Introduction to RSE and GM Paradigm for Rational Fluid Prescribing.

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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. 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". 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. 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. By 1983 Tranbaugh and Lewis were able to state 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."

J Rodney Levick challenged the standard teaching of transvascular filtration being balanced by transvascular absorption in a review article of 1991. 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. In 1992 Emery, Greenough and Gamsu at Kings College Hospital, London asked 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. 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.

Two landmark papers appeared in 2012; in a large randomised clinical trial called SAFE it was found that the volume of human serum albumin solution required to achieve resuscitation was only a little less than the effective volume of 0.9% Sodium Chloride; and 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." 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. 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 has become illogical. In 2009 researchers in Amsterdam confirmed by clinical experiments that reducing colloid osmotic pressure of plasma does not predispose to pulmonary edema, and that

colloid resuscitation does not reduce the risk. In the hope that starch could succeed where albumin had failed, a large randomised controlled trial funded by Fresenius and called CHEST was published in 2012 and confirmed that the plasma substitute hydroxy-ethyl starch has very little volume advantage over 0.9% Sodium Chloride in clinical resuscitation and causes more harm than the isotonic salt solution. Now organisations are calling for a moratorium on the use of hydroxyethyl starch, or all plasma substitutes.

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 osmotic therapies, and can be safely achieved with volumes that are only a little greater than the colloid solution volume requirement would be. With the passing of plasma substitutes many clinicians are resorting to albumin therapy instead. This shows a failure to understand that all biophysical osmotherapies are equally poor at supporting plasma volume. Proteins do have an oncotic role across the endothelial glycocalyx; COP difference opposes but does not reverse Jv. Put another way, any biophysical osmotic solution can only slightly retard filtration of fluid to the interstitium compared to a crystalloid, it cannot absorb tissue fluid. However, the endothelial glycocalyx (EG) is semi-permeable to albumin molecules, and the presence of albumin within the EG is a determinant of its filter function. Note that the full effect of albumin on EG barrier function is achieved when plasma albumin is less than half normal, and advice to treat with albumin for this reason would only be relevant at very low plasma albumin concentrations. The functional unit of EG with its contained albumin is sometimes referred to as the endothelial surface layer. Plasma albumin concentration is the major determinant of the plasma COP in health, but in congenital analbuminaemia or acquired hypoalbuminaemia, other proteins become more important. Albumin molecules distribute through the ECF and in health, it is estimated that about 40% of the total body albumin is intravascular. In inflammation, the intravascular proportion of albumin will decrease and the extravascular proportion will increase. The measured transcapillary escape rate of albumin to the tissues (TCERA) is said to be an index of 'vascular permeability'. The normal TCERA is about 5% of the plasma albumin per hour, but this can double during surgery and may be increased to 20% or more in septic shock. The gallium-transferrin pulmonary leak index can be used as an index of pulmonary permeability, and it has been found to be inversely related to plasma albumin and plasma transferrin concentrations in both septic and non-septic intensive care patients with acute lung injury.

Clinicians rely on the original Starling principle as a reason to transfuse plasma or albumin to preferentially resuscitate the intravascular volume. The revised Starling equation and the glycocalyx model lead us to expect that the transendothelial protein concentration difference will regulate Jv after plasma or albumin resuscitation, but the no absorption rule will preclude any significant benefit for the intravascular volume. This could explain some of the clinical observations relating to albumin therapy. These include the following:

Hypoalbuminaemia is a marker of disease severity and a predictor of complications in surgical patients, but treatment of hypoalbuminaemia is of no clinical benefit.

Acute respiratory distress syndrome (ARDS) patients (lung injury score 2.5 or more) have low plasma albumin and transferrin concentrations, but hyperoncotic human albumin solution with or without a diuretic produces no improvement in pulmonary oedema.

Negative fluid balance rather than COP difference improves the alveolar to arterial oxygen tension ratio in ARDS patients.

