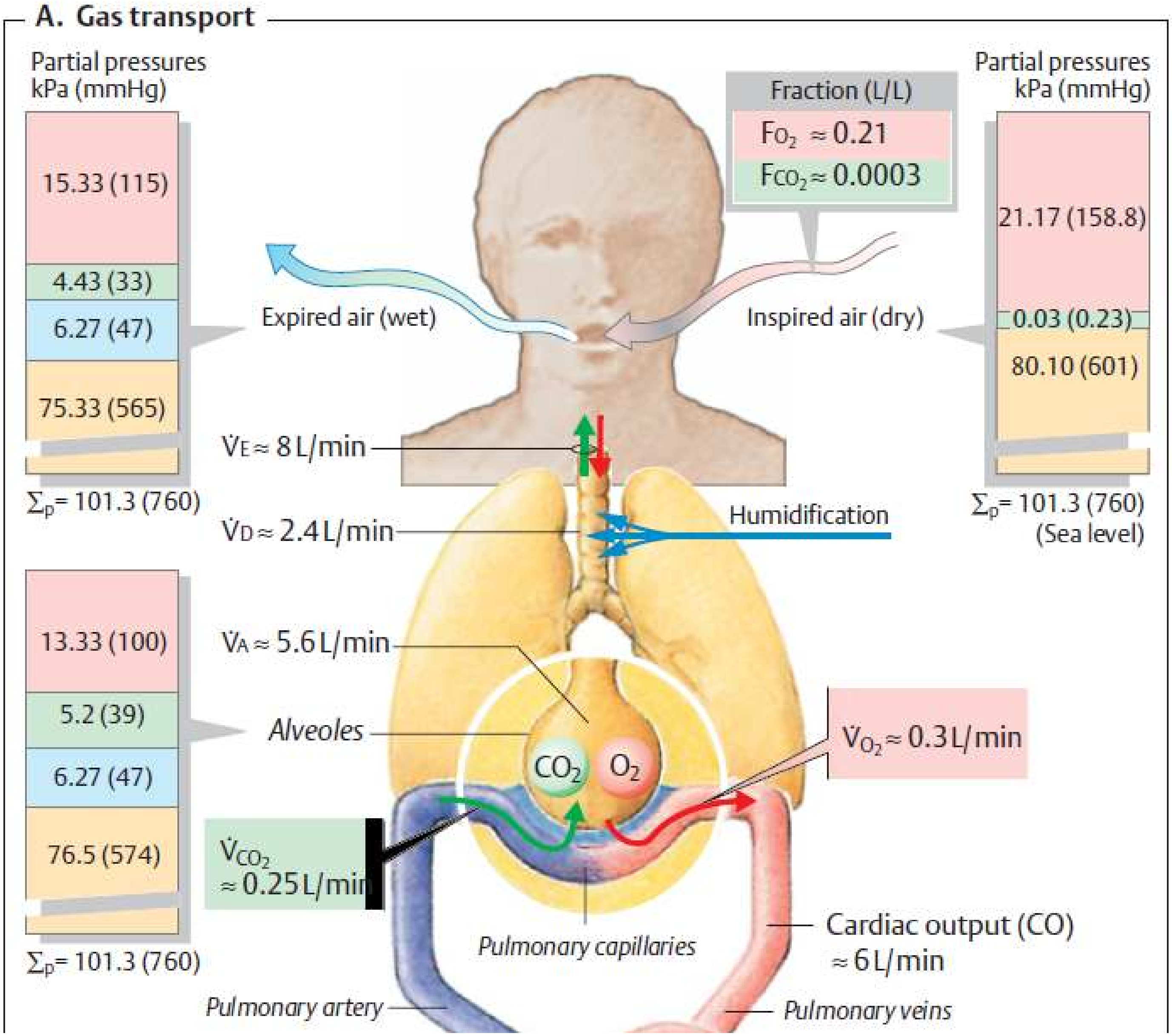
PATHOPHYSIOLOGY OF THE RESPIRATORY SYSTEM 1

RESPIRATORY INSUFFICIENCY
and
acute (adult) respiratory distress syndrome (ARDS)

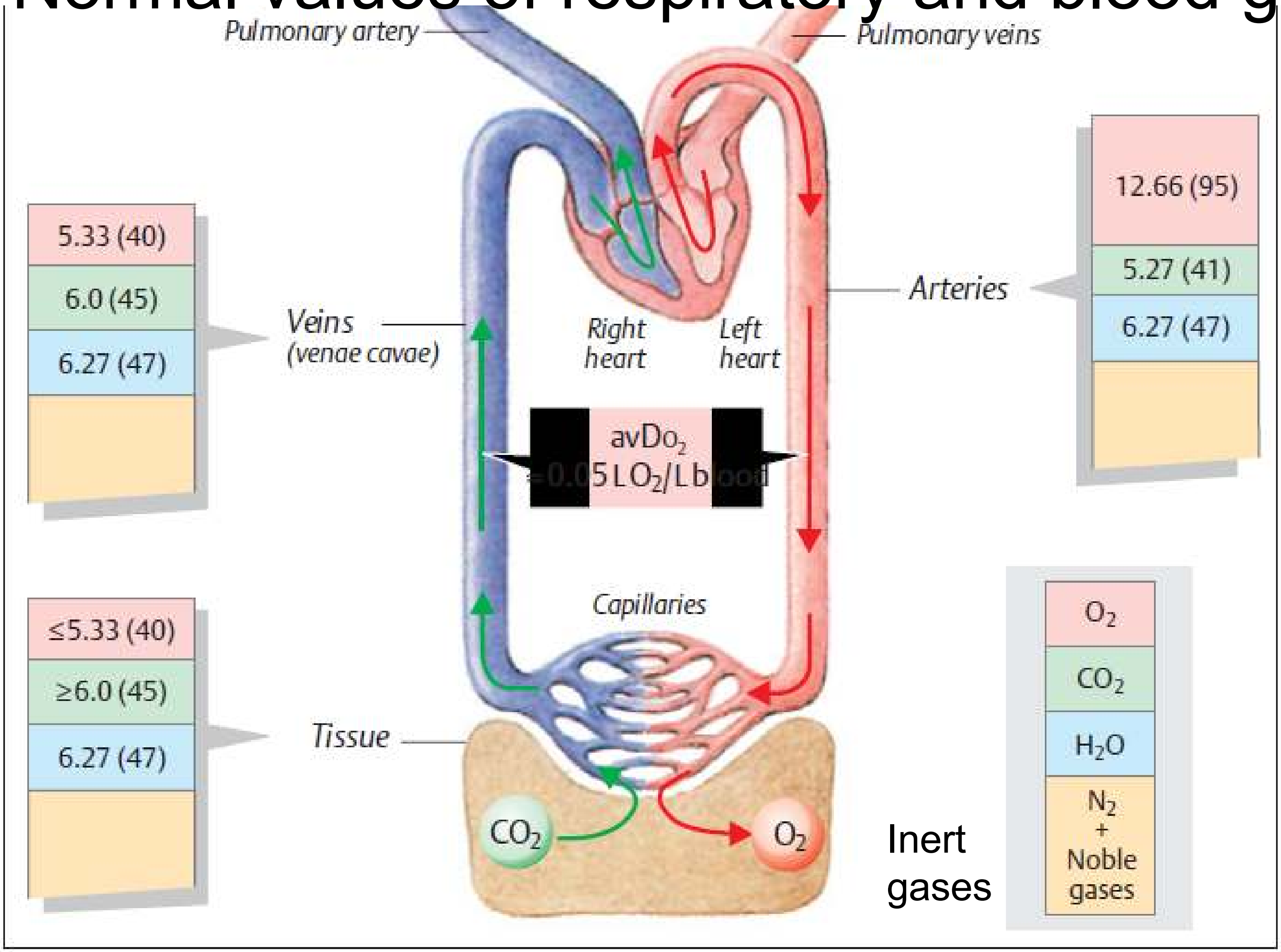
Outline

- **Reminder: respiratory gases, hypoxia, polycytemia, etc.**
- **Introduction**
- **Patophysiology of respiratory insufficiency type 1 and 2**
- **Mechanisms of lower p_aO_2 in respiratory diseases**
  - alveolary hypoventilation
  - diffusion block
  - pulmonary shunt
- **Reactive pulmonary hypertension**
- **Hyperkapnia in respiratory insufficiency type 2 (global)**
- **ARDS (acute respiratory distress syndrome)**
- **Remarks about oxygenotherapy**

Normal values of respiratory and blood gases



Normal values of respiratory and blood gases



Some values, definitions:

760 mmHg=101 kPa=1000 cmH_2O=100%

STPD – Standard Temperature and Pressure, Dry (air), 0/15/20 °C, 101 kPa

BTPS – Body Temperature and Pressure, Saturated (air), 37 °C, 100 % humidity

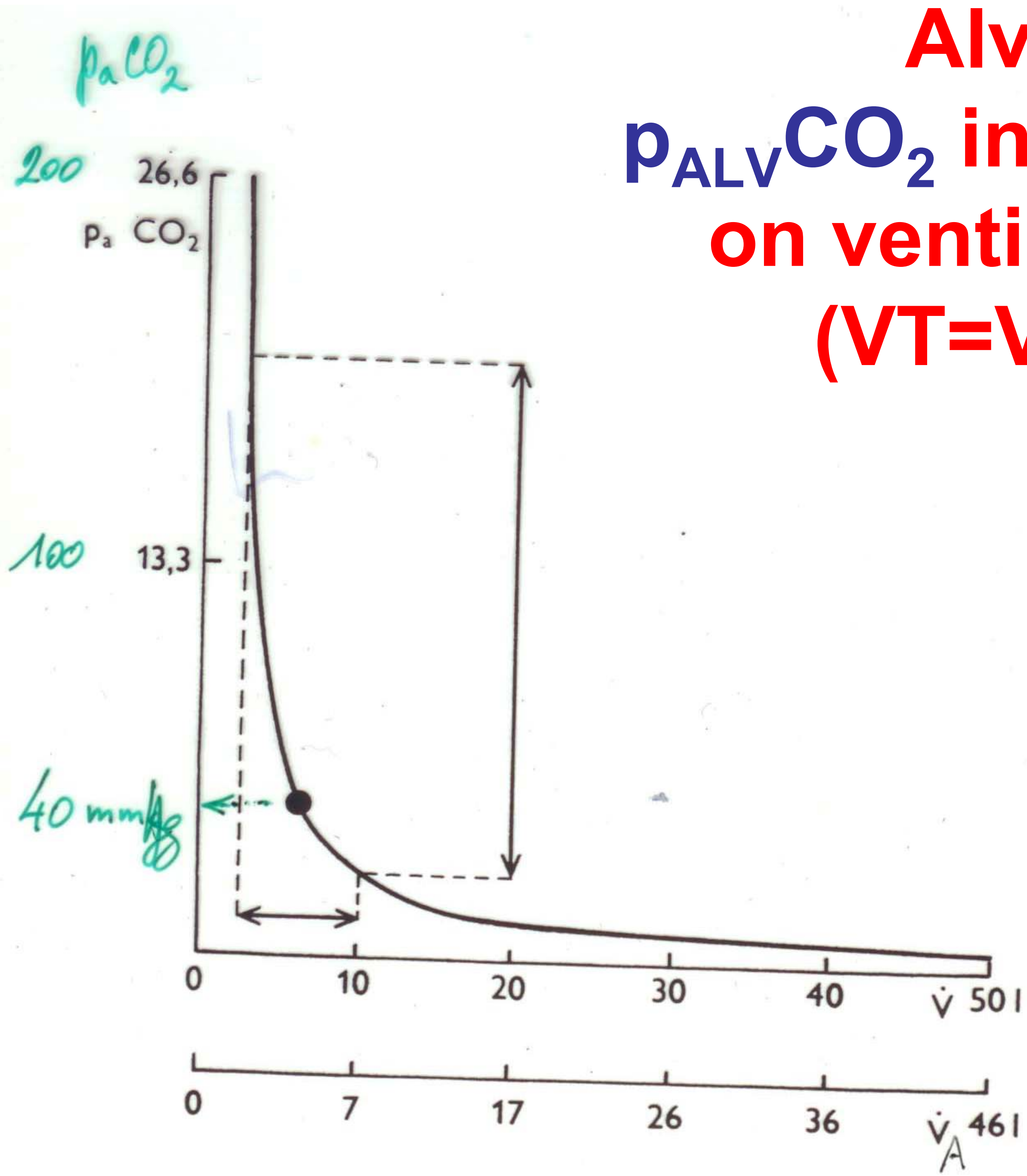
Atmospheric CO_2: 300 ppm = 0.03 kPa

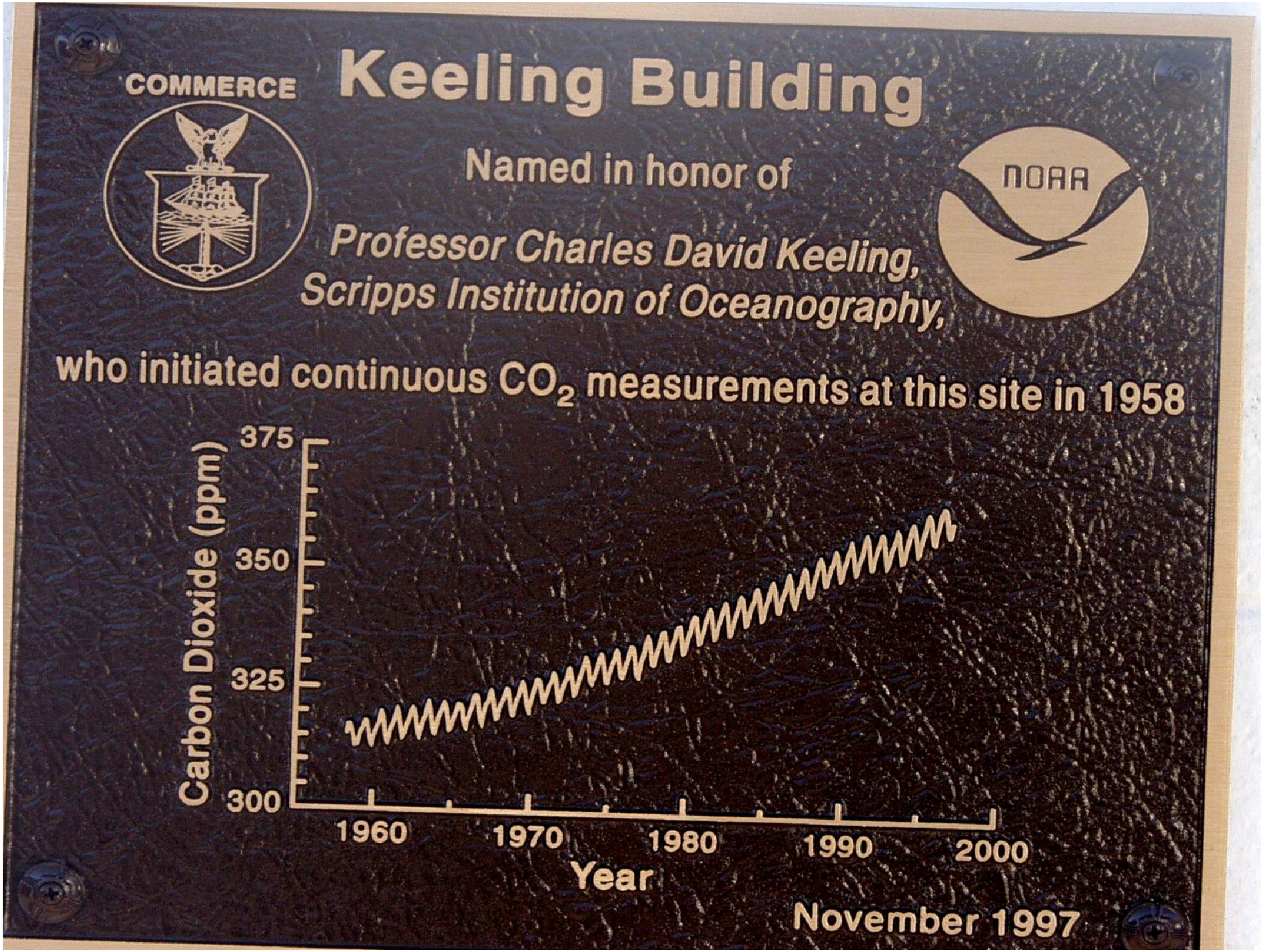
Exhaled CO_2 : 4.4 … 5.2 % = 5.2 kPa

Atmospheric O_2 : 21 % = 21 kPa

Exhaled O_2 : 15.3 % = 15.3 kPa

Alveolar $p_{ALV}CO_2$ in dependence on ventilation V(T) (VT=VD+VA)




COMMERCE
Keeling Building
Named in honor of
Professor Charles David Keeling,
Scripps Institution of Oceanography,
who initiated continuous CO_2 measurements at this site in 1958
Carbon Dioxide (ppm)
375
350
325
300
1960
1970
1980
1990
2000
Year
November 1997

Eero Antero Mäntyranta

(born 1937) is a former Finnish skier and multiple Olympic Champion. With his seven medals from four Winter Olympics, he is one of the most successful skiers Finland has ever produced.

