# PATHOPHYSIOLOGY OF THE RESPIRATORY SYSTEM

# lecture no. 1
# RESPIRATORY INSUFFICIENCY
# and
# acute (adult) respiratory distress syndrome (ARDS)

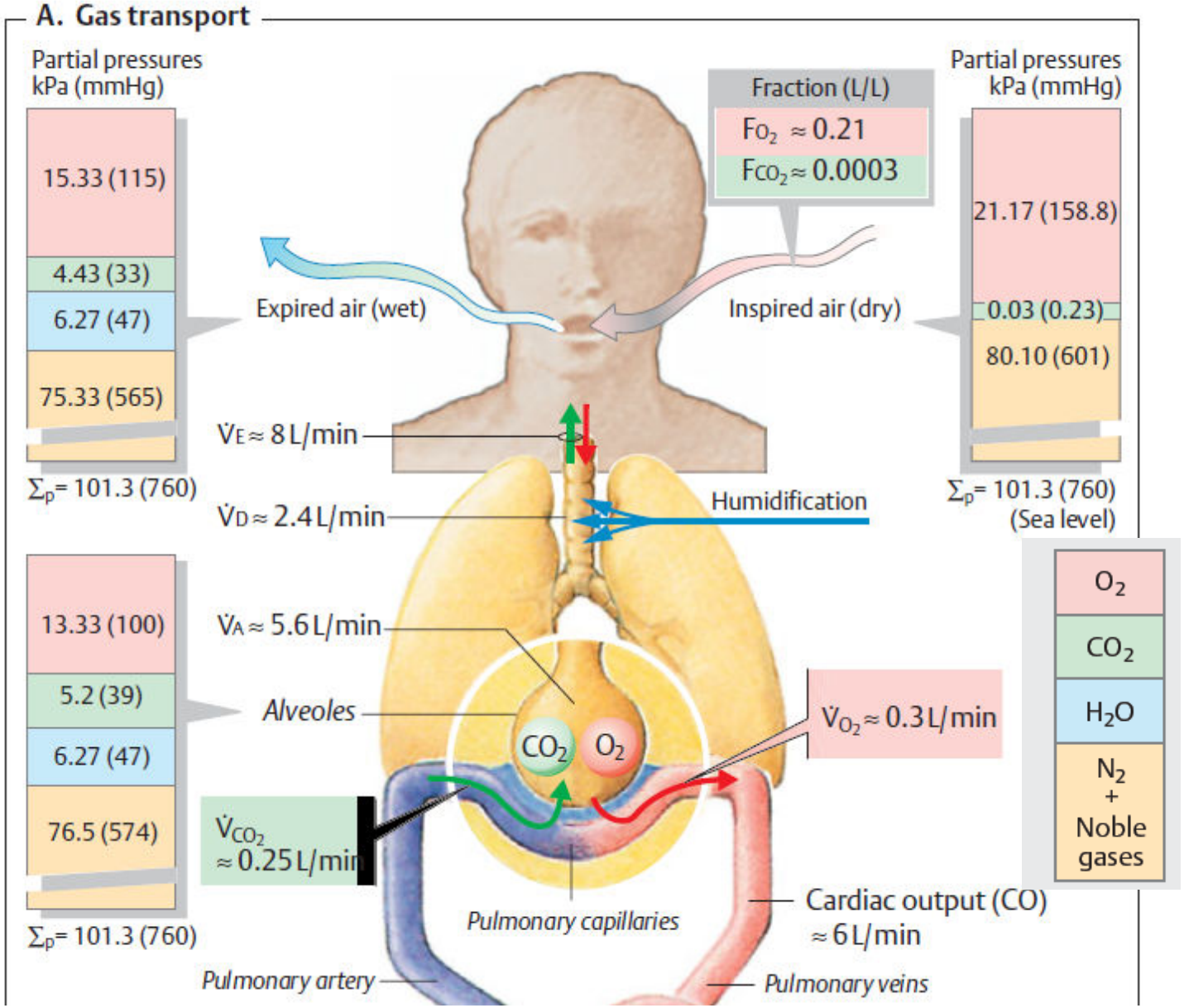
P. Marsalek, (with J. Kofranek, E. Necas),
one of next lectures also by Z. Humlova

# Outline

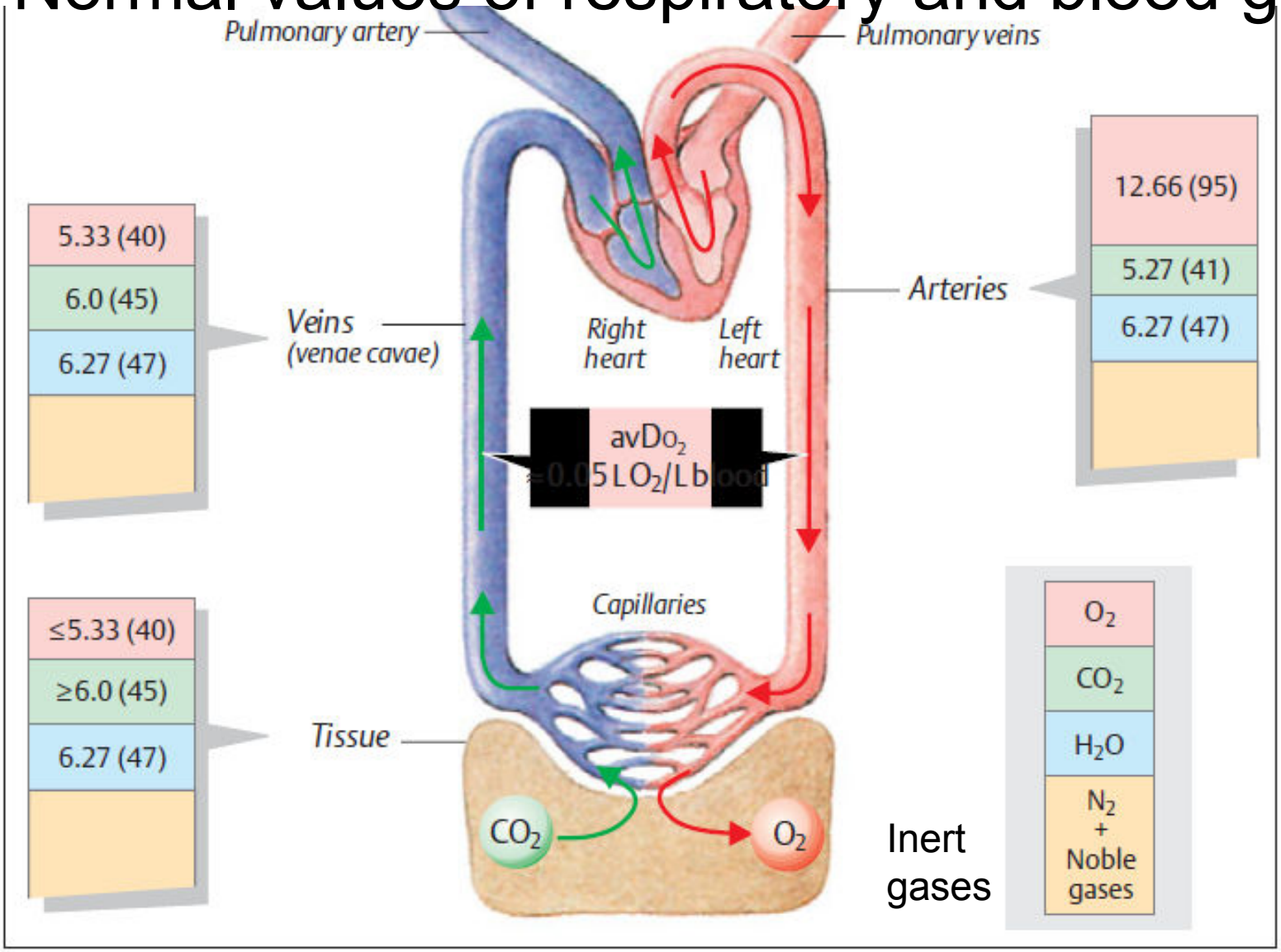
- We use definitions of:
respiratory gases, hypoxia, polycytemia, etc.
- Introduction
- Patophysiology of respiratory insufficiency type 1 and 2
mechanisms of lower
- $p_aO_2$, and
- $p_AO_2$ (in our notation it is $p_{art}O_2$, and $p_{ALV}O_2$ )
in respiratory diseases
  - alveolary hypoventilation
  - diffusion block
  - pulmonary shunt
- Reactive pulmonary hypertension
- Hyperkapnia in respiratory insufficiency type 2 (global)
- ARDS (acute respiratory distress syndrome)
- Remarks about oxygenotherapy

(notation: p: pressure, C: concentration, F: fraction…)

# Normal values of respiratory and blood gases



# Normal values of respiratory and blood gases



# Normal values, definitions

**1atm=**

**=760 mmHg=101 kPa=1000 cm$H_2O$=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**

**$FiO_2$ : fraction of inspired oxygen**

COMMERCE

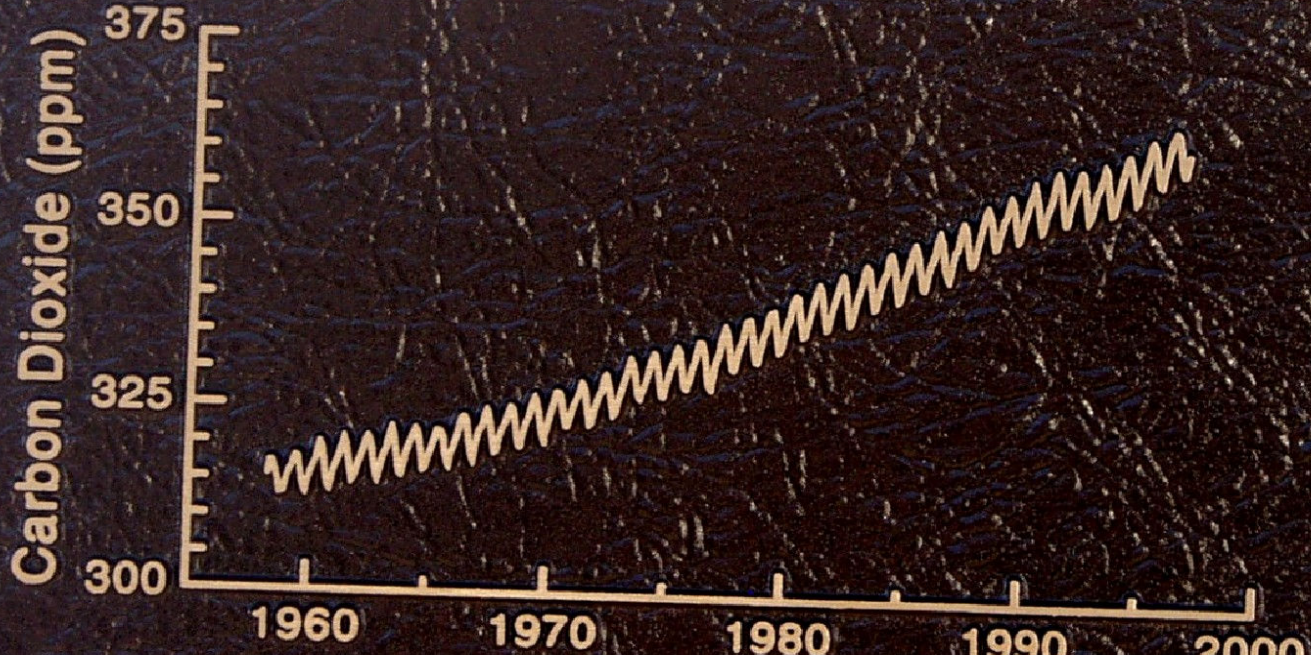
# Keeling Building

NOAA

Named in honor of

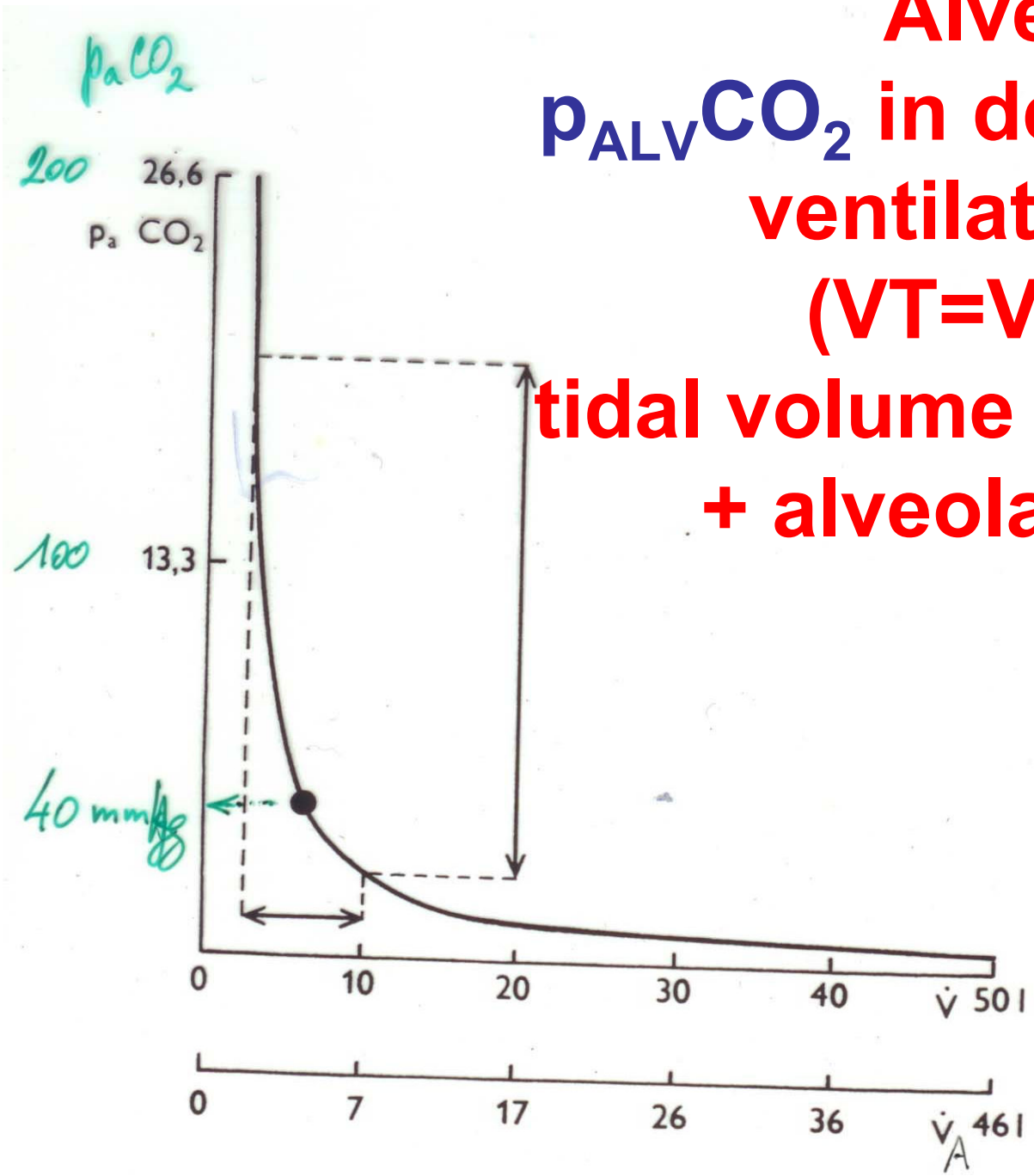
*Professor Charles David Keeling,*
*Scripps Institution of Oceanography,*

who initiated continuous $CO_2$ measurements at this site in 1958.




November 1997

# Alveolar $p_{ALV}CO_2$ in dependence on ventilation V(T) (VT=VD+VA, tidal volume = dead space + alveolar space )



# Eero Antero Mäntyranta

(*1937-+2013) was a Finnish skier and multiple Olympic Champion. With his seven medals from four Winter Olympics, he was one of the most successful skiers Finland has ever produced.

