Hypoxia（缺氧）

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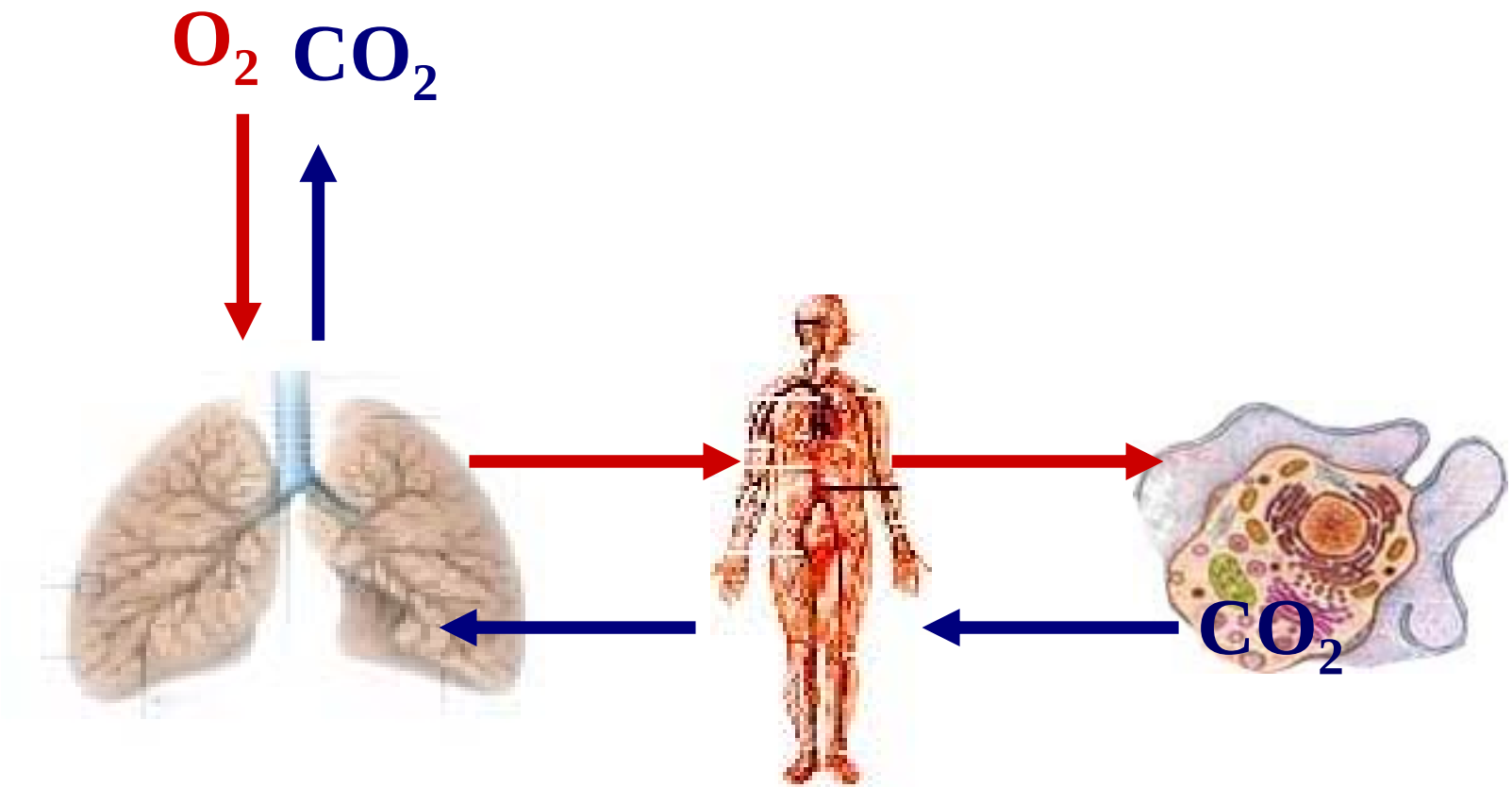
Clinical Example

- In 1875 three French scientists ascended in a balloon. A height of over 26,000 feet was reached. They lost consciousness at about 25,000 feet. When Tissandier regained consciousness the balloon was falling rapidly, but his two accompaniers were dead. Oxygen containers were carried in this ascent but Tissandier records that his arms became powerless and so he was unable to raise the mouthpiece to his lips.
- **What is the dead cause of two scientists ?**

Normal Oxygen Delivery & Utilization



External respiration

Circulation

Internal respiration

What is hypoxia?

Hypoxia is a pathologic process, O_2 supply to tissue or O_2 utilization by cells is interrupted, it leads to changes in metabolism, function and even structure of cells and organs of body.

Deficiency of O_2 supply

Disturbance of O_2 utilization

Metabolisms Functions Structures

Section I. Parameters of the Blood Oxygen

- 1. Partial pressure of oxygen (PO_2)
- 2. Oxygen capacity (CO_2 max)
- 3. Oxygen content (CO_2)
- 4. Ca-vO_2动静脉血氧含量差
- 5. Oxygen Saturation (SO_2)
- 6. P_{50}

1. Partial pressure of oxygen (PO_2)

- **The pressure (tension) produced by oxygen molecules physically dissolved in plasma.**

Normal value : PaO_2= 13.3kpa (100mmHg)

PvO_2 = 5.3kpa (40mmHg)

Influence factor: (1) PO_2 of inhalation air

(2) function of external respiration

(3) shunting of blood

2. Oxygen capacity (CO_2 max)

- Maximum amount of O_2 that can be combined to Hb in 100ml of blood

Normal value : $CaO_2max=CvO_2max=20ml/dl$

Influence factor: Hb
- Quantity
- Quality
- Affinity with O_2

3. Oxygen content (CO_2)

- The total amount of O_2 carried in 100ml blood, including the dissolved and that carried by Hb.

