Doctor 022

Physiology

Modified no.

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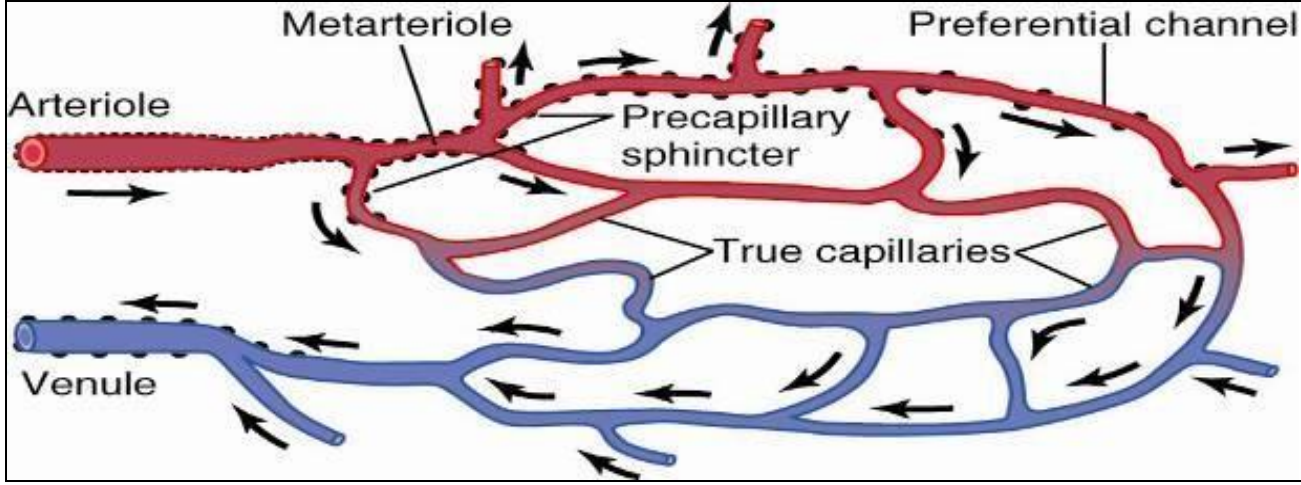
Overall Objectives

- Microcirculation is part of the cardiovascular system which composed of the heart and the circulatory system (the blood vessels), the main function of the cardiovascular system is to provide supplement (oxygen, nutrients)into the cells and also to get rid of wast products and CO2 from the cells to the organs that responsible for elimination of these wastes that’s the most important function of the cardiovascular system.
- As we said the cardiovascular system is composed of the heart which is a pump that pumps the blood that carries these supplies , and from blood vessels which are the tubules in which the blood is carried to reach the tissues or the cells

- The types of the blood vessels:
- Large arteries, Connected to the heart, (conducting arteries)
- Smaller arteries (connecting arteries)
- Arterioles (smaller in diameter but they have more smooth muscle cells. the activity of these cells changes the diameter to a large extent. The smooth muscle cells in the arteriols when they contract there will be large constriction for these cells so the diameter will change drastically. if they relax, they will largely dilate, so the diameter could be wide or extremely constructed to almost closed.)
- Capillaries (they characterized that they are *consist of only* single layer of endothelial cells without the smooth muscles layer they rest on basement membrane only (like chair). If we return to their function, we will find that they are the site of exchange between blood , the interstitium and the cells. so having only single layer it serves the function (it facilitates easier exchange)).so single layer provides easier exchange between the blood inside the capillaries and the outside that is why they are the main site of exchange (capillaries).
- Part of the basement membrane is usually ECM , but mostly it consist of fibers (collagen fibers, actin fibers and other fibers and usually negatively charged) proteoglycans consist of hyaluronic acid.

- The basement membrane isn't an insulator layer , it is fibrous and the proteoglycans is like gelly .so the basement membrane only forms a simple coat of gelly and provides an attachment site for cells to be more stable ,but it isn't an insulator or large barrier it is simple barrier.
- The microcirulation mainly consists of capillaries but it attaches to arterioles from one side and vunules from the other.
- (the microcirculation is referred to the capillaries and the arterioles that's the nearest to the capillaries)).
- Know the structure and function of the microcirculation
- Know how solutes and fluids are exchanged in capillaries
- Know what determines net fluid movement across capillaries

