HYPOXIA, ACCLIMATIZATION, CYANOSIS, OXYGEN THERAPY

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DEFINITION AND TYPES OF HYPOXIA

❑*Hypoxia is O2 deficiency at the tissue level.* It is a better term than *anoxia* (= complete 02 lack at the tissues) because the latter never occurs clinically.

❑On the other hand, *hypoxaemia refers to 02 deficiency in the blood.*

❑Depending on the cause, hypoxia is classified into *4 main types*:

1. Hypoxic hypoxia.
2. Anaemic hypoxia.
3. Stagnant hypoxia.
4. Histotoxic hypoxia.

(1) HYPOXIC HYPOXIA

- In this type, the *hypoxia occurs secondary to hypoxaemia.* The P02 and 02 content as well as the % saturation of Hb with 02 are all decreased in *both the arterial and venous blood*

- There is also cyanosis due to *presence of excessive amounts of reduced Hb in the blood*. The common causes of hypoxic hypoxia include the following :

1. Breathing air that contains low 02 % than normal (e.g. in high altitudes) and places that are not properly ventilated (e.g. mines).

2. Inadequate pulmonary ventilation *(respiratory pump failure)* : This results from *defective breathing* which may occur due to either :

a- Depression of the respiratory centre (e.g. in morphine poisoning).
b- Weakness or paralysis of the respiratory muscles (e.g. in poliomyelitis).
c- Fatigue of the respiratory muscles (e.g. in bronchial asthma).
d- Pneumothorax, hydrothorax, chest deformities and emphysema.
e- Shallow rapid breathing (e.g. in pulmonary congestion or embolism).

3. Gas exchange failure: This occurs in diseases that cause *alveolo-capillary block* (e.g. pulmonary fibrosis or edema and pneumonia) or *ventilation perfusion imbalance.*

4. Right to left cardiac shunts (e.g. atrial and ventricular septal defects) : These transfer venous blood to the left side of the heart (without oxygenation in the lungs), resulting in hypoxaemia and consequently hypoxia.

(2) ANAEMIC HYPOXIA

- In this type, the hypoxia occurs due to *deficiency of the amount of Hb available to carry 02 .* In the arterial blood, the 02 content is decreased but the PO2 is normal, while both are decreased in the venous blood.

- Its common causes include the following :

1. All types of anaemia.
2. Transformation of Hb by certain toxins and drugs into compounds that are unable to carry 02 e.g. sulph-Hb and metHb (refer to blood).
3. Carbon monoxide (CO) poisoning.

Carbon monoxide (CO) poisoning

- CO combines with Hb and forms carboxv-Hb CCOHb). The affinity of Hb to CO is about *250 times its affinity to 02,* and *COHb cannot bind to* 02 (because CO binds to the ferrous atoms in the Hb molecule).

- CO also *shifts the O2Hb dissociation curve to the left* and this further decreases delivery of oxygen to the tissues, resulting in severe hypoxia (which is fatal if 70 - 80 % of Hb is converted to COHb)

Symptoms

1. Symptoms of other types of hypoxia *(see below)* specially *headache and nausea* (however, since the arterial *P02* is normal, the peripheral chemoreceptors are not stimulated, so *respiration is little stimulated)*

2. The skin and mucous membranes are *cherry red* (colour of COHb)

3. Symptoms of brain damage (mental changes & parkinsonism like state) appear with exposure to small doses of the gas.

Treatment

1. Removing the patient away from the source of the gas, keeping him at complete rest and improving his ventilation by *artificial respiration*

2. Breathing a mixture of 95 % *02* and 5 % C02. *02* helps COHb dissociation, while C02 stimulates respiration. *Hyperbaric 02* (02 under high pressure) can also be used

3. *Exchange blood transfusion* may be required in severe cases.

