Plasma Volume and Tissue Edema: Balancing Two Extracellular Fluid Circulations of Albumin and Its Solvent

Thomas Edward Woodcock MB.B.S, M.Phil, FFARCS Eng.
fluidphysiology.org , Hampshire, United Kingdom.

For about a decade, now it has been clear that most capillaries do not reabsorb filtered fluid, with the corollary that interstitial fluid is in a vital steady- state circulation at about 5–10 ml min^{-1}, and capillary filtration rate can increase to 100 ml min^{-1} or more with rapid 1 litre fluid bolus. Applying a paradigm that views extracellular fluid (ECF) as two linked circulations rather than two relatively static compartments changes our deductions as to what constitutes rational fluid therapy, and explains many if not all of the otherwise inexplicable clinical and experimental findings. Colloid therapy to support plasma volume has been promoted by international experts and the pharmaceutical industry since Bayliss and Starling recommended gum saline for the treatment of wound shock in 1916, and so this kinetic paradigm based on the steady-state Starling principle may not be readily accepted in some quarters.

Enteral fluid absorbed by the intestinal mucosal capillaries and parenteral fluid infused into a vein enter a central volume of distribution. The capillary filtration rate (or the transendothelial flow of solvent Jv) is a primary determinant of the redistribution of fluid from the central to the peripheral volume of distribution. See Figure 1. Michel and Weinbaum are jointly credited with a new interpretation of the Starling principle which recognizes that the protein osmotic pressure difference (delta Π) opposing filtration is developed across the luminal endothelial glycocalyx layer. This seemingly minor change has some major consequences for our understanding of ECF kinetics.

(i) The diagram, represented in almost every physiology textbook, of fluid being filtered to the interstitium at the beginning of blood's transit through a capillary, and then reabsorbed as it approaches the venules, is incorrect.

(ii) Staverman's reflection coefficient sigma, which modifies the measured delta Π to the effective delta Π in the Starling equation, is a characteristic of the glycocalyx layer and its interaction with albumin.

(iii) At steady state, the hydrostatic pressure difference (delta P) driving filtration Jv is always larger than sigma delta Π and so capillaries produce filtrate along their entire length. The traditional teaching of filtration being balanced by reabsorption as the dominance of hydrostatic and colloid osmotic pressure differences shifts does not occur. This is the steady-state no-reabsorption rule.

(iv) The traditional view of lymph flow being compensation for a slight net positive filtration–reabsorption balance is obsolete. Sigma delta Π opposing filtration is much greater, and so Jv is much less than previously believed, and the ultrafiltrate is almost all returned to the blood circulation as the volume flow of lymph Qlymph.

The presence of an intravascular gel phase, the glycocalyx layer, separating free-flowing plasma from the junction breaks within intercellular cleft has clinical consequences. Attempts have been made to estimate the intravascular volume of the glycocalyx layer by indicator dilution, but Michel and Curry have pointed out the methodological difficulties in obtaining a clinically meaningful value. For the purposes of a paradigm that explains clinical experience, I have suggested that a bolus of an isosmotic plasma substitute has a central volume of distribution which approximates the free-flowing plasma, while a bolus of an isotonic salt solution has a central volume of distribution that includes the intravascular gel phase and approximates the whole of the intravascular volume. The concept is supported by consistent clinical reports that adequate resuscitation with an isosmotic plasma substitute can be achieved with slightly smaller volumes than adequate resuscitation with a crystalloid, but at the expense of much diluted hematocrit. The ability of plasma and plasma substitutes to cause anemia is still widely misinterpreted as indicating that the colloids are 'better volume expanders'. It has been traditional to think of intravascular plasma volume as a measurable mass of fluid within a bucket to which one can add a colloid solution, and from which a colloid-free solution rapidly redistributes. The better concept is of two compartments through which exctracellular fluid circulates, while we manipulate the inflow and outflow rates.