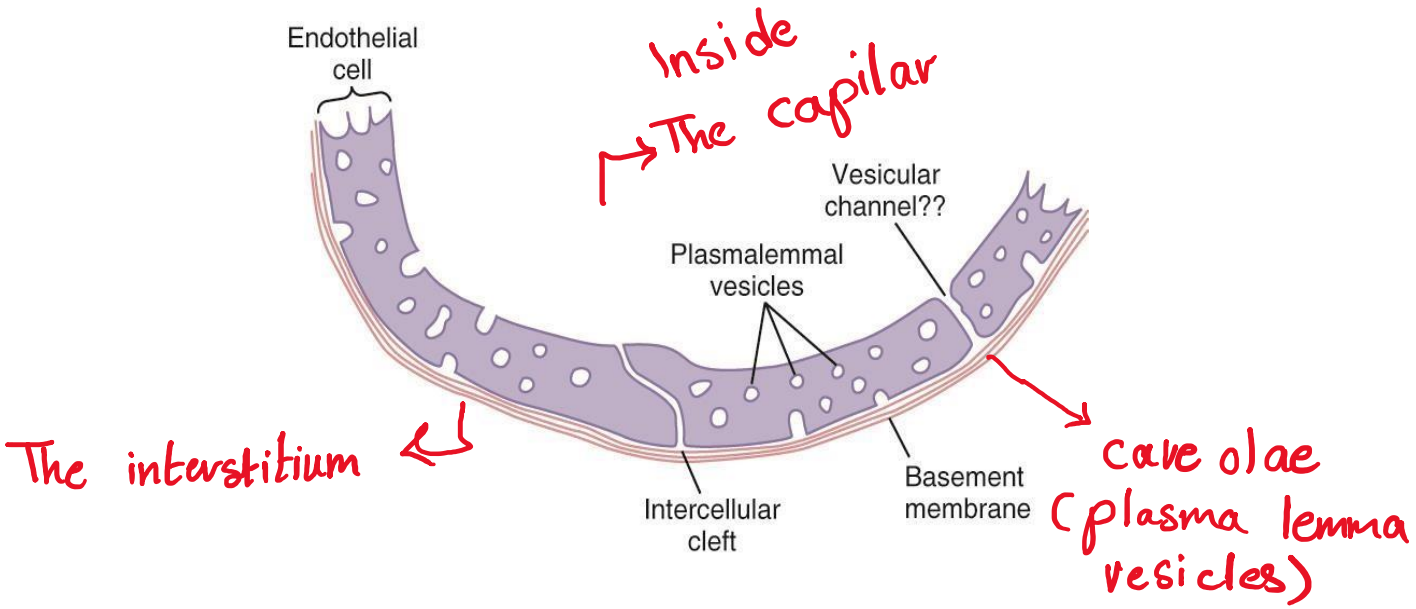
- Important in the transport of nutrients to tissues
- Site of waste product removal
- Over 10 billion capillaries with surface area of 500-700 square meters perform function of solute and fluid exchange



- As you can see at the picture: we have the blood coming from the heart through the arteries then it reaches the arterioles. the arterioles (بيطلع منها) capillaries which are the ones that don't have smooth muscle.if it has smooth muscle ,it is still arterioles.
- (The arterioles have smooth muscle and the capillaries don't have smooth muscle)
- The last part of the arterioles that connects to the capillary it is called meta arterioles .the meta arterioles consist of areas that have large number of smooth muscles (like rings around the vessel(the meta arterioles)) that smooth muscles when it is contracted ,it narrows the vessel (it might close the vessel) so it prevents the blood from reaching (it reduces the blood flow into the capillaries) that will form a sphincter that's called precapillary sphincters (found on the meta arterioles).because they open and close just like the sphincter found on the top of the stomach (it opens when we eat and closes after that to prevent the gastric juice from returning to the oesophagus.if it is relaxed, the gastric juice will return to the oesophagus

- and you will feel heartburn (it is called reflux because the sphincter doesn't work properly (relaxed)).so the sphincter is like the tap (faucet) either you close it so you cease (stop) the flow of water , you open a little bit of it (weak flow) or you fully open it (strong or great flow of water) so it depends the knob .
- So these sphincters control how much flow is going to pass through these rings or these precapillary sphincters so they determine how much flow inside the capillaries. These sphincters is controlled by the local tissue's needs(if the tissue needs oxygen and glucose , they open.and if the tissue doesn't need them or it has low metabolic activity they close).there are factors that make these sphincters open when there's high activity and close in the case of low activity (the tissue doesn't need oxygen and glucose). **So according to the metabolic demands of the tissue the local circulation (the circulation inside the microcirculation it is called local circulation) is controlled. So the blood flow inside the local circulation is controlled according to tissues' or cells' requirements and needs (**tightly

- controlled to tissue's needs ,don't give more or less than the needs there is matching between the needs and the flow that is going to be inside .for example: if someone is running ,the muscles of the sphincters are opened.why ?because the muscle is utilising(consuming) oxygen and high glucose so it needs higher blood ,but if you were at rest (sleeping) ,will the sphincters be relaxed ?no ,the blood flow will be very low in the microcirculation of the muscles in your leg (for example).why ? Because of the low demands .
- So if we want to see the number of capillaries, there will be large number of this kind of blood vessels . The surface area of these capillaries(that almost equal eighth of football field's area in the human body)that is prepared for transport.even though they are micro ,but because of their large number they give large surface area available for transport (exchange).so this serves the function(to facilitate efficient exchange)of the capillaries.



- Composed of unicellular layer of endothelial cells surrounded by a basement membrane
- Diameter of capillaries is 4 to 9 microns
- (that is why is called micro circulation.why? Because its size is in micrometers)
- Solute and water move across capillary wall via *intercellular cleft* (space between cells) or by *plasmalemma vesicles (Caveolae)*
- If we took the cross section of the capillaries ,we would see single layer of cells resting at the basement membrane .if a substance moves from the blood to the interstitium , it will move across the capillary's wall .it has two choices either it moves through the space between the cells which is the intercellular cleft (between two endothelial cells).(a fluids and a substances dissolved in these fluids can pass through this cleft and it will move from inside the vessel to outside the vessel via the intercellular cleft) or the substances can be transported by pinocytosis and endocytosis (vacuoles or vesicles evacuate its contents into the interstitium) (transcellular across the cell itself).sometimes the vacuoles might be close to each other (بيفتحوا على بعض) and form a channel

- (a number of vacuoles next to each other) .a channel for substances to be transferred directly from inside the vessel to outside it (there is a theory that says a channels consist of vacuoles might be there).these vacuoles are called caveolae or plasma lemma vesicles.
- The solutes dissolved in water are mainly transported either via the intercellular clefts or via the caveolae .why? Because the water doesn't like to pass through the phospholipid .so it needs either aquaporin (the aquaporins (channels) don't give efficient transport because it has limited number)or intercellular clefts which are found between all the cells (the wall of the capillaries is consist of huge numbers of cells).the intercellular clefts give better option for water and solute to be transported .

