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From Transfusion Alternatives in Transfusion Medicine

Perioperative Optimization of Oxygen Delivery

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Posted: 11/11/2010; Transfusion Alter Transfusion Med. 2010;11(3):22-29.

Abstract and Introduction

Abstract

The concept of perioperative hemodynamic optimization was developed by Shoemaker in the early 1980s. The controversy concerning optimization of oxygen delivery persists as recent studies show that the timing of this optimization appears to be an essential factor. At the initial stage of aggression (operative period, initial phase of septic shock), optimization of volume replacement decreases morbidity and mortality, while at a later period excess volume replacement can be harmful for the patient. The aim of this article is to review the physiological methods and indications for optimization of oxygen delivery.

Introduction

The concept of perioperative hemodynamic optimization was developed by Shoemaker[1] in the early 1980s. The observation that patients dying after surgery had lower oxygen delivery (DO_2) and oxygen consumption (VO_2) than survivors[2] led to the hypothesis that non-surviving patients presented a high risk because of their low physiological reserves to deal with the metabolic requirements of the perioperative period. Inability to activate adaptive defense mechanisms was suggested to be responsible for an oxygen debt starting in the preoperative period and subsequently amplified by the surgical procedure, leading to organ failure or even death.[3–5] This hypothesis was confirmed in 1988 by a randomized, prospective trial comparing a conventional approach to an interventional approach designed to induce higher than normal values (cardiac index > 4.5 L/minute/m^2, VO_2 > 170 mL/minute/m^2, DO_2 > 600 mL/minute/m^2).[6] This optimization decreased mortality.[4] This approach was applied to patients at high risk as a result of the clinical setting (renal, cardiovascular, cerebral, hepatic or respiratory disease, malnutrition, age > 70 years, shock, sepsis, acute abdominal disease) and the type of surgery (cardiac and aortic surgery, hepatic and major abdominal surgery). Classical supraphysiological objectives were cardiac index > 4.5 L/minute/m^2 with DO_2 > 600 mL/minute/m^2 and VO_2 > 170 mL/minute/m^2. Recommended treatment modalities were plasma expansion, packed red blood cell transfusion, positive inotropic drugs and vasodilators. Similar results were published by Boyd *et al*.[7] In these studies, optimization of oxygen delivery was performed before the onset of organ

failure. A meta-analysis published in 2002 confirmed the rationale of this approach in the perioperative setting.[8] However, subsequent studies conducted in intensive care patients in shock demonstrated the value, in terms of mortality, of systematically targeting higher than normal values when organ failure has already occurred.[9,10] The controversy concerning optimization of oxygen delivery persists, as recent studies show that the timing of this optimization appears to be an essential factor. At the initial stage of aggression (operative period, initial phase of septic shock), optimization of volume replacement decreases morbidity and mortality,[11–16] while at a later period, excess volume replacement can be harmful for the patient.[17–19] The aim of this article is therefore to review the physiological methods and indications for optimization of oxygen delivery.

Physiology of Oxygen Delivery

Basic physiology: Tissue Oxygen Delivery and Oxygen Consumption[20]

Oxidative degradation of high-energy substrates is an essential feature of all living organisms. Aerobic organisms have developed complex chemical reactions, grouped under the term 'respiratory chain', in which oxygen plays the central role on mitochondria. The absence of oxygen reserve explains the importance of a constant oxygen supply adapted to needs.

At rest, basal metabolism requires a VO_2 of 250–300 mL/minute, i.e. 3.5 mL/kg. Many states either increase (pain, anxiety, sepsis, fever) or decrease VO_2 (hypothermia, anesthesia, hypothermia).

According to the Fick principle, VO_2 is calculated as the product of the difference between arterial oxygen content (CaO_2) and mixed venous blood oxygen content (CvO_2, in the pulmonary artery) multiplied by cardiac output (CO):

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

Oxygen delivery (DO_2) is defined it by the product of CaO_2 and CO:

$$DO_2 = CaO_2 \times CO$$

Arterial and mixed venous oxygen contents are mainly determined by hemoglobin, hemoglobin oxygen saturation and the oxygen-binding capacity of hemoglobin, as only a negligible proportion of oxygen is dissolved directly in blood:

$$CaO_2 = 1.34 \times [Hb] \times SaO_2$$
$$CvO_2 = 1.34 \times [Hb] \times SvO_2$$

