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CORE TRAINING FOR DOCTORS

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Cyanosis

Cyanosis is a physical sign defined by many, including Snider (1990) and Weng et al (2009), as a bluish or purplish discolouration of the skin and mucous membranes. It is considered as 'peripheral' or 'central' depending upon the distribution of the discolouration and the underlying cause. The word 'cyanosis' comes from the Greek 'cyanos' meaning dark blue. In peripheral cyanosis the extremities are cyanosed (*Figure 1*) but the tongue remains a healthy pink colour. In central cyanosis, the extremities and the tongue and mucous membranes both have a bluish or purplish colour (*Figure 2*).

Figure 1. Cyanosis of the feet of an 86-year-old woman caused by peripheral vascular disease.

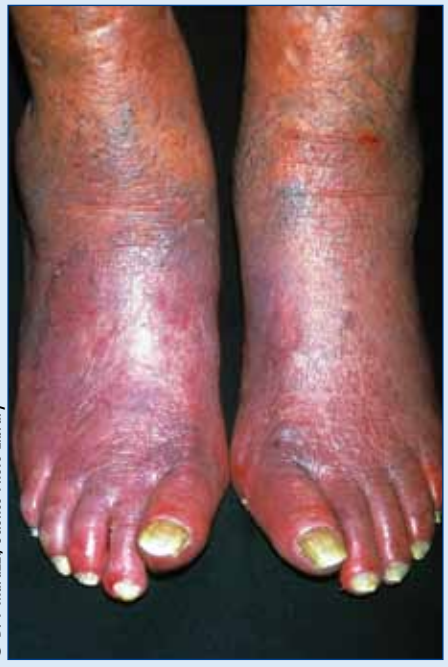

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Figure 2. Purple lips caused by central cyanosis in a 71-year-old man. This patient has chronic obstructive pulmonary disease and bronchiectasis lung disorder.

Detection

The colour of skin is normally determined by a combination of pigments from oxyhaemoglobin, deoxyhaemoglobin, melanin and carotene, and from the optical effect of scattering. Kienle et al (1996) described that the bluish colouration of cyanosis arises as a result of the scattering of different wavelengths of light, the absorption characteristics of the skin, the oxygenation state of blood (which affects its absorption properties), the diameter and the depth of blood vessels, and our visual perception.

Lighting is also important and intense light can make cyanosis less readily apparent: 20 footcandles (~200 lux) is regarded as optimal. This is equivalent to natural light on a cloudy day. As Snider (1990) described, inspection for cyanosis should ideally take place at body sites containing minimal melanotic pigment, that have a capillary bed close to the skin surface, and that are well perfused. Examples include the lips, ears, trunk, nail beds, hands and conjunctiva. The tongue is regarded as the most sensitive area and the lips the most specific.

Mechanism of cyanosis

In peripheral cyanosis the blood leaving the heart is oxygenated as it should be (*Figure 3*) whereas, as described by Stadie (1919), central cyanosis is caused by incomplete oxygenation of arterial blood which can arise for a number of different reasons (*Figure 4*). Haemoglobin absorbs light at different wavelengths depending

Any condition that results in slowing of the peripheral circulation will cause peripheral cyanosis. The appearance of cyanosis under these circumstances is often transient. Low blood flow may result from decreased arterial perfusion caused by poor cardiac output (cardiogenic shock), by fixed arterial narrowing (atherosclerosis), or by reflex arteriolar narrowing (cold weather or hypothermia). Venous obstruction slows capillary blood flow and may be caused by local (venous thrombosis) or central (congestive heart failure) mechanisms. This slowing of blood flow allows more time for the extraction of oxygen from haemoglobin. In cases of peripheral cyanosis the peripheries are usually cold to touch as well as appearing blue.

Figure 3. Causes of peripheral cyanosis.

Central cyanosis is usually accompanied by a reduction in arterial oxygen saturation except in very uncommon causes such as methaemoglobinaemia, sulfhaemoglobinaemia and some haemoglobinopathies. There are multiple causes of central cyanosis which can broadly be divided as follows:

1. Problems with the heart – congenital heart disease with right to left shunts, cardiac arrest, heart failure
2. Problems with the lungs – any lung disease causing a ventilation/perfusion mismatch, e.g. severe pneumonia, chronic lung disease, pulmonary embolus, pulmonary hypertension
3. Alveolar hypoventilation secondary CNS disturbance which could be caused by drug overdose (e.g. sedatives, benzodiazepines) or head injury
4. Altitude
5. Problems with haemoglobin – methaemoglobinaemia, sulphaemoglobinaemia
6. Impaired oxygen use, e.g. cyanide poisoning.

