DO_2/VO_2 relationships

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Introduction

Most cellular activities require oxygen, primarily obtained from the degradation of adenosine triphosphate (ATP) and other high-energy compounds. Oxygen must, therefore, be present in the mitochondria in sufficient amounts to maintain effective concentrations of ATP by the electron transport system. Cells must perform various activities in order to survive, including membrane transport, growth, cellular repair, and maintenance processes. They often also have facultative functions, such as contractility, electrolyte or protein transport, motility, or various biosynthetic activities. If oxygen availability is limited, cellular oxygen consumption may fall, and become supply-dependent. Facultative functions are the first to be affected, leading to cellular and, ultimately, organ dysfunction. If the situation becomes more serious, obligatory functions can no longer be maintained, and irreversible alterations may occur resulting in cell death. Maintaining sufficient oxygen availability to the cell is thus fundamental for cell survival: the hypoxic cell is doomed to become malfunctional and to die.

Oxygen delivery vs oxygen availability

The amount of oxygen available in the cell is determined by a number of central and peripheral factors. The central factors depend on the adequacy of cardiorespiratory function (cardiac index and PaO_2) and the hemoglobin concentration, according to the formulas given in Table 1. Peripheral factors depend on the distribution of cardiac output to the various organs, and the regulation of the microcirculation, which is determined by the autonomic control of vascular tone, local microvascular responses, and the degree of affinity of the hemoglobin molecule for oxygen.

Among the central factors, cardiac output is a more important determinant of oxygen delivery (DO_2) than the arterial oxygen content (Table 1), as a fall in hemoglobin or SaO_2 can be compensated by an increase in cardiac output, whereas the opposite is not true. If cardiac output falls, SaO_2 cannot rise above 100% and hemoglobin concentration cannot increase acutely. Furthermore, an increase in red blood cell mass does not efficiently increase DO_2, because cardiac output usually decreases as a result of the associated increase in blood viscosity. Hence,

Table 1. The determinants of oxygen delivery, oxygen consumption, and oxygen extraction

Oxygen delivery (DO_2) = CO x Hb x SaO_2 x C x 10
Oxygen consumption (VO_2) = CO x (CaO_2 CvO_2) x 10 (Neglecting the dissolved oxygen) = CO x Hb x (SaO2-SvO2) x C
Oxygen extraction (O_2ER) = VO_2/DO_2 = (CaO_2-CvO_2)/CaO_2
or neglecting the dissolved oxygen = (SaO_2-SvO_2)/SaO_2
where CO represents the cardiac output, Hb the hemoglobin concentration, SaO_2 and SvO_2 the arterial and the mixed venous oxygen saturations, respectively, and C the constant value representing the amount of oxygen bound to 1 g of Hb (this value is usually 1.34 or 1.39).

cardiac output is the most important factor in the constant adaptation of the body's oxygen needs in physiological conditions.

The peripheral factors can change substantially in inflammatory conditions (including sepsis), when local control of the vascular tone may be altered, the formation of microthrombi may shut down some capillaries, and edema may develop. Changes in hemoglobin oxygen affinity can also influence the peripheral delivery of oxygen.

Basic concepts: The Relationship between VO_2 and DO_2 and the concept of VO_2/DO_2 Dependency

A number of animal experiments using different models [1–4] have shown that oxygen uptake (VO_2) remains independent of DO_2 over a wide range of values, because oxygen extraction (O_2ER, which is the ratio of VO_2 over DO_2) can readily adapt to the changes in DO_2. When cardiac output is acutely reduced by acute blood withdrawal, tamponade, anemia, or hypoxemia, O_2ER increases (SvO_2 decreases) and VO_2 remains quite stable, until DO_2 falls below a critically low threshold (DO_2crit), when VO_2 starts to fall. An abrupt increase in blood lactate concentrations then occurs, indicating the development of anaerobic metabolism (Fig. 1). In the presence of sepsis mediators, as after the administration of endotoxin or live bacteria [5, 6], oxygen extraction capabilities are altered so that the DO_2crit is higher and the critical O_2ER is typically lower than in control conditions. In these conditions, VO_2 can become dependent on DO_2 even when DO_2 is normal or elevated. Altogether, these observations help to characterize the four principal types of circulatory shock (Fig. 2).

Although such studies performed in anesthetized animals can hardly be reproduced in humans, an acute reduction in DO_2 can be observed in the intensive care unit (ICU) during withdrawal of life support [7]. In these dying patients, VO_2 remained relatively constant until DO_2 fell below very low values.

