



Research approaches for studying flow-induced thromboembolic complications in blood recirculating devices

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The advent of implantable blood recirculating devices has provided life-saving solutions to patients with severe cardiovascular diseases. Recently it has been reported that ventricular assist devices are superior to drug therapy. The implantable total artificial heart is showing promise as a potential solution to the chronic shortage of available heart transplants. Prosthetic heart valves are routinely used for replacing diseased heart valves. However, all of these devices share a common problem – significant complications such as hemolysis and thromboembolism often arise after their implantation. Elevated flow stresses that are present in the nonphysiologic geometries of blood recirculating devices, enhance their propensity to initiate thromboembolism by chronically activating the blood platelets. This, rather than hemolysis, appears to be the salient aspect of blood trauma in devices. Limitations in characterizing and controlling relevant aspects of the flow-induced mechanical stimuli and the platelet response, hampers our ability to achieve design optimization for these devices. The main objective of this article is to describe state-of-the-art numerical, experimental, and *in vivo* tools, that facilitate elucidation of flow-induced mechanisms leading to thromboembolism in prosthetic devices. Such techniques are giving rise to an accountable model for flow-induced thrombogenicity, and to a methodology that has the potential to transform current device design and testing practices. It might lead to substantial time and cost savings during the research and development phase, and has the potential to reduce the risks that patients implanted with these devices face, lower the ensuing healthcare costs, and offer viable long-term solutions for these patients.

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The advent of implantable blood recirculating devices has provided life saving solutions to patients with severe cardiovascular diseases. Recently, it has been reported in the REMATCH (Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure) study [1] that left ventricular assist devices (LVAD) are superior to drug therapy, paving the way for their ultimate use – a long-term heart replacement therapy for patients not eligible for heart transplants. In North America there are over 45,000 patients annually in end-stage heart disease awaiting transplant with only 2000 transplants available. The implantable total

artificial heart (TAH) is showing promise as a potential solution to this chronic shortage. The LVAD, if approved for destination therapy, has only a 30% 2-year survival rate, and still has an unacceptable complication rate of thrombosis/stroke. Prosthetic heart valves (PHVs) are routinely used today for replacing diseased heart valves. However, all of these devices share a common problem – significant complications such as hemolysis, platelet destruction, and thromboembolism (TE) often arise after implantation. This attendant risk for cardioembolic stroke remains an impediment to these devices. The mandatory life-long anticoagulant drug

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regimen they require, which induces vulnerability to hemorrhage and is not a viable therapy for some patients, does not eliminate this risk.

Patients with mechanical heart valves (MHVs) are predisposed to thromboembolic disorders and must undergo lifelong anticoagulation therapy. Despite this therapy, these patients develop thromboembolic complications at a linearized rate of between 0.7 and 6.4% per patient each year [2–5]. In such patients platelets are chronically activated [6–9]. Transcranial Doppler (TCD) was used to detect microembolic events in patients with MHVs [10], resulting in the detection of high-intensity transient signals (HITS). The amount of HITS vary significantly according to the prosthesis [11–13], implicating local flow conditions in their genesis. Kleine and colleagues demonstrated in a pig model a significant effect of valve rotation and downstream turbulence on HITS frequency [14]. Measurement of hemostatic indexes in conjunction with TCD in patients with ventricular assist devices (VADs) support the hypothesis that microembolic signals are related to increased hemostatic activity, even in the presence of aggressive anticoagulant therapy [15]. Elevated neurobiochemical markers were found in valve replacement as compared with coronary artery bypass graft (CABG) patients, attributed to the higher number of cerebral embolic events in those patients [16].

One of the major culprits in blood recirculating devices is the emergence of nonphysiologic (pathologic) flow patterns that enhance the hemostatic response. Elevated flow stresses that are present in the nonphysiologic geometries of blood recirculating devices, enhance their propensity to initiate TE. Mechanically-induced blood trauma in these devices was almost exclusively studied with respect to red blood cell (RBC) damage (hemolysis). In recent years it has been demonstrated that flow-induced thrombogenicity, caused by chronic platelet activation and the initiation of thrombus formation, is the salient aspect of this blood trauma. This lends itself to the hypothesis that TE in prosthetic blood recirculating devices is initiated and maintained primarily by the nonphysiological flow patterns and stresses that activate and enhance the aggregation of blood platelets, increasing the risk of TE and cardioembolic stroke.

The aim of this article is to describe work that pertains to the interaction between flow-induced stresses and the blood constituents, and that supports the hypothesis that TE in prosthetic blood recirculating devices is initiated and maintained primarily by the nonphysiological flow patterns and stresses that activate and enhance the aggregation of blood platelets, increasing the risk of TE and cardioembolic stroke. Such work includes state-of-the-art numerical, experimental, and *in vivo* tools used to elucidate flow-induced mechanisms leading to TE in prosthetic devices. The latter part of this article describes several aspects of the work performed at the author's laboratory pertaining to this hypothesis.

Background

Platelets have long been regarded as the pre-eminent cell involved in physiologic hemostasis and pathologic thrombosis. Platelet activation under tightly controlled flow shear stress

was methodically investigated in the past. Constant stress experiments have established a threshold for platelet activation [17], forming the foundation for shear-induced platelet activation (SIPA) on a basic time-averaged blood flow model. Yet, in prosthetic devices the pathological blood flow patterns that arise are far more complicated. Furthermore, the effect of the loading history of a blood corpuscle should also be taken into account [18]. Rheologic variables related to pulsatility, eddy formation, and turbulence, may predominate under many physiologic and pathologic conditions. Limitations in characterizing relevant aspects of the mechanical stimuli and the ability to control them still obscure the physical relationships between mechanical loading and platelet response, hampering our ability to achieve design optimization for prosthetic blood recirculating devices.

Platelets are ellipsoid discs 2–4 μm in diameter. Upon activation platelets start secreting procoagulant and self-stimulating substances from granules, adhere to surfaces, and aggregate. Aggregation is promoted by agonists secreted from the platelets' α -granules [19,20], and by fibrinogen that binds to the platelet surface via GPIIb/IIIa [21]. Thrombin is generated when Factor Xa is assembled with cofactor Factor Va on the surfaces of activated platelets expressing anionic phospholipids [22]. The resulting prothrombinase complex cleaves the soluble fibrinogen into insoluble fibrin. There is clear evidence that the platelet α -granule-derived Factor V (20% of its amount in blood [23]) dominates the prothrombinase complex and the rapid thrombin generation in the platelet-rich thrombus [24].

Many research groups have used rheological methods to study the effects of shear stresses on platelets and it is well accepted that shear stress causes platelet activation [25]. Exposure to fluid shear stresses will aggregate platelets irreversibly in the absence of any exogenous agonist, showing consistent dose-and time–response characteristics of equivalent chemical agonists [26,27]. Under abnormal flow conditions, SIPA can cause both aggregation (adhesion of platelets to each other in the presence of fibrinogen) and – through provision of anionic phospholipid – thrombin generation. Fluid mechanical factors implicated in platelet activation and aggregation include high rates of shear and deformation, turbulence, and areas of flow stagnation or recirculation that are characterized by low shear and longer retention time [28–30]. Pathologic shear stress levels in stenosed human coronary arteries activated platelets within physiological transit times [31]. Hellums and colleagues compiled numerous experimental results to depict a locus of incipient shear-related platelet activation on a shear stress–exposure time plane, which is commonly used as a standard for platelet activation threshold. This threshold was established in experiments in which the shear level was kept constant while the time to reach activation was measured, i.e. the exposure time [32]. However, platelets exposed to pulsed and elongational stresses, such as those that may be found in devices, were activated at lower shear rates and formed larger aggregates [20,33,34]. The cumulative effect of varying flow stresses and exposure times along

individual platelet trajectories in stenosed arteries and past MHVs further indicates that platelet activation criteria should be established under more realistic flow conditions [35–38].

