MUNI
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Microcirculation

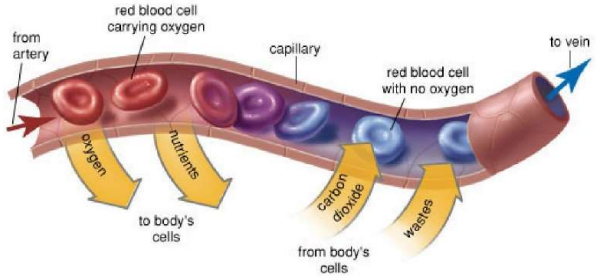
Faculty of Medicine, Masaryk University

Microcirculation

Microcirculatory function is the main prerequisite for adequate tissue oxygenation and thus organ function.
The microcirculation is formed by the smallest blood vessels (<100 μm diameter), and consists of arterioles, capillaries, and venules.
Its purpose

1) provides access for oxygenated blood to the tissues and appropriate return of volume;
2) maintains global tissue flood flow, even in the face of changes in central blood pressure
3) ensures adequate immunological function and,
4) links local blood flow to local metabolic needs

The main cell types
endothelial cells
smooth muscle cells (mostly in arterioles),
circulating blood cells



Microcirculation

The structure and function of the microcirculation is highly heterogeneous in different organ systems

Main determinants of capillary blood flow

driving pressure,
arteriolar tone,
hemorheology
capillary patency

Starling Equation

$$J_V = K_f [(P_C - P_i) - \sigma(\pi_C - \pi_i)]$$

where:

J_V	Net fluid flux
K_f	Filtration coefficient
P_c	Capillary hydrostatic pressure
P_i	Interstitial hydrostatic pressure
σ	Reflection coefficient
π_c	Capillary oncotic pressure
π_i	Interstitial oncotic pressure

and

$[(P_c - P_i) - \sigma(\pi_c - \pi_i)]$ is the Net driving pressure

Transport of substances through capillary membrane

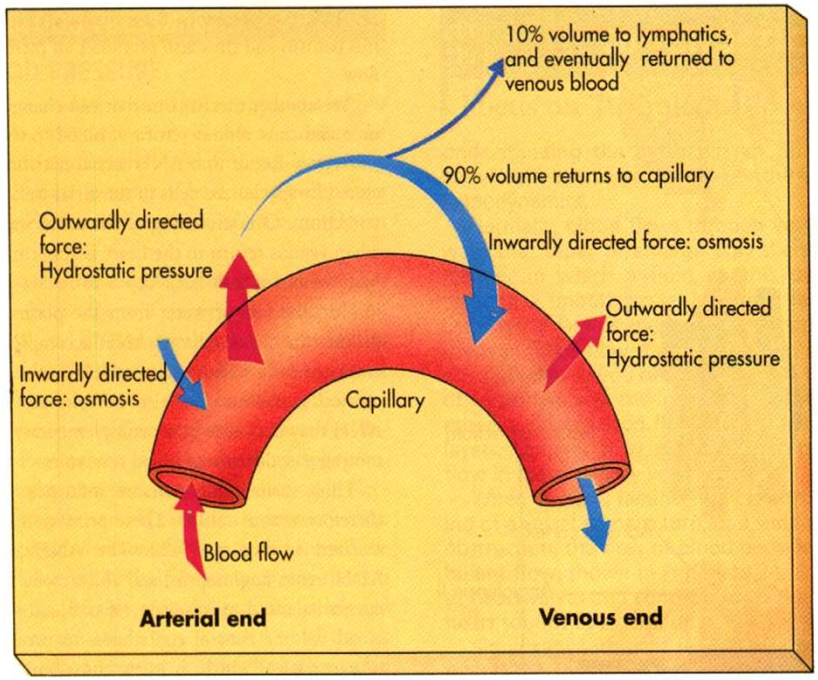


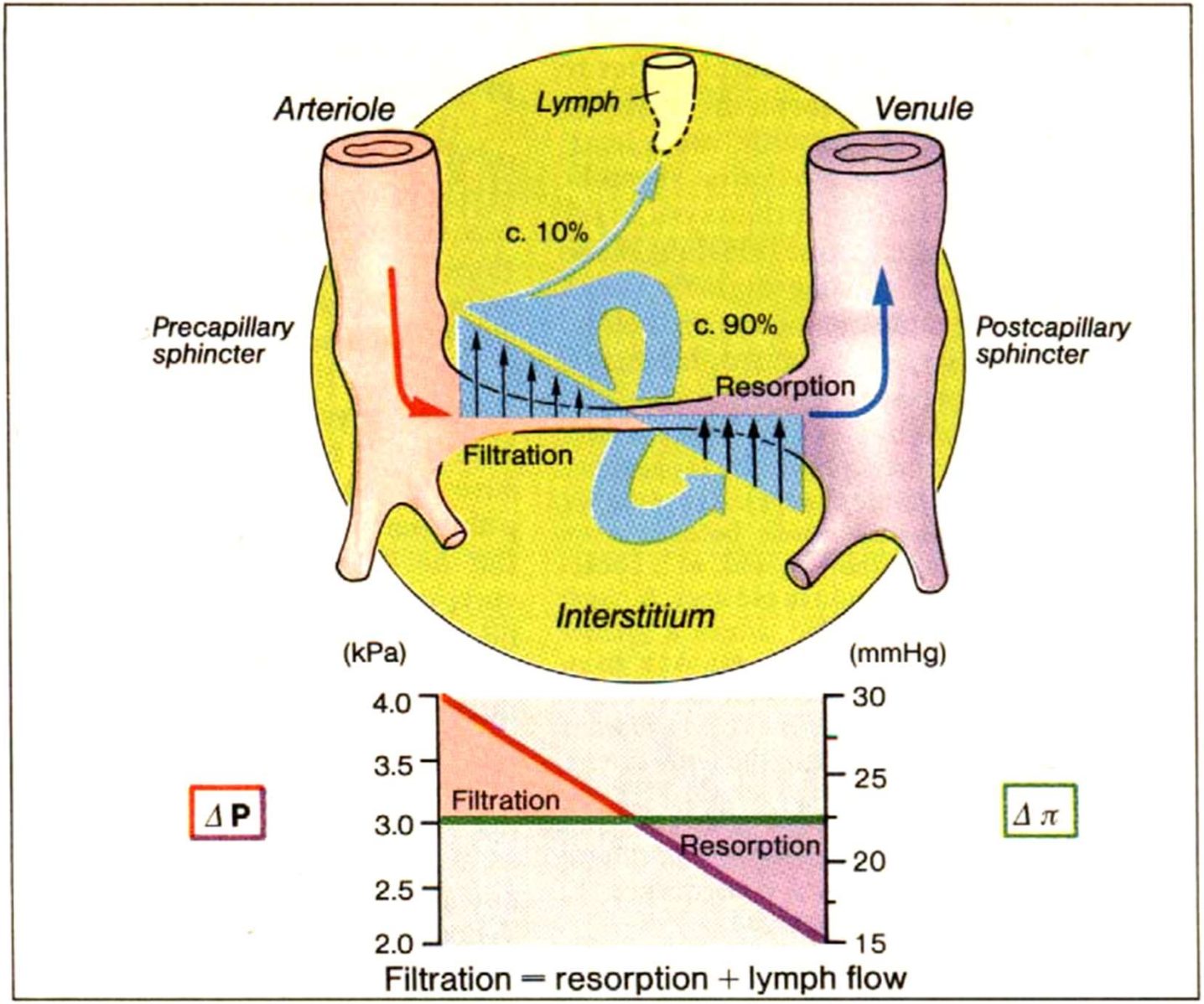
Figure 19-21 **Starling's law of the capillaries.** At the arterial end of a capillary the outward driving force of blood pressure is larger than the inwardly directed force of osmosis—thus fluid moves out of the vessel. At the venous end of a capillary the inward driving force of osmosis is greater than the outwardly directed force of hydrostatic pressure—thus fluid enters the vessel. About 90% of the fluid leaving the capillary at the arterial end is recovered by the blood before it leaves the venous end. The remaining 10% is recovered by the venous blood eventually, by way of the lymphatic vessels (see Chapter 20).

