Cardiovascular Physiology

33. Hemodynamics: basic biophysical principles.
34. Hemorheology.

Ferenc Domoki, November 6, 2019.

Instead of an introduction: the three major players responsible for the cardiovascular function

- The blood
- The heart
- The vascular system

The cardiovascular physiology discusses the features, interactions and regulation of these three factors.
Hemodynamics- definitions

- **Flow**: the fluid volume flowing through the cross-section of the tube in a given time period (\(\Delta V/\Delta t\)), when applied for the whole circulation: the **cardiac output (CO)**.
- Designated as \(Q\), unit of measurement volume/time (e.g., liter/min).
- Attention! flow \(\neq\) flow velocity (v), the latter describes the average linear velocity of the fluid particles (m/s).
- \(Q = A \cdot v\), where \(A\) is the cross-sectional area of the vessel.

Laminar blood flow

- Fluid sheets (laminae) gliding over each other.
- In tubes the sheets can be considered as concentric circles, the linear velocity of the flowing molecules decreases from center to periphery.
- A parabola-shaped velocity gradient profile develops.
Turbulent flow

Irregular flow with whirlpools always presents as increased viscosity increasing resistance. Turbulent flow is promoted by wide tubing, tube irregularities (branching, curving, partial occlusion), high flow velocity, and low viscosity.

Reynolds number: an indicator of the likeliness of turbulent flow development

- No physical unit
- \( \text{Re} = d \cdot v \cdot \rho / \eta \), where \( d \) is diameter, \( v \) is velocity, \( \rho \) specific gravity, and \( \eta \) viscosity (measured in cm, cm/s, g/cm\(^3\), and Poise, according to the CGS system).
- If the number is greater than 2000, turbulence is likely to occur.
- In the circulation, arterial blood flow is most likely to become turbulent (big diameter+big velocity).
Hemodynamics- definitions

- **Blood pressure**: the pressure exerted by the blood on the wall of the blood vessel. Its value depends on cardiac activity and also on the position of the vessel with respect to the heart.
- Designated with \( P \), the SI unit is Pascal Pa, but in physiology traditionally mmHg is used.
- Between two points in the vascular system, flow develops if there is a difference in pressure in the fluid (blood) filling the tube (vessel). This is called **perfusion pressure (pressure gradient)**, designated as \( \Delta P = P_1 - P_2 \).
- In the circulation, the \( \Delta P \) pressure gradient is developed by the backward sucking-forward pumping activity of the heart!

Hemodynamics- definitions

- At a given pressure gradient, the flow will be determined by the **hydraulic resistance**, when applied for the systemic circulation it is called total peripheral resistance (TPR).
- Designated as \( R \) (TPR), its unit is pressure·time/volume (mmHg·min/liter)
The major law of hemodynamics: Ohm’s law

- Flow = Perfusion pressure/hydraulic resistance

\[ Q = \frac{\Delta P}{R} \quad (\Delta P = Q \cdot R; \ R = \Delta P/Q) \]

- \( \text{CO}_{\text{systemic circ.}} = \frac{(P_{\text{aorta}} - P_{\text{right atrium}})}{\text{TPR}} \)

- \( \text{CO}_{\text{pulmonary circ.}} = \frac{(P_{\text{a.pulm}} - P_{\text{left atrium}})}{R_{\text{lung}}} \)

- \( \text{CO}_{\text{systemic circ.}} = (\geq) \text{CO}_{\text{pulmonary circ.}} \)

Which factors determine resistance?
HAGEN-POISEUILLE’S law

Pressure

\[ Q \propto \Delta P \]

Length

\[ Q \propto \frac{1}{L} \]

Radius

\[ Q \propto r^4 \]

Viscosity

\[ Q \propto \frac{1}{\eta} \]

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

\[ R = \frac{L\eta}{8 \pi r^4} \]

Which factors determine hydraulic resistance?

