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DI TRENTO

# Biophysics of the cardiovascular system, mathematical modeling, and marfan syndrome

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# Viscosity

## Viscosity

The *viscosity* of a fluid is a measure of its resistance to deformation at a given rate.

$$F = \mu A \frac{u}{y}$$

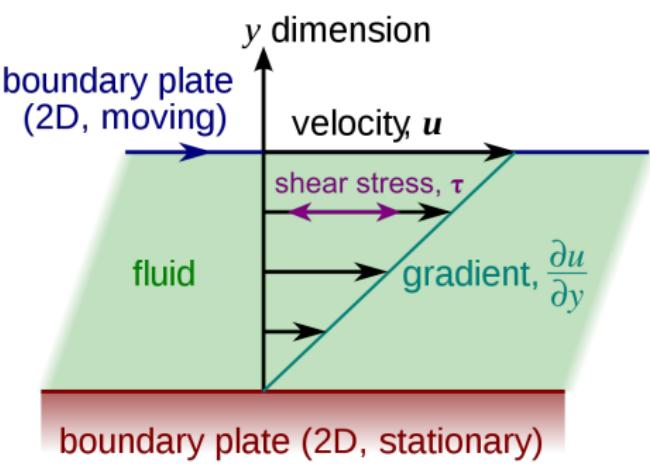
$A$  - Area of plate

$u$  - velocity

$\mu$  - (dynamic) viscosity

$y$  - distance between plates

$$[\mu] = \frac{N}{m^2} \cdot t = Pa \cdot t$$



## Rate of shear deformation / shear velocity

The fraction  $\tau = \frac{u}{y}$  is called *rate of shear (deformation) or shear velocity*.

If  $u$  does not vary linearly with  $y$ , a generalization is:

## Generalized shear stress (Newton-Stokes law)

*Shear stress* can be generally defined as:  $\tau = \mu \frac{\partial u}{\partial y} (= \frac{F}{A})$ .

By evaluating the partial derivative at  $y = 0$  we get the *wall shear stress* that expresses the retarding force (per unit area) from a wall in the layers of a fluid flowing next to the wall.

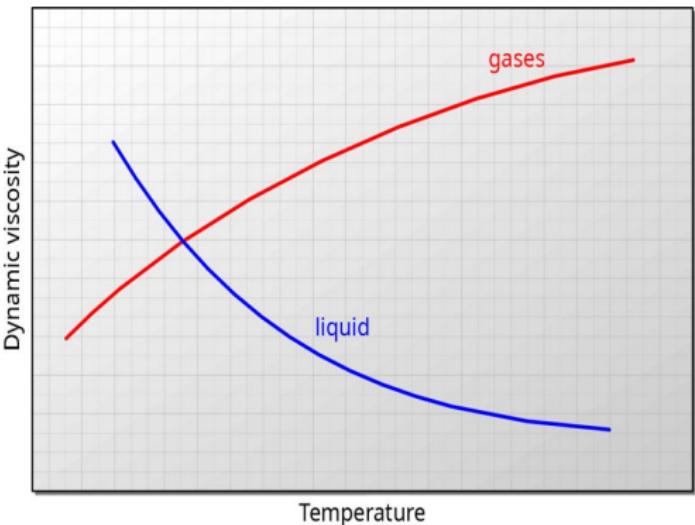
Fluids that follow this law are called **Newtonian fluids**.

# Viscosity depends on temperature



## Viscosity of water

Temperature (°C)	Viscosity (mPa·s)
10	1.3059
20	1.0016
30	0.79722
50	0.54652
70	0.40355
90	0.31417



For liquid, there is an asymptotic value of viscosity at infinitely high temperature.



## Hemorheology

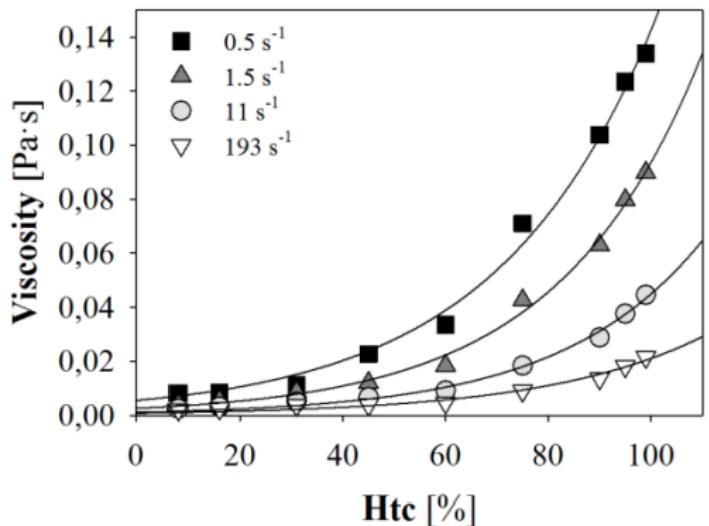
*Hemorheology* is the study of flow properties of blood and its elements of plasma and cells.

Proper tissue perfusion can occur only when blood's rheological properties are within certain levels.

Blood viscosity is determined by:

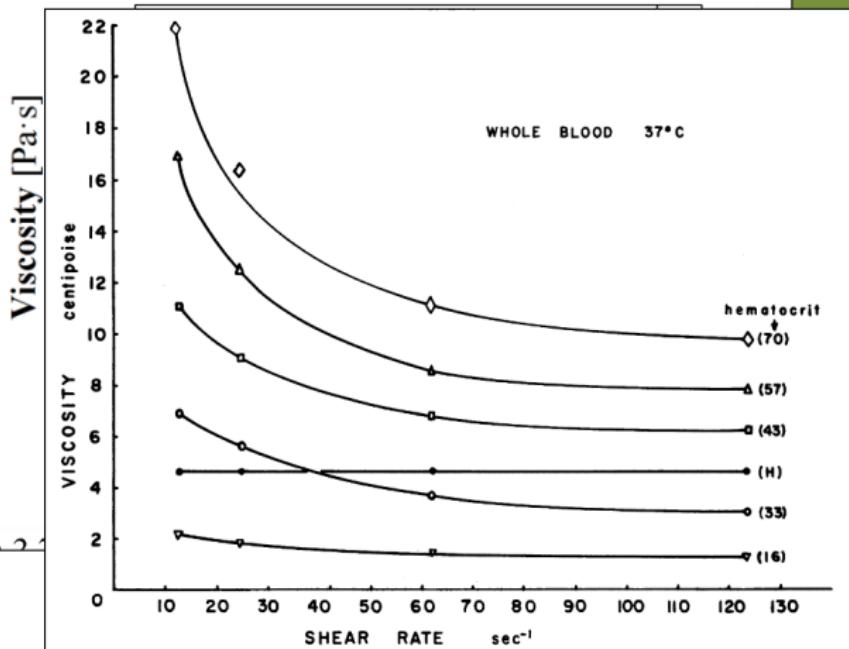
- Plasma viscosity
- Hematocrit
- Mechanical properties of red blood cells ( $\Rightarrow$  blood is non-Newtonian fluid: **shear thinning**)