Solute and Fluid Exchange Across Capillaries

- Most important means by which substances (specially lipids insoluble substances)are transferred between plasma and interstitial
- fluid is by *diffusion*
- *(Bulk diffusion)*
- *Lipid soluble* substances diffuse directly through cell membrane of capillaries (I.E.CO2, O2) (more rapidly) (steroids , short fatty acids and lipid soluble vitamins)
- *Lipid insoluble* substances such as H2O(polar), Na, Cl, glucose(large polar) and ions cross capillary walls via intercellular clefts (80 times more than bld flow in cap) (bulk diffusion)
- *Concentration differences* across capillary enhances diffusion (only slight is enough)
- The bulk diffusion (the total diffusion via the clefts) : large amounts (like the flood from side to side or like the water coming out of strainer(مُنْخُل) *is called bulk flow).*

- The lipid soluble substances is transferred by simple diffusion (because it have all the length of membrane (the whole area of plasma membrane not only the intercellular clefts) to move from anywhere on the membrane that's why the lipid soluble substances have the highest rate of diffusion .
- Is it important to have concentration gradient for substances that are going to be transported? Even by diffusion?yes, a simple gradient must be there for (glucose ,urea) to move down the gradient .so the gradient is important even oxygen , now the oxygen will move even though it is soluble and the paths are all available for it, but there must be (gradient), the oxygen must be inside the blood vessel higher than the outside of it so it can move from inside the blood vessel to the outside of it. But the slight gradient is enough, only the slight gradient because of the high surface area so it is enough.

Effect of Molecular Size on Passage Through Capillary Pores

- The *width of capillary intercellular slit* pores is 6 to 7 nanometers
- Now the intercellular cleft, does it have a specific size? or is it big to the point that the size doesn't matter? It has a specific size, so, moving the substances through the intercellular clefts is limited to the size of molecules , okay maybe the substance can be moved with the water through the intercellular cleft but if the size of it was bigger than the cleft, will it move? No. Then there is a limitation in the size.
- But some capillaries have a bigger size , and some capillaries have a smaller size, it depends on the type of the capillary and the tissue. The capillaries are types. So the permeability of the capillaries with different tissues or organs differs. For example,in the brain , we know that in the brain, there is something called blood brain barrier (The capillaries in the brain have something on it like a ceil , there are cells that surround it from central nervous system in a way that they cover the clefts. Okay? And the clefts are so tight and don't allow for any substance to get in, so there is a selectivity in the substances , like there is a guard that specifies if a substance could come from the blood and enter the brain cells or could

- not ? We call this blood brain barrier, this is a type of protection to the brain, not every substance that entered the blood or a drug can enter the brain immediately.
- The testicles also have a barrier.
- In the liver it is the opposite, the capillaries have large number of vacuoles .So these vacuoles are also found in the basement membrane .so in the liver there are wide clefts, pores on the cell (on the membrane itself) and there are also
- Pores in the basement membrane so it allows larger molecules and even a cell can pass through these capillaries that found in the liver and it's called sinusoid.it also found in the bone marrow.
- The capillaries in the kidney are called glomerular capillaries which have higher permeability than the classical ones found in the tissues like skin ,muscles and guts, but it is lower than

- the sinusoid.they allowed higher filtration than the filtration occurs in any normal capillary bed in the body .why ?because the filtration of blood is the function of the kidney so the filtrations must be more efficient than the filtration in the muscle tissue or in the guts or in any normal tissue.
- The *permeability* of the capillary pores for different substances varies according to their *molecular diameters*
- The capillaries in different tissues have *extreme differences* in their permeabilities (brain, liver, kidney)

Relative Permeability of Muscle Capillary Pores to Different-sized Molecules

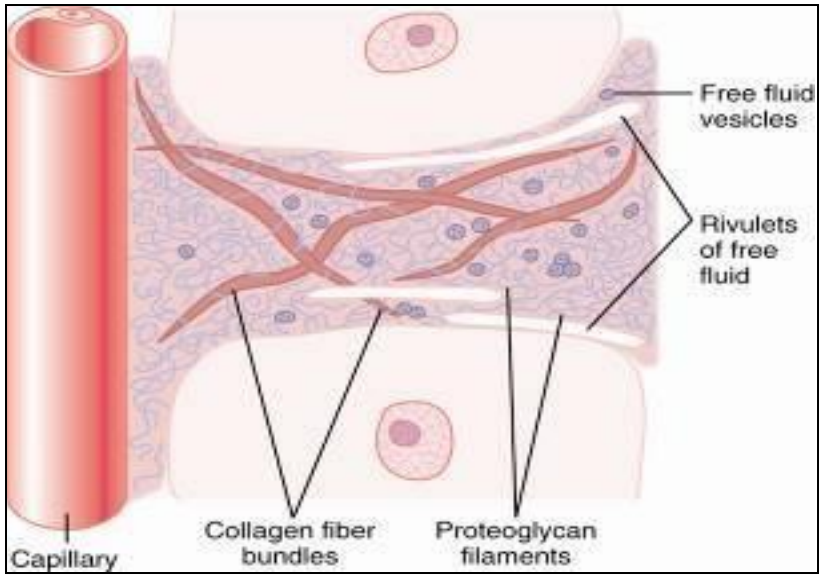
Water	**18**	**1.00**
NaCl (less than one)	**58.5**	0.96
Urgent (less than one)	**60**	0.8
Glucose (much less than one)	**180**	0.6
(Almost half)		
Sucrose (less than half)	**342**	0.4
Insulin (¼)	**5000**	0.2
Myoglobin	**17,600**	0.03
Hemoglobin (lower negative charge)	**69,000**	0.01
Albumin (higher negative charge	**69,000**	.0001

