

# Revised Starling equation and the glycocalyx model of transvascular fluid exchange: an improved paradigm for prescribing intravenous fluid therapy

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## Editor's key points

- The classic Starling principle does not hold for fluid resuscitation in clinical settings.
- The endothelial glycocalyx layer appears to have a major role in fluid exchange.
- A revision of Starling incorporating the glycocalyx model appears to explain better the responses seen clinically.

**Summary.** I.V. fluid therapy does not result in the extracellular volume distribution expected from Starling's original model of semi-permeable capillaries subject to hydrostatic and oncotic pressure gradients within the extracellular fluid. Fluid therapy to support the circulation relies on applying a physiological paradigm that better explains clinical and research observations. The revised Starling equation based on recent research considers the contributions of the endothelial glycocalyx layer (EGL), the endothelial basement membrane, and the extracellular matrix. The characteristics of capillaries in various tissues are reviewed and some clinical corollaries considered. The oncotic pressure difference across the EGL opposes, but does not reverse, the filtration rate (the 'no absorption' rule) and is an important feature of the revised paradigm and highlights the limitations of attempting to prevent or treat oedema by transfusing colloids. Filtered fluid returns to the circulation as lymph. The EGL excludes larger molecules and occupies a substantial volume of the intravascular space and therefore requires a new interpretation of dilution studies of blood volume and the speculation that protection or restoration of the EGL might be an important therapeutic goal. An explanation for the phenomenon of context sensitivity of fluid volume kinetics is offered, and the proposal that crystalloid resuscitation from low capillary pressures is rational. Any potential advantage of plasma or plasma substitutes over crystalloids for volume expansion only manifests itself at higher capillary pressures.

**Keywords:** fluid therapy; intensive care

Twenty-five years ago, Twigley and Hillman announced 'the end of the crystalloid era'. Using a simplified diagram of plasma, interstitial and intracellular fluid compartments, and their anatomic volumes, they argued that colloids could be used to selectively maintain the plasma volume.<sup>1</sup> Plasma volume being about 20% of the extracellular fluid (ECF), it was presumed that the volume equivalence for resuscitation from intravascular hypovolaemia would be of the order of 20 ml colloid to 100 ml isotonic salt solution (ISS). Moreover, it was presumed from Starling's principle that transfusion of hyperoncotic colloid solutions would absorb fluid from the interstitial fluid (ISF) to the intravascular volume. This simple concept of colloid for plasma volume and ISS for ECF replacement has been continued and developed.<sup>2-4</sup> Two trials in critically ill patients have found that over the first 4 days of fluid resuscitation, 100 ml ISS is as effective as 62-76 ml human albumin solution<sup>5</sup> or 63-69 ml hyperoncotic plasma substitute.<sup>6</sup> In blunt trauma patients during the first day of resuscitation, 100 ml ISS was as effective as 97 ml isosmotic plasma substitute, while in gunshot or stabbing victims, 100 ml was as effective as 67 ml.<sup>7</sup> A trial of paediatric resuscitation practices in resource-poor facilities in

Africa demonstrated no advantages of bolus therapy with albumin compared with ISS, and a survival advantage for slow ISS resuscitation without bolus therapy.<sup>8</sup> A series of volume kinetics experiments have demonstrated that the central volume of distribution of ISS is much smaller than the anatomic ECF volume,<sup>9</sup> and an editorial had to conclude that 'Fluid therapy might be more difficult than you think'.<sup>10</sup> This review attempts to reconcile clinical trial data and bedside experience of fluid therapy with recent advances in microvascular physiology to improve our working paradigm for rational prescribing.