A number of studies have correlated the VO_2/DO_2 dependency phenomenon to profound circulatory alterations. Bihari et al. [8] showed that an increase in VO_2 during a prostacyclin infusion was a characteristic of non-survivors. A number of

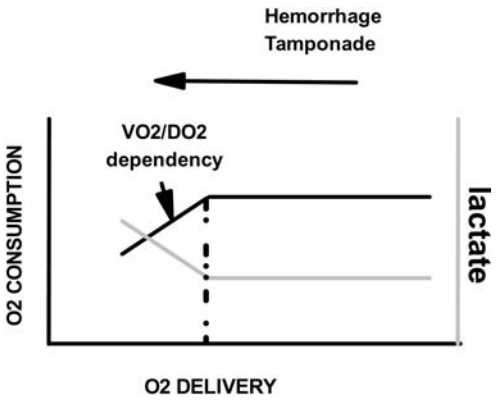

Fig. 1. Relationship between oxygen uptake (VO_2) and oxygen delivery (DO_2) when DO2 is acutely reduced by tamponade or hemorrhage in anesthetized animals. Note that blood lactate levels increase as soon as DO_2 falls below DO_2crit.

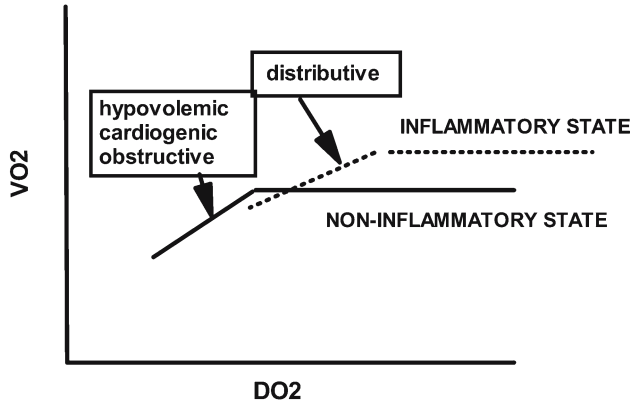

Fig. 2. The four types of acute circulatory failure.

investigators have also reported that patients with acute circulatory failure with increased blood lactate concentrations demonstrate an increase in VO_2 when DO_2 is acutely increased by fluid infusion [9], blood transfusions or dobutamine administration [10]. Such a phenomenon has not been observed in stable patients with normal lactate concentrations [9–12].

Others have challenged these observations, arguing that the VO_2 was usually determined from the Fick principle rather than determined independently from expired gas analysis. Hence, VO_2 and DO_2 were calculated from the same variables, i.e., cardiac output, hemoglobin concentrations, and SaO_2, resulting in mathematical coupling of data.

Indirect calorimetry also has its limitations and sources of error, and becomes very imprecise when high FiO_2 are delivered. Incidentally, many authors have argued that VO_2 is *calculated* using the Fick equation, but *measured* when obtained by indirect calorimetry. This is clearly wrong: With both techniques, VO_2 results from a calculation of the product of flow (blood flow or gas flow) and oxygen content differences (between arterial and venous blood or between inspired and

Table 2. Calculation of oxygen uptake by indirect calorimetry

$$VO2 = \frac{FiO_2 \times (1 - FeO_2 - FeCO_2)}{(1 - FiO_2 - FeO_2)} \times VE$$

where FeCO2 is the expired CO2 fraction, FiO2 and FeO2 the inspired and expired oxygen fraction, respectively, and VE the expiratory flow rate

expired gases). In fact, the formula used to calculate VO_2 by indirect calorimetry is quite complex (Table 2).

In addition, this reasoning can itself be criticized. First, the effect of mathematical coupling of data does not seem to be major if the changes in DO_2 are of sufficient magntitude [13]. Second, this limitation cannot explain how the changes in VO_2 can be observed in some individuals and not in others. It is important to note that all studies using indirect calorimetry to determine VO_2 included only stabilized patients: this is largely due to the time needed to install the material used for VO_2 determinations. The same applies to the studies arguing that changes in VO_2 can be observed only in patients with high lactate concentrations: these studies included stabilized patients in whom signs of shock had already resolved. Admittedly, the interpretation of elevated blood lactate concentrations is not always straightforward, as hyperlactatemia can be influenced by decreased lactate clearance. Also, in sepsis, hyperlactatemia does not necessarily reflect anaerobic metabolism secondary to cellular hypoxia, but other mechanisms, like increased glycolysis or abnormal pyruvate metabolism [14]. Hence, hyperlactatemia should complement the clinical evaluation of circulatory shock, including arterial hypotension and signs of altered tissue perfusion like altered sensorium, altered cutaneous perfusion, and decreased urine output.