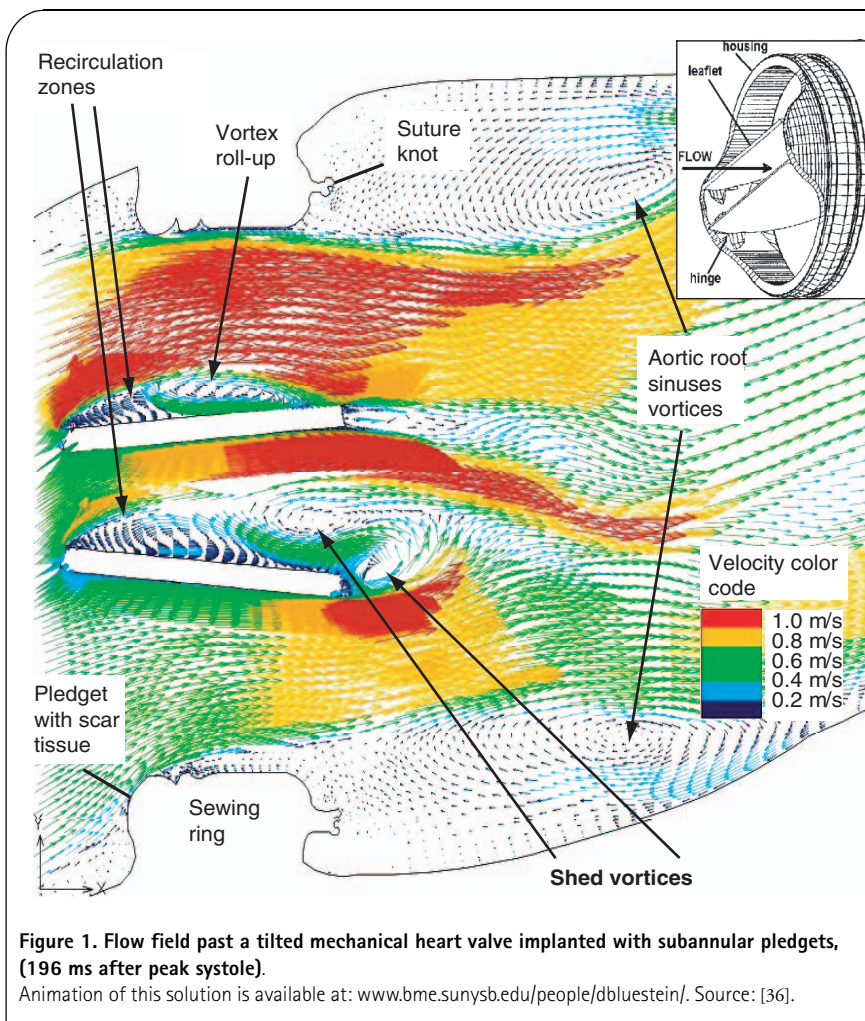
Thromboembolic complications remain one of the major problems for blood recirculating devices such as VADs, and TAH. While hemolysis testing has become a standardized development tool [39–41], very few data on flow-induced thrombogenic aspects are currently available. It is more difficult to quantify due to the complexity of the blood coagulation system, where flow-induced mechanical stresses act synergistically with material contact activation and biochemical agonists. A variety of approaches for studying device-induced thrombogenicity are currently in progress by a few groups [39,42–47]. Hypercoagulopathy in devices is not a result of flow-induced shear stresses alone.

Further reasons for thromboembolic complications in VADs, for example, are the contact between blood components and the foreign surfaces of the assist device system as well as altered rheologic conditions with different velocities of blood flow and blood stasis in the recipient heart [48]. Furthermore, the native heart itself represents a source of TE. Clots may form in ventricles with poor contractile function, in the case of atrial fibrillation and artificial valves. In addition, septic complications and insufficient anticoagulation are responsible for thromboembolic events. In the clinical setting, not only thromboembolic events but also (simultaneously) bleeding complications can occur as a consequence of anticoagulant treatment and/or platelet defects [49]. However, flow-induced thromboembolic complications in devices were mostly overlooked in the past, and appear to be a central mechanism which is directly related to the device hemodynamics.

The mechanism underlying flow-induced thromboembolic complications is poorly understood. One of the culprits in PHVs and similar blood recirculating devices, is the nonphysiologic flow patterns generated by the valve. PHVs generate very high shear stresses, with portions of the flow cycle becoming turbulent [38,50–54]. A recent example of flow-induced MHV TE is the Medtronic Parallel™ valve that was voluntarily withdrawn during clinical trials, due to an unacceptable incidence of thrombus formation in valve recipients [55]. Laser Doppler anemometry (LDA) measurements [56,57] revealed elevated turbulent stresses within the hinges of the valve, linked to the thrombus formation. Current US Food and Drug Administration (FDA) and International Organization for Standardization standards are re-examined in lieu of these findings. Similarly, TE and the attendant risk of stroke (2–47%, [58,59]) remains an impediment to VAD chronic application [60]. VADs induce changes to the coagulation system by activating platelets [15,61–63] despite aggressive anticoagulant therapy. The flow patterns within VAD were implicated as the underlying risk for TE [64]. Jesty and Bluestein have developed an innovative Platelet Activity State (PAS) assay, which enables near real-time measurements of the thrombogenic potential induced by flow through devices [42]. This technique was applied to *in vitro* measurements of flow-induced platelet activation in MHVs mounted in a LVAD [65,66].

After removal of the annular tissue during PHV implantation surgery, the larger annulus is a tempting target for an oversized prosthesis, sometimes implanted by wedging the valve. Inadequate valve orientation may distort its presentation to the axis of blood flow, exceeding the normal restraints of the prosthesis design. DeWall and Ellis indicated that as the prosthesis is designed with consideration for axial flow, tilting the valve in implantation will likely result in a dysfunctional valve [67]. Valves with a larger opening angle, such as the St Jude Medical™, are more susceptible to dysfunction with a tilted implantation. An oblique tilt of 5 or more degrees, which is difficult to visualize at operation, can result in one of the leaflets opening past the axis of flow with delayed, asynchronous, closure and resultant regurgitation [68]. Omoto and colleagues found that improper orientation in patients with St Jude prostheses resulted in higher maximal transprosthetic velocity, greater maximal pressure gradient, and marked turbulence [69]. Surgeons generally agree that for aortic pivoting disc prostheses the major orifice should be directed in the general anterior orientation [70–72], as supported by an *in vitro* fluid mechanics study [73,74]. For bileaflet valves (St Jude Medical) optimal orientation was achieved with one leaflet directed toward the right cusp [75].

Platelet aggregates or gaseous microemboli were suggested as the source of HITS [11,76]. Russell and colleagues and later Braekken and colleagues measured HITS associated with solid emboli introduced into rabbit aorta [77,78], while Markus and colleagues introduced solid emboli and measured HITS in the distal carotid artery of sheep [79]. Georgiadis and colleagues excluded thrombi as an underlying embolic material because of lack of correlation with thrombin-sensitive markers [80]. However, they did not use platelet markers, thus excluding microemboli that are rich in platelets. Dewanjee and colleagues quantified platelet microthrombi and microemboli from cardiopulmonary bypass in organs using radioactive-labeled platelets [81]. The debate regarding the consistency of microemboli is not yet settled due to the use of different approaches in analyzing TCD microembolic signals, particularly in distinguishing between gaseous, or solid emboli and artifacts. Droste and colleagues suggested oxygen inhalation as a method to distinguish between gaseous and solid emboli [82,83], but Conger and colleagues found little evidence that blood gas concentrations had an effect on HITS frequency (measured in MHVs implanted in pigs) [84]. Droste and colleagues improved the detection of circulating emboli by using bigated TCD that takes into account the motion of the embolus [82]. Georgiadis and colleagues developed a method to distinguish between HITS and artifacts using an arbitrary sample volume technique [85]. Devuyst and colleagues suggested a new analyzing method of characterizing HITS based on wavelet analysis [86]. Recently, a method was developed to monitor platelet microemboli formation *in vivo* [87]. A significant effect of valve rotation and orientation on downstream turbulence and HITS frequency was found for two valve designs (bileaflet versus monoleaflet) implanted in patients [75,88] and in pigs [14].



