Mechanics and Molecular Transport, and Regulation in Microcirculation

Last Class:
1. Fluid Mechanics & Rheology
   N-S Equation, Dimensionless Numbers, Bernoulli Equation, Newtonian Flow, etc.
2. Wave Propagation Phenomenon
3. Vascular Impedance to Blood

Today’s Contents:
1. Structure of Microcirculation
2. Types of Capillaries & Functional Properties of Blood
3. Flow-related Mechanical characteristics of Microcirculation
4. Methods of Capillary Exchange
5. Regulation of Blood Flow
Structure of the Microcirculation

The function of the cardiovascular system is to provide a homeostatic environment for the cells of the organism. The exchange of the essential nutrients and gaseous materials occurs in the microcirculation at the level of the capillaries. These microvessels are of extreme importance for the maintenance of a balanced constant cellular environment. Capillaries are known as the main exchange vessels where the interchange between the contents in these walls and the interstitial space occur across their walls.
Capillary

The diameters of blood vessels forming the microcirculation range from a few hundred microns down to a few microns, while the diameter of a freely suspended human red blood cell is about $8 \, \mu m$.

Poiseuille equation

Vascular impedance
The vascular network consists of both small and large vessels specifically designed to accommodate varying levels of blood flow and pressure, depending upon the location within the body (e.g. large conduit vessels versus small microvessels within the capillary beds in tissues). The single layer of smooth muscle cells terminates at the capillaries and reappears at the level of small venules.
The Capillary Circulation

The extensiveness of the organizational structure of the network of capillaries is necessary for efficient cellular transport and diffusion processes to take place. These processes are slow in comparison to blood perfusion. For this reason, a capillary is normally in the neighborhood and within reach to any single cell at a distance of about three to four cells apart. A given capillary can have a length of about 1 mm and a diameter of 4-10 μm.

http://www.chelationtherapyonline.com/articles/p198.htm
**Types of the Capillary**

*Continuous* - They are continuous in the sense that the endothelial cells provide an uninterrupted lining, and only allow small molecules, like water and ions to diffuse through tight junctions which leave gaps of unjoined membrane which are called intercellular clefts.

[Diagram of a capillary with labels for Pericyte, Red blood cell in lumen, Intercellular cleft, Basement membrane, Tight junction, Endothelial cell, Endothelial nucleus, Pinocytotic vesicles, and (a).]

In leaky junctions...

http://classes.midlandstech.com/carterp/Courses/bio211/chap19/chap19.html
**Types of the Capillary**

*Fenestrated* - Fenestrated capillaries have pores in the endothelial cells (60-80 nm in diameter) that are spanned by a diaphragm of radially oriented fibrils and allow small molecules and limited amounts of protein to diffuse. In the renal glomerulus there are cells with no diaphragms called podocyte foot processes or "pedicels," which have slit pores with an analogous function to the diaphragm of the capillaries.

In kidney and intestine

http://classes.midlandstech.com/carterp/Courses/bio211/chap19/chap19.html
**Types of the Capillary**

**Sinusoidal** - Sinusoidal capillaries are a special type of fenestrated capillaries that have larger openings (30-40 μm in diameter) in the endothelium. These types of blood vessels allow red and white blood cells (7.5μm - 25μm diameter) and various serum proteins to pass using a process that is aided by a discontinuous basal lamina.

http://classes.midlandstech.com/carterp/Courses/bio211/chap19/chap19.html

In kidney, liver, and bone marrow
Size of Red Blood Cells

If we compare the size of red cells from various mammals, we find the perhaps surprising fact that their diameters seem to be rather uniform and independent of mammalian body size. This is summarized in the following Table.

Table 7.1.1: Diameters of red blood cells (RBC) of some mammalian species.

