ASYMMETRY IN CAPILLARY FILTRATION: THE STEADY-STATE STARLING PRINCIPLE

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Edema is a common sign of trauma and inflammation, heart failure and fluid overload. Every clinician has been taught that every capillary has high hydrostatic pressure at it's arteriolar origin and much lower hydrostatic pressure at the point of its confluence to form a venule. Hydrostatic pressure difference (capillary – interstitial) drives filtration of solvent to the interstitium. There are, however, capillary and interstitial osmotic pressures and the difference between them is in the opposite direction, i.e. favouring absorption of interstitial fluid to the capillary. In every healthy capillary, we were taught, there will first be filtration of solvent to the tissues followed by reabsorption. Any excess interstitial fluid after reabsorption forms lymph and is drained back to the veins via lymph nodes and the thoracic duct. J Rodney Levick, Professor of Physiology at St Georges Hospital, University of London, was one of the first to point out that even in this anatomically symmetric model reabsorption of solvent would bring interstitial proteins up close to the capillary creating a rising pericapillary concentration of protein so that the difference between plasma and interstitial concentrations falls and reabsorption ceases. If he was right,then clinicians were wasting millions of dollars infusing expensive oncotic and hyperoncotic solutions in the belief that they would increase fluid reabsorption into capillaries, increasing plasma volume and reducing tissue fluid volume (edema). Clinicians of the day were not in the habit of reading physiology science publications. Laboratory students were able to reproduce experiments in which the traditional Starling forces could be manipulated and the resulting filtration/ reabsorption observed. In particular, acute reduction in capillary pressure resulted in an instantaneous reversal of filtration to absorption. The fact that absorption soon decreased and then ceased was put down to a limitation of the experimental model. In 2004 Adamson and colleagues published experiments that proved that reabsorption in response to acute reduction in capillary pressure was only transient, soon returning to a steady-state situation of reduced filtration. With slower changes, compensatory mechanisms ensured that reabsorption did not occur at any point of blood passage along a capillary. Some call this the glycocalyx model, Levick proposes naming the model after the men who separately predicted it; the Michel-Weinbaum model.

We now know that the anatomic path of interstitial fluid circulation is extremely asymmetric and that reversal of flow is as unimaginable as the reversal of cardiac output. Starting with intravascular free flowing plasma, water and small-pore permeable solutes such as ions, glucose, urea and exogenous Dextran 40 can enter the slow-moving gelatinous intravascular layer we call the endothelial glycocalyx (EG). Albumin and other soluble larger molecules can enter the EG, indeed they are constituent parts of it, but the EG acts as a filter that mostly keeps albumin upstream while freely passing the solvent. The solvent can then leave the intravascular space through junctional strand breaks in the junction strand that bind endothelial cells at their edges. Think of the fried egg shaped cells having a bead of glue running along their edges to hold the tubular sheet of cells together. The bead of glue is, however, discontinuous and it is through the occasional strand breaks (also called gaps) that filtered solvent may exit the intravascular space. Rate of flow of the solvent is Jv, conventionally positive when flowing from capillary to interstitium. Note that the EG is the reason why intravascular albumin concentration is higher than interstitial; degradation of the glycocalyx barrier function leads to redistribution of albumin to the

tissues with fall in plasma albumin concentration. Albumin is not lost, and infusion of exogenous albumin is also soon redistributed to the detriment of the patient.