Normal value : CaO_2 = 19ml/dl

CvO_2 = 14ml/dl

Influence factor: PO_2

CO_2max : quantity and quality of Hb

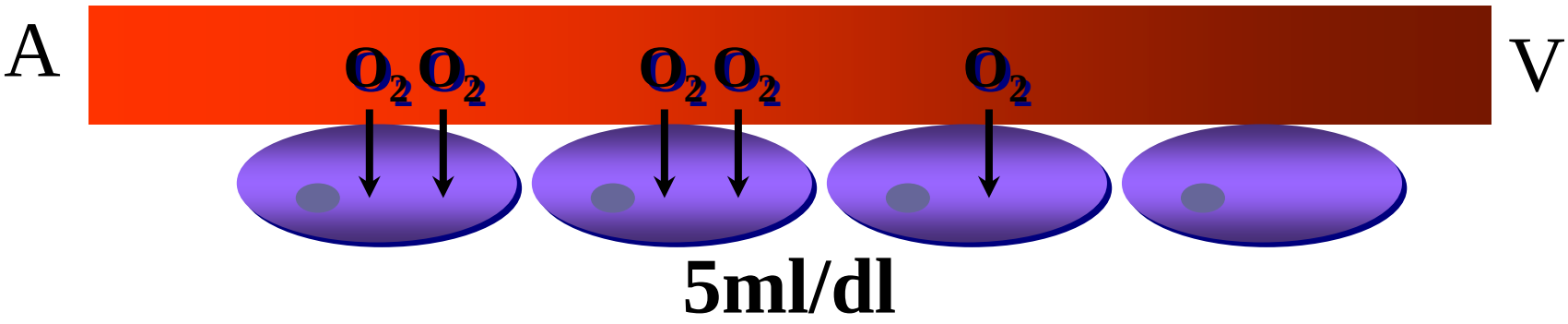
CaO_2<normal value→**hypoxemia**（低氧血症）

4.Ca-vO_2动静脉血氧含量差

The Difference between oxygen content in artery and vein, it reflect the O2 volume that tissue cells obtain from 100ml blood

(CaO_2 – CvO_2) = 5ml/dl

19ml/dl **14ml/dl**



5ml/dl

5. Oxygen saturation (SO_2)氧饱和度

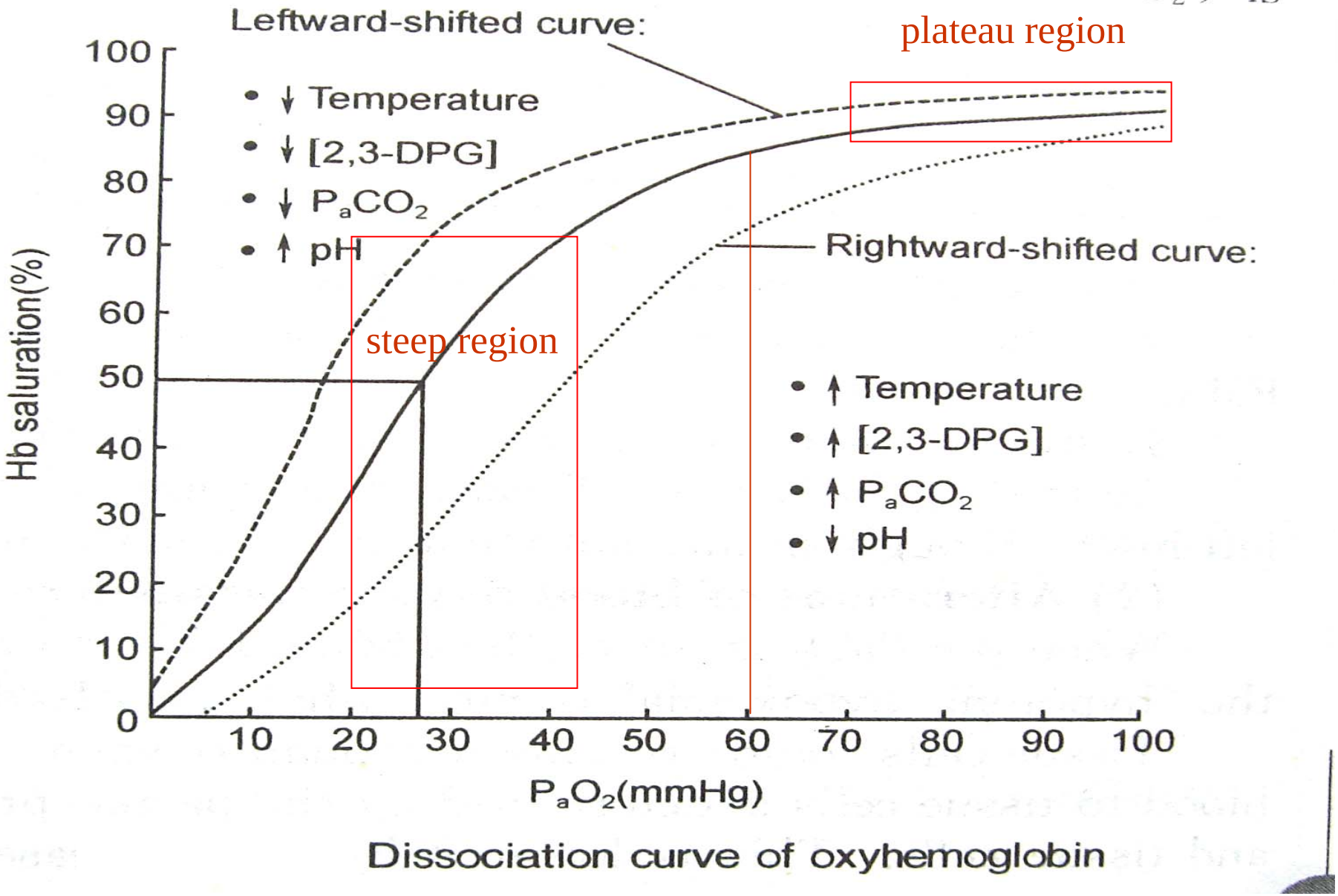
- The ratio of the actual amount of oxygen carried by Hb to oxygen capacity