At arterial end of capillary the difference in hydrostatic pressures is higher than the difference in osmotic pressures

which causes filtration.

At arterial end of capillary the difference in hydrostatic pressures is lower than the difference in osmotic pressures

which cause reabsorbtion.



A. Capillary fluid exchange

Regulation of blood supply

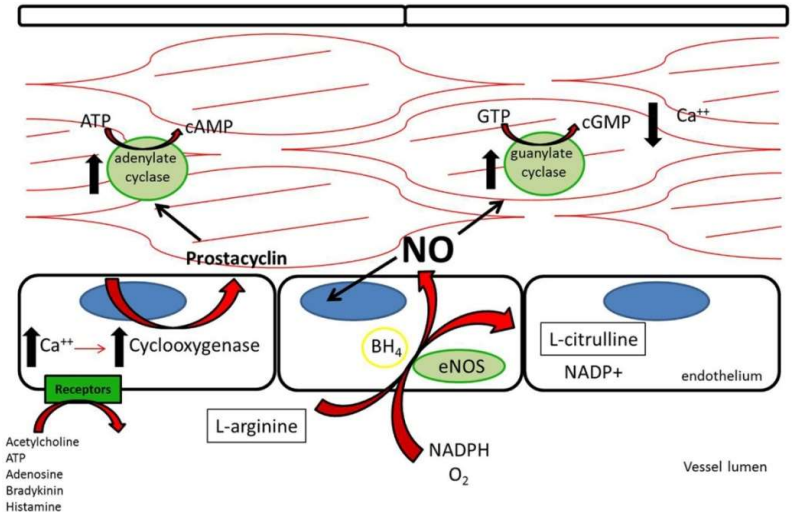
a) short-term regulation

Vasodilatation

NO – produced in the endothelium by constitutive (eNOS) and inducible (iNOS) synthase
prostacyclins
catecholamines
histamine
bradykinin
pO_2, pCO_2 ,pH
cGMP, cAMP

Vasoconstriction

Endothelin
ATII
ADH
Catecholamines
Ca^{2+}



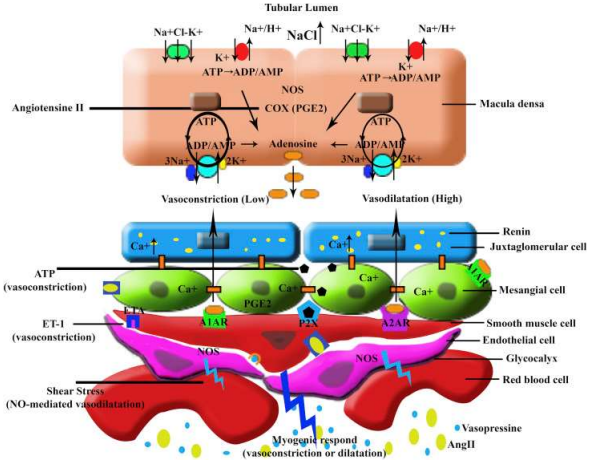
Special mechanisms

Kidney
Tubuloglomerular feedback

Brain
Vasodilation as a response to elevated pCO2 in CSF

Skin
Blood flow control is linked to the control of body temperature

Lungs
hypoxia – vasoconstriction



<u>Large vessels</u>
Mainly NO

Regulation of blood supply

b) Long-term regulation

Days, months or years

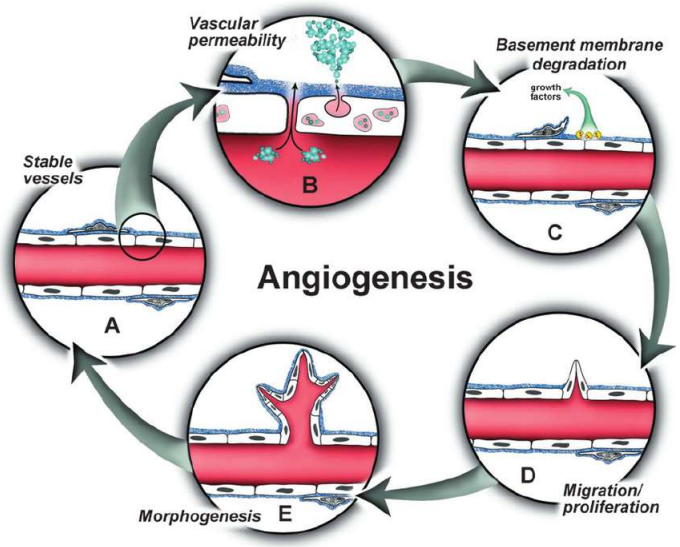
Mechanisms

The blood vessels supplying the tissues increase their

a. physical sizes
b. Numbers

Angiogenesis (buds from existing vessels)

vs. vasculogenesis (de novo)



