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Research Article

Advancements in Blood Rheology and Hemodynamics Simulation with a Brief History

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Abstract

Blood rheology is a complex field of study that investigates blood flow behavior, vital for understanding its role in physiological and pathological conditions. This article delves into various rheological models that describe blood behavior, ranging from Generalized Newtonian models to more sophisticated thixotropic and elastoviscoplastic models. One such model, the Horner-Armstrong-Wagner-Beris (HAWB) model, offers valuable insights into the dynamic interplay of reversible and irreversible phenomena in blood flow. Recent advancements, such as the mHAWB framework, provide enhanced accuracy and versatility in modeling blood rheology, holding great potential for diagnostic and therapeutic applications. Moreover, microscopic and mesoscopic simulations have paved the way for deeper insights into blood behavior, bridging the gap between theory and experiment. Multiscale models offer a promising approach to capturing the complexities of blood rheology at various length scales. Finally, we explore the clinical implications of blood rheology, including its significance in conditions like polycythemia, neonatal respiratory distress, and circulatory inadequacy. By understanding blood rheology comprehensively, we can advance our knowledge of complex blood flow dynamics and its potential applications in healthcare.

Introduction

Red Blood Cells (RBCs), white Blood Cells (WBCs), and platelets are solid cellular components suspended within a liquid plasma, constituting an aqueous solution comprising proteins, chemical compounds, and minerals. Blood is a highly concentrated solution of platelets and blood cells, with RBCs being the predominant component, accounting for approximately 45% of the total blood volume. In contrast, WBCs, platelets, and other remaining particles constitute less than 1% of the total blood volume. The scientific field of "blood rheology" investigates blood's biophysical and flow characteristics. Among the well-established hemorheological parameters, blood viscosity holds significant importance. Factors such as plasma viscosity, hematocrit level, and the deformability and aggregating capacity of RBCs under specific hemodynamic conditions collectively influence blood viscosity.

The pioneering work of the French doctor Poiseuille [1] marks the first endeavor to apply fluid flow principles for understanding blood circulation. He formulated a fundamental equation describing the relationship between pressure gradient and flow in a cylindrical tube as follows:

$$Q = \frac{\Delta p.\pi.\gamma^4}{8L.\eta} \quad (1)$$

Here, Q represents the volumetric flow rate through a tube with a r radius, experiencing a pressure difference of P across its length L. The fluid viscosity is denoted as η. The derived law from Poiseuille's work highlights that vascular geometry primarily dictates blood flow resistance, often relegating the consideration of blood viscosity and other hemorheological parameters. Poiseuille's law has been extensively employed in numerous scientific and medical investigations, with ongoing research focusing on the crucial aspects of blood rheology within cardiovascular physiology.

Hemorheology Attributes

Blood exhibits many non-Newtonian rheological properties, including shear thinning, yield stress, and viscoelasticity. Additionally, blood possesses a distinctive thixotropic activity, as evidenced by the emergence of hysteresis loops across three shearing cycles [2]. These non-Newtonian characteristics have significant implications beyond flow patterns and fluid transportation [3], particularly in irregular lumen geometries such as stenosed arteries. The mechanical stress induced by these properties affects blood vessel walls and surrounding tissues, potentially leading to long-term lesions and the formation of sediments inside vessel walls.

The impact of non-Newtonian properties extends to other transport phenomena, including pulse wave propagation in arteries [4]. The presence and amplification of non-Newtonian effects are contingent on the deformation rate, often accentuated in low shear rate flow regimes. Shear and elongation represent two non-Newtonian effects influenced by the type of deformation [2]. Various scenarios, such as abnormal blood rheology, flow in stenosed arteries, and stent placement, can magnify the influence of non-Newtonian effects. Surprisingly, studies have shown that the non-Newtonian nature of blood can act as a regulatory mechanism, reducing flow resistance and wall shear stress as stenosis size increases, thereby aiding

the body's defense [5]. Specifically, shear thinning is crucial in facilitating blood flow through stenotic vessels. Blood predominantly exhibits shear-thinning behavior, with the most pronounced non-Newtonian effects observed under steady flow conditions. Shear thinning is persistent and evident at various biological flow rates, driven by the disaggregation of red blood cells under high shear rates.

The observed thixotropic behavior of blood arises from the disruption of organized blood cell aggregation due to shearing forces with increasing deformation time [6]. Moreover, the blood's microstructure is critical in generating other non-Newtonian processes. The viscoelastic properties of blood primarily originate from its corpuscular microstructure, with red blood cells playing a central role due to their remarkable elastic deformability and ability to form three-dimensional rouleaux formations. These viscoelastic characteristics are more pronounced at low shear rates, where aggregation is most evident, highlighting the non-Newtonian behavior of blood [7]. The pulsatile nature of blood flow further enhances or activates viscoelastic effects. When considering the impact of viscoelasticity on blood circulation, it is essential to account for the properties of blood vessels, porous tissue, and the blood itself. These viscoelastic effects are integral to blood circulation, influencing and being influenced by the overall circulation process. The interaction between blood, artery walls, and porous tissue is inevitable due to blood's viscoelastic nature [8].

Moreover, blood exhibits yield stress, although there is some disagreement. At low shear rates, red blood cells aggregate to form rouleaux microstructures, obstructing the flow and leading to the development of yield stress. Studies have shown a strong association between yield stress and the levels of fibrinogen protein, hematocrit, and blood plasma. Additionally, mineral concentration could be an essential additional parameter influencing yield stress. Fibrinogen levels significantly control or affect various blood rheological features, particularly the non-Newtonian properties [9]. When the hematocrit level falls below a specific threshold, the yield stress property of blood seems to diminish or become negligible. Yield stress may play a role in forming blood clots (thrombosis) and vascular obstructions in certain pathological conditions, such as strokes, as well as in the clotting process following injuries and during subsequent healing. However, numerous clinical and experimental studies indicate that the magnitude of yield stress is insignificant and, consequently, has no discernible impact on the flow profile (and thus the flow rate) in large and medium-sized blood arteries within the physiological flow ranges. Instead, yield stress is expected to have a more notable influence in tiny capillaries and other porous structures where flow occurs at extremely low shear rates. The magnitude and effect of yield stress could be exacerbated in certain disease states related to blood rheology, such as polycythemia vera, or structural abnormalities in blood vessels, like stenoses [10]. In such cases, the impact of yield stress on blood flow patterns could become more apparent and potentially contribute to pathological conditions characterized by abnormal blood flow and clot formation.

The intimate relationship between shear thinning and thixotropic behavior in the blood leads to its manifestation as a thixotropic fluid, as empirically verified by multiple investigations. Other non-Newtonian properties may also contribute to the observed thixotropic-like behavior, potentially explaining discrepancies regarding the thixotropic nature of blood. While thixotropy is a transient characteristic, its impacts on blood circulation can have long-term consequences due to the pulsatile nature of blood flow. Viscoelastic effects in blood follow a time-dependent pattern, with thixotropy becoming increasingly evident at slow shear rates over extended time scales. However, thixotropy seems to play a relatively minor role in blood flow compared to other non-Newtonian effects, such as shear thinning [11]. This could account for the limited number of studies focusing on this specific characteristic. It is important to note that the thixotropic behavior of blood exhibits significant sensitivity to blood composition, leading to variations between individuals and under different biological circumstances.

