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Summary of article:

This article explains and emphasises the importance of oxygen delivery for medical students to apply to clinical practice through the usage of several common clinical cases.

Keywords: oxygen delivery, tissue hypoxia, medical students

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Abstract

Introduction: Oxygen delivery to tissues is a vital physiological process in the human body and an essential topic for all medical practitioners. Studying the topic strengthens understanding about the vital signs, in particular heart rate, blood pressure, respiratory rate, and oxygen saturation. It further grants insight into common clinical interventions such as supplemental oxygen and intravenous fluids. However, oxygen delivery is a concept that often goes underappreciated by medical students and junior doctors. This is an educational article that seeks to improve understanding and clinical application around the topic.

Case overview: We use six common clinical scenarios (gastroenteritis, haemorrhagic shock in trauma, reactive polycythaemia, sepsis, status epilepticus, and peripheral vascular disease) to present the causes and management of tissue hypoxia, as well as the body's physiological responses.

Discussion overview: Tissue hypoxia occurs when the whole body or a region of the body is deprived of adequate oxygen supply to meet tissue metabolic demands. There are four types of tissue hypoxia: hypoxic, stagnant, anaemic, and histotoxic hypoxia. Consideration of the underlying cause of a patient's tissue hypoxia aids rapid assessment and targeted management of the patient.

Highlights

1. Hypoxia and hypoxaemia are terms that should not be used interchangeably. Hypoxia refers to inadequate delivery of oxygen to tissues, while hypoxaemia refers to inadequate PaO2 in blood.
2. The causes of tissue hypoxia can be logically deduced from the Oxygen Delivery Equation and comprise reduced cardiac output or regional blood flow ('stagnant hypoxia'), true or functional anaemia ('anaemic hypoxia'), reduced PaO2/SaO2 ('hypoxic hypoxia') as well as histotoxic hypoxia.
3. Common interventions addressing specific mechanisms of tissue hypoxia include fluids and inotropes for reduced cardiac output, RBC transfusions for anaemia and supplemental oxygen and positive pressure ventilation for reduced PaO2/SaO2.

Introduction

Cells use oxygen to produce energy through aerobic respiration. Inadequate delivery of oxygen to tissues results in a cascade of complications: anaerobic respiration, lactic acidosis, cell death, and eventual organ dysfunction [1].

The term *hypoxia* should first be distinguished from *hypoxaemia*. Hypoxaemia refers to reduced arterial oxygen tension or partial pressure of oxygen in blood (PaO_2) below normal values, which is positively related to the oxygen saturation (SaO_2) by the oxygen-haemoglobin dissociation curve [2]. Hypoxia is a broader term that refers to inadequate oxygen delivery to tissues and can be affected by any factor contributing to oxygen delivery and consumption, as elaborated upon below [2]. Hypoxia can be classified as either localised (affecting a region of the body) or generalised (affecting the whole body).

Global oxygen delivery to tissues (DO_2) is the amount of oxygen delivered to tissues per minute. It is the product of cardiac output (volume of blood delivered to tissues per minute) and the arterial oxygen content (the amount of oxygen in that blood). Formally, it is expressed by the Oxygen Delivery Equation (ODE) as follows:

$DO_2 = CO \times [Hb \times 1.34 \times SaO_2 + [0.003 \times PaO_2]]$, where:

- DO_2 = Delivery of oxygen, in ml/min,
- CO = Cardiac output, in L/min,
- Hb = Haemoglobin concentration, in g/L,
- SaO_2 = Arterial oxygen saturation, in %,
- And PaO_2 = Arterial partial pressure of oxygen, in mmHg [3]

The (0.003 x PaO2) component represents the small amount of dissolved oxygen in blood not bound to haemoglobin. Due to the numerical insignificance of this value, the equation can be simplified to:

$$\mathbf{DO_2 \propto CO \times Hb \times SaO_2}$$

That is, the global delivery of oxygen is proportional to the product of the cardiac output, haemoglobin concentration, and the arterial oxygen saturation. Cardiac output is the product of heart rate and cardiac stroke volume (CO = HR x SV) and is approximately equal to 5 L/min for a healthy person at rest. DO_2 is approximately equal to 1000 ml O_2/min for such a person.

