Available online at www.sciencedirect.com

ScienceDirect

Current Opinion in Biomedical Engineering

Mathematical and computational modeling of device-induced thrombosis

Keefe B. Manning[1], Franck Nicoud[2] and Susan M. Shea[3]

Abstract

Given the extensive and routine use of cardiovascular devices, a major limiting factor to their success is the thrombotic rate that occurs. This poses direct risk to the patient and requires counterbalancing with anticoagulation and other treatment strategies, contributing additional risks. Developing a better understanding of the mechanisms of device-induced thrombosis to aid in device design and medical management of patients is critical to advance the ubiquitous use and durability. Thus, mathematical and computational modeling of device-induced thrombosis has received significant attention recently, but challenges remain. Additional areas that need to be explored include microscopic/macroscopic approaches, reconciling physical and numerical timescales, immune/inflammatory responses, experimental validation, and incorporating pathologies and blood conditions. Addressing these areas will provide engineers and clinicians the tools to provide safe and effective cardiovascular devices.

Addresses

[1] Department of Biomedical Engineering, The Pennsylvania State University, University Park, PA, USA

[2] CNRS, IMAG, Université de Montpellier, Montpellier, France

[3] Division of Critical Care Medicine, Department of Pediatrics, Washington University School of Medicine, St. Louis, MO, USA

Corresponding author: Manning, Keefe B. (kbm10@psu.edu)

Current Opinion in Biomedical Engineering 2021, **20:**100349

This review comes from a themed issue on **Biomechanics & Mechanobiology: Mathematic Modeling and Biophysical Characterization of Thrombosis**

Edited by **Mark Alber, Aaron Fogelson** and **Kathryn Link**

Received 13 November 2020, revised 30 July 2021, accepted 13 September 2021

Available online xxx

https://doi.org/10.1016/j.cobme.2021.100349

Keywords

Cardiovascular, Devices, Thrombosis, Modeling.

Abbreviations

CFD, computational fluid dynamics; CGMD, Coarse Grained Molecular Dynamics; CV, cardiovascular; DPD, Dissipative Particle Dynamics; ECMO, extracorporeal membrane oxygenation; FXII, Factor XII; GPIb, glycoprotein Ib; IgG, immunoglobulin G; IVC, inferior vena cava; MCS, mechanical circulatory support; NS, Navier-Stokes; PDE, partial differential equation; REBOA, resuscitative endovascular balloon occlusion of the aorta; TAH, total artificial heart; TAVR, transcatheter aortic valve replacement; VAD, ventricular assist device; vWF, von Willebrand Factor.

Introduction

Blood-contacting medical devices are used to treat a variety of cardiovascular (CV) and cardiopulmonary diseases. These devices perturb hemostasis, resulting in complications that manifest in the patient as thrombosis and hemorrhage. Thrombosis is not only a frequent source of device failure [1], but excessive clotting and/or bleeding may also pose direct risks to the patient [2].

Nevertheless, devices have emerged as the standard-of-care for many CV disease conditions [3]. Current device use, incidence of adverse events, and material surfaces, and upcoming and novel/controversial devices, are summarized in Table 1.

Although disease etiologies and patient populations vary among blood-contacting devices and their applications, they all share the same overarching challenges: (1) device-induced thrombosis is not fully understood and therefore is clinically unpredictable, and (2) clinical trials can be extremely difficult and risky in these patient populations, sometimes to the point of being prohibitively so. Therefore, *in silico* studies are a critical tool to complement *in vitro*, *ex vivo*, and *in vivo* studies to contribute to overcoming these challenges. Device thrombosis modeling can be used to inform on device design in the preclinical stage and to inform on treatment and clinical handling of current patients, by developing guidelines and on-demand treatments.

In this review, the initial focus is a discussion on the pathophysiology of device thrombosis. We then assess modeling efforts posterior to Fogelson and Neeves' 2015 review [4], with a focus on model assumptions to facilitate discourse on the physiological relevance of different mathematical and computational approaches.

Device perturbation of hemostasis: Virchow's triad

As is widely appreciated, Virchow theorized, rather correctly, that hemostasis is a delicate balance between the blood state, surface, and flow [5]. Although there have been recent adaptations to his theory, the basic concept remains applicable to devices, which we have summarized in Figure 1.

Table 1

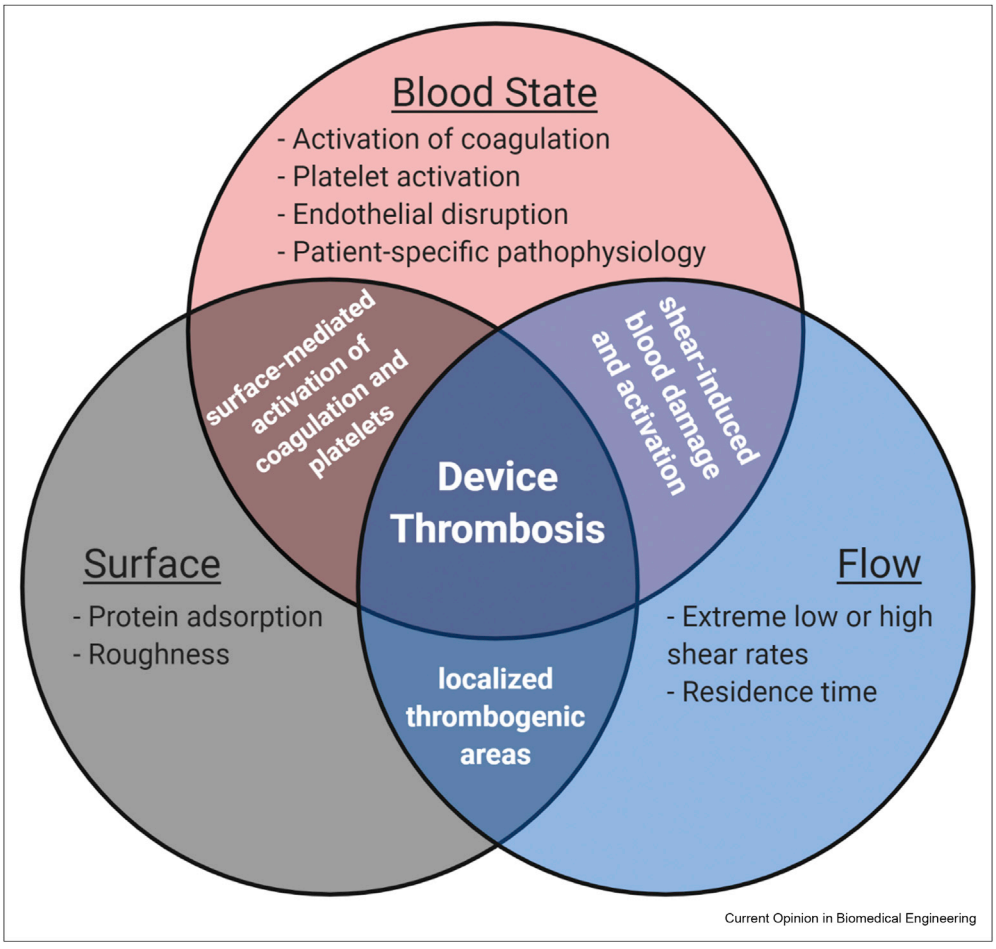
Overview of blood-contacting medical devices.

