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Analyzing Blood Clot Formation through Fluid Mechanics

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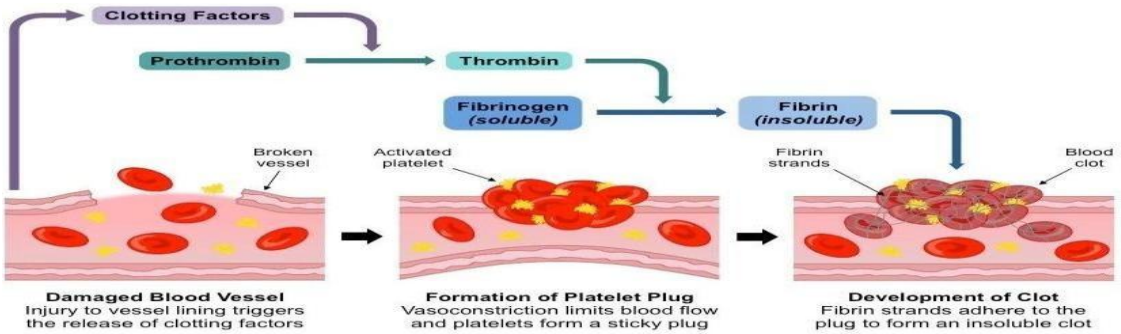
Abstract
Blood clot formation, or thrombosis, is a critical physiological process that helps prevent excessive bleeding after injury but can also lead to severe health issues when uncontrolled. Fluid mechanics plays a vital role in understanding the dynamics of blood flow and how it influences the clotting process.Various hemodynamic factors, such as shear stress, flow velocity, and vessel geometry, directly affect platelet aggregation, fibrin network formation, and thrombus growth. This study delves into the complexinteraction between blood flow and clot formation by exploring how fluid dynamics impact thrombus development in both normal and pathological conditions. Using advanced computational models based on fluid mechanics, researchers can simulate blood flow in micro vessels and larger arteries, providing insights into the triggers of clotting events and the progression of thrombotic diseases like deep veinthrombosis, stroke, and heart attacks. These simulations, when combined with experimental data, help uncover the underlying mechanisms that contribute to abnormal clotting, offering potential for early diagnosis and more effective treatments. The integration of computational fluid dynamics (CFD) tools allows for the accurate prediction of clotting behavior, improving our understanding of thrombotic disorders and guiding the development of personalized therapies. By analyzing blood clot formation through fluid mechanics, we gain a deeper appreciation of the complex relationship between blood flow and hemostasis, ultimately aiding in better management and prevention of clot-related diseases.

Keywords: Blood clot formation, Fluid mechanics, Hemodynamic, Thrombosis, Computational modeling

1.1 Introduction

Blood clot formation is a multifaceted and dynamic process influenced by several factors, with fluid dynamics playing a crucial role in the way blood components interact under various flow conditions. Jesty and Fenton (1999) conducted a study that focused on the kinetics of clot formation in a shear flowsystem. Their research emphasized how shear stress, a force experienced by blood cells as they flowthrough blood vessels, can significantly impact platelet aggregation and the subsequent formation offibrin, the protein that solidifies the clot. Wong et al. (2009) expanded on this by exploring the role ofplatelet aggregation and fibrin formation in thrombus development under flow conditions, highlighting how variations in flow influence the progression of clotting, especially in pathological settings such as arterial injury.



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Shaoetal.(2009) took a more detailed approach by utilizing micro scale simulations to study the mechanisms of blood clotting in environments characterized by shear flow. Their simulations providedvaluable insights into how the microscopic interactions between blood cells, platelets, and fibrinogenoccur under fluid shear, offering a deeper understanding of the mechanical processes that drive clotformation. Furthermore, Sarmiento et al. (2014) modelled the dynamics of clot formation in micro vesselflow, underscoring how the complexity of small-scale hemodynamic, such as flow in capillaries andarterioles, contributes significantly to thrombosis. Their work highlights the crucial role of fluid dynamics not just in clot initiation, but also in the stability and growth of thrombi with in micro vessels.

Simpson et al. (2005) provided a broader perspective by investigating the fluid mechanics of blood clotformation in the context of vascular diseases. Their research revealed how altered blood flow, as seen inconditions like atherosclerosis,

can influence the development and progression of blood clots, potentially leading to severe cardio vascular events like stroke or heart attack. These studies collectively emphasizethe importance of understanding fluid dynamics in blood clot formation, not only in normal physiological conditions but also in various disease states, there by offering a foundation for improving diagnostic toolsand therapeutic interventions in the management of thrombosis and homeostasis. Through these insights, future research may continue to refine our understanding of how hemodynamic influence clotting, leading to more effective treatments and preventive strategies.