Accordingly, the causes of tissue hypoxia are either inadequacies in cardiac output, regional blood flow (‘stagnant hypoxia’), true or functional anaemia (‘anaemic hypoxia’), or reduced PaO_2 (‘hypoxic hypoxia’). ‘Histotoxic hypoxia’ is an additional uncommon cause of tissue hypoxia where tissues are unable to utilise oxygen that is delivered, classically described in cyanide poisoning. Excessive tissue oxygen demands may also result in tissue hypoxia if oxygen delivery cannot be increased sufficiently, although it is not typically considered part of this classification. The types of hypoxia are summarised in Table 1 [5].

Cause of hypoxia	Brief description	Examples
Stagnant hypoxia	Decreased blood flow to tissues, either from reduced cardiac output (resulting in global hypoxia) or reduced regional blood flow (resulting in local hypoxia)	Hypovolaemia Arrhythmias such as ventricular tachycardia, ventricular fibrillation, bradyarrhythmias Acute myocardial infarction Peripheral vascular disease Acute vessel embolisms
Anaemic hypoxia	Decreased ability to transport oxygen, either from reduced haemoglobin concentration or reduced functionality of haemoglobin	Anaemia, for example, iron deficiency anaemia, anaemia of chronic disease Carbon monoxide poisoning
Hypoxic hypoxia	Decreased PaO_2 (hypoxaemia)	High altitude Hypoventilation Many respiratory conditions, for example, asthma, pulmonary embolism, pneumonia
Histotoxic hypoxia	Decreased tissue ability to properly utilise oxygen that is delivered	Cyanide poisoning Tissue oedema

Table 1. Causes, brief descriptions, and examples of tissue hypoxia.

Blood pressure is notably not a parameter included in the ODE. The mean arterial pressure (MAP) is the product of cardiac output and systemic vascular resistance (MAP = CO x SVR). MAP is commonly used in the clinical assessment of organ perfusion as a less-invasive surrogate measure of cardiac output. However, the relationship between MAP and cardiac output is altered and becomes difficult to interpret in conditions with large changes in the SVR, such as sepsis-induced vasodilation or severe vasoconstriction in haemorrhagic shock [4].

Six common clinical cases below apply these concepts to explain the body's physiological responses to tissue hypoxia and how medical interventions might preserve oxygen delivery during these situations.

Case 1 – Stagnant hypoxia (global)

Consider the case of Daniel, a 34-year-old previously healthy male presenting with three days of acute diarrhoea. He has been passing watery stools 10 times a day with inadequate fluid replacement, and reports that he has not voided for 12 hours. On examination, he has dry mucous membranes and a low jugular venous pressure. He is tachycardic at 115 beats per minute (bpm) and his blood pressure is 120/80 mmHg. An electrocardiogram (ECG) shows sinus tachycardia.

Question: What is the pathophysiology of Daniel's tachycardia and what would be the appropriate treatment?

Discussion

Tachycardia can be understood as being a rise in heart rate either secondary to increased sympathetic outflow (producing sinus tachycardia) or a non-sinus tachyarrhythmia. An ECG differentiates between the two and is therefore a key investigation in the workup of tachycardia [6].

This patient has hypovolaemia secondary to acute gastroenteritis which has resulted in sinus tachycardia without compromising blood pressure.

Recall that cardiac output is the product of heart rate and stroke volume (CO = HR x SV). In this case of an otherwise healthy young man, hypovolaemia results in reduced stroke volume and therefore cardiac output due to reduced venous return. Through baroreceptor-mediated reflex mechanisms, the body compensates by activating the sympathetic nervous system which raises the heart rate and contractility of the ventricles to maintain CO [7]. Caution is therefore advised in patients with cardiac disease or medications affecting heart rate, for example, beta-blockers, as such physiological compensation may be impeded.

These physiological responses can be reasoned out using the ODE. Upon a transient decrease in cardiac output, global oxygen delivery is lowered. To avoid resultant tissue hypoxia, the body compensates by increasing the heart rate. Worsening hypovolaemia would have the potential to overwhelm this compensatory mechanism and cause tissue hypoxia.

