LECTURE 8

We have seen that, for a blood vessel, the flux of blood moving through depends on the pressure drop along the vessel:

$$\underbrace{Q = \frac{1}{R}\Delta P}_{\text{non-compliant vessel model}} \qquad \underbrace{Q = \frac{1}{R}\Delta P\left[1+\gamma\left(P_0+P_1\right)+\frac{\gamma^2}{3}\left(P_0^2+P_0P_1+P_1^2\right)\right]}_{\text{compliant vessel model}}$$

We have also seen that the amount of blood in the circulatory system depends on the net volume of blood pumped at each stroke:

$$\tilde{V}_{stroke} = V_{max} - V_{min} + C_d\tilde{P}_v - C_s\tilde{P}_a$$

average venous and arterial pressures

Now the question is: how can we use these relationships to develop a model of the entire circulatory system?

To answer this question, we need to make preliminary decisions, i.e.:

A) Components to be specifically modeled

B) Simplifying assumptions

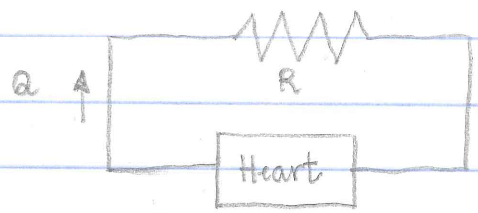
C) Features in each component to be included

As a result of our choices at point A), B), and C), we may derive a model and we may determine whether it can be solved. For instance:

- Regarding A), the circulatory system includes many venous and arterial vessels: which ones do we model? Do we model the heart pumping blood in the system? $\Rightarrow$ • We model the total flux through the vessels
  • We model the heart as the terminal of the flux

- Regarding B), we assume that the heart can be represented as a single chamber (i.e., no separation between ventricles and atria). We also assume that - since we are interested in the total flux - the vessels are lumped into one equivalent vessel

- Regarding C), we may decide to make the equivalent vessel non-compliant and the single-chambered heart compliant, i.e.:



In terms of equations, we have:

equiv. vessel:

$$Q = \frac{\tilde{P}_a - \tilde{P}_v}{R}$$

$\tilde{P}_a \triangleq$ average arterial pressure

$\tilde{P}_v \triangleq$ average venous pressure

equiv. one-chambered heart:

$$Q = CO = F\left(V_{max} - V_{min} + C_d \tilde{P}_v - C_s \tilde{P}_a\right)$$

cardiac output

$C_d, C_s \triangleq$ equivalent diastolic and systolic value of the heart compliance

By combining, we have:

$$\tilde{P}_a - \tilde{P}_v = RF\left(V_{max} - V_{min} + C_d \tilde{P}_v - C_s \tilde{P}_a\right)$$

$$\Updownarrow$$

$$(1 + RFC_s)\tilde{P}_a - (1 + RFC_d)\tilde{P}_v = RF\left(V_{max} - V_{min}\right) \qquad (*)$$

The formula (*) is the resultant model of the circulatory system. Note:

(*) is an algebraic relationship between $\tilde{P}_a$ and $\tilde{P}_v$ $\Rightarrow$ No time is involved. Hence it only applies to steady-state conditions

(*) can be satisfied by an infinite number of pairs $(\tilde{P}_a, \tilde{P}_v)$ $\Rightarrow$ The model is not enough to univocally determine $\tilde{P}_a$ and $\tilde{P}_v$ given the measurements of F, R, and $V_h \triangleq V_{max} - V_{min}$.

$$\Downarrow$$

We need to refine the model by reconsidering one of the choices made at point A), B), or C). For instance, let us assume that the equivalent vessel is compliant (i.e., we revise the choices at point C) above):

$$Q = \frac{1}{R}(\tilde{P}_a - \tilde{P}_v)\left[1 + \gamma(\tilde{P}_a + \tilde{P}_v) + \frac{\gamma^2}{3}(\tilde{P}_a^2 + \tilde{P}_a\tilde{P}_v + \tilde{P}_v^2)\right]$$

$$= \frac{1}{3\gamma R}\left[(1+\gamma\tilde{P}_a)^3 - (1+\gamma\tilde{P}_v)^3\right]$$

$$\Downarrow$$

$$(1+\gamma\tilde{P}_a)^3 - (1+\gamma\tilde{P}_v)^3 = 3\gamma RF(V_h + C_d\tilde{P}_v - C_s\tilde{P}_a) \qquad (**)$$

