Basic Biomedical Sciences 1

Lecture 3: Dynamics of Microcirculation and Lymphatics

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DYNAMICS OF MICROCIRCULATION AND LYMPHATICS

FUNCTIONS OF THE MICROCIRCULATION

Functions of the microcirculation

- Transport of nutrients to the tissues
- Removal of cell excreta.
    - The peripheral circulation of the entire body has about 10 billion capillaries, with a total surface area estimated to be **500 to 700 square meters**.

STRUCTURE OF THE MICROCIRCULATION AND CAPILLARY SYSTEM

- The microcirculation of each organ is organized to serve that organ's specific needs. In general, each nutrient artery entering an organ branches 6-8 times before the arteries become small enough to be called **arterioles**, which generally have internal diameters of only 10 to 15 micrometers. Then, the arterioles branch 2-5 times, reaching diameters of 5 to 9 micrometers at their ends, where they supply blood to the capillaries

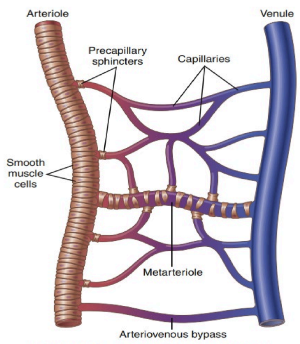

Figure 16-1. Components of the microcirculation.

Arterioles

- Highly muscular, coated with smooth muscle cells, and their diameters can change by many times.
    - **Metarterioles (terminal arterioles)**: do not have a continuous muscular coat, but smooth muscle fibers encircle the vessel at intermittent points.
    - **Precapillary sphincter:** At the point where each true capillary originates from a metarteriole, a smooth muscle fiber usually encircles the capillary (smooth muscles are intermittent and not continuous).

Venules

- Larger than the arterioles, have a much weaker muscular coat, and the pressure in the venules is much less than that in the arterioles, but the venules can still contract considerably, despite the weak muscle

Structure of the Capillary Wall

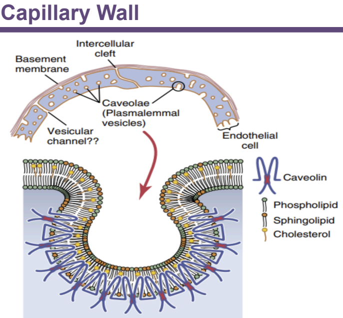

Figure 16-2. Structure of the capillary wall. Note especially the *intercellular cleft* at the junction between adjacent endothelial cells. It is believed that most water-soluble substances diffuse through the capillary membrane along the clefts. Small membrane invaginations, called *caveolae*, are believed to play a role in transporting macromolecules across the cell membrane. Caveolae contain caveolins, which are proteins that interact with cholesterol and polymerize to form the caveolae.

- 0.5 micrometer thick
- Internal diameter: 4 to 9 micrometers
- Composed of a unicellular layer of endothelial cells and is surrounded by a thin basement membrane on the outside of the capillary.
- 2 small passageways connecting the interior with the exterior.
    - **Intracellular cleft:** passageways of nutrients and molecules; the thin-slitted, curving channel between adjacent endothelial cells
    - **Short ridges of protein attachments** that hold the endothelial cells together but, between these ridges, fluid can flow freely throughout the cleft.
    - Diffusion of water, water-soluble ions, and small solutes between the interior and exterior of the capillaries.
- **Caveolae:** believed to play a role in endocytosis and transcytosis of macromolecules across the interior of endothelial cells
    - Many minute plasmalemmal vesicles present in the endothelial cells associated with molecules of cholesterol and sphingolipids.
    - These imbibe small packets of plasma or extracellular fluid that contain plasma proteins, and some of these vesicles may coalesce to form vesicular channels.

