



Device thrombogenicity emulation: A novel methodology for optimizing the thromboresistance of cardiovascular devices

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ARTICLE INFO

Article history:

Accepted 15 November 2012

Keywords:

Mechanical circulatory support (MCS)
Ventricular assist devices (VAD)
Thrombogenicity
Blood flow
Platelets
Device optimization
Device thrombogenicity emulation (DTE)

ABSTRACT

Thrombotic complications with mechanical circulatory support (MCS) devices remain a critical limitation to their long-term use. Device-induced shear forces may enhance the thrombotic potential of MCS devices through chronic activation of platelets, with a known dose–time response of the platelets to the accumulated stress experienced while flowing through the device—mandating complex, lifelong anticoagulation therapy. To enhance the thromboresistance of these devices for facilitating their long-term use, a universal predictive methodology entitled device thrombogenicity emulation (DTE) was developed. DTE is aimed at optimizing the thromboresistance of any MCS device. It is designed to test device-mediated thrombogenicity, coupled with virtual design modifications, in an iterative approach. This disruptive technology combines *in silico* numerical simulations with *in vitro* measurements, by correlating device hemodynamics with platelet activity coagulation markers—before and after iterative design modifications aimed at achieving optimized thrombogenic performance. The design changes are first tested in the numerical domain, and the resultant device conditions are then emulated in a hemodynamic shearing device (HSD) in which platelet activity is measured under device emulated conditions. As such, DTE can be easily incorporated during the device research and development phase—achieving minimization of the device thrombogenicity before prototypes are built and tested thereby reducing the ultimate cost of preclinical and clinical trials. The robust capability of this predictive technology is demonstrated here in various MCS devices. The presented examples indicate the potential of DTE for reducing device thrombogenicity to a level that may obviate or significantly reduce the extent of anticoagulation currently mandated for patients implanted with MCS devices for safe long-term clinical use.

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1. Introduction

The advent of mechanical circulatory support devices has provided life-saving solutions to patients with severe cardiovascular diseases. The REMATCH trial (Stevenson et al., 2004) was one of the first major studies to demonstrate that left ventricular assist devices (LVAD) are superior to drug therapy for advanced heart failure, paving the way for their use as long-term heart replacement therapy for patients ineligible for heart transplantation. Despite the success of this study the MCS heart demonstrated significant limitations with unacceptable complication rates (Portner et al., 2001), and strokes (Lazar et al., 2004). Second and third generation continuous-flow VADs that have emerged clinically in recent years have improved the clinical outcomes.

However, in the recent HeartMate II VAD Destination-Therapy Trial patients still suffered 11% disabling stroke rate (Slaughter et al., 2009), attributed to the increased shear stress, offering the possibility that improved VAD design could prevent this problem in the future (Geisen et al., 2008). The AbioCor artificial heart, was developed as a possible solution to the chronic shortage in availability of human hearts for transplantation. In the pilot trial of the AbioCor TAH (ABIOMED, Inc.), a high rate of thromboembolic complications made the clinical outcomes disappointing (Frazier et al., 2004) stemming from design and valvular issues. mechanical heart valve (MHV) patients develop thromboembolic complications at a rate of 0.7–6.4% per patient year (Butchart et al., 2001, 2003). In these patients, platelets are chronically activated (Edmunds, 1996; Edmunds et al., 1997). All these devices, as well as new emerging MCS devices, progressively share common limitations of thromboembolism and hemolysis.

The formation of thromboemboli in MCS devices is potentiated by contact with foreign surfaces and regional flow phenomena that stimulate blood clotting, in particular via activation of platelets.

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The non-physiologic flow patterns generated in a device are considered as one of the major culprits in enhancing the hemostatic response. The well-known “Virchow’s triad” of altered blood, surface, and flow, establishes the blood-artificial surface interaction problem as a multifactorial one. The flow component, perhaps the most complex part of the triad, combines all three, i.e. flow—local flow patterns play a substantial role in coagulation reactions, blood—platelet aggregation, and surface—local deposition on activated surfaces. It determines where a thrombus will form, its size and composition, and whether or not it will remain locally or embolize (Sorensen et al., 1999a,b). Thrombus and thrombo-emboli generated in cardiovascular devices are composed primarily of platelets, with less fibrin involvement than one would encounter in situations associated with low-shear thrombosis (Harker and Slichter, 1970).

Flow-induced shear platelet activation causes both aggregation and thrombin generation, showing consistent ‘dose’ and time response characteristics of equivalent chemical agonists (O’Brien and Salmon, 1990). A commonly used threshold for platelet activation under constant shear level was established by Hellums et al. (Hellums et al., 1987), forming the foundation for shear-induced platelet activation (SIPA). In prosthetic devices the pathological blood flow patterns related to pulsatility, eddy formation, and turbulence, may predominate the platelets response (Alveriadou et al., 1993; Folie and McIntire, 1989). The cumulative effect of varying flow stresses and exposure times along platelet trajectories was studied in stenoses and past MHV (Bluestein, 2004; Bluestein et al., 1997, 2000, 2002, 2004; Cao and Rittgers, 1998).

In PHV and CVS devices portions of the flow cycle may become turbulent, (Bluestein et al., 1994, 2000), with elevated stresses within MHV hinges (Yoganathan et al., 1998). VADs induce changes to coagulation through activation of platelets (Rothenburger et al., 2002; Wilhelm et al., 2001) despite aggressive anticoagulant therapy, with flow patterns implicated in the underlying risk for their thromboembolism (Jin and Clark, 1993), especially cerebral embolism (e.g., rates ranging from 7.4% for the Heartmate I VAD to approx. 50% for the Novacor VAD system) (El-Banayosy et al., 2001). Platelet aggregates are the source of microembolic signals (MES) measured in patients with PHV (Grosset et al., 1996). A significant effect of valve hemodynamics on platelet activation for two differing valve designs (bileaflet. vs. monoleaflet) was also observed in patients (Laas et al., 2003).