Predicting time-dependent effects in blood flow involves considering several factors, including thixotropic, viscoelastic, or other rheological properties. The pulsatility of blood flow and the rapid changes in deformation circumstances during the systolic-diastolic heart cycle are two significant factors. Additionally, the marked disparity in shear rates among arteries, capillaries, porous tissue, and venous segments of the circulatory system is another influential factor [12]. The irregular geometry of blood flow conduits, such as bends and converging-diverging formations, constitutes a third factor capable of triggering or amplifying time-dependent effects. The fourth factor is the variation in deformation rates between ventricular systole and diastole. The lower shear rates anticipated during diastole than systole may explain why certain studies have found non-Newtonian effects more pronounced. Many reported non-Newtonian rheological parameters and other physical characteristics of blood stem from in vitro measurements, which can introduce significant errors when attempting to infer in vivo values. Ambient conditions, experimental requirements, and procedures (e.g., additives to preserve and fluidize blood samples) can contribute to variations in reported parameters. Furthermore, the choice of measurement technique can significantly influence the reported values. The inherent variations and uncertainties are further compounded by individual differences and conditions, such as dietary intake before measurements, which are challenging to regulate or quantify. Consequently, careful consideration is necessary when using these values, particularly for in vivo and patient-specific modeling and research [13]. Acknowledging and accounting for these uncertainties is crucial for accurate and meaningful interpretations of blood rheological data and their clinical implications.

Methods

Literature search strategy

An extensive and systematic literature search was conducted to compile this state-of-the-art review on blood rheology with a brief history. A comprehensive collection of scholarly databases was utilized, including PubMed, IEEE Xplore, ScienceDirect, Google Scholar, and Web of Science. The search encompassed articles, research papers, and reviews from the earliest available records up to September 2023. A combination of keywords and controlled vocabulary terms related to blood rheology, rheological models, simulations, clinical implications, and relevant terminologies were employed. Boolean operators such as "AND" and "OR" were used to refine search queries, ensuring a broad yet pertinent selection of articles.

Selection criteria

Articles were included in this review based on their relevance to blood rheology, rheological models, and related computational simulations. Inclusion criteria encompassed peer-reviewed research papers, reviews, and scholarly articles. To maintain the review's integrity, non-English articles and those with insufficient methodological details were excluded.

Data extraction and synthesis

Extracted data consisted of information on blood rheology models, microscopic and mesoscopic simulations, multiscale modeling approaches, and clinical implications of blood rheology. Data was systematically organized, including model descriptions, simulation techniques, clinical findings, and relevant contextual information. A critical analysis of the selected literature was performed, categorizing studies based on the focus of their investigations.

Review framework

The gathered information was structured following a comprehensive framework. The review began with an introduction to blood rheology, followed by detailed sections discussing rheological models, simulation methodologies, clinical implications, and future perspectives.

Quality assessment

The quality of the selected literature was assessed by critically evaluating the rigor of research methods, data collection, analysis, and overall contribution to the field of blood rheology. This assessment aimed to ensure the inclusion of high-quality, scientifically sound research in the review.

Ethical considerations

Ethical standards and guidelines for academic research and publication were followed throughout the review process. Proper citation and attribution of original authors were ensured.

Historical Background

Fishman and Richards and their colleagues presented a comprehensive history of the theories that have shaped our understanding of blood circulation [14]. The roots of this understanding can be traced back to ancient civilizations, where early insights into the peripheral pulse and the rhythmic movement of the heart were documented as early as 3000 B.C., as depicted in hieroglyphics. The Greeks and Romans also contributed significantly to the knowledge of cardiovascular anatomy. Historical records suggest

that they thoroughly understood the heart and major blood vessels. The Roman literature, for instance, indicated an awareness of the heart's valves, recognizing their role in facilitating one-directional flow. However, the concept of blood circulating within a closed circuit was yet to be established at that time. Instead, the prevailing belief was that blood moved in waves akin to the motion of the ocean. The Greek physician Galen (131-201 A.D.) harnessed the knowledge of the pulse as a valuable indicator of the patient's health condition. His observations and insights into the significance of the pulse contributed to the early understanding of blood circulation in ancient medicine. Throughout history, these early observations and concepts paved the way for developing more sophisticated theories and scientific investigations, eventually leading to our modern understanding of blood circulation and cardiovascular physiology. Fishman and Richards' work provides a historical account of the gradual evolution of these ideas, highlighting the invaluable contributions made by ancient civilizations in unraveling the mysteries of blood circulation (Figure 1).

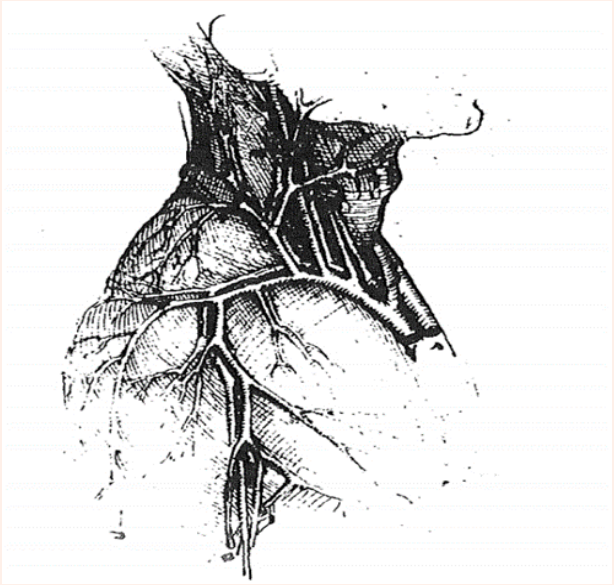

Figure 1: Illustration of great vessels at the root of neck by Leonardo da Vinci [14].

Erasistratos, dating back to 280B.C., observed that the pulse appeared later in arteries farther from the heart, providing an early indication of the pulse as a wave propagation phenomenon. However, this insight did not lead to a comprehensive understanding of circulation, as it did not consider the concept of blood circulation as a closed circuit. During the Renaissance, anatomical studies marked the emergence of the scientific method, yet knowledge of circulation remained somewhat comparable to that of ancient Greeks and Romans during the Middle Ages. Leonardo da Vinci (1452-1519) was an exceptional observer who integrated structural study with functional research. Through detailed illustrations and annotations on the circulatory system, he correctly described auricular and ventricular contractions, the arterial pulse wave, and even mentioned atherosclerosis (thickening of artery walls with aging). Although his work was influenced by ancient theories, including the notion of blood moving in an ebb and flow pattern, it significantly contributed to understanding cardiovascular physiology.

