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Review

Hemodilution both ways: phenomenon and tool
Narrative review

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“All models are wrong, some are useful.”
George Box - British statistician

Abstract

Hemodilution refers to the dilution of blood components. Whether it is an iatrogenic effect of volume replacement or intentional as a treatment, it also occurs as a consequence of disease. Hemodilution affects blood viscosity with a significant impact on blood rheology. The prevalence of hemodilution anemia is high and therefore a common clinical phenomenon. Hemodilution can also be considered as a tool when applied intentionally, as an opportunistic therapeutic option, as a specific treatment, or as a blood-sparing technique.

Keywords: **Anemia, hemodilution, blood viscosity, oxygen transport, fluids.**

Introduction

While dilution of blood components, and more specifically RBCs (red blood cells), is a common clinical finding as anemia, a symptom, it is also a frequent side effect of volume replacement, whether or not intentional[1]. Critical care physicians are familiar with varying degrees of HD (hemodilution) in patients following intravenous infusions during major surgery, blood loss, and trauma[2]. Acute, intentional normo- or hypervolemic HD were once widely adopted as blood conservation techniques whenever significant blood loss was expected.

Like ketchup, blood behaves as a shear-thinning, non-Newtonian fluid: solid at rest and thinner when shaken[3]. Crucial to this viscosity-dependent rheological behavior of blood is the deformability of RBCs and their tendency to aggregate, which even occurs at normal Hct (hematocrit) levels[4]. Viscosity modification through HD is a way to manipulate blood rheology in both the macro- and microvasculature[5]. Arthur Guyton described the specific physiological interplay between blood viscosity and VR (venous return) in his famous curves demonstrating the relationship between RAP (right atrial pressure) and CO (cardiac output)[6,7]. Besides possible acid-base disturbances and toxicity of the exogenous solution itself, intravenous fluids used to induce HD can also affect the osmotic and oncotic balances with shifts to and from other fluid spaces (interstitial and intracellular) and even fluid overload[8]. When it comes to HD, awareness and close monitoring are necessary for an optimal patient care, such as keeping a patient as euvolemic as possible and maintaining adequate levels of all blood components[9]. In experienced hands, intentional ANHD (acute normovolemic hemodilution) has been shown to be useful as part of blood conservation programs and an adjuvant to the treatment of acute organ ischemia (e.g. stroke, intermittent claudication) and other medical conditions involving poor microcirculation or blood flow maldistributions[10,11].

A targeted literature review was conducted, focusing on various sources regarding HD such as randomized controlled trials, retrospective and prospective cohort studies, specific books, and relevant papers.

Discussion

Viscosity

Non-turbulent blood flow through most of the macrovascular parts is laminar and organized in uniaxial concentric and contiguous fluid layers (Figure 1). These layers contain formed blood

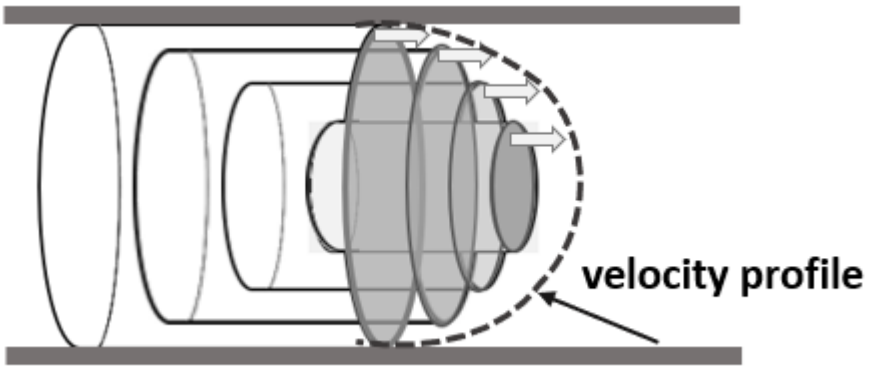

Fig. 1 — Representation of non-turbulent laminar flow in concentric, cylindrical fluid layers in a vessel, resulting in a parabolic velocity profile.

