Ernest Starling and the colloid delusion.

KEY MESSAGES.

- Biophysical colloid therapies for the treatment of shock have been popular for almost a century.
- The red cell dilution efficiency of colloid solutions is up to 5 times that of crystalloids and this fact has long been claimed by pro-colloid experts to prove that colloids are superior "volume expanders".
- The resuscitative efficiency of colloids is now generally agreed to be only about 1.5 times that of crystalloids.
- Defenders of colloid therapy are now trying to argue that leaky capillaries are the problem, and that colloids can continue to be used in non-septic (typically surgical and haemorrhagic) cases. This is not true.
- A better account of fluid hyperfiltration and increased capillary permeability is given to explain that colloids will cause harm in all patients.

An historical account of colloid therapy.

Ernest Starling's name is celebrated whenever critical care physicians discuss fluid therapy for haemodynamic resuscitation. The Frank - Starling law of the heart still underpins therapy of acute and chronic heart failure. Starling's Principle of fluid exchange with the tissues, on the other hand, has been less successful in describing what we see in patient care. Starling himself recognised the limitations of his experiments. He indicated his reservations when he said that oedema is probably absorbed directly by blood vessels, and that the osmotic pressure of serum is probably responsible for absorption of isotonic fluid from the tissues to the blood stream which ensues on any general lowering of capillary pressures. (1) During the Great War, Starling and his brother-in-law William Maddock Bayliss, Professor of General Physiology at University College London, were called to sit on the "Special Investigation Committee on Surgical Shock and Allied Conditions" of the Medical Research Committee. Bayliss believed that intravenous therapy would be more effective if it included a substance to maintain the viscosity of the blood, and experimented with 5% solutions of gelatine or gum acacia. He also noted that such solutions had a colloid osmotic pressure comparable to that of serum, and the concept of a biophysical treatment for shock was conceived. In 1917 Bayliss went to France, and many moribund soldiers were given a bottle of "gum saline" to observe its effects on "wound shock". (2) Underpinned by an undisputed physiological principle, the rationale for biophysical colloid resuscitation was accepted around the world, and survived for almost a century.

With the establishment of intensive care units in the 1970s it became possible to stabilise and to study patients with shock. (3) The pulmonary artery flotation catheter and the thermal - green dye technique for the estimation of extravascular lung water at the bedside were particularly powerful tools for the investigation of the effects of colloids. At the 1978 Hyland Symposium on

pulmonary oedema Civetta explained how physiological considerations lead to the surprising conclusion that oncotically active substances can only serve to enhance the formation of interstitial oedema. (4) The following year Virgilio presented data from surgical patients which "seriously question the the necessity to maintain colloid osmotic pressure by using protein solutions during acute haemodynamic resuscitation". (5) By 1983 Tranbaugh and Lewis were able to state firmly that analysis of the Starling microvascular forces operative in the lung did not provide a reason to prefer colloid resuscitation, and they had data confirming that crystalloids were both safe and effective. Of colloids, they said "one wonders how their further use can be justified." (6)

J Rodney Levick challenged the standard teaching of transvascular filtration being balanced by transvascular absorption in a review article of 1991. (7) Absorption, he argued, cannot be maintained across most low-pressure exchange segments because there is a rise in pericapillary interstitial oncotic pressure as filtration slows and then ceases, keeping the transvascular oncotic pressure difference smaller than the reduced hydrostatic pressure difference. The critical care community seems not to have noticed this remarkable revision of fluid physiology, which makes an oncotic pressure therapy for resuscitation unlikely to be effective. In neonatal practice Emery, Greenough and Gamsu asked the pertinent question whether it is the dose of colloid (albumin) or the volume of the solution that achieves resuscitation. Their subjects, sixty hypotensive pre-term infants, received their resuscitation fluid at 5 ml kg-1 h-1. Twenty received the full dose of colloid as 20% Human Albumin Solution delivered in one hour, while twenty received plasma and twenty received 4.5% Human Albumin Solution 15 ml kg-1 h-1 over three hours. The total dose of protein was therefore similar between groups, while the hyperoncotic albumin group received a smaller volume. The degree of resuscitation was similar in all three groups ofter one hour, but after three hours restoration of blood pressure was better in the higher-volume (15 ml kg-1) groups. They thereby showed that it is the volume infused rather than colloid load that is important in producing a sustained increase in blood pressure. (8) The next question was whether albumin was necessary at all, and it was answered in 1997 by So, Fok, Ng and colleagues. Sixty three hypotensive pre-term neonates were treated with an infusion of either 5% albumin or isotonic sodium chloride at 10 ml kg-1 h-1 until they were adequately resuscitated. Albumin did not reduce the volume of fluid required to achieve resuscitation, but it was associated with post-resuscitation fluid retention. (9)