In addition, the compliance of the equivalent vessel implies that the volume of this vessel is (check eq. 11.20 in the textbook):

$$V = \frac{3}{4}V_0\left[\frac{(1+\gamma\tilde{P}_a)^4 - (1+\gamma\tilde{P}_v)^4}{(1+\gamma\tilde{P}_a)^3 - (1+\gamma\tilde{P}_v)^3}\right]$$

$V_0 \triangleq$ volume when no pressure is applied.

Because the model is focused on the average behavior under steady-state conditions, it is reasonable to expect that $V \cong$ constant $\Rightarrow$ We can write:

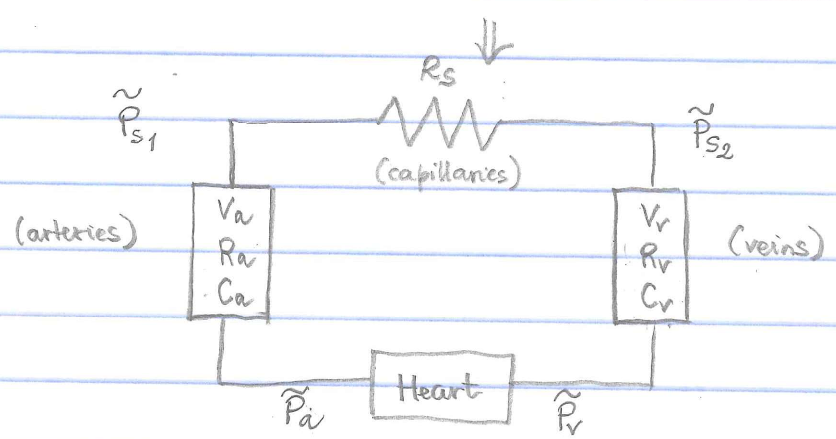
$$\frac{(1+\gamma\tilde{P}_a)^4-(1+\gamma\tilde{P}_v)^4}{(1+\gamma\tilde{P}_a)^3-(1+\gamma\tilde{P}_v)^3} = \underbrace{\frac{4}{3}\frac{V}{V_0}}_{\text{constant}} \qquad (***)$$

Equations (**) and (***) are a system of two equations in two variables (i.e., $\tilde{P}_a$ and $\tilde{P}_v$) and will have a unique solution given the average volume V and V_0

* A more realistic (linear) model of the circulatory system

Let us relax a few of the (many) approximations made to obtain the model above. Specifically, let us choose:

- Regarding B): Let us model 3 vessels connected in series, one for arteries, one for veins, and one for capillaries
- Regarding c): Let us model arteries and veins as compliant vessels and capillaries as non-compliant vessels



$\tilde{P}_{s_1} \triangleq$ average pressure at the border arteries - capillaries

$\tilde{P}_{s_2} \triangleq$ average pressure at the border capillaries - veins

Note that the separation between arteries/veins and capillaries is somehow arbitrary and depends on the section of the vessels, i.e., we model the larger vessels as compliant and the smaller vessels as non-compliant

Heart: $Q = CO = F\left(V_h + C_d \tilde{P}_v - C_s \tilde{P}_a\right)$ $\quad (a_1)$

Arteries: $$Q = \frac{1}{R_a}\left(\tilde{P}_a - \tilde{P}_{s1}\right)\left[1 + \gamma\left(\tilde{P}_a + \tilde{P}_{s1}\right) + \frac{\gamma^2}{3}\left(\tilde{P}_a^{\,2} + \tilde{P}_{s1}\tilde{P}_a + \tilde{P}_{s1}^{\,2}\right)\right]$$

$$V_a = \frac{3}{4} V_0 \left[\frac{(1+\gamma \tilde{P}_a)^4 - (1+\gamma \tilde{P}_{s1})^4}{(1+\gamma \tilde{P}_a)^3 - (1+\gamma \tilde{P}_{s1})^3}\right]$$

