Danny Bluestein
State University of New York at Stony Brook, Department of Biomedical Engineering, NY 11794–8181, USA
Tel.: +1 631 444 2156
Fax: +1 631 444 6646
danny.bluestein@sunysb.edu

Towards optimization of the thrombogenic potential of blood recirculating cardiovascular devices using modeling approaches

'The minimally invasive percutaneous valve delivery approach...has demonstrated a huge promise for patients who cannot tolerate cardiothoracic surgery.'

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In recent years, implantable blood recirculating devices have become a viable alternative for destination therapy for treating patients with end-stage heart failure. The Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) trial has demonstrated that they have a significant advantage over traditionally administered drug therapy [1,2]. These devices also offer a potential solution to the chronic shortage of heart transplants. After reviewing 2 years of results from the REMATCH trial, the US FDA granted a premarket approval for the Thoratec HeartMate® Ventricular Assist Device (VAD) to be used for destination therapy [3]. A substantial number of implantable blood recirculating devices, for example, new VAD designs and new prosthetic heart valve (PHV) designs, are currently being developed and tested for safety and efficacy. Recently, the minimally invasive percutaneous valve delivery approach, involving the delivery of a collapsible stented valve (either bioprosthetic or polymer valves) via the arterial system, has demonstrated a huge promise for patients who cannot tolerate cardiothoracic surgery [4,5]. However, thromboembolism and the attendant risk for cardioembolic stroke remains an impediment to all these devices. The mandatory life-long anticoagulant drug regimen that most of them require, which induces vulnerability to hemorrhage and is not a viable therapy for some patients, does not eliminate this risk. The thromboembolic complication rates for patients implanted with these devices and the ensuing healthcare costs are far from desirable. A prudent approach to developing these devices towards a cost-effective utility should include optimization of these devices for thrombogenic performance, desirably before going into expensive preclinical and clinical trials.

In an executive summary issued by the National Heart, Lung and Blood Institute (NHLBI) 2004 Working Group for Next Generation Ventricular Assist Devices for Destination Therapy [3], a major recommendation was to develop improved antithrombotic therapies and device technologies to reduce thromboembolic events, based on successful computational and experimental fluid dynamic studies within PHVs that should be further developed and applied to VADs. Design of PHVs and VADs is traditionally concerned with hemocompatibility, durability and thromboresistance, with hemodynamic characteristics somewhat taking a back seat. Hemodynamic optimization is aimed at avoiding the formation of stagnant zones and regions of elevated stresses, while achieving good washout characteristics. Elucidating the hemodynamics of devices via sophisticated fluid dynamics and thrombogenic testing is far from trivial, and the identification and/or

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interpretation of pertinent design parameters is subtle. Prosthetic valves are geometrically very complex and the shape and/or motion of their leaflets are not known *a priori*, rather, it evolves dynamically in response to the instantaneous flow conditions [6]. For mechanical heart valves (MHVs) this is somewhat alleviated through several accepted design parameters [7,8], for example, leakage flow upon valve closure, intended to scour critical areas of the valve such as the hinges and the areas between the leaflet edges and the housing. However, traditional design matrix approaches for optimizing such devices are only of limited utility, as the optimization process is very specific to the device design characteristics and its inherent geometric constraints. Accordingly, in the cardiovascular device industry, designing and manufacturing device prototypes and testing them *ad hoc* represents a common practice. This lags behind common practices in the research and development phase of aircrafts, automobiles and other engineering devices that function in a flow environment. All use modeling approaches such as computational fluid dynamics (CFDs) extensively during the design process, so that by the time a prototype design is to be tested, its design optimization is pretty well established.

With the inherent design constraints of blood recirculating devices (a few examples were briefly outlined above) this is clearly a formidable challenge. While there is no established set of parameters for achieving design optimization, the ultimate goal is to minimize the thrombogenicity of the device – preferably to a level that will not require anticoagulation (as is the case for bioprosthetic valves for example). Clearly, a modeling approach represents an efficient way to economically test design modifications to realize whether they indeed achieve this design goal. However, it requires a numerical approach that goes beyond the common quantitative flow mapping within the device – a nontrivial undertaking to begin with, given the complexity of the geometries in devices and the complex nature of blood as a fluid. It should incorporate an accountable model that is able to provide quantitatively accurate predictions of flow-induced blood hemoastatic activation, resulting from accurately resolved flow fields within the device and the stresses they induce on the blood-borne particulates. In recent years it was shown that platelet activation and the initiation of thrombus formation is the salient aspect of mechanically induced blood trauma in devices [9,10]. Accordingly, the mechanical loading environment of platelets in flowing blood within devices should be characterized, and incorporated into an accountable model for cellular trauma by means of an activation/damage accumulation hypothesis [11].

Such an approach was partially developed for modeling hemolysis in devices, and while the process of platelet activation is more complex than red blood cell (RBC) hemolysis, the conceptual framework is similar. Briefly, exposure to fluid shear stresses will activate and aggregate platelets irreversibly in the absence of any exogenous agonist, showing consistent 'dose' and time response characteristics of equivalent chemical agonists [12]. Hemolysis response is very similar, and several models for hemolysis have been developed over the years, for example, local rate of hemolysis as a power function of the average local rate of mechanical energy dissipation [13], and relating hemolysis to shear stress [14,15]. In these predictive phenomenological models, which are based on the theory of damage in solid mechanics, 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 [16], or as weight average damage accumulation over a number of cycles. The latter is important for the ability of a model to correspond to the blood flow conditions within the device once implanted in a patient. The blood constituents, and specifically platelets, may be exposed to elevated stresses in their passage through the device, but only intermittently, followed by a refractory period of lower stresses while flowing through the vasculature. With each consecutive passage through the device, the question arises as to what is the effect of the previous load history, or senescence of the platelet, on its activation potential. Previous damage history, as well as incorporation of statistical weighting functions corresponding to the fact that blood constituents will not replicate their trajectories with each successive passage through the device, that is, will not patently flow through the 'hot spot' regions within the device, are essential for successful predictions by such models.