Neovascularisation

Important for tissues with high metabolic requirements

Mechanisms

1. **Increase of vascularity**

Examples:

scar tissue

tumours

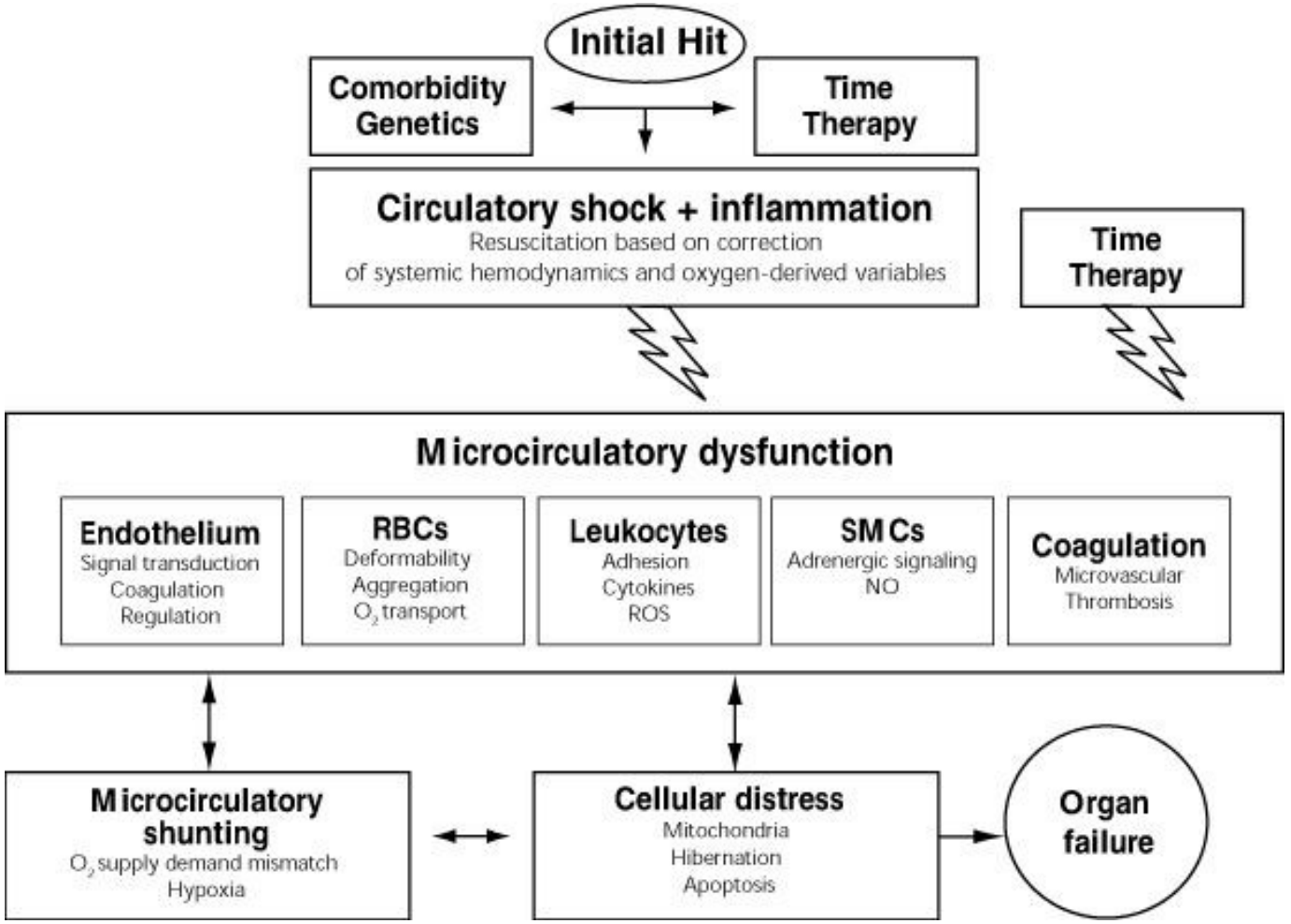
Slow process in terminally differentiated tissues

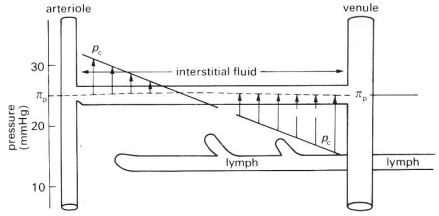
2.Development of collateral circulation from already existing vessels

When the flow is blocked, other collateral vessels open

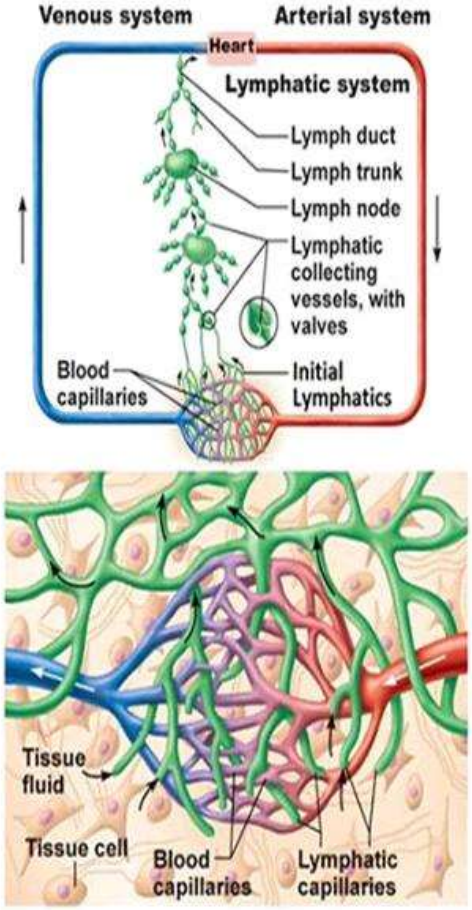
Dilation in the acute phase (neurogenic and metabolic factors)

Remodelation and enlargement in the long term


Initial Hit
Comorbidity
Genetics
Time
Therapy
Circulatory shock + inflammation
Resuscitation based on correction
of systemic hemodynamics and oxygen-derived variables
Time
Therapy
Microcirculatory dysfunction
Endothelium
Signal transduction
Coagulation
Regulation
RBCs
Deformability
Aggregation
O_2 transport
Leukocytes
Adhesion
Cytokines
ROS
SMCs
Adrenergic signaling
NO
Coagulation
Microvascular
Thrombosis
Microcirculatory
shunting
O_2 supply demand mismatch
Hypoxia
Cellular distress
Mitochondria
Hibernation
Apoptosis
Organ
failure


arteriole
venule
p_c
interstitial fluid
30
π_p
π_p
pressure (mmHg)
20
p_c
lymph
lymph
10

