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Mechanisms underlying the volume regulation of interstitial fluid by capillaries: a simulation study

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ABSTRACT

Background: Control of the extracellular fluid volume is one of the most indispensable issues for homeostasis of the internal milieu. However, complex interdependence of the pressures involved in determination of fluid exchange makes it difficult to predict a steady-state tissue volume under various physiological conditions without mathematical approaches.

Methods: Here, we developed a capillary model based on the Starling's principle, which allowed us to clarify the mechanisms of the interstitial-fluid volume regulation. Three well known safety factors against edema: (1) low tissue compliance in negative pressure ranges; (2) lymphatic flow driven by the tissue pressure; and (3) protein washout by the lymph, were incorporated into the model in sequence.

Results: An increase in blood pressure at the venous end of the capillary induced an interstitial-fluid volume increase, which, in turn, reduced negative tissue pressure to prevent edema. The lymphatic flow alleviated the edema by both carrying fluid away from the tissue and decreasing the colloidal osmotic pressure. From the model incorporating all three factors, we found that the interstitial-fluid volume changed quickly after the blood pressure change, and that the protein movement towards a certain equilibrium point followed the volume change.

Conclusion: Mathematical analyses revealed that the system of the capillary is stable near the equilibrium point at steady state and normal physiological capillary pressure. The time course of the tissue-volume change was determined by two kinetic mechanisms: rapid fluid exchange and slow protein fluxes.

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1. Introduction

Quantitative analysis of microcirculation at the capillary bed is indispensable when studying systemic circulation. Fluids that circulate through the vessels filter in and out through the membrane at the capillary bed in organ tissues. In order to comprehend the dynamics of complex fluid regulation, it is important to estimate the amount of fluid exchanged at the capillaries quantitatively.

Volume regulation, which includes fluid filtration, reabsorption, and formation of lymph, had been discussed using analogue computer simulations in the 1970s and 1980s.[1–3] They succeeded in simulating steady-state levels and transient responses of the essential physiological parameters involved in volume regulation, such as plasma volume, interstitial volume, and lymphatic flow (LF). However, such system analyses put emphasis on understanding the fluid balance in the whole body, and detailed analysis of the volume change and protein flux at the level of capillary was not feasible in those analyses due to the lack of computational capacity.

At a single capillary level, Curry and Michel[4] suggested the fibre-matrix theory of capillary permeability in 1980. This theory led to the revision of Starling's principle (1886) after a centennial of belief (see Levick's[5] review article). In line with the revision, Adamson et al[6] introduced the idea of subglycocalyx fluid oncotic pressure (Π_g) instead of Π_{isf} in calculating effective filtration pressure. In this revised theory, they estimated that, in case of steady-state filtration, a subglycocalyx protein concentration was lower than the interstitial protein concentration, and there were smaller gradients between Π_{isf} and Π_g, which was assumed to be 70–90% of Π_{isf}. However, in case of steady-state absorption, they confirmed that the reversed flow of the interstitial fluid caused reflected protein to accumulate in the subglycocalyx space, and Π_g became larger than Π_{isf} to cease the absorption within a few minutes. Although a thorough revision of the hypothesis was a landmark study to look into the detailed function of the capillaries, it is also widely accepted that continuous vasomotion with a cycle time of ~15 seconds keeps all of the parameters in the system in a transient state. Therefore, in the first stage of our single capillary model, we adopted the classical Starling's principle consisting of four primary forces to move fluids across the capillary membrane: the capillary plasma pressure (P_{pl}), the interstitial fluid pressure (P_{isf}), the capillary plasma colloidal osmotic pressure (Π_{pl}), and the interstitial fluid osmotic pressure (Π_{isf}), to evaluate the averaged function of multiple capillaries within tissue. There is also a tissue specific nonlinear relationship between P_{isf} and the interstitial fluid volume (V_{isf}), which plays a key role in preventing edema. Additionally, the LF, which is regulated by interstitial fluid pressure, carries protein as well as fluid away from the tissue.

In this study, we aimed to construct a realistic and versatile model of fluid exchange based on Starling's principle and included general features of tissue, such as the nonlinear relationship between P_{isf} and V_{isf} (tissue compliance) and the P_{isf} dependency of the LF. Then we applied mathematical analyses to the models to understand the mechanisms of the fluid volume regulation, quantitatively.

2. Methods

2.1. Governing equations for capillary filtration

In the present study, the involvement of the crystalloid osmotic pressure is entirely excluded, and the fluid filtration (J) across the capillary is determined by the following equation based on Starling's principle:

$$J = K \times P_E \cdot (\mathrm{mL/ms/mm}) \quad (1)$$

K (mL/ms/mmHg/mm) is the endothelial hydraulic conductance, which is a measure of the capacity of the capillary membrane to filter water per unit capillary length. P_E is the effective net filtration pressure that is the sum of four primary forces to move fluids across the membrane, P_{pl}, P_{isf}, Π_{pl} and Π_{isf};

$$P_E = \left(P_{pl} - P_{isf}\right) - \left(\Pi_{pl} - \Pi_{isf}\right) \ (\mathrm{mmHg}) \quad (2)$$

When P_E is positive, there will be a fluid filtration across the capillary membrane. Inversely, if P_E is negative, there will be a fluid absorption from the interstitial space into the capillary. Standard pressure values used in calculating P_E in the model are listed in Table 1.

2.2. Structure of the model

2.2.1. A capillary vessel model

The conformation of the capillary is assumed to be a cylinder (Fig. 1A). Parameters used in the capillary model are listed in Table 2. The internal radius of the capillary model (r) is 5 μm, and the length of the vessel from the arterial end to venous end (L) is 0.6 mm. It is well known that blood flow through each capillary is intermittent because of vasomotion, which is caused by intermittent contraction of metarterioles and precapillary sphincters. There are so many capillaries present in living tissue that their overall function becomes averaged. Therefore, in the present model, the average function of the capillary will be discussed.

Table 1 – Pressures used for calculating fluid effective filtration pressure

	Arterial end (mmHg)	Venous end (mmHg)
Capillary blood pressure (P_{pl})	25	15
Plasma colloidal-osmotic pressure (π_{pl})	28	
Tissue interstitial-fluid pressure (P_{isf})	−3	
Tissue interstitial-fluid colloidal osmotic pressure (π_{isf})	8	
Effective filtration pressure (P_E)	13	−7

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