INVITED ARTICLE

# Physiology of Oxygen Transport and its Determinants in Intensive Care Unit

Sumesh Arora[1], Pratik Tantia[2]

## Abstract

Transport of oxygen is one of the most important functions of blood. How oxygen moves from the air, where its partial pressure is about 150 mm Hg to mitochondria, where it drops down to a single digit is an evolutionary marvel. In this article, we discuss the physiology of oxygen transport from the alveoli to the tissue, the alveolar gas equation and the oxyhemoglobin dissociation curve. In the applied physiology section, we discuss the impact of high altitude, hyperbaric conditions, carbon monoxide poisoning on the transport of oxygen. Some common pitfalls in the interpretation of pulse oximetry and arterial blood gas are also discussed. Finally, we talk about the methods of increasing oxygen delivery, the compensation for hypoxia and some indications of venous oxygen saturation measurement.

**Keywords:** Arterial blood gas analysis, Hemoglobin, Hyperbaric oxygen therapy, Hypoxia, Oxygen saturation, Pulse oximetry

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Oxygen is vital for functioning of every cell in the body. Oxygen needs to be transported from the atmospheric air to the mitochondria. In this article, we will review mechanism of oxygen transport in the blood, factors affecting oxygen delivery and the clinical implications of this knowledge in day-to-day practice. Table 1 consists of lists of abbreviations used in this article.

## Transport of Oxygen in Blood — From Alveoli to the Tissues

While transport of oxygen from the atmosphere to mitochondria is a continuous process, for the purpose of discussion, we will divide it into smaller steps. The steps are outlined together in Flowchart 1.

### Oxygen in the Atmosphere

Atmospheric air is a mixture of gases, wherein each constituent gas has a partial pressure which is the notional pressure of that gas if it were to occupy the entire volume of the gas mixture at the same temperature. Dalton's law of partial pressure states that the total pressure of a mixture of gases is equal to the sum of partial pressures of individual gases.

### Oxygen Reaches Alveoli

Expected partial pressure of oxygen in the alveoli may be calculated using the alveolar gas equation:

[1]Department of Intensive Care Medicine, Prince of Wales Hospital, Sydney, New South Wales, Australia

[2]Department of Intensive Care, Ananta Institute of Medical Sciences and Research Centre, Rajsamand, Rajasthan, India

**Corresponding Author:** Sumesh Arora, Department of Intensive Care Medicine, Prince of Wales Hospital, Sydney, New South Wales, Australia, e-mail: sumesharora1@gmail.com

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$$PAO_2 = PiO_2 - \frac{PaCO_2}{R}$$

