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Endothelial glycocalyx: Role in body fluid homeostasis and fluid management

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Review Article

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ABSTRACT

Endothelial glycocalyx layer (EGL) coating the luminal surface of vascular endothelium plays an essential role in maintaining the normal fluid homeostasis of the body. This highly fragile layer can be damaged by a number of pathophysiological conditions and interventions. Disease state management should be directed to maintain EGL integrity to improve patient's outcome. When intravenous (IV) fluids are used, appropriate type, rate and amount of fluid should be determined by the pathophysiology of the condition and measures to maintain the integrity of the EGL. This review depicts the structure and function of the EGL, its alteration in common pathological states and the rationale of IV fluid management to preserve EGL in such conditions.

Key words: Endothelial glycocalyx, fluid homeostasis, intravenous fluid therapy, Starling equation

INTRODUCTION

Glycocalyx, the sugar protein coating of the vascular endothelium, forms an integral part of the vascular barrier and contributes to 2% of the plasma volume [Figure 1a]. The endothelial glycocalyx layer (EGL) plays a pivotal role in body fluid homeostasis, modulation of inflammatory reactions, adhesion of platelets and leukocytes and is breached in conditions such as trauma, sepsis, diabetes, electrolyte imbalance, surgery and overzealous fluid management.[1,2]

Intravenous (IV) fluid administration plays an integral part in the management of a patient. As described by Malbrain *et al.*,[3] there are four major indications for IV fluid administration, namely, resuscitation, maintenance and supplementation of fluid and electrolytes, as a carrier for IV drugs and for parenteral nutrition. Improper administration of IV fluid can cause serious alteration of normal physiology including damage of the vital EGL layer.

This review was undertaken to describe the structure, physiology and functional basis of the EGL, its relevance in body fluid homeostasis and IV fluid management in various clinical and pathological conditions.

A thorough literature search was done from inception to September 2018 using databases/search engines (Medline, Embase, Scopus, PubMed, Google Scholar and websites of National Societies for IV fluid management). The articles were manually searched by the authors for cross-referencing. All the articles published in English were searched. We used the following keywords "endothelial glycocalyx," "intravenous fluid therapy," "fluid homeostasis," "Starling equation," "Revised Starling equation," "Liver failure," "Nephrotic syndrome," "Heart failure," "Oedema," "Albumin," "Sepsis" and "ARDS." The relevant information pertinent to the role of EGL in various conditions were included.

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STRUCTURE OF EGL

The composition of the EGL varies according to the microenvironment. The most prominent constituents of EGL are proteoglycan, glycoproteins and glycosaminoglycans (GAGs) along with other soluble components such as proteins [primarily albumin along with antithrombin-III (ATIII), apolipoproteins], hormones, enzymes such as extracellular superoxide dismutase-3 (SOD3), angiotensin-converting enzyme, growth factors, chemokines and adhesion molecules (selectins and integrins)[1] [Figure 1b].

The central protein core is made up of proteoglycans to which the negatively charged highly sulphated GAGs remain attached. Syndecan and glypicans are the major proteoglycans having a firm connection to the cell membrane forming the backbone of the EGL. The other proteoglycans such as mimecan, perlecan and biglycan are secreted later and contribute to the soluble portion of the glycocalyx.[1]

There are five types of GAG chains, namely, heparan sulphate, chondroitin sulphate, dermatan sulphate, keratan sulphate and hyaluronan (or hyaluronic acid). Hyaluronic acid is the only nonsulphated, uncharged GAG not usually attached to any core protein. It is usually attached to cell surface proteins (CD44)[4] and forms a viscous solution by exhibiting water-retaining characteristics. Glycocalyx forms a meshwork in which proteins and soluble GAGs get attached. It has a fixed part which remains attached to the endothelial layer and a dynamic part, which is in equilibrium with circulating blood volume. Proteins <70 kDa such as extracellular SOD, ATIII and albumin are present in the dynamic part of the EGL layer which have variable structure and composition [Figure 1b]. The adhesion molecules such as platelet endothelial cell adhesion molecule (PECAM), vascular cell adhesion molecule (VCAM) and intercellular adhesion molecule (ICAM) are also embedded within the structures.

