Oxygen Delivery and Consumption: A Macrocirculatory Perspective

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Despite decades of investigation, severe sepsis continues to be a leading cause of death and resource use throughout the world. Deaths attributable to complications of infection now are thought to be on par with those secondary to acute myocardial infarction. In 2001, Angus and colleagues,¹ using data obtained from all nonfederal hospitals in a seven state area as an estimate of national figures, calculated the number of severe sepsis cases in the United States to be somewhere in the neighborhood of 751,000 cases per annum with an associated mortality of 28.6% or 215,000 deaths overall. This figure was roughly twice that estimated by the Centers for Disease Control (CDC) at the beginning of the 1990s. Moreover, they predicted that the incidence of severe sepsis would continue to increase at an annual rate of 1.5%. This trend was borne out in a longitudinal study using information from a national hospital database representing roughly 20% of nonfederal short-term institutions. Over the period from 1993 to 2003, Dombrovskiy and colleagues² reported a doubling in hospitalizations for severe sepsis from 64.7 to 134.6 cases per 100,000 population. In addition, the investigators noted an increase in the percentage of patients developing multiple organ dysfunction during their stay. Whereas acuity of illness and crude severe sepsis rate were clearly increasing, the associated case-fatality rate fell approximately 7% during the decade under study. Not surprisingly, the cases were disproportionately concentrated in the elderly, with patients over the age of 65 accounting for roughly three-fifths of hospitalizations. The expense of caring for patients with this syndrome is staggering. During the calendar year 1995, the cost

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per case of severe sepsis was estimated to be $22,100, which translated into national expenditures approaching $16.7 billion.\(^1\)

Over the last 5 decades, remarkable advances in our understanding of the pathophysiology of sepsis have occurred. A crucial aspect of the syndrome involves cardiovascular dysfunction that was first appreciated by Waisbren\(^3\) in the 1950s. Early observations suggested that the lactic acidosis and organ dysfunction seen in septic states were occurring in the setting of normal or high oxygen delivery to tissues and, therefore, represented a unique form of shock. Indeed, experimental models revealed that the critical level of oxygen delivery in sepsis was significantly higher than that seen in anemic, stagnant, and hypoxic hypoxia.\(^4\) Another poorly understood phenomenon also seemed to be occurring in septic animals and patients: normal compensatory increases in O\(_2\) extraction to meet tissue demand appeared to be limited, suggesting that the optimal means to meet increased demand would be through an increase in global oxygen delivery.\(^4,5\)

The problem of meeting cellular oxygen needs and maintaining tissue and organ viability in sepsis has become increasingly complex with the modern demonstration of marked microcirculatory disturbances along with early organelle injury and dysfunction. A variety of studies suggest that augmenting convective transport in the macrocirculation often has little impact on the distribution of microcirculatory blood flow or measured oxygen consumption.\(^6,7\) Other studies suggest that oxygen tension within a variety of tissues may be more than adequate for normal cellular respiration implying that as shock progresses treatment strategies based on enhanced convective transport are not likely to be successful.\(^8,9\)

Cellular and organelle injury appears to occur very early on in severe septic conditions. Brealey and colleagues,\(^10\) studying mitochondria obtained from septic patients within the first 24 hours of admission to an ICU, frequently found abnormal activity in electron transport complexes I and IV along with marked alterations in the levels of ATP and the ADP-ATP ratio. Even though initially patients were clinically indistinguishable, nonsurvivors had roughly half the amount of ATP contained within mitochondria than did survivors. Curiously, there also may be important bioenergetic differences in mitochondria from different tissues obtained from patients suffering multiple organ dysfunction and also from patients with different ancestry.\(^11,12\) What does seem clear is that morphologic changes evident on electron microscopy correlate with the organelle’s ability to efficiently use oxygen and the cell’s ability to function normally. When exposed to lipopolysaccharide, mitochondria undergo changes in size, shape, and density thought secondary to the development of a so-called permeability transition pore. As the process advances, a number of mitochondria may undergo organelle death and subsequent autophagy.\(^13,14\)

Surprisingly, autopsied organs obtained from patients dying of sepsis demonstrate little evidence of ischemic necrosis when assessed by light microscopy. Hotchkiss and colleagues\(^15\) investigating patients within an hour and a half of death found scant amounts of focal necrosis near central veins in hepatic lobules and in organs (heart, kidney, and brain) where infarction had occurred before death. Apoptosis of lymphocytes and endothelial cells was noted on immunohistochemical staining in several organs, but rarely exceeded 5% of the cells examined. These findings, along with a host of other observations in natural and experimental settings, have lead many in the field to develop a new paradigm to explain these discordant findings. Rather than cells undergoing a fatal loss of function secondary to injury or ischemia, cellular processes may be down-regulated in an effort to limit oxidant stress, high-energy phosphate depletion, or other injurious processes as a means to allow for later recovery similar to the hibernation seen in chronically ischemic myocardial tissue.\(^16\)
Although this may prove to be adaptive, at present we do not have the ability to discern the point at which the process becomes maladaptive nor the capability to recover the function of these failing organs.