William Harvey (1578-1658), an English physician, established the modern understanding of blood circulation. His pioneering work, based on numerical measurements and deductions, represented a paradigm shift in observation and reasoning. Another significant event was minister Stephen Hales (1677-1761) taking the first blood pressure reading. Hales conducted quantitative measurements of artery diameters, flow velocities, and heart output, and he emphasized the role of diastolic contraction in directing stroke volume through the small vessels of circulation after partial storage in major arteries. However, their quantitative work focused more on geometric and kinematic characteristics and did not incorporate calculations now considered part of solid or fluid mechanics [15,16].

In 1775, Leonhard Euler published the first mathematical study on blood flow, introducing the equations for the inviscid flow of an incompressible fluid in an elastic tube, known today as the one-dimensional equations. Euler also proposed a nonlinear relationship between the cross-sectional area of a blood artery and its pressure at every point inside. Although Euler couldn't solve the equations then, he acknowledged that the heart could be likened to a positive displacement pump and provided a reasonably thorough explanation of the governing equations for blood flow in arteries [17]. Thomas Young, a physician, and natural philosopher, is known for Young's modulus and was the first to derive the pulse wave's propagation speed in blood flow in 1809. He formulated his equation by comparing sound propagation in elastic solids and compressible fluids. Overall, the historical journey of understanding blood circulation involved brilliant minds and their contributions to the gradual evolution of scientific knowledge in this field. Thomas Young significantly contributed to our understanding of blood flow and fluid mechanics. He emphasized the role of elastic stress in the tube wall, which produces pressure in the fluid similar to the stress in a compressed solid or gas in the case of an incompressible fluid enclosed in the tube. Young's formula, in contemporary notation, is expressed as:

$$C_o = \left(\frac{h.E}{2a.p}\right)^{\frac{1}{2}} \quad (2)$$

Here, h represents the thickness of the tube wall, E is Young's modulus of the tube material, a is the tube radius, and p is the fluid density. Young applied this formula to blood flow in arteries [18]. Young also calculated the pressure decrease resulting from viscous losses in various arterial segments. Although his calculations were not as precise as later work by Poiseuille, Young provided reasonably accurate estimations. For instance, he projected that the pressure would only be approximately 2 inches of water lower in arterioles (with a diameter similar to a human hair) compared to the main arteries. Young's experiments involved measuring blood pressure in the arteries of a mare, with the data used to estimate blood viscosity to be around four times higher than that of water. The currently accepted standard value for blood viscosity is about 3.5. [1,18]. Moving forward in history, Marcello Malpighi and his colleagues observed capillary blood vessels firsthand in 1961, about three decades after William Harvey proposed the existence of "porosities of the flesh" through which blood must travel from arteries to veins. Furthermore, in 1688, A. van Leeuwenhoek witnessed individual red blood cells flowing single file in the tiniest veins of a living tadpole's tail. His observations depicted red blood cells as tiny globules filling the capillary lumen and separated by gaps filled with clear plasma [16,19,20].

In the early 19th century, researchers such as Young et al. [18] estimated the diameter of red blood cells within the generally recognized range of 7.1 to 8.5μm. This period marked the qualitative and somewhat limited statistical understanding of the circulatory system's main anatomical characteristics, flow rates, pressures, wave propagation, and viscous loss phenomena. During the late 19th century, several researchers, including Moens and Korteweg et al. [21] in 1878, and Lamb et al. in 1898, rederived the equation for pulse wave velocity (equation 1) in different ways. More comprehensive research was also conducted on viscous pressure drops in blood arteries. Poiseuille accurately measured pressure drops using water, alcohol, and mercury in glass tubes in 1840. His results were expressed in equations (3) and (4), now known as Poiseuille's law, which quantitatively describes tube viscous flow [21,22]. The understanding of viscous effects in blood flow stagnated after Poiseuille's law was derived [23]. It wasn't until 1929 and 1931 that Fahraeus and Lindqvist et al. [24] made a significant discovery, demonstrating that blood's apparent viscosity decreases as the tube diameter drops from 500 to 40μm. This effect can be attributed to the tube's lower hematocrit than the feeding reservoir, as demonstrated by Fahraeus. Additionally, a slight movement of red blood cells away from the artery wall is linked to decreased hematocrit. This effect is now known as the Fahraeus-Lindqvist effect and has been confirmed by other investigators [23,24].

Advancements in the understanding of wave propagation in the circulatory system were initiated in the 1950s by McDonald and Womersley, who utilized linearized solutions. Nonlinear theories were revisited by Lambert et al. in 1958 [25]. Over the past 25 years, significant progress has been made in analyzing and understanding blood flow, particularly in typical physiology. However, there is a need to apply these developments to specific pathologies, diagnostic methods, and surgical procedures. This necessitates closer collaboration between mechanically skilled engineers and medical professionals dealing with common medical issues.

Recent advances in Blood Rheology

Experimental methods

Blood's material characteristics have been extensively studied using rheometry, both historically and in modern research. In 1959, industrial rheologist Scott Blair and colleagues employed the Casson model to characterize flow curves obtained from human and animal capillary data The Casson model is described by equation (3),

$$\sigma_{12}^{\frac{1}{2}} = \sigma_{y,c}^{\frac{1}{2}} + (\eta_\infty \gamma)^2 \quad (3)$$

where σ_{12} represents the shear component of stress, $\sigma y,c$ is the Casson model yield stress, γ is the shear rate, and $\eta\infty$ is the corresponding viscosity. These early investigations into steady shear flow already identified the complex nature of blood rheology, with manifestations of yielding and shear thinning. They also suggested a more comprehensive rheological characterization of blood's dynamic behavior, considering the pulsatile nature of natural blood circulation in the arterial system [12,26]. Evaluating blood rheology accurately and consistently, especially at low shear rates, is challenging due to its "living" character, interface interactions, coagulation propensity, and the wall, as mentioned above, cell-free layer. To optimize dimension area and vertical length while minimizing free surface area and pattern quantity, the double-wall concentric cylinder is now the preferred geometry for general shear rheometry. Using titanium and stainless-steel cells ensures proper cleaning and minimal interaction with plasma proteins.

Researchers employ various techniques to remove memory effects during rheological measurements, including using a solvent lure, temperature control, and appropriate preconditioning strategies (such as shearing at mild to high shear rates for 30-60 seconds). Introducing an anticoagulant, preferably EDTA, during blood withdrawal is necessary unless the focus of observation is specifically on blood coagulation. Blood samples are used for various examinations, with routine shear being the most common. Additional measurements have been published in the literature, employing different transient deformation methods, such as Small Amplitude Oscillatory Shear (SAOS), triangular ramp, Large Amplitude Oscillatory Shear (LAOS), step shear change, and Unidirectional Large Amplitude Oscillatory Shear (UD-LAOS) experiments [27]. The UD-LAOS model was specifically developed to accurately capture the kinematics of pulsatile blood flow in arteries. It is critical to conduct blood rheological measurements promptly after withdrawal, as biological changes like ATP deficiency and physical changes, such as protein adsorption to interfaces, can occur in as little as 4 hours. Moreover, cooling blood between acquisition and measurement can result in a hysteretic effect that persists even after the blood is reheated to body temperature [28]. These considerations underscore the importance of careful experimental design and handling of blood samples to obtain accurate and reliable rheological data. To validate computer-assisted measures of vessel diameter, red cell velocity, and hemoglobin saturation, as well as to demonstrate the effect of muscle activation on blood flow and O_2 consumption, preliminary studies were conducted. Due to their substantial size and steady diameter during muscle tension, venules were selected for these preliminary studies conducted by Robert et al. (1998) before, during, and after twitch stimulations [29,30].