The AbioCor TAH study indicated that while no evidence of significant hemolysis was observed in animal or human patients studies (Dowling et al., 2004; Samuels et al., 2005), the majority of patients died of stroke related complications. Regrettably, very few data on flow-induced thrombogenic aspects are currently available (Charron et al., 1994). Several approaches for studying device-induced thrombogenicity were developed by a few groups (Paul et al., 1998; Travis et al., 2002; Jesty and Bluestein, 1999; Jesty et al., 2003). Jesty and Bluestein developed an innovative platelet activity state (PAS) assay, facilitating measurements of the thrombogenic potential induced by flow in devices. This technique was applied to *in vitro* measurements of flow-induced platelet activation in MHVs mounted in an LVAD (Yin et al., 2004), and in bioprosthetic and polymer valves (Yin et al., 2005), which are targeted for minimally invasive, percutaneous valve delivery (Feldman, 2006; Mesana, 2006)—the breakthrough technique with a huge promise for patients who cannot tolerate cardiothoracic surgery. The goal is for polymer valves, which are better suited for catheter-based stented delivery, to have thrombogenic potential comparable to the latter thereby obviating the need for mandatory anticoagulation therapy. Leakage gap width within bileaflet MHV pivots was demonstrated to have a significant effect on platelet damage (Travis et al., 2001).

Thrombus formation was investigated in blood flow through orifices simulating these MHV hinges region using a thrombin-antithrombin -III (TAT) assay (Fallon et al., 2006).

Vortex shedding was observed experimentally and computed numerically in the wake of MHV leaflets and in various MCS devices. Shed vortices were studied in the wake of MHVs (Bluestein et al., 2001, 2002; Reif et al., 1990) which promote hemostatic reaction 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. Elevated turbulent stresses (1200–2000 dynes/cm²), which were measured in such wakes (Grigioni et al., 2001; Yoganathan et al., 1986), reiterated their role in activating platelets. Prior activation and the extrusion of platelets pseudopodia, potentially induced by the elevated shear stresses globally preceding vortex shedding, increases their effective hydrodynamic volume by several folds, resulting in an increased collision rate (Wurzinger et al., 1985). Numerical simulation in the wake of a MHV depicted the wake dynamics and complex behavior of vortex shedding (Huang et al., 1994; Kelly et al., 1999; King et al., 1997; Krafczyk et al., 1998). First unsteady turbulent Reynolds Averaged (URANS) simulations using the transient turbulence Wilcox $k-\omega$ model (Bluestein et al., 2000, 2002) quantified stress histories of platelets along pertinent trajectories. Advanced URANS and direct numerical simulations (DNS) included a damage accumulation in repeated passages past valves (Alemu et al., 2010), and FSI simulation comparing the thrombogenic potential of ATS and St. Jude Medical MHVs (Dumont et al., 2007).

Few models for hemolysis have been developed over the years, e.g., as a function of mechanical energy dissipation (Bluestein and Mockros, 1969), or shear stress (Apel et al., 2001; Bludszweit, 1995; Burgreen et al., 2001). In these predictive phenomenological models, that are adaptable to platelets, the normalized internal damage accumulates until a critical value of damage is reached, 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. *In vitro* hemolysis indices were investigated numerically over 3D device domains for the purpose of design optimization (Garon and Farinas, 2004), and by integrating hemolysis and platelet lysis indices along trajectories in the flow field of MHV (Goubergrits and Affeld, 2004). Several models examined the interaction of activated platelets with the blood field (Kuharsky and Fogelson, 2001; Sorensen et al., 1999a), and platelet deposition (Reininger et al., 1999; Worth Longest and Kleinstreuer, 2003). Such modeling efforts provide insight into the areas where platelets have a high probability for activation, leading to thrombus formation and thromboembolism.

2. Methods

2.1. The device thrombogenicity emulation (DTE) methodology and its components

DTE is an iterative optimization process, summarized in a composite flow chart schematic (Fig. 1). Briefly: ‘hot spot’ platelet trajectories (extreme flow trajectories which expose platelets to the highest stress-loading conditions) are extracted from extensive advanced numerical simulations of the blood flow in the device. Those are resolved to quantify the stress loading waveforms, which are programmed into a hemodynamic shearing device (HSD) where the stress loading conditions within the device are emulated. Samples of gel filtered platelets exposed to these stress loading waveforms are removed from the HSD and assayed to measure thrombin generation rates, a surrogate marker for platelet activation, using the platelet activity state (PAS) assay (Jesty and Bluestein, 1999; Jesty et al., 2003). Designs may then be iteratively modified to reduce the thrombogenic potential, as computed in the virtual (modeling) domain, and the resultant stress loading waveforms programmed and further tested in the HSD. This iterative process involves changing design parameters specific to the device and repeating the numerical simulations of the blood flow through the redesigned device. When optimized thromboresistance is achieved via DTE. A prototype of the