Acute viral gastroenteritis is usually self-limiting, and treatment is largely supportive with fluid repletion [8]. This maintains the patient's stroke volume and thereby preserves cardiac output and oxygen delivery. A return of heart rate towards normal would constitute an appropriate response to fluid therapy and be a useful way to assess efficacy of treatment.

Compare the treatment aims of gastroenteritis with that of Case 2:

Case 2 – Stagnant hypoxia (global) and anaemic hypoxia

Betty, a 65-year-old female pedestrian, has been brought in by ambulance to the emergency department after being struck by a motor vehicle at a speed of 40 km/hr. She has a history of hypertension and hyperlipidaemia managed well with perindopril and atorvastatin. She is conscious and complaining of abdominal pain.

On primary survey, her airway is patent and a cervical collar is in place. Her respiratory rate is 22 breaths per minute with SpO_2 of 98% on room air. Her heart rate is 125 bpm and her blood pressure is 85/50 mmHg. Abdominal examination finds generalised tenderness with

some guarding. A focused assessment with sonography for trauma (FAST) scan is performed which shows a large amount of intraperitoneal free fluid.

Question: While awaiting a laparotomy in theatre, what would be the appropriate immediate management of this patient?

Discussion

This is a patient who most likely has stage 3 haemorrhagic shock secondary to trauma [9]. Both Betty's heart rate and blood pressure are compromised, with her antihypertensive agent further impairing her ability to compensate for the blood loss.

As with Daniel in Case 1, the goal of initial resuscitation would be to preserve Betty's volume status via the rapid infusion of intravenous fluids, thereby preserving her stroke volume and cardiac output.

However, there are factors apart from cardiac output that affect global oxygen delivery. Recalling the ODE ($DO_2 \propto CO \times Hb \times SaO_2$), it can be observed that while the administration of intravenous fluids would preserve cardiac output, it would reduce the haemoglobin concentration in this actively bleeding patient, reducing oxygen delivery.

This explains the adage "Replace blood with blood", with the next appropriate step being the provision of packed red blood cell (PRBC) transfusions [9]. In emergency situations, type O negative blood may be used due to insufficient time for cross-matching donor and recipient blood.

In Betty's case, it is important to note that these are only temporising measures, with a laparotomy in theatre being the definitive treatment to control the source of bleeding.

Case 3 – Hypoxic hypoxia

The third case pertains to John, a 72-year-old male presenting to the emergency department with an infective exacerbation of chronic obstructive pulmonary disease (COPD), which he has had for the past 15 years. He responds well to salbutamol burst therapy and on review his vital signs have all returned to within normal limits apart from an SpO2 of 93% on room air. He is prepared for discharge to home with a short course of antibiotics and steroids. However, a full blood count (FBC) returns showing a polycythaemia with a haemoglobin concentration of 180 g/L. His other cell line counts are within normal limits and no previous records are available. He does not have hepatosplenomegaly and denies constitutional and hyperviscosity symptoms.

Question: Would it be worthwhile to work John up for sinister causes of polycythaemia such as an erythropoietin (EPO) secreting tumour or haematological malignancy with serum EPO levels and JAK-2 mutations respectively?

Discussion

This case relates to the Hb and SaO_2 components of the ODE.

In states of chronic hypoxaemia, the body compensates for the reduced oxygen delivery by increasing the secretion of EPO which may result in polycythaemia [10]. Examples of such conditions include advanced COPD, sleep apnoea, and living at a high altitude.

Polycythaemia is most commonly secondary to one of these hypoxaemia-associated conditions. Rarely, it can be the result of an EPO-secreting tumour or be the manifestation of a primary haematological malignancy such as polycythaemia vera (PV) or other myeloproliferative neoplasms [10].

In this scenario, where there is an obvious explanation for the polycythaemia and an absence of red flag signs or symptoms, it would likely not be worthwhile to work John up further for such rare causes [10].

It is worthwhile noting that reactive polycythaemia does not occur in acute hypoxic states, as the production of haemoglobin is a relatively slow process [10]. This explains why reactive polycythaemia was not present in Cases 1 and 2.