Figure 4. Causes of central cyanosis.

upon whether it is in its reduced or oxygenated form. When saturated with oxygen (i.e oxyhaemoglobin is present), blood is bright red. Haemoglobin (and therefore blood) appears bluish after giving up oxygen. The presence of cyanosis depends upon the absolute amount of deoxygenated haemoglobin in the vessels, not the deoxygenated:oxygenated ratio or the relative lack of oxygenated haemoglobin. Lundsgaard and Van Slyke (1923) established that the amount of deoxygenated haemoglobin in the capillaries needed for cyanosis to occur is 5 g/dl. They stated:

'It is the blood in the capillaries, and possibly in the arterioles and venules of the subpapillary plexus as well, which produces the cyanotic skin color'.

This threshold of 5 g/dl of deoxyhaemoglobin in mean capillary blood has not been confirmed or refuted by more sophisticated measurement techniques available today.

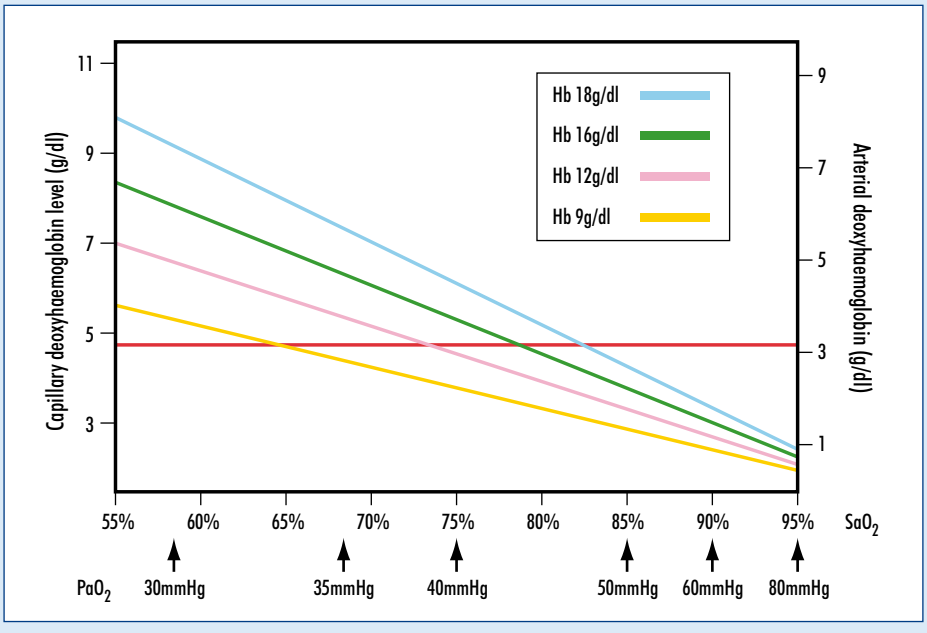
In previous literature, there has been some misinterpretation of the location of the 5 g/dl change with some studies quoting this change in the arterial and others the venous circulation. As it is difficult to obtain measurements for deoxyhaemoglobin concentration in the capillaries, Lundsgaard and Van Slyke (1923) proposed that this measurement could be estimated by averaging the amount of deoxyhaemoglobin in arterial blood with that in venous blood. Goss et al (1988) translated this requirement of 5 g/dl of reduced haemoglobin in the capillaries to a reduced haemoglobin content of 3.4 g/dl in arterial blood. Martin and Khalil (1990) concluded that at this level of capillary deoxyhaemoglobin, if the total haemoglobin concentration is 12 g/dl cyanosis should only be detectable when the oxygen saturation as measured by pulse oximetry is relatively low at between 73% and 78%.

Limitations of cyanosis as a clinical sign

Cyanosis is not a reliable clinical sign. Detection can be extremely difficult, particularly in mild cases. Lundsgaard (1923) and Comroe (1947) previously reported that variability in the detection of cyanosis arises for a number of different reasons including differences in skin colour, tissue perfusion and inter-observer variation.

