# Introduction

Monitoring of hemodynamic status of critically ill patients in intensive care units is one of the main objectives of therapeutic management ***(Hett & Jonas, 2003).***

In the initial treatment of a critically ill patient, blood pressure, heart rate, urine output, and central venous pressure guide resuscitative efforts. Despite normalization of these variables, global tissue hypoxia may still persist and has been implicated in the development of multiorgan failure and increased mortality ***(Rivers et al., 2001).***

Global tissue hypoxia attributable to inadequate oxygen delivery is often exacerbated by a microcirculatory injury and increased tissue metabolic demands this may be further compounded by cytopathic hypoxia attributable to mitochondrial dysfunction ***(Fink, 2002).***

Shock is best defined as a life-threatening medical condition that occurs due to inadequate oxygen for aerobic cellular respiration. The typical signs of shock are low blood pressure, tachycardia and signs of poor end-organ perfusion ***(Gutyon et al., 2010).***

While hypotension is an important marker of shock, it is clear that blood pressure alone cannot be used as the sole determinant of shock. Shock models have demonstrated that the body can develop an oxygen debt in the setting of normal blood pressure ***(Wo et al., 1993).***

This concept underscores the importance of evaluating organ function and microcirculatory perfusion in patients who have normal vital signs despite inadequate organ perfusion ***(Sakr et al., 2004).***

Therefore, measurements of tissue perfusion and oxygenation are necessary to determine whether the ultimate goal of resuscitation, and adequate oxygen supply to tissues, has been attained ***(Ahrens, 2006).***

# AIM OF THE WORK

The aim of this essay is to discuss defects in tissue oxygenation encountered in many critically ill patients, different methods of monitoring and current strategies for optimization of tissue oxygenation.

# Physiology of Tissue Oxygenation

Tissue oxygenation is determined by:-

## *I- Oxygen delivery*

## *Definition:-*

Global oxygen delivery ($DO_2$) is the amount of oxygen delivered to the whole body from the lungs. It is the product of total blood flow or cardiac output (CO) and the oxygen content of arterial blood ($CaO_2$) and is usually expressed in ml/min ***(Hebert et al., 2008).***

Oxygen delivery may be calculated as follows:

$$DO_2 = CO \times CaO_2.$$

Where CO is the cardiac output and $CaO_2$ is arterial $O_2$ content. The formula may include the cardiac index (CI), which is the cardiac output divided by the body surface area. The formula would then be:

$$DO_2I = CI \times CaO_2.$$

Calculation of $CaO_2$ may be performed using the following formula**:**

$$CaO_2 = (Hb \times 1.39 \times SaO_2) + (PaO_2 \times 0.003).$$

Where Hb represents the hemoglobin level, $SaO_2$ the arterial saturation, $PaO_2$ the arterial tension, and 0.003 is the solubility coefficient of oxygen in human plasma. Each gram of hemoglobin is capable of carrying 1.39 ml of oxygen. The amount of oxygen carried on the hemoglobin is Hb x 1.39 x $SaO_2$. The oxygen content is essentially dependent on the oxygen carried by hemoglobin and oxygen dissolved in plasma does not make a significant contribution to $CaO_2$ this concept is illustrated in ***Table (1-1).*** Thus, it is usually acceptable to use the abbreviated formula for oxygen content: $CaO_2$ = Hb x 1.39 x $SaO_2$. However, if a high $FiO_2$ is used, the amount of dissolved $O_2$ may be significant, and the entire formula should be used ***(American Thoracic Society and American College of Chest Physicians, 2009).***

***Table (1-1): Relative influence of anemia on oxygen delivery (Hebert et al., 2008).***

| Parameter | Normal | Anemic | Anemic with $O_2$ therapy |
|---|---|---|---|
| Inspired oxygen (%) | 21 | 21 | 100 |
| $PaO_2$ (mmHg) | 90 | 90 | 640 |
| $SaO_2$ (%) | 98 | 98 | 98 |
| Hb concentration (g/L) | 150 | 75 | 75 |
| Dissolved oxygen (ml/L) | 3 | 3 | 19 |
| Hb-bound oxygen (ml/L) | 197 | 98 | 98 |
| Total $CaO_2$ (ml/L) | 200 | 101 | 117 |
| $DO_2$ (ml/min) assuming cardiac output is 5 L/min | 1000 | 505 | 585 |