With this background, the authors examine the relationship of oxygen delivery to oxygen use under varying conditions and review the concept of the critical dissolved oxygen (DO₂crit), the point at which oxygen consumption falls with further decrease in oxygen delivery. In addition, this article addresses the concerns over shared measurement errors in obtaining estimates of oxygen consumption, review the seminal articles in this area, and explore the practice of early goal-directed therapy (EGDT).

**CONVECTIVE TRANSPORT AND THE DELIVERED OXYGEN–OXYGEN CONSUMPTION RELATIONSHIP**

To sustain aerobic metabolism, cells require a constant supply of oxygen. At the level of the mitochondria, the amount needed seems impossibly small. Under basal conditions, an oxygen partial pressure of ~1 mmHg in the vicinity of the mitochondria meets the organelles' metabolic requirements.¹⁷ This supply is maintained through convective and diffusive transport of oxygen and relies heavily on the association properties of hemoglobin (Hgb) for oxygen. Mathematically whole body oxygen delivery (DO₂) is expressed by the following formula:

\[
DO₂ = \frac{\text{Arterial oxygen content}}{\text{Cardiac Output}} \times 10
\]

or

\[
DO₂ = \frac{CaO₂}{CO} \times 10
\]

Where \(CaO₂ = [\text{Hgb} \times 1.39 \text{ mL/gm of Hgb} \times \text{Saturation of Hgb}] + [\text{PaO₂} \times 0.0031]\). A normal arterial oxygen content is generally between 18 and 20 mL per deciliter of blood. In the setting of a normal cardiac output, total bulk transport in the systemic circulation is then between 900 and 1,100 mL per minute. When indexed to body surface area, a range of 530 to 600 mL/min/m² is obtained.

Estimating oxygen consumption (VO₂) can be accomplished in the clinical setting either by expired-gases analysis or through the reverse Fick method. The latter is the more popular approach and uses a mixed venous blood gas obtained from a pulmonary artery catheter to calculate venous oxygen content in the same manner as done on the arterial side of the circulation. Substituting mixed venous central (Cv) and tension (Pv) values into the above equation leads to the following formula: CvO₂ = \([\text{Hgb} \times 1.39 \text{ mL/gm of Hgb} \times \text{saturation of Hgb}] + [\text{PvO₂} \times 0.0031]\). The venous oxygen content under usual conditions runs 13 to 16 mL/dL leading to an arterial-venous (A-V) O₂ content difference of ~3–5 mL/dL. Multiplying the oxygen content difference by the cardiac output obtained from thermodilution measurements then provides a reasonable estimate of total body oxygen consumption. The values obtained are slightly lower than those derived from expired gas analysis that includes O₂ consumption from the alveolar compartment. The reverse Fick equation is expressed mathematically as the following:

\[
VO₂ = A - VO₂ \text{ content difference} \times CO \times 10
\]

The percentage of oxygen consumed to that delivered is termed the extraction ratio (ER). Normally the ER is around 25%, but can vary significantly depending on the metabolic activities of the tissue and the conditioning of the subject. In well-trained
athletes, for example, the extraction ratio near their anaerobic threshold may approach 60%. Extraction ratios can be calculated in one of two ways:

$$\text{ER} = \frac{\text{VO}_2}{\text{DO}_2}$$

or

$$\text{ER} = \frac{(\text{CaO}_2 - \text{CvO}_2)}{\text{CaO}_2}$$

Intermittent or continuous monitoring of venous oxygen tension in the superior vena cava or pulmonary artery also can often provide important early information with regard to the adequacy of oxygen delivery. By rearranging the following formula and ignoring the small contribution from dissolved oxygen we can demonstrate that when VO\(_2\) is stable venous oxygen saturation (SvO\(_2\)) will vary with DO\(_2\).

$$\text{DO}_2 = \frac{\text{VO}_2}{\text{SaO}_2 - \text{VO}_2}$$

Originally, it was thought that SvO\(_2\) might serve as an indicator of cardiac output but the correlations in critically ill patients have been disappointing because DO\(_2\) can be influenced by changes in hemoglobin and the partial pressure of oxygen and VO\(_2\) can vary with temperature, activity, nursing interventions, oxygen delivery, and the tissues’ ability to extract.