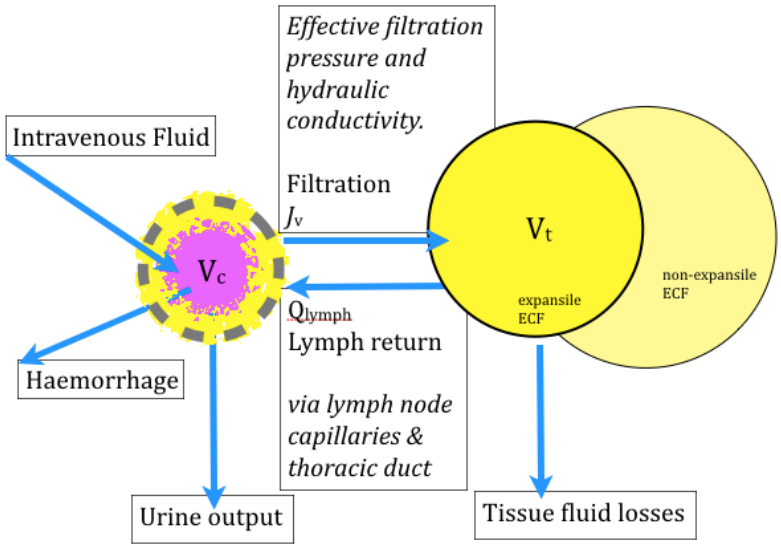

Figure 1: balancing circulating fluid solvent between central and peripheral volumes, or plasma and interstitial fluids, is achieved by manipulating Jv and lymphatic return.

In health, indicator dilution studies give a 70 kg adult about 3 litre of plasma which contains around 210 g protein (70 g litre^{-1}), 1 litre EG gel phase and about 12 litre interstitial gel phase which contains 240–360 g protein (20–30 g litre^{-1}). Only about 8 litre of the interstitial fluid is within an anatomic space that allows contraction or expansion, so in kinetic terms, the peripheral distribution volume of infused isotonic saline is substantially less than the total interstitial fluid volume.

The ability of capillaries to filter only 5-10 ml min^{-1} Jv from the 3 litre of plasma that pass through each of the pulmonary and systemic microcirculations per minute is a remarkable feat of autoregulation. If, in an experiment on healthy adult human subjects, capillary pressure is acutely elevated by bolusing a litre of isotonic saline i.v. in <10 min, haematocrit dilution studies suggest that Jv increases transiently to around 100 ml min^{-1}. In laboratory studies, acute reduction in capillary pressure to less than sigma delta Π upsets the steady state and results in an immediate reversal of capillary filtration to reabsorption, but this physiological autotransfusion is transient (<30 min) and limited (<500 ml in the 70 kg adult) before a new steady-state condition of reduced filtration is re-established.

Small reductions in the regional vascular resistance of a tissue bed below normal lead to substantial increases in capillary ptressure and Jv. Precapillary vasodilators therefore cause edema as a side-effect, while α-1 adrenergic agonists help keep capillary pressure low by precapillary arteriolar constriction. They minimize delta P and therefore Jv and so are an effective anti-edema therapy. Examples include epinephrine treatment of anaphylaxis/ anaphylactoid reactions and anti-hypotensive infusions of norepinephrine or phenylephrine in anaesthetic practice.

Paracellular ultrafiltrate accounts for most of the baseline 8 litre day^{-1}. In steady-state conditions, afferent lymphatic fluid is also formed at the rate of about 8 litre day^{-1} and has the same protein concentration as the interstitial fluid (20–30 g litre^{-1}). Diaphragm-fenestrated blood capillaries within lymph nodes are able to absorb lymphatic fluid and return it to the circulation at the rate of about 4 litre day^{-1}, leaving around 4 litre day^{-1} of proteinaceous (circa 60 g litre^{-1}) efferent lymph to return to the venous system via the thoracic duct. Lymph flow is not entirely passive. There is smooth muscle associated with many lymphatics whose contraction and relaxation acts as a pump. While inflammatory mediators and opioids may inhibit lymphatic contractility, so promoting oedema, norepinephrine is known to stimulate contractility.

One of the first consequences of inflammation is a decrease in the interstitial pressure as integrins change the conformation and hydration of structural collagen fibres. Delta P and Jv therefore increase, beginning the shift of ECF balance from the intravascular to the extravascular compartment. Precapillary vasodilation increases the capillary pressure and so further increases Jv. If the haemodynamic reflexes are working, arterial pressure is maintained by increased cardiac output (capillary recruitment increasing the surface area for filtration), which is another factor increasing Jv in the early phase of systemic inflammation. Notice that I have accounted for a substantial increase in Jv to the interstitium and so far have not had to appeal to the 'leakiness' of the capillary expressed as the hydraulic

conductivity, or Staverman's reflection coefficient sigma. Histamine and other autocoids are known to increase the length and number of intercellular junction breaks, especially in the distal part of the capillary and the venules. The surface area for filtration A within each capillary and the hydraulic conductivity Lp are both thereby increased and further increase the Jv. Fragmentation of the glycocalyx, and failure of the repair mechanisms eventually reduce sigma so that the effective delta Π (sigma delta Π) opposing filtration is reduced.