1.34: oxygen-binding capacity of hemoglobin

[Hb]: patient's hemoglobin concentration (identical in arterial and venous territories)

SaO_2: arterial oxygen saturation of hemoglobin

SvO_2: oxygen saturation of hemoglobin in mixed venous blood in the pulmonary artery

Arterial oxygen delivery and oxygen consumption are therefore dependent on cardiac output, hemoglobin, and arterial and venous oxygen saturation (the latter reflecting tissue O_2 extraction):

$$DO_2 = CaO_2 \times CO = 1.34 \times Hb \times CO \times SaO_2$$

$$\begin{aligned} VO_2 &= CO \times (CaO_2 - CvO_2) \\ &= 1.34 \times CO \times Hb \times (SaO_2 - SvO_2) \end{aligned}$$

Under physiological conditions, VO_2 is independent of DO_2. In order to maintain a constant VO_2, the body can respond by increasing oxygen extraction (corresponding to a reduction of SvO_2) and/or by increasing cardiac output. These mechanisms are described during normovolemic hemodilution.[20] In case of increased VO_2 (e.g. during effort), the body ensures the necessary oxygen by increasing cardiac output and by increasing O_2 extraction. Theoretically, SvO_2 cannot be considered to be normal without determining the individual's VO_2. A healthy individual has a SvO_2 of 70% at rest and SvO_2 decreases during effort. In contrast, if DO_2 decreases (decreased cardiac output and/or decreased hemoglobin), tissue oxygen extraction (corresponding to a fall in SvO_2) increases in order to maintain a constant VO_2.

In the presence of a marked reduction of DO_2, the compensatory mechanism of increased oxygen extraction is no longer sufficient to maintain a constant VO_2. VO_2 decreases in proportion to DO_2 (Figure 1). VO_2 is said to be 'DO_2 dependent'. The level of DO_2 below which this dependence between DO_2 and VO_2 is observed is called the critical oxygen delivery. Below this value, the anaerobic metabolic pathway is used to ensure adequate energy production, resulting in the formation of lactic acid, a marker of deficiency of the aerobic pathway and tissue oxygen debt.

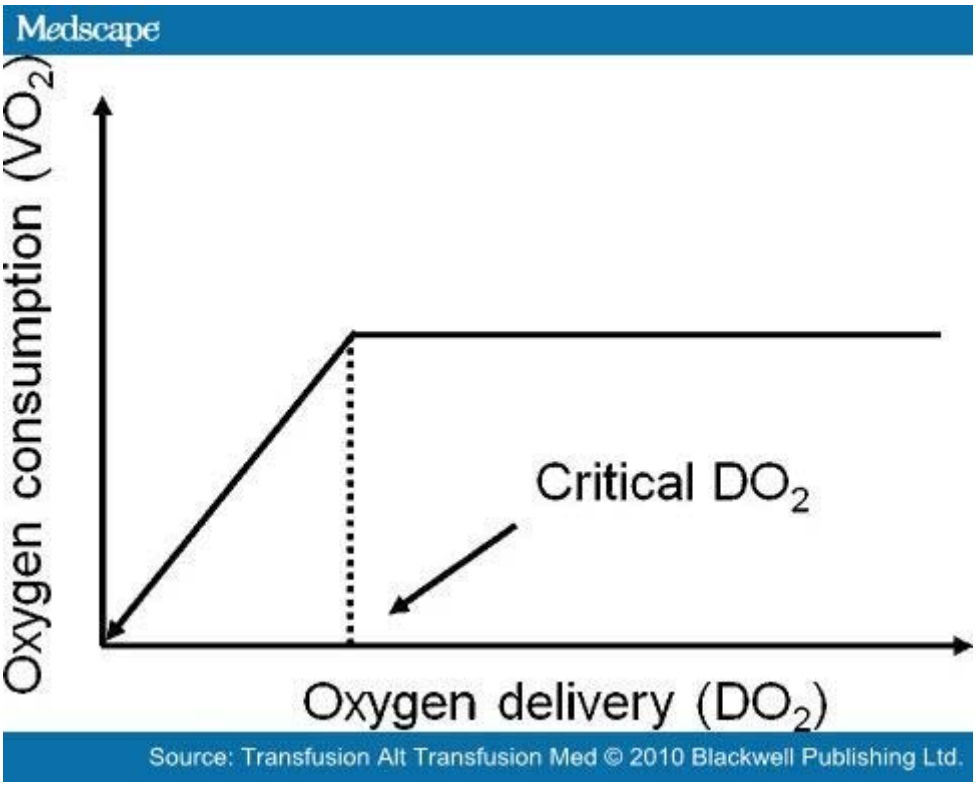

Figure 1. Critical oxygen delivery (DO_2): above this value, VO_2 is independent of DO_2. Below this value, VO_2 becomes DO_2-dependent and extraction capacities are no longer sufficient. The anaerobic pathway is activated resulting in lactic acid production.