Case 4 – Stagnant hypoxia (global) and hypoxic hypoxia

The next patient is Diane, a 62-year-old previously well female presenting with four days of worsening fever, cough, and shortness of breath. She was brought to the hospital by her husband today after she developed rigors and appeared confused.

Her airway is patent, respiratory rate is 32 breaths per minute with SpO_2 of 86% on room air, her heart rate is 120 bpm and her initial blood pressure is 95/50 mmHg. Her temperature is 38.5 degrees Celsius, her Glasgow Coma Scale (GCS) score is E4V4M6 and her blood sugar level is within normal limits. A chest X-ray reveals right lower lobe consolidation.

Question: What would be the appropriate management for this patient?

Discussion

This patient has sepsis likely secondary to a chest infection, with a qSOFA score of 3 [11]. Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection [11]. It causes tissue hypoxia, in part due to systemic arterial and venous dilatation that results in reduced preload, stroke volume, and cardiac output.

According to the "sepsis bundle" [12], it is important that patients with sepsis are commenced on the following within the first hour of presentation: intravenous fluid resuscitation of 30 ml/kg, supplemental oxygen to keep SaO_2 greater than 94%, as well as empiric intravenous antibiotics. The other recommendations are to obtain blood cultures and measure serum lactate. Failure of the patient to respond to these measures indicates the need for escalation of care and possible admission to an intensive care unit.

These recommendations can be understood by considering the ODE. The administration of intravenous fluids raises cardiac output, while supplemental oxygen preserves SaO_2. Empirical antibiotics treat the presumed bacterial infection to eventually halt the systemic vasodilatory and inflammatory response. Thus, these measures improve tissue oxygenation and limit organ dysfunction.

Case 5 – Excessive oxygen consumption

The next case pertains to James, a 30-year-old man brought in by ambulance to the emergency department for status epilepticus. He has had a generalised onset tonic-clonic seizure lasting 15 minutes which was eventually terminated by paramedic-administered benzodiazepines. His airway remained patent and oxygen saturations were adequate

throughout the seizure. However, a severe lactic acidosis with a pH of 6.90 is noted on the venous blood gas performed after the seizure episode.

Question: What is the cause of tissue hypoxia in this case?

Discussion

This scenario of oxygen balance looks at global oxygen consumption – the amount of oxygen consumed by tissues per minute. Global oxygen delivery (DO_2) in a normal person at rest is approximately 1000 ml O_2/min, while oxygen consumption (VO_2) for the same is approximately 250 ml O_2/min. Tissues extract oxygen from incoming arterial flow while veins carry blood away from tissues, explaining why the typical mixed venous oxygen saturation is approximately 75% [13].

During periods of increased metabolic activity, such as during exercise or, as in this case, a seizure, tissue oxygen demands increase significantly to facilitate energy production through aerobic respiration. Hypoxia, anaerobic respiration, and lactic acidosis result when tissues are unable to extract enough oxygen from capillaries and have negative net oxygen balance [13]. Treatment involves maintaining a clear airway and breathing while preventing further seizures and looking for seizure precipitants. The tissue hypoxia should resolve with these definitive measures as metabolic demands return to normal.

Case 6 – Stagnant hypoxia (local)

The last case moves away from global oxygen balance and considers another factor that may affect oxygen balance of specific tissues.

Shane is a 68-year-old male with a known history of poorly controlled type two diabetes mellitus, hypertension, hyperlipidaemia, and peripheral vascular disease. He presents to the emergency department with right lower limb claudication and pain at rest worsening over the past two weeks. On examination, his right lower limb is pale and cool distal to the knee joint. Popliteal, dorsalis pedis, and posterior tibial pulses are absent. The ankle-brachial index is 0.3, indicating critical limb ischaemia. An arterial Doppler ultrasound shows severe stenosis of the right femoral artery. Shane's vital signs are all normal and he is not anaemic.

Question: Given that Shane's cardiac output (as inferred from blood pressure), haemoglobin concentration, and SaO_2 are all unimpaired, what is the mechanism of his tissue ischaemia?