elements and (macro)molecules that slide past each other at different speeds due to mutual friction and intermolecular forces. According to Newton, viscosity is a measure of the internal resistance to flow exerted by the friction between fluid layers[11]. To model this, consider a plate in a laminarly flowing fluid with area A, separated from other layers by a distance Y. By accelerating the upper plate with a tangential force F, it pushes the underlying plates forward. This creates friction between the plates, which opposes their motion and causes the fluid layers to move at different speeds (Figure 2 a and b). Since the relationship of force and velocity is linear, the speed V of every single plate is inversely proportional to the distance between it and the upper plate. The F/A ratio is defined as the shear stress and the V/Y ratio as the shear rate, the velocity gradient across the layers per unit distance[11]. Viscosity is the ratio of shear stress to shear rate. Fluids are classified as Newtonian or non-Newtonian, depending on whether their viscosity is constant or not (Figure 3).

Like ketchup, blood has inherently a non-Newtonian nature and subsequently an inconsistent viscosity, which at lower shear rates is primarily determined by the concentration of RBCs and their stiffness or deformability[11]. RBC flexibility can be reduced by hypoxia and acidosis, among others[12,13]. Normally, 8-micron RBCs bend to flow freely and independently through arterial capillaries, where the shear rates are high. However, at lower shear rates, RBCs tend to aggregate like stacked coins forming so-called rouleaux, which increases blood viscosity[14]. This means that blood viscosity is always apparent, context-sensitive, and depends on the actual flow conditions. Even at physiological Hb (hemoglobin) or Hct levels, low shear rates can provoke this nonlinear increase in blood viscosity through the formation of rouleaux, mainly in the larger postcapillary venules[11]. There, the decelerating blood reaches its nadir shear rate, which causes blood to sludge. Stacks of RBCs further connect to each other by long cathodic molecules such as fibrinogen, a process intensified by acute phase molecules and immunoglobulins under pathological conditions[11]. Such inflammatory molecules force RBCs to aggregate even in the more proximal microcapillaries, thus impeding the microcirculatory flow (shock)[15].

In summary, the Hct is the most fundamental determinant of blood viscosity, followed by

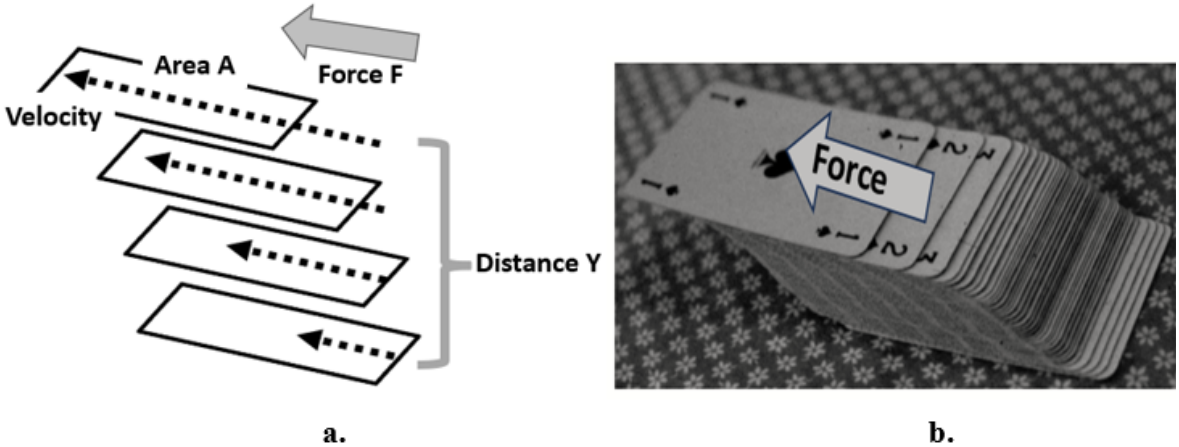

Fig. 2 — a. The tangential force F causes tension stress on the top plate with area A and accelerates it. This force is transferred to the underlying layers. The velocity of every single layer is inversely proportional to the distance between it and the upper plate. See text for more explanation. b. Playing cards analogy of the viscosity model.