THE ISSUE OF MATHEMATICAL COUPLING

Early studies in the area of DO\(_2\)-VO\(_2\) covariance relied on the reverse Fick equation to estimate consumption rather than measuring VO\(_2\) independently through techniques such as indirect calorimetry. This methodology led to concerns that systematic or random errors in shared variables such as cardiac output and SaO\(_2\) might force a relationship during regression analysis where in fact none existed. This conclusion was supported by Phang and colleagues in a study of acute respiratory distress syndrome (ARDS) patients. When VO\(_2\) was measured by expired gas analysis during manipulation of oxygen delivery, DO\(_2\) dependence was not apparent, leading to the conclusion that measurement errors in the common elements of the Fick equation were the source of the previously described covariance. This controversy continues to find its way into the literature and can be an ongoing source of confusion for the practitioner. A number of recent papers, however, have provided key insights into the impact of measurement error when common variables are used to establish DO\(_2\)-VO\(_2\) dependency and have suggested approaches to mitigate the effect.

Analysis of the problem can be quite complex and is beyond the scope of this article. The interested reader can find in-depth discussions in papers by Squara, De Backer, and Granton and colleagues. The essential elements, however, can be distilled down to (1) the effect of pooled versus individual measurements, (2) the heterogeneity of patient populations, (3) the impact of changing DO\(_2\) in the setting of low cardiac output, and (4) the effect of two versus multiple measurements. Granton and colleagues point out that if the change in DO\(_2\) is large (50–100 mL/min/m\(^2\)) and multiple measurements are obtained, then the reverse Fick technique and indirect calorimetry approximate each other. Also, if measurement error in cardiac output
estimates can be kept to a minimum, then the change in slope of the \( \text{DO}_2-\text{VO}_2 \) relationship attributable to mathematical coupling will be modest and, by itself, inconsistent with supply dependency.\(^{25,27}\)

It is also important to remember that biologic coupling should not be easily dismissed as a statistical aberration. A number of studies have demonstrated markedly different outcomes across groups depending on the presence or absence of supply-dependency.\(^{28-31}\) If systematic or random errors were forcing statistical relationships, then one would expect \( \text{DO}_2-\text{VO}_2 \) covariance to be similar between groups and not predictive of patient outcome.

In experimental settings and clinical studies, the slope of the \( \text{DO}_2-\text{VO}_2 \) relationship during supply dependency is quite steep with a range of 30% to 50%. Above \( \text{DO}_2\text{crit} \), the slope falls to less than 10% but rarely plateaus (Fig. 1). The modest slope in oxygen consumption above \( \text{DO}_2\text{crit} \) has been attributed to increased metabolic work necessitated by higher individual organ blood flow, the thermogenic effect of catecholamines, and the conformation of organs to a richer oxygen environment. In light of these observations and the known impact of measurement error, it has been suggested that supply dependency not be diagnosed until the slope of the \( \text{DO}_2-\text{VO}_2 \) relationship is well in excess of 10%.\(^{26}\)

**THE “CRITICAL” \( \text{DO}_2 \)**

Normally, changing oxygen needs of the body are easily met through abundant basal flow and a variety of compensatory mechanisms including increased stroke volume and heart rate, vascular redistribution of blood flow, capillary recruitment, and changes in hemoglobin binding affinity. Recently, it has also been shown that the red blood cell itself may be playing an important role in local control of flow through hypoxic regions by generating dilatory nitric oxide from membrane associated nitric oxide synthase.\(^{32}\) The point at which these compensatory mechanisms fail to meet tissue requirements has been termed the critical \( \text{DO}_2 \) or anaerobic threshold. At this point, a decrease in oxygen delivery is associated with a fall in oxygen consumption.

![Oxygen Delivery and Consumption](image)

**Fig. 1.** The classic biphasic \( \text{DO}_2-\text{VO}_2 \) relationship. \( \text{DO}_2\text{crit} \) represents the point at which oxygen consumption falls (becomes dependent on \( \text{DO}_2 \)) with further reduction in oxygen delivery. In states of pathologic \( \text{DO}_2 \) dependency, the slope of the relationship is altered and covariance is thought to occur over a much wider range of \( \text{DO}_2 \). Serum lactate arising from anaerobic metabolism will increase when oxygen delivery falls below \( \text{DO}_2\text{crit} \).
along with an increase in lactate generation. The $\text{DO}_2$-$\text{VO}_2$ relationship is generally biphasic with a supply-dependent and a supply-independent region. The point of transition and the slope of the $\text{VO}_2$-$\text{DO}_2$ relationship will vary depending on the conditions under which measurements are obtained and individual patient characteristics (see Fig. 1).