Altogether, these studies indicate that the VO_2/DO_2 dependency phenomenon can be observed but only in patients who are clearly unstable, during shock resuscitation; it is a hallmark of acute circulatory failure (shock) [15].

A more important limitation is that the global VO_2/DO_2 assessment is not precise enough to be useful clinically and, more specifically, to guide therapy. Furthermore, VO_2/DO_2 dependency may occur regionally, especially in the hepatosplanchnic region [16] (Fig. 3). Comparisons of VO_2 and DO_2 are useless, because obtaining these derived variables is hard to interpret and the plot of VO_2 vs DO_2 is limited by the problem of mathematical coupling of data. However, evaluation of the relationship between cardiac output and oxygen extraction may be very useful to evaluate the adequacy of the cardiac output response [17]. Such a CI/O_2ER relationship has no problem of mathematical coupling of data (Fig. 4). Increased lactate concentrations remain a reliable prognostic indicator, actually superior to DO_2 and VO_2 values [18]; increasing DO_2 to higher values when blood lactate levels are normal has not been shown to be beneficial.

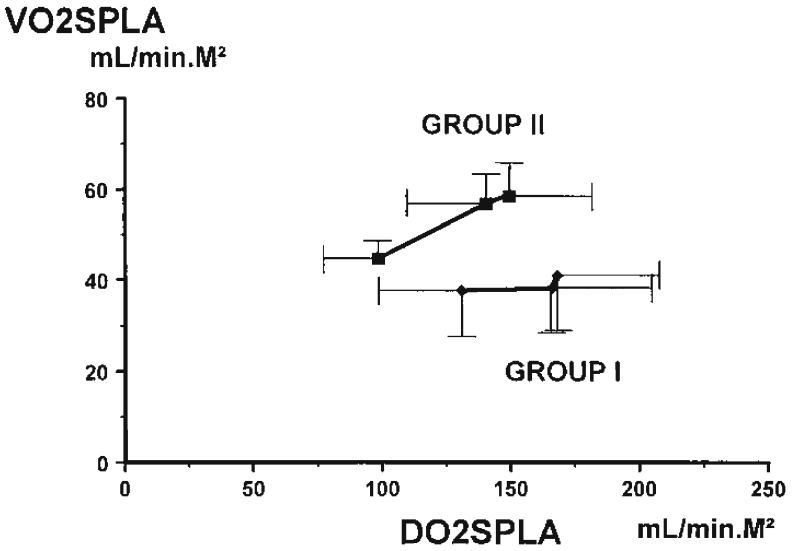

Fig. 3. Regional VO_2/DO_2 relationship in the splanchnic circulation in patients with severe sepsis. Group I: patients with gradient between mixed venous and hepatic venous oxygen saturation lower than or equal to 10%. Group II: patients with gradient between mixed venous and hepatic venous oxygen saturation higher than 10%. Data are presented as mean ± SEM. (From [16] with permission)

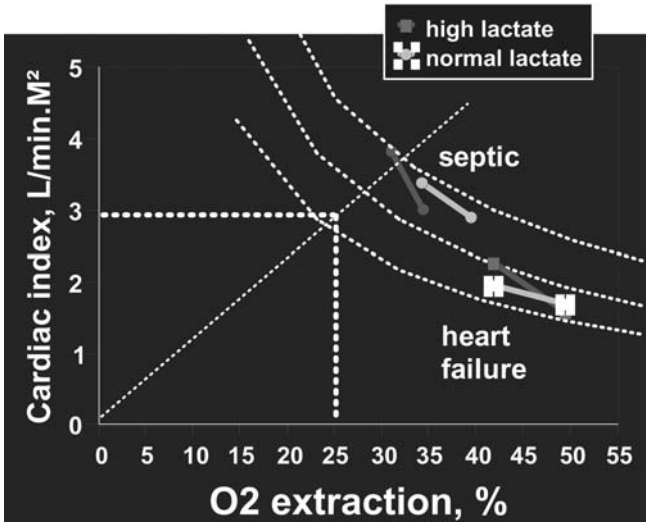

Fig. 4. Cardiac index/O_2ER diagram during a short term dobutamine infusion indicating VO_2/DO_2 dependency in patients with increased lactate levels but not in those with normal lactate levels (data from [10]).

