

MODELING OF BLOOD FLOW AS THE RESULT OF FILTRATION-REABSORPTION PROCESSES IN CAPILLARIES

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In our previous article (*Am J Physiol Adv Physiol Educ* 272: S26–S30, 1997) we proposed a model that permits analysis for the change of hemodynamics in vessels with local stenosis. This problem is connected with the blood-tissue metabolism. This article continues the classroom research on concepts related to blood flow physiology. We take into consideration the problem of the blood-tissue fluid exchange. A model based on basic principles of hydrodynamics and mathematics is proposed for analysis of “filtration-reabsorption equilibrium” and its disturbances under different external influences. It permits medical students to develop a scientific analytic approach to the solution of physiological and pathophysiological hemodynamics problems.

ADV PHYSIOL EDUC 23: 32–39, 2000.

Key words: blood-tissue exchange; filtration-reabsorption equilibrium; analytic approach

The study of processes in the microcirculation system has an important place in physiology and pathophysiology courses. The microcirculation system is part of the cardiovascular system. It realizes the substance exchange between the blood and the tissue. Many facts can influence the blood flow in capillaries and, consequently, the substance exchange (1–3). The purpose of this article (this lesson) is to show medical students what pathological processes can take place in the system of substance exchange under different external influences on the organism such as radiation, defibrillation, burns, toxins, metabolites, and so on. These effects influence simultaneously both microcirculation and lymphatics (1, 2, 4, 5). However, for the first stage of consideration, we have submitted this article for the examination of capillary damage. Interaction of the capillary and lymphatic system under external action is to be considered for the next article (next lesson).

All of the above-mentioned effects cause damage to the capillary wall and thus increase capillary permeabil-

ity. In addition, there may be disturbances of hemodynamic parameters. For better teaching and learning about this problem in a biophysics course that precedes physiology and pathophysiology courses, students are encouraged to investigate the problem of the peculiarities of substance exchange under the following conditions: 1) when the hemodynamic parameters of blood flow are changed, and 2) when the ultrastructure of the capillary wall is disturbed.

Physiologists more commonly use the conceptual basis for the problem of blood-tissue exchange. However, the analytic approach should be useful for quantitative estimation of exchange parameters and for prediction of new results. Therefore, in this article (lesson) we have used the analytic approach.

For solving this problem we propose the use of mathematical modeling. This approach permits results to be obtained using the basic law of hemodynamics, Poiseuille’s law, in differential form. The sug-

gested model can be used to calculate the space distribution of hemodynamic parameters along the capillary, to estimate numerically the water balance between the capillary and the tissue, and to estimate the blood flow in the blood capillary and through its wall.

THE FILTRATION-ABSORPTION MECHANISM

One of the mechanisms providing substance exchange between the vessel and the tissue is filtration and reabsorption, occurring in the capillary set. As a result of these processes, water moves across the capillary endothelial wall because of the *nonuniformity* of its ultrastructure. Capillary walls contain pores, clefts, and fenestrations that permit rapid exchange of the water and solutes with the interstitial fluid. For example, some of the porous capillaries (e.g., in the kidney and intestine) contain fenestrations as large as 100 nm that are very permeable to water.

In accordance with the Starling theory, the plasma flow across the capillary wall is determined by the hydrostatic and oncotic pressures of the blood in the capillary and the tissue

$$q = f[P_{hc} - P_{ht}] - (P_{oc} - P_{ot})$$

where q is the plasma flow across the capillary wall, P_{hc} is the hydrostatic pressure of the plasma in the capillary, P_{ht} is the tissue pressure (interstitial fluid pressure), P_{oc} is the oncotic pressure of the plasma, P_{ot} is the oncotic pressure of the tissue fluid, and f is the filtration constant, or coefficient of the capillary permeability for the capillary wall, which depends on the distance (l) across the capillary wall (i.e., the thickness), the viscosity of the fluid (η), the radius of the pore (r), and the number of pores per capillary wall surface (N).