- **If we look at one type of the capillaries and at the substances that is going to be transferred via the intercellular cleft (mainly lipid insoluble).the water is the best transported substance via the intercellular cleft so we give its permeability one .any other substance's permeability will be in relation to water .**
- At the second column we have the molecular weight.
- **As the molecular weight increases, the permeability decreases.**
- so as the size increases the harder it gets for these substances to be transported via the intercellular cleft.
- Hemoglobin and albumin have the same molecular weight ,but different permeability.why? Because of the charge . The basement membrane is negatively charged so the substance that has higher negative charge (albumin)repulses with the basement Membrane and don't pass through (more difficulty).so the charge is also an important factor **,the more negative charges in the molecule the harder it becomes to pass through basement membrane .the more neutral, more positive charges the easier it becomes.** So the size and the charge together are important factors.
- Not important: when a more positive substance pass through the basement membrane it will be attracted to it ,but it can pass because it is dissolved in fluid.

Interstitium and Interstitial Fluid

➢Space between cells is called interstitium;fluid in this space is called interstitial fluid .

➢Two major types of solid structures in interstitium Are collagen fibres and proteoglycan filaments (coiled molecules composed of hyaluronic acid)



- Almost all fluid in interstitium is in form of *ge*l (fluid proteoglycan mixtures); there is very little
- free fluid under normal conditions
- If we look at the composition of the interstitium :
- In the interstitium there is a lots of fibers (collagen fibers) and proteoglycans which are type of carbohydrates these proteoglycan absorb the water

- ال proteoglycans بتمتص الماء وبتعمل زي ال polymerisation الي بصير لل gelly،لما تعملوا gelly بتجيبوا مي بتخلطوها مع ال gelly powder بكون monomersبعدين بصير له polymerisation بعد هيكsetting لما يصير في setting لل gellyهل بتقدروا تسحبوا المي من ال gelly؟هل اذا وقع ال gelly على الأرض هل المي بتنكب ؟اذا ما بتكون free waterداخل ال gelly

- The water in the interstitium mainly is trapped in this gel like structure (proteoglycans) . There is small amount of free water (like small vacuoles contain free water that can move from one place to another) unlike the trapped one that can’t move .so inside the interstitium isn’t a pool of water, it is like gel but has spaces that is filled with water (small percentage) .so the interstistium will be resistant to volume changes (changes in volume happen when changes in fluids and osmolarity in compartment happen but it won’t be drastic , it is a kind of protection).

Determinants o Net Fluid Movement across capillaries

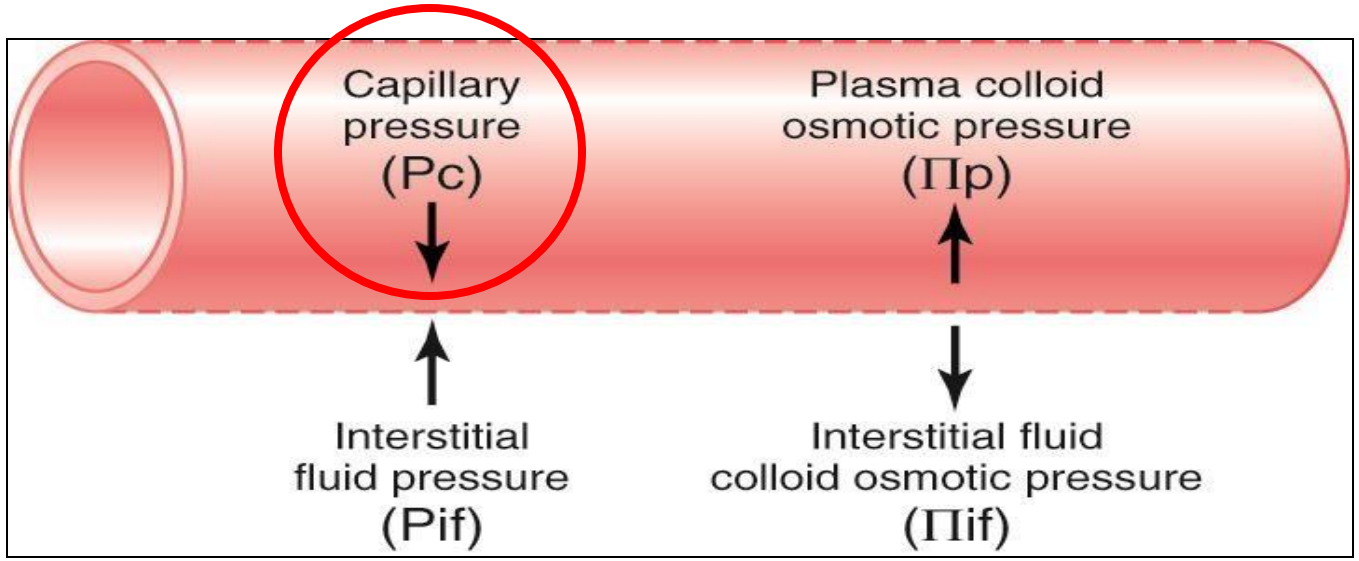
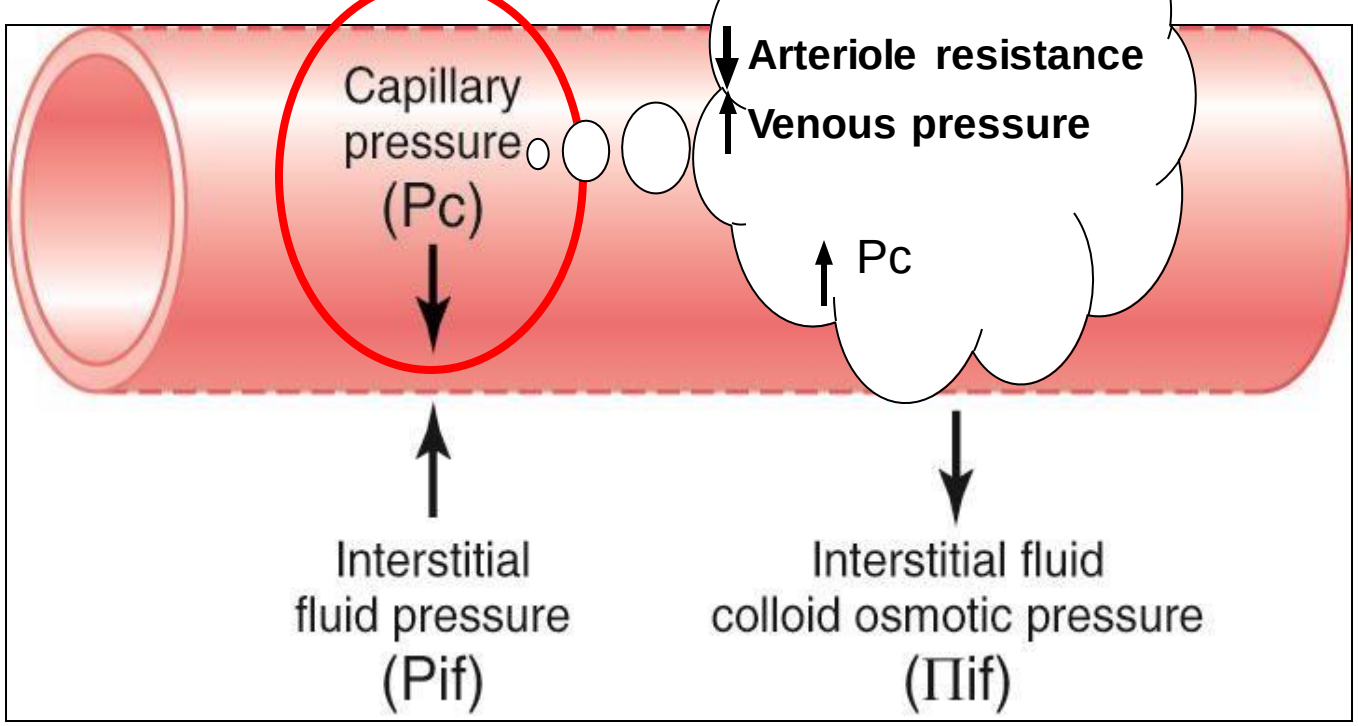