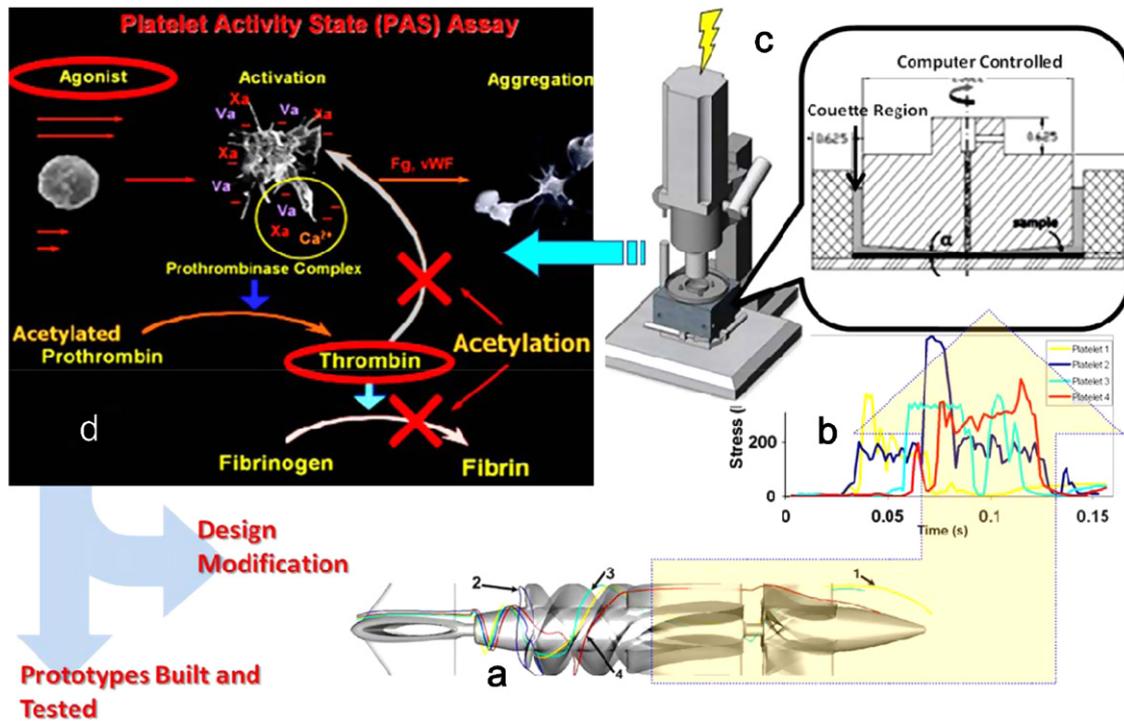


Fig. 1. DTE methodology iterative optimization flow chart: (a) 'hot spot' platelet trajectories extracted from the numerical simulation in the device (VAD in this case) are resolved to determine the (b) stress loading waveforms, which are programmed into the (c) HSD, where the stress loading conditions within the device are emulated. Samples are removed from the HSD and assayed to measure the thrombin generation rates using the (d) PAS assay. The procedure is reiterated by changing design parameters specific to the device and repeating the numerical simulation of the blood flow through the redesigned device. After the iterative process achieves a significant reduction in platelet activity, the iterations are stopped and an optimized prototype is built and tested.

optimized device may then be built and tested to validate that optimization was achieved by comparing it to the baseline or predicate device design prior to optimization.

The numerical simulations of blood flow through the devices (modeled as a two-phase fluid with the platelets suspended in plasma (Gosman and Ioannides, 1983) combine fluid structure interaction (FSI) with Unsteady Reynolds Averaged Navier-Stokes (URANS) CFD. Highly resolved computational grids (currently up to 20 million elements) are generated as required for the two equation $k-\omega$ turbulence model (Wilcox, 1994). This simulation approach is further described in detail in our previous publications (Alemu et al., 2010; Xenos et al., 2010). Typical platelet trajectories in the flow field of a VAD and their corresponding stress-loading histories (computed with the combined effect of shear stress and exposure time (Alemu and Bluestein, 2007; Apel et al., 2001; Hellums, 1994) are shown (Fig. 1a and b)). Currently up to 65,000 such histories are collapsed into a quantitative probability density function (PDF) which serves as the 'thrombogenic footprint' of the device (Alemu et al., 2010; Xenos et al., 2010)—mapping where the cumulative stress of each trajectory will end up in the distribution of the stress accumulation (SA) range characterizing the specific device. For improved thromboresistance it is desired that the dominant mode of the distribution be shifted to the lower SA range, i.e. a "leftward shift," and as few trajectories as possible residing in the riskier higher SA range (where platelets are likely to activate).

The HSD (Fig. 1c) combines features of cone and plate, and Couette viscometers to dynamically expose a population of platelets to a uniform shear stress field of rapidly varying levels (Girdhar and Bluestein, 2008), which are programmed into the device according to the loading waveforms extracted from advanced numerical simulations of blood flow through a device (Fig. 1b). The PAS assay employs a modified prothrombinase method using a real-time chromogenic assay to measure thrombin formation—a universal marker of platelet activation. It quantifies the propensity of any blood recirculating device to induce thrombosis by measuring the contribution of the device to the induction of platelet activation and the hemostatic response (Jesty and Bluestein, 1999; Jesty et al., 2003). Thrombin formation is monitored as blood flows through device prototypes or within the HSD, and as the positive feedback loop is blocked in this assay (as well as the cleaving of the soluble fibrinogen into insoluble fibrin) the extent of measured thrombin generation is directly coupled to the prothrombinase activity, i.e., the platelet activation and aggregation induced by the agonist-flow induced shear stress (Fig. 1d).

For VAD recirculation experiments whole blood (120 ml) was obtained from healthy adult volunteers ($n=10$) in accordance with Stony Brook University IRB regulations. Purified platelets (15×10^6 ml) or platelets and red cells (800×10^6 ml) were diluted in modified Tyrode's buffer. Timed samples (0, 10, 20, 30 min) were obtained from platelets or platelets+red cells exposed within the VAD flow loop and activation measured with the PAS assay as

described above. The slope of normalized platelet activation was fitted to a linear model and reported as platelet activation rate (PAR). For the studies comparing the efficacy of VAD optimization to that of using anticoagulants reported below, platelets in buffer as previously described (Aspirin (ASA) treatment), or platelets in buffer with the addition of red blood cells (Dipyridamole treatment) were recirculated in the flow-loop through the non-optimized VAD \pm ASA or Dipyridamole, both at a concentration of $20 \mu\text{M}$; corresponding to plasma concentrations from low-dose formulations of both drugs. These *in vitro* dosages were equivalent to the maximal possible absorption of the metabolized drug in a subject's circulation.

We have previously applied the DTE methodology for optimizing the thrombogenic performance of various MCS and prosthetic heart valves, e.g., MHV (Xenos et al., 2010), polymer valves (Claiborne et al., 2011) and VADs (Girdhar et al., 2012). In the following section an example of utilizing DTE for achieving optimal thromboresistance in a VAD is demonstrated and also compared *in vitro* to the equivalent effect achieved by the anti-thrombotic therapy.

3. Results

The efficacy of DTE was demonstrated in VADs by comparing two rotary blood pump prototypes (DeBakey Micromed vs Heart Assist 5, Micromed Inc., Houston, TX). Geometric features of the original VAD design (DeBakey Micromed) that were implicated in the thrombogenicity of this device were modified to create the optimized VAD design (Heart Assist 5). The design modifications included: the inlet flow straightener (4 blades reduced to 3), streamlined inlet hub and bearing taper, impeller region (blade leading edge and pitch angle, blade profiles), impeller-shroud gap and near wall region, and the impeller-diffuser interface. The original and optimized designs are shown in Fig. 2a. Numerical simulations (URANS FSI-25 rotations at 9000 rpm) were used to calculate the cumulative stresses along thousands of flow trajectories through both devices (before and after the optimization) and collapsed into PDFs—the 'thrombogenic footprint' of each device prototype. Following the specific design changes, the extensive numerical simulations conducted clearly indicate that