- The flowing fluid’s own material property: viscosity \( \eta \)
- Tube geometry: directly proportional to tube length \( L \), inversely proportional to the 4th! power of tube radius \( r \)
- Hagen-Poiseuille’s law:

\[ Q = \Delta P \frac{\pi}{8} \times \frac{r^4}{L} \times \frac{1}{\eta} \]

\[ R = \frac{8}{\pi} \times \frac{L\eta}{r^4} \times \eta \]
The criteria of Hagen-Poiseuille’s laws compared to the facts of the circulation

<table>
<thead>
<tr>
<th>Hagen-Poiseuille’s laws</th>
<th>Circulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cylindrical, rigid, tubes, no branches</td>
<td>Elastic, branching vessels, veins are not cylindrical</td>
</tr>
<tr>
<td>Newtonian fluid</td>
<td>Non-newtonian fluid, the blood</td>
</tr>
<tr>
<td>Constant flow</td>
<td>Pulsatile flow (arteries)</td>
</tr>
<tr>
<td>Laminar flow</td>
<td>Sometimes turbulent flow</td>
</tr>
</tbody>
</table>

The equation thus cannot be possibly true for the circulation, however, the law identifies all the important factors.

Haemorheology: the science of blood as a fluid

<table>
<thead>
<tr>
<th>Haemorheology</th>
</tr>
</thead>
<tbody>
<tr>
<td>„rhei” greek word meaning stream, widely known because of the famous aphorism „Panta rhei!”- Everything flows!- (in the meaning of nothing stays constant)</td>
</tr>
<tr>
<td>Characterization of laminar flow; Newton’s law of viscosity, introducing shear rate, shear stress, viscosity</td>
</tr>
<tr>
<td>Viscosity of non-newtonian fluids, such as the blood</td>
</tr>
<tr>
<td>Characterization of blood viscosity as the blood flows in the vessels, the adaptation of the red blood cell to flow</td>
</tr>
<tr>
<td>Turbulent flow, Reynolds number</td>
</tr>
</tbody>
</table>
Newton’s law of viscosity I.

- Moving the glass plate creates fluid flow beneath the plate, the fluid flows (slides) in parallel sheets (laminae) with respect to each other.
- This velocity gradient \( \frac{dv}{dx} \) in the fluid is homogenous, and proportional to the force \( F \) moving the glass plate.

Newton’s law of viscosity II.

- **shear stress**: the tangential force that makes the layers (unit surface area) glide over each other, signed with \( \tau \), unit of measurement \( N/m^2 \) (Pa)
- **shear rate**: the velocity \( (v) \), with which the layers in \( x \) distance move related to each other, signed \( \gamma = \frac{dv}{dx} \), unit of measurement \( 1/s \)
- Newton’s law of viscosity states, that in simple (newtonian) fluids there is a simple proportionality between shear stress and shear rate, the proportionality coefficient is called viscosity. Viscosity’s sign is \( \eta = \tau/\gamma \), unit of measurement is \( \text{Pa}\cdot s \) (SI) or \( \text{P} \) (poise, in CGS). Conversion factor: 1 \( \text{Pa}\cdot s = 0.1 \text{ P} \). Viscosity is inversely proportional to temperature (try pouring cold vs. warm honey)
Factors determining blood viscosity

- The blood plasma is a Newtonian fluid, its viscosity depends on the concentration of plasma proteins (dehydration!). The blood, however, is a non-Newtonian fluid ($\eta \neq \tau / \gamma$), thus viscosity changes as a function of shear, and modified by tube geometry as well.
- 1. **Hematocrit.** Increasing hematocrit will increase viscosity.
- 2. **Shear thinning.** Increasing shear rate will reduce viscosity.
- 3. **Fähræus-Lindquist effect.** Decreasing vessel size below 300 µm will reduce viscosity.
- These unique features of the blood are largely explained by the red blood cell membrane's non-elastic deformability (fluidity).