The colloid vs crystalloid debate continued to fill many journal pages and consume many Congress hours. Another blow was dealt in 2004 by two landmark papers. In a large randomised clinical trial comparing albumin and saline for fluid resuscitation in a general intensive care patient population it was observed that the volume of human serum albumin solution required to achieve resuscitation on the first day (mean 1.2 litres) was only a little less than the effective volume of 0.9% Sodium Chloride (mean 1.6 litres), and that albumin-treated patients received more red cell transfusions in the first two days. (10) In a laboratory study it was shown

that "colloid osmotic forces opposing filtration across non-fenestrated continuous capillaries are developed across the endothelial glycocalyx and that the oncotic pressure of interstitial fluid does not directly determine fluid balance across microvascular endothelium." (11) Students must now familiarise themselves with the glycocalyx model, also known as the Michel - Weinbaum glycocalyx - junctional break model of fluid exchange in a continuous capillary. (12) (13) Starling's hypothesis that "absorption from the tissues ... ensues on any general lowering of capillary pressures" does not occur, and biophysical colloid osmotic pressure therapy in resuscitation is no longer supported by physiological reason. In 2009 researchers in Amsterdam confirmed by clinical experiments in both septic and non-septic patients that reducing colloid osmotic pressure of plasma does not predispose to pulmonary oedema, and that colloid resuscitation does not reduce the risk. (14) In the hope that hydroxyethyl starch might succeed where albumin had failed, a large randomised controlled trial was published in 2012 and confirmed that the plasma substitute causes more harm than isotonic salt solution and has very little volume advantage in clinical resuscitation. (15) In 2013 it was shown that peri-operative stroke volume optimisation goal-directed fluid therapy is possible with crystalloid, and there is no evidence of a benefit in using hydroxyethyl starch. The authors declared that "the concept of the 1:3 replacement ratio in hypovolaemic patients is obsolete." (16) August organisations have called for a moratorium on the use of hydroxyethyl starch, (17) and the Cochrane collaboration continues to advise against all plasma substitutes. (18)

A new paradigm for the prescription of intravenous fluid therapy.

Prescribers of intravenous fluids who wish to do so rationally need a paradigm based on current physiology to guide them. The Revised Starling Equation & Glycocalyx Model (RSE&GM) Paradigm explains why isotonic salt solution resuscitation from low capillary pressure is to be preferred to biophysical therapies, and can be safely achieved with volumes that are only a little greater than the colloid volume requirement would be. (19) At low capillary pressures the transvascular solvent filtration rate Jv is very low and essentially uninfluenced by the colloid osmotic pressure of plasma. The fact that a bolus dose of colloid reduces the haematocrit much more than the same volume of crystalloid should not be misrepresented as evidence that the colloid is the superior resuscitating solution. RSE&GM raises concern that high molecular weight colloids that do not permeate the glycocalyx layer will dehydrate and compress it. RSE&GM predicts that colloid therapy could be superior to crystalloid therapy for isovolaemic haemodilution (20) and hypervolaemic hyperdynamic goal-directed therapy, if evidence can be found that these strategies can be implemented without causing pulmonary oedema and can improve postoperative outcomes.

The colloid delusion.

