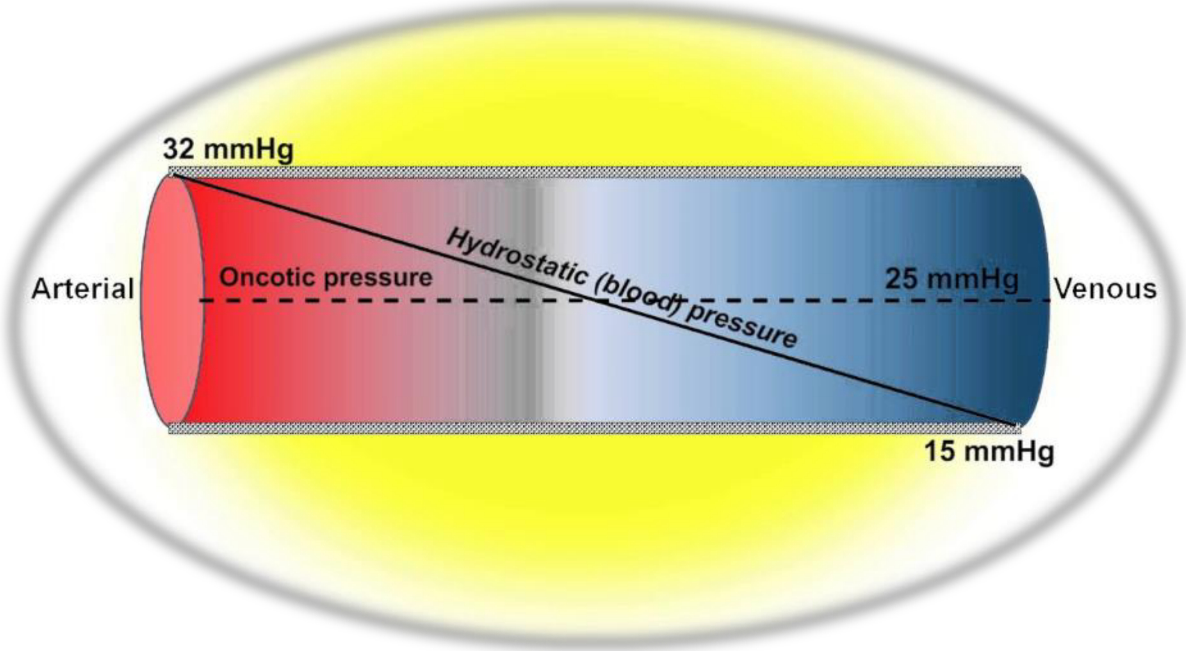
Introduction to Physiology

Final Exam Material

Dr. Yanal Shafagoj

Lecture 4

"Microcirculation and Edema"



Comprehensive File

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What are the factors that lead to formation of edema?

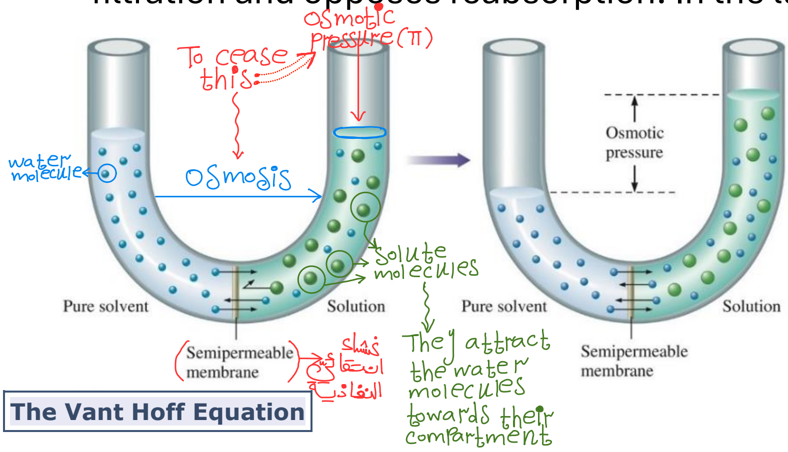
In this lecture we will continue talking about the 4 starling forces.