In septic and non-septic patients, fluid loading against central venous pressure produces greater increases in cardiac output with human albumin solution than with isotonic salt solution but there are no benefits for pulmonary edema nor for the lung injury score.

Red cell dilution studies of hyperoncotic human albumin solution transfusion have been interpreted as showing osmotic absorption of fluid from the extravascular to intravascular compartment. Without information from an indicator of the whole intravascular volume, such as Dextran 40, such a conclusion is not justified. An acute increase in circulating plasma COP would be expected to draw water from the non- circulating part of the intravascular volume within the EGL. Studies reporting red cell dilution data that do not take into account the EG intravascular volume should be interpreted with caution.

Plasma substitutes are used to maintain or raise the plasma COP, although they displace albumin from the circulation. Moreover, by elevating COP, they suppress hepatic albumin synthesis. Little is known of their effect on the EG, but they would not be expected to support EG filter function as albumin does. The need to consider the contribution of the EG to red cell volume of distribution changes as noted above for studies of hyperoncotic albumin solutions applies equally to studies of hyperoncotic plasma substitutes. In normovolaemic volunteers made

hypervolaemic, modified fluid gelatin or hydroxyethyl starch solutions were distributed to the ISF more slowly than isotonic salt solutions as explained by the revised Starling equation, but there was no difference in arterial pressure, urine output, or renal hormone concentrations in plasma. In the expectation that they will be more effective than isotonic salt solutions at inducing hyperdynamic circulation, these plasma substitutes are commonly preferred for haemodynamic goal-directed therapy. However, the volume kinetic experiments have shown that the clearance of isotonic salt solutions from the central (intravascular) compartment (presumed to reflect Jv) is substantially slower in anaesthetized patients than in unanaesthetized subjects, and it has been shown that isotonic salt solution can be used to achieve hyperdynamic goals. This phenomenon is called context sensitivity. In contrast, a volume kinetic experiment in volunteers undergoing euvolaemic haemodilution with hydroxyethyl starch found that the elimination rate constant from central to peripheral fluid compartments was not reduced, as is the case for isotonic salt solution, but increased during anaesthesia compared with awake subjects. The duration of resuscitation attributable to hydroxyethyl starch after removal of a unit of blood was therefore shorter in subjects during desflurane anaesthesia. The extent to which context sensitivity can be attributed to reduced transendothelial pressure difference is not clear, but reduced filtration response to crystalloid loading of hypovolaemic subjects has been demonstrated, and crystalloids given during the vasodilation induced by spinal anaesthesia ('co-loading') are more effective than 'preload' crystalloids. Mean arterial pressure is an important determinant of the distribution of isotonic salt solutions from the intravascular space in patients undergoing general or regional anaesthesia, so that the lower the pressure, the slower the clearance of crystalloid from the circulation. One aspect of albumin therapy which may confer the benefit looked for in septic patients is the potential for anti-inflammatory or immune regulatory properties. Analysis of published data does not show that plasma substitutes are equivalent to albumin in this respect, or better than an isotonic salt solution.

The paradigm I recommend is as follows. The intravascular space contains three compartments of interest. If we define the intravascular fluid volume as that contained by the endothelial cells, we can measure it as the Dextran 40 dilution volume and it approximates to the central volume of distribution of infused isotonic salt solution. Dextran 70 is excluded from the non-circulating EG and its dilution volume consists of circulating plasma. There is a degree of exclusion of red cells from plasma at the EG boundary, so the volume of distribution of red cells is rather less than the Dextran 70 dilution volume. Compaction of the EG can have significant effect on the balance of total intravascular fluid and red cell dilution volumes. EG volume compaction by inflammation or hyper-osmotic colloid infusion must be considered in red cell dilution studies of the intravascular volume. Acute reduction of transendothelial pressure difference by pre-capillary vasoconstriction, post-capillary vasodilation, or hypovolaemia can result in transient absorption of fluid to the plasma volume, equivalent to as much as a 500 ml 'auto- transfusion' in human physiology, but this effect lasts only for a few minutes. See Figure 1 the left cartoon.