(3) STAGNANT (ISCHAEMIC) HYPOXIA

❑ In this type, the hypoxia occurs due to blood stagnation (or slow circulation) in the tissues. Both the *PO2 and 02 content are normal in the arterial blood but decreased in the venous blood*, leading to cyanosis in the affected areas. Blood stagnation may be either :

1. Generalized (i.e. allover the body) e.g. in congestive heart failure, circulatory shock, and polycythaemia vera

2. Localized e.g. in areas of venous thrombosis or V.C. (the latter is characteristic of Raynaud's disease, in which severe V.C. occurs in the tips of the lingers and toes, specially on exposure to cold)

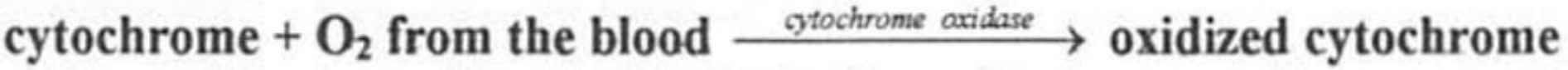
(4) HISTOTOXIC HYPOXIA

- In this type, the hypoxia occurs due to *blockage of the enzymes* involved in tissue (or internal) respiration (= the process of gas exchange in the cells).

- Thus, although the arterial PO2 and 02 content are normal, yet 02 cannot be extracted, and consequently, *their levels are increased in the venous blood* and approach their levels in the arterial blood

- Tissue respiration depends on a haem-like substance called *cytochrome* and certain enzymes, specially *cytochrome oxidase.* These are concerned with 0 2 transport from the blood to the tissues by the following reaction :

- The oxidized -cytochrome –releases its 02 to the tissues and becomes reduced. The reduced cytochrome then gets 02 from the blood and becomes oxidized, and the cycle is repeated. The commonest cause of histotoxic hypoxia is cyanide poisoning



Cyanide poisoning

- The cyanide salts block the cytochrome oxidase enzyme, so the cells become hypoxic because they become unable to extract *02* from the blood.

- The condition can be improved by hyperbaric oxygenation and also by giving methylene blue or nitrite salts (these substances convert Hb into metHb, which reacts with cyanide and form the non-toxic compound cyan-metHb).

❑The following table shows the P02 and *0 2* content in the arterial and venous blood in various types of hypoxia :

	ARTERIAL BLOOD		VENOUS BLOOD	
	P_{O2}	O_2 content	P_{O2}	O_2 content
HYPOXIC HYPOXIA	decreased	decreased	decreased	decreased
ANAEMIC HYPOXIA	normal	decreased	decreased	decreased
STAGNANT HYPOXIA	normal	normal	decreased	decreased
HISTOTOXIC HYPOXIA	normal	normal	increased	increased

SYMPTOMS OF HYPOXIA

- Sudden severe hypoxia is fatal due to deprerssion of the respiratory centre. On the other hand, mild and moderate hypoxia lead to the following :

1. *Nervous symptoms* e.g. headache, fatigue, disorientation and drowsiness.
2. *Digestive symptoms* e.g. anorexia (loss ofappetite), nausea and vomiting.
3. Respiratory symptoms (tachypnea and may be periodic breathing).
4. Cardiovascular symptoms: Tachycardia, high cardiac output and hypertension, followed by fainting in long-standing cases.

- In chronic hypoxia, the alveolar hypoxia causes pulmonary V. C., which may lead to pulmonnary hypertension and overstraining of the right ventricle.

ACCLIMATIZATION

- This term refers to the adaptive mechanisms that occur in high altitudes (i.e. on prolonged exposure to low 02 pressures). The body tries to compensate and improve O2 delivery to the tissues.

- At high altitudes, the composition of air remains constant but its total pressure falls. This results in marked reduction of the PO2 in atmospheric air

- The minimal alveolar PO2 that can be tolerated without loss of consciousness is *40 mmHg (at* which Hb is about 75% saturated with 02). The altitude at which this occurs *varies according to whether the subject is breathing air or 100% O2:*

- If the subject was *breathing air,* this P02 is reached when the atmospheric pressure decreases to 350 mmHg (at an altitude of about 6100 meters) while if the subject was breathing 100% O2, it is reached when the atmospheric pressure decreases to 120 mmHg (at an altitude of about 13700meters)

ACUTE MOUNTAIN SICKNESS

- This is a condition that may occur in some individuals when they ascend to high altitudes for the first time. It occurs within 8 - 24 hours and lasts for 4-8 days.

- Its symptoms include *headache, dizziness, irritability, insomnia, fatigue, dyspnea, palpitation, anorexia, nausea and vomitting.*

- Its cause is probably *cerebral edema* (which is often produced secondary to V.D. of the cerebral vessels that occurs as a result of the low arterial P02) because the symptoms markedly improve when the cerebral edema is treated.