The lymphatic system



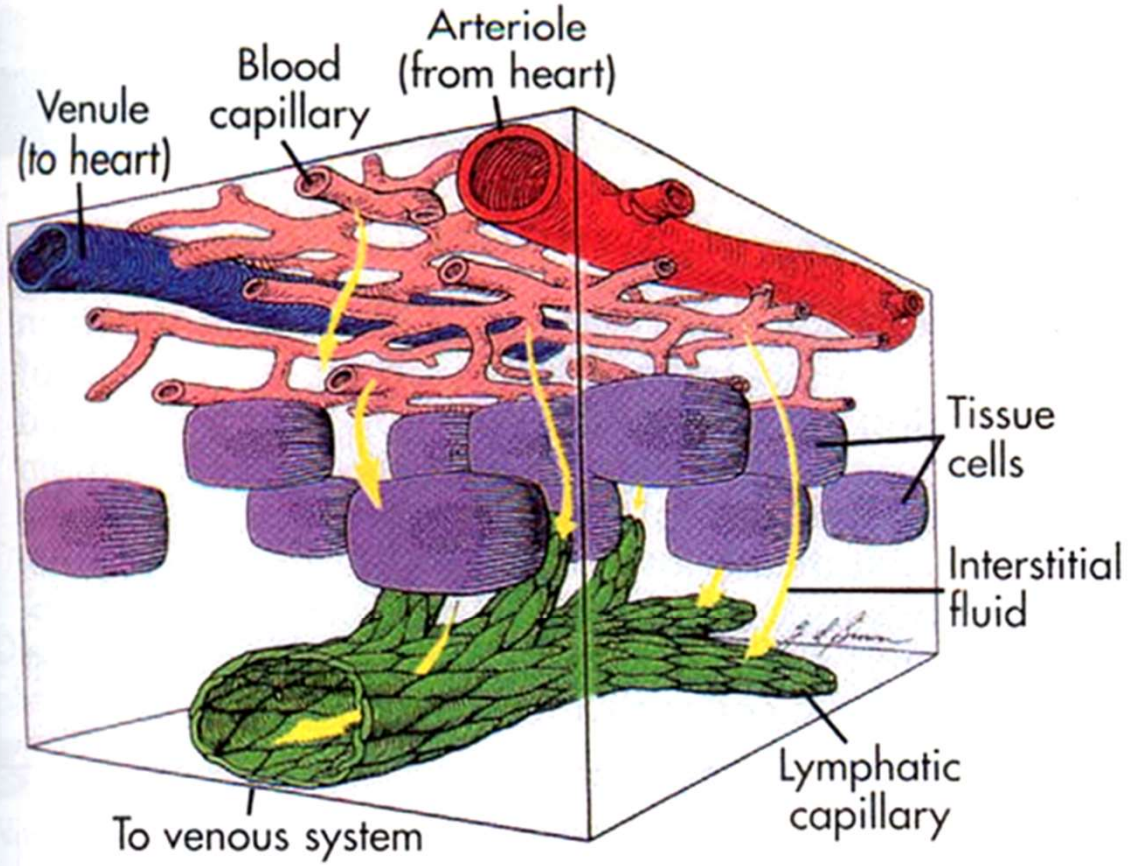


Figure 20-1 Role of the lymphatic system in fluid balance. Fluid from plasma flowing through the capillaries moves into interstitial spaces. Although much of this interstitial fluid is either absorbed by tissue cells or reabsorbed by capillaries, some of the fluid tends to accumulate in the interstitial spaces. As this fluid builds up, it tends to drain into lymphatic vessels that eventually return the fluid to the venous blood.

Lymphatic circulation

The interstitial fluid enters lymphatic capillaries through loose junctions between endothelial cells.
Lymph flow back to the thoracic duct is promoted by contraction of smooth muscle in wall of lymphatic vessels & contraction of surrounding skeletal muscle (lymphatic pump)
Lymph carry proteins that cannot pass the capillary wall – necessary for maintaining the circulating protein concentration (failure leads to death within 24 hours)
Lymphatic drainage is also the main way of lipid absorption in GIT
Pathogens are eliminated in the lymphatic nodes

Lymph flow

Is increased when the fluid filtration from the capillaries to the interstitium is increased

a) Elevated capillary hydrostatic pressure
b) Decreased capillary oncotic pressure
c) Increased interstitial oncotic pressure
d) Increased capillary permeability

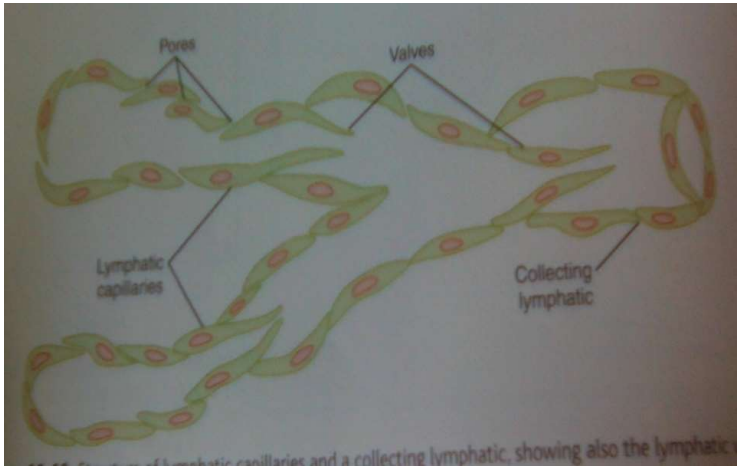
-Lymphatic pump generates the negative hydrostatic pressure in the interstitium

-When the interstitial pressure is permanently elevated to +1 - +2 mmHg, a compression of larger lymphatic vessels may occur

Lymphatic pump

A. intrinsic

Contraction of vessel wall
following its dilation
Generates pressure
between 50 – 100 mmHg