Because the compliance coefficient C_a in the arteries is usually very small, we can make the following approximations:

$$C_a \cong 0 \Rightarrow \gamma \triangleq C_a / V_0 \cong 0 \Rightarrow \quad Q \cong \frac{\tilde{P}_a - \tilde{P}_{s1}}{R_a} \qquad (a_2)$$

$$V_a \cong \frac{C_a}{2}\left(\tilde{P}_a + \tilde{P}_{s1}\right) + V_0$$

The approximated formula for V_a is obtained as follows:

$$\frac{(1+\gamma \tilde{P}_a)^4 - (1+\gamma \tilde{P}_{s1})^4}{\underbrace{(1+\gamma \tilde{P}_a)}_{a}{}^3 - \underbrace{(1+\gamma \tilde{P}_{s1})}_{b}{}^3} = \frac{a^4 - b^4}{a^3 - b^3} = \frac{(a^2+b^2)(a+b)(a-b)}{(a^2+ab+b^2)(a-b)} =$$

$$= \frac{\left[(1+\gamma\tilde{P}_a)^2 + (1+\gamma\tilde{P}_{s1})^2\right]\left[2+\gamma(\tilde{P}_a + \tilde{P}_{s1})\right]}{\left[(1+\gamma\tilde{P}_a)^2 + (1+\gamma\tilde{P}_a)(1+\gamma\tilde{P}_{s1}) + (1+\gamma\tilde{P}_{s1})^2\right]} =$$

we neglect the terms in γ^2

$$= \frac{\left[2 + 2\gamma(\tilde{P}_a + \tilde{P}_{s1}) + \gamma^2(\tilde{P}_a^{\,2} + \tilde{P}_{s1}^{\,2})\right]\left[2+\gamma(\tilde{P}_a+\tilde{P}_{s1})\right]}{3(1+\gamma(\tilde{P}_a+\tilde{P}_{s1})) + \gamma^2(\tilde{P}_a^{\,2} + \tilde{P}_a\tilde{P}_{s1} + \tilde{P}_{s1}^{\,2})} \cong \frac{2}{3}\left[2+\gamma(\tilde{P}_a+\tilde{P}_{s1})\right] \Rightarrow$$

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$$V_a \cong \frac{3}{4} V_0 \cdot \frac{2}{3}\left[2+\gamma(\tilde{P}_a+\tilde{P}_{s1})\right] = V_0 + \frac{\gamma V_0}{2}(\tilde{P}_a+\tilde{P}_{s1}) = V_0 + \frac{C_a}{2}(\tilde{P}_a+\tilde{P}_{s1})$$

Veins:

$$Q = \frac{1}{R_v}(\tilde{P}_{s2}-\tilde{P}_v)\left[1+\hat{\gamma}(\tilde{P}_{s2}+\tilde{P}_v)+\frac{\hat{\gamma}^2}{3}(\tilde{P}_{s2}^2+\tilde{P}_{s2}\tilde{P}_v+\tilde{P}_v^2)\right]$$

$$V_v = \frac{3}{4}\hat{V}_0\left[\frac{(1+\hat{\gamma}\tilde{P}_{s2})^4-(1+\hat{\gamma}\tilde{P}_v)^4}{(1+\hat{\gamma}\tilde{P}_{s2})^3-(1+\hat{\gamma}\tilde{P}_v)^3}\right]$$

where: $\hat{V}_0 \triangleq$ volume of the veins under no pressure drop

$\hat{\gamma} \triangleq C_v/\hat{V}_0$

By using the same argument used for the arteries, we can write:

$$Q \cong \frac{\tilde{P}_{s2}-\tilde{P}_v}{R_v} \qquad V_v \cong \hat{V}_0 + \frac{C_v}{2}(\tilde{P}_{s2}+\tilde{P}_v) \qquad (a_3)$$

