

Course:	Medical Physiology
Lecture:	Capillary Circulation
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**Textbook: Guyton & Hall. Medical Physiology. 12<sup>th</sup> Edition, pp. 177-189; 244-245.**

- I. Introduction**
- II. General Properties of Capillaries**
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- IV. Precapillary Sphincter Control**
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- VI. Bulk Flow & Starling Forces**
- VII. Effective Capillary Pressure**
- VIII. Pathological Conditions that Change Effective Capillary Pressure**
- IX. Edema**

## **OBJECTIVES**

After reviewing lecture notes and related material in the practice quiz or textbooks, the student should be able to:

1. List the major functions of the capillaries (e.g. nutrient exchange -- including O<sub>2</sub>; waste exchange -- including CO<sub>2</sub>).
2. List the characteristics of capillaries that facilitate the exchange processes.
3. List three factors which are important in controlling the opening and closing of precapillary sphincters. (Realize that all factors have some role in all tissues, but that some tissues rely most heavily on specific factors. For example, heart sphincters are controlled predominately by adenosine. The brain relies most heavily on CO<sub>2</sub>.)
4. Explain the primary mechanisms whereby blood flow increases to active skeletal muscle during exercise.

5. Explain why in increasing blood flow to a tissue it is more advantageous to open additional capillaries rather than to force more blood through the same number of capillaries.
6. List the four "Starling Forces."
7. Identify each of the "Starling Forces" as to whether it favors filtration or reabsorption.
8. List three conditions that may lead to edema.
9. Explain why each of the conditions listed in Objective #7 leads to edema.
10. List two functions of lymphatic capillaries.
11. Explain how starling forces help compensate for blood loss.

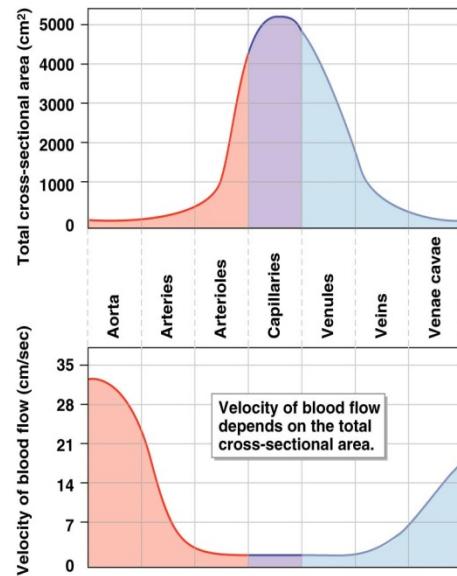
## I. Introduction

Capillary vessels are ideally designed for the exchange of fluids, dissolved gases, and small solute molecules between blood and interstitial fluid. During this lecture we will examine capillaries in terms of their structure & function and describe the various types of flow characteristics that are present.

## II. General Properties of Capillaries

Capillaries are the “business end” of circulation - essentially all of the functional activity of the circulation takes place at the capillary level. These include:

1. Nutrient Exchange:
  - Glucose
  - Oxygen
  - Free Fatty Acids
  - Other Nutrients
2. Waste Exchange:
  - CO<sub>2</sub>
  - Lactate & Ammonia
  - Other metabolic byproducts
3. Most exchange processes that take place are dependent on simple diffusion.
4. Characteristics of capillaries that facilitate simple diffusion:
  - Capillaries have thin walls - one cell thick
  - Therefore, the distance traveled by



*Silverthorn, Human Physiology, 4<sup>th</sup> Ed.*

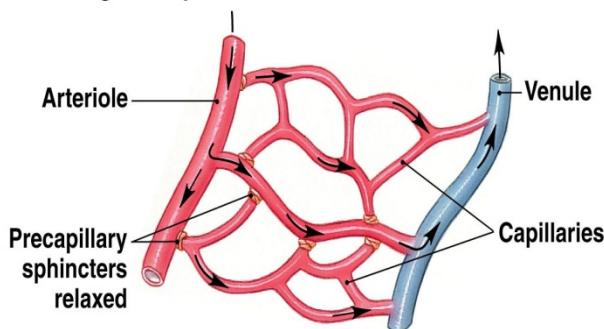
- diffusion particles (i.e. O<sub>2</sub> & CO<sub>2</sub>) is short
- Capillaries have a high total surface area
- Flow velocity through capillaries is slow because of the large cross sectional area of capillary beds in the circulation. This will facilitate diffusion.