The presence of sulphated GAGs renders a negative charge to the glycocalyx. Hence, its interaction varies with varying charge of molecules and also acts as a barrier repelling the negatively charged molecules like red blood cell (RBC), white blood cell (WBC) and platelets, forming a "cell exclusion zone." The layer also acts as a sieve, restricting passage of molecules >70 kDa. However, the amphoteric nature of albumin and size of 67kDa helps it to bind tightly to the glycocalyx. Some albumin even leaks through the glycoprotein layers. This attachment of albumin reduces the hydraulic conductivity across vasculature.[1]

There are several techniques to visualise the vital EGL layer both *in vivo* and *in vitro*. *In vitro* visualisation started with transmission electron microscopy which gained accuracy over decades by development of glycocalyx-sparing fixation techniques. *In vivo* techniques comprise confocal laser scanning microscopy which allows 3D reconstruction of the EGL. However, its less penetration makes it less useful in visualising EGL of large vessels. Two-photon laser scanning microscopy is one of the most promising technique allowing fairly accurate EGL visualisation both *in vivo* and *in vitro*.[5] Real-time visualisation by handheld videomicroscopy is the latest trend. Based on the mean distance between RBC and vessel wall, an assessment of EGL thickness is calculated by *post hoc* software analysis.[6]

FUNCTIONAL IMPORTANCE OF GLYCOCALYX

The negatively charged GAGs are arranged like branches covering the glycoprotein receptors[1,7] [Figure 2]. The
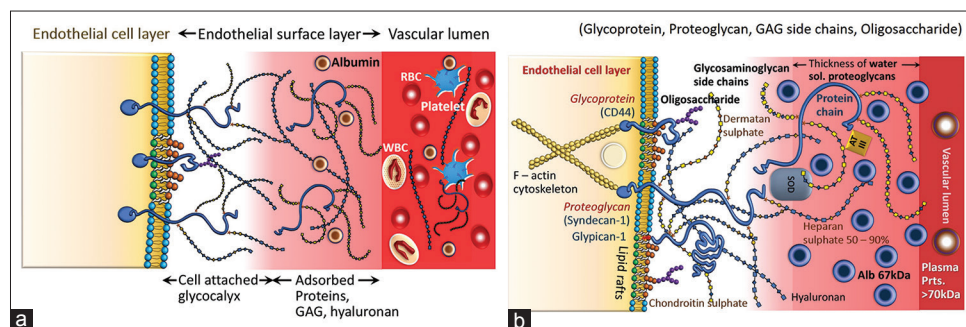
**Figure 1:** Structure of endothelial glycocalyx (EGL). (a) 2% of the non-circulating portion of the intravascular volume formed by EGL. RBC, WBC and platelets are excluded from the non-circulating EGL, which is in dynamic equilibrium with plasma. (b) Structure and various constituents of EGL layer. RBC – Red Blood Cell, WBC – White Blood Cell, Alb – Albumin, SOD – Superoxide dismutase, ATIII – Antithrombin III

adhesion receptors are therefore protected by the GAG branches. These receptors are mostly of two types: selectins and immunoglobulins. Histamine, thrombin, interleukins and tumor necrosis factor bind to the selectin while immunoglobulins have adhesive molecules for ICAM, VCAM and PECAM.

External or internal insults like loss of flow (thrombosis, arteriosclerosis), inflammation (systemic inflammatory response, diabetes, trauma, sepsis) and rapid administration of fluid can damage the glycocalyx. This results in exposure of the receptors of the glycocalyx to combine with the noxious ligands that result in signal transduction. Hence, damage to glycocalyx significantly affects the microcirculation.[8]

REVISED STARLING PRINCIPLE

As per Starling's model,[9] the net force at the arteriolar end of the capillaries pushes fluid out as a result of high hydrostatic pressure and at the venous end fluid re-enters the vessels because of osmotic attraction. The Starling equation reads as follows: $J_v = K_f ([P_c - P_i] - \sigma [\pi_c - \pi_i])$, where J_v is
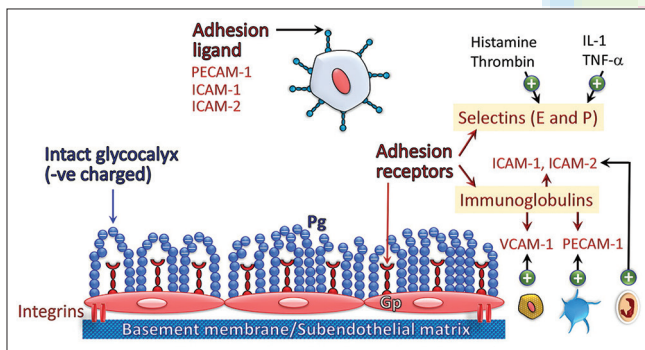