Capillaries: $$Q = \frac{\tilde{P}_{s1}-\tilde{P}_{s2}}{R_s} \qquad (a_4)$$

At this point $(a_1)-(a_4)$ provide a system of 6 equations for 7 unknown variables, i.e., $\tilde{P}_a, \tilde{P}_v, \tilde{P}_{s1}, \tilde{P}_{s2}, \tilde{V}_a, \tilde{V}_v$, and $Q \Rightarrow$ We need one more equation. This eq. can be obtained by observing that the total volume of arteries and veins is on average constant, i.e.: $V_a + V_v = V$ - constant $\Rightarrow$ By using this, $(a_1)-(a_4)$ provides a unique solution.

Let us solve $(a_1)-(a_4)$ under the following simplifying conditions:

$$\left.\begin{array}{l} V_h \ll C_d\tilde{P}_v - C_s\tilde{P}_a \\ C_s \cong 0 \end{array}\right\} \Rightarrow \qquad Q \cong F C_d \tilde{P}_v \qquad (a_1')$$

$$\left.\begin{array}{l} R_a \cong 0 \\ V_0 \ll \dfrac{C_a}{2}\left(\tilde{P}_a + \tilde{P}_{s1}\right) \end{array}\right\} \Rightarrow \begin{array}{l} \tilde{P}_a \cong \tilde{P}_{s1} \\ V_a \cong C_a \tilde{P}_a \end{array} \qquad (a_2')$$

$$\left.\begin{array}{l} R_v \cong 0 \\ \hat{V}_0 \ll \dfrac{C_v}{2}\left(\tilde{P}_{s2} + \tilde{P}_v\right) \end{array}\right\} \Rightarrow \begin{array}{l} \tilde{P}_{s2} \cong \tilde{P}_v \\ V_v \cong C_v \tilde{P}_v \end{array} \qquad (a_3')$$

From $(a_1')-(a_3')$ we obtain:

$$Q = \frac{\tilde{P}_a - \tilde{P}_v}{R_s} \qquad (a_4')$$

$$C_a \tilde{P}_a + C_v \tilde{P}_v = V \text{ - constant}$$

The solution for the simplified system $(a_1')-(a_4')$ is:

$$\tilde{P}_v = \frac{V}{C_v + C_a(1 + F C_d R_s)} \qquad \tilde{P}_a = \frac{1 + F C_d R_s}{C_v + C_a(1 + F C_d R_s)} V$$

$$Q = \frac{F C_d}{C_v + C_a(1 + F C_d R_s)} V$$

Note that the solution indicates:

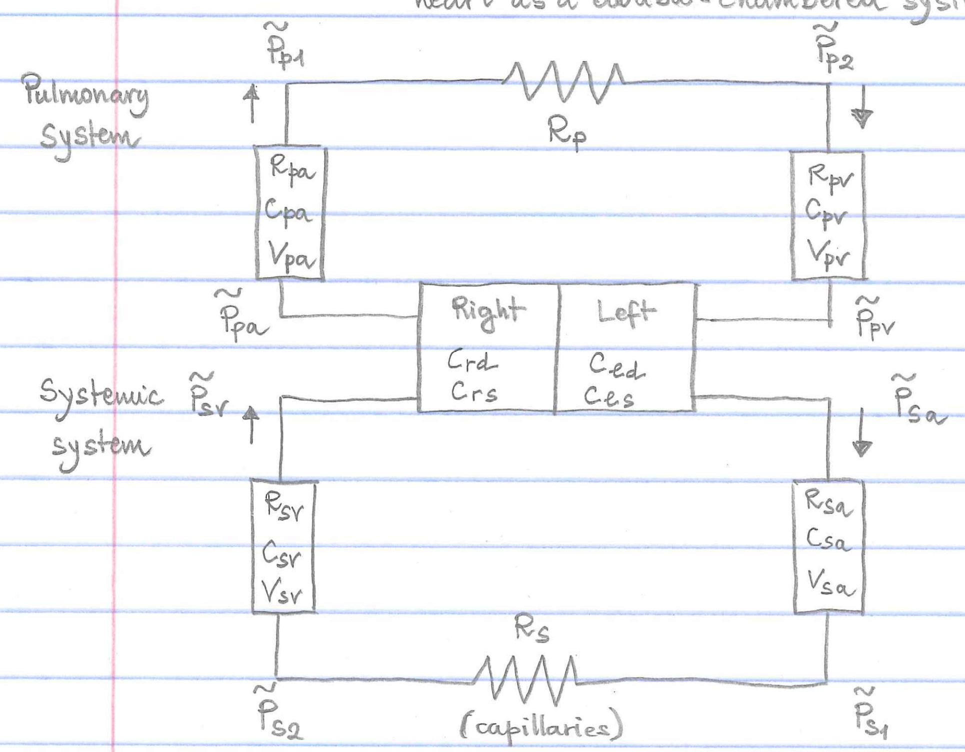
- As F increases (e.g., during exercise) $\tilde{P}_a \to V/C_a$
- As F decreases (i.e., $F \to 0$) $\tilde{P}_a \to V/(C_a + C_v)$ and $\tilde{P}_a \to \tilde{P}_v$