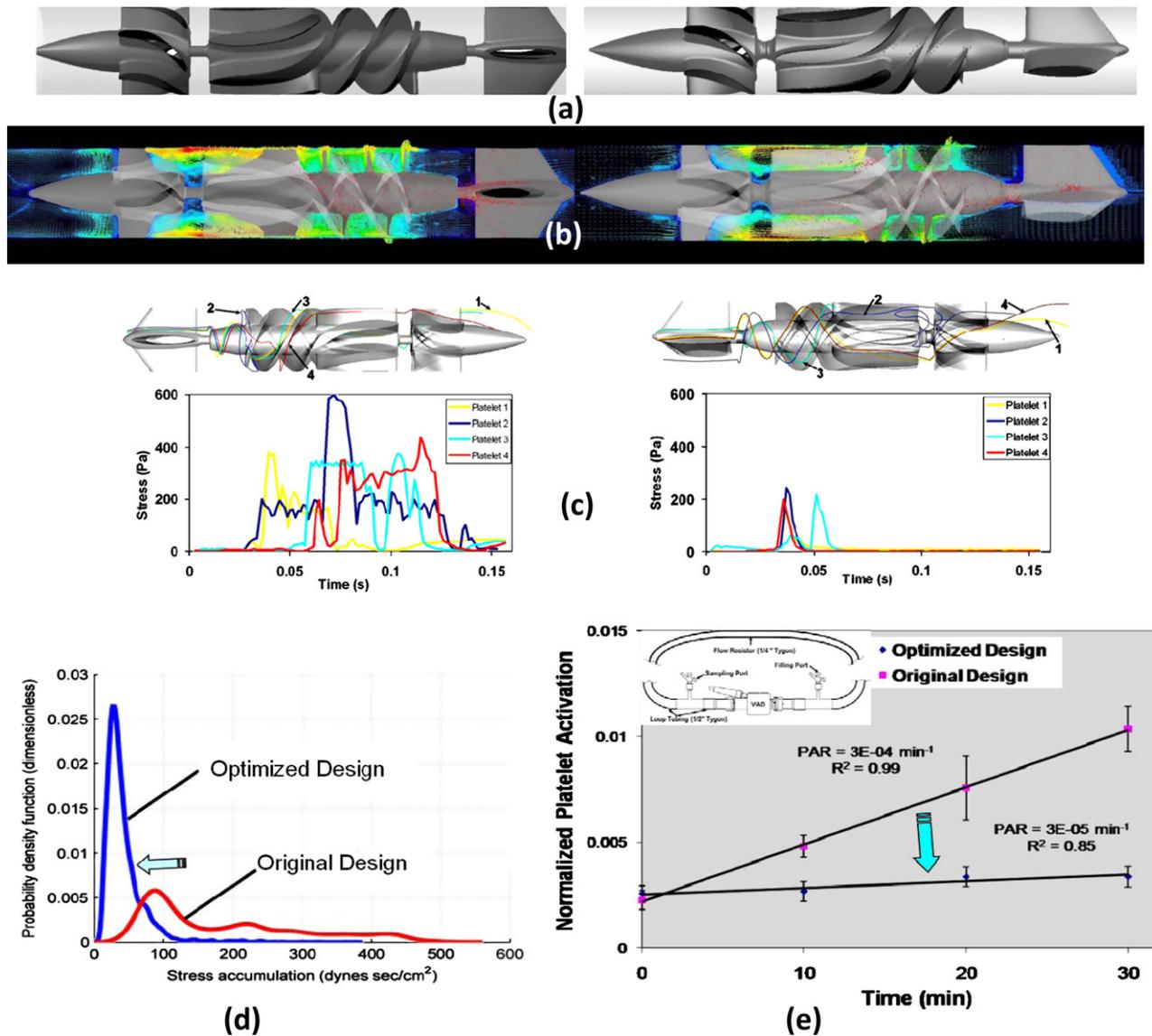


Fig. 2. Optimization of a VAD using the DTE methodology: (a) The original Micromed DeBakey (left) and the optimized Heart Assist 5 (right). (b) The flow field with platelets dispersion patterns superimposed showing flow velocities and stresses in the device before (left) and after the optimization (right). (c) 'Hot spot' trajectories and the corresponding waveforms used for emulation in the HDS before (left) and after optimization (right) showing a very significant reduction in the loading stresses. (d) PDF of the stress accumulation showing a very significant shift towards lower SA values for the optimized VAD. (e) Comparative measurements of platelet activity in the VAD prototypes performed in a recirculation flow loop ($CO=4$ L/min) before and after the optimization, showing an order of magnitude reduction of the platelet activity rate (PAR—the slope of the platelet activation over 30 min recirculation).

the PDFs of the optimized design point to significantly reduced overall thrombogenicity, i.e. a marked shift to the left (lower stress accumulation values), (Fig. 2c). 'Hot spot' trajectories and the corresponding waveforms used for emulation in the HDS before (left) and after optimization (right) (Fig. 2 b) similarly show a significant reduction in the levels of dynamic loading stresses.

Comparative platelet activity measurements were performed in a recirculation flow loop with both pump prototypes (pre- and post-optimization) running under clinical operating conditions (speed—9500 rpm, cardiac output 4 L/min, pressure rise—80 mm Hg). The measurements showed that an order of magnitude lower platelet activity rate (PAR) was achieved for the optimized device (non-optimized VAD $PAR=3 \times 10^{-4}$, Optimized VAD $PAR=3 \times 10^{-5}$, $p < 0.01$). This clearly demonstrates the efficacy of the DTE methodology for attaining safe and cost-effective pre-clinical MCS thombo-optimization.

In order to further examine the efficacy of the DTE optimization, we conducted a comparative study of the level of platelet

activity reduction achieved via optimization alone to that achieved by the addition of conventional antithrombotic pharmacologic agents. The effect of the reduction achieved by the optimization (with the optimized HA5 VAD) was compared to that achieved by Aspirin (ASA) and Dipyridamole, which were added to the non-optimized VAD operating in the recirculation flow loop under the same operating conditions described above. The non-optimized VAD, with no addition of the antithrombotic agents, served as the control for all cases studied. While a significant decrease in platelet activation rate (PAR) was observed for both the ASA and the Dipyridamole treatments, it was markedly less than that achieved via VAD optimization: approximately a third for the Aspirin (PAR reduced from 3×10^{-4} to 2×10^{-4}) as compared to that achieved by the optimization (PAR reduced from 3×10^{-4} to 3×10^{-5}), and similarly approximately a third for the Dipyridamole (PAR reduced from 7×10^{-4} to 5×10^{-4}) as compared to approx. 90% reduction achieved by the optimization (PAR reduced from 6×10^{-4} to 6×10^{-5}) (Fig. 3).