A) Hydrostatic pressures (due to fluid volume):

1. Blood hydrostatic pressure (BHP or P_c) is a force which favors filtration and opposes reabsorption.
2. Interstitial fluid hydrostatic pressure (IFHP or P_{IF}) is a force which opposes filtration and favors reabsorption. This is true if P_{IF} is +ve such as in Bowman's capsule in the kidney, but if it is -ve it will favor filtration such as in the lung.

B) Colloid Osmotic pressures (due to presence of large proteins such as albumin and globulin):

3. Blood colloid osmotic pressure (BCOP or Π_c) is a force which opposes filtration and favors reabsorption.
4. Interstitial fluid osmotic pressure (IFOP or Π_{IF}) is a force which favors filtration and opposes reabsorption. In the lungs, it is 14 mmHg.



As we studied earlier, this figure shows that water moves to the compartment with higher osmolarity. Π is the required pressure to stop the movement of water.

The osmolarity depends on the # of particles and not the size.

The osmosis depends on the numebr of solute molecules and not their sizes (differnet sizes for the same number of molecules give the same effect of attraction water molecules

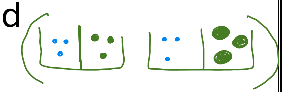
The Vant Hoff Equation

Osmotic pressure = n x (c/M) x RT

The osmotic pressure (Π; capital π) is determined by 5 factors:

$$\Pi = \sigma nRTC$$

σ: reflection constant; ranges *from* 0 *to* 1; how much it is reflected



0 → completely permeable (not reflected from the membrane)

1 → impermeable (totally reflected)

n: dissociation constant; the # of particles resulting from the dissociation

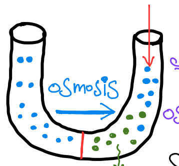
for glucose (not ionic), n=1; for NaCl, n=2; for $CaCl_2$, n=3…

NaCl 2 particles Ca^{+2} $2Cl^-$

R: ideal gas constant

T: absolute temperature (in Kelvin)

C: molar concentration (before dissociation if present)



1 mOsm/L (of any plasma protein) yields 19.3 mmHg of osmotic pressure.

Total concentration of proteins in the plasma is 6 – 8 g/dL.

The blood colloid osmotic pressure in the capillary ≈ 28 mmHg.

We refer to proteins when talking about Π since they have very low permeability (very high σ) → strong effect on Π. Other particles such as ions (Na^+, K^+, Cl^-, Ca^{2+}...) and small molecules such as glucose do not contribute to Π due to their equal concentrations on both sides of the capillary wall.

The osmotic pressure in blood plasma is determined mainly by 2 proteins:

Protein	Concentration in capillaries	Molecular weight	Contribution to Π_c
Albumin	3.5 – 5.5 g/dL	69,000 g/mol	22 mmHg
Globulin	2 – 4 g/dL	150,000 – 200,000 g/mol	6 mmHg

Albumin is more important than globulin for Π_c due to 2 reasons:

1. Higher concentration
2. Lower molecular weight → more particles for a given mass.

Because albumin is the dominant factor in determining Π, the osmotic pressure grows linearly with the concentration of albumin, but after a critical concentration, a small change in albumin concentration will yield a huge change in Π.

X-axis: Albumin concentration; Y-axis: Osmotic pressure.

Red: Expected osmotic pressure after critical concentration – linear.

Blue: Real osmotic pressure after critical concentration – non-linear.

It is believed that after this critical concentration albumin (due to its negative charge) will attract cations leading to increased particles and thus increased osmolarity → increased Π.

Suppose the albumin concentration is 4 g/dL which is equal to 40 g/L.

Let's calculate the molarity.

$$Molarity\ [\frac{mol}{L}] = \frac{concentration\ [\frac{g}{L}]}{molecular\ weight\ [\frac{g}{mol}]}$$

$$= \frac{40\,\frac{g}{L}}{70{,}000\,\frac{g}{mol}} = 0.0006\,\frac{mol}{L} = 0.6\,\frac{mmol}{L}$$

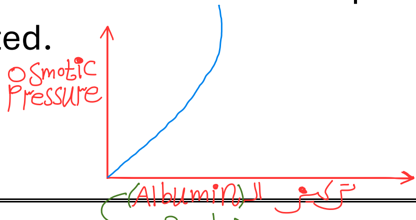
Since albumin does not dissociate, the osmolarity will be equal to the molarity. So, the albumin osmolarity is 0.6 mOsm/L.