# Blood viscosity: properties

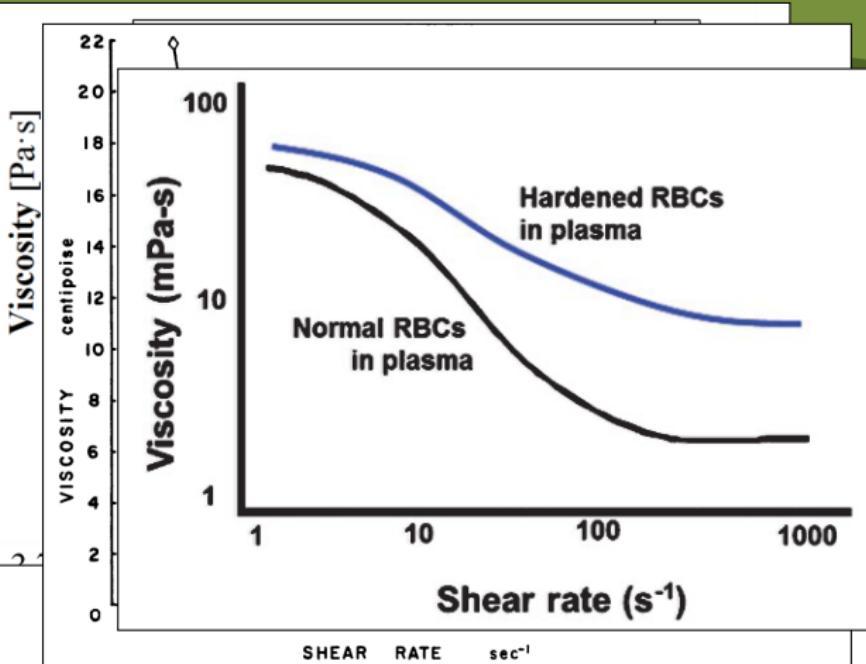


2.7 Viscosity as a function of Hct at four different shear rates

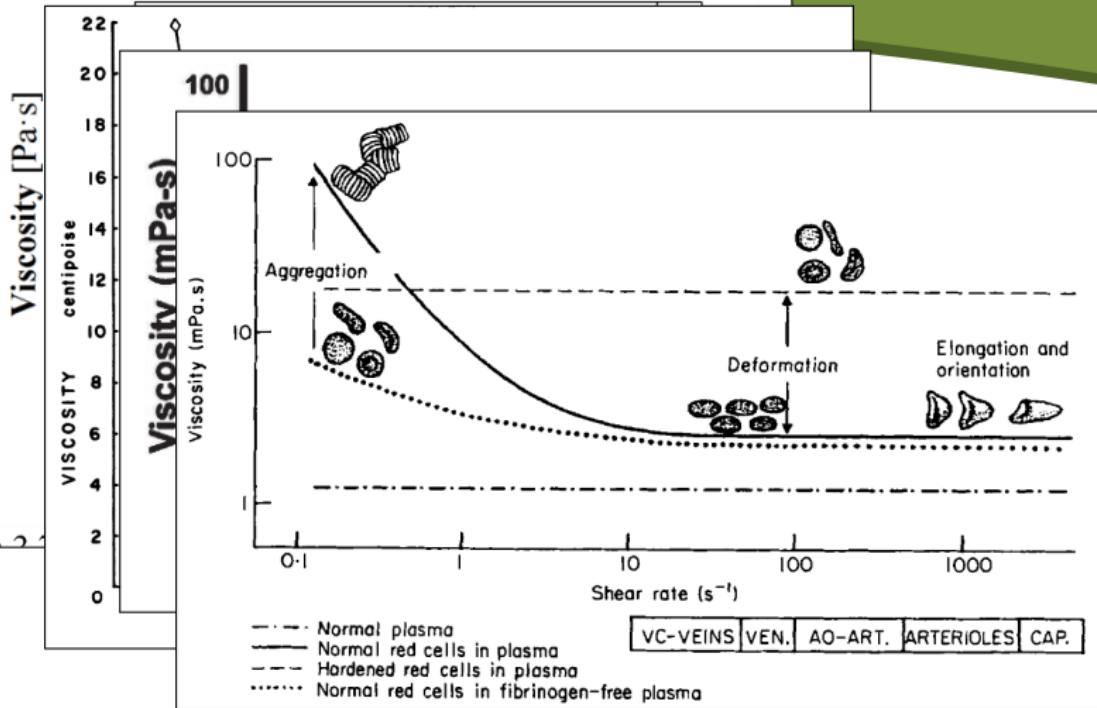
# Blood viscosity: properties



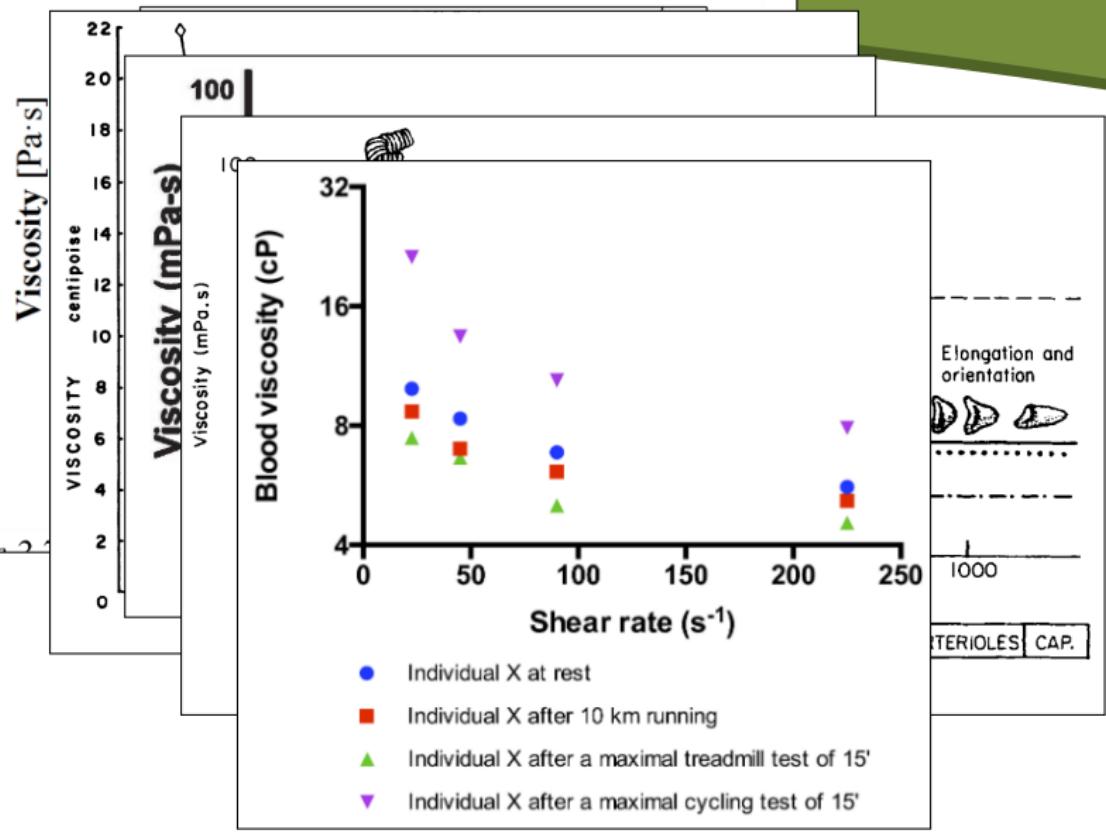
# Blood viscosity: properties



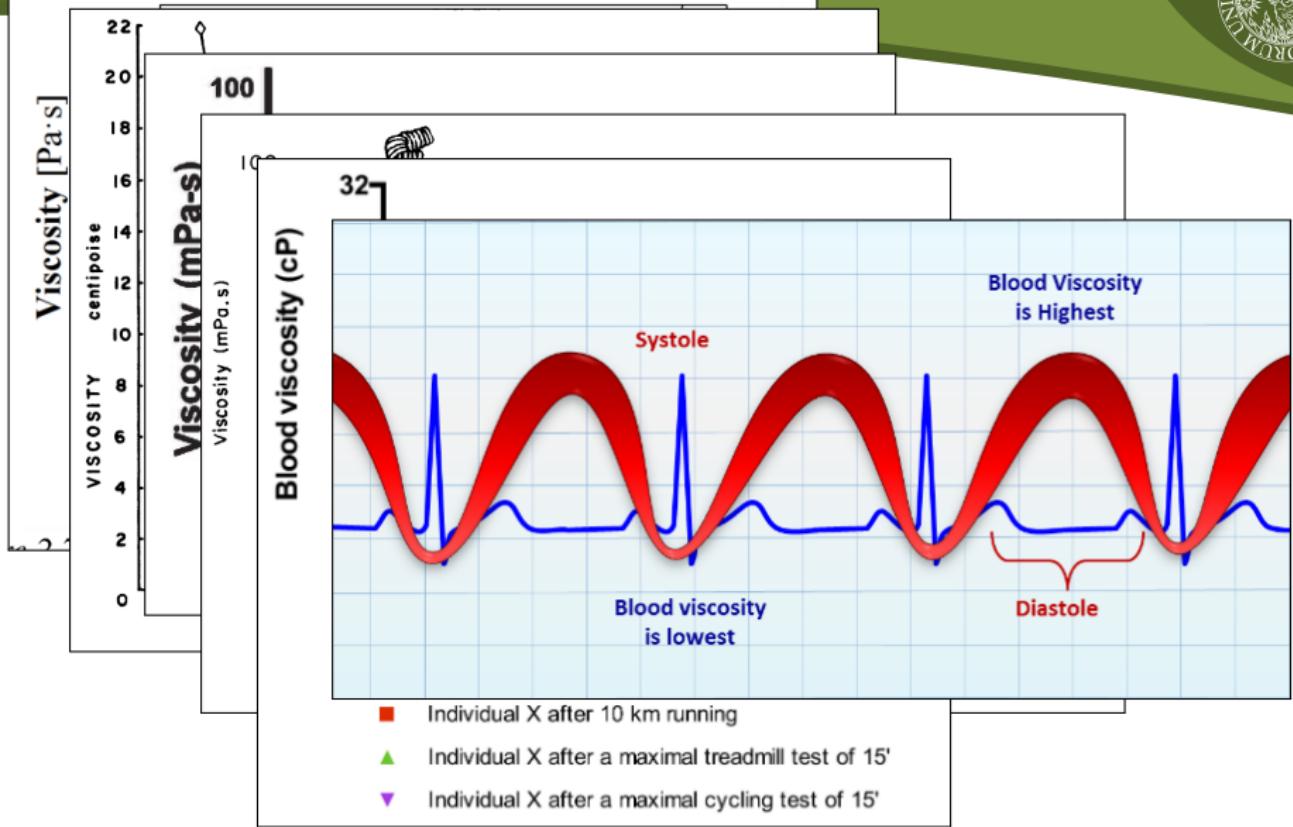
# Blood viscosity: properties



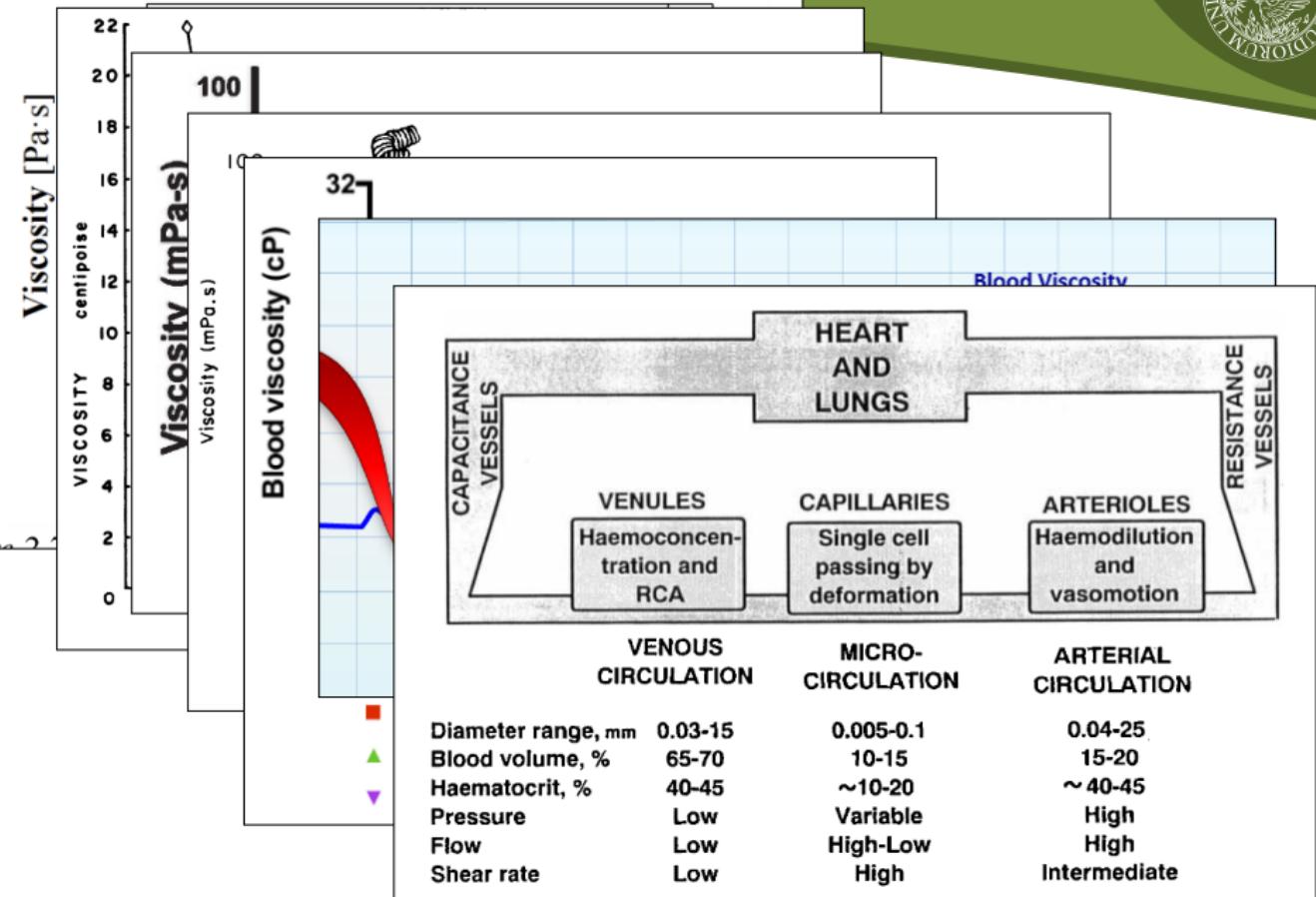
# Blood viscosity: properties



# Blood viscosity: properties



# Blood viscosity: properties





## Laws of flow: continuity equation

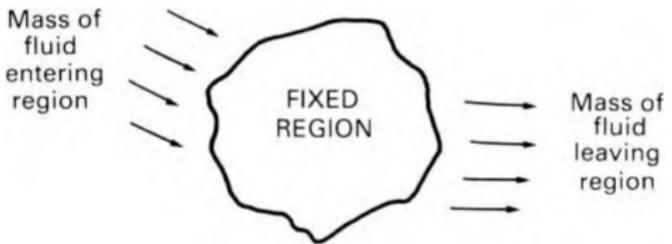
## Principle of mass conservation

Matter can neither be created nor destroyed.