Normally, changing oxygen needs of the body are easily met through abundant basal flow and a variety of compensatory mechanisms including increased stroke volume and heart rate, vascular redistribution of blood flow, capillary recruitment, and changes in hemoglobin binding affinity, recently, it has also been shown that the red blood cell itself may be playing an important role in local control of flow through hypoxic regions by generating dilatory NO from membrane associated nitric oxide syntheses ***(Gladwin & Patel, 2008).***

# ***II- Oxygen consumption***

## *Definition:-*

Global oxygen consumption ($VO_2$) is the volume of oxygen consumed by the tissues per minute. Under aerobic conditions, oxygen is consumed to generate energy so that $VO_2$ corresponds to the metabolic rate. Measurements of $VO_2$ are sometimes used to assess the adequacy of $DO_2$ on the assumption that if $DO_2$ is inadequate $VO_2$ becomes supply-dependent. $VO_2$ can be measured directly by analysis of respiratory gases or derived from cardiac output and arterial and venous oxygen contents. Calculation from cardiac output and arterial-mixed venous oxygen saturation is simpler and can be done using a pulmonary artery catheter, (the reverse/ inverse Fick's principle) is used: $VO_2 = CO \times (CaO_2 - CvO_2)$ ***(Hebert et al., 2008).***

This equation highlights the importance of mixed or central venous blood oxygen saturation as a parameter to monitor cardiopulmonary function. Any impairment in these factors will result in a lack of tissue oxygenation or hypoxia, which when severe is life-threatening ***(American Thoracic Society and American College of Chest Physicians, 2009).***

## III- Oxygen extraction ratio

### Definition:-

The oxygen extraction ratio ($O_2ER$) is the ratio of $VO_2$ to $DO_2$ and represents the fraction of oxygen delivered to the microcirculation that is taken up by the tissues.

$$O_2ER = VO_2/DO_2$$

The normal $O_2ER$ is 0.2 to 0.3, indicating that only 20–30% of the delivered oxygen is utilized. This spare capacity enables the body to cope with a fall in $DO_2$ without initially compromising aerobic respiration and $VO_2$. $O_2ER$ varies between organs; the heart has a high $O_2ER$ (~0.6) so it is particularly sensitive to reductions in coronary artery $DO_2$ ***(Hebert et al., 2008)***.

## IV- Respiratory Exchange Ratio

### Definition:-

The ratio of carbon dioxide output to oxygen uptake is called the respiratory exchange ratio (R), that is:

$$R = \frac{\text{Rate of carbon dioxide output}}{\text{Rate of oxygen uptake}}$$

The value for R changes under different metabolic conditions. When a person is using exclusively carbohydrates for body metabolism, R rises to 1.00. Conversely, when a person is

using exclusively fats for metabolic energy, the R level falls to as low as 0.7. The reason for this difference is that when oxygen is metabolized with carbohydrates, one molecule of carbon dioxide is formed for each molecule of oxygen consumed; when oxygen reacts with fats, a large share of the oxygen combines with hydrogen atoms from the fats to form water instead of carbon dioxide. In other words, when fats are metabolized, the respiratory quotient of the chemical reactions in the tissues is about 0.70 instead of 1.00. For a person on a normal diet consuming average amounts of carbohydrates, fats, and proteins, the average value for R is considered to be 0.825 ***( Jones et al., 2010).***

## *V-Oxygen transport and diffusion*

Oxygen must be transported effectively from the atmosphere to the tissues in order to sustain normal metabolism. An understanding of oxygen delivery is therefore central to the management of patients during anesthesia, resuscitation and during critical illness ***(Hebert et al., 2008).***