$$PAO_2 = FiO_2\,(PB - PH_2O) - \frac{PaCO_2}{R}$$

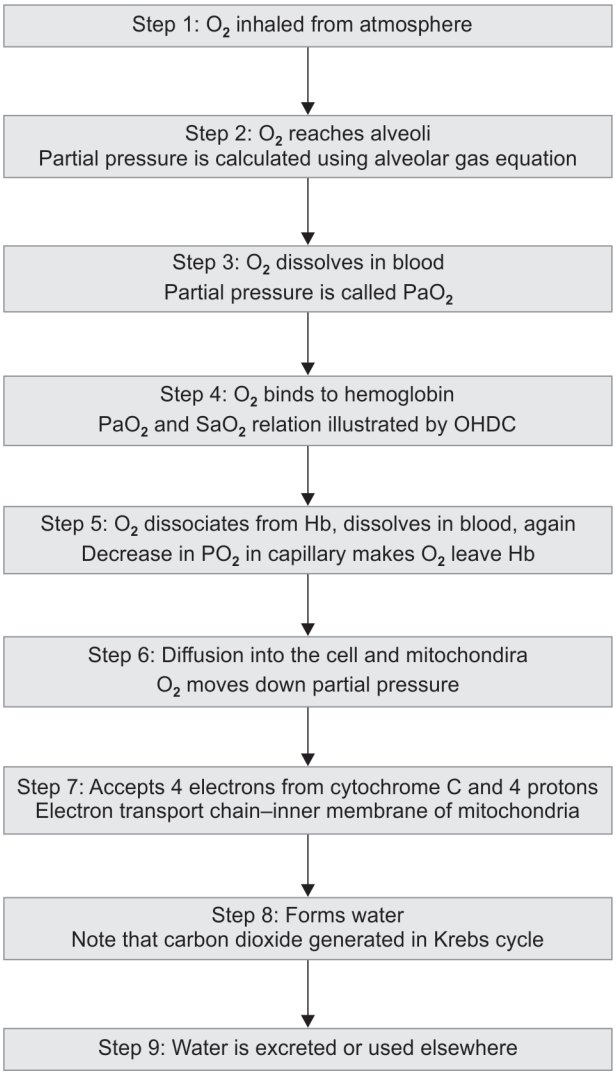
### Oxygen Dissolves in Blood

From alveoli, oxygen diffuses into blood. Dissolved oxygen in blood also exerts partial pressure. This pressure is labeled as $PaO_2$ (Fig. 1). The solubility of oxygen in blood is directly proportional to the

**Table 1:** List of abbreviations

| | | | |
|---|---|---|---|
| ABG | Arterial blood gas | $PiO_2$ | Partial pressure of inspired oxygen |
| atm | Atmospheres pressure | $PO_2$ | Partial pressure of oxygen |
| $CaO_2$ | Arterial oxygen content | psi | Pounds per square inch pressure |
| $DO_2$ | Oxygen delivery | Q | Cardiac output |
| OHDC | Oxyhemoglobin dissociation curve | $SaO_2$ | Oxygen saturation on cooximetry (e.g. using arterial blood gas analysis) |
| $PaCO_2$ | Partial pressure of carbon dioxide in arterial blood | $ScvO_2$ | Central venous oxygen saturation |
| $PAO_2$ | Partial pressure of oxygen in alveoli | $SJO_2$ | Jugular venous oxygen saturation |
| $PaO_2$ | Partial pressure of oxygen in arterial blood | $SpO_2$ | Oxygen saturation on pulse oximetry |
| PB | Barometric pressure | $SvO_2$ | Mixed venous oxygen saturation |
| $PH_2O$ | Partial pressure of water vapor at 37°C | $VO_2$ | Oxygen consumption |

**Flowchart 1:** Diffusion of oxygen from plasma to RBC and binding to hemoglobin. (Drawn with permission from www.gotheextramile.com - Quiz Time in Critical Care Pty Ltd, Sydney, Australia)




partial pressure of oxygen that it is exposed to. This relationship is known as **Henry's law.** The difference between $PAO_2$ and $PaO_2$ is popularly called 'A-a' gradient.

## Oxygen Binds to Hemoglobin

How much oxygen binds to hemoglobin, and therefore how much oxygen is carried by blood, is determined by $PaO_2$. In pulmonary capillaries blood, $PO_2$ is high; therefore, hemoglobin takes up oxygen dissolved in plasma (Fig. 2). Plasma in turn draws more oxygen from the alveoli.

Each hemoglobin molecule has four protein chains, carrying a heme molecule. In deoxyhemoglobin, the hemoglobin molecule is in a 'tense' conformation having relatively low affinity for oxygen. In oxyhemoglobin, it adopts a relaxed state and the affinity for oxygen increases than in the 'tense' state. The combination of oxygen to first heme increases the affinity of second heme for oxygen and so on.

The relationship between $PaO_2$ and $SaO_2$ when plotted on a graph results in a sigmoid-shaped curve commonly known as the oxygen hemoglobin dissociation curve (OHDC). Binding of oxygen to hemoglobin also depends on certain factors like $PaCO_2$, pH, temperature and 2, 3 Diphosphoglycerate (DPG) levels in RBCs. These factors lead to either a rightward or leftward shift of the OHDC. The $PO_2$ at which hemoglobin is 50% saturated is called the $P_{50}$ (normally 27 mm Hg in adult) and is used to measure the shift. Thus, depending on other variables, $SaO_2$ may vary for the same $PaO_2$ value. Various physiological parameters that result in a shift in OHDC are illustrated in Figure 3.