Figure 2: Protective mechanism of EGL. Adhesion molecules remain embedded in EGL layer refraining adhesion of endothelial cells and inflammatory mediators. Gp – Glycoprotein, Pg – Proteoglycan, ICAM – Intercellular Adhesion Molecule, VCAM – Vascular Cell Adhesion Molecule, PECAM – Platelet Endothelial Cell Adhesion Molecule

the net fluid movement between compartments and $[P_c - P_i] - \sigma [\pi_c - \pi_i]$ is the net driving force, P_c is the capillary hydrostatic pressure, P_i is the interstitial hydrostatic pressure, π_c is the capillary oncotic pressure, π_i is the interstitial oncotic pressure, K_f is the filtration coefficient – a proportionality constant, and σ is the reflection coefficient). Starling stated that these forces are balanced [Figure 3a].

However, it was later demonstrated that the effect of π_i on transvascular fluid exchange is significantly less than predicted by the standard Starling's equation due to the presence of EGL.[10] Hence, the revised Starling's principle considers the presence of EGL which comprises adsorbed albumin molecules and exerts a significant osmotic pressure than interstitium as was thought earlier. Just below the EGL, there is an empty subglycoclyx space[11] [Figure 4]. Albumin is transported across the cell membrane by the process of endocytosis, whereas the circulating albumin in the blood is adsorbed over the GAG side chains and contributes to the soluble layer of the EGL. The zone below the soluble portion of EGL is an acellular zone also known as the red cell exclusion zone. The adsorbed albumin in the soluble portion of EGL contributes to 60% of colloid osmotic pressure (COP) of the total intravascular COP that is higher than the circulating plasma. Hence, an osmotic gradient is created between the EGL and subglycocalyx zone (protein-free zone in the intercellular cleft between cells below the glycocalyx). The revised Starling's equation incorporates π_g (glycocalyx oncotic pressure) instead of π_i, and is stated as $J_v = K_f ([P_c - P_i] - \sigma [\pi_c - \pi_g])$ [Figure 3b].

Hence, the oncotic pressure difference is not built up between the intravascular and the interstitial tissue spaces, but within a small protein-free zone beneath the glycocalyx surface layer (subglycocalyx space). The capillary hydrostatic pressure and subglycocalyx
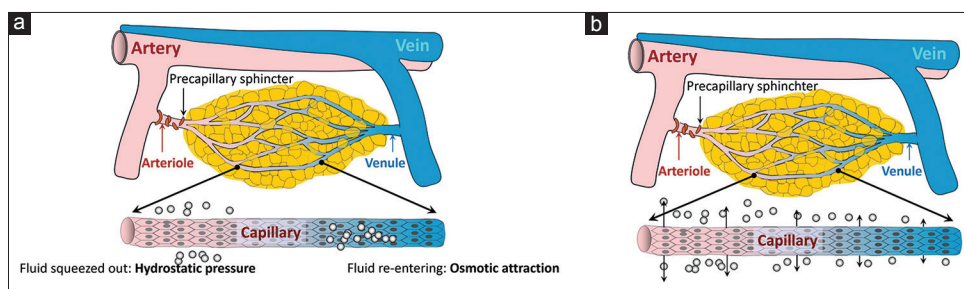
Figure 3: (a) Original Starling's equation Jv – Kf ([Pc – Pi] – σ [πc – πi]. Fluid pushed out at the arteriolar end equals fluid reabsorbed at the venular end. (b) Modified Starling's equation taking EGL layer into consideration Jv – Kf ([Pc – Pi] – σ [πc – πg]). Lymph plays a major role in returning fluid back into the circulation

pressure help draw the fluid in the interstitial space. This fluid that filters out forms the "ultrafiltrate." In the interstitium, the hydrostatic and the osmotic pressure are much low, hence negligible fluid goes back to the capillaries at the venous end to cause any venous reabsorption. The lymphatics play all important role to remove the excess fluid which comes to the interstitial space and is put back into circulation [Figure 4]. The revised Starling's equation states that (a) intravascular volume comprises circulating RBC volume, plasma volume and glycocalyx volume instead of only plasma and cellular elements, (b) ultrafiltrate is produced due to filtration across glycocalyx and no venous reabsorption occurs at the venous end and (c) lymph forms the major route for return of fluid into circulation as it removes the fluid from the interstitial space.
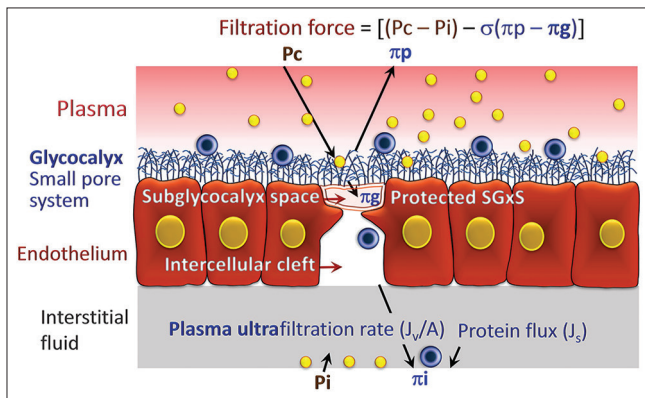

