Physiological regulations - confrontation with pathology and diseases

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Outline

- General/ versus Special (patho)-physiology

- Physiologic/ vs. pathologic regulation

- **Vicious circles**
- **Feedback in general: positive/ vs. negative**
- **Best shown on these two examples:**
- **1) circulation**
- **2) thermo-regulation**

- Etc.

What came first
((Czech) textbook vol 2 and 3)
2 and 3 - Special pathological physiology

Analysis and mechanisms of disorders of tissues, organs and systems

- Blood
- Cardio-vascular system, cardio-pulmonary system
- GIT, nutrition and metabolism
- Uro-genital tract, reproductive system
- Central and peripheral nervous system
- Endocrine system
- Etc.

What comes next
((Czech) textbook vol. 1)
1. General pathological physiology

- Analysis of common general mechanisms and processes involved in patho-genesis of several diseases
- Defensive and adaptive mechanisms: inflammation, fever, hyper-termia, shock, stress, oedema, failures and disorders of control systems, metabolic disorders, inherited disorders, other genetic mechanisms, etc. ….

http://mlab.lf1.cuni.cz/mlab/ marsalek-UPF/

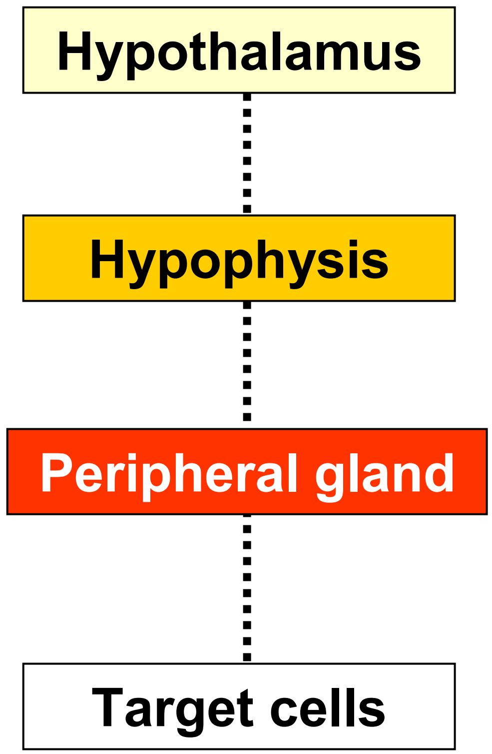
These are the alternative, „half-wild“ web pages of our group

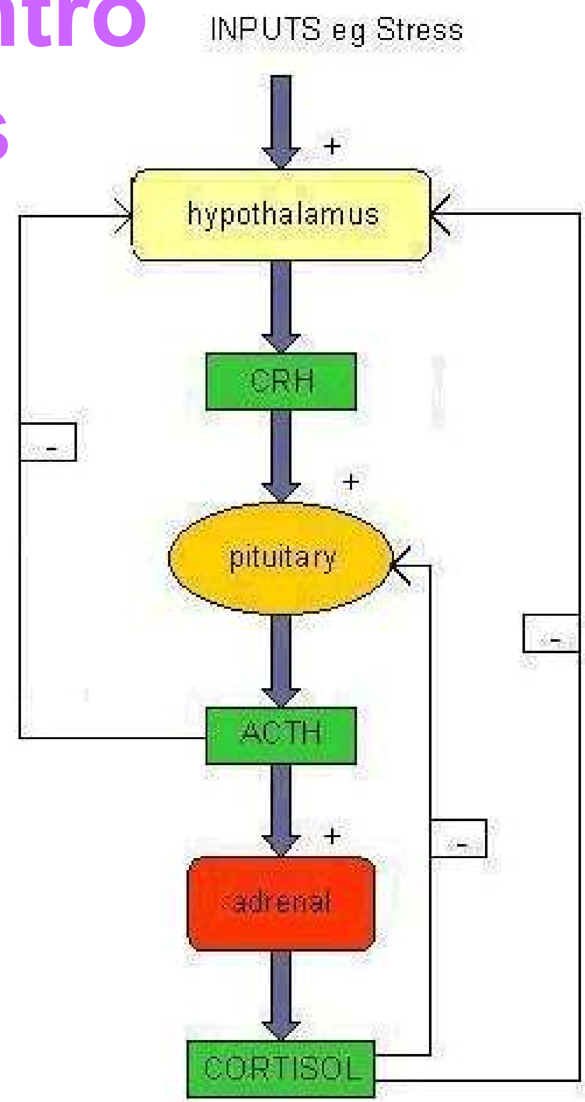
at the DPF (= UPF in Czech)

Let us recall the general intro to endocrine disorders

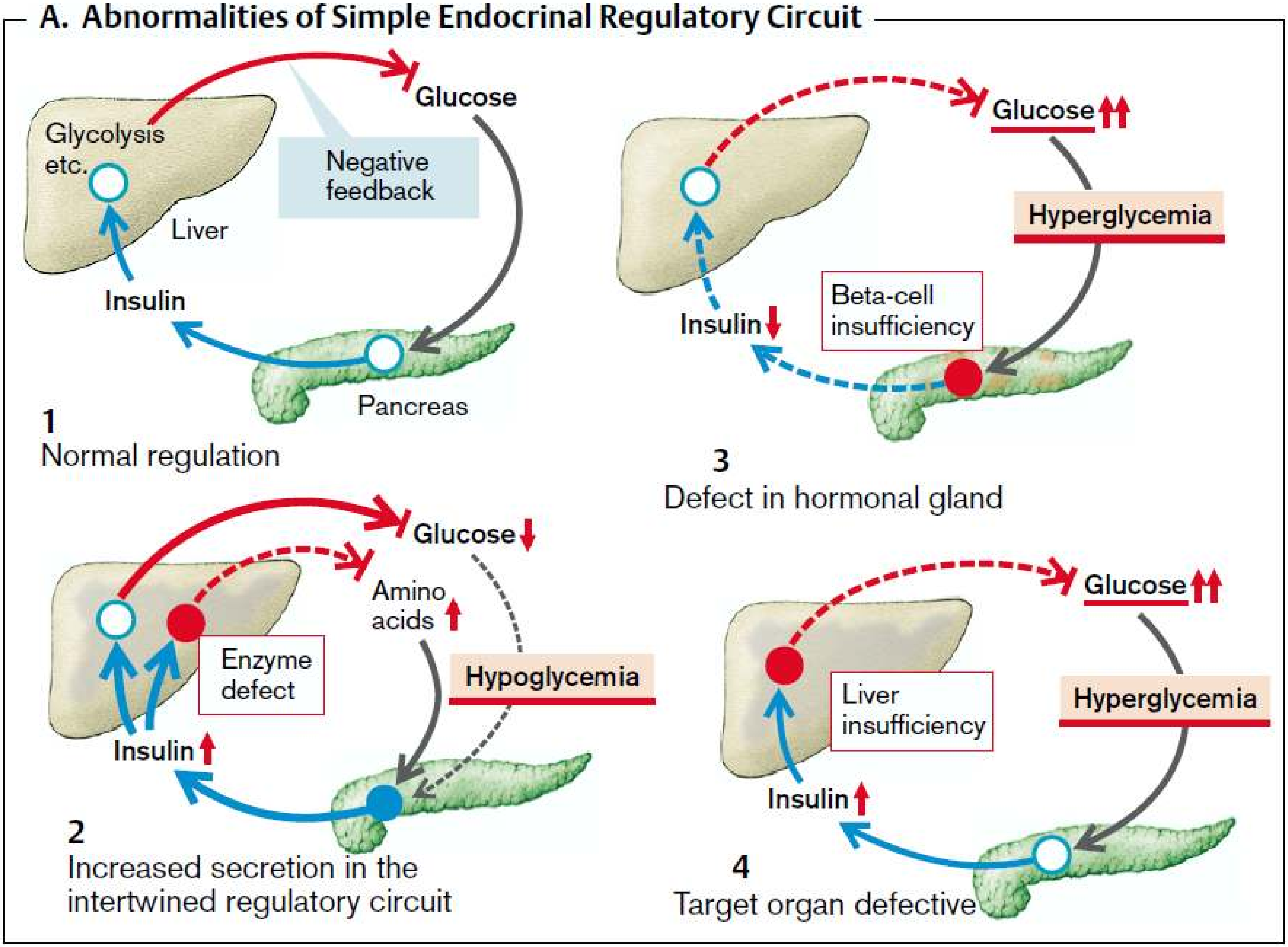
Negative feed-back

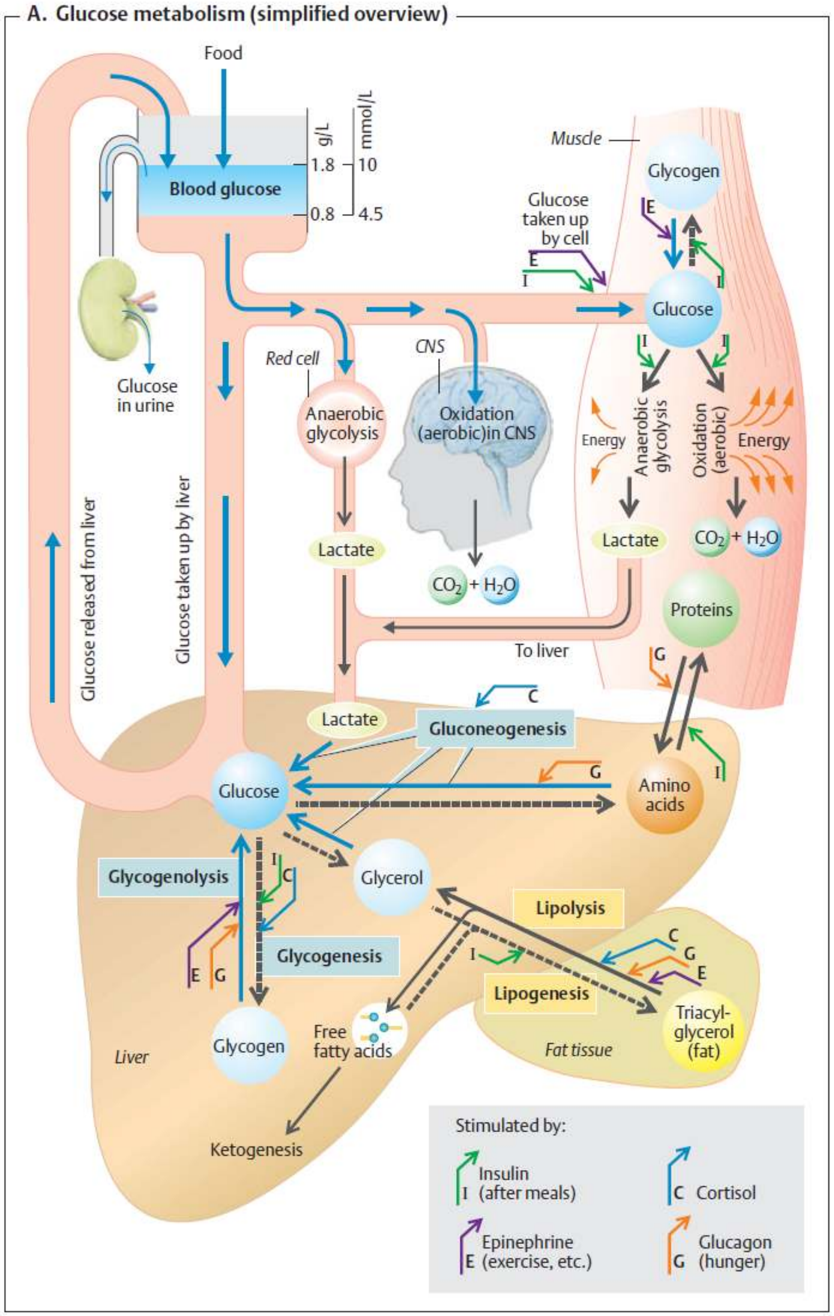
- **short / lonng feed-back**
- **system stability…**