# „Advantageous mutation“ of erytropoietin receptor

Mäntyranta had 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

High Altitude Hypoxia

$O_2$

$CO_2$

Respiratory Hypoxia

Circulatory Hypoxia (ischemic)

Histotoxic Hypoxia

Saccharides
Fats
Proteins

$+ O_2 \rightarrow CO_2$

$H_2O$

*mitochondrion*

*cell*

Bone marrow

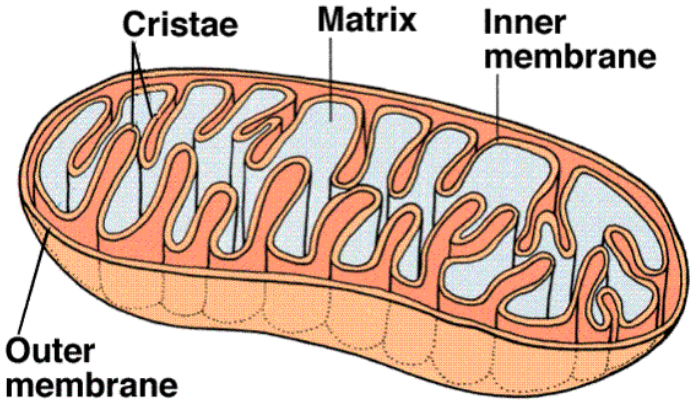
erythropoesis

erythropoetin

pO2

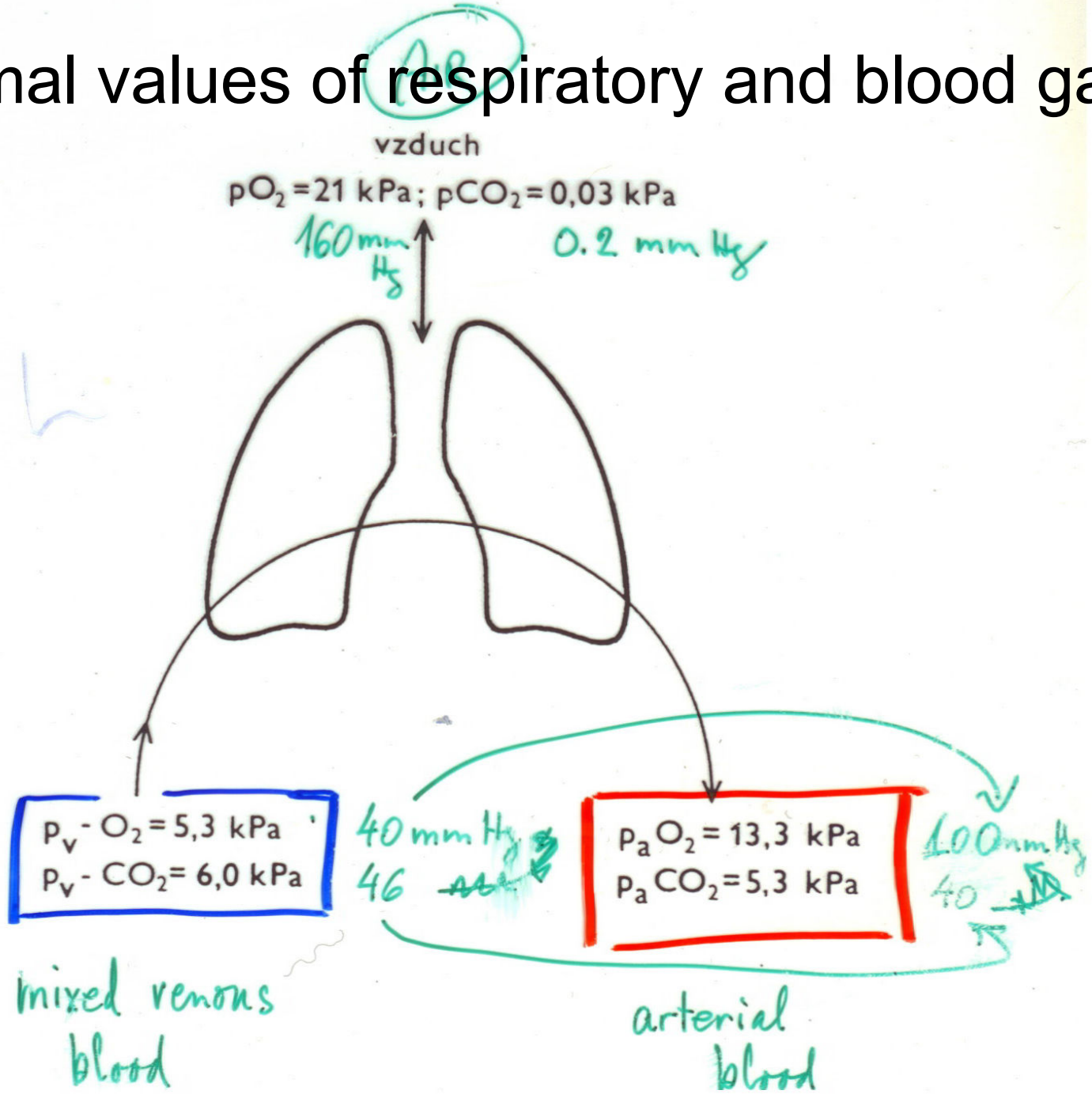
kidneys

Hypoxia from Anemia




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 adequately fulfilled:

- **$p_{art}O_2$ 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**

# RESPIRATORY INSUFFICIENCY

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

Why it is?: 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)
- $p_aCO_2$ is 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 $p_{art}O_2$

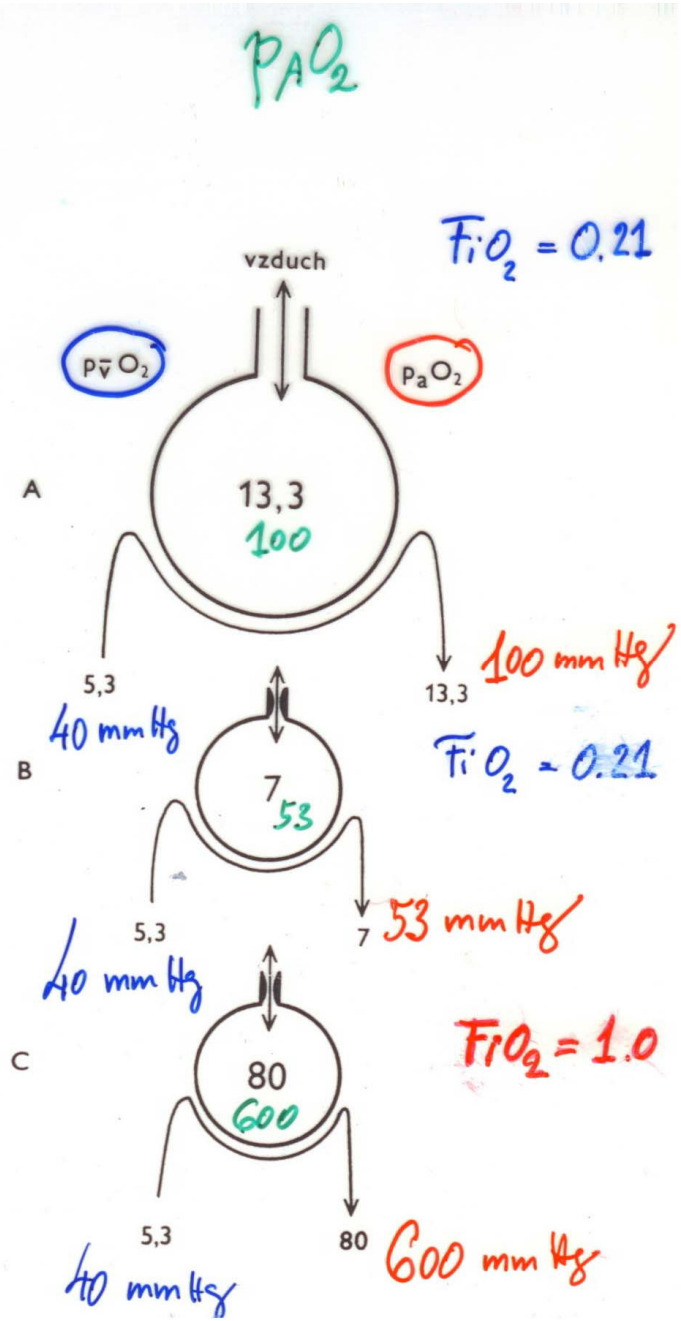
- **Total alveolar hypoventilation**
- **Local alveolar hypoventilation**
- **Pulmonary shunt**
- **Diffusion block**

**(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 (see oxygenotherapy)
- $p_{ALV}O_2$ values lower than 100 mmHg DECREASE oxygen content in the blood significatly

# Oxygenotherapy



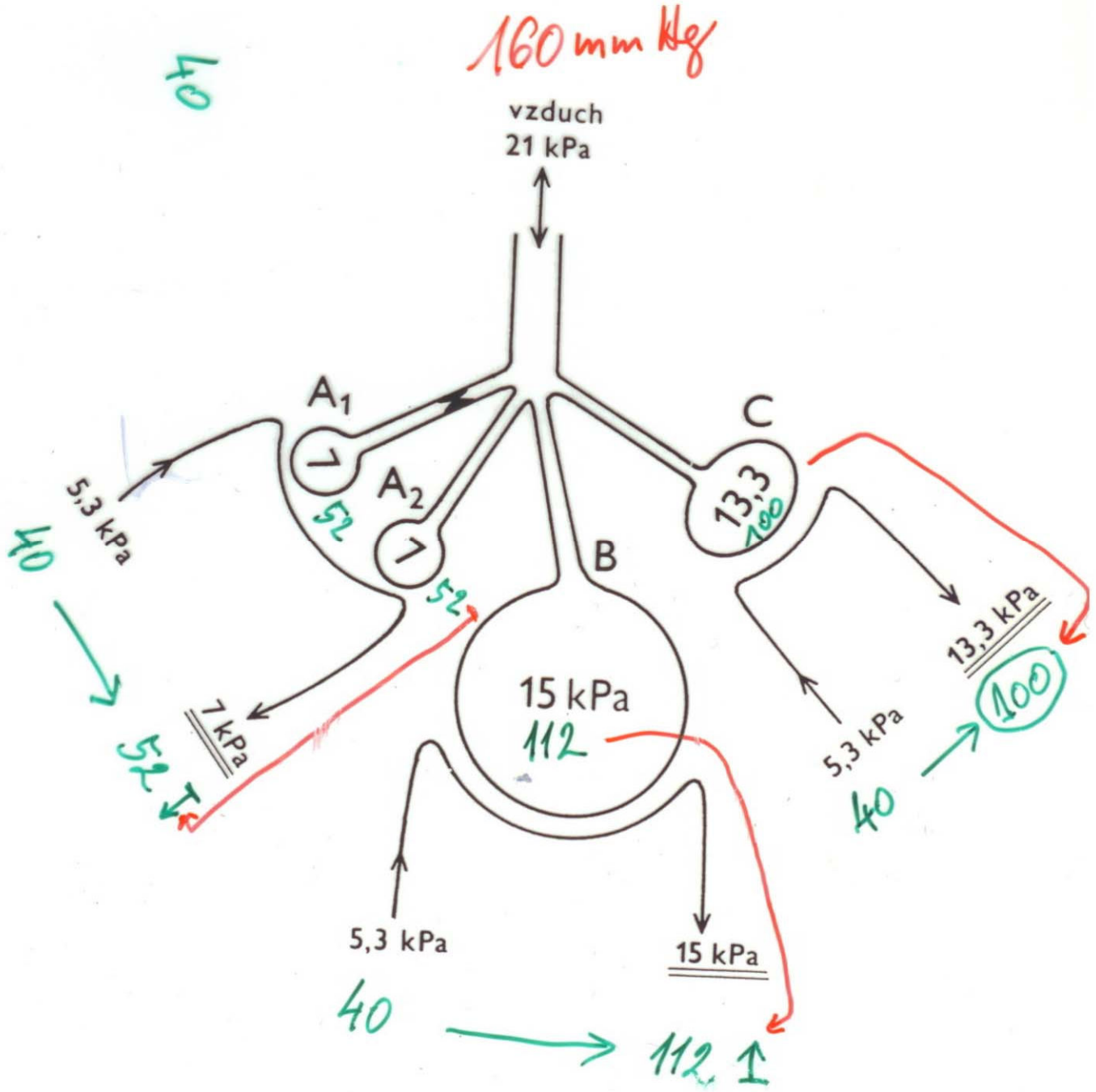

- normal (21 %) $\mathbf{O_2}$ breathing in norm

- normal (21 %) $\mathbf{O_2}$ breathing in pathology

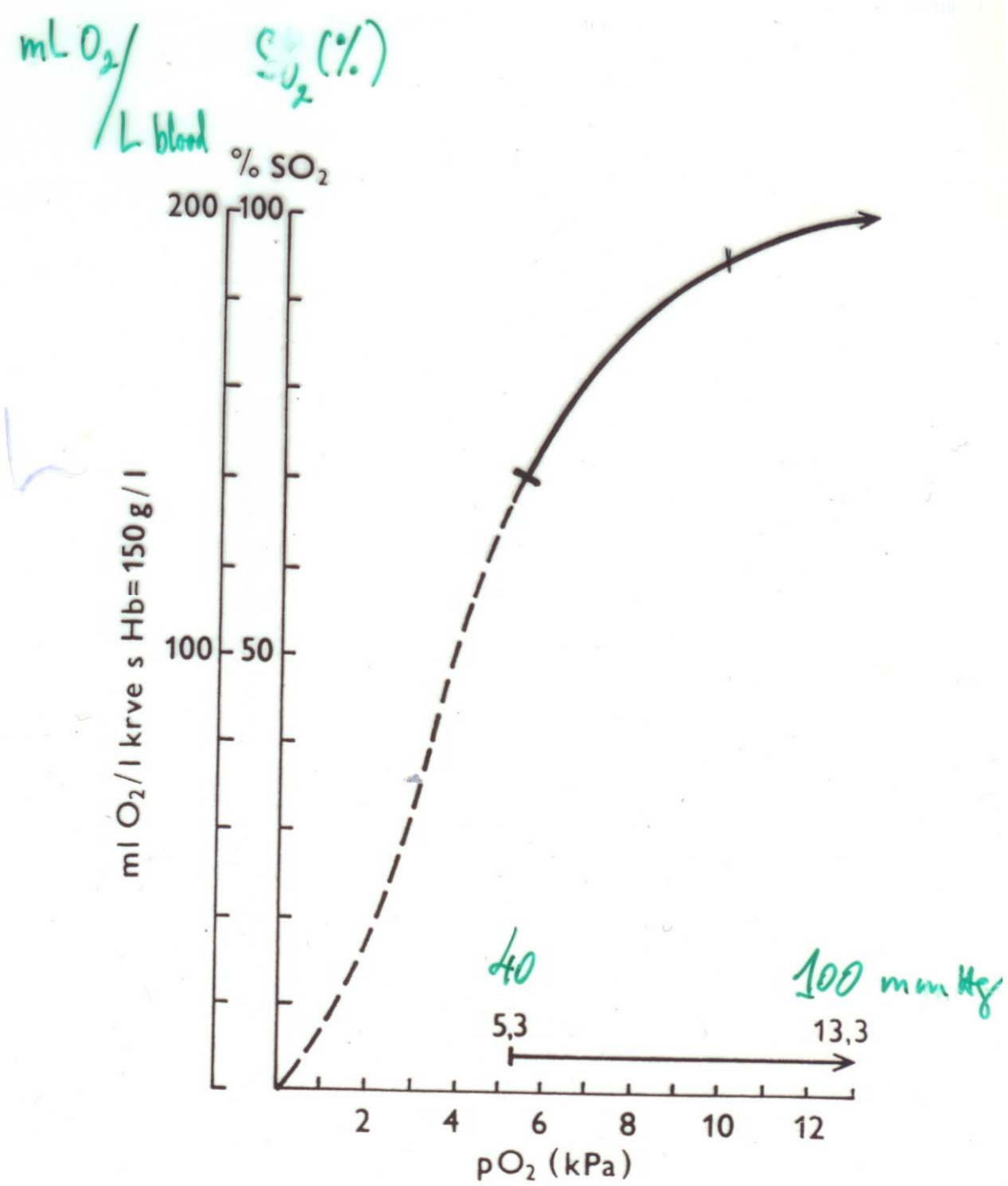
- high (up to 100 %) $\mathbf{O_2}$ breathing in pathol.,can be (even higher = hyperbaric)