Device	Refs	Clinical indication for use	Rate of failure or adverse events	Material surface(s)	Notes
Stents	[67,68]	Arterial obstructions	Thrombosis <1%; restenosis 10%	Metal (e.g. nitinol, stainless steel)	
Grafts	[69]	Vascular repair or bypass	20–40% not patent at 5 years	Saphenous vein, polymer (e.g. nylon, Polytetrafluoroethylene (PTFE))	
Catheters	[70]		Central venous catheters 14–18%; peripherally inserted central catheters 5–15% in-hospital	Silicone rubber, polyurethane	
Heart valves		Valvular heart disease			
Bioprosthetic valves	[71]		Thrombosis $\leq$2–3%/year	Fixed biologic tissues can be on stent/graft scaffold	
Mechanical valves	[72]		Thrombosis $\leq$2–3%/year, up to 6%/year if insufficient anticoagulation		Requires lifelong anticoagulation
Transcatheter aortic valve replacement (TAVR)	[73]	Aortic stenosis	Thrombosis 9.3%	Fixed biologic tissues on stent/graft scaffold	Increasing in use
Mechanical circulatory support (MCS)		Heart failure			
Ventricular assist devices (VADs)	[74–76]		Thromboembolic events as high as 30% in HeartMate II (adult) and Berlin Heart EXCOR (pediatrics)	Metals, ceramics, plastics	Decreases over time
Intra-aortic pumps	[77]		1% thrombosis, 27% bleeding	Polyethylene, polyurethane	
Cardiopulmonary bypass	[78]	Cardiac surgery	2–10% myocardial infarction, 3% stroke	Plastics	Many other complex complications, both surgical and related to critical illness
Total artificial hearts (TAHs)	[79,80]		20% bleeding, 1.6% embolus, 2% stroke	Polyurethane	
Extracorporeal membrane oxygenation (ECMO)	[19,81]	Heart and/or lung failure	$\geq$90% some clot formation in circuitry; balance of bleeding risk with the anticoagulation level	Mainly plastics, metals	Notable pediatric patient population; encompasses many devices assembled into circuitry
Inferior vena cava (IVC) filters	[82]	Pulmonary embolism risk	$\leq$30% thrombosis, Deep vein thrombosis (DVT) as high as 43%	Metals (e.g. nitinol, stainless steel)	Intended to cause obstruction; reports of incidence vary widely
Endovascular coils	[83]	Cerebral aneurysm	9.1% total complication rate, including rebleeding, ischemia, and rupture	Metals (e.g. platinum alloy)	Intended to cause thrombosis
Resuscitative endovascular balloon occlusion of the aorta (REBOA)	[84]	Hemorrhage	Unclear; may increase mortality	Plastics used by the catheter/guidewire	Use still controversial
Dialysis	[85]	Kidney disease	<1%/year	Plastics	
Microparticles and nanoparticles	[86,87]	Thrombosis	n/a	Charged polymers	Novel

Blood state

Blood is a suspension containing erythrocytes, leukocytes, platelets, factors, ions, and glycoproteins, which all have critical roles to maintain hemostasis and perform other physiological functions [6]. Coagulation, a critical physiological function, occurs by initiation via either vascular injury or foreign body contact and comprises dozens of cellular species and nearly 100 reactions to form a stable thrombus [7]. With the introduction of a device in the CV system, the surface-mediated pathway (foreign body) is stimulated along with the activation of the tissue-mediated pathway (vascular injury) as the endothelium is disrupted by the device during implantation. Whether these events are separate or simultaneous remains unknown, and although the question may be moot because both lead to thrombosis, elucidation of

Figure 1



Virchow's triad for device thrombosis. The driving mechanisms of device thrombosis can be viewed through the lens of Virchow's triad. The blood state, device surface, and device flow patterns have concomitant effects that ultimately result in thrombosis.

the interactions and timeline could inform therapeutic inhibition of either or both pathways.

In addition to coagulation, platelets are significant contributors to clotting and interface with other cellular components such as von Willebrand factor (vWF) and fibrin (ogen). Their impact on devices can be substantial, including total device failure. Given the mechanical and chemical sensitivities of platelets, their response is critical to gauge device thrombogenicity. Platelets can be stimulated by high shear, the surface-mediated pathway, and activated by biochemical means [8]. For example, when activated platelets attach to vWF adsorbed to the device surface, this creates a foundational support for the clot (along with contributions from other clotting factors). vWF can also be pathologically compromised, as has been shown in patients with extracorporeal membrane oxygenation and the ventricular assist device (VAD) who develop bleeding events [9].

These cellular components are currently thought to have the most significant impact on devices, but as this area continues to be studied, more may be revealed. Thus the blood state, which includes its constituents, is quite integral to determining device success. However, the device surface itself can dramatically influence clotting.