B. extrinsic

Intermittent compression
from outside

During exercise, the
lymphatic flow increases up
to 30-fold

Oedema

Cellular (cytotoxic) oedema – fluid collection in the cells

usually caused by ischemia → ionic pumps failure → ↑ cellular osmolarity

most important inside the skull

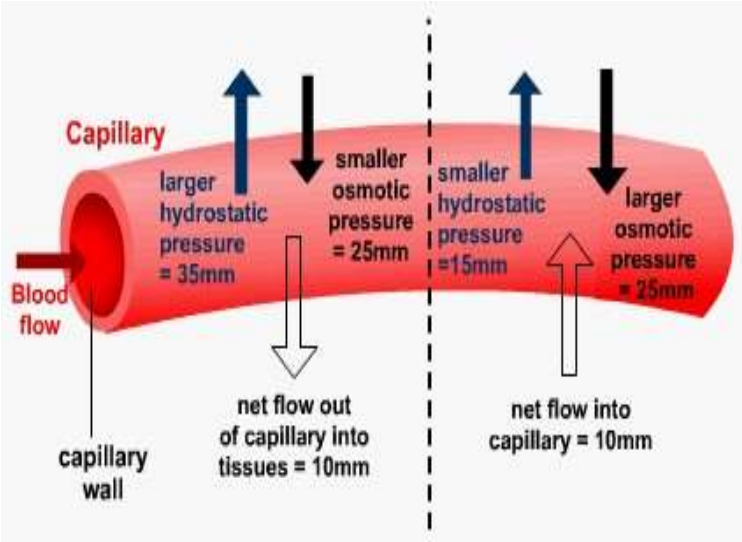
Interstitial oedema – fluid collection in the interstitium

local vs. systemic causes – see further

Effusion – fluid collection in body cavities

Starling forces

Actually pressures, or pressure gradients
$F = A \cdot K \cdot [(P_v - P_t) - \sigma(\pi_v - \pi_t)]$, where:
F…filtration
A…filtration area
K…membrane permeability coefficient (for water)
σ…membrane reflection coefficient (for proteins)
The pressure gradient is directed outside at the arterial end and inside at the venous end of a capillary
Exception: glomerular capillaries (high hydrostatic pressure – cave shock)
Pulmonary capillaries – filtration slightly prevails all along the capillary (low both hydrostatic and oncotic pressure gradient)



