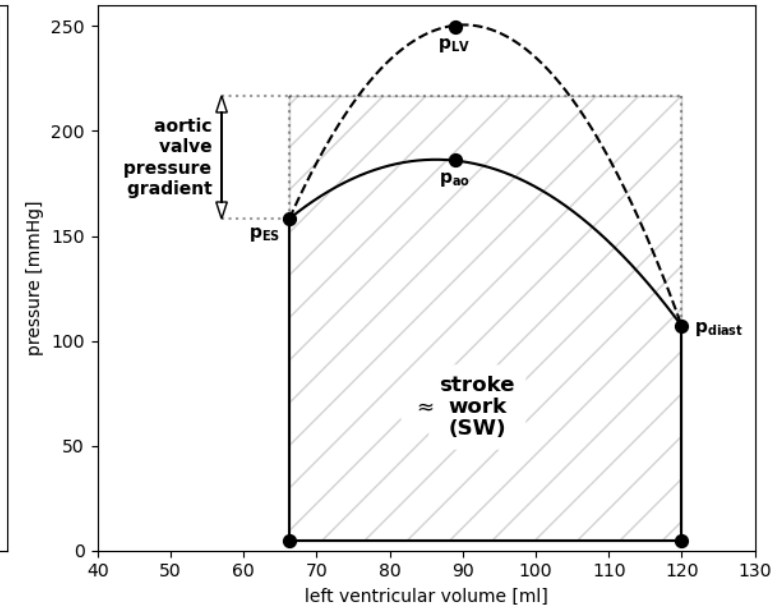
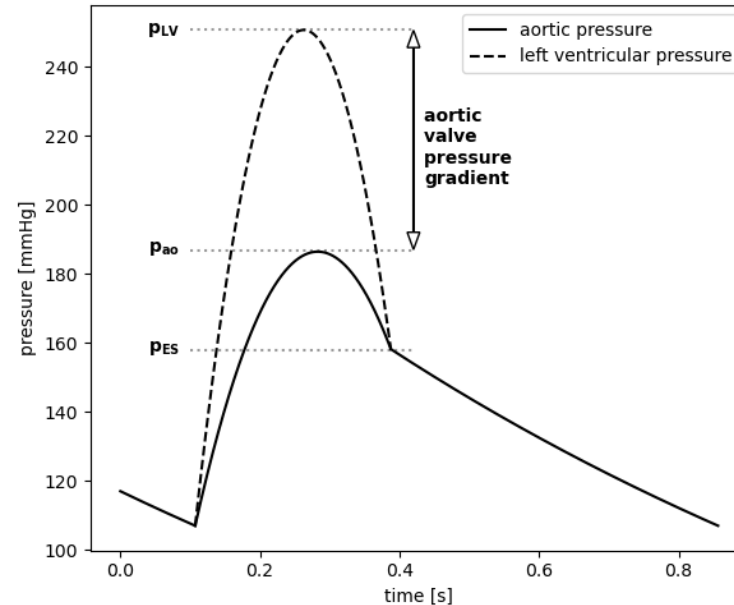


Matematické modelování

význam pro hemodynamiku

Michal Šitina

ARK, FNUSA, Brno



$$E_{\text{out}} = A \cdot \left\{ \frac{1}{2} p_{\text{ES}} (V_{\text{ED}} - V_0 - \text{SV}) + \left[\frac{1}{2} \rho \left(\frac{\text{SV}}{T_E \cdot S_{\text{ao}}} \right)^2 + p_{\text{ES}} \right] \cdot \text{SV} \right\} + B$$

Matematické modelování význam pro hemodynamiku

- náhlá smrt u těžké aortální stenózy
 - stagnující intenzivní medicína
 - co nás posouvá ?
 - místo matematického modelování v medicíně
- 
- 
- matematické modelování v hemodynamice – jak podávat krystaloidy u těžkého krvácení?

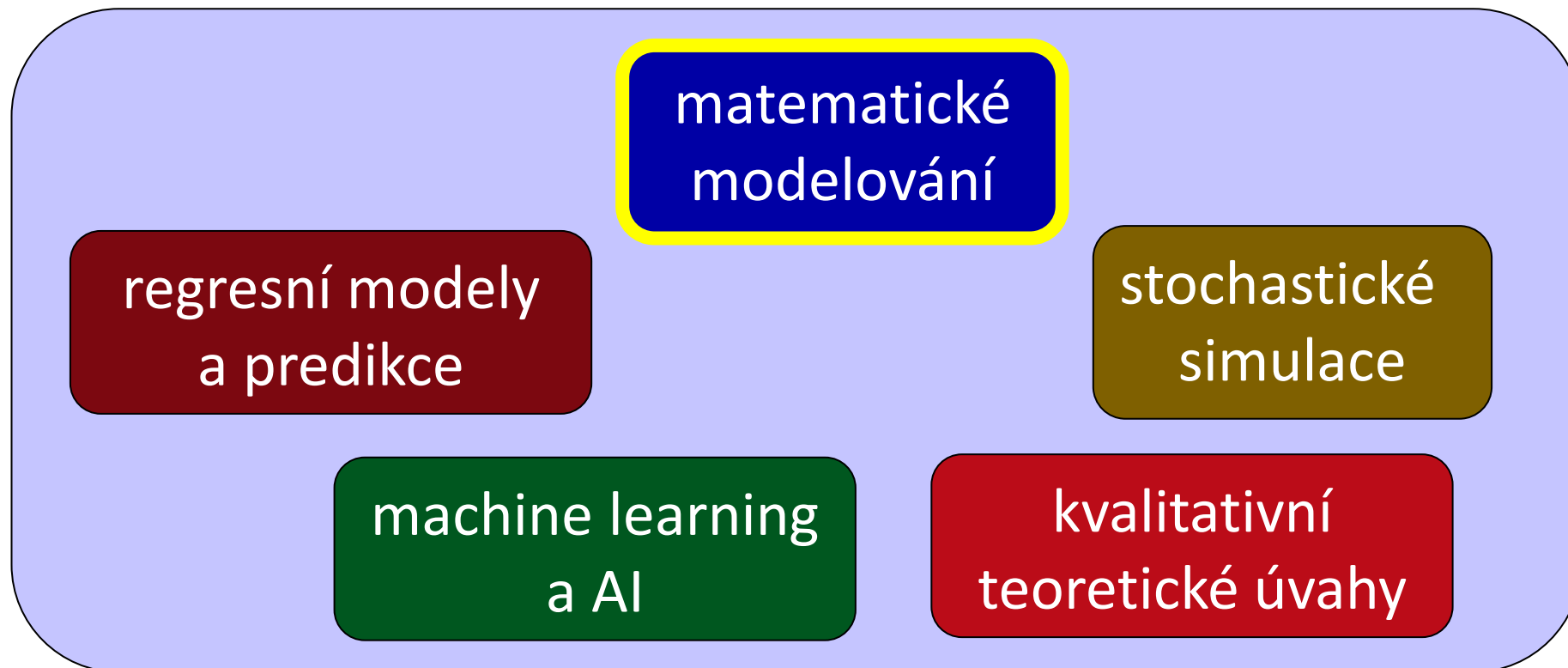
Kde lze potkat matematické modely?

- software hemodynamických přístrojů
- software KS/ICD...
- prediktivní skóre – např. EuroSCORE II
- technické aplikace
 - aneuryzma aorty
 - TAVI
 - biomechanika – ortopedie, traumatologie...