  Moreover, $\tilde{P}_v$ has an evolution that is opposite to $\tilde{P}_a$, i.e., it increases as F decreases and it decreases as F increases $\Rightarrow$ The condition $\tilde{P}_a \cong \tilde{P}_v$ (i.e., no pressure drop) determines no blood flow and it is typical during heart failure
- As R_s increases, Q decreases (i.e., less cardiac output), $\tilde{P}_v$ decreases, while $\tilde{P}_a$ increases $\Rightarrow$ V_a increases while V_v decreases

* A more realistic (multicompartment) model of the circulatory system

The predictions of the previous model are qualitative consistent with the clinical observations. However, the assumption that all the capillaries can be lumped into one single systemic resistance R_s does not take into account that capillaries in different regions may have different values for R_s or that, despite large variations in the value of R_s, the cardiac output does not experience large changes $\Rightarrow$ We need to refine the model:

- Regarding 3): Let us preserve the model with 3 vessels (i.e., veins, arteries, and capillaries) but let us have different vessels for pulmonary and systemic system.
  Because of two circulatory subsystems, let us model the heart as a double-chambered system



(1) Equations for the Systemic system:

Arteries:

$$Q \cong \frac{\tilde{P}_{sa} - \tilde{P}_{s1}}{R_{sa}}$$

$$V_{sa} = V_{0s} + \frac{C_{sa}}{2}\left(\tilde{P}_{sa} + \tilde{P}_{s1}\right)$$

Veins:

$$Q \cong \frac{\tilde{P}_{s2} - \tilde{P}_{sv}}{R_{sv}}$$

$$V_{sv} = V_{0v} + \frac{C_{sv}}{2}\left(\tilde{P}_{sv} + \tilde{P}_{s2}\right)$$

Heart and capillaries:

$$Q = F\left(C_{ld}\tilde{P}_{pv} - C_{ls}\tilde{P}_{sa}\right)$$

$$Q = \frac{\tilde{P}_{s1} - \tilde{P}_{s2}}{R_s}$$

(2) Equations for the Pulmonary system:

Arteries:

$$Q \cong \frac{\tilde{P}_{pa} - \tilde{P}_{p1}}{R_{pa}}$$

$$V_{pa} \cong V_{0p} + \frac{C_{pa}}{2}\left(\tilde{P}_{pa} + \tilde{P}_{p1}\right)$$

Veins:

$$Q \cong \frac{\tilde{P}_{p2} - \tilde{P}_{pv}}{R_{pv}}$$

$$V_{pv} = \hat{V}_{0v} + \frac{C_{pv}}{2}\left(\tilde{P}_{pv} + \tilde{P}_{p2}\right)$$

Heart and capillaries:

$$Q = F\left(C_{rd}\tilde{P}_{sv} - C_{rs}\tilde{P}_{pa}\right)$$

$$Q = \frac{\tilde{P}_{p2} - \tilde{P}_{p1}}{R_p}$$

Typically, the constant values V_{0v} and $\hat{V}_{0v}$ are neglected. The total volume is kept constant on average $\Rightarrow$ $V_{sa} + V_{sv} + V_{pa} + V_{pv} = V$ - constant (3)

The combination of equations (1)-(3) provides a system of 13 equations in 13 variables (pressures, volumes, and Q) $\Rightarrow$ There is a unique solution.

