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Hyperoxia in Extreme Hemodilution

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Key Words

Acute normovolemic hemodilution · ANH · Hyperoxia · Hyperoxemia

Abstract

Intraoperative surgical blood loss is initially replaced by infusion of red cell-free, cristalloidal or colloidal solutions. When normovolemia is maintained the ensuing dilutional anemia is compensated by an increase of cardiac output and of arterial oxygen extraction. In the ideal case, a surgical blood loss can entirely be 'bridged' without transfusion by intraoperative normovolemic hemodilution. However major blood loss results in extreme hemodilution and the transfusion of red blood cells may finally become necessary to increase arterial oxygen content and to preserve tissue oxygenation. When transfusion has to be started before surgical control of bleeding has been achieved, parts of the red blood cells transfused will get lost, thereby increasing intraoperative transfusion needs. Beside red blood cell transfusion, arterial oxygen content can be rapidly increased by ventilating the patient with 100% oxygen (hyperoxic ventilation), thus enhancing the amount of physically dissolved oxygen in plasma (hyperoxia). In experimental and clinical studies hyperoxic ventilation has emerged as a simple, safe and effective intervention to enlarge the margin of safety for hemodynamic compensation and tissue oxygenation in hemodiluted subjects experiencing major bleeding. The hyperoxia-associated microcirculatory dysregulation and impaired tissue oxygenation known to take place in the presence of a physiologic hemoglobin concentration are not encountered in hemodiluted subjects. Hyperoxic hemodilution i.e. the combination of intraoperative extreme hemodilution and hyperoxic ventilation may therefore be considered a cost-effective, safe and efficient supplement to reduce allogeneic transfusion during surgical interventions associated with high blood losses. The vast majority of the experimental and clinical investigations this new concept is based on was initiated and performed under the guidance of Prof. Konrad Messmer.

Fluid Replacement of Surgical Blood Loss

The transfusion of allogeneic blood is expensive and – although safer than ever before – still associated with potential complications (acute transfusion reaction due to 'clerical error', transfusion-related bacterial and viral infection, immunosuppression). To reduce both, costs and immanent risks, allogeneic transfusion should either be completely avoided or at least minimized during surgical procedures. This can be achieved by (1) intraoperative transfusion of autologous blood collected preoperatively (autologous blood donation, acute normovolemic hemodilution) or intraoperatively (blood salvage), (2) reduction of the amount of blood loss (skillful surgical technique, deliberate hypotension, administration of antifibrinolytic drugs), and (3) acceptance of low intraoperative hemoglobin (Hb) concentrations.

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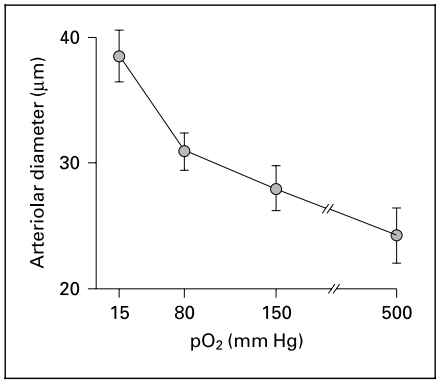

Fig. 1. Oxygen response of parenchymal arterioles of the hamster cheek pouch in situ (intravital microscopy). Arterioles were suffused with a normal saline solution equilibrated to different oxygen partial pressures (x-axis). The mean arteriolar diameter (± SEM) is depicted on the y-axis. Adapted from Jackson and Duling [25].