co NENÍ matematické modelování

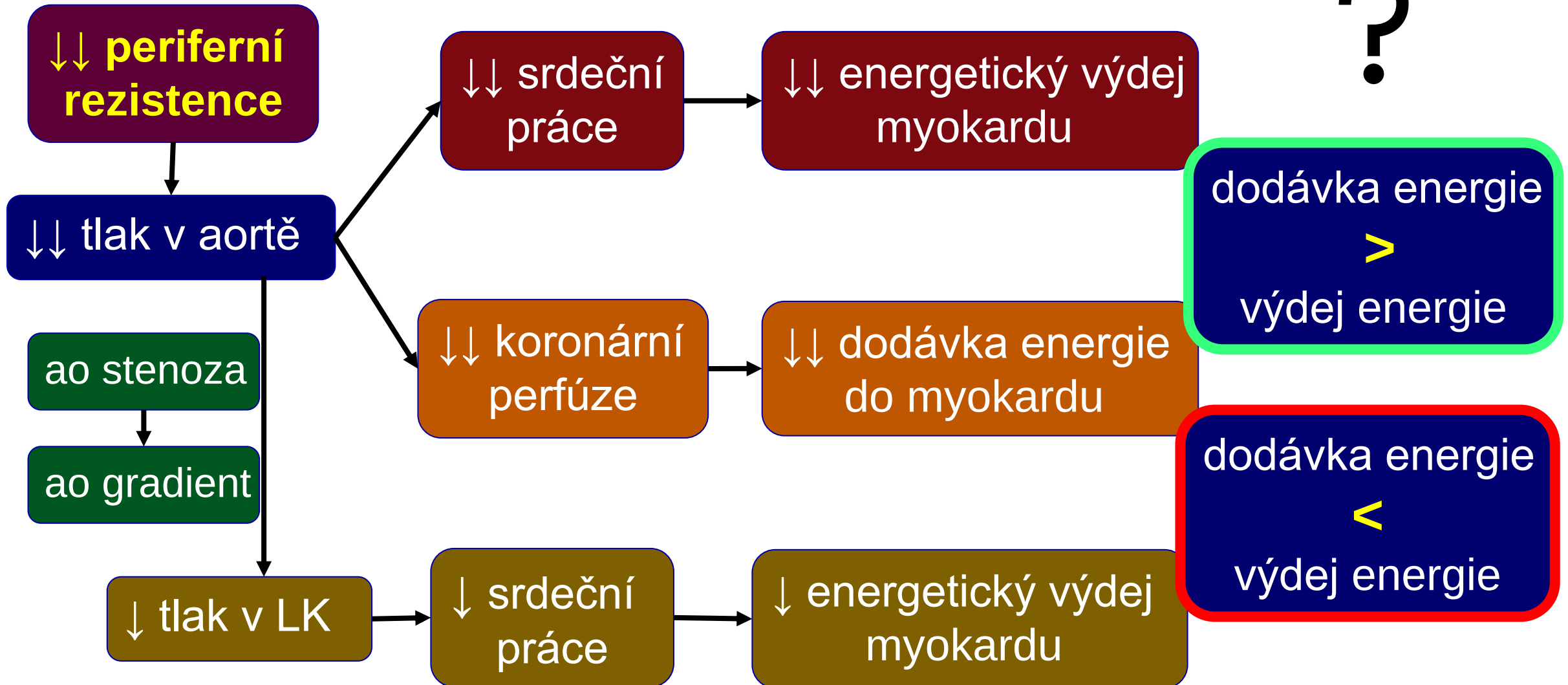
- statistická analýza změřených dat

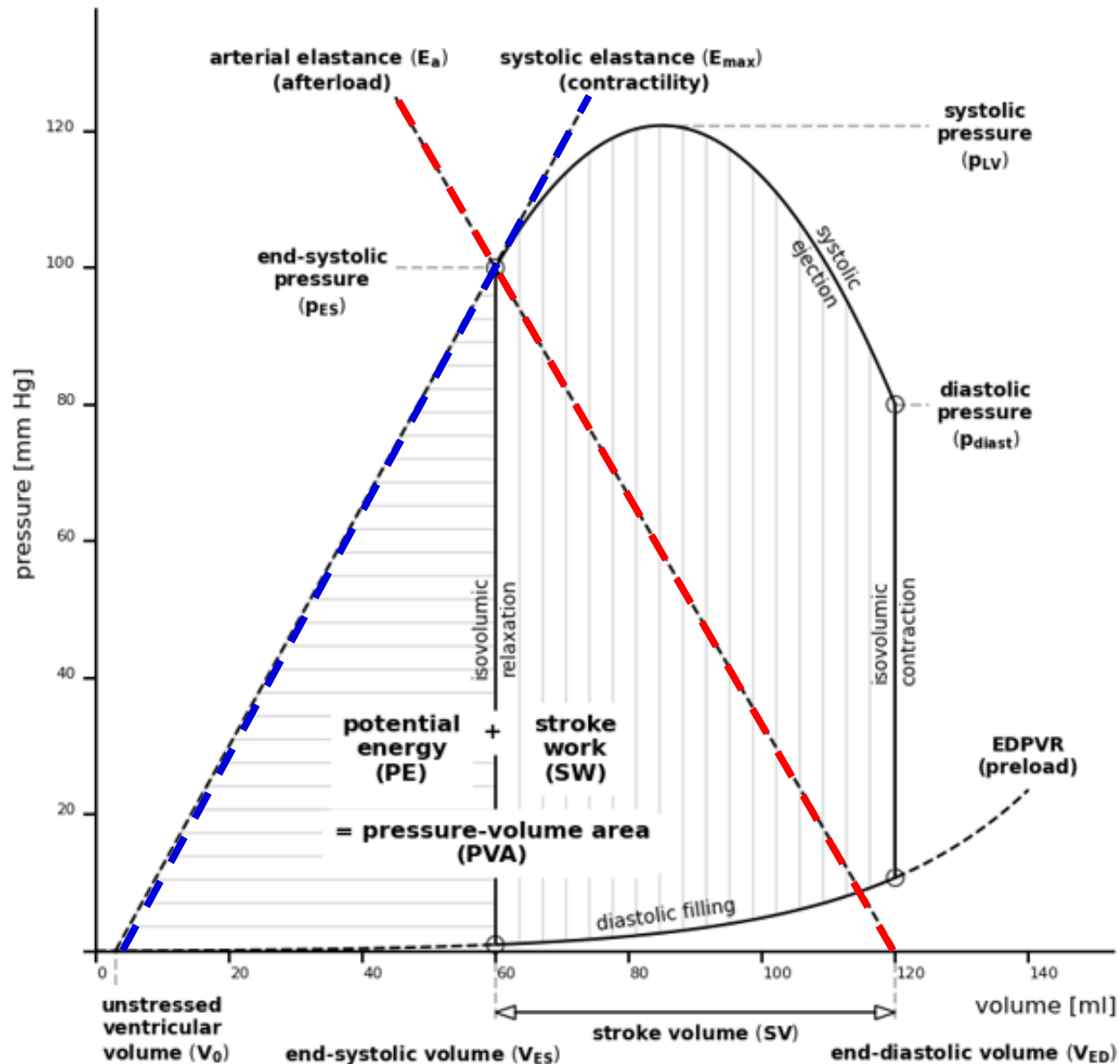
teoretické/výpočetní přístupy



Náhlá smrt u těžké aortální stenózy

?





- ventricular energetics theory
- ventriculoarterial coupling theory
- Windkessel arterial model

Náhlá smrt – matematický model

APPENDIX

Mathematical model of cardiac hemodynamics and energetics

The mathematical model is based on the two-element Windkessel model of arterial hemodynamics (22), the ventriculoarterial coupling model (23), and the ventricular energetics model (24). The model compares the energy delivered to the heart by the coronary circulation (E_{in}) and the energy expenditure of the heart (E_{out}).

Energy expenditure of the heart

For energy expenditure of the heart (E_{out}), an empirical relationship

$$E_{out} = A \cdot PVA + B \quad (A1)$$

has been established (24, 25), where PVA denotes the area inside the pressure-volume diagram of the left ventricle (Fig. 1). It represents the work of the left ventricle, given by the sum of the stroke work (SW) and the elastic potential energy (PE), $PVA = PE + SW$. The constant B represents unloaded cardiac energy consumption, indicating the energy consumed by the heart for non-contractile activities of the cardiac cells (25), such as basal metabolism or excitation-contraction coupling. The constant A represents the contractile efficiency of the heart. More precisely, the inverse value of A indicates the percentage of energy consumed by the heart (after subtraction of unloaded cardiac energy consumption) that is converted to the mechanical activity (24).

The elastic potential energy (PE) corresponds to the rectangular triangle in the pressure-volume diagram (Fig. 1), given by the equation

$$PE = \frac{1}{2} p_{ES} (V_{ED} - V_0 - SV), \quad (A2)$$

where p_{ES} denotes the end-systolic pressure in the left ventricle, V_{ED} the end-diastolic volume of the left ventricle and V_0 the unstressed volume of the left ventricle, i.e. the intersection of the end-systolic pressure-volume relationship (ESPVR) with the volume axis of the diagram. In calculating the PE, the minor contribution of the end-diastolic pressure-volume relationship (EDPVR), related to the non-zero end-diastolic pressure, is neglected.

The stroke work (SW) corresponds to the area inside the systolic part of the left ventricular pressure-volume diagram (Fig. 1), which can be approximated as a rectangle. For the SW follows (24, 27)

$$SW = p_{ES} \cdot SV, \quad (A3)$$

where SV denotes the stroke volume of the left ventricle. The end-systolic pressures in the left ventricle and in the aorta must be the same and are approximately 10-15% lower than the maximum systolic pressure in the aorta p_{ao} (28, 29),

$$p_{ao} = \frac{p_{ES}}{0.85}. \quad (A4)$$

In the case of aortic stenosis, during ejection phase of left ventricular systole, the left ventricular pressure is significantly higher than aortic pressure by the pressure gradient across the stenotic aortic valve (PG) (Fig. 2). Consequently, the stroke work must be calculated as

$$SW = (p_{ES} + PG) \cdot SV. \quad (A5)$$

The PG can be approximated as

$$PG = p_{LV} - p_{ao} \approx \frac{1}{2} \rho v_{ao}^2, \quad (A6)$$

where ρ is the density of blood and v_{ao} the mean systolic flow velocity through the aortic valve (30). Blood density is held constant value of $\rho = 1.065$ g/ml (42). At the end of systole, the flow velocity decreases and the left ventricular pressure returns to the level of aortic pressure (p_{ES}), at which point the aortic valve begins to close.

