

# Capillary dynamics, interstitial fluid and the lymphatic system

Andrew Haggerty

Mahesh Nirmalan

## Abstract

The regulation of small blood vessels (arterioles, venules and capillaries) and the formation of interstitial fluid at the capillary beds is an important process in the understanding of the healthy circulation. Traditionally, the Starling forces have been at the very heart of our understanding of this system. However more recent work shows that the trans-vascular fluid flux is significantly lower than what one would expect on the basis of Starling's forces alone and hence alternative explanations have been sought to understand the process of tissue fluid formation. In this context the role of the endothelial glycocalyx layer (or EGL) has drawn substantial interest. The EGL is a dynamic, active interface between the blood and the endothelial cells. It is formed by membrane-bound glycoproteins, proteoglycans and polysaccharides, producing a hydrated gel-like layer on the luminal surface of the vascular endothelium of approximately 500–2000 nm thickness. In this paper we review some of these emerging concepts and propose alternative ideas to understand some frequent clinical conditions and their treatment.

**Keywords** Circulating volume; endothelial glycocalyx; oedema; Starling's forces; sub-glycocalyx space

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The microcirculation was originally described by Malpighi in 1661, who with the aid of a single lens microscope was the first person to describe the functional capillary unit as we now know it.<sup>1</sup> It represents a complex interface between the macro-circulation and individual cellular structures. It is a highly integrated, functional system, maintaining the local milieu and thus facilitating essential cellular function. Evolutionarily it has developed as organisms have evolved into multicellular structures and diffusion alone was ineffective in supplying the essential needs of tissues. For example, based on Fick's principles at a distance of 0.1  $\mu\text{m}$  (the distance between the erythrocyte and the capillary endothelial cell) diffusion of an oxygen ( $\text{O}_2$ ) molecule would take 2  $\mu\text{secs}$ , but when extended to 1 cm the time taken for diffusion becomes several hours. Our

**Andrew Haggerty** MBChB (Hons) FCICM FRCA MCEM PGCEd is a Senior Fellow in Intensive Care Medicine, Manchester Royal Infirmary, Manchester, UK. Conflicts of interest: none declared.

**Mahesh Nirmalan** MD, FRCA, PhD, FFICM is a Consultant in Intensive Care Medicine and Professor of Medical Education, Manchester Royal Infirmary, University of Manchester, UK. Conflicts of interest: none declared.

## Learning objectives

After reading this article, you should be able to:

- provide an abbreviated and abridged review of Starling's principles
- describe the structural differences between arterioles, venules and capillaries
- describe the functional anatomy of the 'interstitium' or the 'interstitial compartment' and elaborate how the different components may behave in health and disease
- describe the endothelial glycocalyx layer (EGL) and the separation of the intravascular volume into the effective circulating volume and the subglycocalyx space (SGS)
- elaborate the possible role of the endothelial glycocalyx layer (EGL) in sepsis and oedema formation
- elaborate the potential consequences of albumin therapy when the EGL is damaged or disrupted in disease

understanding of the microcirculation has come some way since Harvey<sup>2</sup> in 1628 postulated the existence of invisible '*pores to the flesh*'. Much of our understanding of the functions of the microcirculation as a concept derives from Starling's original work.<sup>3</sup> The aim of this article is to provide an abridged review of Starling's principles while exploring new concepts that build upon these original constructs.

## Structure of the microcirculation

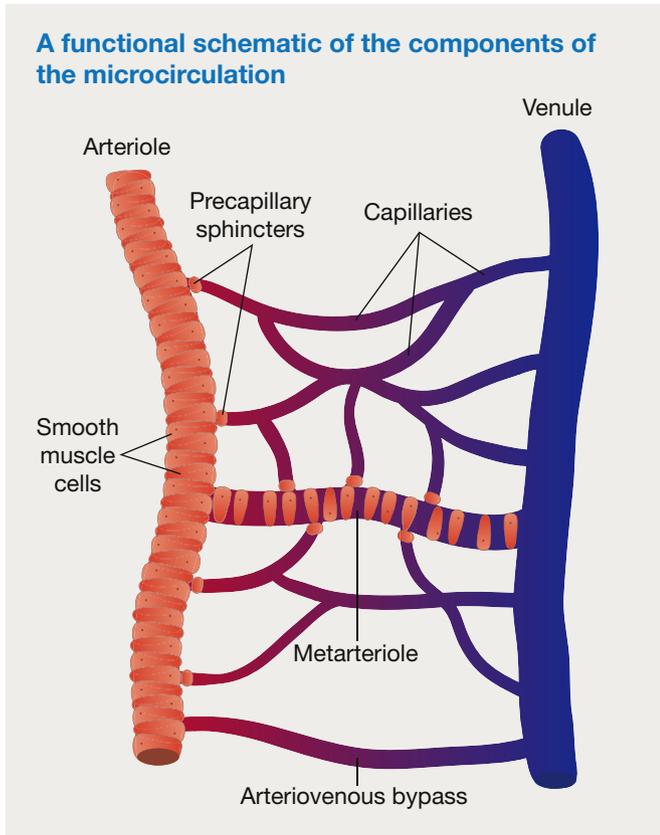
The term microcirculation includes terminal arterioles, capillary beds and venules. In addition we include the surrounding interstitial fluid (ISF), lymphatic channels and collecting ducts (Figure 1). In reality it is a complex, dynamic system comprised of up to 10 billion capillary beds,<sup>4</sup> continually fluctuating between their perfused and collapsed state under the influence of systemic and local factors. Often for simplicity the description is of the average net perfusion of these units, although inherently these units are independent and fluctuate rapidly.

