Peripheral circulation

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Circulation's raison d'être

- Securing adequate blood flow (O_2, nutrients, „waste") that the individual organs need at the whole range of their activity
- Possibilities:
  - ~~Max flow everywhere all the time~~
  - Organ blood flow regulation according to actual need

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Regulation of circulation

- Tools
- How the tools are used for regulation

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Tools

- Resistance vessels (arterioles), precapillary sphincters: changes in diameter
  - Vasodilation
  - Vasoconstriction

Prerequisite: basal tone
- nerve-independent
- sympathetic tone

- Changes in the diameter of open vessels
- Changes in the number of open vessels („recruitment“)

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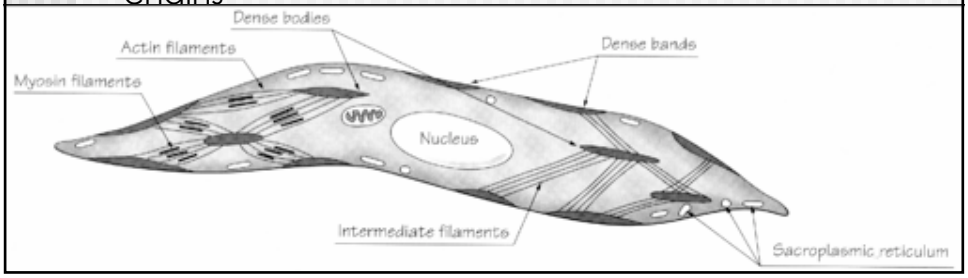
Vascular smooth muscle (VSM) contraction

- Actin (thin filaments)
  - attached to *dense bodies* made of α-actin (in cytoplasm & inner side of membrane)
- Myosin (thick filaments)
  - hexamere of 2 heavy & 2 different pairs of light chains



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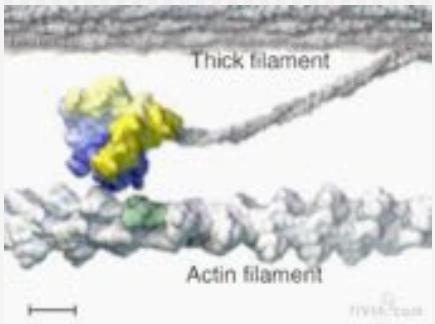
Vascular smooth muscle contraction



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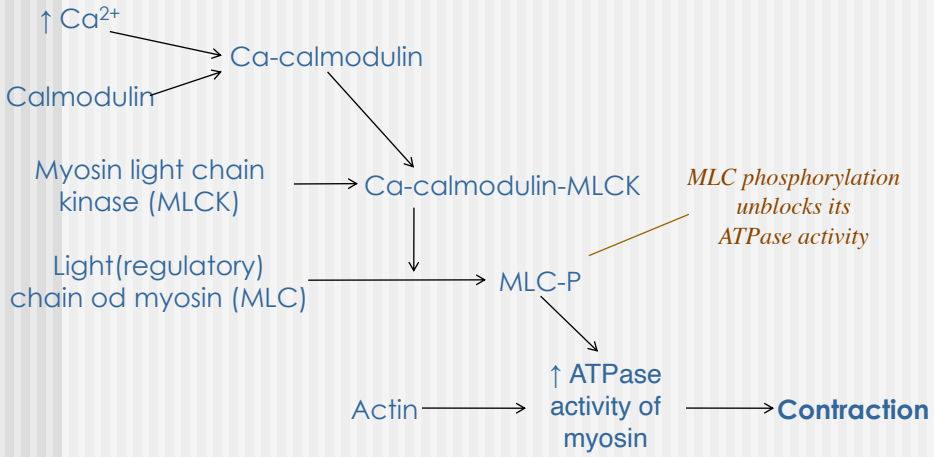
Activation of VSM contractile apparatus



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VSM inactivation

- ↓ $[Ca^{2+}]_i$
  - ↓ influx
  - pumping outside
    - Ca^{2+} ATPase
    - Na/Ca antiport
  - pumping to reticulum (SERCA)
- Ca^{2+}-independent MLC phosphatase prevails over MLCK → ↓ phosphorylation (→ activity) of MLC

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Excitation-contraction coupling

- Electromechanical
  - voltage-gated Ca^{2+} channels (VOC)
- **Pharmacomechanical**
  - receptor-operated Ca^{2+} channels (ROC)
  - Ca^{2+} from sarcoplasmic reticulum (IP_3)
  - Sensitization
    - Rho kinase → MLC phosphorylation
    - A, C, G kinases → MLC phosphatase inhibition

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Vascular tone regulation

- Local (mainly ♥, brain, kidney): autoregulation of blood flow
- Neural (mainly skin, GIT): inter-organ distribution
  - important where local flow can be reduced for the sake of the whole body (blood pressure maintenance)
  - almost not at all in brain & ♥
- Humoral - total PVR