<table>
<thead>
<tr>
<th>Species</th>
<th>Body weight (kg)</th>
<th>RBC Diameter (um)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shrew</td>
<td>.01</td>
<td>7.5</td>
</tr>
<tr>
<td>Mouse</td>
<td>.20</td>
<td>6.6</td>
</tr>
<tr>
<td>Rat</td>
<td>.50</td>
<td>6.8</td>
</tr>
<tr>
<td>Dog</td>
<td>20</td>
<td>7.1</td>
</tr>
<tr>
<td>Man</td>
<td>70</td>
<td>7.5</td>
</tr>
<tr>
<td>Cattle</td>
<td>300</td>
<td>5.9</td>
</tr>
<tr>
<td>Horse</td>
<td>400</td>
<td>5.5</td>
</tr>
<tr>
<td>Elephant</td>
<td>2000</td>
<td>9.2</td>
</tr>
</tbody>
</table>
Blood is the principal vehicle and medium that serves to provide nutrients and remove waste products throughout the complex multicellular constituents of the body organs. Blood plasma is about 90-95% water and contains numerous dissolved materials that include proteins, lipids, carbohydrates, electrolytes, hormones and pigments. Here we can define the solubility which is related to the concentration \( c_i \) of the gas, and its partial pressure

\[
p_i = f_i P \\
P = C_c RT \\
C_c = \frac{n}{N_A V}
\]

where \( N_A \) is the Avogadro's number (6.02\times10^{23}/\text{mole}); \( f_i \) is the molar fraction of the gas; \( R \) is the gas constant; \( n \) is the number of gas molecules and \( V \) is the gas volume.
Table 2.3.1 Solubility of gases in blood plasma.

<table>
<thead>
<tr>
<th>Gas</th>
<th>Solubility in Molar/mmHg</th>
</tr>
</thead>
<tbody>
<tr>
<td>O₂</td>
<td>1.4 x 10⁻⁶</td>
</tr>
<tr>
<td>CO₂</td>
<td>3.3 x 10⁻⁵</td>
</tr>
<tr>
<td>CO</td>
<td>1.2 x 10⁻⁶</td>
</tr>
<tr>
<td>N₂</td>
<td>7 x 10⁻⁷</td>
</tr>
<tr>
<td>He</td>
<td>4.8 x 10⁻⁷</td>
</tr>
</tbody>
</table>
Flow-Related Mechanical Characteristics of the Microcirculation

Pressure, flow and forces are drastically smaller in the microcirculation as opposed to the macro-circulation. We know that the Reynolds number as defined by

\[ Re = \frac{\rho \bar{U} d}{\eta} \]

is very small as compared an artery. For instance, the Reynolds number may be 0.03 for a 100 \( \mu \)m arteriole.

Steady flow is assumed in many hemodynamic and rheological studies. This is because the Womersley’s number, defined as

\[ \alpha_W = r \sqrt{\frac{\omega \rho}{\eta}} \]

is very small. Womersley’s number can be viewed as the ratio of oscillatory flow to steady flow. When \( a_w \) approaches zero, the approximation of a steady flow is a reasonable one.
In relation to entrance length, it is now small compared with the diameter of the microvessels. Thus, the flow becomes fully developed towards a parabolic profile, despite the relatively short length of the vessels. The well-known Fahraeus-Lindqvist effect explains the decreasing blood viscosity in very small vessels. Nevertheless, the Poiseuille’s equation has been viewed as important in the microcirculation, in that the flow is determined by the driving force of the pressure gradient and the resisting force of viscosity.

\[ \Delta P = \frac{8 \eta l}{\pi r^4} Q \]

These initially confusing results can be explained by the concept of a plasma cell-free layer, a thin layer adjacent to the capillary wall that is depleted of red blood cells.
There are actually two factors which promote cell-free layer formation.

1. For deformable particles (such as red blood cells) flowing in a tube, there is a net hydrodynamic force that tends to force the particles towards the center of the capillary. This is known as the Segre–Silberberg effect.

2. It is clear that red blood cells cannot pass through the capillary wall, which implies that the centers of red blood cells must lie at least one red blood cell half-thickness away from the wall. This means that, on average, there will be more red blood cells near the center of the capillary than very near the wall.
Others that Cause the Decrease of Blood Viscosity

The organizational alignment of red blood cells reduces the resistance.