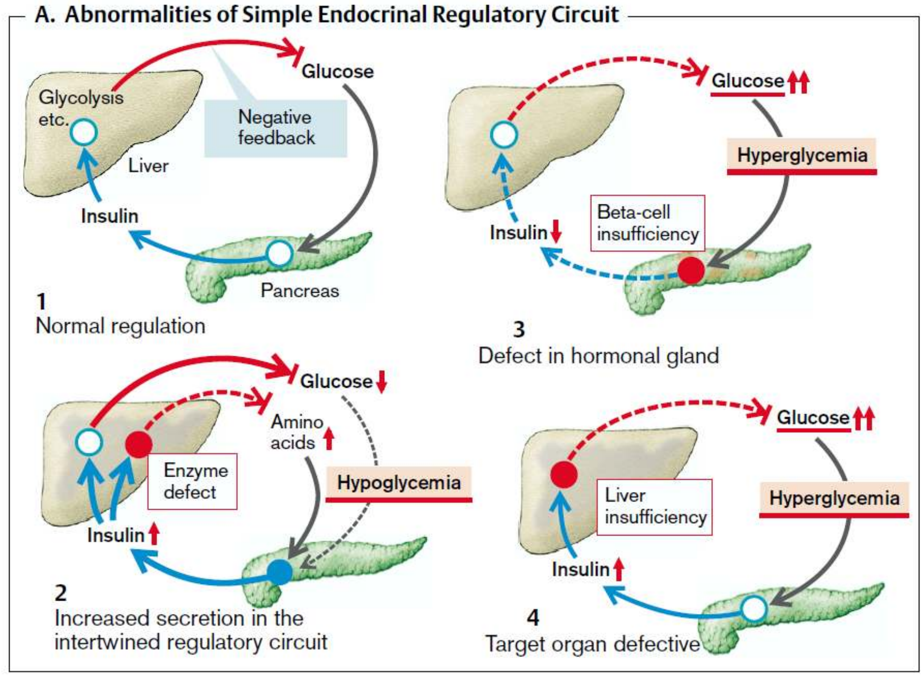


Example1: glycemia control by insulin





Despopoulos, Color Atlas of Physiology © 2003 Thieme



C. Hormonal effects on carbohydrate and fat metabolism

Hormone / Function	Insulin (Satiated ◄— Buffer)	Glucagon (Buffer —► Hungry)	Epinephrine (Stress, exercise)	Cortisol (Supply)
Glucose Uptake by cell	+ Muscle, fat		+ Muscle	− Muscle, fat
Glycolysis	+	−	+	−
Gluconeogenesis (liver)	−	+	+	+
Glycogen Synthesis ← → Lysis	Liver, muscle ←	Liver →	Liver, muscle →	Liver ←
Fat Synthesis ← → Lysis	Liver, fat ←	Fat →	Fat →	Fat →

C. Hormonal effects on carbohydrate and fat metabolism

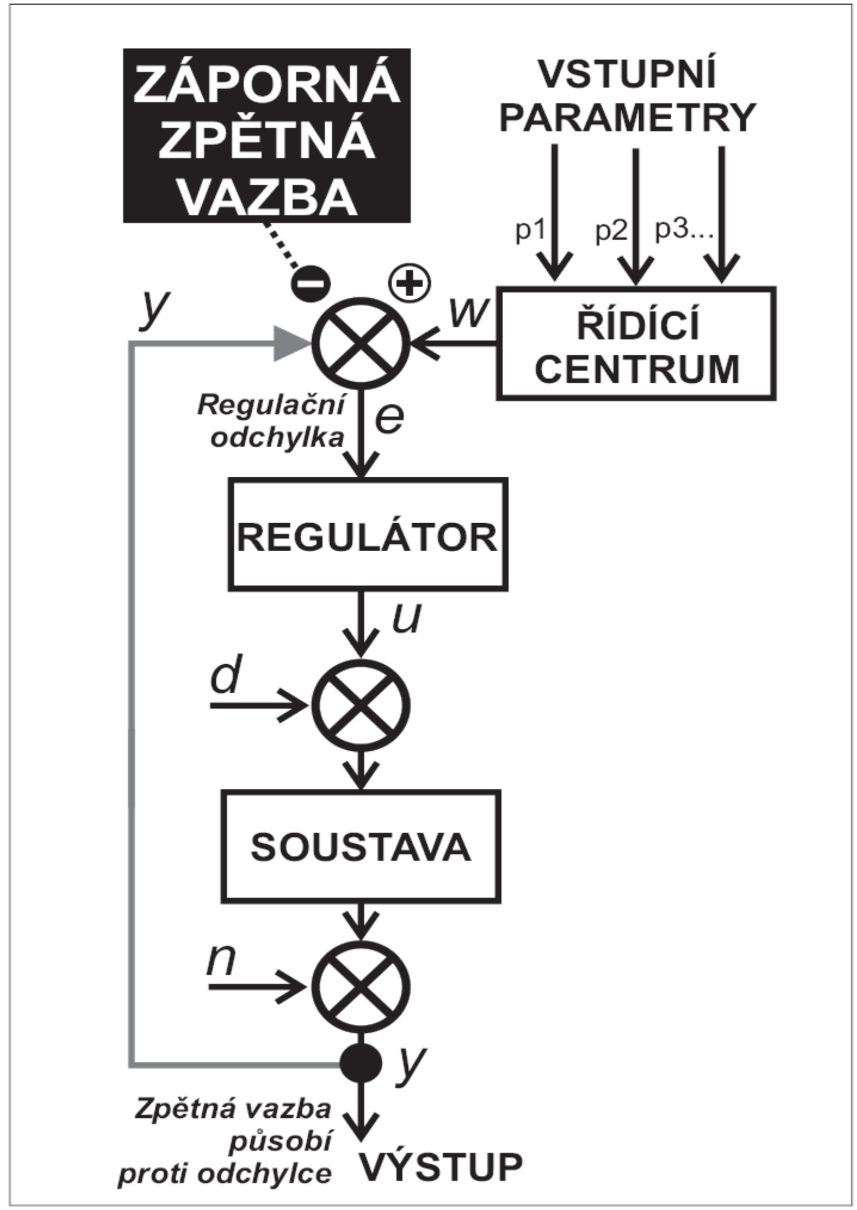
Hormone **Function**	Insulin Satiated ← Buffer	Glucagon → Hungry	Epinephrine Stress, exercise	Cortisol Supply
Glucose				
Uptake by cell	+ Muscle, fat		+ Muscle	− Muscle, fat
Glycolysis	+	−	+	−
Gluconeogenesis (liver)	−	+	+	+
Glycogen Synthesis ⇄ Lysis	Liver, muscle ←	Liver →	Liver, muscle →	Liver ←
Fat Synthesis ⇄ Lysis	Liver, fat ←	Fat →	Fat →	Fat →

General description of control systems

Control system: Negative feed-back

*y…*controlled variable, i/o
*w…*pre-set value
*e…*error signal
*u…*actuating variable
*d,n…*disturbance variables

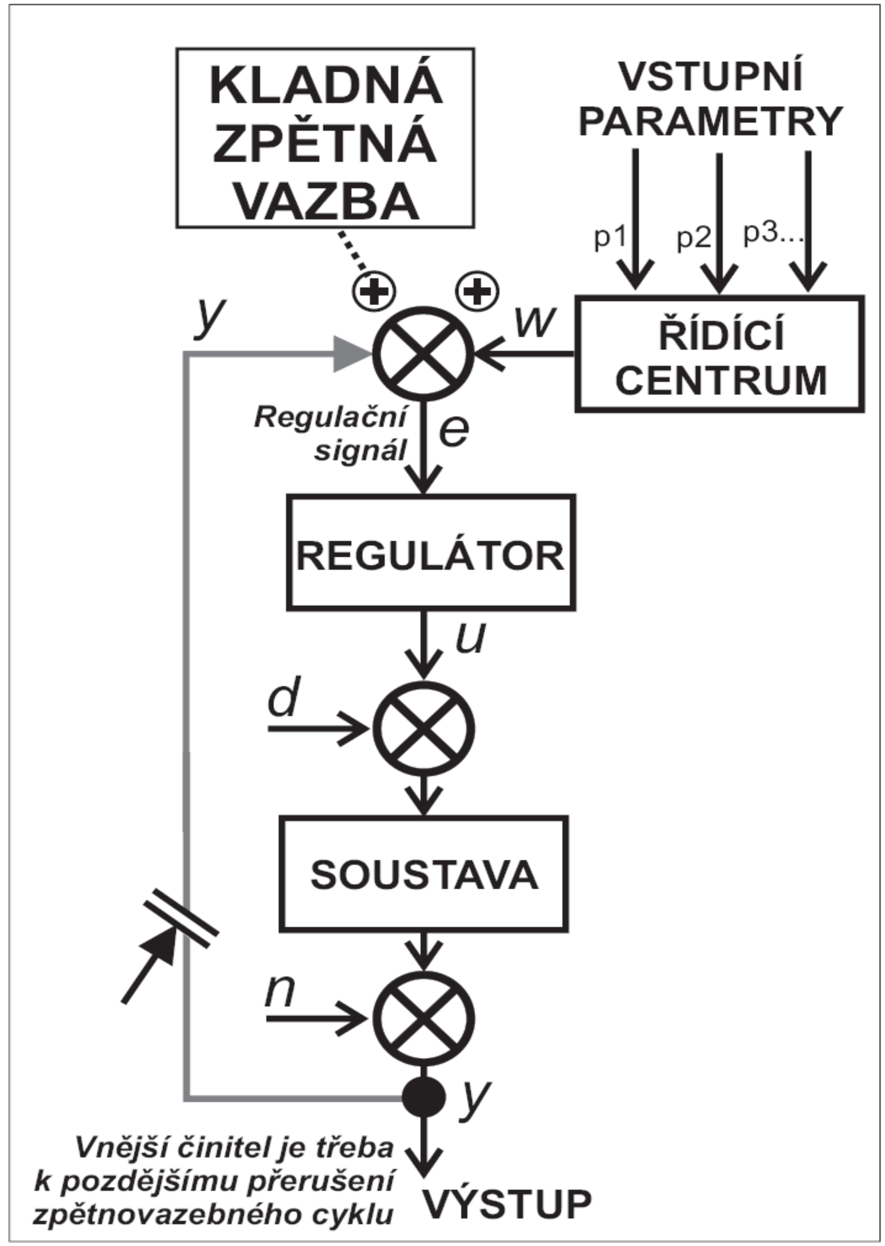
In **negative** feed-back, error signal *e* used for control is obtained by **subtraction** of the controlled variable (-*y*) from the pre-set value (+*w*), $e = w - y$.



Control system: Positive feed-back

*y…*controlled variable, i/o
*w…*pre-set value
*e…*error signal
*u…*actuating variable
*d,n…*disturbance variables

In **positive** feed-back, error signal *e* used for control results from **addition** of the controlled variable (+*y*) to the pre-set value (+*w*),
$e = w + y$.