Matching of oxygen requirements and DO_2 can be achieved by decreasing VO_2, increasing DO_2 or a combination of both.

Decreased Oxygen Consumption

VO_2 decreases under conditions of hypothermia and anesthesia. Hypothermia less than 35°C is associated with clotting disorders because of decreased enzymatic activity. The beneficial effects of decreased VO_2 during hypothermia must be weighed up against the risks related to warming during recovery. Under these conditions, VO_2 can increase to levels approaching the maximum VO_2 and can represent a real stress test.[21] Anesthesia also decreases VO_2, partly explaining the indication for sedation in shock. However, it is essential to avoid the hypotensive effects of anesthetic drugs that can compromise organ perfusion and therefore peripheral oxygen delivery.

Increased Oxygen Delivery

Theoretically, an increase of DO_2 can be due to an increase of one of the three determinants of DO_2, i.e. increased oxygen extraction ($EO_2 = SaO_2 - SvO_2$), increased cardiac output or increased hemoglobin concentration.

Increased Oxygen Extraction *Increased SaO_2.* Optimal SaO_2 can be easily achieved during anesthesia by avoiding the harmful effects of ventilation. Ventilatory practices in the operating room appear to be very disparate both in terms of tidal volume (twofold range) and the positive end-expiratory pressure levels used. Although protective ventilation (tidal volume < 8 mL/kg) has been shown to decrease mortality of acute respiratory distress syndrome in intensive care patients, the use of high tidal volumes in anesthesia appears to be associated with activation of inflammation. These potential harmful effects require further studies.[22,23]

Decreased SvO_2 (Real Increase of EO_2). Pharmacological manipulations of SvO_2 are difficult to envisage, despite the fact that all anesthetics, except for ketamine, decrease oxygen extraction capacities.[5,6] It must be remembered that, physiologically, maintenance of a certain degree of acidosis (between 7.25 and 7.38) or hypercapnia (in the absence of intracranial hypertension) allows greater peripheral oxygen delivery without altering the oxygen-binding capacities in the lungs. In the presence of altered lung compliance, maintenance of normocapnia and normal pH appear to be more harmful because of the risk of lung lesions than maintenance of a certain degree of acidosis and/or hypercapnia.[24–26]

Improvement of Microcirculation. Improvement of the microcirculation can improve perfusion of peripheral territories with the corollary of improved oxygen extraction. Improvement of the microcirculation corresponds to elimination of shunts. This phenomenon is similar to the lungs when homogenization of ventilation–perfusion ratios improves gas exchange and therefore PaO_2.

Increased Cardiac Output Cardiac output is the product of heart rate by stroke volume (SV) and SV is the difference between end-diastolic (EDV) and end-systolic (ESV) ventricular volumes. An increase of SV is due to increased ESV or decreased EDV.

Increase of End-diastolic Volume or Preload.[27–30] The Frank–Starling curve of ventricular function shows that an increased cardiac preload induces a marked increase of SV on the left side of the curve (preload-dependent part of the curve). This preload dependence is a physiological condition for functioning of the cardiocirculatory system at baseline conditions allowing the body to adapt venous return as rapidly as possible to meet metabolic demands according to the required activity.

Decrease of End-systolic Volume. This situation corresponds to increased contractility and/or decreased ventricular outflow obstruction or postload. Increased contractility is only indicated in the case of heart failure, sometimes frequent in certain diseases. The use of positive inotropic drugs to improve hemodynamics does not appear to be indicated in patients with normal systolic function, as it induces tachycardia and increased oxygen consumption, which can be harmful. Vasodilators and inodilators could be theoretically indicated, but they regularly induce hypotension. Dobutamine can also induce decreased blood pressure because of its beta-2 vasodilator effects.