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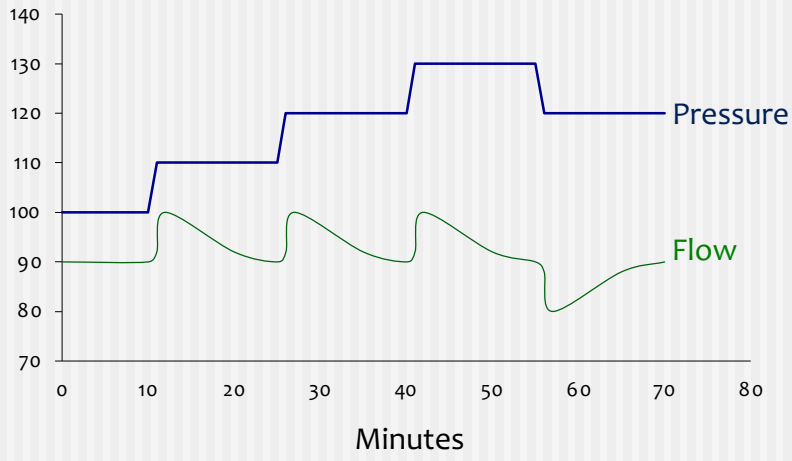
Local autoregulation of blood flow



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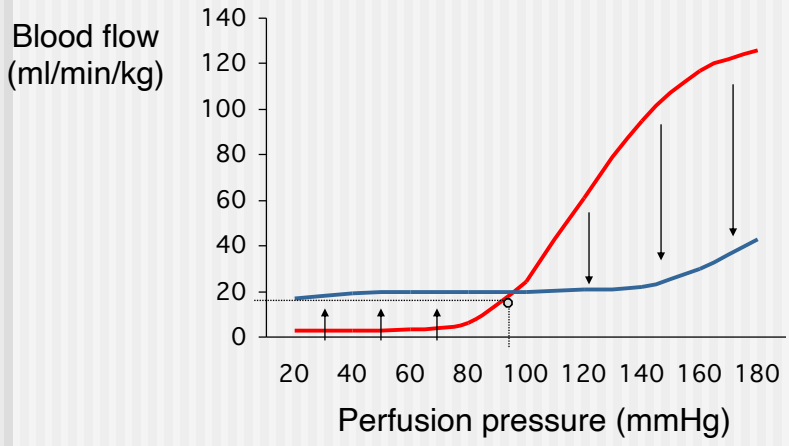
Local autoregulation of blood flow



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Blood flow autoregulation

- Importance:
  - Adjusts perfusion to metabolic needs
  - Constant flow during pressure alterations
  - Rises towards periphery
- Mechanisms:
  - Myogenic response
  - Metabolic regulation

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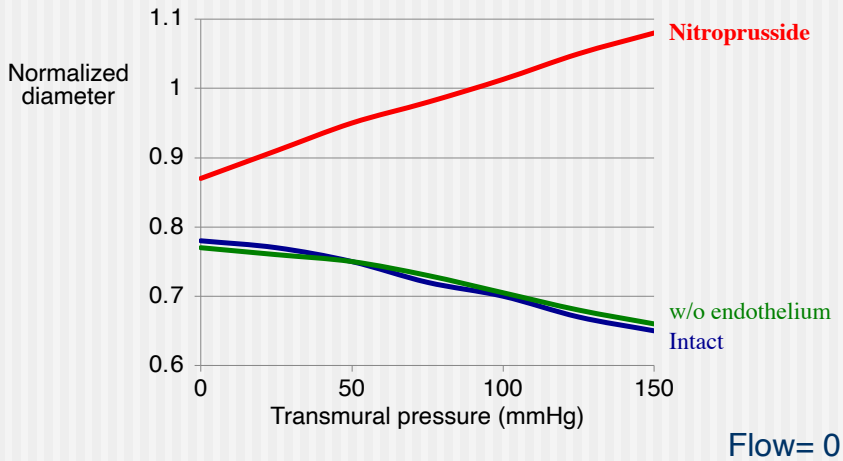
Myogenic response to Δ pressure (Bayliss effect)



Flow= 0

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Myogenic response

- Mechanisms not entirely clear
  - Stretch-activated cation channel
  - Ca^{2+} influx
- Important e.g. for orthostasis
  - upright $\rightarrow \uparrow$ transmural pressure in legs
  - myogenic vasoconstriction prevents excessive redistribution of blood to legs & edema

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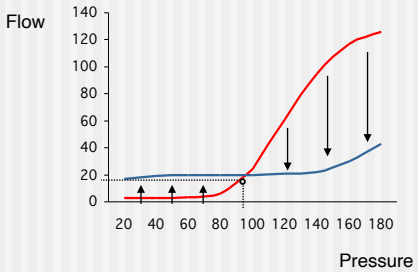
Metabolic regulation