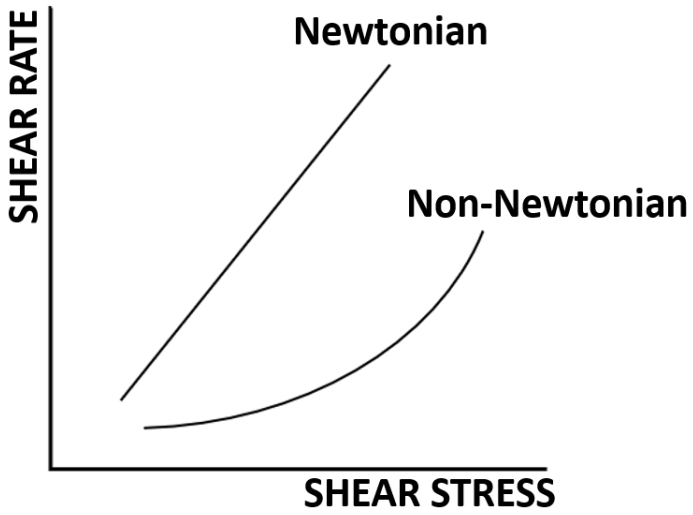

Fig. 3 — Viscosity as the ratio of shear stress (x-axis) to shear rate (y axis) and the difference between Newtonian and non-Newtonian fluids, respectively. A linear relationship means that the viscosity is constant and the fluid is Newtonian.

temperature[16]. By lowering the Hct or the levels of large proteins (e.g. fibrinogen) to limit RBC aggregation, the blood can be converted into a near-Newtonian fluid[11,17]. This is most easily achieved by diluting the mass of RBCs. As a side effect, HD increases the dimensionless Reynolds number, a risk indicator of turbulence, which is inversely related to viscosity. The latter occurs at high flow points, such as arterial branches and narrowed stenotic vessels or valves. Besides the enhancement of auscultatory murmurs and also heart sounds, the clinical impact of more turbulence during clinical HD is unclear[18]. Furthermore, a kind of physiological anemia was observed in association with prolonged bed rest and longer stays in space, supporting the hypothesis that a hematocrit-related viscosity reduction may provide natural protection against thromboembolic events[19,20]. Although now considered obsolete, it was once a practice to reduce blood viscosity with, for example, dextran to prevent postoperative deep vein thrombosis[11].

Oxygen transport, rheology and hemodynamics

Blood circulates to and from the microcirculation, the body's largest available cross-sectional area for gas exchange and molecular interaction. DO_2(oxygen delivery) is the content of O_2(oxygen) in the blood, both Hb-bound and gaseous, that leaves the left ventricle per minute to be distributed across the microvascular network [DO_2=CO•(1.34•Hb•O_2Saturation+pO_2•0.0031)]. As shown in Figure 4, Hint's seminal paper, published in this journal in 1968, demonstrated that a supramaximal O_2-transport capacity can be realized under resting conditions at lower Hb levels, despite the associated reduction in blood O_2-content[21]. Hint expanded on previous findings and demonstrated that this beneficial effect can only be achieved if the circulating blood volume is strictly maintained[22]. These findings are repeatedly confirmed by others[23]. Paradoxical at first glance, the underlying physics are clear: Hb as independent parameter decreases linearly, while viscosity, a dependent rheological variable, decreases exponentially. So do vascular resistances, changing smoothly and evenly with the viscosity, at the same rate and extent, as determined by the Hagen-Poiseuille linear relationship between viscosity and resistance. According to the Frank-Starling law, illustrated by Guyton, the viscosity-related decrease in (venous) resistance induces a subsequent increase in VR and CO, compensating for the lower O_2-content to maintain O_2-transport at normal levels within a Hct range of roughly 25%-45%. Furthermore, supramaximal O_2-transport is achieved at Hct levels of circa 30%, which triggers an optimal CO reflex, due to the non-proportional relationship between the simultaneous decrease in Hb and the viscosity-dependent venous and arterial resistances[6,7]. However, this beneficial discrepancy between O_2-content and supramaximal O_2-transport only occurs in subjects with sufficient preload and cardiac reserves, at rest or under basal metabolic conditions, such as sedation or possibly well-dosed anesthesia[23].