If q is positive, there is filtration, and if it is negative, there is reabsorption (Fig 1A). According to the Starling hypothesis, the values P_{ht} , P_{ot} , and P_{oc} are not dependent on the coordinate x . The average values for a normal physiological state are as follows: $P_{ht} \approx 3$ mmHg, $P_{ot} \approx 5$ mmHg, and $P_{oc} \approx 25$ mmHg.

The hydrostatic pressure is ~ 32 mmHg at the arterial end of capillary ($P_{hc,a}$) and ~ 15 mmHg at the venous end ($P_{hc,b}$). Because of the gradient of the hydrostatic

pressure along the capillary, filtration usually occurs at the arterial end of the capillary and reabsorption at its venous end.

Fluid and protein that have escaped from the blood capillaries enter the lymphatic capillaries and are transported via the lymphatic system back to the blood vascular compartment (Fig. 1B). Both the lymphatic and microcirculation systems provide unique conditions for steady hydrostatic and oncotic pressures in blood and tissue fluid. Thus there is a filtration-reabsorption equilibrium under normal physiological conditions.

As a result of the Starling theory, there is a typical graph (Fig. 1A) that has been represented in a series of physiology textbooks. This graph indicates that, for normal physiological parameters: 1) the pressure curve $P_{hc}(x)$ is a straight line, with the gradient of P_{hc} constant; 2) there is a specific point A on the graph, and consequently in the capillary, at which both filtration and reabsorption are absent, called the point of equilibrium state; and 3) there is a balance of volumes of the fluids filtrated at the arterial end and reabsorbed at the venous end of the capillary. Under normal physiological conditions $\sim 10\%$ of the filtrated fluid remains in the tissue and then returns to the blood vascular compartments via the lymphatic system.

However, it may be supposed that the dependence $P_{hc}(x)$ is linear (gradient of P_{hc} is constant) under the assumption that the flow q across the capillary wall is much smaller than the flow Q along the capillary: $qL \ll Q$, where L is the length of the capillary.

In general, the functions $q(x)$, $Q(x)$, and $P_{hc}(x)$ influence each other and thus are nonlinear. Actually, the decrease of flow Q as caused by flow q results in a diminishing gradient of P_{hc} in the region of filtration. On the contrary, in the region of reabsorption the increase of Q caused by flow q entering the capillary flow from the tissue results in an increasing gradient of P_{hc} along the venous part of the capillary. Thus the dependence $P_{hc}(x)$ is not linear in common.

In the case of nonlinear hemodynamic parameters along the capillary, the equilibrium region may be extended. If we knew the function $q(x)$, we could