### Arteriole

The arterioles are well-innervated vessels, encircled by smooth muscle, meaning their diameter can change many fold in response to autonomic nervous inputs. Arterioles branch multiple times before reaching the diameter of 5–9  $\mu\text{m}$  where they supply blood to the capillaries under the control of the pre-capillary sphincter. The arterioles terminate in the met-arteriole, differentiated by a non-continuous encircling of smooth muscle. This too provides direct branches to the capillary bed, under the control of the pre-capillary sphincter. Direct vessels may branch off the arteriole side without an associated pre-capillary sphincter and can be defined as an arteriovenous bypass.

### Venule

Venules are larger and have a less established smooth muscle coat. Flow through the venule system is of much lower pressure, and as such despite the poor formation of the muscular layer, it is



**Figure 1** Adapted from Guyton and Hall textbook of medical physiology. 13th Edn. Philadelphia, PA: Elsevier, 2016.

still able to generate significant changes in flow in response to changes in autonomic nervous tone.

### Capillary

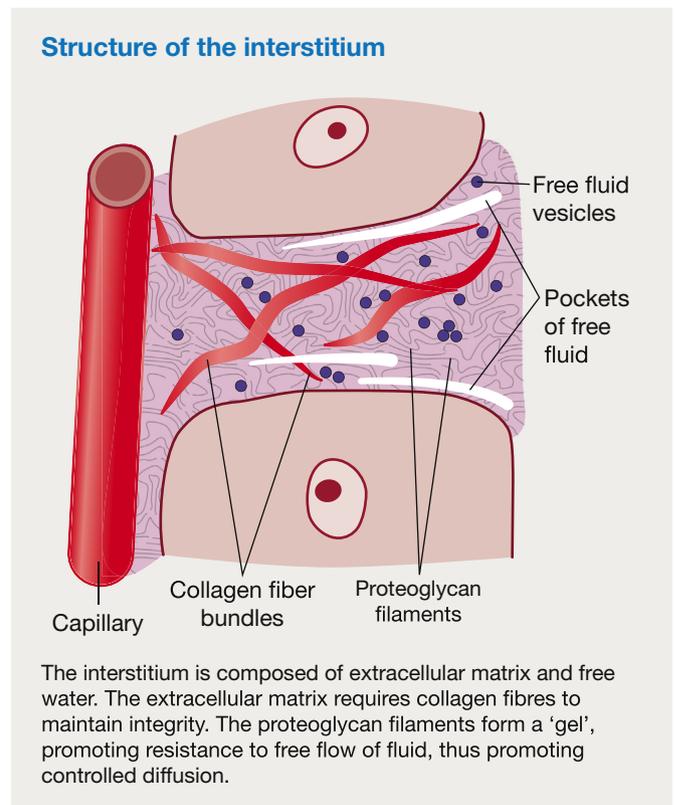
Capillary walls are formed by a single layer of endothelial cells surrounded by a basement membrane. They are devoid of surrounding intima or smooth muscle, having a wall thickness of 0.5  $\mu\text{m}$ . The vessel diameter of 5–9  $\mu\text{m}$  is just large enough to facilitate the passage of erythrocytes, although their flow through these vessels is often dependent on their inherent deformability. In pathological states, this deformability may be impaired, resulting in the obstruction to flow through the capillary bed. Such abnormal or poor capillary flow may also be observed when the viscosity of blood is increased in states of dehydration. The permeability of these capillaries is highly tissue specific, and largely dependent on the presence and size of the inter-cellular clefts. These clefts are formed at the junctions of adjacent endothelial cells, and are approximately 6–7 nm in diameter, slightly smaller than the diameter of an albumin protein molecule. These clefts theoretically produce no resistance to the passage of water and most water-soluble substances. Variations on these pores occur in specific tissues. For example within the brain the endothelial cells are connected by ‘tight junctions’, which regulate the passage of constituents between luminal and extraluminal spaces, selectively facilitating the free passage of small elements such as water, carbon dioxide ( $\text{CO}_2$ ) and  $\text{O}_2$  only. Conversely, in the liver the wider intracellular clefts allow almost uninterrupted passage of substances, facilitating its essential

metabolic and immunological functions. All other tissues lie somewhere within this spectrum, largely individualized for their specific functions.

