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Blood viscosity modulates tissue perfusion: sometimes and somewhere

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SUMMARY

Each organ possesses specific properties for controlling microvascular perfusion. Such specificity provides an opportunity to design transfusion fluids that target thrombo-embolic or vasospasm-induced ischemia in a particular organ or that optimize overall perfusion from systemic shock. The role of viscosity in the design of these fluids might be underestimated, because viscosity is rarely monitored or considered in critical care decisions. Studies linking viscosity-dependent changes of microvascular perfusion to outcome-relevant data suggest that whole blood viscosity is negligible as a determinant of microvascular perfusion under physiological conditions when autoregulation is effective. Because autoregulation is driven to maintain oxygen supply constant, the organism will compensate for changes in blood viscosity to sustain oxygen delivery. In contrast, under pathological conditions in the brain and elsewhere, increases of overall viscosity should be avoided – including all the situations where vascular autoregulatory mechanisms are inoperative due to ischemia, structural damage or physiologic dysfunction. As latter conditions are not to identify with high certainty, the risks that accompany therapeutic correction of blood viscosity are outweighing the benefits. The ability to bedside monitor blood viscosity and to link changes in viscosity to outcome parameters in various clinical conditions would provide more solid foundation for evidence-based clinical management.

INTRODUCTION

The realization that regulatory properties of tissue perfusion may be organ specific is a critical element that could be key to the development of strategies for dealing with thrombo-embolic episodes or vasospasm in brain, heart or other tissue. However, extensive research in these pathologies has not yet provided a precise understanding of the mechanisms of hypoperfusion at the microcirculatory level. Physical models that equate blood flow and tissue perfusion to the parameters of the Hagen-Poiseuille equation (HPE) describing flow in tubes, provide estimates of vascular resistance and blood flow related to the available perfusion pressure and the prevailing blood viscosity. Notably, this approach is seldom able to predict tissue perfusion, as the HPE perfectly describes flow of Newtonian (incompressible uniform-viscous) fluid through a cylindrical tube. Blood flow *in vivo*, however, differs for a variety of reasons: it is neither laminar, nor are blood vessels cylindrical tubes, nor is blood a non-corpuscular

Newtonian fluid. Moreover, all known models do not contemplate the action of mechanisms that regulate oxygen delivery in proportion to the metabolic needs of the tissue. In fact, ignoring the metabolic regulation of perfusion, as well as other regulatory mechanisms dependent on myogenic tone and endothelial shear stress, in many instances leads to the conclusion that tissue perfusion does not obey simple physical laws.

There are many examples showing discrepancies between the predictions of the pressure/flow/viscosity relationship and the behavior of microvascular perfusion. A recent publication demonstrated the maintenance of tissue oxygen delivery in combination with a significant increased blood viscosity resulting from hematocrits around 0.85.¹ At the other end of the spectrum, the extreme reduction of hematocrit by exchanging transfusion with a molecular hemoglobin-based oxygen carrier did not affect oxygen delivery.² These examples raise the question whether blood viscosity is a factor in the regulation of tissue perfusion and oxygen delivery, when there is sufficient oxygen carrying capacity in blood.

Assessing the impact of blood viscosity on tissue perfusion

Assessment of viscosity is characterized by three fundamental problems: (i) measurement; (ii) functional; and (iii) anatomical characteristics of each tissue. Blood viscosity is inextricably related to oxygen delivery, as it is primarily determined by hematocrit. The basic difficulty is that the viscosity measured by viscometric techniques is only approximately representative of the effective blood viscosity *in vivo*, because hematocrit is not homogeneous in the circulation. Each tissue possesses different functional capacity to autoregulate blood flow following changes in perfusion pressure and metabolic demand. Consequently, each tissue will respond differently to changes in oxygen delivery and presumably to changes in viscosity. This physiologic heterogeneity renders a complex picture for evaluation of the role of viscosity in setting perfusion. The third problem is that specialized anatomical features of the microcirculation of each tissue complicate the prediction how blood viscosity affects tissue perfusion in the microcirculation.

The non-homogeneity of circulatory hematocrit, leading to the variability of blood viscosity in the circulation, is mostly due to axial migration and plasma skimming resulting from the Fahraeus-Lindqvist effect, whereby viscosity of blood declines with decreasing vessels diameter. Additional effects are contributed by the presence of an endothelial surface layer, whose rheological impact is, at present, not completely understood. The endothelial glycocalyx introduces an uncertainty in the determination of the effective diameter of capillaries and small microvessels.