What defines this $\text{DO}_2\text{crit}$ threshold and whether this threshold changes appreciably based on the physiologic condition of the subject, has long been a subject of study. Initial work in various animal species suggested that the critical $\text{DO}_2$ was in the range of 5 to 10 mL/kg/min depending on study design. It was not until the 1980s, however, that systematic investigation of $\text{DO}_2\text{crit}$ was undertaken in human beings. In the setting of high-risk surgery and ARDS, the values obtained varied widely suggesting that basal conditions could lead to dramatic differences in $\text{DO}_2\text{crit}$. In an effort to establish minimum delivery requirements, Lieberman and colleagues iso-volemically bled normal volunteers down to a Hgb of 5 g/dL then infused esmolol to blunt compensatory tachycardia. None of the participants produced lactate despite an average delivery of 7.3 mL/kg/min establishing that $\text{DO}_2\text{crit}$ is below this point in normal resting adults. However, mild cognitive and memory changes were described raising the possibility that important individual organ susceptibility may occur and cannot be excluded on the basis of systemic lactate levels or estimated $\text{DO}_2$. Having the subjects breathe high fractional concentrations of oxygen ($\text{FiO}_2$) mitigated the effects of the prior interventions, suggesting that clinically relevant increases in tissue $\text{O}_2$ tension can be achieved in anemic hypoxia by increasing the soluble component of $\text{O}_2$ transport. Shibutani and colleagues, and, later, Komatsu and colleagues, studied patients immediately before coronary artery bypass grafting and then again 15 minutes after coming off bypass. Both studies demonstrated a $\text{VO}_2$ plateau in the majority of patients as $\text{DO}_2$ exceeded 300 to 330 mL/min/m$^2$. Post-bypass, however, there was a subset of patients who for unclear reasons demonstrated a proportional increase in $\text{VO}_2$ over the range of $\text{DO}_2$ studied suggesting that within this group a higher critical $\text{DO}_2$ existed. The most extreme example of critical $\text{DO}_2$, however, comes from hemodynamic measurements obtained from an 84-year-old patient who for religious beliefs refused blood products in the perioperative period. At the end of the operation, hemoglobin had fallen to 2.6 g with a measured $\text{DO}_2$ of 146 mL/min/m$^2$. The patient went on to die 8 hours postoperatively with a preterminal $\text{DO}_2$ of 78 mL/min/m$^2$. Utilizing best-fit regression lines the investigators estimated the $\text{DO}_2\text{crit}$ to be $\sim 184$ mL/min/m$^2$ (4.9mL/kg/min) while fully ventilated and undergoing sedation and muscle relaxation.

In the situations described above, one would expect compensatory mechanisms to be fully active and that oxygen consumption would proceed normally. Indeed, in the latter case, the extraction ratio was found to be 60% before death. The situation with sepsis has always been considered to be more complex with a much higher range needed to achieve supply independency.