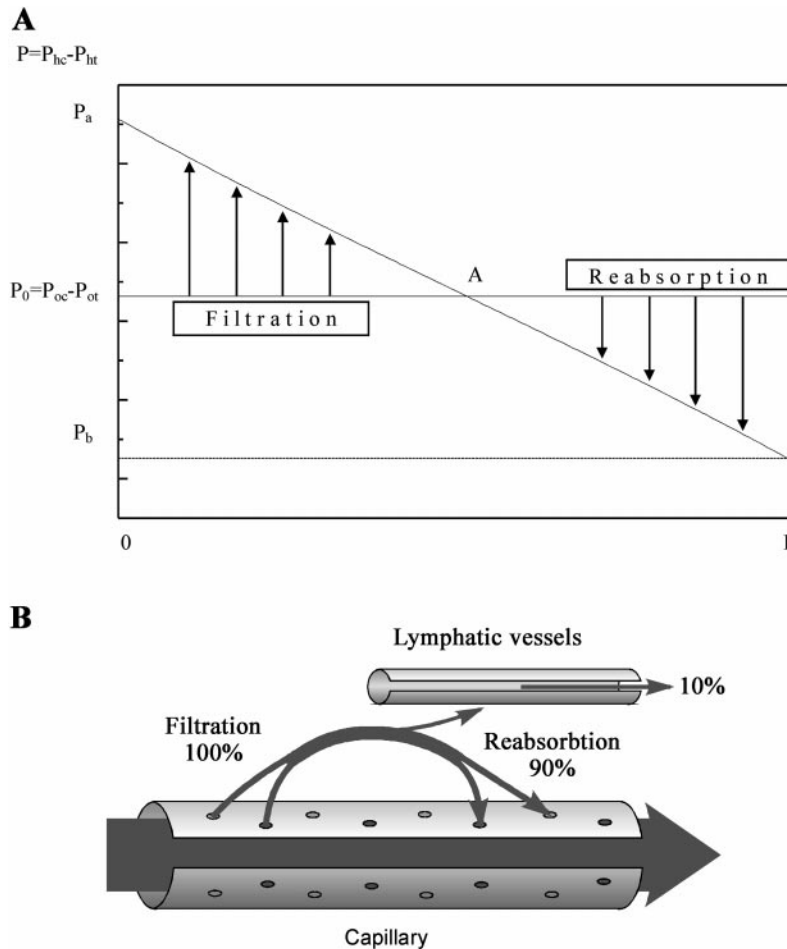


FIG. 1.
A: scheme of pressure distribution along capillary and flow exchange between capillary and tissue in muscle. *P*, pressure; P_{hc} , hydrostatic pressure of blood in capillary; P_{ht} , tissue hydrostatic pressure; P_a , pressure at arterial end of capillary; P_b , pressure at venous end of capillary; P_o , oncotic pressure; P_{oc} , oncotic pressure of plasma; P_{ot} , oncotic pressure of tissue fluid; L , length of capillary. **B:** scheme of blood-tissue fluid exchange in blood capillary and lymphatics.

calculate the integral of the filtrated and reabsorbed fluids, and thus we could estimate the fraction of the fluid that remained in the tissue. This is important for the study of possible mechanisms of the balance disturbances.

MODEL OF BLOOD FLOW THROUGH PORES IN CAPILLARIES

Let us consider the plasma flow in the capillary with the following porous structure (Fig. 2). The plasma is moving in the capillary in two directions simulta-

neously: along the vessel (longitudinal flow Q) and perpendicular to it (lateral flow q) through hydraulic cylinder pores. Considering this system as distributed, we introduce the specific characteristics.

The perpendicular flow through the pores qdx equals the decrease dQ of the longitudinal flow at the distance dx , expressed as $dQ = -qdx$, where $q(x)$ is the lateral flow through all the pores on the surface of the capillary of unit length. $Q(x)$ is the longitudinal plasma flow along the capillary.

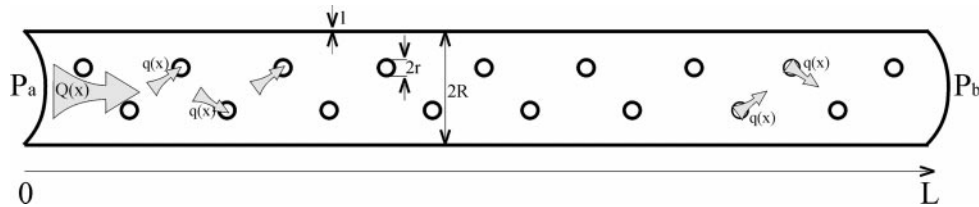


FIG. 2.

Model of capillary with pores in its wall. P_a and P_b are pressures at arterial ($x = 0$) and venous ($x = L$) ends of capillary, where x represents distance along length of capillary. $2R$, diameter of capillary; $2r$, diameter of pore; $Q(x)$, flow along capillary; $q(x)$, flow through pores.