I apply this to a flowing fluid, considering a fixed region in the flow:

## Principle of mass conservation for fluids

$$\text{Mass of fluid entering per unit time} = \text{Mass of fluid leaving per unit time} + \text{Increase of mass of fluid in the control volume per unit time (accumulation)}$$



# Continuity equation: steady flow



For a steady flow (i.e. does not change in time) the mass of fluid in the control volume is constant:

Principle of mass conservation for fluids: steady flow

$$\text{Mass of fluid entering per unit time} = \text{Mass of fluid leaving per unit time}$$

# Continuity equation in a tube



Applying this principle to a streamtube we obtain:

$$\begin{array}{lcl} \text{Mass of fluid entering} & = & \text{Mass of fluid leaving} \\ \text{per unit time at section 1} & = & \text{per unit time at section 2} \end{array}$$

Hence:

$$\rho_1 A_1 u_1 = \rho_2 A_2 u_2$$

If the fluid can be considered incompressible, i.e.  $\rho_1 = \rho_2$ , then:

$$A_1 u_1 = A_2 u_2 = Q$$

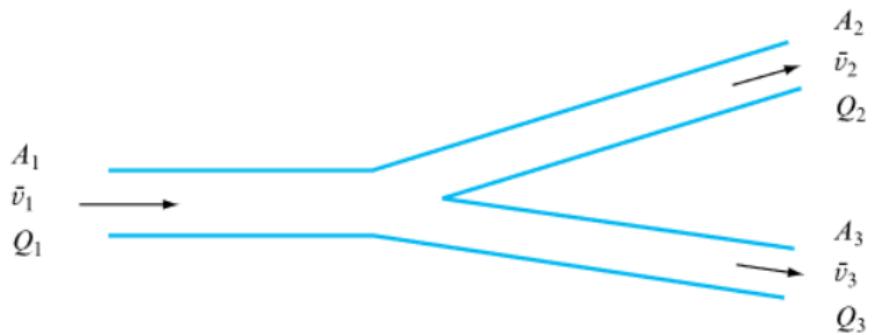
where  $Q$  is the volumetric flow rate.

# Continuity equation: junction



Clearly in junction the equation holds:

$$\text{Total inflow to junction} = \text{Total outflow from junction}$$

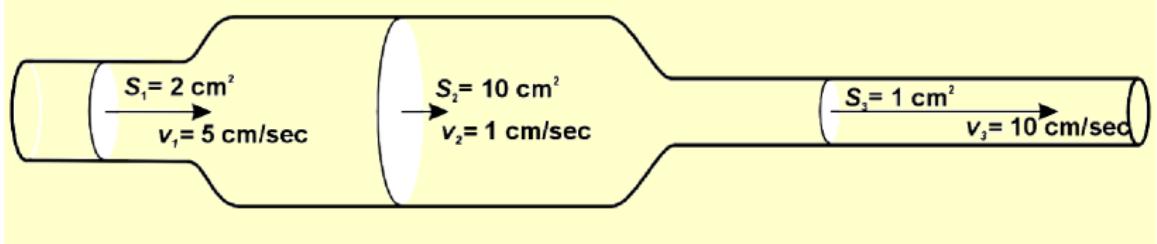


$$\rho_1 Q_1 = \rho_2 Q_2 + \rho_3 Q_3$$

# Continuity equation: cardiovascular system



For the same volume of fluid per second passing from section area  $S_1$  to section area  $S_2$ , which is five times greater, the velocity of flow diminishes to one fifth of its previous value.



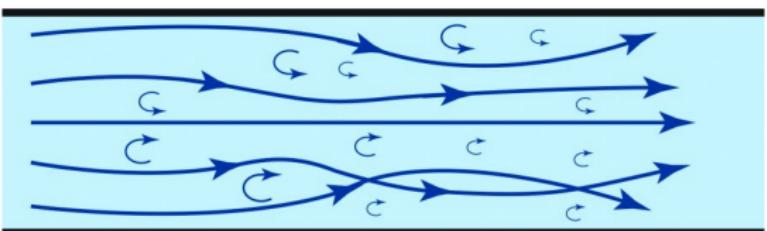


## Laws of flow: Hagen–Poiseuille law

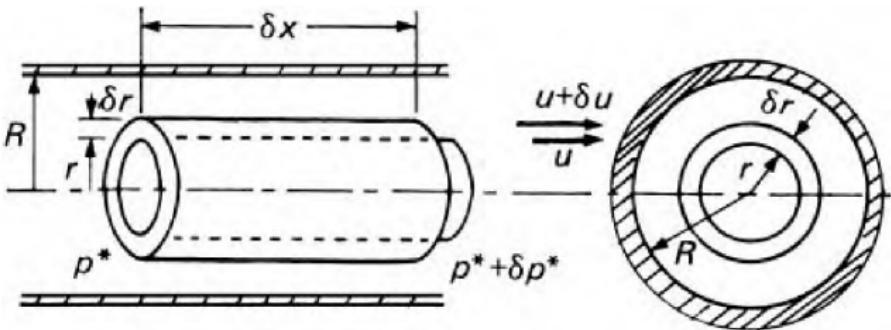
## Laminar Flow



## Turbulent Flow



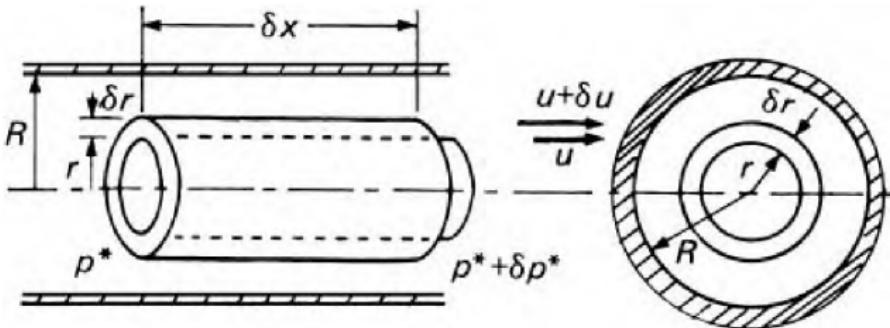
# Laminar flow in circular pipes



In laminar flow the paths of individual particles do not cross, so the pattern of flow may be imagined as a number of thin, concentric cylinders which slide over one another.

The diagram shows a cylinder of radius  $r$ , moving from left to right with velocity  $u$  inside a slightly larger cylinder of radius  $r + \delta r$  moving in the same direction with velocity  $u + \delta u$

# Laminar flow in circular pipes

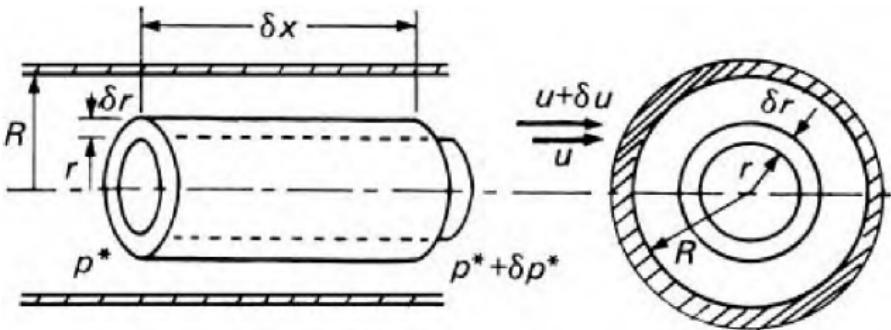


Force balance on the inner cylinder:

$$p^* \pi r^2 - (p^* + \delta p^*) \pi r^2 + \tau 2\pi r \delta x = 0$$

$$\Rightarrow \tau = \frac{(p^* + \delta p^*) - p^*}{\delta x} \frac{r}{2} \xrightarrow{\delta x \rightarrow 0} \frac{r}{2} \frac{dp^*}{dx}$$

# Laminar flow in circular pipes



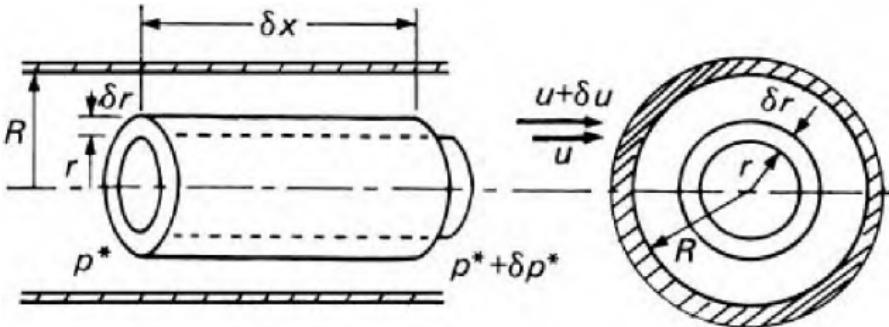
Hence:

$$\mu \frac{du}{dr} = \tau = \frac{r}{2} \frac{dp^*}{dx} \Rightarrow \frac{du}{dr} = \frac{r}{2\mu} \frac{dp^*}{dx}$$

Integrating:

$$u = \frac{r^2}{4\mu} \frac{dp^*}{dx} + A$$

# Laminar flow in circular pipes



To define  $A$  we need boundary conditions: we assume that there is no slip at the wall of the pipe:

$$u|_{r=R} = 0 \quad \Rightarrow \quad A = -\frac{R^2}{4\mu} \frac{dp^*}{dx}$$

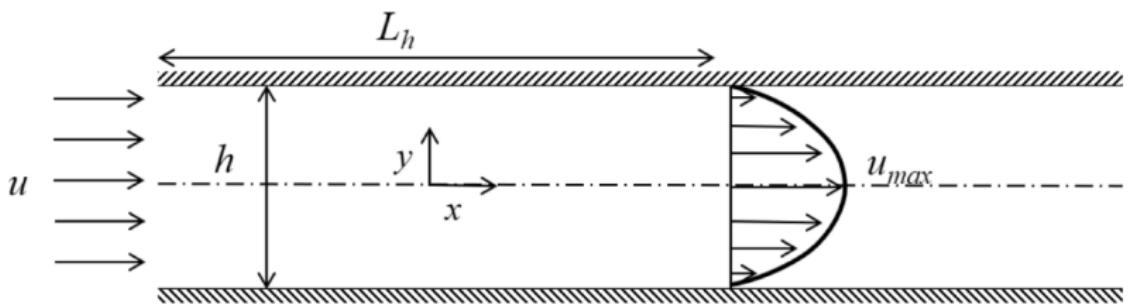
Hence:

$$u = -\frac{1}{4\mu} \frac{dp^*}{dx} (R^2 - r^2)$$

# Laminar flow: velocity profile



$$u = -\frac{1}{4\mu} \frac{dp^*}{dx} (R^2 - r^2)$$





## Discharge

The discharge of a canal can be computed as:

$$Q = VA$$

where  $V$  is the average flow velocity,  $A$  is the area of the cross-section.