ACCL MATIZATION MECHANISMS

❑The compensatory mechanisms involved in acclimatization usually starts within *one week. They aim at increasing 02 delivery to the tissues,* and they include the following:

1. Increase of the pulmonary ventilation: This occurs as a result of stimulation of the respiratory centre by signals discharged from the *peripheral chemoreceptors* (which are excited when the arterial Po2 drops below 60 mmHg).

❑The initial response is relatively small because the resulting hyperventilation washes C02 in the expired air resulting in *alkalosis* (which tends to inhibit the respiratory centre).

❑However, within a few days ventilation markedly increases due to :

a- *Correction of the alkalosis* through excessive excretion of HC03, by the kidneys in the urine (so the urine pH in high altitudes is alkaline).

b- *Stimulation of the central chemoreceptors by the lowered brain pH* (which is produced as a result of development of lactic acidosis, as well as shift of HC03- from the brain to the plasma).

2. Increase of the blood O2- carrying capacity: This occurs as a result of *stimulation of erythropoiesis* under the effect of the *erythropoietin hormone* (which is secreted by the kidneys in response to O2 lack).

- The red cell count increases up to 8 million/mm3 (= *physiological polycythemia)* and the Hb content may increase by 50 % (which increases the 0 2-canying capacity of the blood) and in addition, the *haematocrit value increases up lo 60 %and the blood volume by 20 30 %*.

3. Increase of the circulatory rate: Signals from the peripheral chemoreceptors stimulate the vasomotor centre, resulting in *tachycardia and an increase of both the cardiac output and arterial blood pressure.*

- In *addition, peripheral V.D. and angiogenesis* also occur under the effect of 02 lack. All these effects increase the blood flow to the tissues.

4. Increase of 02 liberation at the tissues: This is produced through *stimulation of 2-3 DPG synthesis* in the red blood cells at high altitudes, which facilitates *02* liberation from Hb02 by shifting the 02-Hb dissociation curve to the right

❑2-3 DPG *antagonizes the effect of alkalosis* (which tends to shift the O2Hb dissociation curve to the left) and produces *a net increase of the P50.*

5. Cellular compensatory changes: In response to the low arterial *PO2,* all the following increase in the cells :
a- The mitochondria (the site of oxidative reactions).
b- The myoglobin content in skeletal muscles.
c- The oxidative enzymes (specially the cytochrome oxidase enzyme).

❑What is the role of the kidneys in high altitudes with respect to acclimatization?

- Over subsequent weeks and months most people acclimatize to living at high altitude, although the ability to perform strenuous exercise may be limited.

No human communities live permanently above 5500m because further acclimatization becomes impossible; instead there is slow deterioration in all aspects.

- The various compensating mechanisms:

1. Respiratory functions: Hyperventilation continues; pulmonary diffusion capacity can increase upto threefold as a result of more open pulmonary capillaries; increased pulmonary capillary blood volume and greater alveolar surface area. Cyanosis may be absent at rest.

2. Kidney functions: they excrete HC03 and eventual correction of the respiratory alkalosis. This takes 2-3 weeks

3. Cardiovascular functions: Perfusion and heart rate tend to come back to sea level values. Hypoxic vasoconstriction leads to pulmonary hypertension and right ventricular hypertrophy. The vasoconstriction also precipitates muscularization of pulmonary arterioles, which are normally devoid of smooth muscle.

4. Tissue function: there is an increase in the capillary of many tissues and in the concentration of cytochrome oxidase; the former improves O2 transfer and the latter permits the mitochondria to utilize the O2 more effectively. The myoglobin content of the skeletal muscles also increase, which raises the reserve store of O2; myoglobin may also facilitate intracellular diffusion.

5. Blood: there is an increase in 2,3 BPG production which shifts the OxyHb curve to the right, to enable O2 to be offloaded to the tissues more easily. Hypoxia increases, erythropoeitin production leading to polycythemia. Hb concentration may increase to as much as 20gm/dL and despite los PO2 and % saturation of Hb with O2, O2 content will not fall as much. What is the disadvantage to this?

- Some individuals successfully acclimatize gradually or even suddenly fail in their compensation response.
- Their ventilation falls producing dyspnoea and cyanosis.
- Hematocrit and pulmonary arterial pressure iincreases further, leading to right heart failure.
- In sudden failure, pulmonary oedema is the most dominant feature.
- These are all the symptoms of chronic mountain sickness

Colour of the skin in various types of hypoxia

1. In **hypoxic hypoxia**, there is *cyanosis* (i.e. the skin is *bluish)* because of presence of abnormally great amounts of reduced Hb in the blood.