As mentioned before, each mOsm/L yields 19.3 mmHg of Π.

Theoretically, 0.6 mOsm/L will yield about 12 mmHg.

This contradicts the data in the table above which is 22 mmHg.

As we said before, the relation between Π and the concentration of albumin is not linear but shifts upward after a critical concentration. This explains why we have a higher value for Π than expected.



Capillary exchange

Almost all fluid in the interstitium is in the form of gel (fluid proteoglycan mixtures); there is very little free fluid under normal conditions.

There are 3 ways by which capillary exchange – movement of substances between blood and ISF – occurs.

1. Diffusion (most important for solute exchange):

Diffusion is the random movement of particles, and net diffusion is determined by the concentration gradient (higher to lower).

O_2 and essential nutrients move: blood in capillaries → ISF → body cells.

CO_2 and wastes move: body cells → ISF → blood in capillaries.

In the blood-brain barrier, tight junctions limit diffusion.

In general, large molecules such as proteins cannot cross the capillaries.

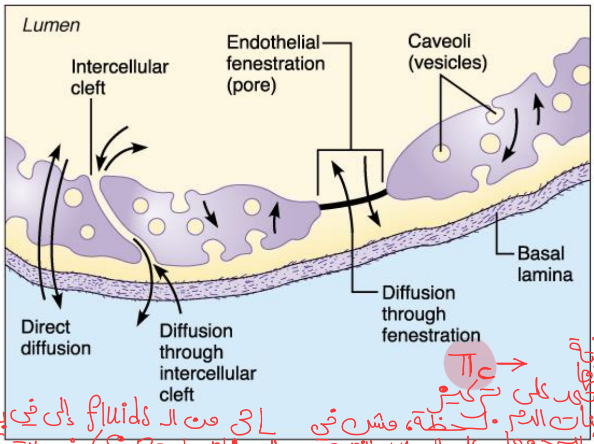
In some places, sinusoids, proteins and even blood cells can cross the capillaries.

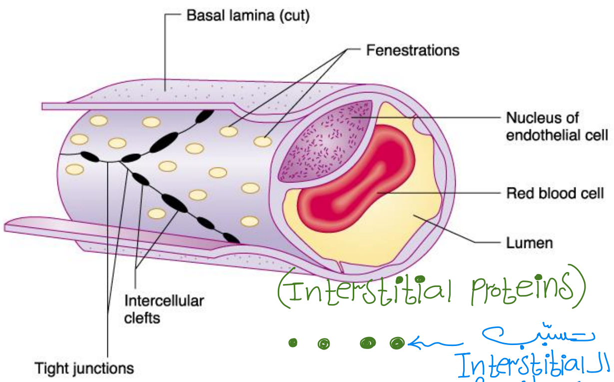
2. Transcytosis:

It is the transport of large molecules that cannot cross capillary walls, and it uses both endocytosis (on one end) and exocytosis (on the other end).

3. Bulk flow (or simply flow; most important for regulation of relative volumes of blood and the ISF):
   a. Passive process in which large numbers of ions, molecules, or particles in a fluid move together in the same direction.
   b. Based on pressure gradient (starling forces).

In general, solutes and water move across capillary wall via intercellular cleft (space between cells) or through fenestrations (pores in the endothelial lining of the capillaries) or by plasmalemma vesicles in transcytosis.





Interstitial protein concentration is different among different tissues. In muscles 1.5 g/dL, subcutaneous 2 g/dL, intestines 4 g/dL and in liver 6 g/dL.

75% of the total colloid osmotic pressure of plasma results from the presence of *albumin* and 25% is due to *globulins*.