We consider that the central equation governing the relationships among Q , pressure P , and hydraulic resistance W is Poiseuille's law

$$Q = - \frac{1}{W} \frac{dP}{dx} \quad (1)$$

The value $P(x) = P_{hc}(x) - P_{ht}$ constitutes the driving force for filtration. The value W is the specific hydraulic resistance of the capillary of the unit length

$$W = \frac{8\eta}{\pi R^4}$$

where $2R$ is the diameter of the capillary. Let the plasma be considered a Newtonian fluid with a constant viscosity η .

According to the Starling theory, the flow q through the pores depends on the algebraic sum of pressures

$$q = \frac{P - P_0}{\omega} \quad (2)$$

The value $P_0 = P_{oc} - P_{ot}$ is the resulting oncotic pressure, which is conditioned by the different concentrations of proteins in the capillary plasma and in the tissue fluid. This value P_0 is the key factor that restrains fluids loss from the capillary.

The hydraulic resistance ω of all the pores at the surface of the capillary of the unit length is

$$\omega = \frac{4\eta l}{\pi^2 r^4 R n}$$

where $2r$ is the diameter of the pore; l is its length, otherwise known as the capillary thickness; and n is

the number of pores per unit area (1 mm^2), otherwise known as the pores density.

Taking into account *Eqs. 1 and 2* and designating

$$\lambda = \sqrt{\frac{\omega}{W}} = \sqrt{\frac{R^3 l}{2\pi r^4 n}}$$

we get the second-order differential equation

$$\frac{d^2P}{dx^2} - \frac{P}{\lambda^2} = - \frac{P_0}{\lambda^2} \quad (3)$$

The boundary conditions for this equation are the values of hydrostatic pressure at the arterial ($x = 0$) and venous ($x = L$) ends of the capillary

$$\begin{cases} P(x = 0) = P_a \\ P(x = L) = P_b \end{cases}$$

All the parameters in these equations can be changed. If the permeability of the capillary wall, for example, is increased under radiation, r and n will be increased. If there is a spasm of arterioles, P_a will be decreased. If the protein is not removed from the interstitial spaces by the lymph vessels, it will accumulate in the interstitial fluid and act as oncotic force to draw fluid from blood capillary, thus P_{ot} is increased and P_0 is decreased. There is regulation in microcirculation and lymphatic systems. Lymph flow is increased by any mechanism that enhances the rate of blood capillary filtration. At the next lesson we shall use the indicated mathematical approach to take into account the interaction between microcirculation and lymphatics.

And now let us make the following assumptions: *1*) the external factors influence mainly the blood capil-

lary parameters; 2) the drainage capacity of the lymphatics is steady; the pressure oncotic tissue and hydrostatic tissue pressure are fixed by lymphatics; and 3) the difference in protein concentration between tissue and blood is the same because of the lymphatic system; P_0 is not dependent on r .

The solutions of *Eqs. 1-3* are represented in the APPENDIX.

ANALYSIS OF SOLUTION

Spatial distribution of hemodynamic characteristics.

The functions $P(x)$, $Q(x)$, and $q(x)$, being nonlinear, are varied essentially if the parameters of the cardiovascular system are changed.

One of the main factors influencing the spatial distribution of these functions is the radius and the number of pores. Calculations show that when the diameter of the pore is small (<20 nm), the function $P(x)$ is almost a straight line as in the "ordinary" Poiseuille's law (Fig. 3, *curve k*; see Fig. 1). When the diameter is increased (>50 nm), the dependence $P(x)$ becomes essentially nonlinear (Fig. 3, *curves l and m*).

It is not difficult to see the essential change of the topography of substance exchange in the capillary. The increase of r tends toward extension of the region of filtration-reabsorption equilibrium. At the middle of the capillary the extended region is increased where the blood-tissue exchange is greatly reduced compared with that during normal exchange. Actually, in Fig. 3, *curve m* shows that the region of active exchange is restricted only by $10 \mu\text{m}$ from the arterial and venous ends of capillary, and at all middle zones ($\sim 500 \mu\text{m}$) exchange is reduced approximately to zero. This distortion of the exchange topography will tend to pathologies such as local tissue necrosis.