Mechanically-induced blood trauma in blood recirculating devices was almost exclusively studied with respect to RBCs damage (hemolysis). In recent years it has been shown that platelet activation and the initiation of thrombus formation is the salient aspect of mechanically-induced blood trauma [89]. RBCs are much more resistant to mechanical damage due to their 'tank-treading' motion and membrane flexibility. RBCs experience less shear forces than platelets [90,91] as they predominantly flow in core regions (Fahraeus-Lindqvist effect). Hemolysis occurs with shear stress levels of 1500–2500 dynes/cm² and exposure times of 102 s [92–95], while platelet activation occurs at stress levels almost one order of magnitude lower; 100–300 dynes/cm² and 102 s [96,97]. Recently, Travis and colleagues have exactly measured this range of turbulent stress in MHV leakage flow [44].

The measured scale of turbulent eddies in blood flow past MHVs poses a direct threat to the platelets [98]. Their smaller size causes them to respond more exclusively to viscous shearing since they are smaller than the typical Kolmogorov length scales characterizing the turbulent energy cascade in MHV flows [99,100]. Additionally, the relative rigidity of platelet membrane as compared with that of RBCs is a major mechanism for a

higher strain to dissipate across the platelet membrane [45,46]. These recent studies contrasted hemolysis by leakage flow through MHVs [101] with platelet activation measurements, and demonstrated that while hemoglobin levels (hemolysis indicator) barely increased, platelet activation markers, such as annexin V, were greatly increased [45,46]. This is further supported by Klaus and colleagues who exposed human and porcine blood to elevated shear stresses in a Couette-type device, and found that hemolysis was not started until critical shear rates of about 80,000/s, while significant impact on platelets happened at lower shear rates (starting at 55,000/s); likely to set stronger limits to the design layout of devices than hemolysis [99]. The growing recognition that thrombosis, rather than hemolytic anemia, is the primary clinical problem associated with blood recirculating devices, suggests that markers of thrombogenic potential should be studied, rather than hemolysis. This is further accentuated by the pioneering AbioCor™ Implantable Replacement Heart System recently implanted in several patients. While no evidence of significant hemolysis was observed in animal [102] or human patient studies [103,104], several of the patients died of stroke-related complications.

Vortex shedding, a complex flow phenomenon of interacting vortices in the wake of bluff bodies [105], was observed experimentally and computed numerically in the wake of MHV leaflets [36,38,106–109], in models of arterial stenosis [110], and in various blood recirculating devices. LDA measurements of increased turbulent stresses (1200–2000 dynes/cm²) conducted in MHV wakes [53,111], reiterated the role of the wake dynamics in activating platelets, and the dominant role in the recruitment and aggregation of platelets that were activated in previous flow phases. If the shed vortices are large, the cells will simply flow within them, rather than being acted on by the forces at their boundaries. Nevertheless, it is postulated that these shed vortices are the origin of cerebrovascular microemboli associated with prosthetic devices. They provide the necessary conditions for the hemostatic reaction to proceed by providing optimal mixing for platelet aggregation, increasing the procoagulant surfaces needed for the coagulation reactions to proceed, and dispersing the clotting factors in the process. Prior activation and the extrusion of platelet pseudopodia, which may be induced by the elevated shear stresses globally preceding vortex shedding, increases their effective hydrodynamic volume by several fold, resulting in an increased collision rate [112]. The ensuing turbulent eddies enhance mixing and cascade energy

to ever smaller spatial scales, while dissipating it the Kolmogorov cascade. When scales are comparable with cellular scales, eddies directly interact with the cells, damaging their membranes [100].

While limited to laminar flow in lower than physiologic Reynolds numbers (Re), the pioneering work of McQueen and colleagues of 3D unsteady simulations of flow in the human heart, opened the field of modeling cardiovascular flows [113–117]. In recent years attention is increasingly paid to the flow dynamics in the valve's wake. Huang and colleagues conducted the first high-resolution unsteady laminar flow numerical simulation in the wake of a MHV that depicted the complex behavior of vortex shedding [118]. They estimated the turbulent stresses associated with the vortex shedding to be as high as 3900 dynes/cm^2 , potentially playing a dominant role in aggregating activated platelets. Recent laminar 3D simulations [119–121] depicted the effects of transient flow past MHVs and the wake dynamics. However, the laminar flow assumption hampers the applicability of these simulations for studying MHV thrombogenicity, as turbulent stresses may easily exceed their laminar counterparts by an order of magnitude, and are critical in activating the hemostatic system [37]. The limitations of most existing turbulence models in handling complex valvular flows (pulsatility entails intermittent turbulence in the transition range, which violates the isotropic turbulence assumption most turbulence models use), restricted the success of their application for solving MHV flows. Kiris and colleagues were one of the first groups to solve the steady 3D Reynolds-averaged Navier-Stokes (RANS) equations in MHV flow, albeit using a simplistic mixing-length turbulence model [122]. Bluestein and colleagues were the first to perform unsteady turbulent simulations using the innovative Wilcox $k-\omega$ model, which is capable of handling transient turbulence [36,38]. The simulations depicted the intricate dynamics of the shed vortices in the wake and quantified stress histories of platelets along pertinent trajectories, with results validated using digital particle image velocimetry (DPIV).

While some correlations exist for relating platelet activation to shear stress exposure, no satisfactory model for platelet activation under flow conditions exists. Few models for shear-induced hemolysis have been developed in recent years, relating hemolysis to shear stress [123–129]. In these predictive models the normalized internal damage accumulates in a RBC until it reaches a critical value of damage, either as a function of the instantaneous stress level and the previous damage history, or as weight average damage accumulation over a number of cycles. Several numerical works directly examined the interaction of platelets with blood flow leading to coagulation products [130–133].

As mentioned previously, the limitations in characterizing the flow-induced stimuli and the ability to control them still obscure the physical relationships between mechanical loading and platelet response, hampering our ability to achieve design optimization for prosthetic blood recirculating devices. There is an urgent need to bridge this gap by characterizing the mechanical loading environment of platelets in flowing blood, and incorporate it into an accountable model for cellular trauma by means of an activation/damage accumulation hypothesis. With an accountable model for flow-induced thrombogenicity developed and validated, such a methodology has the potential to transform current device design and testing practices, leading to substantial time and cost savings during the research and development (R&D) phase.

This need is best illustrated in the case of implantable blood recirculating cardiovascular devices design process. To date, the design methodology of PHVs, VADs and other blood recirculating devices lags behind those practiced in the R&D phase of aircrafts, automobiles, and other engineering devices that function in a flow environment. All of which use computational fluid dynamics (CFD) extensively during the design process. Unfortunately, a reliable methodology capable of providing quantitatively accurate predictions of design parameters pertinent to TE in devices is emerging only recently. Device flow dynamics are mainly investigated using experimental techniques, which are limited in their ability to resolve the intricate small-scale flow phenomena involved in TE. Currently, CFD is incorporated only at a late stage of the device design process, having limited utility for effective design alterations. The utility is further limited by inadequate characterization of the complex flow fields and their interaction with the blood-borne particulates.

