

## Acute and Short Term Hyperoxemia: How about Hemorheology and Tissue Perfusion?

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### Abstract


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Tissue perfusion is a major factor determining the prognosis, morbidity and mortality in ICU patients. Perfusion may carry on via uninterrupted delivery of sufficient substrate and oxygen to the tissues. From this point of view, determinants of tissue perfusion that routinely mentioned are cardiac output, vascular tonus, oxygen diffusion and transportation. The impact of blood viscosity and related hemorheological factors on microcirculation and tissue perfusion is frequently neglected. Under physiological circumstances, compensatory mechanisms maintain the stability of perfusion. However, it is well-established that the changes in aggregation and deformability of red blood cells are concomitant with alterations in blood fluidity at hypoxic conditions and this fact enhances the severity of hypoxemia. On the contrary, acute hyperoxemia is performed to achieve therapeutic goals or to prevent predicted hypoxemia during ICU facilities. Although the effects of hyperoxemia on vessel reactivity and ROS generation were previously indicated, its impact on hemorheology and tissue perfusion are not clear. Further studies are needed to disclose the influence of acute hyperoxemia performed during cardiopulmonary resuscitation, intubation, sedation, tracheal suction, etc., on tissue perfusion in critically ill patients.

**Keywords:** Hyperoxemia; Hemorheology; Perfusion; Viscosity; Aggregation; Deformability

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Oxygen therapy has been used to prevent or treat hypoxemia more frequently in intensive care unit (ICU) setting for years. Oxygen demand of the patients is predicted by evaluating blood gases, organ insufficiency indicators and physiological findings of progressing hypoxia. However, the ratio of fractioned inspired oxygen (FiO<sub>2</sub>) needed to be administered to patient to overcome the adverse effects of hypoxemia while avoiding deleterious effects of oxygen is a matter of debate. Many studies have proven the existence of oxygen toxicity due to increased formation of reactive oxygen species (ROS) especially in conditions of hypoxia/reperfusion. While these effects are particularly pronounced during long term administration, i.e., beyond 12-24 h, several retrospective studies suggest that even hypoxemia of shorter duration is also associated with increased mortality and morbidity [1]. The efficacy of short term ventilation with high FiO<sub>2</sub> (0.8-1.0) during perioperative period (i.e., anesthesia induction or weaning, patient transport), sedation for

invasive procedures (i.e., catheterizations, endoscopic attempts) or cardiopulmonary resuscitation (CPR) is not currently proven in terms of microcirculation and organ perfusion.

Exchange of gases, nutrients and metabolites between the blood and tissues via the microcirculatory network is the cornerstone of tissue perfusion and organ function. A concept covering both oxygen delivery, tissue oxygen transport and oxygen consumption of the cells could be named tissue oxygen perfusion [2]. There are various non-invasive methods to estimate the tissue perfusion and oxygenation like body temperature gradient, pulse-oximetry, near-infrared spectroscopy, orthogonal polarizing spectrophotometry, laser Doppler flowmeter, transcutaneous oximetry and sublingual capnography [3]. All these methods are partially capable of monitoring the essential components of perfusion as cardiac output, systemic vascular resistance, hemoglobin oxygen saturation and integrity of microcirculation.

Blood supply and oxygen delivery to tissues are estimated via these methods and oxygen therapy is maintained to achieve the targets of sufficient oxyhemoglobin saturation and blood flow. However the effects of hemorheological properties are frequently neglected.

Hemorheology deals with the flow and deformation behavior of blood and its formed elements (i.e., RBCs, WBCs, platelets) [4,5]. Because blood is a two-phase liquid (plasma and cellular elements), its fluidity at a given shear rate and temperature is determined by the rheological properties of the plasma and cellular phases and by the volume fraction (i.e., hematocrit) of the cellular phase. In addition to the concentration of cellular elements in blood, their rheological properties are important determinants of blood fluidity. RBCs are the major determinant of this effect, with these cells exhibiting a very special rheological behavior. Normal RBCs are highly deformable bodies and tend to orient themselves with the flow streamlines, especially if the shear forces are high enough to slightly deform these cells. Another important rheological feature of RBCs is their tendency to aggregate into linear arrays, termed rouleaux, in which they are arranged like stacks of coins. Linear aggregates then interact to form three-dimensional structures [6]. Fibrinogen and other large plasma proteins promote RBC aggregation, with aggregation dependent on the magnitude of shearing forces acting on the cells. Increased shear disrupts the aggregates, whereas reduced shear favors aggregation [4]. Because of the increased effective particle size, the disturbance of flow streamlines becomes more pronounced when RBC aggregates are formed and blood viscosity is significantly increased. Red blood cell aggregation is thus the major determinant of blood viscosity under low shear conditions [4]. Studies linking viscosity-dependent changes of microvascular perfusion to outcome-relevant data suggest that whole blood viscosity and relevant hemorheologic parameters are negligible as a determinant of microvascular perfusion under physiological conditions when autoregulation is effective. Because

autoregulation is driven to maintain oxygen supply constant, the organism will compensate for changes in blood viscosity to sustain oxygen delivery [4,7]. However, when the physiological compensatory mechanisms are hampered due to pathological courses or therapeutic interventions (i.e., mechanical ventilation, sedation etc.) hemorheological alterations may lead to perfusion disturbances.

Acute hyperoxemia is proved to be related with cerebral vasoconstriction, neuronal cell death, decreased cardiac index and heart rate while increased peripheral vascular resistance [8]. Despite the rapidly growing information about the deteriorating effects of high  $\text{FiO}_2$  therapy on perfusion via decreased blood flow and ROS related cytotoxicity, there are limited data on the impact of hyperoxemia on blood rheology which is directly correlated with tissue perfusion, especially in critically ill patients. Recent two studies showed that acute hyperoxemia due to hyperbaric oxygen therapy or normobaric ventilation with high  $\text{FiO}_2$  did not have significant effect on blood viscosity, red blood cell aggregation or deformability [9,10]. Despite the well-known perfusion disrupting effects of hypoxia like decreased red blood cell deformability, blood viscosity, plasma viscosity and increased red blood cell aggregation, hyperoxemia seems to be inefficacious and/or harmless in terms of tissue perfusion via blood liquidity.

High  $\text{FiO}_2$  inhalation is used in seriously ill or healthy subjects with various indications. Acute and chronic respiratory insufficiencies are major indications in ICU patients. Moreover, CPR and many other invasive procedures as tracheal suctioning, catheterization, intubation and extubation are performed under high  $\text{FiO}_2$ . Recent data verify the application of high  $\text{FiO}_2$  to avoid hypoxemia for acute and short term procedures facing the risks of potential oxygen toxicity and impaired microcirculation. More studies are needed to define the 'safe interval and duration' for oxygen therapy in order to contribute to improve oxygenation rather than frustrating tissue perfusion.

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