## Starling's principle

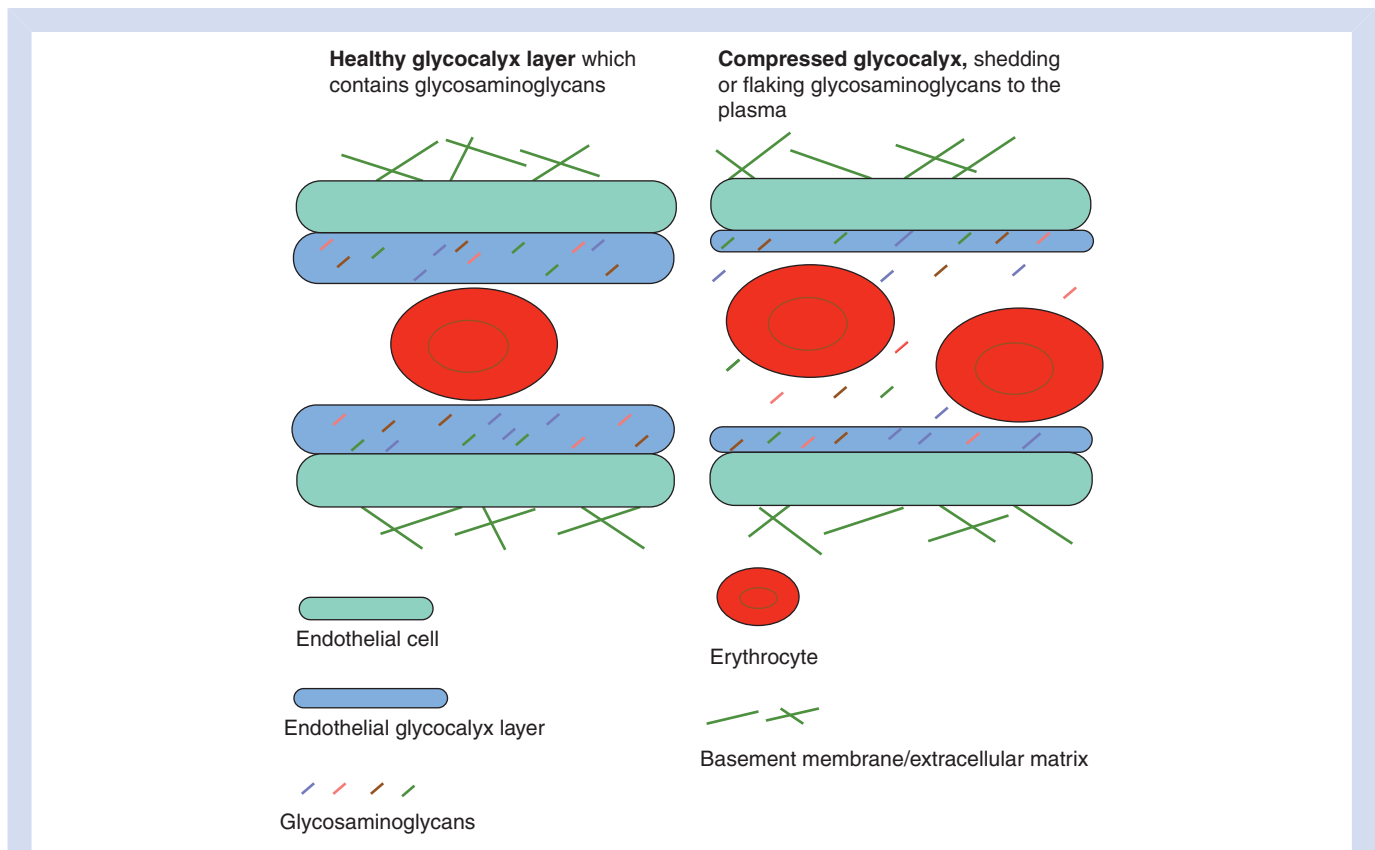
From experiments injecting serum or saline solution into the hindlimb of a dog, Starling deduced that the capillaries and post-capillary venules behave as semi-permeable membranes absorbing fluid from the interstitial space.<sup>11</sup> The work of Krooh and colleagues<sup>12</sup> developed Starling's principle in human physiology. With adoption of reflection coefficient<sup>13</sup> and pore theories,<sup>14</sup> the familiar paradigm of raised venous pressure and reduced plasma protein concentration

leading to oedema in clinical practice emerged.<sup>12–15</sup> Luft<sup>16</sup> revealed ‘the fine structure of the capillary and the endocapillary layer’ in 1966, and Curry and Michel<sup>17–18</sup> proposed a theory ‘that the molecular sieving properties of the capillary wall reside in a matrix of molecular fibres which covers the endothelial cells and fills the channels through or between them’ in 1980. Transvascular exchange depends on a balance between hydrostatic and oncotic pressure gradients. Fluid is filtered to the interstitial space under a dominant hydrostatic pressure gradient (capillary pressure  $P_c$  minus ISF pressure  $P_{is}$ ) at the arteriolar portion of capillaries, and it was believed that it is absorbed back under a dominant colloid osmotic pressure (COP) gradient (capillary COP  $\pi_c$  minus ISF COP  $\pi_{is}$ ) at the venular end. In 2004, Adamson and colleagues<sup>19</sup> showed that the effect of  $\pi_{is}$  on transvascular fluid exchange is much less than predicted by the standard Starling equation, which therefore has to be revised.<sup>20</sup> It is now established that non-fenestrated capillaries normally filter fluid to the ISF throughout their length. Absorption through venous capillaries and venules does not occur.  $\pi_c$  opposes, but does not reverse, filtration. Most of the filtered fluid returns to the circulation as lymph. Levick and Michel<sup>21</sup> now propose that the small pore system of the transvascular semi-permeable membrane is the endothelial glycocalyx layer (EGL) where it covers the

endothelial intercellular clefts, separating plasma from a ‘protected region’ of the subglycocalyx space which is almost protein-free. Subglycocalyx COP ( $\pi_{sg}$ ) replaces  $\pi_{is}$  as a determinant of transcapillary flow ( $J_v$ ).<sup>19–22</sup> Plasma proteins, including albumin, escape to the interstitial space by a relatively small number of large pores, which are responsible for the increased  $J_v$  observed in the early stage of inflammation,<sup>21</sup> and may be susceptible to pharmacological intervention.<sup>23–25</sup> The fact that low protein concentration within the subglycocalyx intercellular spaces accounts for the low  $J_v$  and lymph flow in most tissues is a critical insight and the basis of the glycocalyx model.<sup>21</sup>

