

The Role of Blood Viscosity in Hemodialysis Patients

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ABSTRACT

Hemodialysis typically increases blood viscosity. Increased blood viscosity plays a role in accelerating atherosclerosis, in anemia, and in decreasing life expectancy in hemodialysis patients. Elevated blood viscosity increases the risk of thrombosis, decreases tissue perfusion, and increases systemic vascular resistance. Elevated blood viscosity also reduces the efficiency of hemodialysis, which can contribute to electrolyte abnormalities. Inefficient removal of protein-bound uremic toxins decreases the erythrocyte zeta potential, augmenting erythrocyte aggregation and low-shear blood viscosity. This contributes to accelerated atherosclerosis, which may be the most common cause of death in hemodialysis patients. The interaction of the systemic vascular resistance response and the renin-angiotensin-aldosterone system regulates blood viscosity

even in renal failure patients. This regulation is accomplished in part by modulation of the hematocrit, which causes the anemia of renal failure. Erythropoiesis-stimulating agents interfere with this homeostatic response, increasing the risk of atherosclerosis and death. The change in intravascular volume caused by hemodialysis correlates with the change in blood viscosity, suggesting that viscometry may provide useful data in assessing a patient's volume status. Capillary viscometry is the best method for measuring blood viscosity. On-site testing in a free-standing hemodialysis facility is feasible.

Key words: Blood Viscosity; Renal Failure; Hemodialysis

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INTRODUCTION

Elevated blood viscosity causes pathology via several mechanisms. First, blood viscosity is inversely related to blood flow. Thus, hyperviscosity causes underperfusion of all tissue. Elevated blood viscosity predisposes to thrombosis by causing sluggish blood flow. It also increases systemic vascular resistance and contributes to hypertension. Elevated blood viscosity impacts the prognosis of renal failure patients by accelerating atherosclerosis, explains the occurrence of anemia in chronic renal failure, and contributes to the decreased life expectancy of patients despite hemodialysis. Because blood viscosity is under homeostatic control, measuring blood viscosity helps in assessing the volume status of hemodialysis patients.

THE BASICS OF BLOOD VISCOSITY

Experience with the viscous behavior of fluids such as water, ethanol, and gasoline is not applicable to blood. Unlike those fluids—but like ketchup—the viscosity of blood decreases as its flow velocity (i.e., shear rate) increases, making blood a non-Newtonian fluid (Figure 1). Shear rate is expressed as inverse seconds (1/sec).

Blood flow can occur at either high shear rates, $\geq 100/s$, or low shear rates, $\leq 10/s$. High-shear flow occurs in arteries during systole, especially in long straight arteries. Low-shear conditions occur in veins, capillaries, and, in some patients, in areas of changing arterial geometry, such as branches, curves, focal constrictions, and dilatations. In those arterial segments, decreased arterial compliance or obstructions such as arterial plaques can cause blood to flow at high velocity. Flow separation develops, leading to low-shear conditions. Flow separation allows pools or eddies to develop adjacent to rapidly flowing blood (Figure 2). This has implications for atherothrombosis.

Next to shear rate, the most powerful variable determining blood viscosity is the hematocrit (Hct). Less powerful variables include plasma viscosity—which varies with the concentration, size, and shape of circulating proteins—erythrocyte aggregation, and erythrocyte deformability.

ERYTHROCYTE AGGREGATION

Blood viscosity increases exponentially as the shear rate decreases because of progressive, reversible erythrocyte aggregation, which forms stacks of erythrocytes called *rouleaux*^[1] (Figure 3). Erythrocyte

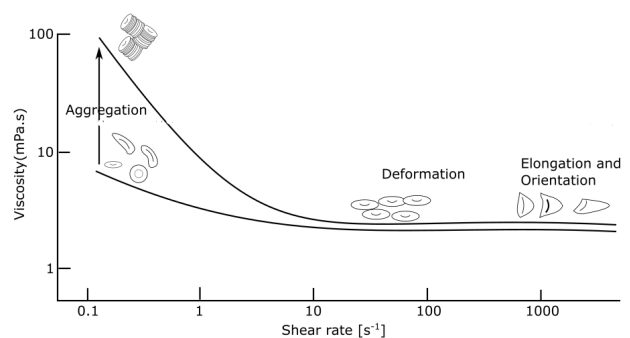


Figure 1 The relationship of blood viscosity to shear rate. Blood viscosity decreases as shear rate increases. Erythrocytes aggregate at low shear rates and reversibly deform from discocytes into ellipsoids. One centipoise (cP) equals one millipoise (mPa.s). The lower curve is the viscosity of defibrinated blood, which has much less erythrocyte aggregation. Courtesy of MagMedics, LLC.