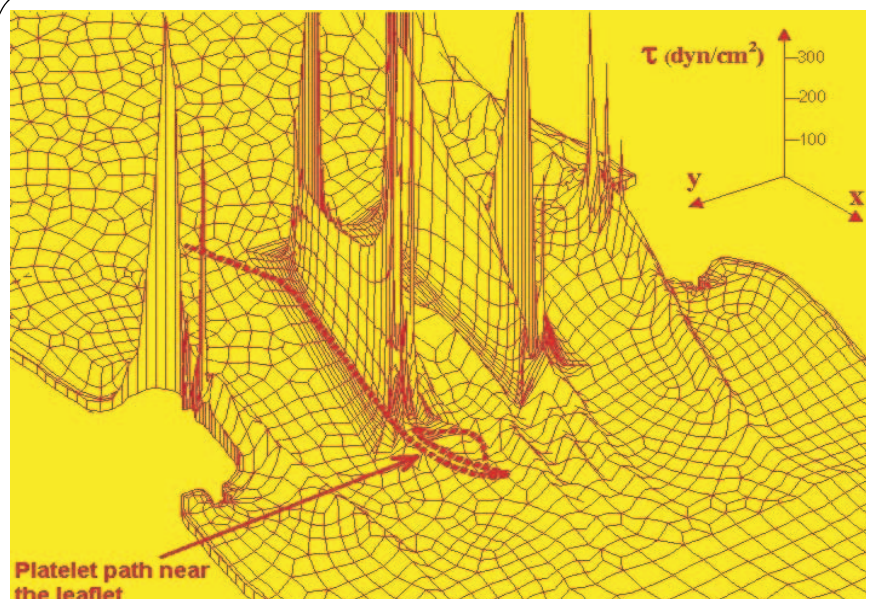


Figure 2. Perspective of shear stress (τ) distribution around the valve's leaflets (85 ms after peak systole). A typical turbulent path exposes the platelet to high shear levels, leading to entrapment in the wake. Source [36].

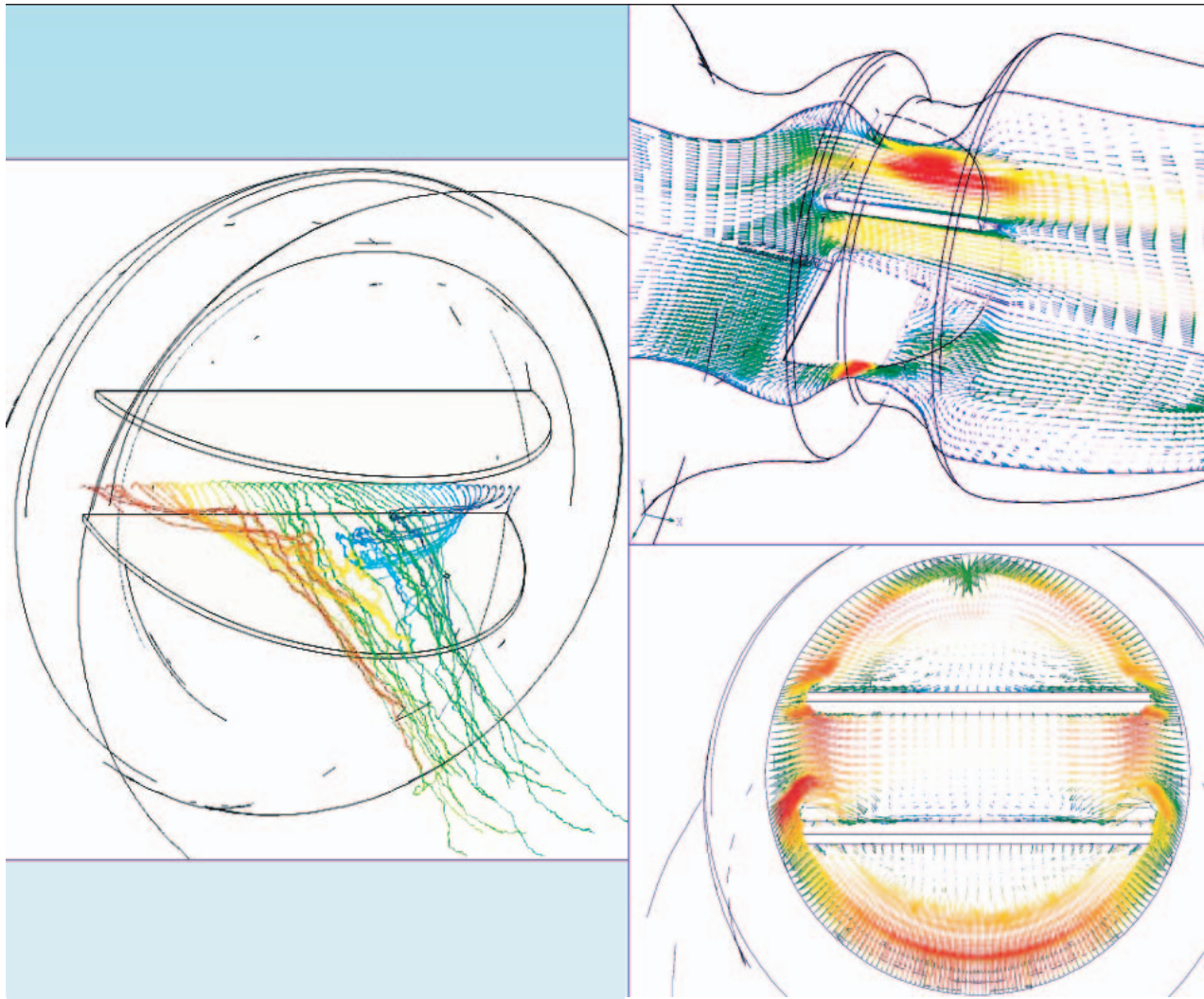


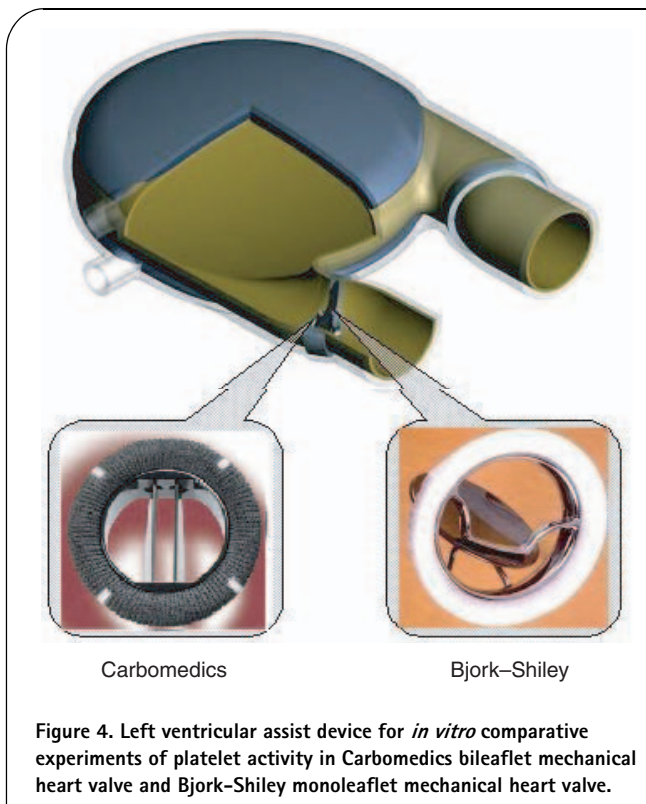
Figure 3. 3D turbulent/transient non-Newtonian simulation of blood flow past a St Jude mechanical heart valve in the aortic position. Turbulent platelet trajectories (left panel) depict the complex 3D flow patterns leading to entrapment of platelets within the shed vortices in the valve's leaflets wake. Acceleration of the flow (lower to higher velocity vectors) is represented by the blue to red range correspondingly (two right panels).