1.2 Understanding blood clot formation through fluid mechanics

Understanding blood clot formation through fluid mechanics is crucial for studying the dynamics of thrombosis and the processes involved in thrombus development. Research by **Shao et al. (2012)** delves in to the role of blood flow in thrombus formation, using computational models to highlight how different flow conditions and shear stress affect platelet aggregation and clot formation in arteries. This study underscores the significance of flow-mediated effects, which help in understanding how thrombosis develops in arterial environments and provide insights for the development of treatments to prevent clots. Similarly, **Jesty et al. (1994)** introduced a kinetic model for platelet aggregation, offering a step-by-step explanation of how platelets accumulate and form clots in response to vascular injury. Their work emphasizes the role of blood flow in determining the speed and efficiency of platelet aggregation, which is critical for clot formation.

Fenton and Kottke-Marchant (1998) contributed a theoretical model based on fluid dynamics, showing that variations in shear rate and flow patterns are vital for triggering the clotting cascade, ultimately leading to thrombus formation. Their findings are particularly relevant in understanding clot growth and predicting potential clotting disorders. Lastly, **Coupier et al. (2008)** focused on hemodynamic and platelet aggregation in micro vessels, where the flow patterns differ significantly from larger vessels, typically characterized by low shear rates. Their research emphasizes how such flow conditions influence clotting behavior in smaller vessels, such as capillaries and small arteries, and highlights the complexity of clot formation in these narrower spaces. Together, these studies reveal how fluid mechanics is essential to understanding the underlying mechanisms of thrombosis, offering valuable insights for both diagnostics and treatment strategies for clotting disorders.

1.3 Platelet Transport and Margination Modelling

The exact mechanism of platelet margination, or the movement of platelets toward the vessel wall, remains a subject of ongoing investigation, though it is likely influenced by various hydrodynamic forces.

A significant factor is the Fa˚hræus-Lindqvist effect, which describes how small vessels (10–500 μm) experience a reduction in hematocrit and apparentviscosity due tothe exclusion of red blood cells (RBCs) from the walls. This results in the formation of an RBC depletion zone. The thickness of this layer is influenced by a lift force that pushes RBCs away from the wall, counter balanced by hydrodynamic collisions that push them back toward it. Models of RBC dynamics suggest that thethickness of the depletion zone is inversely proportional to the square root of the hematocrit. The lift forcearises from local velocity disturbances caused by the deformable nature of RBCs, while shear-induced diffusion (SID), which describes the random motion of particles due to collisions in the flowing blood, counteracts this force (Gillespie et al., 2010). These collisions are not rigid body impacts but instead arise from flow-induced stresses and lubrication forces between particles.

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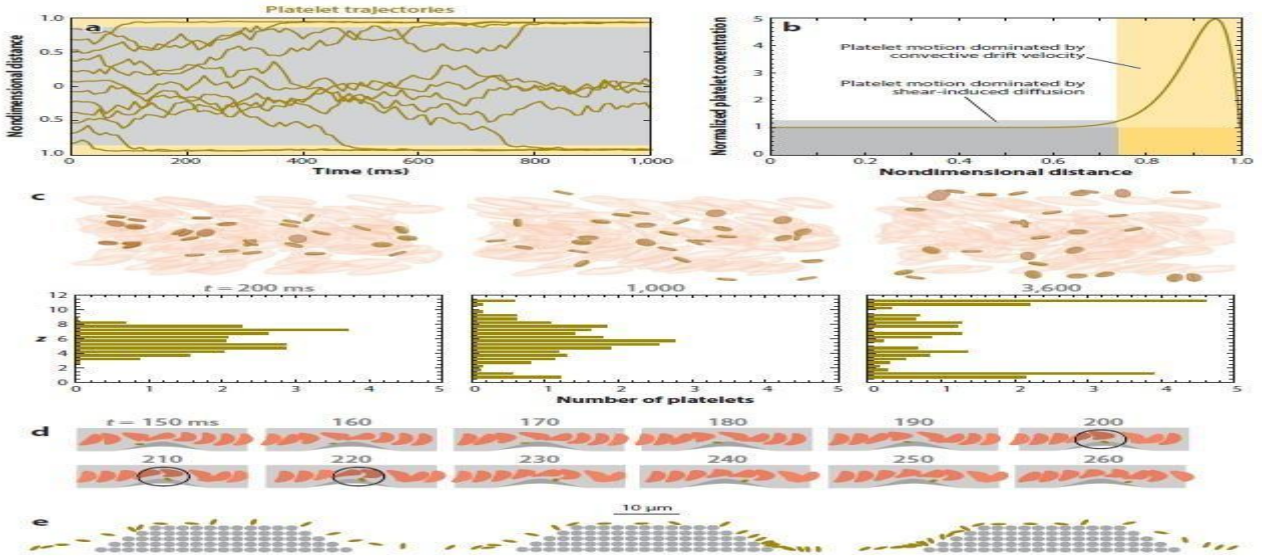