Using the above equation, the discharge  $\delta Q$  through the annular space between radii  $r$  and  $r + \delta r$  is  $\delta Q = u2\pi r \delta r$ , hence:

$$\delta Q = -\frac{1}{4\mu} \frac{dp^*}{dx} (R^2 - r^2) 2\pi r \delta r = -\frac{\pi}{2\mu} \frac{dp^*}{dx} (R^2 r - r^3) \delta r$$



We can obtain the discharge through the entire section by integrating  $r$  in  $[0, R]$ :

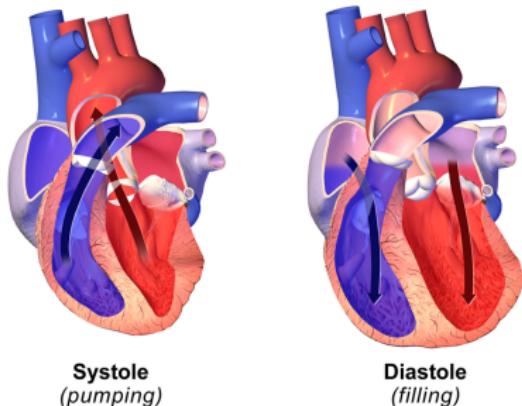
$$Q = \int_0^R \delta Q \, dr = -\frac{\pi R^4}{8\mu} \frac{dp^*}{dx}$$

That is called the **Hagen - Poiseuille law**.

For a pipe of length  $l$  over which the pressure drops from  $p_1$  to  $p_2$ , it can be written as:

$$Q = \frac{\pi R^4}{8\mu l} (p_1 - p_2)$$

# In the cardiovascular system: cardiac output



- $CO$  - Cardiac Output, analogue of  $Q$
- $MAP$  - Mean Arterial systolic Pressure, analogue of  $p_1$
- $MVP$  - Mean diastolic ventricular pressure, analogue of  $p_2$

Then we can write:

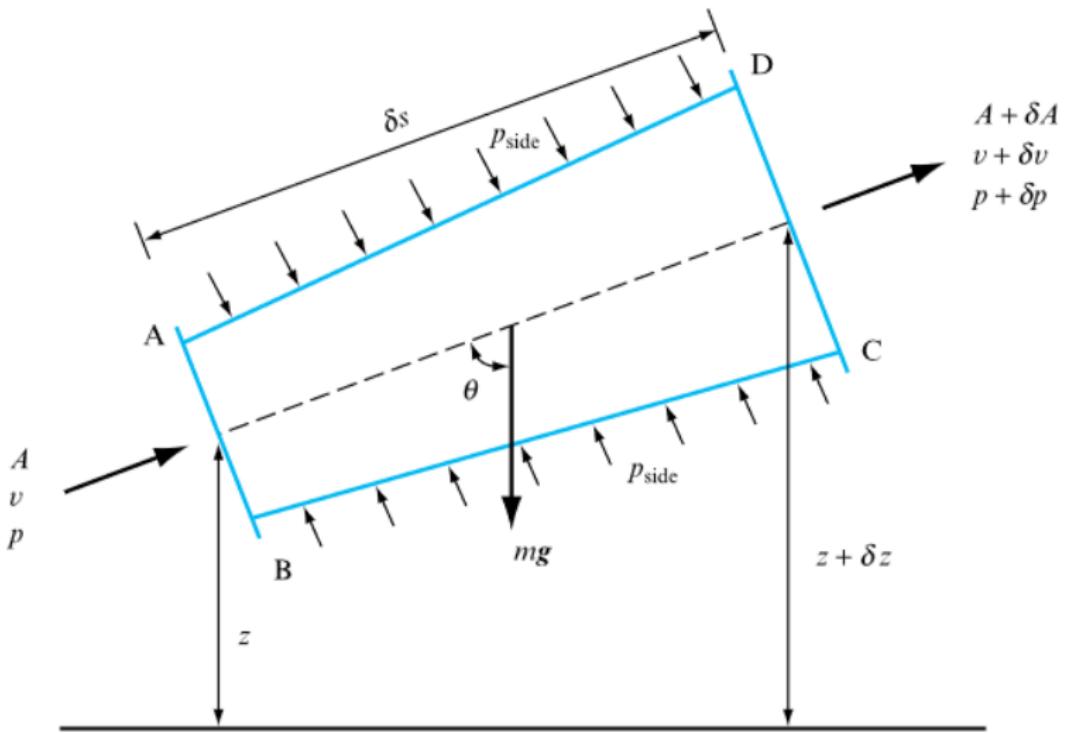
$$CO = \frac{\pi R^4}{8\mu l} (MAP - MVP)$$



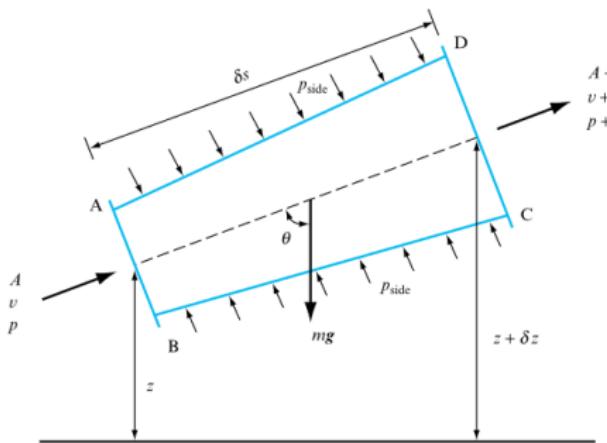
## Laws of flow: Bernoulli's equation

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# Euler's equation



# Euler's equation



Mass per unit time flowing:

$$\rho A v$$

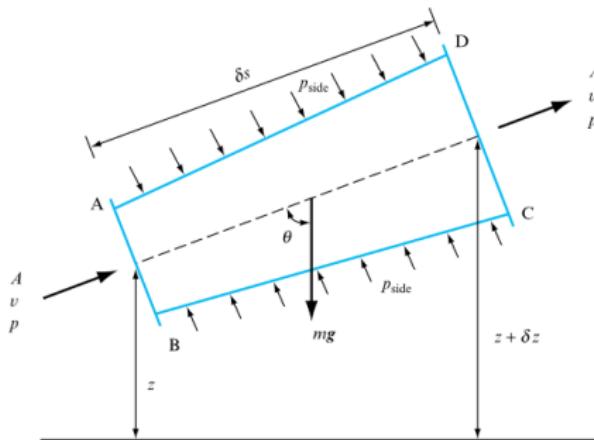
Rate of increase of momentum from AB to CD:

$$\rho A v [(v + \delta v) - v] = \rho A v \delta v$$

# Euler's equation



Forces acting to produce the change of momentum in the direction of motions:



$$F \text{ due to } p = pA$$

$$F \text{ due to } p + \delta p = (p + \delta p)(A + \delta A)$$

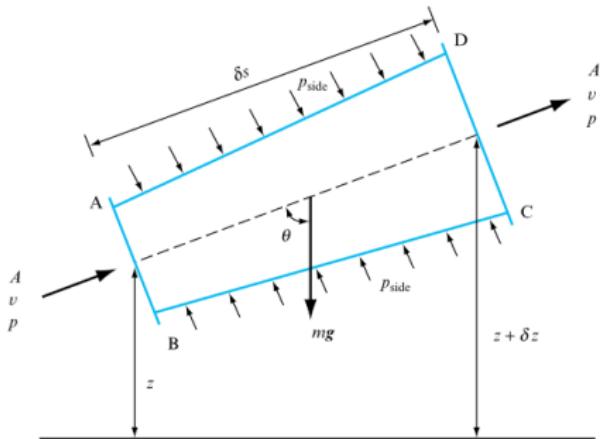
$$F \text{ due to } p_{\text{side}} = p_{\text{side}}\delta A$$

$$F \text{ due to } mg = mg \cos(\theta)$$

Resultant force in the direction of motion:

$$pA - (p + \delta p)(A + \delta A) + p_{\text{side}}\delta A - mg \cos(\theta)$$

# Euler's equation



$$\begin{array}{l} A + \delta A \\ v + \delta v \\ p + \delta p \end{array}$$

One can rewrite:

$$\begin{aligned} mg &= (\rho \times \text{Volume}) \cdot g \\ \Rightarrow mg &= \rho(A + \frac{1}{2}\delta A)\delta s \cdot g \end{aligned}$$

And:

$$\cos\theta = \delta z / \delta s$$

Hence, I rewrite resultant force in the direction of motion:

$$-\rho\delta A - A\delta p - \delta p\delta A + p_{\text{side}}\delta A - pg \left( A + \frac{1}{2}\delta A \right) \delta s (\delta z / \delta s)$$

# Euler's equation



Neglecting product of small quantities, the resultant force in the direction of motion:

$$-A\delta p - \rho g A \delta z$$

Applying Newton's second law to the rate of increase of momentum:

$$\rho A v \delta v = -A\delta p - \rho g A \delta z$$

Dividing by  $\rho A \delta s$ :

$$\frac{1}{\rho} \frac{\delta p}{\delta s} + v \frac{\delta v}{\delta s} + g \frac{\delta z}{\delta s} = 0$$

For  $\delta s \rightarrow 0$  we get the **Euler's equation**:

$$\frac{1}{\rho} \frac{dp}{ds} + v \frac{dv}{ds} + g \frac{dz}{ds} = 0$$

# Bernoulli's equation



In order to integrate we need to know the relationship between density  $\rho$  and pressure  $p$ . Assuming an incompressible fluid where  $\rho$  is constant we can integrate with respect to  $s$ :

$$\frac{p}{\rho} + \frac{v^2}{2} + gz = \text{constant}$$

That is the **Bernoulli's equation**.

# Bernoulli's equation: interpretation



Writing it in the *pressure form*:

$$\underbrace{p}_{\text{Pressure energy}} + \underbrace{\frac{\rho v^2}{2}}_{\text{Kinetic energy}} + \underbrace{\rho g z}_{\text{Potential energy}} = \text{constant}$$

We get a *conservation of energy law*.

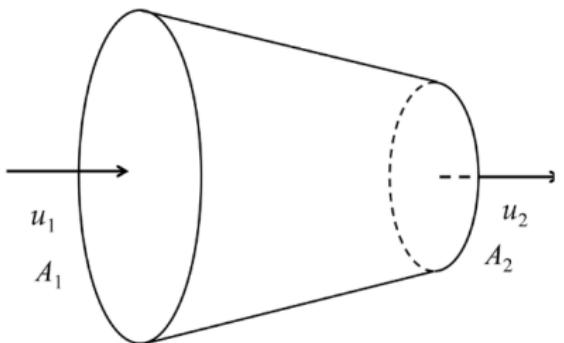
# Bernoulli's equation: shrinking vessel



In figure we see a schematic depiction of an artery that is changing in shape shrinking.