$$SO_2 = (CO_2 - \text{dissolved } O_2 / CO_2 max) \times 100\%$$

Normal value : SaO_2 = 95%

SvO2 = 70%

Influence factor: PO2



Dissociation curve of oxyhemoglobin

6. P_{50}

- A parameter of the affinity of Hb to oxygen, is the PO2 at the 50% SO2

Normal value : P_{50} = 26-27mmHg

Influence factor: right shift → P50 ↑ left shift → P50 ↓

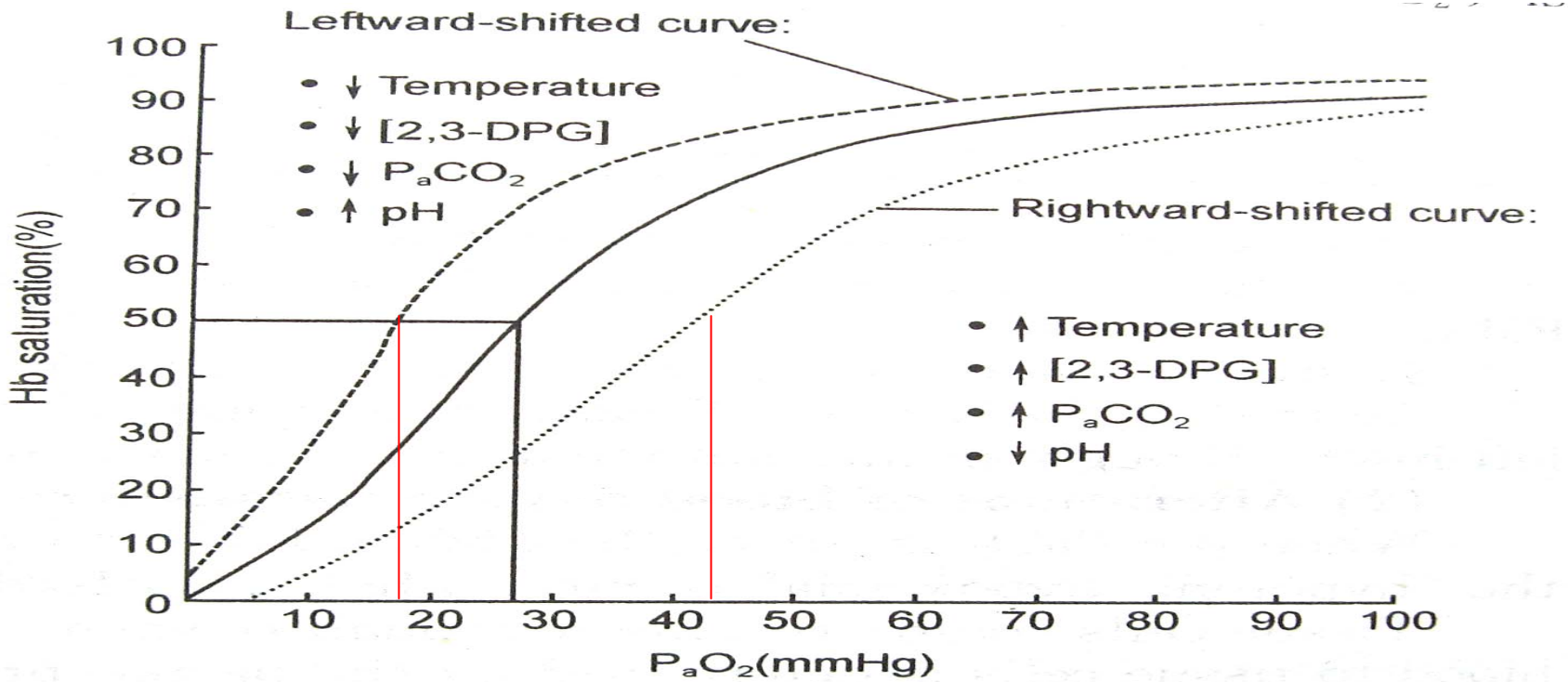
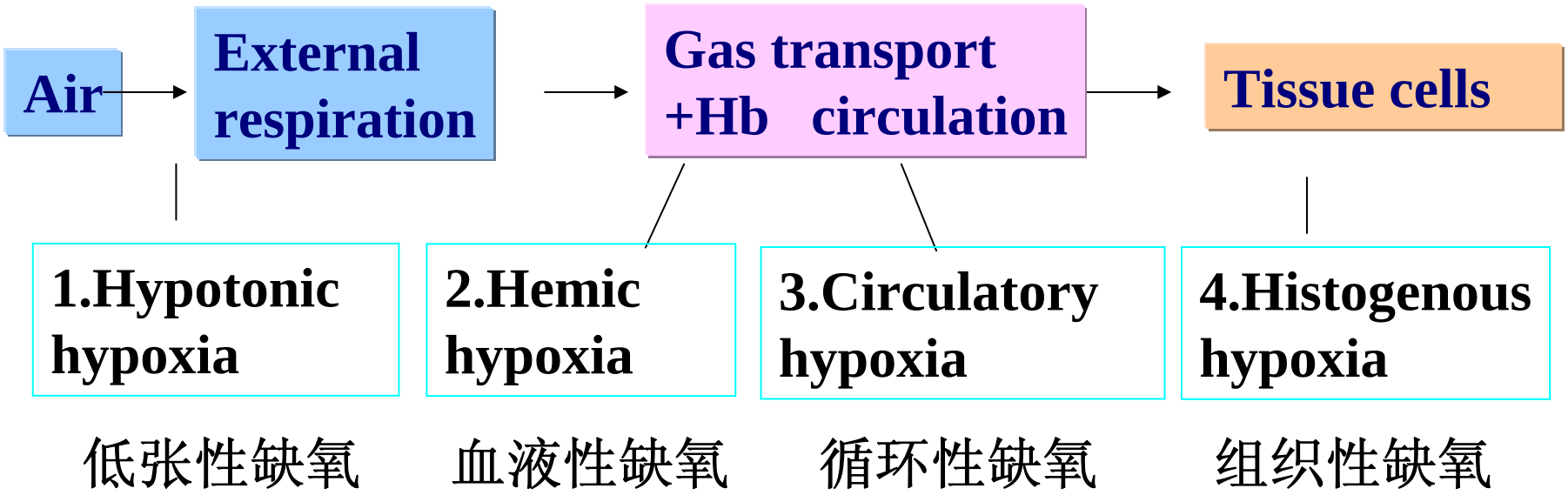


Figure 4-1 Dissociation curve of oxyhemoglobin

Section II. Classification, etiology and mechanisms of hypoxia



Uptake → Carry → Transport →Utilization

1.Hypotonic hypoxia低张性缺氧

Uptake → Carry → Transport →Utilization

Feature: $PaO_2 \downarrow \rightarrow CaO_2 \downarrow \rightarrow O_2$ supply $\downarrow$

(1) Underlying causes

1) Decreased oxygen pressure in the inspired air
(upper air, highland, poor ventilation)

2) Disturbance of outer respiration
(hypoventilation- respiratory hypoxia)

3) A shunt of blood from vein to artery (congenital heart disease)

(2) Characteristics of blood oxygen and mechanisms of tissue hypoxsia

Characteristics of blood oxygen

PaO_2, CaO_2, SaO_2 : all decresed

CaO_2 max : normal

CaO_2 - CvO_2 : Decresed (e.g. 16-13=3ml/dl)