The other factors affecting these functions are the pressures, particularly P_0 , P_a , and P_b . Figure 4 shows the distributions of functions for different P_a .

Estimations of blood flow in the capillary and through its wall.

Under ionizing radiation, an organism may have arterio-lymphatic spasms. Because of this phenomenon, P_a will be

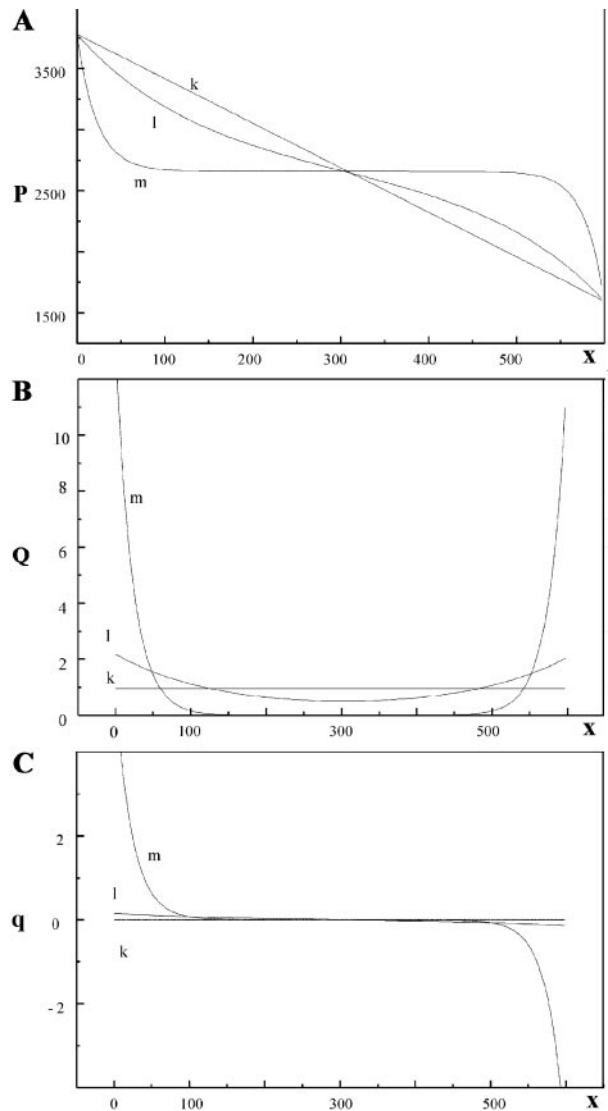


FIG. 3.

Distribution of hemodynamic parameters along capillary for different radius (r) of pore (for curves *k*, *l* and *m*, $r = 10, 100$, and 250 nm, respectively). *A*: $P(x)$; *B*: $Q(x)$; *C*: $q(x)$. $P_a = 28.4$ mmHg, $P_b = 12$ mmHg, $P_0 = 20$ mmHg, $L = 600 \mu\text{m}$, $l = 0.6 \mu\text{m}$, $R = 3 \mu\text{m}$, $N = 1.3 \times 10^{12} \text{ m}^{-2}$, and viscosity (η) = $0,0012 \text{ Pa}\cdot\text{s}$. In *A*, P is represented in units of Pa; in *B*, Q is represented in units of $10^{-13} \text{ m}^3/\text{s}$; and in *C*, q is represented in units of $10^{-8} \text{ m}^2/\text{s}$. In *A-C*, x is represented in units of μm .

decreased (Fig. 4, *curve k*). In this case, the flow Q in the capillary is decreased. The calculations show that there is essentially a decrease of plasma flow q through the capillary wall. The effects may be associated with such conditions as infarct and insult. In this

