

The Oxygen Delivery Debate-A Review

J Raghuram,**MB, BCh, MRCP (UK)*, P Eng,***FAMS, M Med (Int Med), FCCP*, Y Y Ong,****FAMS, M Med (Int Med), FRACP*

Abstract

Tissue hypoxia is an important cause for the development of multisystem organ failure in the critically ill. Achieving adequate haemodynamic support of oxygen demand is the mainstay of treatment in these patients. Controversies regarding therapeutic end-points do exist but in general maintaining oxygen delivery by ensuring adequate cardiac output, oxygen saturation and haemoglobin is important in the critically ill.

Ann Acad Med Singapore 1998; 27:404-8

Key words: *Oxygen consumption, Oxygen extraction, Pathologic supply dependency, Tissue hypoxia*

Introduction

Multisystem organ failure occurs in a large proportion of critically ill patients and is a major cause of death in this group of patients. The mechanisms responsible for the development of multisystem organ failure in the critically ill patient are unknown. Tissue hypoxia may be a major factor leading to multisystem organ failure.¹ Impaired oxygen delivery, oxygen extraction at the tissue level and oxygen consumption may all contribute to the occurrence of tissue hypoxia. The aims of this article are to address the relationship between oxygen delivery (DO₂) and oxygen uptake (VO₂) and to review the trials to date of increased oxygen delivery in the critically ill patient.

VO₂ and DO₂ Relationship

Oxygen delivery is the product of cardiac output and arterial oxygen content. The uptake of oxygen by organ systems of the body remains relatively constant when DO₂ is altered under normal circumstances. The extraction of oxygen [extraction fraction (EF)] by tissues adjusts readily to small changes in oxygen delivery thus maintaining a constant VO₂.²

This relationship between DO₂ and VO₂ is illustrated in Figure 1. There are 3 phases to this relationship. The line emanating to the right of point A represents the situation that occurs during exercise when there is increased cellular metabolic demand.³ It shows a rise in DO₂ as VO₂ rises during exercise. This rise in DO₂ is

primarily mediated by an augmentation of cardiac output. Anaerobic threshold is reached when increase in DO₂ is insufficient to match the rise in VO₂. Beyond the anaerobic threshold, anaerobic metabolism occurs with a rise in blood lactate level.⁴ To the left of point A, i.e. as DO₂ falls, a plateau phase is seen in which VO₂ is independent of DO₂. Further reduction in DO₂ results in a physiologic dependence phase in which a concomitant reduction in VO₂ can be seen. As DO₂ falls, VO₂ is maintained up to a critical point beyond which a further reduction in DO₂ will result in a concomitant reduction in VO₂. This point at which VO₂ becomes supply-dependent on DO₂ is termed the critical DO₂, and in anaesthetised humans it is approximately 8 ml/kg/min.^{5,6} VO₂ is maintained constant as DO₂ decreases by progressive increase in the oxygen EF. Figure 2 shows the relationship between EF and DO₂. The EF is defined as the ratio of the difference between the arterial (CaO₂) and mixed venous (CvO₂) oxygen concentrations and the arterial oxygen concentration $[(CaO_2 - CvO_2) / CaO_2]$. Below the critical DO₂ point, EF continues to increase but not enough to maintain a constant VO₂.

Adequate oxygen delivery depends on the integrated action of the cardiorespiratory and microvascular systems. EF must increase in order to maintain VO₂ as DO₂ falls. This increment in EF may be brought about by the redistribution of blood flow between organs and within organs.¹ However, failure to redistribute blood flow and to increase microvascular perfusion within tissues may

* Registrar

** Consultant Chest Physician

*** Senior Consultant and Head

Department of Respiratory and Critical Care Medicine

Singapore General Hospital

Address for Reprints: Dr J Raghuram, Department of Respiratory and Critical Care Medicine, Singapore General Hospital, 1 Hospital Drive, Singapore 169608.

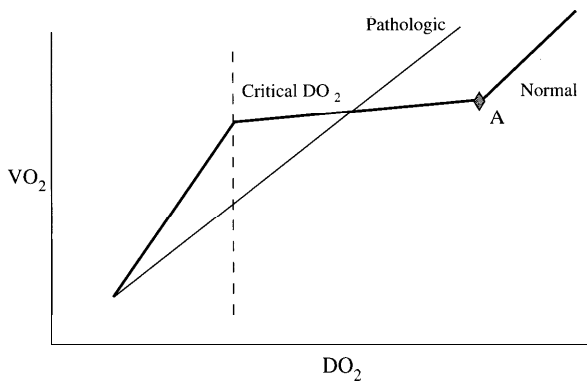


Fig. 1. The relationship between DO_2 and VO_2 in normal and pathologic states are shown. The line emanating to the right of point A represents the relationship between VO_2 and DO_2 , during exercise where VO_2 is the independent variable. To the left of point A is the plateau phase which is characterised by a constant VO_2 despite a reduction in DO_2 , under normal circumstances. As DO_2 continues to decrease below the critical DO_2 point, VO_2 becomes physiologically dependent on DO_2 . In pathological states (sepsis, ARDS, etc), VO_2 is supply dependent on a wide range of DO_2 .