Since it is known for a long time that adequate tissue oxygenation does not depend on a 'normal' hemoglobin concentration [1] an intraoperative blood loss is initially replaced by erythrocyte-free, i.e. cristalloidal or colloidal solutions (e.g. Ringer's lactate, dextran, hydroxyethyl starch, gelatine). As long as normovolemia is maintained the resulting dilutional anemia is compensated without risk of tissue hypoxia through an increase of cardiac output (through an increase of ventricular stroke volume) and enhanced arterial oxygen extraction [2, 3]. In the ideal case, a surgical blood loss can be 'bridged' without allogeneic blood transfusion by intraoperative normovolemic hemodilution. However, once the Hb has dropped to values recommended as the lower intraoperative limit (Hb 6 g/dl in healthy subjects or Hb 8–10 g/dl in patients with preexisting cardiovascular disease [4, 5]) or once so-called 'transfusion-trigger' parameters (e.g. oxygen consumption, mixed-venous oxygen partial pressure, ST segment depression in ECG) indicate the exhaustion of the compensatory mechanisms for dilutional anemia , as a rule transfusion of red blood cells is initiated to increase arterial oxygen content and to preserve a margin of safety for tissue oxygenation and organ function. When transfusion has to be started prior to definite surgical control of bleeding, the overall need for transfusion increases due to the partial loss of the red blood cells transfused.

Effects of Hyperoxic Ventilation in Extreme Hemodilution

Hyperoxia

As an alternative to the immediate transfusion of red blood cells, ventilation with 100% oxygen (hyperoxic ventilation) can be employed to rapidly raise arterial oxygen content by increasing the amount of physically dissolved oxygen in plasma (hyperoxia). Because of the linear relationship between arterial partial pressure of oxygen, paO_2, and arterial oxygen content in plasma, the quantity of oxygen dissolved depends only upon arterial pO_2 and plasma volume. Since in hemodiluted subjects the plasma compartment is significantly increased, plasma becomes an important source of oxygen [6].

Hyperoxic Vasoconstriction

Molecular oxygen causes vasoconstriction. This effect of hyperoxia on large vessels as well as on microvessels (arterioles, venules) has been extensively demonstrated in vitro (isolated vessel segments [7]) and in vivo (intravital microscopy [8], laser doppler flowmetry [9] etc.; see fig. 1). It seems to be locally mediated [10] by products of the arachidonic acid metabolic pathway (e.g. 20-hydroxy-eicosa-tetraenoic acid, briefly 20-HETE [11]) and can be completely blocked by indomethacin [12] and cytochrome P-450 inhibitors [11]. Hyperoxia has been shown to increase systemic vascular resistance and to decrease cardiac output and oxygen consumption in subjects with normal hemoglobin concentration [13]. The simultaneously observed deterioration of tissue oxygenation has been interpreted as to reflect impaired local oxygen delivery due to hyperoxic vasoconstriction and abnormal spatial and temporal distribution of microvascular blood flow [14]. As a consequence hyperoxia at normal hemoglobin concentrations is considered harmful concerning tissue integrity and function.

In our own experiments carried out in hemodiluted dogs (Hb 7 g/dl) [6] hyperoxia completely reversed the hemodilution-induced increase of cardiac index and partially reversed the decrease of systemic vascular resistance (fig. 2). Nevertheless, the normal Gaussian distribution of single tissue pO_2 values measured by means of an oxygen-sensitive multiwire surface electrode was preserved during hyperoxia (fig. 3). A higher number of hypoxic tissue pO_2 values (0–15 mm Hg) was not detected and the shifting of the histograms to the right (increase of tpO_2 median) may even indicate improved tissue oxygenation. Moreover non-linear analysis of blood flow distribution did not reveal any increase in heterogeneity of microcir-

