Functional heterogeneity of oxygen supply with blood and hemoglobin-based oxygen carriers in porcine models of hemorrhagic shock
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**General Introduction**

To ensure adequate blood flow and diffusion of oxygen to the mitochondria of cells, there is a complex regulation of global, regional, neuronal, and humoral factors, as well as intrinsic metabolic and vascular pathways. Therefore, normal cell, tissue, and organ functions depend not only on oxygen supply but also on oxygen demand. The balance between oxygen supply and oxygen demand determines whether the tissue is healthy or dysoxic (in which the oxygen need exceeds the oxygen supply), leading to damage to the cells, tissues, or even whole organs.

If regional dysoxia in compromised vascular beds is great enough, this state can be detected by techniques that assess global hemodynamic- and oxygenation-related parameters. Early detection of tissue dysoxia, however, requires techniques for measuring regional oxygen supply, oxygen consumption, or ideally the oxygen supply-consumption ratio. Although the measurement of metabolic parameters, such as plasma lactate, venous oxygen saturation, and regional carbon dioxide level, is clinically applicable, these measurements are only indirect parameters of the adequacy of tissue oxygenation and are therefore limited in their usefulness. Methods for direct, quantitative assessment of microcirculatory oxygen tension utilize either the electrochemical properties of metals, such as oxygen electrodes, or the optical properties of hemoglobin and indicator dyes, such as fluorimetry and phosphorimetry. Measurement with oxygen electrodes requires the insertion of one or more electrodes into the organ to map oxygenation in depth. This requirement is related to cell damage and bleeding, which severely limit the applicability of this technique.

Fluorimetry, a non-invasive technique for intracellular oxygen measurement, but due to short fluorescence lifetimes, highly specialized equipment is required, which has limited its use.

The Pd-porphyrin phosphorescence technique is a non-invasive and online monitoring method for microcirculatory oxygenation. It provides a direct measurement of the oxygen supply-consumption ratio. This quantitative measurement of oxygen in vivo is based on the oxygen-dependent quenching of the phosphorescence of palladium porphyrin. The oxygen concentration or partial oxygen pressure is calculated using the phosphorescent decay curve. This method has enabled the fiber-based detection of oxygen in various tissues during different types of shock. Because of the required administration of a dye, this technique has only been used in animal models.

In sepsis and during the treatment of sepsis, it has been shown that monitoring of the microcirculation is important because its behavior differs from the changes in monitored macrocirculatory parameters. The disparity between the macro- and
microcirculation is thought to be due to microvascular dysfunction induced by inflammatory activation associated with infectious, inflammatory or hypoxic conditions and resulting in the shunting of vulnerable microcirculatory beds.

Hemorrhage, characterized by reductions in both hemoglobin concentration and blood volume, results in heterogeneity of the blood flow between, as well as within organs.\(^\text{10}\) Depending on the severity of shock, this heterogeneity might result in a disturbed balance between oxygen delivery to and oxygen consumption by tissues.\(^\text{11}\) It is known that in trauma patients, hemorrhage is related to high mortality and morbidity via early stage failure of the heart or intestinal ischemia, which subsequently can result in multiple organ failure.\(^\text{12}\) To determine the severity of hemorrhage and the efficacy of resuscitation, it seems obvious to monitor oxygenation at the microcirculatory level.

For the treatment of hemorrhage, transfusion of allogeneic blood can be life-saving, but it is associated with logistical constraints, side effects, and biological limitations. Therefore, for more than a century, there has been a search for alternatives to blood. Of these alternatives, the development of hemoglobin-based oxygen carriers (HBOCs) is the most substantial and was introduced in 1933 by Amberson.\(^\text{13}\) Most developed products are made from outdated human donor blood and consist of acellular hemoglobin molecules obtained after lysing the red blood cells. This process offers important advantages in that these products do not require blood typing or cross-matching, which are required with the transfusion of allogeneic blood. Furthermore, these products are essentially free from viral pathogens and can be stored for long periods of time. Compared with the hemoglobin within red blood cells, however, acellular hemoglobin made from human blood has increased oxygen affinity, and the tetramer structure of the hemoglobin easily breaking down into dimers and monomers; this process results in a short intravascular half-life and in nephrotoxicity.\(^\text{14}\) The production of stroma-free hemoglobin, cross-linking, and polymerization have resulted in less nephrotoxicity, improved intravascular retention time, and reduction of the oxygen affinity of the hemoglobin. Of utmost concern, however, is the vasoactivity of HBOCs. Believed to be due primarily to the binding by artificial hemoglobin of nitric oxide (NO) as a natural vasodilator,\(^\text{15}\) there are various characteristics of the hemoglobin molecule itself, such as hemoglobin concentration, viscosity, colloid osmotic pressure, oxygen affinity, and molecular weight, that are involved in this regulation.

As HBOCs were primarily developed for the improvement of disturbed microcirculatory oxygenation during hemorrhage, it is important to know how the combination of vasoactivity and oxygen transport capacity affects the distribution of oxygen supply and oxygen consumption in various tissue beds during shock and resuscitation.