An analytical solution can be derived under the following simplifying assumptions:

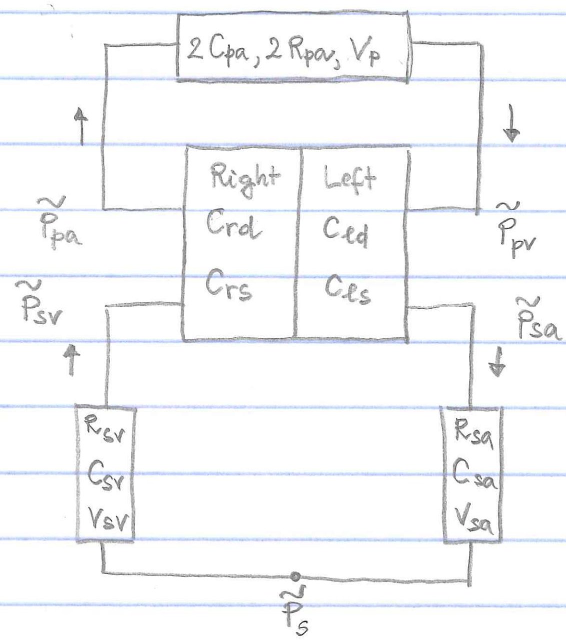
$$\left.\begin{array}{l} \bullet\ \tilde{P}_{pa} \cong \tilde{P}_{p1} \\ \bullet\ \tilde{P}_{pv} \cong \tilde{P}_{p2} \\ \bullet\ \tilde{P}_{s1} \cong \tilde{P}_{s2} \end{array}\right\} \text{This reduces the system to 10 equations in 10 variables}$$

- $R_s \cong 0$
- $R_p \cong 0$

$\Rightarrow$ The capillary resistances are neglected

- $C_{pa} \cong C_{pv}$
- $R_{pa} \cong R_{pv}$

$\Rightarrow$ The pulmonary system is represented as a single compliant vessel with volume $V_p \triangleq V_{pa} + V_{pv}$



In this case, the equations become:

$$Q = \frac{\tilde{P}_{pa} - \tilde{P}_{pv}}{2R_{pa}} \qquad Q = \frac{\tilde{P}_{sa} - \tilde{P}_{s}}{R_{sa}}$$

$$V_p = V_{op} + \frac{2C_{pa}}{2}\left(\tilde{P}_{pa} + \tilde{P}_{pv}\right) \qquad V_{sa} = V_{os} + \frac{C_{sa}}{2}\left(\tilde{P}_{sa} + \tilde{P}_{s}\right)$$

$$Q = F C_{rd} \tilde{P}_{sv} \qquad Q = F C_{ed} \tilde{P}_{pv}$$

$$Q = \frac{\tilde{P}_{s} - \tilde{P}_{sv}}{R_{sv}} \qquad V_{sv} = \frac{C_{sv}}{2}\left(\tilde{P}_{sv} + \tilde{P}_{s}\right)$$

$$V_{sv} + V_{sa} + V_p = V - \text{constant}$$

The solution results:

$$\tilde{P}_{sa} = Q\left(R_{sa} + R_{sv} + \frac{1}{FC_{rd}}\right)$$

$$\tilde{P}_{sv} = \frac{Q}{FC_{rd}}$$

$$\tilde{P}_{pa} = Q\left(\frac{1}{FC_{ed}} + 2R_{pa}\right)$$

$$\tilde{P}_{pv} = \frac{Q}{FC_{ed}}$$

$$Q = \frac{V_t - V_{os} - V_{op}}{\underbrace{R_{sv}\left(C_{sa} + \frac{C_{sv}}{2}\right) + \frac{R_{sa}C_{sa}}{2} + 2C_{pa}R_{pa}}_{\alpha} + \frac{2C_{pa}}{FC_{ed}} + \frac{C_{sv} + C_{sa}}{FC_{rd}}}$$