The flow from the capillary little exceeds the reabsorption – lymphatic drainage

Causes of interstitial oedemas and effusions

Higher capillary hydrostatic pressure

hypervolemia

hyperperfusion

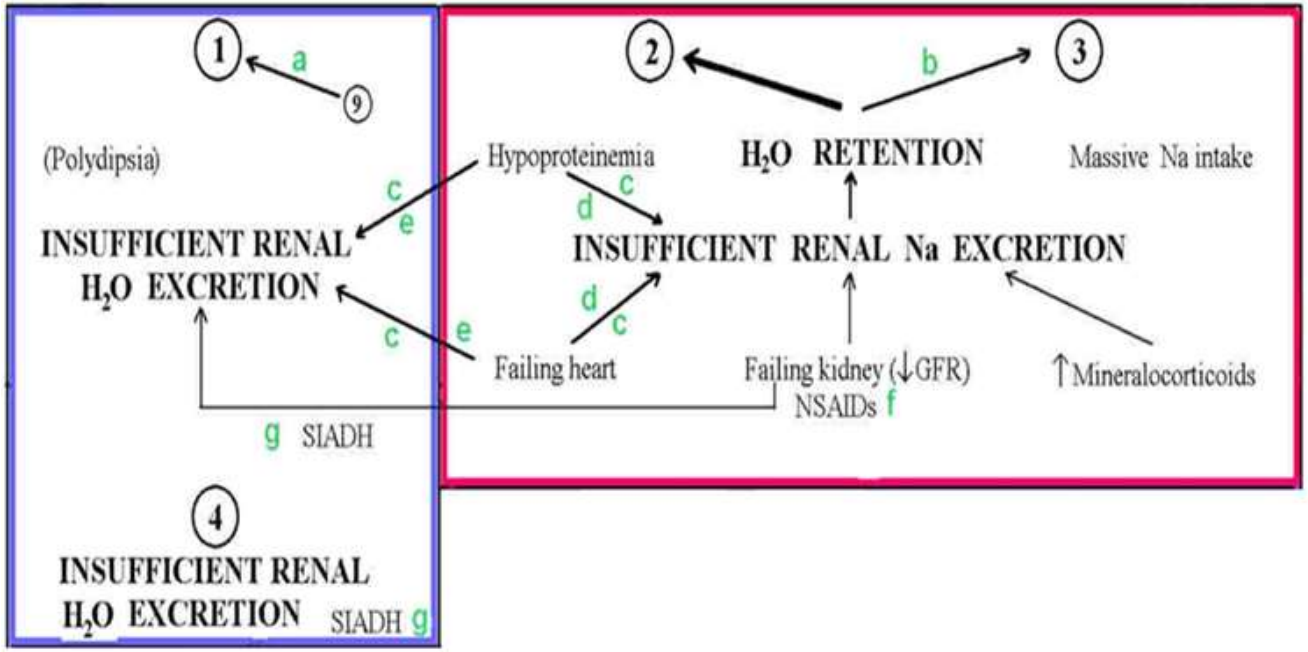
↓ venous return

Lower plasma oncotic pressure

Increased capillary wall permeability

Obstruction of the lymphatic vessels

Hypervolemia - etiology



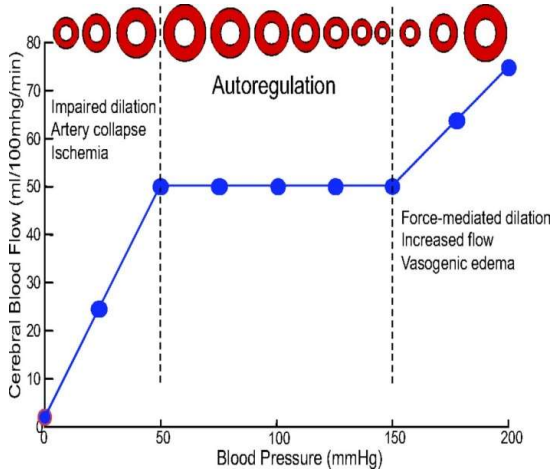
hyponatremic hypervolemia

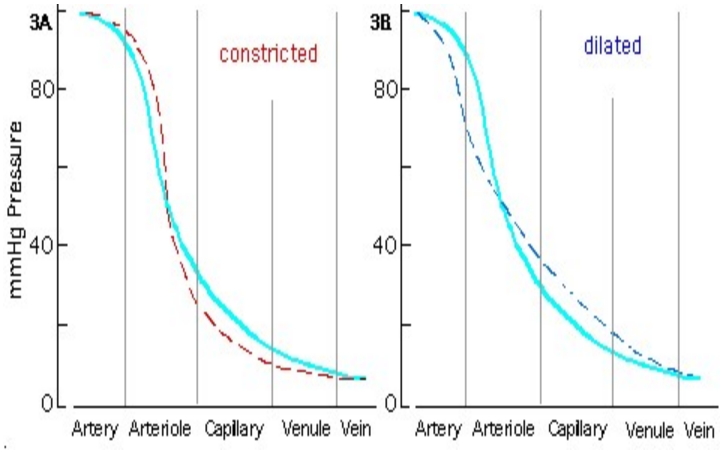
normo/hypernatremic hypervolemia

Capillary hyperperfusion and oedema

Oedema during hypertensive crisis – important in brain circulation

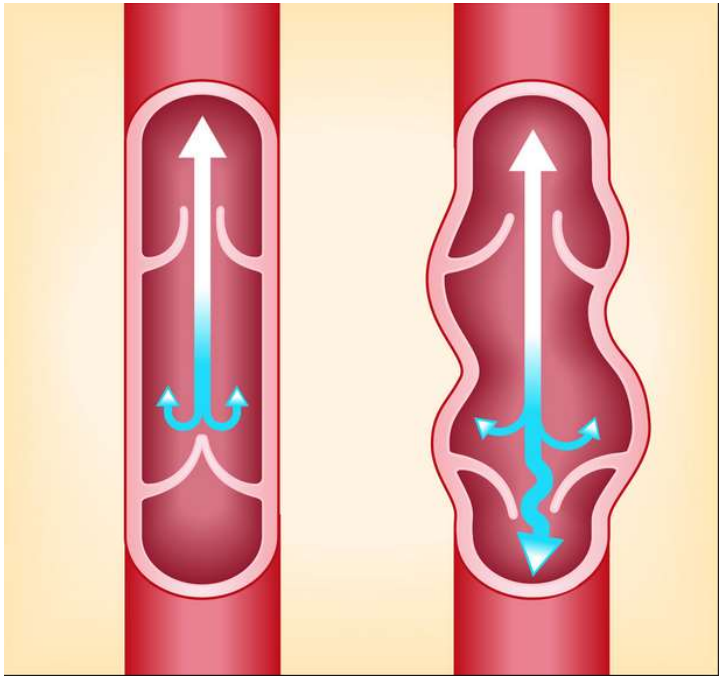
Oedema as a side effect of vasodilation treatment





Odemas in venous diseases

↑hydrostatic pressure at the venous end of a capillary
Most often caused by venous valves insufficiency
Deep venous thrombosis – asymmetric oedema
Leg ulcers – most often of venous origin
Increased filtration → increased capillary permeability → protein leak → „fibrin cuff“→ tissue ischemia → ulcer



Heart failure and oedema

- Left-sided failure
  - backward
    - ↑hydrostatic pressure in pulmonary capillaries → pulmonary oedema
    - Respiratory failure, pleural effusion (transudate)
    - Pulmonary hypertension → secondary right-sided failure
  - forward
    - Systemic hypotension→ shock
    - Organ failure (liver, kidneys, GIT, brain)
    - Muscular weakness, fatigue, cachexia

Right-sided failure

backward

↑ hydrostatic pressure at the venous and of systemic capillaries
Oedemas in systemic circulation
anasarca (systemic oedema)
hepatomegaly, ascites

forward

Isolated is a rarity
Leads into ↓ left ventricle preload → left-sided forward failure

Pulmonary oedema and pleural effusion

Pulmonary oedema: fluid accumulation in the lung tissue („swamp“)

- interstitial
- alveolar

Both fluid filtration and resorption from/to pulmonary circulation

Treatment: medication

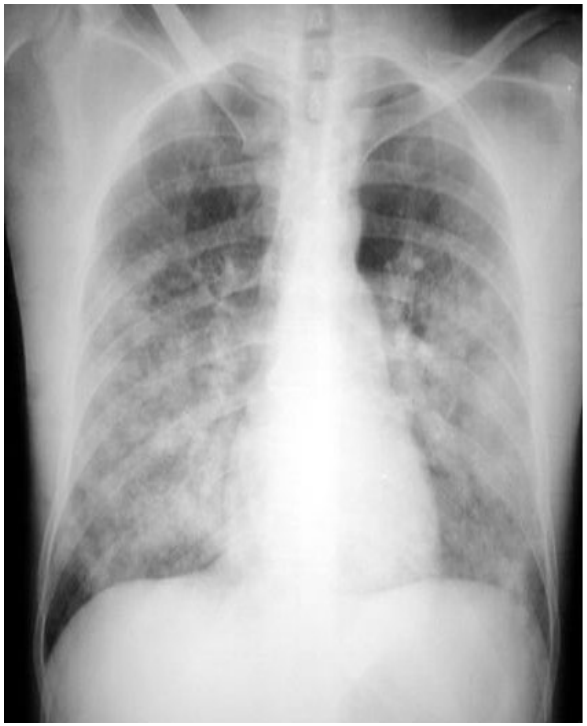
Pleural effusion: fluid between the parietal and visceral pleura („lake“)

Fluid is filtrated mainly from the systemic circulation and reabsorbed mainly into the pulmonary circulation

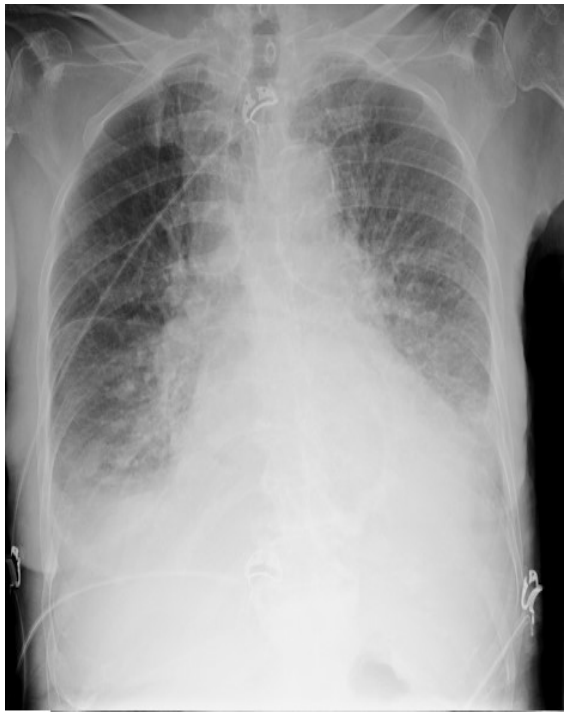
Treatment: medication or surgery

In transudates, pulmonary oedema is often combined with pleural effusion

X-ray



Pulmonary oedema



Bilateral pleural effusion

Exudate vs. transudate

Exudate

↑proteins

↑LD

↓glucose

cells present

Etiology:

1) inflammation
2) tumour
3) Pulmonary embolism (results from local necrosis)
4) TBC

Transudate

↓proteins

↓LD

↑glucose

cells absent

Etiology:

1) heart failure
2) hyperhydration
3) hypoproteinemia (liver failure, nephrotic syndrome)