Given that the entire stroke volume (SV) must flow across the aortic valve of area S_{ao} during the ejection phase of the left ventricular systole of a duration T_E , it follows that

$$T_E \cdot S_{ao} \cdot v_{ao} = SV. \quad (A7)$$

A substitution of all the equations into Eq. 1 yields an expression for the total energy expenditure of the heart, E_{out} ,

$$E_{out} = A \cdot \left\{ \frac{1}{2} p_{ES} (V_{ED} - V_0 - SV) + \left[\frac{1}{2} \rho \left(\frac{SV}{T_E \cdot S_{ao}} \right)^2 + p_{ES} \right] \cdot SV \right\} + B \quad (A8)$$

The end-systolic pressure (p_{ES}) can be expressed by the maximum end-systolic left ventricular elastance E_{max} (24) as

$$p_{ES} = E_{max} \cdot (V_{ED} - V_0 - SV) = E_{max} \cdot (V_{ED}^{eff} - SV), \quad (A9)$$

where $V_{ED}^{eff} = V_{ED} - V_0$ is referred to as effective end-diastolic volume (27).

According to the ventriculoarterial coupling theory (23), the stroke volume is described by the equation

$$SV = \frac{V_{ed}^{eff}}{1 + E_a/E_{max}} \quad (A10)$$

where E_a denotes the effective arterial elastance and is given by

$$E_a = TPR / [T_E + \tau(1 - e^{-T_D/\tau})] \quad (A11)$$

where T_D is a duration of diastole and τ , the time constant of diastolic pressure decline, is the product of the total peripheral resistance TPR and the arterial compliance C, $\tau = TPR \cdot C$. After substituting Eqs. 9-11 into Eq. 8, we obtain a relationship describing the total energy expenditure of the heart during one cardiac cycle expressed as a function of S_{ao} , E_{max} , V_{ED} , C, TPR and HR, considered in the model as independent variables.

$$E_{out} = B + A \cdot \left\{ \frac{1}{2} E_{max} \left[\frac{V_{ed}^{eff} TPR}{TPR + E_{max} \left(T_E + \tau - \tau e^{-\frac{T_D}{\tau}} \right)} \right]^2 + \frac{\rho}{2 T_E^2 S_{ao}^2} \left[\frac{V_{ed}^{eff} E_{max} \left(T_E + \tau - \tau e^{-\frac{T_D}{\tau}} \right)}{TPR + E_{max} \left(T_E + \tau - \tau e^{-\frac{T_D}{\tau}} \right)} \right]^2 + TPR \left(T_E + \tau - \tau e^{-\frac{T_D}{\tau}} \right) \left[\frac{E_{max} V_{ed}}{TPR + E_{max} \left(T_E + \tau - \tau e^{-\frac{T_D}{\tau}} \right)} \right]^2 \right\} \quad (A12)$$

Energy delivery to the heart

The pressure in aorta during diastole declines exponentially in dependence on TPR, C and HR (22), as described by the equation

$$p(t) = p_{cv} + (p_{ES} - p_{cv}) e^{-\frac{t}{\tau}}, \quad (A13)$$

where p_{cv} is the central venous pressure in the right atrium. For the sake of simplicity, we assume a constant value of $p_{cv} = 5$ mmHg (36) for all simulations.

During one diastole, a volume of blood V_{blood} flows through the coronary arteries in dependence on the resistance of the coronary circulation (R_{cor}) and the pressure gradient between the aorta ascendens and the end-diastolic pressure (p_{ED}) in the left ventricle (34). Similarly to p_{cv} , we assume a constant value of $p_{ED} = 10$ mmHg (35) throughout the diastole and for all simulations. The following equation can be derived for V_{blood} .

$$V_{blood} = \int_0^{T_D} \frac{p(t) - p_{ED}}{R_{cor}} dt \quad (A14)$$

Hence, final solution is

$$V_{blood} = \frac{p_{ES} - p_{cv}}{R_{cor}} \cdot \tau \left(1 - e^{-\frac{T_D}{\tau}} \right) + \frac{p_{cv} - p_{ED}}{R_{cor}} T_D. \quad (A15)$$

The blood volume V_{blood} transports a volume of oxygen $V_{O_2} = V_{blood} \cdot cO_2$, where cO_2 denotes the volume of oxygen in a volume unit of blood and was set to a constant value of 0.2 ml O_2 /ml blood (43). Only a fraction of the oxygen supplied (ε) is extracted by the myocardium and used for energy produce.

Given that metabolic conversion of 1 ml of oxygen delivers energy of 20 J (24), the energy delivery to the heart (E_{in}), in J/beat, can be expressed as

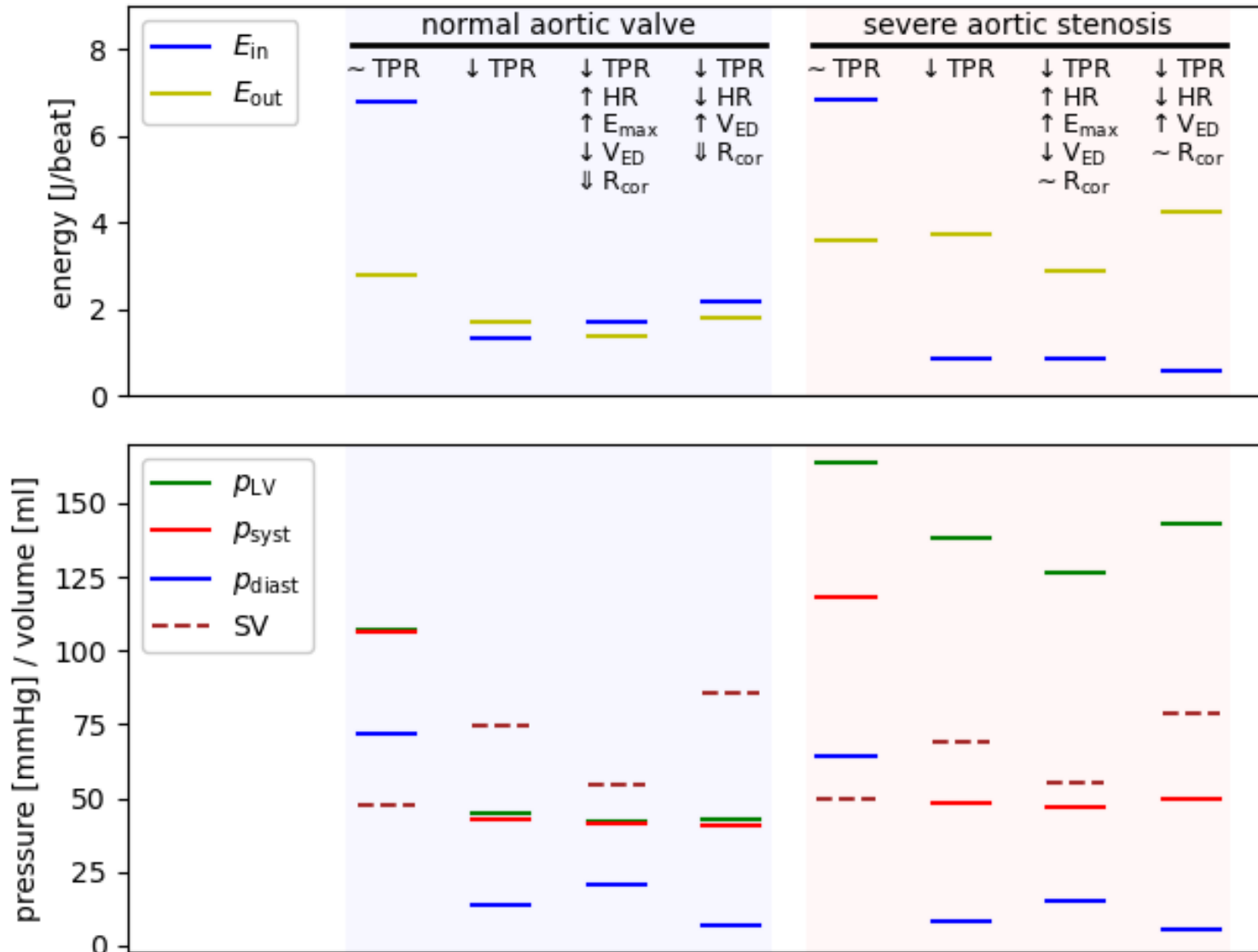
$$E_{in} = 20 \cdot \varepsilon \cdot V_{O_2} = 20 \cdot \varepsilon \cdot V_{blood} \cdot cO_2 \quad (A16)$$

The duration of diastole (T_D) and of the left ventricular ejection phase (T_E) can be expressed as functions of heart rate (HR) according to empirical equations (32)