##### 5. Types of Flow in Capillaries:

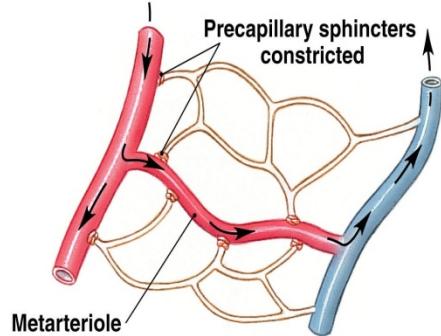
- A. **Bulk Flow:** Bulk flow is the term to describe flow across the capillary wall and is unique to capillary flow. There are two types of bulk flow that occur and are named according to their direction of flow:
1. Filtration – movement out of the capillary and into the interstitial space.
  2. Reabsorption (absorption) – movement from the interstitial space back into the capillary.
- B. **Normal Flow:** Normal flow is flow that occurs down the lumen of the capillary, and is determined primarily by the opening and closing of precapillary sphincters, and has several characteristics:
1. In contrast to arterioles, which are typically always patent to some degree depending upon the level of sympathetic tone, capillary sphincters can close completely, therefore the capillary is intermittent and either on or off.
  2. The mechanism by which increased tissue perfusion is achieved is by opening additional sphincters as needed.
  3. Note that the effects of opening additional sphincters are to increase total surface area and to decrease velocity of flow.

### III. Organization of the Microcirculation

**(a)** When precapillary sphincters are relaxed, blood flows through all capillaries in the bed.



**(b)** If precapillary sphincters constrict, blood flow bypasses capillaries completely and flows through metarterioles.



Silverthorn, Human Physiology, 4<sup>th</sup> Ed.

Notice in the diagrams above, that the “capillary bed” is in between an arteriole and venule. (B) Blood flow can pass from arteriole to venule without passing through the capillary bed by traveling through the metarteriole (or through an AV shunt). (A) As perfusion requirement arises, sphincters are opened and blood is shunted through the capillary bed. Most of the time, capillary beds are shut off. When

open, blood flow occurs - blood passes through the capillaries one cell at a time! In fact, RBCs take on an elongated shape to fit through the lumen of the capillaries. Therefore RBCs must be quite flexible in order to have efficient flow, and in conditions such as sickle cell anemia, the deformation of the shape causes inflexibility and can lead to occlusion of the vasculature, a painful and serious peripheral vascular condition.

A precapillary sphincter exists at each branch of a capillary that gives rise to an arteriole. In addition, at each capillary branching from a metarteriole there is a precapillary sphincter. Note that precapillary sphincters do not exist in regions where capillaries branch from other capillaries. The reason for this is that a sphincter is formed from muscle tissue, and there is no muscle tissue in capillaries. The precapillary sphincter is a component of the arteriole.

#### **IV. Pre-capillary Sphincter Control**

As a general rule, the primary controlling parameter of the precapillary sphincter, regardless of the tissue or organ type, is the generation of metabolites within the local environment. Each tissue may rely more or less heavily on different metabolic components to produce an opening of the precapillary sphincters. Also, in general, when we refer to dilation throughout this discussion, the capillary sphincters will also open. Thus, they are not the same events - but when vessels dilate due to local metabolic effects, then opening of the precapillary sphincters will generally follow.

In the case of skeletal muscle: decreased O<sub>2</sub> partial pressure, increased CO<sub>2</sub> partial pressure, production of metabolic acids - all drive the opening of capillary sphincters. Note that CO<sub>2</sub> will also cause vasodilation. Skeletal muscle, however, responds slightly more to hypoxia than to the other metabolites. Once the metabolites are washed out, the precapillary sphincters will again close. The process is a continual on/off cycle. The amount of time in which the sphincters remain open will depend upon the metabolic activity of the muscle.