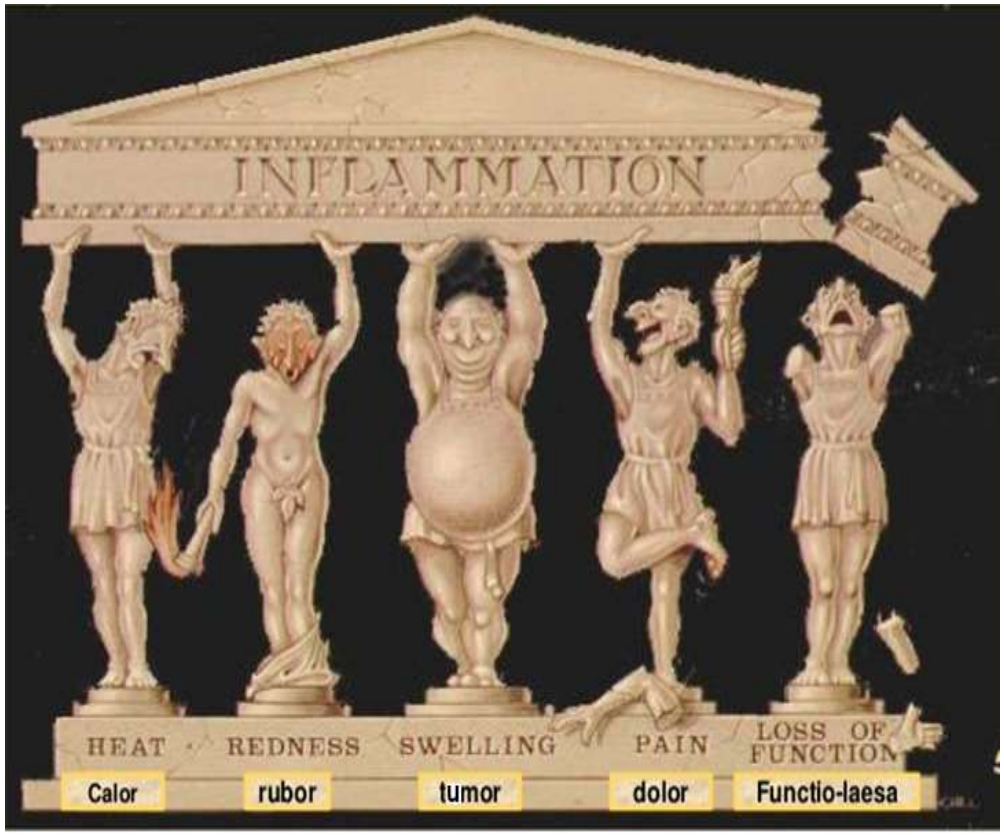
Hypoproteinemia

Normal blood protein level approx. 62 – 82 g/l

Decrease:
malnutrition (kwashiorkor)
malabsorption
liver failure
nephrotic syndrome

There is no pulmonary oedema (low both hydrostatic and oncotic pressure gradient in pulmonary capillaries)!

Inflammation and oedema



Mechanisms of endothelial permeability

Transcellular transport

vesiculo-vacuolar organelles (VVO)

fenestrations (GIT, kidneys, endocrine glands) – with or without (glomerulus) a membrane

Paracellular transport

adherent junctions – formed mainly by cadherins

- dissolve when stimulated by:
  - histamine
  - bradykinin
  - VEGF
  - NO

Tight junctions(esp. brain) – form a barrier

Vascular mechanisms of inflammation

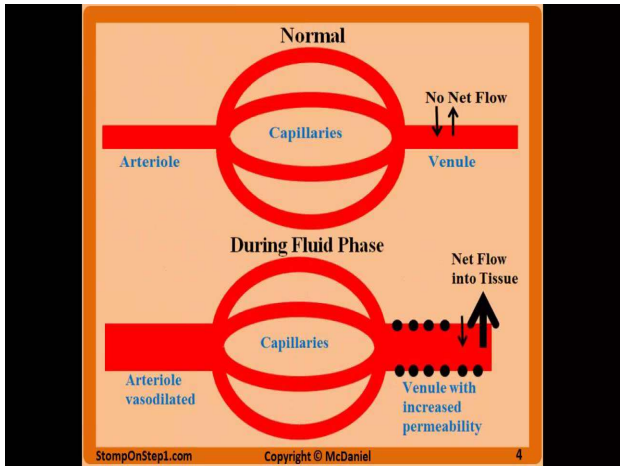
Contraction of arterioles followed by vasodilation and

increase in capillary permeability

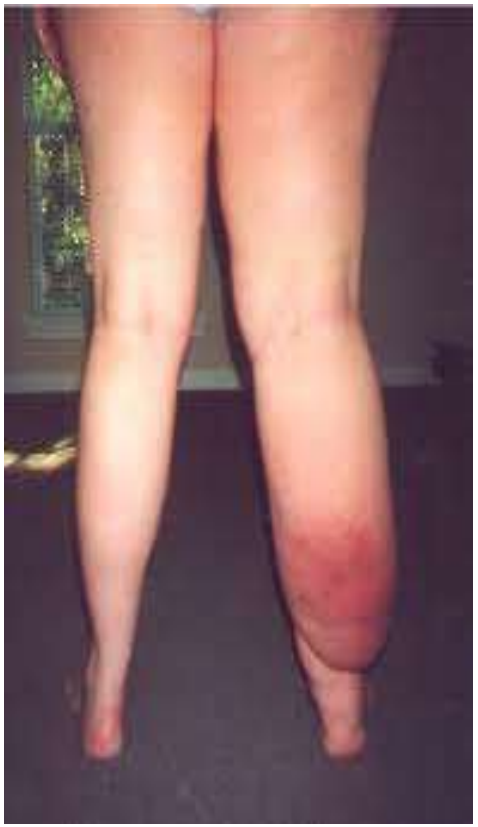
Vasoconstriction: endothelin, TXA2, PAF

Vasodilation: iNOS, PGI2, bradykinin

Cytokine production



Lymphatic oedema



Result of the impaired lymphatic drainage

- Primary lymphatic oedema

Idiopathic, a disorder of lymphatic system development
Occurs usually during adolescence or early adulthood
Sporadic or familiar occurrence

- Secondary lymphatic oedema

Secondary obstruction of lymphatic vessels (tumour, inflammation, trauma, iatrogenic – surgery radiation therapy, node extirpation)
Filariasis in the tropics
Oncologic diseases and their treatment in Europe

Lymphatic oedema and tumours

Mechanic compression of lymphatic vessels by a tumour
Interstitial oedema around the tumour (inflammation, VEGF) → compression of lymphatic drainage
Lymphatic node metastases