2. In **anaemic hypoxia**, the skin *is pale,* except in CO poisoning in which the skin is *cherry red* (which is the colour of carboxyHb).

3. In **stagnant hypoxia**, there is *cyanosis* (i.e. the skin is *bluish)* because of presence of abnormally great amounts of reduced Hb in the venous blood as a result of blood stagnation in the tissues.

4. In **histotoxic hypoxia**, the skin is *red* because the amount of oxyHb in the arterial blood is normal *while that in the venous blood is increased*

CYANOSIS

- Cyanosis is a *blue discolouration of the skin and mucous membranes* due to presence of an abnormally great amount of reduced Hb in the superficial capillaries.

- It is easily seen in the nail beds, mucous membranes, and the areas that have thin skin e*g.* the ear lobes. *lips* and fingers

THRESHOLD OF CYANOSIS: This is the minimal concentration of reduced Hb in the capillary blood that leads to appearance of cyanosis. Under normal conditions, the threshold of cyanosis is 5 gm reduced Hb */* 100 ml of capillary blood.

**Cyanosis does not occur normally because the amount of reduced Hb in the capillary blood is calculated to be only 2.1 gm/100 ml as follows :

a- The arterial blood contains 3 % reduced Hb, and since the Hb concentration in the blood averages 15 gm %, then the amount of reduced Hb in the arterial blood = ***15 x 3 / 100 = 0.45 gm / 100 ml.***

b- The venous blood contains 25 % reduced Hb, so the amount of reduced Hb in the venous blood = ***15 x 25 / 100 = 3.75 gm / 100 ml.***

c- The amount of reduced Hb in the capillary blood is the average of the amounts present in the arterial and venous blood =

[0.45] + [3.75] ÷ 2 = 2.1 gm / 100 ml blood

CAUSES OF CYANOSIS

1. Hvpoxic hypoxia (because both the arterial and venous blood contain abnormally greater amounts of reduced Hb).
2. Stagnant hypoxia (due to much reduction ofHb in the venous blood).
3. Asphyxia (in which there is both hypoxia and hypercapnia).

*** *In high altitudes, the threshold of cyanosis is more easily reached* because the total amount of Hb is markedly increased.

****Cyanosis does not occur in anaemic hypoxia* (because the totalamount of Hb is decreased) specially in CO poisoning (because of the cherry red colour ofcarboxyHb).

****Cyanosis does not also occur in histotoxic hypoxia* (because the venous blood contains a smaller amount of reduced Hb than normal).

***Normal subjects frequently develop cyanosis in cold weather* due to slowing of the blood flow in the sign as a result of V.C.

- However cyanosis may be *absent in very cold weather* because the release of 02 from Hb in this case is much decreased (due to reduction of the tissue activity and shift of the *O2H*b dissociation curve to the left).

- In the latter condition, the skin colour may be *reddish* because the severe V C leads to tissue ischaemia. and this increases the formation of metabolites, which accumulate and lead to V D. (resulting in the reddish colour of the skin).

DEPTH OF CYANOSIS

- There is usually no relation between the severity of the condition and the depth of cyanosis This is shown in the following examples

1. In cases of hypoxic hypoxia, bleeding improves cyanosis (due to loss of reduced Hb) although the condition becomes worst (due to loss of HbO2)

2. In high altitudes, persons may be very deeply cyanosed although they live almost normally (because the blood contains sufficient amounts of oxyHb).

TYPES OF CYANOSIS

1. Central cyanosis : This is *generalized* (allover the body) and it occurs in cases of hypoxic hypoxia that are due to central causes specially .

a- Cardiac diseases e.g. congestive heart failure and various septal defects.

b- Diseases that interfere with ventilation or,gas exchan_ge in the lungs.