## The endothelial glycocalyx layer

The EGL is a web of membrane-bound glycoproteins and proteoglycans on the luminal side of the endothelial cells, associated with various glycosaminoglycans (GAGs) (mucopolysaccharides) which contribute to the volume of the layer (Fig. 1).<sup>26</sup> It is the active interface between blood and the capillary wall.<sup>27</sup> Visualization of the EGL is technically demanding, but has helped to emphasize its physiological importance.<sup>28–29</sup> From indocyanine green dilution studies of patients given a large dose of i.v. colloid, the human EGL volume was estimated to be about 700 ml,<sup>30</sup> and presuming



**Fig 1** A cartoon illustrating that the intravascular volume contains the non-circulating glycocalyx fluid volume and the circulating plasma volume. Red blood cells are excluded from the glycocalyx layer. Compaction of the glycocalyx layer increases plasma volume and the red cell dilution volume independently of changes in intravascular volume.

that the endothelial surface area approximates 350 m,<sup>2 31</sup> an average EGL thickness of about 2  $\mu$ m was suggested. Fluid within the EGL is a non-circulating portion of the intravascular volume with a protein concentration gradient between the free-flowing plasma and the endothelial intercellular clefts. The EGL is thinner where it covers the microcirculation (as little as 0.2  $\mu$ m) and thicker in larger vessels (up to 8  $\mu$ m).<sup>29</sup> The EGL is semi-permeable with respect to anionic macromolecules such as albumin and other plasma proteins, whose size and structure appear to determine their ability to penetrate the layer.<sup>32</sup> The healthy EGL is impermeable to Dextran molecules of 70 kDa or more, and the glycocalyx-plasma boundary can be visualized as that part of the intravascular space that excludes fluorescein-labelled Dextran 70.<sup>32 33</sup> Red blood cells are also excluded from the EGL, and the intravascular red cell exclusion volume is larger than the Dextran 70 exclusion volume.<sup>34</sup> Dextran 40 is small enough not to be excluded by the EGL, and studies measuring the distribution volumes of Dextran 40 and erythrocytes in human subjects indicate an EGL in health of about 1700 ml, much larger than the indocyanine green dilution method.<sup>35</sup> Microvascular EGL thickness can be measured in sublingual tissues of patients using orthogonal polarization spectral imaging, and correlates well with dilution estimations.<sup>36</sup>

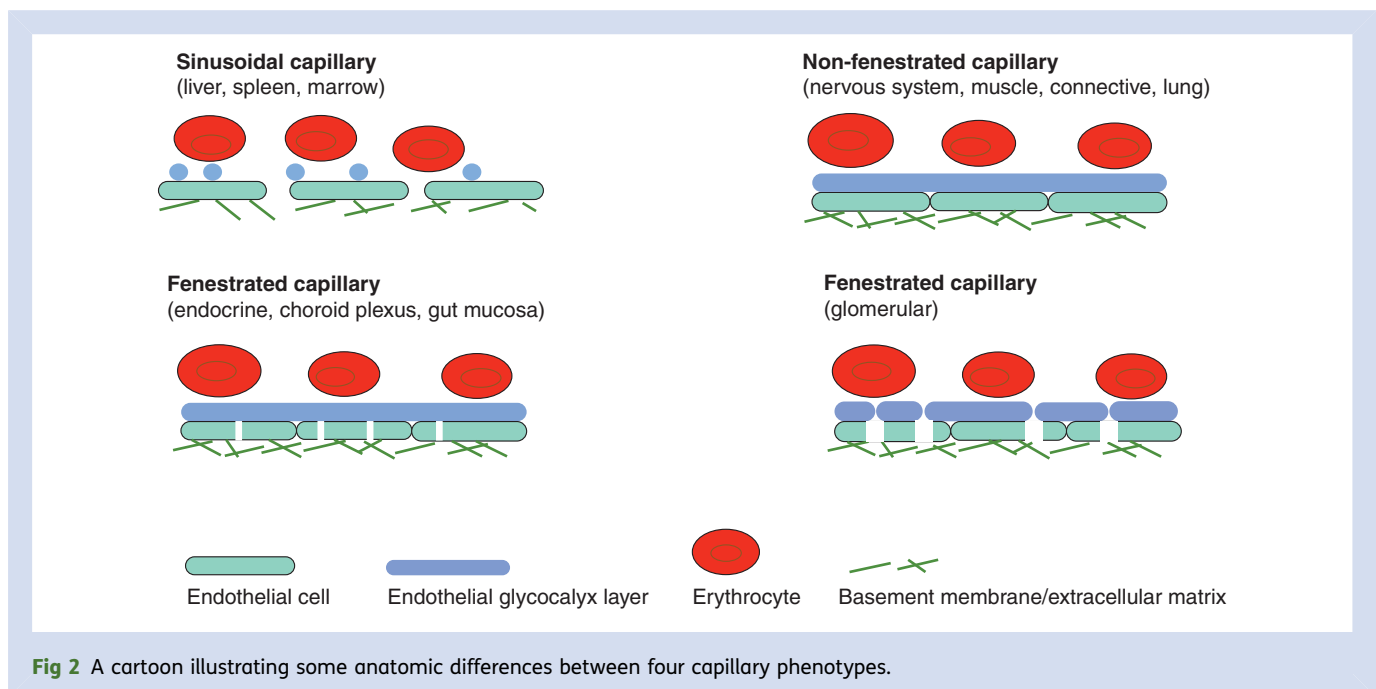
By removing GAGs and measuring volume reduction (compaction) of the EGL, the major ones appear to be heparan sulphate, chondroitin sulphate, and hyaluronic acid.<sup>33 37</sup> Compaction of the EGL by removal of GAGs preserves its resistance to filtration, despite loss of thickness and possible reduction in permeability.<sup>37</sup> Compaction of the EGL and the increase in heparan,<sup>38 39</sup> hyaluronic acid,<sup>40</sup> or chondroitin<sup>41</sup> in plasma are considered markers of glycocalyx injury, described as