Figure 2 An area of flow separation (white arrow) caused by high-velocity flow due to an obstruction in the common carotid artery. Flow in the jugular vein is blue. Flow in the common carotid artery is in the opposite direction and velocity of flow are indicated on the color scale at upper right. Flow in the common carotid is from right to left. Note that the flow velocity increases as it encounters the obstruction, turning from red to yellow. An area of very slow, retrograde flow, dark blue in color, is present at the distal end of the obstruction. The obstruction is gray in color and located against the arterial wall. Courtesy of Robert S. Perret, MD.

aggregation increases blood viscosity by increasing the effective mass of erythrocytes, thereby increasing their inertia and the force, called *shear stress*, required to move them. Erythrocyte aggregates are weak and break when sufficient shear stress is applied to them.

Erythrocyte aggregates form when large proteins such as fibrinogen and low-density lipoprotein (LDL) act like glue and simultaneously bind two erythrocytes. The fibrinogen receptor on the erythrocyte is the integrin $\alpha v\beta 3$ ^[2]. LDL binds to an incompletely characterized receptor^[3]. Significantly, high-density lipoproteins compete for binding to approximately 60% of LDL receptors, decreasing blood viscosity.

Erythrocyte aggregation mediated by fibrinogen causes the elevated erythrocyte sedimentation rate (ESR) commonly observed in inflammation. Erythrocyte aggregation greater than normal is called *hyperaggregation*. The ESR and plasma fibrinogen concentration are similarly elevated in end-stage renal disease in both nephric and anephric patients, demonstrating that nephritis does not cause the finding^[4].

An electrical field called the *zeta potential* prevents erythrocytes from spontaneously aggregating^[5]. The more negative the zeta potential, the less likely that erythrocytes will spontaneously aggregate. The zeta potential derives from the negative charge at the erythrocyte surface caused by sialic acid. This attracts a cloud of sodium cations and the anions they attract, predominantly chloride (Figure 5). This cloud prevents the closer approach of other erythrocytes. Thus, binding molecules and particles with a large diameter are necessary to foster erythrocyte aggregation, because they will not be hindered by the repulsion between the negatively charged erythrocytes.

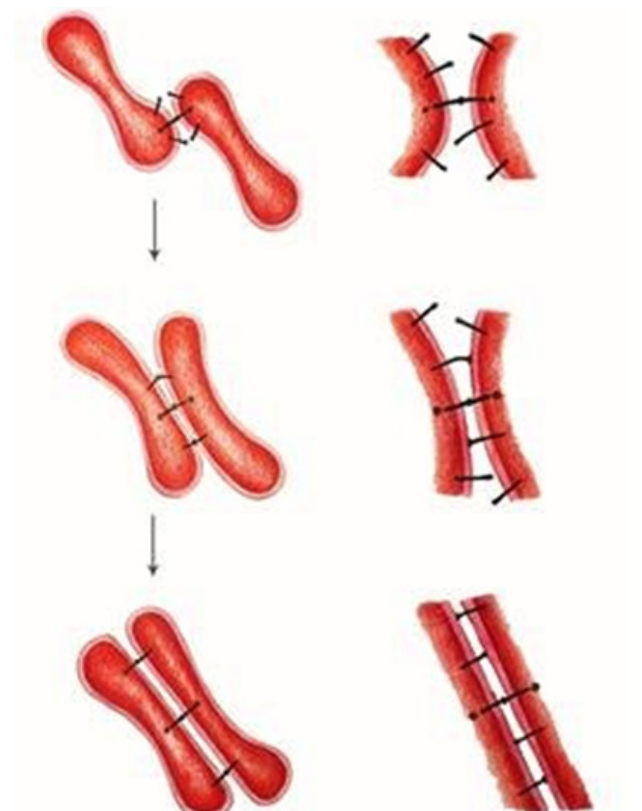


Figure 3 The formation of an erythrocyte aggregate. Molecules or particles with a large diameter, such as fibrinogen or low-density lipoprotein, can act like glue and bind two erythrocytes. When the erythrocyte zeta potential decreases, smaller molecules such as IgG can also foster erythrocyte aggregation. Ultimately, this process gives rise to rouleaux. Courtesy of Pop *et al.*[1].

ERYTHROCYTE DEFORMABILITY

At high shear rates, shear stress causes an erythrocyte to reversibly deform from a biconcave disc into an ellipsoid, decreasing the resistance offered by its leading edge (Figure 1). Erythrocytes also entrain, allowing them to draft, reducing resistance and the energy needed for flow. These phenomena decrease blood viscosity at high shear rates. Reduced deformability increases blood viscosity, especially at high shear rates.

Because the diameter of an erythrocyte is greater than the diameter of a capillary, erythrocytes must deform to circulate through them. Erythrocytes are the most deformable biomaterial known^[6]. Optimal performance is possible only when each component performs normally. In the erythrocyte, these components include the cell membrane, cytoskeleton, and cytosol. Given that each of these can deteriorate or malfunction, it is not surprising that abnormalities of erythrocyte deformability are common and nonspecific. For example, repetitive deformation inevitably causes mechanical fatigue so that erythrocytes stiffen with age.