Another difficulty in evaluating the impact of viscosity on tissue perfusion is the interaction of various functional mechanisms that actively regulates perfusion to maintain oxygen supply to the tissues. As a consequence, vessel perfusion models based on the analysis of flow in single vessels, or even networks of these vessels do not demonstrate the effect of hemorheological disorders on tissue perfusion. For example, vasodilatation induced *in vitro* by an increased viscosity³ is most likely counteracted *in vivo* by a reduced perfusion pressure.

The complex nature of interactions that determine tissue perfusion suggests that the effects of changing blood rheology should be evaluated by (i) measurement of the tissue perfusion *per se*; and (ii) consideration of the result in the context of tissue survival and overall outcome. Techniques to measure tissue perfusion use tracers or microspheres with an inherent precision error; they are laborious and most frequently only applicable in experimental models. Just a few parameters are representative prerequisites of tissue survival. For example, the number of functional capillaries per unit volume of tissue (FCD) successfully predicts the survival of animals subjected to hemorrhagic shock, independent from tissue oxygenation.⁴ In this

context, this parameter becomes the ‘outcome’ or gauge with which to evaluate rheological changes.

In the following, we shall attempt to identify the role of viscosity in tissue perfusion in terms of changes of an ‘outcome’ parameter, and the impact of viscosity on maintenance of oxygen delivery.

Low viscosity

At the same oxygen content, reduction of blood viscosity can be produced by hemodilution using an artificial oxygen carrier (AOC)^{5,6} (ideally without nitric oxide scavenging properties⁷) or by inducing hemodilution in combination with hyperbaric oxygenation⁸ (which also reduces vessel diameter by hydrostatic atmospheric pressure).

Under physiological conditions, during hemodilution with and without an artificial hemoglobin solution, in oxygen content matched groups, cerebral blood flow (CBF) was greater in animals with decreased viscosity.⁹ In the brain, a 4-fold variation of blood viscosity at the same oxygenation level does not produce a change of the local CBF.² Thus, at reduced blood viscosity, tissue perfusion increases to maintain oxygen delivery and *vice versa*.

Whole blood viscosity is the sum of plasma viscosity (mainly determined by colloid components such as albumin) plus the density and packing of all blood cells and their rigidity. Normally, shear stress-independent plasma viscosity contributes only to a tenth or less to whole blood viscosity.¹⁰ However, plasma viscosity is more important for the regulation of tissue perfusion than blood viscosity.^{2,11,12} Following hemodilution from 60% to a hematocrit below 20%, a 33% increase in plasma viscosity at the same oxygen content increased tissue PO₂ levels on the surface of liver and skeletal muscle.¹² Increasing plasma viscosity may be used to offset the concomitant decrease in blood viscosity due to lowered hematocrit in hemodilution.¹¹ Experimental studies show that high plasma viscosity is beneficial in shock resuscitation.¹³

Correction of plasma viscosity, though, should be performed carefully. Over-treatment should be avoided even under physiological conditions. This is supported from the analysis of viscosity-dependent flow dynamics. A therapeutic attempt to increase systemic whole blood viscosity may increase dramatically flow resistance in small bore tubes. These relationships are strongly affected by blood cell deformability and concentration, red cell aggregation, and white cell interactions with the red cells and endothelium.¹⁴ However, data obtained in rigid glass tubes do not account for the effects of vascular responses. Under physiological conditions with an intact vasomotion, shear stress-dependent vasodilation should occur in the microvasculature as a reaction to increased viscosity. However, because alterations of the endothelial glycocalyx function depend in various organs on resuscitation fluid characteristics,^{15,16} vascular damage might be induced by iatrogenic viscosity increases in metabolically compromised tissues with impaired endothelial function.

