PHYSICAL FINDINGS
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Cyanosis

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Descriptions of cyanopathia or *Morbus caeruleus* (cyanosis) have populated medical literature since the time of Hippocrates, although the actual pathophysiology behind its development eluded physicians until the advent of objective anatomy and physiology. Morgagni, "accurate anatomist," philosopher, and one of the fathers of contemporary medicine, is often credited with having first described cyanosis (in association with stasis due to pulmonic stenosis [1761]),[1] however, it was actually deSenac, personal physician to King Louis XV (and the first to elucidate the relationship between atrial fibrillation and mitral stenosis), who first described the pathophysiology of cyanosis (albeit not entirely correctly!) in 1749.[2] It was not until over 2 centuries later, however, that Christen Lundsgaard actually quantified the amount of deoxygenated hemoglobin that was required to produce that bluish discoloration that produces the clinical finding of cyanosis.[2]

FEATURES OF CYANOSIS

Cyanosis is an abnormal bluish discoloration of the skin and mucous membranes; it is caused by high levels of deoxygenated (reduced) hemoglobin (or its derivatives) circulating within the superficial dermal capillaries and subpapillary venous plexus (*not*, as commonly taught, the deeper arteries and veins).[1] Hypoxemia, not to be confused with hypoxia (which reflects tissue oxygenation), is the deficient oxygenation of blood that leads to cyanosis.[3]

Whether or not cyanosis is apparent to the human eye depends on dermal thickness, cutaneous pigmentation, and state of the cutaneous capillaries.[4] In light of this, cyanosis is best appreciated in areas of the body where the overlying epidermis is thin and the blood vessel supply abundant, such as the lips, malar prominences (nose and cheeks), ears, and oral mucous membranes (buccal, sublingual); it is better appreciated in fluorescent lighting.[1]

Cyanosis is classified as being either peripheral or central (**Figure**). As its name implies, in addition to the hands and feet, central cyanosis is apparent at the lips, tongue, and sublingual tissues. Peripheral cyanosis, on the other hand (pun intended!), spares the oral mucosa but causes bluish discoloration of the hands and feet; it is the result of vasoconstriction and diminished peripheral blood flow from various causes (**Table**). Pseudocyanosis can mimic peripheral cyanosis, however, there is no response to attempted "blanching" of the skin by applying pressure; pseudocyanosis is generally due to drug exposure (such as amiodarone) and much more rarely these days, metal exposure (chrysiasis, argyria).[1]

PATHOPHYSIOLOGY

In order for circulating blood to appear blue, it requires an elevated amount of blue pigment to accumulate. Central cyanosis is generally of greater concern, as it requires reduced arterial oxygen saturation (PaO_2) or abnormal hemoglobin derivatives to be present (methemoglobin or sulfhemoglobin), and is generally a relatively late finding in the course of illness. The increased amount of deoxygenated hemoglobin is due to either an increased amount of venous admixture (due to vasodilatory effects on the venous plexi) or by reduced arterial oxygen tension in the capillaries.

In central cyanosis, either SaO_2 is reduced or abnormal (nonfunctional) hemoglobin is present, which is why central structures and mucosae are affected; this is in contrast to peripheral cyanosis, where there is a normal SaO_2 but increased extraction of oxygen in the setting of peripheral vasoconstriction and thus, decreased peripheral blood flow.

As McGee[1] astutely notes, historically there has been (and exists still in the teaching of medical students today) great confusion about the actual levels of deoxyhemoglo-

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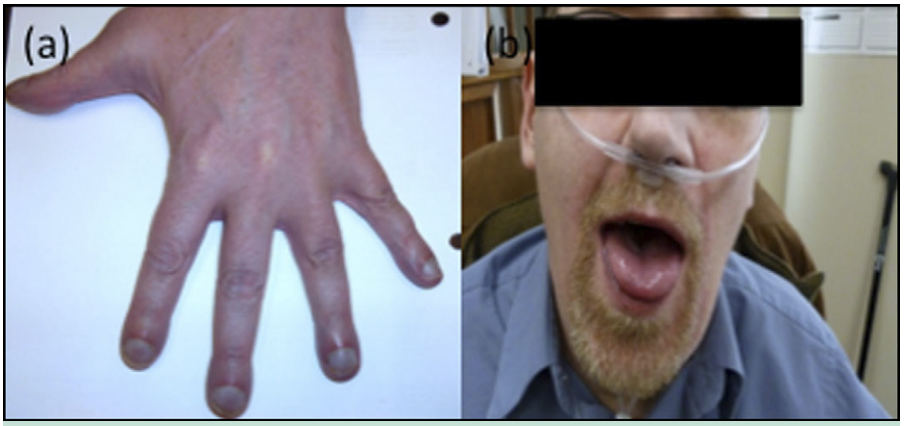