Surface

When blood contacts a biomaterial surface, a series of complex systems initiate potentiate thrombosis via the pathways described in the previous section. Proteins are adsorbed immediately to the surface [1,10,11], a process which is controlled initially by diffusion but dominated by protein−surface affinity over time (Vroman Effect, [12]). Device materials are typically hydrophobic and have affinity with many proteins [13]. The most commonly adsorbed plasma proteins are albumin, fibrinogen, immunoglobulin G, fibronectin, and vWF. As mentioned previously, vWF and fibrinogen appear to be the most critical factors for platelet activity [14]. In the adsorption process, proteins undergo conformational changes to expose hydrophobic domains, which results in expression of receptor sites, causing subsequent

immune crosstalk, and further potentiating thrombosis [15–17]. The phenotype of the end surface is dependent on the biomaterial; thus, a multitude of unique surfaces exists.

However, the device surface is absorbed in its entirety, yet thrombosis tends to be localized [18,19]. Flow is thus the final key mechanistic driver.

Flow

Flow has been demonstrated to be quite potent in determining the effectiveness and long-term viability of a device. Fundamentally, flow regimes (i.e. laminar, transitional, and turbulent) can affect cellular responses by creating pathologically low- and high-stress regions, whereby shear stress can induce platelet activation [3,20], the combination of shear stress and its exposure time can induce hemolysis and thus potentiate coagulation [21], and recirculating flows and wakes can facilitate clotting [22,23]. Experimental studies have demonstrated the impact of shear stress on platelet activation/aggregation [24–26] and thrombosis [27]. Pathologic flows created by the presence of devices and actions associated with them can influence hemostasis with examples of recirculating flows/wakes in extracorporeal membrane oxygenation circuitry and inferior vena cava filters, and extremely high shear stress associated with prosthetic heart valves and VADs (examples found in Table 1). Residence time of platelets and factors is another crucial factor that may enhance clotting [24].

Flow, the blood state, the biomaterial surface, and their concomitant effects are thus the essential elements to understanding the unique qualities of device thrombosis (Figure 1) and therefore determine their ultimate success.

Modeling approaches available

Despite much effort and tremendous progress, thrombosis modeling remains extremely challenging because of the variety and complexity of the phenomenon. Recently, modeling studies (Table 2) are in fact more relevant to natural thrombosis in the setting of the vasculature [28]. As detailed in the previous section, device thrombosis has additional mechanisms which must be considered in the modeling effort, making the challenge even greater.

Biomarkers deduced from pure computational fluid dynamics results

The device's presence in the CV system leads to thrombus formation after an unknown delay, which may be hours, days, or even months. Thus, to maximize clinical and/or design utility, a computational tool for device thrombosis should forecast clotting and predict if, when, and where thrombosis occurs. Because some processes operate at very short time scales (1 ms, say, flow convection or fast biochemical reactions), practical approaches often neglect all the 'details' and try to guess the thrombotic response from the analysis of the stationary flow field obtained from classical computational fluid dynamics (CFD). The typical fluid mechanics markers used to predict thrombosis in devices include low-velocity region [29], residence time [30–35], flow recirculation [36], low wall shear stress [31,37,38], washout [33,34], kinetic energy density [34], (platelets) stress accumulation [32,35,39], (platelets) shear/convection/aggregation [40], and activation indices [41]. These approaches can provide relevant information at low cost about the flow structure and how geometric changes can reduce thrombogenicity [42]. Of course, they do not inform about the size, evolution, and thrombus quality.

An extension of the pure CFD approach was proposed [43,44] to predict the time of occlusion in high-velocity stenotic channels. In this situation, vWF adsorption on the artificial surface, platelet adhesion via glycoprotein Ib–vWF, and subsequent activation and aggregation of flowing platelets lead to thrombus formation. Assuming that these processes can be abstracted by a correlation between the local hemodynamic shear rate and the thrombus growth rate, this approach relies on a set of pure CFD simulations to predict the occlusion time [43,44]. Of course, the approach can only be justified if the shear rate–growth rate correlation indeed exists and if it can be calibrated in advance.

Physical-based models

Simulations aiming at describing thrombosis should include models for the coagulation cascade [45–47] and platelet dynamics [20,48,49]. Given the numerous interactions between fibrin formation and platelets during thrombosis, proper *in silico* models should consider these two ingredients. The most advanced formulation to date is likely that of Yazdani et al. [50], where a set of 24 partial differential equations are resolved for fluid flow and 20 biochemical species interacting in the clotting cascade are implemented (following the pattern set forth by Anand et al. [51]) with a set of Lagrangian particles (platelets) that can be chemically activated and produce agonists. The key element that makes this Eulerian–Lagrangian approach capable of representing thrombosis in low and high shear flows is a shear-dependent platelet adhesive model set to correctly reproduce data *in vivo* and *in vitro*. Surprisingly, FXII, whose activation on the artificial surface may trigger the intrinsic pathway, was not considered by Yazdani et al. [50]; instead, thrombus formation was triggered by imposing nonzero concentration of the TF-VIIa complex at a site of injury. The initiation of thrombin formation (and therefore fibrin) without explicitly defining an injury site, but rather by relying solely on the activation of

Table 2

Summary of recent approaches and assumptions.

Flow regime	Refs	Flow domain	Coagulation	Platelets	Clot	Contact system	Injury site	Gap to the device
High shear	[48]	3D Navier-Stokes (NS) 10^{-3} m	None	Particles	No	No	Yes	Domain size/biochemistry/ contact/clot
	[20]	3D Dissipative Particle Dynamics (DPD) 10^{-5} m	None	Coarse Grained Molecular Dynamics (CGMD)	No	No	Yes	Domain size/biochemistry/ contact/clot
	[49]	3D DPD 10^{-4} m	None	Particles	Yes	No	Yes	Domain size/biochemistry/ contact
	[58]	3D NS 10^{-2}–10^{-1} m	None	Pseudo particles	Yes	No	Yes	Biochemistry/contact
Low shear	[45,46]	2D DPD 10^{-4} m	8 species	None	Yes	No	Yes	3D/domain size/contact system/platelets
	[47]	2D NS 10^{-2} m	20 species	None	No	Yes	No	3D/platelets/clot
All flow regimes	[53]	2D NS 10^{-2} m	1 species	2 scalar quantities	Yes	No	No	3D/biochemistry/clot retraction on flow
	[88]	2D DPD 10^{-4} m	3 species	Particles	Yes	No	Yes	3D/domain size/contact/ platelet–protein coupling
	[18,54,55]	3D NS 10^{-1} m	5 species	5 scalar quantities	Yes	No	No	Contact
	[52]	3D NS 10^{-2}–10^{-1} m	1 species	3 scalar quantities	No	No	No	Biochemistry/clot retraction
	[50]	3D NS 10^{-4} m	20 species	Particles	Yes	Yes w/o XII	Yes	Domain size/FXII
	[89]	2D NS 10^{-4} m	8 species	Particles	Yes	No	Yes	3D/domain size/contact
	[56]	3D NS 10^{-2}–10^{-1} m	5 species	3 scalar quantities	Yes	No	No	Specific to flow diverters in aneurysms/contact
	[57]	3D NS 10^{-2} m	5 species	2 scalar quantities	Yes	No	No	Specific to stenosis geometries/contact

