Review

Impact of revised Starling hypothesis on fluid therapy

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Intravascular fluid therapy has been in use for treating critically ill patients for almost two centuries, since the time of the cholera pandemic.[1] Our understanding of distribution of intravenous fluids has been influenced by assumptions based on the classical Starling principle.[1] Initially, it was believed that crystalloids and colloids both expand intravascular volume, and colloids aid in reabsorbing interstitial oedema.[1] However, these assumptions have been challenged with the discovery of the endothelial glycocalyx and its inclusion in the "revised" Starling hypothesis.

The "classic" Starling model

Ernest Henry Starling's influential research paper presented findings from experiments on the hind limb of a dog supporting the transfer of fluid from body tissues into the bloodstream and vice versa.[2] In that paper, he put forward the hypothesis that a harmonious equilibrium between the hydrostatic and osmotic pressures across the walls of capillaries maintains the circulation of blood within a network of permeable vessels designed to carry water.[2] With the pioneering work by Pappenheimer & Soto-Rivera providing experimental proof, the Starling hypothesis became the Starling principle. [3]

Starling principle states that the rate of volume filtration across the endothelial surface (Jv) depends on the difference in hydrostatic pressures across that membrane and the difference in oncotic pressures-the so-called Starling forces. [4,5,6,7]Towards the arteriolar end of the capillaries, the outward hydrostatic pressure from intravascular fluid is stronger than the inward oncotic pressure from plasma proteins, causing fluid to filter from the intravascular compartment to the interstitial fluid compartment. As the blood flows through to the venular end of the capillaries, the capillary hydrostatic pressure reduces and the inward oncotic pressure gradient increases due to filtration of protein less fluid. [2] The Starling principle is depicted in a mathematical model as follows,[7]

$$Jv = Lp\ [(P_C - P_i) - \sigma\ (\pi_c - \pi_i)]$$

Lp is the filtration coefficient, Pc and P_i are the hydrostatic pressures of the lumen of the micro vessel and the interstitial fluid (ISF) in the tissue, respectively. The colloid oncotic pressure (COP) of lumen of the micro vessel and the ISF is represented by π_c and π_i respectively. Due to very low π_i, it is often not considered. σ signifies the Staverman's reflection coefficient which is a measure of the leakiness of the endothelial barrier to macromolecules. The value of σ ranges from 0 to 1.[4,7]

Why was the revision required?

With the progression of laboratory techniques evaluating microcirculation, many compelling pieces of evidence started to accumulate that questioned the Starling principle.[4,5,6] The basic Starling equation mentioned earlier fails to account for the restrictive characteristics of the barrier to solutes.[6] Experimental studies could not find any single vascular bed where absorption was demonstrated at the venular end.[7] The direct influence of interstitial fluid's oncotic pressure on fluid balance across the microvascular endothelium is also not significant.[8] Previously, μ_i was thought to be near zero, but recent evidence suggests it may be 40% of μ_c in certain vascular beds.[4] The current understanding is that non-fenestrated capillaries typically filter fluid into the ISF along their entire length. The process of absorption does not take place through most venous capillaries and venules.[6]

To understand the revised Starling theory, it is important to recapitulate the basic structure and types of capillaries. The capillaries are thin-walled microcirculatory structures that

allow the exchange of nutrients and gases between blood and tissue. The capillary wall is formed by endothelial cells supported on the basement membrane, with a sub-endothelial layer in between. With the improvement of techniques of electron microscopy, an endothelial surface layer (ESL) comprising a proteoglycan and glycoprotein mesh called endothelial glycocalyx (EGL) and absorbed proteins and glycosaminoglycans (GAG), has been seen to coat the endothelium and restrict blood cells from coming in contact with the endothelium.[4]

The size of the core proteins, the number of GAG side chains, and their binding to the cell membrane may vary. The glycocalyx forms a luminal mesh that provides endothelial cells with a framework to bind plasma proteins and soluble GAGs. Once bound, it forms the physiologically active ESL. The glycocalyx has a net negative charge because of the GAG side chain sulfation, and changes in the sulfation patterns affect protein binding and vascular permeability. The EGL usually repels all negatively charged molecules except albumin, which, although negatively charged, binds tightly to the glycocalyx due to its amphoteric nature. [9] The EGL permits the passage of fluid and electrolytes freely while being selectively permeable to macromolecules such as albumin, which are absorbed into the mesh network of the EGL. The protein-poor layer located beneath the EGL at intercellular clefts is known as the subglycocalyceal layer (SGL). The EGL preserves the permeability of the capillaries, and inflammation, diabetes, trauma, sepsis, and overzealous fluid administration can affect it.[10]

Based on the type of connection between endothelial cells, the presence of fenestrations, and the continuity of the EGL, capillaries can be classified as non-fenestrated continuous or fenestrated continuous capillaries. [6] The barrier provided to water and solutes and the dynamics of fluid flow from them depend on their characteristics. Thus, the interplay of Starling forces is unique for each of them.[6,7]