Measuring the non-shear parts of the stress tensor for blood is generally more challenging. Past attempts to determine the typical stress under shear flow for a cone and plate apparatus were unsuccessful [31,32]. Therefore, probing the additional stress components under extensional flow is simpler. For this purpose, a microfluidic hyperbolic contraction or a CaBER (Constant Area Birefringence) approach can be employed. In the hyperbolic contraction method, a high-speed camera measures the sample diameter as the sample is uniaxially stretched between two plates. However, interfacial effects can influence these measurements, leading some researchers to suggest submerging the sample in an oil solution. The Fåhræus effect and the high volume fraction of Red Blood Cells (RBCs) make it more challenging to carry out these tests on whole blood. However, they have been successfully employed for analog and diluted blood solutions [33].

Microfluidics has also been utilized for measuring blood viscosity. Various configurations, such as droplet-based devices, gravity-driven flow in a rectangle shape, flow via a slit device, and devices with multiple capillaries arranged in parallel, have been proposed in the literature [34]. While these instruments can measure blood viscosity with very little blood, their main limitation is often the inability to achieve low shear rates. Additionally, interfacial effects can significantly impact the data if free surfaces are present. For dynamic blood measurements, spatial velocity measurements can be acquired using different techniques under both in vivo flow conditions and in vitro methods, such as bulk rheology or microchannel flow. Particle image velocimetry (PIV) and Particle Tracking Velocimetry (PTV) are commonly used. These techniques involve employing a high-speed camera to track particles scattered throughout the blood and then utilizing a computer program to gather velocity data and particle paths. However, standard tracer particles for blood tend to agglomerate, leading to inaccurate measurements. Blood's opaqueness and heterogeneity also pose challenges for investigations using single-particle tracking passive micro-rheology to detect the dynamic moduli values related to the linear viscoelasticity of blood [35]. One approach to overcome these challenges is to track individual red blood cells (RBCs), which often requires sample dilution. Nonetheless, combining various techniques makes it possible to obtain spatial velocity measurements in dynamic blood flow, which is essential for understanding blood behavior under different flow conditions and in different experimental setups.

In the study conducted by Lima et al. [36] in 2009, a portion of Red Blood Cells (RBCs) was subjected to fluorescent labeling to enhance their tracking capabilities. Another approach involved the creation of hydrophobic PEGylated particles to prevent agglomeration, achieved by coating regular tracer particles with Polyethylene Glycol (PEG). In addition to Particle Image Velocimetry (PIV) and Particle Tracking Velocimetry (PTV), Magnetic Resonance Microscopy (MRM) and Laser Doppler Velocimetry (LDV) measurements were employed as alternatives to track blood velocity [36]. Furthermore, significant advancements have been made in the field of microscopic simulations of blood, particularly in the study conducted by Jamali et al. [37] in 2021. These simulations can greatly enhance the analysis and interpretation of microfluidic observations related to blood flow behavior [37].

Models in Blood Rheology

Constitutive blood modeling

The scientific recognition of blood rheology's non-Newtonian character dates back more than a century, running parallel to the development of rheology as a science. However, until the early 2000s, many blood flow simulations conveniently assumed Newtonian behavior. In fluid mechanics, the continuum hypothesis, based on conservation principles, simplifies the representation of matter as a continuum of macroscopic quantities like density, velocity, and temperature, effectively averaging out microscopic details. This simplification allows the enforcement of conservation principles but disregards microscopic fluctuations [38]. Nevertheless, subsequent research has shown that even at high shear rates, where non-Newtonian effects might be expected to be minimal, significant non-Newtonian behavior is observed in blood flow [39]. Blood rheology exhibits four non-Newtonian characteristics: Shear thinning, yield stress, thixotropy, and viscoelasticity. The first two characteristics, shear thinning and yield stress, can be described using various generalized non-Newtonian equations, with the Casson model being historically significant for describing blood viscosity [40]. The Casson model captures the square root dependence of shear stress on shear rate, and its parameters have been extensively studied for their dependence on important physiological factors like hematocrit and fibrinogen concentration.

In its natural form, the Casson model yields the expression for the equivalent generalized shear viscosity ((γ)) as a function of shear rate. Advances in research have thus highlighted the importance of considering non-Newtonian effects in blood rheology, even in scenarios with high shear rates. Understanding the interplay between non-Newtonian properties and physiological factors can lead to more accurate blood flow simulations and models, with potential implications for diagnostics and medical treatments.

$$\eta(\gamma) = \left\{ \left[\frac{(\sigma_{y,c})}{[\gamma]} \right]^{\frac{1}{2}} + [\eta_\infty]^{\frac{1}{2}} \right\}^2 \quad (4)\eta(\gamma) = \left\{ \left[\frac{(\sigma_{y,c})}{[\gamma]} \right]^{\frac{1}{2}} + [\eta_\infty]^{\frac{1}{2}} \right\}^2 \quad (4)$$

In computational simulations, approximations are often necessary to handle complex models like the Casson model for blood rheology. The Casson model's attractiveness lies in the availability of several expressions that correlate its parameters with physiological factors, notably the pioneering work by E. W. Merrill et al. [40]. One of the most comprehensive parameterizations of the Casson model was developed by Apostolidis and Beris, which links the model's viscosity and yield stress to the hematocrit (H), fibrinogen concentration (cf), and temperature (T):

$$\frac{\eta_\infty}{\eta_p} = (1 + 2.07H + 3.72H^2)^{-7.03\left(1-\frac{T_0}{T}\right)} \quad (5)$$

$$\sigma_{y,c} = \begin{cases} (H - H_c)^2(0.508c_f + 0.452)^2, & H > H_c \\ 0, & H \le H_c \end{cases} \quad (6)$$

$$\sigma_{y,c} = \begin{cases} 0.313c_f^2 - 0.468c_f + 0.176 & c_f > 0.75 \\ 0.0012, & c_f > 0.75' \end{cases} \quad (7)$$

In this model, T_0 represents the reference temperature at which the plasma viscosity is measured, and H_c is the critical hematocrit. The hematocrit is expressed as a fraction between 0 and 1. It is important to acknowledge that certain constants in the model have been rounded to three significant digits. Moreover, the yield stress is measured in dyn/cm², fibrinogen concentration in g/dL, and temperature in Kelvin (K).