Proteins such as albumin are transported from the intravascular to extravascular space by two pathways: first, as the glycocalyx is an imperfect filter (reflection coefficient sigma for albumin <1.0) some albumin passes through intercellular clefts ('paracellular pathway') as part of the convection current, and second via a diffusive caveolation from the luminal to the abluminal side of the endothelial cell ('transcellular pathway'). Expressed as a mathematical formula, the mass flow of a solute such as albumin (Js albumin) is the sum of the convective and the diffusive components. Js can be measured as the transcapillary escape rate (TCER) of a radio-labelled marker. Using I131, TCER albumin is about 5% h^{-1}, or about 10 g h^{-1} when the plasma albumin concentration is normal. In health, while Jv is low, transcellular pathway for Js predominates. However, when paracellular hyperfiltration occurs, this pathway for Js predominates. TCER albumin increases by up to 300% (i.e. to 15% h^{-1}) in surgical patients, in cancer patients, and in sepsis.

Even in health, there is at any moment more extracellular albumin within the interstitial fluid than in the plasma. During hyperfiltration and hyperpermeability, plasma albumin concentration decreases because of net redistribution of circulating albumin to the interstitial space. Transfused albumin is also rapidly redistributed so that there is soon more of it in the tissues than in the plasma volume. Transfusion of albumin will cause edema, every gram of albumin holding about 18 ml water in the interstitial gel.

As Jv is close to zero at low capillary pressures, plasma volume expansion from hypovolaemia can equally well be achieved with an isotonic salt solution, an isosmotic albumin solution, or a plasma substitute. Only when capillary pressure (or more accurately delta P) has been restored to the point at which the convection jet of ultrafiltrate emerging from each junction strand break has maximized the opposing sigma delta Π will further fluid loading lead to a proportionate increase in Jv. I have described this flow–pressure relationship as a J curve and suggested that the inflection point be called the J point. The more severe the hypovolaemia, the greater the case for preferring crystalloid resuscitation to repay the autotransfusion and re-establish a subglycocalyx protected space. This logic runs counter to the suggestion by some authorities that colloid solutions may be preferred in more extreme cases of hypovolaemia 'because it stays in the circulation longer'. Moreover, statim boluses are expected to cause transient peaks of capillary pressure that lead to transient hyperfiltration. This may account for the finding of the FEAST trial that large bolus resuscitation was harmful to children.

The capillary filtration unit needs almost continuous maintenance and tonic regulation of its permeability. The key regulating parts of the capillary filtration unit are the adherens junctions, the continuity of the tight junctional strands (length and number of breaks), and the balance of synthesis and degradation of glycocalyx layer components. The small GTP-ase enzymes which maintain the near-impermeability of the capillary filtration unit require a continuous supply of intracellular cyclic adenosine monophosphate and a continuous supply of sphyngosine-1-phosphate (S1P), generated within circulating erythrocytes and carried to the endothelium by plasma albumin. Inflammation reduces activation of the small GTP-ases and so reduces the near-impermeability of the capillary filtration unit.

Albumin is a glycocalyx component and a carrier of S1P but laboratory experiments suggest a plasma concentration as low as 10 g $litre^{-1}$ is enough to support endothelial barrier integrity. The ALBIOS trial found no therapeutic advantage in keeping the plasma albumin concentration >30 g $litre^{-1}$. 'Leaky capillaries' are not a reason to give pharmaceutical preparations of albumin solution.

An important endocrine regulator of plasma volume is atrial natriuretic peptide (ANP) whose actions are essentially the reverse of aldosterone. ANP is secreted in response to vascular distension and acts on intra-renal and extra-renal guanylate cyclase (GC-A) receptors to reduce the effective plasma volume by at least three important actions. Intra-renal GC-A receptor stimulation brings about natriuresis by increasing glomerular filtration pressure (the efferent arterioles constrict) and inhibiting tubular sodium reabsorption. Secondly, extra-renal GC-A receptor stimulation increases the TCER of albumin (Js), so that the delta Π opposing Jv is not increased by the loss of salt and water from the circulation. Thirdly, GC-A receptors generally relax vascular smooth muscle.