Patients with normal haemoglobin levels can appear cyanosed at higher oxygen saturation values than patients with anaemia. The higher the haemoglobin content in an individual's blood, the more readily cyanosis will appear as the oxygen saturations fall. This is explained further in *Figure 5*. A polycythaemic patient may appear cyanosed with relatively little hypoxia. In contrast, an anaemic patient may become dangerously desaturated without appearing cyanosed. Reduced arterial oxygenation can arise if the amount of oxygen in the

Figure 5. Oxygen and haemoglobin (Hb) values at which central cyanosis occur. The values for capillary and arterial reduced haemoglobin are depicted on the y axis. The per cent saturation of haemoglobin in arterial blood (SaO_2) and corresponding arterial pressure of oxygen in arterial blood (PaO_2) are shown on the x axis. Each diagonal line represents different haemoglobin contents of blood. The red line denotes a capillary deoxyhaemoglobin level of 5 g/dl.



alveoli is lowered. Cyanosis can occur even with normal arterial oxygenation if there is increased extraction of oxygen at the capillary level (and therefore increased amounts of deoxyhaemoglobin) such as occurs with reduced flow through capillaries.

Uncommon causes of central cyanosis

Methaemoglobin

Methaemoglobin is an oxidized haemoglobin in which iron is in the ferric form and therefore does not bind to oxygen. Some methaemoglobin is normally formed in the body, but this is usually reduced to deoxyhaemoglobin by the NADH (nicotinamide adenine dinucleotide) methaemoglobin reductase system. If this enzyme system is deficient or if it becomes overloaded, elevated blood levels of methaemoglobin result. The level of methaemoglobin capable of producing cyanosis is thought to be about 1.5 g/dl.

Methaemoglobin imparts an intense bluish tinge to the skin. The cyanosis that develops with methaemoglobinaemia is not related to reduced haemoglobin but to oxidized haemoglobin. Methaemoglobinaemia usually occurs as a drug reaction, especially to nitrite or nitrate-containing compounds (e.g. nitroglycerin), dapsone and to some topical anaesthetics. Although excess methaemoglobin reduces measured oxygen saturations, the partial pressure of oxygen in arterial blood is not affected. If arterial partial pressure of oxygen is low in a patient with methaemoglobinaemia a concomitant pulmonary problem should be sought.

Sulfhaemoglobin

Sulfhaemoglobin is not normally formed in the body and its chemical composition is not well defined. The mechanism of its formation is not known, although many of the same toxins that result in the oxidation of deoxyhaemoglobin to methaemoglobin can also produce sulfhaemoglobin. Once formed, the sulfhaemoglobin molecule is stable and is not converted back to deoxyhaemoglobin. Cyanosis is detectable at sulfhaemoglobin levels as low as 0.5 g/dl. Sulfhaemoglobin is similar to methaemoglobin in causing low oxygen saturation but not affecting arterial partial pressure of oxygen and in imparting an intense bluish colour to the skin.

Congenital haemoglobinopathies

Haemoglobinopathies as described by Mounts et al (2010) are an uncommon cause of cyanosis and low oxygen saturation on pulse oximetry and usually limited to the paediatric population. They arise as a result of a group of abnormal haemoglobins (haemoglobin M) in which amino acid substitutions take place either in the alpha or beta chains resulting in facilitation of oxidation of haemoglobin to yield excess methaemoglobin. This in turn leads to cyanosis. The five variants of haemoglobin M are inherited in an autosomal dominant pattern. Individuals in whom an alpha chain substitution has occurred are cyanotic from birth. Those in whom beta chain substitution has occurred often do not become cyanotic until 3–6 months of age because of the normal changeover from gamma to beta chain synthesis during that time.

Pseudocyanosis

Pseudocyanosis is a bluish tinge to the skin and/or mucous membranes that is not associated with either hypoxaemia or peripheral vasoconstriction. Most causes are related to metals (e.g. silver nitrate, silver iodide, silver, lead) or drugs (e.g. phenothiazines, amiodarone, chloroquine hydrochloride). Ingestion of substances containing gold or silver can produce bluish skin colouration most commonly seen in sun-exposed portions of the body. The bluish skin colour associated with haemosiderin deposition is more apparent in parts of the body with less melanotic pigment. Polymers of the oxidation products of chlorpromazine, when deposited in the skin and other organs, can result in a blue/purple colour.

Relevance to clinical practice

Not only is cyanosis difficult to detect, the presence of cyanosis itself is not a reliable tool for detecting arterial hypoxaemia. Comroe and Botelho (1947) studied a group of normal individuals breathing various concentrations of oxygen and noted that cyanosis was not apparent to 25% of observers even at arterial oxygen saturations of 71–75%. They also found that 17% of observers believed cyanosis to be present when arterial oxygen saturations were 91–95%.