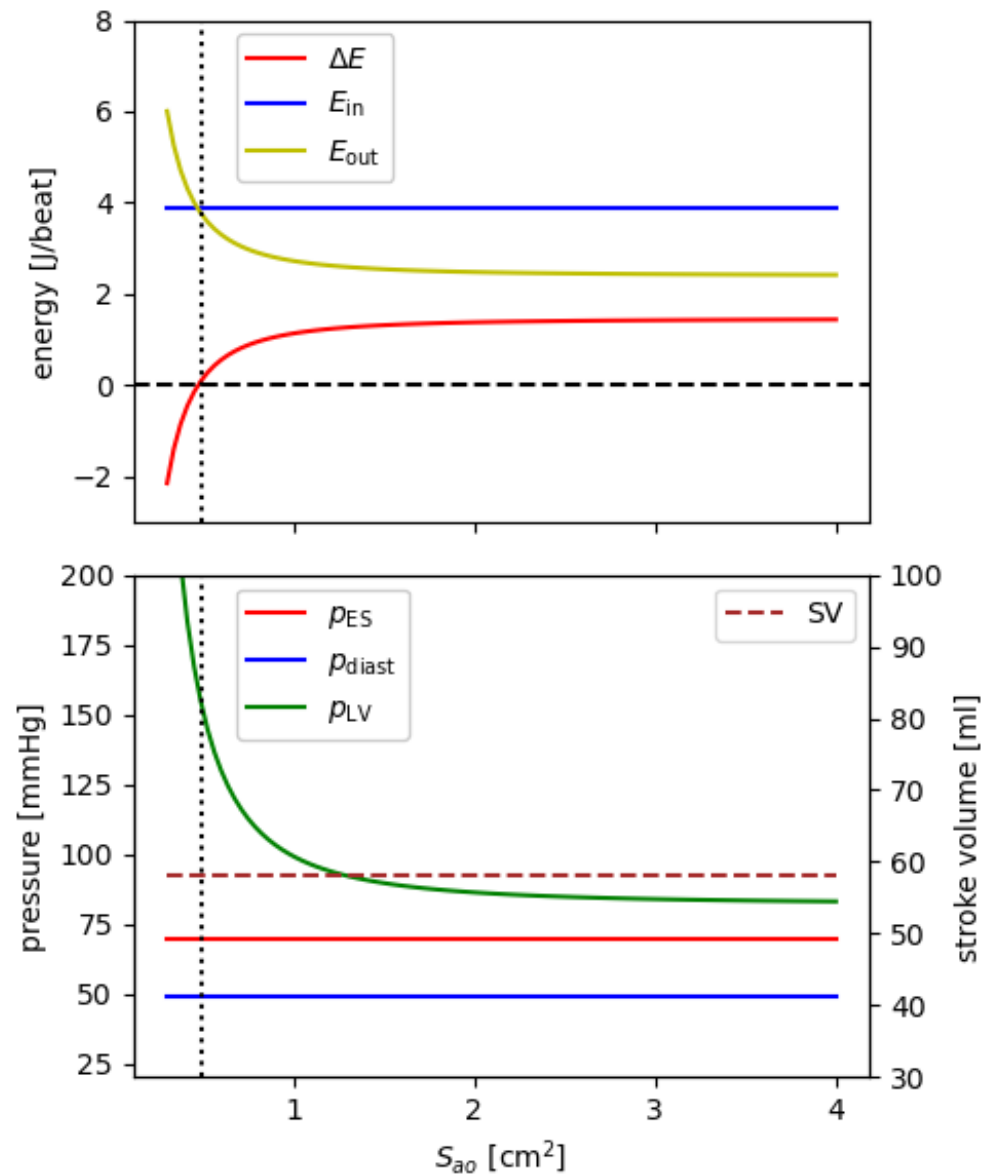
$$T_E = (371.15 - 1.14 HR) / 1000 \quad (A17)$$