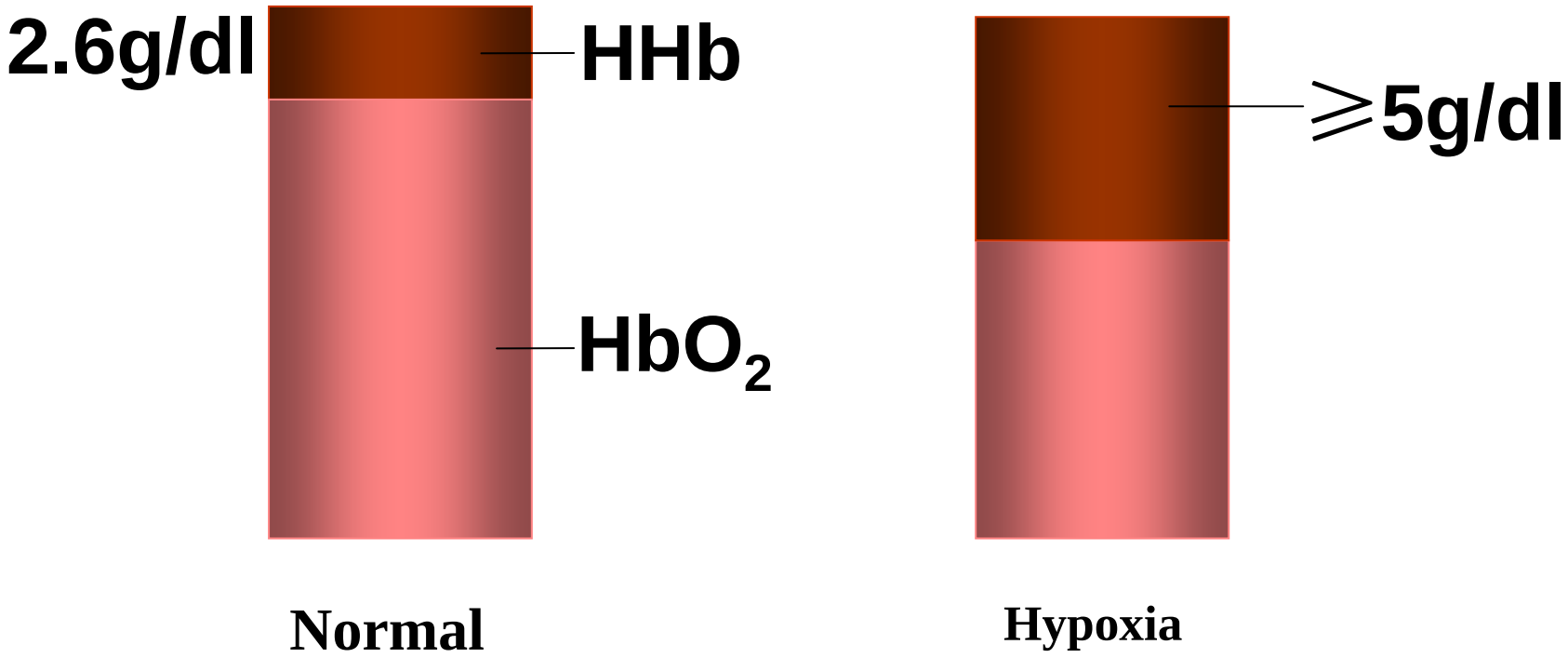
kept normal (if a compensative increase of cellular ability to use oxygen occurs in chronic hypoxia)

Mechanisms of tissue hypoxsia

$PaO_2 \downarrow \Rightarrow$ rate of O_2 diffusion $\downarrow$

Clinical feature- Cyanosis 紫绀

hypotonic hypoxia → PaO2 ↓ → HbO2 ↓ →HHb ↑， HHb ↑ > 5g/dl→ cyanosis
(bluish discoloration of the skin, nail bed and mucous membranes)



血液性缺氧

2.Hemic Hypoxia (isotonic hypoxemia)

Uptake → Carry → Transport →Utilization

- Caused by ***reduced quantity*** or *alternative quality* of Hb, which may decrease CO_2 or interfere O_2 release from Hb leading to tissue hypoxia, although PO_2 is normal.

- As PO_2 is normal, it is also called isotonic hypoxemia.

(1) Underlying causes

decrease CO_2

1) **Anemia**贫血

2) **Carbon monoxide poisoning** 碳氧血红蛋白血症

3) **Methemoglobinnemia** 高铁血红蛋白血症

4) **Abnormal high affinity of Hb to oxygen**

Infusion of alkali fluid or stored blood (2,3- DPG content is low) may shift the O_2 dissociation curve to the left and increase the affinity of hemoglobin to oxygen.

alternative quality of Hb

Anemia贫血

O_2 change in blood for health and anemia when 100ml blood through Cap and released 1mlO_2

			when 100ml blood through cap and released 1ml O_2	
health	HbX	CO_2max 20ml/dl	SO_2	PO_2（mmHg）
			95%→90%	100→63
anemia	1/2X	10ml/dl	95%→85%	100→53

Anemia: CO_2 ↓ , O_2 diffusion ↓ → (A-V) ↓ tissues hypoxia

CO poisoning (Carboxyhemoglobinemia)

HbO_2 + CO $\rightleftharpoons$ HbCO (carboxyhemoglobin) +O_2

① The affinity of Hb for CO is 210 times as its affinity for O2 and COHb release CO very slowly.

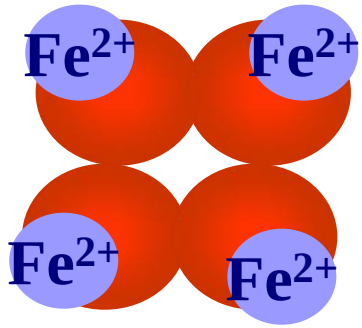
② CO reduces 2，3- DPG amount in RBC, the dissociation curve of HbO_2 is shift to left ,so that O_2 release from HbO_2 at the tissue level is more difficult.

Methemoglobinemia

$$\mathbf{Hb \cdot Fe^{2+}}\ \textbf{(}\text{deoxyhemoglobin)} \xrightarrow[\text{oxidant}]{} \mathbf{Hb \cdot Fe^{3+} \cdot OH}\ \textbf{(}\text{methemoglobin)}$$

① When oxidants (nitrites) poisoning , Hb is oxidized to MHb, which losing the function of carrying O_2

② MHb can increase the affinity of Hb combine to O_2, so the dissociation curve of HbO_2 is shift to left.