Clinical implications

The Supranormal DO_2 Approach

William Shoemaker and his colleagues proposed that DO_2 should be maintained at supranormal values (at least 600 ml/min.M²) in all patients at risk of complications, to ensure sufficient oxygen availability to the cells [19]. This proposal was based on the observation that survivors from sepsis or trauma usually generate higher DO_2 than non-survivors [20]. Although this approach may have merits in some populations [21, 22], it is limited by two important aspects. One is that patients with higher DO_2 are more likely to survive, simply because they have a better physiological reserve, allowing them to generate a higher cardiac output. The second is that increasing DO_2 to supranormal values in all patients 'at risk' may be beneficial to some, still underresuscitated, but harmful to others, already well resuscitated, who would thus receive too much fluid and adrenergic agents like dobutamine.

This concept is an oversimplification of a complex phenomenon. When applied to a mixed group of critically ill patients, such strategies have been shown to be ineffective [23] and may even be harmful, especially if high doses of dobutamine are administered [24].

The Titrated Approach

It is more meaningful to have a titrated approach, individualized according to results of a careful clinical evaluation and some paraclinical tests including measurements of cardiac index, SvO_2, blood lactate concentrations, and perhaps regional PCO_2. This requires a complete understanding of the pathophysiologic alterations

As mentioned above, the relationship between CI and SvO_2 does not have the problem of mathematical coupling of data associated with the evaluation of the relationship between VO_2 and DO_2 when both are obtained from the same values of cardiac output, hemoglobin concentrations, SaO_2, and SvO_2. The study of such variables also avoids cumbersome calculations, as cardiac index is a primary variable and O_2ER is very simply calculated (Table 1). In most cases, the relationship between CI and SvO_2 or even central venous oxygen saturation ($ScvO_2$) alone may suffice. There are, however, two reasons why the relationship between CI and O_2ER would be better (Fig. 4.). One is that the relationship between CI and SvO_2 is curvilinear, rendering the data interpretation more difficult. The second, is that even when hypoxemia is avoided, SaO_2 can still vary between about 90 and 99% in the acutely ill patient, i.e., a 10% variation in the variable. Nevertheless, SvO_2, or maybe even $ScvO_2$ alone, may be used in an algorithm for resuscitation. Rivers et al. [25] showed that monitoring $ScvO_2$ could result in a significantly lower mortality rate in patients with severe sepsis and septic shock. Likewise, Polonen et al. [26]found, in cardiac surgery patients, that maintaining SvO_2 at normal or high levels shortens hospital stay and lowers the degree of organ dysfunction at time of discharge from hospital. Nevertheless, lactate concentrations remain valuable in

shock states. Although one may argue that lactate concentrations reflect other cellular abnormalities than anerobic metabolism secondary to hypoxia, persistently raised lactate levels should represent an alarm signal. Hence, in addition to clinical evaluation, repeated measurements of SvO_2 and blood lactate may be helpful.

Conclusion

Maintenance of adequate DO_2 is essential to preserve organ function, as a low DO_2 is a straightforward path to organ failure and death, and treatment must be titrated to the individual based on the integration of several factors including clinical examination and available oxygenation and hemodynamic parameters. The relationship between VO_2/DO_2 remains an important concept, even though its simple application to guide therapy may be too simplistic. The relationship between cardiac index and O_2ER (or its simplification SvO_2) can be helpful.