Figure 4: The oncotic pressure difference is build up between the adsorbed albumin in the soluble EGL layer a small protein free zone (subglycocalyx space) leading to the revised Starling's equation

EGL AND FLUID THERAPY

IV fluid should be administered when the fluid or electrolyte needs cannot be met orally or enterally or IV fluid has to be given as a medium for giving drugs. As per the National Institute of Health and Care Excellence (NICE) guidelines,[12] 5 Rs (Resuscitation, Routine maintenance, Replacement, Redistribution and Reassessment) should be kept in mind while prescribing IV fluids and early de-escalation is warranted.

Crystalloids are solution of inorganic ions and small organic molecules in water and are divided according to tonicity in to iso, hypo or hypertonic solutions. Overadministration of acidic crystalloids with strong ion difference like normal saline (NS) with chloride of 153 mmol/L can lead to hyperchloremic metabolic acidosis and damage the EGL and result in acute kidney injury (AKI) and impaired clotting functions[13] [Figure 5a]. Rapid NS administration can initiate excess plasmin activity and auto-heparinisation from EGL shedding resulting in diffuse coagulopathy specially in a background of trauma or sepsis.[14,15] Balanced crystalloids like lactated Ringer (Cl 109 mmol/L) and plasmalyte A (Cl 98 mmol/L) are more physiological and are similar in composition to human plasma [Figure 5b]. They are more compatible with EGL. Large randomised clinical trials like SMART[16] and SALTED[17] in both critically ill and noncritically ill patients have shown that major adverse renal events (AKI and requirement of renal
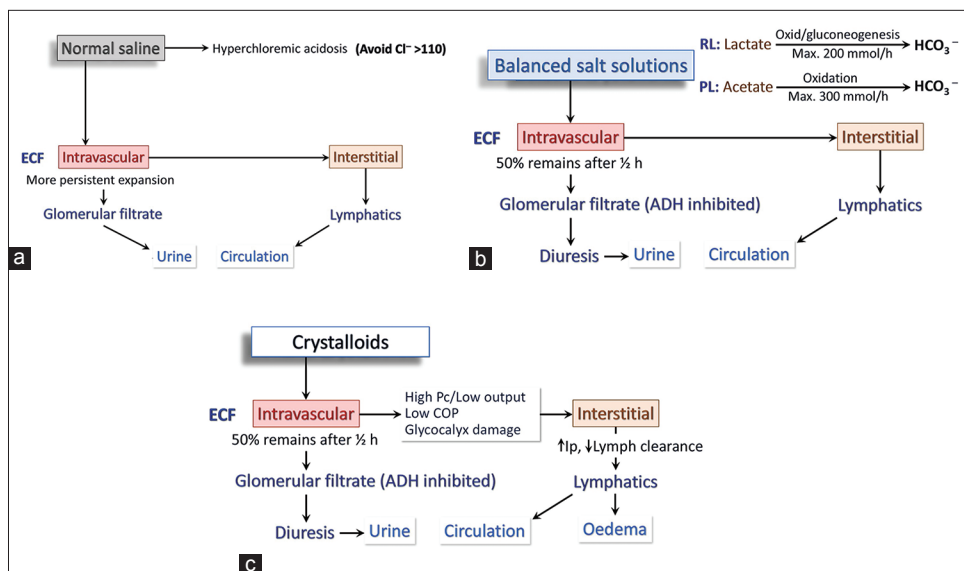
Figure 5: (a) Distribution and excretion of normal saline (0.9% NS) after intravenous administration. The high chloride load is above physiological limit and can contribute to hyperchloremic metabolic acidosis. (b) Distribution, metabolism and excretion of balanced salt solution (Ringers lactate and Plasmalyte A) with intact EGL layer. (c) Distribution and excretion of balanced salt solution (Ringers lactate and Plasmalyte A) with damaged EGL layer leading to edema formation. ECF – Extracellular fluid, RL – Ringer's Lactate, PL – Plasmalyte A, Cl- – Chloride, HCO3— – Bicarbonate