Hb: α2β2

(2) Characteristics of blood oxygen of tissue hypoxia

Characteristics of blood oxygen

PaO_2, SaO_2 : normal (normal outer respiratory)

CaO_2max :

- decresed
  - reduced quantity or alterative quality of Hb $\Rightarrow CaO_2 \downarrow$
- normal
  - abnormal high affinity of Hb to oxygen $\Rightarrow$ release $O_2 \downarrow$

$(CaO_2 - CvO_2)$: reduced (e.g. 16 – 13 = 3

or 19 – 16 = 3)

Mechanisms of tissue hypoxia

$CaO_2 \downarrow$ or O_2 release from Hb$\downarrow$

$\rightarrow PaO_2$ decreased rapidly during the transport process

$\rightarrow PO_2$ in capillary $\downarrow$ Tissue hypoxia

Clinic features

Discoloration of the skin:

1) Anemia --- pallid苍白

2) Carbon monoxide poisoning --- cherry red or pallid

3) Methemoglobinnemia --- brown (similar to cyanosis)

Enterogenous cyanosis肠源性紫绀

3.Circulatory hypoxia (hypokinetic hypoxia)

Uptake → Carry → Transport →Utilization

Caused by reduced oxygen supply to tissue due to reduced tissue blood flow and also called hypokinetic hypoxia

May be divided into two types:

Ischemic hypoxia

arterial pressure ↓ or arterial occlusion

tissue blood flow ↓ ⇒ O_2 supply ↓

venous pressure ↑ or venous occlusion

Congestive hypoxia

(1) Underlying causes

1) Generalized circulation deficiency (Shock, Heart failure)

2) Local circulation deficiency (Embolism, Atherosclerosis, thrombosis)

(2) Characteristics of blood oxygen and mechanisms of tissue hypoxia

PaO_2, SaO_2, CaO_{2max} CaO_2 : 1 all normal

Slowed blood flow
- 2 O_2 diffuse ↑ ⇒ C_vO_2 ↓ ⇒ $C_aO_2 - C_vO_2$ ↑
- 3 → **Cyanosis**
- Tissue blood flow ↓ ⇒ tissue hypoxia

(normal: 19–14ml/min slowed: 19 –12ml/2min=3.5ml/min)

4.Histogenous Hypoxia组织性缺氧

Uptake → Carry → Transport →Utilization

It is caused by impaired cellular utilization of oxygen

(1) Underlying causes

1) Histotoxic hypoxia (Cyanide, sulfide, arsenide)

Inhibit cytochrome oxidase (Cyanide can combine with Fe^{3+})

⇒ interrupt electron transfer in the respiratory chain

2) Cell injury (radiation, bacterial toxin ⇒ mitochondria damage)

3) Impaired synthesis of respiratory enzymes (deficiency of vitamins) e.g. VB_1 is the coenzyme of pyruvate dehydrogenase

(2) Characteristics of blood oxygen

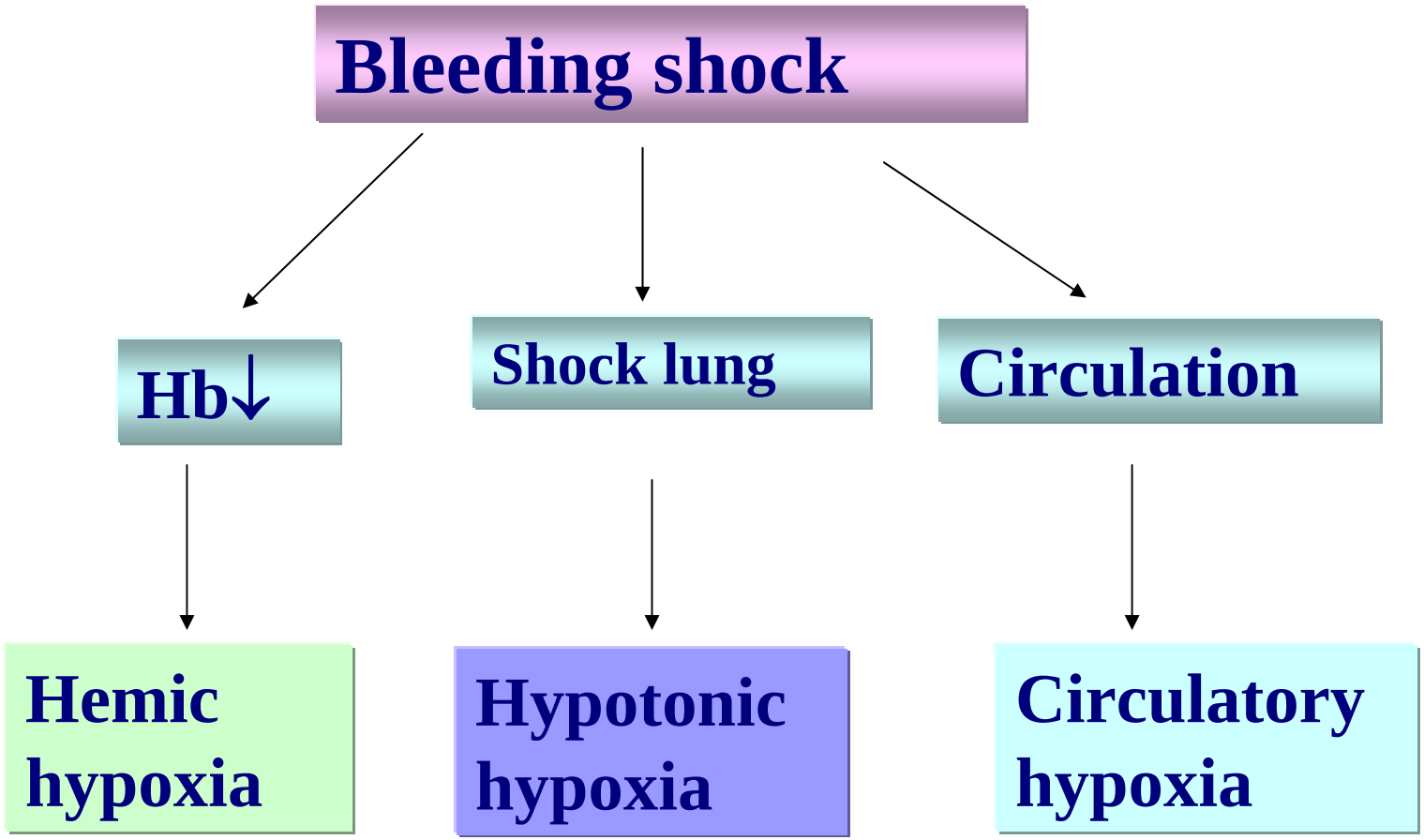
PaO_2, SaO_2, CaO_2max, CaO_2 : normal

$C_aO_2 - C_vO_2$: decresed (utilization of oxygen by tissues↓)

Blood O_2 characteristics in different kinds hypoxia

Types of hypoxia	PaO_2	CO_2max	CaO2	SaO_2	CaO2-CvO2
Hypotonic hypoxia	↓	N	↓	↓	↓ or N
Hemic hypoxia	N	↓ or N	↓ or N	N	↓
Circulatory hypoxia	N	N	N	N	↑
Histogenous hypoxia	N	N	N	N	↓

Mixed Hypoxia



Section Ⅲ. Functional and Metabolic Changes of the Body in hypoxia

The effects of hypoxia on the body depending on：

the velocity, extent, duration of hypoxia

the functional and metabolic status of the body.