Cell membranes become less fluid when long, saturated fatty acids replace shorter saturated and unsaturated fats in the lipid bilayer because long carbon chains form more van der Waals attractions. Uremia also decreases cell membrane fluidity. Decreased erythrocyte membrane fluidity increases blood viscosity at both low and high shear rates^[7]. Spherocytes and echinocytes are less deformable than discocytes. The important subject of erythrocyte deformability has been reviewed by Baskurt and Meiselman^[8].

BLOOD VISCOSITY IS INVERSELY PROPORTIONAL TO BLOOD FLOW

Viscosity affects blood flow as described by the Hagen-Poiseuille equation: $Q = \Delta P \pi r^4 / 8 \ell \eta$, where Q = flow, ΔP = the blood pressure gradient, r = vessel radius, ℓ = vessel length, and η = blood viscosity. Thus, flow is inversely proportional to viscosity. Experimentally, an increase in blood viscosity causes a threefold decrease in blood flow^[9]. This decreases the delivery of oxygen, glucose, and all other

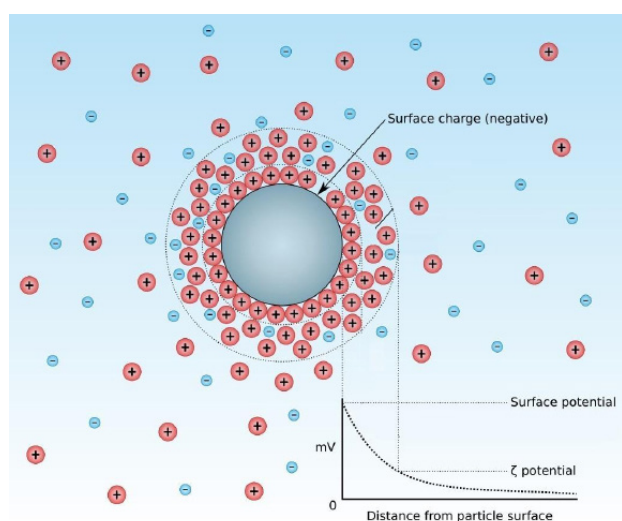


Figure 4 Zeta potential. A charged particle, known as a colloid, suspended in water attracts dissolved ions. This results in the zeta potential, which varies with the magnitude of the surface charge and the concentration of ions. If the zeta potential is too low, colloids can spontaneously agglutinate or flocculate, which limits the shelf life of some medications. In blood, erythrocytes are colloids, and the dissolved ions include sodium, chloride, and organic ions. Courtesy of Wikimedia Commons, Mjones1984, and Laryyisgood.

metabolic substrates to tissue and reduces the delivery of carbon dioxide to the lungs and other metabolic wastes to the kidneys.

Another consequence of the inverse relationship of blood viscosity to flow is an increased risk of thrombosis. Sluggish blood flow is simply the manifestation of elevated blood viscosity. Sluggish blood flow was first noted to be a risk factor for thrombosis by the 19th-century pathologist Rudolph Virchow. Slow blood flow allows initial erythrocyte aggregation to occur, which increases blood viscosity. This decreases blood velocity, leading to more aggregation, even slower flow, further aggregation, etc. This process creates larger areas of lower shear and even localized stasis.

Fibrinolytic activity normally eliminates the microthrombi that develop on morphologically normal intima^[10]. Sluggish blood flow limits the influx of fibrinolytic activity and dispersion of activated clotting factors. Areas of sluggish flow are also prothrombic because of decreased shear-mediated endothelial production of nitric oxide and prostacyclin, molecules with antiplatelet activity. Thus, endothelial dysfunction is often the result of sluggish blood flow and extensive low shear^[11].