factor XII, was made by Méndez Rojano et al. [47], where the backward facing step experiment was computed. A significant concentration of thrombin was present only in the region where thrombus formation had been observed experimentally by Taylor et al. [23], suggesting the flow–contact system interaction is a key element in thrombus location within devices, at least in the low shear regime.

The Eulerian–Lagrangian method developed by Yazdani et al. [50] is too computationally demanding to be applied to actual devices; the fundamental reason is the tremendous number of particles (1.5 μm each) that must be accumulated to form a thrombus of a typical size of 1 cm. A way to significantly reduce the overall computational load is to represent platelets by Eulerian fields [18,52–57], instead of particles. Wu et al. [18] applied 14 coupled partial differential equations: 4 for fluid flow, 5 for biochemical species to represent coagulation, and 5 for different platelet types. This approach has shown good potential for complex devices such as the HeartMate II VAD.

Recently, the concept of pseudo-platelets was introduced [58] to reduce the computational effort while keeping the Lagrangian description of platelets, by far, more realistic than the Eulerian framework. In this view, the spherical particles transported by the flow change their size (from 1.5 to 90 μm) once activated and adhered, thus reducing the required number of particles that form the thrombus. This numerical treatment, although not physically based, produces reasonable thrombus formation according to Zheng et al. [58] and allows increasing size of the affordable computational domains from sub-millimetric, as implemented in the study by Yazdani et al. [50], to centimetric [58]. In the latter study, a mapping from the particle aggregation step to a phase-field representation of the thrombus material properties and permeability was also first proposed. This methodology opens new perspectives in terms of thromboembolic event prediction, although necessary adaptations to accommodate device thrombosis remain.

Future directions

As efforts continue to develop device-induced models, it should be noted that the U.S. Food and Drug Administration and other regulatory bodies are keenly interested, and increasingly likely, to accept properly validated models as part of the device approval process. With this context, the future directions to facilitate impactful device modeling are paramount.

Microscopic versus macroscopic approaches

Currently, there are two modeling approaches to device-induced thrombosis: either considering the individual cells and factors (microscopic) or considering the domain as a continuum and the cells as bulk concentrations (macroscopic). Both approaches have advantages and disadvantages with the associated limitations. However, developing a synergistic strategy and collaboration between the macroscopic approaches that could implement the microscopic, or even nanoscopic, results could yield significant progress to capture the truly salient features for thrombosis [59]. Within this context, careful consideration of the intent (and setting) of the proposed device is significant, considering endovascular coils aim to clot aneurysms, whereas mechanical circulatory support devices must avoid thrombosis.

Reconciling physical and numerical timescales

Thrombosis may be visible days, weeks, or months after device implantation, whereas multiphysics simulations representing flow–coagulation–platelet–surface interactions can only represent fractions of seconds or minutes depending on the model's spatial scales. On top of purposely increasing reaction rates and/or diffusivity coefficients [18], current efforts to reduce the complexity of kinetics schemes [60,61] or model the near wall transport phenomena [62] may improve the situation, but will most probably be insufficient to fill the gap. A proper way to drastically increase the physical time that a simulation can demonstrate would be to have access to the thrombus growth rate. Then, the entire process could be represented by a set of simulations performed at different stages over the thrombus evolution, using the last computed growth rate to extrapolate from one instant to the following one. This strategy was successfully followed by Mehrabadi et al. [43] in the very simple case where the growth rate can be inferred from the local shear rate issued by pure CFD. This approach could be made more general by leveraging a multiphysics simulation at each step. Thus, future efforts should focus on modeling the thrombus growth rate rather than simply their size.

Immune/inflammatory

The persistent inflammatory stimulus resulting from blood contact with the device surface induces a perpetual immune response [15]. Adsorbed proteins, in addition to regulating activation of coagulation and platelets, also regulate the activation of complement and immune cells. Fibrinogen on the biomaterial surface can activate circulating monocytes, initiating the inflammatory response [15]. The presence of factors on the membranes of these and other cells can also contribute to activation and propagation of coagulation on the device surfaces. Complement is also activated via binding to the adsorbed surface [17], generating C3a and C5a at the device site [15], and both contribute to further inflammatory activation and stimulate coagulation. Devices can increase circulating platelet–leukocyte aggregates ([63]), which are associated with thromboinflammatory diseases [63,64] and linked to CV events [65]. Including

some description of the complement and inflammatory systems, and their crosstalk with thrombosis, should be considered in future modeling efforts.

Validation

Results from *in vitro* and *in vivo* experiments, as well as from clinical data, are necessary both to validate *in silico* efforts and to provide biological and mechanistic information as inputs into such models. The gold standard preclinical experiment is a large animal model with appropriately long timescales; however, this can be both practically challenging and expensive. Benchtop *in vitro* studies thus have less logistical and financial burden for implementation, thereby increasing throughput, but can encounter the same challenges discussed in the sections Microscopic versus macroscopic approaches and Reconciling physical and numerical timescales: timescale and selection of parameters and endpoints. Both types of experiments can provide useful information to identify thrombogenic hotspots. Clinical data on the location and incidence of thrombosis in devices are ideal for validation but can be challenging to obtain. New methodologies for obtaining validation data, both in preclinical experiments and from device patients, are needed.