Though colloid solutions are very effective for diluting the erythrocyte concentration (i.e. Inducing anaemia), they are much less effective for restoring or preserving haemodynamic stability after haemorrhage (20). It is salutory to consider how so many doctors practicing

volume resuscitation with colloids and crystalloids over so many decades failed to notice that biophysical therapies are much less effective than expected. Those who perpetuated the Starling Principle in their undergraduate teaching and textbooks were unfamiliar with critical care practice, and practitioners were pleased to believe the simplistic mantra, elevated to Guideline status by some experts, that one should give plasma or plasma substitutes to increase the intravascular fluid volume, and isotonic salt solution for the whole of the extracellular fluid. Those who did prefer crystalloids felt obliged by this teaching to give three to five times the estimated intravascular volume deficit, sometimes resulting in iatrogenic pulmonary oedema which was labelled "adult" or "acute" respiratory distress syndrome. Practitioners in the United Kingdom were particularly persuaded of the apparent necessity to resuscitate with colloids. Pharmaceutical manufacturers of colloids are generous sponsors of professional educational programs and Specialist societies in the UK, and the colloid - crystalloid controversy is a popular perennial topic. Joachim Boldt, one of the men often invited to give lectures at international conferences and commissioned to write review articles for the leading Journals, has been found to have fabricated data in at least ten publications, concealing the harm that hydroxyethyl starch causes. (21) In an effort to preserve the market for tetrastarch in non-hypovolaemic surgical practice Fresenius Kabi commissioned a meta-analysis of published data involving 2139 healthy surgical patients given tetrastarch in 59 studies. It concluded that tetrastarch is safe in surgical practice, but did not question whether these expensive medicines with recognised side-effects are necessary for optimal clinical outcome. (22) A similar meta-analysis included trauma patients, and also found the mortality with colloid therapy to be no better than crystalloid therapy in trial patients. Accepting the risks of nephrotoxicity and anaphylaxis, they nonetheless called for restrictions on colloid use to lifted. (23) It is now generally accepted that those still clinging to their faith in biophysical volume therapies have to deliver a randomised clinical trial of a selected colloid against the crystalloid gold standard. (24) Until then, the view that untested synthetic colloids should not be given to patients outside of an ethically-approved clinical trial should be respected.

Understanding "leaky capillaries".

Many of the clinical challenges of critical care are attributed to what we call leaky capillaries. Pushed to elaborate, even the experts may recall 'the reflection coefficient', but few can elaborate further.

The in vivo capillary filtration unit needs almost continuous maintenance and tonic regulation of its permeability. (25) The key regulating parts of the capillary filtration unit are;

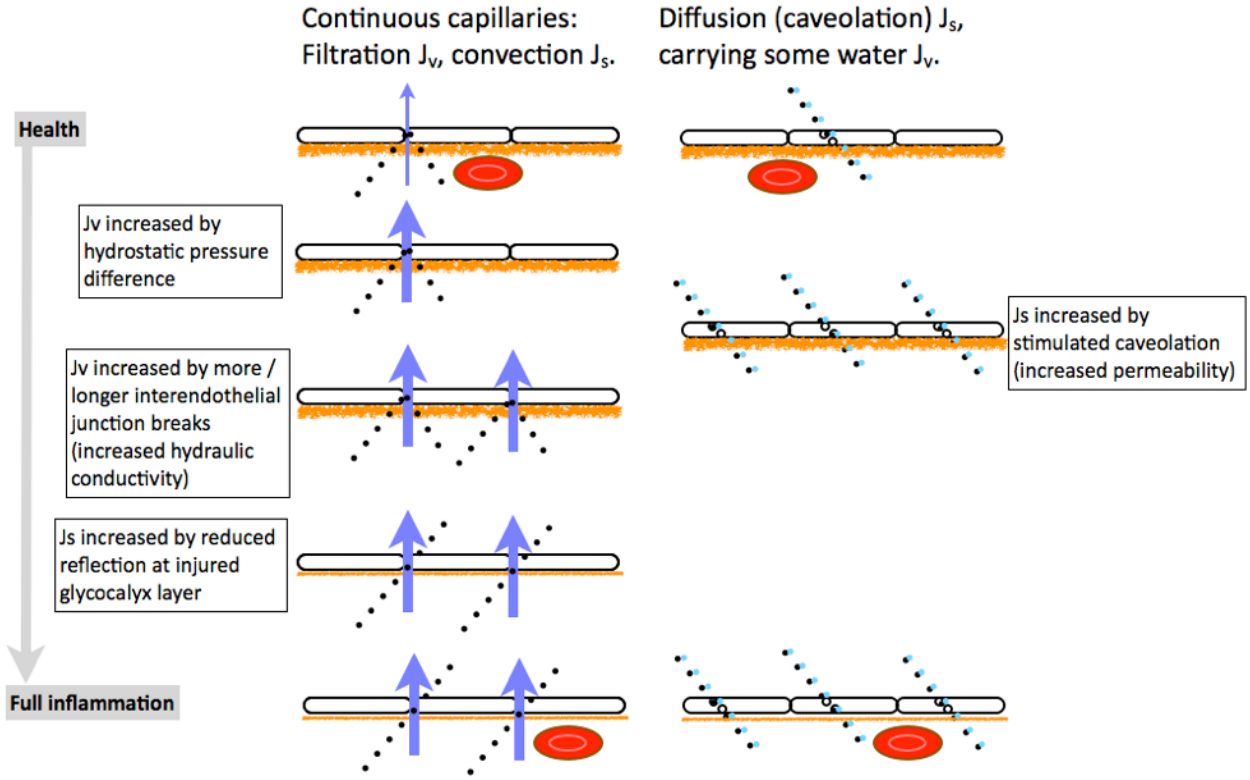
- the adherens junctions,
- the continuity of the tight junctional strands (length and number of breaks), and
- the balance of synthesis and degradation of glycocalyx layer components.