THE EFFECT OF RENAL FAILURE AND HEMODIALYSIS ON BLOOD VISCOSITY

Because of fluid overload and the anemia of renal failure, blood

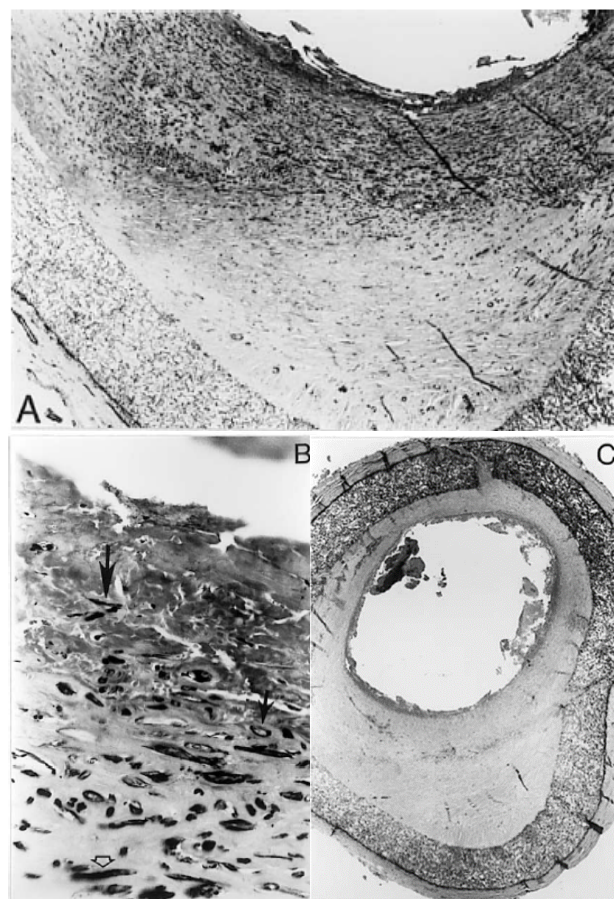


Figure 5 An atherosclerotic plaque within a Dacron arteriovenous graft used for hemodialysis stained for smooth muscle actin. Panels A and B are stained for smooth muscle actin. Positive cells stain darkly and are indicated by arrows in panel B. Panel C is a low-power image of an atherosclerotic plaque stained with hematoxylin and eosin. Like atherosclerotic plaques in native arteries, the plaque is an asymmetric, not concentric, thickening. The graft is indicated by a long arrow. A thin layer of fibrin on the plaque surface is indicated by the short arrow. Original magnification: panel A, 40 \times ; panel B, 750 \times ; panel C, 20 \times . Reference [25].

viscosity at high shear rates in chronic renal failure typically is normal to slightly decreased before hemodialysis. Blood viscosity at low shear rates is typically normal to slightly increased. This may be due to treatment with erythropoiesis-stimulating agents (ESA) or increased erythrocyte aggregation, as reflected in the increased ESR in these patients. Unfortunately, most studies of blood viscosity in chronic renal failure do not report a normal reference range, only the change caused by hemodialysis.

Hemodialysis typically increases blood viscosity^[12-17]. Erythrocyte cell membrane fluidity improves slightly with dialysis^[18]. The effect of hemodialysis on blood viscosity in a patient depends on the dominant abnormality before dialysis and how it responds to hemodialysis. Thus, hemodialysis can increase or decrease blood viscosity.

Vaisman et al. published quantitative data on the effect of hemodialysis on blood viscosity in thirty patients^[19]. Several attributes make their data particularly useful. They published normal values of blood viscosity at both shear rates reported. Blood viscosity was measured before and 3.5 hours after hemodialysis. This allows re-equilibration of plasma concentrations of protein-bound uremic toxins (PBUT). Some of these can augment erythrocyte aggregation by lowering the erythrocyte zeta potential [vide infra].

In their study, blood viscosity was determined by capillary viscometry. This method is more sensitive than rotational viscometry to the effect of erythrocyte aggregation on low-shear blood viscosity. Erythrocyte aggregates form in the low-shear environment in the center of the column of flowing blood in a capillary viscometer, whereas they are disrupted by the shear applied in a rotational viscometer.^[4] Further, this study reported quantitative data on each patient, highlighting the interindividual variation in blood viscosity and response to hemodialysis. The study population was anemic, with a mean Hct of 34%. The hematocrit of individual subjects was not reported. Data from this study will be discussed in detail.

At a shear rate of 5/sec, five patients had abnormally high pre-dialysis blood viscosity, >14 cP in this study. Low-shear blood viscosity increased in nineteen subjects after hemodialysis. Nine patients had abnormally high blood viscosity at 5/s after hemodialysis. Blood viscosity increased by 140% in three patients. Viscosity decreased in four subjects with high pre-dialysis values, normalizing in three.

At a high shear rate (300/s), pre-dialysis blood viscosity was less than or nearly normal, 3.2 cP, in all but two patients, despite anemia. This value is similar to the normal mean blood viscosity, 3.26 cP, determined in a population of 126 healthy adults with a mean hematocrit of 42.3% and measured at 100/s^[20]. Measured 3.5 hours after hemodialysis, high-shear blood viscosity increased in twenty-three patients, becoming abnormally high in four additional patients. There was a significant correlation between the change in blood viscosity and the weight of fluid removed at dialysis, $R^2 = 0.405$.

ACCELERATED ATHEROTHROMBOSIS

In some studies, cardiovascular disease is the most common cause of death in hemodialysis patients. Patients with chronic renal failure have a 5- to 10-fold increased risk of cardiovascular disease compared to age-matched controls^[21], a finding that traditional risk factors explain only incompletely^[22]. This increased risk is due to elevated low-shear blood viscosity.

This was demonstrated by the study of Canaud et al., which showed that low-shear blood viscosity was higher in hemodialysis patients who died of cardiovascular disease ($n = 8$) than in those

who died of other causes ($n = 20$)^[12]. The increased cardiovascular risk caused by elevated low-shear blood viscosity is not limited to hemodialysis patients. Low-shear blood viscosity is a stronger predictor of cardiovascular events than high-shear blood viscosity in hypertensive men as well, independent of the effect of other risk factors^[23].