Plasma Skimming Effect:

Hematocrit in the branch (Hd)

Hf > Hd

Hematocrit in the main channel (Hf)
Factors that Influence Blood Viscosity

Low blood viscosity results in heart failure (hypotension) but high viscosity increases the workload of heart (hypertension).

- **Platelet**: (less significant)

- **Cholesterol**: 

- **Hematocrit**: 

- **Plasma Protein**: aggregation of red blood cells
Starling’s hypothesis describes the filtration and absorption of fluid across capillary walls. The capillary wall is known to consist of endothelium with a basement membrane that is highly permeable to allow fluid exchange. Several factors govern such exchange: (1) hydrostatic capillary blood pressure, $P_c$ (2) osmotic pressure of plasma proteins, $\pi_c$, (3) hydrostatic interstitial fluid pressure, $P_i$ and (4) osmotic pressure, $\pi_i$, of the proteins in the interstitial fluid. These define the Starling’s hypothesis under equilibrium.

For this reason, the transcapillary flow is given

$$Jv/A = Lp \left[ (P_c - P_i) - \sigma (P_c - P_i) \right]$$

where $k_c$ is capillary permeability and $S$ is the cross-sectional area available for the exchange.
Osmosis

**Osmosis** is the movement of solvent molecules through a selectively permeable membrane into a region of higher solute concentration, aiming to equalize the solute concentrations on the two sides.
Pressure-Related Mechanical Characteristics of the Microcirculation
It should be noted here that the diameters of microvascular vessels change continuously throughout the cardiac cycle. Thus, the compliance change must follow the nonlinear behavior as we have shown earlier for the arteries. In other words, the compliance is pressure-dependent, thus time-varying.
Pulse Transmission Characteristics (1)

The steady flow concept assumed for the microcirculation is in accordance with the windkessel theory that peripheral vessels act as stiff tubes. This would protect the small vessels against sudden surges in flow and rapid changes in pressure.

Schematic illustration of the pulse transmission path from the ascending aorta to the index finger artery.

\[ c = \frac{1}{4} d \sqrt[4]{\frac{\omega}{\eta D}} \]  

Propagation speed
Pulse Transmission Characteristics (2)

http://www.as.miami.edu/chemistry/2086/Chapter_21/NEW-Chap21_class_part2.htm
Methods of Capillary Exchange

1. **Paracellular diffusion** – between the cells
   1. Leaky cell-cell junctions

2. **Transendothelial transport (transcytosis) through the cells**
   1. *Endo- and exocytosis, diffusion through the endothelial cell*

3. **Bulk flow**: mass movement of H$_2$O and dissolved solutes as result of hydrostatic or osmotic pressure
   - Filtration – flow direction out of capillaries
   - Absorption – flow direction into capillaries
Transport of Gases

One of the most important functions of the microcirculation is the delivery of $O_2$ to tissue and the removal of waste products, particularly of $CO_2$, from tissue. $O_2$ is required for aerobic intracellular respiration for the production of adenosine triphosphate (ATP). $CO_2$ is produced as a by-product of these biochemical reactions.

**Diffusion** describes the spread of particles through random motion from regions of higher concentration to regions of lower concentration. The time dependence of the statistical distribution in space is given by the diffusion equation. The concept of diffusion is tied to that of mass transfer driven by a concentration gradient, but diffusion can still occur when there is no concentration gradient (but there will be no net flux).
Diffusion of Small Molecules

\[ D \quad d_p \]

Simple diffusion of lipid-soluble molecules through plasma membrane

www.shutterstock.com · 46393198
Transport of O$_2$

http://www.bmj.com/content/317/7169/1370.full
The primary role that the capillaries play is in the oxygen exchange. The quantity of oxygen extracted from the blood during its flow through capillaries is determined by the relationship between the rate of oxygen utilization and the blood flow.
The binding of oxygen with hemoglobin provides an efficient transport system to deliver and maintain a desirable amount of tissue and organ oxygenation. Since the slope of the curve changes greatly at this level, hemoglobin can easily give up its carrying oxygen readily when the metabolic need arises. Thus, the oxygen transport system is ideally designed to perform the tasks of on-demand metabolic adjustments.
Transport of CO$_2$
Bohr Effect