**Interstitium and interstitial fluid (ISF):** This space is often perceived as a passive reservoir, holding all filtrated fluid from the microcirculation before returning it via the lymphatic system to the general circulation. However, this is structurally complex space contains two major structural components, together forming the *extracellular matrix*. Key components of the matrix include (Figure 2):

- collagen fibre bundles – provide tensile strength and structural support.
- Proteoglycan filaments – small filaments, composed almost universally of hyaluronic acid (98%) and protein. They form a ‘brush’ of fine reticular filaments, trapping water to prevent movement by mass flux.
- Free water comprises approximately 1% of ISF in health, although there is a significant increase in this component (often >50%) in the development of tissue oedema.

**Lymphatic system:** It is essential for returning filtrate from the interstitium back to the intravascular compartment. This ultimately occurs at the thoracic duct at the junction of the left internal jugular vein (IJV) and subclavian veins (SCV), or the right lymphatic duct which drains at the junction of right IJV and SCV. Total daily lymphatic flow is approximately 2–3 L/day, the majority of which is derived from the enteric circulation. In addition to ultrafiltrate, lymphatics also carry fats, with an



**Figure 2** Adapted from Guyton and Hall textbook of medical physiology. 13th Edn. Philadelphia, PA: Elsevier, 2016.

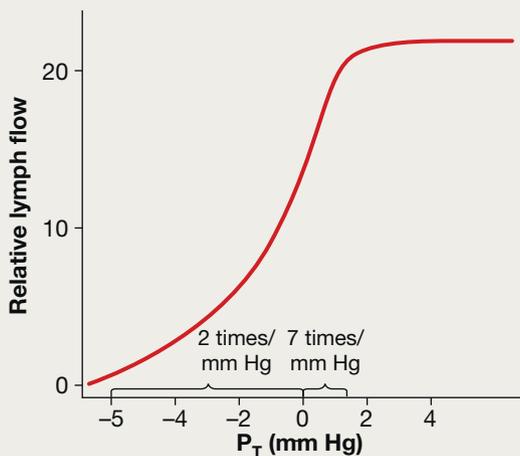
observed large surge in the fat content following consumption of meals. Lymphatic flow has inherent reserve, and can increase almost 20-fold in response to increased interstitial volume and pressure.<sup>4</sup> An increase in interstitial pressure ( $P_i$ ) will increase centripetal lymphatic flow, while reducing ultrafiltrate production by opposing transcapillary flux ( $J_v$ ). Thus transcapillary pressures in health will oscillate around an equilibrium. However, under extreme circumstances, as often seen during significant microcirculatory dysfunction, there is a significant increase in  $P_i$ , to values of 1–2 mmHg above atmospheric pressure. This results in direct external compression of lymphatic vessels, impeding lymph flow. Ultimately this results in a plateauing of lymph flow with increasing  $J_v$  (Figure 3). This uncoupling of  $J_v$  and lymphatic flow results in further interstitial oedema, and its subsequent detrimental effects.

The presence of valves ensures flow remains unidirectional and this constant flow ensures the maintenance of relative negative interstitial pressures. Flow through the lymphatic system is augmented by two discrete mechanisms.

- inherent contractility – sequential segmental contraction in response to stretching occurs throughout the system
- external intermittent compression – caused by movement, skeletal muscle contraction and pulsatility of nearby arterial vessels. In exercise this can increase lymphatic flow by 20- to 30-fold,<sup>4</sup> whereas in the sedated patient this may be markedly decreased.

Total lymphatic flow is dependent on relative hydrostatic and oncotic pressures, capillary permeability and lymphatic drainage. This can be summarized utilizing Starling's theorem of transcapillary haemodynamics.

### The relation between interstitial fluid pressure and lymphatic flow in dogs



Notice that at pressures only 4–6 mmHg above standard interstitial pressures, lymphatic flow can increase 10- to 20-fold. This reaches a maximum when interstitial pressure rises just above atmospheric pressure, at which point there is direct extrinsic compression of lymphatic vessels, causing lymphatic flow to plateau.

(Courtesy of Drs Harry Gibson and Aubrey Taylor from Guyton and Hall's Textbook of Medical Physiology, 13th Edn 2015).

Figure 3

### Starling theorem

$$\text{Transcapillary flow } (J_v) = (P_c - P_i) - (\Pi_c - \Pi_i)$$

Starling's theorem evolved following experiments tracking the dispersion of saline and serum solutions into the hind legs of dogs.<sup>3</sup> It is based upon the interaction of four primary 'Starling forces' at the capillary level, the net fluid movement balanced between forces promoting the outward movement of fluid and forces promoting the inward movement of fluid into the capillaries.