From this, we obtain: $Q_\infty = \lim_{F \to \infty} Q = \frac{V_t - V_{os} - V_{op}}{\alpha}$ - The CO saturates as the heart rate increases

Moreover, the solution for Q indicates that the CO depends on the excess blood volume beyond that at zero pressure $\Rightarrow$ In trauma, if the loss of blood is not compensated by increased heart rate (e.g., via drugs) or changes in compliance and resistance, the CO can rapidly drop.

* Expanding the model with regulation mechanisms

All the models provided thus far give an instantaneous relationship between CO, pressures, and resistances. $\Rightarrow$ If the conditions change (e.g., we consider the circulatory system during intense physical exercise vs. rest; while the body is supine vs. standing up; etc.) we expect changes in pressures and, hence, variations in vessel volumes and CO $\Rightarrow$ However, this does not happen!

The body implements numerous mechanisms to maintain CO and pressures as constant and uniform as possible despite the occurrence of exogenous events

⇓

Three mechanisms are in place to cope with short-term (i.e., seconds to hours) fluctuations:

- AUTOREGULATION → It acts locally at the level of individual tissues and modulates the blood flow in response to oxygen needs while keeping the arterial pressure constant

- BARORECEPTOR REFLEX → It acts at the level of heart and veins by modulating the heart rate and the venous resistance to maintain the arterial pressure and CO constant

- HUMORAL CONTROL → It acts on the fluidodynamic properties of the blood (e.g., density and viscosity) via release of hormones and other substances to regulate pressures

Let us expand our models to encompass the (local) effects of autoregulation:

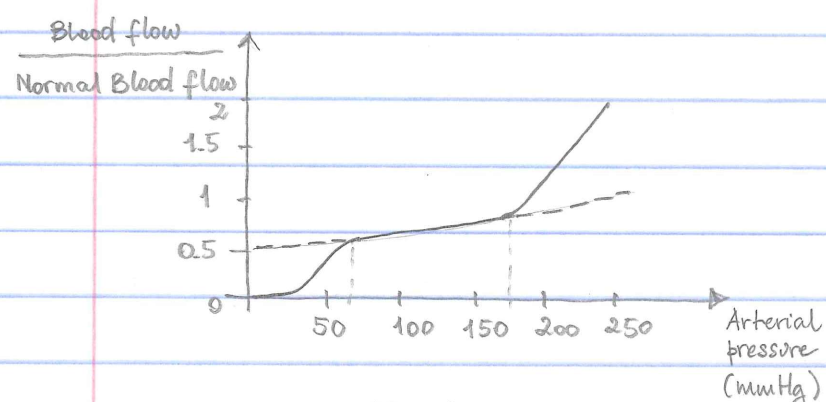


Fig. 1

⇐ In our models, the blood flow grows with arterial pressure. However, from real measurements (see figure) one can see that large changes in pressure cause small changes in blood flow

Hence, there must be a local mechanism to increase the blood flow regardless of the arterial pressure, just in response to the need for oxygen. One option is:

More O_2 is needed than available from the blood stream $\Rightarrow$ Cells degrade ATP to extract additional O_2 and - in doing so - they release adenosine in the blood stream $\Rightarrow$ Adenosine works as a local vasodilator, i.e., it relaxes the muscle fibers surrounding the vessels $\Rightarrow$ The arterial vessels locally dilate and thus reduce the systemic resistance

A possible way to model this in a tissue is:

$M \triangleq$ metabolic rate (i.e., oxygen consumption/time)