Otherwise, during intense exercise and hyperdynamic states with an elevated CO and accelerated blood flow, resulting in faster shear rates and thus lower blood viscosity, higher Hct values might be required to optimize O_2-transport[24]. It can be assumed that each flow rate corresponds to a specific Hct value, with a match between blood viscosity and the maximum achievable O_2-transport[25]. So, cyclists and other athletes benefit

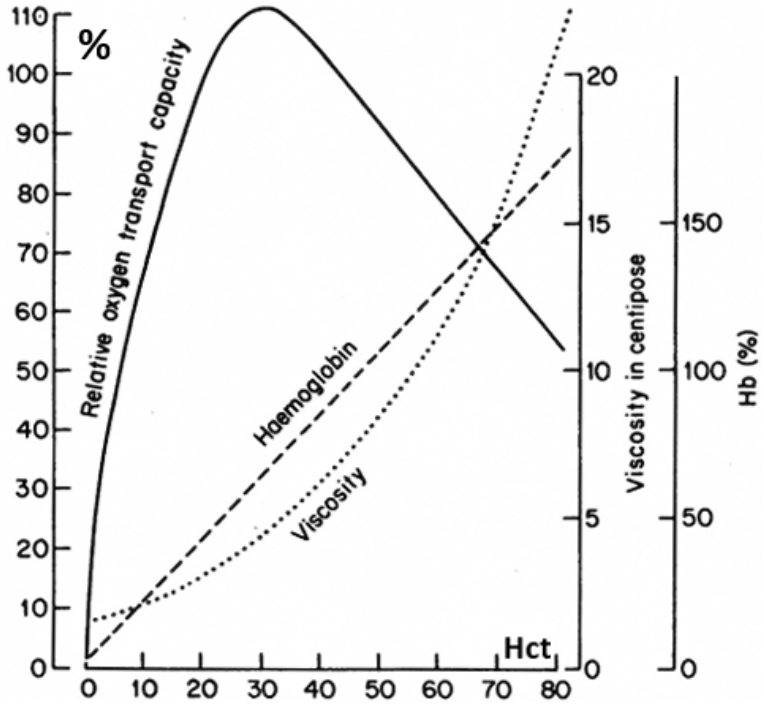

Fig. 4 — Relationship between hemoglobin, viscosity and relative oxygen transport capacity. Reproduced with permission - picture courtesy[21].

from an increased Hct caused by high-altitude training or erythropoietin doping[26].

Conversely, HD is indicated during hypothermic CPB (cardiopulmonary bypass) to avoid hyperviscosity related complications. Using 'clear primes' instead of whole blood to prime (= filling up) extracorporeal circuits prevented harmful complications of hypothermic CPB, documented since the early days of cardiac surgery[27,28]. Calculation of SVR (systemic vascular resistance), corrected with Vand's equation, can eliminate the effects of both temperature and Hct changes[29]. This afterload surrogate reflects more accurately the vascular tone in hemodiluted and hypothermic or pyrexial patients[30].

As postulated by Guyton and, although refuted by some but nevertheless useful for this context, is the P_{MCF} (mean circulating filling pressure)[31,32,33]. It is a static pressure, which is uniformly present throughout the whole circulation during circulatory standstill. This filling pressure is generated by a portion of the circulating blood, the so-called Vs (stressed volume), the pressure of which is mainly realized by the arterial vascular elasticity[34]. The difference P_{MCF} minus RAP directly controls the VR to the heart and thus CO. The Vu (unstressed volume), on the other hand, represents the venous capacity and its magnitude depends on the venous vascular tone[35]. Vu can be modeled as a balloon to store blood as a reserve, which is immediately available for recruitment[36]. Approximately 70-75% of the total blood volume consists of Vu, while Vs takes up 25-30%. Determined mainly by transmural pressures and intravascular tensions, Vs and Vu are just functionally separated components, balancing in a dynamic equilibrium. The relevance to the current topic of this Vs and Vu concept is illustrated by the well-known bathtub analogy (Figure 5). The tap represents the arterial flow rate and the water level of the tub reflects the total blood volume[35]. Water below the overflow hole is Vu, and water rising above it is Vs. The size of the hole and the outflow tube are respectively analogs of the venous resistance and the VR, through which the water is pumped back to the faucet tap. In such a closed system, the net outflow from the tap can never be greater than the return flow through the drain to the tap (Frank-Starling similarity). Imagine a thought experiment replacing water by a viscous oil, while all the bath's pipes and plumbing remain identical. Even if ignoring the Navier-Stokes equations for a moment, it follows intuitively that at steady state both the oil levels above and below the overflow hole will be the same as in a water filled bathtub. However, flow rates then have to be lower due to the higher intrinsic impedance of the viscous oil[37]. This implies, theoretically, that changing viscous resistances should only affect flows (VR and CO) and not the Vs and Vu. Physiologically, CO increases are possible with minimal Vs and Vu changes[38].