#### Forces promoting net flux of fluid out of the capillaries

**Capillary hydrostatic pressure ( $P_c$ ):** This can be measured directly and when done so shows significant variability. This is clearly an adaptive process, and is dependent on the 'function' of that particular tissue. The resistive properties of the arterioles and pre-capillary sphincters ensure regulation of flow over significant pressure variables, but become a primary site of the observed capillary dysregulation during sepsis.

**Interstitial colloid oncotic pressure ( $\Pi_i$ ):** Formed by diffusion through a semi-permeable membrane and by transcytosis of larger proteins, resulting in an average  $\Pi_i$  of 8 mmHg, but in many tissues this approaches that of  $\Pi_c$ . This discrepancy forms part of the rationale for the argument against the Starling principle.

#### Forces promoting net flux of fluid into the capillaries

**Plasma colloid oncotic pressure ( $\Pi_c$ ) (Table 1):** Formed by the sum of oncotic pressures of plasma proteins, nucleic acids, polyphosphates and polysulfated moieties. There is an associated Gibbs–Doonan equilibrium, established by charged constituents attracting smaller counter ions in an attempt to maintain electroneutrality, increasing the total osmotic effect. The normal human  $\Pi_c$  averages approximately 28 mmHg; approximately 19 mmHg due to the direct oncotic effects of plasma proteins, and a further 9 mmHg attributable to the Gibbs–Donnan effect.

**Interstitial hydrostatic pressure ( $P_i$ ):**  $P_i$  is tissue dependent and although not universally subatmospheric, it is, in health, universally negative *in relation to its surrounding tissue*.<sup>4</sup> Encapsulated tissues (eye, brain, kidney, muscles) have a pressure exerted upon them by their encasements. In non-encapsulated tissue pressure is usually subatmospheric, in the region of -2 to -4 mmHg.<sup>4</sup> In most tissues there is high resistance to the interstitial space being passively loaded with fluid. Connective tissues are held together under mild compression by collagen fibrils, which are  $\beta$ -1 Integrin bonded to fibroblasts, opposing the inherent tendency of the interstitium to expand.

**Changes along the capillary bed:** Hydrostatic pressure is the predominant variable along the capillary bed, reducing by as much as 25 mmHg between arterial and venous ends. In principle this results in net filtration at the proximal capillary and net reabsorption at the distal end. The transition point and the net movement of fluid will depend upon the exact