Finally, there are some specialized capillary beds to consider. The continuous endothelial cells of the pulmonary capillaries are exposed to the whole right ventricular output, but perfused by much lower arterial pressure.

Traditionally, it is taught that pulmonary capillary wedge pressure >18 mm Hg leads to pulmonary oedema. It has been observed that increase in capillary pressure activates a heparan sulfate–nitric oxide-dependent pathway that fragments the glycocalyx layer and reduces transendothelial resistance, so accelerating the increase in Jv which causes oedema formation. In other words, hydrostatic pulmonary oedema is soon followed by permeability oedema and is not always rapidly reversed by reducing capillary pressure. Keeping the lymphatic drainage pressure (central venous pressure) low is likely to be of benefit.

Glomerular filtration is a remarkable special case, by which around 120 ml min^{-1} ultrafiltrate leaves the plasma via glomerular open fenestrated capillaries to enter the renal tubule system. Glomerular glycocalyx injury leads to albuminuria. Peritubular diaphragm-fenestrated capillaries participate in secretion and reabsorption of solutes, while vasopressin/ antidiuretic hormone modifies the final reabsorption of water from the distal parts of the nephron to regulate extracellular fluid osmolality.

Sinusoidal capillaries of the bone marrow, spleen, and liver have discontinuous basement membranes and glycocalyx layers, so that they do not filter proteins, and there is no delta Π opposing Jv. Hepatocytes are therefore able to regulate plasma protein synthesis by osmotic pressure in the Space of Diss. Around one-fifth of the left ventricular output passes through the hepatic microcirculation, and the liver contributes more to the lymphatic circulation than any other organ. In stabilized sepsis, as much as 50% of the left ventricular output perfuses the liver.

The capillaries of the central nervous system have fully continuous basement membrane and glycocalyx layer, with several lines of tight junction in every interendothelial cleft forming a very impermeable blood–brain barrier. Cleft exit microdomains appear to be associated with closely placed pericytes. Anatomically, there are no lymphatic vessels draining the interstitial fluid of the central nervous system, but a lymph-like flow of interstitial fluid around glial cells has been reported and is referred to as the glymph system. Anesthesia and sleep are associated with increased glymph flow, which is speculated to wash potentially neurotoxic metabolites away.

References:

Woodcock TE. Plasma volume, tissue oedema, and the steady-state Starling principle. BJA Education, 2016, 1–5.

Levick JR, Michel CC. Microvascular fluid exchange and the revised Starling principle. Cardiovasc Res 2010; 87: 198 – 210.

Levick JR. An Introduction to Cardiovascular Physiology, 5th Edn. London: Hodder Arnold, 2010; Chapters 9–11.

Michel CC, Curry FR. Glycocalyx volume: a critical review of tracer dilution methods for its measurement. Microcirculation 2009; 16: 213–9.

Woodcock TE, Woodcock TM. Revised Starling equation and the glycocalyx model of transvascular fluid exchange: an improved paradigm for prescribing intravenous fluid therapy. Br J Anaesth 2012; 108: 384–94.

Maitland K, Kiguli S, Opoka RO et al. Mortality after fluid bolus in African children with severe infection. N Engl J Med 2011; 364: 2483–95.

Curry FR, Adamson RH. Tonic regulation of vascular permeability. Acta Physiol (Oxf) 2013; 207: 628–49.

Caironi P, Tognoni G, Masson S et al. Albumin replacement in patients with severe sepsis or septic shock. N Engl J Med 2014; 370: 1412–21.

Lin YC, Samardzic H, Adamson RH et al. Phosphodiesterase 4 inhibition attenuates atrial natriuretic peptide-induced vas- cular hyperpermeability and loss of plasma volume. J Physiol 2011; 589: 341–53.

Collins SR, Blank RS, Deatherage LS, Dull RO. Special article: the endothelial glycocalyx: emerging concepts in pulmonary edema and acute lung injury. Anesth Analg 2013; 117: 664–74.

Xie L, Kang H, Xu Q et al. Sleep drives metabolite clearance from the adult brain. Science 2013; 342: 373–7.

Keywords:

Plasma Volume.
Endothelial Glycocalyx.
Atrial Natriuretic Peptide.
Sphingosine-1-Phosphate.
Lymph.
Edema