Incorporation of pathologies and blood state

Modeling is most frequently implemented with idealized parameters. Biological variability and patient pathophysiology may play key roles in the lack of translation of modeling results to the patient. Patients will likely be treated with pharmacological agents that modify hemostatic and thrombotic function, *e.g.* virtually all patients with mechanical circulatory support will be anticoagulated. In addition, devices can alter the blood state, induce pathologies, and perturb the endothelial environment during implantation. This endothelial disruption can cause deleterious effects like restenosis of coronary stents and potentiate platelet activation and thrombus formation [66]. Incorporation of these clinically relevant blood states may increase the translatability of modeling efforts.

Conclusion

Because of the inherent complexity of the CV system, thrombosis modeling of high integrity is challenging. However, while the current tangible application is device design, computationally guided patient care is the 'science fiction' of today but will be the needed 'reality' in the future.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

K.B.M. acknowledges support, in part, by U.S. National Institutes of Health grant HL136369. F.N. acknowledges support by ANR (the French National Research Agency) under the 'Investissements d'avenir' programme with the reference ANR-16-IDEX-0006.
Figure 1 was created with BioRender.com.

References

Papers of particular interest, published within the period of review, have been highlighted as:

* of special interest
** of outstanding interest

1. Jaffer IH, Fredenburgh JC, Hirsh J, Weitz JI: **Medical device-induced thrombosis: what causes it and how can we prevent it?** *J Thromb Haemostasis* 2015, **13**:S72–S81.

2. Susen S, Rauch A, Van Belle E, Vincentelli A, Lenting PJ: **Circulatory support devices: fundamental aspects and clinical management of bleeding and thrombosis**. *J Thromb Haemostasis* 2015, **13**:1757–1767.

3. Slepian MJ, Sheriff J, Hutchinson M, Tran P, Bajaj N, Garcia JGN, Scott Saavedra S, Bluestein D: **Shear-mediated platelet activation in the free flow: perspectives on the emerging spectrum of cell mechanobiological mechanisms mediating cardiovascular implant thrombosis**. *J Biomech* 2017, **50**:20–25.

4. Fogelson AL, Neeves KB: **Fluid mechanics of blood clot formation**. *Annu Rev Fluid Mech* 2015, **47**:377–403.

5. Virchow R: *Gesammelte abhandlungen zur wissenschaftlichen medicin.* 1856.

6. Fåhraeus R: **The suspension stability of the blood**. *Physiol Rev* 1929, **9**:399–431.

7. Smith SA, Travers RJ, Morrissey JH: **How it all starts: initiation of the clotting cascade**. *Crit Rev Biochem Mol Biol* 2015, **50**:326–336.

8. Yun SH, Sim EH, Goh RY, Park JI, Han JY: **Platelet activation: the mechanisms and potential biomarkers**. *BioMed Res Int* 2016, **2016**.

9. * Rauch A, Susen S, Zieger B: **Acquired von Willebrand syndrome in patients with ventricular assist device**. *Front Med* 2019, **6**.
A review of acquired von Willebrand syndrom (AVVS), which has recently been observed in mechanical circulatory support patients. AVVS is caused by damaging shear stress in medical devices that cause a loss in high molecular weight von Willebrand factor (vWF) multimers, resulting in increased bleeding risk.

10. Basmadjian D, Sefton MV, Baldwin SA: **Coagulation on biomaterials in flowing blood: some theoretical considerations**. *Biomaterials* 1997, **18**:1511–1522.

11. Sperling C, Fischer M, Maitz MF, Werner C: **Blood coagulation on biomaterials requires the combination of distinct activation processes**. *Biomaterials* 2009, **30**:4447–4456.

12. Vroman L, Adams AL: **Identification of rapid changes at plasma–solid interfaces**. *J Biomed Mater Res* 1969, **3**:43–67.

13. Thevenot P, Hu W, Tang L: **Surface chemistry influences implant biocompatibility**. *Curr Top Med Chem* 2008, **8**:270–280.

14. Grunkemeier JM, Tsai WB, Horbett TA: **Co-adsorbed fibrinogen and von Willebrand factor augment platelet procoagulant activity and spreading**. *J Biomater Sci Polym Ed* 2001, **12**:1–20.

15. * Labarrere CA, Dabiri AE, Kassab GS: **Thrombogenic and inflammatory reactions to biomaterials in medical devices**. *Front Bioeng Biotechnol* 2020, **8**.
A very recent review discussing the mechanisms of thrombosis both in arterial and venous systems and with devices. The authors discuss the importance of the development of nonthrombogenic surfaces that mimic passive biological surfaces (e.g. endothelium), as this would help not only to mitigate thrombosis, but inflammation as well.

16. Gorbet MB, Sefton MV: **Biomaterial-associated thrombosis: roles of coagulation factors, complement, platelets and leukocytes**. *Biomater Silver Jubil Comp* 2004, **25**:5681–5703.

17. Franz S, Rammelt S, Scharnweber D, Simon JC: **Immune responses to implants - a review of the implications for the design of immunomodulatory biomaterials**. *Biomaterials* 2011, **32**:6692–6709.

18. Wu WT, Yang F, Wu J, Aubry N, Massoudi M, Antaki JF: **High fidelity computational simulation of thrombus formation in Thoratec HeartMate II continuous flow ventricular assist device**. *Sci Rep* 2016, **6**:1–11.

19. Hastings SM, Ku DN, Wagoner S, Maher KO, Deshpande S: **Sources of circuit thrombosis in pediatric extracorporeal membrane oxygenation**. *Am Soc Artif Intern Organs J* 2017, **63**:86–92.

20. * Gupta P, Zhang P, Sheriff J, Bluestein D, Deng Y: **A multiscale model for recruitment aggregation of platelets by correlating with in vitro results**. *Cell Mol Bioeng* 2019, **12**:327–343.
Coarse grained molecular dynamics for platelets at the microscale and dissipative particle dynamics for the shear flow at the macroscale are coupled to study the aggregation of platelets. Results indicate that assuming a rigid-platelet model underestimates the contact area and the detaching force by approximately 90%.

21. Litvinov RI, Weisel JW: **Role of red blood cells in haemostasis and thrombosis**. *ISBT Sci Ser* 2017, **12**:176–183.