Figure **(A)** peripheral cyanosis (with clubbing); **(B)** central cyanosis.

bin required to produce clinically apparent cyanosis. This is because many clinicians erroneously equate arterial levels of deoxyhemoglobin with capillary levels—and it is the capillary levels, *not* the arterial ones, that yield the blue color we observe. Another important point is that it is the *absolute*, not relative, quantity of deoxygenated hemoglobin that matters; this means that for a given patient, the level of SaO_2 at which cyanosis becomes apparent depends on their *total hemoglobin concentration*. Because of this, severely anemic patients with marked arterial desaturation might not be cyanosed, yet polycythemic patients develop obvious cyanosis at much higher SaO_2.

ASSOCIATED CONDITIONS

Associated conditions are those causing hypoxemia, as outlined in the **Table**, and are predominantly cardiopulmonary in nature, although shock of any kind also may cause cyanosis. The most commonly associated clinical finding in those with chronic conditions causing cyanosis is clubbing (for a detailed description, see Marrie and Brown[5]); those with clubbing of the digits warrant a close examination for cyanosis and its associated conditions, and vice versa.

ANCILLARY

Clinicians should be wary when attempting to measure or follow pulse oximetry in the cyanotic patient. Bedside pulse oximetry relies on the red and infrared light absorption characteristics of oxy- and deoxygenated blood (hemoglobin), therefore, its accuracy is affected in those patients with peripheral cyanosis (potentially leading to a *falsely positive* low PaO_2, ie, implying a low arterial saturation). This can be circumvented with an arterial blood gas sample, as co-oximetry now readily distinguishes deoxyhemoglobin from abnormal types of hemoglobin, and will demonstrate a low PaO_2 in patients with central cyanosis.[1]

Table Causes of Cyanosis (Modified from Kasper et al[4])

Central Cyanosis	Peripheral Cyanosis
Decreased arterial oxygen saturation	All causes of central cyanosis can cause peripheral cyanosis
Decreased atmospheric pressure (altitude)	Reduced cardiac output (left ventricular failure or shock)
Impaired pulmonary function (extensive pneumonia, pulmonary embolism, obstructive lung disease, pulmonary edema, etc.): alveolar hypoventilation, ventilation-perfusion mismatch, impaired oxygen diffusion	Cold exposure
Anatomic shunts (Venous blood → arterial circulation): Congenital heart disease ("cyanotic" types, pulmonary arteriovenous malformations [AVMs], multiple small intrapulmonary shunts)	Redistribution of blood flow from extremities
Hemoglobin with low oxygen affinity	Arterial or venous obstruction
Hemoglobin abnormalities	
Methemoglobinemia (hereditary or acquired)	
Sulfhemoglobinemia (acquired)	
Carboxyhemoglobinemia (not true cyanosis, "chocolate" cyanosis)	

APPROACH TO PATIENT

The approach to the patient with cyanosis is simple, yet it is of vital importance to determine the underlying cause—a standard history and physical examination answering the following 4 questions: 1) What is the *timing of onset* of cyanosis (ie, is it congenital or acquired?); presence of cyanosis at or from birth suggests congenital heart disease; 2) Is it *central or peripheral*? On examination one should rule out pseudocyanosis (as above) and warm cool extremities to abolish peripheral cyanosis, in addition to seeking evidence of coexistent cardiopulmonary disease; 3) Is there clubbing present? Cyanosis and clubbing narrow the differential to congenital heart disease, suppurative pulmonary disease, and right-to-left shunting (cardiac and intrapulmonary); 4) what do the arterial blood gas and pulse oximetry show? These are generally straightforward; however, if pulse oximetry is indeterminate, perform co-oximetry for abnormal hemoglobin types.

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