'shedding', 'flaking', or 'fragmentation' (Fig. 1). Rapid crystalloid infusion in volunteers results in elevated plasma levels of hyaluronic acid and may therefore be injurious.<sup>42 43</sup> Increased plasma concentrations of GAGs have been found in septic shock patients, and they appear to reduce the antibacterial properties of plasma.<sup>44</sup> The volume of the EGL can be reduced by  $\geq 1$  litre in diabetes<sup>40</sup> or acute hyperglycaemia.<sup>35</sup> A number of other molecules, derived both from the endothelium and from the plasma and involved in coagulation and inflammation, exist within the EGL. The proteoglycan syndecan is a major glycocalyx component which increases in the plasma when EGL shedding occurs.<sup>38 45-47</sup>

It appears, on the evidence from human studies to date, that the EGL is compromised in systemic inflammatory states such as diabetes,<sup>40</sup> hyperglycaemia,<sup>35</sup> surgery,<sup>38</sup> trauma,<sup>47</sup> and sepsis.<sup>45</sup> Inflammatory mediators which have been implicated so far include C-reactive protein,<sup>48</sup> A<sub>3</sub> adenosine receptor stimulation,<sup>49 50</sup> tumour necrosis factor,<sup>34</sup> bradykinin,<sup>51</sup> and mast cell tryptase.<sup>52</sup> Therapeutic options for the protection or restoration of the EGL emerge from such studies. *N*-acetyl cysteine,<sup>35</sup> antithrombin III or hydrocortisone,<sup>53-56</sup> and even sevoflurane anaesthesia<sup>57 58</sup> could be beneficial. Compacted EGL volume can be restored by infusion of the GAGs chondroitin sulphate and hyaluronic acid.<sup>33</sup>

## Vascular endothelial cells

The reticuloendothelial capillaries of the sinusoidal tissues (liver, spleen, and bone marrow) are of phago-endothelial phenotype (Fig. 2). They express uptake receptors for hyaluronic acid, and by actively removing this important GAG, they prevent development of an effective EGL. In hepatic



**Fig 2** A cartoon illustrating some anatomic differences between four capillary phenotypes.

sinusoids, open fenestrations are the primary pathway for macromolecules as large as chylomicrons and lipoproteins to pass between plasma and ISF. The upper effective pore size of human hepatic sinusoidal capillaries is estimated to be about 180 nm.<sup>59</sup> Albumin synthesis is proportional to hepatic  $\pi_{is}$ , so an increase in other plasma proteins (acute phase proteins) or transfusion of colloids will displace albumin to the extravascular compartment and suppress albumin synthesis.<sup>43 60 61</sup> Being limited by fibrous capsules, the sinusoidal tissues have little or no compliance to accommodate ISF expansion. Filtration to the ISF will be dependent on hydrostatic pressure gradients, as there is no COP mechanism to oppose filtration, and return to the circulation is via the lymphatics. The liver is observed to account for around 50% of the body's total lymph production, with higher than average protein concentration, and is therefore the major site of transcapillary escape of plasma proteins and probably of other macromolecules when capillary function is unimpaired. In resuscitated hyperdynamic septic shock patients, hepatic blood flow is increased to around 50% of the cardiac output.<sup>62</sup>