22. * Yang L, Neuberger T, Manning KB: **In vitro real-time magnetic resonance imaging for quantification of thrombosis. *Magn Reson Mater Physics***. *Biol Med* 2020. https://doi.org/10.1007/s10334-020-00872-2.
An experimental study demonstrating the first real-time clot growth to provide researchers a validating data set for device-induced thrombosis models at the macroscopic scales.

23. Taylor JO, Witmer KP, Neuberger T, Craven B a, Meyer RS, Deutsch S, Manning KB: **In vitro quantification of time dependent thrombus size using magnetic resonance imaging and computational simulations of thrombus surface shear stresses**. *J Biomech Eng* 2014, **136**:1–11.

24. Nobili M, Sheriff J, Morbiducci U, Redaelli A, Bluestein D: **Platelet activation due to hemodynamic shear stresses: damage accumulation model and comparison to in vitro measurements**. *Am Soc Artif Intern Organs J* 2008, **54**:64–72.

25. Shi X, Yang J, Huang J, Long Z, Ruan Z, Xiao B, Xi X: **Effects of different shear rates on the attachment and detachment of platelet thrombi**. *Mol Med Rep* 2016, **13**:2447–2456.

26. Navitsky MA, Taylor JO, Smith AB, Slattery MJ, Deutsch S, Siedlecki CA, Manning KB: **Platelet adhesion to polyurethane urea under pulsatile flow conditions**. *Artif Organs* 2014, **38**:1046–1053.

27. Casa LDC, Deaton DH, Ku DN: **Role of high shear rate in thrombosis**. *J Vasc Surg* 2015, **61**:1068–1080.

28. Belyaev AV, Dunster JL, Gibbins JM, Panteleev MA, Volpert V: **Modeling thrombosis in silico : frontiers , challenges , unresolved problems and milestones**. *Phys Life Rev* 2018, **1**:1–39.

29. Bounouib M, Benakrach H, Es-Sadek Zeriab M, Taha-Janan M, Maazouzi W: **Numerical study of a new ventricular assist device**. *Artif Organs* 2020, **44**:604–610.

30. Zhang J, Chen Z, Griffith BP, Wu ZJ: **Computational characterization of flow and blood damage potential of the new maglev CH-VAD pump versus the HVAD and HeartMate II pumps**. *Int J Artif Organs* 2020. https://doi.org/10.1177/0391398820903734.

31. Chen HY, shin Tien W, Chambers SD, Dabiri D, Kassab GS: **Search for an optimal design of a bioprosthetic venous valve: in silico and in vitro studies**. *Eur J Vasc Endovasc Surg* 2019, **58**:112–119.

32. Chivukula VK, Beckman JA, Prisco AR, Dardas T, Lin S, Smith JW, Mokadam NA, Aliseda A, Mahr C: **Left ventricular assist device inflow cannula angle and thrombosis risk**. *Circ Hear Fail* 2018, **11**.

33. Liao S, Neidlin M, Li Z, Simpson B, Gregory SD: **Ventricular flow dynamics with varying LVAD inflow cannula lengths: in-silico evaluation in a multiscale model**. *J Biomech* 2018, **72**:106–115.

34. Liao S, Wu EL, Neidlin M, Li Z, Simpson B, Gregory SD: **The influence of rotary blood pump speed modulation on the risk of intraventricular thrombosis**. *Artif Organs* 2018, **42**:943–953.

35. Aliseda A, Chivukula VK, McGah P, Prisco AR, Beckman JA, Garcia GJM, Mokadam NA, Mahr C: **LVAD outflow graft angle and thrombosis risk**. *Am Soc Artif Intern Organs J* 2017, **63**:14–23.

36. De Nisco G, Gallo D, Siciliano K, Tasso P, Lodi Rizzini M, Mazzi V, Calò K, Antonucci M, Morbiducci U: **Hemodialysis arterio-venous graft design reducing the hemodynamic risk of vascular access dysfunction**. *J Biomech* 2020:100.

37. Ghodrati M, Maurer A, Schlöglhofer T, Khienwad T, Zimpfer D, Beitzke D, Zonta F, Moscato F, Schima H, Aigner P: **The influence of left ventricular assist device inflow cannula position on thrombosis risk**. *Artif Organs* 2020. https://doi.org/10.1111/aor.13705.

38. Buck AKW, Groszek JJ, Colvin DC, Keller SB, Kensinger C, Forbes R, Karp S, Williams P, Roy S, Fissell WH: **Combined in silico and in vitro approach predicts low wall shear stress regions in a hemofilter that correlate with thrombus formation in vivo**. *Am Soc Artif Intern Organs J* 2018, **64**:211–217.

39. Buck AKW, Goebel SG, Goodin MS, Wright NJ, Groszek JJ, Moyer J, Singh S, Bluestein D, Fissell WH, Roy S: **Platelet stress accumulation analysis to predict thrombogenicity of an artificial kidney**. *J Biomech* 2018, **69**:26–33.

40. Stiehm M, Wüstenhagen C, Siewert S, Ince H, Grabow N, Schmitz KP: **Impact of strut dimensions and vessel caliber on thrombosis risk of bioresorbable scaffolds using hemodynamic metrics**. *Biomed Tech* 2019, **64**:251–262.

41. Zlobina KE, Guria GT: **Platelet activation risk index as a prognostic thrombosis indicator**. *Sci Rep* 2016, **6**.

42. Chen HY, Diaz JA, Lurie F, Chambers SD, Kassab GS: **Hemodynamics of venous valve pairing and implications on helical flow**. *J Vasc Surg Venous Lymphat Disord* 2018, **6**:517–522.e1.

43. Mehrabadi M, Casa LDC, Aidun CK, Ku DN: **A predictive model of high shear thrombus growth**. *Ann Biomed Eng* 2016, **44**:2339–2350.

44. Ku DN, Casa LDC, Hastings SM: **Choice of a hemodynamic model for occlusive thrombosis in arteries**. *J Biomech* 2017, **50**:110–113.