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.

The equations we are told are Starling's were in fact proposed many years after his death. The most frequently cited equation explains the transvascular solvent filtration rate Jv in terms which describe the net hydrostatic pressure difference and net colloid osmotic pressure difference across the semipermeable microcirculation. Less often taught, but equally important to understanding the pathophysiology, is the equation explaining a solute transfer rate Js as the sum of the mass of that solute carried with the microvascular filtrate (convection) and the mass of that solute that permeates the microcirculation independently of flow (diffusion). In clinical considerations the solute of interest is albumin. Researchers who measure Js of albumin or another marker molecule in disease states often presume that Jv will be increased with Js and cause oedema. Figure one is a cartoon illustrating some of the ways inflammation affects Js and Jv. Note that increase in true permeability is just one way Jv and Js are increased.

One of the first consequences of inflammation is a fall in the interstitial pressure Pint as integrins change the conformation and hydration of structural collagen fibres. Jv therefore increases, beginning the shift of extracellular fluid balance from the intravascular to the extravascular compartment. Pre-capillary vasodilation increases the capillary pressure Pcap and so further increases Jv. If the haemodynamic reflexes are working, blood pressure is maintained by increased cardiac output (capillary recruitment) which is another factor



Endothelial glycocalyx layer in orange color. Blue arrow indicates solvent flux J_v, and dotted line indicates albumin solute flux J_s.

increasing Jv in the early phase of systemic inflammation.

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 within each capillary and the hydraulic conductivity Lp are thereby increased and further increase the Jv. Note that in some versions of the Starling equation for Jv, the product of surface area and hydraulic conductivity is called the filtration coefficient Kfc. Lee and Slutsky have reviewed the biology and potential for therapeutic manipulation of the proteins that zip adjacent endothelial cells together, or unzip them creating the junction breaks. (26)

Now consider the endothelial glycocalyx layer (EGL). It is easily compressed in volume by almost anything we do to our patients. It entraps and retains albumin molecules, in part by electrostatic means, restricting their free passage through it and so behaving as an imperfect filter. It has been claimed that it is too fragile to have any clinical relevance, but only a few glycoprotein and proteoglycan fibres on the luminal aspect of the endothelial junction breaks could perform a filter function. With extensive endothelial injury exposed coagulant molecules in the endothelial membrane will cause fatal disseminated intravascular coagulation. Inflammation damages the EGL and thereby reduces the reflection coefficient sigma for albumin, with EGL components such as the glycosaminoglycans (GAGs) appearing in blood samples. Sigma is an index of the effective as opposed to measured colloid osmotic pressure effect on Jv. As such, a reduced sigma limits the colloid osmotic pressure opposition to Jv and gives free rein to the hydrostatic pressure filtration driver. However, even if sigma approaches zero the resistance to fluid filtration caused by the basal membrane and extracellular matrix gel remains substantial.