Discussion

The ODE describes global oxygen delivery. However, for adequate oxygen delivery to specific tissues, there must be sufficiently patent local vasculature in addition to adequate global oxygen delivery [1]

In Shane's case, management would focus on timely improvement of his right lower limb arterial supply before local tissue necrosis occurs, rather than correcting cardiac output, haemoglobin concentration, or the arterial oxygen saturation. This could be achieved using medical or surgical therapy.

Local arterial insufficiency is the pathophysiological basis of many common clinical conditions with tissue hypoxia. Improving the vasculature is typically the most effective treatment, as seen from the following examples. Myocardial tissue hypoxia from type one acute myocardial infarction may be managed with percutaneous coronary intervention or

thrombolysis. Brain parenchymal hypoxia from embolic ischaemic stroke may be treated with thrombolysis or removal of the clot by endovascular means. Patients with Raynaud's phenomenon are managed with arterial vasodilating agents to restore perfusion to the fingers in addition to treating any underlying autoimmune disease.

Summary of cases

In summary, the four types of tissue hypoxia are stagnant hypoxia, anaemic hypoxia, hypoxic hypoxia, and histotoxic hypoxia. Histotoxic hypoxia has not been expounded on in this article due to its relative uncommonness.

Figure 1 summarises the causes and the commonly used directed management strategies of tissue hypoxia as described in this article. Note that this list of strategies is not exhaustive; for instance, it omits arrhythmia correction as a management strategy for low cardiac output.

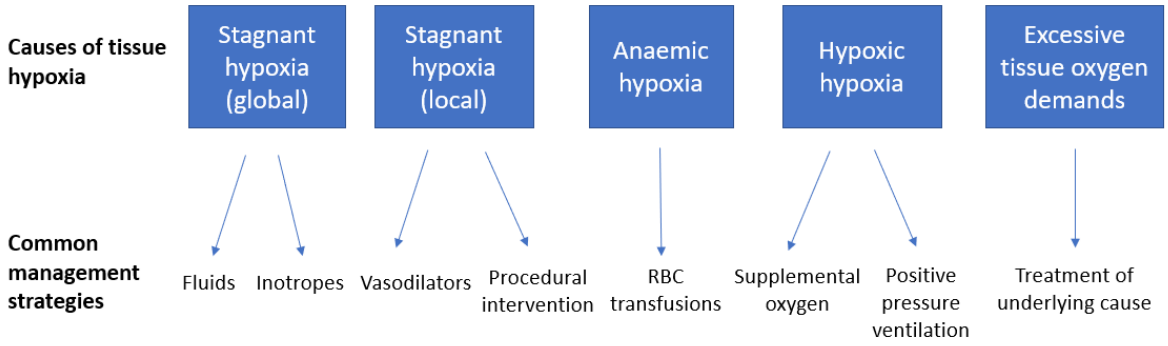

Figure 1: Causes of tissue hypoxia and their commonly used directed management strategies. Stagnant hypoxia globally (reduced cardiac output) is often treated with fluid administration or inotropes, while locally (reduced regional blood flow) is managed medically or procedurally depending on the cause. Anaemic hypoxia is typically managed with red cell transfusions. Hypoxic hypoxia is overcome with supplemental oxygen or positive pressure ventilation delivered through various oxygen delivery devices. Excessive tissue oxygen demands are managed according to the underlying cause.

Article Limitations

This article does not cover detailed guidelines about oxygen therapy, shock management, or other mentioned topics and should not be taken as such. It is intended for medical student education as a general approach to oxygen delivery and tissue hypoxia.

Many research studies have looked at the potentially adverse effects of hyperoxia (excessively high PaO2) and supranormal oxygen delivery in various patient groups. This is beyond the scope of this paper.

Conclusion

It is our opinion that oxygen delivery is an essential medical topic that provides a structured framework to approach causes and management of tissue hypoxia.

Medical students and junior doctors should actively engage the above framework in assessing the deteriorating patient. Consideration of the underlying cause of a patient's tissue hypoxia aids rapid assessment and targeted management of the patient.

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