Flow-induced thromboembolism in MHVs: numerical, *in vitro* & *in vivo* studies

Turbulent and transient simulations of flow past a St Jude MHV were conducted in order to capture the intricate dynamics of the shed vortices that appear in the wake of the valve leaflets during the deceleration phase after peak systole, and are postulated to be the foci of free emboli formation. While the combination of transient and turbulent simulation in a non-Newtonian fluid is very demanding computationally and notoriously difficult to converge, it is mandatory for solving the flow field past a MHV, as the local Reynolds number of the blood flow past the valve may easily reach 7000, putting it exclusively in the turbulent range. However, under the pulsatile flow conditions past the valve, the turbulence is intermittent in nature, peaking during the deceleration phase after peak systole [54,109]. Thus, the use of traditional turbulence models that assume isotropic turbulence throughout the flow cycle, e.g the $k-\omega$ model, is inadequate. To resolve this anomaly, the innovative Wilcox $k-\omega$ model [134]

which is primary intended for simulating globally low-Re internal flows (intermittent turbulent flows in the transitional range) was employed. The unsteady Reynolds-averaged Navier-Stokes (URANS) equations were solved using a non-Newtonian blood flow model.

The simulations were conducted in a 2D geometry, aimed at investigating the effects of valve orientation and suturing techniques on the thromboembolic potential of the valve [36]. A St. Jude medical MHV implanted in the aortic position using sub-annular suturing (including the scar tissue formed over the pledgets a week or two after implantation), in a geometry that included the left ventricle and the aortic root after aortic valve replacement (AVR), with partially dissected aortic root and sinuses, was modeled. The effect of valve orientation was simulated by tilting the valve 15° with respect to the blood flow axis. The velocity vectors shown in FIGURE 1 indicate that the protrusion of the bottom pledget into the flow field, combined with the decreased cross-sectional area, produced jet flow through



the bottom orifice. Typical velocity vectors during the deceleration phase (196 ms after peak systole) are shown in FIGURE 1. Three jets were formed: one jet was formed past the central orifice of the valve between the valve leaflets, and two jets were formed between the upper surfaces of the leaflets and the aortic wall. The wake of the valve revealed an intricate pattern of shed vortices that rolled on top of each other (vortex pairing), and extended as far as twice the leaflet length downstream. The dynamics of this wake of shed vortices during the deceleration phase provide the flow conditions that may promote the formation of large platelet aggregates, as evidenced by the vortex pairing phenomenon that occurs repeatedly within the wake. Previous numerical results using a similar numerical approach were validated with Digital Particle Image Velocimetry [38]. An inherent limitation of this 2D study is that it does not include the eccentricity of the physiological flow profile across an implanted MHV with the highest flow velocities along the noncoronary leaflet [135]. This asymmetrical flow causes turbulence and might contribute to the elevated shear stresses in a tilted aortic heart valve prosthesis, especially in bileaflet valves.

Turbulent particle paths were computed using a Lagrangian approach of particulate two-phase flow. A stochastic model was applied that simulates the interaction between turbulence and platelets, in which the instantaneous velocities in the carrier phase are used to solve particle velocities by adding random fluctuations obtained from the $k-\omega$ simulation [136,137]. A typical trajectory following a platelet path below the bottom leaflet superimposed on a 3D perspective of the shear stress map (FIGURE 2) indicated that a large portion of the platelets that are exposed to the elevated shear

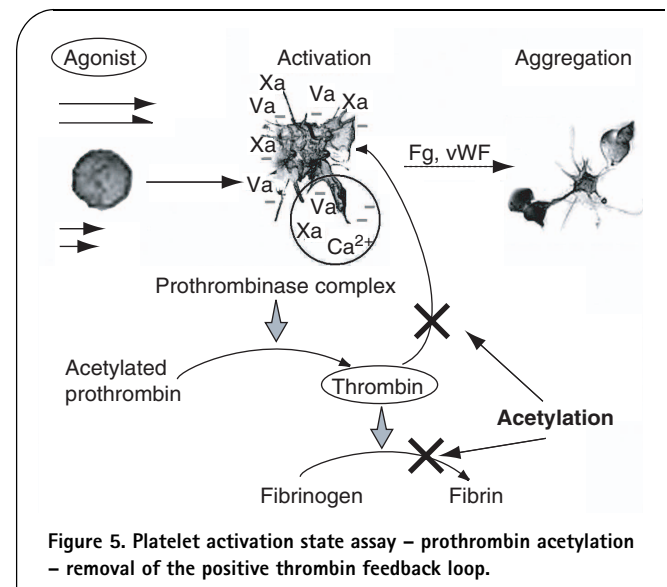
stresses around the leaflets (their projections accentuated by the high shear stress surrounding them) get trapped within the wake of shed vortices, where optimal conditions exist for enhanced mixing and interaction between activated platelets and coagulation factors, potentially leading to thromboemboli formation.

To quantify the shear stress histories of the platelets, the values of viscosity, turbulent viscosity, kinetic energy, dissipation and strain rate were extracted from the numerical solution and used to compute the platelet stress histories along the trajectories. Briefly, the cumulative effect of shear stress (τ) and exposure time (Δt) was computed by summation of the product of their instantaneous absolute values in each computational node along the platelet path, i.e. $\sum (\tau \times \Delta t)$. This parameter is termed the 'Level of Activation' parameter [37]. The total stress, laminar plus turbulent, was computed using the Boussinesq approximation [138] and multiplied by the instantaneous exposure time to this stress (Δt_i) along the platelet trajectory, according to the following formulation:

$$\sum_{i=t_0}^{t_{max}} \left(\frac{(\varepsilon_i + \varepsilon_{i+1})}{2} \times (\mu_i + \rho \mu_i^t) + KE_i \times \rho \right) \times \Delta t_i$$

where ε_i is the strain, μ_i is the viscosity, μ_i^t is the turbulent viscosity, ρ is the density, KE_i is the turbulent kinetic energy and Δt is the time step.

After establishing pertinent platelet trajectories, the level of activation was computed along two characteristic platelet paths for each geometry (tilted, or misaligned valve, and untilted valve); one in the region of highest shear stresses near the leaflet, the other in the core flow region used as a reference activation level for both geometries. The computation was carried out during deceleration, from $T = 183$ ms to $T = 313$ ms, corresponding to the phase during the cardiac cycle in which most of the shed vortices were formed and the turbulence peaked. The level of activation of platelets flowing near the



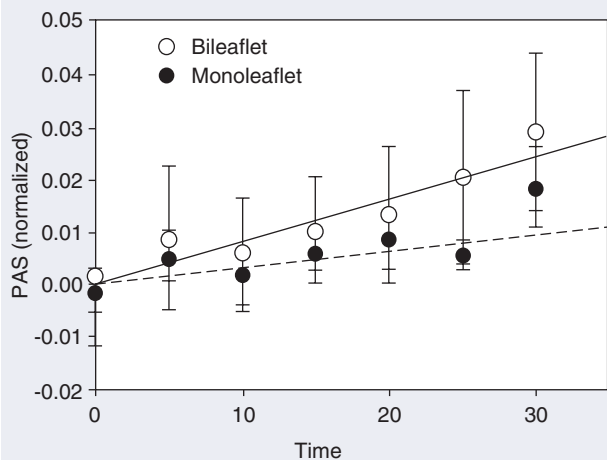


Figure 6. *In vitro* platelet activity measurements in left ventricular assist devices. The bileaflet mechanical heart valve (slope = $8.114 \times 10^{-4}/\text{min}$) generated higher PAS activities than the monoleaflet mechanical heart valve (slope = $3.143 \times 10^{-4}/\text{min}$). The difference between the two slopes was significant ($p < 0.05$). PAS: Platelet Activation State. Source [66].

leaflets was much higher compared with those flowing in the core flow region, with the tilted geometry producing a steep and rapid increase in the activation level, demonstrating how the valve's misalignment directly affects platelet activation. The shear stress histories along these trajectories depict a rapid increase in the platelets level of activation, reaching a value of $20 \text{ dynes} \times \text{s}/\text{cm}^2$ over a short span and single passage, compared with the activation threshold of $35 \text{ dynes} \times \text{s}/\text{cm}^2$ [32]. The level of activation computation was later applied for comparing the thrombogenic potential of monoleaflet and bileaflet MHV designs (FIGURE 7), and correlated to *in vitro* platelet activity measurements performed in LVADs (FIGURE 6).