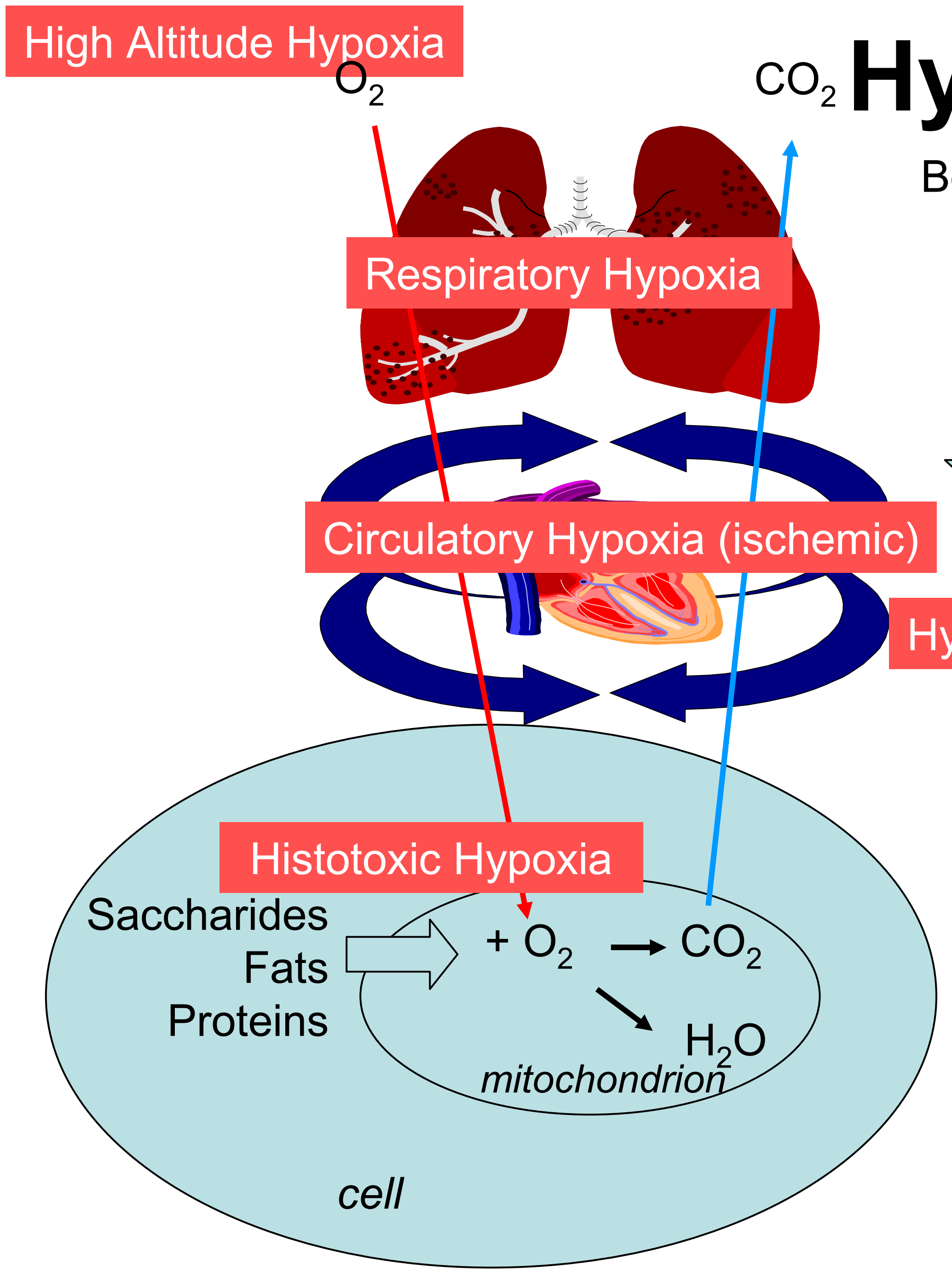
„Advantageous mutation“ of erytropoietin receptor

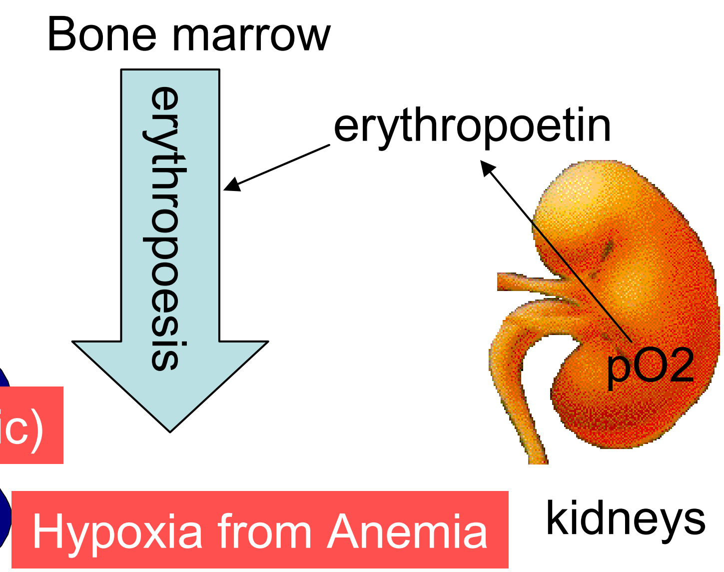
Mäntyranta has Primary familial and congenital polycythemia (PFCP) causing increase in red blood cell mass and hemoglobin due to a mutation in the erythropoietin receptor (EPOR) gene, which was identified following a DNA study done on over 200 members of his family, as reported in 1993

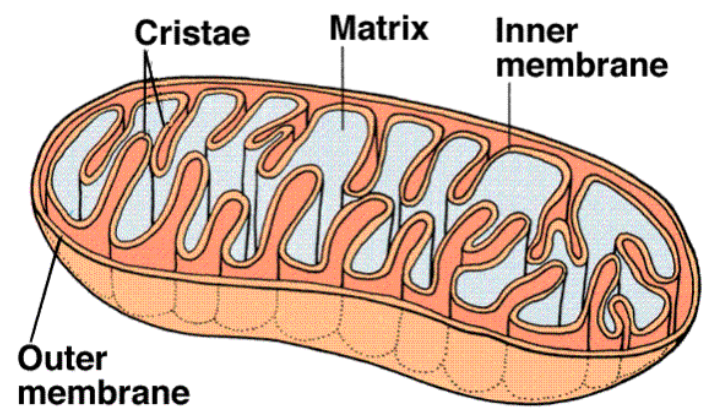
Polycytemia in winter olympics winner: Eero Mantyranta

Hb 231 g/L
Hct 68%

Hypoxia examples

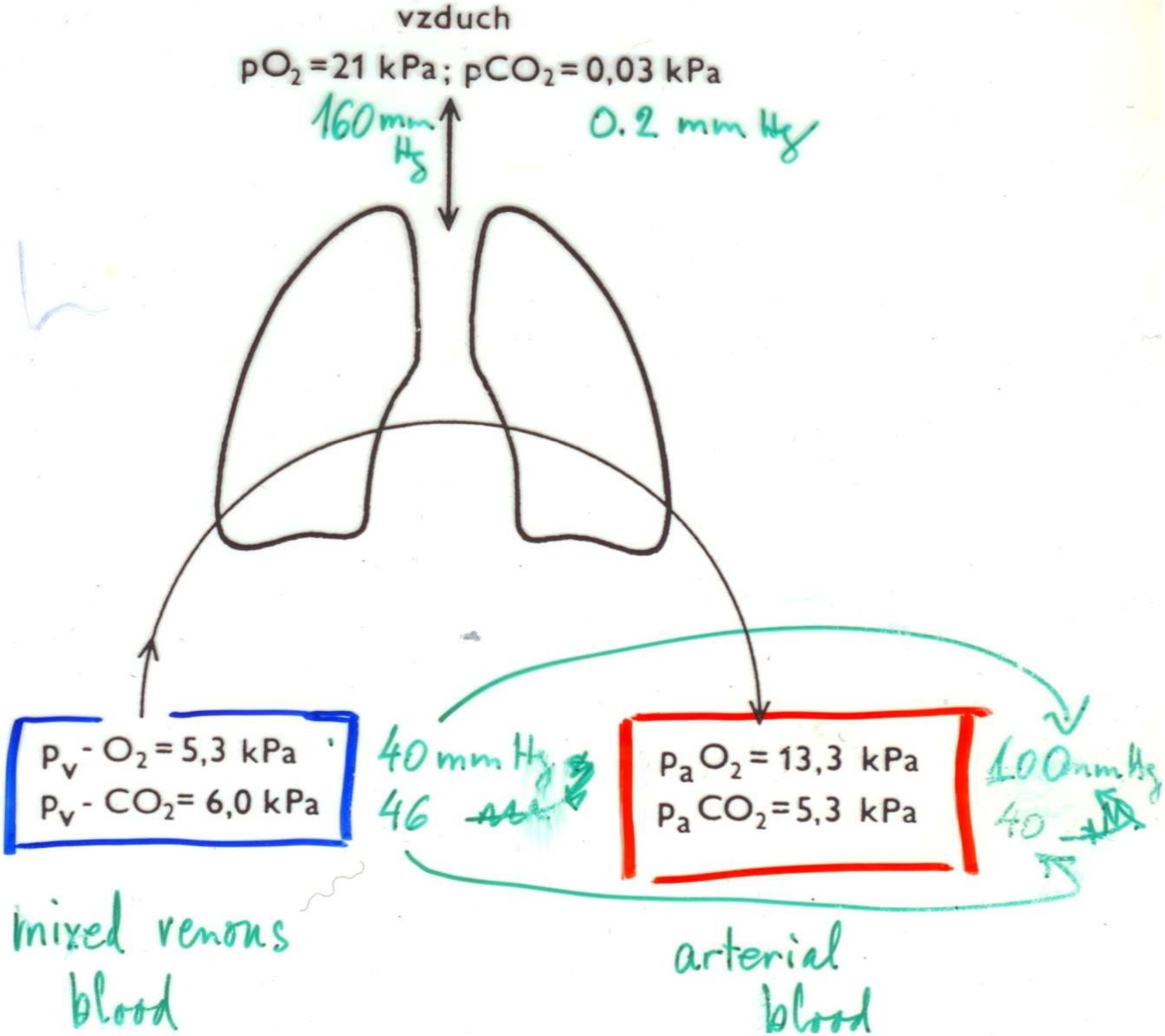






mitochondrion

Normal values of respiratory and blood gases



RESPIRATORY INSUFFICIENCY

Type I (partial, hypoxemic, low O_2)

Type II (global, ventilatory, low O_2 , high CO_2)

RESPIRATORY INSUFFICIENCY

Functions of the respiratory systems are not adequatelly fulfiled:

- **$p_{art}O_2$ does not attain 12.6 .. 13.15 kPa =**

= 95 .. 100 mmHg

- **$p_{art}CO_2$ may (but not necessarily does) exceed 5.25 kPa = 40 mmHg**

$p_{art}CO_2$ may be normal – even decreased while $p_{art}O_2$ will be always decreased (low)

the explanation is in different compensatory possibilities of total lungs to vary pCO_2 and pO_2 in individual alveoli

–

such possibility is large for pCO_2 but effectively it is lacking for pO_2

RESPIRATORY INSUFFICIENCY

RESPIRATORY INSUFFICIENCY type I (partial), (hypoxemic)

- p_aO_2 does not reach 13 kPa (100 mmHg)
- p_aCO_2 is normal or, often decreased (hypocapnia)

RESPIRATORY INSUFFICIENCY type II (global), (ventilatory)

- p_aO_2 does not reach 13 kPa (100 mmHg)
- p_aCO_2 over 5.25 kPa (40mmHg = hypercapnia)

Respiratory Insufficiency – Type I

- **low $p_{art}O_2$ because of a respiratory system pathology**

- **$p_{art}CO_2$ normal or even decreased (hypocapnia), due to regulation**

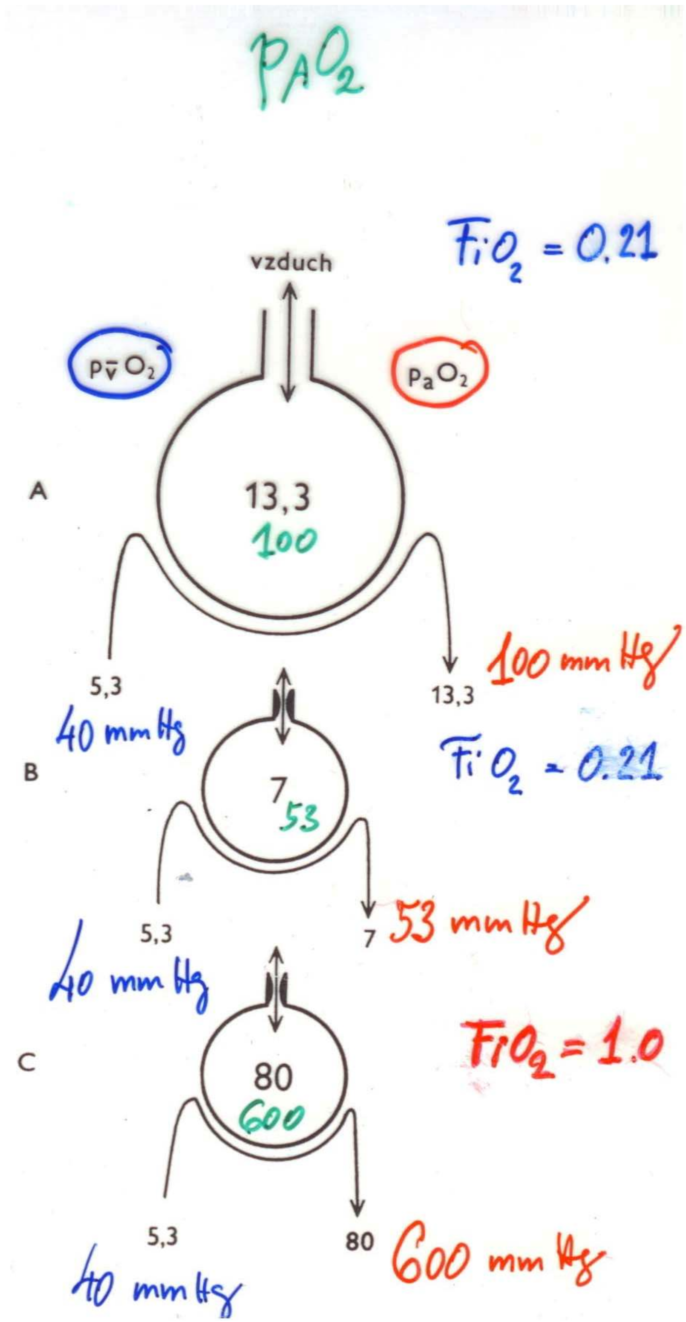
Four pathogenetic mechanisms of decreased $p_{art}O_2$

- Total alveolar hypoventilation
- Local alveolar hypoventilation
- Pulmonary shunt
- Diffusion block

(other classification according to etiology is possible…)

$p_{ALV}O_2$ determines $p_{art}O_2$ ($C_{art}O_2$)

- $p_{art}O_2$ in the arterial blood is given by $p_{ALV}O_2$ value in the particular alveolus
- $p_{ALV}O_2$ values exceeding 100 mmHg DO NOT INCREASE oxygen content in the blood significantly
- $p_{ALV}O_2$ values lower than 100 mm Hg DECREASE oxygen content in the blood significatly



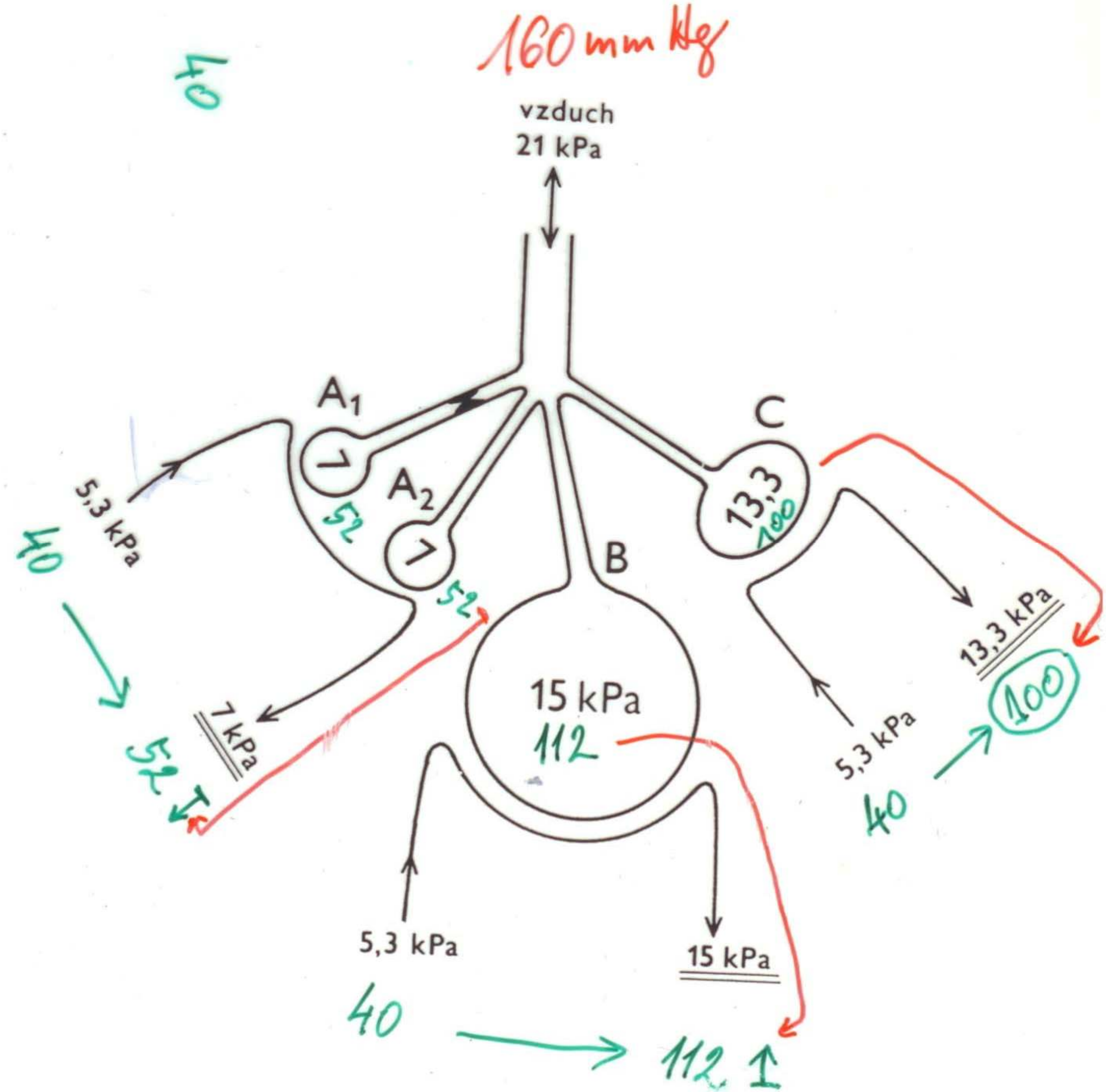
- normal (21 %) **O_2** breathing in norm

- normal (21 %) **O_2** breathing in pathology

- high (up to 100 %) **O_2** breathing in pathol.,can be (even higher = hyperbaric)