Vasodilatory metabolites (complement each other):

- O_2
- CO_2
- H^+
- lactate
- K^+
- adenosine



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Organs without autoregulation (skin,…)

- Metabolic component minimal due to low metabolism
- Myogenic component suppressed by NO
  - NO inhibition unmasks skin myogenic autoregulation

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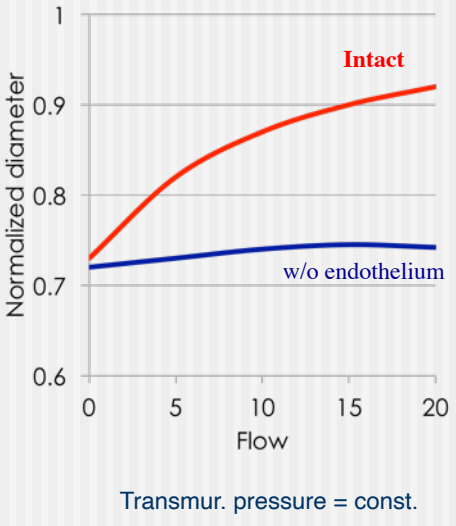
Coordination of arterial & arteriolar dilation

- Vasodilation of peripheral arterioles accelerates flow in larger feeding arteries
- Shear stress ↑
- NOS activation
- Arterial relaxation
- NO in this situation indispensable



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Endothelium

- Nitric oxide (NO)
  - vasodilation via cGMP → G kinase
- Prostacyclin (PGI_2)
  - vasodilation via cAMP → A kinase
- Endothelin (mainly ET-1, also -2 a -3)
  - 21 amino acids from pro-ET-1 (38 AA) by endothelin converting enzyme
  - receptors via G-proteins:
    - ET_A on VSM (mainly intracellular Ca^{2+})
    - ET_B releases NO & PGI_2 from endothelium
- Angiotensin conversion

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Neural regulation of vascular tone

- Essentially only **sympathicus**
  - Mostly adrenergic
  - Mainly vasoconstriction
- Parasympathicus only a bit in face, colon, bladder & genital (erection)
  - Cholinergic
  - Vasodilation
- From pressoric & depressoric area of the cardiovascular center in medulla

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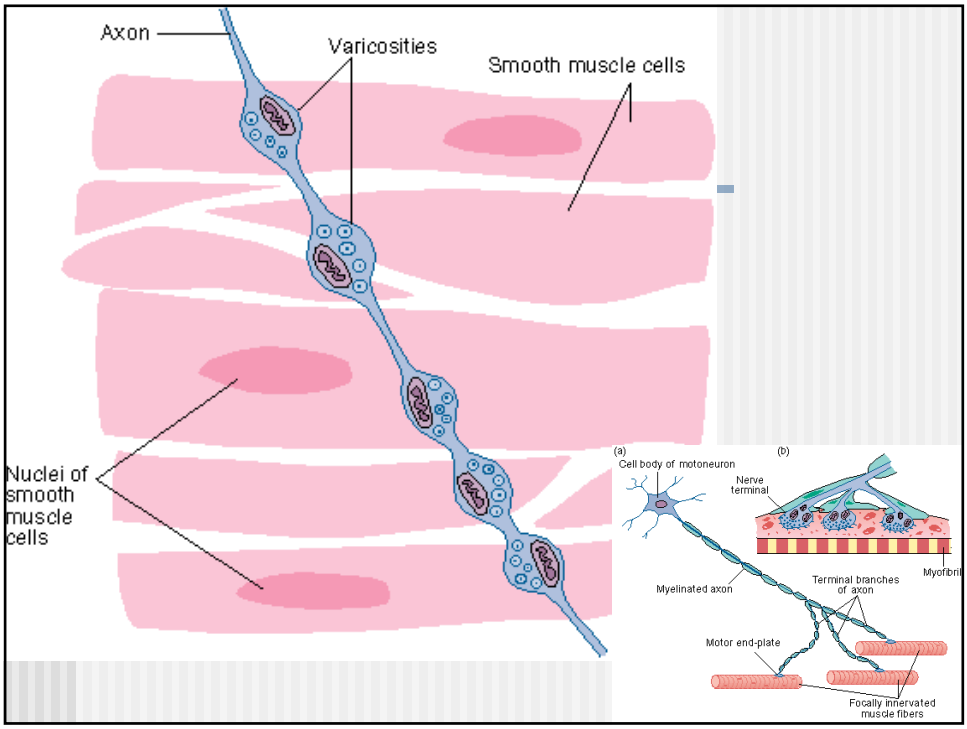

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Sympathicus: NA terminals

- α receptors - vasoconstriction
  - more sensitive to NA from nerve terminals than to circulating adrenaline
  - predominant in skin, kidney,...
- β receptors - vasodilation
  - more sensitive to circulating adrenaline than to NA
  - predominant in skeletal muscle
  - similar expression of α a β in coronary & GIT vessels

    flow redistribution to muscle during exercise
- Some SNS terminals in vessels are cholinergic
  - vasodilation
  - skeletal muscle
  - importance ?? (↑ muscle flow when exercise anticipated ?)