Flow

The **flow** of fluids is determined by the sum of the 4 starling forces:

NFP (net filtration pressure) = filtration forces – reabsorption forces

$$Flow = [(filtration\ forces) - (reabsorption\ forces)] * K$$

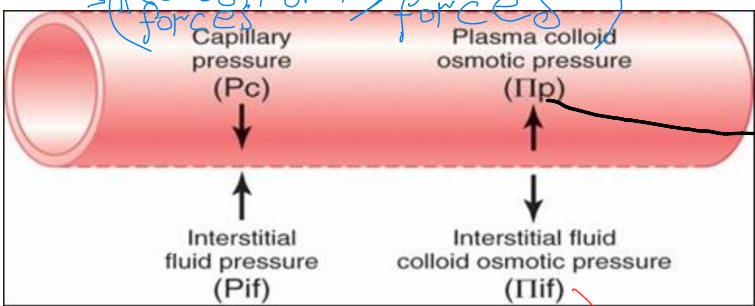
$$Flow = [(P_c + \Pi_{IF}) - (P_{IF} + \Pi_c)] * K; K\ is\ the\ permeability$$

Refer to the top of page 1 for the definitions of the 4 forces.

Since we are using NFP, the following sign convention must be used:

If the flow is positive → filtration occurs.

If the flow is negative → reabsorption occurs.



Starling's Law

3 of the 4 forces usually have constant values along the capillary, however P_c has a varying value depending on the location along the capillary.

On the arterial end of the capillary, P_c is high (say 40 mmHg), and on the venous end, P_c is lower (say 20 mmHg).

On the arterial end, the sum of forces favoring filtration is higher than the ones favoring reabsorption due to the high value of P_c and thus filtration occurs (positive value for the flow in the equation).

On the venous end, the sum of forces favoring filtration becomes lower than the ones favoring reabsorption due to the relatively lower value for P_c and thus reabsorption occurs (negative flow).

This explains the behavior of ideal capillaries (such as in skeletal muscles).

About 85% of the fluid filtered at the arterial end is reabsorbed at the venous end.

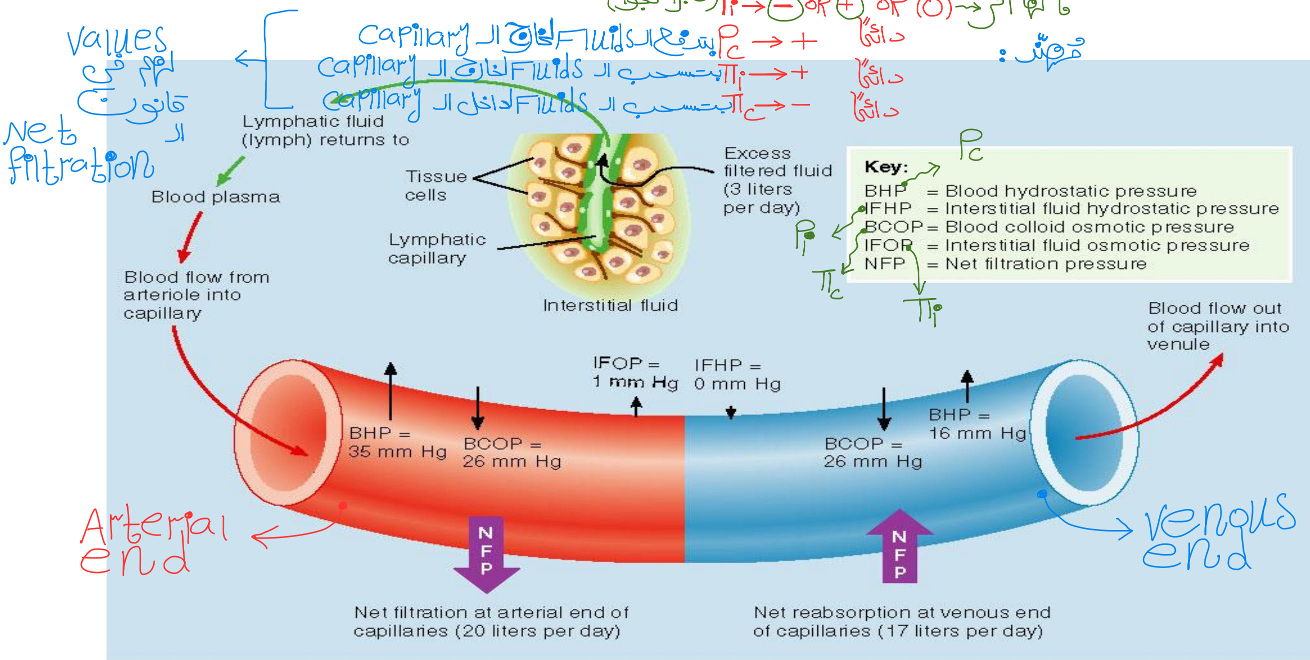
The leftover (15%) enters lymphatic capillaries to return to the blood.