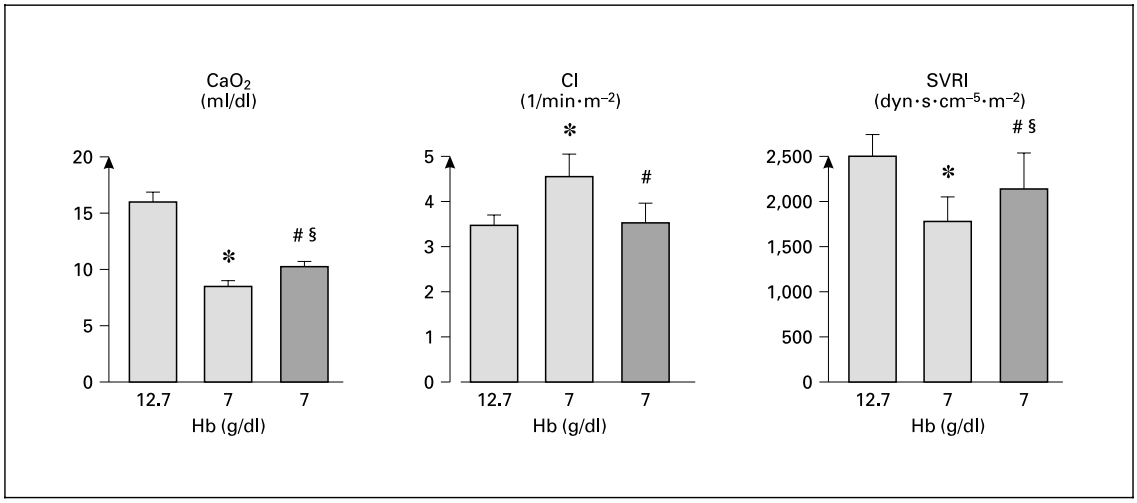

Fig. 2. Changes in arterial oxygen content (CaO_2), cardiac index (CI) and systemic vascular resistance index (SVRI) upon normovolemic hemodilution on room-air ventilation (21% oxygen) to a hemoglobin concentration of 7 g/dl (filled bars) and after subsequent onset of hyperoxic ventilation (100% oxygen; hatched bar). Adapted from Habler et al. [6]. * $p < 0.05$; 'Hb 12.7 g/dl, room-air' vs. 'Hb 7 g/dl, room-air'; # $p < 0.05$; 'Hb 7 g/dl, room-air' vs. 'Hb 7 g/dl, hyperoxic ventilation'; § $p < 0.05$; 'Hb 12.7 g/dl, room-air' vs. 'Hb 7 g/dl, hyperoxic ventilation'.