# 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

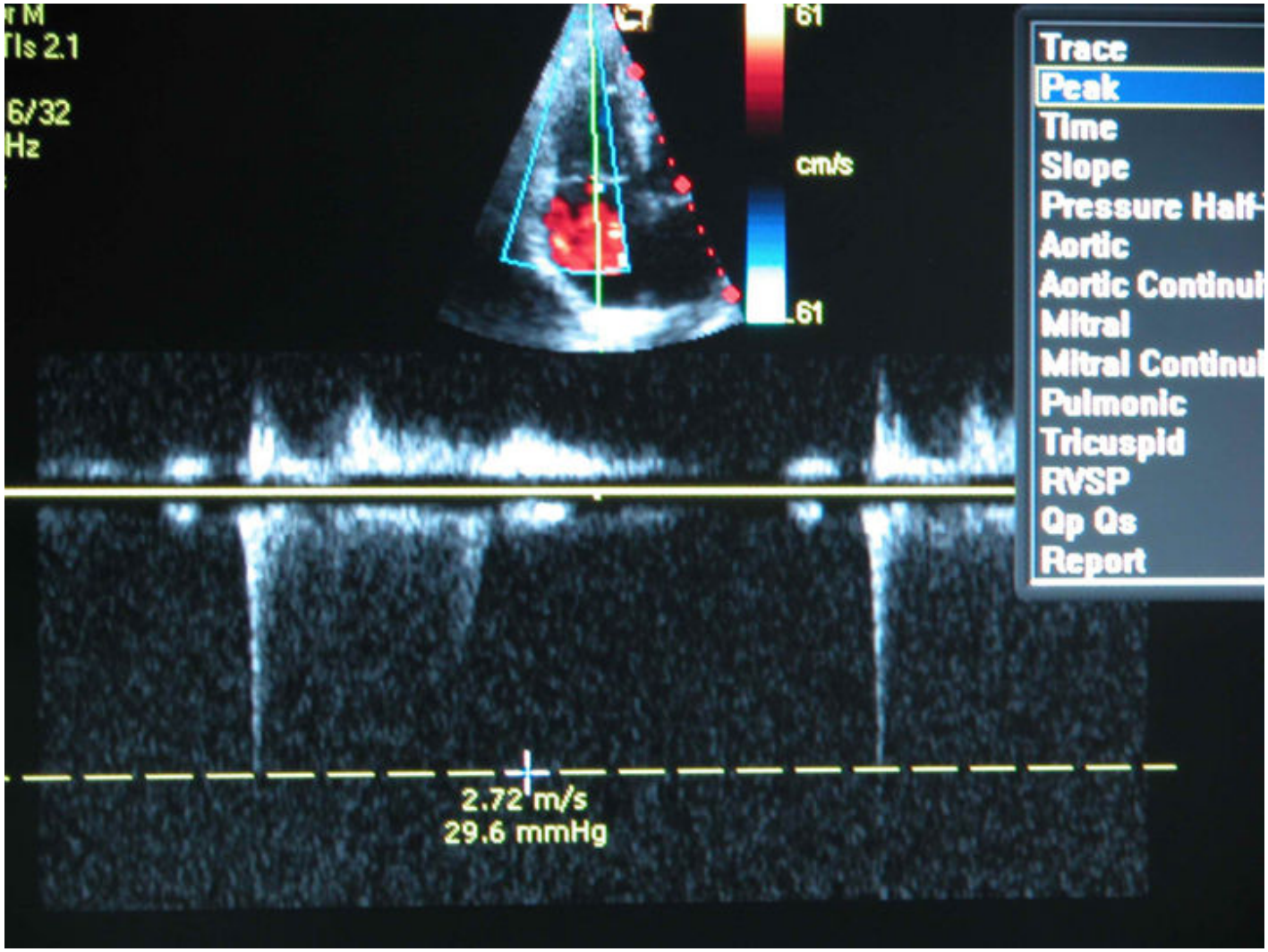
# The „S – shape“ of the oxygen dissociation curve

- **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



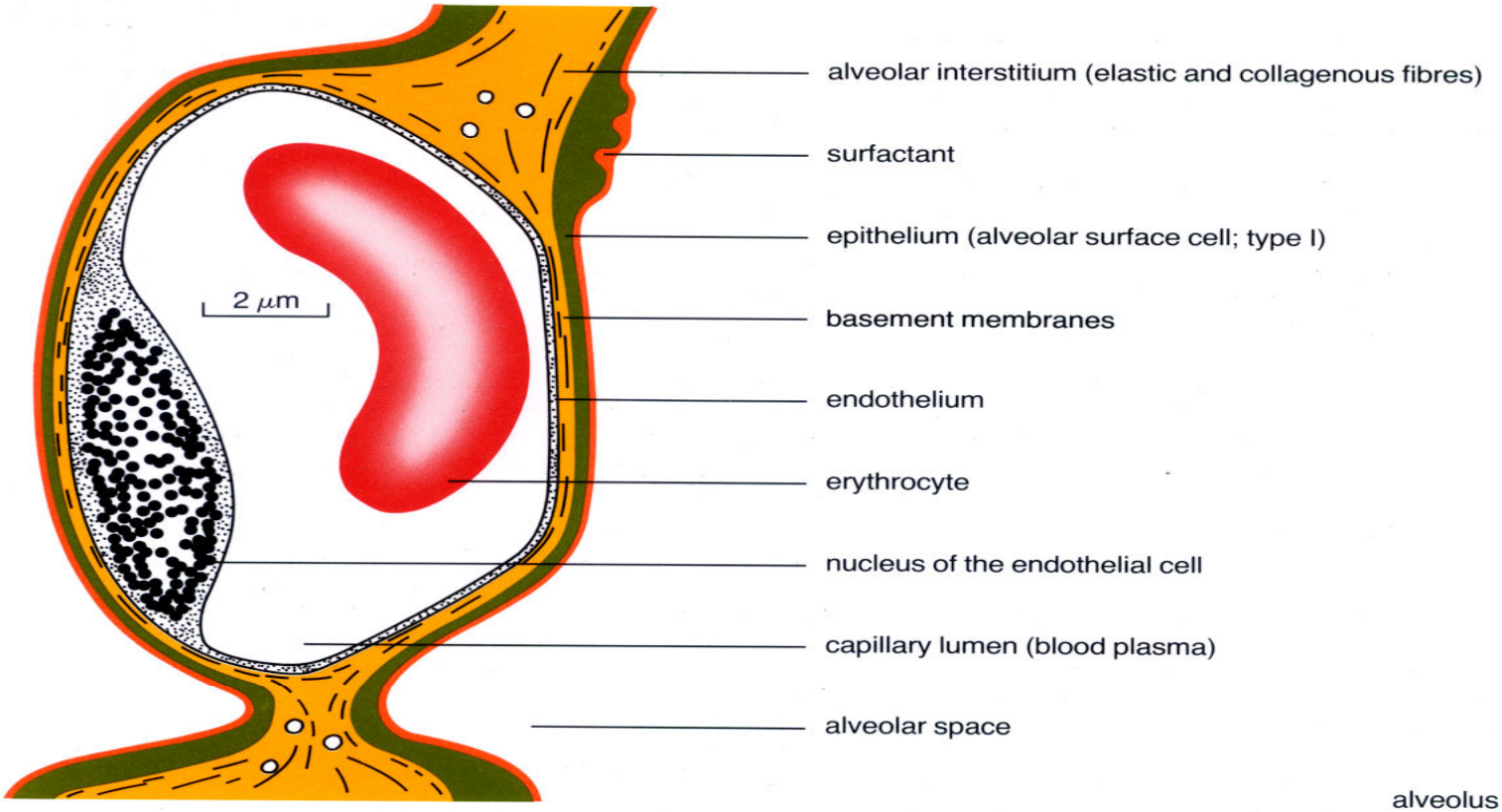
# Arterial hypoxia stimulates respiratory centers 1

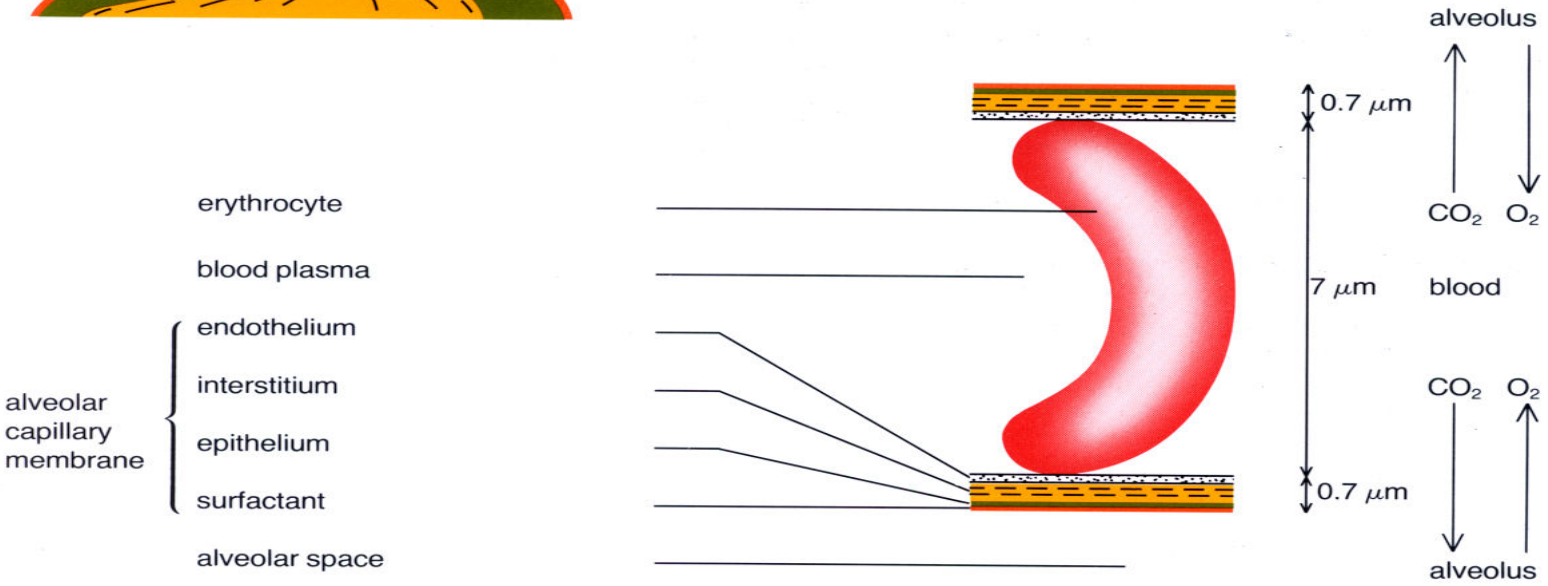
- **Arterial hypoxia (a low $p_aO_2$) stimulates respiratory centers through activation of peripheral chemoreceptors *(glomus caroticum, corpus aorticum)***

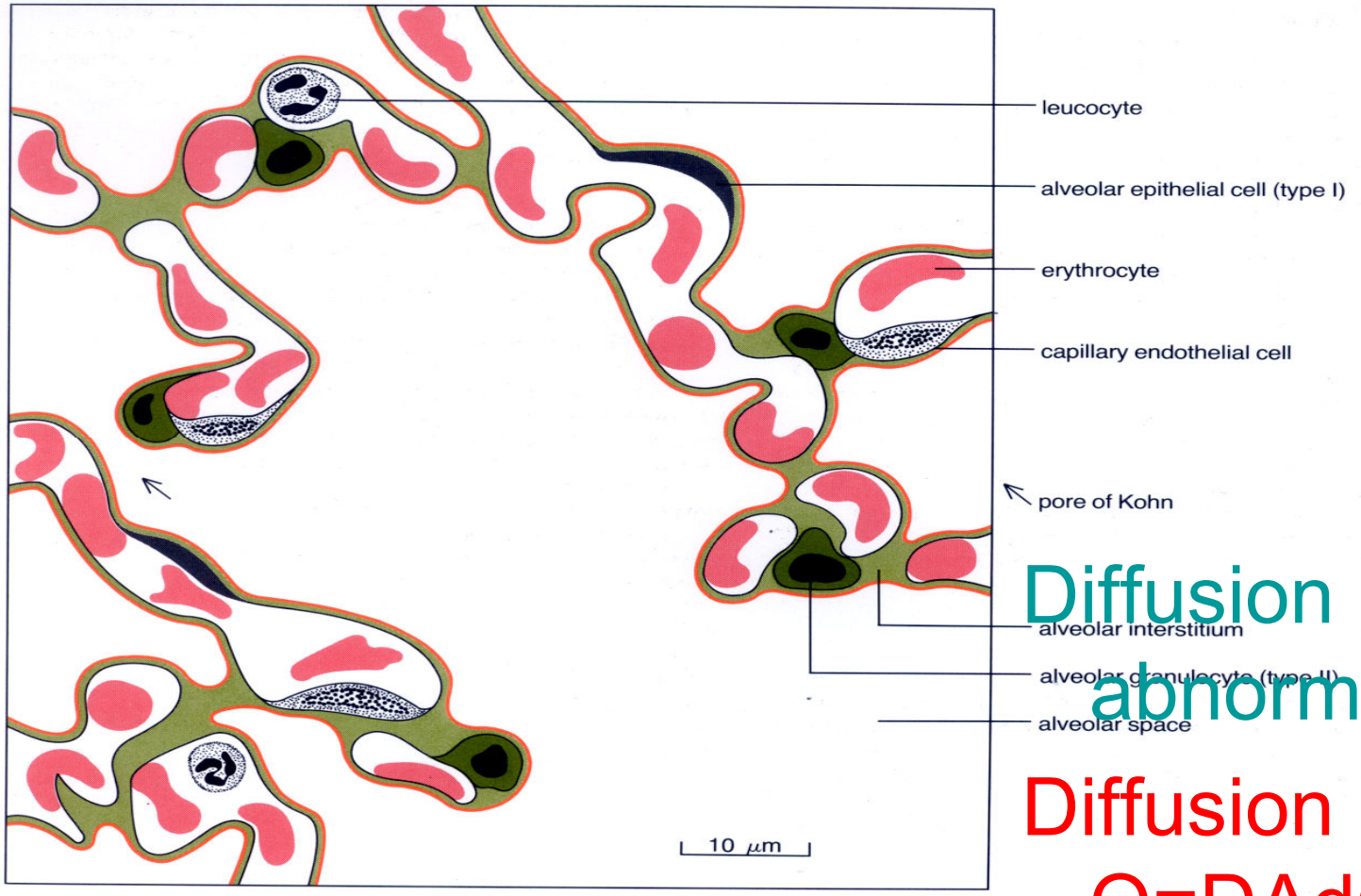
- **This is a fundamental change in control of the lung ventilation which normally depends on $CO_2$ produced by the metabolism (blood pH is maintained)**

# 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


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


erythrocyte
blood plasma
alveolar capillary membrane
endothelium
interstitium
epithelium
surfactant
alveolar space
0.7 μm
7 μm
0.7 μm
alveolus
CO2
O2
blood
CO2
O2
alveolus




| 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

schematized from E. R. Weibel, 1963

Diffusion abnormalities

Diffusion law:

Q=DAdC/L,

Q=flow,D=coeff.,

A=area, L=length

dC=conc.diff.

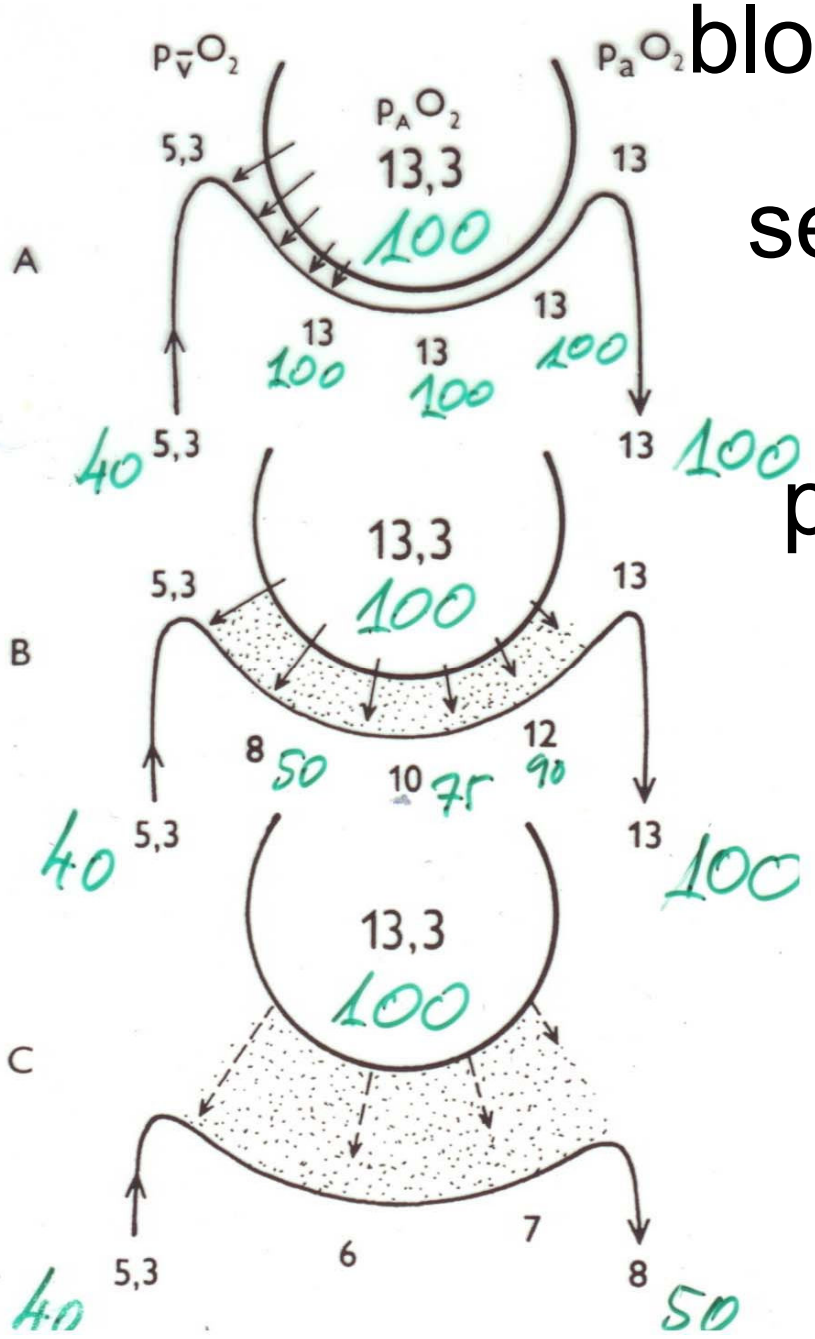
# Diffusion block

- 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 – 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...