As noted above, elevated low-shear blood viscosity increases the risk of thrombosis. If a thrombus persists long enough, it undergoes fibrous remodeling, or *organization*, the process in which stem cells differentiate into granulation tissue and form a scar. This process causes healing by secondary intention and fibroplasia of exudates and clots.

Leu et al. demonstrated in the 1980s that a thrombus can be organized entirely by circulating cells. They suspended a thrombogenic Dacron surface within a sheep aorta in such a way that it had no connection with the endothelium. Over a period of 84 days, the investigators noted collagen synthesis and differentiation of circulating stem cells into endothelial cells, myofibroblasts, and fibroblasts^[24].

Organization of mural thrombi in Dacron arteriovenous grafts used for hemodialysis access results in lesions that are morphologically and immunohistochemically indistinguishable from atherosclerotic plaques in native arteries. These atherosclerotic plaques in synthetic grafts have been the subject of several reports^[25] (Figure 4). Further, the smooth muscle cells in atherosclerotic plaques are immunohistochemically distinct from the smooth muscle cells in the vessel tunica media^[26].

Blood flow in Dacron arteriovenous grafts is extremely high velocity, resulting in turbulence. This is evidenced by audible bruits and palpable thrills. This allows platelets activated by high shear to cause mural thrombosis in areas of flow separation. The existence of atherosclerotic plaques in synthetic grafts has several implications for atherothrombosis theory. Atherosclerotic plaques do not require years of low-grade inflammation to develop. Smooth muscle cells do not migrate from the arterial media into the intima to form a plaque. Atherothrombosis is a thrombotic, not an inflammatory, disease. Thus, thrombosis causes both atherothrombotic complications such as myocardial infarction and ischemic stroke, as well as the underlying plaque itself^[11,25].

The thrombogenic theory of atherosclerosis was originally proposed in the 19th century by Rokitsansky. It was confirmed in the mid-20th century by the pathologist John Duguid after finding that serial sectioning of an atherosclerotic plaque revealed continuity with granulation tissue. This paradigm dominated atherogenesis thought until the evolving awareness that hypercholesterolemia is a risk factor for atherothrombosis. In familial hypercholesterolemia patients, extreme elevations of plasma LDL particle concentrations cause marked increases of blood viscosity, leading to accelerated atherothrombosis and deep vein thrombosis^[11]. Marked inflammation causing extreme elevations of interleukin 6 and fibrinogen in coronavirus disease 2019 (COVID-19) results in hyperviscosity and arterial and venous thrombosis^[2]. However, interventions to reduce cholesterol concentrations or inflammation in people without extreme elevations of either have enjoyed only modest success in decreasing morbidity and mortality due to atherothrombosis^[27].

Protein-Bound Uremic Toxins Increase Blood Viscosity at Low Shear Rates

Erythrocyte aggregation due to decreased zeta potential may be the most important cause of accelerated atherothrombosis in some hemodialysis patients. This decreased zeta potential results from

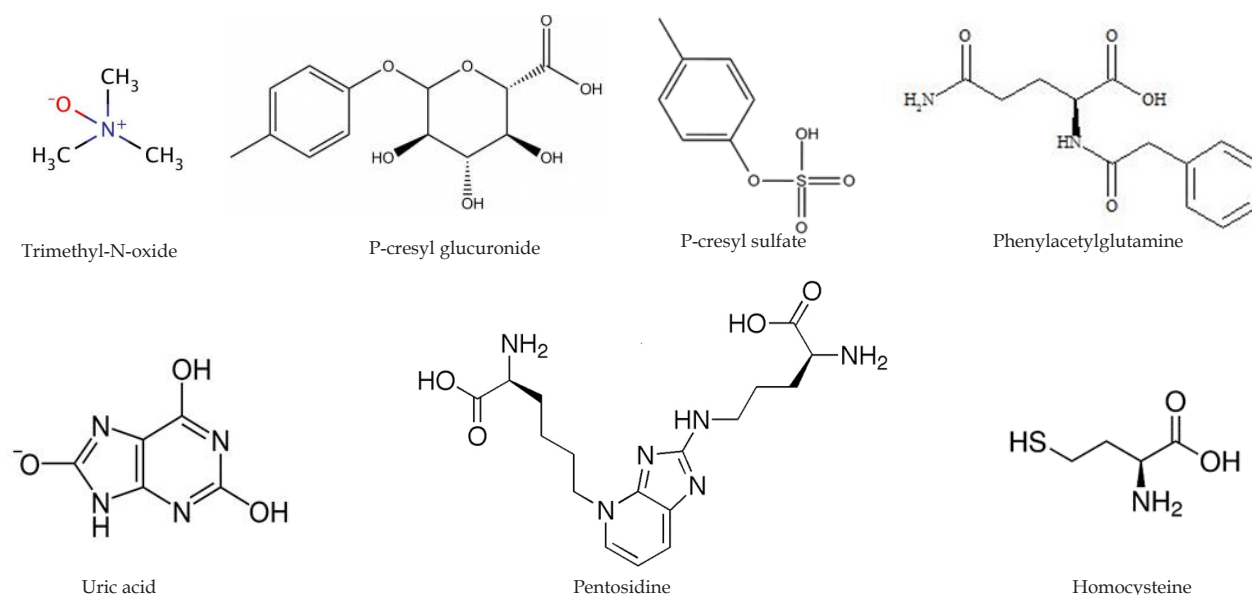


Figure 6 Organic ions. These molecules decrease the erythrocyte zeta potential when they are incorporated into the ion cloud surrounding an erythrocyte.

elevated plasma concentrations of protein-bound uremic toxins (PBUT). Normally, these molecules are eliminated by transporter proteins in the proximal renal tubular epithelium. Because PBUT are highly protein-bound, removal by hemodialysis is incomplete, and equilibrium plasma concentrations are quickly restored.