Total versus Local Alveolar Hypoventilation

- **Total alveolar hypo-ventilation = the sum of ventilations of all alveoli is insufficient to eliminate CO_2 produced in the metabolism**
- **Local alveolar hypo-ventilation = some part of alveoli is hypoventilated while others are hyperventilated – the sum is adequate to CO_2 produced in the metabolism or is even excessive *(resulting in hypocapnia)***

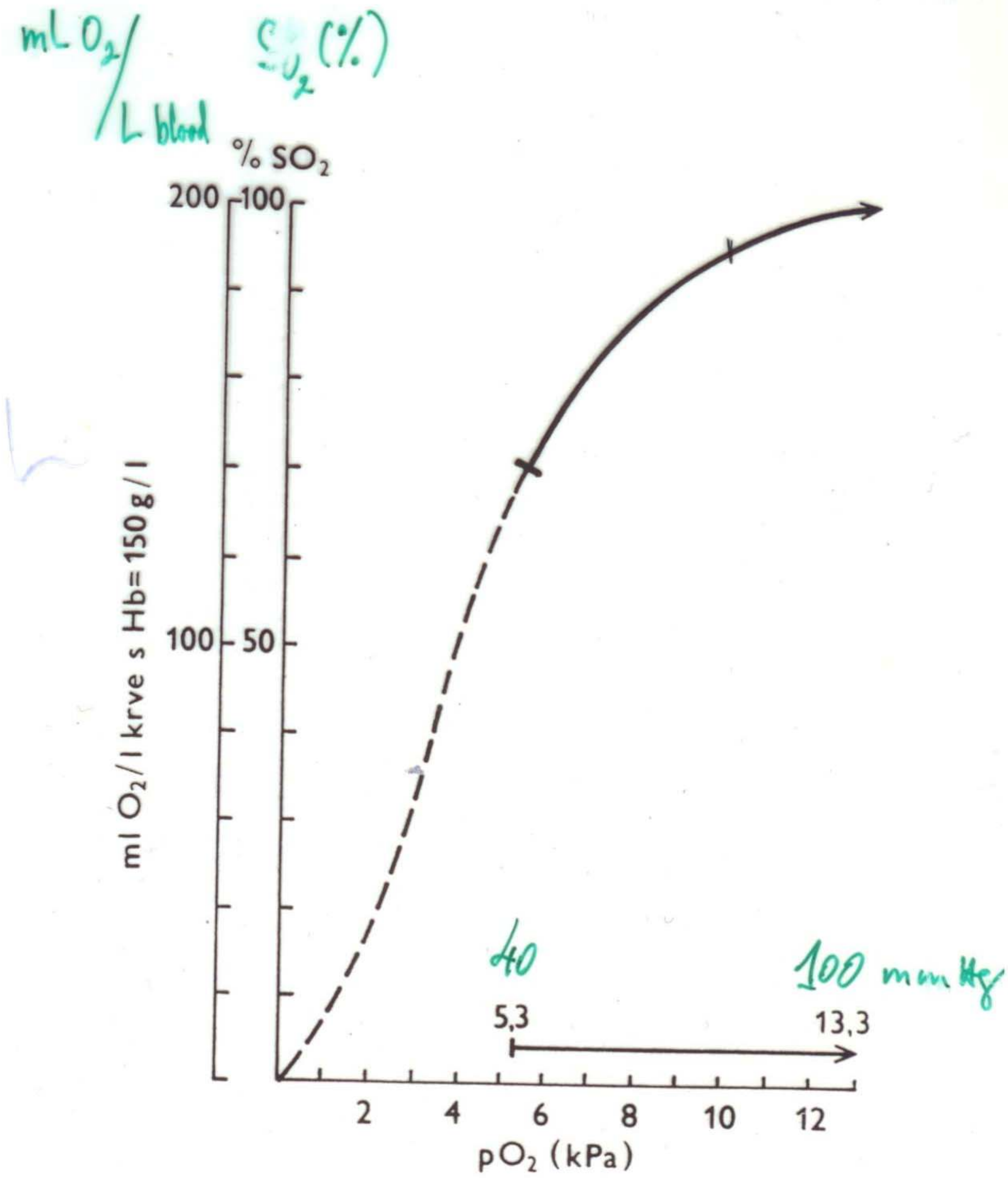


A_1, A_{2}- - hypo-ventilated

B – hyper-ventilated

C- normally ventilated alveolus;

summary V/Q ratio is OK



The S – shape of the oxygen to HB binding curve

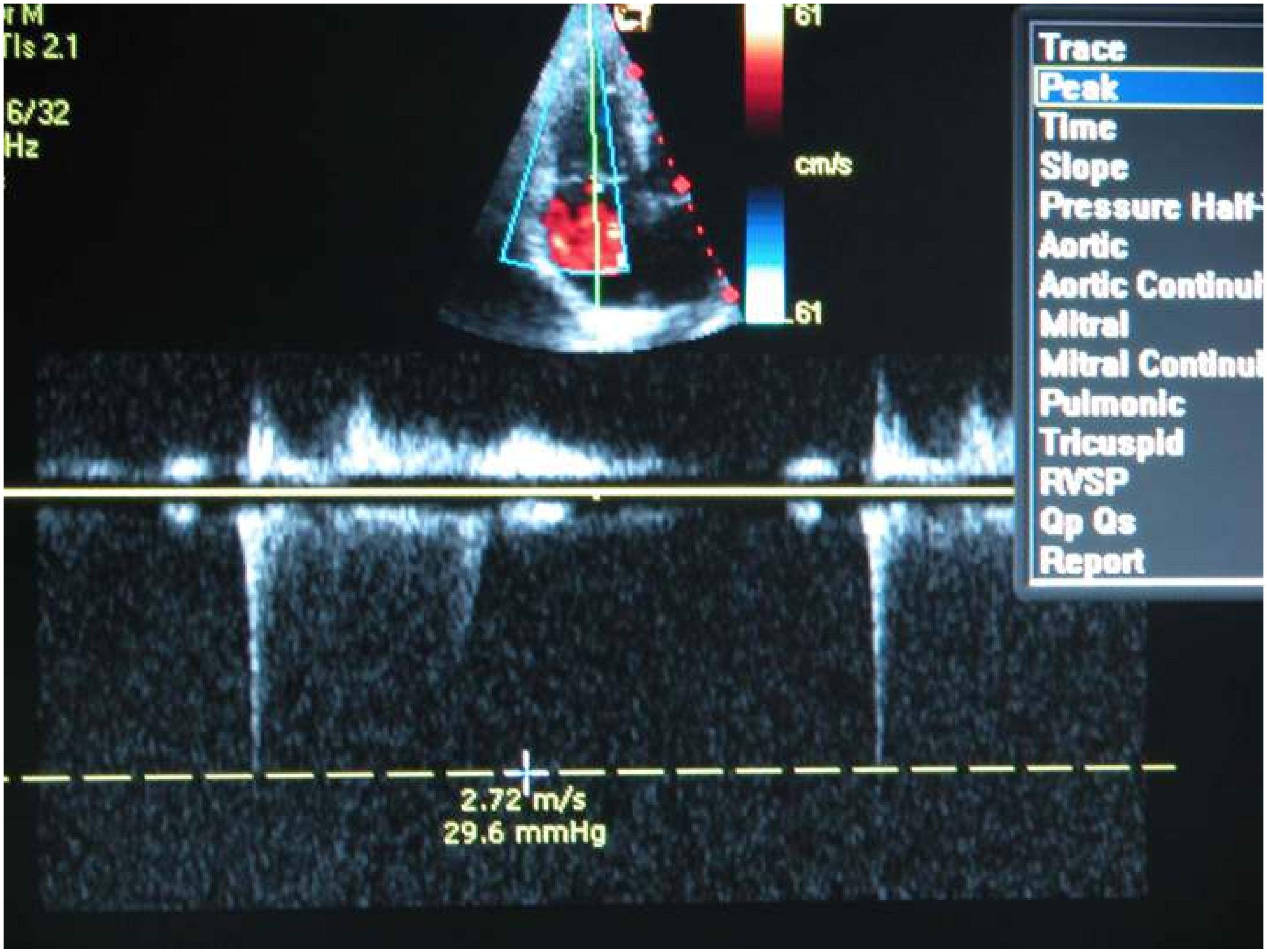
The „S – shape“ of the oxygen dissociation curve

- **The „S – shape“ form of the oxygen dissociation curve protects against effects of a mild hypoxia in the arterial blood (a low decrease in p_aO_2)**
- **Respiratory insufficiency may progress rapidly after hemoglobin saturation in the arterial blood decreases below 85 to 80 % because the oxygen dissociation curve becomes steep (vic. circ. …)**

Alveolar hypoxia causes pulmonary hypertension

- **Alveolar hypoxia (low p_AO_2) shifts pulmonary perfusion to regions with higher oxygen tension (p_AO_2) through vasoconstriction**
- **The vasoconstriction causes pulmonary hypertension („reactive“ - due to alveolar hypoxia)**
- **This creates a problem in patients with chronic alveolar hypoventilation *(chronic bronchitis, emphysema)***
- **Chronic pulmonary hypertension leads to hypertrophy and dilatation of the right heart (cor pulmonale)**

Pulmonary hypertension on echocardiography

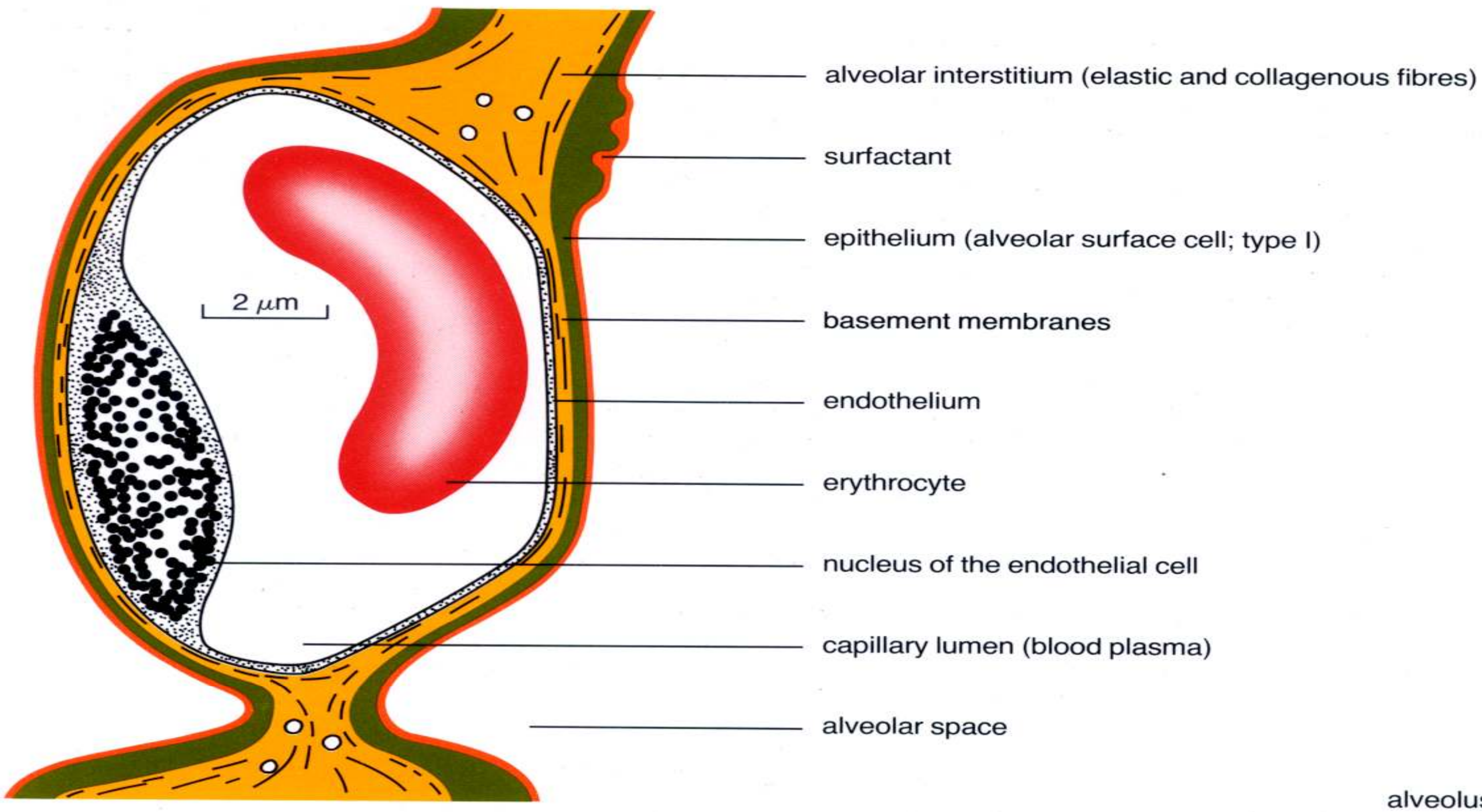


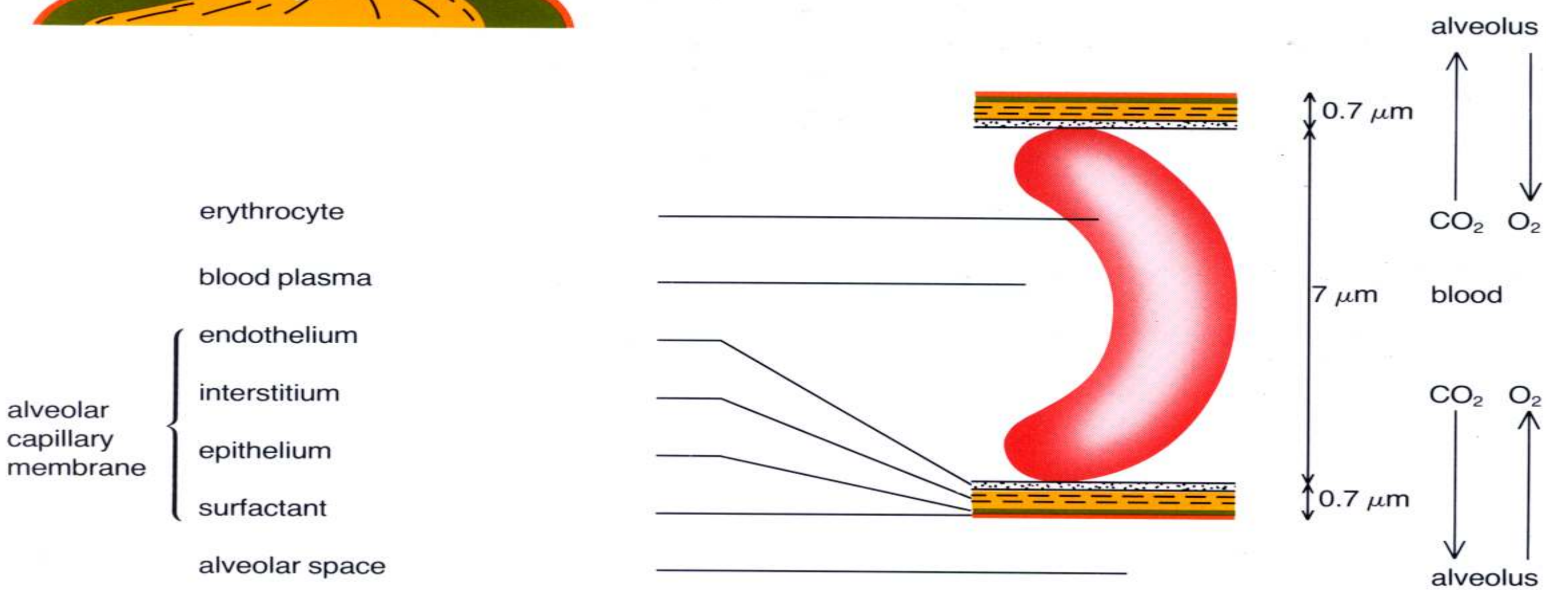
Arterial hypoxia stimulates respiratory centers 1

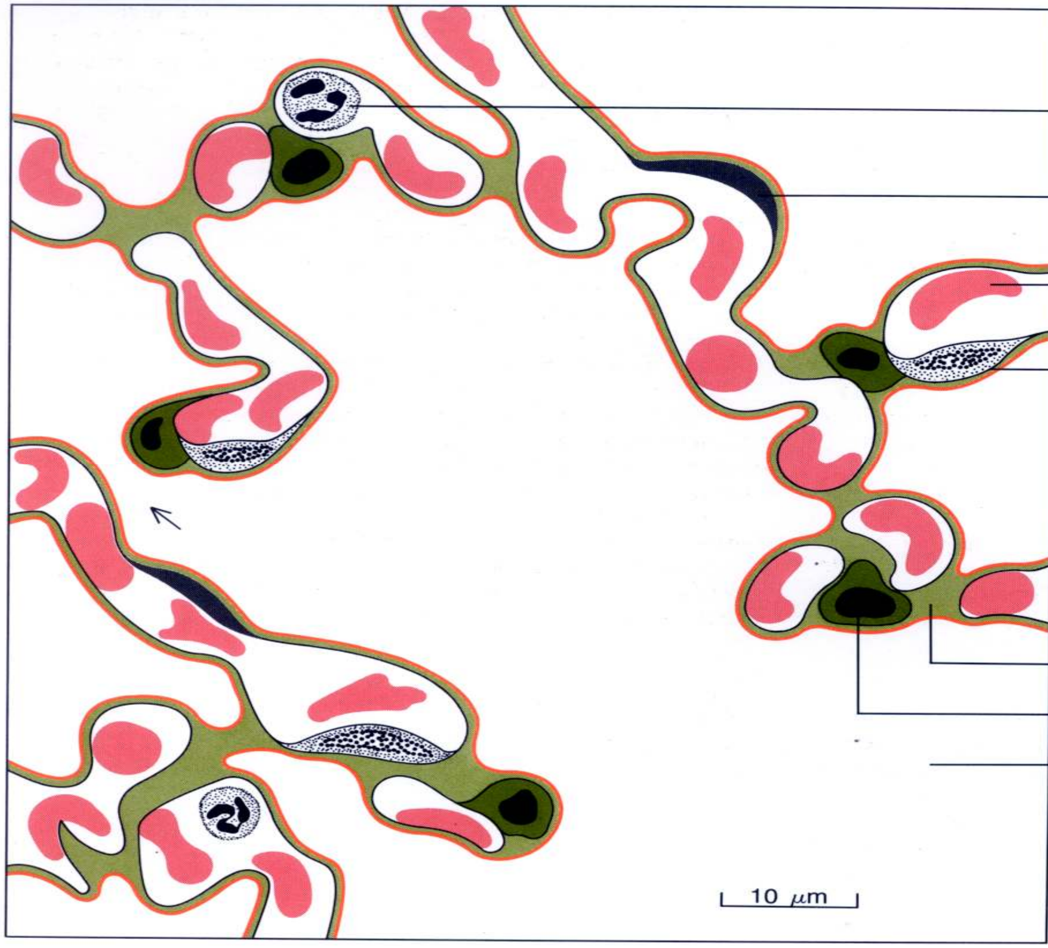
- **Arterial hypoxia (a low p_aO_2) stimulates respiratory centers through activation of peripheral chemoreceptors *(glomus caroticum, corpus aorticum)***
- **This is a fundamental change in control of the lung ventilation which normally depends on CO_2 produced by the metabolism (blood pH is maintained)**