Oxygen diffuses from the alveoli into the pulmonary capillary blood because the oxygen partial pressure ($PO_2$) in the alveoli is greater than the $PO_2$ in the pulmonary capillary blood. In the other tissues of the body, a higher $PO_2$ in the capillary blood than in the tissues causes oxygen to diffuse into the surrounding cells. Conversely, when oxygen is metabolized in the cells to form carbon dioxide the intracellular carbon dioxide pressure ($PCO_2$)

rises to a high value, which causes carbon dioxide to diffuse into the tissue capillaries. After the blood flows to the lungs, the carbon dioxide diffuses out of the blood into the alveoli, because the $PCO_2$ in the pulmonary capillary blood is greater than that in the alveoli. Thus, the transport of oxygen and carbon dioxide by the blood depends on both diffusion and the flow of blood. The $PO_2$ of the gaseous oxygen in the alveolus averages 104 mmHg, whereas the $PO_2$ of the venous blood entering the pulmonary capillary at its arterial end averages only 40 mmHg because a large amount of oxygen removed from this blood as it passes through the peripheral tissues. Therefore, the initial pressure difference that causes oxygen to diffuse into the pulmonary capillary is 104 – 40, or 64 mmHg ***(Richardson, 2010).***

About 98% of the blood that enters the left atrium from the lungs has just passed through the alveolar capillaries and has become oxygenated up to a $PO_2$ of about 104 mmHg. Another 2% of the blood has passed from the aorta through the bronchial circulation, which supplies mainly the deep tissues of the lungs and is not exposed to lung air. This blood flow is called **"**shunt flow" meaning that blood is shunted past the gas exchange areas. On leaving the lungs, the $PO_2$ of the shunt blood is about that of normal systemic venous blood, about 40 mmHg. When this blood combines in the pulmonary veins with the oxygenated blood from the alveolar capillaries, this so-called venous admixture of blood

causes the $PO_2$ of the blood entering the left heart and pumped into the aorta to fall to about 95 mmHg ***(Piiper, 2010).***

When the arterial blood reaches the peripheral tissues, its $PO_2$ in the capillaries is still 95 mmHg. The $PO_2$ in the interstitial fluid that surrounds the tissue cells averages only 40 mmHg. Thus there is a tremendous initial pressure difference that causes oxygen to diffuse rapidly from the capillary blood into the tissues so rapidly that the capillary $PO_2$ falls almost to equal the 40 mmHg pressure in the interstitium. Therefore, the tissue $PO_2$ is determined by a balance between:

(1) The rate of oxygen transport to the tissues in the blood.

(2) The rate at which the oxygen is used by the tissues ***(Roy & Popel, 2010).***

Normally, about 97% of the oxygen transported from the lungs to the tissues is carried in chemical combination with hemoglobin in the red blood cells. The remaining 3% is transported in the dissolved state in the water of the plasma and blood cells. Thus, under normal conditions, oxygen is carried to the tissues almost entirely by hemoglobin. The oxygen molecule combines loosely and reversibly with the heme portion of hemoglobin. When $PO_2$ is high, as in the pulmonary capillaries, oxygen binds with the hemoglobin, but when $PO_2$ is low, as in the tissue capillaries, oxygen is released from the hemoglobin; this is

the basis for almost all oxygen transport from the lungs to the tissues ***(Spahn & Pasch, 2010).***

## Oxygen-Hemoglobin Dissociation Curve

Oxygen-hemoglobin dissociation curve demonstrates a progressive increase in the percentage of hemoglobin bound with oxygen as blood $PO_2$ increases, which is called the percent saturation of hemoglobin ***Figure* (1-1).** Because the blood leaving the lungs and entering the systemic arteries usually has a $PO_2$ of about 95 mmHg, one can see from the dissociation curve that the usual oxygen saturation of systemic arterial blood averages 97% ***(Nikinmaa, 2010).***

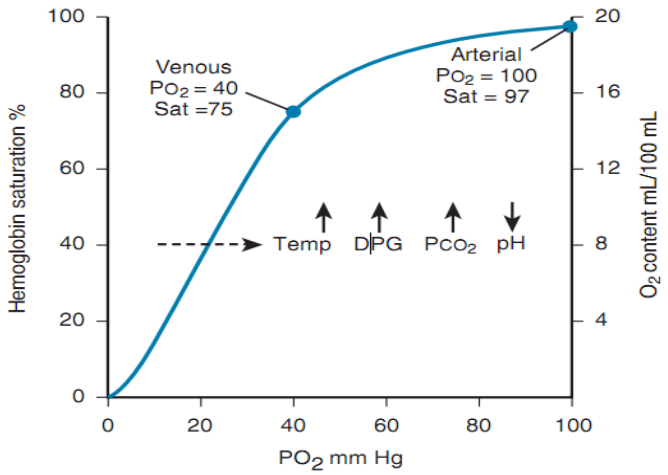


***Figure (1-1): Oxygen dissociation curve showing typical values for arterial and mixed venous blood. The curve is shifted to the right by increases of temperature, $PCO_2$, 2, 3-diphospho-glycerate (DPG), and H concentration (West et al., 2008).***