45. Bouchnita A, Tosenberger A, Volpert V: **On the regimes of blood coagulation**. *Appl Math Lett* 2016, **51**:74–79.

46. Bouchnita A, Galochkina T, Kurbatova P, Nony P, Volpert V: **Conditions of microvessel occlusion for blood coagulation in flow**. *Int J Numer Method Biomed Eng* 2017, **33**, e2850.

47. * Méndez Rojano R, Mendez S, Nicoud F: **Introducing the procoagulant contact system in the numerical assessment of device-related thrombosis**. *Biomech Model Mechanobiol* 2018, **17**:815–826.
In this computational study, the initiation of thrombin formation (and therefore fibrin) is performed without explicitly defining an injury site, but rather by relying solely on the activation of factor XII (contact system and intrinsic pathway). Thrombin accumulates in larger quantity where thrombus formation is observed *in vitro*.

48. Tomita A, Tamura N, Nanazawa Y, Shiozaki S, Goto S: **Development of virtual platelets implementing the functions of three platelet membrane proteins with different adhesive characteristics**. *J Atherosclerosis Thromb* 2015, **22**:201–210.

49. Wang L, Chen Z, Zhang J, Zhang X, Wu ZJ: **Modeling clot formation of shear-injured platelets in flow by a dissipative particle dynamics method**. *Bull Math Biol* 2020:82.
DPD is used to study how the fact that platelets can be injured by non-physiological shear stresses in VADs and can modify clot formation;

results suggest quicker but more easily breakable blood clots at injury sites.

50. Yazdani A, Li H, Humphrey JD, Karniadakis GE: *A general shear-dependent model for thrombus formation*. 2017. https://doi.org/10.1371/journal.pcbi.1005291.

51. Anand M, Rajagopal K, Rajagopal KR: **A model for the formation, growth, and lysis of clots in quiescent plasma. A comparison between the effects of antithrombin III deficiency and protein C deficiency**. *J Theor Biol* 2008, **253**:725–738.

52. Taylor JO, Yang L, Deutsch S, Manning KB: **Development of a platelet adhesion transport equation for a computational thrombosis model**. *J Biomech* 2017, **50**:114–120.

53. * Taylor JO, Meyer RS, Deutsch S, Manning KB: **Development of a computational model for macroscopic predictions of device-induced thrombosis**. *Biomech Model Mechanobiol* 2016. https://doi.org/10.1007/s10237-016-0793-2.

A macroscopic thrombosis model that focused on devices or biomaterial surfaces and was validated using experimental data collected with magnetic resonance imaging.

54. Wu WT, Zhussupbekov M, Aubry N, Antaki JF, Massoudi M: **Simulation of thrombosis in a stenotic microchannel: the effects of vWF-enhanced shear activation of platelets**. *Int J Eng Sci* 2020:147.

• A macroscopic, heuristic model for the role of vWF on shear activation of platelets is proposed. Results show fair agreement with the experimentally observed formation of vWF-mediated thrombus in a stenosis.

55. Wu WT, Jamiolkowski MA, Wagner WR, Aubry N, Massoudi M, Antaki JF: **Multi-constituent simulation of thrombus deposition**. *Sci Rep* 2017, **7**.

56. Sarrami-Foroushani A, Lassila T, Hejazi SM, Nagaraja S, Bacon A, Frangi AF: **A computational model for prediction of clot platelet content in flow-diverted intracranial aneurysms**. *J Biomech* 2019, **91**:7–13.

57. Hosseinzadegan H, Tafti DK: **A predictive model of thrombus growth in stenosed vessels with dynamic geometries**. *J Med Biol Eng* 2019, **39**:605–621.

58. ** Zheng X, Yazdani A, Li H, Humphrey JD, Karniadakis GE: **A three-dimensional phase-field model for multiscale modeling of thrombus biomechanics in blood vessels**. *PLoS Comput Biol* 2020:16.

A fully-Eulerian, three-dimensional framework is presented which includes a phase-field model of thrombus that is calibrated with existing *in vitro* experimental data. This is the first study integrating the initiation of a thrombus through platelet aggregation with its subsequent viscoelastic responses.

59. Zhang P, Zhang L, Slepian MJ, Deng Y, Bluestein D: **A multiscale biomechanical model of platelets: correlating with in-vitro results**. *J Biomech* 2017, **50**:26–33.

60. Hansen KB, Shadden SC: **Automated reduction of blood coagulation models**. *Int J Numer Method Biomed Eng* 2019, **35**.

61. Mendez Rojano R, Mendez S, Lucor D, Nicoud F: **Sensitivity analysis, model reduction and parameter estimation for thrombosis modeling for CFD**. In *SIAM conference on computational science and engineering*; 2019.

62. Hansen KB, Shadden SC: **A reduced-dimensional model for near-wall transport in cardiovascular flows**. *Biomech Model Mechanobiol* 2016, **15**:713–722.

63. Radovancevic R, Matijevic N, Bracey AW, Radovancevic B, Elayda M, Gregoric ID, Frazier OH: **Increased leukocyte-platelet interactions during circulatory support with left ventricular assist devices**. *Am Soc Artif Intern Organs J* 2009, **55**:459–464.

64. Finsterbusch M, Schrottmaier WC, Kral-Pointner JB, Salzmann M, Assinger A: **Measuring and interpreting platelet-leukocyte aggregates**. *Platelets* 2018, **29**:677–685.

65. Liu C, Yang Y, Du L, Chen S, Zhang J, Zhang C, Zhou J: **Platelet-leukocyte aggregate is associated with adverse events after surgical intervention for rheumatic heart disease**. *Sci Rep* 2019, **9**:1–10.

66. Tesfamariam B: **Endothelial repair and regeneration following intimal injury**. *J Cardiovasc Transl Res* 2016, **9**:91–101.

67. Ohkata I: **Medical applications of superelastic nickel-titanium (Ni–Ti) alloys**. In *Shape memory and superelastic alloys*. Elsevier; 2011:176–196.

68. Byrne RA, Joner M, Kastrati A: **Stent thrombosis and restenosis: what have we learned and where are we going? the Andreas Grüntzig Lecture ESC 2014**. *Eur Heart J* 2015, **36**:3320–3331.