Turbulent/transient URANS 3D simulations of flow past a St Jude MHV in anatomically correct aortic position implantation (subannular suturing) were conducted (FIGURE 3). The intricate dynamics of the shed vortices in the wake of the valve's leaflets during the deceleration phase after peak systole, are depicted by the turbulent trajectories and the complex 3D flow structures revealed. 3D helical vortices entrained fluid span-wise from the leaflet leading edge into the wake of shed vortices. Those are postulated to trap activated platelets, enhancing free emboli formation and the risk of TE.

A comparative study was conducted to measure *in vitro* the procoagulant properties of platelets induced by flow through bileaflet and monoleaflet MHVs in a

LVAD. The LVAD (FIGURE 4) was the implantable part of a pneumatic heart assist system developed by Professor Affeld (Charité – University Medicine Berlin, Germany). The procoagulant activity of the platelets was measured using a platelet activation state (PAS) assay based on a modified prothrombinase method [42]. Briefly, the PAS assay is an innovative technique based on the modification of the prothrombinase method, in which acetylated prothrombin is used. The prothrombinase complex assembles on the activated platelet surface in the presence of Factor Xa bound to the two essential cofactors provided by activated platelets: Factor Va and anionic phospholipids [139]. The thrombin generated in the assay, is a powerful platelet agonist that reactivates the platelets in a positive feedback loop. The acetylated prothrombin reacts with the prothrombinase complex to produce a thrombin species that does not activate platelets. Removing the positive feedback activation (FIGURE 5) results in easily measurable thrombin, which accurately reflects the flow-induced procoagulant activity of the platelet. The author's group has previously shown that PAS measurements correlate with flow cytometry of negative phospholipid exposure measured by annexin V binding [47].

Gel-filtered (plasma-free) platelets in a buffer (derived from platelet-rich plasma) were recirculated through the LVAD, mounted with Carbomedics bileaflet MHVs and Bjork–Shiley monoleaflet MHVs. The amount of acetylated thrombin generated was measured using a chromogenic assay. The PAS measurement indicated that the Carbomedics bileaflet MHV activated platelets at a rate of more than two-fold than that observed with the Bjork–Shiley monoleaflet MHV ($P < 0.05$, FIGURE 6). CFD simulations of turbulent, transient, non-Newtonian blood flow patterns generated by the two designs were

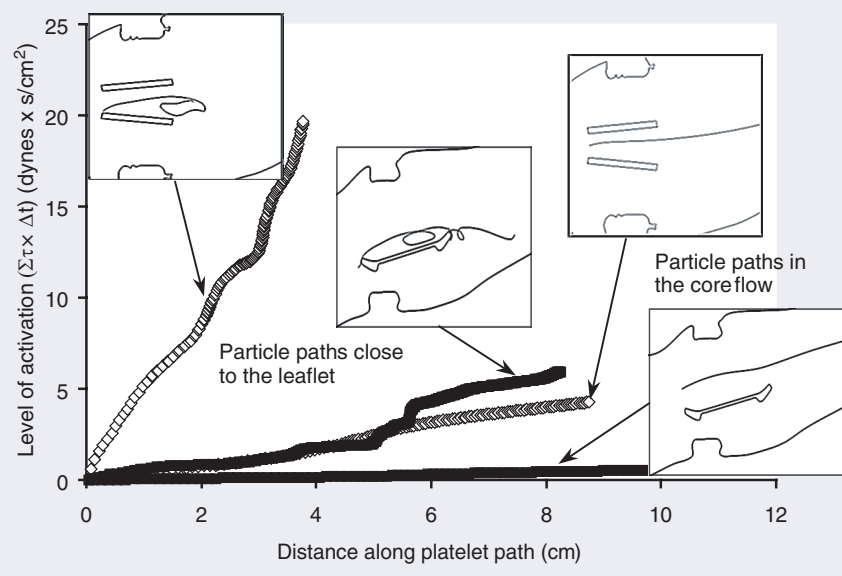


Figure 7. Comparison of shear stress histories of platelets (level of activation) along the platelet path in the core flow and near the valve leaflet for the bileaflet MHV and monoleaflet MHV. Platelets were activated faster in bileaflet than in monoleaflet MHV in both the core flow and near the valve leaflets. MHV: Mechanical heart valve. Source [66].

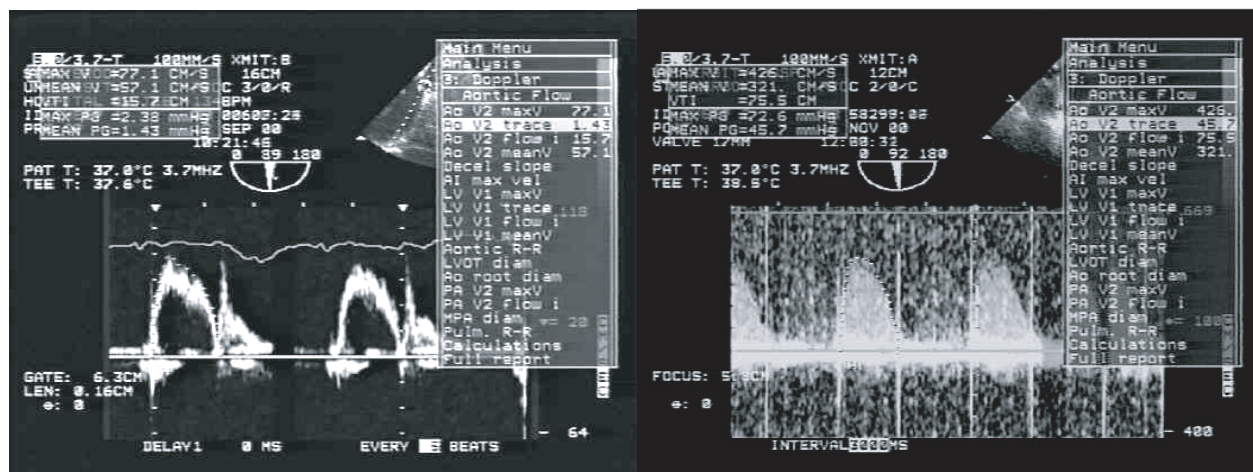


Figure 8. Pulse Doppler of the sheep native aortic valve (preoperative, left), as compared with continuous wave Doppler of St Jude Medical mechanical heart valve (10 weeks postoperative, right).

conducted using the Wilcox $k-\omega$ turbulence model. Platelet shear stress histories (cumulative effect of shear stress and time) through the two MHVs were calculated and compared with the PAS measured *in vitro*. Turbulent flow patterns could be seen in CFD simulations in both valves, and the computed platelet shear stress history along pertinent trajectories in the core flow of the valves and near the leaflets, where the platelets encounter elevated shear stresses (FIGURE 7), clearly indicated that the Car-bomedics bileaflet MHV induced a higher level of stimulation (the platelet 'Level of Activation' parameter), correlating with the *in vitro* PAS measurements (FIGURE 6).