Arterial hypoxia stimulates respiratory centers 2

- **The fundamental change in control of the lung ventilation in patients with a low p_aO_2 makes them sensitive to oxygen administration**
- **Total alveolar hypoventilation may be worsened by adminstration of oxygen**
- **This may lead to a dramatic worsening of hypercapnia and respiratory acidosis**


2 μm
alveolar interstitium (elastic and collagenous fibres)
surfactant
epithelium (alveolar surface cell; type I)
basement membranes
endothelium
erythrocyte
nucleus of the endothelial cell
capillary lumen (blood plasma)
alveolar space


alveolus
0.7 μm
erythrocyte
CO_2 O_2
blood plasma
7 μm
blood
endothelium
interstitium
alveolar capillary membrane
epithelium
CO_2 O_2
surfactant
0.7 μm
alveolar space
alveolus



Diffusion abnormalities

dimensiones of the alveolar-capillary membrane

overall thickness:	0.30–1.00 μm
alveolar epithelium:	0.15–0.35 μm
epithelial basement membrane:	0.05–0.20 μm
endothelial basement membrane:	0.05–0.40 μm
capillary endothelium:	0.05–0.25 μm

2.10 Structure and function of the alveolus

Diffusion law: Q=DAdC/L,

Q=flow,D=coeff.,

A=area, L=length

dC=conc.diff.

schematized from E. R. Weibel, 1963

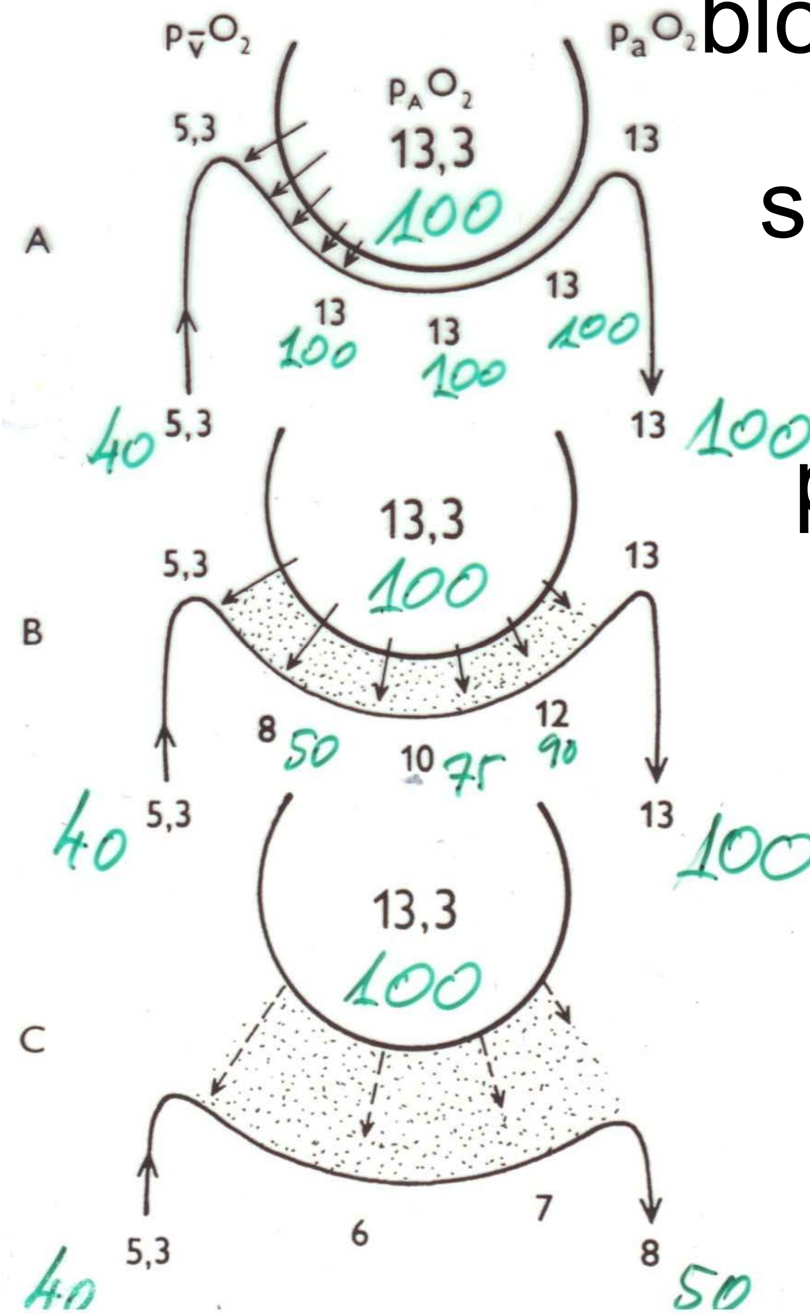
Diffusion block

- A widening of the alveolo-capilary lung barrier results in „diffusion block“

- The amount of O_2 and CO_2 transferred between blood and the alveolar air depends on: $(Q=DAdC/L)$
  - exchange area A (surface)
  - difference in partial pressures (dC, „concentration gradient“)
  - diffusion coefficient (D, higher for CO2 compared to O2)
  - **diffusion distance, L**

Diffusion block – a special case of the „Latent Respiratory Insufficiency“

- p_aO_2 may be normal in cases of „diffusion block“ (p_AO_2 is also normal)
- To a certain stage of the pathology p_aO_2 may be normal and decrease only during exercise (therefore „latent“)
- Respiratory insufficiency manifests only in connection with a more rapid blood flow that occurs during exercise



block is due to widening of the barrier separating the alveolar air from the blood passing in the pulmonary capillaries

Diffusion abnormalities

Diffusion law: Q=DAdC/L,

Q=flow,D=coeff.,

A=area, L=length

dC=conc.diff.

Pulmonary shunt 1

- **A fraction of blood passing the lungs DOES NOT get into a gases exchanging contact with the alveolar air.**
- **This functionally resembles the cardiac shunts causing the „right-to-left“ circulatory shunts**
- **„Pulmonary shunt“ refers to the functional analogy, there is no anatomical shunt in the blood circulation**

Pulmonary shunt 2

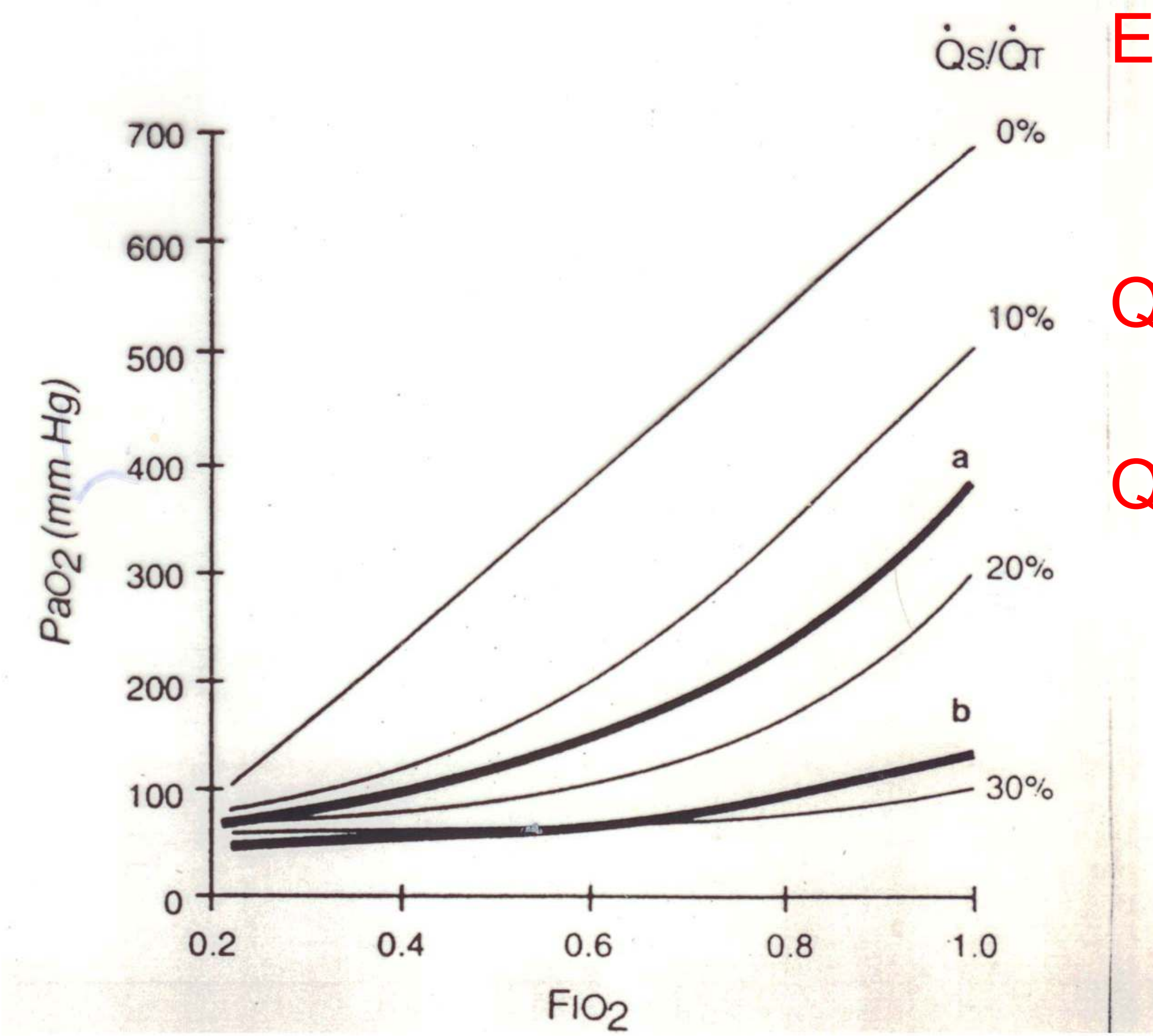
- **„Pulmonary shunt“ has a devastating effect on p_aO_2 values causing severe hypoxemia highly refractory to administration of oxygen**

- **Conditions of patients with pulmonary shunts may worsen dramatically when the extent of the shunt is enlarged**

ARDS

- ARDS – Adult (or Acute) Respiratory Distress Syndrome
- Compare to: (Infant) Respiratory Distress Syndrome - of immature newborn, lack of surfactant

...atelectasis is one of the common effects...



Effects of pulmonary shunt

QS = shunt perfusion

QT = total perfusion

Hypercapnia –
Respiratory Insufficiency Type II

- **There is only a single pathogenetic cause of hypercapnia (increased p_aCO_2) and this is the total alveolar hypoventilation.**

- **This is why this type of respiratory insufficiency is sometimes characterized as „ventilatory“.**

Respiration
and acid-base balance

$$pH = pK + \log \frac{[HCO_3^-]}{[H_2CO_3]} \quad [H_2CO_3] = k \cdot pCO_2$$

$$7{,}4 = 6{,}1 + \log \frac{24{,}0\ mM}{1{,}3\ mM} \ldots\ \underline{\underline{5{,}3\ kPa\ pCO_2}}$$

pCO_2 will be in hypoventilated alveoli increased and pO_2 decreased …

consequently

also in the blood leaving affected alveoli partial pressures of these gases will be adequatelly changed

… also in the blood leaving affected alveoli partial pressures of these gases will be adequatelly changed

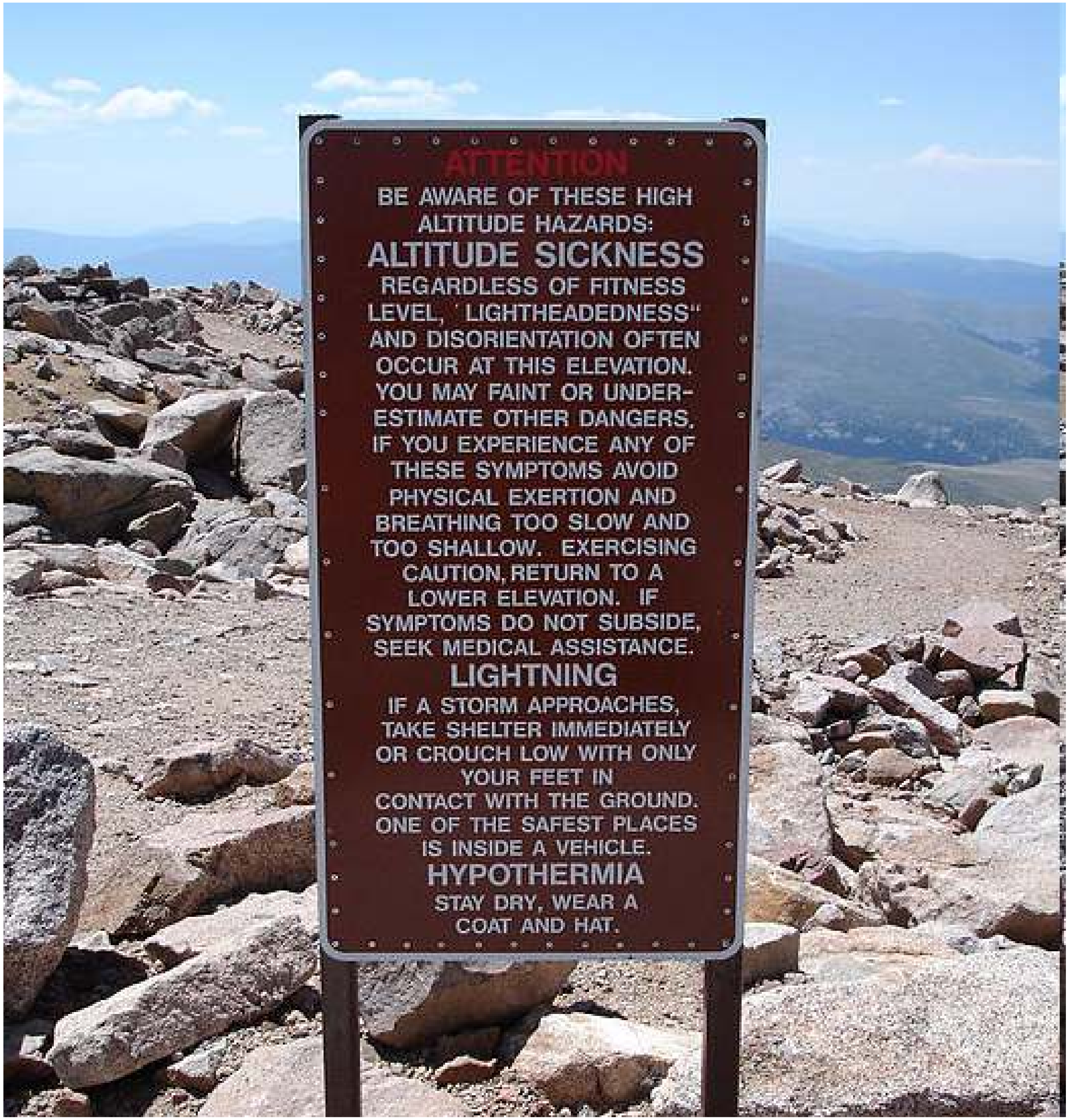
accordingly, P_aCO_2 should be increased

… however

after sampling the arterial blood and meassurig P_aO_2 and P_aCO_2

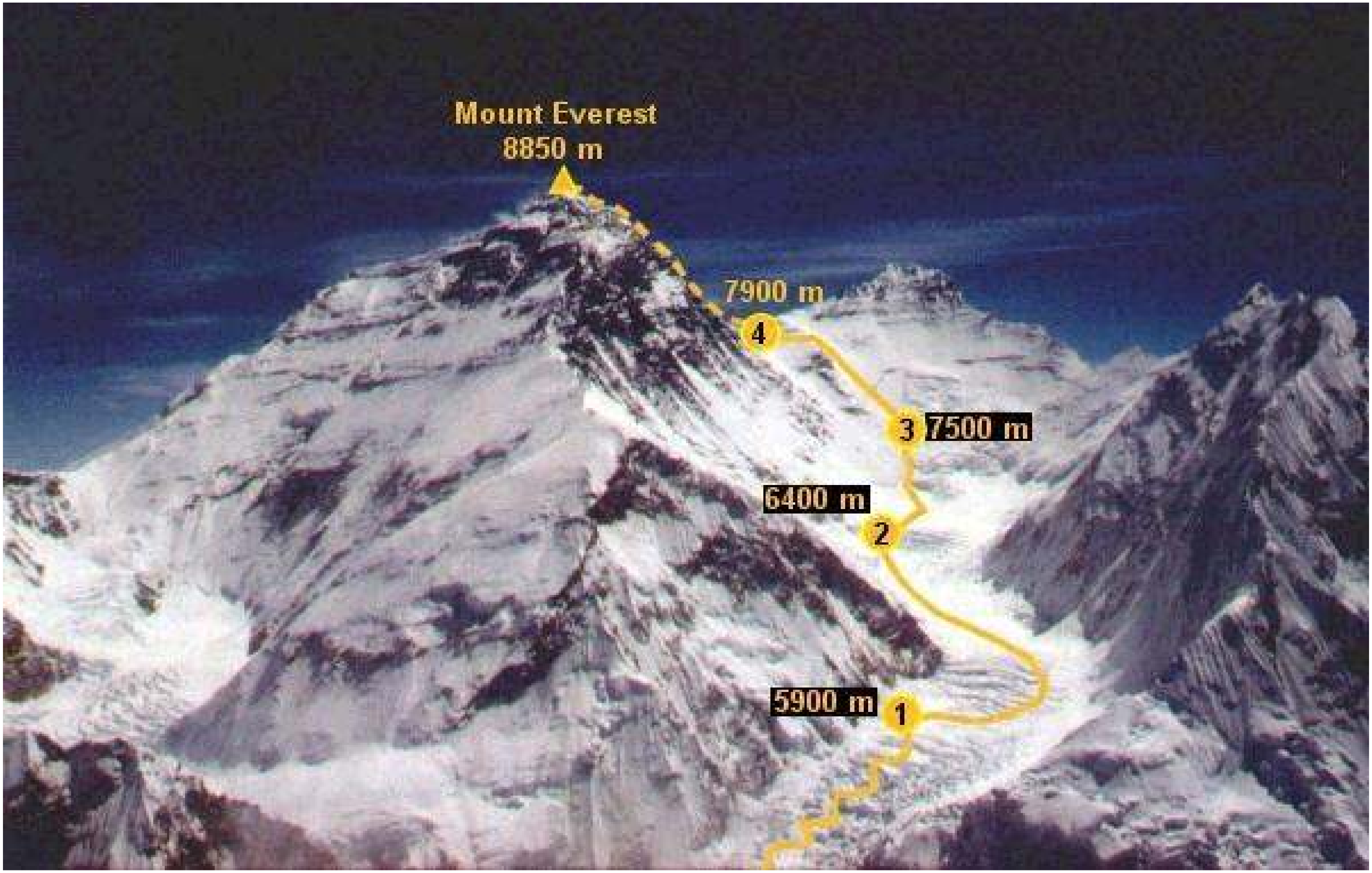
a little surprisingly

P_aCO_2 may be normal – even decreased (!)