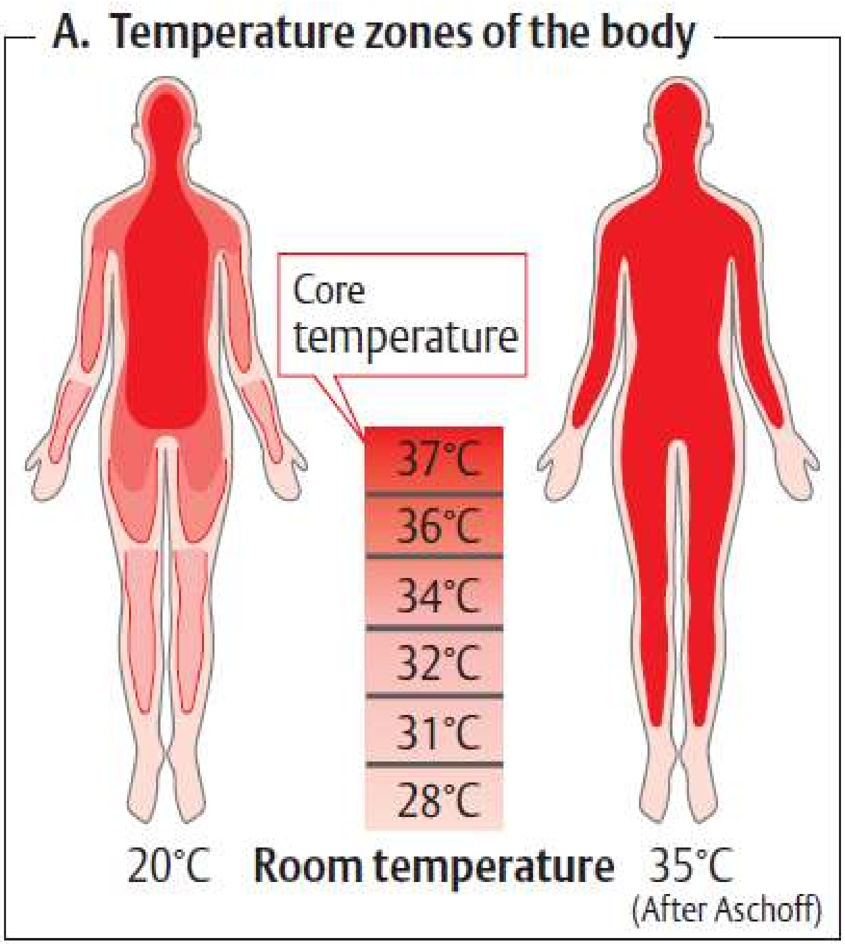
Examples – negative and positive feed-back

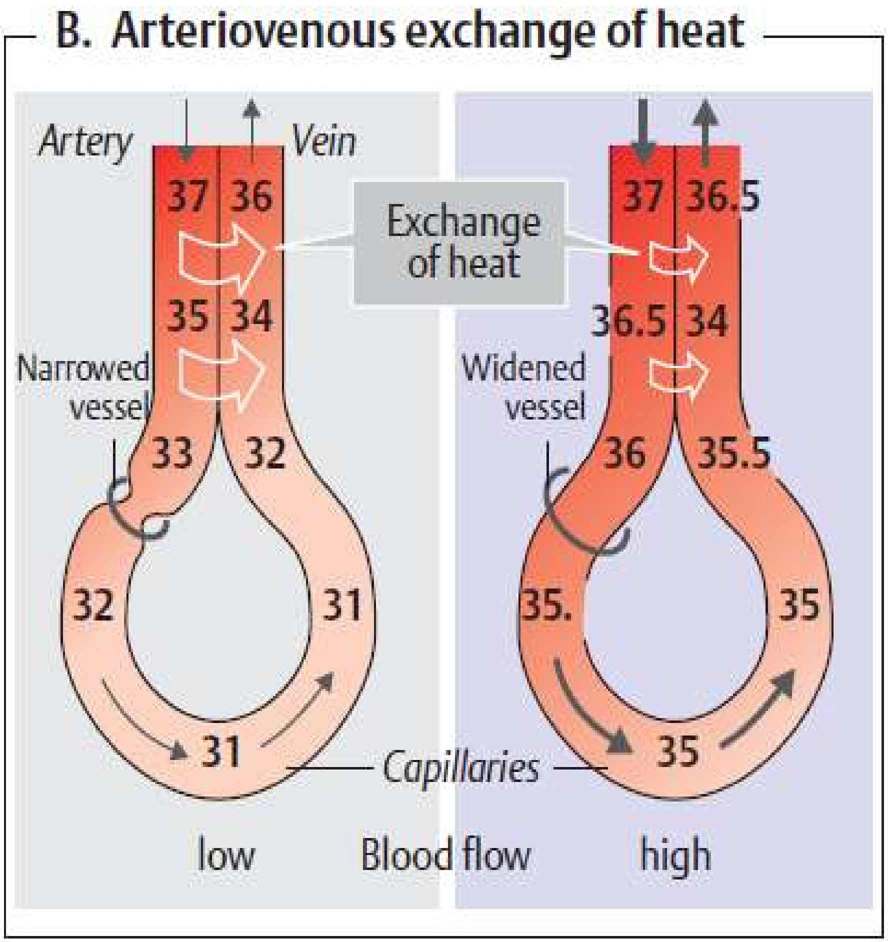
Negative feed-back – easy, almost everything is controlled this way:
blood pressure, temperature, glycemia, …
in general – homeostasis…

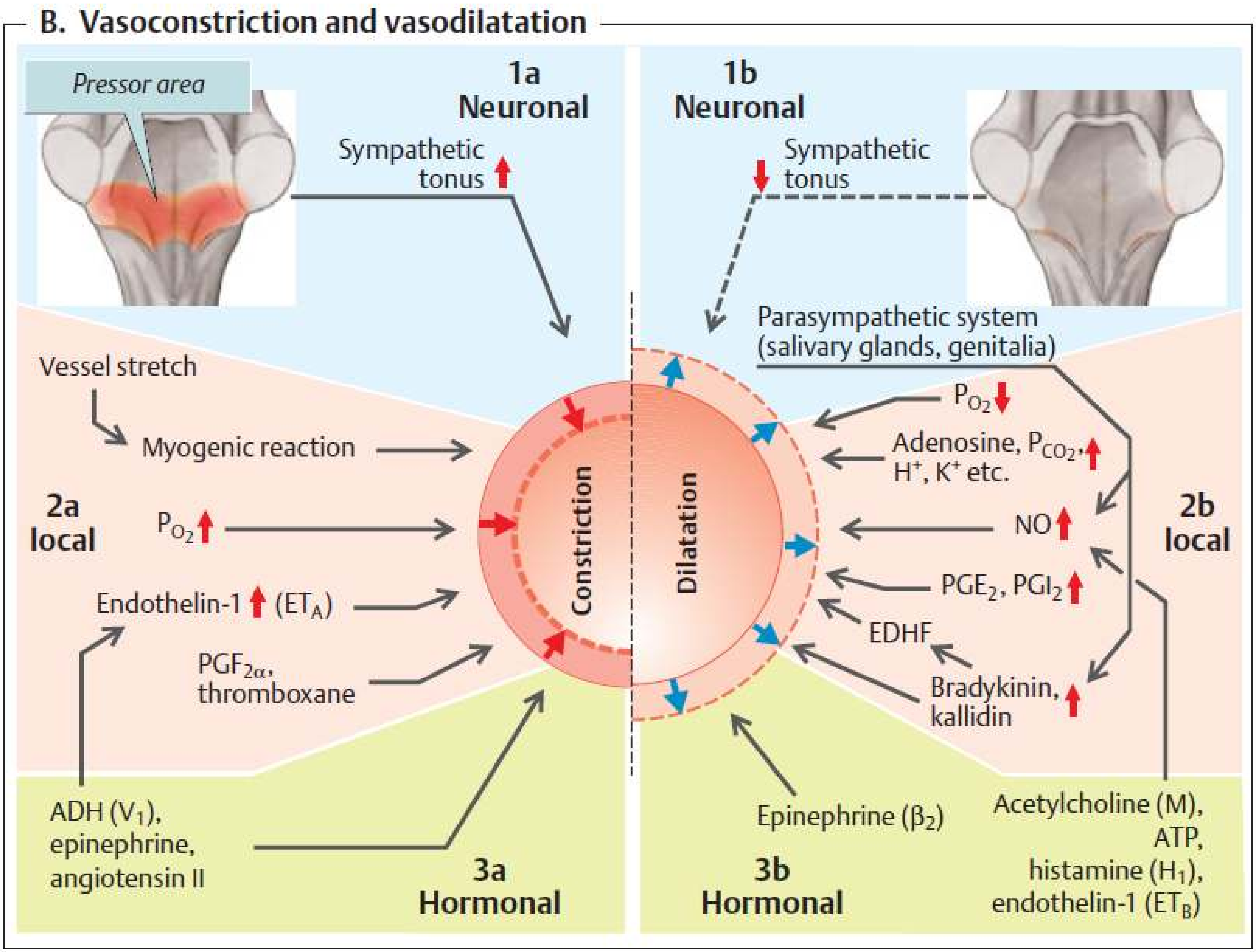
positive feedback – fewer examples, more difficult:
1) in physiology/ pato-physiology:
Ovulation, sex hormones in large, „avalanche-like“ trigger reactions:
hemocoagulation, division of lymfocytes
during the immune reaction (e.g the pneumonia crisis)

2) Pathology (pathologic values of variables, vicious circles, failures).
Building up of a new, pathologic equilibrium, example: adaptation to the lower PO2
failure of blood pressure control -> shock, hypo-perfusion, hypoxia…

Example 2: temperature control, fever

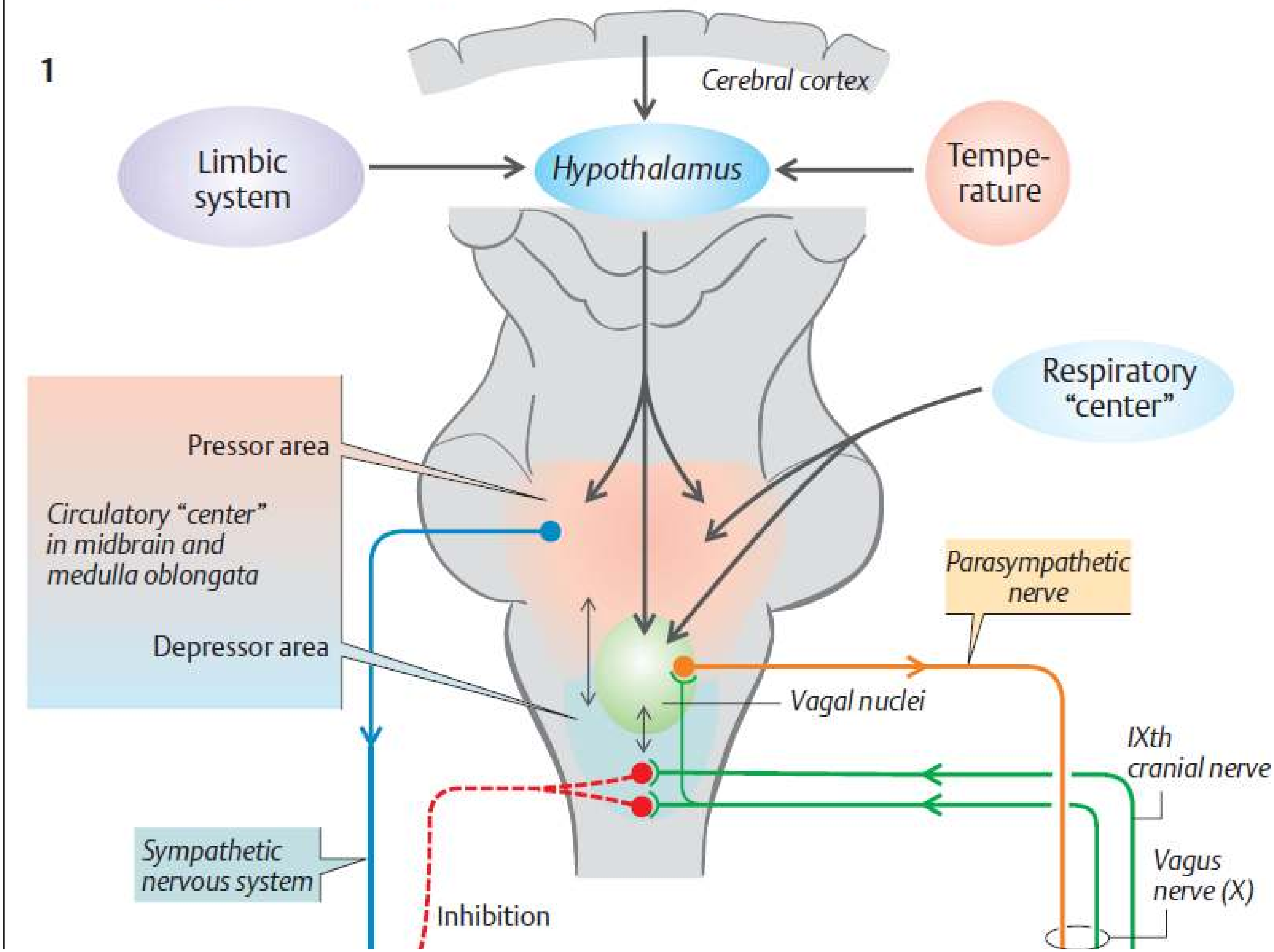

A. Temperature zones of the body
Core temperature
37°C
36°C
34°C
32°C
31°C
28°C
20°C
Room temperature
35°C
(After Aschoff)


