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Hyperviscosity syndromes; hemorheology for physicians and the use of microfluidic devices

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Abstract

Purpose of review—Hyperviscosity syndromes can lead to significant morbidity and mortality. Existing methods to measure microcirculatory rheology are not readily available and limited in relevance and accuracy at this level. In this review, we review selected hyperviscosity syndromes and the advancement of their knowledge using microfluidic platforms.

Recent findings—Viscosity changes drastically at the microvascular level as the physical properties of the cells themselves become the major determinants of resistance to blood flow. Current, outdated viscosity measurements only quantify whole blood or serum. Changes in blood composition, cell number, or the physical properties themselves lead to increased blood viscosity. Given the significant morbidity and mortality from hyperviscosity syndromes, new biophysical tools are needed and being developed to study microvascular biophysical and hemodynamic conditions at this microvascular level to help predict those at risk and guide therapeutic treatment.

Summary—The use of "lab-on-a-chip" technology continues to rise to relevance with point of care, personalized testing and medicine as customizable microfluidic platforms enable independent control of many in vivo factors and are a powerful tool to study microcirculatory hemorheology.

Keywords

hyperviscosity syndromes; hemorheology; microfluidic technology; lab on a chip; point of care

Introduction

William Harvey, an English physician, became the founder of physiology after correctly first describing human circulation in his "De Motu Cordis" published in 1628 [1]. Factors involved in blood flow remained largely unknown interesting Jean Leonard Marie Poiseuille to answer this question by studying blood flow through glass tubes. He found blood too

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Conflicts of interest

None.

difficult to use, with inconsistent results, so most of his studies used simpler liquids such as water and alcohol. From this, Poiseuille's Law characterizes the relationship of the flow rate of a liquid as a function of driving pressure, radius and length of the tube and viscosity of the liquid [2].

Viscosity, a material property of a fluid, describes its internal resistance to shearing motions, in which different parts of the fluid move with different velocities [3] (Figure 1). Isaac Newton hypothesized viscosity is independent of fluid characteristics, an intrinsic property of that fluid, termed Newtonian fluid [4].

The Ancients were the first to recognize the complexity, or four humours of blood: yellow bile, mucous, blood and black bile, what we now recognize as a suspension of plasma, buffy coat, erythrocytes and deoxygenated red cells [2]. Further, blood plasma is a complex suspension of macromolecules (fibrinogen, immunoglobulin, albumin, lipoproteins) and organic/inorganic substances in an electrolyte solution [5].

Whole blood and serum viscosity can be measured using capillary, falling-sphere, or rotational viscometers, but these techniques assume blood is a "continuum" fluid, meaning its physical properties do not change at different size scales, and becomes problematic when considering viscosity at the level of the microvasculature for the following reasons [6,7].

The diameter of blood vessels forming human circulation range from a few centimeters down to a few microns, while the diameter of a single erythrocyte is approximately eight microns [3,8]. The complexity of blood viscosity increases substantially at the microvascular level as the physical properties of the cells themselves become the major determinants of resistance to blood flow. As blood does not behave as a homogenous, Newtonian fluid in these miniscule vessels, consideration of blood flow in the microvasculature must consider the complex physical properties of the cells, their sizes, properties and number in suspension. Poiseuille's difficulty with using blood ex-vivo was in part to blood's non-Newtonian characteristics, as its viscosity is not constant and decreases with increasing shear rate [9] (Figure 2). This becomes relevant inside the body as blood travels from larger vessels to the microcirculation. Viscosity is also a strong function of hematocrit and because of several non-Newtonian effects in the microvasculature, the hematocrit of blood actually changes in smaller vessels, further changing viscosity yet again.

In 1965, Fahey coined the term "hyperviscosity syndrome" to describe the mucous membrane bleeding, retinopathy and loss of vision and neurological disorders associated with elevated serum viscosity [10] (Figure 3). Simply, blood becomes hyper-viscous when there is an increased number of blood cells or plasma proteins, plasma proteins are altered, decreased cell deformity or increased cell adhesion/aggregation, as detailed in selected hyperviscosity syndromes below. This increased viscosity results in impaired circulatory blood flow. Symptoms manifest in the lungs as dyspnea, hypoxia, hemorrhage and respiratory failure; the central nervous system as confusion, headache, focal neurological deficits and coma; along with impaired vision, retinal hemorrhages, myocardial and limb ischemia, renal vein thrombosis and priapism [11].

Given current viscosity measurements only quantify whole blood or serum and viscosity changes drastically at the microvascular level as single cells travel, one can argue, especially physician engineers like ourselves, that new, readily accessible tools are necessary to quantify effective viscosity at the microvascular level given the significant morbidity and mortality from hyperviscosity.