The effects include：

Compensatory responses

Mild (PaO_2 30-60mmHg)

injurious changes

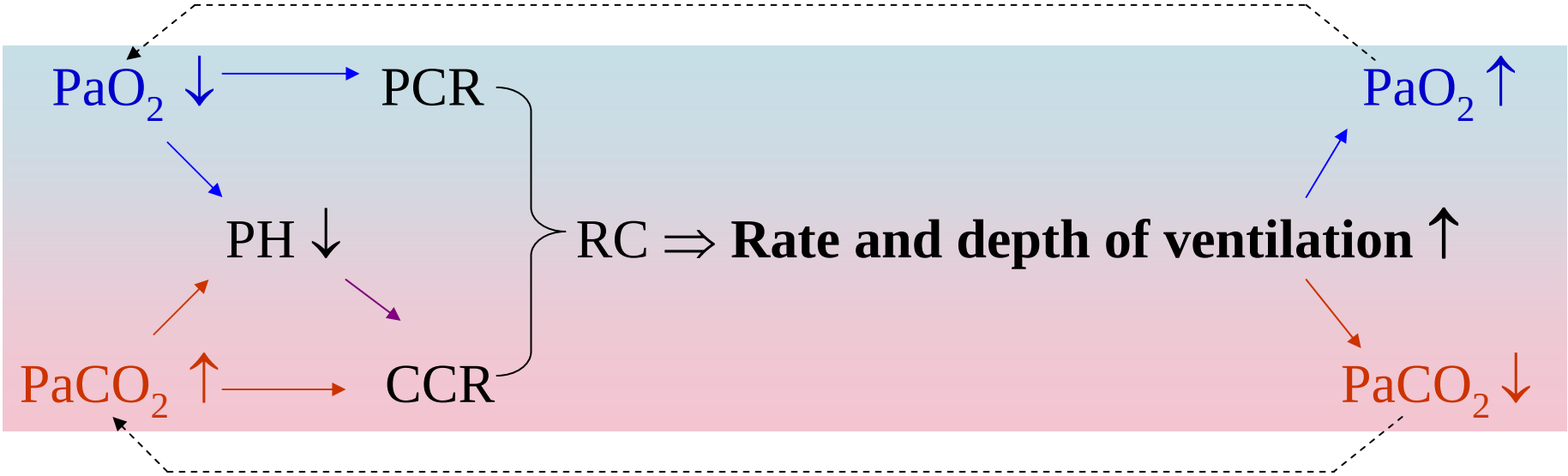
Severe(PaO_2 <30mmHg) or Rapid

The responses and alterations caused by different types of hypoxia may various, although there are some common features.

The followings are take the hypotonic hypoxia as an example:

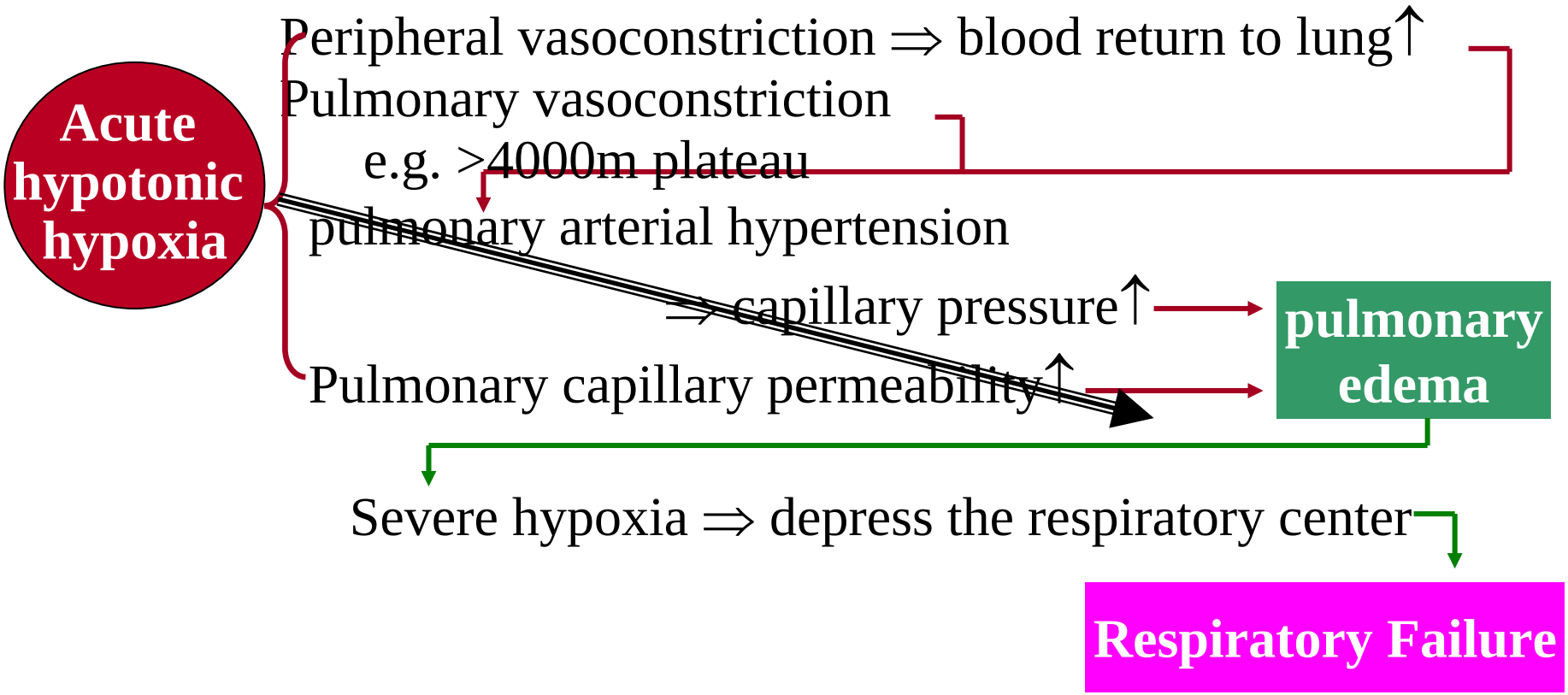
1. Respiratory system

(1) Compensatory responses



(PCR= peripheral chemoreceptor; CCR= central chemoreceptor; RC= respiratory center)