Pore theory speaks of large pores which pass albumin molecules, and small pores which retain them. But what are the anatomic equivalents of these biophysically defined concepts? Permeability as it appears in the equation for Js is an index of how readily albumin appears to diffuse across a capillary if it were a simple semipermeable membrane dividing static fluid spaces. It is not. Albumin is actively transported across continuous capillaries via a membrane-associated protein that has been called gp60 or PV-1 and is now referred to as caveolin. (26) (27) Caveolin deficiency is incompatible with life. The rate of transfer of albumin, and other proteins having their own transport system, to the interstitium will appear to be a change in the number of large pores. Plasmalemmal vesicles (caveolae) carry some water with the albumin, but the convective inter-endothelial pathways predominate. Places where the fibrematrix covering a junction break is thinned will also behave like more large pores.

The circulation of tissue fluid to lymphatic vessels and return to the intravascular space.

RSE&GM recognises that the microvasculature is not a passive biophysical barrier separating the vascular and interstitial compartments of the extracellular fluid's circulation. The collecting (afferent) lymph vessels have barrier properties comparable to the venules and carry filtered tissue fluid to

the lymph nodes whose capillaries are diaphragm fenestrated and capable of fluid absorption. (28) As much as 50% of the fluid arriving at a lymph node is reabsorbed there, so the lymph in the efferent lymphatics has a high protein concentration and is pumped to the thoracic duct. It is thought that most of the efferent lymph re-enters the venous system via the thoracic duct, but other lymphatic - venous collaterals can be recruited if the duct is tied off. Radiation ablation of lymph nodes predisposes to oedema, a clear practical demonstration that non-fenestrated capillaries outside the lymph nodes are not capable of significant absorption of tissue fluid. The spontaneous contractility of the lymphatics is enhanced by adrenergic agents and suppressed by inflammatory mediators. It's worth recalling that 25% of the cardiac output goes to the discontinuous capillary circulations of the liver, spleen and bone marrow, where sigma for albumin and any other large molecule is very low, and that more than 50% of the high-protein lymph in the thoracic duct originates from the liver. In resuscitated hyperdynamic sepsis the proportion of blood going to the liver rises to as much as 50% so that higher molecular weight molecules will be easily lost from the blood stream.

Was Ernest Starling wrong?

Let's go full circle back to Starling's laboratory more than a century ago. He deduced the following;

1. Salt solutions, isotonic with the blood-plasma, can be and are absorbed directly by the blood vessels. This statement probably holds good for dropsical fluids containing small percentages of proteids.
2. A backward filtration into the vessels is mechanically impossible in the connective tissues of the limbs, of the muscles and of the glands similar in structure to the submaxillary.
3. The proteids of serum have an osmotic pressure of about 30 mm. to 40 mm. Hg. Absorption of isotonic salt solutions by the blood vessels is determined by this osmotic pressure of the serum proteids. The same factor is probably responsible for the absorption from the tissues which ensues on any general lowering of capillary pressures e.g. artificial anaemia.
4. The proteids of the tissue fluids, when not used up in the tissues themselves, are probably absorbed mainly, if not exclusively, by the lymphatic system.

So he correctly concluded that injected isotonic salt solutions are absorbed directly by the blood vessels, it was only his hypothetical extrapolation of this finding to the absorption of 'dropsical fluids' that was mistaken. How are they different? It will be a useful exercise to consider the Michel - Weinbaum glycocalyx - junctional break model of fluid exchange in a continuous capillary once more and see if you can find the reason for yourself before reading the final paragraph.

Fluid filtered by the EGL is almost protein-free and creates a low colloid osmotic pressure "microdomain" at the interendothelial cleft exit. However, if filtration slows tissue proteins almost immediately diffuse back into the cleft, raising the colloid osmotic pressure, diminishing the colloid osmotic pressure difference and preserving a low rate of filtration. In the case of injected protein-free isotonic salt solution, the volume of the low colloid osmotic pressure domain at adjacent cleft exits is relatively immense, and there is no available protein to diffuse back into the cleft.

Absorption can therefore occur until the injected volume has been taken up and tissue proteins can again enter the cleft, restoring the normal equilibrium of low filtration. If you, not unreasonably, thought that raised interstitial pressure at the site of injection might reverse the hydrostatic filtration pressure difference, look again at Starling's second statement that "backward filtration is mechanically impossible".

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