The capillaries of the renal glomeruli have a full basement membrane and EGL, but they are generously fenestrated. Anatomically, the fenestrations are as wide as 65 nm, but their effective pore size is only about 15 nm, attributable to EGL flanking over the open fenestrations. The effective pore size for glomerular filtration beyond the capillary basement membrane is limited to about 6 nm by filtration slit diaphragms at the level of podocyte foot processes. Thus, albumin and larger molecules are normally not filtered into tubular fluid. It has been presumed that albuminuria is an index of capillary permeability,<sup>63</sup> but the mechanism is probably more complex.<sup>64</sup> Protein filter function is impaired by hyperglycaemia,<sup>65</sup> and probably by other kidney injuries.

Fenestrated capillaries with specialized functions also exist in the endocrine and exocrine glands and the choroid plexus. The fenestrated capillaries of the kidney cortex and medulla (peritubular capillaries and the vasa recta), the gastrointestinal mucosa, and the lymph nodes are notable exceptions to the principle of no fluid absorption.<sup>21</sup> The basement membrane of these capillaries is continuous, and their diaphragmed fenestrations are induced by vascular endothelial growth factors. Their upper pore size is in the range of 6–12 nm.<sup>59</sup>

Non-sinusoidal non-fenestrated capillaries have continuous basement membrane and EGL. Breaks within the inter-endothelial cell junctions constitute the primary pathways for transvascular fluid filtration, and the increased porosity seen in inflammation may be due to an increase in these normally infrequent discontinuities.<sup>19 25 59 66</sup> An alternative interpretation of pore theory, called the 'glycocalyx-junction-break model', proposes that pore size (small or large) is a function of the spaces between the matrix fibres of the EGL, while the area for fluid exchange is a function of the length of the junction breaks between adjacent endothelial cells.<sup>22</sup> In the capillaries of the brain and spinal cord, endothelial cell membranes are tightly opposed

by zona occludens tight junctions with few breaks, resulting in very small effective pore size of barely 1 nm.<sup>59</sup> The blood–brain barrier is therefore only permeable to the smallest non-lipid soluble molecules. Non-sinusoidal non-fenestrated capillaries of muscles, connective tissues, and lungs have macula occludens loose junctions to their intercellular clefts, and the effective pore size there is up to 5 nm, making them permeable to molecules as large as myoglobin. The tissues that can accumulate substantial amounts of ISF after trauma and sepsis (i.e. the more compliant tissues) are loose connective tissues, muscles, lungs, and gastrointestinal mesentery and mucosa. For example, extravascular lung water measured by double indicator dilution can increase from around 500 ml to 2.5 litre in pulmonary oedema, while the loose connective tissues and muscles can expand to many litres of peripheral oedema.

Aquaporins are present within vascular endothelial cell membranes, particularly in muscles. Their effective pore size is very small and it is believed they contribute little to transvascular filtration. There is controversy about the significance of transcellular large-pore systems for transport of proteins from plasma to the ISF in systemic inflammation. If they exist, their effective pore size is >50 nm. An increase in large pore numbers is an important component of the inflammatory increase in  $J_v$ .<sup>21</sup> Endothelial cells may undergo phenotype changes in response to physical and chemical stresses, which contributes to endothelial dysfunction.<sup>22</sup>

This consideration of the four types of body tissue and their capillaries helps to explain some otherwise unexpected clinical observations. A series of experiments on the volume kinetics of rapidly infused i.v. fluids measured the haemoglobin concentration of arterial or venous blood and modelled a central and a peripheral volume which represent the intravascular and extravascular fluid volumes, respectively.<sup>9</sup> Acutely, the peripheral volume is found to be 6–8 litre, less than the anatomic ISF volume. As volume kinetics measure only the volume which can be expanded, and this will therefore not include spaces limited by rigid structures such as the bone (brain, marrow) or fibrous capsules (liver, spleen, kidney).<sup>9</sup> This goes some way to explaining why ISS are more efficient plasma expanders than we might expect if we were to presume their distribution throughout the whole ECF. In systemic capillary leak syndrome, so much fluid goes to the soft tissues of the limbs that it can cause compartment syndromes.<sup>67</sup>