PBUT are typically ionized at physiologic pH (Figure 6). Commonly, this is due to the presence of carboxyl, amino, or sulfate groups. Because these molecules are larger than chloride and sodium ions, they can have a lower charge density than those smaller ions and decrease the zeta potential when incorporated into the ion cloud, lowering the barrier to erythrocyte aggregation. This allows smaller molecules such as IgG to foster aggregation, resulting in hyperaggregation^[28]. This was demonstrated *ex vivo* using elevated urate concentrations^[5]. Erythrocyte hyperaggregation due to decreased zeta potential increases low-shear blood viscosity and contributes to the increased risk of cardiovascular disease in gout.

Many PBUT are produced by the gut microbiome and are also known as *gut-derived uremic toxins* (GDUT). Twenty-five GDUT have been described to date^[29]. Their role in atherothrombosis was demonstrated in an elegant study by Bogiatzi *et al.*^[30]. Those investigators defined three groups based on the degree of carotid atherosclerosis: those whose disease was explained by traditional risk factors, those whose disease was not explained by traditional risk factors, and those who didn't have disease despite having traditional risk factors. The concentrations of four GDUT—trimethylamine N-oxide, P-cresyl sulfate, P-cresyl glucuronide, and phenylacetylglutamine—were highest in those whose disease was not explained by traditional risk factors and lowest in those who didn't have disease despite the presence of traditional risk factors. All are ionized at physiologic pH and decrease the erythrocyte zeta potential. Except for phenylacetylglutamine, these molecules are highly protein-bound.

Another class of GDUT is advanced glycation endproducts (AGE).^[29] Circulating AGE can be formed by nonenzymatic covalent binding of reducing sugars to the amino acids lysine, arginine, or cysteine.^[31] The plasma concentration of one AGE, pentosidine, is considerably higher in hemodialysis patients than those with stage 1-2 chronic kidney disease: 1.7 (0.6-3.1) μmol versus 0.2 (0.2-0.3) μmol (data expressed as median [10-90 percentile]).^[32]

It is reasonable to conclude that the accumulation of organic

ions, the consequence of renal failure, a pathologic gut microbiome, and hyperglycemia could decrease the erythrocyte zeta potential and increase cardiovascular risk. This is especially true because the erythrocyte zeta potential is in the range said to confer *incipient instability*; that is, the repulsive forces preventing spontaneous aggregation are only slightly greater than the attractive forces favoring spontaneous aggregation. Indeed, erythrocytes spontaneously aggregate when the zeta potential is less than -7 mV. The zeta potential of human erythrocytes is calculated to be between -13.07 mV and -18 mV. The weak zeta potential of human erythrocytes decreases the energy cost of two vital natural processes, hemoconcentration in postcapillary venules in inflammation and clot retraction in thrombosis, both of which require extreme packing of erythrocytes approaching a hematocrit of 100%.^[5] A zeta potential with an absolute value of > 61 mV is said to confer excellent stability.

The erythrocyte zeta potential cannot be measured directly. Quantification of erythrocyte aggregation by light microscopy has been the most widely utilized surrogate marker. Erythrocyte aggregates can also be detected by flow cytometry. Improvement of the prognosis of hemodialysis patients will require improvements in removing protein-bound uremic toxins. This is likely to occur only when the pathologic significance of the erythrocyte zeta potential and hyperaggregation is widely recognized. Currently, some still question a causal relation between PBUT and atherothrombosis.^[33]

ANEMIA OF CHRONIC RENAL FAILURE

The blood viscosities of healthy adults^[21] and anemic hemodialysis patients before hemodialysis^[20] are similar because blood viscosity is under homeostatic control. Without the ability to control blood viscosity, decreased renal blood flow would result in a vicious cycle: increased erythropoietin production would increase red blood cell mass and blood viscosity, which would further reduce renal blood flow, further upregulating erythropoietin production and blood viscosity, etc. Negative feedback of erythropoiesis prevents renal artery stenosis from causing terminal polycythemia.