Recent advancements in blood rheology have made efforts to incorporate the effects of cholesterol and triglyceride levels into the Casson model. These developments build upon early experimental investigations conducted by Moreno and coworkers. A notable application of this parametrized model, with consideration of the local hematocrit, has been its integration with a widely used stress migration model. This combination can accurately represent hematocrit margination in continuum simulations of blood flow through microvascular bifurcations. Impressively, these simulations have shown a remarkable level of agreement with microscopic simulations, underscoring the model's ability to capture the intricate dynamics of blood flow. The successful application of this improved model in understanding blood flow behavior further reinforces its potential as a valuable tool for studying blood rheology in both healthy and pathological conditions [41]. Prior to the parametrization described above, a significant obstacle in blood rheology research was the limited availability of well-characterized data and a standardized experimental protocol. However, a significant breakthrough was achieved by Horner et al. in 2018, who validated a data collection protocol and expanded it to encompass both steady and transient shear experimental procedures. This advancement resulted in a comprehensive and well-documented experimental data set for human and animal blood samples.

The availability of such data not only deepened our understanding of non-Newtonian blood rheology in transient flows, a phenomenon that cannot be adequately captured by inelastic, generalized Newtonian approaches but also led to essential adjustments in predictions made by the Casson model and the square root law, even in terms of steady-state shear viscosity. The improved predictive capability of the model demonstrates its potential to enhance our comprehension of the intricate dynamics of blood flow, offering valuable insights into both physiological and pathological conditions. It is important to acknowledge previous significant research in this field, where researchers adopted a viscoelastic modeling approach utilizing models like Giesekus, Phan-Thein, Tanner, and thermodynamically based models developed by Raja Gopal and colleagues. However, to achieve a more comprehensive understanding, further efforts may be required to establish correlations between model parameters and additional blood physiochemistry beyond the explored factors such as hematocrit, fibrinogen, and cholesterol levels. Consideration of other factors like blood type, oxygenation levels, age, and various pathological conditions could also be crucial in enhancing the model's predictive capabilities.

The pace of research in this area is rapidly advancing, underscoring the emerging significance of blood rheology as a diagnostic tool. Although the current modeling primarily focuses on physiologically healthy conditions, it establishes a critical baseline for potential future applications of hemorheology as a diagnostic resource. As research continues to evolve, the potential for blood rheology to provide valuable insights into various medical conditions and aid in diagnostics becomes increasingly promising (refer to Figure 2).

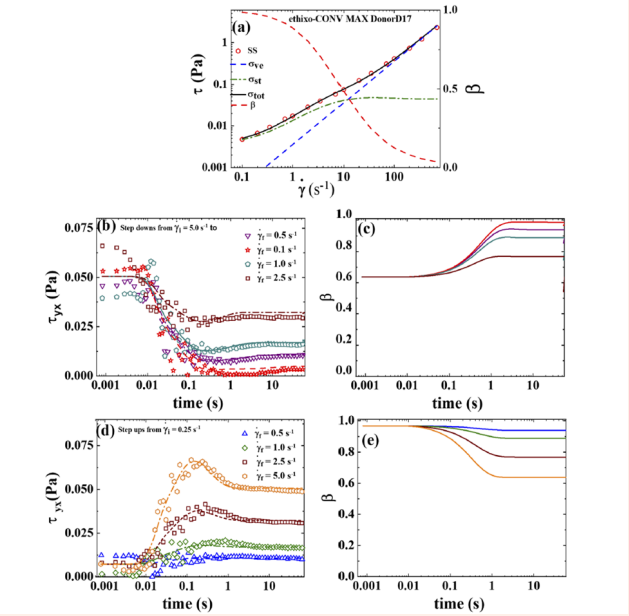

Figure 2: Ethixo-convected Maxwell model fit for (a) steady state human blood data; (b) set of four step-downs in the shear rate from ˙γ= 5.0 s–1 to 0.1 s–1, 0.5 s–1, 1.0 s–1, and 2.5 s–1; (c) corresponding structure parameter curves (colors of structure parameter curves match their respective colors from stress evolution curves); (d) step-up in the shear rate from ˙γ=0.25 s–1 to 0.5 s–1, 1 s–1, 2.5 s–1, and 5 s–1; and € corresponding structure parameter curves (donor 1) (dataset 1). Reproduced from Tussing 2020 [42].

Thixotropic/elastoviscoplastic models for blood

Generalized Newtonian models are computationally inexpensive to implement but cannot predict accurately transient (thixotropic/hysteretic) changes in the viscosity which are relevant as blood flows naturally under pulsatile conditions. A viscoelastic model can be used to better account for the transient effects. One example of this is the Anand-Kwack-Masud (AKM) model which is a generalization of the Oldroyd-B model.

One of the most successful thixotropic models for blood is the Horner-Armstrong-Wagner-Beris (HAWB) model52 which uses this approach to describe the rouleaux contribution to the shear stress σR,12 as:

$$\sigma_{R,12} = \lambda^3 \eta_R \dot{\gamma}_p + \lambda G_e \gamma_e \quad (8)$$

$$\frac{d\lambda}{dt} = \frac{1}{\tau_\lambda}\left[(1-\lambda) + (1-\lambda)\tau_\alpha|\dot{\gamma}_p| - \lambda(\tau_b|\dot{\gamma}_p|)^2\right] \quad (9)$$

where λ represents the level of microstructure (rouleaux formation) from [0,1], where 0 represents absence of structure, i.e., full individual RBCs, and 1 fully formed rouleaux, $\lambda 3$ represents the best (for the HAWB) power-law dependence of the rouleaux to an effective viscosity with $\eta\eta RR$ as the viscosity of fully formed rouleaux, GR is the yield stress modulus, γe is the elastic strain, $\tau\lambda$, $\tau\tau aa$, τb are three characteristic times for Brownian aggregation, shear-induced aggregation and shearinduced breakage, respectively, and γp˙ is the plastic strain rate. In the context of the HAWB (Hemodynamic-Aware Wall-Bounded) model, the strain and strain

rate are decomposed into plastic and elastic components, denoted as $\gamma tot=\gamma e+\gamma p$ and $\dot{\gamma} tot=\dot{\gamma} e+\dot{\gamma} p$, respectively. This decomposition follows the principles of the kinematic hardening theory of plasticity and was first introduced by Dimitriou in 2019. Subsequently, it was further refined by Apostolidis et al. in 2015 and Horner et al. in 2020.

The elastic component (γe) in this modeling paradigm characterizes reversible processes, representing deformations that can be fully recovered once the applied stress is removed. On the other hand, the plastic component (γp) is integrated into the model to capture irreversible processes, specifically related to the aggregation and disaggregation of rouleaux formations. The HAWB model, with its decomposition of strain and strain rate into plastic and elastic components, enables a more comprehensive understanding of blood flow dynamics, particularly in the context of complex rheological behaviors. By incorporating both reversible and irreversible phenomena, this model holds promise for exploring blood flow dynamics under diverse conditions and gaining insights into the hemorheological characteristics of blood in various physiological and pathological contexts.