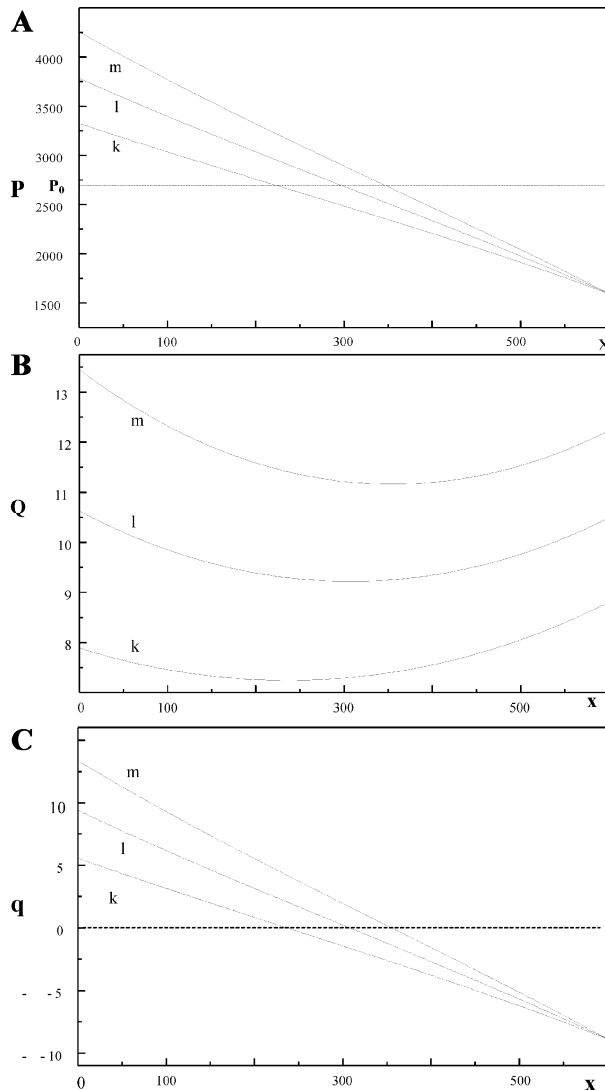


FIG. 4.

Distribution of hemodynamic parameters along capillary for different P_a (for curves k , l , and m , $P_a = 25$, 28.4 , and 32 mmHg, respectively). **A:** $P(x)$; **B:** $Q(x)$; **C:** $q(x)$. In **A**, P is represented in units of Pa; in **B**, Q is represented in units of 10^{-13} m³/s; and in **C**, q is represented in units of 10^{-11} m²/s. In **A-C**, x is represented in units of μm .

case, we have a quantitative conformity with the phenomenon discussed in our previous article (3). The increase in P_a tends to lead to edema (Fig. 4, curves m).

The fluid pressure and geometric factors of capillaries influence the location and expansion of the equilib-

rium region, where the flow into and out of the vessel is almost balanced.

The forms of $P(x)$, $Q(x)$, and $q(x)$ could be essentially changed under different pathologies.

Numerical estimations of the plasma fraction remaining in the tissue: the possible mechanism of edema.

Let us introduce the value

$$k = \frac{q_+ - |q_-|}{q_+} 100\%$$

which characterizes the plasma fraction remaining in the tissue. The value q_+ is the integral of $q(x)$ from the beginning of the capillary $x = 0$ to the equilibrium point $x = x_A$. Thus it is the total filtered flow. Correspondingly, q_- is the integral of $q(x)$ from $x = x_A$ to the end of the capillary $x = L$. This is the total reabsorbed flow.

According to our model, $k = 10\%$ for the normal physiological parameters ($R = 3 \mu\text{m}$, $P_a = 29$ mmHg, $P_b = 12$ mmHg, $P_0 = 20$ mmHg, $r = 50$ nm, $\eta = 0.012$ Pa·s). These data correspond to the experimental physiological data.