Microfluidics

In vivo studies on hemorheology are nearly impossible due to difficulty in visualizing and manipulating animal microvasculature therefore creating a need for physiologic in vitro investigations. Microfluidic technology rose to popularity within the science and engineering fields in the 1980's. These "miniaturized total analysis systems," or "lab-on-a-chip," enable study at the microscopic level [12]. Photolithography masks, commonly silicon wafers, are etched with complete control of size, down to the submicron scale, and geometry of microfluidic channels. This fabrication technology is akin to computer microchip circuits. Polydimethylsiloxane (PDMS) is used atop these chips for molding. PDMS allows for cost effectiveness, easy in fabrication and batching. PDMS is also transparent allowing for direct optical data collection [13] (Figure 4).

Today, this technology remains integral in biomedical research due the ability to mimic desired in vivo environment. Uses range from study of single cell mechanics to endothelialized microvessels and organs on a chip [14-16]. Required sample size typically is very low, conserving precious samples. These devices are often scalable, resulting in ease in reproducibility and cost efficiency [13]. In addition, microfluidic systems also allow for independent control of many in vivo factors to further study various contributors to pathophysiology in healthy and diseased states [12,17**].

Hyperviscosity syndromes

The patients Fahey reported suffered from macroglobulinemia or multiple myeloma, but more disease states are now linked to hyperviscosity.

Acute leukemia

Hyperleukocytosis, defined as a peripheral blood leukocyte count greater than one hundred thousand per microliter, is an emergency in acute leukemia. The increased viscosity is multifactorial but predisposes to occlusion of the microvasculature, termed leukostasis. The high blast count and leukocyte aggregates result in stasis in the smaller blood vessels. Leukocyte blasts promote adhesion to self and the vascular endothelium. The damaged endothelium leads to loss of vascular integrity, modifying the endothelial phenotype from antithrombotic to prothrombotic phenotype [11].

Leukemia cells themselves have been shown to be less deformable than non-pathologic leukocytes [18], with stiffness varying among leukemia cell types [19], and further stiffened after chemotherapy exposure [20].

Complicating the issue, hematocrit often decreases as leukemic cell counts rise and acute leukemia patients often present with anemia. As hematocrit is a major determinant of whole blood viscosity, red cell transfusions are avoided unless hemodynamically unstable to avoid furthering the hyperviscosity [21]. Intravenous fluids are given at increased rates and leukapheresis can also be performed in attempts to decrease viscosity [22].

Emergency initiation of chemotherapy can be used to quickly reduce blast count; often before specific leukemia diagnosis is made. As treatment of acute promyelocytic leukemia is vastly different from other myeloid subtypes, Emde et al designed a microfluidic for rapid detection of PML-RARα in less than one hour [23].

Sickle cell disease

Sickle cell disease (SCD) is the most frequent genetic disease in the world and results from a single nucleotide mutation in the beta globin gene. This amino acid change results in hemoglobin polymerization, changing the erythrocyte from biconcave to “sickled” shape when deoxygenated [24]. These sickled cells are rigid with decreased deformability, aggregating at low shear rates and increasing viscosity. Sickled erythrocytes increase blood viscosity through intrinsic properties of the sickled cells as well as abnormal interactions of these cells with leukocytes, platelets, vascular endothelium, and clotting factors.

The disease is characterized by hemolytic anemia and vaso-occlusive events, leading to blood cell adhesion to endothelium, resulting in a strong inflammatory state, ischemia and reperfusion [25]. Sequela of this hyperviscosity syndrome manifests with painful vaso-occlusive crises, acute chest, strokes, vasculopathy and kidney disease, among others.

Various commercial methods, such as ektacytometry, micropore filtration assay, micropipette aspiration and atomic force microscopy, can quantify the deformability of erythrocytes but these are not easily accessible or clinically relevant for heterogenous small volumes or single cells. Guruprasad et al paired a microfluidic microvasculature device with automated particle tracking program to measure single-cell deformability on heterogenous red blood cell (RBC) populations [26]. Szafraniec combined microfluidics with computational technologies to study the effective viscosity under varying oxygen conditions [27**]. Alapan et al designed microfluidic devices to evaluate RBC deformability and endothelium adhesion [28,29]. Monitoring RBC deformability has implications to monitor for clinical events and changes with therapies. Zhang et al designed a microfluidic device combined with a principal component analysis to quantify microvascular occlusion and SCD severity [30*].

Hydroxyurea, the standard of care medication to treat SCD, upregulates production of non-sickled hemoglobin F, decreasing sickled cells and viscosity. Using a microfluidic with endothelialized, bifurcating channels, Tsai et al showed in patients on hydroxyurea, less than 10% of channels occluded, compared to half of the channels occluding in patients not on this disease-modifying medication [16].

The hyperviscosity of SCD is also impacted by plasma osmolality. Inability to concentrate urine is a hallmark of sickle cell nephropathy and sickle red cells are chronically

dehydrated due to dysfunctional ion channels. Intravenous fluids are a hallmark of treatment during vaso-occlusive crises, yet the specific type of intravenous hydration remains controversial. Work by Carden et al showed modifying the extracellular fluid tonicity altered deformability, adhesivity and occlusion risk on microfluidic vascular models [31].