## The extracellular matrix and basement membrane

The glycocalyx is the first and the major fibre matrix resistor in the current of fluid and solutes between plasma and lymph. The basement membrane and extracellular matrix are the second and third resistances in a series.<sup>68</sup> The basement membrane, where it exists, is a specialized part of the extracellular matrix 60–100 nm in thickness, composed of type IV collagen and laminin and closely adherent to the cell membrane.<sup>59 69</sup> The extracellular matrix is a web of

collagen fibrils within the interstitial space upon which glycoproteins such as fibronectin and proteoglycans (protein molecules with GAG side chains) are arranged, and contain free GAGs. Toll-like receptors are found within the extracellular matrix and are believed to have a pivotal role in the early development of systemic inflammatory response<sup>70</sup> and ventilator-induced lung injury.<sup>71</sup> Integrins and their receptors modulate cell locomotion through the extracellular matrix, and it has been discovered that they can modulate  $P_{is}$  by bringing about conformational changes to collagen which allow the GAGs to become hydrated. An acute reduction in  $P_{is}$  occurs in inflammatory conditions, increasing the transendothelial pressure difference and thereby increasing  $J_v$  by as much as 20-fold independently of other causes of capillary 'leak'.<sup>72 73</sup>

## Plasma proteins

Proteins have an oncotic role across the endothelial glycocalyx and COP difference opposes but does not reverse  $J_v$ . The EGL is semi-permeable to albumin molecules, and the presence of albumin within the EGL is an important determinant of its filter function.<sup>74</sup> The functional unit of EGL 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.<sup>61</sup> 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.<sup>75</sup> 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  $J_v$  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,<sup>76-78</sup> but treatment of hypoalbuminaemia is of no clinical benefit.<sup>79 80</sup>
- Acute respiratory distress syndrome (ARDS) patients (lung injury score 2.5 or more) have low plasma

albumin and transferrin concentrations,<sup>81</sup> but hyperoncotic human albumin solution with or without a diuretic produces no improvement in pulmonary oedema.<sup>82</sup>

- Negative fluid balance rather than COP difference improves the alveolar to arterial oxygen tension ratio in ARDS patients.<sup>83 84</sup>
- In septic and non-septic patients, fluid loading against central venous pressure produces greater increases in cardiac output with human albumin solution than with ISS,<sup>85</sup> but there are no benefits for pulmonary oedema nor for the lung injury score.<sup>86</sup>

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.<sup>87</sup> 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 EGL intravascular volume should be interpreted with caution (Fig. 1).

## Plasma substitutes

Plasma substitutes are used to maintain or raise the plasma COP, although they too displace albumin from the circulation.<sup>43</sup> Moreover, by elevating COP, they suppress hepatic albumin synthesis. Little is known of their effect on the EGL, but they would not be expected to support EGL filter function as albumin does. The need to consider the contribution of the EGL to red cell volume of distribution changes as noted above for studies of hyperoncotic albumin solutions applies equally to studies of hyperoncotic plasma substitutes.<sup>88</sup>

In normovolaemic volunteers made hypervolaemic, modified fluid gelatin or hydroxyethyl starch solutions were distributed to the ISF more slowly than ISS as explained by the revised Starling equation, but there was no difference in arterial pressure, urine output, or renal hormone concentrations in plasma.<sup>89</sup> In the expectation that they will be more effective than ISS at inducing hyperdynamic circulation, these plasma substitutes are commonly preferred for haemodynamic goal-directed therapy.<sup>90-95</sup> However, the volume kinetic experiments have shown that the clearance of ISS from the central (intravascular) compartment (presumed to reflect  $J_v$ ) is substantially slower in anaesthetized patients than in unanaesthetized subjects,<sup>9</sup> and it has been shown that ISS can be used to achieve hyperdynamic goals.<sup>96 97</sup> This phenomenon is called context sensitivity.<sup>9</sup> 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 ISS, but increased during anaesthesia compared with awake subjects.<sup>98</sup> 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,<sup>99</sup> and crystalloids given during the vasodilation induced by spinal anaesthesia ('co-loading') are more effective than 'preload' crystalloids.<sup>100</sup> Mean arterial pressure is an important determinant of the distribution of ISS 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.<sup>101</sup>

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.<sup>102–106</sup> Analysis of published data does not show that plasma substitutes are equivalent to albumin in this respect, or better than ISS.<sup>107</sup>

### COP in practice

A paradigm founded on the standard Starling principle attaches great importance to the COP of plasma in clinical practice. However, there is no difference between the COP of plasma in septic and non-septic patients,<sup>23</sup> it does not influence pulmonary transcapillary filtration in patients with pulmonary oedema,<sup>108</sup> and it was not found to be a determinant of outcome in an intensive care practice.<sup>109</sup> In a patient study, human albumin transiently raised plasma COP compared with hydroxyethyl starch or ISS, but neither fluid balance nor the development of peripheral or pulmonary oedema were different between the treatment groups.<sup>110</sup> In a study of post-surgical patients with acute lung injury, it was found that plasma substitute resuscitation worsened the total thoracic compliance compared with normal saline, and that the type of fluid used for volume loading did not affect pulmonary permeability or oedema.<sup>111</sup> Properties other than the effect on COP contribute to the capillary 'sealing' effect of albumin or plasma substitutes, and this has been called the 'COP paradox'.<sup>74</sup>