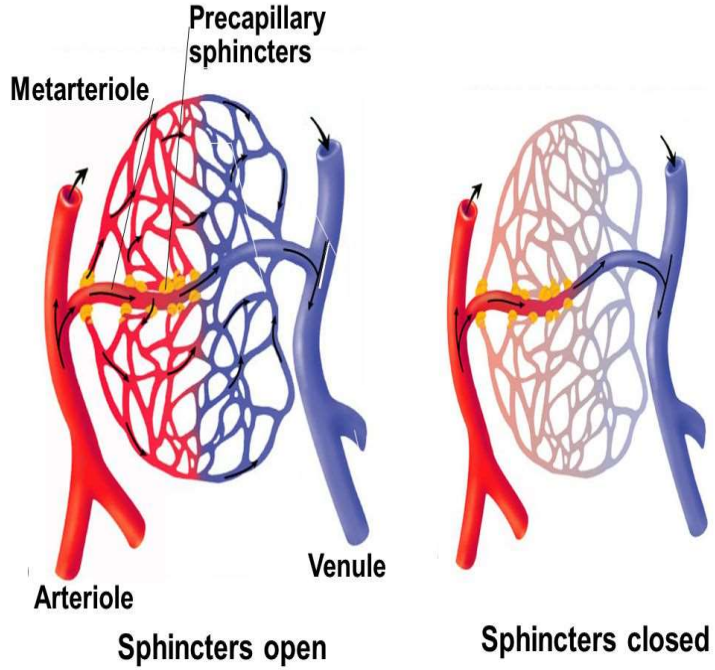
„pitting and „non-pitting“ oedema

In the low-protein oedema (heart failure, liver failure, nephrotic syndrome), a pit remains after pressing by a finger
In high-protein oedema (lymphatic oedema, inflammation, chronic oedema), no pit is present

Splanchnic circulation

Precapillary sphincters

Under normal circumstances, only some capillaries allow the blood passage
When the precapillary sphincters open, more blood passes into the microcirculation
The mechanism is present mainly in the splanchnic circulation



Catecholamine-induced Changes in the Splanchnic Circulation

Volumes and flows in the splanchnic region (normovolemic healthy male adult)

blood volume of approximately 70 ml/kg body weight.

splanchnic organs constitute 10% of the body weight, but contain 25% of the total blood volume.

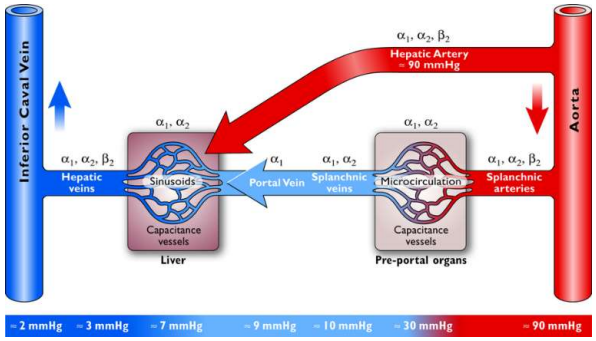
nearly two thirds of the splanchnic blood (*i.e.* > 800 ml) can be autotransfused into the systemic circulation within seconds.

liver 300 - 400 ml

intestine 300 - 400 ml

spleen 100 ml

splanchnic vasculature serves as an important blood reservoir for the circulatory system.



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The Journal of the American Society of Anesthesiologists, Inc.

From: Catecholamine-induced Changes in the Splanchnic Circulation Affecting Systemic Hemodynamics
Anesthes. 2004;100(2):434-439.

Distribution of Adrenoceptor Subtypes in the Splanchnic Vasculature

Receptor subtype	Vascular bed: Pre-portal arterial	Hepatic arterial	Pre-portal venous	Hepatic venous
α_1	+++	+++	+++	++
α_2*	++	+	+	+
β_2	---	--	-?	---

+ depicts vasoconstriction; - depicts vasodilation; the number of +'s or –'s depicts the relative density of adrenoceptor subtypes; based on references 3 and 4.

Vasoconstriction decreases arterial flow, decreases venous capacitance, impedes venous outflow. Vasodilation increases arterial flow, facilitates venous outflow (see text for details).

* refers only to peripheral α_2-adrenoceptors; activation of central α_2-adrenoceptors decreases sympathoadrenal tone.

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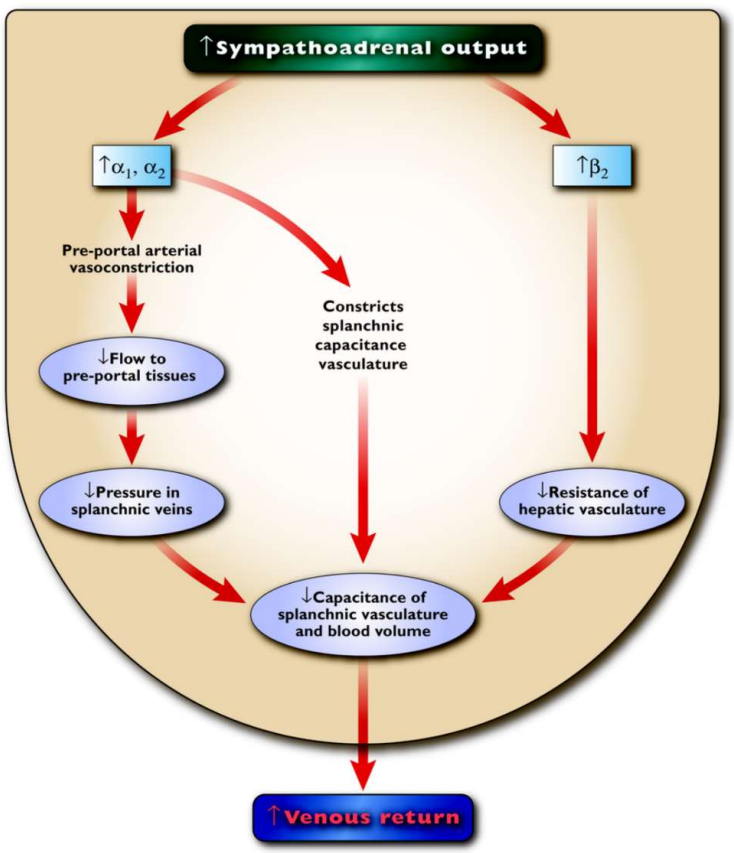

Experiment

Murine mesentery
Adrenaline → arterial vasoconstriction (mainly α_1 receptors)
Histamine → arterial vasodilation (mainly H_1 receptors)