It should be noted that only small amount of oxygen is transported in dissolved form. For Hb of 15 g/dL, at 100% saturation and $PaO_2$ of 100, approximately 20 mL/dL is transported bound to hemoglobin while only 0.3 mL/dL is transported dissolved in blood (1 dL = 100 mL). Oxygen content of blood may be calculated using the following equation.

$$CaO_2 = \text{Hb bound } O_2 + \text{Dissolved } O_2$$

$$CaO_2 = (Hb \times K \times SaO_2) + (\alpha \times PaO_2)$$

K is **Huffner's constant** (1.39 mL $O_2$/gram Hb) – Maximum amount of oxygen that can bind to Hb

$\alpha$ is the **solubility coefficient** for $O_2$ at 37°C (0.00314 mL/dL/mm Hg).

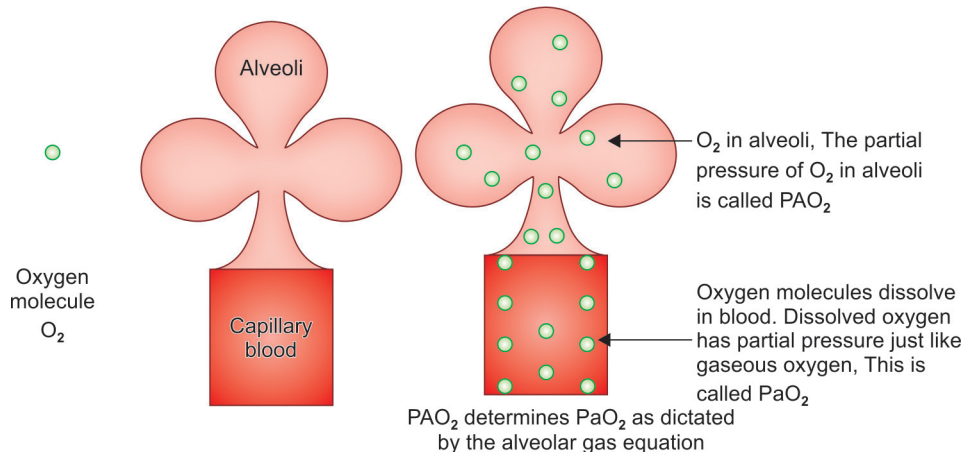



**Fig. 1:** Entry, transport in blood and metabolic role of oxygen

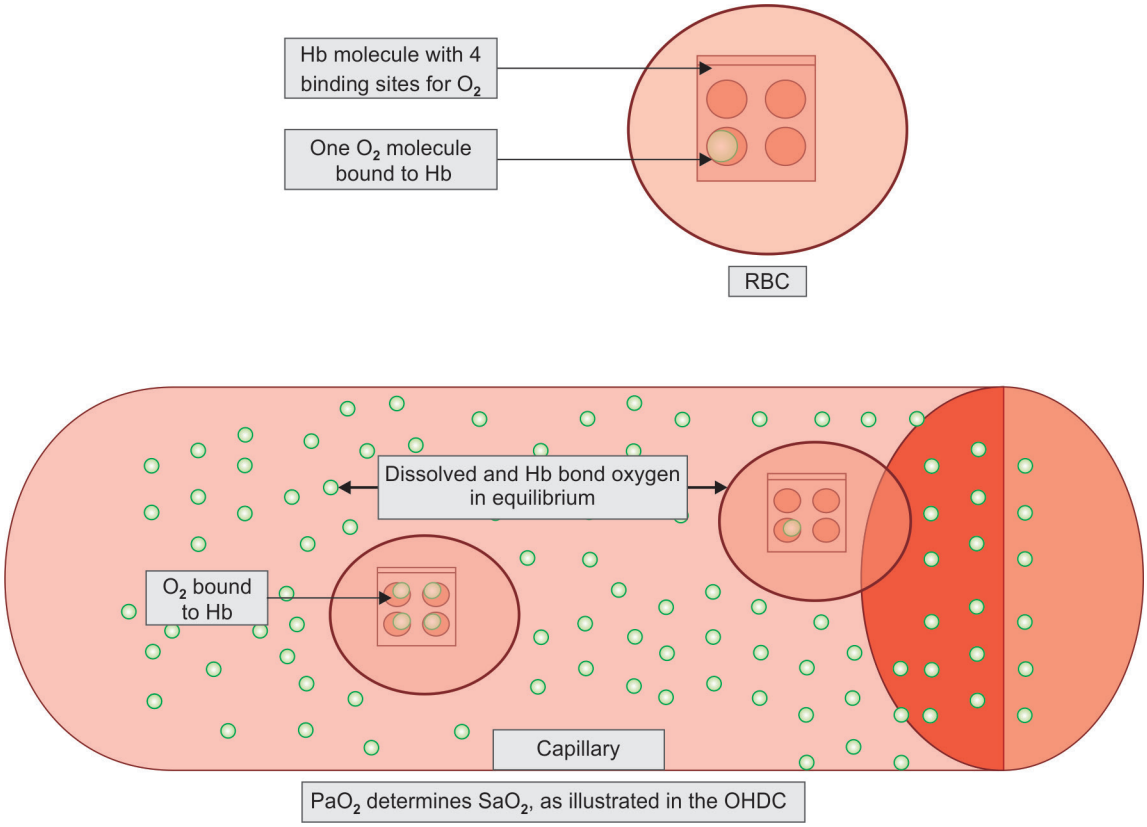



**Fig. 2:** Diffusion of oxygen from alveoli to plasma (Drawn with permission from www.gotheextramile.com - Quiz Time in Critical Care Pty Ltd, Sydney, Australia)

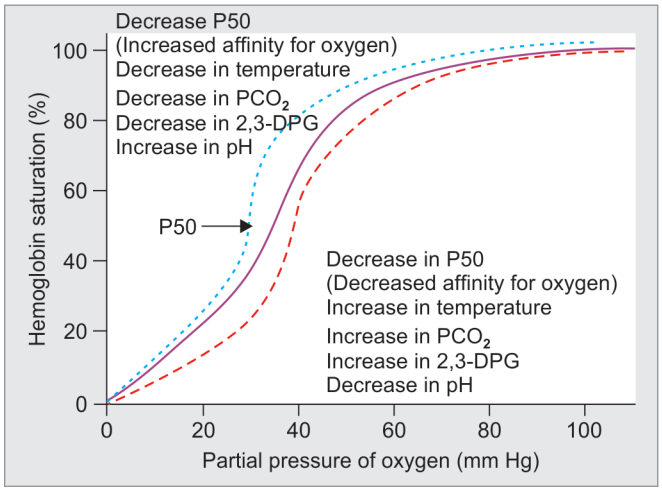



**Fig. 3:** Oxyhemoglobin dissociation curve and factors that results in a shift to right or left (Drawn with permission from www.gotheextramile.com - Quiz Time in Critical Care Pty Ltd, Sydney, Australia)

## Hemoglobin Releases Oxygen in Capillaries

In the tissue cells, the $PO_2$ is low. As a result, oxygen dissolved in the capillary blood diffuses into the tissues. This reduces the capillary oxygen $PO_2$, which decreases the affinity of oxygen for hemoglobin. In the capillaries, therefore, oxygen dissociates from hemoglobin and diffuses down the concentration gradient into the cells.

## Oxygen Entry into Cell and Metabolic Pathway

Oxygen enters the cells and is primarily utilized via cytochrome-C oxidase in electron transport chain located in the inner mitochondrial membrane. Here, one molecule of oxygen accepts 4 hydrogen nuclei (protons) and 4 electrons, resulting in formation of two molecules of water and ATP. Note that carbon dioxide is produced in the Krebs cycle and contains the oxygen molecule derived from glucose. Oxidative metabolism of each glucose molecule results in production of 38 ATP. When the level of oxygen in mitochondria falls to around 1–2 mm Hg (**Pasteur point**), oxidative phosphorylation stops. Anaerobic metabolism of glucose results in synthesis of lactic acid yielding just 2 ATP per glucose. Other enzymes like cytochrome P450 hydroxylase also utilize oxygen and are involved in detoxification.