Experimental studies have shown that small tracer particles suspended in RBCs exhibit random motion atlow shear rates, indicating that platelet movement can be modeled using a diffusive flux equation. In this model, the effective diffusion coefficient (Deff) governs lateral platelet transport, with the volume fraction of blood cells (hematocrit) playing a crucial role. The diffusion coefficient of platelets, based onthe Stokes-Einstein equation, is estimated at around O(10−9) cm²/s, while solute transport models suggesta larger value of O(10−7) cm²/s. This discrepancy suggests that platelet motion is primarily driven byinteractions with RBCs or fluid disturbances caused by RBC movement, rather than Brownian motional one (He &Karniadakis, 2010).

However, a constant diffusion coefficient does not explain the net movement of platelets toward the vessel wall. To account for this, additional factors are needed, such as a non-constant diffusion coefficientor a directional bias in platelet motion. SID theory provides a framework for modeling these non-constant diffusion coefficients, which depend on hematocrit and shear rate. The effective diffusion coefficient is proportional to the square of the particle volume fraction for rigid spheres, and for deformable particles like RBCs, the maximal SID occurs at a hematocrit of approximately 0.55,with diffusion decreasing as hematocrit approaches 1 due to particle crowding. Alternatively, empirical power-law expressions have been used to model Deff as a function of shearrate and hematocrit (Shaoetal., 2006).

To further explain the movement of platelets, a drift-diffusion model can be applied. This model incorporates both the drift velocity and effective diffusion, offering an explanation for the biased motionof platelets toward the wall. The drift velocity is related to the spatial gradient in RBC concentration,which is highest near the depletion zone where RBC collisions are most frequent. By using this velocity expression in a stochastic differential equation, researchers can model the biased random walk of platelets, and these models have been found to align closely with experimental data and simulations (Gillespie et al., 2010). Such insights are critical for understanding the fluid dynamics of blood flow and thrombus formation in vessels.

1.4 Simulations of Platelet Margination Using Direct Cell Models

In the past decade, direct simulations of blood cell suspensions under flow conditions have become feasible, offering valuable insights into the mechanisms of platelet margination at the cellular scale. Arecent review article outlines the methods and challenges involved in these simulations (Wong et al.,2009).One significant approach involves a twodimensional lattice Boltzmann immersed boundary method, which has been used to investigate the effects of red blood cell (RBC) anti margination, volume exclusion, and the timescales associated with the drift-diffusion process. For example, Crowl & Fogelson(2009) simulated pressure-driven flow in a 50-µm channel at shear rates of 400 and 1,100 s−1, with hematocrit values of 0.2 and 0.4. Their results, which would be challenging to replicate experimentally, showed that the timescale for platelet margination was independent of the initial RBC distribution, whether uniform or anti marginated. This suggests that platelet margination is not directly caused by RBC antimargination during the formation of the RBC-depletion layer. However, the exclusion of volume bytightly packed RBCs in the core does play a role in platelet margination, although it does not fully explainthe experimentally observed dip in platelet concentration between the depletion layer and the core. By comparing the results of direct cell simulations with a stochastic model of flux, they found that a non-constant diffusion coefficient was needed to match the platelet fluctuations observed in the core. Platelet

diffusion was fastest at the midline, decreasing sharply as platelets neared the depletion layer. The drift mechanism, potentially driven by the orientation and tank-treading motion of RBCs adjacent to the depletion zone, is necessary to push platelets into thelayer.