In the case of the heart: The adenosine mechanism, which was previously discussed, is a major producer of dilation in cardiac tissue (coronary arteries). Cardiac tissue will also dilate in response to hypoxia, increased CO<sub>2</sub> and decreased pH.

The brain regulates its intrinsic flow according to the presence of the same metabolites - but is more sensitive to PCO<sub>2</sub> than to the others.

There are other chemicals (some blood borne while others are locally released) that have influence on the microcirculation. These are summarized in the three tables below.

Local environment – primary determinant of opening and closing of precapillary sphincters.

##### Skeletal Muscle:

- PCO<sub>2</sub>
- pH
- PO<sub>2</sub>

##### Brain

- PCO<sub>2</sub>
- Adenosine
- PO<sub>2</sub>

##### Heart

- Adenosine
- PO<sub>2</sub>
- PCO<sub>2</sub>
- pH

a. Recall that vascular smooth muscles have both  $\alpha_1$  &  $\beta_2$  receptors and that epinephrine will stimulate both  $\alpha_1$  &  $\beta_2$  receptors. The effect of epinephrine (contraction vs. dilation) will depend on the relative concentration of receptors within a given capillary bed.

b. The primary response of norepinephrine will be to cause a constriction since it will activate predominantly via  $\alpha_1$  receptors.

c. Dopamine - Dopaminergic receptors are abundant in the kidney & gut. At low doses, dopamine will cause a drop in peripheral resistance and a selective perfusion of the kidney. At higher doses, dopamine will activate  $\alpha_1$  receptors causing vasoconstriction. Clinically you will learn about this as a "renal dose of dopamine" in the treatment of shock.

d. Angiotensin II is a physiologically important vasoconstrictor.

e. Kinins, such as Bradykinin, are all vasodilators.

f. Adenosine: In the heart and most other places, adenosine acts to vasodilate while in the kidney, adenosine acts to vasoconstrict.

g. Hypoxia, Increased  $\text{CO}_2$ ,  $\text{K}^+$  &  $\text{H}^+$ : when present systemically, all tend to produce vasodilation.

h. Krebs Cycle Intermediates: presence of these indicate increased metabolism, will cause vasodilation.

g. Endothelin (constriction) & Nitric Oxide (NO, aka: Endothelium Derived Relaxing Factor (dilation))- are released from the endothelium.

Substance	Constrictor	Dilator
Catecholamines		
Epinephrine	X – via $\alpha_1$	X – via $\beta_2$
Norepinephrine	X – via $\alpha_1$	
Dopamine	X – high dose, constriction via $\alpha_1$	X – low dose, dilation in renal, gut via D
Amine		
Histamine		X
Acetylcholine		X

Substance	Constrictor	Dilator
Polypeptides		
Angiotensin II	X	
Kinins		X
Vasopressin (ADH)	X	
Vasoactive Intestinal Peptide (VIP)		X

Substance	Constrictor	Dilator
Adenosine	X – via A <sub>1</sub>	X – via A <sub>2</sub>
Hypoxemia		X
$\text{H}^+ / \text{K}^+$		X
Hypercapnia ( $\text{CO}_2$ )		X
Kreb's Cycle Intermediates		X
Endothelin	X	
Nitric Oxide (NO)		X

## V. Control of Skeletal Muscle Blood Flow During Exercise

Blood flow to active muscle increases dramatically during exercise. The primary mechanism responsible for this increase is the accumulation of metabolites (adenosine, lactate etc.) within the muscle that acts to elicit vasodilation of local arterioles and relaxation of precapillary sphincters. This causes an increased blood flow, which interestingly is not due to an increase in the total velocity of flow through the skeletal muscle capillaries as the recruitment of more surface area for flow allows total flow to increase without any change in blood flow velocity.