(2) Dysfunction of respiration



2. Circulatory system

- **(1) Compensatory responses**
- 1) Increase of cardiac output (heart rat ↑, myocardial contractibility↑, venous return ↑)
- 2) Blood redistribution (skin and abdominal organs → heart and brain)
- 3) Pulmonary vasoconstriction (effect of sympathetic nerve, humoral factors and and direct effect on SMC)
- 4) Capillary proliferation (increased expression of VEGF)

(2) Dysfunction of circulation

1) Pulmonary arterial hypertension

2) Abnormality of cardiac function and structure
(Decrease of myocardial contractility and extensibility, arrhythmia, etc.)

3) Decreased venous return

3. Hemic system

- **1) Increase of RBC**

  chronic hypoxia → erythropoietin ↑

- **2) Rightward shift of oxyhemoglobin dissociation curve**

  2,3-DPG ↑ → Affinity of Hb to oxygen ↓

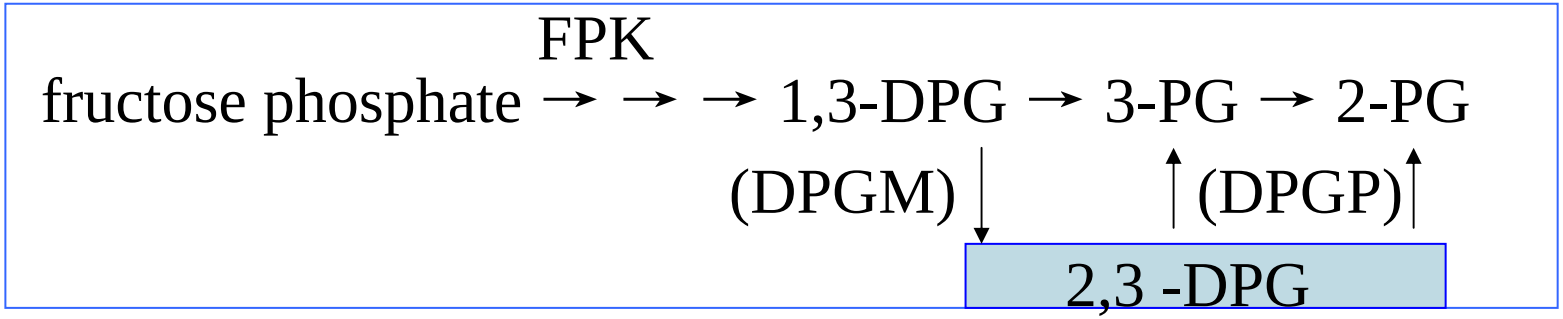
  → release of oxygen from Hb ↑

Mechanisms of rightward shift of ODC by increased 2,3-DPG

① 2,3-DPG combined with HHb →combination of HHb with O_2 ↓

② 2,3-DPG ↑ → pH in RBC ↓ → affinity of Hb with O_2 ↓

Mechanisms of increase of 2,3-DPG in hypoxia:



① Hypoxia → HbO_2 ↓ HHb ↑ → free 2,3-DPG in RBC ↓

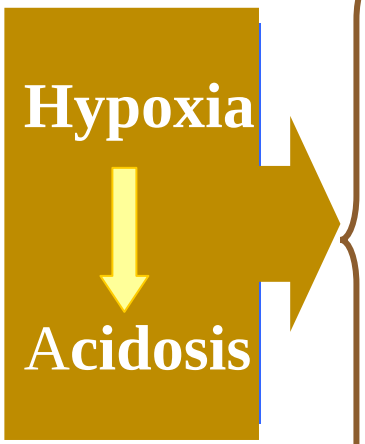
→ inhibitory effect of 2,3-DPG on fructose phosphate kinase and DPGM ↓ → production of 2,3-DPG ↑

② Hypoxia → Compensatory hyperventilation → respiratory alkalosis

→ pH ↑ → activating fructose phosphate kinase → glycolysis ↑ → production of 2,3-DPG ↑

→ activity of DPGP ↓ → degradation of 2,3-DPG ↓

4. Changes in CNS



- decreased RMP
- decreased synthesis of neurotransmitter
- decreased generation of ATP
- increased free Ca^{2+} in the cells
- lysozyme release
- cell edema→ intracranial pressure ↑
- vasodilation↗

Disturbance Of CNS

PO_2 in cerebral vein:

- 34mmHg → Normal
- 28mmHg → insanity
- 19mmHg → unconsciousness
- 12mmHg → life threaten

5. Changes in tissue and cells

(1) Compensatory responses

1) Enhanced ability of tissue and cell for oxygen utilization

Number and membrane area of mitochondria ↑

Activity of enzymes in respiratory chain ↑

2) Enhanced anaerobic glycolysis

ATP ↓ → ATP/ADP ↓ → activity of fructose phosphate kinase ↑

3) Increased myoglobin

(may release more oxygen when PO_2 in tissue decreased)

4) Low metabolic status (may decrease cellular energy consumption)

(2) Hypoxic cell damage

1) Cell membrane injury $\Rightarrow$ permeability $\uparrow$

$\Rightarrow$ Na^+ and Ca^{2+} go into cells; K^+ go out.