$$T_D = 60 / HR - T_E. \quad (A18)$$

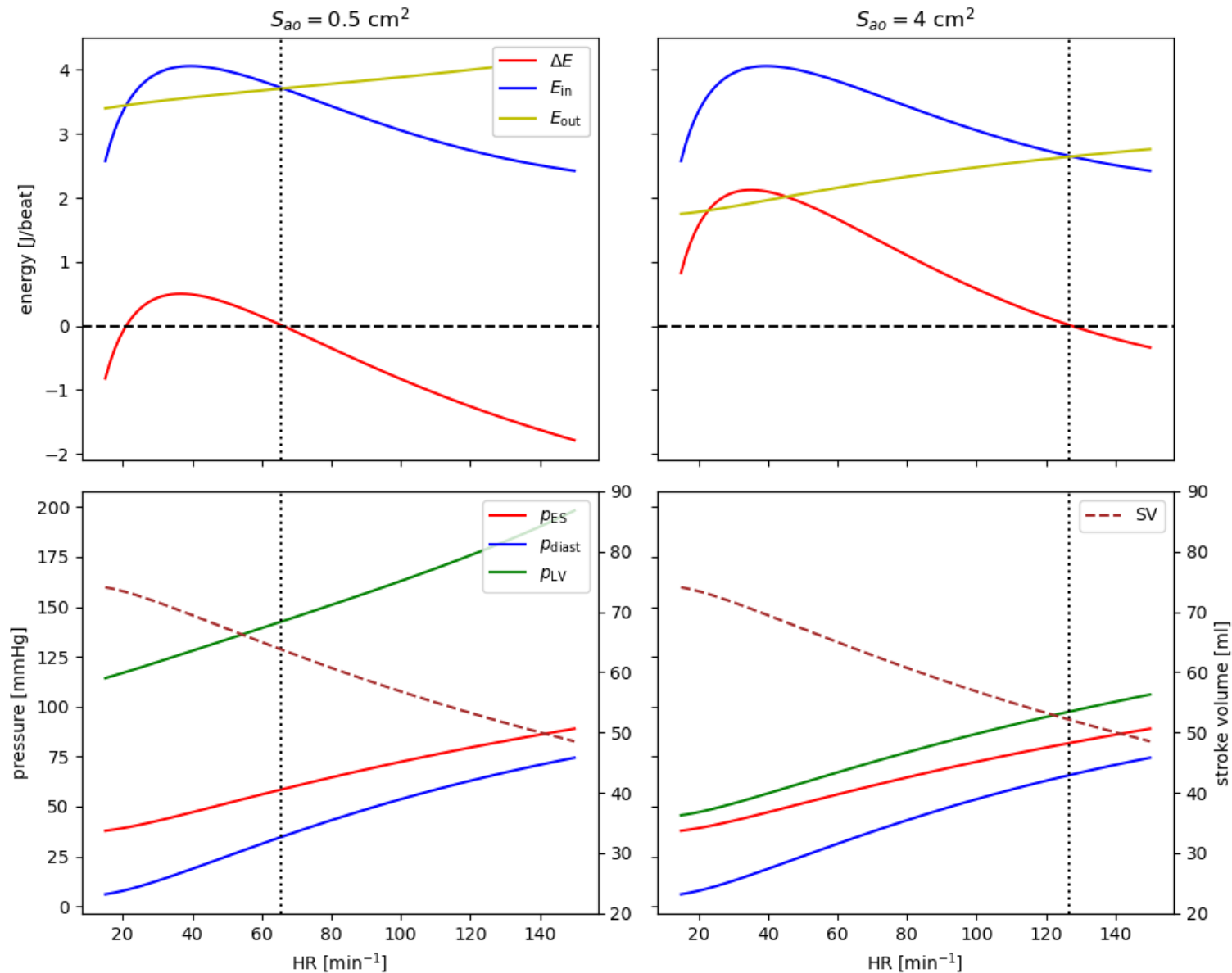
Náhlá smrt u těžké aortální stenózy

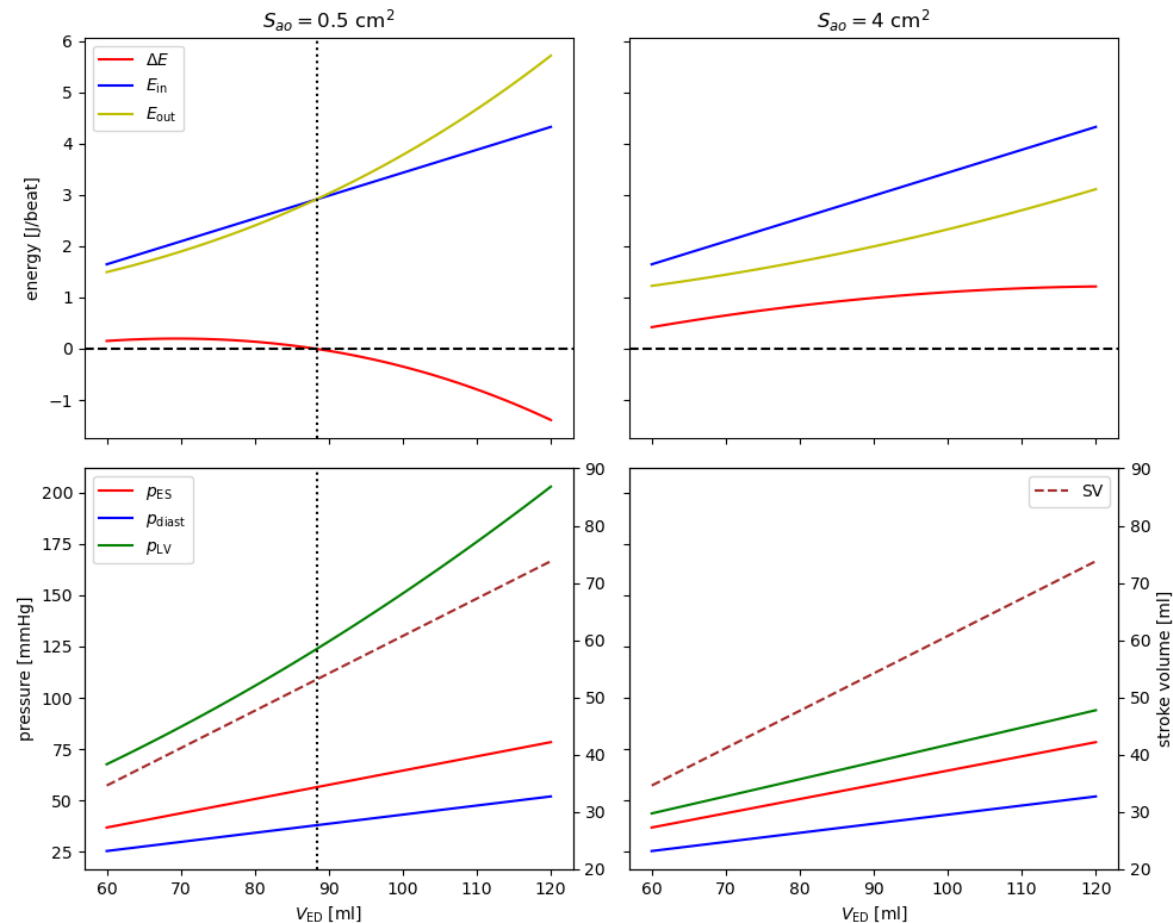
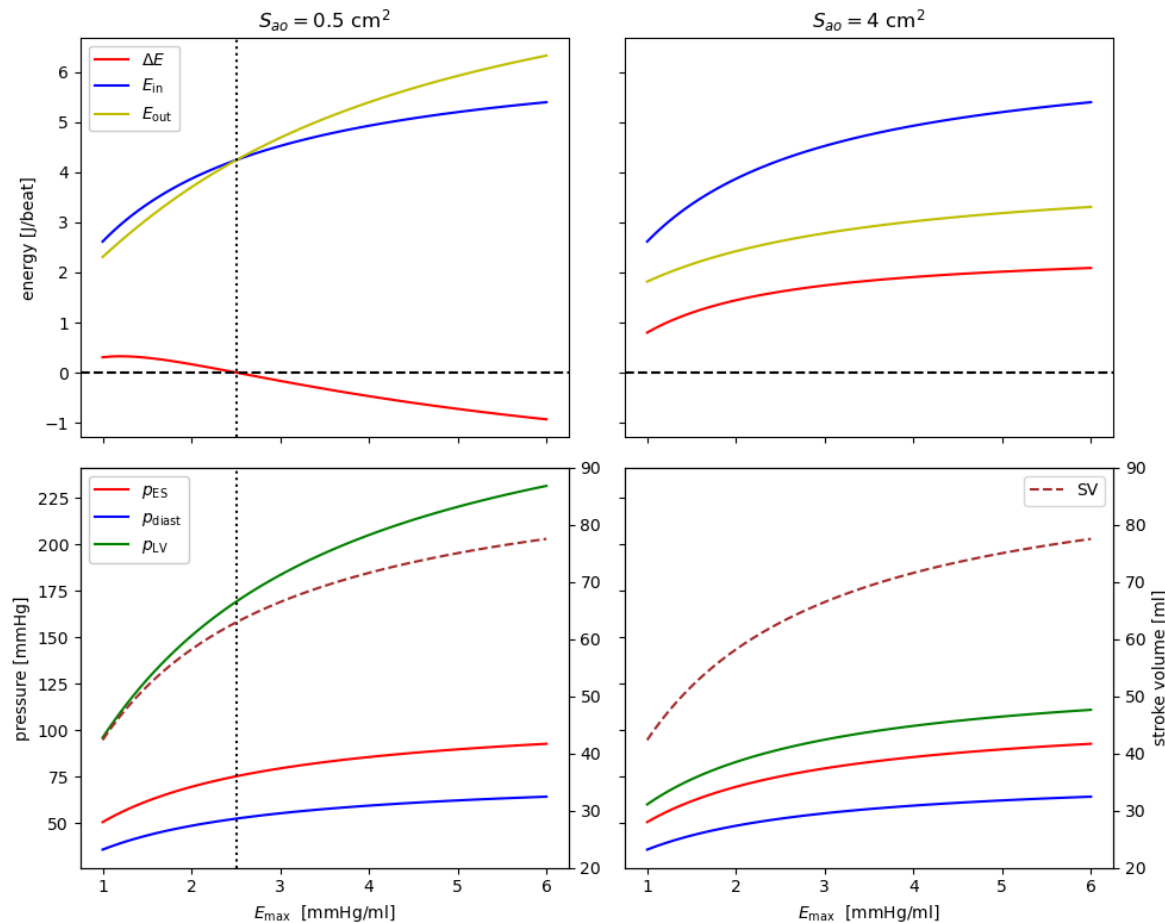


Náhlá smrt u těžké aortální stenózy



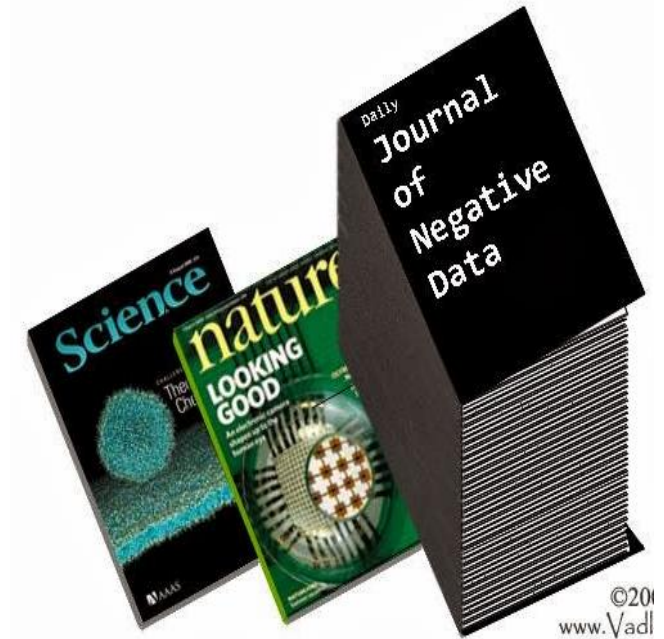
Náhlá smrt u těžké aortální stenózy





Stagnuje intenzivní medicína ?

- ne
- ano
 - optimalizace
- hemato-onkologie
 - CAR-T
 - bispecifické protilátky
 - iFLT3
 - iBCL-2
 - iIDH1/IDH2
 - iBTK
 - iPI3K
 - iProteazomu
 - iHiston deacetyláz



Je věda na konci svých sil? Průlomových objevů ubývá, kvalita výzkumu klesá



David Busta vedoucí redaktor investiční rubriky
19. 5. 2024 15:13 • Aktualizováno • 4 min. čtení ► [PŘEHRÁT ČLÁNEK](#)

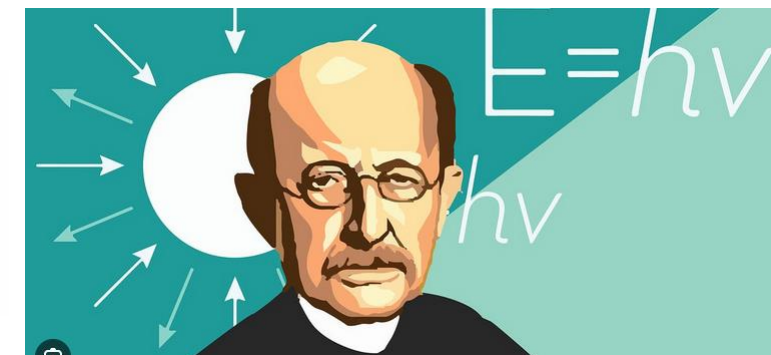


EVOLUTION NEUROSCIENCE & MIND

Is the End of Science Near?