Sympathetic outflow to skeletal muscle vasculature actually increases during exercise (as it does systemically to also increase heart rate and force of contraction of the heart to elevate cardiac output). Although this may seem paradoxical considering your knowledge of how important sympathetic tone is to eliciting vasoconstriction, this is actually a very important response. Because of the large skeletal muscle mass subjected to metabolic vasodilation during exercise, if it were not for the sympathetic vasoconstrictor drive that "checks" the metabolic vasodilation, blood pressure would fall during exercise. This would then lower systemic blood pressure and reduce skeletal muscle blood flow since there would be little driving pressure or perfusion pressure present to maintain systemic blood flow to skeletal muscle. This mass increase in total body sympathetic discharge is also important for elevating heart rate, contractility and strongly vasoconstricting areas that have low metabolic demand during exercise (gastrointestinal system etc.). This is essential for raising cardiac output and redistributing blood flow from inactive to active tissue beds so that the body can meet the demands of the exercise.

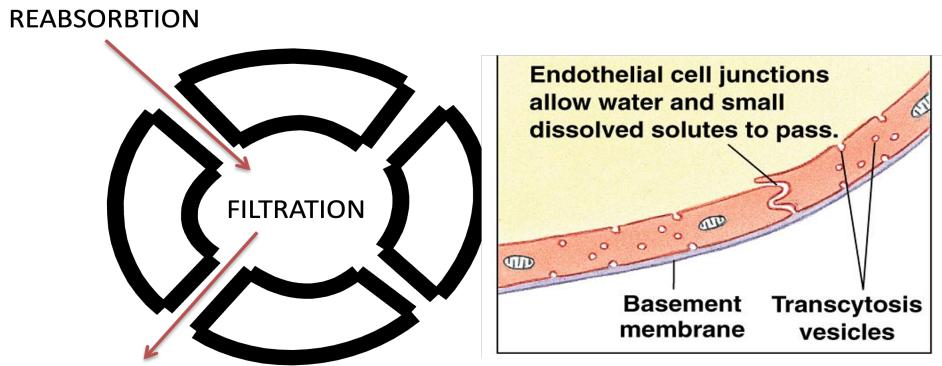
## VI. Bulk Flow & Starling Forces

Bulk Flow (illustrated below) is the movement of a plasma ultrafiltrate through the capillary wall.

Filtration is the movement from the capillary into the interstitium.

Reabsorption is the movement from interstitium into the capillary.

Bulk Flow properties vary with tissue type. Skeletal muscle, for example, have large pores ( $\sim 60 \text{ nm}$ ) between the endothelial cells.



*Silverthorn, Human Physiology, 4<sup>th</sup> Ed.*

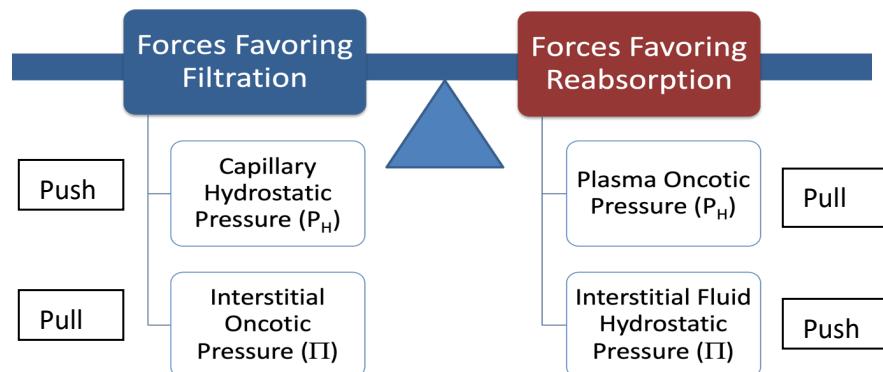
Chemicals such as  $\text{H}_2\text{O}$ ,  $\text{Cl}^-$ ,  $\text{HCO}_3^-$ ,  $\text{Na}^+$ , urea - will readily diffuse through capillaries in skeletal muscle. Therefore, a chemical gradient is unlikely to exist.

Proteins are generally excluded from exiting the capillary. Their exclusion is due to both size of the molecule and charge of the molecule. Proteins are generally negatively charged and the pores of the capillaries are also negatively charged.

Albumin is the most abundant serum protein. These negatively charged proteins exert an osmotic (oncotic) force. That is they attract and hold water. Under normal circumstances then, proteins in the capillary circulation are a primary factor in driving reabsorption and thus prevent too much fluid from leaving the circulation through filtration. Loss of these proteins results in loss of fluid.