Changes in the hemodynamic parameters of the cardiovascular system or a breach of the capillary ultrastructure tends to induce disturbances in the hydrostatic-oncotic balance. This may result in disease. One of the pathologies connected with the disturbance of filtration-absorption equilibrium is extracellular fluid edema. Tissue *edema* means the presence of excess fluid in the tissues of the body. The excess interstitial fluid will accumulate and cause extracellular edema if 1) the volume of interstitial fluid exceeds the drainage capacity of the lymphatics (too much fluid filters from the capillaries into the interstitium) or 2) lymphatic blockage prevents the return of the interstitial fluid to the circulation, as in elephantiasis.

The factors that can increase the leakage of fluid into tissue are increased capillary pressure P_a ; decreased plasma proteins, and consequently decreased oncotic pressure P_0 ; and increased capillary permeability f .

Increased capillary pressure. P_a may rise because of decreased arteriolar resistance (e.g., in the cases of excessive body heat, paralysis of sympathetic nervous system, or effects of vasodilator drugs).

In accordance with the suggested model, when $P_a = 40$ mmHg the fraction of water remaining in the tissue is $k = 55\%$. It is greater than that in the normal steady state.

In the cases of contraction or relaxation of arterioles, the calculation of k is connected with the problem of local stenosis or expansion of vessels, as discussed in detail in Ref. 3.

Decrease of plasma protein concentrations. A decrease in plasma protein concentration causes the plasma oncotic pressure to fall to a very low value, so it cannot prevent the filtration of fluid from the capillaries into the tissue (1, 2).

The plasma protein concentration is reduced in nephrosis because great quantities of these proteins are lost in the urine. Another reason for the decrease of plasma proteins may be a failure to produce proteins in cases of liver disease or protein or caloric malnutrition.

Figure 5 shows hemodynamic parameters for different oncotic pressures. Calculations show that if $P_0 = 20$ mmHg (normal), then $k = 10\%$. If $P_0 = 18$ mmHg (low

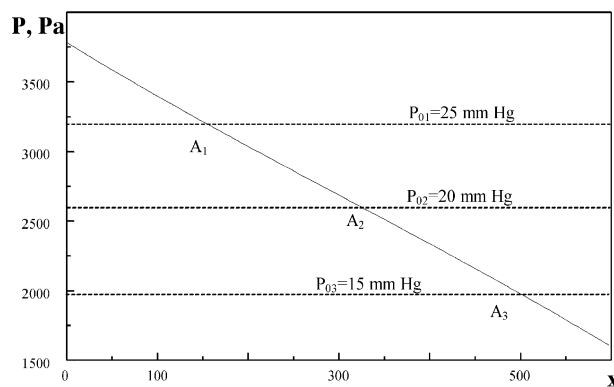


FIG. 5.

Influence of P_0 on filtration-reabsorption equilibrium. A_1 – A_3 are equilibrium points for oncotic pressures P_{01} – P_{03} . P is represented in units of Pa, and x is represented in units of μm .

concentration of proteins), then $k = 52\%$. In this case edema may arise.

Increased capillary permeability. An increase in capillary permeability allows excessive leakage of both proteins and fluid through the porous wall. Increase of the coefficient f may be due to different factors, particularly immune reactions that cause release of histamine and other immune products in response to burns, radiation, toxins, bacterial infections, vitamin deficiency, or prolonged ischemia.

If the radius is >600 nm, the fraction of remaining water is rapidly increased, resulting in edema.

Often, edema is the result of the *combination of different phenomena*. For example, when the diameter of the capillary pores becomes as large as the proteins, proteins can move into the interstitial space with the fluid, and consequently the oncotic pressure in the capillary plasma will be decreased. The diminishing of the restraining factor of fluid loss causes additional plasma loss from vascular system and may lead to edema. In this case, our mathematical model gets complicated by the dependence $P_0(r)$.

The complicated phenomena arise as a result of radiation effects on tissues. Disturbance of prolonged biochemical processes may cause change in the capillary ultrastructure, and consequently the effects described above may arise. At the same time, damage to the cardiovascular system as a whole may decrease the hydrostatic pressure gradient, and, in particular, P_a may be decreased and P_b may be increased. The combination of pressure and ultrastructure changes lead to disturbances in filtration-reabsorption processes and, consequently, to edema.