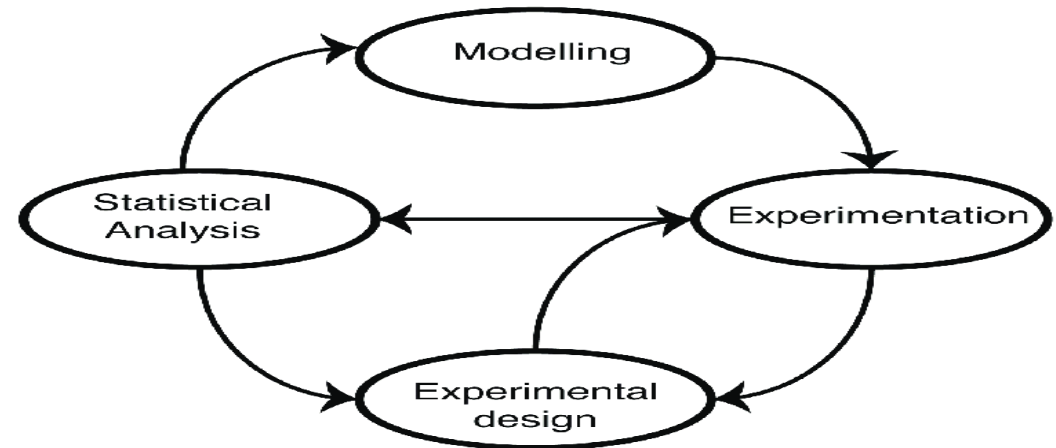
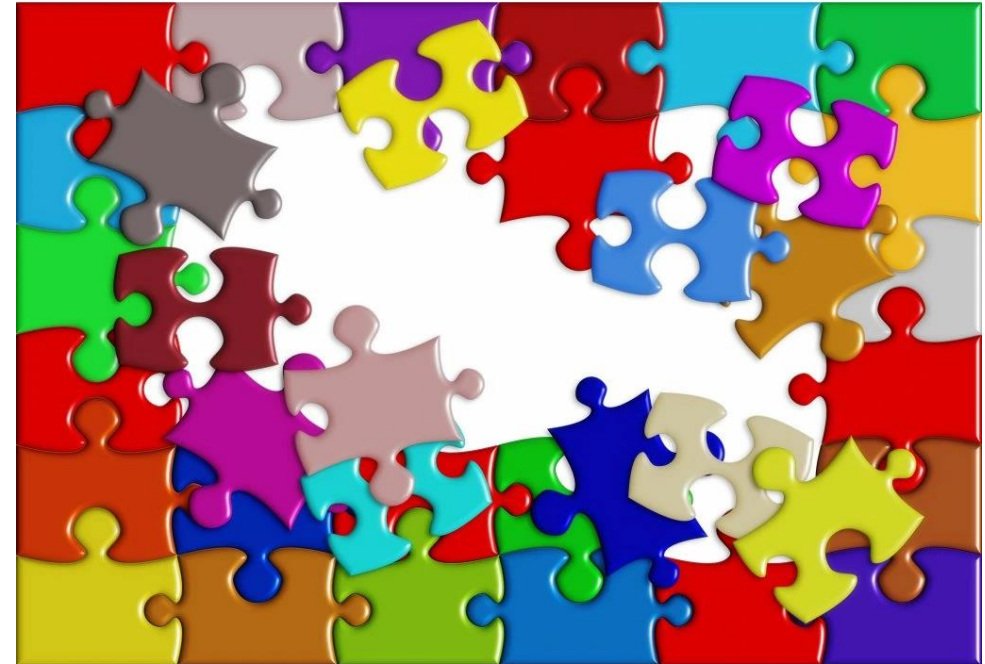
Evolution News

January 12, 2023, 6:55 AM

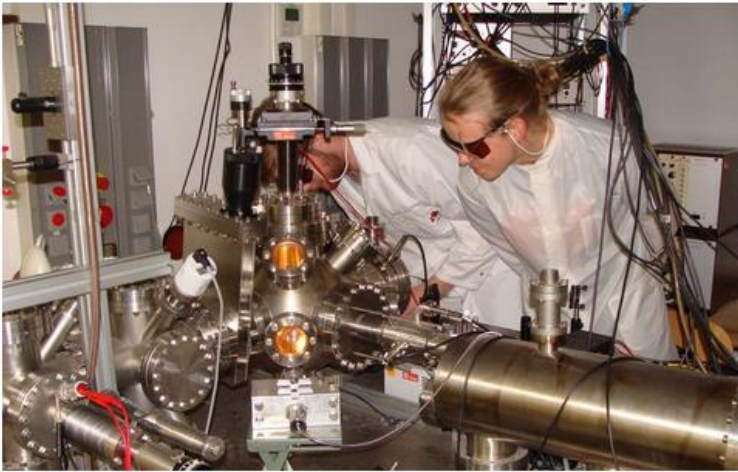


Výzkumné metody

- pozorování
- experiment
- úvaha
 - dovozování nových poznatků z obecnějších teorií
 - ventricular energetics theory
 - ventriculoarterial coupling theory
 - Windkessel arterial model



experimentální
fyzika

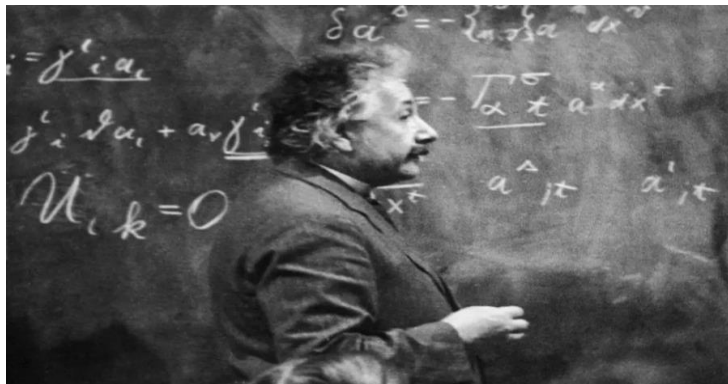


experimentální
biologie

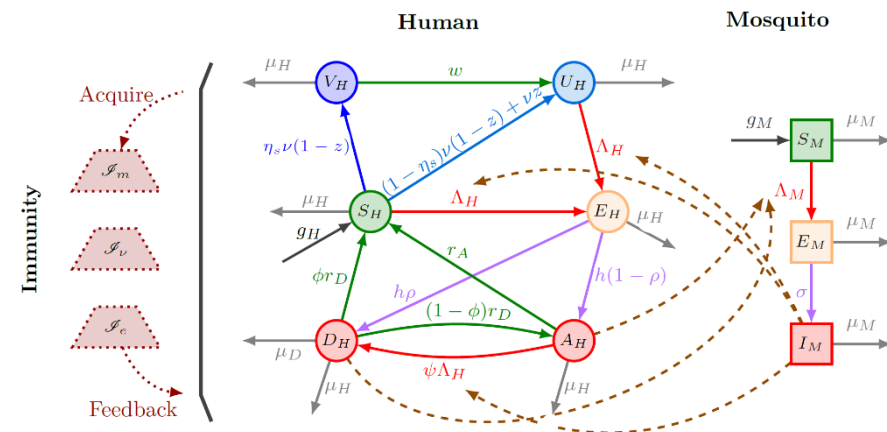


teoretická
fyzika

$$i\hbar \frac{\partial \psi(x,t)}{\partial t} = -\frac{1}{2} \frac{\hbar^2}{m} \frac{\partial^2 \psi(x,t)}{\partial x^2}$$