**Starling Forces:**

There are **four forces** that drive bulk flow - two that favor filtration and two that favor reabsorption. It is the balance of these forces that will ultimately decide whether fluid has a net loss from the circulation or is retained within the circulation.



#### **Starling Forces that Favor Filtration:**

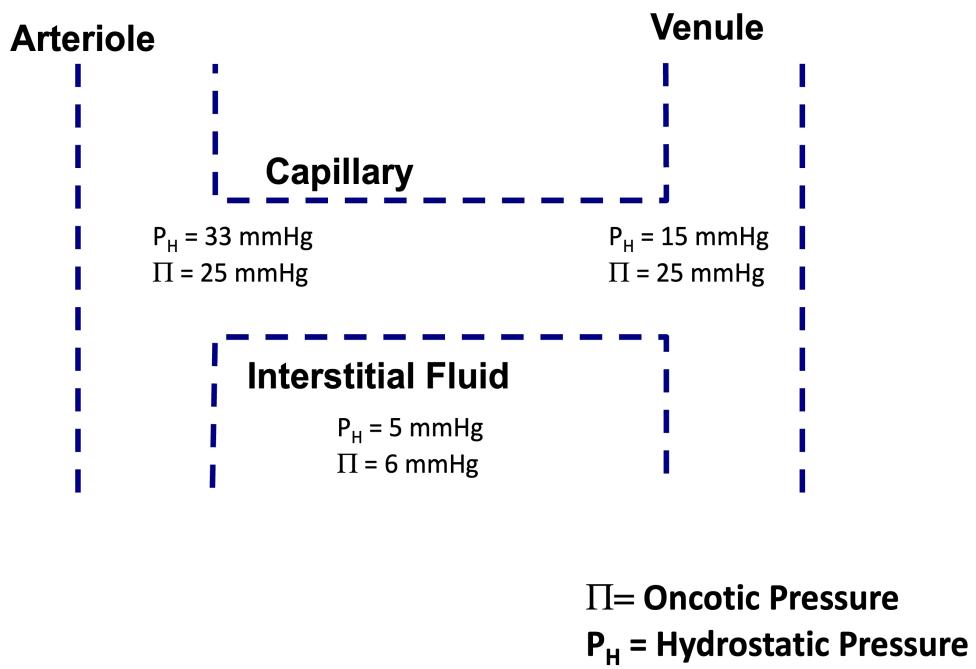
- **Capillary Hydrostatic Pressure:** is simply the force that occurs due to blood pressure within the capillary that tends to drive (push) fluid outward and through the endothelial pores. (There are other meanings ascribed to "hydrostatic pressure". We have picked this usage because it is the usage in Berne & Levy and your Internal Medicine texts.)
- **Interstitial Fluid Oncotic Pressure:** The word oncotic is used to describe the osmotic effect due to capillary protein. Oncotic pressure then is simply a colligative property. In this case - we are describing the influence of proteins which are present in the interstitium - their osmotic tendency to pull fluid out to the interstitium from within the capillaries.

#### **Starling Forces that Favor Reabsorption:**

- **Capillary Oncotic Pressure:** This is the same type of pressure described above; only fluid movement is in the opposite direction. So, capillary oncotic pressure is the osmotic driving force - due to

the presence of proteins inside the capillary - and tends to retain fluid within the capillary and pull fluids from outside the capillary into the lumen the capillary.

- **Interstitial Fluid Hydrostatic Pressure:** This is equivalent to its counterpart described above, only movement occurs in the opposite direction. This force tends to push fluid back into the capillary. (For this discussion, we are assuming that interstitial fluid pressure is positive. The magnitude and the sign of the pressure is still hotly debated. )