A three-dimensional model of platelet margination using a Stokes flow boundary-integral method also explored simple shear and channel flow in a 34-μm channel to examine platelet margination in relation tothe RBC capillary number (Ca), which is defined as Ca = μγ R/E. Here, μ represents plasma viscosity, γ is the shear rate, R is the RBC radius, and E is the membrane shear modulus (Shao et al., 2009). For shearrates greater than 2,000 s−1 (Ca > 1), platelet diffusion was found to scale linearly with shear rate, as predicted by shear-induced diffusion (SID) theory. At lower Ca, however, there was a non monotonic dependence on shear rate due to increased fluctuations in RBC shape and orientation, which contrasts with the aligned prolate ellipsoid shape of RBCs at high Ca. Similar trends were observed in channel flow, where the hematocrit gradient produced a non-constant diffusion coefficient in the core. A peak inlateral platelet motion was observed near the RBC depletion layer, consistent with findings from the earlier two-dimensional simulations. The estimated diffusion coefficients from the three-dimensional simulations were an order of magnitude smaller than those from the two-dimensional models, but the overall platelet motion was in good agreement.

A lattice Boltzmann spectrin-link method in another three-dimensional simulation investigated the effectsof hematocrit, viscosity ratios between internal RBC fluid and external plasma, and platelet size and shape within a 41-μm tube (Sarmiento et al., 2014). This study found that platelet margination increased with higher hematocrit (ranging from 0.2 to 0.4) and that lower viscosity ratios led to faster margination due to the faster tank-treading motion of RBC membranes near the vessel wall. Conversely, rigid RBCs did not experience margination because they lacked tanktreading motion. Furthermore, platelet shape influenced margination, with ellipsoids and disks showing slower margination compared to spherical platelets. Notably, disks tended to remain adjacent to RBCs at the edge of the depletion region rather than interacting directly with the vessel wall.
The deformability of platelets compared to RBCs also plays a role in margination. Kumar & Graham(2012) developed a model for binary suspensions of particles with different deformabilities, finding that stiff particles (representing platelets) marginate more easily than floppy particles (representing RBCs) when the stiff particles are present in dilute concentrations, as in the case of platelets in blood. This particle segregation primarily results from the differential collision dynamics between the rigid and flexible particles.

Finally, the presence of a clot growing in the vessel lumen can alter the size of the depletion layer and the distribution of platelets within it. Modeling a thrombus as a porous structure suggests that increasing porosity narrows the depletion layer, which may compress platelets in to the thrombus, potentially enhancing platelet aggregation (Shao et al., 2009). Even without interstitial fluid flow, the presence of astenosis in a vessel can further promote platelet deposition, as suggested by studies on vessel narrowing (Wonget al., 2009).

1.5 Dual-Stage Aggregation

For many years, it was believed that platelet aggregation—where platelets clump together—required activation by soluble agonists. This theory posed challenges, particularly under fast flow conditions, since soluble agonists would not likely be present far upstream of a thrombus. As a result, platelets would needto be activated almost instantaneously by agonists in the immediate vicinity of the thrombus (Marchioli etal., 2002).

Recent understanding suggests that the formation of additional platelet layers, similar to the initially the vessel surface, follows a two-step process. First, inactivated platelets transiently bind to the thrombus using their GPIb receptors, attaching to von Willebr and factor (vWF) molecules immobilized on the surface of the platelets already adhered to the vessel. This binding slows the platelets, providing enough time for soluble agonists or signals triggered by GPIb-vWF interactions to activate the platelets,which in turn enables the formation of stronger, longer-lasting αIIbβ3-mediated bonds (Boussel et al.,2004).These bonds are crucial for maintaining cohesion among platelets as the thrombus grows.

As platelets accumulate and form a structure that projects into the vessel, the platelets must with stand increasing detachment forces. To support this, many strong, long-lived bonds are necessary. The bond between αIIbβ3 (in its highaffinity state) and fibrinogen has dissociation rates ranging from 0.15 to 0.25s−1 under applied forces up to 50 pN, with a typical breaking force of around 90 pN (Shao &Karniadakis,2003).These off rates are much slower than those of GPIb-vWF bonds, which makes the αIIbβ3-fibrinogen bond particularly effective in supporting firm platelet adhesion and inter-platelet cohesion under high shear conditions.
Platelet aggregation under flow conditions is now understood to involve both fibrinogen and vWF at all physiological shear rates, with vWF becoming particularly important at higher shear rates. At high shearrates (1,500–1,800s−1) and in