Transfusion support is a mainstay therapy in SCD, whether preventing or treating adverse events. Transfusion support balances increasing the oxygen carrying capacity of blood by decreasing sickled cells and increasing AA hemoglobin with the increase in blood viscosity which can decrease tissue perfusion [24]. As such, simple transfusion guidelines are in place for target post transfusion hematocrit values [32]. Work by Schmalzer et al showed simple transfusion alone is not as beneficial as exchange transfusion as viscosity is affected by total hematocrit level as well as the deformability of the cells [33]. This was supported by Lu et al with use of a microfluidic device to mimic exchange and simple transfusions and showed exchange transfusion had a significant effect on improving velocity under hypoxic conditions whereas the latter did not [34].

Waldenström macroglobulinemia

Waldenström macroglobulinemia (WM), is an indolent malignancy of B lymphocytes, resulting in overproduction of the monoclonal protein, immunoglobulin M. IgM is pentameric, with a high axial length-to-width ratio making it the largest immunoglobulin, resulting in significant increases in serum viscosity with slight increases in levels [7,35]. Hyperviscosity syndrome is commonly observed in WM, affecting 10-30% of patients [35]. This was first reported in 1944 by Jan Waldenström who cared for two patients with oronasal bleeding, elevated erythrocyte sedimentation rates, and elevated viscosity with macroglobulinemia [36]. Not all patients with WM require treatment at all, or at the time of diagnosis. Hyperviscosity is an indication to initiate treatment, though the ability to measure plasma viscosity is not readily available [37]. Noting this in 1965, Fahey commented on the large inability to measure viscosity and provided readers instructions on how to measure using either a ten dollar device purchased at a local instrument supply store or a 0.1 milliliter pipette [10].

The consensus panel from the Second International Workshop on WM recommended those with smoldering WM be followed and not treated until symptomatic, regardless of serum IgM levels.[38] Predictors of development of symptomatic hyperviscosity in WM patients remain sparse. Abeykoon et al found serum IgM and viscosity to be statistically significant predictors of symptomatic hyperviscosity, while MacKenzie et al reported a direct correlation between whole blood viscosity and relative serum viscosity among their patients, there was note of a symptomatic patient with low serum viscosity but high whole blood viscosity, indicating red cell paraprotein interaction [39,40]. Gustine et al studied serum IgM levels at which it would be reasonable to initiate treatment given the risk of developing symptomatic hyperviscosity, though commented results were limited as most patients did not have serum viscosity measurements [41].

Once hyperviscosity syndrome develops, rapid treatment focuses on plasmapheresis as short term treatment with occasional initiation of chemotherapeutic agents, such as ibrutinib, to maintain response and prevent recurrence [35]. Recent work by Karel et al used

microfluidics with and without atherosclerotic stenosis to study the effect of the Btk inhibitor ibrutinib on thrombus formation using WM patient's blood [42*]. Ibrutinib reduced platelet deposition, thrombus size and contraction around the stenotic microfluidic vessel.

Polycythemia vera

Polycythemia vera (PV) is the most common myeloproliferative neoplasm characterized by the V617F activating mutation in the tyrosine kinase JAK2, resulting in clonal proliferation of multipotent hematopoietic cells [43]. Classical presentation is characterized by erythrocytosis, leukocytosis, and thrombocytosis [44]. The prominent feature of this disease is elevated RBC mass from uncontrolled proliferation of erythroid lineage, resulting in increased hemoglobin concentration, hematocrit value and blood viscosity [45].

It has also been shown PV erythrocytes demonstrate pro-adhesive features to the endothelium, further increasing the risk of circulatory complications [43,46]. Patients with PV are at high risk for vaso-occlusive events including cerebral ischemia, hemorrhage and stroke, which may be a presenting symptom in 15% or more patients [47*]. Cerebral ischemic events result from increased blood viscosity and platelet activation within the central nervous system vessels.

Wang et al developed a point of care microfluidic for JAK2 testing within one hour with high accuracy, operability, and cost efficiency [48]. Lin et al designed a microfluidic capable of distinguishing PV based off erythrocyte hemagglutination using a single finger prick of whole blood [49].

SARs-Co-V2

Coronavirus disease 2019 (COVID-19), caused by the novel coronavirus SARS-CoV-2 is the newest hyperviscosity syndrome. The estimated rate of spread of SARS-CoV-2 is 40-fold higher than SARS-CoV, making it more difficult to control and the need for quick, accurate, inexpensive and widely accessible testing, patient monitoring and treatment [50**].