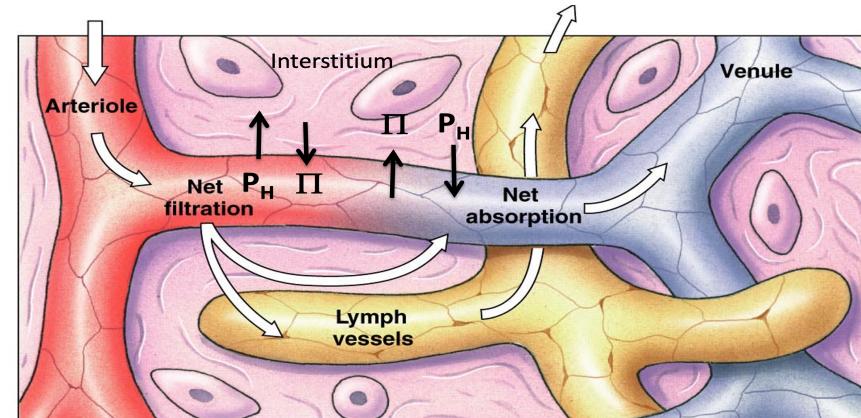


#### The Starling Hypothesis:

According to the Starling Hypothesis, if all four forces are summed, the net direction of fluid movement can be determined. The example in the above diagram is as follows:

1. Blood flow occurs from the arteriole through the capillary and into the venule. The pressure of the blood in the arteriole and entering the capillary is 33 mmHg. This pressure is the capillary hydrostatic pressure.
2. As blood passes through the capillary, there is a pressure drop. The inlet pressure is 33 mm Hg and the outlet pressure is 15 mm Hg.
3. The protein concentration in the blood is such that it is equivalent to 25 mm Hg. This value is the capillary oncotic pressure.
4. The interstitial hydrostatic pressure is given as 5 mm Hg and the interstitial oncotic pressure is given as 6 mm Hg.
5. The diagram below shows the arithmetic for balancing the forces and determining flow.

6. The forces that favor and oppose filtration are listed and summed for the arterial side. Notice that there will be a net filtration on the arterial side.
7. On the venous side, notice that the overall force will favor reabsorption.
8. Overall, the fluid that is filtered on the arterial side will be reabsorbed on the venous end.



$\Pi$  = Oncotic Pressure

$P_H$  = Hydrostatic Pressure

Silverthorn, Human Physiology, 4<sup>th</sup> Ed.

### Arterial Side of Capillary

Forces Favoring Filtration

$$\begin{array}{r} P_H = 33 \text{ mmHg} \\ \Pi = 6 \text{ mmHg} \\ \hline 39 \text{ mmHg} \end{array}$$

Forces Favoring Reabsorption

$$\begin{array}{r} P_H = 5 \text{ mmHg} \\ \Pi = 25 \text{ mmHg} \\ \hline 30 \text{ mmHg} \end{array}$$

### Venous Side of Capillary

Forces Favoring Reabsorption

$$\begin{array}{r} P_H = 5 \text{ mmHg} \\ \Pi = 25 \text{ mmHg} \\ \hline 30 \text{ mmHg} \end{array}$$

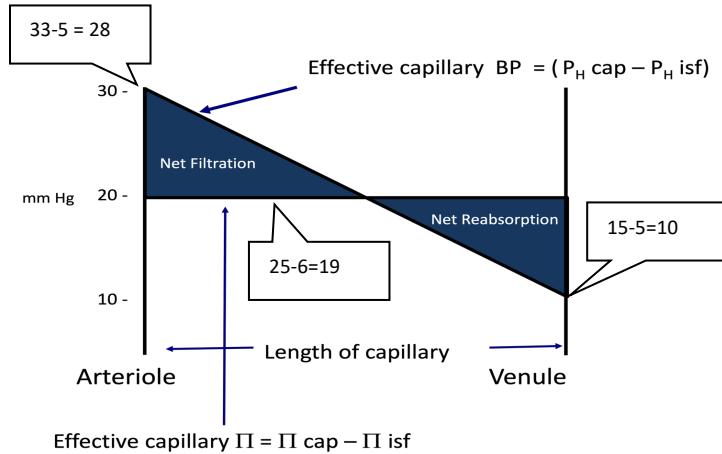
Forces Favoring Filtration

$$\begin{array}{r} P_H = 15 \text{ mmHg} \\ \Pi = 6 \text{ mmHg} \\ \hline 21 \text{ mmHg} \end{array}$$

$$\text{Net Filtration Pressure} = 39 - 30 = 9 \text{ mmHg}$$

$$\text{Net Reabsorption Pressure} = 30 - 21 = 9 \text{ mmHg}$$

## VII. Effective Capillary Pressure



The diagram at the left represents an alternative method for analysis. In this case we calculate the effective capillary pressures as follows.