replacement therapy) are less with administration of balanced salt solution having low chloride content (<110 mmol/L) compared with NS. However, balanced crystalloids are hypotonic compared with extracellular fluid and are associated with metabolic alkalosis, hence they are not completely harmless. With damaged EGL, the distribution of the balanced salt solution changes contributing to interstitial oedema [Figure 5c].
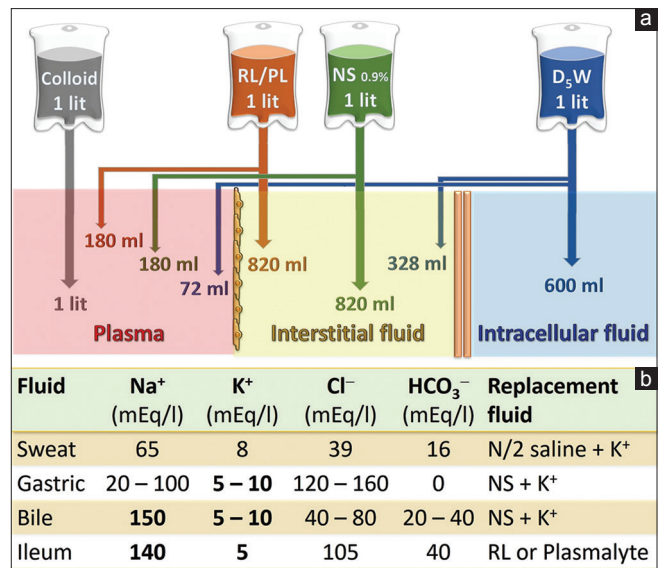
Colloids due to their large molecular size are expected to stay in the intravascular space for a longer time thereby creating an increase in oncotic pressure. Colloids commonly used are natural (albumin) or artificial (gelatin, dextran and hydroxy ethyl starch). Albumin has lower molecular size (67 kDa) and is part of soluble part of EGL.[18] Presence of hypoalbuminaemia has shown to contribute to increased EGL damage in trauma and sepsis along with increased leakage of albumin into the interstitial space when compared with patients with normal albumin levels. Albumin (5%) helps maintain the integrity of the EGL and is advised as an early modality of treatment in trauma with the exception of traumatic brain injury.[19] Artificial/semisynthetic colloid administration is associated with increased incidence of anaphylactoid reactions, coagulopathy and AKI. Newer generation 6% hydroxy ethyl starch (HES) (130/0.42) was presumed to offer a wider safety and efficacy range. However, Scandinavian[20] and CHEST[21] trials have demonstrated increased long-term mortality and AKI.

Revised Starling equation's implication

At subnormal capillary pressure, infusion of colloid solution preserves plasma COP, raises capillary pressure and increases Jv. While infusion of crystalloids also raises capillary pressure, it lowers COP and thus increases Jv more than the same colloid solution volume. At subnormal capillary pressure, infusion of crystalloid is therefore a better choice as first line of fluid management [Figure 6a].

Inflammation, trauma, shock (hypovolemic, septic), hyperglycemia, ischaemia and reperfusion, electrolyte imbalance and iatrogenic causes like rapid administration of fluids and surgery cause damage to the EGL. Ageing, lack of moderate exercise, high-sugar diet and smoking are also important predisposing factors that contribute to EGL damage.

EGL takes 6–8 h to regenerate under normal physiological conditions. In pathological conditions, the regeneration time varies from hours to days

Fluid	Na+ (mEq/l)	K+ (mEq/l)	Cl− (mEq/l)	HCO3− (mEq/l)	Replacement fluid
Sweat	65	8	39	16	N/2 saline + K+
Gastric	20 – 100	5 – 10	120 – 160	0	NS + K+
Bile	150	5 – 10	40 – 80	20 – 40	NS + K+
Ileum	140	5	105	40	RL or Plasmalyte

Figure 6: (a) Distribution of various commonly used fluids (crystalloids and colloids) in different body compartments. (b) Composition of various transcellular fluids in human body and the type of replacement fluids to be used depending on the type of fluid loss. RL – Ringer's Lactate, PL – Plasmalyte A, NS – Normal Saline, D5W – 5% Dextrose, Na+ – Sodium, K+ – Potassium, Cl- – Chloride, HCO3- – Bicarbonate

depending on the extent of the ongoing insult and the volume of glycocalyx damaged. In experimental model of enzymatic degradation, EGL takes 5–7 days or more to attain the previous thickness.[22]