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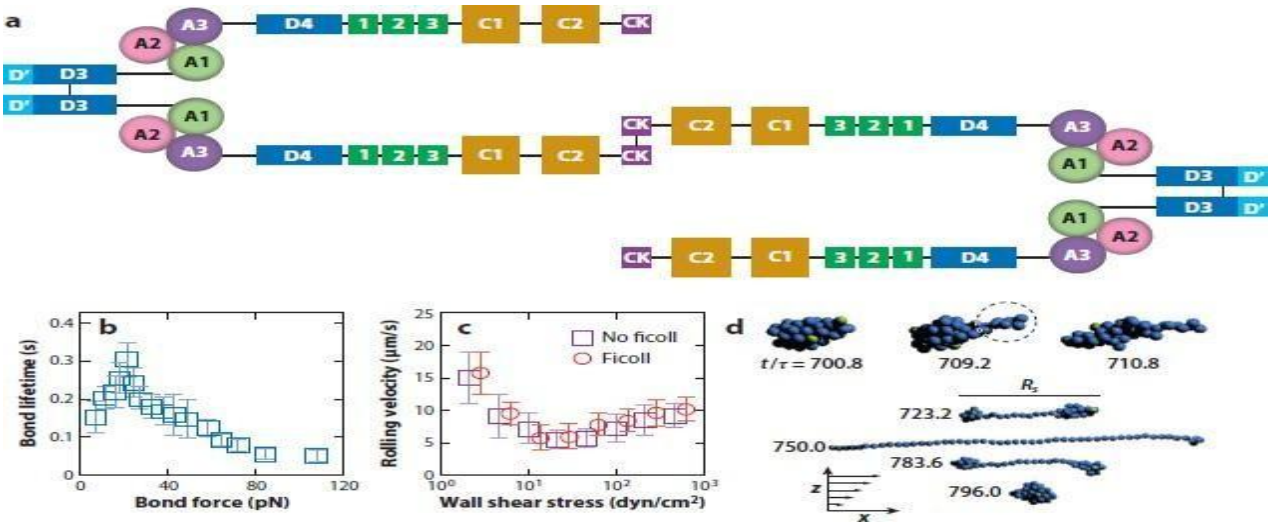
the absence of fibrinogen, platelet aggregates form rapidly but are unstable, disintegrating as platelets shed individually or in small groups, leaving behind a monolayer of adhered platelets (Marchiolietal.,2002). In contrast, when both vWF and fibrinogen are present, aggregates form more slowly but remain stable and intact overtime. Experimental studies have shown that vWF is essential for attaching platelets to the regions of the aggregate exposed to fast-flow conditions. In the interior of the aggregate, where flow is slower, fibrinogen gradually replaces vWF as the primary mediator of platelet cohesion (Boussel et al., 2004).



Most studies on platelet aggregation have been conducted using anticoagulated blood to prevent thrombin or fibrin production, isolating the platelet-surface and platelet-platelet interactions. However, thrombin and fibrin, which are generated during coagulation, can influence platelet accumulation by activating additional platelets and stabilizing the thrombus. Therefore, results from these anticoagulated experiments cannot be directly applied to in vivo situations where coagulation is also occurring. Recent studies examining platelet aggregation and coagulation under flow conditions have provided valuable data, enhancing the accuracy of mathematical models and simulations of clot formation in arteries. These insights are essential for better understanding the complexities of thrombus formation in vivo (Shao &Karniadakis, 2003).

(a) A schematic representation of a von Willebrand factor (vWF) multimer, highlighting its key domains.The A1, A3, and C1 domains are involved in binding to GPIb, collagen, and αIIbβ3, respectively, whilethe A2 domain contains the cleavage site that is targeted by ADAMTS-13.(b) Measurements from asingle-molecule study showing the lifetime of a vWF-GPIb bond under mechanical force.(c) The velocity at which a platelet moves along a vWF-coated surface in response to varying shear stress.(d) Images from a Brownian dynamics simulation illustrating the behavior of a vWFlike polymer under shear flow. The dashed circle represents a thermally induced protrusion, which is pulled by the shear forces. This results in the near-complete extension of the molecule. Following this, the polymer rotates, leading to shear-induced compaction.