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Baroreceptors

- Carotid sinus (more sensitive) & aortic arch
- Activation by stretch
  - Via glossopharyngeal nerve to medulla (nucleus tractus solitarius)
  - Sympathetic tone ↓
- Sensitivity ↓ in hypertension (stiffer carotid sinus)
- Sometimes hypersensitivity → hypotension & fainting because of tight collar

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Chemoreceptors

- Peripheral (O_2 in carotid & aortic bodies): only small, supportive role
- Central (CO_2/pH in hypothalamus): massive vasoconstriction (protects CNS from ischemia)

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Humoral regulation of VSM: circulating hormones

- **Adrenaline**: (importance < NA from SNS)
  - Skeletal muscles: β vasodilation @ low dose, α vasoconstriction @ high dose
  - Skin & other organs: only α vasoconstriction
- Angiotensin II:
  - ACE from A-I, A-I from angiotensinogen by renin (released from kidny in hypotension or ↓ volume)
  - mainly AT_1 receptors
  - AT_2 opposite effects, but little AT_2 in vessels
    - (their activation can ↑ during AT_1 inhibition because of feed-back ↑ A II - therapeutic significance)

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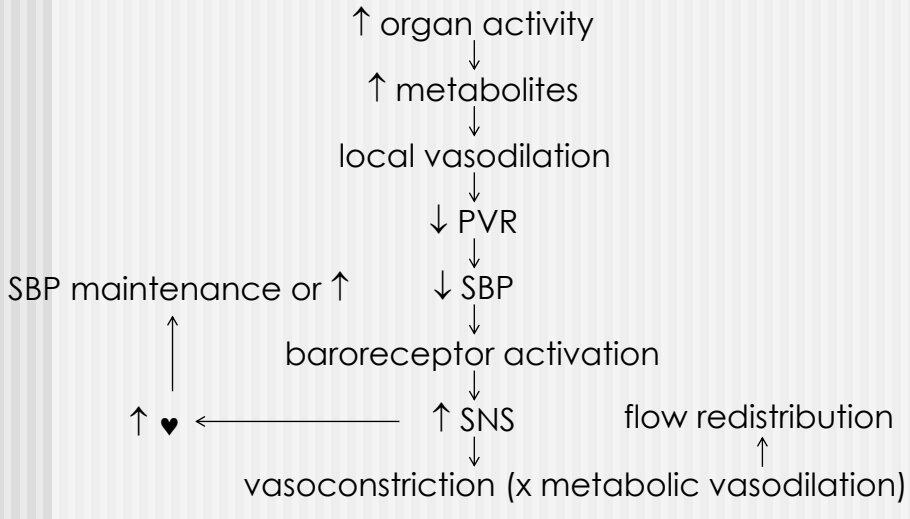
Circulatory Δ with ↑ organ activity



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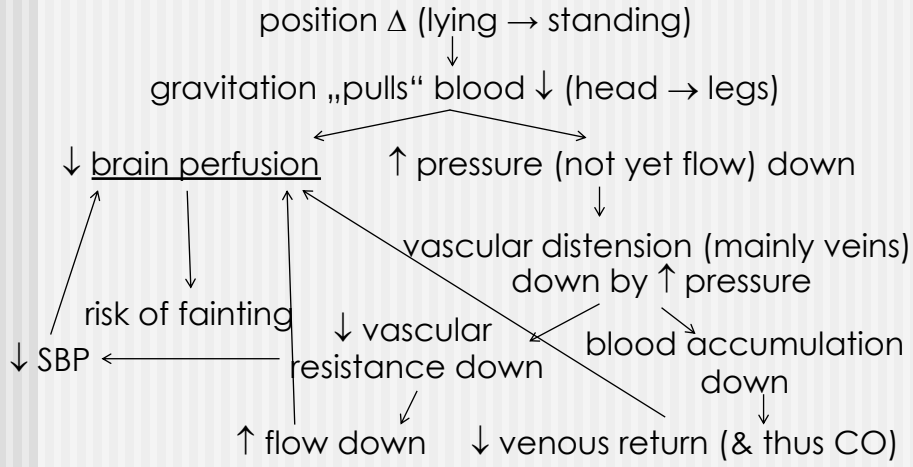
Orthostasis - problem