69. Park KM, Kim YW, Yang SS, Kim DI: **Comparisons between prosthetic vascular graft and saphenous vein graft in femoropopliteal bypass**. *Ann Surg Treat Res* 2014, **87**:35–40.

70. Wall C, Moore J, Thachil J: **Catheter-related thrombosis: a practical approach**. *J Intensive Care Soc* 2016, **17**:160–167.

71. Rashid HN, Gooley RP, Nerlekar N, Ihdayhid AR, McCormick LM, Nasis A, Cameron JD, Brown AJ: **Bioprosthetic aortic valve leaflet thrombosis detected by multidetector computed tomography is associated with adverse cerebrovascular events: a meta-analysis of observational studies**. *Euro Interven* 2018, **13**:e1748–e1755.

72. Whitlock RP, Sun JC, Fremes SE, Rubens FD, Teoh KH: **Antithrombotic and thrombolytic therapy for valvular disease: antithrombotic therapy and prevention of thrombosis, 9th ed: American college of chest physicians evidence-based clinical practice guidelines**. *Chest* 2012, **141**:e576S–e600S.

73. Yanagisawa R, Tanaka M, Yashima F, Arai T, Jinzaki M, Shimizu H, Fukuda K, Watanabe Y, Naganuma T, Higashimori A, *et al.*: **Early and late leaflet thrombosis after transcatheter aortic valve replacement: a multicenter initiative from the OCEAN-TAVI registry**. *Circ Cardiovasc Interv* 2019, **12**.

Analysis of data from 485 transcatheter aortic valve replacement (TAVR) patients who underwent computed tomography (CT) post-TAVR to investigate leaflet thickening and reduced motion, which is indicative of leaflet thrombosis. The authors found that early thrombosis occurred in 9.3% of patients, and that late leaflet thrombosis occurred up to 3 years.

74. Jordan LC, Ichord RN, Reinhartz O, Humpl T, Pruthi S, Tjossem C, Rosenthal DN: **Neurological complications and outcomes in the berlin heart EXCOR® pediatric investigational device exemption trial**. *J Am Heart Assoc* 2015, **4**, e001429. e001429.

75. Ho A, Schultz J, John R, Goodwin K, Kluis A, Pritzker M, Missov E, Liao K, Cogswell R: **Incidence of early and late pump thrombosis on HeartMate II LVAD support**. *J Heart Lung Transplant* 2018, **37**:S369.

76. Upshaw JN, Kiernan MS, Morine KJ, Kapur NK, De Nofrio D: **Incidence, management, and outcome of suspected continuous-flow left ventricular assist device thrombosis**. *Am Soc Artif Intern Organs J* 2016, **62**:33–39.

77. Zeymer U, Bauer T, Hamm C, Zahn R, Weidinger F, Seabra-Gomes R, Hochadel M, Marco J, Gitt A, Eberli F, *et al.*: **Use and impact of intra-aortic balloon pump on mortality in patients with acute myocardial infarction complicated by cardiogenic shock: results of the Euro Heart Survey on PCI**. *Euro Interven* 2011, **7**:437–441.

78. Ball L, Costantino F, Pelosi P: **Postoperative complications of patients undergoing cardiac surgery**. *Curr Opin Crit Care* 2016, **22**:386–392.

79. Copeland JG, Smith RG, Arabia FA, Nolan PE, McClellan D, Tsau PH, Sethi GK, Bose RK, Banchy ME, Covington DL, *et al.*: **Total artificial heart bridge to transplantation: a 9-year experience with 62 patients**. *J Heart Lung Transplant* 2004, **23**:823–831.

80. Copeland J, Copeland H, Nolan P, Gustafson M, Slepian M, Smith R: **Results with an anticoagulation protocol in 99 syncardia total artificial heart recipients**. *Am Soc Artif Intern Organs J* 2013, **59**:216–220.

81. Hastings SM, Deshpande SR, Wagoner S, Maher K, Ku DN: **Thrombosis in centrifugal pumps: location and composition in clinical and in vitro circuits**. *Int J Artif Organs* 2016, **39**:200–204.

82. Grewal S, Chamarthy MR, Kalva SP: **Complications of inferior vena cava filters**. *Cardiovasc Diagn Ther* 2016, **6**:632–641.

83. Imamura H, Sakai N, Satow T, Iihara K: **Factors related to adverse events during endovascular coil embolization for ruptured cerebral aneurysms**. *J Neurointerventional Surg* 2020, **12**:605–609.

84. Barnard EBG, Morrison JJ, Madureira RM, Lendrum R, Fragoso-Iñiguez M, Edwards A, Lecky F, Bouamra O, Lawrence T, Jansen JO: **Resuscitative endovascular balloon occlusion of the aorta (REBOA): a population based gap analysis of trauma patients in England and Wales**. *Emerg Med J* 2015, **32**: 926–932.

85. Tennankore KK, D'Gama C, Faratro R, Fung S, Wong E, Chan CT: **Adverse technical events in home hemodialysis**. *Am J Kidney Dis* 2015, **65**:116–121.

86. Cicha I: **Thrombosis: novel nanomedical concepts of diagnosis and treatment**. *World J Cardiol* 2015, **7**:434.

87. Griffin MT, Zhu Y, Liu Z, Aidun CK, Ku DN: **Inhibition of high shear arterial thrombosis by charged nanoparticles**. *Biomicrofluidics* 2018, **12**.
As arterial platelet thrombosis leads to heart attack and stroke, and current antiplatelet therapies are ineffective in parts of the population, the authors investigate a novel way to inhibit thrombosis using negatively charged nanoparticles.

88. Tosenberger A, Ataullakhanov F, Bessonov N, Panteleev M, Tokarev A, Volpert V: **Modelling of platelet–fibrin clot formation in flow with a DPD–PDE method**. *J Math Biol* 2016, **72**: 649–681.

89. * Bouchnita A, Volpert V: **A multiscale model of platelet-fibrin thrombus growth in the flow**. *Comput Fluids* 2019, **184**:10–20.
A multiscale model of platelet-fibrin thrombus growth in the flow is presented, where the coagulation cascade is described by PDEs, blood flow by the Navier–Stokes equations, the clot is a porous medium and discrete spheres mimic platelets. The model proves able to represent both arterial and venous thrombus formation.