The final equations of the HAWB model, which describe the evolution of the elastic strain rate, are as follows:

$$\dot{\gamma}_e = \begin{cases} \dot{\gamma}_p - \frac{\gamma_e}{\gamma_{\max}}|\dot{\gamma}_p|, & \frac{d\gamma\max}{dt} \geq 0 \\ \dot{\gamma}p - \frac{\gamma e}{\gamma_{\max}}|\dot{\gamma}_p| + \frac{\gamma_e}{\gamma_{\max}}\frac{d\gamma_{\max}}{dt} & \frac{d\gamma\max}{dt} < 0 \end{cases} \quad (9)$$

in which the maximum elastic strain sustained by the rouleaux, γ_{max}, is defined

$$\gamma_{\max} = \dot{\gamma}.R\lambda \quad (11)$$

The specific plastic component of the rate of strain on the rouleaux can be evaluated by

$$\dot{\gamma}_p = \begin{cases} \frac{\dot{\gamma}}{2-\frac{\gamma_e}{\gamma_{\max}}}, & \dot{\gamma} \geq 0 \\ \frac{\dot{\gamma}}{2+\frac{\gamma_e}{\gamma_{\max}}} & \dot{\gamma} < 0 \end{cases} \quad (12)$$

Additional considerations beyond the rouleaux stress contribution have been made to enhance the accuracy of the blood rheology model, especially at higher shear rates. These considerations involve including a separate contribution to the stress tensor (σc) resulting from the individual red blood cells and the plasma. In the original HAWB model, this contribution was introduced as a viscoelastic stress, which was defined through an extended White-Metzner model

$$a_c + \left\{\frac{[\eta_c(a_c)]}{G_c}\right\} a_c \Delta = \eta_c(a_c)\gamma \quad (13)$$

where η_c is so defined as a function of the primary invariant of the stress tensor σ_1, C, in this kind of way as to reduce to Cross viscosity healthy of the shear thinning behavior because of man or woman RBCs for hardened RBCs. The authentic HAWB, and its subsequent adjustments are the best fashions with the ability to unify viscoelasticity and thixotropy, which changed into shown to be vital whilst modeling temporary blood rheology. A evaluation of the original HAWB version, the AKM model, and the Apostolidis-Armstrong-Beris (AAB) model101 is proven for human blood under Unidirectional Large Amplitude Oscillatory Shear (UD-LAOS) conditions.

Despite the success of the original HAWB model, several limitations were identified, prompting researchers to make subsequent modifications to address these issues. One notable improvement was the development of the mHAWB framework by Horner et al. in 2019. This framework introduced a reduced λ evolution equation without shear-induced aggregation and with a modified shear-induced breakage. The non-dimensional structure parameter, λ, evolves according to a kinetic rate equation:

$$\frac{d\lambda}{dt} = \frac{1}{t_\lambda}(1-\lambda) - \lambda_t|\lambda| \quad (14)$$

Furthermore, Armstrong and his colleagues extended this modeling framework to encompass the Oldroyd-8 and Giesekus families of viscoelastic equations, showcasing its remarkable versatility. By incorporating the structural contributions from the rouleaux, they linearly combined them with the contributions from each of the Oldroyd-8 models, resulting in stress predictions along various directions, including xx, yy, zz, and yy [42]. This enhanced modeling approach has yielded valuable insights into the complex dynamics of blood flow, paving the way for advanced investigations in hemorheology and potential applications in diagnostics and medical treatments.

In addition, Armstrong and his coworkers performed extensive testing on various variants of the AAB model, introducing additional terms to more accurately describe the physics of the structural evolution equation. They also incorporated a structural contribution to total stress, including a variant that involved a viscoelastic time constant specifically for the contribution to total stress arising from the rouleaux [42]. Furthermore, Armstrong and colleagues explored other thixotropic model frameworks proposed by Wei et al. [43,44], building upon the original work by Oldroyd and Saramito, which included elastic pre-yield viscoplastic behavior within a combined tensorial viscoelastic framework. These frameworks draw heavily on the foundational work by Dimitriou et al. [45] and theories of plasticity and yielding [42,45]. In both of these works, the viscoelastic contribution to total stress from the plasma and individual red blood cells, a critical aspect of the mHAWB construct, was not considered.

The extension of the modeling framework to encompass the Oldroyd-8 and Giesekus families of viscoelastic equations highlights its robustness in addressing a broader range of blood flow dynamics. By skillfully combining the structural contributions from the rouleaux with those from each model, this framework allows for stress predictions in multiple directions, offering comprehensive insights into the intricate rheological behavior of blood. This enriched modeling approach holds tremendous potential for advancing our understanding of hemorheology and its possible applications in diagnostics and medical treatments. It provides a solid foundation for gaining valuable insights into complex blood flow dynamics, unlocking new avenues for cutting-edge research in this field [42].

$$\frac{D}{Dt}\frac{1}{G_R\lambda}\sigma_{R,12} + \max\left(0, \frac{\left|\sigma_{R,12} - \left(\frac{\sigma_{y,0}}{\gamma_{0,R}}\right)\right|}{\eta R\lambda^m}\right) sign(\sigma_{R,12}) = \dot{\gamma} \quad (15)$$

In light of the recent advancements in the mHAWB model, three noteworthy extensions have emerged, focusing on modifications to the modeling of the rouleaux contribution to stress while retaining the modeling of the viscoelastic contribution of RBC deformation and plasma as provided by the equation. The first extension, introduces the Enhanced Structural Stress Thixo-Viscoplastic Model (ESSTV) [46]. In this model, the total rouleaux contribution to stress is described using a thixo-viscoplastic approach, taking into account the history-dependent structural evolution equation of the mHAWB model.

Second, this equation has been extended into a full tensorial description, t-ESSTV, as

$$\frac{D}{Dt}\frac{1}{G_R\lambda}\sigma_R + \max\left(0, \frac{\left|\sigma_R - \left(\frac{\sigma_{y,0}}{\gamma_{0,R}}\right)\gamma_e\right|}{\eta R\lambda^m}\right) sign(\sigma_R) = \dot{\gamma} \quad (16)$$

Furthermore, in the mHAWB model, the original viscoelastic rouleaux contribution, referred to as the extended Thixo-Viscoelastic Model (ETV), has undergone further development by adopting a tensorial representation, giving rise to the t-ETV model. Notably, this advancement has facilitated the formulation of a fully thermodynamically compatible framework, incorporating an internal conformation tensor **C**, which evolves according to rigorous thermodynamic principles. Looking towards the future, the completion of the full tensorial description of constitutive modeling remains a challenge. This includes developing an evolution equation for the structural parameter that is fully compatible with non-equilibrium thermodynamics and applicable to various types of flows beyond just shear flow. Additionally, a more direct connection to the evolving microstructure is desirable, and efforts towards that goal are described in a subsequent section of this review. It is important to note that the comprehensive models developed for human blood can also be adapted for use with popular animal blood. Efforts in this direction and some early experimental findings in the context of animal blood are discussed in a subsequent segment of this review.