The revised starling hypothesis

The revised Starling hypothesis incorporates the significance of the EGL and the SGL in determining the extravasation of fluid across capillaries. Experimental findings suggest that the COP of interstitial fluid does not directly influence the transcapillary flow.[8] Rather, the COP gradient between plasma and the SGL acts as a crucial Starling force that opposes the filtration of fluid driven by hydrostatic pressure. The revised Starling hypothesis can be mathematically represented as: [11]

$$Jv = Lp\ [(P_c - P_i) - \sigma \times (\pi_c - \pi_g)]$$

It should be noted that π_i has been replaced by π_g, which represents the COP of the subglycocalyceal layer.[11]

In situations where there is a gradual decrease in capillary pressure without disturbing the steady state, the non-fenestrated capillaries maintain filtration at a minimal rate without experiencing a phase of fluid absorption because of the rebalancing of the Starling forces. This is known as the "no steady-state absorption rule."[6] However, Mitchel and Phillip have demonstrated transient fluid absorption due to an abrupt lowering of capillary pressure below μc.[12] This absorption is short lived because the pericapillary COP quickly rises as Jv decreases (Jv and μi are inversely related) and a new steady state is established. In clinical settings, it has been noted that during a sudden decrease in blood volume, such as during acute haemorrhage, there is a temporary absorption of fluid into the plasma volume. This "autotransfusion" is short-lived and limited to approximately 500 ml.[6] Instead of the traditional steady-state filtration-absorption model, the current understanding is that the plasma, interstitial fluid, and lymph are connected in series with a steady flow of fluid from one compartment to the other. The fluid that is filtrated at the capillaries is returned to circulation by the lymphatic system. A few exceptions to the "no steady-state absorption" rule are seen in the capillaries of renal glomeruli, lymph nodes, gut mucosa, and liver.[7]

Clinical Implications

Intravascular volume effects intravenous fluid kinetics

The revised Starling equation suggests that the effect on intravascular volume of crystalloids and colloids is influenced by the pre-existing capillary pressures and their interaction with the EGL. Initially, it was thought that crystalloids distributed uniformly in plasma and interstitium, on the contrary, colloids were believed to remain largely in the intravascular compartment.[13] It is now understood that crystalloids initially distribute in the plasma and SGL volumes, whereas colloids distribute only in the plasma volume.[13] At subnormal capillary pressure, as Jv approaches zero, both crystalloids and colloids will be distributed solely in the intravascular space and achieve similar intravascular volume expansion.[14] More specifically, colloid will solely increase plasma volume, while crystalloids get distributed and thereby increase the volume of plasma and EGL. Therefore, the amount of isotonic saline needed for resuscitation is comparable to the amount of colloid required in low capillary pressure situations.[14] Recent data from randomized controlled trials reveals that the intravascular expansion achieved with 1 litre of colloid is similar to that achieved with approximately 1.4 litre of crystalloid, contrary

to the previously held belief of a 1:5 ratio.[13,14,15,16] After the capillary pressure becomes normal or supranormal, filtration resumes, and Jv is increased by colloid and crystalloid infusions by increasing capillary pressure. Crystalloid infusion also reduces the plasma COP and, thereby, increases Jv more than colloid infusion for an equivalent rise in capillary hydrostatic pressure.

Effect of exogenous colloid on interstitial oedema

The "steady-state no absorption" rule implies that increasing plasma COP by infusing exogenous colloid will not lead to reabsorption of interstitial oedema. Physiological and clinical studies have not demonstrated the beneficial role of colloids in reducing oedema.[17,18] In fact, no therapeutic advantage is obtained by keeping the plasma albumin concentration >30 g/liter in patients with severe sepsis or septic shock.[13]

Preservation of EGL as a clinical strategy to reduce capillary permeability

The damage to EGL can lead to increased capillary permeability and oedema formation.[12] The integrity of EGL is hampered by inflammation, trauma, hyperglycemia, sepsis, and overzealous fluid infusions.[10,12] Goal-directed fluid management should be employed to prevent the destruction of EGL by overzealous fluid infusions. The influence of intravenous fluids on EGL is an active area of research.[12] Several agents are being investigated for their possible roles in preserving EGL, examples being N-acetylcysteine, steroids, sevoflurane anesthesia, and antithrombin-III.[6]

The balancing act

The core of the revised Starling hypothesis is similar to that of the Starling principle, and both are based on observations in isolated vascular systems carried out under strict laboratory considerations. [5,19] Unlike observations obtained during steady state in laboratory conditions, the human vascular system is extremely dynamic.[19] Thus, the revised Starling hypothesis may not be able to fully explain the dynamics of transvascular fluid movement, despite the enthusiasm.[19]

It's important to note that, while there may be exceptions or limitations to the Starling principle or its revised version, it still provides a useful framework for understanding fluid dynamics in normal physiological conditions. However, these observations highlight the complexity of fluid movement in various pathological states and the need to consider additional factors described by Starling himself and his successors.

Conflict of Interest: Nil

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