Everything was unknown as this disease quickly became a global pandemic and COVID-19 associated coagulopathy and thrombosis was quickly reported, especially among critically ill patients. Elevations in factor VIII and fibrinogen, circulating prothrombotic microparticles were thought to lead to hyperviscosity [51*,52**]. Hyperviscosity is known to cause endothelium damage and therefore a risk factor for thrombosis. Grobbelaar et al using a microfluidic showed SARS-CoV-2 spike protein S1 induced fibrinogen, a major determinant of blood viscosity, to elevated levels and resistant to fibrinolysis [53*]. This hyperviscosity, along with hypercoagulability from endothelial dysfunction and platelet activation, leading to abnormal blood flow along with hypoxia and immune dysfunction were postulated to lead to thrombogenesis in COVID-19 [54].

Mungmunpuntipantip et al reported increased blood viscosity on admission in cases resulting in fatality versus non-fatal cases [55*]. Renoux et al showed different hemorheological profiles among COVID-19 patients compared to healthy controls with COVID-19 patients having increased RBC aggregation and decreased deformability [56*]. Nader et al demonstrated COVID-19 patients had increased blood viscosity and RBC

aggregation with lower hematocrits than healthy controls; plasma fibrinogen was shown to strongly drive to RBC hyper-aggregation in vitro. Furthermore, RBC aggregation and blood viscosity was increased in hypoxic COVID-19 versus normoxic COVID-19 patients [57*]. Lakshmanan et al designed a microfluidic bleeding device to evaluate antithrombotic agents for use in COVID-19 patients [58].

Buzhdygan et al used a microfluidic with the SARS-CoV-2 spike protein to model its proinflammatory response altering the blood brain barrier, possibly explaining some of the neurological complications seen in these patients [59].

As point of care testing became widespread, microfluidic assays were advantageous, using little reagents and quickly providing precise results; Biomérieux's BioFire system is just one example of microfluidic technology granted emergency use authorization [60*,61].

Conclusions

Hyperviscosity syndromes can lead to significant morbidity and mortality. Existing methods to measure microcirculatory rheology are not readily available and limited in relevance and accuracy at this level, given blood's non-Newtonian properties in small vessels. Clearly, there is a need for simple and inexpensive devices that can provide rapid information about microcirculatory hemorheology. Microfluidic platforms are a powerful tool with which to study related factors from a different perspective to help predict and guide treatment. As evidenced by the widespread use of microfluidic platforms in the study of the novel SARs-CoV-2 pandemic, microfluidics will continue to advance to the forefront of diagnostic and laboratory testing.

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References and Recommended Reading

1. Pasipoularides A Historical Perspective: Harvey's epoch-making discovery of the circulation, its historical antecedents, and some initial consequences on medical practice. J Appl Physiol. 2013 Jun 1;114(11):1493–503. [PubMed: 23558385]
2. Baskurt OK, editor. Handbook of hemorheology and hemodynamics. Amsterdam ; Washington, DC: IOS Press; 2007. 455 p. (Biomedical and health research).
3. Pries AR, Secomb TW. Blood flow in microvascular networks. :34.
4. Késmárky G, Kenyeres P, Rábai M, Tóth K. Plasma viscosity: a forgotten variable. Clin Hemorheol Microcirc. 2008;39(1–4):243–6. [PubMed: 18503132]
5. Katritsis D, Kaiktsis L, Chaniotis A, et al. Wall shear stress: theoretical considerations and methods of measurement. Prog Cardiovasc Dis. 2007 Mar;49(5):307–29. [PubMed: 17329179]
6. Rosencranz R, Bogen SA. Clinical laboratory measurement of serum, plasma, and blood viscosity. Pathol Patterns Rev. 2006 Jun 1;125(suppl_1):S78–86.
7. Gertz MA. Acute hyperviscosity: syndromes and management. Blood. 2018 Sep 27;132(13):1379–85. [PubMed: 30104220]
8. Warkentin TE, Moore JC, Anand SS, et al. Gastrointestinal bleeding, angiodysplasia, cardiovascular disease, and acquired von Willebrand syndrome. Transfus Med Rev. 2003 Oct;17(4):272–86. [PubMed: 14571395]

9 *. Pialot B, Gachelin J, Provost J, Couture O. Exploitation of blood non-Newtonian properties for ultrasonic measurement of hematocrit. Sci Rep. 2021 Dec;11(1):10208. [PubMed: 33986398] New technique for measuring blood hematocrit using medical tube and Doppler ultrasound.

10. Fahey JL. Serum hyperviscosity syndrome. JAMA J Am Med Assoc. 1965 May 10;192(6):464.

11. Röllig C, Ehninger G. How I treat hyperleukocytosis in acute myeloid leukemia. Blood. 2015 May 21;125(21):3246–52. [PubMed: 25778528]

12. Sackmann EK, Fulton AL, Beebe DJ. The present and future role of microfluidics in biomedical research. Nature. 2014 Mar;507(7491):181–9. [PubMed: 24622198]

13. Raj MK, Chakraborty S PDMS microfluidics: A mini review. J Appl Polym Sci. 2020 Jul 15;137(27):48958.

14. Fay ME, Myers DR, Kumar A, et al. Cellular softening mediates leukocyte demargination and trafficking, thereby increasing clinical blood counts. Proc Natl Acad Sci. 2016 Feb 23;113(8):1987–92. [PubMed: 26858400]