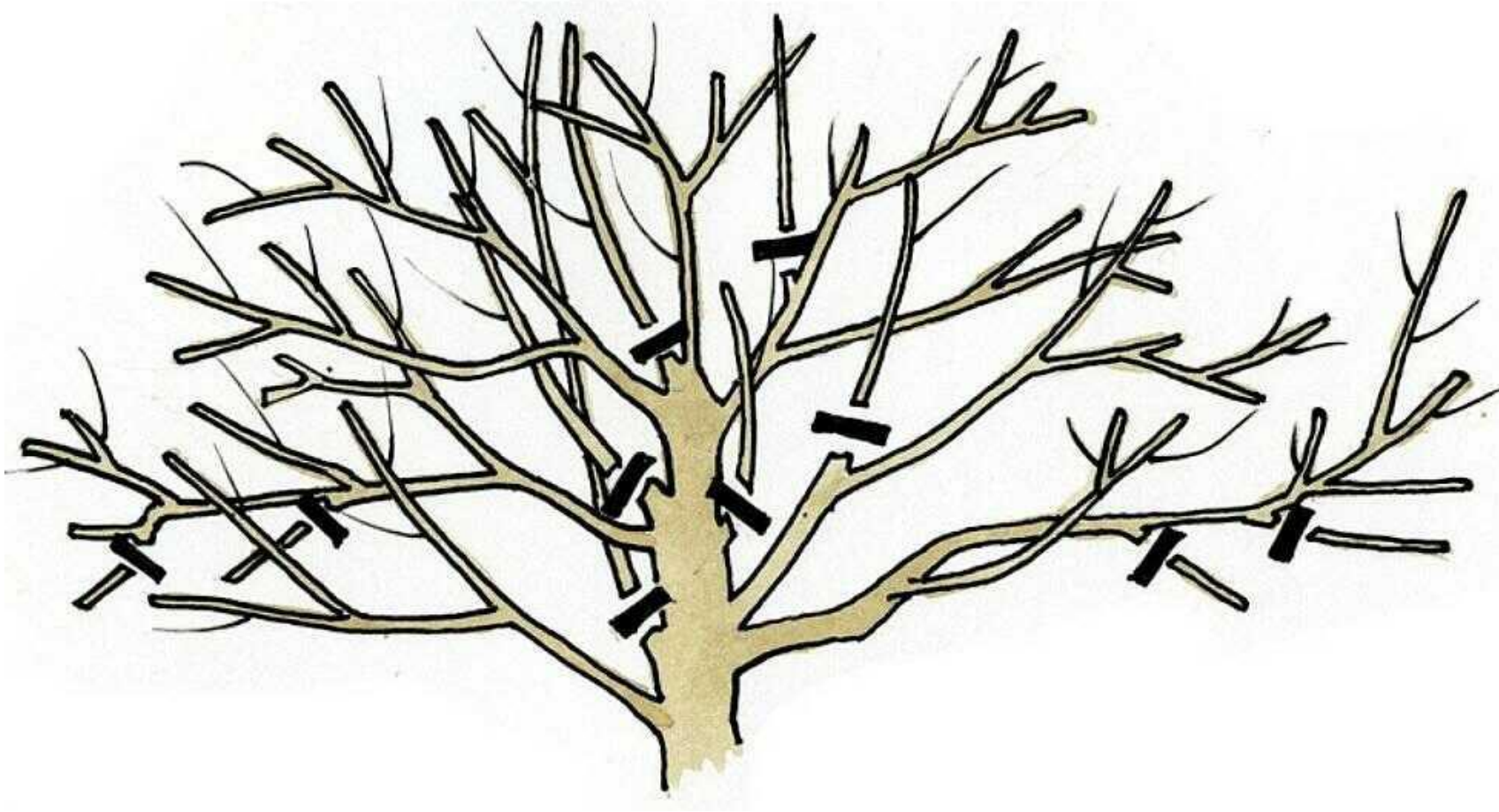
teoretická
biologie



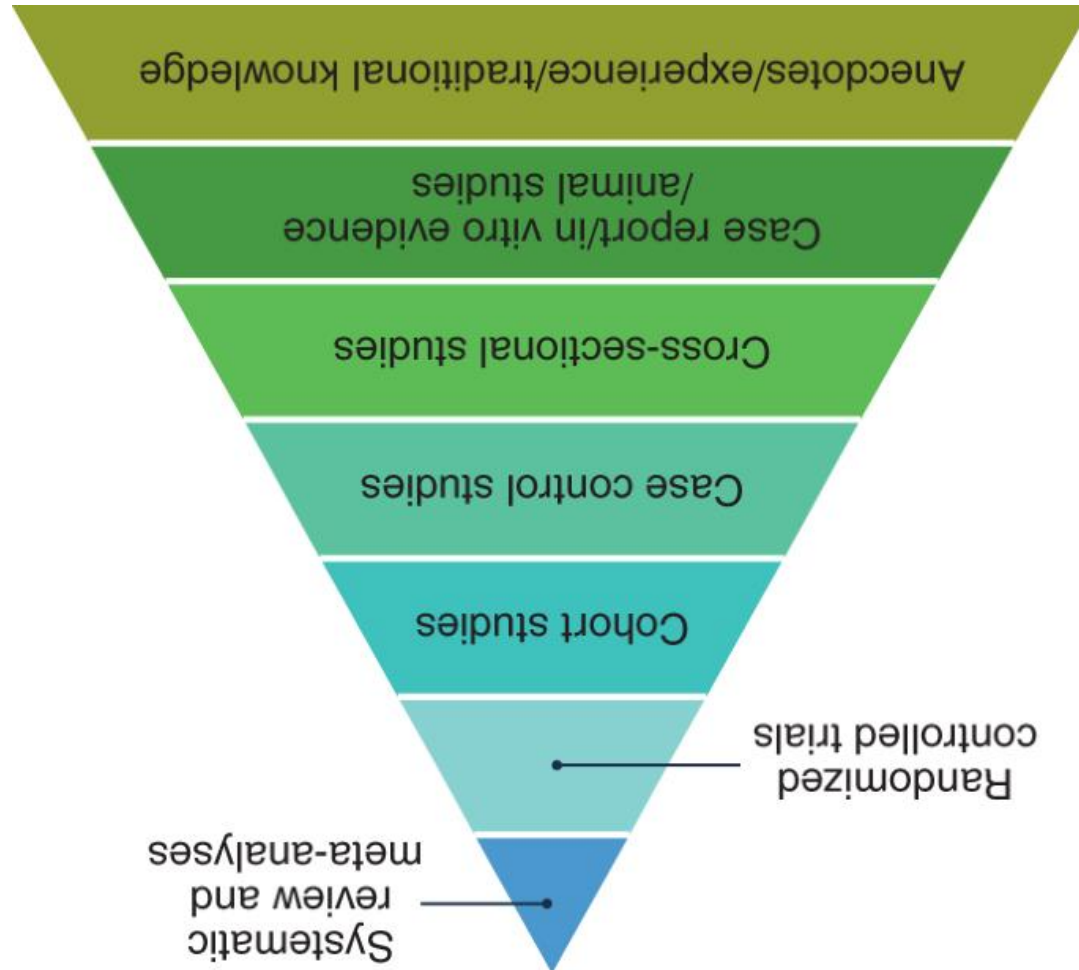
Co nás posouvá v poznání?



Jak nás v poznání posouvají RCT ?



Co nás posouvá v poznání?



- nové poznání, nové směry
- optimalizace
- (systematické) testování

Vývoj v intenzivní medicíně vs. hemato-onkologii

- zkoumatelnost
 - vzorek krve
 - časový vývoj
- komplexita
- molekulární biologie
- „onkologové jsou vědci“... ??



teoretické metody ...?

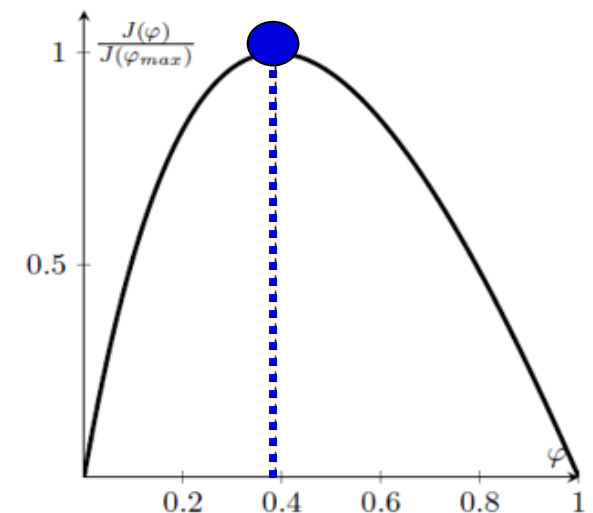


“Sepsí nelze spočítat”

- biologii nelze odvodit z fyziky
- princip evoluční optimality v biologii

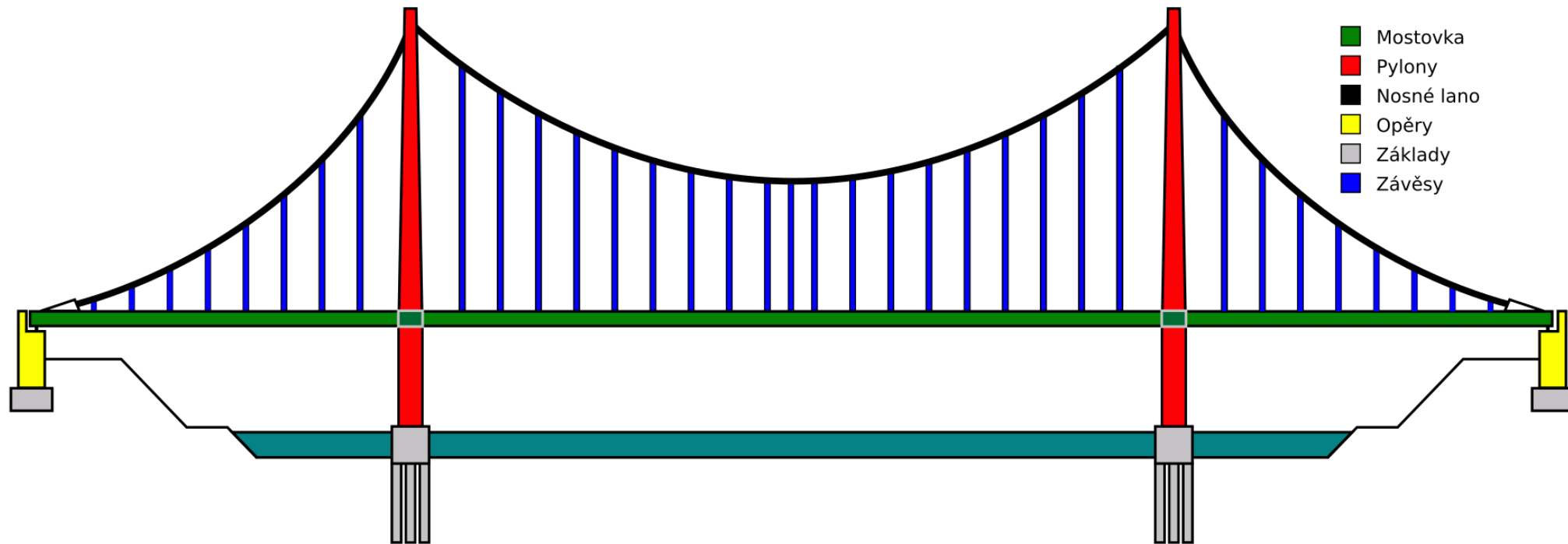
matematická formulace

$$S(a, x, y....) \longrightarrow a_{max} = \max_a S(a, x, y....) \longrightarrow \frac{\partial S}{\partial a} = 0$$



Problémy matematického modelování

- složitost systému, neznámá data



- matematici se nezabývají medicínou, lékaři se nezabývají matematikou

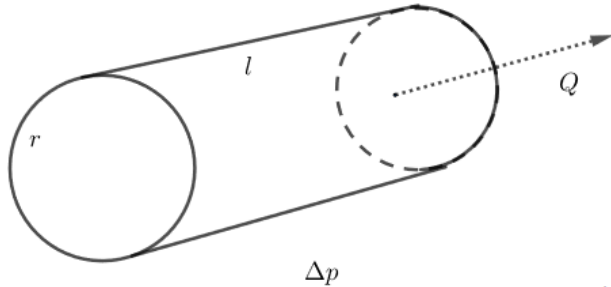
Přínos matematického modelování

- vysvětlení, identifikace podstatného
- kvantifikace protichůdných faktorů vs. kvalitativní úvaha
 - vyšší hematokrit → vyšší dodávka kyslíku ?
- predikce
- zkoumání obtížně zkoumatelného



Co je > 0 ?