### Hematocrit dependency of blood viscosity

<table>
<thead>
<tr>
<th>HEMATOCRIT (%)</th>
<th>RELATIVE VISCOSITY</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>10</td>
<td>2</td>
</tr>
<tr>
<td>20</td>
<td>3</td>
</tr>
<tr>
<td>30</td>
<td>4</td>
</tr>
<tr>
<td>40</td>
<td>5</td>
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<tr>
<td>50</td>
<td>6</td>
</tr>
<tr>
<td>60</td>
<td>7</td>
</tr>
<tr>
<td>70</td>
<td>8</td>
</tr>
</tbody>
</table>

- Normal value
- Water
- Plasma

Ad 1.
RBC aggregates ≠ blood clots

- When shear rate is low, the RBCs form aggregates, these „money rolls” increase blood viscosity. The RBC aggregation depends on the blood plasma proteins, globulins increase it.
- This reversible aggregation is the basis of RBC sedimentation rate (increased when plasma albumin/globulin ratio is decreased).

In response to shear stress, the RBC membrane will start to rotate, and the cell will assume an elongated shape.
Experimental record: red blood cells in shear assume a different shape, membrane-attached tags reveal the rotation of the plasma membrane.

Ad 2.

SHEAR THINNING. By increasing shear, blood viscosity is reduced because:
- 1. DISPERSION: during stasis, red blood cells form aggregates (money roll formation, globulin-dependent) that are dispersed by shear.
- 2. DEFORMATION (shape change) and ORIENTATION of red blood cells (RBCs) in shear.
Blood viscosity starts to reduce when vascular diameter becomes less than 300 µm, at ~7-10 µm diameter it approaches plasma viscosity. This is the Fåhraeus-Lindquist effect.

The scientists: Robert Sanno Fåhraeus (1888-1968)
Johan Torsten Lindquist (1906-?)
Swedish hemato-pathologists
The Fåhraeus-Lindquist effect: mechanisms

1. Axial migration and 2. plasma skimming: red blood cells flow along the main axis, where velocity is higher and shear stress is lower, at the endothelium there is a cell free plasma layer where velocity is smaller. As a combined effect, the effective hematocrit decreases, decreasing viscosity. This mechanism is more important in bigger microvessels (30-300 µm).

3. In the capillaries, red blood cells flow as a single file, their fluid droplet adaptation will become the most perfect, their shape will assume the paraboloid velocity profile. Capillary blood viscosity is however, increased by more rigid white blood cells...

White blood cells elevate capillary blood viscosity
Take home messages:

- The red blood cells in the circulation never resemble bakery products (donuts, cookies etc), but will passively assume any form dictated by shear forces!
- The ADAPTATION of red blood cells both in the micro- and macrocirculation serves to REDUCE viscosity – thus resistance
- The red blood cell was a key to the evolutionary success of birds and mammals!

The mammalian red blood cell is a key to the evolutionary success!

Frog (left), and human (right) red blood cell and capillary
The mammalian red blood cell is a key to the evolutionary success!

Using the same blood volume, mammals may perfuse 16 times more capillaries than the frog. Reducing diffusion distances was a major achievement that made the building of organs with high metabolic rates (brain) possible!

What is important from rheology for a physician?

- Blood viscosity does not CONTROL hydraulic resistance under physiological conditions, but it can significantly affect it.
- High hematocrit (polycythemia, dehydration) will increase viscosity, and thus resistance.
- Low hematocrit may result in too low viscosity that can cause arterial turbulence (with murmurs) increasing resistance and promoting vascular damage.
- Sluggish blood flow results in red blood cell aggregation, leading to structural viscosity increases, starting a vicious circle.
- Any congenital or acquired defect (smoking, diabetes mellitus) of red blood cell membrane fluidity will deteriorate deformability, leading to increases in viscosity, resistance, and impairing blood flow.
Can the physician check the rheology status of the patient? YES! : Rheology tests

- **viscosity**
- Osmotic gradient
- Ektacytometry: deformability index
- **Critical stress:** minimum shear that disperses RBC aggregates, etc...