# ARDS

Symptoms:

-lung injury of acute onset, within 1 week of clinical insult, with progression of respiratory symptoms

-bilateral opacities on chest imaging not explained by other pulmonary pathology
(pleural effusion, pneumothorax, cancer, et cetera)

-respiratory failure not explained by heart failure or volume overload

-decreased arterial $P_{art}O_2/ FiO_2$ ratio:

-mild ARDS: ratio is 201 - 300 mmHg (≤ 39.9 kPa)

-moderate ARDS: 101 - 200 mmHg (≤ 26.6 kPa)

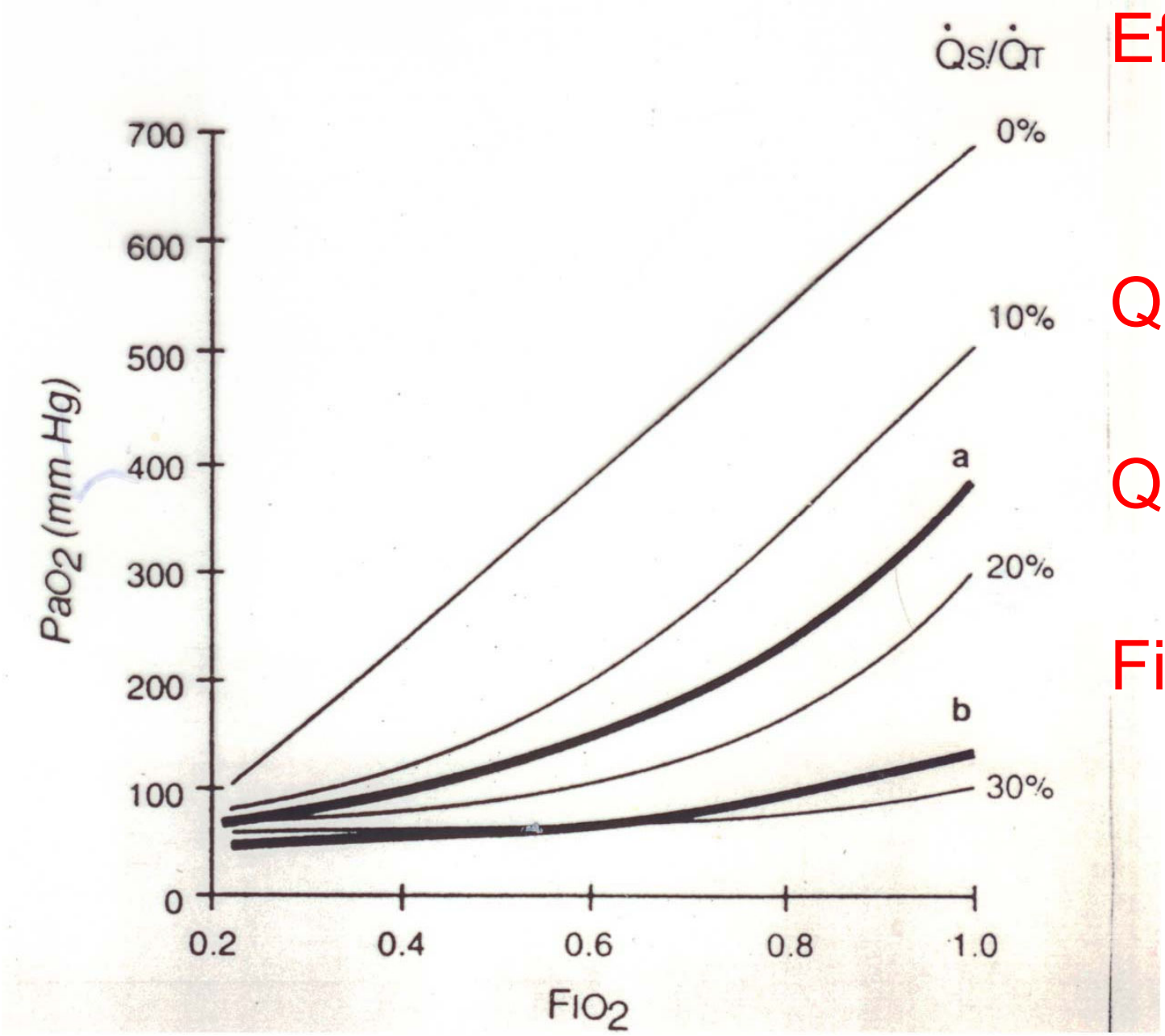
-severe ARDS: ≤ 100 mmHg (≤ 13.3 kPa)

# ARDS

causes: Sepsis, multiple blood transfusions, pulmonary contusion, aspiration of gastric contents, drug abuse or overdose, burns, pancreatitis, smoke inhalation, pneumonia and near drowning. The inhalation of irritants, chemical warfare agents such as phosgene, chlorine gas and such can also cause ARDS.

ethio-pathogenesis:

Edema and decreased surfactant production may cause whole alveoli to collapse or to be flooded. Loss of ventilation contributes further to the right-to-left shunt in ARDS. As the alveoli contain progressively less gas, the blood in alveolar capillaries is less and less oxygenated, resulting in massive intrapulmonary shunting. Collapsed alveoli and small bronchi do not exchange gases. $PaO_2$ drops to 60 mmHg (8.0 kPa) ane less despite mechanical ventilation with 100% inspired oxygen.




Effects of pulmonary shunt

QS = shunt perfusion,

QT = total perfusion,

$FiO_2$ = Fractional inspiratory oxygen.

# 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

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

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

# $pCO_2$ 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*

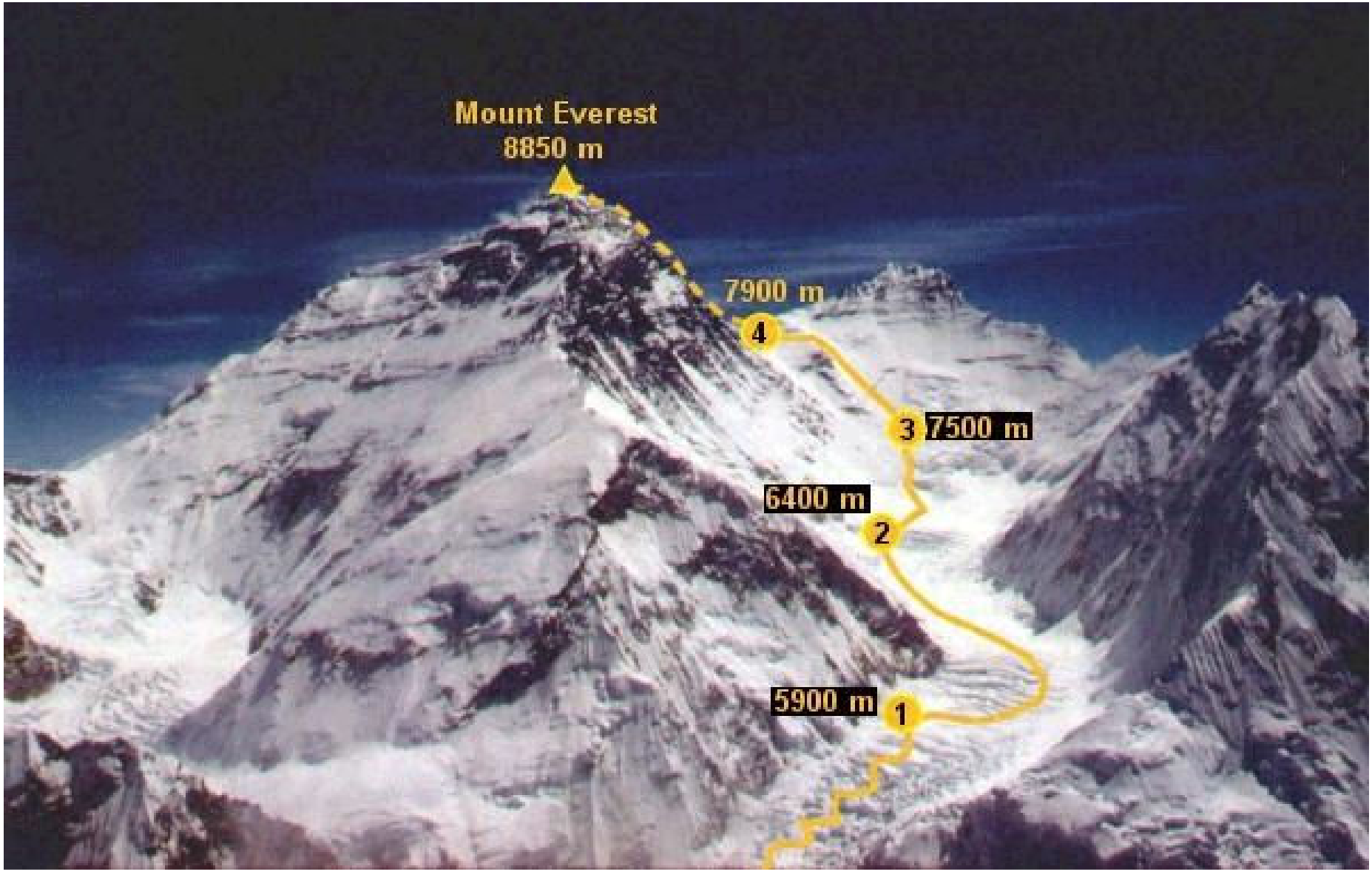
after sampling the arterial blood and meassurig $P_aO_2$ and $P_aCO_2$