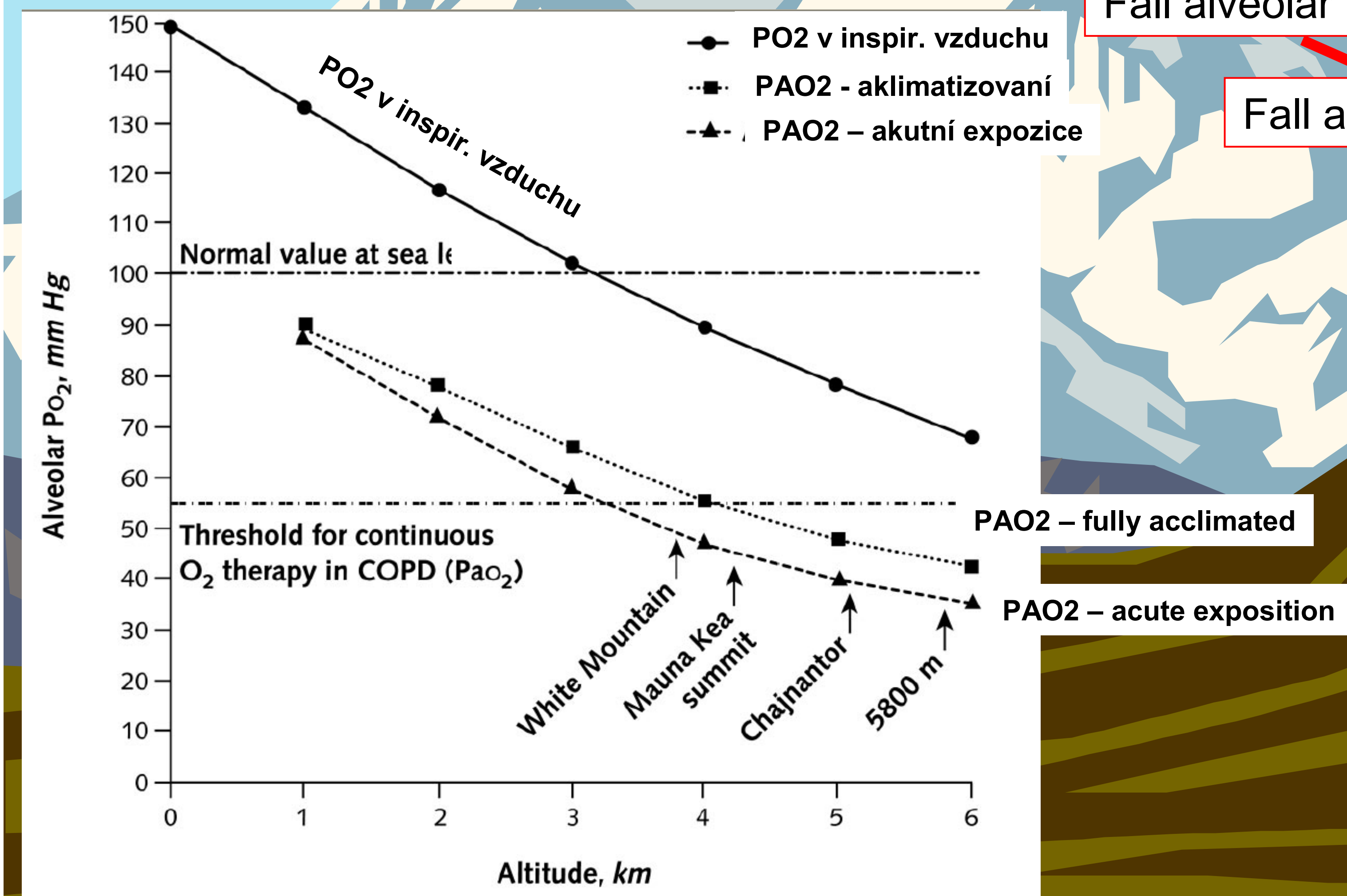
Effects of Altitudes higher than 2000 m/ 6500 ft Above sea level, Ambient press < 80 kPa

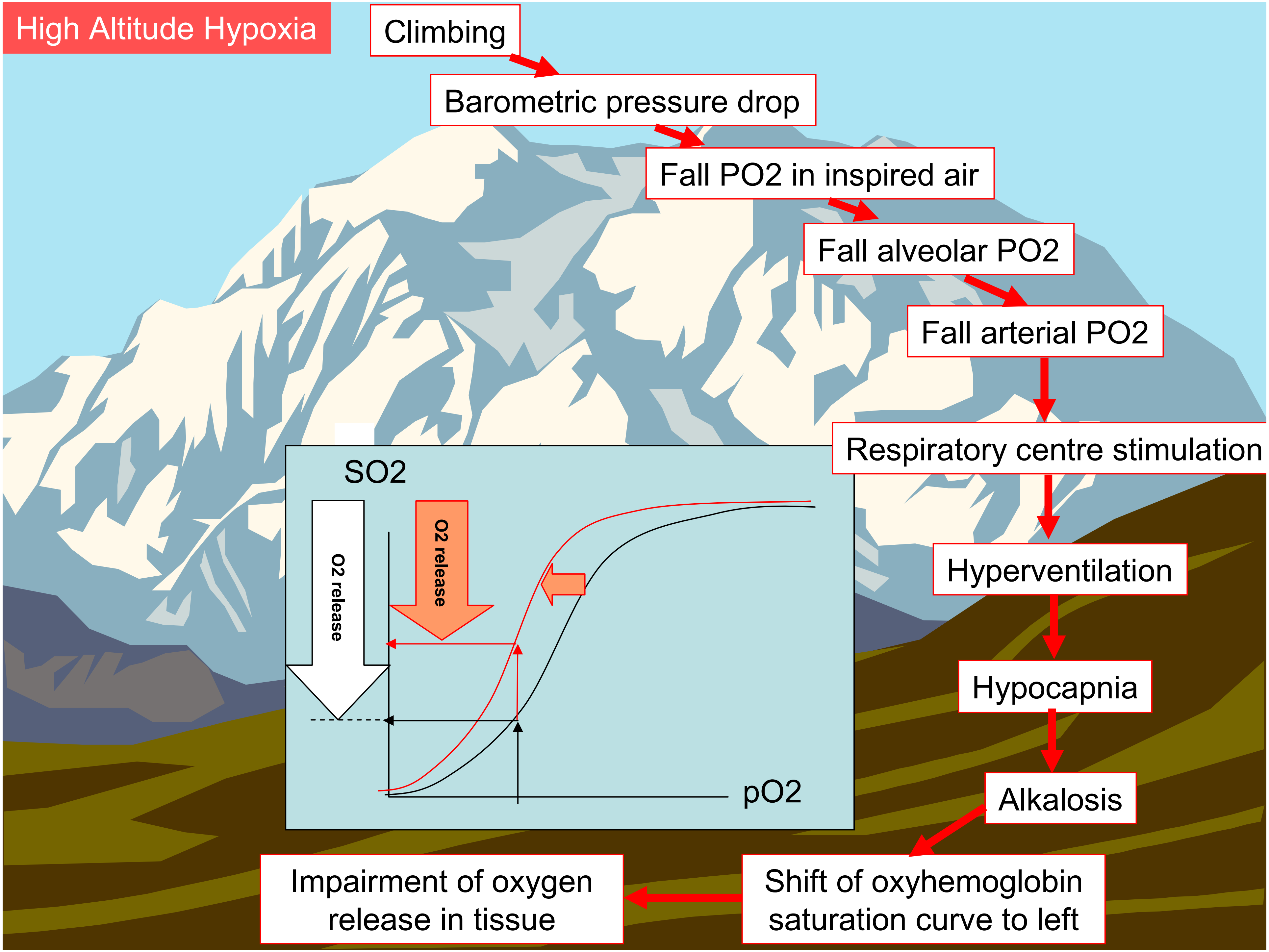
Type I or Type II „Respiratory Insuficiency“?



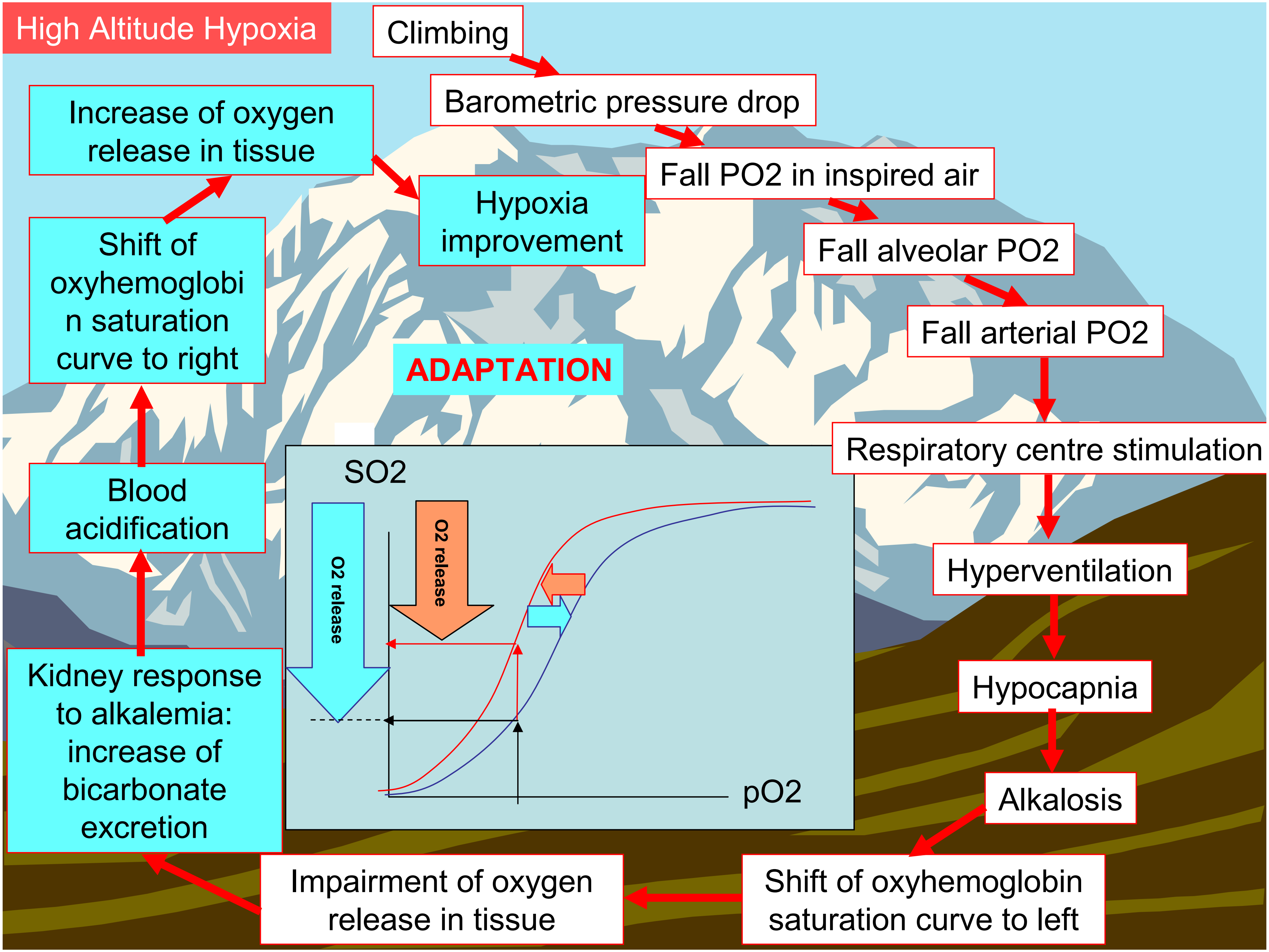
High Altitude Hypoxia

Climbing → Barometric pressure drop → Fall PO2 in inspired air → Fall alveolar PO2 → Fall arterial PO2





High Altitude Hypoxia
Climbing
Barometric pressure drop
Fall PO2 in inspired air
Fall alveolar PO2
Fall arterial PO2
Respiratory centre stimulation
Hyperventilation
Hypocapnia
Alkalosis
Shift of oxyhemoglobin saturation curve to left
Impairment of oxygen release in tissue
SO2
O2 release
O2 release
pO2