Blood vessels: elastic and branching tubes

- According to Hagen-Poiseuille’s law, length and especially radius of vessels affect hydraulic resistance greatly. In contrast to the criteria of the law, the circulatory system consist of elastic, branching, and not always cylindrical tubes= blood vessels.
- Because of vessel elasticity, increases in distending blood pressure result also in increases in vessel radius (reducing resistance), cross sectional area, and volume.
- Important concepts related to vascular elasticity: transmural pressure, vascular compliance, critical closing pressure, wall tension (Laplace’s law)
Transmural pressure: the pressure distending the blood vessel: $P_{tm} = P_{blood} - P_{inst}$

- "transmural": across the wall
- The difference between the blood pressure and the pressure outside the vessel wall (interstitial pressure)
- The interstitial pressure normally doesn’t play a significant role in determining transmural pressure in the systemic arteries (except in contracting muscle), but very important in the low pressure system (venous circulation)

**Transmural Pressure (mmHg)**

<table>
<thead>
<tr>
<th>Vascular System</th>
<th>Compliance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Venous system</td>
<td>20-24 times larger than arterial compliance</td>
</tr>
<tr>
<td>Arterial system</td>
<td></td>
</tr>
</tbody>
</table>

**Vascular Compliance**: Increase in vessel volume in response to unit increase in pressure. Depends on vessel distensibility and size.

Compliance: The slope of the vessel volume ($V$)-transmural pressure ($P_{tm}$) curve.
Blood vessels collapse, if the transmural pressure falls below the critical closing pressure value

Critical closing pressure in arteries is higher than the mean vascular filling pressure that develops after death (~7 mmHg). Therefore, arteries collapse after death, then fill up with air once the dissection begins. This misled scientists for a thousand years believing the arteries to transport air (reflected in their Greek name, *arteria* means windpipe).

Laplace’s law

\[ T = P \times \frac{r}{h} \]

Wall tension = Transmural pressure \( \times \frac{\text{radius}}{\text{wall thickness}} \)

- Tension of vessels: the tangential force in response to the distending pressure. Wall tension is a force that would tear the vessel wall
- Laplace’s law helps to identify which vessels are at risk
  - veins – low (large radius -low blood pressure)
  - capillaries – low (low blood pressure – small radius)
  - arterioles – low (high pressure – small radius + thick wall)
  - muscular arteries – low (high pressure – moderate radius + thick wall)
  - aorta/ large elastic arteries – high (high pressure – large radius – relatively thin wall)

High blood pressure induced wall rupture is thus most likely in the aorta, wall weakening causes aneurysm formation that sets off a vicious circle.
How can the vascular resistance be described in the branching vasculature?

- Vessels are connected to each other either in series or in parallel.
- The different organs in the systemic circulation are connected in parallel.
- The vessels of the SAME class are connected in parallel (etc arteries, arterioles, capillaries, veins).
- Vessel classes are connected to each other in series (arteries to arterioles, arterioles to capillaries, capillaries to venules etc).

Compound resistance in parallel connected tubes

\[
\frac{1}{R_t} = \frac{1}{R_1} + \frac{1}{R_2} + \frac{1}{R_3}
\]

\[
\frac{1}{R_t} = \frac{1}{5} + \frac{1}{25} + \frac{1}{100} = \frac{23}{100} = \frac{1}{4}
\]

\[
R_t = 4 \text{ RU}
\]

Note that total resistance is always smaller than the smallest individual resistance!
Compound resistance of parallel connected vascular segments

\[ R_{\text{segment}} = \frac{1}{\left( \frac{1}{R_1} + \frac{1}{R_2} + \frac{1}{R_3} + \ldots + \frac{1}{R_n} \right)} \]

\[ R = \frac{1}{C} \] !!!!

or

\[ C_{\text{segment}} = C_1 + C_2 + C_3 + C_4 + \ldots + C_n \]

- Compound vascular resistance in each segment is increasing by larger \( R \) (individual resistance), and by smaller \( n \) (the number of parallel connected vessels). Perhaps it is easier to see that segmental conductance \( C \) is smaller if individual conductances are smaller and the number of parallel connected vessels is smaller. Based on these principles the class of arterioles possess the greatest resistance (large individual \( R \), relatively small \( n \) values)

- The organs of the systemic circulation are connected in parallel

  To describe these systems it is easier to use conductance instead of resistance

  \[ C = \frac{1}{R}, \quad C_{\text{total}} = \frac{1}{TPR} \]

  \[ C_{\text{total}} = C_{\text{coronaries}} + C_{\text{brain}} + C_{\text{muscle}} + \ldots \]

  The figure shows the % of total peripheral conductance values in the systemic circulation

  - The TPR is SMALLER than ANY of the organ resistances in the systemic circulation.

