PDFs indicated that overall the ATS valve is slightly inferior to the SJM valve during the systolic deceleration phase in the $SA < 20$ dyne s/cm$^2$. This may be attributed to the design of the SJM valve that diverts the flow trajectories away from the hinges high shear stress region, owing to its ‘ear’ step design proximal to the hinges. However, in the higher more dangerous range of stress accumulation ($SA > 20$ dyne s/cm$^2$) the ATS performs better than the SJM – as depicted in the inset of Fig. 6. The corresponding experimental results based on platelet response to representative trajectories programmed into the HSD however did not yield a statistical difference between the two MHVs. This may be attributed to the small number of loading waveforms chosen from extracted trajectories, and the small difference in the thrombogenicity between the two valves at the forward flow phase, as predicted from the numerical simulations.

During the regurgitant flow through the closed valve the SJM valve exhibited stronger jets around the perimeter of the leaflet-housing gap annular region and through the hinges, whereas the ATS had slightly stronger jets through the B-datum. The size of these high stress regions however was substantially smaller in the ATS valve. The PDF ‘footprints’ of the stress accumulation during regurgitation correlated very well with the experimental results, with differences in measured platelet activity of all emulated trajectories statistically significant ($p < 0.05$). With similar thrombogenicity during forward flow but much higher thrombogenicity during regurgitant flow, we can confidently state that the SJM

Fig. 8. Platelet experiments in the HSD emulating hinge region trajectories through the valves during forward flow: (a) SJM hinges trajectories (1–5) and the corresponding shear stress loading waveforms (b) ATS hinges trajectories (6–10) and the corresponding shear stress loading waveforms (c) Platelet activation corresponding to 600 repeats of each trajectory, measured with PAS.

valve would be expected to have higher overall thrombogenicity (in agreement with our previous simulations comparing these two valves (Dumont et al., 2007)). The PDF can therefore be used as a predictive measure for the thrombogenic performance ‘footprint’ characteristic of the specific valve.

While our highly resolved simulations were not conducted as FSI per se (Morbiducci et al., 2009), the transient forward flow phase with the leaflets fixed in the fully open position till just before the leaflets snap into closure, fully captures the dynamics essential to platelet activation (e.g., trapping potentially activated platelets in the shed vortices generated in the leaflets’ wake). The contribution of the short rapid closing phase (10–20 ms) is expected to be secondary, would be computationally prohibitive for DNS simulations, and for comparative purposes concentrating on the two phases that contribute the most to platelet activation serves the purpose well.

In order to assess statistical turbulence parameters in direct numerical simulations (DNS), the results should be averaged for several cardiac cycles for achieving converged phase-averaged statistics. Statistically, a normal distribution (e.g., the case of isotropic turbulence with Re > 10,000) would require several averaging cycles (depending on the mesh resolution). In case of anisotropic turbulence in the transition range (such as pulsatile flows) a much higher number of cycles may be required to capture the cycle to cycle variations and converge the phase locked turbulent statistics, although a very fine mesh which is resolved below the smallest Kolmogorov turbulent scales may alleviate this requirement. In future simulations we are planning to simulate dozens of cycles for achieving a smaller confidence interval for the turbulence statistics.

Several approximations were made in the numerical simulations. The stress accumulation model utilized for the PDF statistical distributions followed a linear cumulative shear stress approach. However, cumulative shear stress may follow various power-law formulations (Boreda et al., 1995; Nobili et al., 2008b), in which exposure time is given less weight. The linear cumulative shear stress assumption may mask differences that could be attributed to a power-law dependence on peak shear stress, exposure time and stress loading rate. An inherent experimental limitation is that we cannot possibly test the huge number of platelet trajectories generated by the numerical simulations (approx. 15,000–50,000 for each valve). Instead we measure the platelet activation response to a small number of representative stress trajectories that exhibit the highest shear stress levels – serving as a better basis for comparing the two MHV thrombogenic potentials. A high-throughput system with a multiple-HSD setup to study multiple trajectories simultaneously may offer a partial solution in the future.

While for most cases excellent agreement was established between the numerical and experimental results in this study, the correlation is not a function of cumulative shear stress alone. It is apparent from the experimental results presented here that peak shear stress and stress loading rate may also be important parameters that regulate platelet activation. In concurrent and

![Fig. 9. Platelet experiments in the HSD emulating elevated shear stress trajectories through the valves during regurgitation; grouped into wall trajectories (W1–W3 SJM; W4–W6 ATS) and B-datum trajectories (D1–D3 SJM; D4–D6 ATS) (left) and the corresponding shear stress loading waveforms (right). The corresponding platelet activation in response to 600 repeats of each stress trajectory, measured with PAS appears at the bottom.](image-url)
future studies we plan to address these limitations by formulating a more realistic stress accumulation model based on detailed parametric experimental studies, additionally incorporating the effects of repeated passages through the device while taking into account platelet senescence (Alemu and Bluestein, 2007) and sensitization effects (Sheriff et al., 2010).

Our previous studies (Yin et al., 2004, 2005) provided an overall measure of valves thrombogenicity. Moving further, the new methodology presented here is capable of delineating specific effects of the valve design/geometry on platelet activation, either as a stand-alone prosthetic implant or as components of an MCS device. The next step in the DTE methodology is to use this information in order to optimize the design in the ‘hot-spot’ regions. This can be readily achieved by iteratively changing the design in the virtual numerical domain till optimal reduction in the predicted platelet activity is reached, followed by programming the HSD with the loading waveforms resulting from the optimized design and testing to see whether a reduction in platelet activity was indeed achieved. A prototype of the optimized device can then be fabricated and clinically tested.

In conclusion, we have demonstrated the efficacy of our methodology for estimating the effects of design parameters on device thrombogenicity. We envision that this methodology will be adopted by cardiovascular device manufacturers in order to optimize their devices designs for achieving improved thrombogenic performance. This may reduce or even eliminate the need for anticoagulation that is mandated for most of these devices.

Acknowledgments

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jbiomech.2010.04.020.

References


Conflict of interest statement

The authors have no conflicts of interest for this study.