Figure 16-5

- *Capillary hydrostatic pressure* (Pc)-tends to force fluid outward through the capillary membrane

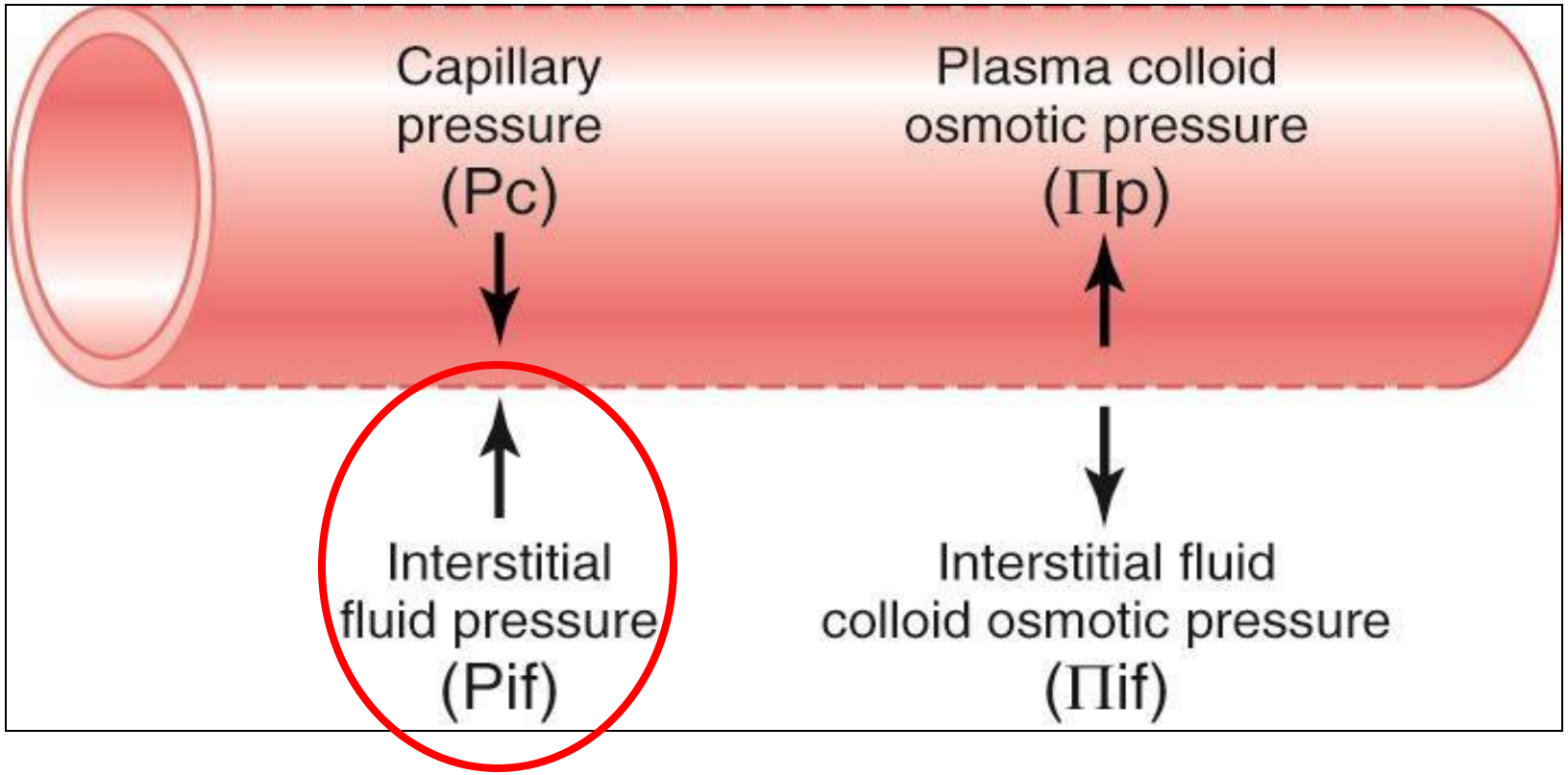


- Now we're going to talk about the forces that govern the exchange process (the exchange process does not occur randomly there are forces (physical forces, our whole body is governed by physical forces)
- The blood inside the capillaries vessels carries the pressure that is originated from the driving force of the pumping activity of the heart (when pumping in the systole of the cardiac (beating)occurs a pumping force for blood is originated and the blood will carry this force (it's a pressure in the aorta (contraction or systole)that's will be the blood pressure (110,120 millimetre) mercury).

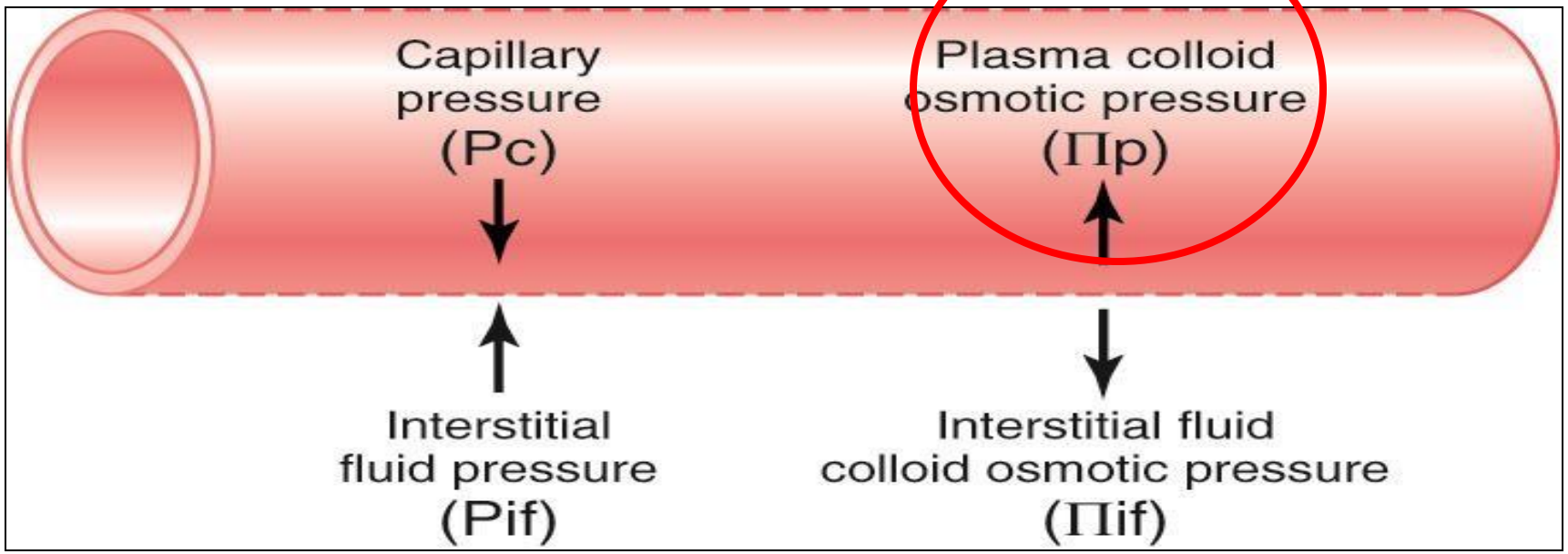
- the blood that carries this pressure will move and will branch into smaller vessels,the greater distance the blood will travel the less pressure it will have .why?because it will be consumed because of(the resistance ,the friction and the distance)the blood will lose part of this energy so the pressure will decline further it go away from the heart (the origin of the force).when the blood reaches the tissue, the pressure won't be 120 millimetre mercury in the arterioles (near the capillaries) , it will be approximately 30 or 50 (it depends on the type of tissue or organ)which is the capillary hydrostatic pressure (the pressure inside the capillary in result of the force that lasts to this point and it depends on the volume of the blood that is filled inside the capillary during the time).
- The hydrostatic pressure will cause a force against the wall.so if there is a cleft near the force that acts on the wall it will draw (push) the fluids away from the capillary if there is a space (فراغ). That will filtrate the blood (filtration) . There is also free fluid in the interstitium this fluid will apply pressure on the wall (against the filtration).this pressure is called interstitial hydrostatic pressure