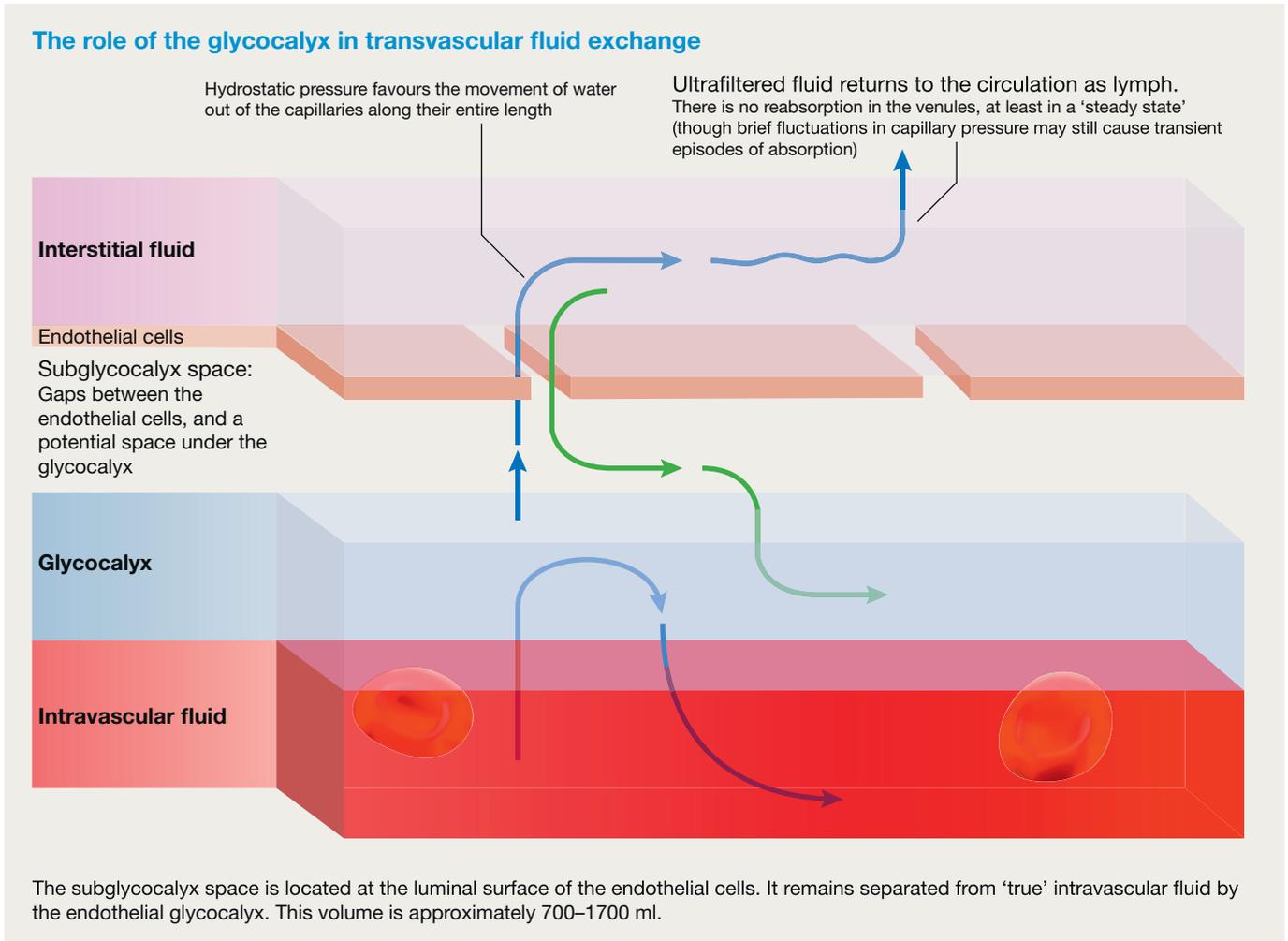


Figure 4

location and function of the capillary bed. This is exemplified in Table 2.

Classical teaching would tell us that approximately 90% of the filtered fluid is reabsorbed. This results in a net filtration rate, in the whole body (excluding kidneys and GFR) of 2 ml/min. This lies well within the functional range of the lymphatic system.

#### Filtration and reflection co-efficients

The work of Krogh<sup>5</sup> and colleagues further developed Starling's theorem with subsequent adaptation of the reflection co-efficient and pore theories. These ultimately reflect the role of the endothelial glycocalyx layer in the selective permeability of the capillary bed.

#### Constituents of colloid osmotic pressure

Component	Molecular Weight (kDa)	Concentration (g/dL)	Effective COP	% contribution to total COP
Albumin	69,000	4.5	21.8	78
Globulin	140,000	2.5	6	21
Fibrinogen	400,000	0.3	0.2	1
TOTAL		7.3	28	

Due to its relative low molecular weight, albumin is the disproportionate determinant of COP, despite accounting for only 60% of the total protein mass. It is a reminder that osmotic activity is proportionate to the number, and not mass, of osmotically active particles.

Table 1

#### A summary of Starling forces affecting microvascular dynamics across a capillary bed

Arteriole end		Venous end	
Forces Out	Forces In	Forces Out	Forces In
$P_c$ 30 mmHg	$\Pi_c$ 28 mmHg	$P_c$ 10 mmHg	$\Pi_c$ 28 mmHg
$P_i$ -3 mmHg		$P_i$ -3 mmHg	
$\Pi_i$ 8 mmHg		$\Pi_i$ 8 mmHg	
TOTAL 41 mmHg	28 mmHg	21 mmHg	28 mmHg
<b>Net filtration pressure 13</b>		<b>Net reabsorptive pressure 7</b>	

Table 2

### The endothelial glycocalyx layer (EGL)

First proposed by Danielli in 1940, it wasn't until the introduction of the electron microscope in 1966 that Luft was able to describe the fine structure of the capillary and endocapillary layer.<sup>6</sup> In 2004 Adamson et al.<sup>7</sup> ultimately dispelled Starling's theorem by showing that observed transvascular fluid flux is actually much less than expected by the calculated Starling's forces.<sup>3</sup> As a result of these developments the collective interest in the EGL and its modulation continues to increase. The EGL is a dynamic, active interface between the blood and the endothelial cells. It is formed by membrane bound glycoproteins, proteoglycans and polysaccharides, producing a hydrated gel-like layer on the luminal surface of the vascular endothelium of approximately 500–2000 nm thickness. The EGL forms a subglycocalyx space (SGS), dividing the intravascular volume into the effective circulating volume and the SGS (Figure 4). SGS is a non-circulating portion of the intravascular volume. Its exact volume remains unclear, dependent on the biomarker utilized, measuring between 700 ml and 1700 ml. The two areas, although anatomically and functionally separate can, under extreme physiological circumstances, interact and behave as a single entity with the SGS forming a 'reserve' for the intravascular volume. This is seen in times of acute reduction in capillary pressures, such as massive haemorrhage, when this reserve may be transiently auto-transfused from the SGS.<sup>6</sup>