$Q \triangleq$ blood flow

$[O_2]_a, [O_2]_v \triangleq$ concentration of O_2 in the arterial (a) and venous (v) component

$$\left.\begin{aligned} M &= Q\left([O_2]_a - [O_2]_v\right) \\ \tilde{P}_a - \tilde{P}_v &= Q R \\ R &= R_0\left(1 + a[O_2]_v\right) \quad a>0 \end{aligned}\right\} \Rightarrow \begin{aligned} [O_2]_v &= [O_2]_a - \frac{M}{Q} \\ Q R_0\left(1+a[O_2]_v\right) &= \tilde{P}_a - \tilde{P}_v \end{aligned} \Rightarrow$$

$$\Rightarrow Q = \frac{1}{1 + a[O_2]_a} \cdot \left(a M + \frac{\tilde{P}_a - \tilde{P}_v}{R_0}\right) \qquad (\Delta\nabla)$$

For $a>0$ this equation captures two facts, i.e., the blood flow grows linearly with the arterial pressure AND the sensitivity of Q to $\tilde{P}_a$ decreases as the availability of O_2 increases. Moreover, it indicates that Q grows linearly with the metabolism.

* How do we estimate a and R_0 from data?

From Fig. 1 (which can actually be constructed from measuraments) one can note that – between $\tilde{P}_a = 75$ mmHg and $\tilde{P}_a = 175$ mmHg – there is a linear relationship between $\tilde{P}_a$ and Q/Q^*, with $Q^* \triangleq$ normal blood flow. If we define Q^* as the blood flow at nominal pressure $\tilde{P}_a = P^* = 100$ mmHg, then we have:

$P^* \cong 100$ mmHg
$\Downarrow$
$Q^* \cong 5.6$ liters/min

$\Rightarrow$ The linear segment has equation:

$$\frac{Q}{Q^*} = \frac{1}{3} + \frac{2}{3}\frac{\tilde{P}_a}{P^*} \qquad (\nabla\Delta\nabla)$$

From $(\Delta\nabla)$ one must have:

$$Q^* = \frac{1}{1+a[O_2]_a^*}\left(aM^* + \frac{P^* - \tilde{P}_v}{R_0}\right)$$

$$M^* = Q^*\left([O_2]_a^* - [O_2]_v^*\right)$$

By using $(\nabla\Delta\nabla)$ and assuming $\tilde{P}_v << \tilde{P}_a, P^*$, we can write:

$$\frac{Q}{Q^*} = \frac{1/Q^*}{1+a[O_2]_a}\left(aM + \frac{\tilde{P}_a}{R_0}\right) = \frac{1}{3} + \frac{2}{3}\frac{\tilde{P}_a}{P^*} \Rightarrow$$

$$\frac{\tilde{P}_a}{R_0 Q^*}\cdot\frac{1}{1+a[O_2]_a} = \frac{2}{3}\frac{\tilde{P}_a}{P^*} \Rightarrow \frac{P^*}{R_0} = \frac{2}{3}Q^*\left(1+a[O_2]_a\right)$$

$$\frac{Ma}{Q^*}\cdot\frac{1}{1+a[O_2]_a} = \frac{1}{3} \Rightarrow 1+a[O_2]_a = 3\frac{Ma}{Q^*}$$

$\frac{p^*}{R_o} = 2Ma$ - Also we have:

$$Q^* = \frac{1}{1+a[O_2]_a^*}\left(aM^* + \frac{p^*}{R_o}\right) = \frac{aM^* + 2aM}{1+a[O_2]_a^*} = \frac{3aM^*}{1+a[O_2]_a^*}$$

Because Q^* is const.

$$\Rightarrow a = \frac{Q^*}{3M^* - Q^*[O_2]_a^*}$$

$$R_o = \frac{p^*}{2aM^*} = \frac{p^*(3M^* - Q^*[O_2]_a^*)}{2Q^*M^*}$$

■

REFERENCE:

Textbook (volume 2): chapter 11, sec. 11.5.1; 11.5.2; 11.5.3; 11.6; 11.6.1