15. Sakurai Y, Hardy ET, Ahn B, et al. A microengineered vascularized bleeding model that integrates the principal components of hemostasis. Nat Commun. 2018 Feb 6;9(1):509. [PubMed: 29410404]

16. Tsai M, Kita A, Leach J, et al. In vitro modeling of the microvascular occlusion and thrombosis that occur in hematologic diseases using microfluidic technology. J Clin Invest. 2012 Jan 3;122(1):408–18. [PubMed: 22156199]

17 **. Myers DR, Lam WA. Vascularized microfluidics and their untapped potential for discovery in diseases of the microvasculature. Annu Rev Biomed Eng. 2021 Jul 13;23(1):407–32. [PubMed: 33863238] Comprehensive review on endothelialized microfluidic devices in study of healthy and diseased states.

18. Lichtman MA. Rheology of leukocytes, leukocyte suspensions, and blood in leukemia possible relationship to clinical manifestations. J Clin Invest. 1973 Feb 1;52(2):350–8. [PubMed: 4509637]

19. Rosenbluth MJ, Lam WA, Fletcher DA. Force microscopy of nonadherent cells: a comparison of leukemia cell deformability. Biophys J. 2006 Apr;90(8):2994–3003. [PubMed: 16443660]

20. Lam WA, Rosenbluth MJ, Fletcher DA. Chemotherapy exposure increases leukemia cell stiffness. Blood. 2007 Apr 15;109(8):3505–8. [PubMed: 17179225]

21. Cowan AQ, Cho DJ, Rosenson RS. Importance of blood rheology in the pathophysiology of atherothrombosis. Cardiovasc Drugs Ther. 2012 Aug;26(4):339–48. [PubMed: 22821616]

22. Jain R, Bansal D, Marwaha RK. Hyperleukocytosis: emergency management. Indian J Pediatr. 2013 Feb;80(2):144–8. [PubMed: 23180411]

23. Emde B, Kreher H, Bäumer N, et al. Microfluidic-based detection of AML-specific biomarkers using the example of promyelocyte leukemia. Int J Mol Sci. 2020 Nov 25;21(23):8942.

24. Connes P, Alexy T, Detterich J, et al. The role of blood rheology in sickle cell disease. Blood Rev. 2016 Mar;30(2):111–8. [PubMed: 26341565]

25. Hebbel RP, Belcher JD, Vercellotti GM. The multifaceted role of ischemia/reperfusion in sickle cell anemia. J Clin Invest. 2020 Mar 2;130(3):1062–72. [PubMed: 32118586]

26. Guruprasad P, Mannino RG, Caruso C, et al. Integrated automated particle tracking microfluidic enables high-throughput cell deformability cytometry for red cell disorders. Am J Hematol. 2019 Feb;94(2):189–99. [PubMed: 30417938]

27 **. Szafraniec HM, Valdez JM, Iffrig E, et al. Feature tracking microfluidic analysis reveals differential roles of viscosity and friction in sickle cell blood. Lab Chip. 2022;22(8):1565–75. [PubMed: 35315465] Combination of microfluidics and computational tracking to study heterogeneity of SCD.

28. Alapan Y, Little JA, Gurkan UA. Heterogeneous Red Blood Cell Adhesion and Deformability in Sickle Cell Disease. Sci Rep. 2015 May;4(1):7173.

29. Alapan Y, Kim C, Adhikari A, et al. Sickle cell disease biochip: a functional red blood cell adhesion assay for monitoring sickle cell disease. Transl Res. 2016 Jul;173:74–91.e8. [PubMed: 27063958]

30 *. Zhang X, Chan T, Carbonella J, et al. A microfluidic-informatics assay for quantitative physical occlusion measurement in sickle cell disease. Lab Chip. 2022;22(6):1126–36. [PubMed: 35174373] Developed a model to quantify disease severity score among SCD patients and effect of hydration on this score.