2. Peripheral cyanosis :This is *localized* to the areas of reduced blood flow e.g. due to V.C., as occurs in *Reynaud's disease*

***Peripheral cyanosis can be differentiated from central cyanosis simply by *warming the skin.* This procedure leads to V.*D which improves peripheral cyanosis but does not affect central* cyanosis *or renders it deeper.*

***Cyanosis is differentiated from skin contusions simply by *applying pressure to the discoloured area.* This procedure *does not affect contusions but improves cyanosis (because it squeezes blood out from the capillaries).*

1. In cases of hypoxic hypoxia, bleeding improves cyanosis (due to loss of reduced Hb) although the condition becomes worst (due to loss of HbO2)

FACTORS THAT AFFECT CYANOSIS

1. Capillary factors: Factors that increase the number of open capillaries or heir diameters e g (heat, *C02* and acid metabolites) increase the depth of central cyanosis but improve peripheral cyanosis

2. Skin thickness: Cyanosis is deeper in thin skin areas and vice versa.

3. Skin presentation: Cyanosis is altered by skin pigmentation, whether physiological (e.g. in yellow races) or pathological (e.g. in jaundice). In dark races cyanosis in the skin is masked, *but it can still be detected in the mucous membrane*

4. Blood composition: The presence of abnormally great amounts of *metHb* produces a cyanotic-like colour. Other abnormalities in the blood composition also alter the depth of cyanosis (e.g lipaemia and leukaemia).

5. The amounts of reduced Hb and oxyHb: Cyanosis becomes deeper if the amount of reduced Hb is increased or the amount of oxyHb is decreases and vice versa.

OXYGEN THERAPY

USES OF OXYGEN THERAPY IN HYPOXIA

1. Oxygen therapy is useful in cases of hypoxic hypoxia, except in cases of right to left cardiac shunts in which blood bypasses the lungs

2. Oxygen therapy is almost not useful in anaemic, stagnant and histotoxic hypoxia, in which it only increases the physically dissolved 0 2 in the blood.

3. Oxygen therapy improves cyanosis and is helpful in CO poisoning.

OXYGEN TOXICITY (HYPEROXIA)

(A) When using I00 % oxygen at one atmospheric pressure

- In this case, the administration of 02 for more than 8 hours causes *tracheobronchial irritation, substernal stress, nasal congestion, sore throat and coughing* and on exposure for 24-48 hours, lung *damage also occurs*

(A) When using I00 % oxygen at high atmospheric pressures

- This is known as *hyperbaric oxygen.* It accelerates the onset of the symptoms of 02 toxicity and, in addition, it causes *twitching of the muscles, ringing in the ears, dizziness, convulsions and coma.*

❑*Hyperbaric oxygenation is useful in the following conditions :*

1- Certain cases of cardiac surgery.

2- Gas gangrene.

3- CO poisoning (and may be *also* cyanide poisoning).

***The exposure to hyperbaric 02 shouldn't exceed 5 hours and at less than 3 atmospheric pressures, due its effects (see above) and dangers

DANGERS OF OXYGEN THERAPY

❑Prolonged exposure to pure 02 (specially hyperbaric O2) causes:

1. Thickening of the respiratory membrane(= *alveolo-capillacy block)*

2. *Decreased formation of the surfactant*.

3. *Decrease of the ATP content in the brain, liver and kidneys* (in rats).

4. *Retrolental fibroplasia* (formation of opaque vascular tissue in the eyes).

5. *Bronchopulmonary dysplasia* (a condition characterized by development of multiple lung cysts and densities). It frequently occurs (and also retrolental fibroplasia) in *premature infants who receive 02 in incubators.*

6. *Acidosis (due to excessive C02 dissolution in the blood)* : This occurs because the tissues obtain their 02 needs from the increased physically dissolved 02 and *not from oxyHb* (which decreases the amounts of reduced Hb and K+ that can carry *C02* in the chemical form.

7. Oxygen therapy may be fatal in the following conditions :

a- *Severe hypercapnia* : When this occurs (e.g. in chronic lung diseases that predispose to pulmonary failure), *the increased arterial Pcm depresses rather than stimulates respiration,* and the *resulting hypoxaemia becomes the main stimulant of the respiratory centre.*Oxygen therapy in these cases abolishes this hypoxic respiratory drive, which may lead to respiratory arrest and death

b- *Deep anaesthesia* : During deep anaesthesia, *the sensitivity of the central chemoreceptors to C02* is *decreased.* Accordingly, respiration is depressed, and the *resulting hypoxaemia becomes the main stimulant of the respiratory centre.* Oxygen therapy *in* these cases abolishes this hypoxic respiratory drive, which may lead to respiratory arrest and death.