#### Functional role of EGL

It is becoming increasingly apparent that the EGL has an extended role beyond that of modulation of transcapillary fluid flux. In summary, the EGL has been implicated in:

- Inflammation – by the modulation of adhesion of inflammatory cells and platelets to the endothelial surface
- Coagulation – retains anticoagulant factors including heparin sulphate, tissue factor inhibitor, protein C and antithrombin, as well as forming a layer to separate plasma from any procoagulant effects in the subendothelial layers.
- Homeostasis – retains protective enzymes such as superoxide dismutase
- Shear force – acts as a mechano-transducer of shear forces to which the endothelium is exposed and nitric oxide production.<sup>8</sup>

#### The importance of new paradigms of microcirculatory functions

Even prior to the proposal of the EGL, the arguments opposing the classical Starling's principles were building. Of significance came from the finding that  $\Pi_i$  often closely resembles that of the intravascular region ( $\Pi_c$ ). Aukland and Reed<sup>9</sup> conclusively showed that the predicted lymphatic flow as calculated by simple Starling forces is often an order of magnitude greater than the observed lymph flow. Zweifach and Intagliatta<sup>10</sup> were amongst many who observed that slight net filtration prevails under steady state conditions *throughout* the capillary. This led them to boldly state, 'We have not to date ... encountered vessels that consistently showed inward filtration'. Finally Levick and Michels<sup>11</sup> experiments showed that at a point approximately 10cm below the level of the heart  $P_c$  must exceed  $\Pi_c$ , and therefore prevent absorption. It is perhaps reasonable to counter

that this postural effect is somewhat negated by the postural vasoconstriction of the pre-capillary sphincter.

#### EGL mechanism of transcapillary fluid flux

EGL forms the major resistor to the movement of fluid. There is also dependence on the basement membrane and extracellular matrix as previously discussed. The role of the EGL was explored by Levick and Michel in their 2010 revision to the original Starling principle.<sup>8</sup> They described two major changes to the original work by Starling:

1. No reabsorption principle. Although  $\Pi_c$  opposes filtration, it does not facilitate the absorption of fluid back into the intravascular space as previously thought. Most of the filtered fluid returns to the circulation as lymph. Endogenously raising  $\Pi_c$  may reduce  $J_v$ , but does not cause reabsorption of interstitial oedema.
2. The proposal that the SGS had a distinct composition, remaining almost protein free with a low oncotic pressure ( $\Pi_s$ ).  $J_v$  was therefore regulated by the maintenance of this trans glycocalyx oncotic pressure gradient ( $\Pi_c - \Pi_s$ ), rather than the transcapillary gradient ( $\Pi_c - \Pi_i$ ) proposed by Starling. The integrity of the EGL is essential in maintaining the low  $\Pi_s$  found within the SGS.

#### How is $\Pi_s$ maintained significantly lower than surrounding oncotic pressures?

For simplification we will consider the continuous capillary structure only. Fenestrated capillaries have an alternative proposed explanation, and we direct readers to the fascinating work by Levick,<sup>12</sup> who proposes that the trans glycocalyx gradient is formed as a direct result of poor mixing and subsequent formation of 'microgradients' of ISF protein. Capillary permeability in continuous capillaries appears to be via two discrete pathways; the 'small pore' and the 'large pore' pathways. The small pore pathway is formed by the EGL, which overlies the entrance to the endothelial intracellular clefts. They have an effective diameter of approximately 8 nm, and are therefore deemed protein reflecting. They are predominantly ultrafiltrating pores, and account for 95% of the total capillary permeability in health. In addition a separate, parallel 'large pore' system transports plasma proteins slowly into the interstitial compartment. This system comprises controversially large (>50 nm) pores and/or vesicular transport. In health it accounts for <5% of capillary permeability, but its clinical importance is seen in disease states, when protein flux through large pores is increased significantly. Put simplistically, the maintenance of a viable and intact EGL is essential in maintaining a protected subglycocalyx space, and thus becomes essential in preventing significant fluid leak out of the capillary vessel.

#### Regulation of microvascular flow

Capillary hydrostatic pressure needs to be regulated to maintain relatively fixed capillary dynamics and trans-capillary flow, essentially ensuring coupling of substrate deliverance to local tissue demand. It is during times of illness that we see uncoupling of this regulation, and a subsequent downward spiral due its pathological sequelae. As our comprehension increases, it is these pathways that will form a target for the

modulation of microvascular failure associated with critical illness. The microcirculation has significant functional reserve, with many capillary beds non-perfused during normal resting state. This provides a means of multi-fold reserve to augment local perfusion. Sustained perfusion of all capillary beds would require a cardiac output of approximately 50 L/min, with an exceptionally low O<sub>2</sub> extraction. Even if we had evolved to be able to sustain this, it would result in an awfully inefficient system. Coupling of regional blood flow to local metabolic needs, appears to be regulated by the vascular endothelium, endothelial glycocalyx and the erythrocyte itself. All result in modulation of the vascular smooth muscle, and capillary resistance. The exact mechanism of modulation remains debatable, and can broadly be divided into myogenic and metabolic theorems.