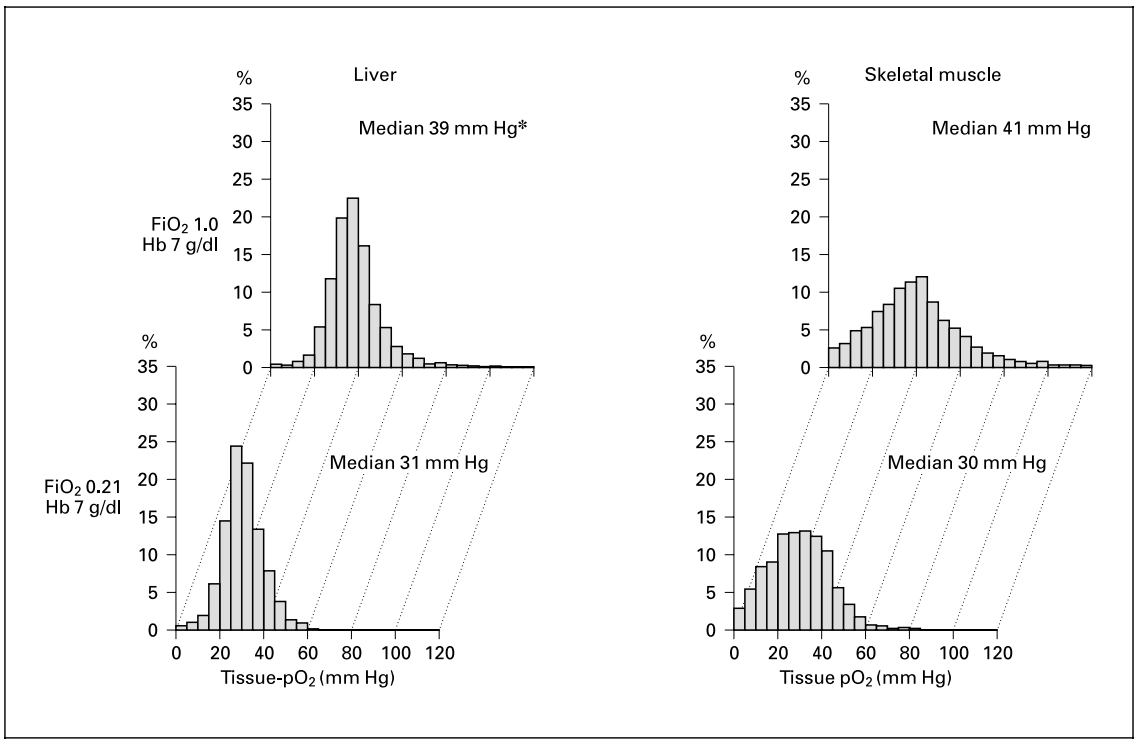

Fig. 3. Frequency distribution of tissue pO_2 values measured on the surface of the liver and a skeletal muscle by use of an oxygen sensitive surface electrode (MDO electrode) in anesthetized dogs hemodiluted to Hb 7 g/dl under room-air ventilation (21% oxygen) and after onset of hyperoxic ventilation (100% oxygen). Adapted from Habler et al. [6]. * $p < 0.05$; 'Hb 7 g/dl, FiO_2 0.21' vs. 'Hb 7 g/dl, FiO_2 1.0'.

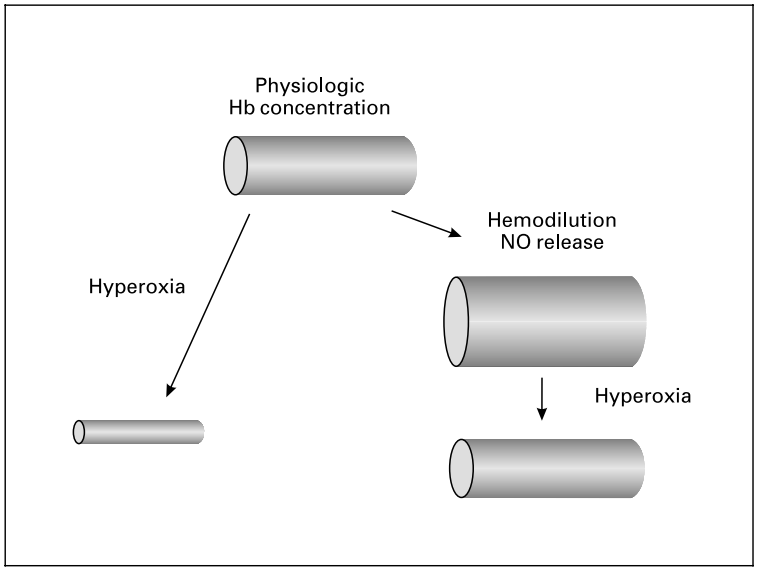

Fig. 4. Schematic depiction of changes in arteriolar diameter when hyperoxic ventilation is performed (1) in subjects with physiologic hemoglobin concentration (left side) and (2) in hemodiluted subjects (right side). Hemodilution-induced vasodilation compensates hyperoxic vasoconstriction [26].