### Capillary pressure in practice

Hahn's experiments show that rapid i.v. infusion of a large volume of ISS in healthy subjects with initially normal  $P_c$  is cleared at rates in excess of  $100 \text{ ml min}^{-1}$ .<sup>9 112</sup> Although this does not take into account the presence of the EGL, we can reasonably deduce that filtration from plasma to ISF ( $J_v$ ) was increased by supranormal  $P_c$  and the transendothelial pressure difference. When albumin or hydroxyethyl starch is used for plasma volume expansion, increased  $J_v$  limits the plasma-expanding effect of the colloid.<sup>4</sup> Nonetheless, colloid infusions have a more sustained plasma expansion effect than crystalloids, probably because maintained plasma COP opposes the increase in  $J_v$ .<sup>89</sup>

When albumin or hydroxyethyl starch is used for normovolaemic haemodilution, keeping the  $P_c$  normal,  $J_v$  is not increased and so most of the infused volume remains intravascular.<sup>4</sup> Hahn has reported increased filtration response to

crystalloid infusion after a colloid infusion,<sup>113</sup> consistent with the paradigm that at supranormal transendothelial pressure difference, further increases in  $P_c$  result in increased  $J_v$ . Rapid infusion of crystalloid to normovolaemic volunteers increases the intrathoracic fluid volume, narrows small airways, and induces hyperventilation.<sup>114</sup> Extreme elevation of  $P_c$  can damage the EGL,<sup>4</sup> and cause stress failure of pulmonary capillaries leading to haemoptysis and oedema.<sup>115</sup> Meta-analysis points to better patient outcomes if fluid balance is maintained.<sup>116</sup>

### An improved paradigm of fluid physiology and therapy

The intravascular space contains three compartments of interest (Table 1). If we define the intravascular fluid volume as that contained by the endothelial cells, we measure it as the Dextran 40 dilution volume and it approximates to the central volume of distribution of infused ISS. Dextran 70 is excluded from the non-circulating EGL and its dilution volume consists of circulating plasma.<sup>117</sup> There is a degree of exclusion of red cells from plasma at the EGL boundary, so the volume of distribution of red cells is rather less than the Dextran 70 dilution volume.

Compaction of the EGL can have significant effect on the balance of total intravascular fluid and red cell dilution volumes. EGL volume compaction by inflammation or hyperosmotic 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 (Fig. 3), but this effect lasts only for a few minutes.<sup>21</sup>

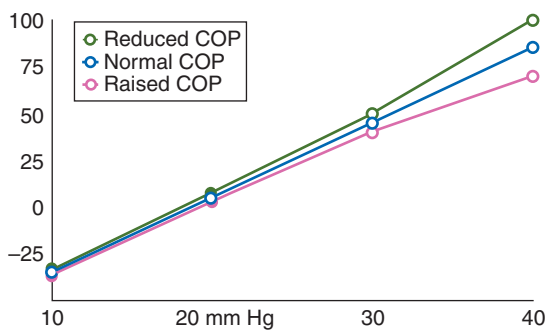
Absorption reverts to filtration as proteins diffuse into the subglycocalyx space from the ISF, diminishing the COP difference that opposes filtration; this is the glycocalyx model. With less acute or extreme disturbance to the equilibrium, the same mechanism preserves filtration, albeit at just a few millilitres per minute, and the no absorption rule applies (Fig. 4).

The pressure at which  $J_v$  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  $J_v$  and  $P_c$  (Fig. 4) 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. 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

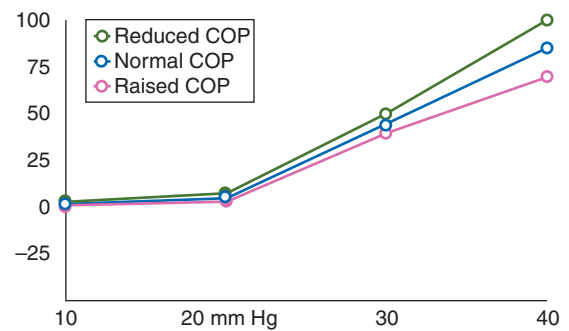
**Table 1** Comparison of the original and revised paradigms for prescribing fluid therapy