## Oxygen Delivery

Since limited amount of oxygen is stored in the body, the cells depend upon continuous supply of oxygen by blood. The oxygen delivered per minute to cells is roughly 4 times the oxygen consumption. Oxygen delivery ($DO_2$) refers to the amount of oxygen delivered by blood to the tissues every minute.

$$DO_2 = Q \times CaO_2$$

Oxygen consumption may be calculated by subtracting oxygen content in venous blood from that in arterial blood

$$VO_2 = Q \times (CaO_2 - CvO_2)$$

Oxygen extraction ratio

$$ER = VO_2 \div DO_2$$

When $DO_2$ is moderately reduced, $VO_2$ remains normal because of increased oxygen extraction. With further reductions in $DO_2$,

**Table 2:** Effect of exposure to hypobaric and hyperbaric conditions on oxygen transport

| *Condition* | *Pathophysiological Effects* | *Response to change in Pressure/ Treatment* | *Comment* |
|---|---|---|---|
| High altitude | $FiO_2$ remains same<br>$PiO_2$ decreases — At Mt Everest (8848 m) the $PiO_2$ is 43 mm Hg (equivalent to $FiO_2$ 0.06 at sea level, $PaO_2$ and $SaO_2$ drops proportionately) | Hyperventilation reduces $PaCO_2$.<br>Acclimatization results in increase in hemoglobin concentration | Sudden exposure to high altitude (decompression of aeroplane) results in rapid hypoxia and loss of consciousness.<br>Commercial flights cruising at altitude of 30,000 feet are pressurized to 11 psi when the outside pressure is 4 psi. 11 psi is equivalent to $FiO_2$ 0.16 at sea level |
| Hyperbaric oxygen therapy | $FiO_2$ remains same<br>$PiO_2$ increases — At 2 atmospheres, $PiO_2$ even at $FiO_2$ 0.21 is 309 mm Hg (equivalent to $FiO_2$ 0.4 at sea level).<br>$PaO_2$ and $SaO_2$ increases proportionately<br>Increase in solubility of oxygen in blood with increase pressure (Henry's law) | At $FiO_2$ 1, at 1 atm. pressure, 2 $mL.dL^{-1}$ $O_2$ is dissolved in plasma<br>At $FiO_2$ 1 at 3 atm. Pressure, 6 $mL.dL^{-1}$ $O_2$ dissolved in plasma, equal to arteriovenous oxygen difference.<br>The pressure rises by 1 atm for every 10 meters depth under water.<br>To reduce risk of decompression sickness, divers should ascend @ <30 feet per minute | Hyperbaric oxygen therapy is used for treatment of decompression sickness, arterial air embolism, carbon monoxide poisoning, anaerobic infections (clostridial myonecrosis, etc.), chronic wounds, radiation osteonecrosis, etc. |

a critical point is reached beyond which $VO_2$ becomes directly proportional to $DO_2$. This state of supply-dependence is associated with progressive lactic acidosis caused by cellular hypoxia.

## Applied Physiology of Oxygen Transport in Blood

### How does Alteration in Ambient Pressure Alter the Oxygen Carriage in the Blood?

At sea level, body is exposed to atmospheric pressure of 760 mm Hg. Altered ambient pressure can have profound effects on oxygen carrying ability of blood. The effects of exposure to hyperbaric or hypobaric conditions is outlined in Table 2.

### Measurement of Oxygen Carriage – Pulse Oximetry and ABG Analysis

*How does Pulse Oximetry Differ from Arterial Blood Gas Analysis?*

Pulse oximetry measurement is based on spectrophotometry. Spectrophotometry utilizes the ratio of absorption of light of specific wavelength by oxyhemoglobin and reduced hemoglobin to calculate their respective concentration. Most pulse oximeters use light at two wavelengths – 660 and 940 nanometers. Using **Lambert–Beer law,** concentration of oxyhemoglobin is measured from the ratio of transmitted light and incident light from pulsatile blood. It should be noted that when we say that $SpO_2$ is 90%, it means there is 90 parts oxyhemoglobin out of 100 parts oxyhemoglobin plus reduced hemoglobin.

Arterial blood gas analysis uses **co-oximetry.** Co-oximetry is spectrophotometry technique that utilizes multiple wavelengths (as opposed to only two in pulse oximetry), so that accurate concentration of oxyhemoglobin, reduced hemoglobin, carboxyhemoglobin and methemoglobin can be measured. Co-oximetry is the gold standard for oxygen saturation measurement. It should be noted that when we say that $SaO_2$ is 90%, it means there is 90 parts oxyhemoglobin out of 100 parts oxyhemoglobin, reduced hemoglobin, carboxy hemoglobin and methemoglobin.