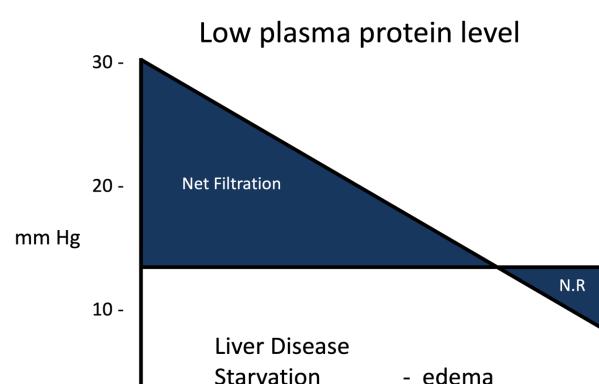
The first line running at a negative slope is called the **Effective Capillary Blood Pressure**. To arrive at the point on the left, we subtract interstitial hydrostatic pressure (5mmHg) from arterial side hydrostatic pressure (33 mmHg) = 28 mmHg

To arrive at the point on the right, we subtract interstitial hydrostatic pressure (5 mmHg) from venule capillary pressure (15 mmHg). This line represents the forces that favor filtration (10 mmHg).

The horizontal line is termed **Effective Capillary Oncotic Pressure**. To arrive at this, we subtract oncotic pressure of the interstitial fluid (6 mmHg) from the oncotic pressure (25 mmHg) within the capillary. = 19 mmHg

Presentation of the data in this fashion readily lends itself to analysis. On the left side, notice that Effective Capillary Blood Pressure (forces favoring filtration) are greater than Effective Capillary Oncotic Pressure (forces favoring reabsorption) - so there will be a net filtration. On the right side, the reverse holds true, so there will be a net reabsorption of fluid. Thus, fluid that was lost from the capillary by filtration is regained by the capillary by reabsorption. So, filtration & reabsorption are approximately balanced. In actuality, filtration slightly exceeds reabsorption with the excess interstitial fluid being picked up by the lymphatics.

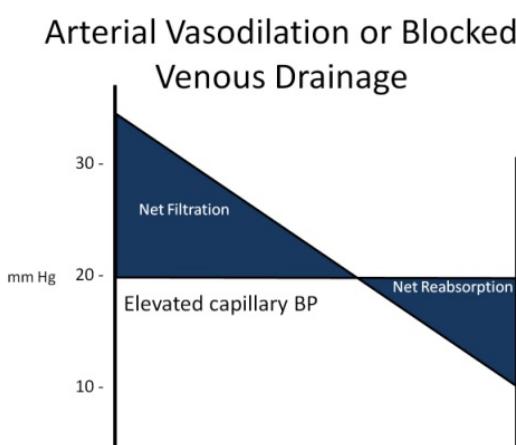
### VIII. Pathological Conditions that Change Effective Capillary Pressure



The patient has a liver disorder (i.e. cirrhosis) in which the production of plasma proteins is diminished.

The Effective Capillary Oncotic Pressure (oncotic pressure of the capillary - oncotic pressure of the interstitium) will be reduced (downward shift on the above graph). Effective Capillary Blood Pressure remains the same as previously.

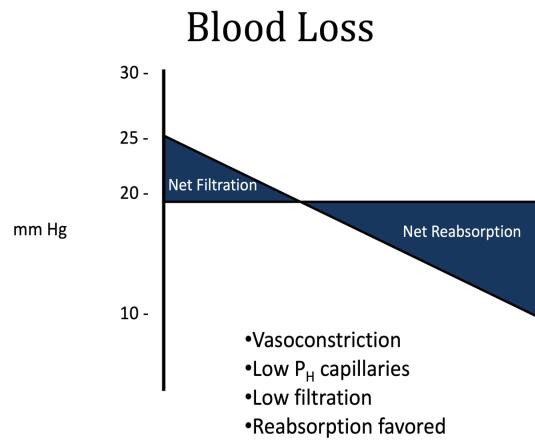
Notice that there is more filtration and less reabsorption in comparison to the previous curve. The net effect may be edema - depending upon the ability of the lymphatics to pick up the extra fluid.