Na^+ inflow $\rightarrow$ intracellular $Na^+\uparrow$ $\rightarrow$ cell edema

K^+ outflow $\rightarrow$ intracellular $K^+\downarrow$ $\rightarrow$ anabolism $\downarrow$

Ca^{2+} inflow $\rightarrow$ intracellular $Ca^{2+}\uparrow$

$\rightarrow$ { inhibiting respiratory function of mitochondria
activating phosphatase $\rightarrow$ lysosome damage
transferring Xanthin dehydrogenase to Xanthin oxidase

$\rightarrow$ free radical generation$\uparrow$

2) Mitochondria injury (swelling, broken)

$\Rightarrow$ ATP generation $\downarrow$

3) Lysosome injury:

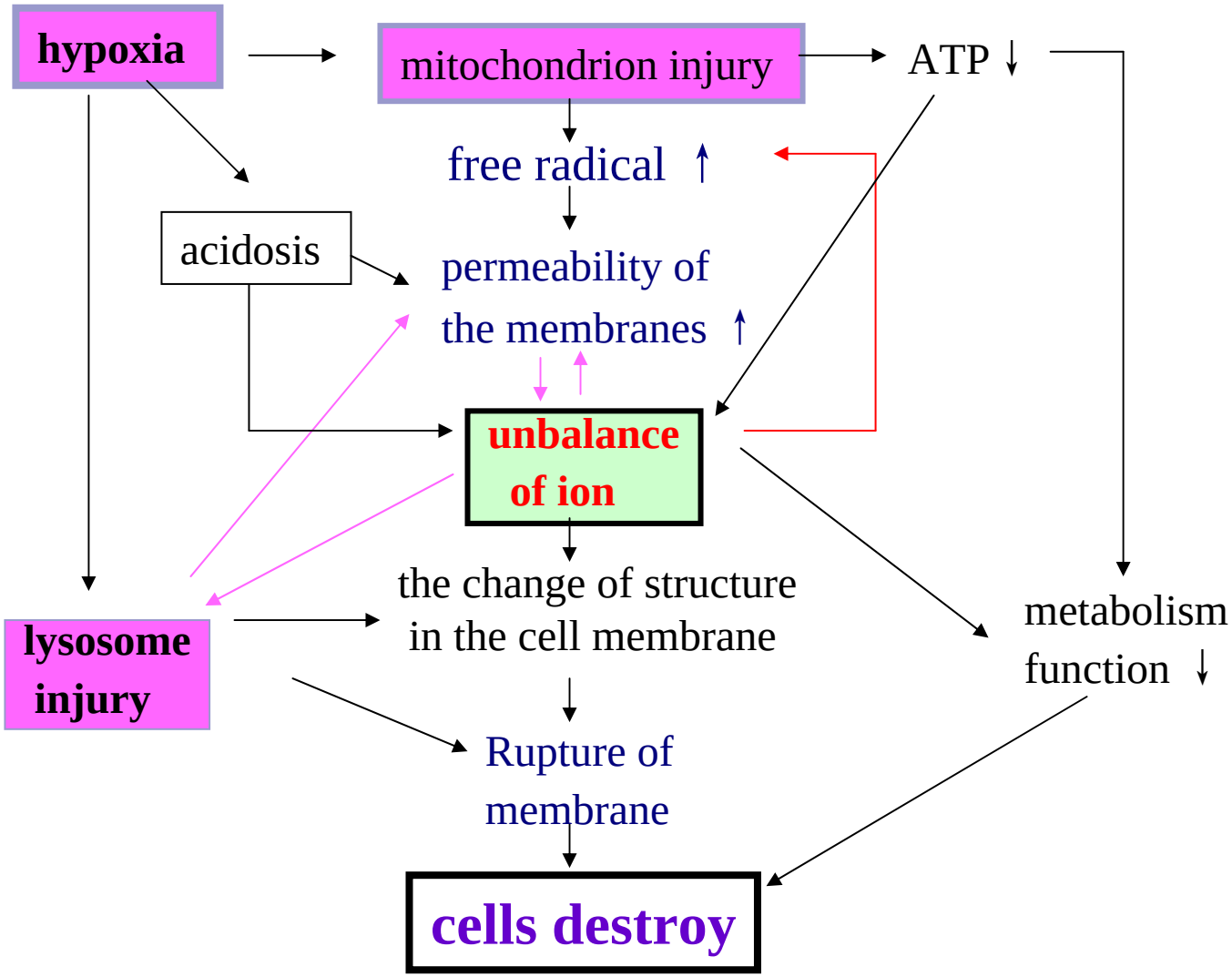
Acidosis $\Rightarrow$ phosphatase activity $\uparrow$

$\Rightarrow$ degradation of membrane phospholipid

$\Rightarrow$ permeability $\uparrow$ $\Rightarrow$ lysosome swell and break down

$\Rightarrow$ lysozyme release $\Rightarrow$ cell lyses and death

The mechanism of cell injury in hypoxia



Section Ⅳ. Factors Influencing the Tolerance to Hypoxia

(1) Oxygen consumption rate of metabolism

Fever, hyperthyroidism, cold, physical activity, agitation

$\rightarrow O_2$ consumption $\uparrow \rightarrow$ tolerance for hypoxia $\downarrow$

Decrease of body temperature, inhibition of CNS

$\rightarrow O_2$ consumption $\downarrow \rightarrow$ tolerance for hypoxia $\uparrow$

(2) Compensatory ability of the body

patients of heart, lung and blood disoders, elder

$\rightarrow$ pulmonary and cardiac reserve $\downarrow$ enzymes activity $\downarrow$

$\rightarrow$ compensatory ability $\downarrow$

It may be improved by exercise

Section Ⅴ. Oxygen therapy and oxygen intoxication

1. Oxygen Treatment

Administration of oxygen-rich gas mixtures is useful for hypotonic hypoxia, but is of very limited value in circulatory, hemic or histogenous hypoxia.

However, it may increase the amount of oxygen dissolved in plasma, which is beneficial for supplying of oxygen to tissue

2. Oxygen Toxicity

Although oxygen is essential for life, it is toxic for all cells when its pressure is high (more then 380 mmHg) and may leading to **oxygen intoxication**, which is thought to be related to the active oxygen including free radical and H_2O_2.

Oxygen toxicity depends on the **partial pressure** and the **inspire duration**. The higher of partial pressure of oxygen and the longer of inspire duration, the more of generation of active oxygen, and may cause tissue damage.

There are two types of oxygen toxicity in human being:

1) pulmonary oxygen intoxication; 2) cerebral oxygen intoxication.

Summary

Hypoxia is referred to a pathological process in which the tissues do not receive adequate oxygen or cannot make use of oxygen, leading to abnormal changes in metabolism, function and structure of tissues.

According to the causes, hypoxia is usually classified into four basic types: hypotonic, hemic, circulatory and histogenous hypoxia.

The effects of hypoxia depending on the velocity, extent, duration of hypoxia and functional and metabolic status of the body. The functional and metabolic changes include compensatory responses to hypoxia and injurious changes caused by hypoxia.

Although administration of oxygen-rich gas mixtures is useful for hypoxia, it is toxic for all cells when its pressure is high.