Finally, the complexity of blood should not be underestimated, as it involves a few factors considered as parameters in current models (e.g., hematocrit) and numerous others. Various pathological factors, nutrition, stress (cytokines), age, sex, blood type, and gases are important in different scenarios. Consequently, model parameters need careful adjustment to account for each specific case. Our own data pattern dependencies have already demonstrated this, and broader samples beyond healthy individuals are expected to enhance parameter adjustment further. Therefore, the importance of experiments and personalized measurements cannot be understated [42].

Microscopic/mesoscopic models of blood

In reality, the inherent complexity of blood can only be accurately captured through microscopic modeling. Blood constitutes a concentrated suspension of deformable, elastic, and aggregating Red Blood Cells (RBCs), alongside other components like platelets, White Blood Cells (WBCs), and various proteins [47,48]. The interactions between these components result in a highly intricate structure, giving rise to blood's complex rheological behavior. This behavior is characterized not only by non-zero yield stress and shear thinning but also by pronounced history effects, such as thixotropy, as discussed earlier. Several attempts have been made to reconstruct the non-Newtonian characteristics of blood using micromechanical models based on first principles. However, due to the complex and poorly understood biological interactions among the constituents, a complete a priori construction of blood rheology remains challenging. Thus, adjustable parameters are still necessary to describe RBC behavior, not only at the macroscopic level but also at the microscopic and mesoscopic levels.

Nevertheless, microscopic and mesoscopic simulations have proven valuable in resolving important flow details. For instance, detailed Dissipative Particle Dynamics (DPD) simulations can predict steady shear viscosity by accounting for RBC aggregation or exclusion, aligning closely with experimental observations of Chien et al. [3,42,49]. Recent simulations have advanced significantly, incorporating factors like fibrinogen to model the aggregation process and even accounting for effects of pathological conditions such as type 2 diabetes mellitus and hyperviscosity based on cell interactions, cell stiffness, and hematocrit. These models have played a crucial role in studying blood hemostasis and thrombosis, with a special focus on the part of platelets and their shear-dependent adhesive dynamics coupled with thrombin formation. Microscopic blood flow simulations offer several advantages. First, they provide theoretical insights into the flow inhomogeneities caused by finite particle sizes, elastic properties, interparticle interaction forces (leading to aggregation), wall exclusion, and hydrodynamic force effects. Second, they generate essential detailed information for constructing and validating coarser-scale models. Third, these simulations hold the potential for connecting to the underlying biology, such as understanding special effects like thrombosis and flow in tiny capillaries involving nanoparticles and inhomogeneous effects. The valuable insights gained from these detailed calculations are indispensable and become particularly essential when modeling specific effects or complex flow scenarios in biologically relevant conditions (Figure 3).

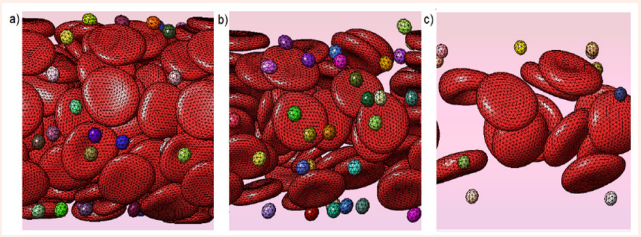

Figure 3: Snapshots of numerical simulations of blood ow with erythrocytes and platelets in the cylindrical channel for three different values of Ht: a) 40%, b) 20%, c) 10%. Blood plasma is modelled with the DPD method. It occupies the remaining volume of the channel (not shown). Reproduced from Bessonov et al. [50].

Multiscale models

Multiscale modeling aims to bridge the gap between nanoscale, mesoscale, and macroscale dynamics while retaining relevant information at small length scales. Systems like blood, which involve a concentrated suspension of deformable Red Blood Cells (RBCs) and numerous other components with strong interactions, exhibit a high degree of complexity, making a multiscale approach particularly advantageous. The choice of a multiscale modeling approach depends on factors such as flow regime, geometry, and available computational resources. One can either couple flow descriptions at multiple length scales to resolve flow-induced inhomogeneities or opt to coarse-grain some aspects of flow physics, reducing computational requirements at the expense of accuracy and microscopic consistency. Substantial progress has been made in increasing the efficiency of multiscale numerical simulations by utilizing Graphic Processing Units (GPU) hardware and parallel Message Passing (MPI) software advances in parallel computing. These advancements enable multiphysics solvers that address different lengths and timescales in a problem and exchange information during runtime. The problem is typically divided into continuum and discrete aspects, with larger blood vessels modeled as continuum (macroscopic) and regions with strong inhomogeneities (mesoscopic) or capillary flow (microscopic) treated as discrete domains. Perdikaris et al. (2016) outline key advancements in simulating blood through such multiphysics schemes in human arterial trees. Due to computational challenges in modeling membrane elasticity and vesicle dynamics for many interacting cells, hierarchical simulations embed smaller micro-level domains into the larger continuum domain and exchange information through overlapping patches. To mitigate error from the randomness of discrete particle-based methods like DPD, replicates can be performed to obtain more reliable data. Current multiphysics software can be linked to simulate physiological blood flow conditions in patient-specific vascular geometries. This hybrid approach has been utilized in research on microscale flow effects and physiological phenomena, such as brain aneurysms, clot formation, and thrombus formation. In simulating the vasculature, it is important to consider the interaction of blood and its components with the elastic walls of blood vessels, necessitating fluid-structure interaction in the flow modeling).

Jariwala et al. [51] proposed a similar approach using a Population Balance Model (PBM) to account for the effect of rouleaux structure formation in blood. This model assumes that red blood cells form low-dimensional self-similar fractal structures, introducing kinetics scaling based on colloidal physics to reduce empirical aspects in determining aggregation-disaggregation behavior. The model assumes spherical symmetry in rouleaux and uses the volume fraction of red blood cells as a metric for structure formation, establishing a connection to the blood hematocrit. By adopting a Smoluchowski kernel for aggregation kinetics, the model captures size-dependent aggregation behavior influenced by Brownian motion and shear. Additionally, the physically-based PBM within a colloidal framework allows for the rational inclusion of more physical phenomena affecting RBC interactions without relying on empirical approaches. This model represents a promising pathway towards a more comprehensive and physically grounded understanding of blood rheology [51].

Clinical Implications

An elevated blood viscosity has been associated with various conditions such as polycythemia, hyperlipemia, and hyperfibrinogenemia and has been implicated in disorders like hypertensive vascular disease, myocardial infarctions, Raynaud's disease, and Waldenstrom's macroglobulinemia [29]. Extensive studies by Gelin et al. [52,53] demonstrated that intravascular red cell aggregation and blood viscosity increase following different types of trauma. These changes were linked to decreased tissue blood flow and were implicated in tissue damage after injury [52]. Gelin observed that the adverse rheological effects of trauma could be reversed by infusing low molecular weight dextran (LMWD, average molecular weight=40,000), a polysaccharide derived from the conversion of sucrose into dextrans by certain bacteria [53]. However, subsequent research showed that much of the data presented in support of the rheological benefits of LMWD were inadequately controlled for red cell and fibrinogen dilution. In experimental animals during hemorrhagic hypotension, the infusion of LMWD did not show any beneficial effects, hemodynamically or rheologically, apart from the effects of hemodilution [9].