  - For instance, coronary circulation has 5% of total conductance that means that its resistance

\[ R_{\text{coronaries}} = \frac{1}{C_{\text{coronaries}}} = \frac{1}{0.05} C_{\text{total}} = 20 \text{ TPR} \]
Combined resistance of in series connection

- $R_{total} = R_1 + R_2 + R_3 + ... + R_n$
- $TPR = R_{aorta} + R_{arteries} + R_{arterioles} + R_{capillaries} + R_{veins}$
- Note that the total resistance is always greater than the largest resistance!

Blood pressure/ segmental resistance in the circulation

- $R_{arterioles} \gg R_{capillaries} > R_{veins} > R_{arteries} > R_{aorta}$
- Blood pressure drop is greatest in the arterioles: this segment has the largest vascular resistance, essentially determining the total peripheral resistance (TPR).
- Control of arterial blood pressure and local blood flow is taking place in the arterioles.
**CLASSES OF VESSELS: STRUCTURE AND FUNCTION**

- **Elastic a.**
- **Muscular a.**
- **Arteriole**
- **Capillary**
- **Vein**
- **Vena cava**

<table>
<thead>
<tr>
<th>Diameter</th>
<th>Wall</th>
<th>Endoth.</th>
<th>Elast. t.</th>
<th>Smooth m.</th>
<th>Conn. t.</th>
</tr>
</thead>
<tbody>
<tr>
<td>25 mm</td>
<td>2 mm</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 mm</td>
<td>1 mm</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30 µm</td>
<td>25 µm</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8 µm</td>
<td>1 µm</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>20 µm</td>
<td>2 µm</td>
<td></td>
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</tr>
<tr>
<td>5 mm</td>
<td>0.5 mm</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>30 mm</td>
<td>1.5 mm</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

**Windkessel function:** Distribution of flow

- **Resistance**
- **Exchange**
- **Protein & cell traffic**
- **Venous return control**

**Cardiac output determination**

**Continuous flow**

**Blood pressure & local flow control.**

**Exchange**

**Protein & cell traffic**

**Venous return control**

**Cardiac output determination**

**CROSS SECTIONAL AREA AND VELOCITY OF FLOW**

\[ Q = A \cdot v \]

<table>
<thead>
<tr>
<th>Vessels</th>
<th>cm²</th>
<th>cm/s</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aorta</td>
<td>4</td>
<td>22.5</td>
</tr>
<tr>
<td>Arteries</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Arterioles</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>Capillaries</td>
<td>2500</td>
<td>0.03</td>
</tr>
<tr>
<td>Venules</td>
<td>250</td>
<td></td>
</tr>
<tr>
<td>Veins</td>
<td>80</td>
<td></td>
</tr>
<tr>
<td>Vv. cavae</td>
<td>8</td>
<td>11.0</td>
</tr>
</tbody>
</table>
DISTRIBUTION OF BLOOD VOLUME

<table>
<thead>
<tr>
<th>%</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart</td>
<td>7</td>
</tr>
<tr>
<td>Aorta</td>
<td>6</td>
</tr>
<tr>
<td>Arteries</td>
<td>6</td>
</tr>
<tr>
<td>Arterioles</td>
<td>2</td>
</tr>
<tr>
<td>Capillaries</td>
<td>6</td>
</tr>
<tr>
<td>Veins</td>
<td>64</td>
</tr>
</tbody>
</table>

Depends on pressure and compliance, most blood is in the **venous system**.