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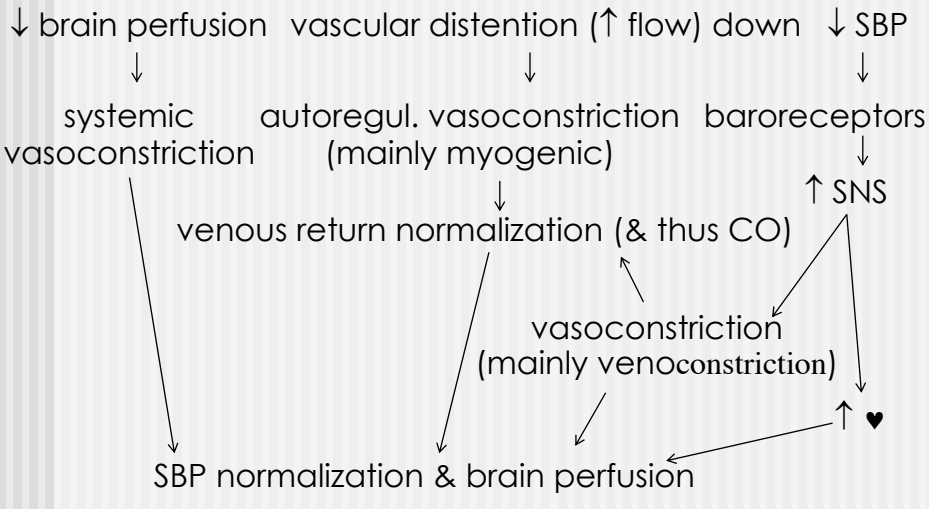
Orthostasis - solution



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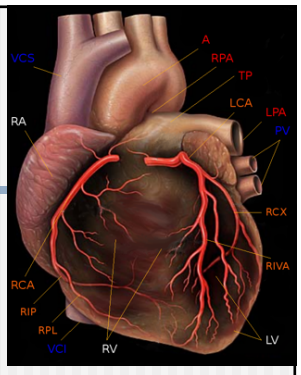
Coronary circulation



- R > L coronary artery:
  - ~ 50 % humans
- L > R coronary artery:
  - ~ 20 % humans
- R = L coronary artery:
  - ~ 30 % humans

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Factors affecting coronary blood flow

- Aortic pressure
- Coronary arteriolar resistance ← myocardial metabolic activity (autoregulation)
- Extravascular compression
  - importance L > R (lower RV pressures)
  - maximal L flow in early diastole

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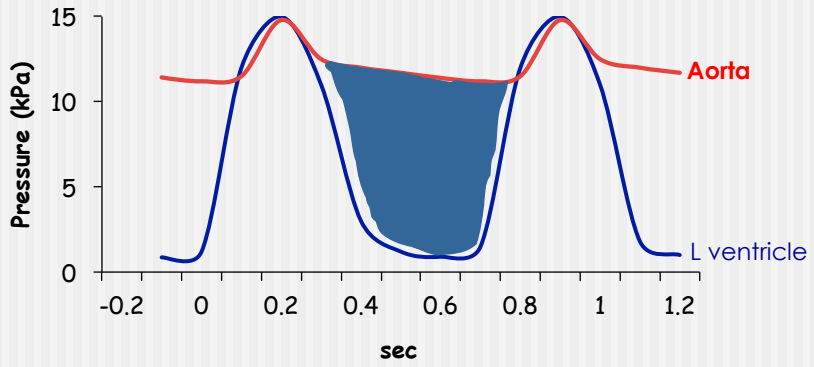
Coronary flow "window of opportunity"



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♥ rate & coronary flow

- Changes in heart rate mainly by changes in the length of diastole
- Tachycardia:
  - ↑ proportion of time spent in systole

    vs.
  - ↑ metabolic needs (→ vasodilation)

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Counterpulsation

- Balloon in thoracic aorta
- Inflated during diastole
  - ↑ coronary pressure when resistance ↓
- Deflated in systole

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SNS stimulation

- Receptors:
  - α (vasoconstrictor)
  - β (vasodilator)
- Direct SNS effect: α vasoconstriction
- Overcome by vasodilation due to ↑ metabolic activity (local regulation dominant)

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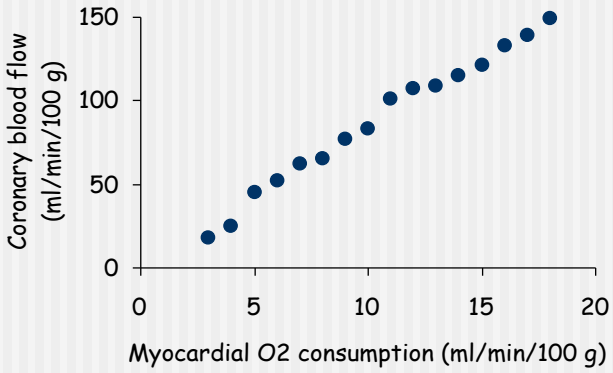
Local metabolic regulation



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O_2 supply to ♥ is flow limited

- Most O_2 extracted from coronaries during a single passage (O_2 extraction near maximal)
- Therefore: ↓ flow → ↓ O_2 delivery