### Myogenic response (Bayliss effect)

First described by Bayliss,<sup>13</sup> an increase in blood pressure at the arteriolar end results in an increase in pre-capillary sphincter tone in an attempt to maintain constant blood flow over a wide range of driving pressures. This is modulated by changes in the stretch-sensitive Na<sup>+</sup> and Ca<sup>2+</sup> membrane ion channels, which can be pharmacologically targeted with the use of calcium antagonists. Myogenic mechanisms do not truly explain microvascular coupling, as pressure and flow are not necessarily equivocal. It is therefore likely that the metabolic autoregulation plays a greater role in coupling flow and tissue requirements.

### Metabolic regulation

The metabolic regulation suggests several possible mechanisms and mediators.

- Humeral and tissue-generated mediators – including angiotensin II, bradykinin, vasopressin, free catecholamines, natriuretic peptides. Act via receptor operated channels of vascular smooth muscle and endothelial cells.
- Local metabolic regulation – changes in metabolic markers; namely PO<sub>2</sub>, PCO<sub>2</sub>, pH, osmolarity, changes in K<sup>+</sup> concentration and released catabolites such as adenosine.
- Antacoids – NO and prostaglandin (Pgl<sub>2</sub>): Likely mediated by endothelial glycocalyx, in response to shear stress and EGL shedding as a consequence of inflammation, ischaemia and other pathological states.
- Erythrocyte (RBC) mediated – there is increasing belief that erythrocytes are the predominant mediator of regional microcirculatory flows, chiefly by O<sub>2</sub> dependent ATP signalling. It is postulated that ATP is released from hypoxic RBCs, via a deoxyhaemoglobin/glycolytic enzyme molecular switch at the inner mitochondrial membrane. This ATP bind to purigenic type 2 (P<sub>2</sub>Y) receptors on endothelial cells and triggers a vascular response via endothelial cells to upstream resistance vessels and pre-capillary sphincters. This appears to be modulated by intermediary nitric oxide (NO). Bateman et al.<sup>14</sup> have shown that this ATP efflux in response to hypoxaemia is severely impaired in sepsis, and may yet represent the key mediator of the observed microvascular failure observed.

Mitochondrial dysfunction alongside microcirculatory failure appears to be a significant feature of sepsis, in which NO is also implicated. The exact mechanism of mitochondrial dysfunction in sepsis is beyond the scope of this article.

### Endothelial dysfunction

Although the EGL is rapidly self-repairing, it is inherently fragile and vulnerable. Due to this vulnerability the EGL may be easily damaged by hypoxia, TNF- $\alpha$ , oxidized lipoproteins and other non-physiological conditions. Glycocalyx dysfunction is the final common pathway in many pathological disease processes, resulting ultimately in its shedding and physical disruption. In addition, thinning of the EGL has been displayed in hyperglycaemia, hyperlipidaemia, smoking, major surgery and ischaemia-reperfusion injury.

Damage to the EGL can be detected by the presence of specific biomarkers in blood. EGL degradation has been implicated in several pathological states including hypercoagulability, platelet activation, autoheparinization and loss of vascular responsiveness (or catecholamine resistance). Syndecan I is the most investigated biomarker in this context and may provide a measure of damage to EGL in these pathological states.

### Clinical application of the microvascular unit

Table 3 summarizes some clinical situations where factors discussed in the previous sections may become highly relevant.

#### Fluid administration

Volume loading and hypervolaemia are often integral pillars of intensive care therapy, resulting in significant alterations in microvascular haemodynamics. The increase in P<sub>c</sub> and reduction  $\Pi_c$  ultimately results in increased formation of ISF and an increase in diffusion distance from capillary lumen to cellular level.

In addition, administration of exogenous fluid also has a detrimental effect on the EGL, both direct and by the production of atrial natriuretic peptide (ANP). Alongside its diuretic, anti-natriuretic and vasodilatory effects, ANP results in a rapid shedding of endothelial glycocalyx, detected by increased syndecan I and hyaluronan. The rate of this fluid administration may also have a significant implication on EGL integrity.

#### Fluid choice

The use of albumin as both resuscitative fluid and in the context of specific pathologies remains controversial. Low albumin levels have been shown to be associated with increased mortality in ICU, but this represents the culmination of a complex multifaceted process, and outcome is uncorrected by simplistically replenishing to 'normal' plasma concentrations. In the context of dysregulated and damaged EGL, subsequent increase in vascular permeability may limit the ability of albumin to have a fluid sparing effect. Albumin administration may result in an increased subglycocalyx volume, and perhaps more importantly an increased  $\Pi_s$ , limiting the resistance to interstitial oedema formation. However, EGL dysregulation represents a dynamic process, and thus the relative timing of albumin administration may be at the heart of the conflicting evidence of its role in sepsis resuscitation to date.