Studies of critically ill patients in the 1980s demonstrated supply dependent $\text{VO}_2$ at much higher levels of $\text{DO}_2$ than previously thought necessary. Mohsenifar and colleagues, using data pooled from patients suffering from ARDS, calculated the critical $\text{DO}_2$ to be 21 mL/kg/min. Later, experimental studies and observations in septic patients suggested that the altered slope of the $\text{VO}_2$-$\text{DO}_2$ relationship and higher $\text{DO}_2\text{crit}$ represented a new type of “pathologic $\text{DO}_2$ dependency” resulting from altered vasomotor activity, $\text{O}_2$ conformity, and metabolic demands of tissue. Based on observational studies, “supranormal” oxygen delivery was recommended as a strategy to avoid incurring oxygen debt and secondary organ dysfunction. The early suggested targets for supranormal delivery were a cardiac index of 4.5 L/min/m$^2$,
Systematically studying $DO_2-VO_2$ dependency is now rarely done in critically ill septic patients. Much of the contemporary approach is based upon achieving hemodynamic goals such as mean arterial pressure (MAP), stabilizing organ function, reducing lactate, and increasing $SvO_2$. In a landmark paper, Ronco and colleagues set out to determine individual anaerobic thresholds in a variety of critically ill patients who were having support withdrawn. Oxygen delivery and consumption were measured repeatedly by independent means to avoid shared measurement errors in the calculation of $DO_2$ and $VO_2$. All patients demonstrated the classic biphasic curve as delivery declined. When comparing $DO_2\text{crit}$ between septic and nonseptic patients, no significant difference was noted. In these heavily sedated patients, the anaerobic threshold averaged $3.8 \pm 1.5$ and $4.5 \pm 1.3$ mL/min/kg respectively. Extraction ratios were also similar and approached those seen in exercising athletes and patients with other forms of shock. The investigators also noted elevated lactate in patients whose baseline oxygen delivery exceeded the measured $DO_2\text{crit}$ by as much as threefold. As consumption began to fall in response to declining delivery, lactate levels rose in all patients, suggesting that hyperlactemia may develop from two independent processes— one tied to deranged cellular metabolism and the other to convective $O_2$ transport. The investigators went on to conclude that $DO_2\text{crit}$ is not increased in the terminal phases of septic shock and that oxygen extraction proceeds normally as well. These findings are difficult to reconcile with numerous clinical and experimental studies demonstrating abnormal supply dependency but may reflect important changes in metabolic activity over the course of illness or particular responses to acute bacteremia and endotoxemia. Resting metabolic rate has been shown to vary considerably over the course of illness. In one study, patients were classified on a daily basis as having sepsis, severe sepsis, or septic shock. The lowest metabolic activity was shown to occur when patients met criteria for septic shock. In one striking example, resting metabolic rate moved in a direction opposite to serum endotoxin levels.

**TRIALS OF $DO_2-VO_2$–GUIDED THERAPY**

The appreciation of this altered $VO_2-DO_2$ relationship and elevated $DO_2\text{crit}$ led to the proposition that organ damage in critically ill patients could result from an inadequate $DO_2$, even in settings where $DO_2$ was normal or modestly elevated. This inadequate $DO_2$ would, in turn, result in a reduction in $VO_2$ and consequent tissue hypoxia, injury, and, eventually, organ failure. In landmark observational studies on high-risk surgical patients, Shoemaker and colleagues observed that patients who were able to generate a high cardiac output, $DO_2$, and $VO_2$ had a significantly higher survival rate than those who did not. This led to the proposition that therapies designed to induce such a “supraphysiologic” state could be life preserving. Based upon median values of survivors noted by Shoemaker and colleagues, the initial targets for these supranormal therapies were a cardiac index of 4.5 L/min/m$^2$, $DO_2$ greater than or equal to 600 mL/min/m$^2$, and a $VO_2$ greater than or equal to 170 mL/min/m$^2$, and several studies were undertaken to assess the potential benefit of $DO_2-VO_2$–guided therapies in the critically ill, particularly among those in severe sepsis and septic shock.

Bihari and colleagues were some of the first investigators to study the impact of increased oxygen delivery on oxygen consumption in a largely septic ARDS population. To augment $DO_2$, vasodilation of the systemic circulation was produced with a fixed dose of prostacyclin (5ng/kg/min$^{-1}$). The change in $DO_2$ was 23% higher in
survivors and 12% in nonsurvivors. Nonsurvivors, however, demonstrated a 19% increase in VO₂ at the end of the 30-minute infusion period compared with 5% in the surviving population. The extraction ratio increased 11% in nonsurvivors with no apparent change in SvO₂. This was in contrast to survivors in whom the ER fell 17% in association with an increase in SvO₂. The investigators understood this to mean that a large oxygen debt was present in those who went on to die and that this debt could be unmasked by increasing global supply or nonspecifically dilating regional vascular beds. Interpretation of the findings, however, is limited by the baseline differences in severity of illness and base deficit, and an incomplete understanding of the cause of death in the nonsurviving population.

In the only randomized, controlled trial limited to septic shock patients of supranormal DO₂ therapy (CI targeted to >6 L/min/m²), Tuchschmidt and colleagues⁴⁶ found a higher mortality rate in the supranormal DO₂ group compared with the normal DO₂ group (72% vs 50%), though this difference was not statistically significant. However, in a subgroup analysis, treatment group patients who were able to achieve the more modest elevations in CI (>4.5 L/min/m²) had a survival advantage over control group patients who were not hyperdynamic (CI<4.5 L/min/m²). This latter finding would seem to suggest that an elevated hemodynamic state confers a survival advantage in septic shock, with or without external intervention. Further, it strongly implies that the inability to achieve a hyperdynamic state in response to septic shock carries a grim prognosis.