Special Types of Pores in Capillaries of Certain Organs

- **Brain:** Tight junctions that only extremely small molecules such as water, oxygen, and carbon dioxide can diffuse
- **Liver:** Almost all dissolved substances of the plasma, including the plasma proteins, can pass from the blood into the liver tissues (since one of the functions of liver is to filter toxic wastes)
- **Gastrointestinal tract:** Midway in size between those of the muscles and those of the liver.
- **Glomerular capillaries of the kidney**- fenestrae penetrate all the way through the middle of the endothelial cells

FLOW OF BLOOD IN THE CAPILLARIES (VASOMOTION)

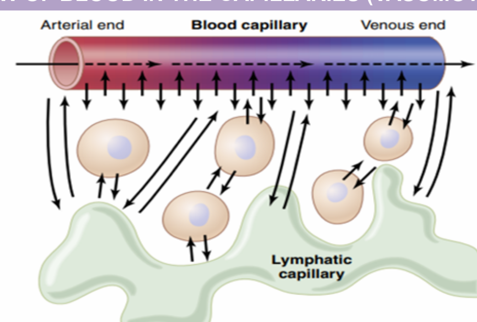

Figure 16-3. Diffusion of fluid molecules and dissolved substances between the capillary and interstitial fluid spaces.

- Blood flows intermittently through the capillaries
    - There is intermittent contraction of the metarterioles and precapillary sphincters.
- The most important factor affecting the degree of opening and closing of the metarterioles and precapillary sphincters is the **concentration of oxygen in the tissues.**
    - When the body senses that a certain part of the body lacks oxygen, there is more vasomotion and the duration of contraction is longer to provide the needed nutrients (oxygen) on that certain area.

EXCHANGE OF WATER AND NUTRIENTS IN THE BLOOD AND INTERSITIAL FLUID

- Diffusion through the Capillary Membrane is the most important means of transferring substances between plasma and interstitial fluid.
- The proteins are the only dissolved constituents in the plasma and interstitial fluids that do not readily pass through the capillary membrane.
  - Proteins are large molecules, that is why proteins should not be seen in the urine. But if there are problems in filtration, proteins will be seen in the urine.
- Lipid-soluble substances diffuse directly through the cell membranes of the capillary endothelium.
  - Exchange of oxygen and carbon dioxide occurs in the alveoli.
- Water-soluble, non-lipid-soluble substances diffuse through intercellular pores in the capillary membrane.

Effect of Molecular Size on Passage Through the Pores

- Width of intercellular cleft pores: 6-7 nm
- The higher the molecular weight, the lesser permeability.

Relative Permeability of Skeletal Muscle Capillary Pores to Different-Sized Molecules		
Substance	**Molecular Weight**	**Permeability**
Water	18	1.00
NaCl	58.5	0.96
Urea	60	0.8
Glucose	180	0.6
Sucrose	342	0.4
Inulin	5000	0.2
Myoglobin	17,600	0.03
Hemoglobin	68,000	0.01
Albumin	69,000	0.001

Diffusion Through the Capillary Membrane Is Proportional to the Concentration Difference Between the Two Sides of Membrane

- The greater the difference, the greater the net movement of the substance in one direction through the membrane.
- The rates of diffusion through the capillary membranes of most nutritionally important substances are so great that even the slightest difference causes more than adequate transport between the plasma and interstitial fluid.

THE INTERSITITUM AND THE INTERSTITIAL FLUID

- **Interstitium**: spaces between the cells
- **Interstitial Fluid**: fluid in the spaces between the cells
- Structure of the interstitium contains <u>**2 major types of solid structures**</u>:
  - **Collagen fiber bundles**- are extremely strong and provide most of the tensional strength of the tissues
  - **Proteoglycan filaments**- are extremely thin, coiled or twisted molecules composed of about <u>**98% hyaluronic acid and 2% protein.**</u>

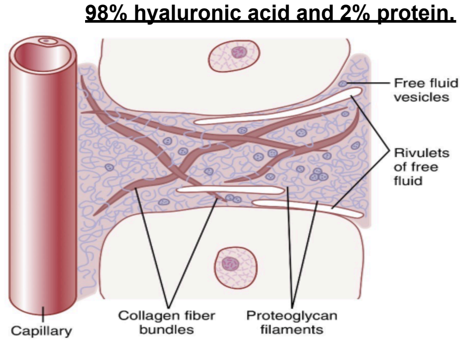

Figure 16-4. Structure of the interstitium. Proteoglycan filaments are everywhere in the spaces between the collagen fiber bundles. Free fluid vesicles and small amounts of free fluid in the form of rivulets occasionally also occur.