High Altitude Hypoxia
Climbing
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Fall PO2 in inspired air
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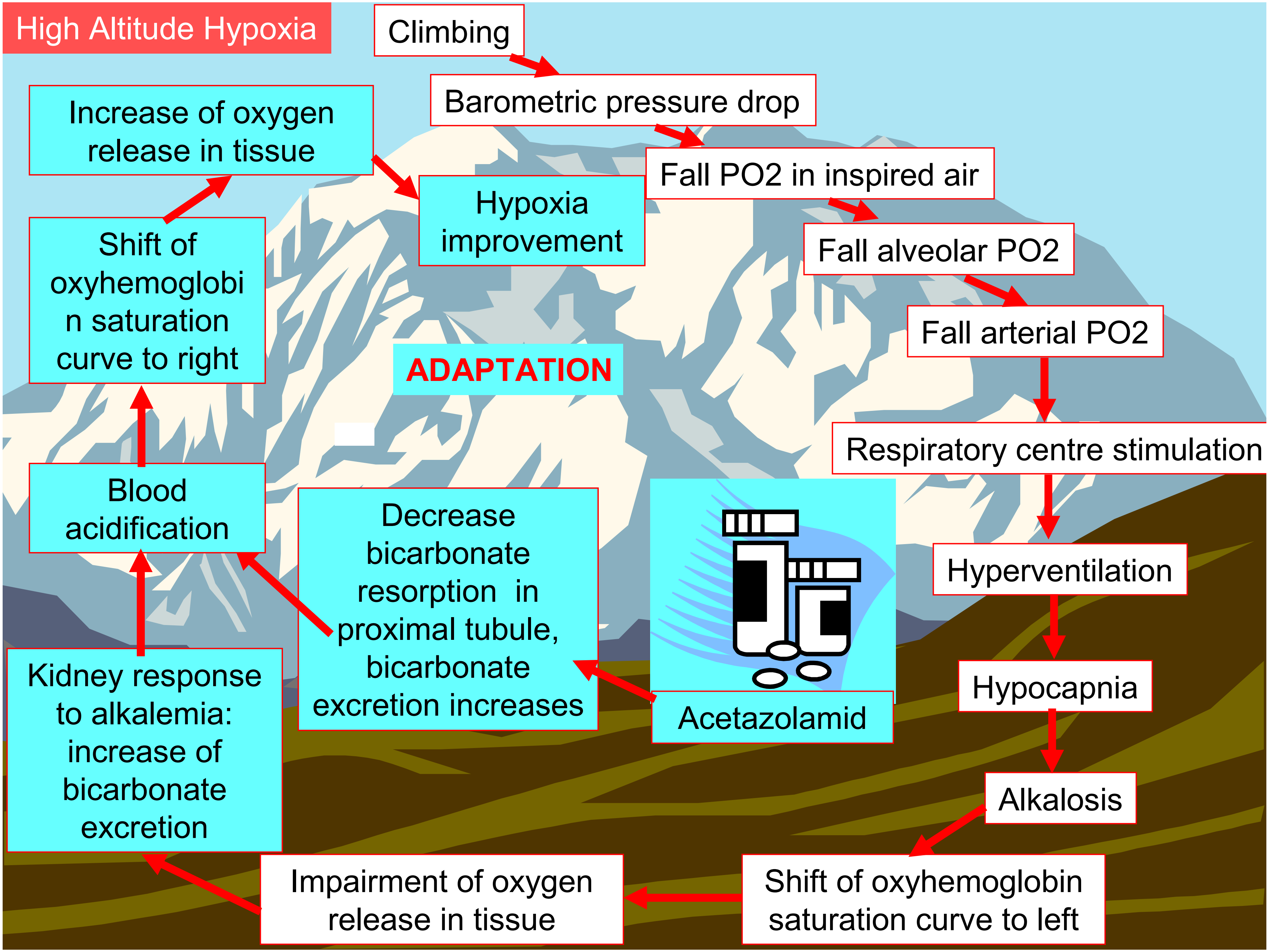
Fall arterial PO2
Respiratory centre stimulation
Hyperventilation
Hypocapnia
Alkalosis
Shift of oxyhemoglobin saturation curve to left
Impairment of oxygen release in tissue
Kidney response to alkalemia: increase of bicarbonate excretion
Blood acidification
Shift of oxyhemoglobi n saturation curve to right
Increase of oxygen release in tissue
Hypoxia improvement
ADAPTATION
SO2
O2 release
O2 release
pO2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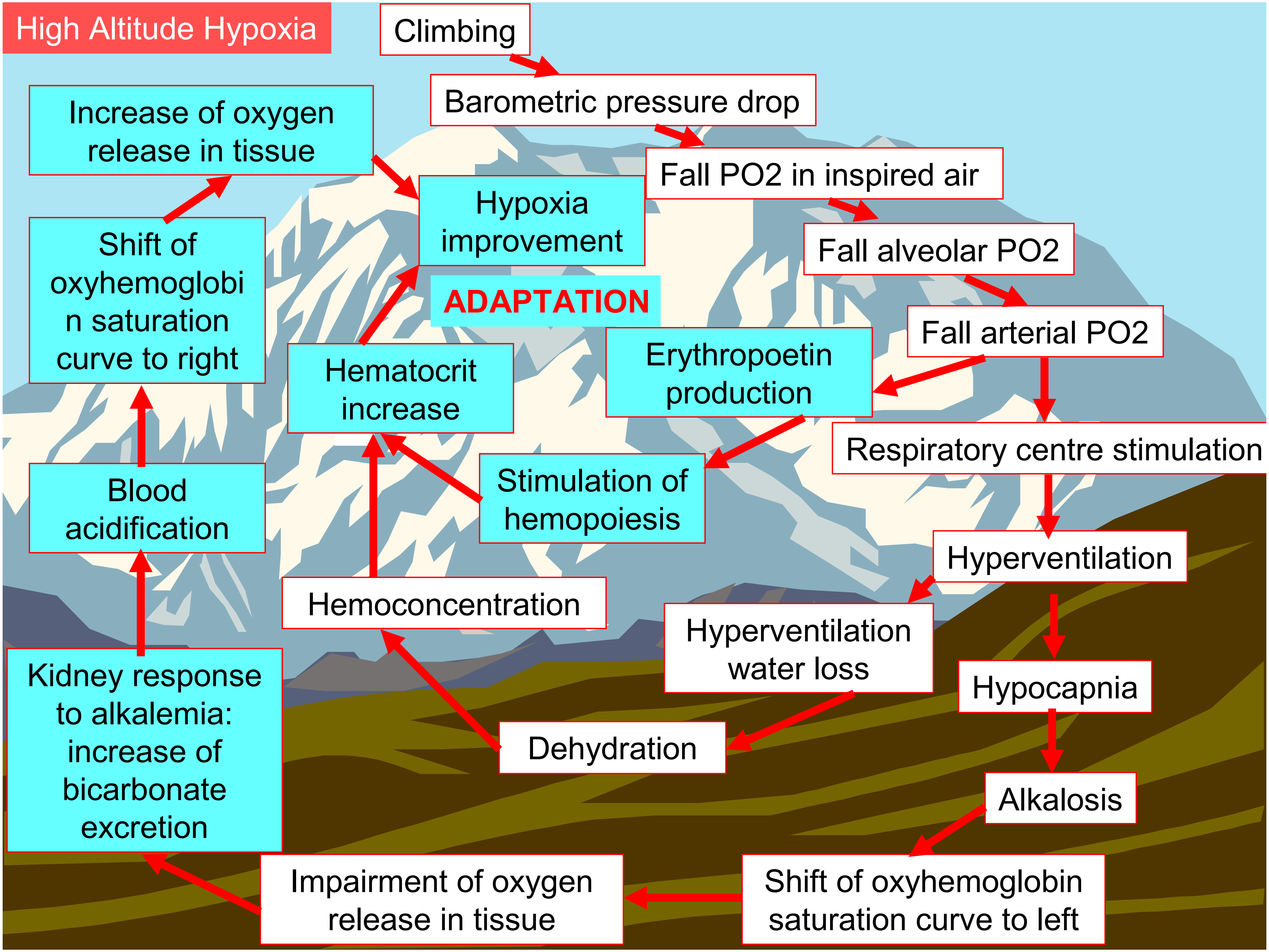
Climbing
Barometric pressure drop
Fall PO2 in inspired air
Fall alveolar PO2
Fall arterial PO2
Respiratory centre stimulation
Hyperventilation
Hypocapnia
Alkalosis
Shift of oxyhemoglobin saturation curve to left
Impairment of oxygen release in tissue
Kidney response to alkalemia: increase of bicarbonate excretion
Blood acidification
Shift of oxyhemoglobin saturation curve to right
Increase of oxygen release in tissue
Hypoxia improvement
ADAPTATION
Decrease bicarbonate resorption in proximal tubule, bicarbonate excretion increases
Acetazolamid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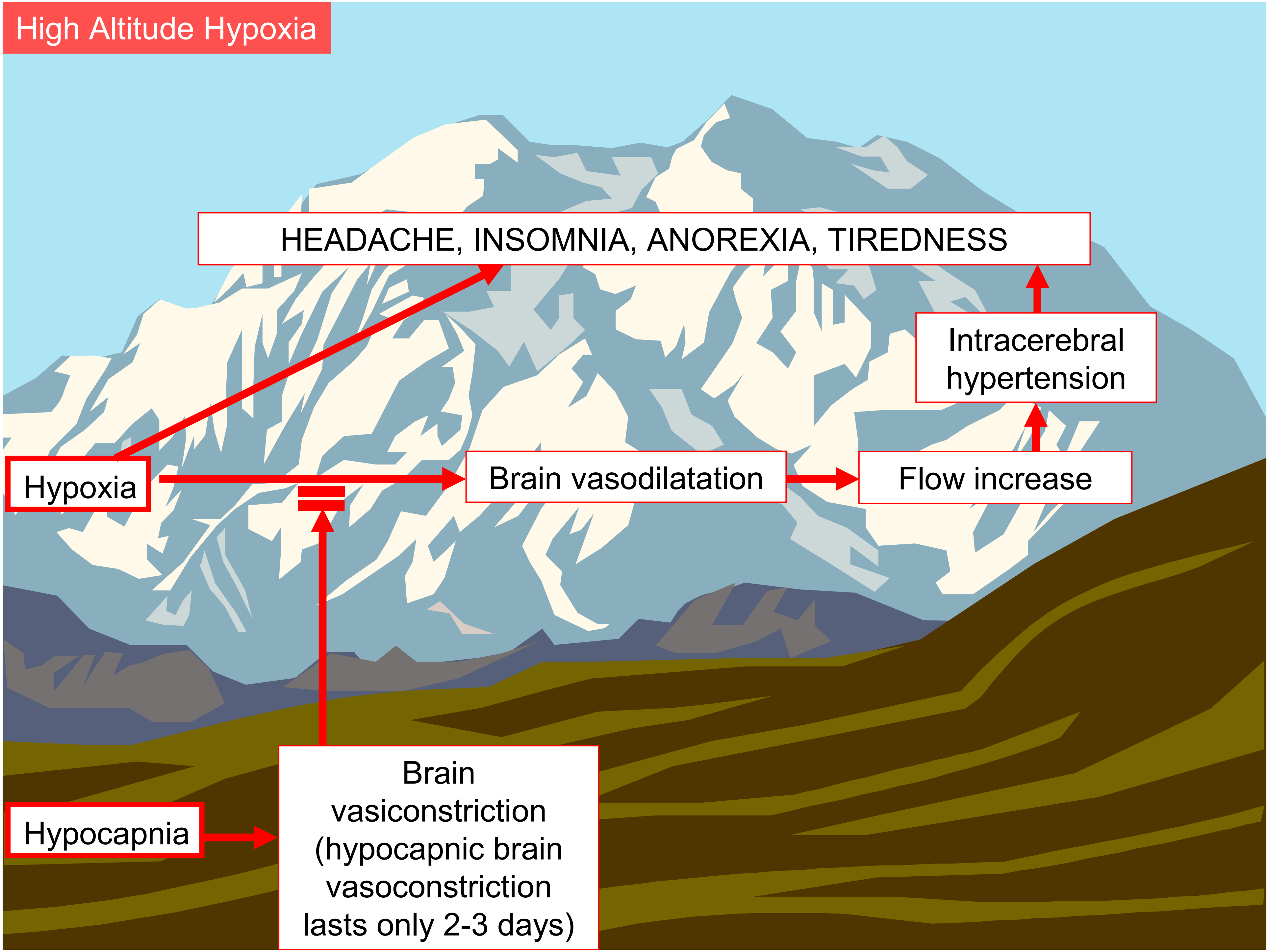
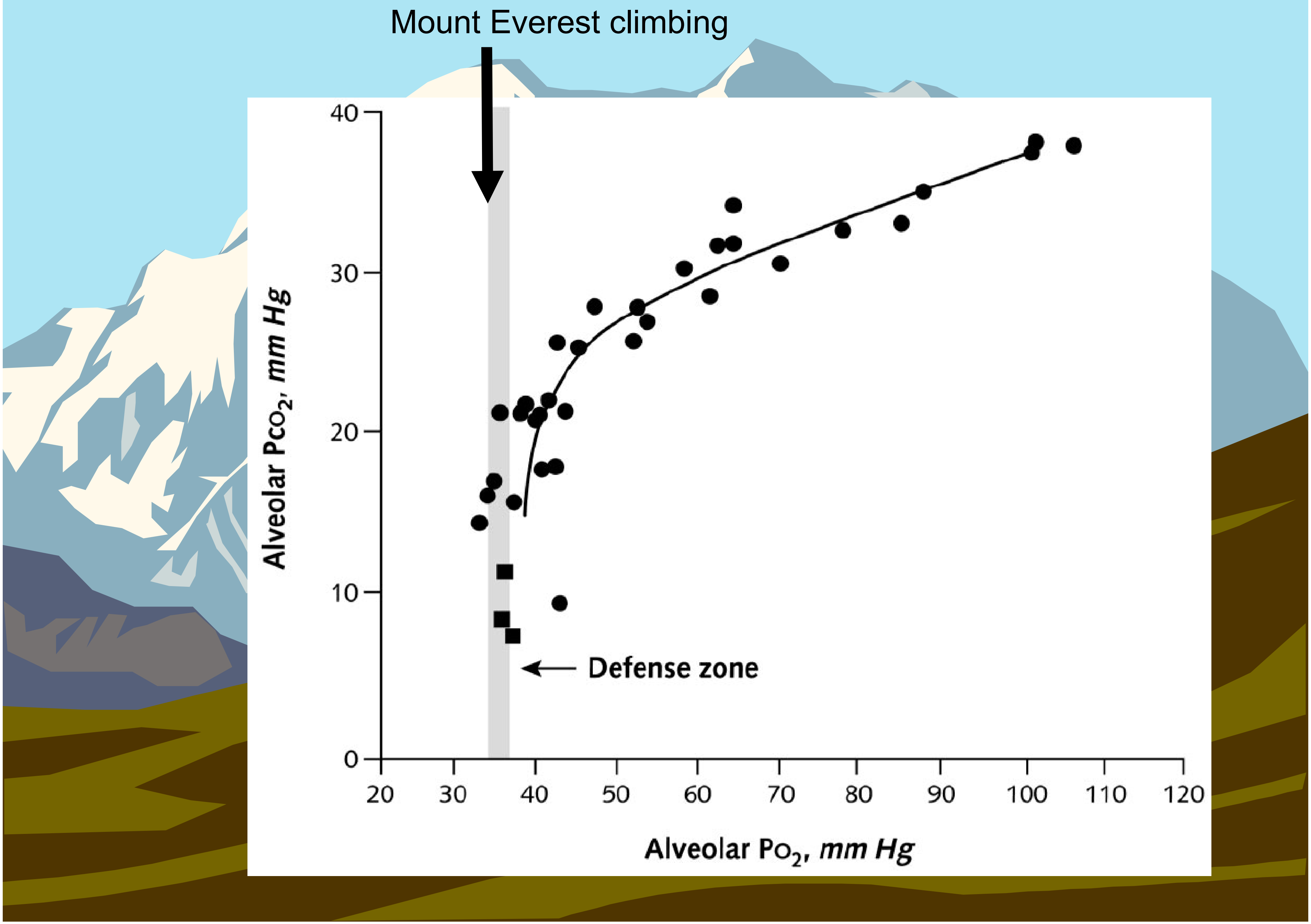
Blood acidification
Shift of oxyhemoglobi n saturation curve to right
Increase of oxygen release in tissue
Hypoxia improvement
ADAPTATION
Hematocrit increase
Erythropoetin production
Stimulation of hemopoiesis
Hemoconcentration
Hyperventilation water loss
Dehydration


High Altitude Hypoxia
HEADACHE, INSOMNIA, ANOREXIA, TIREDNESS
Intracerebral hypertension
Hypoxia
Brain vasodilatation
Flow increase
Hypocapnia
Brain vasiconstriction (hypocapnic brain vasoconstriction lasts only 2-3 days)