B. Arteriovenous exchange of heat
Artery
Vein
37
36
Exchange of heat
35
34
Narrowed vessel
33
32
32
31
31
Capillaries
37
36.5
36.5
34
Widened vessel
36
35.5
35.
35
35
low
Blood flow
high

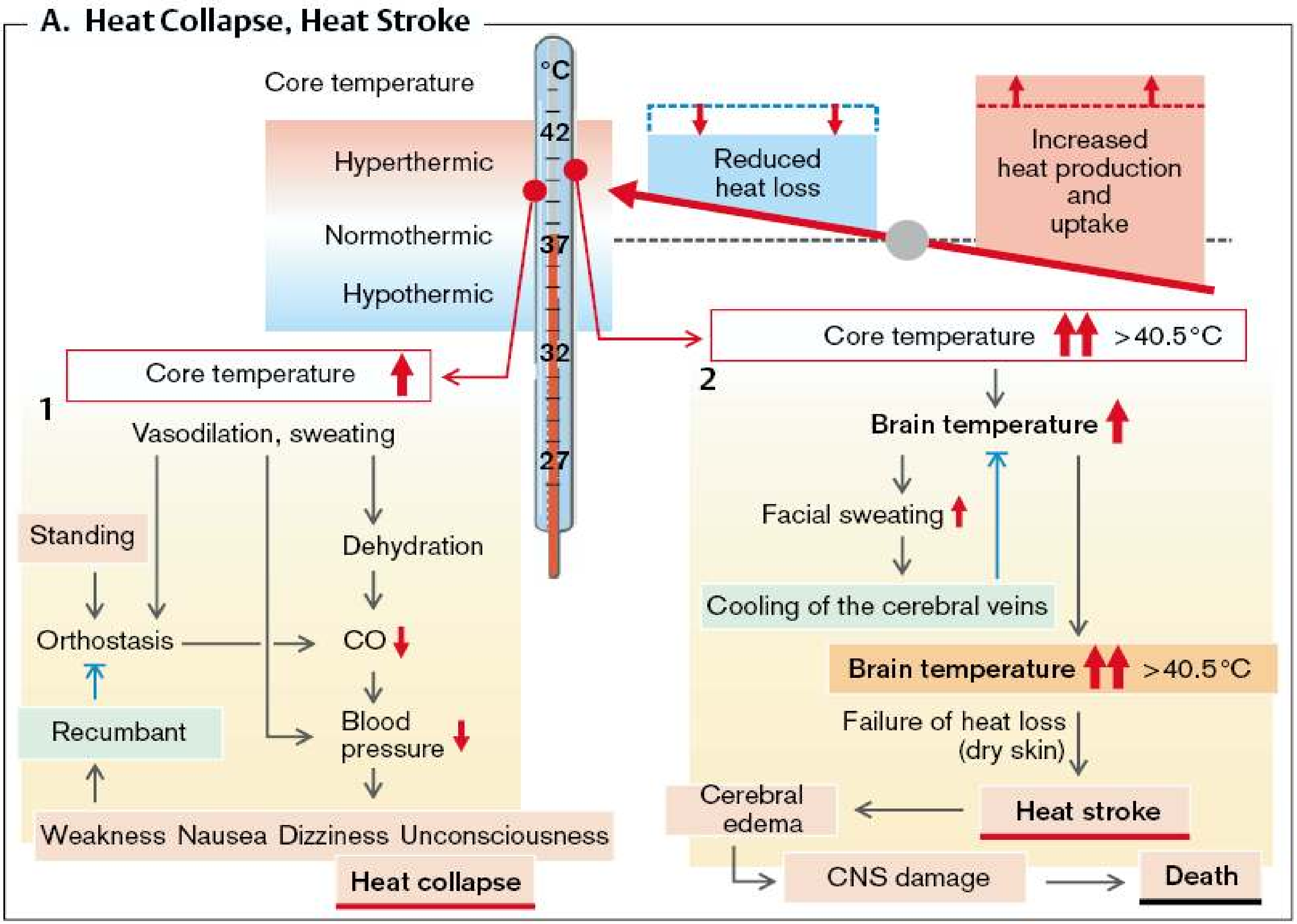


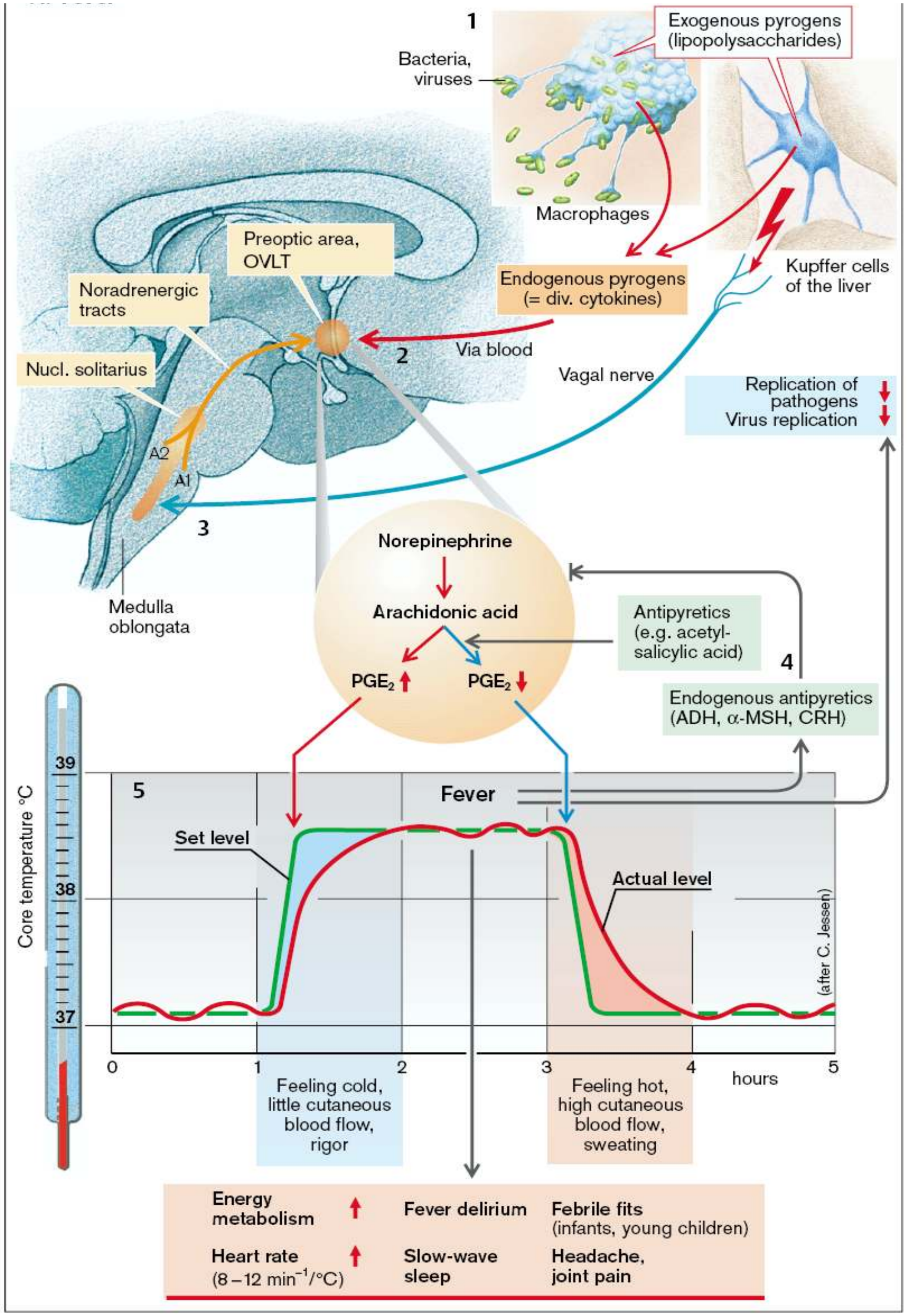
B. Vasoconstriction and vasodilatation
Pressor area
1a
Neuronal
Sympathetic tonus
1b
Neuronal
Sympathetic tonus
Parasympathetic system (salivary glands, genitalia)
Vessel stretch
Myogenic reaction
2a
local
P_{O_2}
Endothelin-1 (ET_A)
$PGF_{2\alpha}$, thromboxane
Constriction
Dilatation
P_{O_2}
Adenosine, P_{CO_2}, H^+, K^+ etc.
NO
2b
local
PGE_2, PGI_2
EDHF
Bradykinin, kallidin
ADH (V_1), epinephrine, angiotensin II
3a
Hormonal
Epinephrine (β_2)
3b
Hormonal
Acetylcholine (M), ATP, histamine (H_1), endothelin-1 (ET_B)