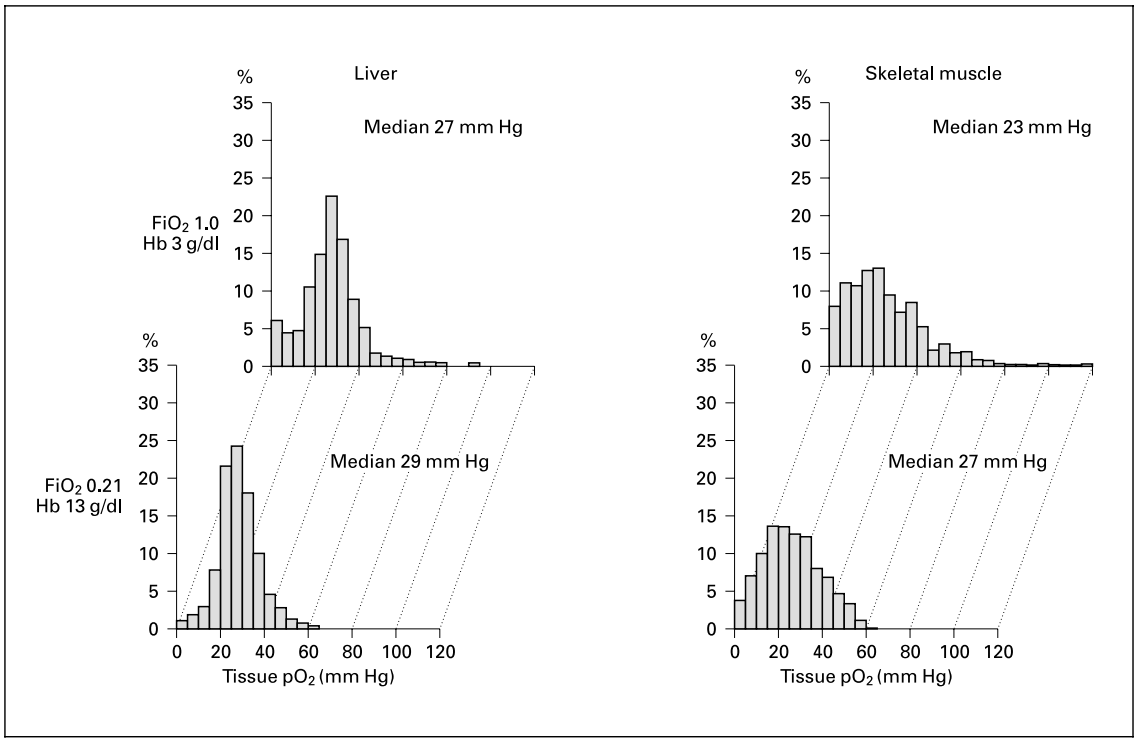

Fig. 5. Frequency distribution of tissue pO_2 values measured on the surface of the liver and a skeletal muscle by use of an oxygen-sensitive surface electrode (MDO electrode) in anesthetized dogs hemodiluted under room-air ventilation (21% oxygen) and physiologic hemoglobin concentration (Hb 13 g/dl) and after extreme hemodilution (Hb 3 g/dl) under hyperoxic ventilation (100% oxygen). Adapted from Habler et al. [6, 19].