Gel in the Interstitium

- The fluid in the interstitium is derived by filtration and diffusion from the capillaries.
- It contains almost the same constituents as plasma except for much lower concentrations of proteins
- The interstitial fluid is entrapped mainly in the minute spaces among the proteoglycan filaments.
- This combination of proteoglycan filaments and fluid entrapped within them have the characteristics of a gel; it is therefore called **tissue gel.**
- Fluid mainly diffuses through the gel by **kinetic thermal motion,** rather than by large numbers of molecules moving together.
  - Diffusion through the gel occurs about **95% to 99%** as rapidly as it does through free fluid.

Free Fluid in the Interstitium

- The amount of free fluid present in most normal tissues is slight, usually **less than 1%**
- When there is <u>**edema**</u>, the small pockets and rivulets expand tremendously until one half or more of the edema fluid becomes free- flowing fluid, independent of the proteoglycan filaments.

FLUID FILTRATION ACROSS CAPILLARIES

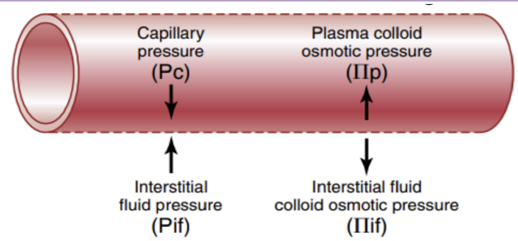

Figure 16-5. Fluid pressure and colloid osmotic pressure forces operate at the capillary membrane and tend to move fluid outward or inward through the membrane pores.

$$NFP = Pc - Pif - \prod p + \prod if$$

4 primary forces that determine whether fluid will move out of the blood
into the interstitial fluid or in the opposite direction (Starling forces):

- **Capillary hydrostatic pressure (Pc)** tends to force fluid outward through the capillary membrane
- **Interstitial fluid hydrostatic pressure (Pif)** tends to force fluid inward through the capillary membrane when Pif is positive but outward when Pif is negative
- **Capillary plasma colloid osmotic pressure (Πp)** tends to cause osmosis of fluid inward through the capillary membrane
- **Interstitial fluid colloid osmotic pressure (Πif)** tends to cause osmosis of fluid outward through the capillary membrane

Interstitial Fluid Pressures in Tightly Encased Tissues

- Some tissues of the body are surrounded by tight encasements, such as the cranial vault around the brain, the strong fibrous capsule around the kidney, the fibrous sheaths around the muscles, and the sclera around the eye.
- In most of these tissues, the interstitial fluid pressures are **positive**.

Interstitial Fluid Pressure in Loose Subcutaneous Tissue

- The interstitial fluid pressure in loose subcutaneous tissue is, in normal conditions, slightly less subatmospheric, averaging about **−3 mm Hg.**
- Intrapleural space (in the lungs): **-8 mm Hg**

- Joint synovial spaces (in the elbows and knees): **-4 to -6 mm Hg**
- Epidural space (in the CNS): **-4 to -6 mm Hg**

Plasma Colloid Osmotic Pressure

	g/dl	Πp (mm Hg)
Albumin	4.5	21.8
Globulins	2.5	6.0
Fibrinogen	0.3	0.2
Total	7.3	28.0

- The proteins of the plasma and interstitial fluids that are responsible for the osmotic pressures on the two sides of the capillary membrane.
- Normal human plasma pressure: approx. **28 mmHg**
- **80%** of the total osmotic pressure is from albumin
- **20%** from globulins

Interstitial Fluid Colloid Osmotic Pressure

- Small amounts of plasma proteins leak into the interstitial spaces through the pores and by transcytosis in small vesicles.
- The total quantity of protein in the entire **12L** of interstitial fluid of the body is slightly greater than the total quantity of protein in the plasma.
- The interstitial volume is four times to the plasma, the average protein concentration of the interstitial fluid is usually **40%** of that in plasma.
- The average interstitial fluid colloid osmotic pressure for this concentration of protein is approx. **8 mmHg.**