C. Central regulation of blood flow

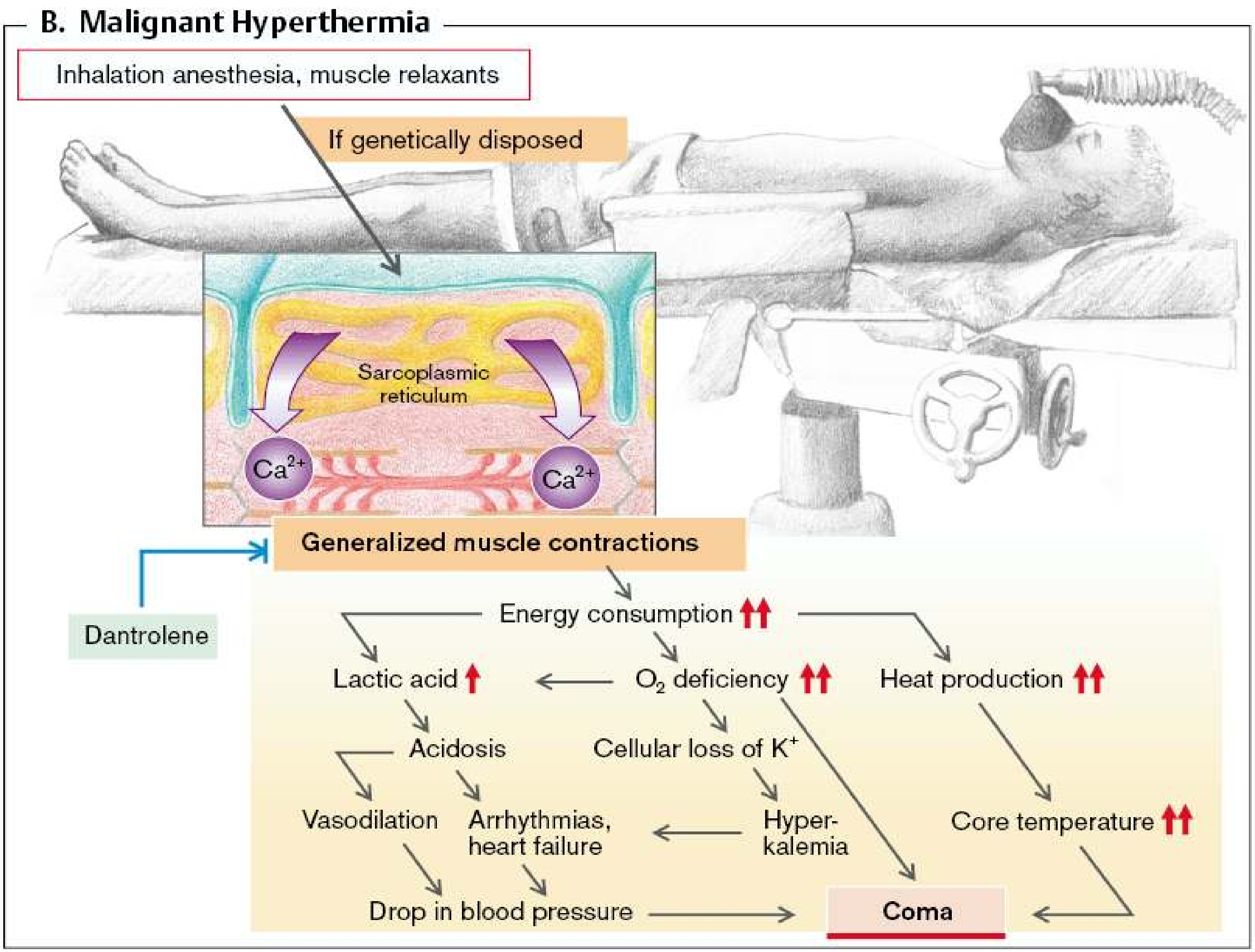


Heat collapse, heat stroke…

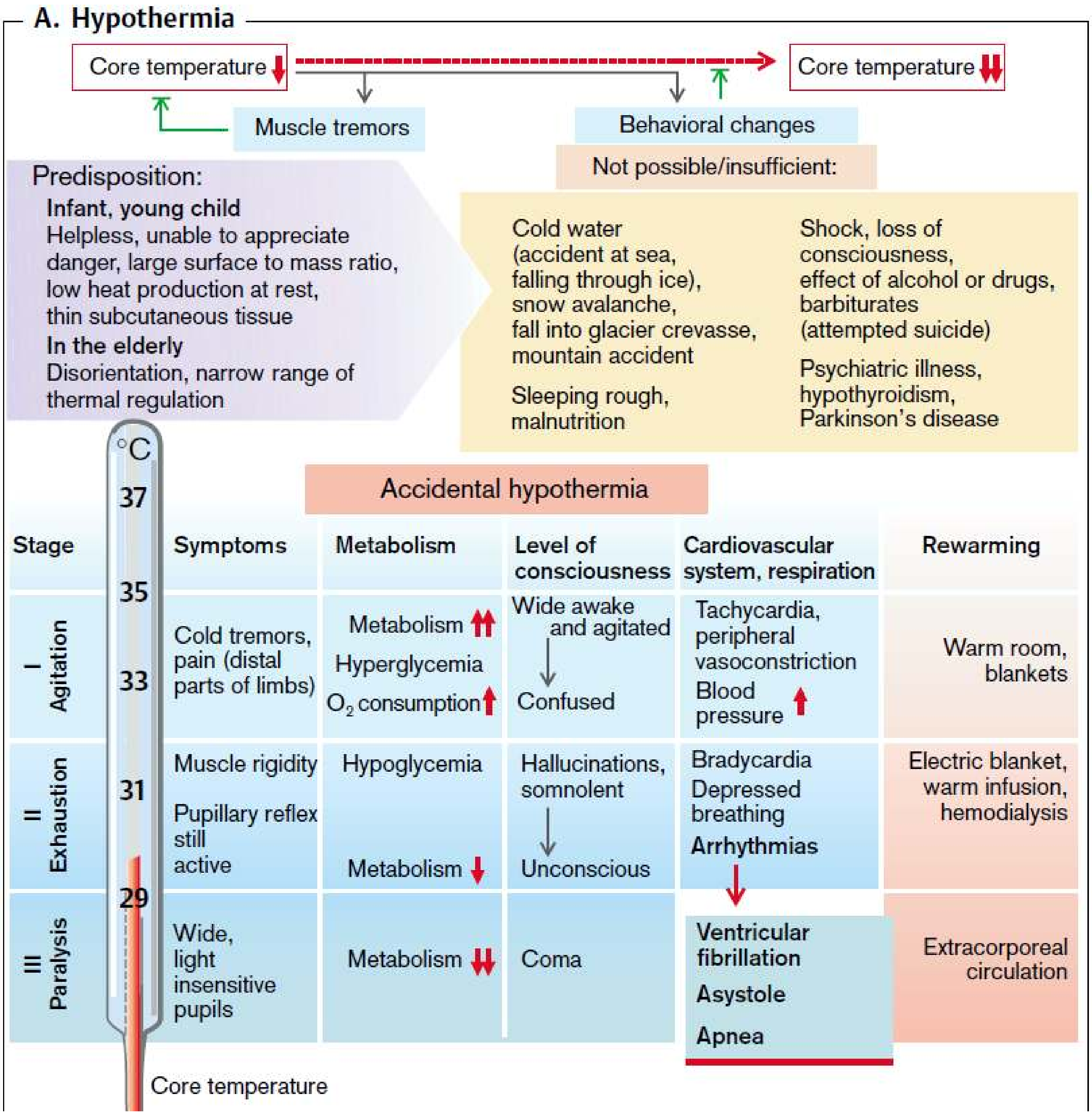




Fever, temperature control

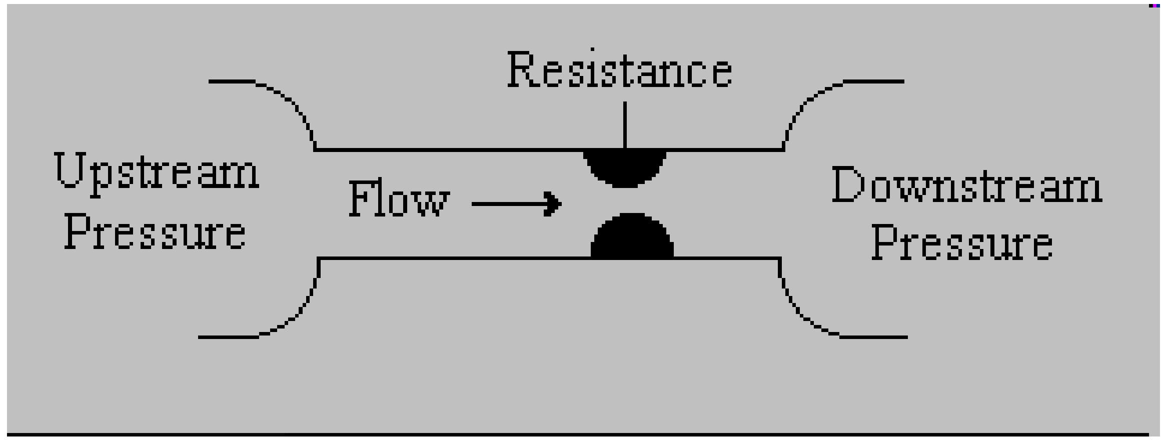

B. Malignant Hyperthermia
Inhalation anesthesia, muscle relaxants
If genetically disposed
Sarcoplasmic reticulum
Ca2+
Ca2+
Generalized muscle contractions
Dantrolene
Energy consumption
Lactic acid
O2 deficiency
Heat production
Acidosis
Cellular loss of K+
Vasodilation
Arrhythmias, heart failure
Hyper-kalemia
Core temperature
Drop in blood pressure
Coma

hypo-thermia



Example 3: blood pressure control

Preliminary thoughts 2 – pressure/ flow/ relation, Ohm's (Poiseulle) law



Pressure-Flow-Resistance Relationship in a Blood Vessel

Blood flow in a blood vessel is equal to the pressure difference along the vessel divided by the vascular *resistance*.

Flow = (Upstream Pressure - Downstream Pressure) / Resistance

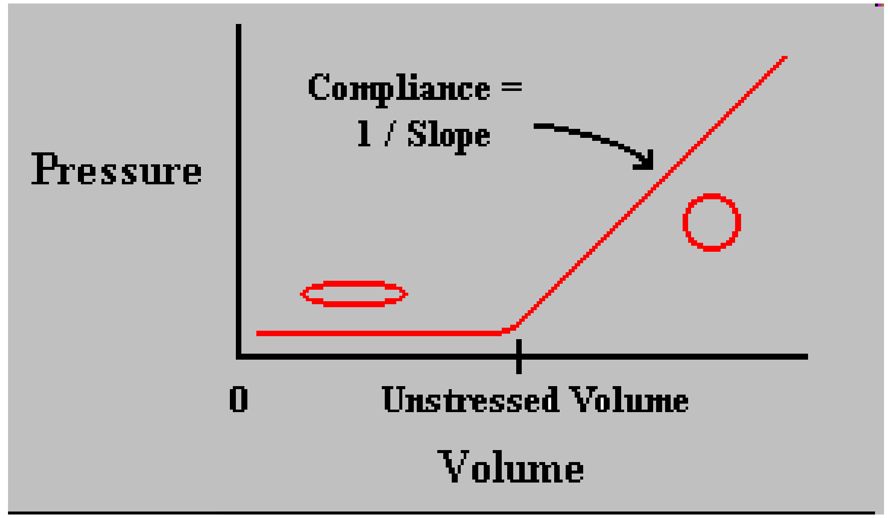
Vascular *conductance* is the reciprocal of vascular resistance. The pressure-flow relationship becomes

Flow = (Upstream Pressure - Downstream Pressure) * Conductance

Typical units for vascular conductance are (ml/min) / mmHg.

Preliminary thoughts 3 – pressure/ volume relation

Blood vessels tend to collapse at low volumes. Internal pressure is equal to external pressure, which is often at or close to zero relative to atmospheric pressure.
As additional volume is added, a critical volume is reached where any added volume causes the internal pressure of the vessel to increase. This critical volume is called the *unstressed* volume. Unstressed volume is usually denoted by V0 or V_0.
***Vascular compliance* is the reciprocal of the slope of the pressure-volume relationship at volumes greater than unstressed volume. The physical units for compliance are typically ml/mmHg.**
Approximate compliance values (ml/mmHg) for an adult male are



Pressure-Volume Relationship in a Blood Vessel

Arteries	**1.5**
Veins	**80**
Whole-Body	**140**

P Pressure (mmHg)

V Volume (ml)

V0 Unstressed Volume (ml)

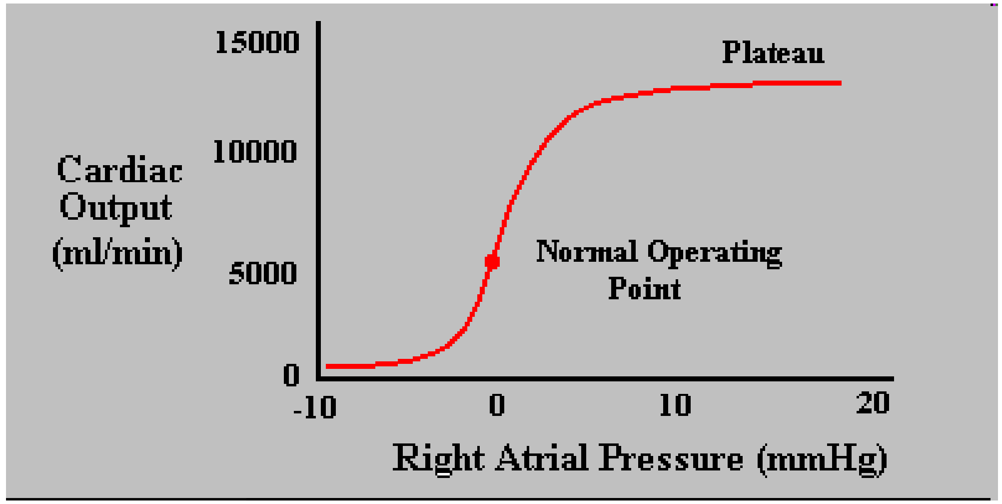
C Vascular Compliance (ml/mmHg)

Equations describing the pressure-volume relationship:

P = 0 when V < = V0

P = (1/C) * (V - V0) when V > V0

Preliminary thoughts 3 – Frank-Starling law



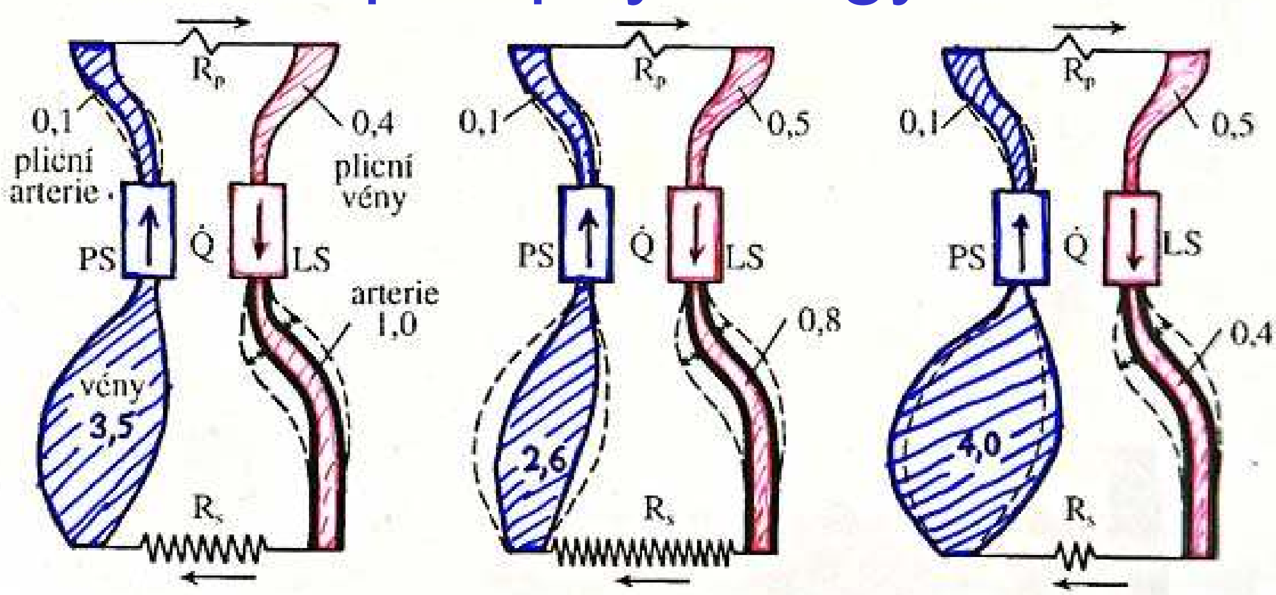
The Frank-Starling relationship may describe the right heart alone, the left heart alone, or the right heart, pulmonary circulation, and left heart combined. This last case is described here.
The Frank-Starling relationship describes the blood pumped by the heart-lung compartment, cardiac output, in terms of the filling pressure, right atrial pressure.