High Altitude Hypoxia

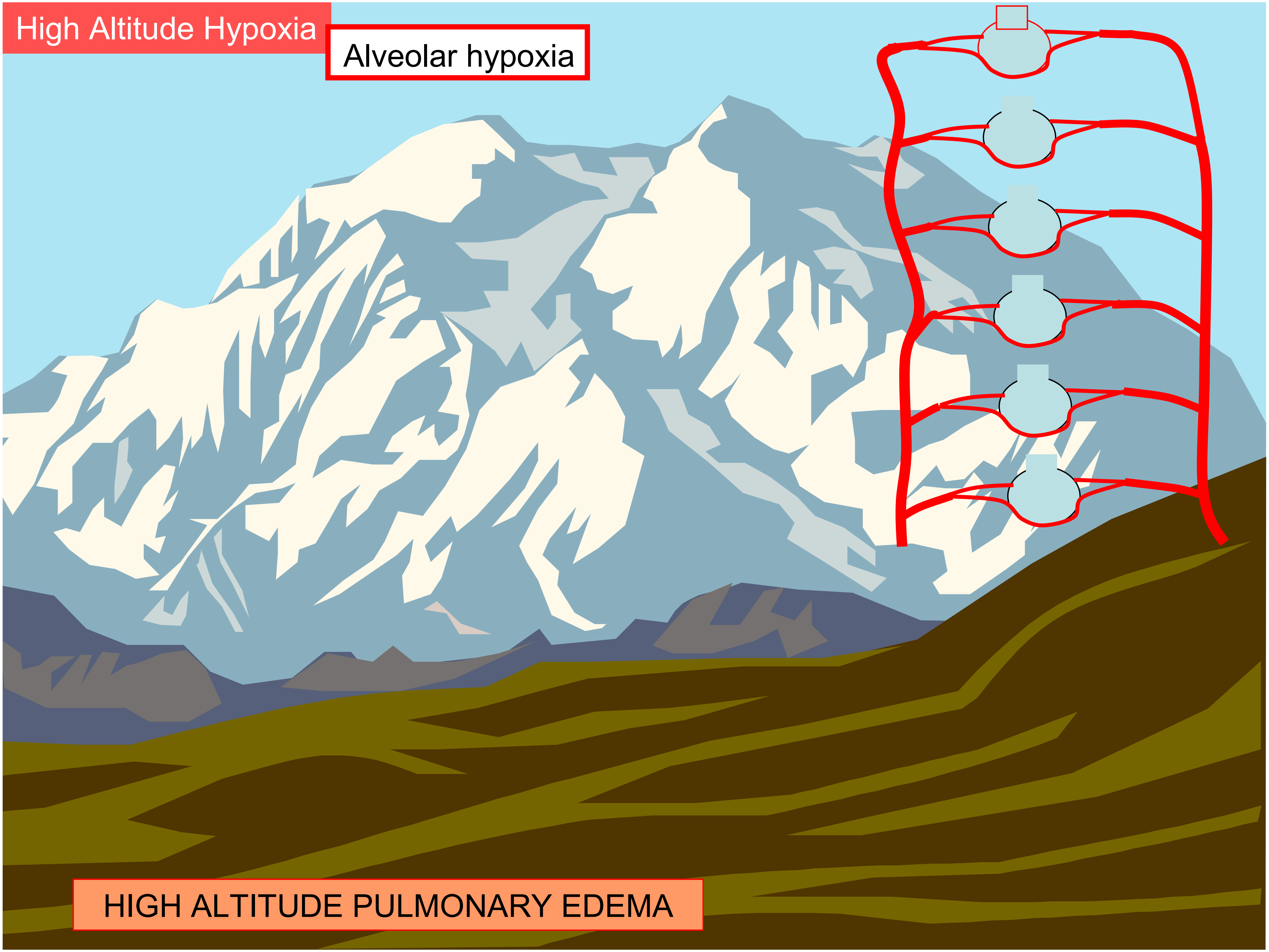


High altitude disease complication

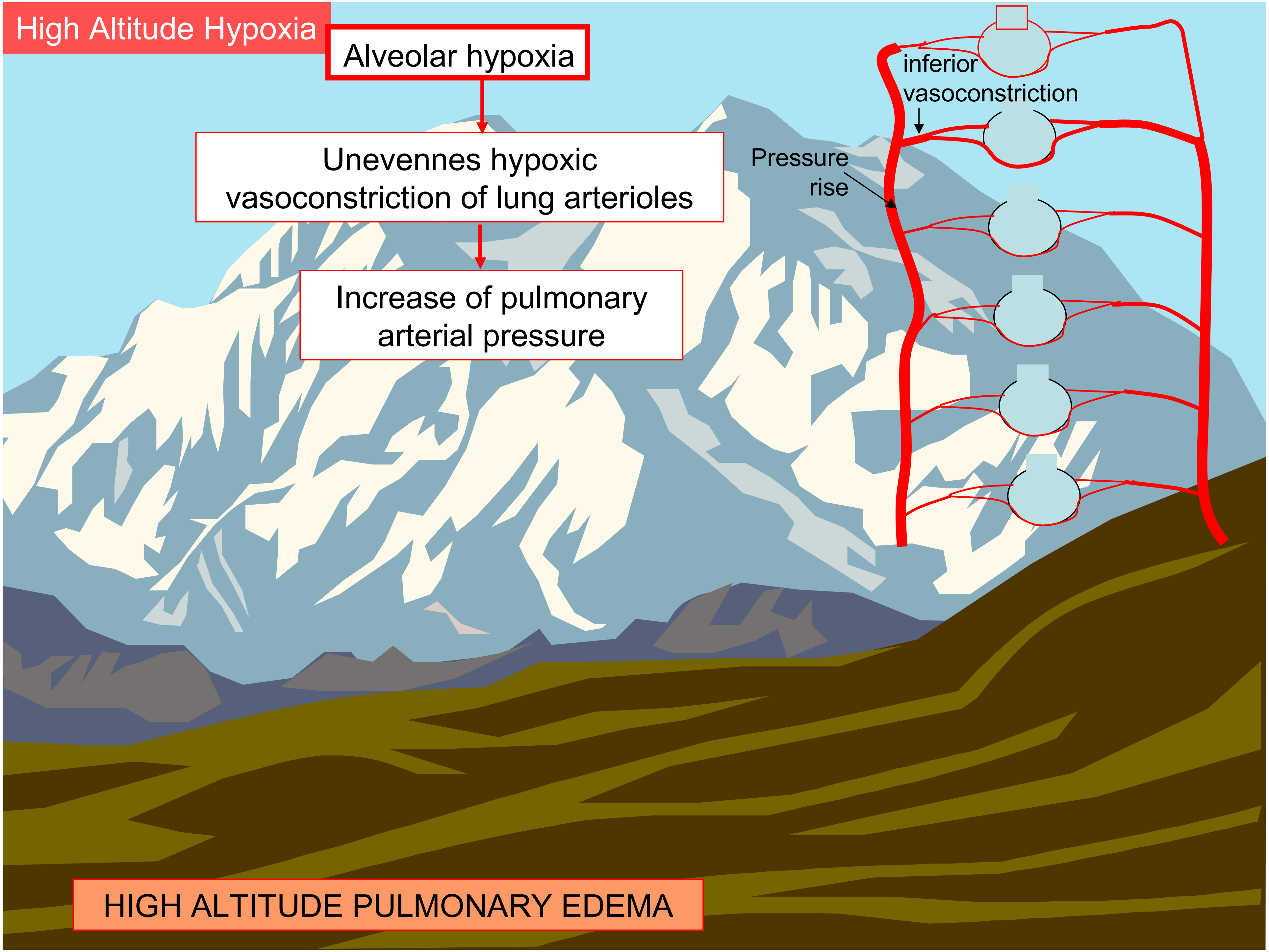
HIGH ALTITUDE PULMONARY EDEMA

HIGH ALTITUDE BRAIN EDEMA

RIGHT VENTRICULAR INSUFFICIENCY



High Altitude Hypoxia
Alveolar hypoxia
HIGH ALTITUDE PULMONARY EDEMA



High Altitude Hypoxia
Alveolar hypoxia
Unevennes hypoxic vasoconstriction of lung arterioles
Increase of pulmonary arterial pressure
inferior vasoconstriction
Pressure rise
HIGH ALTITUDE PULMONARY EDEMA

Hypoxie výšková

Alveolar hypoxia

↓

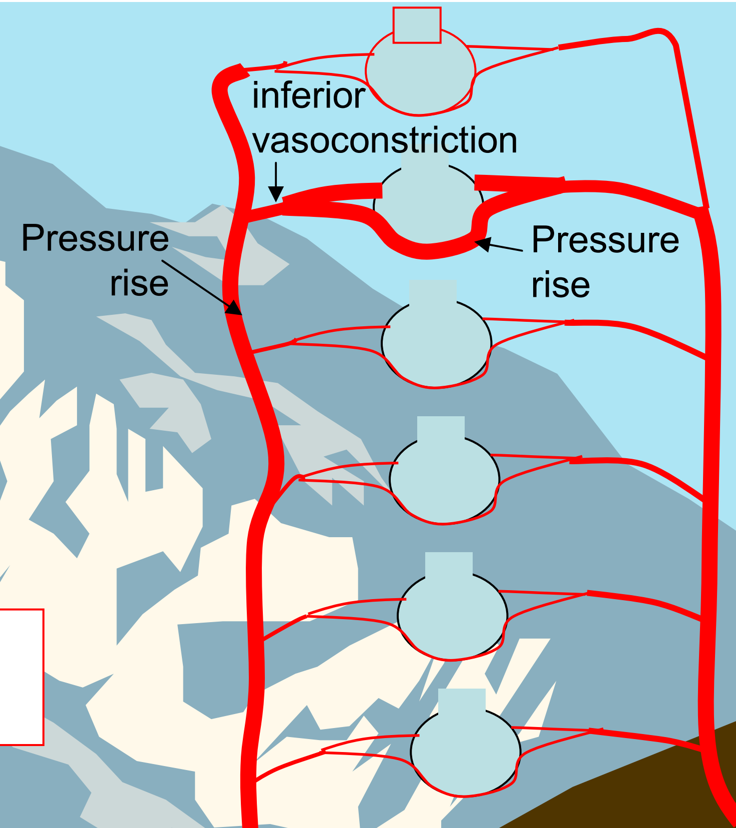
Unevennes hypoxic vasoconstriction of lung arterioles

↓

Increase of pulmonary arterial pressure

↓

Pressure rise in unprotected capillaries



HIGH ALTITUDE PULMONARY EDEMA

Hypoxie výšková

Alveolar hypoxia

↓

Unevennes hypoxic vasoconstriction of lung arterioles

↓

Increase of pulmonary arterial pressure

↓

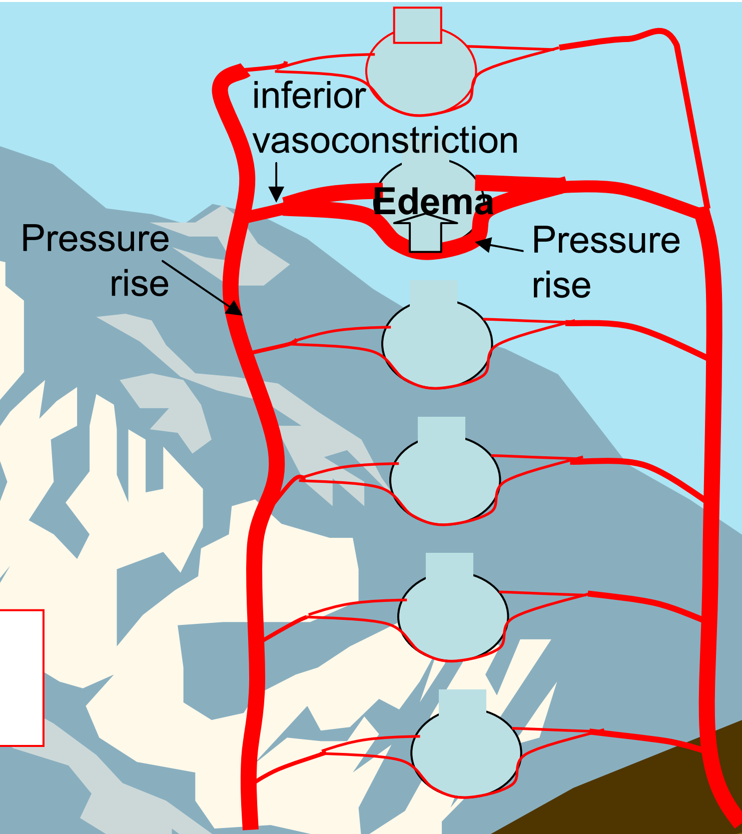
Pressure rise in unprotected capillaries

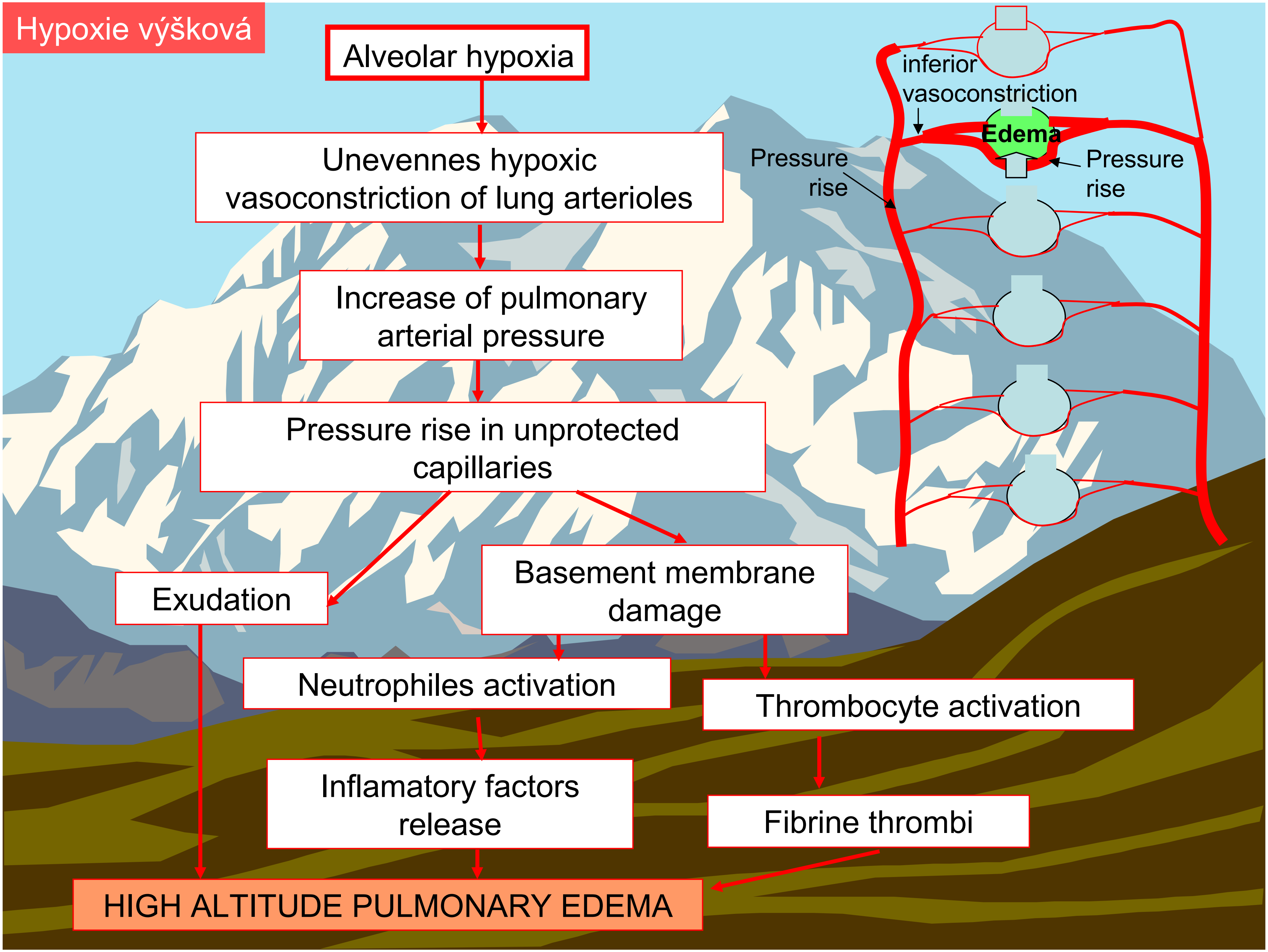
↓

Exudation

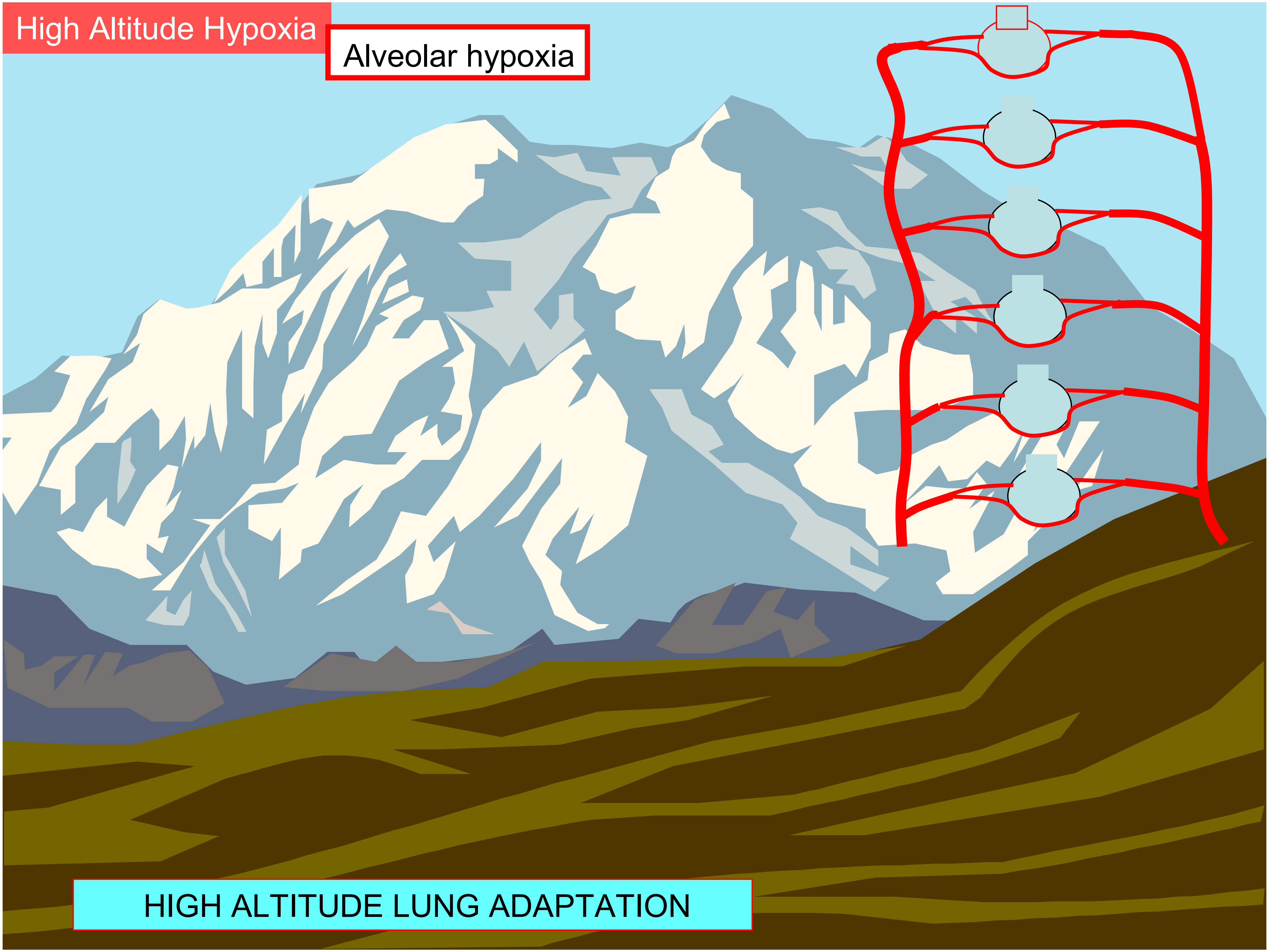
↓

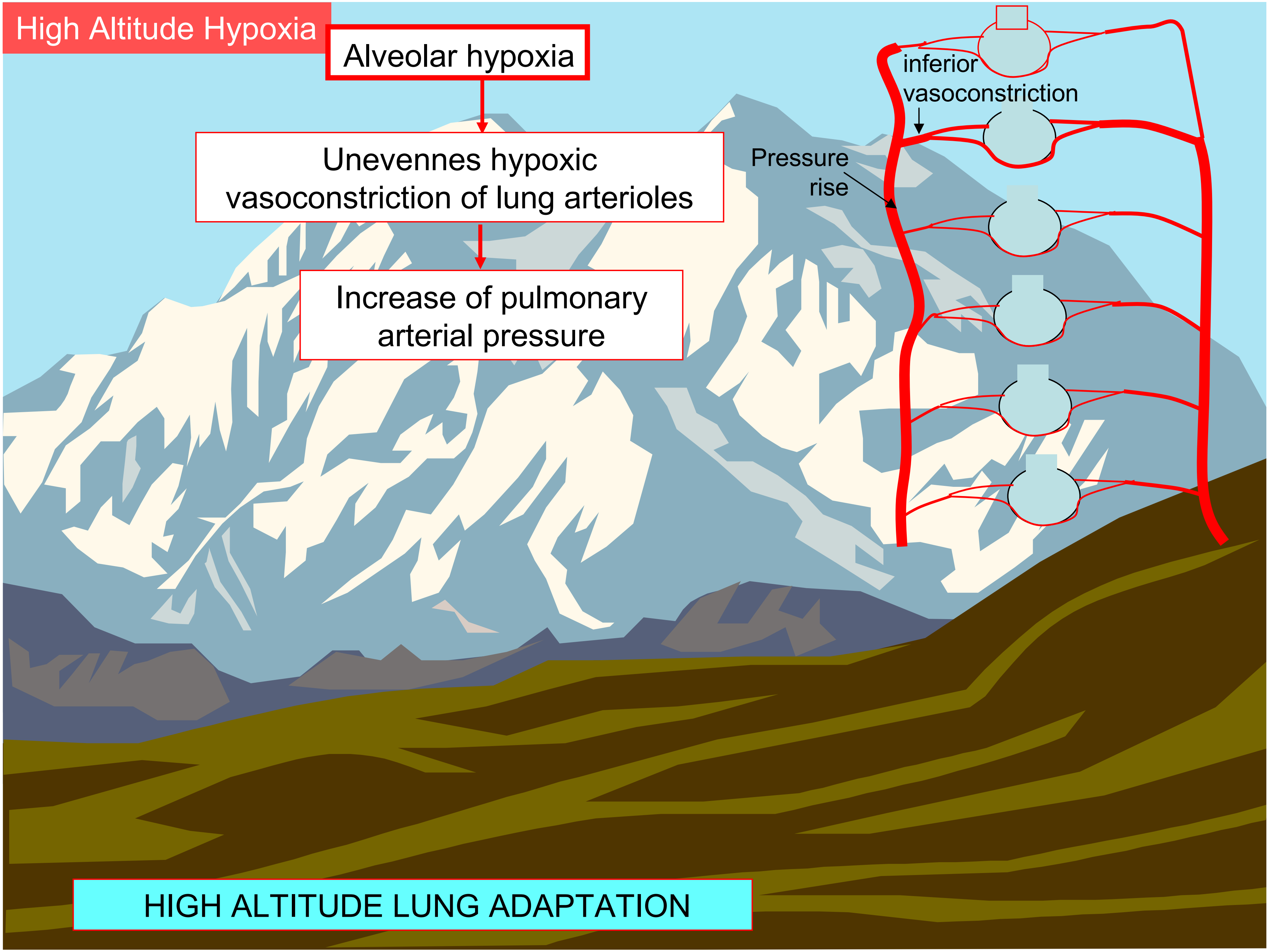
HIGH ALTITUDE PULMONARY EDEMA





Hypoxie výšková
Alveolar hypoxia
Unevennes hypoxic vasoconstriction of lung arterioles
Increase of pulmonary arterial pressure
Pressure rise in unprotected capillaries
Exudation
Basement membrane damage
Neutrophiles activation
Thrombocyte activation
Inflamatory factors release
Fibrine thrombi
HIGH ALTITUDE PULMONARY EDEMA
inferior vasoconstriction
Edema
Pressure rise
Pressure rise