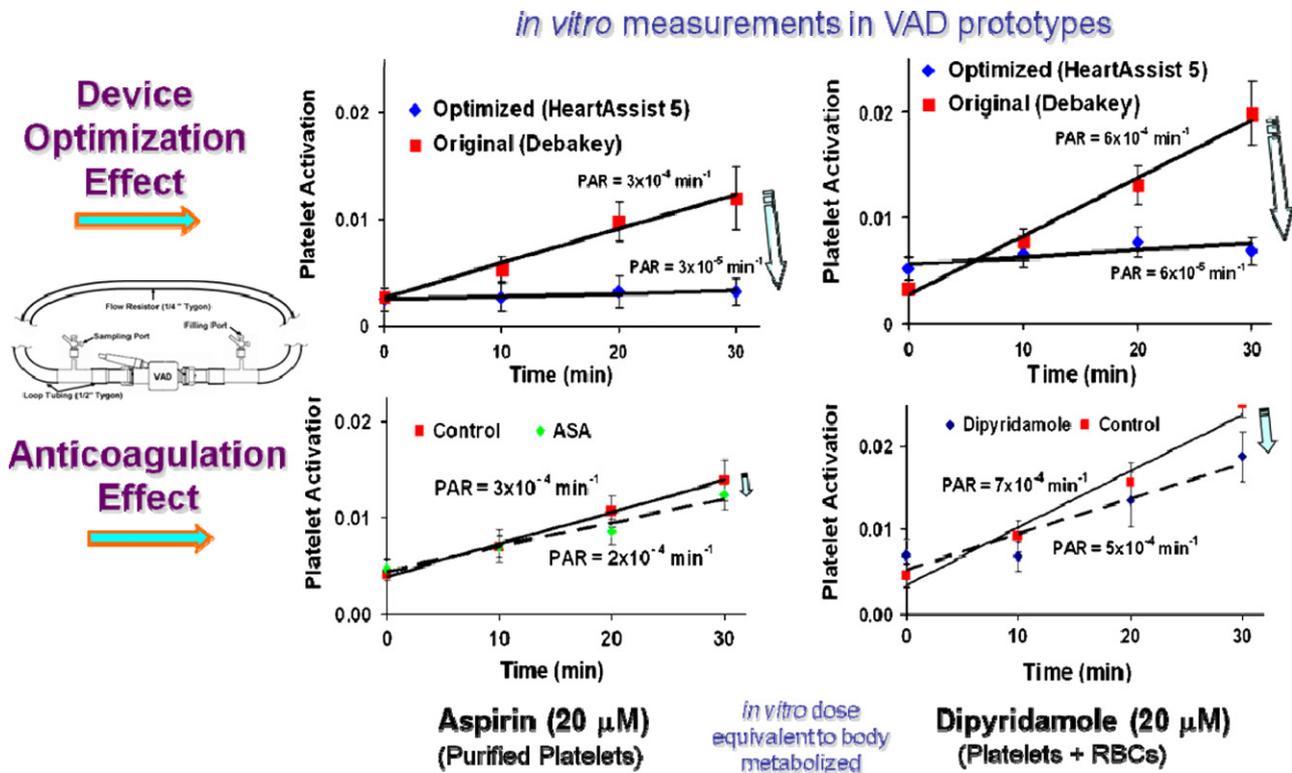


Fig. 3. Comparison of platelet activity reduction achieved by optimization to that achieved by two common antithrombotic agents—Aspirin (ASA) and Dipyridamole. Platelet Activation Rate (PAR) in the optimized (top) and non-optimized VAD+anticoagulation (bottom): platelets (left) and platelets+RBC (right). The non-optimized VAD is the control (red), optimization (blue) ASA (green) Dipyridamole (blue), correspondingly.

4. Discussion

The efficacy of DTE for optimizing the thromboresistance was demonstrated in a redesigned VAD. The marked reduction which was achieved in the platelet activation level (an order of magnitude) far exceeded that which was achieved by the addition of current clinical antithrombotic agents. The DTE methodology allows for a comprehensive evaluation of the thrombogenic potential of devices as a surrogate for initial animal or human testing. This system can identify ‘hot spot’ regions within a device during distinct flow phases and compute flow trajectories and stress load histories within these regions. The programmable HSD which emulates the device conditions is universal, i.e., it is not device specific, thus serving as an ultimate test bed for evaluating almost any type of blood-contacting device design modifications before building costly prototypes.

The DTE methodology as described here for the optimization of a VAD, is based on the premise of allowing for accurate comparisons in both the *in silico* (numerical) and the experimental domains and correlating the two in order to predict the expected thrombogenic performance of the device. In our experimental studies we intentionally use an experimental model that differs in certain aspects from the physiologic scenario. We use purified blood platelets preferentially over whole blood or plasma experiments, as this enables us to isolate and measure the direct effect of pathological shear-induced damage on platelets and their capacity to generate thrombin. In this manner we can directly measure the most relevant coagulation marker (thrombin) which represents the contribution of activated platelets to the coagulation cascade and accurately reflects the flow-induced thrombogenicity of different device designs. It enables us to control and more sensitively measure subtle effects of the various experimental parameters involved in the thrombogenic potential of blood recirculating devices. Our group established the PAS

validity over the years, in addition to its strong correlation to the more traditional platelet surface activation markers, e.g., P-selectin, while enabling near real-time measurements, which are crucial for recirculation experiments (Jesty et al., 2003).

Although currently DTE is primarily used to study MCS devices and prosthetic heart valves, *in vitro* assessment of hemodynamic shearing forces and subsequent platelet activation might be an efficient means of making iterative changes in other potentially thrombogenic cardiac and arterial devices, such as stents. In the case of stents, for example, because of the relative infrequency of thrombosis with current models of stents, demonstrating thrombogenicity reduction in clinical trials of newer stent platforms will likely require tens of thousands of patients. The DTE offers the ability to evaluate new stent designs by emulating their operating conditions. The system is operated under emulated shear stress loading conditions extracted from numerical simulations of blood flow in various device configurations in the circulation—under both normal and/or pathological blood flow conditions, and compared to other designs. The HSD may also be used to study the interaction between flowing platelets and cell-cultured endothelium. It may also be utilized to study the efficacy of various anticoagulation drug regimens under emulated normal and pathological physiological conditions. In this manner, the DTE methodology could allow expeditious assessment of iterative device designs with respect to platelet activation and thrombogenicity, in order to optimize their thromboresistance.