Original Starling principle	Revised Starling equation and glycocalyx model
Intravascular volume consists of plasma and cellular elements	Intravascular volume consists of glycocalyx volume, plasma volume, and red cell distribution volume
Capillaries separate plasma with high protein concentration from ISF with low protein concentration	Sinusoidal tissues (marrow, spleen, and liver) have discontinuous capillaries and their ISF is essentially part of the plasma volume Open fenestrated capillaries produce the renal glomerular filtrate Diaphragm fenestrated capillaries in specialized tissues can absorb ISF to plasma Continuous capillaries exhibit 'no absorption' The EGL is semi-permeable to anionic proteins and their concentration in the intercellular clefts below the glycocalyx is very low
The important Starling forces are the transendothelial pressure difference and the plasma-interstitial COP difference	The important Starling forces are the transendothelial pressure difference and the plasma-subglycocalyx COP difference. ISF COP is not a direct determinant of $J_v$
Fluid is filtered from the arterial end of capillaries and absorbed from the venous end. Small proportion returns to the circulation as lymph	$J_v$ is much less than predicted by Starling's principle, and the major route for return to the circulation is as lymph
Raising plasma COP enhances absorption and shifts fluid from ISF to plasma	Raising plasma COP reduces $J_v$ but does not cause absorption
At subnormal capillary pressure, net absorption increases plasma volume	At subnormal capillary pressure, $J_v$ approaches zero. Auto transfusion is acute, transient, and limited to about 500 ml
At supranormal capillary pressure, net filtration increases ISF volume	At supranormal capillary pressure, when the COP difference is maximal, $J_v$ is proportional to transendothelial pressure difference
Infused colloid solution is distributed through the plasma volume, and infused ISS through the extracellular volume	Infused colloid solution is initially distributed through the plasma volume, and infused ISS through the intravascular volume At supranormal capillary pressure, infusion of colloid solution preserves plasma COP, raises capillary pressure, and increases $J_v$ At supranormal capillary pressure, infusion of ISS also raises capillary pressure, but it lowers COP and so increases $J_v$ more than the same colloid solution volume At subnormal capillary pressure, infusion of colloid solution increases plasma volume and infusion of ISS increases intravascular volume, but $J_v$ remains close to zero in both cases

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**Fig 3** Autotransfusion. Transendothelial filtration rate  $J_v$  is proportional to the capillary pressure, or transendothelial pressure difference if interstitial pressure is not constant. Normal capillary pressure is nominally 20 mm Hg, and the scale for  $J_v$  is arbitrary, although studies show the rate of clearance from the intravascular space during rapid infusion of Ringer's acetate in humans can be as much as 100 ml min<sup>-1</sup>. Raising the plasma COP slows filtration (pink line), while reducing plasma COP increases it (green line).



**Fig 4** The no absorption rule. With less acute reduction in capillary pressure, the glycocalyx model preserves filtration at a very low rate without a phase of absorption, the no absorption rule. We call the inflection on the filtration curve the J point.

pressure difference opposing filtration is maximal and  $J_v$  becomes proportional to  $P_c$ , or transendothelial pressure difference if  $P_{is}$  is not constant.

Porosity increases in inflammatory states, but  $\pi_{is}$  has no direct effect on  $J_v$ . A 10- to 20-fold increase in  $J_v$  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 EGL, they pass easily into the ISF 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  $J_v$  and the transcapillary escape rate of albumin. There is no significant absorption of ISF to the plasma under a COP difference, so colloid therapy does not prevent or improve tissue oedema.

In conclusion, fluid resuscitation studies require us to 'reappraise the basics'.<sup>118</sup> The revised Starling equation and glycocalyx model paradigm appear to be an improvement on the original Starling principle paradigm. Colloids are widely prescribed for resuscitation from hypovolaemia, despite evidence-based protocols and guidelines.<sup>119 120</sup> An important feature of the revised Starling equation and glycocalyx model paradigm is that it explains why albumin or plasma substitutes have no advantage over ISS when  $P_c$  or transendothelial pressure difference is low. The finding that  $\pi_{is}$  has little effect on  $J_v$  focuses our attention on the subglycocalyx space. The EGL is a fragile structure and is disrupted by rapid i.v. infusion of fluids, acute hyperglycaemia, surgery, and sepsis. The glycocalyx model describes how  $\pi_{sg}$ ,  $\pi_{is}$ , and  $J_v$  balance one another, and raises concerns about disease processes or plasma substitute therapies that might disturb the protected low  $\pi_{sg}$ . In the absence of absorption by capillaries and venules, filtered fluid returns to the circulation mostly by lymphatics, and the importance of preserving lymphatic flow is highlighted. The new paradigm provides an explanation of context sensitivity of colloid and crystalloid volume kinetics in awake, anaesthetized, or hypotensive patients, and the rational prescriber will consider the desired effect on  $P_c$  and transendothelial pressure difference. Endothelial dysfunction associated with increased capillary porosity increases  $J_v$  at any  $P_c$ , and lowers the  $P_c$  at which  $J_v$  approaches zero. This J point can be taken into account when faced with a patient with systemic inflammation or sepsis. It is likely that the revised Starling equation and glycocalyx model paradigm will be modified and refined in the light of physiology and clinical trial evidence. In its current form, it strengthens the arguments for preferring ISSs over plasma or plasma substitutes for resuscitation, but accepts a rational use of colloids for euvolaemic or hypervolaemic haemodilution. The use of plasma or plasma substitutes to achieve a

sustained supranormal plasma volume or to reduce tissue oedema is not rational.

## Declaration of interest

None declared.

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