*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

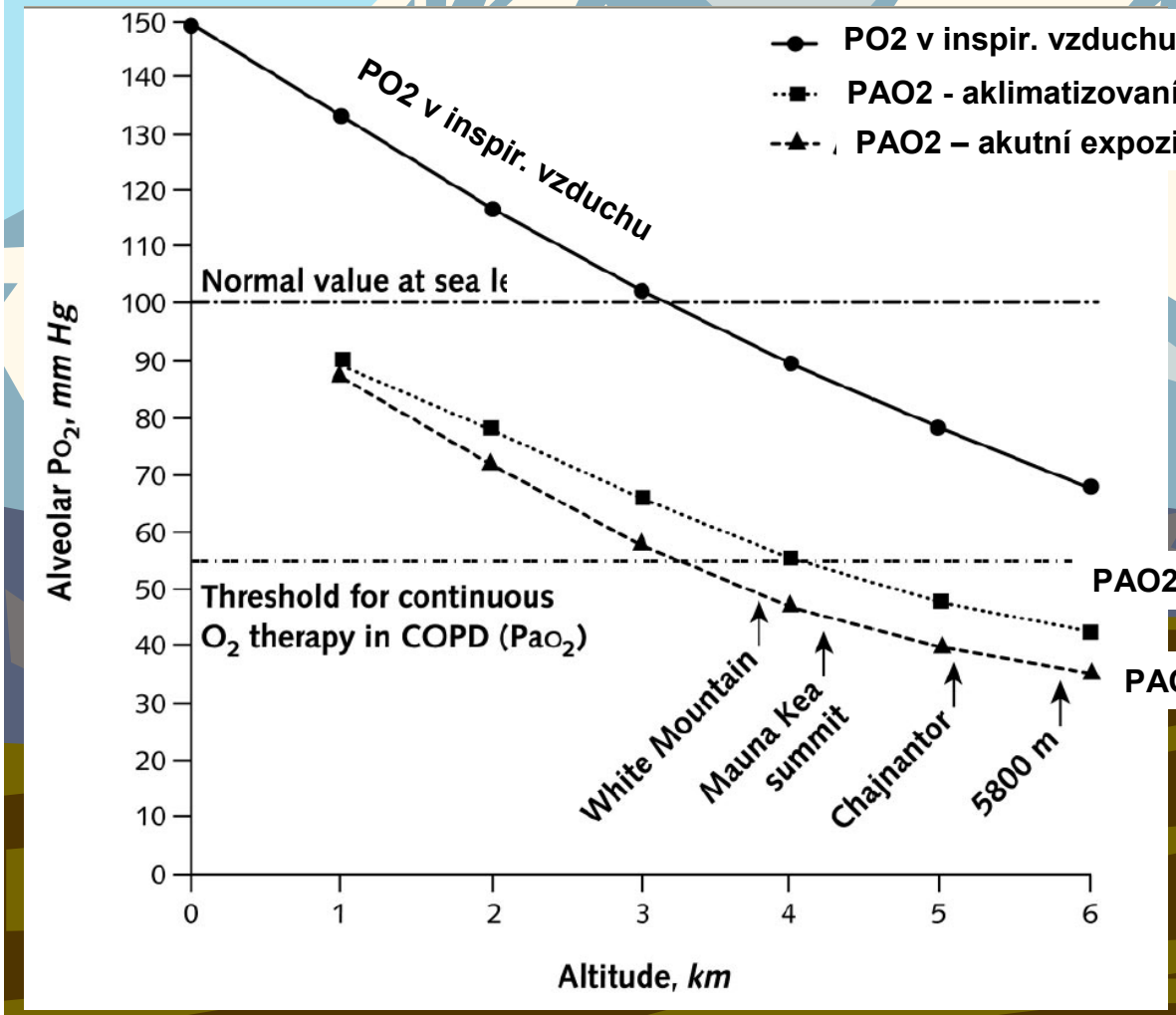
Climbing

Barometric pressure drop

Fall PO2 in inspired air

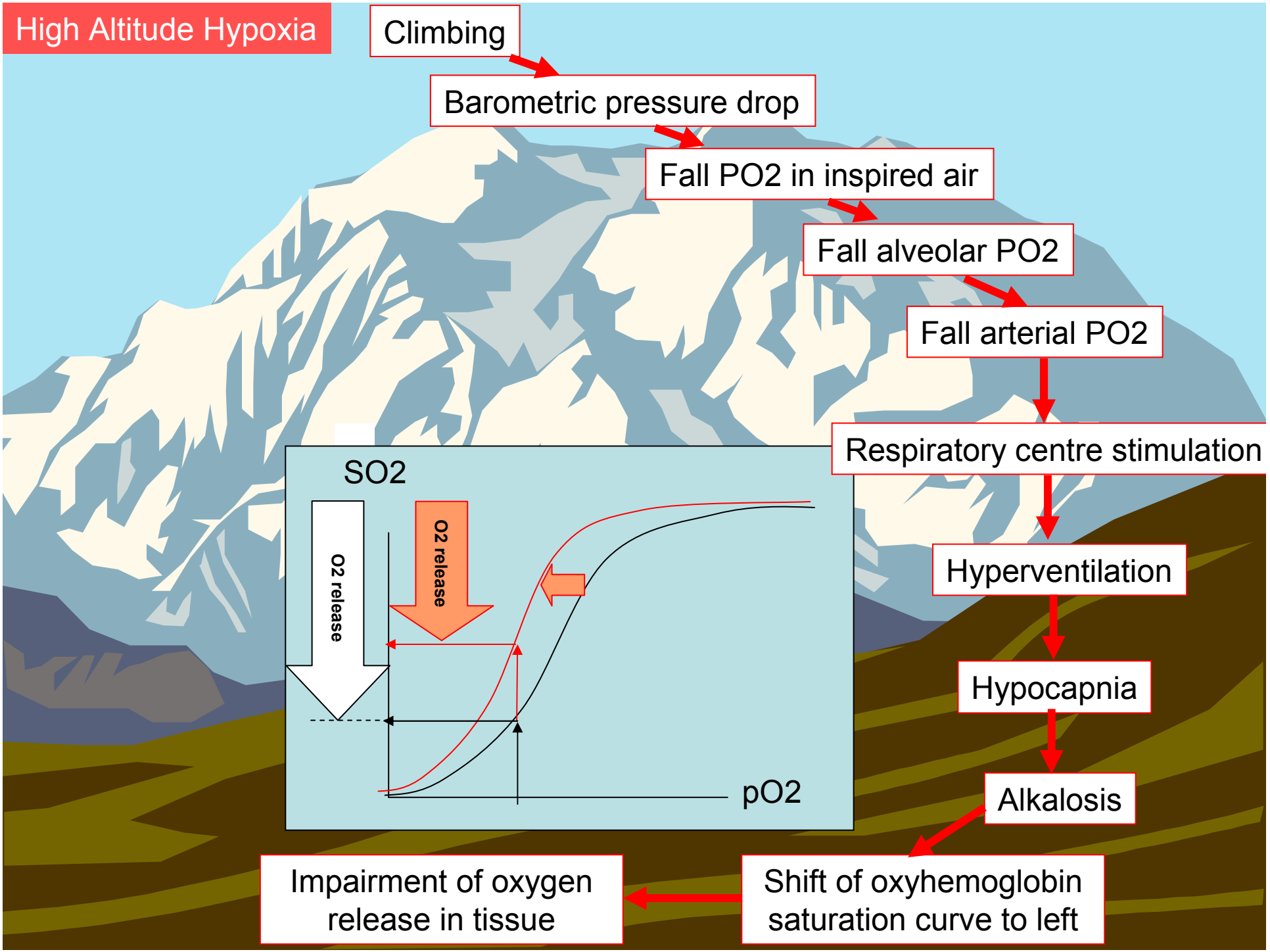
Fall alveolar PO2

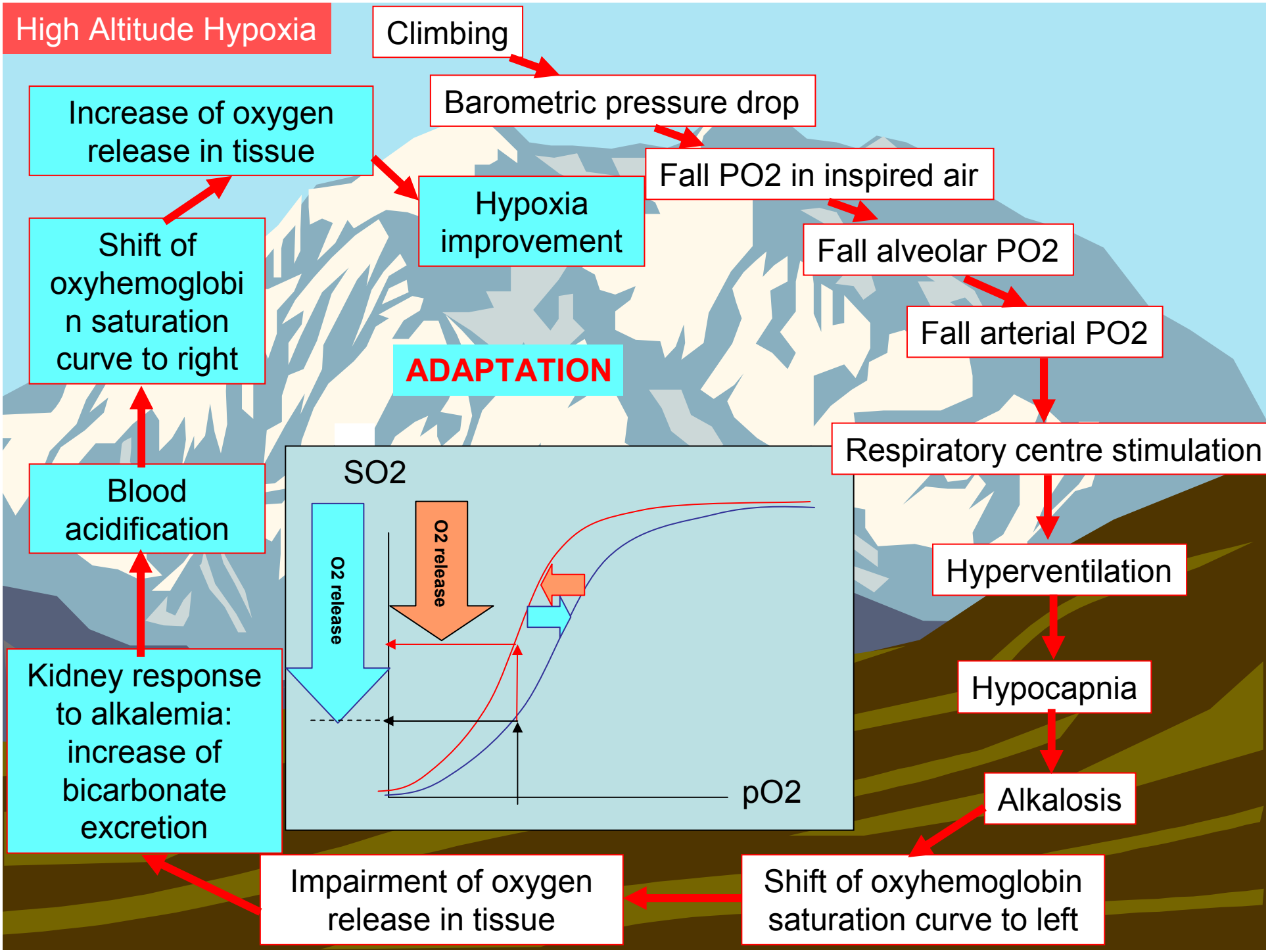
Fall arterial PO2




PAO2 – fully acclimated

PAO2 – acute exposition


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
pO2
O2 release
O2 release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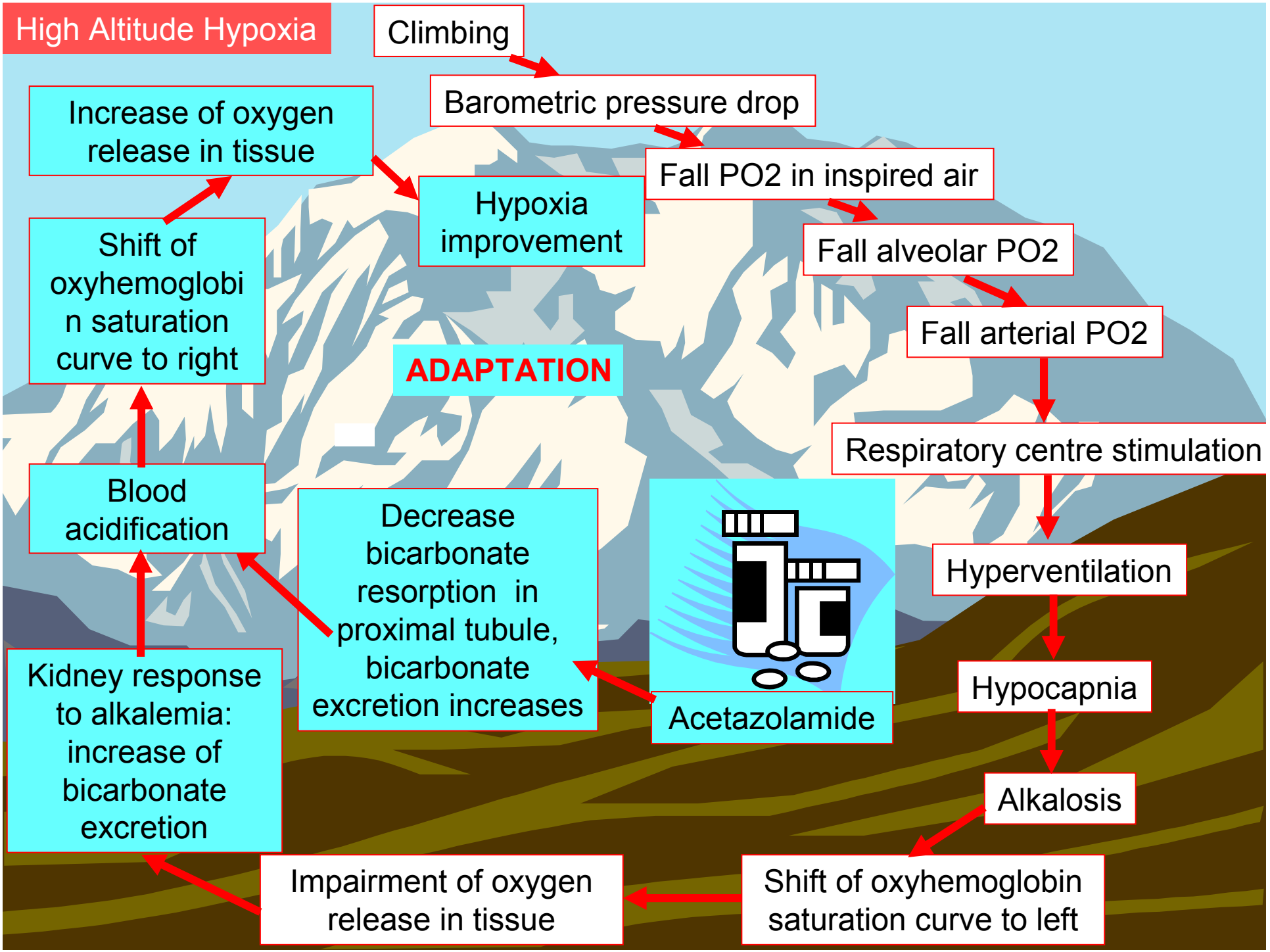
Hypocapnia
Alkalosis
Shift of oxyhemoglobin saturation curve to left
Impairment of oxygen release in tissue
Kidney response to alkalemia: increase of bicarbonate excretion
Blood acidification
Shift of oxyhemoglobin saturation curve to right
Increase of oxygen release in tissue
Hypoxia improvement
ADAPTATION
SO2
pO2
O2 release
O2 release


High Altitude Hypoxia
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Fall arterial PO2
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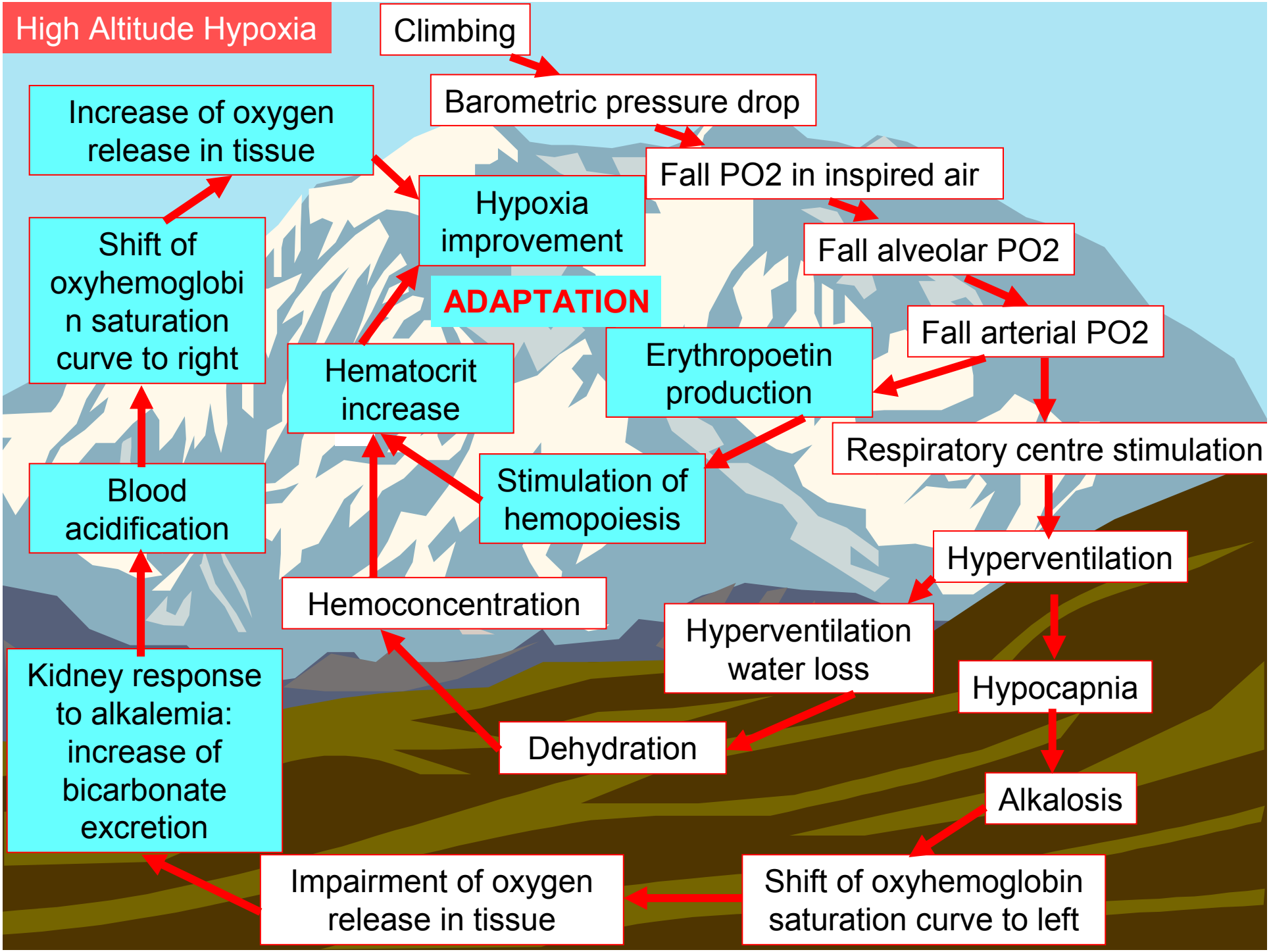
Impairment of oxygen release in tissue
Kidney response to alkalemia: increase of bicarbonate excretion
Blood acidification
Shift of oxyhemoglobi n saturation curve to right
Increase of oxygen release in tissue
Hypoxia improvement
ADAPTATION
Decrease bicarbonate resorption in proximal tubule, bicarbonate excretion increases
Acetazolamide