Conversely, in normal venous blood returning from the peripheral tissues, the $PO_2$ is about 40 mmHg and the saturation of hemoglobin averages 75%. The blood of a normal person contains about 15 grams of hemoglobin in each 100 milliliters of blood, and each gram of hemoglobin can bind with a maximum of 1.34 milliliters of oxygen (1.39 milliliters when the hemoglobin is chemically pure, but impurities such as methemoglobin reduce this). Therefore, 15 times 1.34 equals 20.1, which means that, on average, the 15 grams of hemoglobin in 100 milliliters of blood can combine with a total of almost 20 milliliters of oxygen if the hemoglobin is 100% saturated, this is usually expressed as 20 volumes percent ***(Nikinmaa, 2010).***

- ***Factors that shift the oxygen hemoglobin dissociation curve:***

The strength with which oxygen binds to hemoglobin is affected by several factors ***Table*** **(1-2).** These factors shift the oxyhemoglobin dissociation curve. A rightward shift indicates that the hemoglobin has a decreased affinity for oxygen. This makes it more difficult for hemoglobin to bind to oxygen (requiring a higher partial pressure of oxygen to achieve the same oxygen saturation), but it makes it easier for the hemoglobin to release oxygen bound to it. The effect of this rightward shift of the curve increases the partial pressure of oxygen in the tissues when it is

most needed, such as during exercise or hemorrhagic shock. In contrast, the curve is shifted to the left by the opposite of these conditions. This leftward shift indicates that the hemoglobin has an increased affinity for oxygen so that hemoglobin binds oxygen more easily, but unloads it less easily. Left shift of the curve is a sign of hemoglobin's increased affinity for oxygen ***(Hugger L, 2009).***

***Table (1-2): Factors affecting oxygen hemoglobin dissociation curve (Hugger, 2009).***

| | **right shift (low affinity for $O_2$)** | **left shift (high affinity for $O_2$)** |
|---|---|---|
| Temperature | Increase | Decrease |
| 2.3-DPG | Increase | Decrease |
| $CO_2$ | Increase | Decrease |
| CO (carbon monoxide) | Decrease | Increase |
| pH (Bohr Effect) | Decrease (acidosis) | Increase (alkalosis) |
| type of hemoglobin | adult hemoglobin | fetal hemoglobin |

A shift of the oxygen hemoglobin dissociation curve to the right in response to increases in blood carbon dioxide and hydrogen ions has a significant effect by enhancing the release of oxygen from the blood in the tissues and enhancing oxygenation of the blood in the lungs. This is called the Bohr Effect, which can be explained as follows: As the blood passes through the tissues, carbon dioxide diffuses from the tissue cells into the blood. This increases the blood $PCO_2$ which in turn raises the blood $H_2CO_3$ carbonic acid and the hydrogen ion concentration; these effects shift the oxygen-hemoglobin dissociation curve to the right and downward. Exactly the opposite effects occur in the lungs where carbon dioxide diffuses from the blood into the alveoli. This reduces the blood $PCO_2$ and decreases the hydrogen ion concentration, shifting the oxygen-hemoglobin dissociation curve to the left and upward, therefore, the quantity of oxygen that binds with the hemoglobin at any given alveolar $PO_2$ becomes considerably increased, thus allowing greater oxygen transport to the tissues, the normal DPG in the blood keeps the oxygen-hemoglobin dissociation curve shifted slightly to the right all the time ***(Wagner, 2010).***

2, 3-Disphosphoglycerate (2, 3-DPG) is an organophosphate, which is created in erythrocytes during glycolysis. In hypoxic conditions such as (hypoxemia, chronic lung disease, anemia, and