Homeostatic control of blood viscosity was demonstrated by Kilbridge *et al.* in a 1969 paper titled "The mechanism by which plethora suppresses erythropoiesis"^[34]. The researchers showed in

mice that increasing blood viscosity by transfusion or dehydration decreases erythropoietin activity in response to hypoxia. They also showed that transfusing human erythrocytes containing 100% methemoglobin, which cannot transport oxygen, decreased erythropoietin activity to 10% of controls. These experiments show that mice prioritize blood flow over oxygen delivery. Blood flow is necessary for delivery of glucose and other energy substrates that are essential to life.

Further evidence of negative feedback of erythropoiesis was provided by the experiments of Pagel *et al.*^[35]. They showed in rats that the erythropoietin response to decreased renal oxygen delivery depended on the mechanism by which oxygen delivery was reduced. Clamping both renal arteries, which decreased renal oxygen delivery without changing blood viscosity, resulted in a linear increase in erythropoietin production. In contrast, anemia and reduced blood viscosity caused an exponential increase in erythropoietin production because the absence of negative feedback allowed a faster increase in red cell mass.

Negative feedback to downregulate erythropoietin production is provided by the systemic vascular resistance response (SVRR)^[36]. The anemia of renal failure, like the anemias accompanying congestive heart failure^[37] and hemoglobinopathies, is a homeostatic response to normalize systemic vascular resistance. Combining Ohm's equation, $R = \Delta P/Q$ (in which R represents resistance), with the Poiseuille-Hagen equation shows that $R = ((8 \times l)/(\pi r^4)) \times \eta$, where l is the length of the vessel, r is the vessel radius, and η is blood viscosity^[1]. Thus, systemic vascular resistance is directly related to blood viscosity.

In this response, mechanoreceptors in the left ventricle sense increased systemic vascular resistance and cause cardiomyocyte expression of B-type natriuretic peptide (BNP) and soluble erythropoietin receptor. BNP causes vasodilation and natriuresis and decreases intravascular volume. Soluble erythropoietin receptor is a truncated form of the erythropoietin receptor, which lacks the transmembrane and intracellular domains. It binds and eliminates circulating erythropoietin before it can bind to progenitor cells in the bone marrow. Expressing *decoy receptors* to modulate cytokine hormone activity is common with members of the class I cytokine receptor superfamily. Over the long term, the SVRR decreases the production of erythropoietin mRNA as well.

The activity of the SVRR normalizes systemic vascular resistance, in part by reducing hematocrit. In a study by Fellner *et al.*, eighteen stable renal failure patients on maintenance hemodialysis had slightly increased post-dialysis systemic vascular resistance, 1313 ± 84 dynes-sec/cm⁵ (normal range: 800-1200 dyne-sec/cm⁵) in the presence of anemia, Hct $24.7 \pm 0.9\%$, and low blood viscosity, 2.87 ± 0.11 cP.^[38] The shear rate at which viscosity was measured was not reported. Cardiac output and mean arterial blood pressure were normal. After treatment with erythropoietin, systemic vascular resistance rose to 1568 ± 129 dynes-sec/cm⁵, hematocrit to $36.4 \pm 0.9\%$, and blood viscosity to 3.71 ± 0.18 cP. Mean arterial blood pressure rose to 106 mmHg (normal: 70 to 105 mm Hg). Cardiac output decreased 12% but was still within the normal range.

In a study by Neff *et al.*, forty anemic renal failure patients (Hct $23 \pm 4.1\%$) had normal calculated systemic vascular resistance and increased cardiac output. In a subset of six patients, transfusion to a hematocrit of 40% resulted in an 80% increase in calculated systemic vascular resistance and hypertension. Normal or slightly increased systemic vascular resistance in association with anemia is notable because the typical compensation for anemia is decreased systemic vascular resistance and increased cardiac output to maximize oxygen delivery. The authors concluded that the "anemia

of chronic renal failure may actually serve to protect patients from an otherwise devastating hypertension"^[39]. The data of Fellner *et al.* and Neff *et al.* demonstrate that red blood cell mass is decreased by a physiologic mechanism in order to normalize systemic vascular resistance.

The SVRR also causes erythropoietin resistance, also called *hypo-responsiveness to erythropoiesis-stimulating agents*. In this condition, the dose of ESA required to achieve a target hemoglobin concentration increases because of increased concentrations of soluble erythropoietin receptors^[36].

The SVRR is the physiologic antagonist of the renin-angiotensin-aldosterone system (RAAS). The latter causes vasoconstriction, sodium retention with expansion of intravascular volume, and increased red cell mass and blood viscosity. The plasma renin concentration has been shown to be significantly associated with both hematocrit and blood viscosity at both high and low shear rates^[40]. The erythropoietic activity of the RAAS is seen in post-transplant erythrocytosis, which is defined as a hematocrit $>51\%$ or hemoglobin >17 g/dL after renal transplantation. Ten percent to 30% of patients develop thrombotic events. Blockade of the RAAS is the most effective therapy^[41].

The SVRR does not correct abnormal low-shear blood viscosity. The bulk of vascular resistance is determined by the tone of pre-capillary arterioles, which is a high-shear environment. Flow conditions distal to these (i.e., in capillaries and veins), as well as areas of flow separation in arteries, are not sensed by the mechanoreceptors in the left ventricle. Therefore, erythrocyte hyperaggregation is not detected and cannot be corrected by the SVRR.