Continuity equation:

$$u_1 A_1 = u_2 A_2$$



I assume there is no significant change in elevation, so the Bernoulli's equation becomes:

$$p_1 + \frac{\rho u_1^2}{2} = p_2 + \frac{\rho u_2^2}{2}$$

$$\Rightarrow p_1 - p_2 = \frac{\rho}{2}(u_2^2 - u_1^2)$$

# Bernoulli's equation: shrinking vessel



What we found:

$$u_1 A_1 = u_2 A_2 \quad p_1 - p_2 = \frac{\rho}{2} (u_2^2 - u_1^2)$$

From the continuity equation:

$$u_2 = \frac{A_1}{A_2} u_1 \quad \Rightarrow \quad p_1 - p_2 = \frac{\rho}{2} u_1^2 \left( \frac{A_1^2}{A_2^2} - 1 \right)$$

Notice:

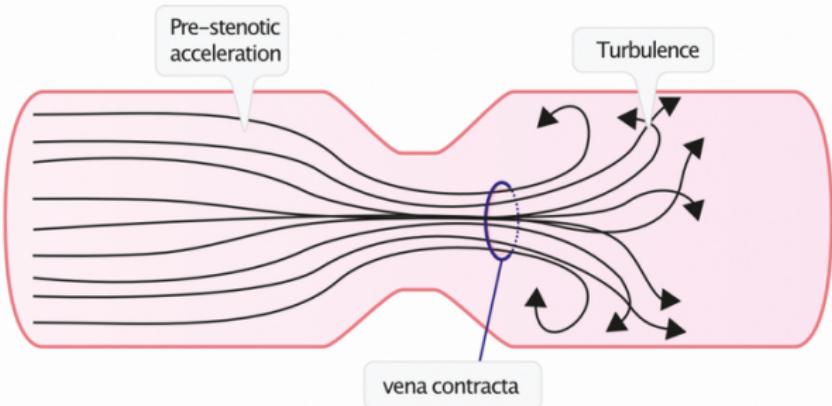
$$A_2 < A_1 \quad \Rightarrow \quad u_2 > u_1$$

$$A_2 < A_1 \quad \Rightarrow \quad \frac{A_1^2}{A_2^2} > 1 \quad \Rightarrow \quad p_1 - p_2 > 0 \quad \Rightarrow \quad p_1 > p_2$$

## Stenosis

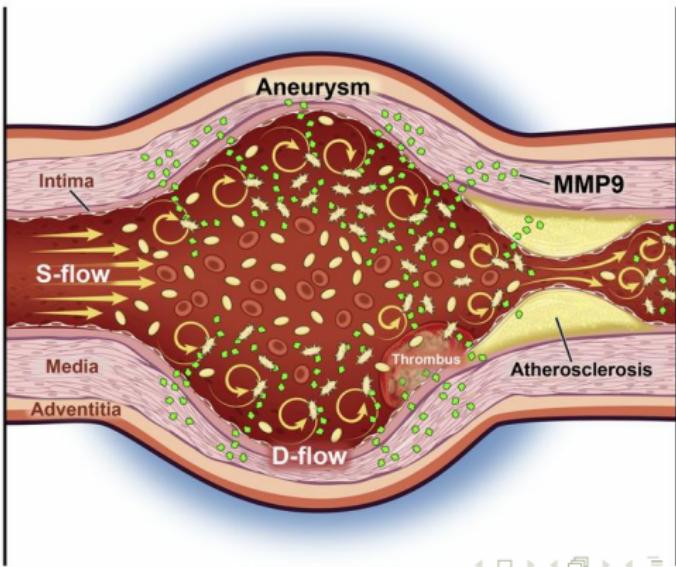
A *stenosis* is an abnormal narrowing in a blood vessel or other tubular organ or structure such as foramina and canals.

### Flow through a stenosis

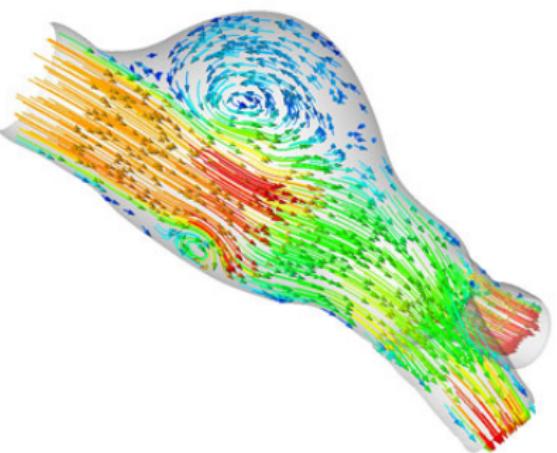
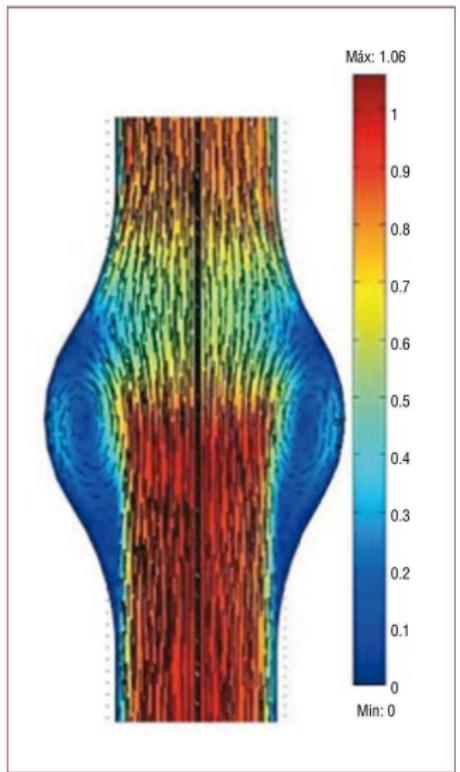


## Aneurysm

An *aneurysm* is an outward bulging, likened to a bubble or balloon, caused by a localized, abnormal, weak spot on a blood vessel wall



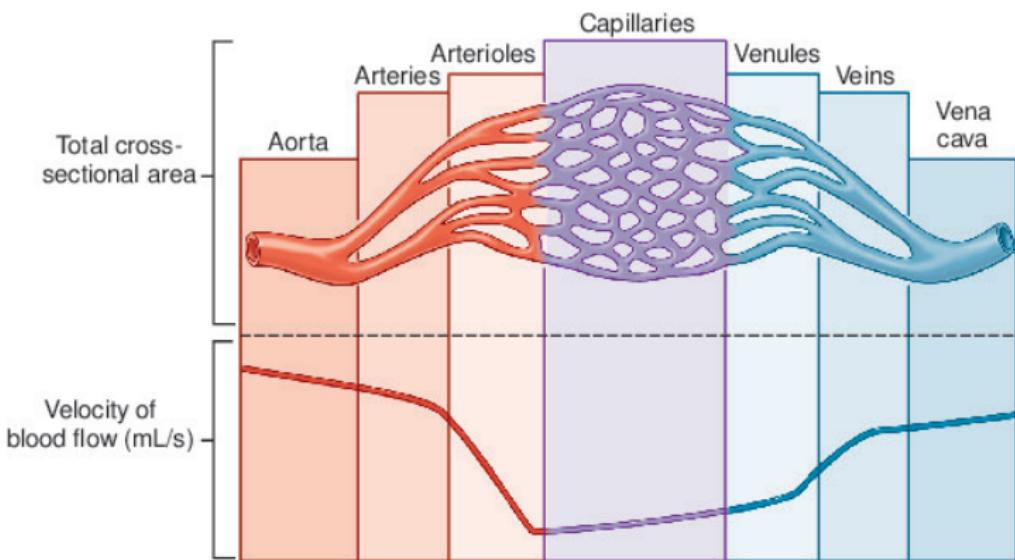
# Bernoulli's equation: aneurysm



# Bernoulli's equation: vessel velocity



	Aorta	Artery	Arteriole	Capillary	Venule	Vein	Vena Cava
Tot. cross-sect. area ( $\text{cm}^2$ )	4.5	20	400	4500	4000	40	18





The Bernoulli's equation holds only if:

- Laminar and steady flow  
Velocity doesn't vary with time
- Inviscid fluid  
Shear forces due to viscosity are negligible
- Incompressible fluid  
Density can be assumed to be constant

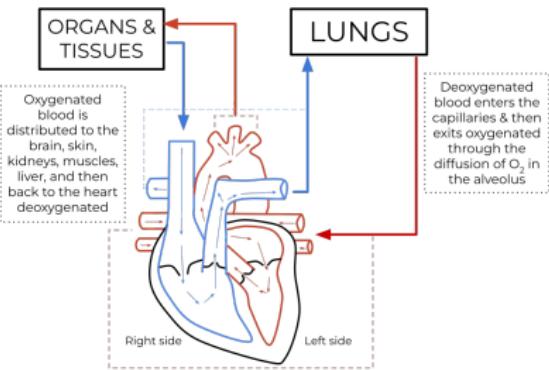
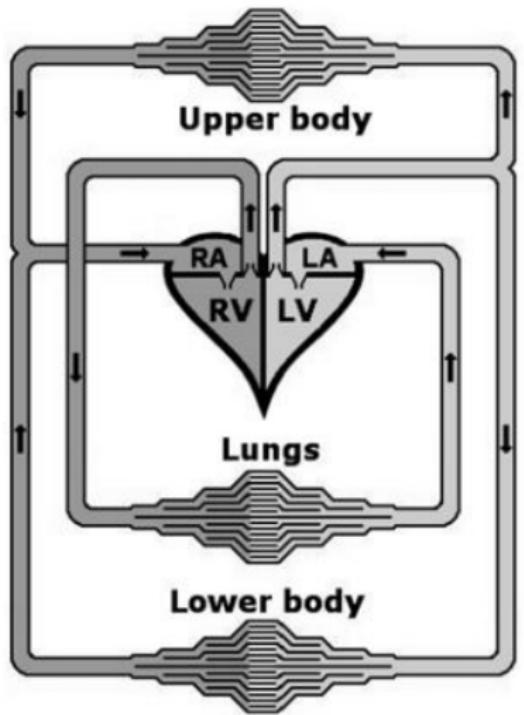
These limitations make the equation inaccurate in certain cases.

Falahatpisheh, Ahmad, '*Simplified bernoulli's method significantly underestimates pulmonary transvalvular pressure drop*', Journal of Magnetic Resonance Imaging 43.6 (2015): 1313–1319



# Introduction to the mathematical problem

# What we want to model



$u$  - velocity

$P$  - pressure

⇒ stress



Navier-Stokes equation for a fixed spatial domain  $\Omega$ :

$$\begin{cases} \frac{\partial u}{\partial t} + (u \cdot \nabla) u + \nabla p - \operatorname{div}(2\nu D(u)) = f & \text{in } \Omega \\ \operatorname{div} u = 0 & \text{in } \Omega \\ u(t = t_0, x) = u_0(x) & \text{in } \Omega \quad (\text{Initial Condition}) \end{cases}$$

We need also **boundary condition**:

- Neumann condition (applied stresses)

$$-Pn + 2\mu D(u) \cdot n = t^e \quad \text{on } \Gamma^n \subset \partial\Omega$$

- Dirichlet condition (prescribed velocity)

$$u = g \quad \text{on } \Gamma^d \subset \partial\Omega$$



# Windkessel models



A simple analogy to understand mathematical model can be between fluidodynamics and electrical circuits:

Electrical	Cardiovascular
electrical charge	blood volume
current ( $I$ )	flow rate ( $Q$ )
potential ( $V$ )	pressure ( $P$ )



As in Ohm's law:  $R_e = \frac{V}{I}$

Blood flowing from wider into smaller vessels encounters resistance.