31. Carden MA, Fay ME, Lu X, et al. Extracellular fluid tonicity impacts sickle red blood cell deformability and adhesion. Blood. 2017 Dec 14;130(24):2654–63. [PubMed: 28978568]
32. DeBaun MR, Jordan LC, King AA, et al. American Society of Hematology 2020 guidelines for sickle cell disease: prevention, diagnosis, and treatment of cerebrovascular disease in children and adults. Blood Adv. 2020 Apr 28;4(8):1554–88. [PubMed: 32298430]
33. Schmalzer E, Lee J, Brown A, et al. Viscosity of mixtures of sickle and normal red cells at varying hematocrit levels. Implications for transfusion. Transfusion (Paris). 1987 May;27(3):228–33.
34. Lu X, Chaudhury A, Higgins JM, Wood DK. Oxygen-dependent flow of sickle trait blood as an *in vitro* therapeutic benchmark for sickle cell disease treatments. Am J Hematol. 2018 Oct;93(10):1227–35. [PubMed: 30033564]
35. Weaver A, Rubinstein S, Cornell RF. Hyperviscosity syndrome in paraprotein secreting conditions including Waldenstrom macroglobulinemia. Front Oncol. 2020 May 19;10:815. [PubMed: 32509586]
36. Waldenström J Incipient myelomatosis or «essential« hyperglobulinemia with fibrinogenopenia - a new syndrome? Acta Med Scand. 2009 Apr 24;117(3–4):216–47.
37. Maqbool MG, Tam CS, Morison IM, et al. A practical guide to laboratory investigations at diagnosis and follow up in Waldenström macroglobulinaemia: recommendations from the Medical and Scientific Advisory Group, Myeloma Australia, the Pathology Sub-committee of the Lymphoma and Related Diseases Registry and the Australasian Association of Clinical Biochemists Monoclonal Gammopathy Working Group. Pathology (Phila). 2020 Feb;52(2):167–78.
38. Kyle RA, Benson JT, Larson DR, et al. Progression in smoldering Waldenström macroglobulinemia: long-term results. Blood. 2012 May 10;119(19):4462–6. [PubMed: 22451426]
39. Abeykoon JP, Zanwar S, Ansell SM, et al. Predictors of symptomatic hyperviscosity in Waldenström macroglobulinemia. Am J Hematol. 2018 Nov;93(11):1384–93. [PubMed: 30121949]
40. MacKenzie M, Lee T. Blood viscosity in Waldenstrom macroglobulinemia. Blood. 1977 Apr 1;49(4):507–10. [PubMed: 402961]
41. Gustine JN, Meid K, Dubeau T, et al. Serum IgM level as predictor of symptomatic hyperviscosity in patients with Waldenström macroglobulinaemia. Br J Haematol. 2017 Jun;177(5):717–25. [PubMed: 28485115]
42 *. Karel MFA, Tullemans BME, D'Italia G, et al. The effect of Bruton's tyrosine kinase inhibitor ibrutinib on atherothrombus formation under stenotic flow conditions. Thromb Res. 2022 Apr;212:72–80. [PubMed: 35247800] Ibrutinib reduces in vitro platelet deposition, thrombus size and contraction around atherosclerotic plaque in vitro.
43. Nemer WE, Grandis MD, Brusson M. Abnormal adhesion of red blood cells in polycythemia vera: a prothrombotic effect? Thromb Res. 2014 May;133:S107–11. [PubMed: 24862129]
44. Spivak JL. Polycythemia vera. Curr Treat Options Oncol. 2018 Feb;19(2):12. [PubMed: 29516275]
45. Shin DW, Gu JY, Kim JS, et al. Increased plasma viscosity in plasma cell dyscrasia and whole blood viscosity in polycythemia vera. Clin Hemorheol Microcirc. 2018 Sep 14;70(1):59–67. [PubMed: 29660912]
46. Wautier MP, El Nemer W, Gane P, et al. Increased adhesion to endothelial cells of erythrocytes from patients with polycythemia vera is mediated by laminin α5 chain and Lu/BCAM. Blood. 2007 Aug 1;110(3):894–901. [PubMed: 17412890]
47 *. Balagopal K, Mathew A, Koshy AG, Jacob JP. Polycythemia vera presenting as hemorrhagic stroke. J Neurosci Rural Pract. 2021 Jul;12(03):601–2. [PubMed: 34295120] PV presenting as hemorrhagic stroke.
48. Wang H, Liu W, Zhang X, et al. Toward point-of-care testing for JAK2 V617F mutation on a microchip. J Chromatogr A. 2015 Sep;1410:28–34. [PubMed: 26235214]
49. Lin JH, Tsai TT, Zeng Q, et al. A multifunctional microfluidic device for blood typing and primary screening of blood diseases. ACS Sens. 2020 Oct 23;5(10):3082–90. [PubMed: 32786388]

50 **. Tang Z, Kong N, Zhang X, et al. A materials-science perspective on tackling COVID-19. Nat Rev Mater. 2020 Nov;5(11):847–60. [PubMed: 33078077] Use of material sciences in novel SARS-CoV-2 pandemic.

51 *. Al-Subaie AM. Coagulopathies in novel coronavirus (SARS-CoV-2) pandemic: emerging evidence for hematologists. Saudi J Biol Sci. 2021 Jan;28(1):956–61. [PubMed: 33169062] Proposes mechanisms for COVID-19 coagulopathy.

52 **. Mazzeffi MA, Chow JH, Tanaka K. COVID-19 associated hypercoagulability: manifestations, mechanisms, and management. Shock. 2021 Apr;55(4):465–71. [PubMed: 32890309] Review on COVID19 coagulopathy.