Millikan et al. [54] reported a syndrome of intermittent carotid and vertebrobasilar insufficiency associated with polycythemia, which responded favorably to phlebotomy with a reduction in hematocrit. This observation corresponds to findings that a marked decrease in cerebral blood flow is associated with the high blood viscosity of polycythemia. Experimental polycythemia in puppies showed modifications in cerebral blood flow following the induction of polycythemia. These were secondary to decreased cardiac output and increased peripheral vascular resistance associated with the significantly increased blood viscosity [54]. Regarding neonatal respiratory distress, a high hematocrit is commonly associated with it, although Inall and colleagues' research suggests that this is not always the case.

Dramatic clinical improvement was reported in an infant with severe respiratory distress and a hematocrit of 78%. In this case, hemodilution was performed by

exchanging 5% dextrose and water for whole blood until the hematocrit was lowered to 45%. A similar case was observed in an infant with severe respiratory distress and congestive heart failure at the Children's Hospital of Boston. This child had a hematocrit of 82% and a plasma fibrinogen concentration of 985mg% (normal range: 200 to 300mg%). Plasma was exchanged for whole blood until the hematocrit reached 50%, and at this point, a significant clinical improvement was evident. The child was discharged from the hospital 10 days later without any signs of heart disease [29]. Improving peripheral circulation by reducing blood viscosity and yield stress through hemodilution and plasma fibrinogen reduction appears to be a promising treatment for patients with circulatory inadequacy. It can complement existing measures used to treat circulatory failure. Since the metabolic requirements of the heart, as assessed by myocardial oxygen consumption, are primarily influenced by the pressure load rather than the flow load, the reduction in peripheral resistance following hemodilution may reduce the metabolic demand of the myocardium and improve tissue perfusion during circulatory failure. Studies by Case et al. demonstrated that when left ventricular work is kept constant, increasing the hematocrit from 32% to 55% led to a significant decrease in left coronary blood flow from 193 to 83ml per minute. This reduction in flow was greater than the relative increase in oxygen-carrying capacity of the blood due to the higher hematocrit [29].

Discussion

Blood rheology, the study of how blood flows, is pivotal in understanding its behavior under diverse physiological and pathological conditions. This comprehensive analysis dives deep into the various rheological models used to characterize blood, encompassing conventional and advanced approaches. Beginning with a discussion on Generalized Newtonian models, we acknowledge their computational efficiency, yet emphasize their limitation in capturing transient viscosity changes - a crucial factor in pulsatile blood flow. Such limitations have led researchers to explore more sophisticated thixotropic and elastoviscoplastic models designed to better represent the dynamic nature of blood flow. One noteworthy model discussed is the Horner-Armstrong-Wagner-Beris (HAWB) model. It extends beyond traditional models by introducing a multi-component strain and strain rate decomposition approach. This innovative concept distinguishes between plastic and elastic components, enabling a more intricate comprehension of blood flow dynamics. Importantly, this approach aligns with the principles of kinematic hardening theory, lending further credibility to the HAWB model. The utilization of the HAWB model, along with its extensions, promises to unravel the complexity of blood flow under varying conditions. By capturing reversible and irreversible phenomena, it offers immense potential for exploring blood behavior in various physiological and pathological contexts. Beyond theoretical models, the article underscores the significance of microscopic and mesoscopic simulations in unveiling the finer intricacies of blood dynamics. These simulations delve into particle-level interactions, considering factors like RBC aggregation and exclusion. Their value extends to providing critical insights for building and validating coarser-scale models, facilitating a stronger bridge between theory and experimentation.

Multiscale modeling is an exceptional approach to addressing the inherent complexities in blood rheology. The article highlights that it can adapt to different flow regimes, geometries, and computational resources. Such flexibility allows researchers to either couple flow descriptions across multiple length scales for high fidelity or selectively simplify aspects of flow physics to conserve computational resources without compromising microscopic consistency. It is well understood that blood rheology is not confined to laboratories but significantly impacts healthcare. Elevated blood viscosity has been associated with various conditions, including polycythemia, hyperlipemia, and hyperfibrinogenemia. This knowledge underscores the importance of understanding blood rheology in a clinical context. Furthermore, the article presents compelling cases where interventions such as hemodilution have shown promise in improving peripheral circulation. The findings open the doors to innovative strategies for addressing circulatory inadequacy. Indeed, by unveiling the complexities of blood flow, this research has far-reaching implications for healthcare, diagnostics, and therapeutic interventions. It symbolizes the synergy between theoretical modeling, computational simulations, and practical healthcare applications. Understanding blood rheology at multiple scales enriches our comprehension of hemodynamics, enhancing our capacity to address physiological and pathological conditions related to blood flow. It stands as a testament to the continuous advancement of science in the service of human health and well-being.

Conclusion

The study of blood flow and its rheological properties has been a subject of continuous investigation and advancement. Blood's complex behavior, as a non-Newtonian fluid, involves various characteristics such as shear thinning, yield stress, viscoelasticity, and thixotropic behavior. These properties are crucial in understanding blood circulation and its implications on physiological and pathological processes. The historical perspective reveals a gradual evolution in our understanding of blood flow dynamics, from early observations by ancient civilizations to the groundbreaking work of researchers like William Harvey, who revolutionized the modern blood circulation. As technology advanced, the field of blood rheology witnessed significant developments in experimental techniques, computer simulations, and mathematical models. Rheometry has become crucial for characterizing blood's material properties, shedding light on its yielding behavior, shear-thinning nature, and dynamic viscoelasticity. Advanced measurement techniques, such as Particle Image Velocimetry (PIV) and Particle Tracking Velocimetry (PTV), have enabled the accurate tracking of blood velocity in both in vivo and in vitro settings, facilitating a deeper understanding of blood flow patterns and behavior.

Despite progress, challenges persist, mainly when dealing with blood's living nature, interactions with interfaces, and propensity to coagulate. Low shear rate measurements, in particular, have been difficult due to the need to minimize interfacial effects. Researchers have proposed innovative solutions, such as microfluidic hyperbolic contractions and single-particle tracking passive micro-rheology, to address these challenges and expand our knowledge of blood rheology. Looking ahead, interdisciplinary collaboration between mechanical engineers, biologists, and medical experts will be crucial to unravel further the complexities of blood flow and its implications on human health. The combination of experimental techniques, numerical simulations, and advanced modeling approaches provides valuable insights into blood circulation and its role in various physiological processes and diseases. Such advancements in blood rheology research will undoubtedly contribute to the development of more accurate diagnostic tools, improved medical treatments, and better patient outcomes in the future.

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