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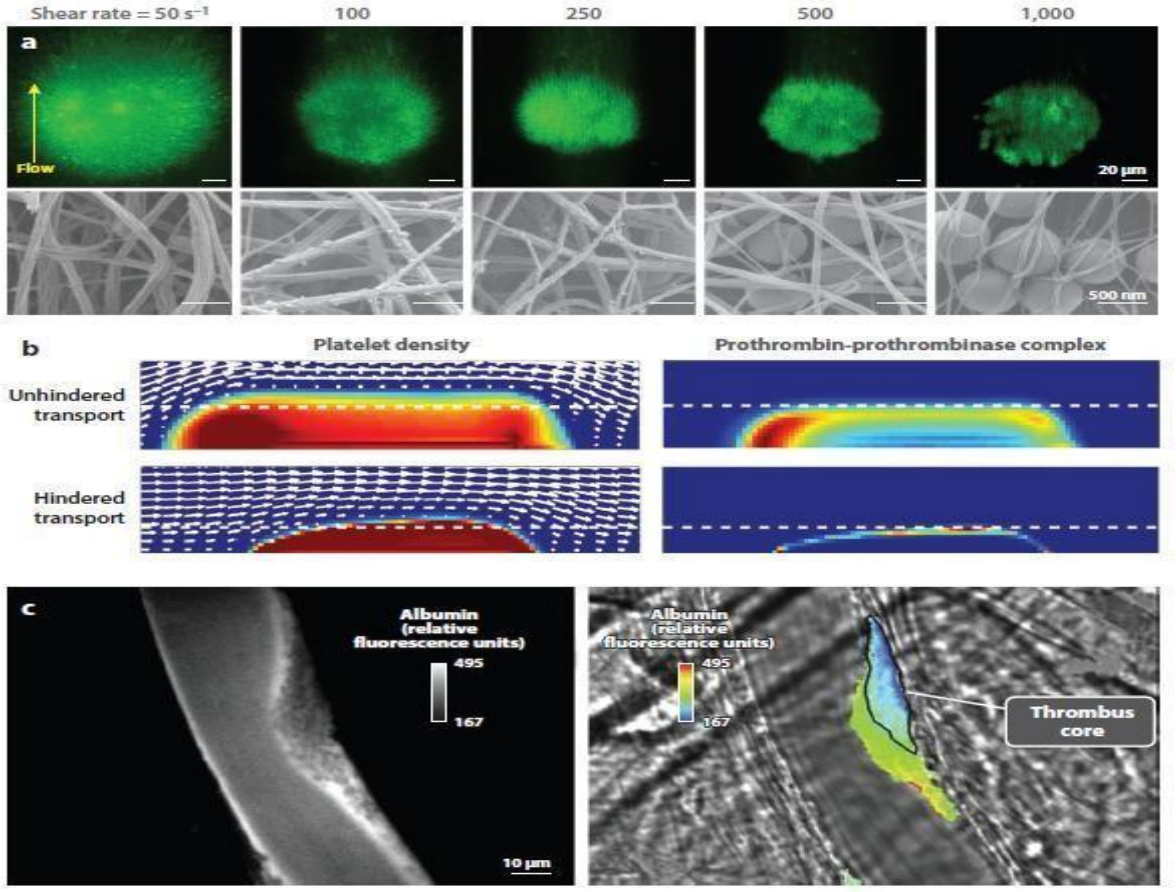
1.6 Mass Transfer Regulation of Surface Coagulation Reactions and Fibrin Polymerization



Three enzyme complexes assemble on the subendothelium and activated platelet surfaces, and their activity is partly regulated by mass transfer limitations. The tissue factor (TF) and factor VIIa (FVIIa) complex, bound to the subendothelial surface, initiates coagulation by converting the zymogens factor X(FX) and factor IX (FIX) to their activated forms, FXa and FIXa. FIXa then binds to FVIIIa on the surface of an activated platelet, forming the FIXa complex (known as tenase), which amplifies FXa production. Similarly, FXa and factor Va (FVa) bind together on platelets to form the FXa complex (prothrombinase), which catalyzes the conversion of prothrombin to thrombin. Blood flow can either promote or inhibit these surface reactions depending on the shear rate. When shear rates are below 600s−1, FXa production by TFis limited by transport, meaning the FXa flux increases with shear rate. Above 600s−1,the production of FXa becomes reaction-limited, and its flux remains constant. When both TF and FVIIIa are present, their combined FXa production is transport-limited over a broad range of shearrates, from 57 to 1,130 s−1. This suggests that blood flow enhances coagulation initiation across all physiological shear rates, provided that normal concentrations of FVIII, FIX, and FX are available. Thrombin production by prothrombinase on a phospholipid bilayer is reaction-limited for shear rates between 100 and 1,000 s−1. Flow acts as an inhibitor here, diluting thrombin and thereby localizing high thrombin concentrations to the immediate vicinity of the clot (Jestyetal.,1994;Fenton&KottkeMarchant,1998; Coupier et al., 2008).
Regardless of the shear rate, a threshold density of TF on the surface is necessary to initiate coagulation.This threshold behavior has been predicted by simulations of clot formation on immobilized TF and confirmed by in vitro blood flow assays. The threshold TF density required to initiate coagulation underflow increases about three fold as the shear rate rises from 100 to 1,000 s−1. A certain injury size is also needed to initiate coagulation both statically and under flow on immobilized TF. This injury size likely ensures that coagulation is initiated only at sufficiently large or deep injuries that expose higher concentrations of TF(Jestyet al., 1994;Fenton&Kottke-Marchant, 1998).
Fibrin polymerization can be either transport-limited or reaction-limited, depending on the thrombin wall flux and shear rate. A kinetic model of fibrin gel formation predicts two grow thregimes based on shear