In a cylindrical vessel with laminar flow:

$$R_c = \frac{\Delta P}{Q}$$

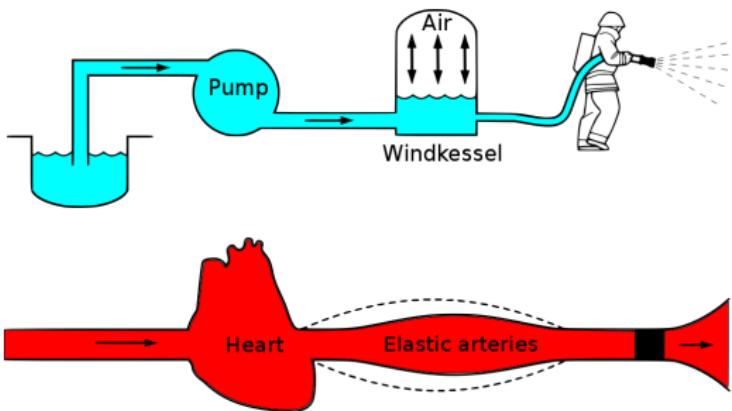
where  $P$  is pressure,  $Q$  is the flow.

Symbol of resistor:



## Windkessel effect

*Windkessel effect* is a term used in medicine to account for the shape of the arterial blood pressure waveform in terms of the interaction between the stroke volume and the compliance of large elastic arteries.



# Vessel and electrical capacitance



The walls of the vessels are surrounded by muscles that change the volume and pressure in the vessel. Let:

$$Q_i \rightarrow \text{flow into vessel} \quad Q_o \rightarrow \text{flow out of vessel} \Rightarrow Q = Q_i - Q_o \rightarrow \text{rate of change of volume}$$

Formula for a capacitor ( $C_e$  is the electrical capacitance):

$$I = C_e \frac{dV}{dt}$$

Since arteries accumulates blood as a capacitor, we have:

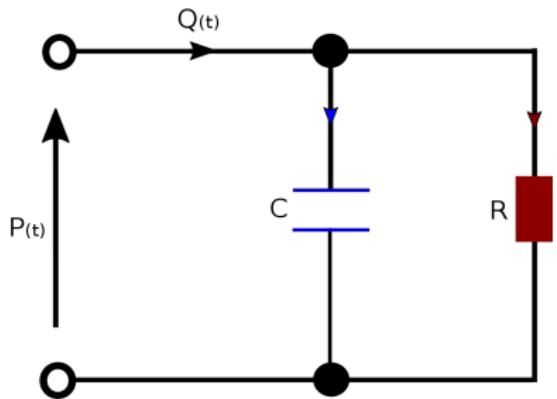
$$Q = C_c \frac{dP}{dt}$$

where  $C_c$  is the compliance of the vessel. Symbol of capacitor:



Stephen Hale in 1733: assumed that the arteries operate like a chamber in an old hand-pumped fire engine which smoothes the water pulses into a continuous flow.

German physiologist Otto Frank formalized Hale's idea in the *2-module Windkessel Model*.



$C$  - arterial compliance

$R$  - resistance to blood as passes from aorta to narrower arterioles

$P$  - aortic pressure

$Q$  - flow in aorta

## 2-Module Windkessel model

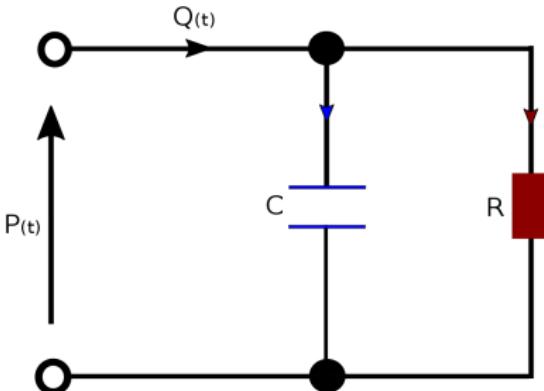


Let  $Q_2$  be the flow through  $C$  and  $Q_3$  be the flow through  $R$ :

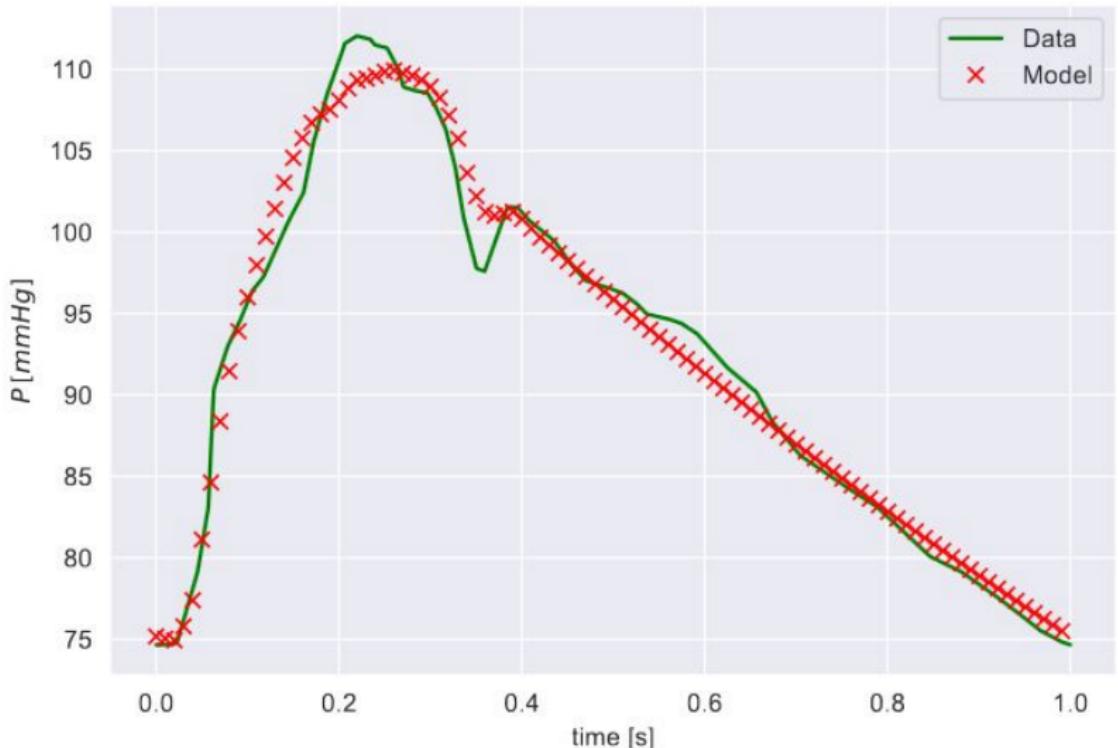
$$Q = Q_2 + Q_3 \quad P = Q_3 R \quad C \frac{dP}{dt} = Q_2$$

Using Kirchoff's we obtain:

$$Q = \frac{P}{R} + C \frac{dP}{dt}$$



# Numerical results





# Fibrillin-1



## Fibrillin-1

*Fibrillin-1* is a protein that in humans is encoded by the FBN1 gene, located on chromosome 15.

It is a large extracellular matrix glycoprotein that serves as a structural component of calcium-binding microfibrils.

These microfibrils provide force bearing structural support in elastic and nonelastic connective tissue throughout the body.

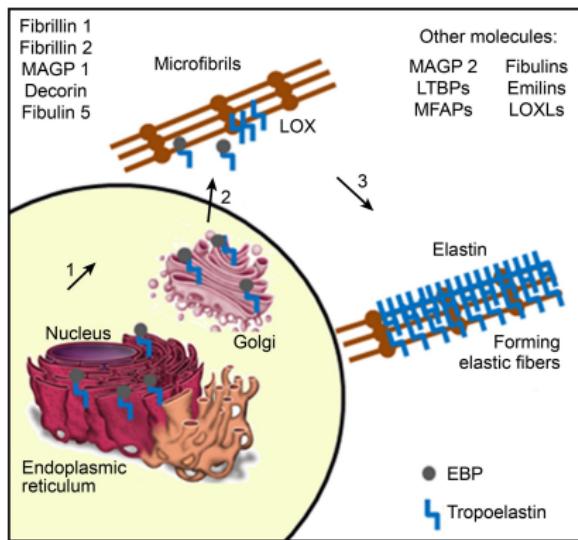
# FBN-1 importance: elastogenesis



FBN microfibrils → scaffold for tropoelastin

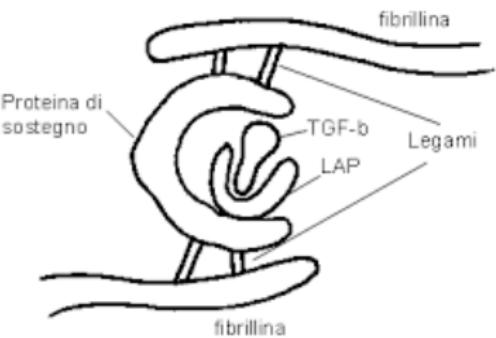
Tropoelastin → oxidized by member of lysyl oxidase family

⇒ Elastogenesis



## Fibrillin-1 second job:

- Store other proteins
- Keeping them inactive
- Activate them and release when needed

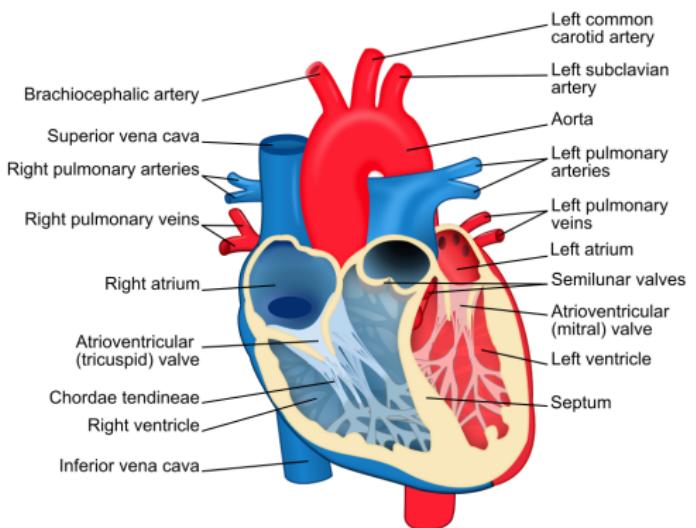


Example:  $\text{TGF-}\beta$  (transforming growth factor beta).

$\text{TGF-}\beta$  helps to control muscle and bone growth.

When fibrillin-1 do not form properly,  $\text{TGF-}\beta$  can act in the wrong places or at the wrong times, affecting a person's growth and development.

# FBN-1 importance: Heart



Formation of elastic fibers in heart valves and aorta require the involvement of FBN-1 and FBN-2.

While expression of FBN-2 decreases significantly after fetal development, expression of FBN-1 continues into adulthood.