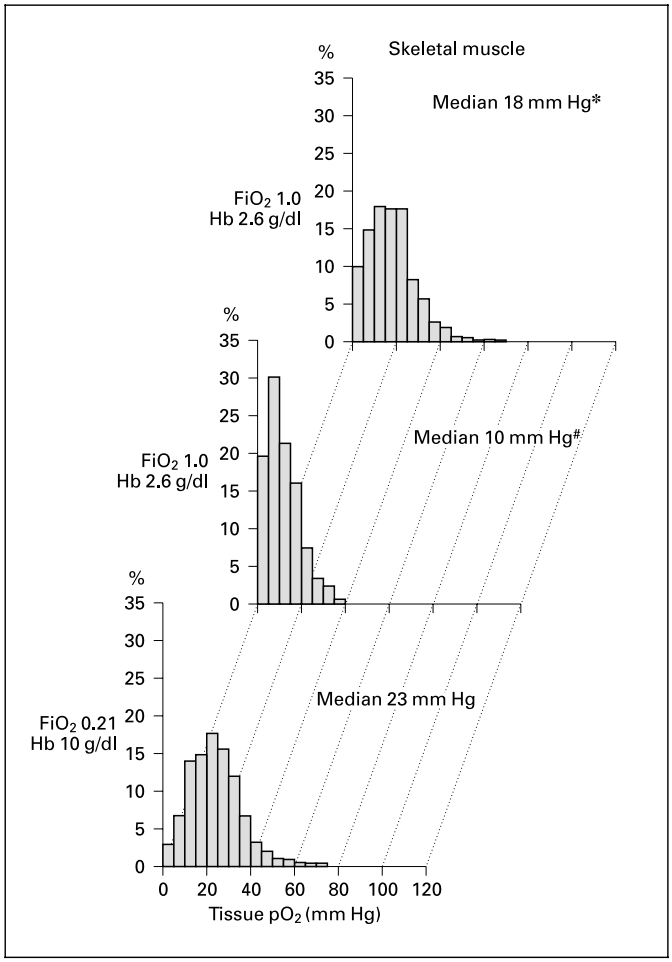

Fig. 6. Frequency distribution of tissue pO_2 values measured on the surface of a skeletal muscle by use of an oxygen-sensitive surface electrode (MDO electrode) in anesthetized pigs hemodiluted under room-air ventilation (21% oxygen) until occurrence of tissue hypoxia (Hb 2.6 g/dl) and after onset of hyperoxic ventilation (100% oxygen). Kemming et al., unpublished data. # $p < 0.05$; 'Hb 10 g/dl, FiO_2 0.21' vs. 'Hb 2.6 g/dl, FiO_2 0.21'; * $p < 0.05$; 'Hb 2.6 g/dl, FiO_2 0.21' vs. 'Hb 2.6 g/dl, FiO_2 1.0'.

culatory blood flow during hyperoxia in hemodiluted animals [15, 16]. These findings demonstrate the pivotal role of the actual Hb concentration on the microcirculatory effects of hyperoxia. The increase of organ blood flow induced by hemodilution (i.e. normovolemic anemia) increases shear stress at the vessel wall which in turn induces the release of endothelium-derived relaxing factor (i.e. nitric oxide, NO) and hence vasodilation [17, 18]. It can therefore be speculated that in dilutional anemia the microcirculatory dysregulation due to hyperoxia is counteracted by NO release (see schematic drawing, fig. 4).

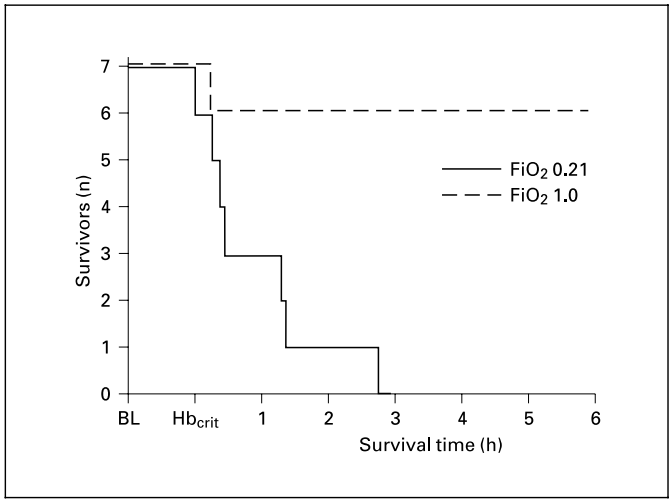

Fig. 7. Survival after acute normovolemic hemodilution (ANH) under room-air ventilation (21% oxygen) to the critical hemoglobin concentration (Hb_{crit}) i.e. until occurrence of manifest tissue hypoxia. For the following 6 h animals were either further ventilated with room air (n = 7, dotted line) or with 100% oxygen (hyperoxic ventilation; n = 7, solid line). Meier et al., unpublished data.