Preliminary thoughts 4, the continuity equation

…almost trivial…, ☺
Left heart flow =
= right heart flow,
and so on

version 3, Czech „patophysiology“, 2003

Nečas et al., Vol 1, p. 147



Objem krve: 5,6 litrů*
R_s: 17,5 mmHg/litr/min
$\dot{Q}$: 5,6 litr/min
TK: 100 mmHg

Objem krve: 4,6 litrů*
R_s: 23,5 mmHg/litr/min
$\dot{Q}$: 4,2 litr/min
TK: 100 mmHg

Objem krve: 5,6 litrů*
R_s: **6,3 mmHg/litr/min**
Q: 6,4 litr/min
TK: 43 mmHg

* 0,6 l je vnitřní objem cirkulačního aparátu, který musí být vyplněn krví, jejíž objem však nepřispívá k roztažení cév (angl. unstressed volume)

Obr. 2.15 Model cirkulace s vyznačením distribuce krve mezi arteriální a venózní části. **A** – normální cirkulace, **B** – cirkulace po ztrátě 1 litru krve a zvýšení systémového odporu tak, aby byl udržen arteriální krevní tlak, **C** – cirkulace po poklesu systémového odporu („vazodilataci“), který způsobí redistribuci 0,5 litru krve z arteriální části cirkulace do části venózní. PS, LS – pravá a levá část srdce, R_s, R_p – odpor v systémové a plicní cirkulaci, $\dot{Q}$ – srdeční výdej, TK – krevní tlak v systémových arteriích

version 1, „physical model“, no date equations only, …almost trivial…, ☺

1. Frank-Starling law
2. Ohm’s law (simplification of Poiseulle law)
3. Compliance of vessels
4. Continuity equation (volumes persist)

$$\dot{Q} = k_{\mathrm{LH}} \overline{p}_{\mathrm{SV}} = k_{\mathrm{RH}} \overline{p}_{\mathrm{PV}}$$

$$I = \frac{U}{R}, \dot{Q} = \frac{(\overline{p}_{\mathrm{IN}} - \overline{p}_{\mathrm{OUT}})}{R}$$

$$V_{\mathrm{VS}} = c_{\mathrm{VS}} \overline{p}_{\mathrm{VS}}$$

$$\sum V_i = V_{\mathrm{TTL}}$$

version 2, „variables and units“, no date…

V …[Litre] blood volume
$\dot{Q}$ …[Litre/sec] minute volume
R_P …[mmHg.sec/Litre] pulmonary resistance
R_S …[mmHg.sec/Litre] systemic resistance
p_{AS}..[mmHg] arterial systemic pressure
…etc.

these variables are in equations, described here and on

$$\dot{Q} = k_{LH}\bar{p}_{SV} = k_{RH}\bar{p}_{PV}$$

$$I = \frac{U}{R}, \dot{Q} = \frac{(\bar{p}_{IN} - \bar{p}_{OUT})}{R}$$

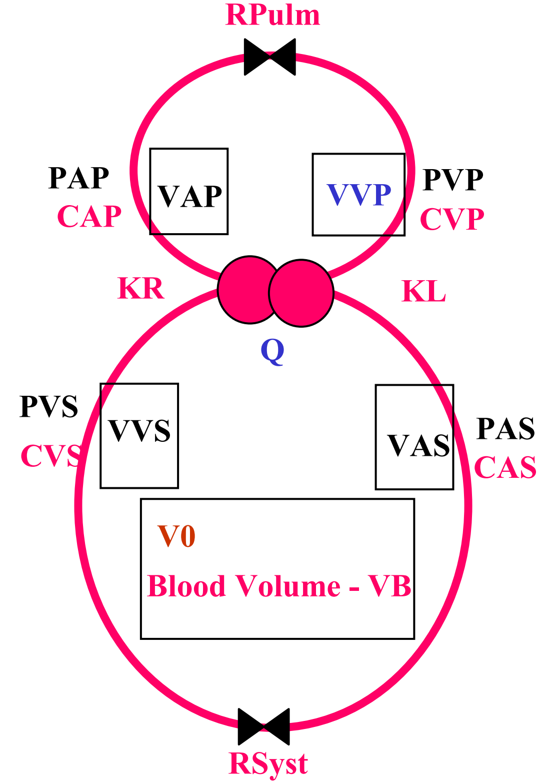
$$V_{VS} = c_{VS}\bar{p}_{VS}$$

$$\sum V_i = V_{TTL}$$

1. Frank-Starling law
2. Ohm’s law (simplification of Poiseulle law)
3. Compliance of vessels
4. Continuity equation (volumes persist)

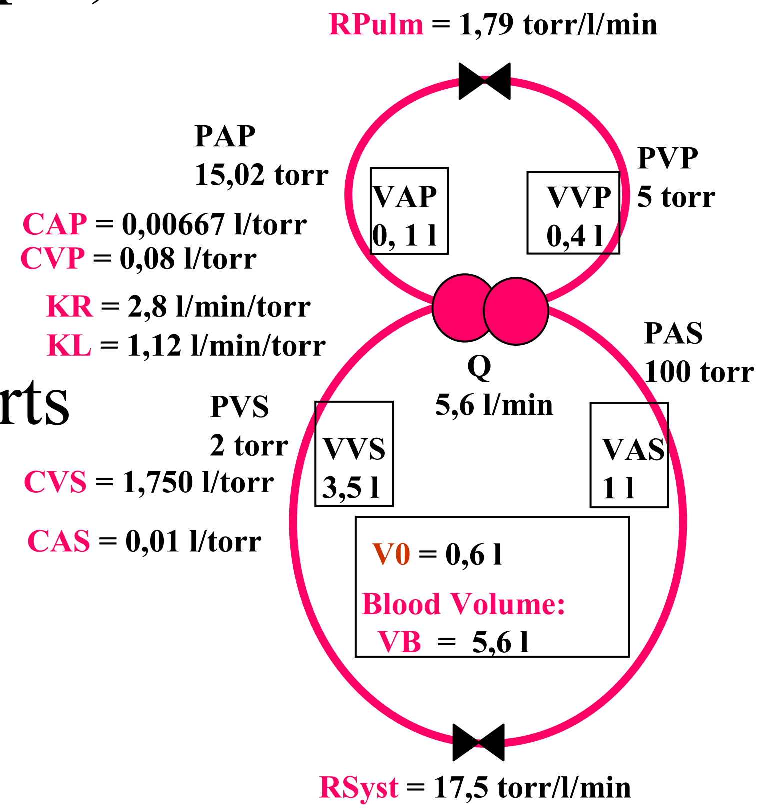
version 4, „physiological model" – for separate parts of circulation, no date

- Frank-Starling law (control by input)
  - Q = KL * PVP
  - Q = KR * PVS
- Ohm's law
  - Q = (PAS - PVS)/RSyst
  - Q = (PAP - PVP)/RPulm
- Vessel compliance in separate parts
  - VB = V0 + VAS + VVS + VAP + VVP
  - VAS = CAS * PAS
  - VVS = CVS * PVS
  - VVP = CAP * PVP
  - VAP = CVP * PAP



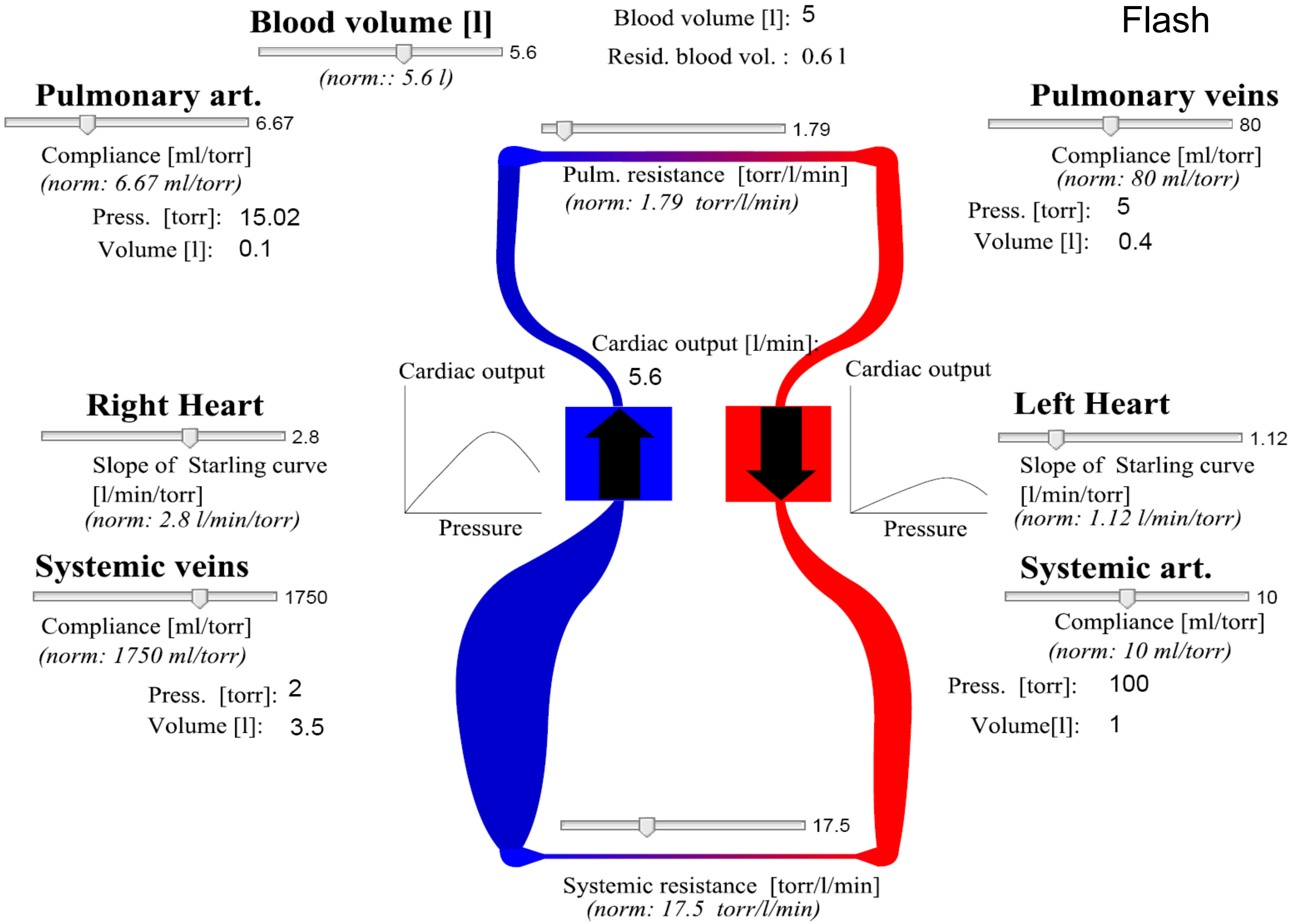
version 5, „physiological model“ with values – for separate parts of circulation, no date