5. Conclusions

We have demonstrated a proof-of-concept applicability of our DTE methodology by comparing the thromboresistance of two continuous-flow rotary VAD designs. Specifically, an order of

magnitude lower platelet pactivity rate (PAR) was measured in the optimized VAD design (Heart Assist 5TM) as compared to the VAD before the optimization, correlating to a very significant overall shift in the mean stress accumulation (SA) to lower values as observed with the optimized design. The overall results of this analysis reflect a most significant design improvement, indicating that recipients of the optimized VAD may not require anticoagulation. Additionally it demonstrates that design changes may offer a more robust alternative to anti-platelet drugs such as Aspirin and Dipyridamole.

Conflict of interest statement

None of the authors has a conflict of interest.

Acknowledgment

This study was funded by grants from the National Institute of Health: NIBIB Quantum Award Phase I R01 EB008004-01 (DB), and Quantum Award: Implementation Phase II-U01 EB012487-0 (DB).

References

- Alemu, Y., Bluestein, D., 2007. Flow-induced platelet activation and damage accumulation in a mechanical heart valve: numerical studies. *Artificial Organs* 31, 677–688.
- Alemu, Y., Girdhar, G., Xenos, M., Sheriff, J., Jesty, J., Einav, S., Bluestein, D., 2010. Design optimization of a mechanical heart valve for reducing valve thrombogenicity—a case study with ATS valve. *ASAIO Journal* 56 (5), 389–396. <http://dx.doi.org/10.1097/MAT.0b013e3181e65bf9>.
- Alveriadou, B., Moake, J., Turner, N., Ruggeri, Z., Folie, B., Phillips, M., Schreiber, A., Hrinca, M., McIntire, L., 1993. Real-time analysis of shear dependent thrombus formation and its blockade by inhibitors of von Willebrand factor binding to platelets. *Blood* 81, 1263–1276.
- Apel, J., Paul, R., Klaus, S., Siess, T., Reul, H., 2001. Assessment of hemolysis related quantities in a microaxial blood pump by computational fluid dynamics. *Artificial Organs* 25, 341–347.
- Bludszuweit, C., 1995. Model for a general mechanical blood damage prediction. *Artificial Organs* 19, 583–589.
- Bluestein, D., 2004. Research approaches for studying flow induced thromboembolic complications in blood recirculating devices. *Expert Review of Medical Devices* 1, 65–80.
- Bluestein, D., Einav, S., Hwang, N.H., 1994. A squeeze flow phenomenon at the closing of a bileaflet mechanical heart valve prosthesis. *Journal of Biomechanics* 27, 1369–1378.
- Bluestein, D., Einav, S., Leonides, C.T.E., 2001. Techniques in the Analysis of Stability of Pulsatile Flow Through Heart Valves in Biomechanics Systems Techniques and Applications: Cardiovascular Techniques. CRC Press LLC, Boca Raton, FL.
- Bluestein, D., Li, Y.M., Krukenkamp, I.B., 2002. Free emboli formation in the wake of bi-leaflet mechanical heart valves and the effects of implantation techniques. *Journal of Biomechanics* 35, 1533–1540.
- Bluestein, D., Niu, L., Schoepfoerster, R.T., Dewanjee, M.K., 1997. Fluid mechanics of arterial stenosis: relationship to the development of mural thrombus. *Annals of Biomedical Engineering* 25, 344–356.
- Bluestein, D., Rambod, E., Gharib, M., 2000. Vortex shedding as a mechanism for free emboli formation in mechanical heart valves. *Journal of Biomechanical Engineering* 122, 125–134.
- Bluestein, D., Yin, W., Affeld, K., Jesty, J., 2004. Flow-induced platelet activation in a mechanical heart valve. *Journal of Heart Valve Disease* 13, 501–508.
- Bluestein, M., Mockros, L.F., 1969. Hemolytic effects of energy dissipation in flowing blood. *Medical and Biological Engineering* 7, 1–16.
- Burgreen, G.W., Antaki, J.F., Wu, Z.J., Holmes, A.J., 2001. Computational fluid dynamics as a development tool for rotary blood pumps. *Artificial Organs* 25, 336–340.
- Butchart, E.G., Ionescu, A., Payne, N., Giddings, J., Grunkemeier, G.L., Fraser, A.G., 2003. A new scoring system to determine thromboembolic risk after heart valve replacement. *Circulation* 108 (1), II68–74.
- Butchart, E.G., Li, H.H., Payne, N., Buchan, K., Grunkemeier, G.L., 2001. Twenty years' experience with the Medtronic Hall valve. *Journal of Thoracic and Cardiovascular Surgery* 121, 1090–1100.
- Cao, J., Rittgers, S.E., 1998. Particle motion within in vitro models of stenosed internal carotid and left anterior descending coronary arteries. *Annals of Biomedical Engineering* 26, 190–199.
- Charron, M., Follansbee, W., Ziady, G.M., Kormos, R.L., 1994. Assessment of biventricular cardiac function in patients with a Novacor left ventricular assist device. *Journal of Heart and Lung Transplantation* 13, 263–267.
- Claiborne, T.E., Girdhar, G., Gallocher-Lowe, S., Sheriff, J., Kato, Y.P., Pinchuk, L., Schoepfoerster, R.T., Jesty, J., Bluestein, D., 2011. Thrombogenic potential of Innovia polymer valves versus Carpentier-Edwards Perimount Magna aortic bioprosthetic valves. *ASAIO Journal* 57, 26–31.
- Dowling, R.D., Gray Jr., L.A., Etoch, S.W., Laks, H., Marelli, D., Samuels, L., Entwistle, J., Couper, G., Vlahakes, G.J., Frazier, O.H., 2004. Initial experience with the AbioCor implantable replacement heart system. *Journal of Thoracic and Cardiovascular Surgery* 127, 131–141.