References

1. Cain SM (1977) Oxygen delivery and uptake in dogs during anemic and hypoxic hypoxia. J Appl Physiol 42:228–234
2. Nelson DP, Beyer C, Samsel RW, Wood LDH, Schumacker PT (1987) Pathological supply dependence of O2 uptake during bacteremia in dogs. J Appl Physiol 63:1487–1492
3. Van der Linden P, Gilbert E, Engelman E, Schmartz D, Vincent JL (1991) Effects of anesthetic agents on systemic critical O2 delivery. J Appl Physiol 71:83–93
4. Zhang H, Spapen H, Benlabed M, Vincent JL (1993) Systemic oxygen extraction can be improved during repeated episodes of cardiac tamponade. J Crit Care 8:93–99
5. Samsel RW, Nelson DP, Sanders WM, Wood LDH, Schumacker PT (1988) Effect of endotoxin on systemic and skeletal muscle O2 extraction. J Appl Physiol 65:1377–1382
6. Zhang H, Vincent JL (1993) Oxygen extraction is altered by endotoxin during tamponade-induced stagnant hypoxia in the dog. Circ Shock 40:168–176
7. Ronco JJ, Fenwick JC, Tweeddale MG, et al (1993) Identification of the critical oxygen delivery for anaerobic metabolism in critically ill septic and nonseptic humans. JAMA 270:1724–1730
8. Bihari D, Smithies M, Gimson A, Tinker J (1987) The effects of vasodilation with prostacyclin on oxygen delivery and uptake in critically ill patients. N Engl J Med 317:397–403
9. Haupt MT, Gilbert EM, Carlson RW (1985) Fluid loading increases oxygen consumption in septic patients with lactic acidosis. Am Rev Respir Dis 131:912–916
10. Vincent JL, Roman A, De Backer D, Kahn RJ (1990) Oxygen uptake/supply dependency: Effects of short-term dobutamine infusion. Am Rev Respir Dis 142:2–8
11. Bakker J, Vincent JL (1991) The oxygen supply dependency phenomenon is associated with increased blood lactate levels. J Crit Care 6:152–159
12. Gilbert EM, Haupt MT, Mandanas RY, Huaringa AJ, Carlson RW (1986) The effect of fluid loading, blood transfusion and catecholamine infusion on oxygen delivery and consumption in patients with sepsis. Am Rev Respir Dis 134:873–878
13. Stratton HH, Feustel PJ, Newell JC (1987) Regression of calculated variables in the presence of shared measurement error. J Appl Physiol 62:2083–2093
14. Gore DC, Jahoor F, Hibbert JM, DeMaria EJ (1996) Lactic acidosis during sepsis is related to increased pyruvate production, not deficits in tissue oxygen availability. Ann Surg 224:97–102

15. Friedman G, De Backer D, Shahla M, Vincent JL (1998) Oxygen supply dependency can characterize septic shock. Intensive Care Med 24:118–123
16. De Backer D, Creteur J, Noordally O, Smail N, Gulbis B, Vincent JL (1998) Does hepatosplanchnic VO2/DO2 dependency exist in critically ill patients. Am J Respir Crit Care Med 157:1219–1225
17. Silance PG, Simon C, Vincent JL (1994) The relation between cardiac index and oxygen extraction in acutely ill patients. Chest 105:1190–1197
18. Bakker J, Coffernils M, Leon M, Gris P, Vincent JL (1991) Blood lactate levels are superior to oxygen derived variables in predicting outcome in human septic shock. Chest 99:956–962
19. Shoemaker WC, Appel PL, Kram HB, Waxman K, Lee TS (1988) Prospective trial of supranormal values of survivors as therapeutic goals in high-risk surgical patients. Chest 94:1176–1186
20. Shoemaker WC, Montgomery ES, Kaplan E, Elwyn DH (1973) Physiologic patterns in surviving and nonsurviving shock patients. Use of sequential cardiorespiratory variables in defining criteria for therapeutic goals and early warning of death. Arch Surg 106:630–636
21. Yu M, Levy MM, Smith P, Takiguchi SA, Miyasaki A, Myers SA (1993) Effect of maximizing oxygen delivery on morbidity and mortality rates in critically ill patients: A prospective, randomized, controlled study. Crit Care Med 21:830–838
22. Lobo SM, Salgado PF, Castillo VG, et al (2000) Effects of maximizing oxygen delivery on morbidity and mortality in high-risk surgical patients. Crit Care Med 28:3396–3404
23. Gattinoni L, Brazzi L, Pelosi P, et al (1995) A trial of goal-oriented hemodynamic therapy in critically ill patients. N Engl J Med 333:1025–1032
24. Hayes MA, Timmins AC, Yau EH, Palazzo M, Hinds CJ, Watson D (1994) Elevation of systemic oxygen delivery in the treatment of critically ill patients. N Engl J Med 330:1717–1722
25. Rivers E, Nguyen B, Havstad S, et al (2001) Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med 345:1368–1377
26. Polonen P, Ruokonen E, Hippelainen M, Poyhonen M, Takala J (2000) A prospective, randomized study of goal-oriented hemodynamic therapy in cardiac surgical patients. Anesth Analg 90:1052–1059