Increase of Hemoglobin Concentration An increased hemoglobin level can theoretically increase DO_2. However, an increased hematocrit is associated with increased blood viscosity leading to increased postload and decreased rheologic properties of the blood. In anesthesia, the opposite situation, i.e. decreased hemoglobin concentration in a context of hemorrhage, constitutes the more serious problem. In the context of acute hemorrhage, the initial major concern is that of decreased blood volume, which decreases venous return, cardiac preload and therefore cardiac output. In this setting, plasma expansion is essential up to a certain hemoglobin cut-off at which oxygen delivery to the cells becomes compromised. Compensation of the volume of blood loss by volume replacement without blood cells induces hemodilution. Decreased hemoglobin is compensated in terms of DO_2 by better rheologic properties not compromising peripheral oxygen delivery. In a healthy individual in whom a normal blood volume is maintained, hemoglobin levels higher than 7 g/dL can be maintained, including in the intensive care setting.[31] In contrast, in patients with severe coronary disease, a hemoglobin level higher than 10 g/dL is recommended. Between these two values, the indication for transfusion can be defined as a function of the type of operation and the clinical setting by measuring SvO_2. An excessively low SvO_2 may indicate the need for transfusion, even before the hemoglobin cut-off value has been reached.[32]

What are the Modalities for Optimization of Oxygen Delivery?

Although optimization of oxygen delivery has been demonstrated to improve the patient's prognosis, clinicians must be aware of the limits of this concept to avoid exposing certain populations to the risks of the treatments used to achieve this optimization. Preoperative assessment remains essential to ensure optimal preparation of the patient for the surgical procedure. For patients at highest risk, aggressive monitoring and intervention can be considered to decrease mortality. For more minor surgical procedures, optimization of cardiac output combined with minimally invasive monitoring can decrease postoperative complications and length of hospital stay.[11–16] The value of optimization of oxygen delivery for more minor surgical procedures has not been clearly demonstrated.

Which Parameters should be Monitored?

Cardiac Output and/or Determinants of Cardiac Output Cardiac output was initially estimated by thermodilution using a pulmonary artery catheter. Although no study has demonstrated any harmful effects of this procedure, it requires an experienced operator to avoid insertion complications and errors of interpretation. Use of this technique requires a certain amount of time, making this technique a tool reserved to the patients at highest risk, especially those undergoing vascular surgery.[7] Less invasive tools can also be used to evaluate cardiac output.[33] The reliability of these tools remains controversial, although their capacity to detect variations of cardiac output appears to be satisfactory, allowing an improvement of the patients' prognosis.[34–36] Other studies have used markers of cardiac preload to optimize this parameter. These markers of preload can be either static [central venous pressure (CVP), EDV, global EDV, corrected flow time] or dynamic (pulse pressure variation).[37] The

improved patient prognosis is due more to the capacity of these markers to avoid serious hypovolemia than to their capacity to optimize cardiac output (by ensuring optimal cardiac output in a given patient). Perioperative optimization of fluid therapy based on CVP and/or systolic aortic flow time measured by esophageal Doppler,[11–13,15] or even invasive dynamic indices such as pulse pressure variation[37,38] or non-invasive dynamic indices (respiratory variations of oximetry)[39–41] can be used to decrease postoperative complications and length of hospital stay. During initial resuscitation of patients with severe sepsis and/or septic shock, optimization of plasma volume expansion using CVP and mean blood pressure targets, decreases mortality. The study by Rivers *et al*. already demonstrated that optimization of initial plasma expansion in patients with this condition could be improved by measuring $ScvO_2$ with a target of 70%.[16] Although total plasma expansion volumes over the first 72 hours were similar in the two groups compared, this approach allowed more rapid fluid replacement during the first 24 hours.

Hemoglobin Concentration Packed red blood cell transfusion theoretically increases arterial oxygen content (CaO_2) when hemostasis is achieved. In 1999 the trial of transfusion requirements in critical care study, performed in 838 intensive care patients, revealed no significant difference in 30-day mortality between the group in which hemoglobin concentration was maintained between 7 and 9 g/dL and the group in which hemoglobin concentration was maintained between 10 and 12 g/dL.[31] As a result of the microbiological, immunological and thrombotic risks of transfusion, as well as the risks related to human errors, low hemoglobin values of about 7 g/dL are considered to be acceptable in patients without severe heart disease. The following cut-off values are currently accepted in patients with normovolemic hemodilution:[42]

- 7 g/dL in populations with no medical history.
- 8–9 g/dL in patients with a history of cardiovascular disease.
- 10 g/dL in patients not clinically tolerating lower hemoglobin concentrations or with documented heart failure or acute coronary insufficiency.