- Dumont, K., Vierendeels, J., van Nooten, G., Verdonck, P., Bluestein, D., 2007. Comparison of the hemodynamic and thrombogenic performance of two bileaflet mechanical heart valves using a CFD/FSI model. *Journal of Biomechanical Engineering* 129, 558–565.
- Edmunds Jr., L.H., 1996. Is prosthetic valve thrombogenicity related to design or material? *Texas Heart Institute Journal* 23, 24–27.
- Edmunds Jr., L.H., McKinlay, S., Anderson, J.M., Callahan, T.H., Chesebro, J.H., Geiser, E.A., Makanani, D.M., McIntire, L.V., Meeker, W.Q., Naughton, G.K., Panza, J.A., Schoen, F.J., Didisheim, P., 1997. Directions for improvement of substitute heart valves: National Heart, Lung, and Blood Institute's Working Group report on heart valves. *Journal of Biomedical Materials Research* 38, 263–266.
- El-Banayosy, A., Korfer, R., Arusoglu, L., Kizner, L., Morshuis, M., Milting, H., Tenderich, G., Fey, O., Minami, K., 2001. Device and patient management in a bridge-to-transplant setting. *Annals of Thoracic Surgery* 71, S98–102, discussion S114–105.
- Fallon, A.M., Shah, N., Marzec, U.M., Warnock, J.N., Yoganathan, A.P., Hanson, S.R., 2006. Flow and thrombosis at orifices simulating mechanical heart valve leakage regions. *Journal of Biomechanical Engineering* 128, 30–39.
- Feldman, T., 2006. Percutaneous valve repair and replacement: challenges encountered, challenges met, challenges ahead. *Circulation* 113, 771–773.
- Folie, B.J., McIntire, L.V., 1989. Mathematical analysis of mural thrombogenesis. Concentration profiles of platelet-activating agents and effects of viscous shear flow. *Biophysical Journal* 56, 1121–1141.
- Frazier, O.H., Dowling, R.D., Gray Jr., L.A., Shah, N.A., Pool, T., Gregoric, I., 2004. The total artificial heart: where we stand. *Cardiology* 101, 117–121.
- Garon, A., Farinas, M.I., 2004. Fast three-dimensional numerical hemolysis approximation. *Artificial Organs* 28, 1016–1025.
- Geisen, U., Heilmann, C., Beyersdorf, F., Benk, C., Berchtold-Herz, M., Schlessak, C., Budde, U., Zieger, B., 2008. Non-surgical bleeding in patients with ventricular assist devices could be explained by acquired von Willebrand disease. *European Journal of Cardio-Thoracic Surgery* 33, 679–684.
- Girdhar, G., Bluestein, D., 2008. Biological effects of dynamic shear stress in cardiovascular pathologies and devices. *Expert Review of Medical Devices* 5, 167–181.
- Girdhar, G., Xenos, M., Alemu, Y., Chiu, W.C., Lynch, B.E., Jesty, J., Einav, S., Slepian, M.J., Bluestein, D., 2012. device thrombogenicity emulation: a novel method for optimizing mechanical circulatory support device thromboresistance. *PLoS One* 7, e32463.
- Gosman, A.D., Ioannides, E., 1983. Aspects of computer simulation of liquid-fuelled combustors. *AIAA Journal of Energy* 7, 482–490.
- Goubergrits, L., Affeld, K., 2004. Numerical estimation of blood damage in artificial organs. *Artificial Organs* 28, 499–507.
- Grigioni, M., Daniele, C., D'Avenio, G., Barbaro, V., 2001. The influence of the leaflets' curvature on the flow field in two bileaflet prosthetic heart valves. *Journal of Biomechanics* 34, 613–621.
- Grosset, D.G., Georgiadis, D., Kelman, A.W., Cowburn, P., Stirling, S., Lees, K.R., Faichney, A., Mallinson, A., Quin, R., Bone, I., Pettigrew, L., Brodie, E., MacKay, T., Wheatley, D.J., 1996. Detection of microemboli by transcranial Doppler ultrasound. *Texas Heart Institute Journal* 23, 289–292.
- Harker, L.A., Slichter, S.J., 1970. Studies of platelet and fibrinogen kinetics in patients with prosthetic heart valves. *New England Journal of Medicine* 283, 1302–1305.
- Hellums, J., Peterson, D., Stathopoulos, N., Moake, J., Giorgio, T., 1987. Studies on the mechanisms of shear-induced platelet activation. In: Hartman, A., Kuschinsky, W (Eds.), *Cerebral Ischemia and Hemorheology*. Springer and Verlag, New York.
- Hellums, J.D., 1994. 1993 Whitaker Lecture: biorheology in thrombosis research. *Annals of Biomedical Engineering* 22, 445–455.
- Huang, Z.J., Merkle, C.L., Abdallah, S., Tarbell, J.M., 1994. Numerical simulation of unsteady laminar flow through a tilting disk heart valve: prediction of vortex shedding. *Journal of Biomechanics* 27, 391–402.
- Jesty, J., Bluestein, D., 1999. Acetylated prothrombin as a substrate in the measurement of the procoagulant activity of platelets: elimination of the feedback activation of platelets by thrombin. *Analytical Biochemistry* 272, 64–70.
- Jesty, J., Yin, W., Perrotta, P., Bluestein, D., 2003. Platelet activation in a circulating flow loop: combined effects of shear stress and exposure time. *Platelets* 14, 143–149.
- Jin, W., Clark, C., 1993. Experimental investigation of unsteady flow behaviour within a sac-type ventricular assist device (VAD). *Journal of Biomechanics* 26, 697–707.
- Kelly, S.G., Verdonck, P.R., Vierendeels, J.A., Riemsdijk, K., Dick, E., Van Nooten, G.G., 1999. A three-dimensional analysis of flow in the pivot regions of an ATS bileaflet valve. *International Journal of Artificial Organs* 22, 754–763.
- King, M.J., David, T., Fisher, J., 1997. Three-dimensional study of the effect of two leaflet opening angles on the time-dependent flow through a bileaflet mechanical heart valve. *Medical Engineering and Physics* 19, 235–241.
- Krafczyk, M., Cerrolaza, M., Schulz, M., Rank, E., 1998. Analysis of 3D transient blood flow passing through an artificial aortic valve by Lattice-Boltzmann methods. *Journal of Biomechanics* 31, 453–462.