Fluid Volume Exchange through the Capillary Membrane

- The average capillary pressure at the arterial ends of the capillaries is **15 to 25 mmHg greater** than at the venous ends.
- Fluid filters out of the capillaries at their arterial ends but at their venous ends, fluid is reabsorbed back into the capillaries.
- **Analysis of the Forces Causing Filtration at the Arterial End of the Capillary**. The approximate average forces operative at the arterial end of the capillary that cause movement through the capillary membrane are shown as follows:

	mm Hg
Forces Tending to Move Fluid Outward	
Capillary hydrostatic pressure (arterial end of capillary)	30
Negative interstitial fluid hydrostatic pressure	3
Interstitial fluid colloid osmotic pressure	8
TOTAL OUTWARD FORCE	41
Forces Tending to Move Fluid Inward	
Plasma colloid osmotic pressure	28
TOTAL INWARD FORCE	28
Summation of Forces	
Outward	41
Inward	28
NET OUTWARD FORCE (AT ARTERIAL END)	13

- **Analysis of Reabsorption at the Venous End of the Capillary.** The low blood pressure at the venous end of the capillary changes the balance of forces in favor of absorption as follows:

	mm Hg
Forces Tending to Move Fluid Inward	
Plasma colloid osmotic pressure	28
TOTAL INWARD FORCE	28
Forces Tending to Move Fluid Outward	
Capillary hydrostatic pressure (venous end of capillary)	10
Negative interstitial fluid hydrostatic pressure	3
Interstitial fluid colloid osmotic pressure	8
TOTAL OUTWARD FORCE	21
Summation of Forces	
Inward	28
Outward	21
NET INWARD FORCE	7

Starling Equilibrium for Capillary Exchange

- The amount of fluid filtering outward from the arterial ends of capillaries are almost exactly equals the fluid that is eventually returned to the circulation.
- The slight disequilibrium that occurs accounts for the fluid that is eventually returned to the circulation by way of the lymphatics.
- The slight excess of filtration is called the net filtration which is normally **2 mL/min.**

Effect of Abnormal Imbalance of Forces at the Capillary Membrane

- If the mean capillary pressure rises significantly above the average value of 17 mmHg, the net force tending to cause filtration of fluid into the tissue spaces rises.
- There will be an imbalance and would result to fluid accumulation in interstitial spaces, resulting to edema.
- If the capillary pressure falls very low, net reabsorption ensues instead of net filtration, and the blood volume will increase at the expense of the interstitial fluid volume.

LYMPHATIC SYSTEM

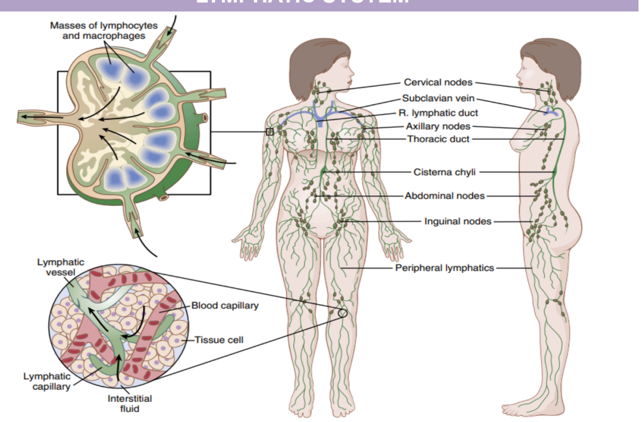

Figure 16-6. The lymphatic system.

- Represents an accessory route through which fluid can flow from the interstitial spaces into the blood.
- The lymphatics can carry proteins and large particulate matter away from the tissue spaces, neither of which can be removed by absorption directly into the blood capillaries.

Lymph Channels of the Body

- **Almost all tissues of the body:** drain excess fluid directly from the interstitial spaces.
- **Thoracic duct:** All lymph vessels from the lower part of the body, left side of the head, left arm, and parts of the chest
- **Right lymphatic duct:** Right side of the head and neck, right arm, and parts of the right thorax.

Terminal Lymphatic Capillaries and Their Permeability

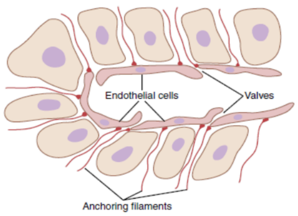

Figure 16-7. Special structure of the lymphatic capillaries that permits passage of substances of high molecular weight into the lymph.