The only way to confirm that arterial hypoxaemia is present and responsible for cyanosis is to analyse a blood sample and determine the partial pressure of oxygen. In the presence of arterial hypoxaemia, central cyanosis is unlikely to occur independently as arterial hypoxaemia also gives rise to other signs and symptoms. Peripheral chemoreceptors may be stimulated by a low partial pressure of oxygen, causing increased ventilation which manifests as dyspnoea and tachypnoea. Sympathetic nervous system stimulation can produce restlessness, sweating, elevation of blood pressure and tachycardia. When hypoxaemia is very severe, cerebral oxygenation may become impaired and confusion or coma can develop.

The routine use of pulse oximetry to identify significant hypoxaemia has meant that physicians need to rely less on cyanosis as a clinical sign. With conditions causing acute hypoxaemia other clinical signs are almost invariably present and an accurate diagnosis of cyanosis is not so important. Perhaps the skill in its detection is most relevant in the outpatient setting, when astute observation could lead to earlier diagnosis of an otherwise unsuspected condition causing chronic hypoxaemia or recognition that the patient has a more severe problem than initially suspected.

Pulse oximetry

Pulse oximetry allows monitoring of the percentage of haemoglobin saturated with oxygen in a non-invasive manner. The percentage displayed on the screen represents the percentage of haemoglobin saturated with oxygen. The advantage of using pulse oximetry is that hypoxia may be detected before the development clinically of cyanosis. The oximeter works by emitting light from a probe at wavelengths of 650 nm and 805 nm. This light is partially absorbed by the haemoglobin in amounts that differ according to whether the haemoglobin is saturated or desaturated. The proportion of haemoglobin oxygenated is then calculated from the absorption at the two wavelengths. When blood flow is sluggish (e.g. in vasoconstriction) then the pulse oximeter may not function.

The cyanotic patient in the PACES exam

In establishing a diagnosis in the PACES exam (*Figure 6*), it is first necessary to establish if cyanosis is central or peripheral.

Cardiovascular	Adult congenital cyanotic heart disease – associated with a heart murmur and clubbing
	Patent ductus arteriosis – tachycardia, breathlessness, heart murmur (machine like), left subclavicular thrill, bounding pulse, widened pulse pressure
	Pulmonary hypertension – loud S2 (pulmonic valve closure sound), (para)sternal heave, raised jugular venous pressure, peripheral oedema, ascites, clubbing, evidence of tricuspid insufficiency
Respiratory	Chronic obstructive pulmonary disease with cor pulmonale – hyper-expanded chest, laboured respiratory effort, intercostal recession, wheeze, signs of right ventricular hypertrophy, raised jugular venous pressure, pan-systolic murmur (tricuspid regurgitation), split second heart sound with loud pulmonary component, peripheral pitting oedema
	Interstitial lung disease – fine end inspiratory crackles, breathlessness and signs of cor pulmonale
	Bronchiectasis – coarse crackles and wheeze, breathlessness and signs of cor pulmonale

Figure 6. Common causes of cyanosis and differential diagnoses for the PACES exam.

The peripheries will be warm in central cyanosis and cold in peripheral cyanosis.

If peripheral cyanosis is present, it is important to look for other features of systemic diseases that are associated with peripheral cyanosis, such as rheumatological disorders.

With respect to central cyanosis, the underlying primary disease will either be cardiac or respiratory in origin. Common cardiovascular causes include adult congenital cyanotic heart diseases, patent ductus arteriosis and pulmonary hypertension. Common stable respiratory conditions in which patients are centrally cyanosed include chronic obstructive pulmonary disease with cor pulmonale, interstitial lung diseases and bronchiectasis. Central cyanosis may be difficult to detect so it is worth looking for other clues as to whether the patient is using oxygen. Candidates may also be asked to explain why cyanosis develops and types of cyanosis. BJHM

KEY POINTS

- Cyanosis is not a reliable clinical sign.
- The presence of cyanosis can be very difficult to detect and depends on a number of factors.
- Central cyanosis is usually accompanied by a reduction in arterial oxygen saturation.
- In peripheral cyanosis the blood leaving the heart is normal.
- The presence of cyanosis itself is not a reliable tool for detecting arterial hypoxaemia.

Conflict of interest: none.

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