Both the simplified bathtub analogy and Guyton's analyses are useful models to illustrate the impact of viscosity on blood rheology. However, they do

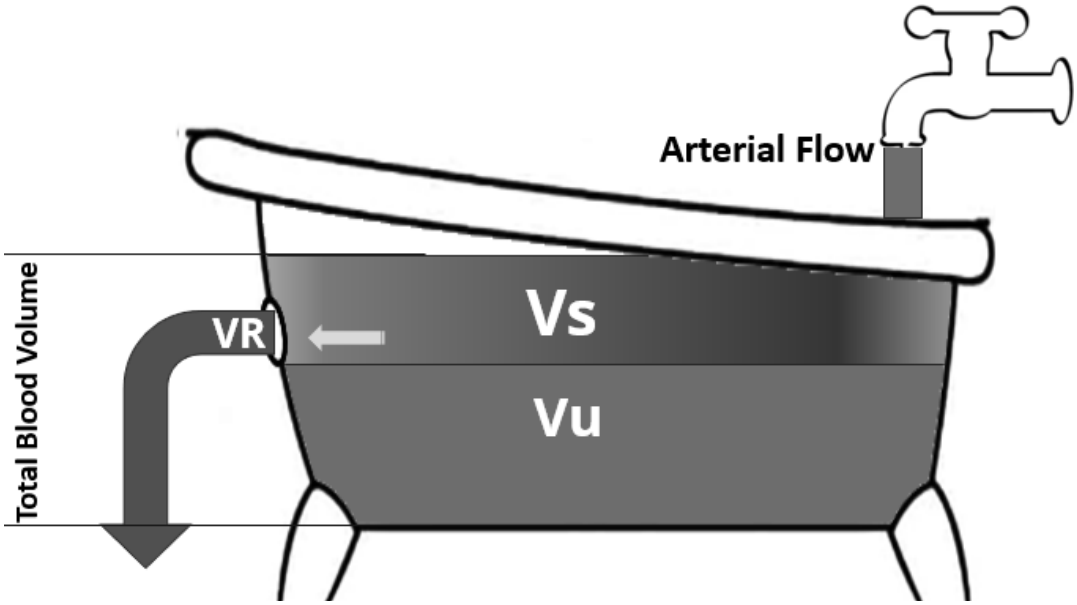

Fig. 5 — Bathtub analogy: tap and outflow represent arterial pressure and flow rate, respectively, and the water level of the tub reflects the total blood volume. Water below the overflow hole is Vu, and water rising above it is Vs; the hole's size and outflow tube are venous resistance and VR. Depiction inspired by S. Magder[40] .

not fully reflect the complexity of the complete vascular system and neglect some characteristics, such as the varying distensibility of blood vessels[11,39,40]. During HD, Vs and Vu may be still influenced by the volume of the harvested blood and the composition or amount of the replacement solution, which can induce fluid exchanges between the intravascular, interstitial and intracellular spaces[10,41,42]. In addition, during surgery under anesthesia, suppressed adrenergic responses and hemodynamic disturbances, including a decreased P_{MCF}, may cause hypotension and vasodilation, resulting in a shift of volume from Vs to Vu[43]. This is currently treated by manipulating the venous tone and capacitance with vasopressors and fluids. Dynamic monitoring of fluid response should be recommended here, as attempts to increase VR and thus stroke volume with fluids are only successful in biventricular preload responders. The latter is the basis of goal-directed-fluid-therapy, which could prevent excessive fluid administration during HD. Non-fluid responders have depleted preload reserves since they are at the high end of their Frank-Starling curve, or even beyond[44-46].