Under pathological conditions, i.e. in situations where normal vascular responses are no longer possible due to damage following hemorrhagic shock or focal brain ischemia, autoregulatory capacity is impaired^{17,18} and the impact of overall viscosity on perfusion becomes more prominent. Following middle cerebral artery occlusion in rats, if a hemoglobin solution is used for hemodilution, a decrease in viscosity, but not a decrease in oxygen content, increases CBF.⁹ In cats, the increase in CBF by oxygenated hemodilution is delayed and affects brain regions heterogeneously.¹⁹ In rats and mice, brain tissue can be rescued by transfusion of cell-free hemoglobin.^{20,21}

Following shock, restoring whole blood viscosity by fresh donor red cells or non-oxygen loaded red cells improves resuscitation independently of the restitution of oxygen-carrying capacity.²²

The role of plasma viscosity might be even more important for pathological conditions. Studies in hemorrhagic shock show that survival is primarily determined by the maintenance of FCD and secondarily by tissue oxygenation. FCD can be maintained by increasing plasma viscosity when hematocrit is reduced beyond the transfusion trigger. This concept postulates the existence of a 'viscosity trigger' in addition to the transfusion trigger.²³

High viscosity

Under natural conditions, an increase of blood viscosity is present in dehydration, blood cell malignancies and dysproteinemias. More often, an increased blood viscosity is induced iatrogenically by infusion of colloids, transfusion, treatment with diuretics and hemodialysis.²⁴ Does increased viscosity have an impact on tissue perfusion overriding tissue oxygenation?

Under physiological conditions, at an extremely high, four-fold increase in whole blood viscosity, capillary and tissue oxygen tensions were normal.²⁵ In the same mice overexpressing erythropoietin resulting in hematocrits of 0.85, cerebral oxygen delivery was normal and matched the brain's oxygen demand.¹ Constriction of the cerebrovascular bed can be produced with hyper-baric oxygen, AOCs, overtransfusion or erythrocytosis. The autoregulatory constriction adjusts CBF such that bulk oxygen delivery is not perturbed. Vasoconstriction in the brain might be produced by endothelin and/or 20-hydroxyecosatetraenoic (20-HETE acid).²⁶ During acute hypertension, 20-HETE contributes to myogenic constriction and thereby modulates CBF autoregulation.²⁷ This potent vasoconstrictor is derived from arachidonic acid converted by cytochrome P450 (CYP) ω -hydroxylase enzymes located in cerebral arterial smooth muscle microsomes. Interestingly, the formation of 20-HETE increases as the PO₂ increases over a 10–80 mmHg range.²⁸ When blood viscosity is decreased at normal oxygen carrying capacity with cell-free hemoglobin polymers, CBF would passively increase and thus increase oxygenation if it were not for arteriolar constriction to maintain CBF and oxygen delivery. This constrictor response relies on oxygen-dependent synthesis of 20-HETE.²⁹ When plasma viscosity is increased above normal levels in the presence of plasma hemoglobin at low hematocrit, the vasoconstriction is converted to vasodilation.³⁰ Conversion to vasodilation may be mediated by loss of 20-HETE synthesis by shear stress-induced increased in NO production leading to inhibition of CYP ω -hydroxylase activity and increased cGMP. Therefore, under physiological conditions, this autoregulatory system is capable of overriding the effect of extremely high viscosities on perfusion and still maintains oxygen delivery.

These results suggest that iatrogenic hemoconcentration *per se* is not necessarily dangerous even if it slows down CBF. Especially when it comes to erythropoietin treatment of renal failure patients, viscosity is not increased in the same extent as with transfusion to a higher hematocrit, because the content of reticulocytes with higher membrane flexibility does not increase viscosity as much as older and stored red cells.¹⁰ Changes in blood viscosity do not result in changes of CBF as long as cerebral vessels can compensate for these changes by vasodilation or vasoconstriction. However, such vascular compensatory adjustments may be exhausted in their response to further pathophysiological conditions in blood vessels that have already been dilated or constricted as a result of changes in blood viscosity.³¹

Under pathological conditions, however, viscosity becomes important. Following stroke, infarct volumes of transgenic mice with extreme erythrocytosis-induced hyperviscosity are much larger, despite higher oxygen content than controls.³² Another example using an experiment with increased and decreased plasma viscosities plus carotid occlusion is that a forebrain ischemia in rats only is inducible with a higher plasma viscosity.³³

In summary, under physiological conditions, in tissues with autoregulatory capacity and high metabolic demand associated with high functional capillary density, perfusion is well regulated to match the oxygen demand. Whole blood viscosity does not exert a major impact on bulk oxygen delivery to the microcirculation because of upstream adjustments in vascular hindrance. In other organs without strong autoregulatory capacity, and with low oxidative metabolism and low functional capillary density, plasma viscosity increases perfusion effectively to increase tissue oxygenation. Under pathological conditions, in all tissues, a higher than normal viscosity should be avoided because it likely hinders flow and worsens the ischemic damage.