53 *. Grobbelaar LM, Venter C, Vlok M, et al. SARS-CoV-2 spike protein S1 induces fibrin(ogen) resistant to fibrinolysis: implications for microclot formation in COVID-19. Biosci Rep. 2021 Aug 27;41(8):BSR20210611. [PubMed: 34328172] Using microscopy and microfluids, investigated SARS-CoV-2 spike protein S1 contribution to hypercoagulability.

54. Ahmed S, Zimba O, Gasparyan AY. Thrombosis in Coronavirus disease 2019 (COVID-19) through the prism of Virchow's triad. Clin Rheumatol. 2020 Sep;39(9):2529–43. [PubMed: 32654082]

55 *. Mungmunpuntipantip R, Wiwanitkit V. Blood viscosity at the first flinical presentation in fatal and non-fatal COVID-19: an observation. Clin Appl Thromb. 2021 Jan 1;27:107602962110067. Compared blood viscosity among fatal and non-fatal COVID-19 patients.

56 *. Renoux C, Fort R, Nader E, et al. Impact of COVID-19 on red blood cell rheology. Br J Haematol. 2021 Feb;192(4). COVID-19 patients have increased red blood cell aggregation and decreased deformability.

57 *. Nader E, Nougier C, Boisson C, et al. Increased blood viscosity and red blood cell aggregation in patients with COVID-19. Am J Hematol. 2022 Mar;97(3):283–92. [PubMed: 34939698] Described clinical outcomes related to increased blood viscosity and red cell aggregation among COVID-19 patients.

58. Lakshmanan HHS, Pore AA, Kohs TCL, et al. Design of a microfluidic bleeding chip to evaluate antithrombotic agents for use in COVID-19 patients. Cell Mol Bioeng. 2020 Aug;13(4):331–9. [PubMed: 32837586]

59. Buzhdygan TP, DeOre BJ, Baldwin-Leclair A, et al. The SARS-CoV-2 spike protein alters barrier function in 2D static and 3D microfluidic in-vitro models of the human blood–brain barrier. Neurobiol Dis. 2020 Dec;146:105131. [PubMed: 33053430]

60 *. Oishee MJ, Ali T, Jahan N, et al. COVID-19 pandemic: review of contemporary and forthcoming detection tools. Infect Drug Resist. 2021 Mar;Volume 14:1049–82. [PubMed: 33762831] Reported on COVID-19 diagnostic tools both approved and under investigation.

61. Zhuang J, Yin J, Lv S, et al. Advanced "lab-on-a-chip" to detect viruses – Current challenges and future perspectives. Biosens Bioelectron. 2020 Sep;163:112291. [PubMed: 32421630]

Key Points

- Hyperviscosity syndromes can lead to significant morbidity and mortality.
- Existing methods to study microcirculatory rheology are not readily available and limited in relevance and accuracy at this level, given blood's non-Newtonian properties in small vessels.
- Microfluidic platforms enable independent control of many in vivo factors and are a powerful tool to study microcirculatory hemorheology in healthy and diseased states in hopes to help predict outcomes and guide treatment.

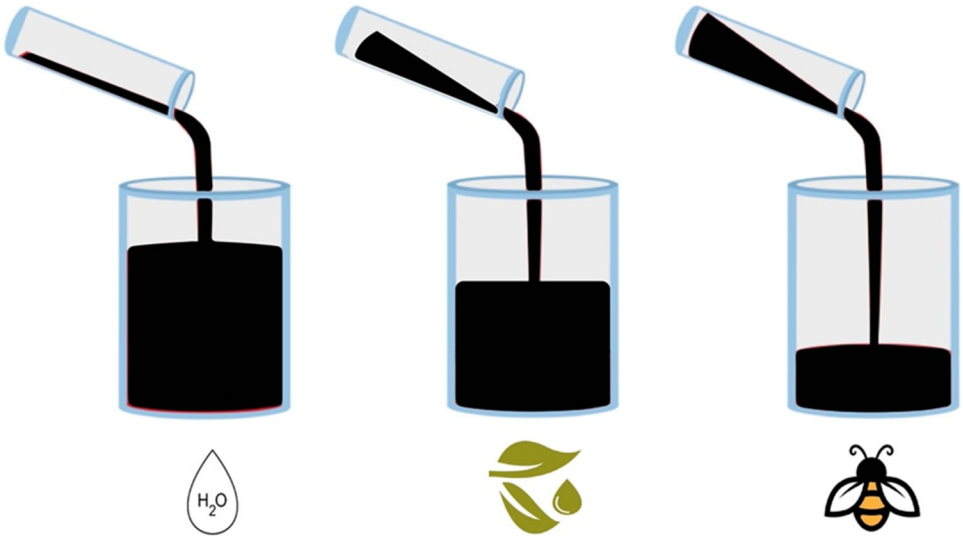

Figure 1. What is viscosity?.

Simply put, a fluid's resistance to flow. Homogenous fluids with increasing viscosity from left to right as depicted with water, olive oil and honey.