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Reduced coronary flow

- Not too strong and/or prolonged (e.g. quickly repaired coronary occlusion)
  → myocardial **stunning** (temporary ↓ contractility)
  - Ca^{2+} overload in ischemia (pump dysfunction)
  - ROS in reperfusion
- Strong and/or prolonged
  → myocardial **infarction** (necrosis)
  - both mechanical & electrical impairment
  - O_2 & substrate depletion, metabolite accumulation

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Tx of angina pectoris

- Coronary vasodilators (e.g. NO_2^-/NO_3^-)
- But:
  - arteries in ischemic regions already fully dilated by metabolic mechanism
  - vasodilation in OK areas can ↓ driving pressure in ischemic areas: **CORONARY STEAL**
- Angina pectoris treated only if coronary steal < pressure work reduction (↓ PVR, ↓ venous return due to peripheral arterio- & venodilation)

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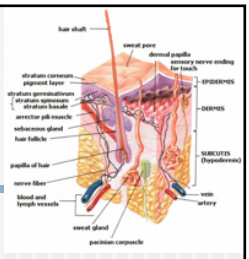
Cutaneous circulation



- Low metabolism
- Blood flow serves mainly thermoregulatory role

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Numerous AV anastomoses

- Thick muscular layer
- Rich nerve supply
- No metabolic autoregulation
- Exclusively under SNS control (can close completely) → thermoregulation

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Neural regulation

- Higher brain centers → SNS:
  - blushing in embarrassment or anger
  - blanching in fear
  - cold and pale skin in shock

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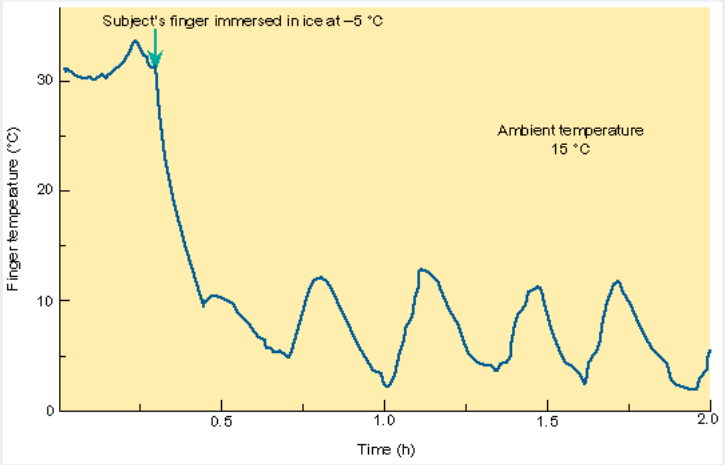
"Hunting phenomenon"



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Raynaud's disease

- Vasoconstrictor hypersensitivity of fingers (& sometimes toes) to cold
- Finger ischemia in cold (tingling, numbness, pain)
- Blanching (no blood) → cyanosis (ischemia) → redness (spasm subsides)
- Idiopathic (mostly young women)

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Countercurrent heat exchange

- Major skin arteries run alongside veins
- In cold: heat taken up from arteries by cooled blood in veins before it reaches surface → heat conservation
- In heat: heat taken up by blood in the surface is given from veins to colder arterial blood → heat not taken up
  (+ ↑ temperature difference from skin to environment → heat dissipation)

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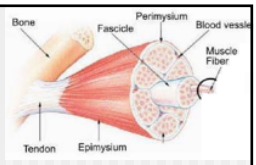
Skeletal muscle circulation



- Blood flow (& capillary density):
  - red (slow-twitch, high oxidative) > white
  - exercise: ↑ up to 15-20x
    - reduction of resting asynchronous intermittent contractions of precapillary sphincters
    - mechanical squeezing by muscle contractions
      - no problem if intermittent
      - can limit tonic contraction

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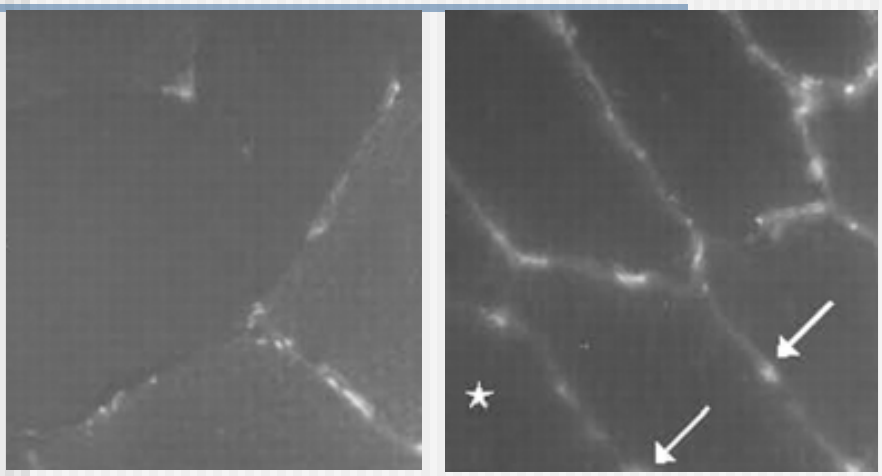
Perfused skeletal muscle capillaries in rest & exercise