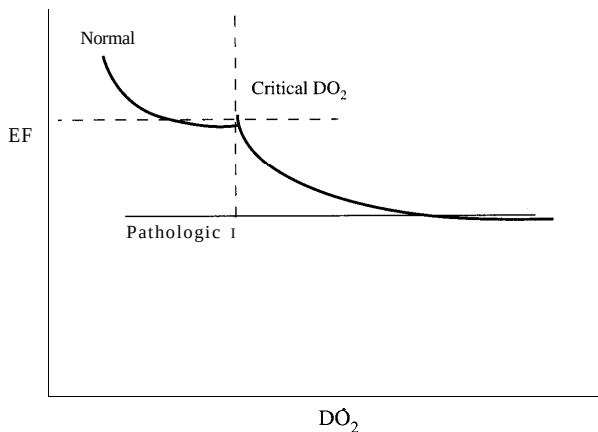


Fig. 2. The relationship between DO_2 and EF in normal and pathologic states are shown. EF increases as DO_2 falls so as to maintain a constant VO_2 under normal circumstances. As DO_2 decreases below critical DO_2 , EF increases but not sufficient to maintain a constant VO_2 . In pathologic states, there is often a small but inadequate increase in EF as DO_2 decreases.

result in a reduction in EF. This reduction in the ability of the tissue to extract oxygen has been observed in pathological states such as sepsis in animal models.^{7,8} Studies in critically ill patients also suggest that VO_2 becomes limited by DO_2 , at normal or even increased levels of DO_2 , with a fixed EF as DO_2 falls.⁹⁻¹¹ In many patients with sepsis syndrome, adult respiratory distress syndrome (ARDS) or septic shock, VO_2 appears to be dependent over a wider range of DO_2 values. This pathological relationship has been described between DO_2 and VO_2 in both animal^{7,8} and in clinical human studies of sepsis.^{2,9} Features that distinguish the pathologic relationship from its physiologic counterpart include higher critical DO_2 , in pathologic dependence, lower critical extraction fraction compared to normal and especially in animal models a higher VO_2 - DO_2 ,

plateau which is attributed to the increased oxygen demand.¹² The exact mechanism resulting in this pathologic supply dependency state is unknown but postulates include local hypoxia, abnormal distribution of blood flow, development of intestinal oedema and release of various inflammatory mediators.^{9,10,13,14} Its presence is associated with increased mortality and as such recognition of this phenomenon may have significant clinical consequences.^{10,14} In many clinical studies, VO_2 and DO_2 , are calculated:

$$DO_2 = Q \times CaO_2 = [\text{stroke volume} \times \text{heart rate} \times \{(\text{Hb} \times \text{SaO}_2 \times 1.39) + (0.003 \times \text{PaO}_2)\}]$$

$$VO_2 = Q \times (CaO_2 - CvO_2) \\ = (\text{stroke volume} \times \text{heart rate}) \times [(\text{Hb} \times (\text{SaO}_2 - \text{SvO}_2) \times 1.39) + \{0.003 \times (\text{PaO}_2 - \text{PvO}_2)\}]$$