This supports the idea that fibrillin-2 dictates the development of early elastic fibers, while fibrillin-1 provides the structural support of mature elastic fibers

# Mutation-induced disease

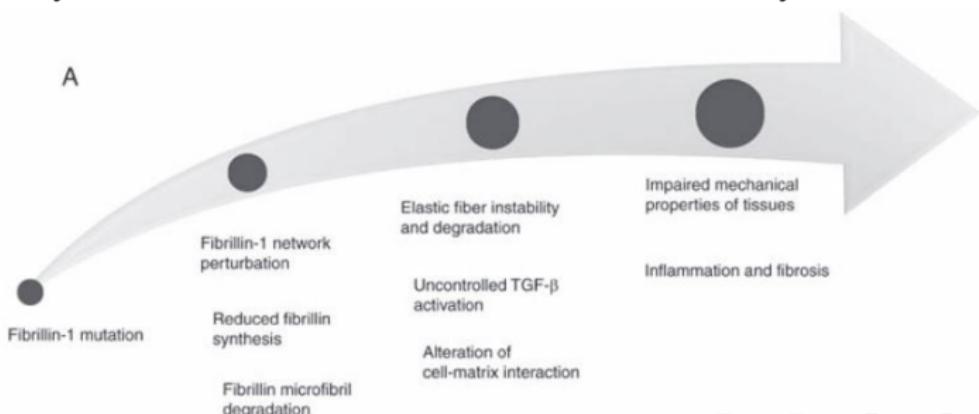


>1000 mutations identified in FBN1 gene, most cause Marfan syndrome.

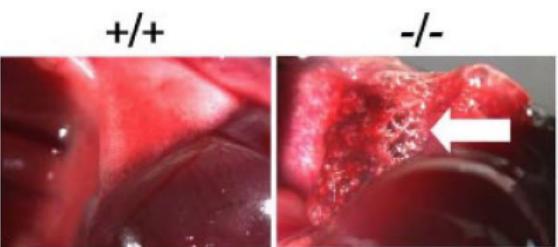
In general, those mutations can lead to:

- Thoracic aortic aneurysm
- Dissection of the aorta
- Different types of dysplasia
- Stiff skin syndrome
- **Marfan syndrome**
- Weill–Marchesani syndrome

Fibrillin-1 is modular  $\Rightarrow$  susceptible to primary effects of FBN1 mutations  
 $\Rightarrow$  destroy native fold of domains  $\Rightarrow$  effects on assembly and stability



FBN-1 knockout mice: can't form functioning elastic fibres + disorganization of elastic fibres + reduction of tissue flexibility/extensibility (arteries, lungs, skin...)



Left: aneurysm of the ascending aorta in newborn mouse and aortic wall rupture

Right: right lungs of wild-type and FBN-1 null mice showing blebs (blister-like protrusion)



# Marfan syndrome



## Marfan syndrome

*Marfan syndrome* is a multi-systemic genetic disorder that affects the connective tissue.

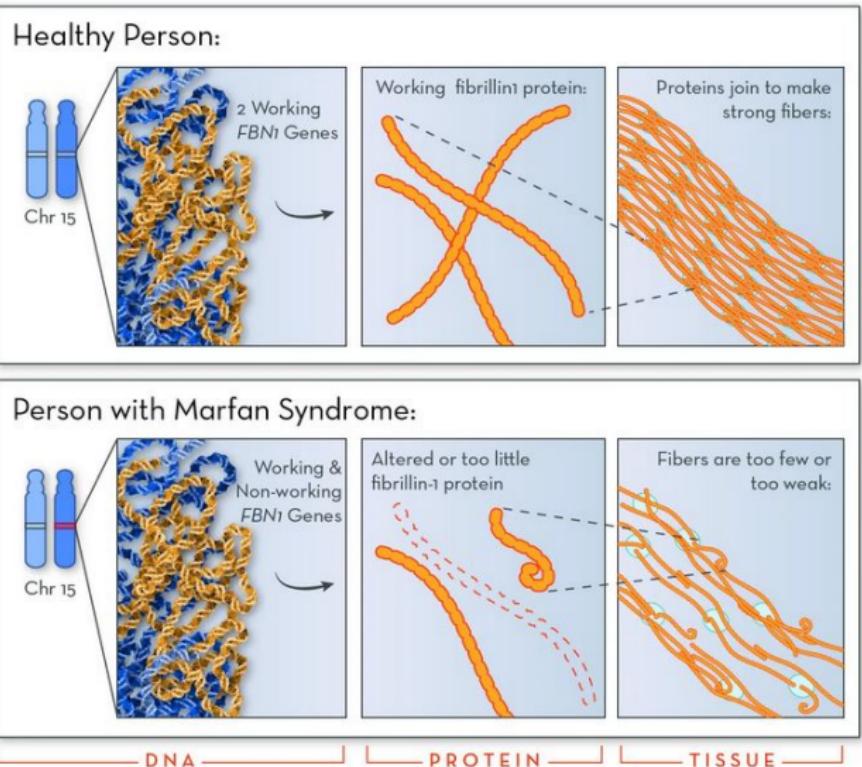
It is an autosomal dominant disorder caused by a mutation in FBN-1 which results in abnormal connective tissue.

In about 75% of cases it is inherited from a parent with the condition while in about 25% it is a new mutation.

Some people are born with clear features of Marfan syndrome, while others develop symptoms as teens or adults.

There is no known cure but many of those with the disorder have a normal life expectancy with proper treatment.

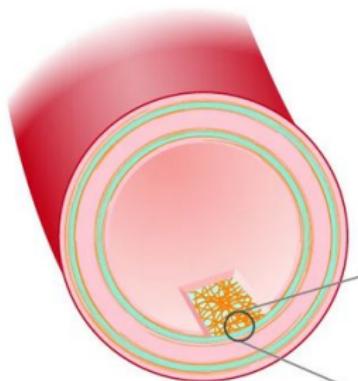
About 1 in 5.000 to 1 in 10.000 people have this syndrome.



# Elastic fiber in body

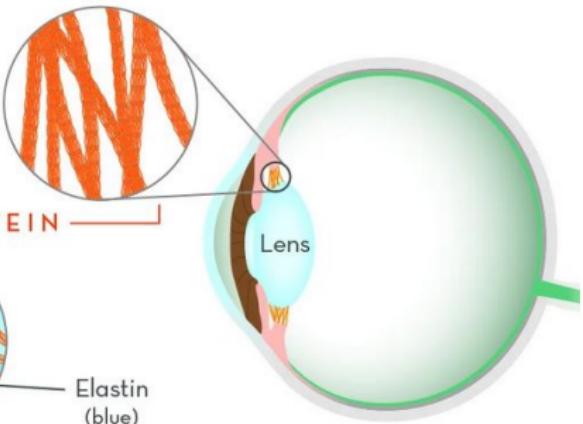


Flexible microfibrils  
wrap around blood vessels.



Blood vessel (cross-section)

Non-elastic microfibrils  
anchor the lens inside of the eye.



Eye (cross-section)

TISSUE / ORGAN

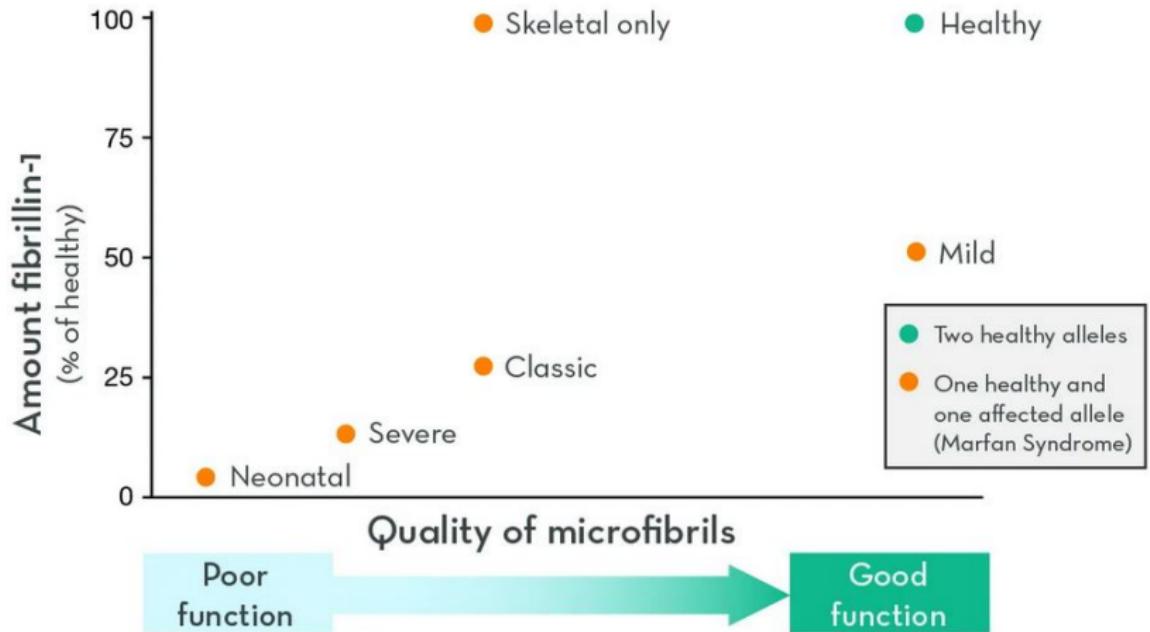


One healthy allele                      some fibrillin-1 protein works  
One disease-causing allele     $\Rightarrow$               some fibrillin-1 protein doesn't work

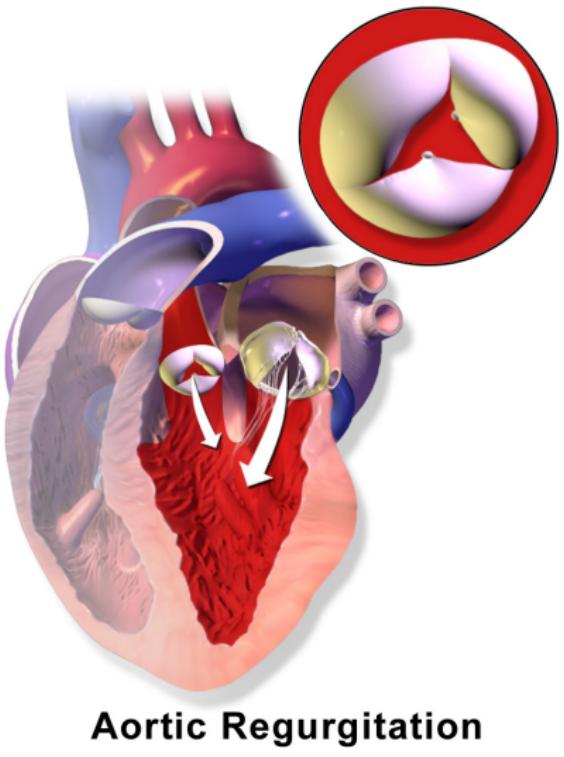
We have two types of non-working fibrillin-1:

	<b>Non-working protein can't be used</b>	<b>Non-working protein is made into microfibrils</b>
Consequence on protein	Few microfibrils	Microfibrils do not work well
Consequences on tissue	Connective tissues are weak	Weak microfibrils, elastin does not stretch properly, microfibrils does not store TGF- $\beta$