High Altitude Hypoxia
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Barometric pressure drop
Fall PO2 in inspired air
Fall alveolar PO2
Fall arterial PO2
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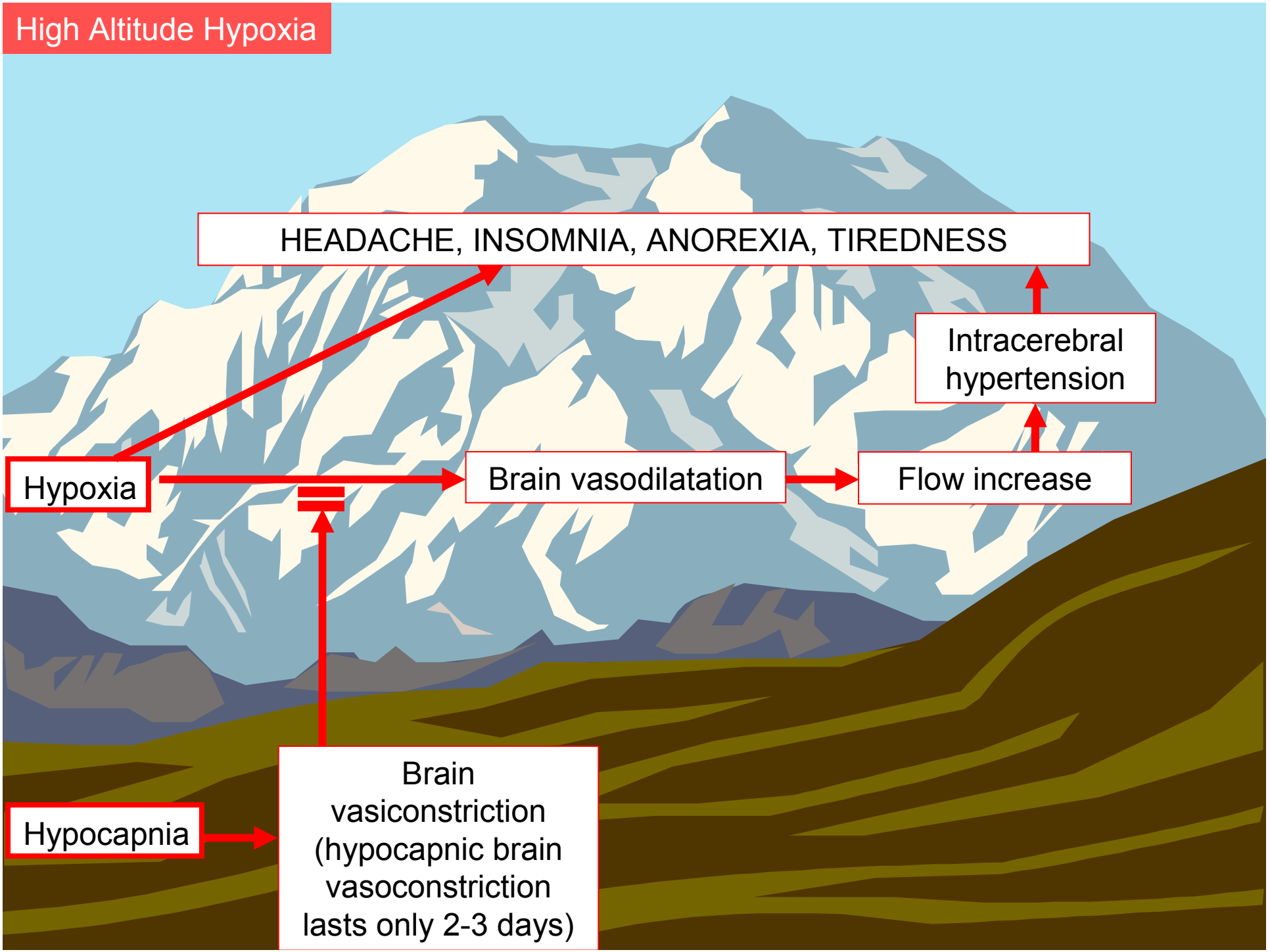
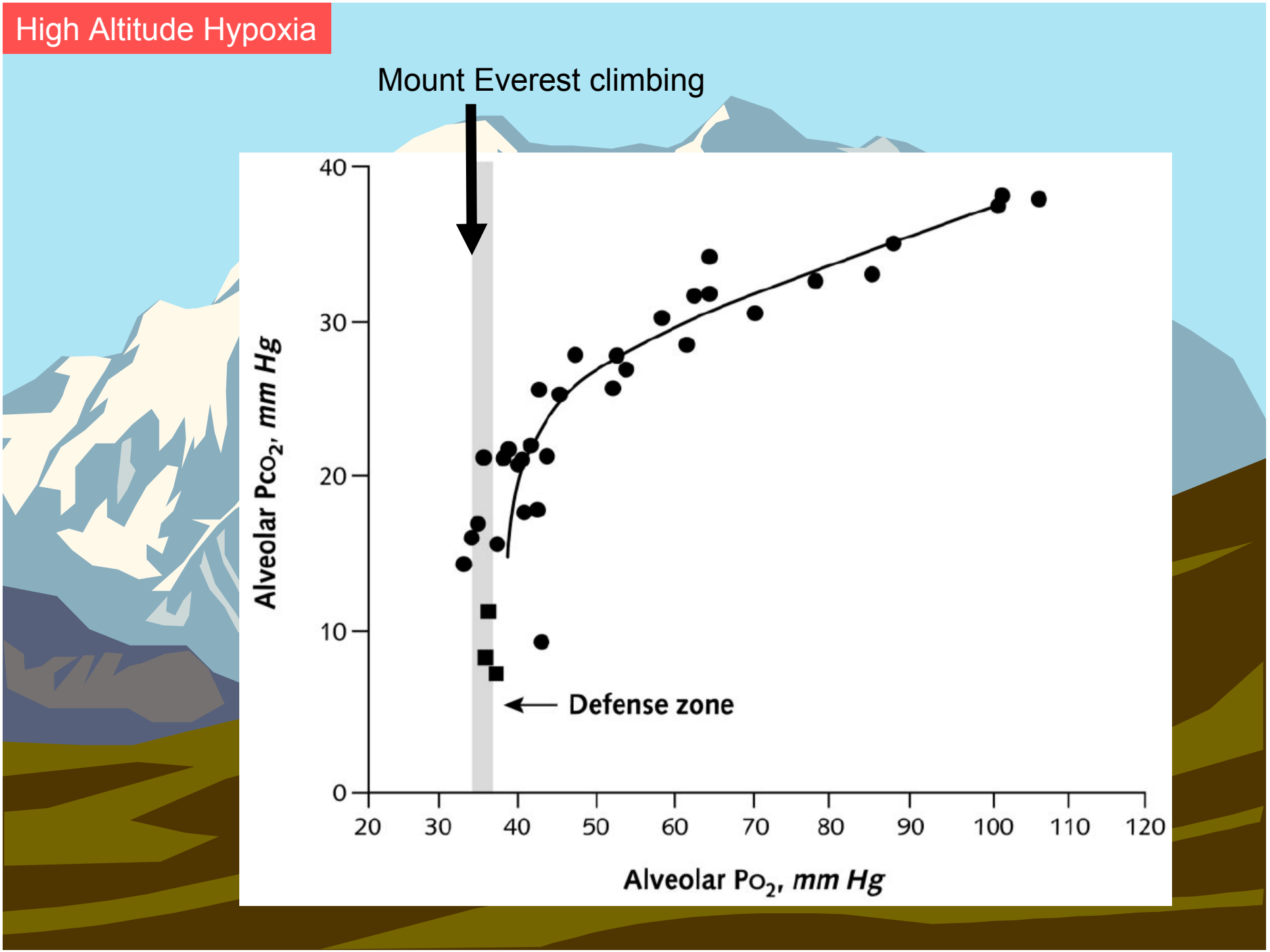
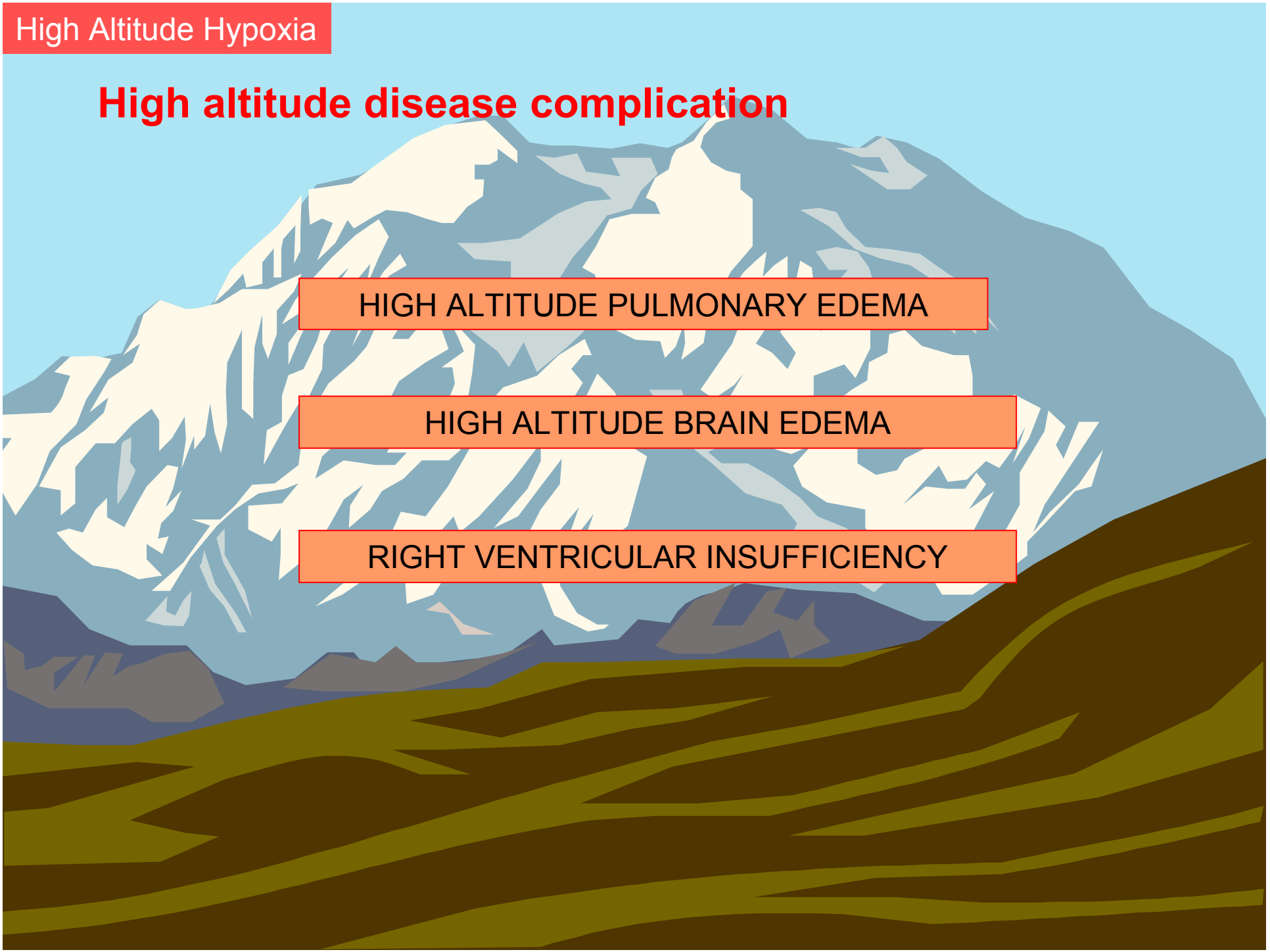
Impairment of oxygen release in tissue
Kidney response to alkalemia: increase of bicarbonate excretion
Blood acidification
Shift of oxyhemoglobin saturation curve to right
Increase of oxygen release in tissue
Hypoxia improvement
ADAPTATION
Hematocrit increase
Erythropoetin production
Stimulation of hemopoiesis
Hemoconcentration
Hyperventilation water loss
Dehydration

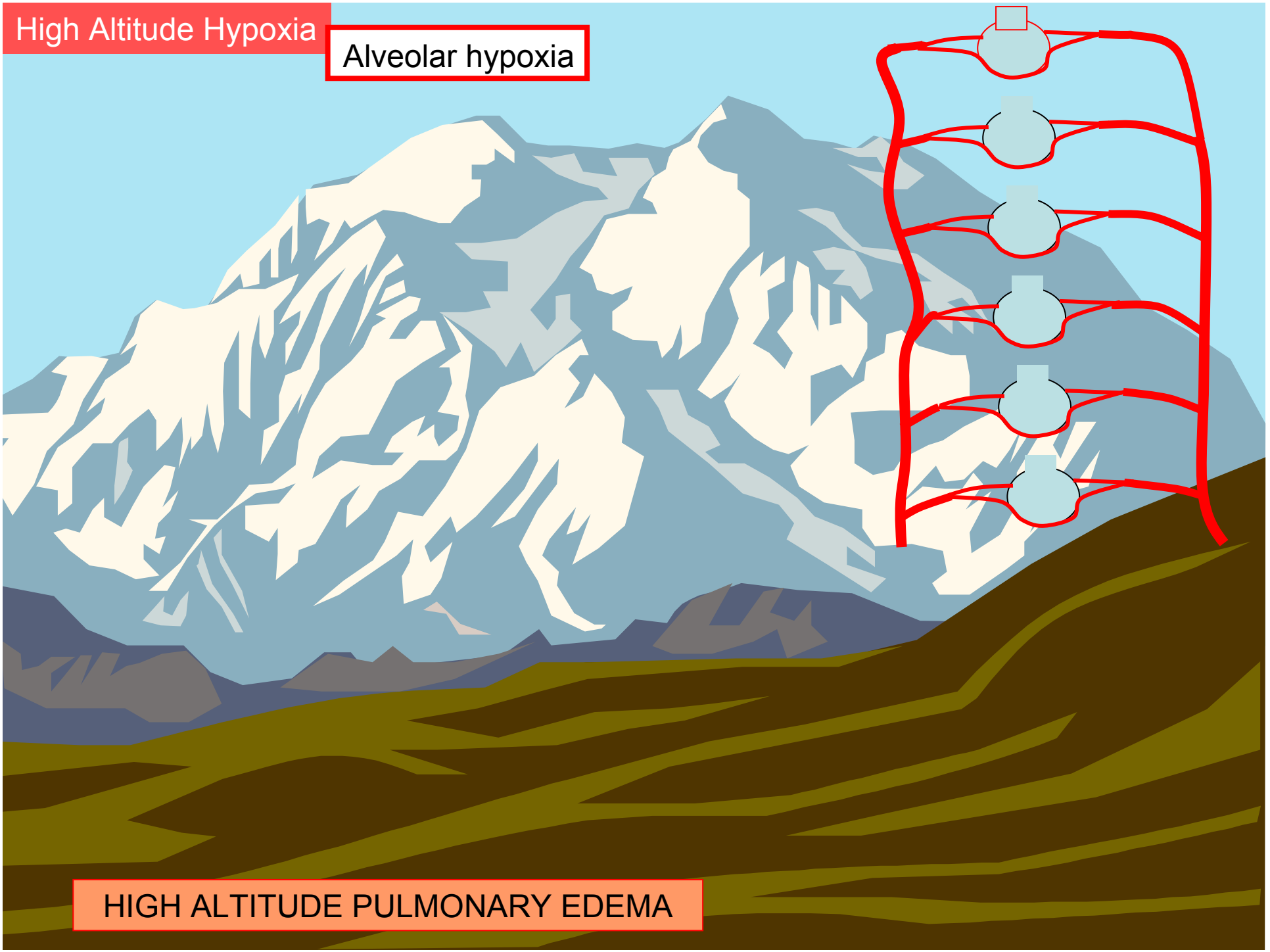

High Altitude Hypoxia
HEADACHE, INSOMNIA, ANOREXIA, TIREDNESS
Intracerebral hypertension
Hypoxia
Brain vasodilatation
Flow increase
Hypocapnia
Brain vasiconstriction (hypocapnic brain vasoconstriction lasts only 2-3 days)