Rate and gel permeability. At low shear rates, fibrin grow this limited by the transport of thrombin from the procoagulant surface to the gel surface. At high shear rates, growth is limited by the dilution of fibrin polymers before they can reach the necessary concentration for gelation. This agrees with experimental findings showing little or no fibrin gelation at shear rates of 100 s−1 on flat surfaces, even at high thrombin concentrations. Surfaces with roughness at the micrometer

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scale provide some protection from dilution by flow, allowing fibrin formation to proceed at higher shear rates. For example, 800-nm TF-coated beads can initiate fibrin formation at a shear rate of 1,000 s−1 when the TF surface density is sufficiently high, but the growth of the fibrin gel into a channel is limited at lower shear rates (100 s−1)(Jestyetal., 1994; Coupieret al., 2008).

1.7 From Flow to Function: How Hemodynamics Dictates Clot Stability and Resolution

Hemodynamicthe study of blood flow and its forces on the vascular system—plays a critical role in the formation, stability, and resolution of blood clots. The dynamic interaction between blood flow, endothelial cells, platelets, and clotting factors determines how well a clot forms, how stable it remains, and how efficiently it is removed after serving its purpose. Understanding this interplay is essential for both diagnosing and treating thrombotic conditions.

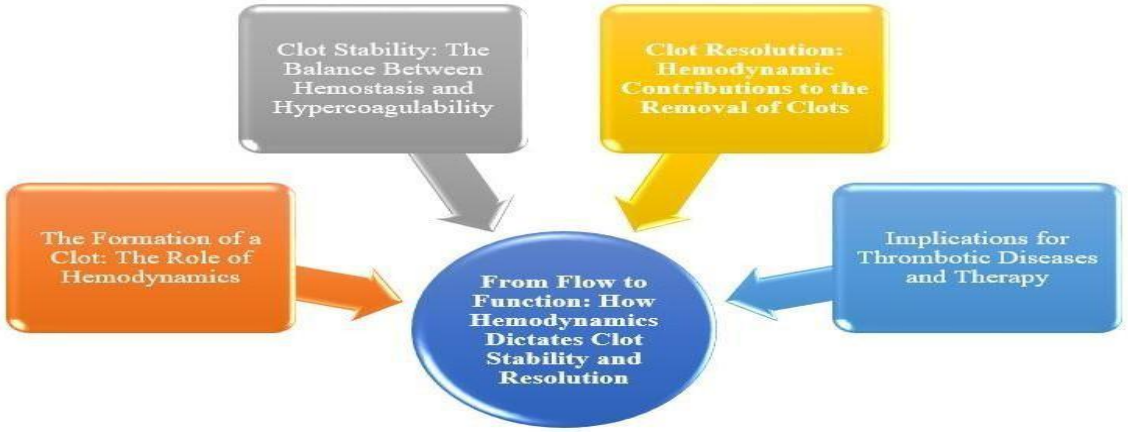

Image: From Flow to Function: How Hemodynamic Dictates Clot Stability and Resolution

1. The Formation of a Clot: The Role of Hemodynamic

Clot formation (or thrombosis) begins when the vascular system is injured, triggering a cascade of events designed to seal the wound and prevent excessive bleeding. The hemodynamic forces—such as shear stress (the frictional force exerted by blood flow on the vessel walls) and blood flow velocity—significantly influence the ability of platelets and coagulation factors to interact and form a clot.