In vivo valve implantation studies

Following Salerno and colleagues (1998) who demonstrated sheep to be a better animal model for chronic evaluation of aortic MHVs as compared with pigs or calves for example, a 17 mm St Jude Medical MHV was successfully implanted in the aortic position in an adult female Dorset sheep. Successful implantation and prolonged survival was achieved after surgical techniques and coagulation treatment during surgery and immediately postoperatively were optimized. Before surgery a Transesophageal Echocardiography (TEE) was performed. Thoracotomy was favored over sternotomy as a less invasive surgical technique, with the additional benefit of better recuperation, as sheep lie on their sternum when recovering from surgery. Another TEE was performed by the end of the procedure. Pre- and postoperative echocardiographic signals (FIGURE 8) indicate the increased gradients and velocities across the MHV as compared with the native valve. The values were similar to those published by Salerno and colleagues (1998) for sheep implanted with bileaflet MHV.

In each sheep experiment in which the animal had died, a detailed autopsy for detection of thrombus formation and its downstream effects, such as disseminated intravascular coagulation (DIC), was carried out, including major internal organs (heart, lungs, brain). Necropsy was conducted and pathological and histological examinations performed in suspected lesions. In one of the

cases, a gross anatomical necropsy of the heart revealed a large thrombus that was stuck between the MHV leaflets (FIGURE 9). Detailed pathological and histological studies also revealed thrombosed cerebral blood vessels in the brain (FIGURE 10) and emboli in the myocardium which indicated coagulative necrosis.

HITS measurement in sheep with TCD

A 19 mm St Jude Medical MHV was implanted in a 201 lb female sheep. TCD and TEE measurements were conducted under anesthesia preoperatively, and at regular intervals postoperatively. The TEE measurements indicated $V_{\max} = 368$ cm/s after valve implantation ($V_{\max} = 78$ cm/s

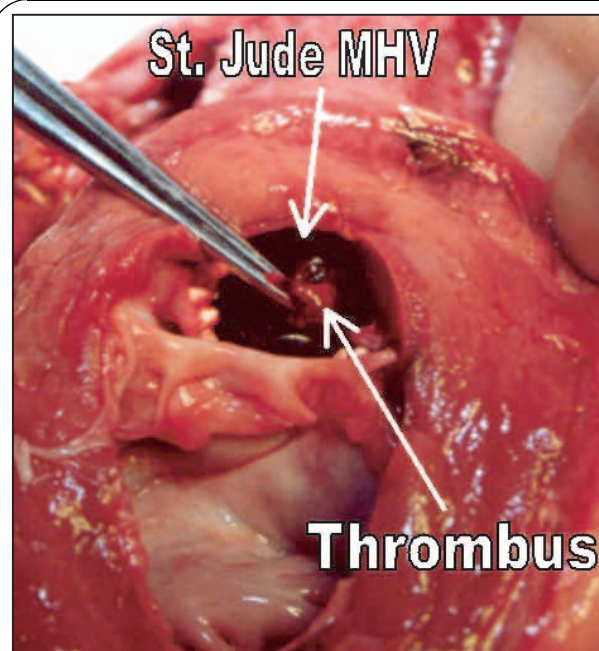


Figure 9. A major thrombus in a St Jude Medical mechanical heart valve in sheep.

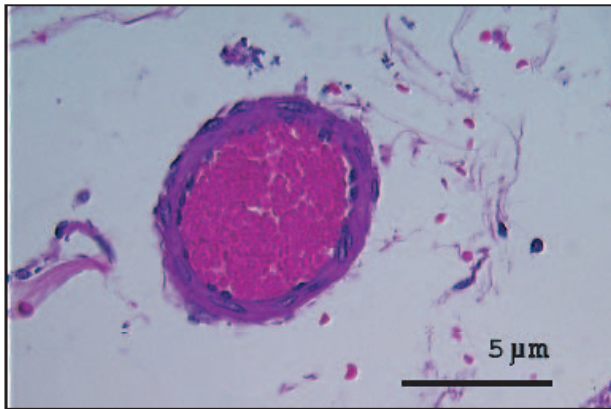


Figure 10. Cerebral blood vessel occluded by thrombosis.

preoperatively) Using a 2 MHz TCD probe attached to the neck of the sheep and a Nicolet Biomedical TCD system, HITS (signifying an emboli passage) were measured in the sheep's left carotid artery for 30 min (sample length gated at 9 mm, focal length 88 mm). HITS were not observed preoperatively. In the postoperative period, the number of HITS ranged from 68 to 123 counts. A typical HITS is shown in FIGURE 11, with postoperative HITS progression indicated and the distribution between gaseous emboli and thromboemboli shown. Spectral analysis of the HITS was performed (FIGURE 12), using the sample volume length (SVL) criterion, aimed at discriminating the riskier thromboemboli from gaseous emboli.

Monitoring sheep platelet activity using the PAS assay

A major advantage of the prothrombinase-based assay of platelet activity is its applicability to platelets of other species. In contrast, the measurement of activation-dependent platelet-membrane antigens with monoclonal antibodies is species-specific, as the antibodies are directed against human platelets. The author's group has confirmed that the assay, using human Factor Xa and acetylated prothrombin, is applicable to the measurement of the activity states of platelets from four mammals studied to date: humans, mice, cattle, and sheep. FIGURE 13 compares the time course of (acetylated) thrombin generation with sheep platelets isolated from a normal control sheep and those from a sheep with an implanted MHV. The upper panel shows that when the platelets are fully activated *in vitro* with a potent platelet agonist (calcium ionophore), their activities are essentially equivalent. In contrast, the platelet activity of the MHV-implanted sheep is twice that of the control, at approximately 8% of the ionophore activated platelets.

This is a strong indication that the MHV is causing significant, measurable, platelet activation in the experimental animal, indicating it is further prone to TE.

Expert opinion

Further elucidation is needed

Thrombogenicity of blood recirculating devices is primarily due to platelet activation, which can be initiated both by contact with foreign surfaces and by nonphysiological flow patterns and/or their combination. Recent efforts in this field strongly indicate that device TE is initiated and maintained primarily by the nonphysiological flow patterns and stresses that activate and enhance the aggregation of blood platelets, increasing the risk of TE and cardioembolic stroke. In this review, research pertaining to the interaction between flow and the blood constituents was described, with an unambiguous emphasis on the flow-induced stresses and flow patterns leading to TE in prosthetic blood recirculating devices. This article described such work, which includes state-of-the-art numerical, experimental, and *in vivo* tools used to elucidate flow-induced mechanisms leading to TE in prosthetic devices.

While anticoagulation medication is readily available and prescribed profusely, most anticoagulants appear to be inefficient in preventing shear-induced platelet activation and aggregation. Kroll and colleagues urged that the current research must go beyond static and steady flow conditions and begin to account for the pertinent rheologic variables that affect physiologic and pathologic responses [17]. Elevated flow-induced stresses that are present in nonphysiological and pathological geometries enhance the propensity to initiate blood coagulation, with rheologic variables related to eddy formation and pulsatility most likely predominating. The precise mechanisms by which platelets convert mechanical stimuli into biochemical signals have yet to be elucidated. Limitations in characterizing

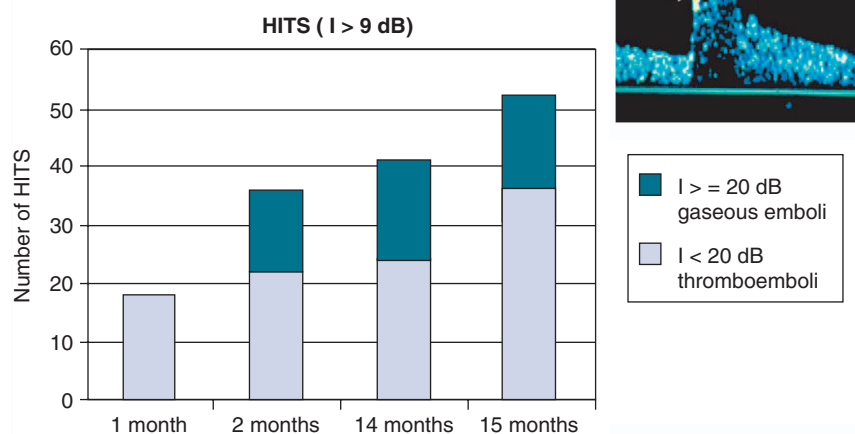


Figure 11. Postoperative measurements of HITS in sheep after mechanical heart valve implantation. HITS: High-intensity transient signals.