Hayes and colleagues⁵⁰ conducted a similar trial in a heterogeneous group of critically ill patients with more modest CI goals (>4.5 L/min/m²), though also using targeted DO₂ (>600 mL/min/m²) and VO₂ (>170 mL/min/m²). This study was actually terminated early due to significantly higher in-hospital mortality rates in the treatment group (54%) than in the control group (34%), with mortality differences attributed to multiple organ failure. In the subgroup of patients with septic shock, in-hospital mortality was 52% in the control group as compared with 71% in the treatment group. Whereas nearly all treatment group patients were able to achieve the specified supranormal CI and DO₂ targets, few were able to achieve the targeted oxygen consumption.⁴⁷ This points to the conclusion that either VO₂ is not in fact wholly dependent on DO₂ or, less likely, that even higher ranges of DO₂ would be required to normalize VO₂. In a smaller study using only a DO₂ target (>600 mL/min/m²), Yu and colleagues⁴⁸ also failed to identify a therapeutic benefit of a supranormal DO₂ strategy over conventional management, though they also noted that there was a significant survival benefit for patients who were able to reach supranormal DO₂ whether self-generated or from treatment (14% vs 56%).

In the largest randomized, controlled trial of supranormal DO₂ in critically ill patients,Gattinoni and colleagues⁴⁹ attempted to assess the effect of raising cardiac indices to supranormal levels (CI>4.5 L/min/m²) and normalizing mixed venous oxygen saturations (SₘᵥO₂ ≥ 70%) as compared with controls. Neither intervention group experienced a reduction in morbidity or mortality (48% in control group, 49% in cardiac index group, 52% in oxygen saturation group). As experienced in prior studies, a large proportion of treatment-arm patients were unable to reach their hemodynamic targets. In this case, only 45% of the cardiac index group and 67% of the mixed venous oxygen saturation group obtained the targeted hemodynamic indices.

Taken collectively, these studies support two conclusions. The first is that supranormal DO₂-based therapeutic strategies are ineffective and potentially harmful. The second is that, although the prognosis for septic patients who can achieve higher than normal oxygen delivery and extraction levels is very good, the prognosis for the substantial number of patients who are unable to increase oxygen consumption despite aggressive inotropic support to increase oxygen delivery is very poor.⁵⁰
However, the premise of directing resuscitation efforts to achieve clearly delineated hemodynamic goals remains an appealing one, though a reorientation of such goals away from achieving supranormal DO$_2$ levels with inotropes is indicated. The fact that in their studies of high-risk surgical patients, Shoemaker and colleagues$^{42}$ were successful in achieving their hemodynamic goals with fluid resuscitation alone in two-thirds of their patients, points to an alternative strategy for the resuscitation of septic patients. Further, as observed by Hayes and colleagues,$^{29}$ inotropic support was frequently not started until the patient had been admitted to the ICU, by which time boosting oxygen delivery may not be able to improve the outcome. This distinction is a crucial one and is highlighted below in the discussion of EGDT.

**DOBUTAMINE AND DO$_2$-VO$_2$**

Whereas intentionally raising DO$_2$ with dobutamine to achieve certain delivery goals has not been shown to improve outcome outside of the early hours of resuscitation, the associated changes in oxygen consumption have been correlated with survival in critically ill and severely septic populations. When Hayes and colleagues$^{47}$ reviewed their experience with high dose dobutamine, they noted that patients who did not achieve all three specified supranormal targets (CI>4.5 L/ min/m$^2$, DO$_2$>600 mL/ min/m$^2$, and VO$_2$>170 mL/min/m$^2$) failed to do so on the basis of inadequate VO$_2$ response 65% of the time. In this group of inadequate responders, lactate levels remained elevated while SvO$_2$ increased in association with very high mortality rates.

Vallet and colleagues$^{31}$ were one of the first groups of investigators to employ short-term infusions of dobutamine in septic patients to identify important physiologic responses and tie these changes to outcome. Their original study population consisted of normolactemic patients with severe sepsis. Baseline hemodynamics and oxygen transport and use measurements were performed before and 1 hour after an infusion of dobutamine. A less than 15% increase in VO$_2$ was considered a positive response based on receiver operating characteristic curves. In the responder group, the average increase in oxygen delivery and oxygen consumption approached 40% while nonresponders had a modest 13% increase in DO$_2$ and no change in VO$_2$. The behavior of lactate was curious, rising ~25% in the nonresponder group despite stable VO$_2$ levels. Among responders the mortality rate was 8.7% while in the nonresponder group mortality was 44.4%.