### When is Pulse Oximetry Inaccurate?

The accuracy of pulse oximeter is based on the following assumptions: Firstly, the oxyhemoglobin and reduced hemoglobin are the only substances that absorb light at the wavelengths used, and secondly, the arterial pulsations are the only cause of pulsatile blood flow. When these assumptions cannot be satisfied, accurate measurement of oxyhemoglobin fraction cannot be made. True hypoxia may exist even when pulse oximeter reading is within normal range. **Oxygen saturation gap** is the difference between the oxygen saturation calculated from a blood gas machine and that from a pulse oximeter.[1] If the gap is >5%, abnormal hemoglobin, e.g. carboxyhemoglobin should be suspected. For example, carboxyhemoglobin has similar absorption at 660 nm as oxyhemoglobin, but not at 940 nm. Even in presence of high carboxyhemoglobin concentration, pulse oximeter continues to read about 90%. Increasing concentration of methemoglobin, on the other hand, results in decrease in $SpO_2$, until it reaches a plateau at about 85%. Fetal hemoglobin or sickle hemoglobin do not alter signal on pulse oximetry. Methylene blue, sometimes used as a rescue therapy in shock, may result in sudden decrease in $SpO_2$ without true arterial hypoxia. In patients with shock, when the pulsatile flow is weak, the pulse oximeters amplify the signal. This results in amplification of the background noise as well, resulting in inaccurate reading.

### Can Arterial Blood Gas Sample Give Erroneous Oxygen Saturation Result?

*Air Bubble or Froth*

Room air bubbles have $PO_2$ of about 150 mm Hg. Change in $PaO_2$ depends upon initial $PaO_2$ in the blood sample. At low Hb saturation ($PaO_2$ <70 or $SaO_2$ ~93%) oxygen absorbed from air bubble binds to the Hb, with minimal change in $PaO_2$. If initial blood $PaO_2$ is 80-140 mm Hg, exposure to air increases $PaO_2$. For initial $PaO_2$ >150, exposure to air decreases $PaO_2$. Air bubbles or froth should be expelled from the syringe before transport. Pneumatic transport system (The CHUTE) results in agitation of sample and a thorough mixing of air bubble with blood, resulting in excessive change in the $PaO_2$ compared delivery by personnel.

**Table 3:** Effects and compensatory mechanisms due to hypoxia

| *Compensatory mechanism* | *Comment* |
|---|---|
| Hyperventilation | Hyperventilation increases the oxygen demand of the diaphragm itself. |
| Hypoxic pulmonary vasoconstriction | Redistribution of pulmonary blood flow for better ventilation-perfusion match. Increase in pulmonary vascular resistance may not be well tolerated in right ventricular failure |
| Sympathetic stimulation | Reflex stimulation due to activation of chemoreceptors in aortic and carotid body |
| Increased cardiac output | Increase in regional blood flow to most organ beds, particularly, brain |
| Rightward displacement of OHDC | Increase in 2,3 DPG and acidosis |
| Anaerobic metabolism | Lactate production to maintain regenerate $NAD^+$ from NADH and maintain glycolysis (which produces 2 ATP/glucose). In the absence of production of lactate, glycolysis will stop, and 2 molecules of ATP generated during glycolysis will no longer be available. While lactate is used as a marker of ischemia, its production is essential and may preserve life by anaerobic metabolism in the absence of oxygen. |
| Increased hemoglobin concentration | Activation of erythropoietin and transferrin gene |

### *Delay in Transfer of Blood to the Lab*

In a blood sample awaiting transfer to the lab $PaO_2$ decreases due to respiration of the blood cells, particularly the WBC and reticulocytes. Samples that cannot be analyzed within 10 minutes should be stored on crushed ice and analyzed within 30 minutes. The change in pH, bicarbonate, and base excess is not significant for up to 30 minutes. There is an upward trend in $PaCO_2$, but the change is not significant at 30 minutes.[2]

### *How does Hypothermia Affect $PaO_2$ on ABG?*

Level of oxygen in a solution is measured using Clarke's electrode. Routinely, blood gas is analyzed at 37°C. Care is required when analyzing the ABG of a hypothermic patient. In **alpha-stat** strategy the sample is analyzed at 37°C while in the **pH-stat** strategy measurement be corrected to the actual core body temperature.