- Kuharsky, A.L., Fogelson, A.L., 2001. Surface-mediated control of blood coagulation: the role of binding site densities and platelet deposition. *Biophysical Journal* 80, 1050–1074.
- Laas, J., Kseibi, S., Perthel, M., Klingbeil, A., El-Ayoubi, L., Alken, A., 2003. Impact of high intensity transient signals on the choice of mechanical aortic valve substitutes. *European Journal of Cardio-Thoracic Surgery* 23, 93–96.
- Lazar, R.M., Shapiro, P.A., Jaski, B.E., Parides, M.K., Bourge, R.C., Watson, J.T., Damme, L., Dembitsky, W., Hosenpud, J.D., Gupta, L., Tierney, A., Kraus, T., Naka, Y., 2004. Neurological events during long-term mechanical circulatory support for heart failure: the Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) experience. *Circulation* 109, 2423–2427.
- Mesana, T., 2006. Percutaneous valve technology: an historical opportunity for cardiac surgeons. *Current Opinion in Cardiology* 21, 94.
- O'Brien, J.R., Salmon, G.P., 1990. An independent haemostatic mechanism: shear induced platelet aggregation. *Advances in Experimental Medicine and Biology* 281, 287–296.
- Paul, R., Marseille, O., Hintze, E., Huber, L., Schima, H., Reul, H., Rau, G., 1998. In vitro thrombogenicity testing of artificial organs. *International Journal of Artificial Organs* 21, 548–552.
- Portner, P.M., Jansen, P.G., Oyer, P.E., Wheeldon, D.R., Ramasamy, N., 2001. Improved outcomes with an implantable left ventricular assist system: a multicenter study. *Annals of Thoracic Surgery* 71, 205–209.
- Reif, T.H., Schulte, T.J., Hwang, N.H., 1990. Estimation of the rotational undamped natural frequency of bileaflet cardiac valve prostheses. *Journal of Biomechanical Engineering* 112, 327–332.
- Reininger, C.B., Lasser, R., Rumitz, M., Boger, C., Schweiberer, L., 1999. Computational analysis of platelet adhesion and aggregation under stagnation point flow conditions. *Computers in Biology and Medicine* 29, 1–18.
- Rothenburger, M., Wilhelm, M.J., Hammel, D., Schmidt, C., Tjan, T.D., Bocker, D., Scheld, H.H., Schmid, C., 2002. Treatment of thrombus formation associated with the MicroMed DeBakey VAD using recombinant tissue plasminogen activator. *Circulation* 106, 1189–1192.
- Samuels, L.E., Holmes, E.C., Entwistle 3rd, J.C., 2005. Swan-Ganz monitoring of the AbioCor artificial heart. *Annals of Thoracic Surgery* 80, 1133.
- Slaughter, M.S., Rogers, J.G., Milano, C.A., Russell, S.D., Conte, J.V., Feldman, D., Sun, B., Tatooles, A.J., Delgado 3rd, R.M., Long, J.W., Wozniak, T.C., Ghumman, W., Farrar, D.J., Frazier, O.H., 2009. Advanced heart failure treated with continuous-flow left ventricular assist device. *New England Journal of Medicine* 361, 2241–2251.
- Sorensen, E.N., Burgreen, G.W., Wagner, W.R., Antaki, J.F., 1999a. Computational simulation of platelet deposition and activation: I. Model development and properties. *Annals of Biomedical Engineering* 27, 436–448.
- Sorensen, E.N., Burgreen, G.W., Wagner, W.R., Antaki, J.F., 1999b. Computational simulation of platelet deposition and activation: II. Results for Poiseuille flow over collagen. *Annals of Biomedical Engineering* 27, 449–458.
- Stevenson, L.W., Miller, L.W., Desvigne-Nickens, P., et al., 2004. Left ventricular assist device as destination for patients undergoing intravenous inotropic therapy: A subset analysis from REMATCH (Randomized Evaluation of Mechanical Assistance in Treatment of Chronic Heart Failure). *Circulation* 110, 975–981.
- Travis, B.R., Leo, H.L., Shah, P.A., Frakes, D.H., Yoganathan, A.P., 2002. An analysis of turbulent shear stresses in leakage flow through a bileaflet mechanical prostheses. *Journal of Biomechanical Engineering* 124, 155–165.
- Travis, B.R., Marzec, U.M., Leo, H.L., Momin, T., Sanders, C., Hanson, S.R., Yoganathan, A.P., 2001. Bileaflet aortic valve prosthesis pivot geometry influences platelet secretion and anionic phospholipid exposure. *Annals of Biomedical Engineering* 29, 657–664.
- Wilcox, D.C., 1994. Simulation of transition with a two-equation turbulence model. *AIAA Journal* 32, 247–255.
- Wilhelm, M.J., Hammel, D., Schmid, C., Stypmann, J., Asfour, B., Kemper, D., Schmidt, C., Morley, D., Noon, G.P., DeBakey, M.E., Scheld, H.H., 2001. Clinical experience with nine patients supported by the continuous flow DeBakey VAD. *Journal of Heart and Lung Transplantation* 20, 201.
- Worth Longest, P., Kleinstreuer, C., 2003. Comparison of blood particle deposition models for non-parallel flow domains. *Journal of Biomechanics* 36, 421–430.
- Wurzinger, L.J., Blasberg, P., Schmid-Schonbein, H., 1985. Towards a concept of thrombosis in accelerated flow: rheology, fluid dynamics, and biochemistry. *Biorheology* 22, 437–450.
- Xenos, M., Girdhar, G., Alemu, Y., Jesty, J., Slepian, M., Einav, S., Bluestein, D., 2010. Device Thrombogenicity Emulator (DTE)—Design optimization methodology for cardiovascular devices: a study in two bileaflet MHV designs. *Journal of Biomechanics*.
- Yin, W., Alemu, Y., Affeld, K., Jesty, J., Bluestein, D., 2004. Flow-induced platelet activation in bileaflet and monoleaflet mechanical heart valves. *Annals of Biomedical Engineering* 32, 1058–1066.
- Yin, W., Gallocher, S., Pinchuk, L., Schoepfoerster, R.T., Jesty, J., Bluestein, D., 2005. Flow Induced Platelet Activation in a St. Jude MHV, a Trileaflet Polymeric Heart Valve and a St. Jude Tissue Valve. *Artificial Organs* 29, 826–831.
- Yoganathan, A.P., Ellis, J.T., Healy, T.M., Chatzimavroudis, G.P., 1998. Fluid dynamic studies for the year 2000. *Journal of Heart Valve Disease* 7, 130–139.
- Yoganathan, A.P., Woo, Y.R., Sung, H.W., 1986. Turbulent shear stress measurements in the vicinity of aortic heart valve prostheses. *Journal of Biomechanics* 19, 433–442.