- Frank-Starling law (control by input)
  - Q = KL * PVP
  - Q = KR * PVS
- Ohm's law
  - Q = (PAS - PVS)/RSyst
  - Q = (PAP - PVP)/RPulm
- Vessel compliance in separate parts
  - VB = V0 + VAS + VVS + VAP + VVP
  - VAS = CAS * PAS
  - VVS = CVS * PVS
  - VVP = CAP * PVP
  - VAP = CVP * PAP



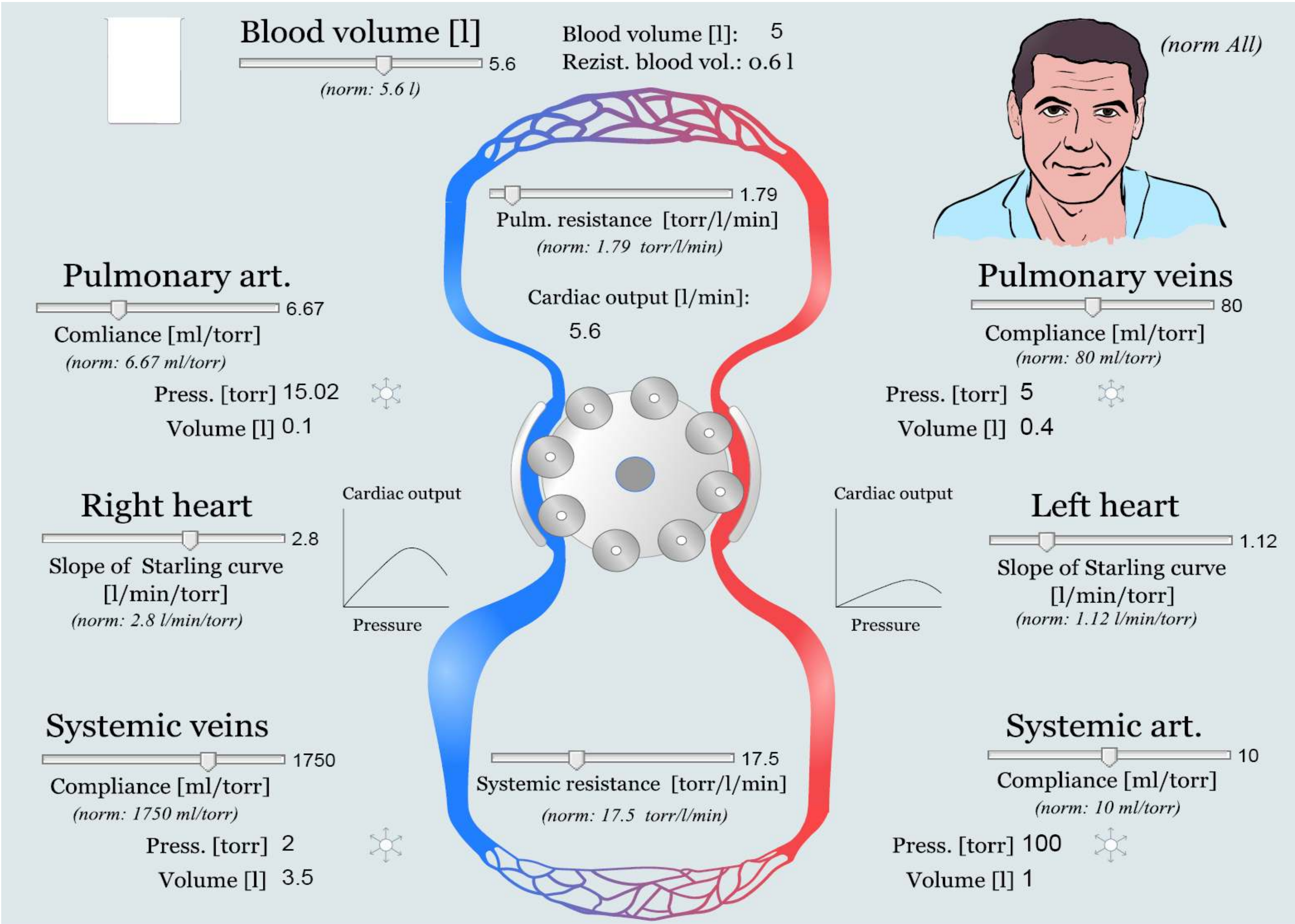
ver. 6 Animation version 2, 2006

Technology: Flash



ver. 7, Animation version 2, 2006

Technology: Flash



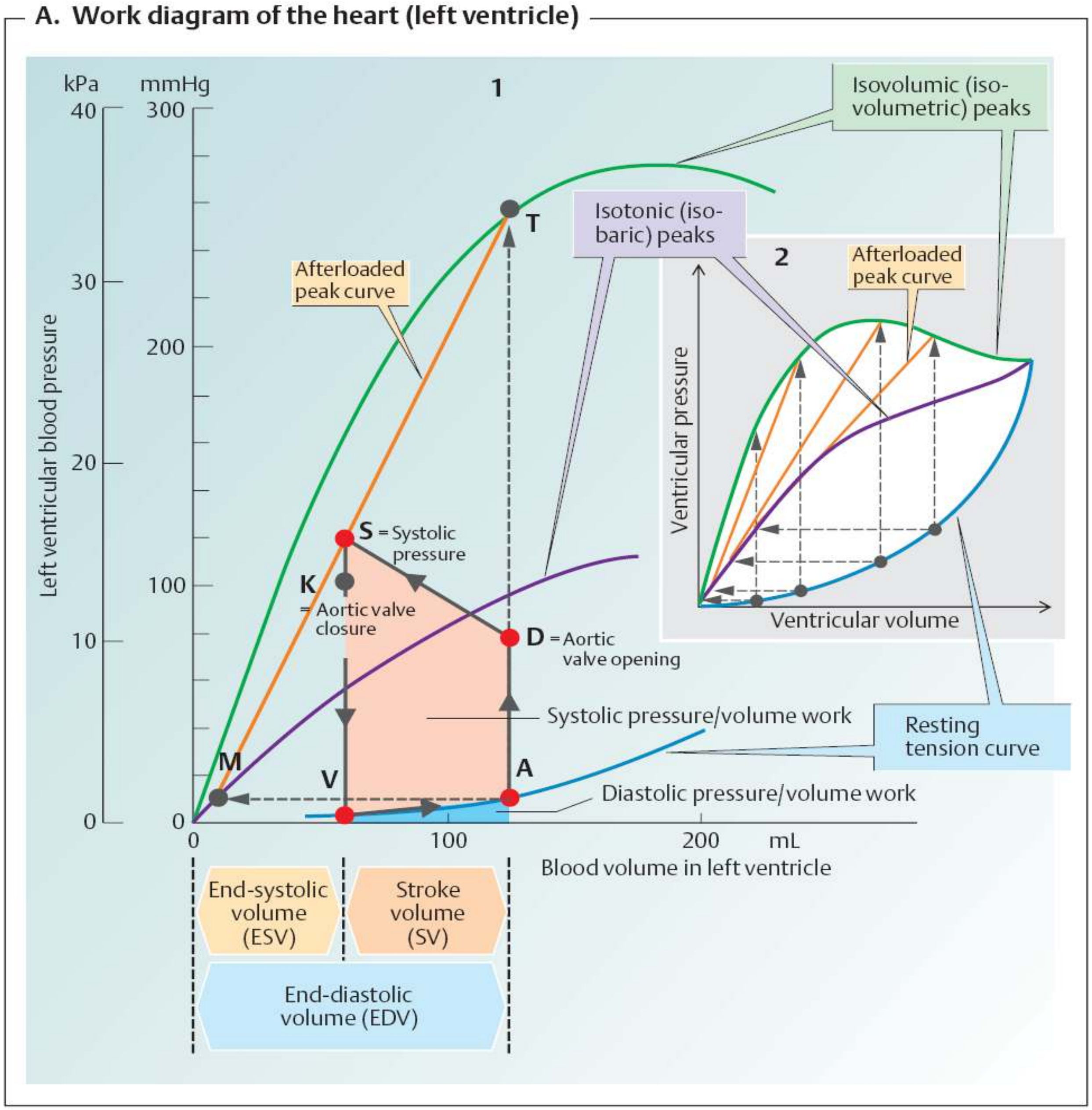
http://www.physiome.cz/atlas/cirkulace/05/SimpleUncontrolledSimulationEC.swf

And what comes next, next animation version, in 2009?

No way, we need more deep understanding to blood pressure control…
No king’s road leads to quantitative description ☹

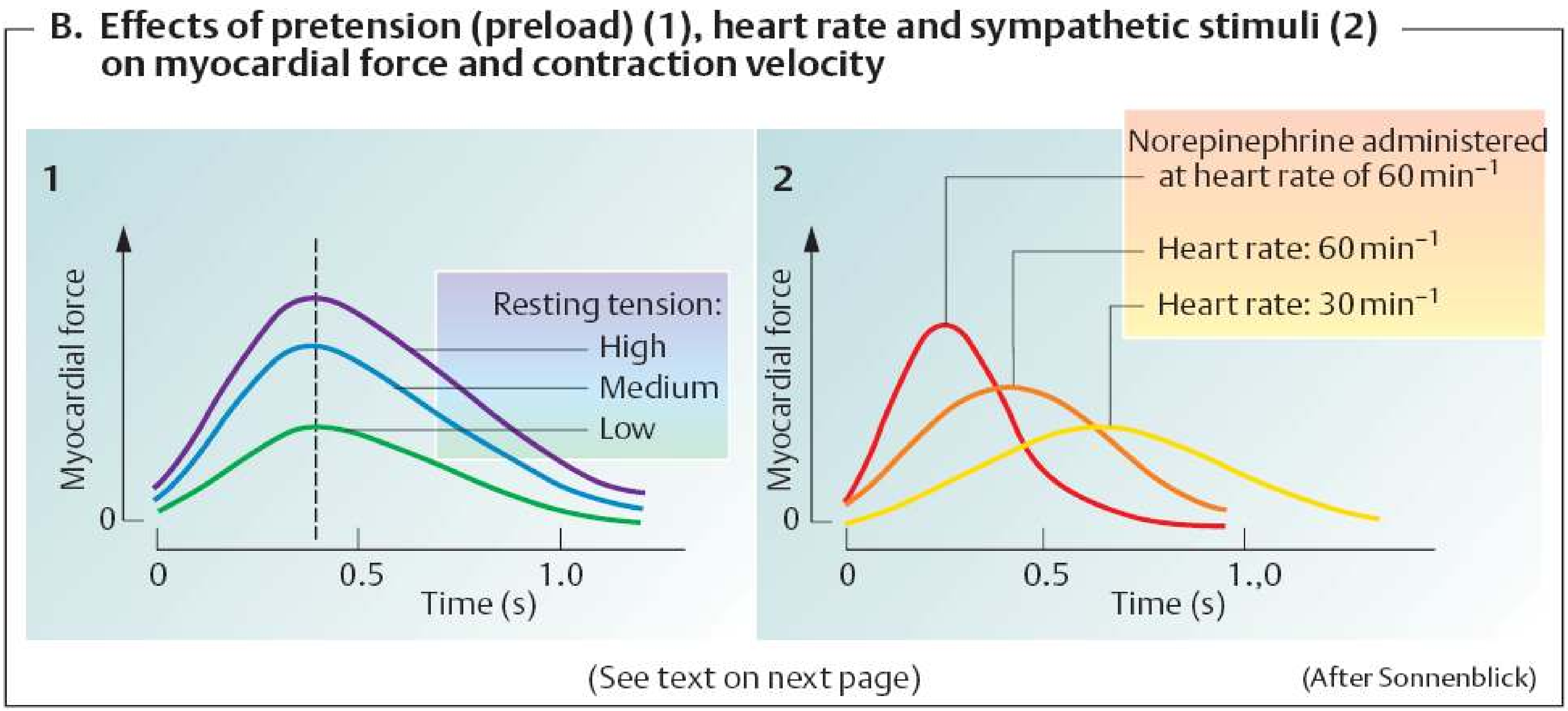
- Main limitations of the model discussed here:

1) Only linear equations, nelinearities present in failure!
2) Only passive control, how to plug in autonomous control?
3) Only time scale in minutes, how is it with Q^dot in longer time scale ?
4) What variables are observables/ what can be estimated?
5) How fast the disorder develops, what are riscs, critical values.?
6) Etc…

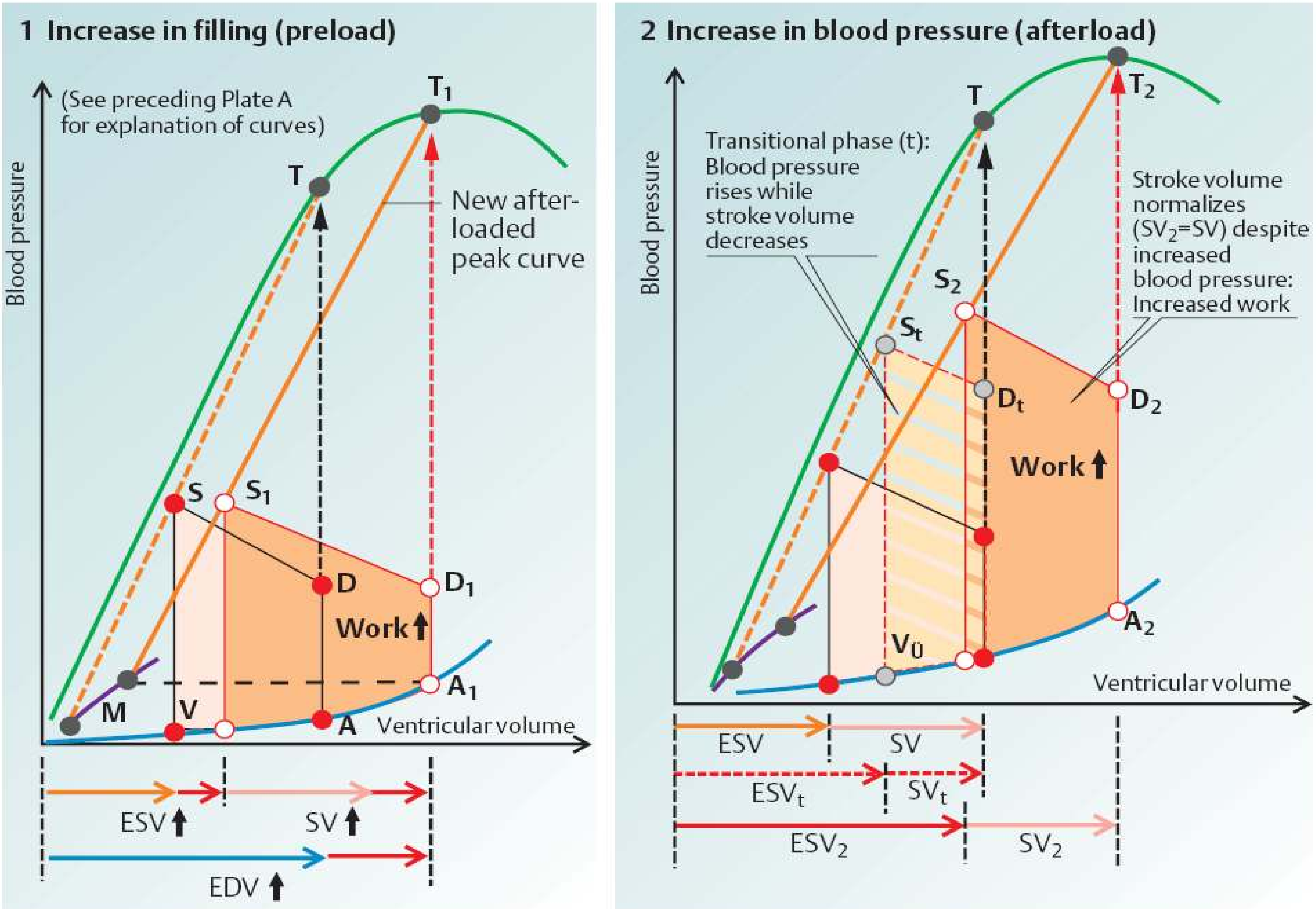


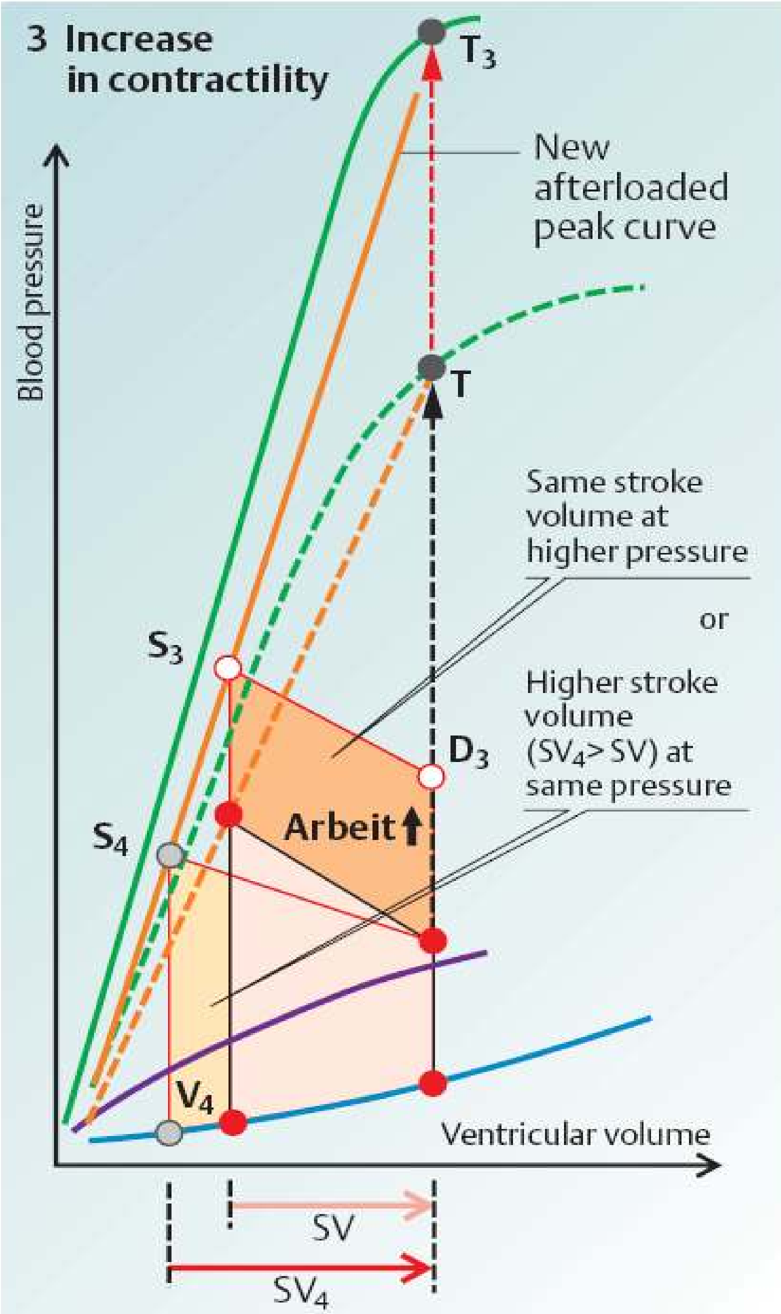
Heart work in circulation, 1 to 4

Preload, afterload

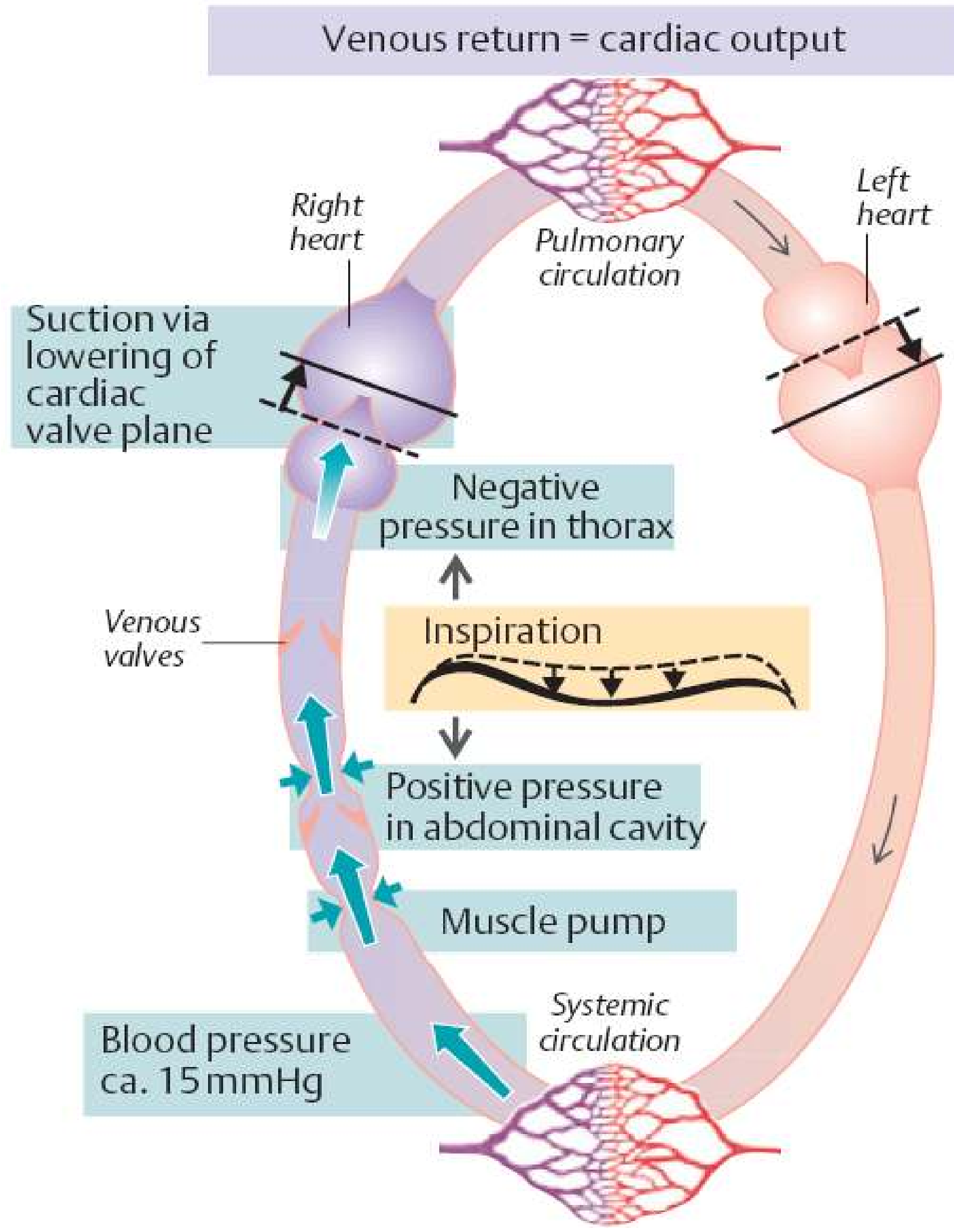


A. Factors influencing cardiac action





B. Venous return



Further properties of control systems– dynamics (= time scale), etc…

- dynamics (time scale, system response)
- linearity vs. non-linearity
- types of controllers (proportional, integral, differential, mixed, state automaton, etc.., etc..)
- system approach
- precision, sensitivity, stability
- demands on energy, information transfer, etc…

Conclusions

- **Feedback in general: positive/ vs. negative**
- **Physiologic/ vs. pathologic regulation**

Shown on these three examples:
1) glycemia control
2) thermo-regulation
3) circulation