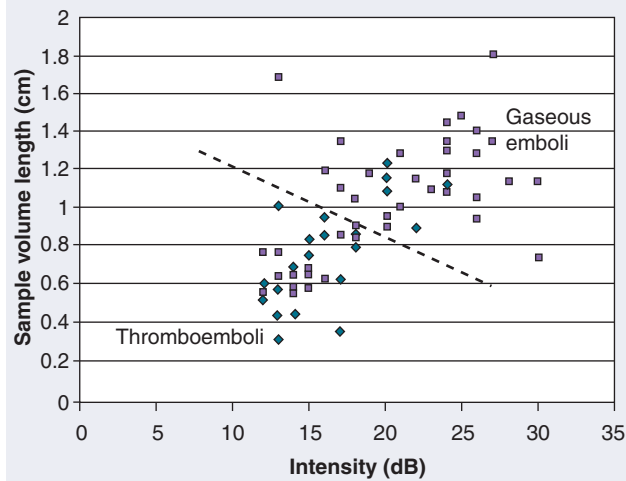


Figure 12. Sample volume length analysis discriminating gaseous emboli from thromboemboli.

relevant aspects of the mechanical stimuli and the ability to control them still obscure the physical relationships between those and the platelet response. To bridge that gap, there is a need to characterize the mechanical loading environment of platelets in flowing blood, to facilitate its replication *in vitro*, and to incorporate it into an accountable model for cellular trauma prediction by means of an activation/damage accumulation hypothesis. If we are to design devices that do not introduce a neodisease, as universally all current devices do, a better understanding of the underlying mechanisms of flow-induced TE is essential. The desired goal is to achieve a minimization of the amount of TE that devices induce, instead of tolerating the fact that it could be clinically manageable through a drug regimen which carries many risks, is unsuitable for many patients, and ultimately does not eliminate the problem.

This article presented numerical modeling approaches, *in vitro* assays which facilitate measuring flow-induced thrombogenicity in devices, and *in vivo* approaches to study the likely devastating end result. As indicated in the title, the emphasis was on research approaches rather than diagnostic clinical modalities. This is intended to circumvent *ad hoc* approaches which unfortunately seem to pervade the field, and to establish a more methodological approach to device development. As mentioned, CFD is incorporated only at a late stage of the device design process, having limited utility for effective design alterations. While there are many reasons for the less than desirable application, it is clear that incorporating CFD in the early stages will greatly benefit the design process, potentially reducing device thrombogenicity. The same is true with respect to the application of relevant *in vitro* thrombogenicity testing techniques, which are currently emerging. Results of such experiments would lead to alterations during the early stages of device development. Such an approach has the potential to significantly cut R&D

costs for the device manufacturers by reducing the number of costly, and at times, redundant *in vivo* testing iterations. It could also prevent unfortunate cases in which devices with unacceptable thromboembolic complication rates were prematurely introduced to the market with devastating consequences. While manufacturers put a certain effort into achieving design optimization, some of their reluctance to invest more in the pertinent research stems from the willingness of the clinical community to accept less than optimal device solutions which can be partially managed through drug therapy. The situation is further complicated by the ambiguity regarding the subject as reflected by the regulatory agencies. Hopefully, with the current surge of studies on flow-induced thrombogenicity in blood recirculating devices, this situation will be rectified by the regulatory agencies mandating new testing protocols.

In summary, by obtaining quantitatively accurate predictions of flow phenomena in prosthetic devices using sophisticated numerical models, correlating them to *in vitro* measurements of flow-induced thrombogenicity, and measuring their end-points *in vivo*, a more accurate depiction of TE may arise and be clinically substantiated. Such methodology may facilitate better

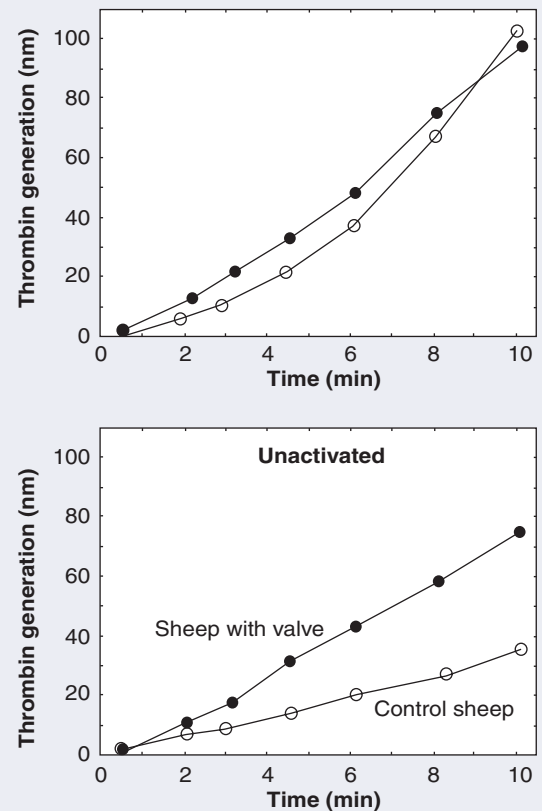


Figure 13. Comparison of sheep platelet activity. Upper panel shows essentially equivalent full activation between MHV-implemented sheep and control sheep. The lower panel shows twice the platelet base activity for the MHV sheep as compared with the control sheep. MHV: Mechanical heart valve.

device design by reducing the risks that patients implanted with these devices face, lowering the ensuing healthcare costs, and offering viable long-term solutions for these patients.

Five-year view

Five years is a relatively short period in the device development life cycle. Nevertheless, there are several strides that could lead to a significant improvement in the design process of blood recirculating devices. Foremost is the rapid advance in numerical modeling techniques and computing capabilities, which facilitate applying relevant and sophisticated CFD modeling techniques for studying blood flow in the complex confines and geometries characterizing devices. This is to be complemented by developing accountable models for flow-induced

blood damage accumulation. With techniques for studying TE *in vitro* becoming more readily available, validation approaches now exist for the numerical predictions, paving the way to achieve within the next 5 years, at least partially, reduction of device thrombogenicity. At the same time, clinical modalities such as TCD enable us to study more carefully the thrombogenic potential of devices *in vivo*. However, given the complexity of this undertaking, it is clear that achieving devices optimization and reducing their thromboembolic rates to more desirable levels may take much longer than 5 years. The success of this endeavor hinges on funding trends, which obviously rely on the recognition in the importance of this type of research by the industry, the regulatory agencies, and the funding agencies.

Key issues

- Thrombosis, rather than hemolytic anemia, is the primary clinical problem associated with blood recirculating devices.
- The attendant risk for cardioembolic stroke remains an impediment to these devices.
- Thromboembolism in prosthetic blood recirculating devices is initiated and maintained primarily by the nonphysiological flow patterns and stresses that activate and enhance the aggregation of blood platelets.
- Platelets are far more sensitive to flow conditions than red blood cells, and they respond to flow-induced stresses by initiating procoagulant activity in several ways.
- Advances in computational fluid dynamics and activation/damage accumulation models can be incorporated into the early stages of the device design process in order to achieve design optimization and reduce their thromboembolic complication rates.
- Techniques for studying flow-induced thrombogenicity can be used to measure *in vitro* procoagulant properties induced by devices, and to validate numerical predictions.
- Clinical modalities, such as transcranial Doppler, can be used to measure device induced thromboemboli *in vivo*.
- Further elucidation is needed to understand the mechanisms by which platelets convert mechanical stimuli into biochemical signals.

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