Hyperoncotic 20% albumin solution may not have the effect of 'drawing in' fluid to the intravascular space-an argument

### Implications of common concepts within critical illness on principles of microvascular function and integrity<sup>a</sup>

P <sub>c</sub>	<ul style="list-style-type: none"> <li>• Vasomotor dysregulation</li> <li>• Fluid resuscitation and hypervolaemia</li> <li>• Mechanical ventilation – venous congestion due to application of positive thoracic pressures.</li> <li>• Abdominal hypertension</li> </ul>
COP	<ul style="list-style-type: none"> <li>• Hypoalbuminaemia of sepsis. A negative phase reactant.</li> </ul>
EGL dysfunction	<ul style="list-style-type: none"> <li>• ‘final common pathway’ in many systemic disease states</li> <li>• Implicated in fluid resuscitation</li> <li>• Increased porosity, loss of vascular integrity</li> <li>• May result in increased interstitial protein deposition which theoretically may promote sustained interstitial oedema</li> </ul>
Lymphatic Flow	<ul style="list-style-type: none"> <li>• Immobility leads to poor lymphatic flow</li> <li>• Mechanical ventilation impeding central flow</li> <li>• Increased P<sub>i</sub>, limiting lymphatic flow reserve</li> <li>• Extrinsic compression: both limiting (circumferential dressings, etc.) and promoting (sequential compression devices)</li> </ul>
P <sub>i</sub>	<ul style="list-style-type: none"> <li>• Initial fall in inflammatory states, independent of microvascular change, due to conformational change in β integrin bonding of collagen to fibroblasts. Increased transendothelial pressure difference, and can increase J<sub>v</sub> by as much as 20-fold, independent of other causes</li> </ul>

<sup>a</sup> These are by no means exhaustive, and many at present will remain just theoretical concepts

**Table 3**

commonly proposed by its advocates. As previously discussed, absorption of fluid at the levels of the capillary bed is yet to be witnessed. In counter argument, the recent ALBIOS study<sup>15</sup> has shown a shorter time to achievement of cardiovascular endpoints, but this is yet to equate to improved patient outcomes. Albumin is commonly used in the non-resuscitative phase to ‘mobilize’ interstitial fluid. At present this is a theorem lacking clinical evidence, but hopefully something that the FADE trial<sup>16</sup> may be able to address. In addition, albumin is likely to have additional effects above and beyond volume restoration. It constitutes the largest pool of thiols in the circulation, and effectively reduces oxidative stress due to its radical-scavenging induced cysteine and methionine residues. It may also mediate protective mechanisms via platelet activation, transport of free fatty acids and hormones, buffering effects and modulation of NO.

#### Sepsis

Sepsis results in a significant multifactorial insult to the integrity of the endothelial cells and the endothelial glycocalyx. Inflammatory mediators released by leukocytes (IFN, TNF, IL-1) can cause direct endothelial cell damage. Apoptotic endothelial cells express adhesion molecules (ICAM-1, VCAM), amplifying the effects of white cells. Apoptotic endothelial cells also externalize negatively charged phosphatidyl-serine on cell membrane, resulting in exposure of blood to procoagulant surface. There is additional release of membrane microparticles. Combination of phospholipid membrane fragments and surface proteins (tissue factor) propagate endothelial dysfunction and participate in DIC. The subsequent loss of EGL and endothelial integrity results in increased permeability observed in sepsis.

#### Mechanical ventilation

Mechanical ventilation significantly alters thoracic pressures, which will have significant implications on the lymphatic and venous systems, which rely on low resistance and subsequent low driving pressures. The negative intrathoracic pressure

associated with spontaneous ventilation will augment central venous and lymphatic return, while the application of positive pressures tenfold that seen in normal physiology will have deleterious effects on this return. In addition, the application of mechanical ventilation is implicated in fluid retention, predominantly regulated by antidiuretic hormone. Application of PPV may additionally reduce atrial stretch, resulting in further fluid retention by the resultant reduced levels of circulating atrial natriuretic peptide (ANP). This fluid retention will have subsequent effects on oncotic gradients, promoting the formation of interstitial oedema.

Greater understanding of the EGL and its involvement in trans-capillary fluid fluxes, inflammation and coagulation has led to a radical rethink of some of our well established concepts in this area. It is most likely that new attempts to manage diseases such as sepsis will focus on aspects of EGL. While some exciting clinical trials have been published and more are currently underway, more work is needed before this new wave of understanding could result in tangible changes to diagnosis, disease stratification and/or clinical management. ◆

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