Furthermore, the lower SVR values observed during HD are not only caused by the decreasing viscosity, but also in part by endogenously released NO from RBCs, which adjust DO_2 and CO_2 removal to local demands through hypoxic microvascular dilatation[47,48]. Those effects put in perspective the concept of a 'global optimal Hct', as this optimum can vary[50,51]. Cerebral desaturation and coronary ischemia during ANHD or blood loss may occur[52,53]. Unpredictable microcirculatory steal effects induced by HD can also exacerbate or mitigate existing microcirculatory disorders, resulting in what is respectively known as a reversed or a not-reversed Robin Hood steal syndrome[4,11,55]. It has also been shown that CO augmentations as a reflex to the HD related SVR reduction might be blunted by anesthetics or a limited cardiac function[56]. The critical point at which O_2-supply really becomes insufficient under all these conditions is not precisely known and can fluctuate[57]. Nevertheless, reduced DO_2 at Hb levels of 4.5-5 g/dl by normovolemic HD has been shown to be well-tolerated in conscious, healthy and young but resting adults[58]. Tolerance to severe HD after massive fluid loading following sudden accidental bleeding has also been demonstrated in Jehovah's and other cases. Moderate hypothermia, 100% O_2, full relaxation and deep anesthesia were able to optimize the O_2 delivery/demand balance[59].

In summary, at rest or under strictly basal conditions moderate hemorheological ANHD, in which a Hct of about 30-32% is reached, contributes to the improvement of O_2-supply, if the cardiac function is not seriously burdened[60,61]. When the Hct falls below 25%, adaptation of coronary flow to the increased CO is usually limited while anoxic anemia can occur as well due to splanchnic and cutaneous vasoconstriction[62-64].

Plasma, fluids and intravascular space

Unlike blood, plasma is Newtonian and its viscosity influences the microvascular function, which is sensitive to changes caused by exogenous solutions[65,66]. Depending on which intravenous solution is used, plasma components are diluted or concentrated during HD. Intravenous fluids contain

molecules in concentrations that often differ from plasma, such as dissolved particles (osmolality) or suspended macromolecules (oncocity). The concentration of crystalloids or colloids, which are particles that respectively are unable to passively cross cell membranes or capillaries, can be higher, equal or lower compared to plasma. Therefore, fluids can be classified to be hypo-, iso- or hypertonic and hypo-, iso-, or hyperoncotic. Solvents can influence the acid-base status solely through physicochemical interactions or, more purposefully, through the adding of buffers or their precursors (balanced solutions)[67]. Dilutional hyperchloremic metabolic acidosis after massive saline infusion is such a well-defined clinical condition[68]. HD can influence pharmacokinetics by diluting circulating substances, such as albumin, which may affect the unbound fraction of drugs and, for instance, prolong a neuromuscular blockade[69]. The effect of exogenous catecholamines can be attenuated by HD[70]. Although coagulation factors are also diluted, hypercoagulability may occur after an episode of HD, while coagulopathy after trauma and hemorrhagic shock is much more complex than just a dilution[71].

Some intravascular macromolecules and plasma are trapped in the negatively charged brush-like glycocalyx layer covering endovascular surfaces: the ESL (Endothelial Surface Layer)[72]. This barrier should regulate and restrict the passage of large molecules and fluid into the extravascular (third) spaces[73]. Shedding and disruption of this fragile ESL is thought to contribute to coagulopathy and fluid or protein leakage from the intravascular space during surgery, trauma, prolonged ventilation, burns, sepsis, hypo/hypervolemia, and other medical conditions[73,74]. Glycocalyx degradation can even stimulate the aggregation of RBCs[75]. However, microvascular modification by glycocalyx shedding does not always and necessarily resulted in substantial increases of vascular permeability after (e.g. colloidal) fluid resuscitation[76]. The oncotic or colloid osmotic pressure response to albumin or artificial colloid infusion may be useful here, as a non-invasive point-of-care monitoring of capillary leaks[77-79]. Although augmented release of ANP (Atrial Natriuretic Peptide) during hypo- or hypervolemia should correlate with ESL degradation, no clear causal relationship was demonstrated[80,81]. ANP administration even protected against capillary leakage under certain conditions[82]. Sometimes the factual data on ESL and fluid administration are conflicting and still not univocal[83]. However, the usual procedure, considered transfusion-sparing, of performing a volume load just before surgery to achieve a hypervolemic HD would disrupt the ESL with a vascular leakage of volume[84]. Hypervolemia related stress on the atrial walls of the heart may stimulate the release of ANP. Therefore, preference should be given to ANHD, using only optimal volumes and gentle infusion rates to maintain circulating intravascular volume without vascular stretch and ESL disruption[85].