There are a number of other events that can lead to a greater net filtration vs. net reabsorption and thus lead to edema. This situation is usually driven by an elevation capillary blood pressure that can occur via one of two mechanisms - vasodilation & obstruction in the circulation.

Vasodilation - recall that in vasodilation, blood will enter the capillary at higher pressure. This will create a situation in which capillary blood pressure is excessively elevated with resultant edema.

Obstruction - such as a venous blood clot will cause the back up of pressure and hence an increase in pressure. Notice in the diagram that filtration will greatly exceed reabsorption.



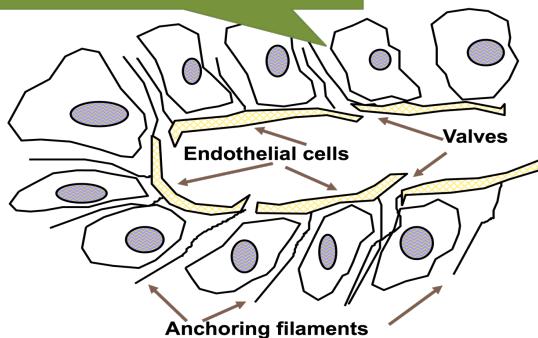
Capillary fluid dynamics change in response to **blood loss** either by donating blood or hemorrhaging. The extent of the change depends on the magnitude of the loss. For example if a modest amount of blood is lost during blood donation, if blood pressure is measured both before and after blood loss - it will more than likely be the same. One reason that pre- and post- blood pressures will remain the same is vasoconstriction will occur (see blood pressure regulation). Vasoconstriction of the arterioles results in decreased capillary blood pressure because less

flow reaches the inlet of the capillary. The net effect is that reabsorption increases. So, the blood loss will be replaced by interstitial fluid. If blood loss is extensive, however, these compensatory mechanisms can become overwhelmed and the drop in hydrostatic capillary pressure can become greater than the capability of fluid to be reabsorbed from the interstitium, resulting in loss in systemic blood pressure.

## IX. Edema

In relation to the circulation, the function of the lymphatics is to take up differential excess between filtration and absorption and return these fluids (and proteins at times) to the central circulation. Generally net filtration exceeds net reabsorption by a small amount, and this difference is taken up by the lymphatic circulation. If the lymphatics are able to perform this task adequately, no edema will result. However, edema will result if interstitial fluid accumulation exceeds uptake by the lymphatics.

Interstitial fluid accumulation opens up lymphatic valves and promotes uptake of fluid.



The structure of the lymphatics is ideally suited for this task. Lymph vessels are much like veins in that they have a very fine layer of smooth muscle which contracts to help propel fluid back toward the central circulation as well as one-way valves that promote unidirectional flow. The lymph vessels contain anchoring filaments which form bridged attachments between endothelial cells and the interstitium. As fluid accumulates within the interstitium this moves apart and naturally opens up the valves that lie between the endothelial cells that comprise the lymphatic vessels. The lymphatic

circulation thus takes up this fluid. If the rate of interstitial fluid accumulation outstrips the rate at which the lymphatics take up the fluid, accumulation of fluid and thus edema will occur. This is why manual massage and manipulation is quite effective at helping clear edematous fluid formation – you are mechanically promoting the clearing of fluid by the lymphatic circulation.

There are a number of circumstances in which edematous fluid formation is promoted. Note that nearly all of these relate to a change one of the four Starling forces that influence capillary fluid dynamics.

### Reduction in plasma proteins.

- This increases filtration and reduces reabsorption.

### Increased capillary hydrostatic pressure.

- Venous clots.
- CHF – fluid backs up in capillary beds – pulmonary edema.
- Vasodilation – arterioles dilate, influx of fluid at capillaries.

### Increased protein permeability in post capillary venules.

- Increases filtration and reduces reabsorption.
- Burns, injury, trauma etc.