Hyperoxia as an Alternative to Red Blood Cell Transfusion in Surgical Blood Loss

Experimental Data

Under the 'protection' of hyperoxia, intraoperative hemodilution may be extended to Hb concentrations lower than those usually accepted as trigger for red blood cell transfusion as demonstrated in experimental and clinical studies [19, 20]. In dogs initially hemodiluted on room-air ventilation to Hb 7 g/dl, subsequent hyperoxic ventilation allowed for further hemodilution to the extreme value of Hb 3 g/dl without encountering significant changes in tissue oxygenation (fig. 5) [19] and cardiac performance [21]. Moreover, in pigs ventilated with room-air and diluted until the occurrence of manifest tissue hypoxia (Hb 2.6 g/dl), subsequent ventilation with 100% oxygen was not only able to effectively reverse tissue hypoxia (fig. 6), but allowed to extend the dilution to Hb 1.2 g/dl i.e. almost complete blood exchange before the signs of tissue hypoxia reoccurred [Kemming et al., unpublished data]. Finally, in the presence of hemodilution-induced tissue hypoxia, an effective tissue utilization of physically dissolved plasma oxygen has been proven evidenced by a significantly higher survival rate of pigs ventilated with 100% oxygen as compared to pigs remaining under room air ventilation (fig. 7; Meier et al., unpublished data).

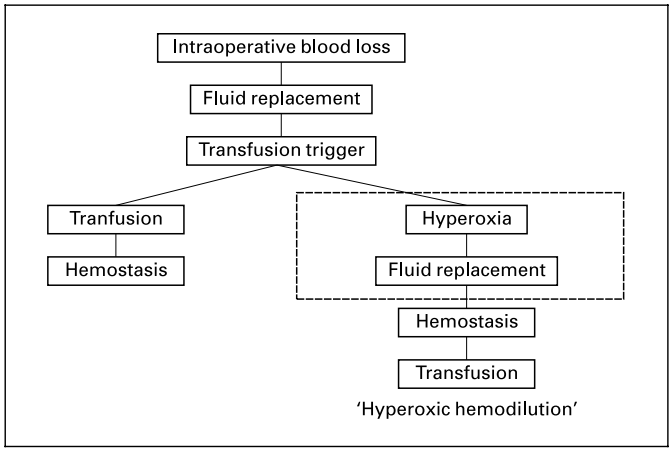

Fig. 8. Hyperoxic hemodilution, i.e. the combination of hyperoxic ventilation and extreme intraoperative hemodilution as an alternative to red blood cell transfusion in patients undergoing elective surgical interventions and experiencing major intraoperative bleeding. Schematic flow diagram. The left branch of the decision tree represents the usual transfusion practice, the right branch depicts the new concept of bridging a surgical blood loss by extreme hemodilution under the protection of hyperoxic ventilation introduced into the literature by our group as 'hyperoxic hemodilution' [24].

Clinical Data

In patients experiencing major intraoperative bleeding during orthopedic surgery, the indication for red cell transfusion (based on the appearence of physiologic trigger parameters) could be reversed in two thirds of the patients by the simple switch from ventilation with 40% oxygen to hyperoxic ventilation with 100% oxygen. This manoeuvre enabled the continuation of intraoperative hemodilution and the definite need for red blood cell transfusion could be postponed for 27–60 min (median 30 min) [20]. This gain in time may at least help the surgeon to definitely control bleeding, or to complete the surgical intervention before red blood cell transfusion becomes necessary. The augmentation of blood oxygen transport capacity indispensible to reduce inspiratory oxygen fraction to values allowing extubation of the patient may then be achieved by exclusive transfusion of allogeneic red blood cells collected in the perioperative period. Moreover advantageous side-effects accompanying perioperative hyperoxia seem to be the reduction of postoperative nausea and vomiting [22] as well as a reduced incidence of perioperative wound infections [23].

Conclusion

Hyperoxic hemodilution, i.e. the combination of normovolemic hemodilution and hyperoxic ventilation [24], represents a safe and effective method to 'bridge' a surgical blood loss exclusively through infusion of erythrocyte-free solutions. This policy may allow to delay the onset of red blood cell transfusion until definite control of surgical bleeding has been achieved (fig. 8). Hyperoxia-related microcirculatory dysregulation and impaired tissue oxygenation both characteristic features at physiologic Hb concentrations are completely absent in hemodiluted subjects. Hyperoxic hemodilution may therefore be considered as an effective supplemental method to reduce perioperative allogeneic transfusion.

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