Resting

Exercise

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Regulation

- SNS (important because the largest vascular bed → great effect on total PVR)
  - prevails at rest
  - NA only vasoconstriction
  - adrenaline vasodilation @ low doses, vasoconstriction @ high
  - some ACh SNS vasodilation
- Local (important because of high metabolism)
  - prevails during exercise
  - high basal tone (→ large vasodilation)

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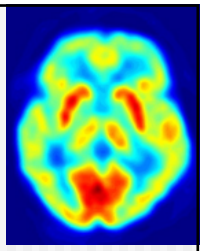
Cerebral circulation



Unique features:

- contained within rigid structure → inflow/outflow dysbalances ↑ pressure
  - Cushing's phenomenon: ↑ systemic BP with ↑ intracranial pressure (e.g. tumor) - by ischemic stimulation of vasopressor center in medulla (helps maintain brain flow)
- Absolute requirement for adequate flow
  - tissue least tolerant to ischemia
    - 5 sec ischemia → loss of consciousness
  - glucose-dependent
  - no contribution to total PVR regulation

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Neural regulation of brain vessels

- Minimal importance (local mechanisms predominate)
- SNS (along carotid & vertebral arteries) - weak vasoconstriction
- Parasympathetic fibers from facial nerve - weak vasodilation

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Local regulation of brain vessels

- Hypoxia
- Very sensitive to CO_2 (vasodilation via changed tissue pH)
- H^+ cannot cross blood-brain barrier → cerebral vasodilation by:
  - local CO_2/tissue pH changes
  - blood CO_2
  - not blood pH (if = CO_2)

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Brain flow autoregulation

- Excellent between 60 and 160 mmHg
- Below 60 mmHg: syncope
- Above 160 mmHg: cerebral edema

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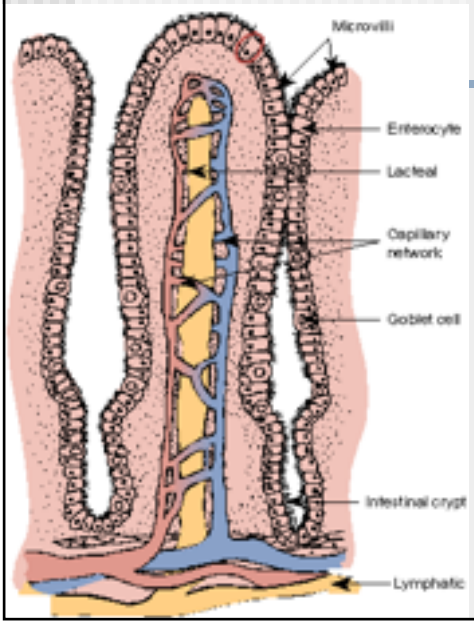
Intestinal circulation



- Countercurrent O_2 exchange (shortcut for O_2 from arteries to veins)
- Flow needed to carry away nutrients, not to bring O_2
- Necrosis of villi with severe flow reduction ($\rightarrow$ bacteremia)

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GIT flow regulation

- Neural:
  - prominent (blood shunted away when needed elsewhere)
  - SNS (NE, α vasoconstriction; β receptors much less expressed)
- Autoregulation less developed
  - functional hyperemia (after meal)
  - gastrin & cholecystokinin ↑ GIT blood flow
  - vasodilation by digestion products (glucose, FFA)

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Hepatic circulation

- Hepatic blood flow ~ 25% CO
  - 3/4 of that via portal vein
    - little O_2
    - mean pressure ~10 mmHg → small driving pressure gradient
      - ↑ hepatic (and central) venous pressure easily transmit upstream → liver edema → transudation to peritoneal cavity (ascites) (also with ↑ portal resistance due to fibrosis in cirrhosis)

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Regulation of liver circulation

- Autoregulation
  - not in portal system
  - hepatic arterioles autoregulate
- SNS
  - constriction of resistance vessels in portal venous & hepatic arterial systems
  - constriction of capacitance vessels more important (blood reservoir)
    - liver contains ~ 15% of all blood
    - 50% of that can be rapidly expelled by SNS