This approach was later applied by Rhodes and colleagues$^{30}$ in a severely septic population that included patients with shock. The groups were characterized based on the VO$_2$ response to 10 mcg/kg/min of dobutamine given over 1 hour’s time. The patients who went on to demonstrate minimal increases in VO$_2$ tended to be older; had higher APACHE (acute physiology and chronic health evaluation) III scores; and required, on average, higher infusion rates of epinephrine and dopexamine at baseline. Hemodynamics, however, were similar in both groups before the initiation of dobutamine. Responders had a brisk increase in cardiac index that came from both chronotropic and inotropic responses, which may have important clinical implications. The nonresponders had varying effects from dobutamine in terms of CI and DO$_2$ but, on average, failed to demonstrate a meaningful increase in either of these parameters. The mortality difference was striking. At 28 days, 86% of the responders were alive compared with just 9% of the nonresponders.

The hemodynamic response to graded amounts of dobutamine also appears to have important prognostic implications. In a recent study performed during the first 48 hours of severe sepsis or septic shock, survivors demonstrated an increase in stroke volume index (SVI) of greater than or equal to 8.5 mL/m$^2$ as dobutamine was
infused up to 15 mcg/kg/min. Although both survivors and nonsurvivors demonstrated a chronotropic response to dobutamine, only the former group seemed capable of improving other aspects of cardiac performance. Left ventricular ejection fraction increased ~12% in survivors, but remained essentially unchanged in nonsurvivors. Right ventricular ejection fraction was affected very little by dobutamine, though indices of lusitropy were shown to improve in the survivor group.51 These findings recapitulate earlier work demonstrating differing hemodynamic responses to septic shock between survivors and nonsurvivors—with the former having, on average, lower heart rates, higher end-diastolic volumes, and better peak systolic pressure to end-systolic volume ratios.52–54 Whether this represents a critical physiologic reserve or an epiphenomenon of generalized organ dysfunction remains a debated question.

**EGDT**

The management of severe sepsis and septic shock changed dramatically with the recognition of the “golden hours”—the critical period of time in which recognition and treatment provide maximal benefit. Lundberg and colleagues55 showed that septic patients on the general wards had a substantial delay in the receipt of intravenous fluids and vasoactive medications in comparison to those in the ICU, with a trend toward decreased survival. In their study of the management of the critically ill in the emergency department, Nguyen and colleagues56 demonstrated that emergency department management (on average 6 hours in duration) was capable of reducing APACHE II scores and reducing down-stream morbidity and mortality. A possible explanation for the failure of the studies led by Tuchschmidt,46 Hayes,29 and Gattinoni49 was not that the theory behind them was unsound, but that they took too long from the onset of illness (and presumably hemodynamic insult) to initiate therapy as all of their studies initiated treatment upon admission to the ICU (and some allowed enrollment up to 72 hours after admission). These delays in the initiation of treatment may have caused any therapeutic strategy to become ineffective.

In 2001, Rivers and colleagues57 published a landmark article in which aggressive EGDT was employed from the outset of the recognition of severe sepsis and septic shock, often before admission to the ICU. Specific goals were set to for the first 6 hours of resuscitation and included the following targets: MAP of 65 to 90, a central venous pressure (CVP) of 8 to 12, and a ScvO2 of ≥70%. The investigators based this approach on the premise that critical underperfusion was poorly recognized in the early hours of sepsis and that this period of inadequate delivery set the stage for later development of life-threatening organ dysfunction.

In the treatment and standard therapy arms, a high percentage of patients had coexisting conditions such as congestive heart failure, diabetes, hypertension, and liver disease. At the time of enrollment, serum lactates averaged 6.9 ± 4.5 to 7.7 ± 4.7, respectively; with greater than 50% of patients having septic shock. By the end of the first 6 hours of treatment, all subjects had achieved a MAP greater than 65 mmHg. Other conventional targets (CVP, urine output) were met by 86.1% of the standard therapy group and 99.2% of the EGDT group. The greatest difference between the groups was found in measures of saturation of superior vena caval blood (ScvO2). The group receiving conventional treatment met or exceeded the ScvO2 target in 60% of cases compared with 95% of cases in the EGDT group. To achieve the ScvO2 goal in the EGDT group, 60% of patients required red cell transfusions and 14% dobutamine. At 6 hours, the EGDT group had received on average 1.5L of additional fluids over the standard therapy group. This translated into a roughly two-point difference in CVP at the end of the resuscitation period. After intervention, the reported MAPs were exceptionally high.
for patients with severe sepsis and septic shock. In the EGDT group, MAPs at 6 hours averaged 95 ± 19 mmHg compared with 81 ± 18 mmHg in the standard arm. Despite the high MAP values in both groups, a significant difference in pH, base deficit, lactate, and organ failure scores was found at the end of 6 hours, which persisted into the 7- to 72-hour observation period despite more aggressive fluid and red cell replacement in the standard therapy group during the later period. When mortality was analyzed, the risk of death was reduced at both the 28- and 60-day mark with all subgroups of sepsis benefiting. The benefit afforded by this approach, however, was limited to a reduction in deaths secondary to “sudden cardiovascular collapse.” Improvement in outcome related to multiple organ dysfunction syndrome did not achieve statistical significance.