where Q = cardiac output

CaO_2 = Arterial oxygen content

CvO_2 = Mixed venous oxygen content

Hb = Haemoglobin concentration

PaO_2 = Arterial oxygen tension

PvO_2 = Mixed venous oxygen tension

SaO_2 = Arterial oxygen saturation

SvO_2 = Mixed venous oxygen saturation

The equations of VO_2 and DO_2 , share common variables namely Q, Hb, SaO_2 and PaO_2 . An artificial relationship between DO_2 and VO_2 can arise due to errors in measurement of these shared variables.^{15,16} This is termed the mathematical coupling of shared measurement error. To circumvent this problem, DO_2 and VO_2 measurements should be established independently. To date, studies on septic patients in which both these variables have been measured independently have not shown any evidence of pathologic dependence of VO_2 on DO_2 .^{11,17-21} In contrast, pathologic dependence of VO_2 on DO_2 , was found in clinical studies where VO_2 and DO_2 , were both calculated.^{2,13,22-24} This would lead to the suggestion that mathematical coupling of shared measurement error could explain the apparent pathologic relationship between DO_2 and VO_2 in septic states. In three studies where VO_2 was calculated and measured (VO_2 measured by analysis of respiratory gases using a metabolic cart) simultaneously and DO_2 , calculated (as shown in the equation above), pathologic dependence of VO_2 and DO_2 , was only seen in the calculated and not in measured values of VO_2 .^{11,18,21} Thus the existence of pathologic dependence of VO_2 on DO_2 , is brought into question.

There are studies which have shown dependence of calculated VO_2 and DO_2 , in one subgroup of patients but not in another. In patients who had increased plasma lactate concentrations, this dependence between calculated VO_2 and DO_2 , was present but not in patients with normal serum lactate concentrations.^{2,13,14,22,25} This sug-

gests that VO_2 may be dependent on DO_2 , under specific conditions.

The evidence thus suggests that the existence of pathologic dependency of VO_2 on DO_2 in sepsis and critical illness depends on common variables used in calculating VO_2 and DO_2 , these being cardiac output and arterial oxygen content. Several investigators have used mathematical concepts to correct for the effects of coupling of shared measurement errors in the determination of VO_2 and DO_2 .^{15,16,26} Using these mathematical simulations, Stratton and colleagues¹⁶ showed that the observed slope of the relationship between DO_2 and VO_2 was a combination of the true slope and the slope caused by shared measurement errors of cardiac output and CaO_2 (Fig. 3). The data scrutinised by Stratton and colleagues were from 2 previous clinical studies.^{9,27} When the analysed data were corrected for the effect of mathematical coupling, the uncoupled slopes in both studies remained statistically significant.¹⁶ They concluded that VO_2 was truly dependent on DO_2 , and could not be explained by mathematical coupling of shared measurement error. Therefore the question of finding a relationship between VO_2 and DO_2 , depends on the method of determining these 2 variables arises. Stratton and several other investigators have suggested that the relationship between calculated DO_2 and calculated VO_2 is not reliable enough to determine adequately whether VO_2 is dependant on DO_2 .^{1,12,16} Therefore it is recommended that DO_2 and VO_2 should be determined using independent methods to avoid problems of mathematical coupling of shared measured errors completely.^{1,12}

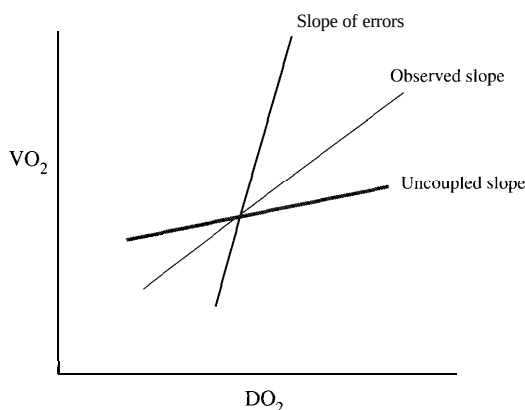


Fig. 3. The slope of errors is caused by the coupling of shared measurement errors. The observed slope is composed of the true slope and the slope of errors. The uncoupled slope is obtained by removing errors from the observed slope.

Supranormal Oxygen Delivery in Critically Ill Patients

It has become increasingly apparent in studies of critically ill patients that survivors have supranormal values of cardiac index (4.5 L/min/m^2), higher DO_2 ($>600 \text{ ml/min/m}^2$) and VO_2 (170 ml/min/m^2) than non-