DECREASED LIFE EXPECTANCY DESPITE HEMODIALYSIS

The average life expectancy of patients on hemodialysis in the United States is less than three years^[42]. Jung *et al.* found that a large change in blood viscosity after dialysis at both high and low shear rates was significantly associated with risk of death: hazard ratio (HR) = 4.69, 95% confidence interval (CI) 1.27-17.3 at 300/s, 3.94, 95%CI 1.06-14.7 at 5/s. Eight of twenty-seven deaths were due to cardiovascular disease, and five were due to cerebrovascular disease^[43]. These data can be explained by volume overload prior to hemodialysis, causing low blood viscosity, or by hemoconcentration after hemodialysis, causing hyperviscosity.

The most common causes of death in hemodialysis patients are cardiovascular disease and infection. The role of elevated blood viscosity in cardiovascular disease was discussed above. Increased blood viscosity decreases the delivery of all metabolic substrates to tissue^[2]. This limits the ability of cells to synthesize biomolecules, including new proteins. The result is decreased physiologic reserve and reduced ability to tolerate an insult to homeostasis. Decreased blood flow slows the delivery of leukocytes and inflammatory mediators to the site of an infection. Inflammation causes further increases in blood viscosity because it is a hyperviscous state owing to several factors: the increased concentrations of fibrinogen and immunoglobins, decreased concentrations of albumin, hemoconcentration due to decreased oral fluid intake, and increased insensible losses due to fever^[44].

Increased blood viscosity causes mortality and morbidity due to overtreatment with ESA^[45,46]. In the United States, ESA are labeled with a black box warning indicating an increased risk of death, serious adverse cardiovascular reactions, and stroke when

administered to achieve a hemoglobin >11 gm/dL. These drugs also increase the risk of venous thromboembolism, hypertension, and shunt thrombosis. Hematocrit is an independent risk factor for coronary heart disease^[47]. These adverse effects are due to increased blood viscosity.

Increased blood viscosity decreases blood flow through the extracorporeal hemodialysis circuit, reducing dialysis efficiency. This problem is worsened by the reversible transformation from discocyte to echinocyte, which often occurs in hemodialysis patients. The degree of echinocytosis correlates with increased high-shear blood viscosity ($r = 0.800$, $p < 0.01$)^[48]. Decreased hemodialysis efficiency in combination with dietary indiscretion can lead to hyperkalemia. Elevated potassium levels are associated with an increased risk of both all-cause and cardiovascular mortality in hemodialysis patients^[49].

ASSESSMENT OF VOLUME STATUS

The accuracy in assessing a patient's volume status may be the most important determinant of the prognosis with hemodialysis using available technology^[50]. Hypervolemia can lead to hypertension, congestive heart failure, pulmonary edema, and hospitalization. Hypovolemia can lead to orthostatic hypotension and underperfusion of the entire body.

Blood pressure and body weight are commonly used to estimate a patient's volume status. The quest to improve the estimation of volume status has resulted in the evaluation of many parameters, including the concentration of BNP and systemic vascular resistance as determined by pulmonary artery catheterization. This subject is reviewed in reference^[50].

Because blood viscosity at high shear rates is determined by the activity of the SVRR and RAAS, the blood viscosity at a high shear rate should provide valuable information about the intravascular volume. The RAAS is active despite renal failure, as shown by the data of Vaisman *et al.*, which suggest that normal blood viscosity is still maintained in the absence of therapy with ESA^[9]. At high shear rates, hypervolemia will correlate with decreased blood viscosity, and hypovolemia with elevated blood viscosity. Kim *et al.* showed that the change in blood viscosity caused by hemodialysis correlated with the change of calculated intravascular volume decrease at both a high shear rate, 300/s, $r^2 = 0.717$, and a low shear rate, 1/s, $r^2 = 0.559$ ^[16].

In patients not treated with ESA, normal blood viscosity can be used to assess the adequacy of a patient's intravascular volume. The vasodilatory, natriuretic, and anti-erythropoietic activity of the SVRR interact with the vasoconstrictive, sodium-conserving, and erythropoietic activity of the RAAS to normalize systemic vascular resistance. Therapeutic administration of ESA interferes with homeostasis and establishes a new baseline blood viscosity. The blood viscosity at the target hematocrit should be used to guide the assessment of a patient's intravascular volume.

MEASURING BLOOD VISCOSITY

Using data on blood viscosity to guide the evaluation of a patient's volume status requires that the data be available quickly. This usually requires on-site testing. Automated analytical instruments to measure blood viscosity are not widely available in the United States. The alternative is testing with a capillary viscometer. Capillary viscometers are widely available and inexpensive. A 37° water bath, timer, and cleaning and drying reagents are also required. Testing is labor-intensive, requiring approximately 10 minutes of technician or technologist time per specimen.

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