**Bohr effect** is a property of hemoglobin first described in 1904 by the Danish physiologist Christian Bohr, which states that an increasing concentration of protons and/or carbon dioxide will reduce the oxygen affinity of hemoglobin. Increasing blood carbon dioxide levels can lead to a decrease in pH because of the chemical equilibrium between protons and carbon dioxide.

When a tissue's metabolic rate increases, its carbon dioxide production increases. Carbon dioxide forms bicarbonate through the following reaction:

\[
\text{CO}_2 + 
\text{H}_2
\text{O} \rightarrow \text{H}_2
\text{CO}_3
\]

Although the reaction usually proceeds very slowly, the enzyme family, carbonic anhydrase in red blood cells accelerates the formation of bicarbonate and protons. This causes the pH of tissues to decrease, and so, promotes the dissociation of oxygen from hemoglobin to the tissue, allowing the tissue to obtain enough oxygen to meet its demands. Conversely, in the lungs, where oxygen concentration is high, binding of oxygen causes hemoglobin to release protons, which combine with bicarbonate to drive off carbon dioxide in exhalation. Since these two reactions are closely matched, there is little change in blood pH.
The **Haldane effect** is a property of hemoglobin first described by the Scottish physician John Scott Haldane. Deoxygenation of the blood increases its ability to carry carbon dioxide; this property is the Haldane effect. Conversely, oxygenated blood has a reduced capacity for carbon dioxide. 

The Haldane effect promotes dissociation of carbon dioxide from hemoglobin in the presence of oxygen. In the oxygen-rich capillaries of the lung, this property causes the displacement of carbon dioxide to plasma as venous blood enters the alveolus and is vital for alveolar gas exchange.

The general equation for the Haldane Effect is: $H^+ + HbO_2 \leftrightarrow H^+Hb + O_2$; however, this equation is confusing as it reflects primarily the Bohr effect. The significance of this equation lies in realizing that oxygenation of Hb promotes dissociation of $H^+$ from Hb, which shifts the bicarbonate buffer equilibrium towards $CO_2$ formation; therefore, $CO_2$ is released from RBCs.
Transport of Nitric Oxide (NO)

NO is a fundamental component in the fields of neuroscience, physiology, and immunology. In mammals including humans, NO is an important cellular signaling molecule involved in many physiological and pathological processes.

The endothelium (inner lining) of blood vessels uses nitric oxide to signal the surrounding smooth muscle to relax, thus resulting in vasodilation and increasing blood flow. Nitric oxide is highly reactive (having a lifetime of a few seconds), yet diffuses freely across membranes. Nitric oxide (NO) contributes to vessel homeostasis by inhibiting vascular smooth muscle contraction and growth, platelet aggregation, and leukocyte adhesion to the endothelium. Humans with atherosclerosis, diabetes, or hypertension often show impaired NO pathways.
Transport of Water and Solutes

The movement of solute molecules across the capillary wall occurs primarily by two mechanisms:

The capillary wall is composed of a single layer of endothelial cells about 1 μm thick. Lipid soluble substances (e.g., O2) can diffuse across the entire wall surface, whereas water soluble substances are restricted to small aqueous pathways equivalent to cylindrical pores 8 to 9 nm in diameter (e.g., glucose in most capillaries; in capillaries with tight junctions and few fenestrations (brain, testes), glucose is predominantly transported). Total pore area is about 0.1% of the surface area of a capillary. The permeability of the capillary wall to a particular substance depends upon the relative size of the substance and the pore (“restricted” diffusion). The efficiency of diffusive exchange can be increased by increasing the number of perfused capillaries (e.g., heart and muscle tissue from rest to exercise), since this increases the surface area available for exchange and decreases the distances across which molecules must diffuse.
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The processes whereby water passes back and forth across the capillary wall are called filtration and absorption. The flow of water depends upon the relative magnitude of hydraulic and osmotic pressures across the capillary wall.
Solvent Drag