Because fluid therapy does not always result in the expected distribution and volume effects, Woodcock & Woodcock re-examined the exposure of semi-permeable capillaries to hydrostatic and oncotic pressures[86,87]. They postulated a modified model of Starling's equilibrium, including ESL and its functioning. However, the implications of this attractive model are not fully proven, as the risks of hypervolemia-induced capillary leakage would be overemphasized by misinterpretation of some measurements[88,89].

Despite all the ongoing and sometimes controversial research, there is no single fluid for HD that meets all requirements. Current volume replacement should be tailored to individual needs based on an old but still valid adage: "the right fluid, the right amount, the right speed, at the right time".

Clinical Applications

Since the 1960s, the knowledge on HD increased and was progressively seen as a potential tool to prevent or reduce exposure to homologous blood. Boosted in the 1980s by the increasing risk of HIV and other known and unknown pathogens, such as hepatitis viruses, intentional ANHD became a prominent blood conservation technique. In theory, blood was removed and replaced with crystalloids or colloids before surgery to reduce allogeneic blood transfusions. The harvested blood was stored as autologous blood to be reinfused later, during or after the surgery. Considered a beneficial effect of ANHD, the spilling of diluted blood also resulted in fewer RBCs and other formed elements lost per volume than whole blood. ANHD can either be performed on the spot, intraoperatively, or as a pre-deposit of blood units, collected weeks before the intervention, stored and tested at a transfusion center[90]. Unfortunately, ANHD did not unambiguously proof to reduce overall transfusion exposure and concerns raised about the true efficacy, as evidenced by inconclusive systematic reviews due to substantial and unexplained heterogeneity[91-93]. Although ANHD is considered safe, it can also be harmful if it is too severe and lasts too long, with potential hypoperfusion and organ damage[94]. In addition, ANHD is not always performed carefully, with

major hemodynamic fluctuations as a disadvantage. Some therefore advocated hypervolemic ANHD or the easy-to-perform intensive preoperative volume loading resulting in systematic overload and even third spacing, which may need to be avoided[43,85,95].

Meanwhile, replacing losses by accurate fluid titration to maintain normovolemia and tolerating a de facto HD became more and more common. The indulgence towards HD is strongly supported by the repeated evidence that Hb levels above 10 g/dL do not improve O_2-transport in critically ill patients at rest[96]. Hb levels between 7-8 g/dL can be tolerated in ICU patients with an adequate oxygenation, unless the patient is symptomatic and has cardiac or brain damage[97,98]. Instead of one-size-fits-all triggers, decision-making nowadays is based on trends and context, using point-of-care laboratories and continuous Hb monitoring to differentiate a transient HD from progressive bleeding or hemolysis. Not every Hb drop requires transfusion and the difference should be made between true anemia by a reduced mass of RBCs and mere dilution[99].

The mixed results and limitations of ANHD as a sole blood conservation practice led to more cautious approaches and other strategies[96]. Multidisciplinary patient blood management guidelines aim to optimize preoperative Hb with iron or erythropoietin, minimizing losses and blood salvage through cell savers and pharmacological interventions[99]. However, a standardized use of ANHD in high-risk surgical bleeding is still recommended as an evidence- and consensus-based blood conservation modality[96].

Conclusion

It looks like nature and evolution helped humans and other species to survive by making circa one-third of their RBCs available for immediate recruitment at any time. This is useful during strenuous physical exertion and protective against all kinds of blood loss. Hypothetically, the benefits of HD could also partly explain the historical success of bloodletting for certain medical conditions over the centuries, especially if this intervention would have been followed by oral fluid intake to compensate for the volume deficit. The body of accumulated knowledge on HD offers an excellent tool in many medical matters and helps to strive for a better critical care. Paraphrasing George Box, we should focus more on whether something can be applied to everyday life in a useful manner than debating if all available answers are correct in all cases[100].

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Permission Editor AAB requested to reproduce one figure from H. Hint[21].

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