However, in the context of serious hemorrhage, the fall in hemoglobin must be anticipated in order to avoid inducing an oxygen debt.

A meta-analysis of 18 studies assessed the impact of blood transfusion on improvement of tissue oxygenation.[43] Four studies did not reveal any change in DO_2. Among the 14 studies reporting an increased DO_2, nine reported no effect on VO_2. These results suggest the importance of adaptive mechanisms to maintain VO_2 independently of DO_2 by increasing cardiac output and tissue oxygen extraction. The hemoglobin cut-off may therefore be ineffective to assess the need for red blood cell transfusion. Evaluation of global or regional oxygenation should be considered to define the indication for blood transfusion. From this point of view, $ScvO_2$ appears to be an accessible and available tool. In an observational study of 60 general surgery patients with a central venous line, $ScvO_2$ was measured before and after blood transfusion decided in the absence of any hemodynamic instability.[32] Almost 30% of transfused patients had an $ScvO_2$ greater than 70% suggesting excessive transfusion.

Oxygen Saturation As the proportion of dissolved oxygen in the blood is negligible compared with the oxygen bound to hemoglobin, oxygen saturation (SaO_2) is the essential parameter. It is important to maintain SaO_2 below 90% to avoid the oblique segment of the hemoglobin dissociation curve, which could then compromise SaO_2 and therefore DO_2.[25,44] In a large proportion of patients, mechanical ventilation raises few problems for anesthetists and intensive care physicians, but the use of high levels of positive end-expiratory pressure, or even recruitment maneuvers may be necessary in the

presence of major hypoxemia.[24] The possible impact of this ventilation on circulation, especially pulmonary circulation, must be evaluated and monitored.[45]

Which Treatment Modalities should be Used?

Plasma Expansion Expansion of intravascular volume is the first-line intervention to increase cardiac output in a patient situated on the vertical part of the Frank–Starling curve. In a French national survey conducted in 1999, hypovolemia was found to be the commonest factor of perianesthetic mortality. Optimization of plasma volume is generally accompanied by a decrease in heart rate and better myocardial performance. Plasma expansion solutions must be at least isotonic. Hypertonic products (hypertonic saline solutions = 7.5% saline) and iso-oncotic or hyperoncotic solutions can be used. However, hypertonic and iso-oncotic or hyperoncotic solutions are not devoid of adverse effects. Hypertonic saline solutions can only be used once because of the hypernatremia induced.[46] High-molecular-weight hydroxyethyl starch solutions (molecular weight > 150 kD) can cause clotting disorders and renal impairment, especially when high doses are used.[47–49] On the other hand, there is no evidence of nephrotoxicity induced by new-generation hydroxyethyl starch solutions (molecular weight < 150 kD) when dose limitations are respected.[50–54]

However, although hypovolemia has a negative impact on oxygen delivery, excessive plasma expansion is just as harmful, as it does not induce any increase of cardiac output and induces interstitial edema responsible for decreased tissue oxygen delivery, leading to organ failure.[26,27] The time factor appears to be particularly important in this context. Studies optimizing plasma expansion during the surgical operation show shortening of the hospital stay, while liberal postoperative plasma expansion is associated with a higher complication rate.

At the present time, experimental arguments suggest that the various plasma expanders are associated with marked effects on the microcirculation and pro- or anti-inflammatory effects,[55] which could have major consequences on the oxygen extraction capacity.

Catecholamines After adequate plasma volume replacement or in case of severe hypotension (diastolic blood pressure < 40 mmHg),[56] the use of catecholamines can be considered provided excessive harmful effects are avoided (tachycardia, hypotension, increased VO_2). The use of positive inotropic drugs should be considered in patients with preexisting or transient heart failure.[57] Levosimendan has not been demonstrated to be effective in terms of morbidity and mortality in this context. Vasopressors remain the drugs most widely used, especially noradrenaline, although adrenaline appears to be a satisfactory substitute. Vasopressor derivatives can also be administered, but their efficacy has not yet been rigorously demonstrated.

Conclusion

Optimization of oxygen delivery improves prognosis, especially that of the most seriously ill patients. However, the indications for this approach and the timing, monitoring and the treatments used must be carefully evaluated, as excessive optimization can have harmful consequences.

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Conflict of Interest

The authors declare no conflict of interest.

Transfusion Alter Transfusion Med. 2010;11(3):22-29.