- Large particles (mainly proteins which can’t pass through the slits because they’re larger than the slits) will course another type of pressure .these large particles that cannot pass through the slits won’t move (will stay remain at its place either it is inside the vessel or outside).if a fluid came out, these particles will try to draw more fluid. **The more concentration of large particles ,these particles will draw more fluid.so the direction of this force is toward the capillary (against the filtration).because the particles draw the fluid toward itself (it can’t go out) to reach the equilibrium (to make dilution).so this force is called capillary oncotic or colloid pressure (against the filtration).**
- **If there are particles exist in the interstitium will cause the same pressure (low).and the colloid pressure will draw (not equal to the capillary colloid pressure) and its direction is with filtration.**
- **When we calculate the net filtration forces ,we give the forces that favouring filtration a positive sign and the forces against filtration a negative sign (we do this before entering the values that are given in the question)**

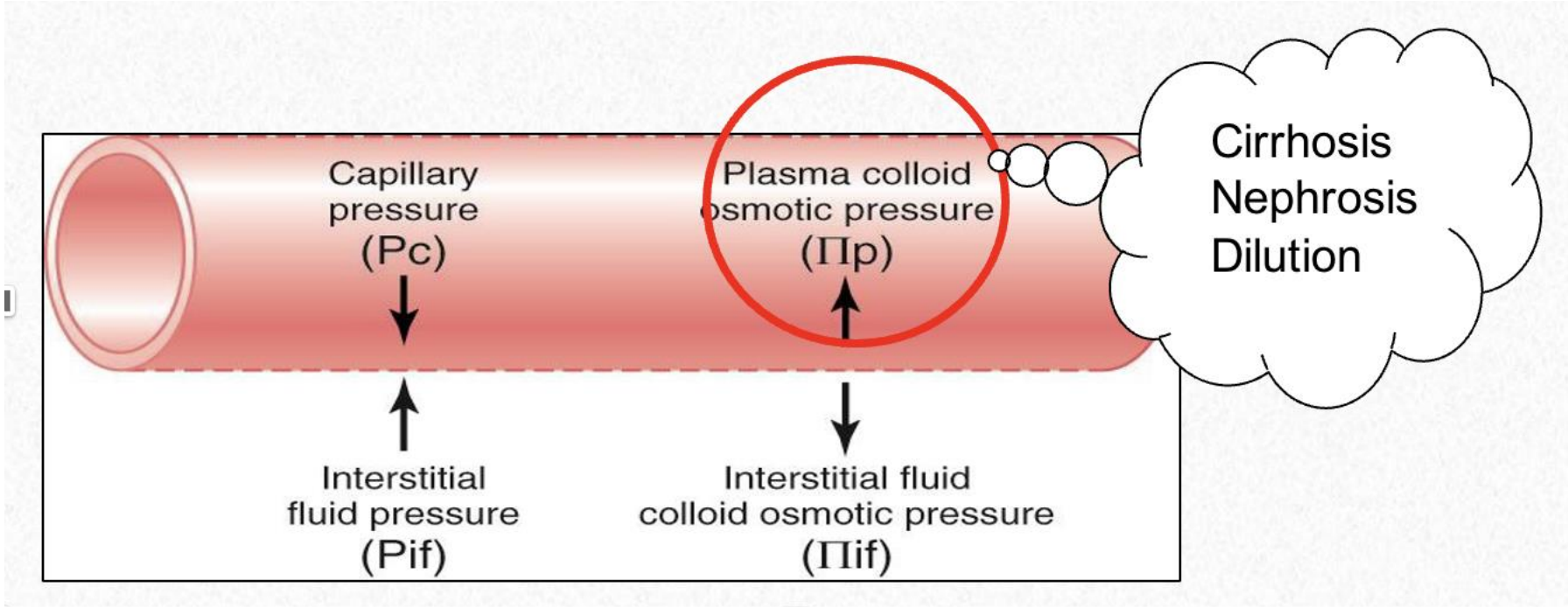
- **If the last value (answer) was positive ,then the net is favouring filtration (a filtration will occur).if the last value was negative, the net will be against the filtration it is called reabsorption .**
- *Capillary hydrostatic pressure* (Pc)-tends to force fluid outward through the capillary membrane