In a subanalysis of the trial, Donnino and colleagues58 advanced the concept of “cryptic septic shock” as an explanation for some of these findings. Post hoc, the group identified a subset of patients who met the criteria for systemic inflammatory response syndrome, or SIRS, and had lactic acidosis, but in whom early blood pressures were in excess of 100 mmHg (mean ~ 116 mmHg) while ScvO2s were in the mid-40%. A markedly lower mortality rate (20% vs 60.9%) was seen in the patients receiving EGDT. If one makes some assumptions (SVR of 1000 dyne/s·cm$^{-5}$) and use average values from the trial, the estimated cardiac output for this group would be in the range of 8 L/min, which is difficult to reconcile with the ScvO2 data. More likely, this group represented a severely hypertensive subset with very limited cardiac reserve. Still, this may be an important group to identify, as aggressive early intervention seems to have lead to a much better outcome.

While the Rivers study has been subject to much analysis and critique in the years since its publication,59 the fact remains that a resuscitation strategy involving the normalization of hemodynamic parameters beyond that of cardiac output and oxygen delivery remains the most effective management strategy for severe sepsis and septic shock. As such, EGDT was quickly and widely embraced, and became one of the cornerstone of the Surviving Sepsis Campaign and its published guidelines.60

Currently a number of studies are underway to assess the value of EGDTs. The questions being addressed include the utility of protocolized care, the value of minimally invasive cardiac assessment, the potential of lactate directed resuscitation, and finally, the benefits of different resuscitation fluids and vasopressors.61

**SURVIVING SEPSIS CAMPAIGN GUIDELINES**

Though a hemodynamic management strategy based primarily on supranormal oxygen delivery has largely been dismissed, the principles behind maintaining normal or even elevated DO$_2$ in the setting of severe sepsis or septic shock to maintain tissue oxygenation remain sound. In the most recent iteration of the evidence-based guidelines for the management of severe sepsis and septic shock, the Surviving Sepsis Campaign incorporated some of the principles of DO$_2$ normalization.60

Along with CVP, MAP, and urine output goals, initial resuscitation recommendations include maintaining a central or mixed venous O$_2$ saturation of greater than or equal to 70%, or greater than or equal to 65%, respectively, as a less-invasive measure of adequate oxygen delivery. If the venous O$_2$ saturation goal is not achieved with fluid resuscitation and vasopressors (norepinephrine or dopamine), then red cell transfusion should be considered if the hematocrit is less than 30%. The use of red blood cell transfusions as a means to increase DO$_2$ outside of the early phase of severe sepsis remains controversial, however, as other studies have shown a survival benefit with more conservative transfusion strategies in general ICU populations.62 The current recommendations are to transfuse for hemoglobin below 7 g/dL, although
a higher hemoglobin could be required in special circumstances such as myocardial ischemia, severe hypoxemia or acute hemorrhage. If ScvO\textsubscript{2} remains below 70% after the above interventions, cardiac output is presumed to be low, and the use of dobutamine to increase delivery is recommended.\textsuperscript{60}

**SUMMARY**

As understanding of the pathophysiology of sepsis has developed so has appreciation of the limited role that supranormal oxygen delivery plays in resuscitation strategies. The window of opportunity to improve outcome through manipulation of convective transport is probably quite narrow and must be exploited at the onset of severe sepsis. EGDT currently offers the best approach to improving outcome. With the completion of a number of ongoing studies, the authors hope that early strategies can be optimized and better endpoints of resuscitation identified. Once cellular injury is well established, increasing delivery of oxygen to the tissues should not be expected to improve oxygen consumption, lactate production and clearance, or outcome.

**REFERENCES**