What can be transferred from the analysis of viscosity effects in the microcirculation to clinical practice?

1. Given the evidence discussed, we may conclude that when there is no vascular damage, and when tissue ischemic events are absent (a condition we name A-Phys), then a higher than normal plasma viscosity may be desirable. In critical organs such as the brain, heart and kidneys, a tight control of oxygen delivery is exerted by myogenic and endothelial derived controls. Even a four-fold increase in viscosity in these organs can be handled when the vascular response is intact.
2. In the case of stroke, infarction or vascular damage (a condition B-Path), outcome is worse if the perfusate's viscosity is above normal value. In this situation, a mild reduction of blood's overall viscosity might improve perfusion in the area of interest such as the recoverable penumbra area around the ischemic core.

In general, there have been few convincing reasons for the inclusion of blood viscosity considerations in daily practice.

One reason is the concept that the best way to the remedy for a health defect is to imitate nature as close as possible. Nature maintains the original high blood viscosity during an uncontrolled hemorrhage – and patients with a delayed correction of blood loss with early low viscosity (low oxygen) fluid resuscitation seem to have a better outcome (although the study needs cautious interpretation³⁴). Keeping viscosity as close as possible to normal seems to be prudent as long as the exact role and function of the blood's viscosity remain unclear.

Thus, viscosity might play a clinical role in the future, but at present, the risks that accompany correction of blood viscosity are outweighing the benefits. Evidence-based clinical data for guidance of volume and transfusion requirements with respect to blood viscosity and its impact on the microcirculation are lacking. Hence, colloids or crystalloid volume resuscitation utilizes a rough estimate of volume loss and intravascular half-life rather than viscosity guidance. The lack of clinically established guidelines and bedside monitors to measure viscosity is the major impediment to viscosity-guided resuscitation.

Application of viscosity-related issues to therapeutic interventions

Volume resuscitation—In general, volume resuscitation is daily practiced peri-operatively. It also is established for hypovolemic and hemorrhagic shock with controlled bleeding. Both clinical situations are representing what we called 'condition A-Phys.' Because critical tissues with an intact auto-regulation, such as in the central nervous system and myocardium, are overriding viscosity decreases during volume replacement for several days before an adaptation occurs,³⁵ whole blood viscosity does not appear to play a very strong role.

However, the aim of volume replacement is to avoid 'condition B-Path', i.e. that critical organs lose vascular control of perfusion that potentially precedes tissue ischemia in case of low-oxygen and low-viscosity volume resuscitation. The loss of autoregulatory capacity in those

organs might be caused by stimuli from remote inflammation in other organs. In that respect, for example, loss of epithelial integrity in the gut followed by bacterial translocation and toxin liberation could, in the long run, potentially cause 'condition B-Path' also in other critical organs.

Therefore, during a prolonged need for volume substitution, plasma viscosity might become important. Indeed, a beneficial outcome results when blood viscosity is maintained. Restoration of blood viscosity to baseline values in the case of volume resuscitation for hemorrhagic shock maintains microvascular and organ perfusion,¹¹ whereas shock and hypoperfusion in the microcirculation (detected indirectly by lactate and base deficit³⁶ or muscle tissue perfusion deficit³⁷) contributes to mortality and morbidity, even if patients are hemodynamically stable.³⁸

Treatment of low-viscosity states with high-viscosity plasma expanders has the potential to improve tissue perfusion and avoid ischemic damage, even in the case of transfusion of a poor oxygen carrier^{10,39} However, current high-viscous volume substitutes are not yet suitable for clinical practice. Polyvinylpyrrolidone (PVP) could be formulated to significantly increase plasma viscosity even above baseline but was taken from the market, because it causes tumor-like granulomas.