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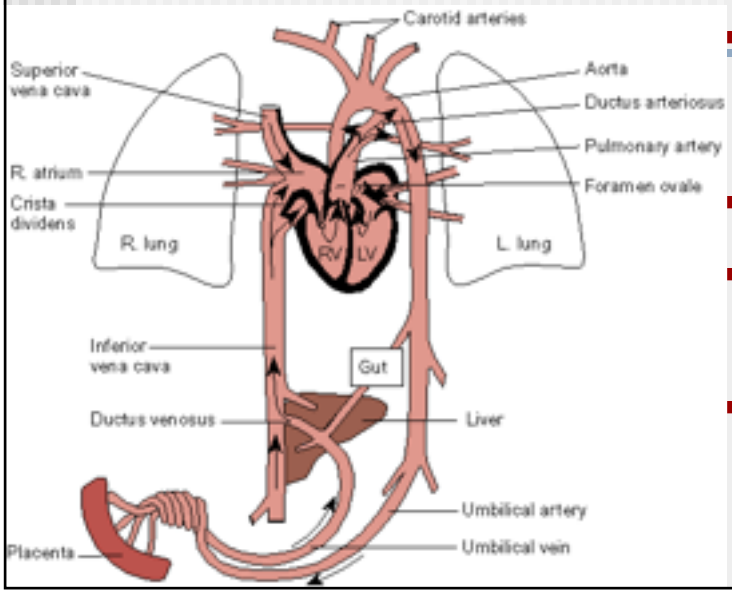
Fetal circulation



- ~50% placental flow returns via ductus venosus
- remainder through liver
- separate streams in IVC (crista dividens)
- stream from d.v. → foramen ovale → LV → carotids

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High fetal pulmonary vascular resistance

- Low O_2 → hypoxic vasoconstriction
- No ventilation → undistended, convoluted vessels
- Shunts ~90% of CO through ductus arteriosus (enters aorta distal to origin of carotid arteries)

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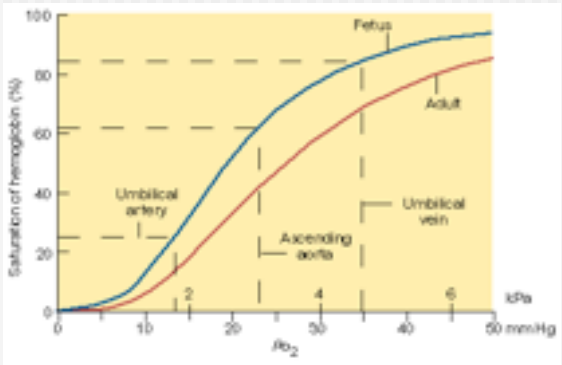
Fetal Hb helps O_2 transfer in placenta



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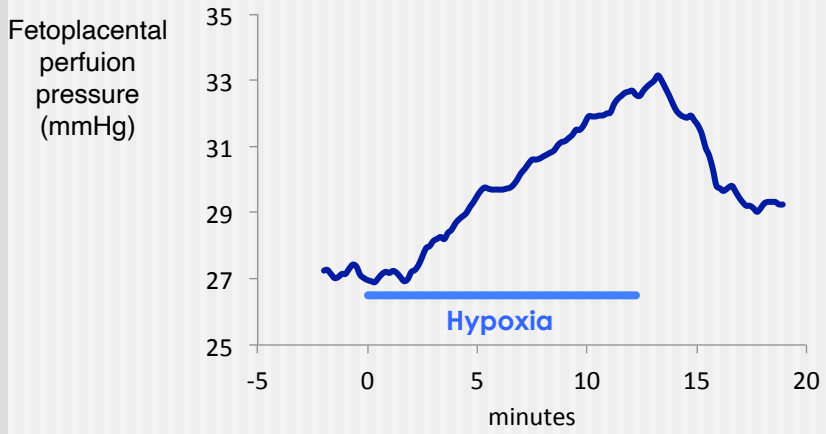
Hypoxic fetoplacental vasoconstriction



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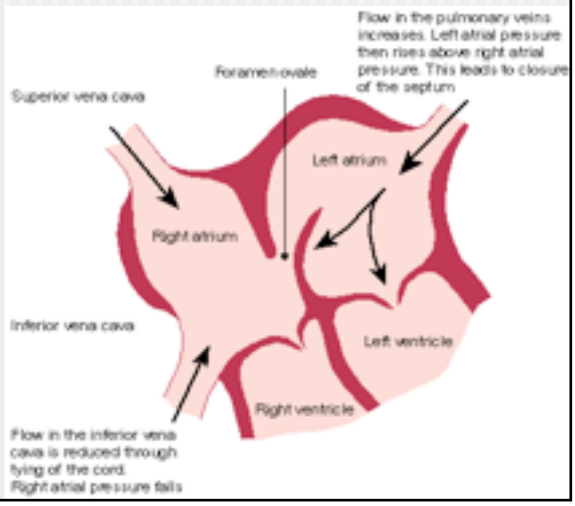
Birth

- Umbilical vessels closed by trauma (if not tied)
- Ductus venosus closes (mech. ??)
- ↑ CO_2 → breathing
- ↑ arterial pO_2 constricts ductus arteriosus (via ↓ vasodil. PGs, Bk; also K channels)



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