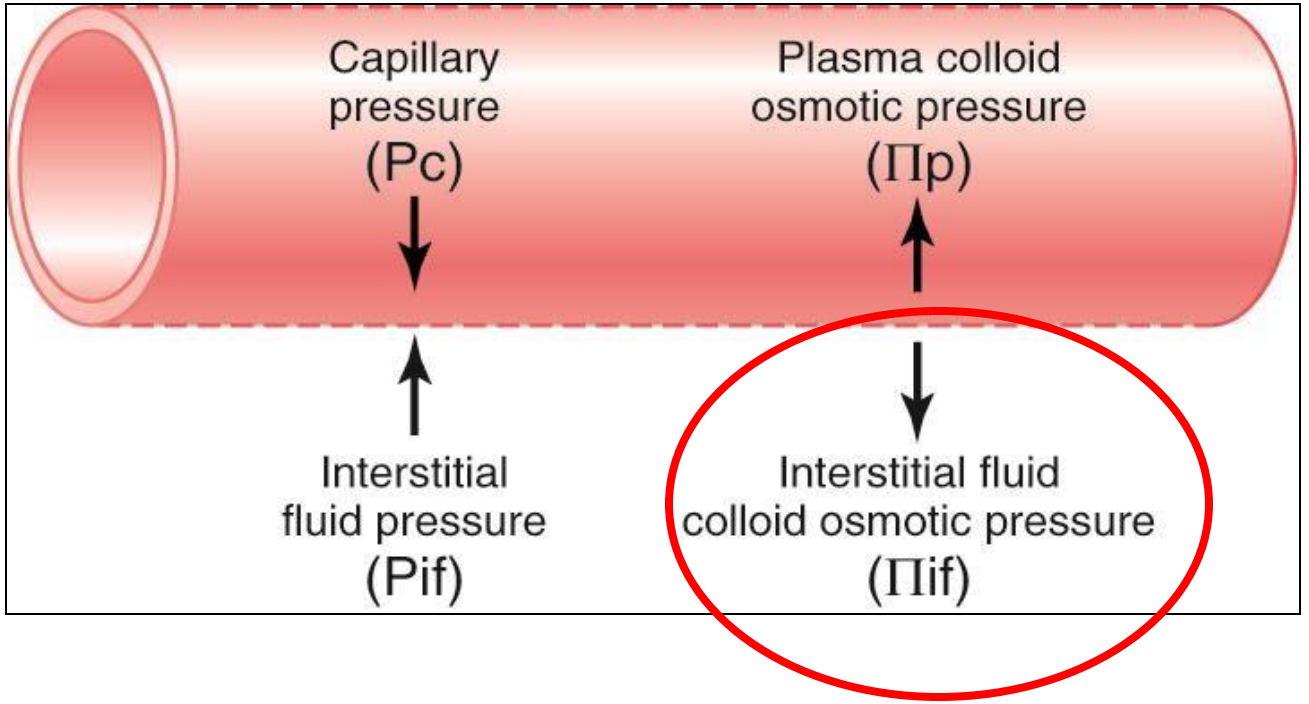
- *Capillary hydrostatic pressure* (Pc)-tends to force fluid outward through the capillary membrane
- *Interstitial fluid pressure* (Pif)- opposes filtration when value is positive



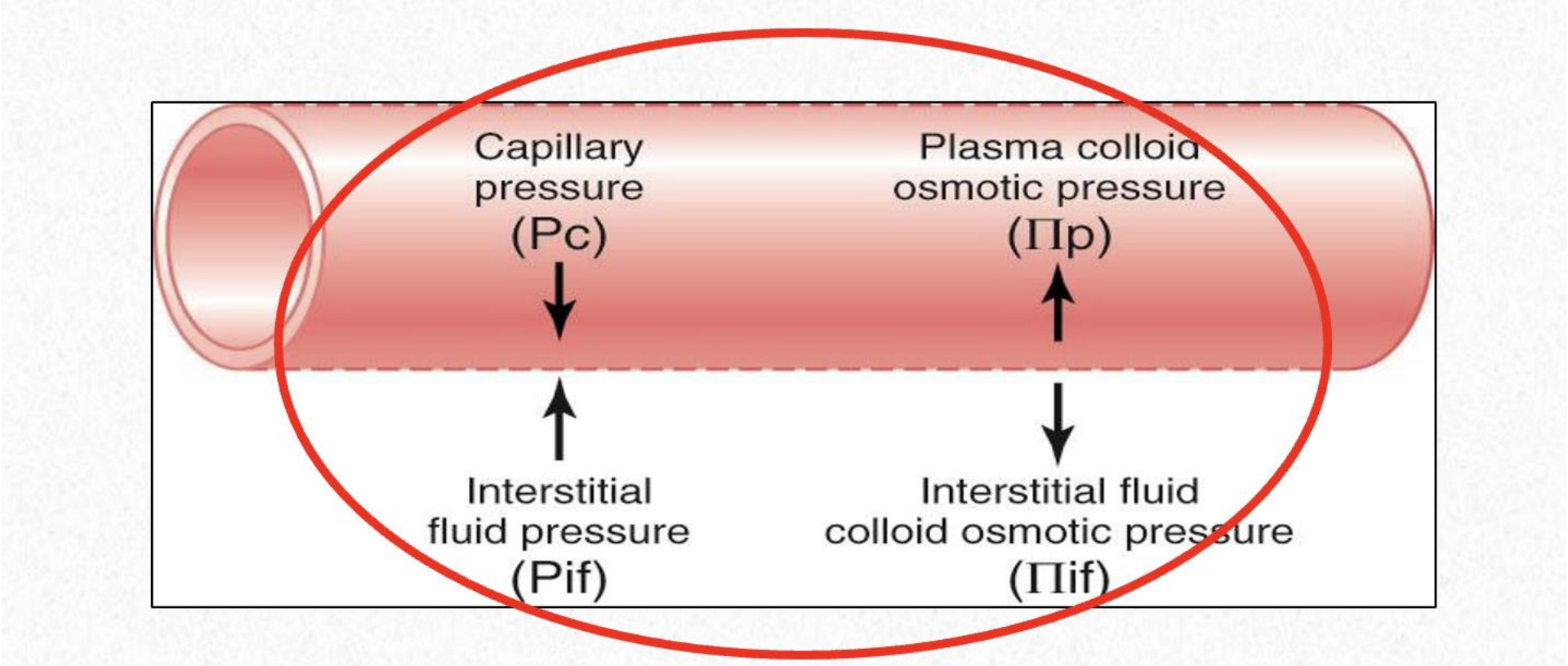
- *Plasma colloid osmotic pressure* - opposes filtration causing osmosis of water inward through the membrane



Plasma colloid osmotic pressure - opposes filtration causing osmosis of water inward through the membrane



- Interstitial fluid colloid pressure- promotes filtration by causing osmosis of fluid outward through the membrane


Capillary pressure (Pc)
Plasma colloid osmotic pressure (Πp)
Interstitial fluid pressure (Pif)
Interstitial fluid colloid osmotic pressure (Πif)

NP = Pc - □ p - Pif + □ if