- $15 + 19 + 74 + 68 + 29$
- $16 - 21 - 61 + 74 - 23$



- vysvětlení, objasnění podstatného vs. AI
- model = zjednodušená realita

- průtok krve tkáněmi

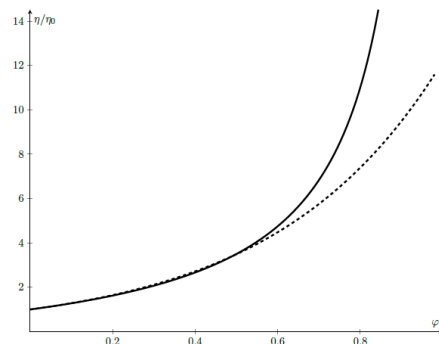
$$Q = \frac{\pi r^4 \Delta p}{8l\eta(\varphi)} \rightarrow Q = K \frac{\Delta p}{\eta(\varphi)}$$

- obsah kyslíku v krvi

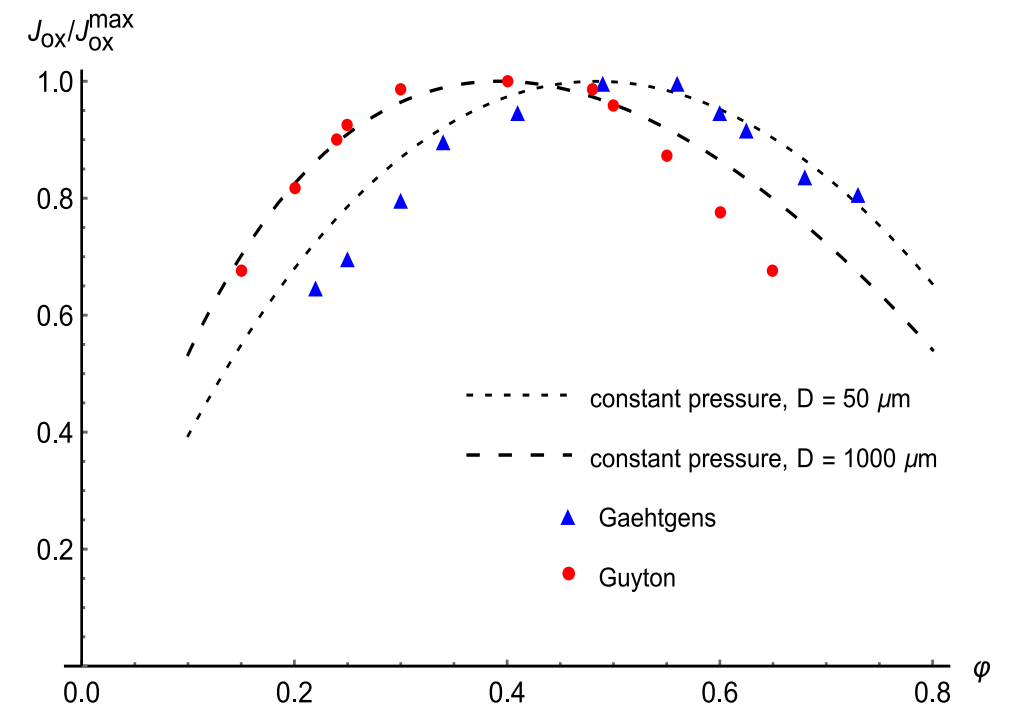
$$C_{ox} = k\varphi$$

- dodávka kyslíku do tkání

$$J_{ox} = C_{ox}Q$$



$$J_{ox} = K' \Delta p \frac{\varphi}{\eta(\varphi)}$$



Zkoumání obtížně zkoumatelného

Jaká je optimální „strategie“ podávání krystaloidů při těžkém krvácení před dostupností transfuze/zástavou krvácení?

■ animální studie

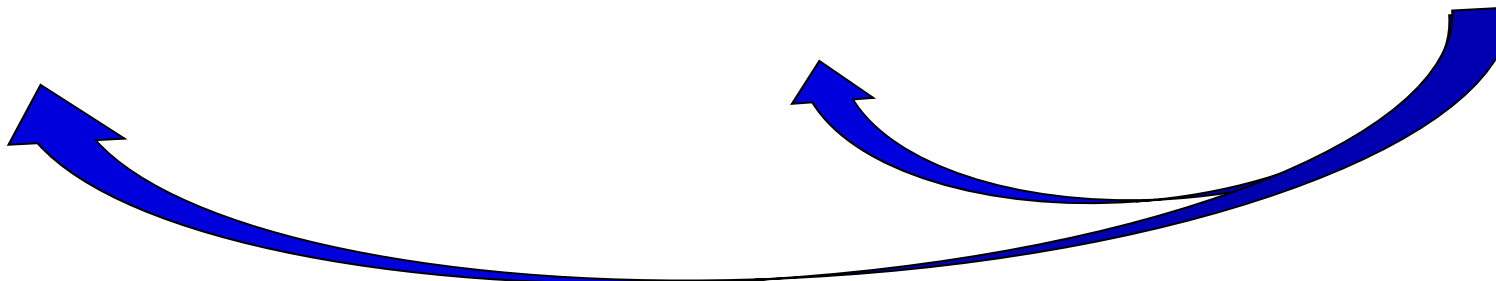
- různá schémata podávání
- limitovaný počet strategií
- počet zvířat
- přímé měření kyslíkového deficitu

■ klinická studie

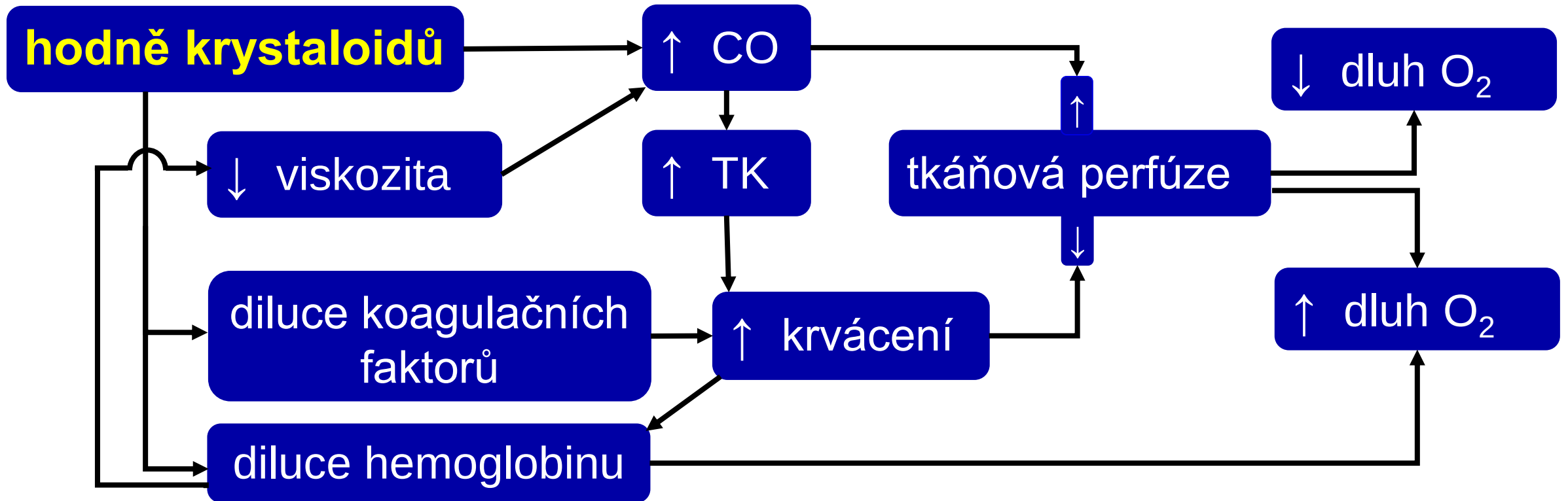
- různá schémata podávání
- variabilita
- počet pacientů
- u všech stejná strategie...??

■ teoretická studie

- detailní matematický popis
- detailní analýza
- verifikace výsledků klinickou či animální studií



- cíl : **minimalizace kyslíkového dluhu ve tkáních do zástavy krvácení**
- protichůdné faktory



- Závisí strategie na odhadované době do zástavy krvácení..?

Matematické modelování význam pro hemodynamiku

- vysvětlení, predikce
- technické aplikace
 - aneuryzma aorty, v softwaru přístrojů...
- příspěvek do mozaiky vědy
- podklad pro další studie

- problém složitosti
- „medicína není matematika“..??
- granty