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It is also clear that such accumulation models rely on the quality of the underlying numerical simulations that are used to establish the platelet trajectories for which the load history is computed. Important considerations that should be taken into account are the following: is the flow laminar, turbulent or in the transition range between laminar and turbulent (dictating the use of different turbulent models according to the expected flow regimen)? Should non-Newtonian features of blood flow be incorporated into the models (relevant if a more accurate depiction of vortical structures within the flow field is desired)? Does the simulation of the flow field through the device need to include moving parts or large deformations (may require fluid structure interaction modeling approach that will possibly limit the incorporation of more complex flow models owing to the currently prohibitive computational costs)? Should the simulation be single phase, two phase (particulate phase and a carrier fluid phase) or multiphase? The latter involves assumptions that are important for accurate trajectory computations. Obviously, a trade-off between accuracy and computational viability should be considered.

A new computational paradigm – discrete particle dynamics modeling, shows a big promise for simulating the interaction between the mechanistic flow approach, which occurs in the macro- to microscales, and the actual interaction it invokes in the smaller scales governing blood constituents and the biochemical reactions of the coagulation cascade leading to

thrombus formation. CFD macroscopic models are limited to only continuum systems [17,18]. This represents a gap from 10 nm to 100 µm between microscopic experimental biochemistry and the macroscopic world. Discrete-particle paradigms do not have such a long history as CFD. However, it possesses the important properties of mesoscopic systems: it can easily model heterogeneous fluids. This allows for simulating processes which are very difficult to model by continuum approaches based on partial differential equations. In interfacing the region where the continuum model and particle model are applied, the continuum model may provide the boundary conditions for a confined region of interest chosen for discrete-particle modeling (where the physical phenomena are too complex to model accurately by a continuum model approach). With this, the particle method can produce the coordinates of all particles (platelets and RBCs, etc.) at any given time which are then mapped, or interpolated, to quantities used in the continuum models. Applying this approach, the microscopic scales of the blood can be regarded as an ensemble of interacting discrete particles representing clusters of matter, which can be conceived as a coarse graining of blood molecules. In its application for studying thromboembolism in devices, it could be envisioned that it will be applied to the smaller confines of devices, for example, the hinge areas in MHV, to elucidate how mechanistic events are converted to biochemical events leading to thrombus formation in these regions. Integrating the continuum approach with the particle dynamics approach may result in a truly multiscale model of blood flow and flow-induced thrombus formation.

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As mentioned above, the inherent design constraints of blood recirculating devices makes it a formidable challenge to integrate the various modeling approaches into a methodology that will facilitate device optimization towards minimizing the thrombogenic potential. Since subtle design features can lead to complicated flow effects, many design parameters reflect confounding optimization demands. A typical example of conflicting design requirements is the gap clearance optimization in MHV. When the gap clearance is reduced, a desired feature for minimizing retrograde flow across the closed valve, a stronger leakage flow is generated, which is implicated in potentially increasing the valve's thrombogenicity. Reconciling such conflicting design considerations is a major challenge that accentuates an acute lack of design parameters for optimizing the thrombogenic potential of devices, and that those existing do not address a multifactorial phenomenon such as flow-induced thrombogenicity.

An approach that uses an integrated modeling methodology, combining accurate quantitative depiction of flow fields and stresses within the device with damage accumulation models predicting the activation levels induced by these flow stresses, will be able to inform the designer how to reconcile such conflicting demands by modifying the device design. Using the above mentioned example of the gap clearance between the valve leaflets and the valve housing, an integrated modeling methodology will be able to inform how, for example, changing the clearance gap or modifying the conduits design around the valve, will affect the thrombogenic potential of the valve, and point to the advantageous design solutions. The efficacy of the process is that once the numerical models are developed and their predictive capabilities demonstrated (through testing), it is a straightforward process to modify the model geometries and quantify the effects of design modifications.

It is anticipated that such an integrated methodology will be able to achieve meaningful clinical outcomes, for instance, device optimization that will lead to a significant reduction in the rate of their cardioembolic complications, in mortality rates and in the ensuing healthcare costs. A longer term goal is to extend these models over the multiscales characterizing the multifactorial phenomenon of clotting in blood flow while efficiently combining biochemical events of the coagulation cascade, morphological changes of the blood constituents during the process and the mechanical flow-induced events leading to that. With the exponential growth in computational power, it is envisioned that multiscale modeling will be fully incorporated into the modeling toolbox, and eventually will be used for device optimization. Such a methodology has the potential to transform current device design and testing practices, by facilitating design changes and optimization by predicting device thrombogenicity before going into preclinical testing. It is envisioned that it will greatly facilitate the use of these devices for long-term therapy. Such innovative modeling approaches will be readily extended and applicable to many types of implantable and extracorporeal blood recirculating devices in which cardioembolic complications are a significant problem, such as the total artificial heart, stents, geometries of vascular surgical reconstruction and tubular constrictions of extracorporeal circulation devices.

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Affiliation

• *Danny Bluestein, PhD*
Associate Professor, State University of New York at Stony Brook, Department of Biomedical Engineering, NY 11794–8181, USA
Tel.: +1 631 444 2156
Fax: +1 631 444 6646
danny.bluestein@sunysb.edu