THE MAIN IDEAS OF THIS LESSON

There are six main ideas that this lesson portrays:

1) This model represents for consideration the analysis of filtration-reabsorption processes under different external effects influencing the microcirculation parameters r , n , P_a , P_b , and P_0 .

2) The model considers the values and spatial distribution of hemodynamic parameters. The functions $P(x)$, $Q(x)$, and $q(x)$ are nonlinear along the capillary.

3) The plasma fraction k remaining in the tissue is estimated numerically. This fraction is essentially increased under specific conditions.

4) The physiological phenomenon of edema can be investigated by the indicated model with the calculation of k .

5) The model makes it possible to estimate the decrease in intensity of blood-tissue fluid exchange under different conditions with the calculation of q . Thus it is possible to examine such a phenomenon as tissue necrosis.

6) The exchange topography may essentially change due to nonlinearity of blood flow along the capillary.

USE OF THE FILTRATION-REABSORPTION MODEL IN THE EDUCATIONAL PROCESS

This model permits one to analyze the different cases of the pathologies in substance exchange between capillary and tissue under different external factors. The calculations and construction of graphs are carried out with the use of personal computers using specially developed computer programs. During the lessons each student works individually. The professor suggests that the students solve five tasks. In particular, the students can alter the hydrostatic and oncotic pressures in tissue and in the capillary as well as the geometric parameters of the capillary and its pores. The computer solves the differential equations and plots $P(x)$, $Q(x)$, and $q(x)$ on the basis of these calculations. By using these curves, it is possible to analyze the filtration-reabsorption equilibrium under different conditions. The students estimate the disturbance of water balance in the case of disease. In particular, the students analyze numerically the different reasons for edema and necrosis with the use of this model. This model is studied by students in the Sechenov Moscow Medical Academy and Moscow State University in their biophysics and physiology courses and used more comprehensively in their pathophysiology courses. Moreover, this model is studied by physicians who wish to improve their specialist qualification. The model is highly efficient-

for education on concepts related to blood flow physiology.

In conclusion, the main purpose of this lesson is to give the student the analytic approach to important problems of hemodynamics and, in particular, of blood-tissue fluid exchange. It permits the student to develop a scientific approach to the solution of physiological and pathophysiological problems.

APPENDIX

$$P(x) = \frac{-(P_b - P_0) + (P_a - P_0)e^{-L/\lambda}}{e^{-L/\lambda} - e^{L/\lambda}} e^{x/\lambda} + \frac{(P_b - P_0) - (P_a - P_0)e^{L/\lambda}}{e^{-L/\lambda} - e^{L/\lambda}} e^{-x/\lambda} + P_0 \quad (4)$$

$$Q(x) = -\frac{1}{\sqrt{W\omega}} \left[\frac{-(P_b - P_0) + (P_a - P_0)e^{-L/\lambda}}{e^{-L/\lambda} - e^{L/\lambda}} e^{x/\lambda} - \frac{(P_b - P_0) - (P_a - P_0)e^{L/\lambda}}{e^{-L/\lambda} - e^{L/\lambda}} e^{-x/\lambda} \right] \quad (5)$$

$$q(x) = \frac{1}{\omega} \left[\frac{-(P_b - P_0) + (P_a - P_0)e^{-L/\lambda}}{e^{-L/\lambda} - e^{L/\lambda}} e^{x/\lambda} + \frac{(P_b - P_0) - (P_a - P_0)e^{L/\lambda}}{e^{-L/\lambda} - e^{L/\lambda}} e^{-x/\lambda} \right] \quad (6)$$

We thank Prof. V. B. Koshelev for constructive discussion and S. A. Ivanov for taking part in the computer calculations.

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Received 23 February 1999; accepted in final form 1 March 2000.

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