- **Shear Stress and Platelet Activation**: In regions of high shear stress (such as arteries), plateletsbecome activated and adhere to exposed subendothelial surfaces. These regions are characterized by rapid blood flow, which tends to limit the accumulation of clotting factors. However, the interaction between platelets and collagen exposed by vessel injury leads to platelet aggregation and clot formation.
- **Flow-Dependent Thrombosis**: In contrast, in low-flow areas (such as veins or aneurysms), clot formation is more efficient due to prolonged contact time between platelets and the vessel wall. The blood flow in these regions may also favor the accumulation of clotting factors, such as fibrinogen, which are necessary for stabilizing the clot.

2. Clot Stability: The Balance between Hemostasis and Hypercoagulability

Once a clot is formed, its stability must be regulated to prevent excessive thrombosis while ensuring that the clot remains in place long enough to stop bleeding. Hemodynamic plays a key role in this regulation.

- **Dynamic Blood Flow and Clot Strength**: As the clot forms, the blood flow around it creates forces that influence the clot's mechanical stability. In areas of high shear stress, the clot may beprone to being dislodged if the adhesive interactions between platelets and fibrin aren't strong enough. Conversely, low-flow environments may encourage thefurther deposition of fibrin and the development of more rigid, stable clots.
- **Fibrinolysis and Hemodynamic Forces**: The clot must eventually be dissolved once it has served its purpose. Fibrinolysis—the process by which fibrin is broken down by plasmin—occurs under the regulation of several enzymes. In areas of high blood flow, fibrinolysis is often more efficient, as increased flow helps distribute tissue plasminogen activator (tPA) and plasminogen to the clot. However, in low- flowregions, fibrinolysis may be impaired, contributing to clot persistence and even clot embolization.
- **Thrombosis in Arterialvs. Venous Systems**: Hemodynamic forces also contribute to why thrombosis manifests differently in arteries compared to veins. In arteries, the high shear stress generally results in the formation of plateletrich

thrombi that are prone to embolization, while venous thrombi are more fibrin-rich and develop in low-flow environments, making them more prone to grow large and persist longer.

3. Clot Resolution: Hemodynamic Contributions to the Removal of Clots

As clot resolution begins, the hemodynamic environment shifts to favor clot removal.

- **Enhanced Flow and Clot Resolution**: Once the wound is sealed andclotting factors are nolonger needed, increased blood flow can help clear away the remnants of the clot. Enhanced shear stress aids in the breaking apart of weaker clot components and accelerates fibrinolysis.
- **Impaired Resolution in Low-Flow States**: On the other hand, in areas of low blood flow, the fibrinolytic system is less efficient, which can delay the resolution of the clot and lead to complications such as post-thrombotic syndromein veins, or reocclusion in arteries.
- **Endothelial Contribution to Clot Resolution**: Endothelial cells also influence clot resolution by releasing factors that modulate clotting and fibrinolysis. For example, when blood flow returns to normal, the endothelium synthesizes tissue plasminogen activator (tPA), which helps degrade the fibrin matrix of the clot.

Conclusion

Analyzing blood clot formation through the lens of fluid mechanics provides invaluable insights into the complex processes that govern thrombus development and stability. Fluid mechanics helps us understand how blood flow, shear stress, and vessel geometry interact to influence clot formation, growth, and detachment. By applying computational models and simulations, we can examine how these factors contribute to both normal hemostasis and pathological conditions such as thrombosis.

The role of shear forces is particularly crucial, as they dictate platelet aggregation and fibrin clot formation in response to vascular injury. For instance, areas of low shear stress, such as in veins or an eurysms, are more prone to excessive clotting, while high shear stress regions, like arteries, can suppress clot formation despite the presence of activated platelets. Furthermore, understanding how blood Viscosity, red blood cell dynamics, and flow turbulence affect clot growth and stability can help identify targets for therapeutic interventions, such as anticoagulant drugs or thrombolytic therapies.
In clinical contexts, particularly with diseases like atherosclerosis, deep vein thrombosis, or hemophilia, fluid mechanics offers a framework for predicting and mitigating clot-related complications. By advancing our understanding of clot dynamics, we can improve the development of personalized treatment strategies, optimize surgical procedures, and design better therapeutic agents. Ultimately, integrating fluid mechanics in to the study of blood clot formation enhances our ability to prevent, manage, and treat clotting disorders more effectively, ensuring improved patient outcomes in various cardiovascular and hematological diseases.

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