Solvent drag, also known as bulk transport, is a phenomenon used to remove both larger and smaller waste molecules. The difference in pressure between your blood and the replacement fluids (known as substitution solution), which creates a solvent drag for small and large waste molecules across the membrane. The solvent drag leads to the removal of waste from your blood. The faster the replacement fluid flows, the more waste is removed from your blood.

Ultrafiltration uses positive pressure on the blood side of the membrane and negative pressure on the fluid side of the membrane to influence the movement of fluid. The gradient, positive to negative, results in fluid removal from the patient. The ultrafiltration rate depends on the pressure applied to the filter, inside and outside the fibers. Minimal waste removal happens by convection during ultrafiltration.

[Diagram showing blood and filtrate with labels for water molecules, blood cells, positive pressure, and negative pressure]

Adsorption may cause limited removal of some waste from your blood. Membrane type affects adsorptive tendencies and effectiveness. High levels of adsorption can cause certain filters to clog and become useless.

The cardiovascular system controls blood flow to individual organs (1) by maintaining arterial pressure within narrow limits and (2) by allowing each organ to adjust its vascular resistance to blood flow so that each receives an appropriate fraction of the cardiac output. There are three major mechanisms that control the function of the cardiovascular system:

**Regulation of Blood Flow**
The role of neural influences on the vasculature varies greatly from organ to organ. Although all organs receive sympathetic innervation, regulation of blood flow in the cerebral and coronary vascular beds occurs mostly through intrinsic local (metabolic) mechanisms. The circulations in skeletal muscle, skin, and some other organs, however, are significantly affected by the sympathetic nerves. In general, the level of intrinsic myogenic activity and sympathetic discharge sets the state of vascular smooth muscle contraction (basal vascular tone) and hence vascular resistance in organs. This basal tone is modulated by circulating and local vasoactive influences.

**Baroreceptors** are located in the carotid sinus and the aortic arch. There are two types of baroreceptors. The unmyelinated baroreceptors are localized in the central cardiovascular system and respond to pressures above normal and initiate reflexes to reduce arterial blood pressure. The myelinated baroreceptors respond to blood pressures below normal and thus protecting the cardiovascular system from prolonged reduction in blood pressure.

**Chemoreceptors** are located in the carotid and aortic bodies. These chemoreceptors respond with an increase in discharge frequency to an increase in $\text{CO}_2$ or to decreases in $\text{O}_2$ and reduced pH of the blood perfusing the carotid and aortic bodies. Because $\text{CO}_2$ and $\text{O}_2$ are intimately related to the ventilation-perfusion process, chemoreceptors are particularly important in regulating ventilation.
Blood Pressure Control Via Sympathetic and Vagal Stimulations
Local Regulation

The site of local regulation is the microcirculation. Examples of local control processes are autoregulation of blood flow, reactive hyperemia, and active (or functional) hyperemia. The mechanisms of local regulation have been identified as (1) the myogenic mechanism based on the ability of vascular smooth muscle to actively contract in response to stretch; (2) the metabolic mechanism, based on a link between blood flow and tissue metabolism; (3) the flow-dependent mechanism, primarily based on the release of NO by endothelial cells in response to shear forces.
Arterioles and venules exhibit vascular tone, that is, their diameter is maximal when smooth muscle is completely relaxed (inactivated). When the vascular smooth muscle is constricted, small arterioles may even completely close their lumen to blood flow, presumably by buckling endothelial cells. Arterioles exhibit a *myogenic response* not observed in other blood vessels.

Stress in the vessel wall can be decomposed into passive and active components. The passive component corresponds to the state of complete vasodilation. The active component determines the vascular tone and the myogenic response.