We do not consider the correction of low blood viscosities to be a clinically relevant option at present. The risk of over-treatment and the risk to endanger tissues where autoregulation is inoperative, i.e. 'condition B-Path' is already present, clearly exist when low viscosity is corrected without guidance. As hyperviscosity cannot be detected rapidly without available bedside measurements, such a monitor is a critical requirement if new high-viscous volume substitutes become available.

Design of artificial oxygen carriers

Alternatives to natural blood have to achieve both delivery of adequate oxygen and preservation of microvascular function. The first generation of AOC so far tended to have low viscosity when compared with blood.⁴⁰ The better formulations did not induce vasomotion and are void of toxicities, had comparatively long intravascular persistence, were effective in small quantities, and did not scavenge nitric oxide. However, most of them provoked strong vasoconstriction due to various components of an unknown mix of mechanisms: the combination of a high-oxygen content (which may increase production of the constrictor 20-HETE), a low viscosity (which may decrease endothelial NO production by decreasing shear rate), and extravasation of hemoglobin tetramers [which will scavenge NO between the endothelium and smooth muscle (the latter mechanism contributes for the greatest part to vasoconstriction)].

Once again, viscosity of an AOC will not be superior to oxygen content in 'A-Phys' conditions and intact auto-regulation. In 'B-Path', i.e. for ischemia, formulations with those properties may not be useful because nutritional flow to the area of need can be hindered. Therefore, the second generation of AOC has increased oxygen affinity, increased viscosity and higher oncotic pressure. This problem may be partly overcome by increasing plasma viscosity of the infused solution to an almost normal value.³⁰ A viscosity higher than normal strictly should be avoided in 'conditions B-Path'. In stroke, the issue of optimal oncotic pressure is complex. Hyperosmotic saline solution administered early after experimental stroke can be detrimental,⁴¹ whereas delayed treatment can reduce brain water content, swelling and intracranial pressure.^{42,43} Results with colloids may be different. Hyperoncotic albumin is neuroprotective in experimental stroke and has led to ongoing clinical trials.⁴⁴ In addition, cross-linked tetrameric cell-free hemoglobin was more effective in reducing infarct volume when infused at a hyperoncotic 20% concentration.⁴⁵ Effects of oncotic pressure in these

studies are difficult to distinguish from direct effects of albumin on scavenging toxic lipids or effects of high hemoglobin concentration on improved oxygen transport.

Small-volume-resuscitation

The assumed mechanism in small-volume-resuscitation (SVR) is to increase intravascular volume by recruitment of water from the interstitial space. This immediate but short lasting effect improves perfusion in shock by blood volume expansion and may be superior to simple crystalloid resuscitation.⁴⁶ However, this concept accepts that viscosity of the perfusate decreases. One improvement could be replacement of hyperosmotic–hyperoncotic SVR in shock with a hyperosmotic–hyperviscous solution. This new approach causes an improved and longer lasting recovery of microvascular perfusion.¹³

Conceptually, increasing viscosity of AOC used in ‘condition A-Phys’ might be beneficial. Repeated dosing might be necessary during ongoing hemorrhage as well as to improve perfusion in prolonged shock. However, whenever ‘condition B-Path’ is assumed to be present, use of high-viscous AOC without tight viscometry might be analogous to drowning the patient that is dying from thirst.

Summary and conclusions

Whole blood viscosity appears to be negligible as a determinant of microvascular perfusion under physiological conditions when autoregulation is effective. Because autoregulation is largely driven for maintenance of oxygen supply, the organism will compensate for changes in blood viscosity to accomplish this apparent goal.

Under physiological conditions and reduced whole blood viscosity, plasma viscosity may play a tissue-dependent relevant role. The role of plasma viscosity might become crucial in organs that normally autoregulate, such as the heart, kidney and the brain, when vasomotion is impaired by vascular damage.

Increases of overall viscosity above normal baseline values should be avoided under pathological conditions in the brain and elsewhere – all situations where vascular autoregulatory mechanisms are inoperative due to ischemia, structural damage or physiologic dysfunction. Experimental evidence shows that treatment of hemorrhagic shock and peri-operative blood loss could benefit from hemodilution and increased plasma viscosity. However, in terms of clinical practice, a safe and effective blood and volume substitute with a high viscosity is not yet available.

Generally, viscosity should be monitored. It should be linked to outcome parameters in all clinical situations where the lowering of blood viscosity is tolerated and evidence based, clinical guidelines should be established.

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