If blood sample of hypothermic, patient is warmed to 37°C (Alpha-stat), decrease in affinity of Hb at higher temperature (due to right shift of OHDC) results in release of large amount of oxygen, resulting in overestimation of $PaO_2$. On the other hand, if the blood sample is analyzed at same temperature as body (pH-Stat), $PaO_2$ will be lower because of higher solubility of oxygen at lower temperature. However, even with low $PaO_2$, the hemoglobin saturation may be higher (due to left shift in OHDC). A simple rule of thumb may be to decrease $PaO_2$ by 5 mm Hg for each 1°C drop in temperature.

## How can We Increase the Capacity of Blood to Deliver Oxygen?

Ensuring that the tissues receive adequate oxygen is a big part of what we do in intensive care. A detailed discussion is beyond the scope of this review. A few points are worth mention.

- *Supplemental oxygen*: The use of supplemental oxygen is so common that we forget it is a drug, with side effects. Supplemental oxygen is vital for treatment of hypoxemia. However, routine use in the absence of hypoxia provides no benefit. The IOTA metanalysis (Improving Oxygen Therapy in Acute-Illness) suggests that liberal oxygen therapy increases mortality without improving any patient-centered outcome.[3]
- *Iron*: It is useful for absolute iron deficiency. Many critically ill patients have anemia of inflammation, for which supplemental iron is not useful. Iron is important for bacterial growth and may increase infection risk. Iron supplementation has not been shown to reduce transfusion requirements.[4]
- *Erythropoietin* appears to be attractive, particularly when restrictive transfusion trigger is used. Its use does not reduce the number of units transfused. Erythropoietin supplementation has not been shown to reduce transfusion requirements.
- *Oxygen carriers*: Hemoglobin-based oxygen carriers (HBOC) and perfluorocarbons are being studied but not yet used in clinical practice.[5]

## Hypoxia — Causes, Signs and Compensation

Hypoxemia ($PaO_2$ <80 mm Hg) presents with vague symptoms and may be difficult to detect unless looked for the compensatory mechanisms that get activated in the setting of hypoxemia are listed in Table 3.

## When should Venous Oxygen Content be Measured?

- *Mixed venous oxygen saturation ($SvO_2$)* refers to the oxygen saturation in mixed venous blood returning from all parts of the body, including heart. For $SvO_2$ measurement, blood should be sampled from the distal port of pulmonary artery catheter. Its normal value is between 60% and 80%. If hemoglobin concentration, $SaO_2$ and oxygen consumption remain constant, decrease in $SvO_2$ reflects a decrease in cardiac output.
- *Central venous oxygen saturation ($ScvO_2$)*: $ScvO_2$, when measured in blood drawn from a central vein in superior vena cava, is 2–4% lower than $SvO_2$ because the blood from kidneys is less deoxygenated. During period of hemodynamic instability, renal and splanchnic blood flow may be lower, and the relationship between $SvO_2$ and $ScvO_2$ will change. The two, therefore, cannot be used interchangeably.[6] The heart has a higher oxygen extraction, and blood from coronary sinus has lower oxygen saturation than from central venous blood.
- *Jugular venous oximetry ($SjO_2$)* is sometimes used in patients with acute neurological injury. The catheter is inserted in the jugular vein but directed cephalad. The normal value ranges from 55–75 mm Hg. Low $SjO_2$ indicates cerebral ischemia. High $SjO_2$ may indicate either cerebral hyperemia, or reduced cerebral metabolism, as may occur after brain death.

## What can Cause the Blood to Boil at 37°C?

We finish the article with a piece of useless trivia. Metaphorically, even trivial things may make our blood boil, but it can really boil if

the ambient pressure is so low that the gas dissolved in blood start to form bubbles. Ebullism, as it is technically called, will occur at an altitude of 29,000 m (Armstrong's line). The astronaut space suits are pressurized to prevent its occurrence.

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