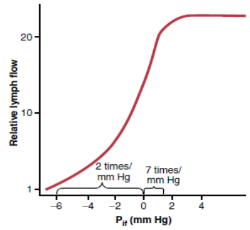

Figure 16-8. Relationship between interstitial fluid pressure and lymph flow in the leg of a dog. Note that lymph flow reaches a maximum when the interstitial pressure (P_{if}) rises slightly above atmospheric pressure (0 mm Hg). (*Courtesy Dr. Harry Gibson and Dr. Aubrey Taylor.*)

- Fluid from the arterial ends of blood capillaries flows among the cells and reabsorbed back into the venous ends of the blood capillaries.
- One tenth of the fluid enters into the lymphatic capillaries and returns to the blood through the lymphatic system.
- **Total lymph: 2-3L per day**
- The fluid return from the lymphatics is extremely important because substances of high molecular weight, such as proteins, cannot be absorbed from the tissues in any other way.
- There are **anchoring filaments** at the junctions of each endothelial cell. There is overlapping, thus forming a minute valve that opens to the interior of the lymphatic capillary.
- Interstitial fluid, along with its suspended particles, can push the valve open and flow directly into the lymphatic capillary.

Formation of Lymph

- Lymph is derived from interstitial fluid that flows into the lymphatics.
- Lymph formed in the **liver** has **6 g/dL protein**.
- Lymph formed in the **intestines** has **3 to 4 g/dL protein**.
- After a **fatty meal**, thoracic duct lymph sometimes contains as much as **1% to 2% fat** (lymphatics is a major route for absorption of fats).
- Large particles, such as bacteria, can push their way between the endothelial cells and enter the lymph almost entirely destroyed.

Rate of Lymph Flow

- About **100 mL/hr** of lymph flows through the **thoracic duct** of a resting
- human
- Approximately another **20 mL** flows into the circulation **each hour**
- Total estimated lymph flow of about **120 mL/hr or 2 to 3 L/day.**

Effect of Interstitial Fluid Pressure on Lymph Flow

- Note that normal lymph flow is very little at interstitial fluid pressures
- more negative than the normal value of **-6 mm Hg.**
- Then, as the pressure rises to **0 mm Hg** (atmospheric pressure), flow increases more than 20-fold. Therefore, any factor that increases interstitial fluid pressure also increases lymph flow if the lymph vessels are functioning normally
- The **lower** the pressure, the **lower** the lymph flow. The higher the pressure, the higher the lymph flow, but there is a limit (plateau).

Factors that increases lymph flow

- Elevated capillary hydrostatic pressure
- Decreased plasma colloid osmotic pressure
- Increased interstitial fluid colloid osmotic pressure
- Increased permeability of the capillaries

Lymphatic Pump Increases Lymph Flow

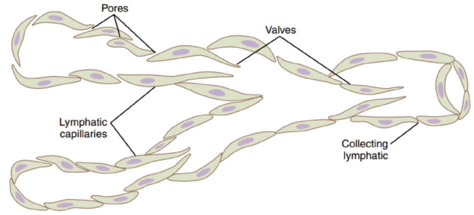

Figure 16-9. Structure of lymphatic capillaries and a collecting lymphatic, with the lymphatic valves also shown.

- When the vessel becomes stretched with fluid, the smooth muscle in the wall of the vessel contracts.
- Each segment of the lymph vessels between successive valves functions as a separate automatic pump.
- The lymphatic pump can generate pressure as high as **50 to 100 mm Hg.**

Pumping Caused by External Intermittent Compression of the Lymphatics

- In addition to the pumping caused by intrinsic intermittent contraction of the lymph vessel walls, any external factor that intermittently compresses the lymph vessel can also cause pumping. **The factors are the following:**
  - Contraction of surrounding skeletal muscles
  - Movement of the parts of the body
  - Pulsations of arteries adjacent to the lymphatics
  - Compression of the tissues by objects outside the body
- The lymphatic pump is very active during exercise, often increasing lymph flow **10- to 30-fold**. Conversely, during periods of rest, lymph flow is sluggish (almost zero).

Lymphatic Capillary Pump

- The terminal lymphatic capillary is also capable of pumping lymph.
- The lymphatic capillary endothelial cells also contain a few contractile actomyosin filaments.
- The lymphatic system also plays a role in controlling the following:
  - Concentration of proteins in the interstitial fluids
  - Volume of interstitial fluid
  - Interstitial fluid pressure