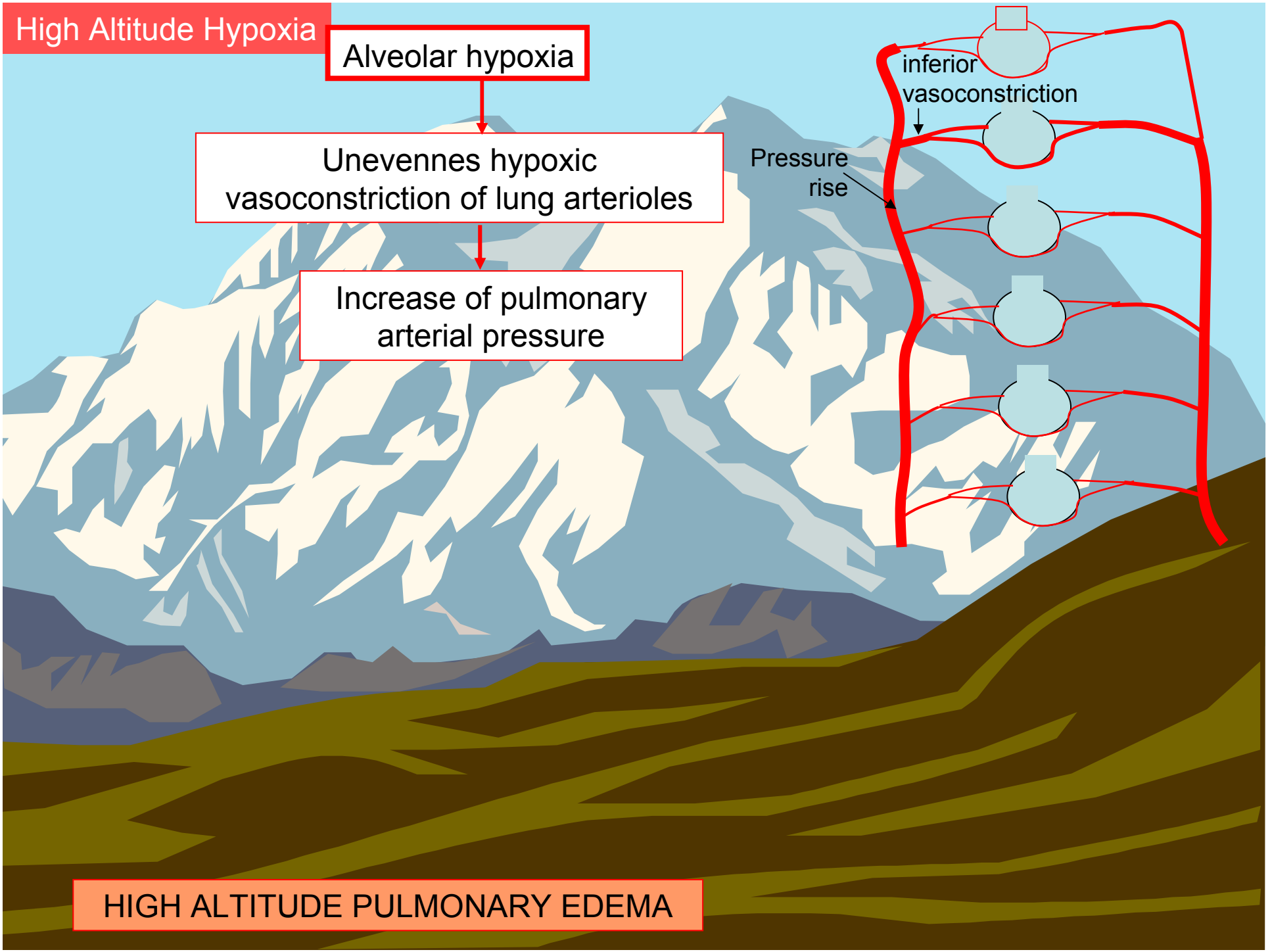
# High Altitude Hypoxia

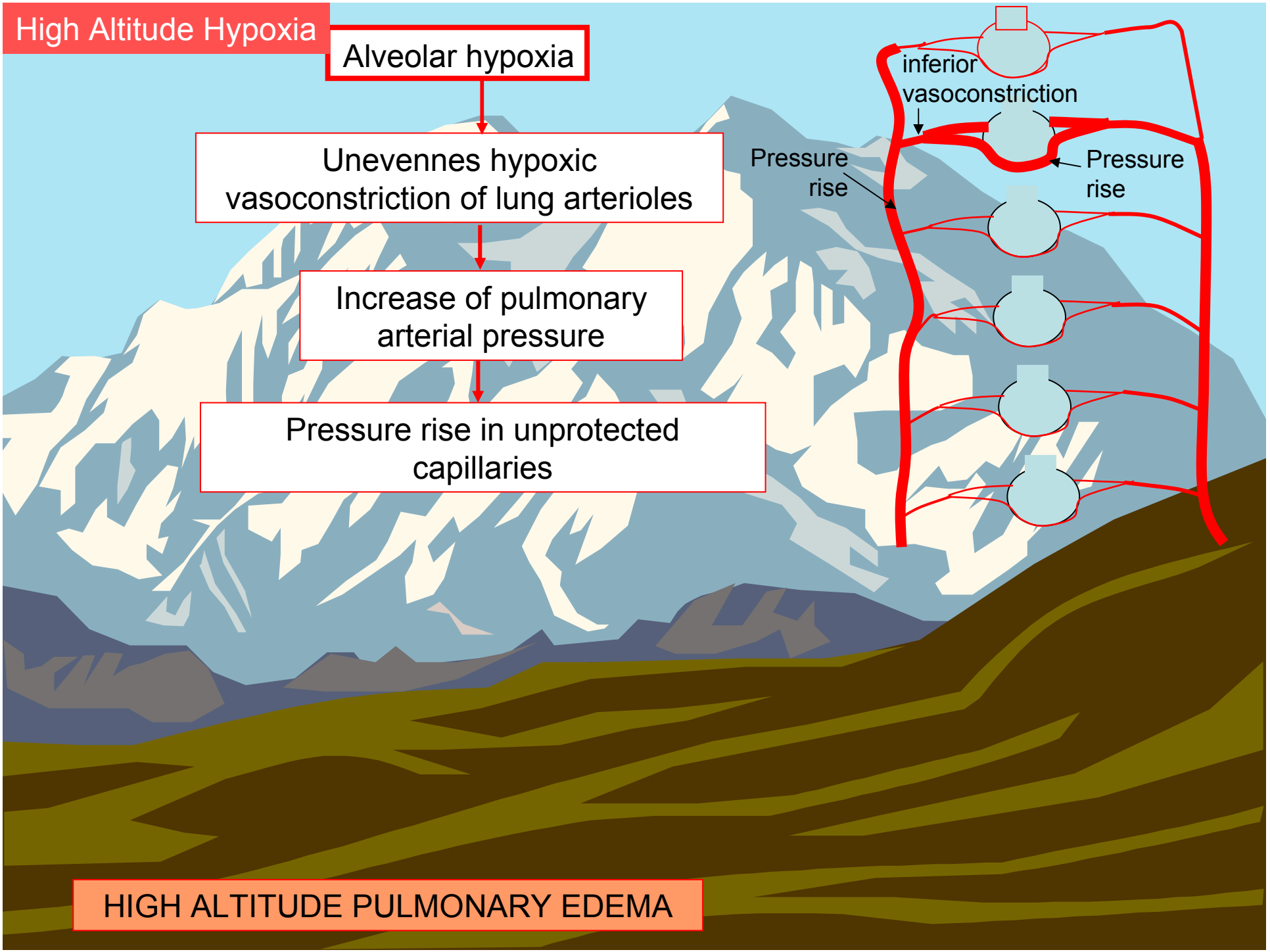


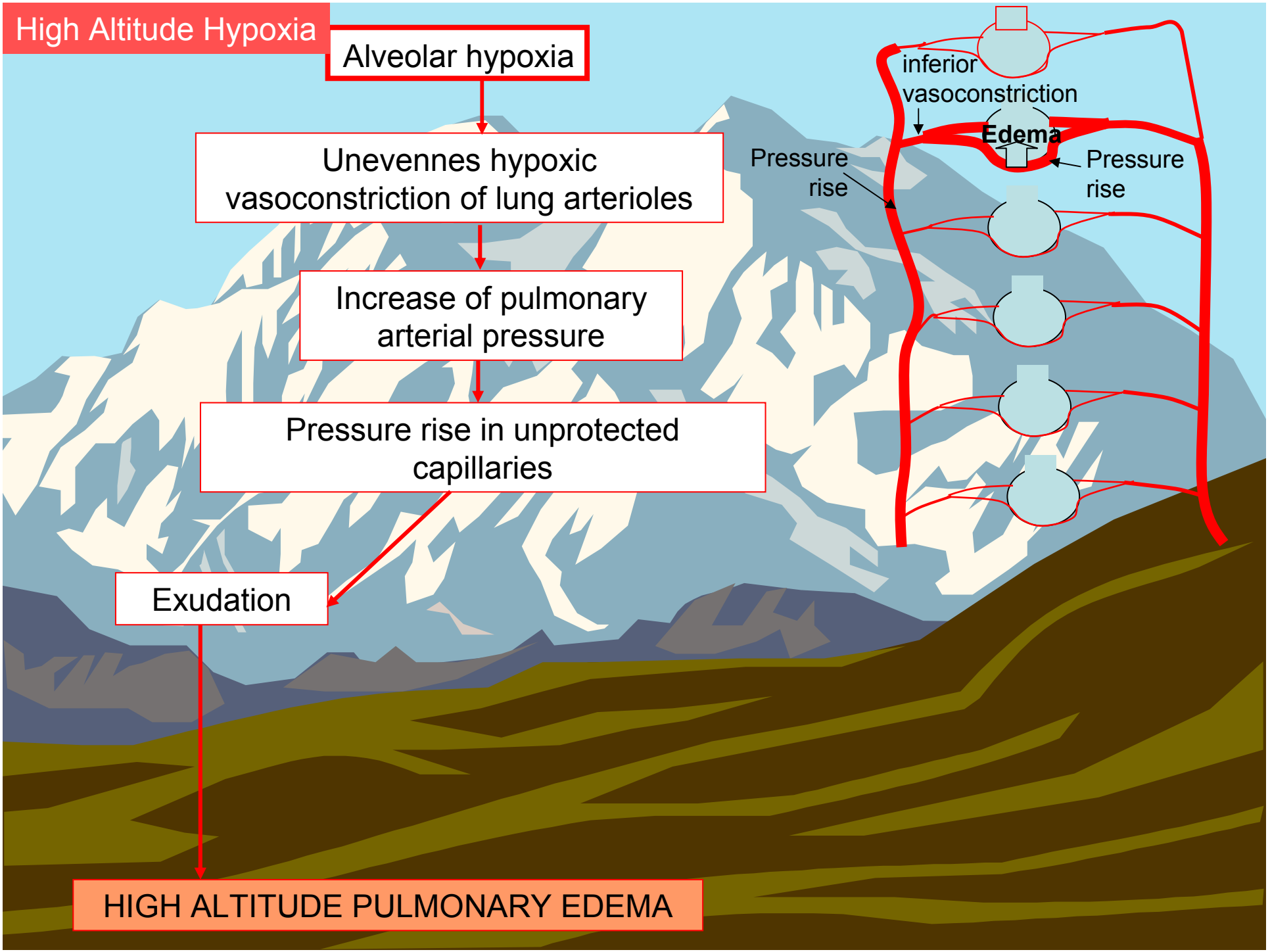
# High altitude disease complication

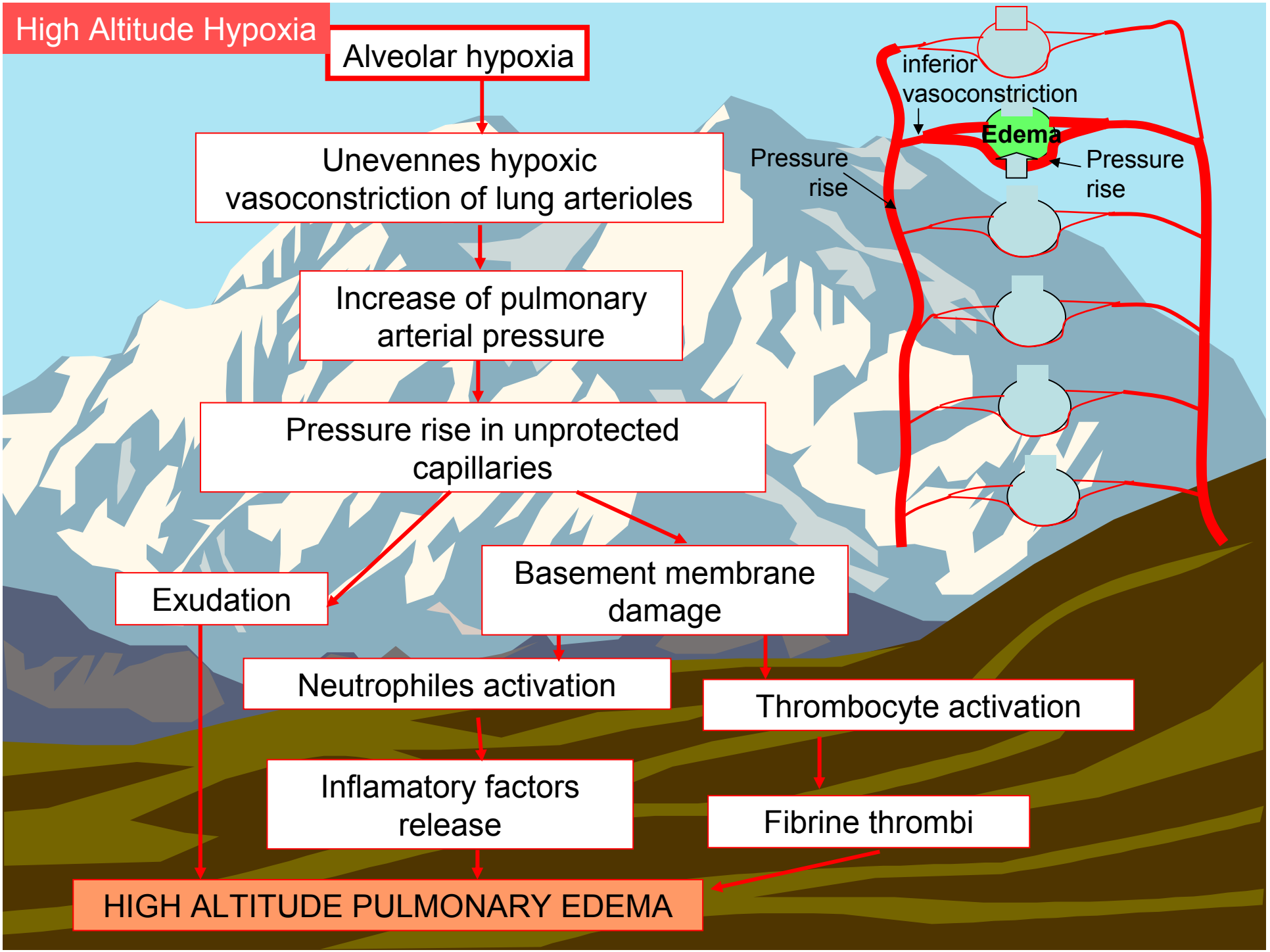


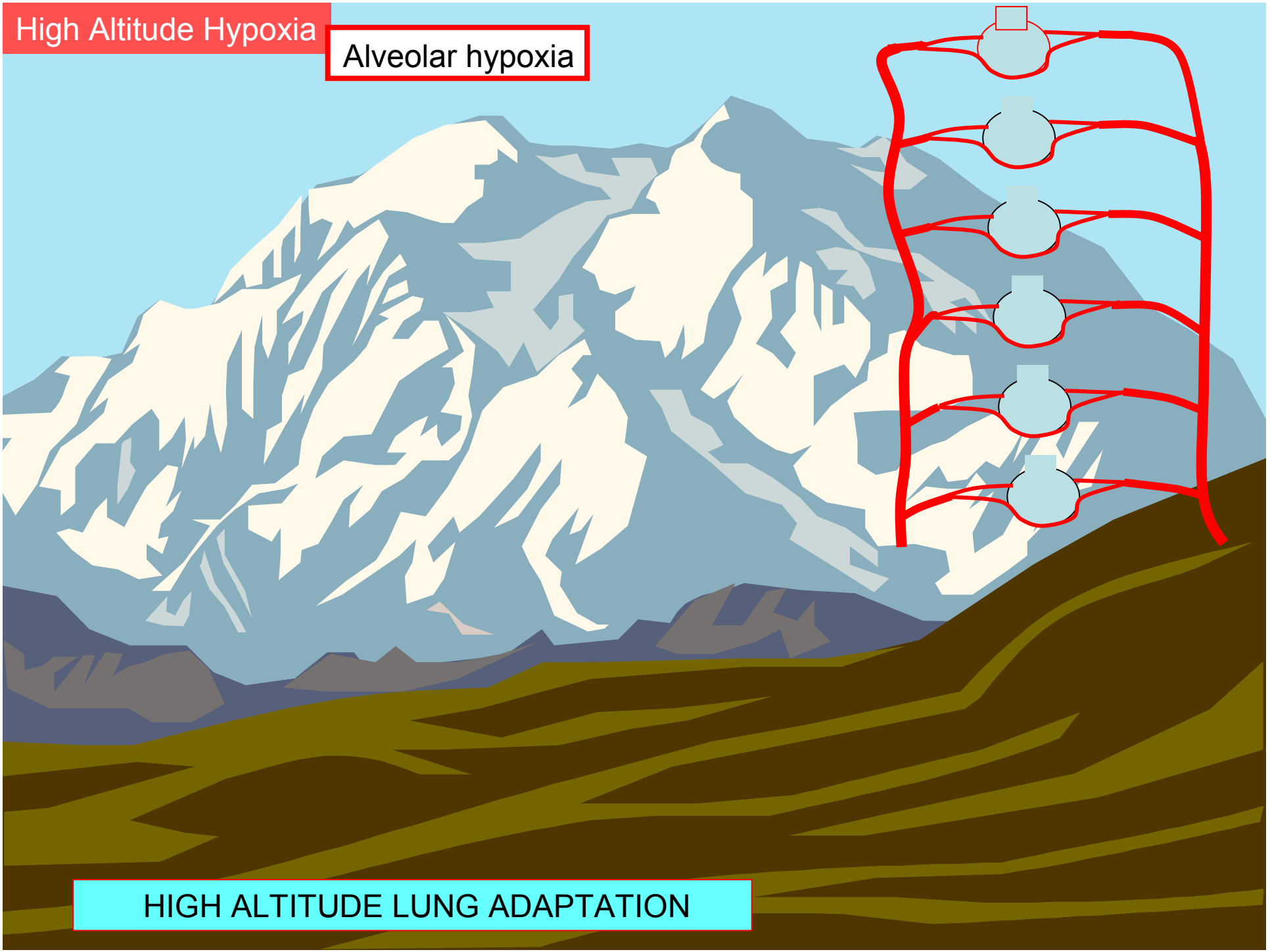

High Altitude Hypoxia
Alveolar hypoxia
HIGH ALTITUDE PULMONARY EDEMA

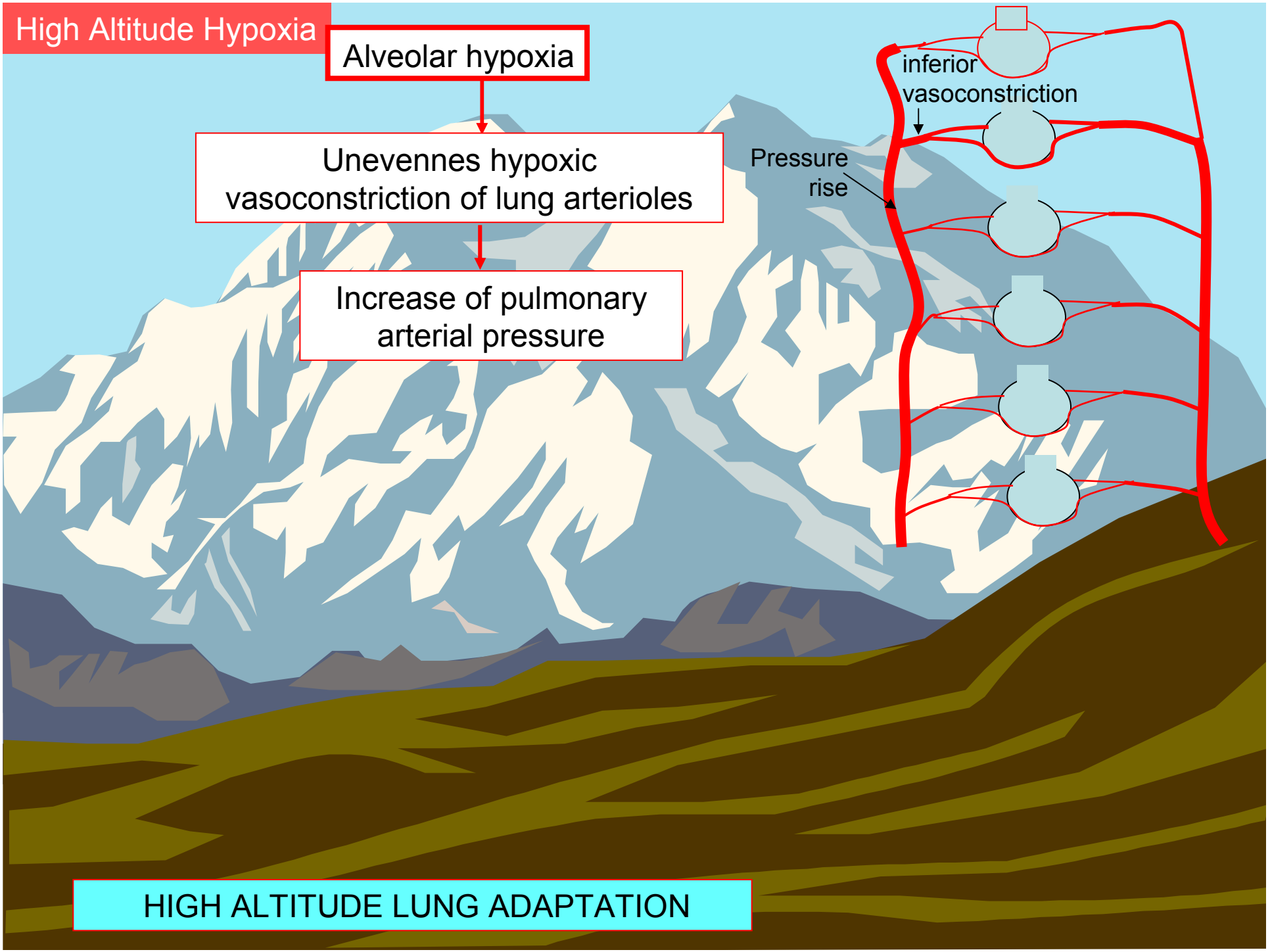

High Altitude Hypoxia
Alveolar hypoxia
Unevennes hypoxic vasoconstriction of lung arterioles
Increase of pulmonary arterial pressure
inferior vasoconstriction
Pressure rise
HIGH ALTITUDE PULMONARY EDEMA