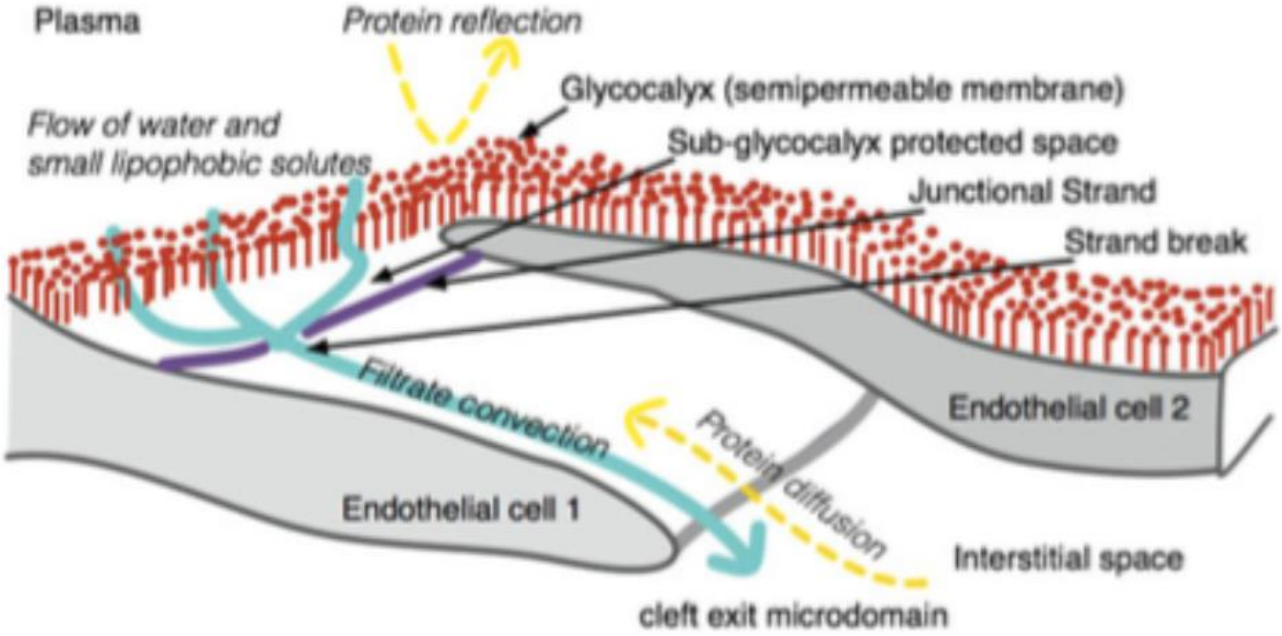

Figure 1: three dimensional cartoon showing endothelial cell 2 cut short to reveal the interendothelial cleft surface of cell 1. Note that proteing diffusion to the subglycocalyx protected zone is turned back by filtrate convection in steady state conditions.

After passing through a tight junction break, a high velocity jet of fluid enters to interendothelial cell cleft which is washed out of protein, making COP there very low. In the cerebral and possibly other circulations pericytes occur close to the cleft exit and create a microdomain within which the compensatory mechanisms occur. There is a collagen condensation of the interstitial matrix adjacent to the endothelial cell which we call the basement membrane. Thereafter circulating solvent and its solutes must permeate the interstitial gel matrix, rich in glycosaminoglycans, just as the EG is, before entering afferent lymphatics and being actively circulated to a lymph node. Some solvent is reabsorbed by lymph node capillaries, the remainder continuing as a high-protein lymph in efferent vessels which discharge into the thoracic duct.

Asymmetry of the capillary membrane creates a one-way valve that supports a mandatory interstitial fluid circulation. No longer is lymph just a safety valve for return of an accumulated filtrate excess. If capillary pressure falls below its normal level, transendothelial filtration of solvent Jv is diminished, the jet of filtrate slows, and the diffusion of proteins back to the subglycocalyx protected space reduces the oncotic pressure difference that might have caused reabsorption. The fact that filtration persists even at subnormal capillary pressure, and reabsorption cannot occur means that the colloid osmotic pressure of a resuscitation fluid is of no consequence. It is dangerous to infuse fluids when the capillary pressure is normal or high; above the J point increases in volume are associated with substantial elevation of capillary pressure which degrades the EG and increases pulmonary and systemic Jv predisposing to edema. Large volume bolus resuscitation is predicted to be harmful as transient peaks of capillary pressure will

cause transient hyperfiltration and so lose infused volume to the tissues. Using a colloid solution will not provide protection!

Resistance to filtrate flow from the capillary to the interstitium where it is collected by motile afferent lymphatic vessels is attributable to the EG, the area of junction strand gaps, the basement membrane and the interstitial matrix. The greatest single contributor can be considered to be the proportion of breaks in the junction strands. The Starling equation includes hydraulic conductance, which is the reciprocal of resistance. I see no reason why critical care teaching should not prefer the concept of transendothelial resistance, which we are more familiar with. The EG is the small pore filter and its condition is indicated by Staverman's reflection co-efficient in the Starling equation. Finally, the COP in the subglycocalyx space replaces the general interstitial COP in the revised equation; its variability maintains steady-state filtration even at subnormal capillary pressure.

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