Rapid administration of IV fluid can cause damage to the EGL in healthy volunteers.[23] However, in hypovolemic or septic shock, IV fluids should be administered through large veins via large bore cannula to avoid fluid jet to prevent damage to the delicate EGL grid. Current evidence suggests that blood products and IV fluids more than 500 mL should be warmed to 37°C which helps in maintaining the core body temperature and protects the EGL.[24]

EGL is destroyed by large volume of fluids or hypervolemia. Atrial natriuretic peptide released from the stretching of atria is considered to be one of the triggers for EGL destruction. NICE guidelines[12] recommend routine maintenance of 25–30 mL/kg/day of water, 1 mmol/kg/day of potassium, sodium and chloride and 50–100 g/day of glucose in patients requiring IV fluids. Addition of glucose is to limit starvation ketoacidosis. However, in old and frail patients with renal impairment and cardiac failure, the total amount should be restricted to 20–25 mL/kg/day. Caution should be exercised in obesity, where the ideal body weight should be considered and IV maintenance fluid should not exceed 3 L/day. Replacement fluids should also be governed by the composition and

amount of fluid loss from different sources (sweat, gastric, bile, pancreas, ileum, colon) [Figure 6b].

Recent meta-analysis[25] suggests that prognosis with restrictive/goal-directed fluid therapy is better compared with liberal fluid administration. The damage of EGL by liberal fluid administration increased leakiness of the endothelium. This extravasation of fluid into the interstitium increases inflammation, wound infection and derangement in coagulation function resulting in increased morbidity and mortality. However, clinical trial recommending liberal fluid over restricted in major abdominal surgeries causing higher rate of AKI in the restrictive fluid group is also a concern.[26] Therefore, calculating the appropriate amount of fluid in critical situation can be tricky and fluid responsiveness of the patient should be assessed specially by dynamic tests which are more sensitive. These tests are based on the principle of inducing short-term changes in cardiac preload, using heart–lung interactions, by the infusion of small volumes of fluid or by passive leg raise and to observe the resulting effect on cardiac output. The passive leg raise is an evidence-based most commonly used bedside test to detect fluid responsiveness of a patient.

Overzealous rapid administration of IV fluids can damage the EGL. Preloading in the presence of normovolemia before induction of general or neuraxial anaesthesia to combat sudden decrease in preload is not justified. Preloading neither decreases the incidence of vasopressor use nor hypotension but increases the morbidity due to destruction of EGL.[27] Rehm M et al.[2] in their study on isolated guinea pig heart showed that unless the EGL is destroyed by enzymes, the endothelial leakiness is not that profound even after ischaemic insults or treatment with heparin. The endothelium gets leaky with the extravasation of fluid only when the protective EGL is destroyed. The study also showed that infusion of 6% HES decreased coronary perfusion pressure significantly, whereas albumin and 0.9% NS had minimal effect.

EGL AND CLINICAL PATHOPHYSIOLOGY

Oedema is the accumulation of fluid in the interstitium with an increase in interstitial compliance. Tissue oedema occurs when the rate of transudation of fluid in the interstitial space from the capillaries surpasses the maximum lymphatic drainage. The mechanism of oedema formation is different in various pathological conditions.

Heart failure

Intact EGL has the ability to buffer an increase in total body sodium without water retention. As a result of heart failure, there is excessive sodium accumulation in the body both from renal retention and EGL degradation. The process of oedema in acute and chronic heart failure is different. In acute heart failure (AHF), redistribution of fluid occurs from splanchnic and peripheral circulation due to sympathetic activation rather than actual increase in intravascular volume which otherwise occurs in chronic heart failure. Hence, in accordance with Starling forces an increase in transcapillary hydrostatic pressure and a decrease in transcapillary oncotic pressure gradient cause the fluid to extravasate into the interstitium resulting in an increase in interstitial pressure due to excessive fluid accummulation that compromises the lymphyatic drainage. Diuretics, ubiquitously used as a first-line treatment of heart failure, decreases capillary hydrostatic pressure and thereby decreases J_v making lymphatic drainage from the interstitium more effective and reducing oedema. However as the protective EGL buffer is destroyed, a large amount of sodium escapes renal clearance and continues to contribute to oedema formation[6] and diuretics alone are not effective. In AHF characterised by volume redistribution, diuretics administered as the first line of treatment can cause a decrease in left ventricular function, an increase in ventricular filling pressure and systemic vascular resistance by activating renin–angiotensin–aldosterone pathway and thereby a decrease in glomerular filtration. A combination of vasodilators like nitrates and hydralazine, positive pressure ventilation and ionotropes might be beneficial in AHF to combat the sudden redistribution of fluid. However, for chronic heart failure where there is actual fluid retention, sodium restriction to less than 2 g/day, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, angiotensin receptor neprilysin inhibitor, beta blockers and aldosterone antagonists along with diuretics can improve oedema and prevent cardiac remodelling.[28]