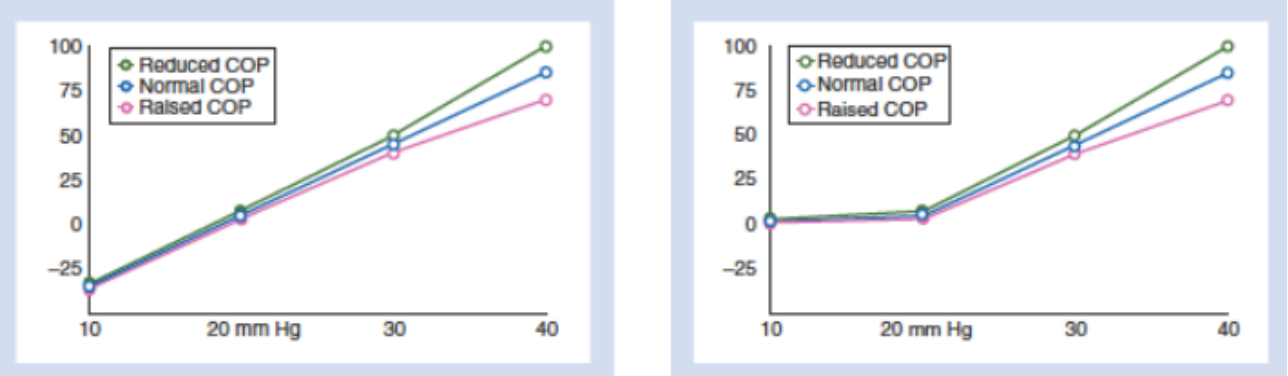

Figure 1: Pressure volume relationships after acute change (left) or in steady-state (right). The inflection of the steady-state J curve is called the J point.

Absorption reverts to filtration as proteins diffuse into the subglycocalyx space from the interstitial fluid, diminishing the COP difference that opposes filtration; this is the Michel-Weinbaum glycocalyx model. With less acute or extreme disturbance to the equilibrium, the same mechanism preserves filtration, albeit at a just a few millilitres per minute, and the no absorption rule applies. The pressure at which Jv approaches zero will depend on capillary porosity, which is the net effect of the various capillaries' hydraulic conductivities, area for fluid exchange, and the reflection coefficient of the macromolecules determining COP. The J-shaped curve describing Jv and capillary pressure

will be shifted to the left with increased capillary porosity, with the inflection on the curve being the J point. Below the J point, any transfused fluid, whether colloid or crystalloid, will appear to be retained within the intravascular space until the transendothelial pressure difference reaches the level at which filtration recommences. See Figure 1 the right cartoon. The glycocalyx model and the no absorption rule explain why the COP properties of plasma or plasma substitutes add little or nothing to plasma volume resuscitation while transendothelial pressure difference is below the J point. Above the J point, the oncotic pressure difference opposing filtration is maximal and Jv becomes proportional to the transendothelial pressure difference. Porosity increases in inflammatory states, but interstitial pressure has no direct effect on Jv. A 10- to 20-fold increase in Jv in the acute inflammatory response is actively regulated by integrins acting upon collagen fibrils in the extracellular matrix, exposing GAGs to take up water, and does not necessarily imply increased capillary porosity. The effects of fluid therapies on this mechanism, if any, are unknown. Changes which compact the EGL releasing GAGs into the circulating plasma are associated with increased transendothelial protein flux, but compaction of the EGL and increased porosity may be separate processes and the association may not be entirely causal. Although transfused macromolecules do not easily permeate an intact EG, they pass easily into the interstitial fluid of the sinusoidal capillaries in the bone marrow, spleen, and liver, equilibrating with interstitial macromolecules and returning to the venous system via lymphatics. An increase in the proportion of the cardiac output going to sinusoidal tissues will increase Jv and the transcapillary escape rate of albumin. There is no significant absorption of interstitial fluid to the plasma under a COP difference, so colloid therapy does not prevent or improve tissue edema.

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Keywords:

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