High Altitude Hypoxia
Alveolar hypoxia
HIGH ALTITUDE LUNG ADAPTATION


High Altitude Hypoxia
Alveolar hypoxia
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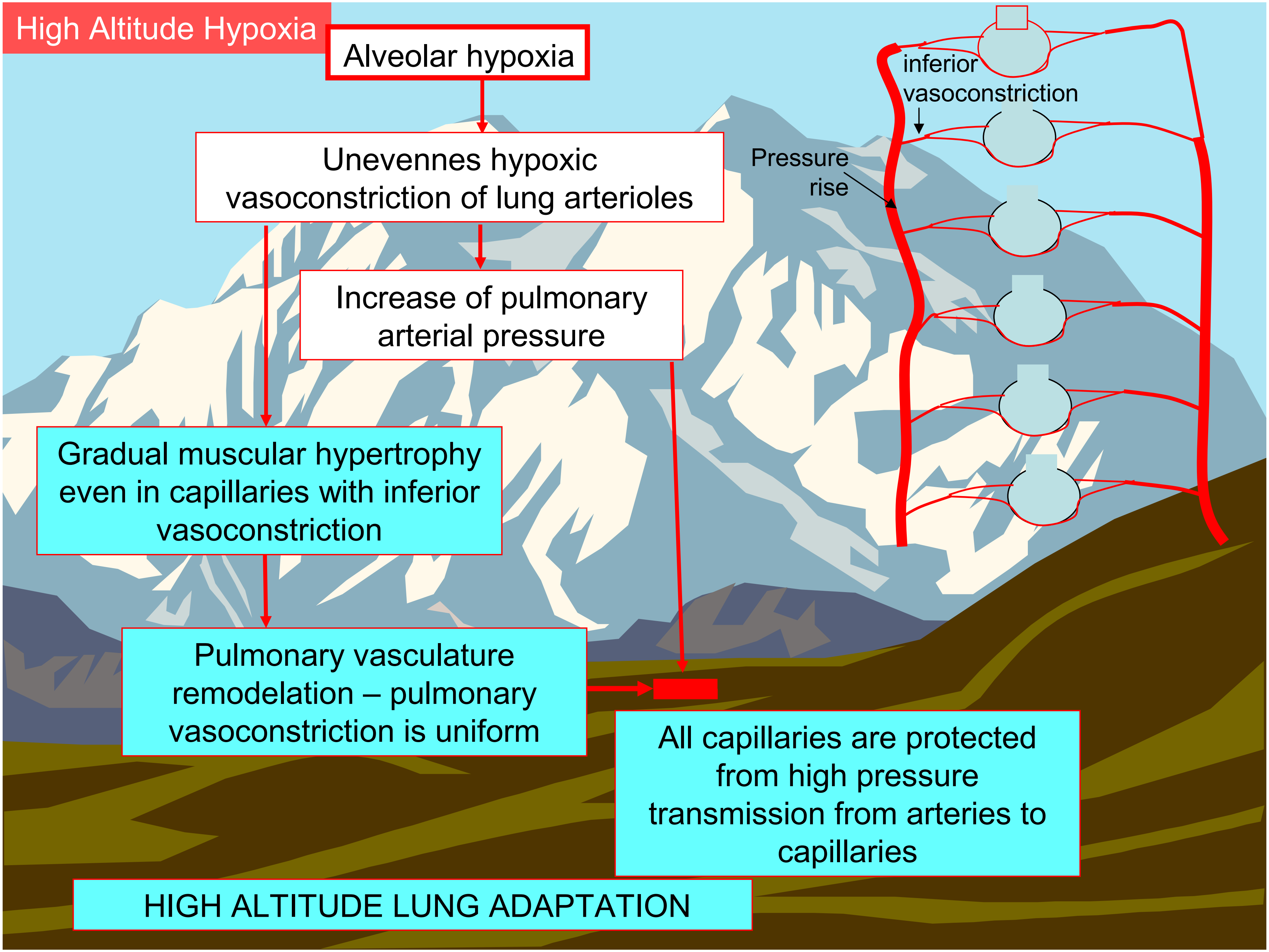
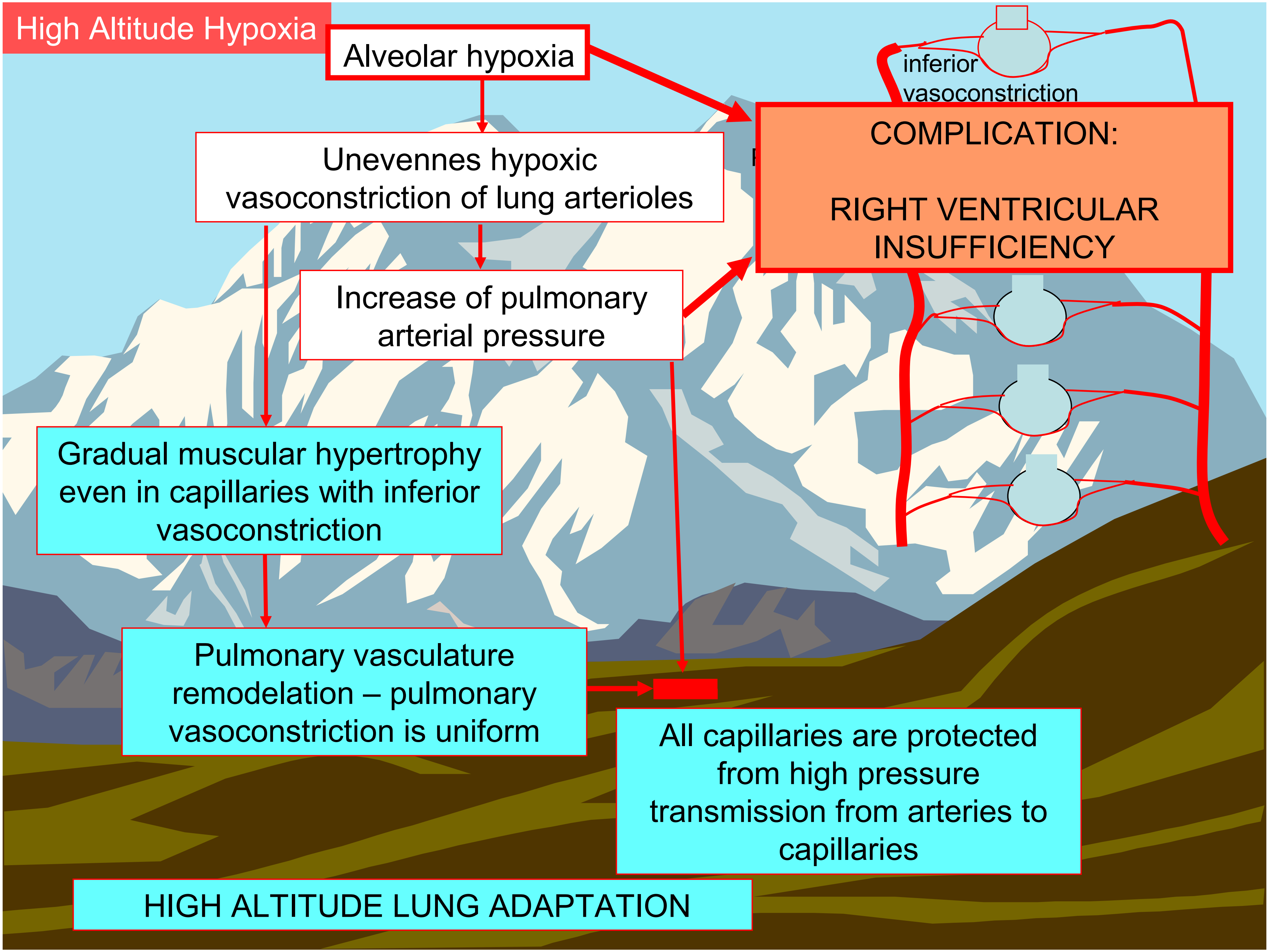
Increase of pulmonary arterial pressure
inferior vasoconstriction
Pressure rise
HIGH ALTITUDE LUNG ADAPTATION


High Altitude Hypoxia
Alveolar hypoxia
Unevennes hypoxic vasoconstriction of lung arterioles
Increase of pulmonary arterial pressure
Gradual muscular hypertrophy even in capillaries with inferior vasoconstriction
Pulmonary vasculature remodelation – pulmonary vasoconstriction is uniform
All capillaries are protected from high pressure transmission from arteries to capillaries
HIGH ALTITUDE LUNG ADAPTATION
inferior vasoconstriction
Pressure rise



High Altitude Hypoxia
Alveolar hypoxia
Unevennes hypoxic vasoconstriction of lung arterioles
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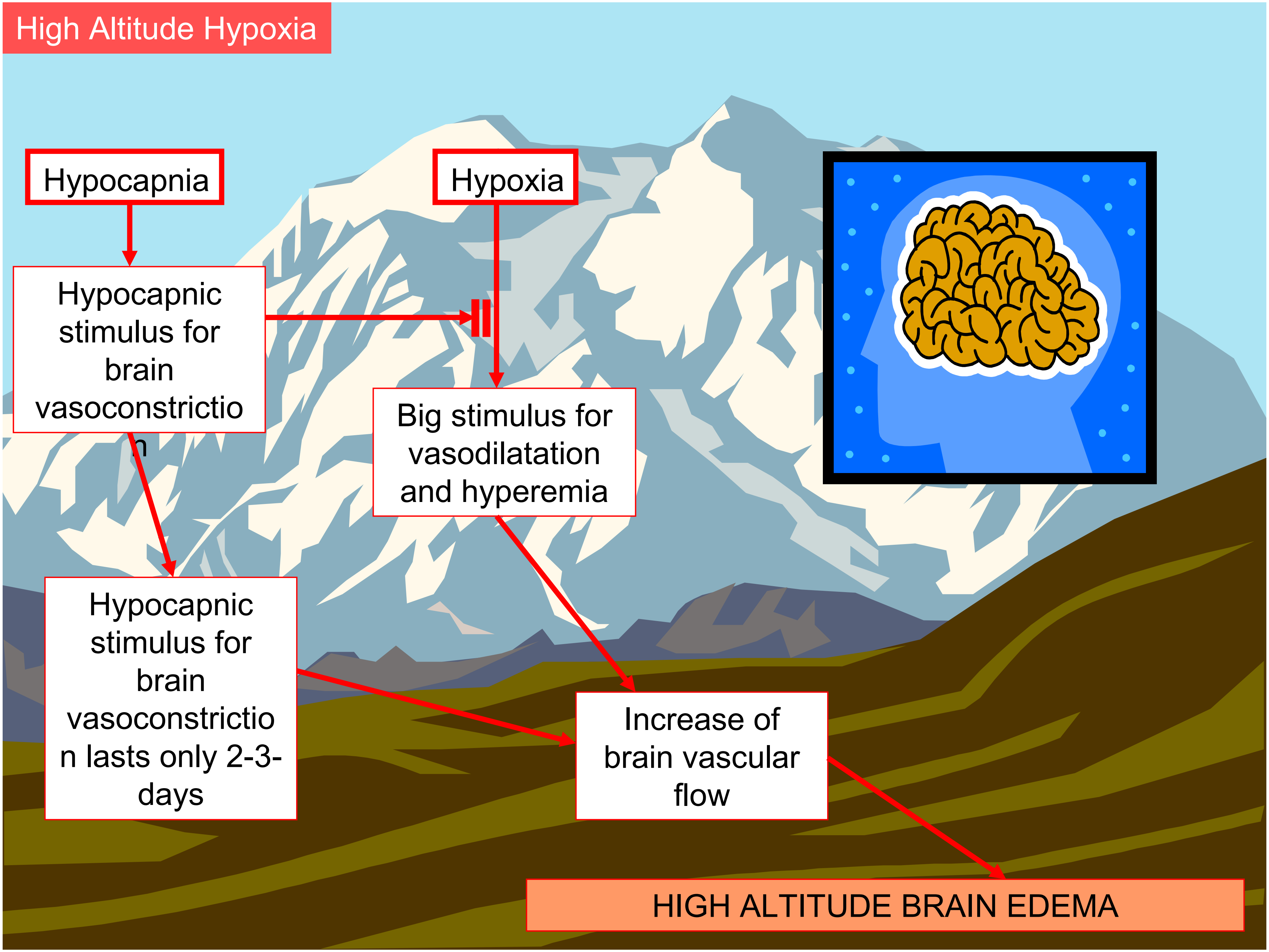
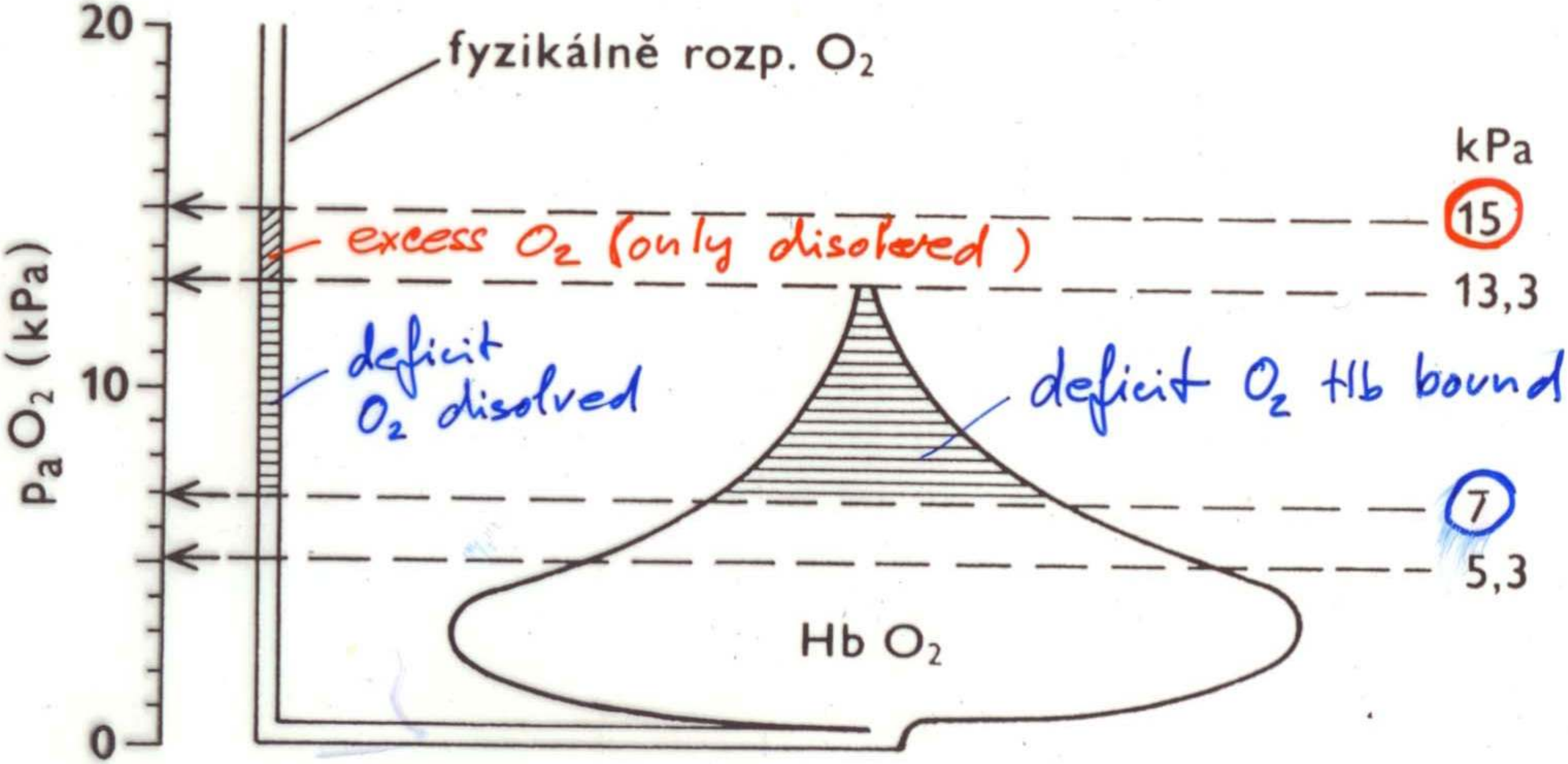
HIGH ALTITUDE LUNG ADAPTATION
inferior vasoconstriction
COMPLICATION:
RIGHT VENTRICULAR INSUFFICIENCY


High Altitude Hypoxia
Hypocapnia
Hypoxia
Hypocapnic stimulus for brain vasoconstrictio n
Big stimulus for vasodilatation and hyperemia
Hypocapnic stimulus for brain vasoconstrictio n lasts only 2-3- days
Increase of brain vascular flow
HIGH ALTITUDE BRAIN EDEMA

END

OF THE LECTURE



20
10
0
p_aO_2 (kPa)
fyzikálně rozp. O_2
kPa
15
13,3
7
5,3
excess O_2 (only disolved)
deficit O_2 disolved
deficit O_2 Hb bound
Hb O_2

Alveolar hypoventilation

- Is a disturbance of the ventilation/perfusion ratio (V_A/Q ratio) when ventilation of an alvelus is insuficient to eliminate CO_2 delivered here by the blood)
- This can be a problem of selected alveoli („local alveolar hypoventilation“) or of all alveoli

In both cases **in the affected alveoli pCO_2 will be increased and pO_2 decreased**.

Heart Defects