survivors.^{28,29} This observation has brought forth the notion that by achieving these supranormal haemodynamic values and patterns of oxygen transport in critically ill patients, mortality may be reduced. Such an approach is thought to prevent or reverse tissue hypoxia which arises as a result of increased oxygen demand resulting from the critical illness itself and maldistribution of blood flow both regionally and in the microcirculatory environment.³⁰ Recent studies have shown that if such treatment measures were instituted in high-risk surgical patients during the perioperative period, a significant reduction in mortality can be achieved.³¹⁻³³ Subsequently, randomised controlled trials in critically ill patients, patients with ARDS and sepsis, septic shock and trauma, achieving supranormal DO_2 , were associated with either no change or increased mortality rate when compared with controls in whom normal DO_2 was achieved.³⁴⁻³⁸ In particular, the study by Hayes et al³⁹ where the median survivor values of oxygen transport were compared with normal haemodynamic values as goals of treatment in a heterogeneous group of critically ill patients, the overall outcome was not improved by using dobutamine to achieve supranormal values of oxygen delivery and consumption. In fact, those patients who received large doses of dobutamine to achieve supranormal values had higher mortality rate (54%) than in patients who were randomised to normal DO_2 , (34%, $P < 0.05$).³⁹ In a recent randomised prospective trial involving 762 critically ill patients Gattinoni and coworkers³⁵ randomly assigned these patients into 3 different categories each with a specific end-point; control group (normal cardiac index), supranormal cardiac index group and the normal mixed venous group. No difference in mortality or organ dysfunction were noted in comparing these 3 groups of patients. Indeed in as many as 55% in the supranormal cardiac index group and 33% in the mixed venous group failed to achieve the target end-points. This may have contributed to the failure to show any improvement in outcome. However, the failure to achieve the target values appears to be a common problem, especially in the elderly and in the severely ill who have impaired cardiac performance and a reduced ability to extract or use oxygen.⁴⁰

Therefore, these studies suggest that increasing DO_2 to supranormal levels confers no survival benefit by attempting to reverse tissue hypoxia in sepsis syndrome and septic shock. Previous studies have shown a significant reduction in mortality especially in high-risk surgical patients.³¹⁻³³ In these studies, one has to note that the patients were resuscitated during the perioperative period such that supranormal DO_2 was achieved during the early stages of the critical illness. This suggests that achieving supranormal DO_2 values may be effective in preventing tissue hypoxia rather than reversing established tissue hypoxia in the critically ill patient.

Conclusion

Despite the lack of evidence for the existence of pathologic dependence of VO_2 on DO , and the absence of survival benefit from supranormal DO , in the critically ill septic patient, tissue hypoxia may still be an important cause of organ dysfunction leading to multiorgan failure.¹² Despite adequate oxygen delivery, tissue hypoxia may still exist because of disturbed utilisation of high-energy compounds and also pre-existing insults resulting from inflammatory mediators. These studies emphasise the importance of the role of haemodynamic therapy in achieving adequate systemic perfusion in the critically ill. Volume replacement, maintenance of blood pressure and judicious use of inotropes are all important in achieving this goal. Volume expansion in the critically ill is important, especially in the early stages, so as to prevent the development of refractory tissue hypoxia. Resuscitation can be monitored with the use of the pulmonary artery catheter. Pulmonary artery catheter has been widely used as a diagnostic tool to define haemodynamic profile in the critically ill patient.⁴¹ Several studies have shown that physicians often make inaccurate predictions of patients haemodynamic profile based on available clinical information.⁴²⁻⁴⁴ These studies further demonstrate that the therapeutic plan is frequently changed based on information obtained from the pulmonary artery catheter. Furthermore, in a large prospective, observational study of 5735 critically ill patients, Connors and colleagues⁴⁵ found that the use of the pulmonary artery catheter was associated with an increased mortality and cost. There certainly is insufficient data to be certain about conditions under which information from pulmonary artery catheter may alter outcome.⁴¹ However, the use of pulmonary artery catheter is generally agreed in patients with shock not responding to aggressive fluid resuscitation and inotropes.⁴¹ The response to volume expansion can be monitored using clinical signs, PCWP readings and serum lactate.⁴⁶ Plasma lactate level may be useful but should be interpreted cautiously. Both hypoxic and non-hypoxic causes of a raised plasma lactate in the critically ill patient should be considered. Gastric tonometry which measures mucosal Pco_2 has emerged as a relatively non-invasive technique of assessing gastrointestinal perfusion and oxygenation by detecting acidosis in the luminal wall of the gut.¹ This technique which involves the placement of a saline filled latex balloon tip catheter placed in the gut allows measurement of intramucosal pH by estimating gas tensions in the surrounding tissues.⁴⁷ Gastric tonometry is a very useful technique as it allows one to monitor specific organ perfusion in the critically ill.¹ Despite the strong evidence favouring its use in critically ill patients, tonometry has still not gained widespread acceptance as it is labour intensive and prone to the introduction of technical errors in determin-

ing the intramucosal pH.⁴⁸ Vasoactive agents such as dopamine or noradrenaline should be used if hypotension persists despite adequate volume replacement and dobutamine or adrenaline if cardiac index is low. Further measures to improve the imbalance between oxygen demand and supply in the critically ill would include mechanical ventilatory support, especially when there is a significant contribution to this imbalance by the increased work of breathing, and control of fever. Both these measures have been shown to reduce VO_2 .^{49,50}

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