P_{IF} (Interstitial fluid hydrostatic pressure) is usually close to zero (negligible) and could be slightly negative due to pumping of the lymphatic system.

Encapsulated organs have positive P_{IF} values.

When it is negative, P_{IF} favors filtration instead of reabsorption.

Quantitative example:



Net filtration pressure (NFP) = (BHP + IFOP) − (BCOP + IFHP)

	Pressures promoting filtration	Pressures promoting reabsorption
	Arterial end	**Venous end**
	NFP = (35 + 1) – (26 + 0) = 10 mm Hg	NFP = (16 + 1) – (26 + 0) = – 9 mm Hg
Result	Net filtration	Net reabsorption

As we can see, net filtration pressure at the arterial end is +10 mmHg while net filtration pressure at the venous end is -9 mmHg (reabsorption occurs at the venous end because the NFP is negative).

The net force is [(+10) + (-9)] = +1 which means that net filtration occurs.

Note: pressure values may differ according to tissue type.

Another example:

Mean forces tending to move fluid outward (filtration):	
Mean Capillary pressure	17.3
Negative interstitial free fluid pressure	3.0
Interstitial fluid colloid osmotic pressure	8.0
Total outward force	28.3
Mean force tending to move fluid inward (reabsorption):	
Plasma colloid osmotic pressure	28.0
Total inward force	28.0
Summation of mean forces:	
Outward	28.3
Inward	28.0
Net force	+0.3 (outward; filtration)

In this example, we used the mean value for P_c between the arterial and venous ends. This calculation gives us the net force in one step instead of calculating the net force for each side then adding both values.

Since the net force is positive, we have net filtration occurring.

To calculate the flow, we multiply the net force (+0.3 mmHg) by the permeability (K).

Experimentally, the net filtration rate is calculated to be **3 L/day** which we have discussed in the previous lecture as the filtered fluid flow (20 L/day) minus the reabsorbed fluid flow (17 L/day).

Causes of Edema

1) Increased P_c.

Ventricular failure (right or left) causing excess fluids in the blood.

2) Decreased Π_c.

The normal albumin concentration range is from 3.5 – 5.5 g/dL.

If it falls below 3.5 g/dL → hypoalbuminemia.

If it rises above 5.5 g/dL → hyperalbuminemia.

One of the causes of edema is hypoalbuminemia which is caused by the low concentration of albumin in the plasma.

This leads to decreased Π_c causing more filtration.

Causes of hypoalbuminemia:

a. Malnutrition (low intake).
b. Malabsorption in intestines (low absorption).
c. Increased loss of albumin from the body in kidneys.
d. Insufficient production of albumin by the liver.

3) Lymphatic capillary blockage:

Excess interstitial fluids are not absorbed by lymphatic capillaries.

This causes the accumulation of fluids in the interstitial space → edema.

4) Leaking capillary wall:

Increase in the permeability (K) which can be caused by the release of histamine during allergic reaction such as after a bee sting.

Most of the interstitial fluid exists in a gel-like state, with a small percentage as free fluid. The amount of free fluid increases in conditions like pitting edema. Non-pitting edema occurs when cells swell, reducing the amount of free fluid, or when fluid clots with fibrinogen (a plasma protein), preventing it from moving freely.