Nephrotic syndrome

The renal basement membrane has fenestrated continuous capillaries and scanty EGL. The fenestrations are normally around 65 nm in size which reduces to 15 nm due to the overlaying of glycocalyx on the fenestrations. The effective filtration pore size at the level of podocytes is only 6 nm contributed by the filtration slit diaphragm. Thus, with intact basement membrane, albumin is not found in the

tubular fluid and its presence depicts a breach in capillary permeablility. In nephrotic syndrome, oedema begins to develop before proteinuria and a decrease in serum albumin is observed. An increase in glycocalyx degradation product (syndecan-1) in blood is observed in early stages of nephrotic syndrome with preserved renal function.

The mechanism of oedema formation in nephrotic syndrome is complex. Decrease serum albumin, intravascular volume status, neurohormonal factors and an integrating mechanism of sodium retention irrespective of intravascular volume due to activation of epithelial sodium channels (ENaC) are thought to be the contributing factors.[29] The mechanism of oedema formation in nephrotic syndrome has been described by two hypotheses, the underfill and the overfill hypotheses. *The underfill hypothesis* states that a decrease in plasma oncotic pressure due to hypoalbuminaemia increases the J_v and causes extravasation of fluid in the interstitial space causing oedema. The intravascular volume loss is sensed as hypovolemia and resultant activation of renin–angiotensin–aldosterone system causing secondary sodium retention. *The overfill hypothesis* states it is the primary renal sodium retention that results in oedema. Albumin can be considered as a modality of treatment if serum albumin is below 2 g/dL, since it helps increase the plasma oncotic pressure. Angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers reduce the amount of protein release in urine and help preserve plasma oncotic pressure in nephrotic syndrome. Diuretics increase the urine output by mobilising the fluid from the intravascular space thereby reducing the Jv and resulting in a decrease in Pi. The initial overburdened lymphatics in the interstitial space because of high Pi can now effectively drain the accumulated fluid in the interstitium. Corticosteroids are useful, since they help in decreasing the inflammation and prevent disease progression.[29]

Liver cirrhosis

In cirrhosis of liver, overexpression of Aplein (APLN) receptors activates hepatic stellate cells leading to tissue remodelling by chronic inflammation, neo-angiogenesis and fibrogenesis.[30] This actively damages the liver sinusoidal endothelial cells and completely disrupts the architecture of the liver. Fibrosis of the liver slows down the normal blood flow through liver and thus increases pressure in the portal vein. An increase in venous hydrostatic pressure increases J_v and causes extravasation of fluid in the interstitial space, causing oedema and ascites. The fibrosis decreases functional hepatic units, hampering the synthetic function of liver. This leads to hypoalbuminaemia since synthesis of albumin is one of the most important functions of liver. A decrease in plasma albumin decreases plasma oncotic pressure, thereby increasing J_v and contributing to the formation of oedema in cirrhosis. The treatment of oedema in cirrhosis is directed towards minimising portal venous pressure as well as increasing the plasma oncotic pressure. Maintaining negative sodium balance, administering diuretics, beta blockers, paracentesis and albumin infusion help in reducing the oedema in such situation.[30]

Sepsis and EGL

Sepsis damages the delicate EGL by directly altering its anionic charge and geometry and by increasing the interendothelial gaps. Expression of endothelial receptor adhesion molecules (ICAM 1, PECAM 1) increases in EGL due to proinflammatory and actute inflammatory mediators. These changes cause leucocyte activation and promote leukocyte rolling, adherence and migration into the interstitium by inflicting direct damage to the vascular endothelium. As a result, the vascular permeability increases causing fluid and albumin to shift to the interstitial space causing generalised oedema. The inflammatory mediators result in loss of vascular tone, peripheral pooling of blood and degradation of heparan sulphate, one of the component of EGL giving rise to a procoagulant state.