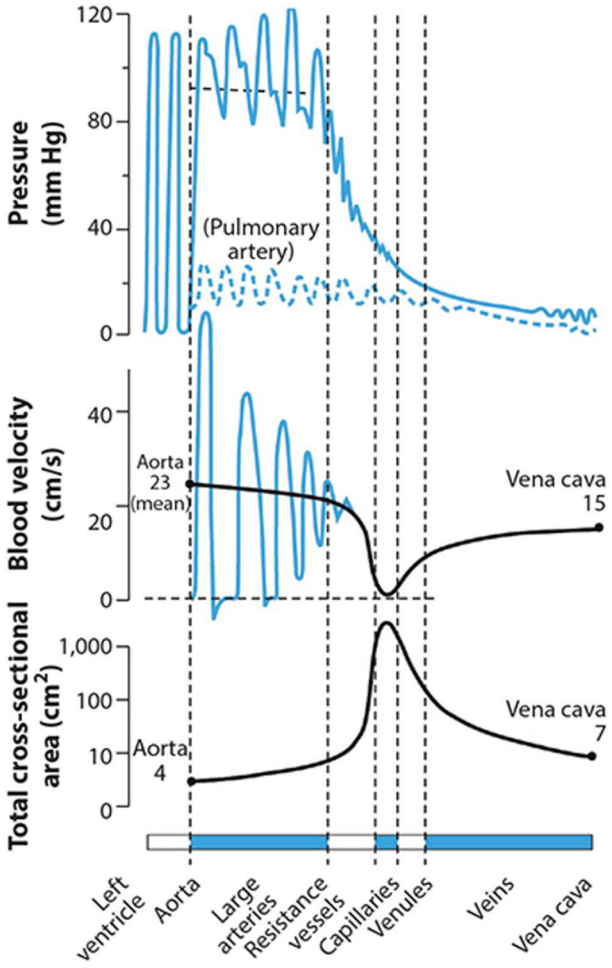

Figure 2. Hemorheology, macro to microcirculation.

As vessel cross-sectional area increases markedly from arterioles to capillaries, applied pressure and blood velocity drop significantly. Travelling from capillaries to venules to veins, cross-sectional area decreases resulting in continued decrease in applied pressure with small increases in blood velocity.

Myers DR, Lam WA. Vascularized microfluidics and their untapped potential for discovery in diseases of the microvasculature. Annu Rev Biomed Eng. 2021 Jul 13;23(1):407–32.

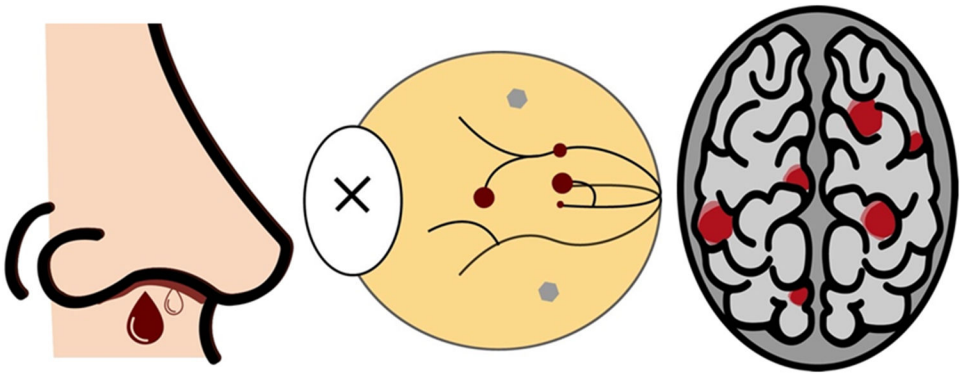

Figure 3. "Hyperviscosity Syndrome."

Characterized by mucous membrane bleeding, retinopathy and loss of vision and neurological disorders associated with elevated serum viscosity.

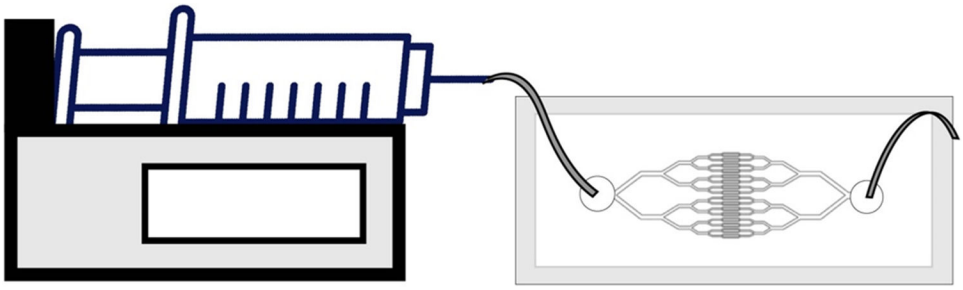

Figure 4. Microfluidic technology.

Illustration depicting microfluidic technology. Sample fluid is pumped at physiologic flowrate into PDMS device designed with specific microvascular geometry and size. Data is collected via videomicroscopy.