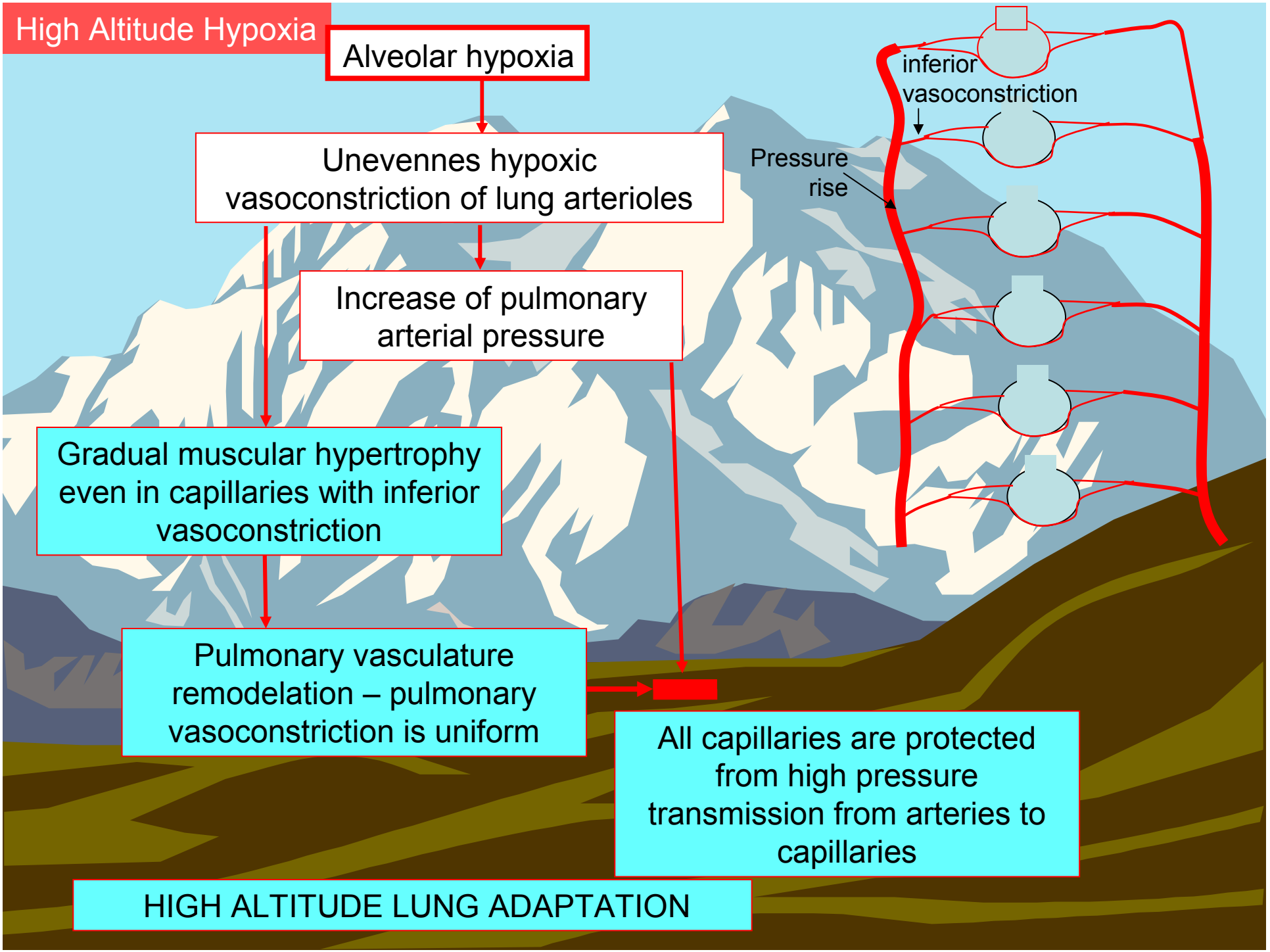

High Altitude Hypoxia
Alveolar hypoxia
Unevennes hypoxic vasoconstriction of lung arterioles
Increase of pulmonary arterial pressure
Pressure rise in unprotected capillaries
inferior vasoconstriction
Pressure rise
Pressure rise
HIGH ALTITUDE PULMONARY EDEMA

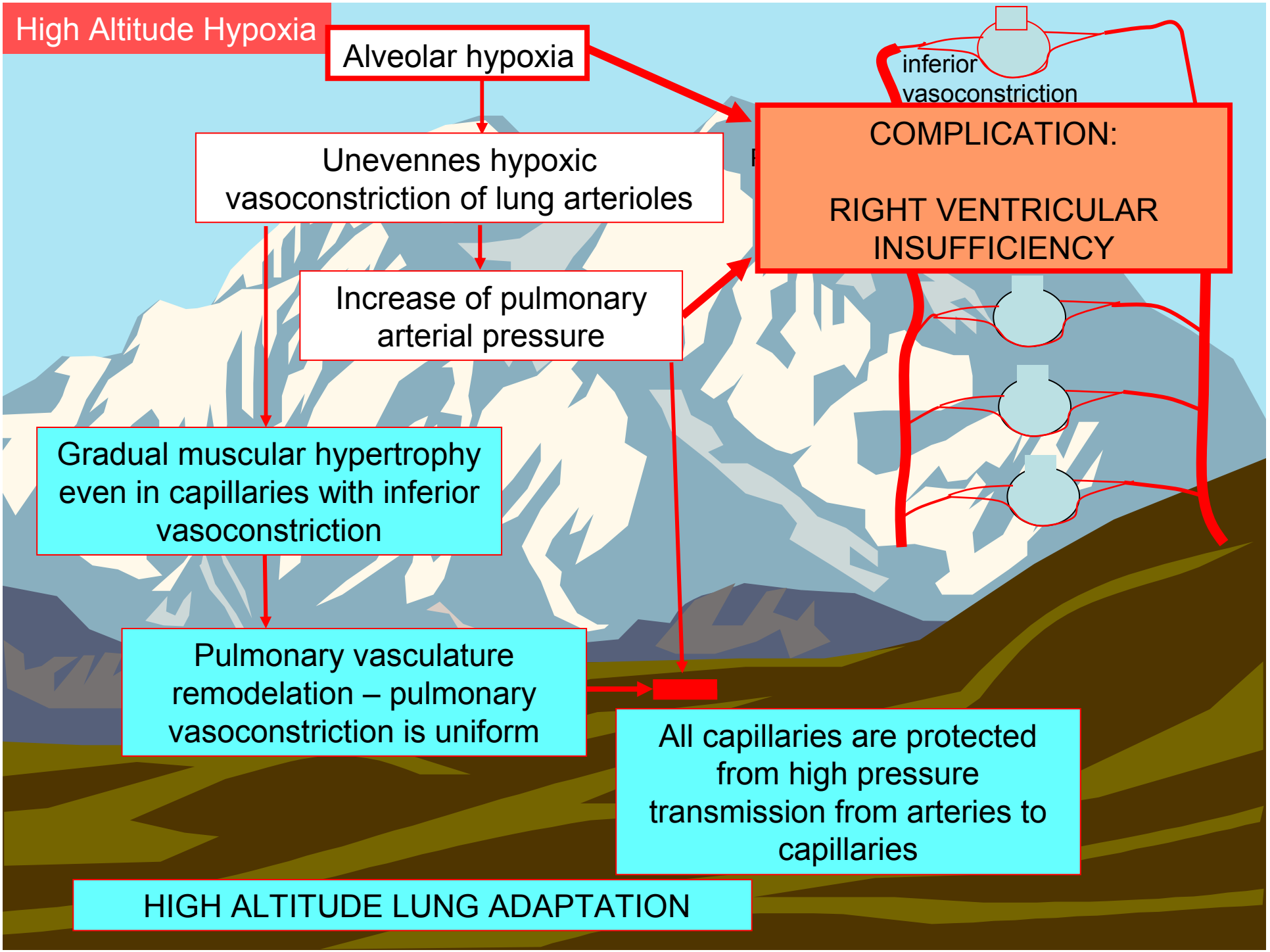

High Altitude Hypoxia
Alveolar hypoxia
Unevennes hypoxic vasoconstriction of lung arterioles
Increase of pulmonary arterial pressure
Pressure rise in unprotected capillaries
Exudation
HIGH ALTITUDE PULMONARY EDEMA
inferior vasoconstriction
Edema
Pressure rise
Pressure rise

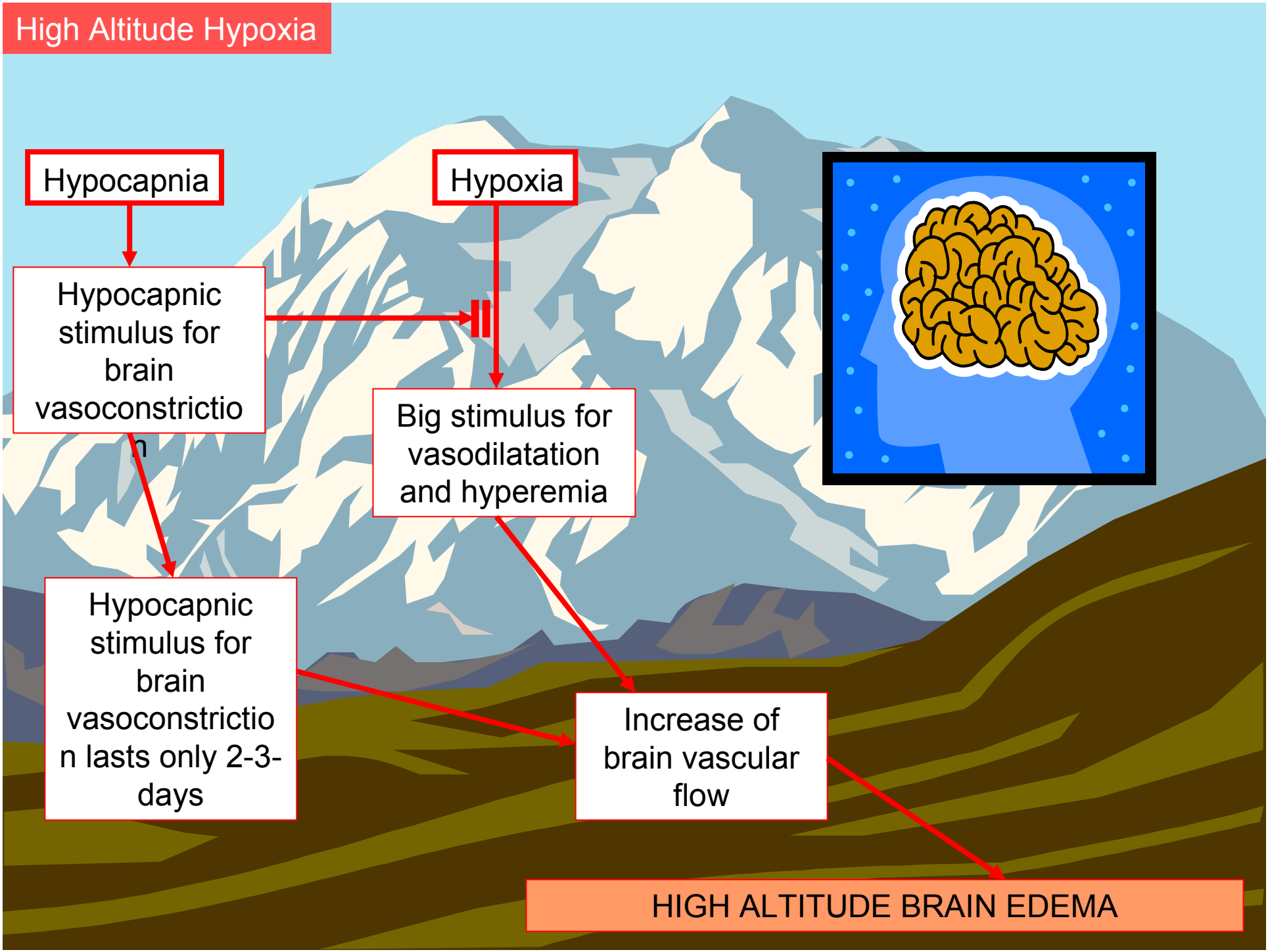

High Altitude Hypoxia
Alveolar hypoxia
Unevennes hypoxic vasoconstriction of lung arterioles
Increase of pulmonary arterial pressure
Pressure rise in unprotected capillaries
Exudation
Basement membrane damage
Neutrophiles activation
Thrombocyte activation
Inflamatory factors release
Fibrine thrombi
HIGH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


High Altitude Hypoxia
Alveolar hypoxia
HIGH ALTITUDE LUNG ADAPTATION


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

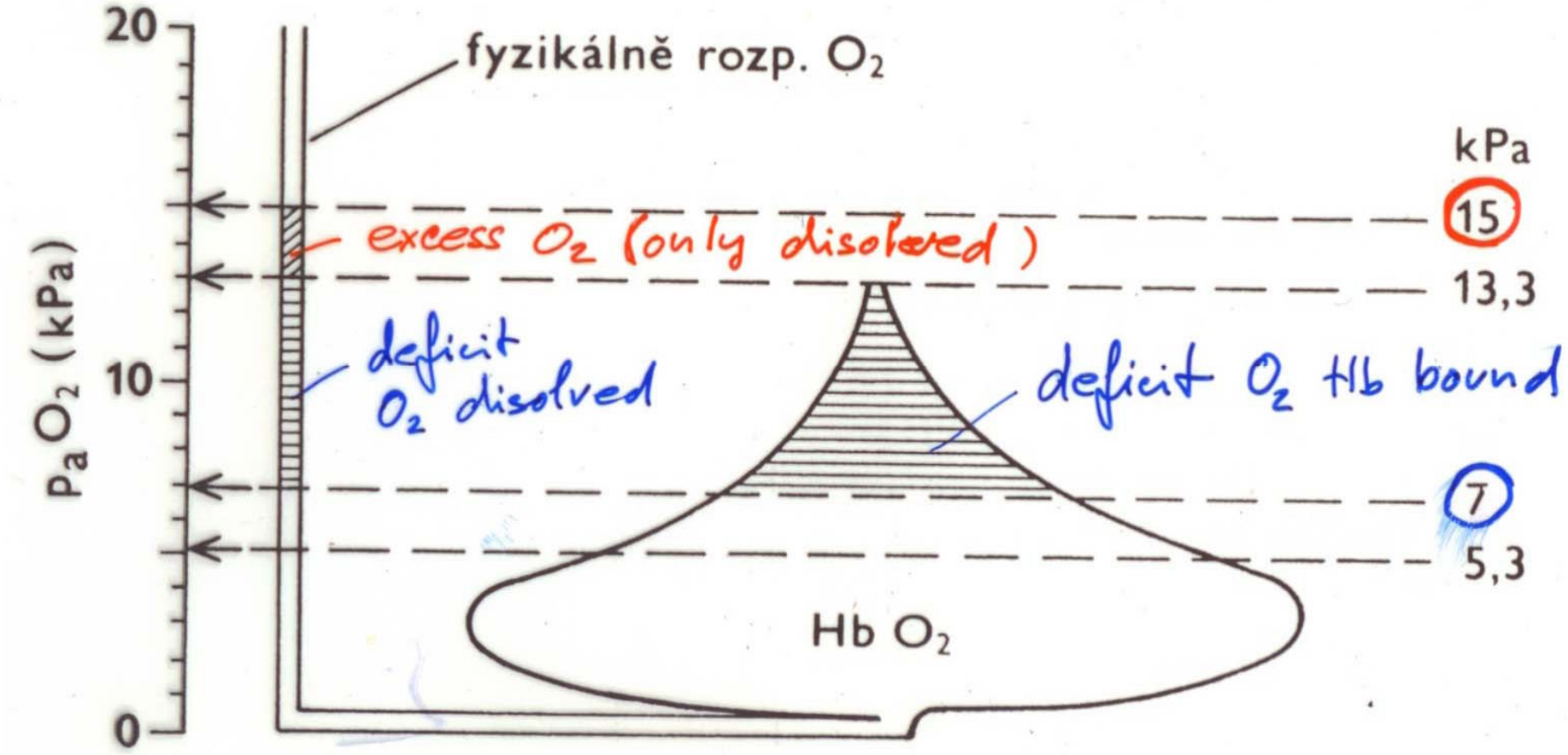

High Altitude Hypoxia
Alveolar hypoxia
Unevennes hypoxic vasoconstriction of lung arterioles
Increase of pulmonary arterial pressure
Gradual muscular hypertrophy even in capillaries with inferior vasoconstriction
Pulmonary vasculature remodelation – pulmonary vasoconstriction is uniform
All capillaries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


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
$P_a O_2$ (kPa)
fyzikálně rozp. $O_2$
kPa
15
excess $O_2$ (only disolved)
13,3
deficit
$O_2$ disolved
deficit $O_2$ Hb bound
7
5,3
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