## Different *FBN1* Alleles Have Different Effects

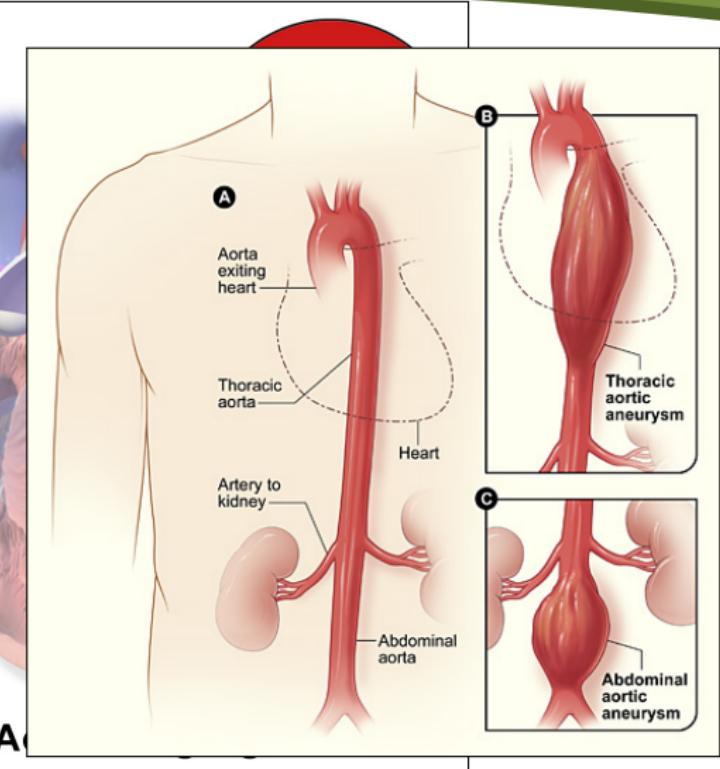


# Diseases caused by mutations

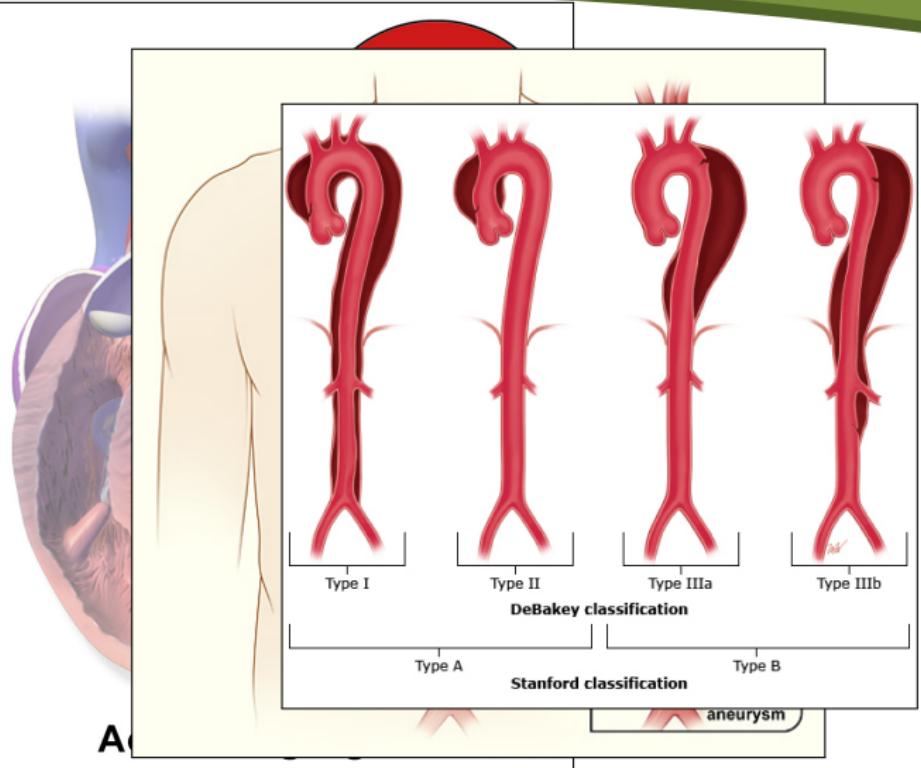


**Aortic Regurgitation**

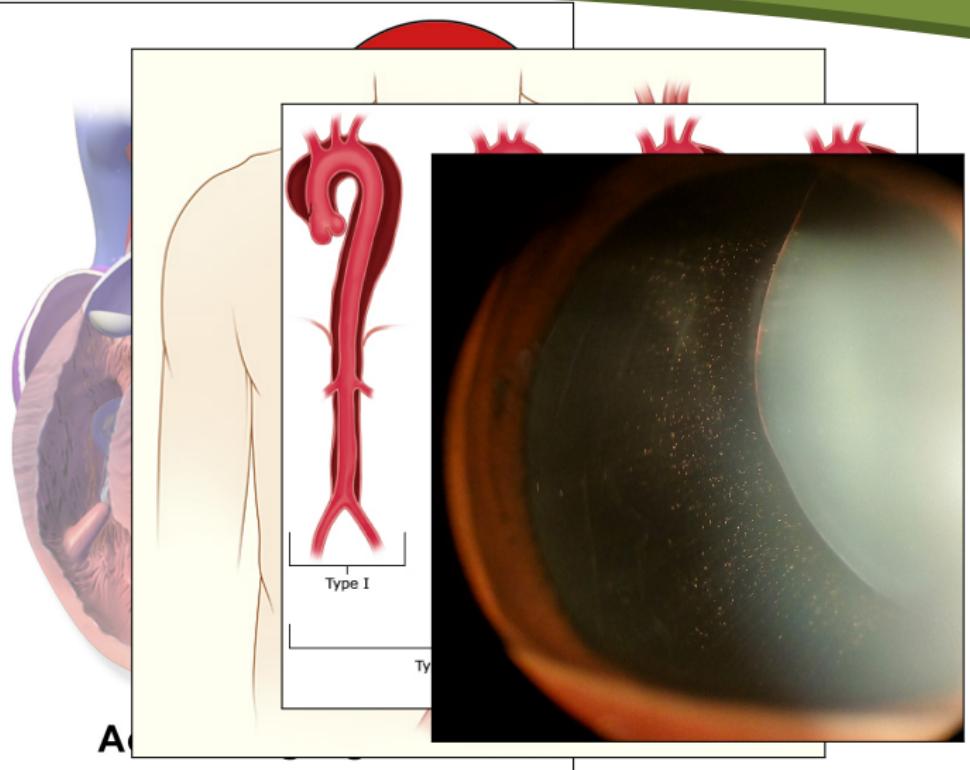
# Diseases caused by mutations



# Diseases caused by mutations



# Diseases caused by mutations



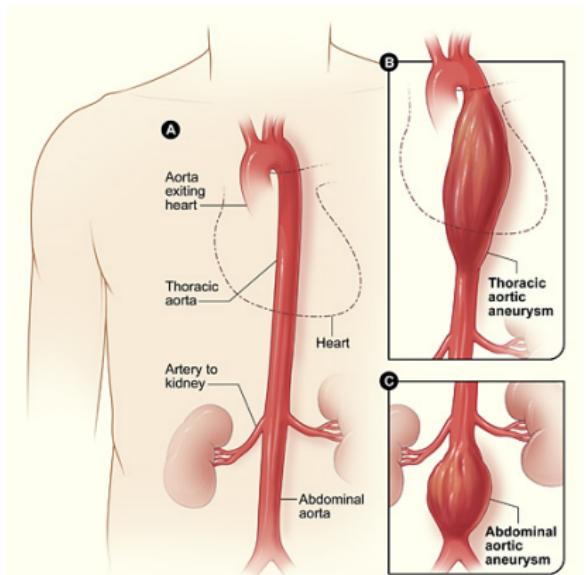
# Diseases caused by mutations





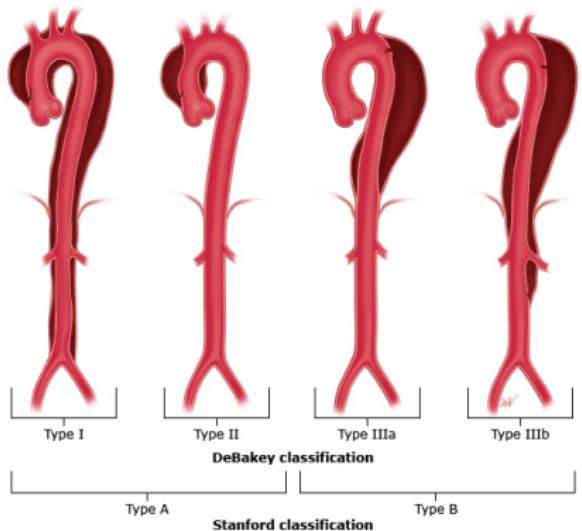
## Mathematical results

# Aortic aneurysm



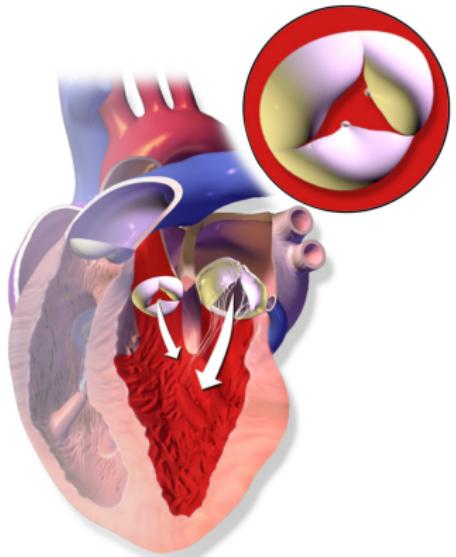
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# Aortic dissection



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- Pirruccello, J. P., Chaffin, M. D., Chou, E. L. et al (2022). **Deep learning enables genetic analysis of the human thoracic aorta.** Nature Genetics. DOI: 10.1038/s41588-021-00962-4

# Aortic regurgitation



**Aortic Regurgitation**

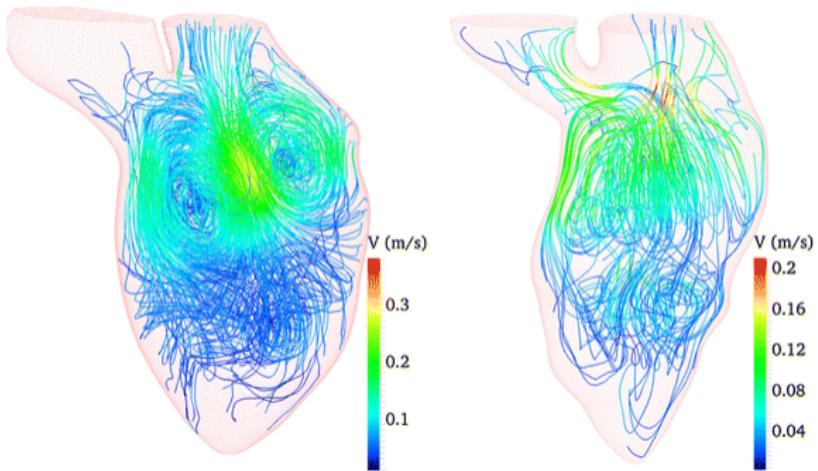
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- Mynard, J. P., Davidson, M. R., Penny, D. J., & Smolich, J. J. (2012). **A simple, versatile valve model for use in lumped parameter and one-dimensional cardiovascular models,** DOI: [10.1002/cnm.1466](https://doi.org/10.1002/cnm.1466)

Summarize:

Biophysics of cardiovascular system

⇒ Mathematical modelling

⇒ Disease treatment



(Sources in the pdf)