HOUR-1 sepsis bundle recommends administration of 30 mL/kg of crystalloids to correct hypotension and lactate more than 4 mmol/L.[31] FEAST trial[32] comparing 40 mL/kg NS or 4% albumin volume resuscitation in septic children had to stop midway due to increased mortality caused by overzealous fluid resuscitation. Buffered isotonic crystalloids are recommended, but administration of large volumes should be avoided. IV fluid intervention helps improve cardiac output, organ perfusion and eventually tissue oxygenation, but the effect is transient due to leakiness and loss of retaining capacity of the damaged endothelium. Therefore, after the initial fluid resuscitation, early use of vasopressors to keep mean arterial pressure ≥65 mmHg by increasing the stressed volume in the venous circulation is recommended. Vasopressors augment the mean systemic filling pressure, cardiac output and perfusion pressure to the vital organs.

Pulmonary vasculature and EGL

The EGL in the pulmonary vasculature is thicker than the systemic vasculature indicating its significant role in maintaining normal pulmonary physiology. EGL plays a major role in mechanotrasduction and vascular permeability. Breech in the integrity of EGL can result in interstitial oedema and hypoxia. EGL serves as a barrier to neutrophils, fluid and protein extravasation. In addition it also plays a role in nitric oxide signalling thereby modifying endothelial permeability. Acute lung injury and acute respiratory distress syndrome can result as a consequence of EGL disruption. Detection of EGL degradation product in blood may serve as an indicator of impending pulmonary damage and its restoration by substances like clinically therapeutic dose of heparin having anti-inflammatory properties can act as a promising therapeutic measure in critically ill patients.[33]

PROTECTION OF EGL

EGL protection is gaining interest as a therapeutic target in modern medicine. Established therapy like blood glucose control and corticosteroids help in protection of the EGL.[34] Some of the experimental therapies to protect the EGL are showing promising results. Attenuating the inflammatory damage of EGL by inhibition of proinflammatory cytokines is one of the suggested options. *Etanercept*, which treats autoimmune diseases by inhibiting tumor necrosis factor (TNF-α), has been tried to preserve EGL function.[35] *ATIII* has shown its efficacy in blocking the activation of the transcription factor, nuclear factor kB which is the regulator of innate and adaptive immune responses, and plays an important role in allergic airway diseases.[34] Etanercept and ATIII block inflammatory cytokines like interleukin-6, TNF-α and tissue factor genes and help protect delicate EGL. *Statins* have shown to protect EGL by combating free radical (oxidised lipoprotein) induced injury to the endothelium and decreasing inflammatory reactants like C-reactive proteins.[36] However, there is lack of evidence in favour of their use especially in patients who are statin-naive and have chronic kidney disease, where studies have shown to increase the incidence of further renal derangement.[37] *Sevoflurane* protects EGL degradation by both preconditioning and early post conditioning. Sevoflurane attenuates liposomal cathepsin B release independent of mast cell degranulation and looks promising in protecting the EGL.[38] *Neferine*, a bisbenzylisoquinoline plant alkaloid, probably has a promising role in protecting the EGL by suppressing the production of mitochondrial ROS.[39] *Sulodexide* is a highly purified mixture of GAGs composed of low molecular weight heparin (80%) and dermatan sulphate (20%) prepared from porcine intestinal mucosa.[40] There is sufficient evidence that sulodexide helps in regeneration of glycocalyx layer particularly in sepsis.[40] EGL degradation markers like syndecan-1, heparan sulphates, heparanase, endocan, hyaluronic acid, chondroitin and angiopoietins are potential markers of glycocalyx damage and can be used as a diagnostic tool for endothelial dysfunction and sepsis severity.

SUMMARY

EGL lining nonfenestrated capillaries plays an important role in body fluid homeostasis. The modified Starling's equation incorporates the importance of EGL and subendothelial glycocalyx space in governing transcapillary forces responsible for ultrafiltration across the endothelial cell layer. Hence, damage to the EGL manifests as oedema in various pathological conditions (heart failure, liver cirrhosis, nephrotic syndrome, sepsis and trauma), which reflects the state of abnormal microcirculation. Therapy directed towards preserving EGL and taking measure towards its regeneration are currently the corner stone of management of disease states. Fluid management in these conditions is an ubiquitous intervention and choosing the right amount and type of fluid is essential to improve the quality of patient care.

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Conflicts of interest
There are no conflicts of interest.

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