Commentary

The International Sepsis Forum’s frontiers in sepsis: high cardiac output should not be maintained in severe sepsis

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Abstract

Abnormal oxygen utilisation is one of the features of septic shock. Some studies have observed that patients that survive septic shock tend to have higher cardiac output and oxygen delivery compared to those that do not. It has been proposed that higher than normal (or "supra-normal") levels of cardiac output and oxygen deliver should be the goal in the management of septic shock. However, randomised controlled trials have not been able to validate that such a goal provides a mortality or morbidity advantage. In this commentary we discuss the various reasons put forward by the proponents of this strategy and review the available evidence.

Keywords cardiac output, oxygen consumption, oxygen delivery, septic shock

Introduction

Septic shock is a syndrome characterized by abnormal oxygen utilization. It has been suggested that maintaining cardiac output (CO) above normal in patients with septic shock should increase oxygen delivery (DO₂) and oxygen consumption (VO₂), decrease any oxygen debt present, and potentially improve survival. However, the tissue extraction of needed oxygen is maintained even at very low levels of DO₂. Furthermore, VO₂ increases with increasing DO₂ only up to a point. Thereafter, subsequent increases in DO₂ do not result in any further increase in VO₂ (Fig. 1). Attempts to increase the DO₂ beyond this point are more likely to be harmful because the methods used (e.g. inotropes) have potential harmful effects (such as increased oxygen demand in tissues, tachyarrhythmias, worsening distribution of blood flow in tissues, and myocardial ischemia).

What is the rationale for maintaining high cardiac output?
The rationale for maintaining high CO comes from studies that found higher levels of cardiac index (CI), DO₂, and VO₂ in patients with septic shock who survived than in those who died [1,2]. However, other studies failed to find a statistically significant difference in these parameters between survivors and nonsurvivors from septic shock [3–5], and one study found VO₂ to be significantly higher in patients with confirmed or suspected sepsis who died, as compared with those who survived [6]. Even assuming that survivors do have higher levels of CI, DO₂, and VO₂ than do nonsurvivors, the question is whether the higher levels of CI, DO₂, and VO₂ actually improve survival or are just markers for patients who are more likely to survive.

Does oxygen consumption increase with increasing oxygen delivery?

In the initial studies showing that an increase in DO₂ is associated with an increase in VO₂ (suggesting that a tissue oxygen debt exists), both DO₂ and VO₂ were calculated using the Fick principle for CO [7–9]. However, if a measured variable is used to determine two parameters, errors in measurement may 'couple' the calculations (i.e. although there may appear to be a relationship between the variables, one may not exist at all) [10]. Hemoglobin, CO, arterial oxygen saturation, and arterial oxygen tension are the shared variables used in calculating both DO₂ and VO₂. To avoid mathematical coupling, it has been suggested that VO₂ be calculated by a
different method from that used for \( \text{DO}_2 \). Four subsequent studies in septic patients using independent methods to calculate the parameters found no correlation between \( \text{DO}_2 \) and \( \text{VO}_2 \) \cite{11–14}, although one study did show a correlation \cite{15}. Thus, there is controversy regarding whether maintaining a high \( \text{CO} \) will result in the desired increase in \( \text{VO}_2 \).

Should an increase in oxygen delivery be the target for treatment?

The studies advocating treatment to achieve supranormal cardiorespiratory values have generally used increased \( \text{DO}_2 \) as the goal of therapy. However, the calculated \( \text{DO}_2 \) only reflects the amount of oxygen ‘dispatched’ from the ventricle into the aorta, rather than the actual delivery of oxygen to the respiring tissues. Thus, it is possible that tissue oxygen deficit could occur despite the presence of a normal or even an elevated \( \text{DO}_2 \). In an experimental model of endotoxic shock in pigs \cite{16}, norepinephrine (noradrenaline) was used to increase mean arterial pressure (MAP) from 52 to 77 mmHg in stages. Despite a dose dependent increase in \( \text{CI} \) and \( \text{DO}_2 \), splanchnic oxygen delivery, jejunal microvascular blood flow and renal blood flow increased during the first, but not the second, increment in MAP.

**Does increasing cardiac output/oxygen delivery improve outcome in sepsis?**

Seven randomized controlled trials have looked at patient outcome with increased \( \text{CO} \) and \( \text{DO}_2 \) in patients with sepsis or septic shock (Table 1). Of these, four studies, predominantly involving patients with sepsis, found no difference in overall survival in the treatment and control groups \cite{17–20}. One study, conducted in 762 critically ill patients, found no difference in overall mortality between the protocol and control groups, and neither was there any difference in mortality in the subgroup of patients with sepsis \cite{21}. Subgroup analysis of patients in whom hemodynamic targets were achieved revealed similar mortality rates. Mortality was significantly increased in the treatment group in one trial \cite{22}, despite significantly higher \( \text{CI} \) and \( \text{DO}_2 \) in the treatment group. Only one study found a survival benefit, but only in the subgroup of patients between the ages of 50 and 75 years \cite{23}; overall mortality data were not given in the report.

A number of the studies \cite{17–19}, with no overall mortality benefit in the protocol groups, subsequently compared the subgroup of protocol patients who achieved high \( \text{CI} \) and \( \text{DO}_2 \) with the subgroup of control patients with normal or low \( \text{CI} \) and \( \text{DO}_2 \) (thus excluding protocol patients with low \( \text{CI} \) and \( \text{DO}_2 \) and control patients with high \( \text{CI} \) and \( \text{DO}_2 \)); they found lower mortality in the former subgroup. Although the authors suggested that this adds to the evidence that a high \( \text{DO}_2 \) should be targeted, this finding more likely represents a

### Table 1

**Randomized controlled trials of high cardiac output in patients with sepsis**

| Ref. | Year | No. of patients | Type of patients | Protocol target | Mortality (%) | Comments |
|------|------|-----------------|------------------|----------------|--------------|----------|
|      |      |                 |                  |                | Protocol     | Control  | \( P \) |
| [17] | 1992 | 51              | Septic shock     | \( \text{CI} \geq 6.0 \) | 72           | 50       | 0.14     |
| [18] | 1993 | 67              | Medical and surgical | \( \text{DO}_2 > 600 \) | 34           | 34       | NS       |
| [22] | 1994 | 100             | Medical and surgical | \( \text{CI} > 4.5, \text{DO}_2 > 600, \text{VO}_2 > 170 \) | 54           | 34       | 0.04     |
| [21] | 1995 | 762             | Medical and surgical | Protocol group 1: \( \text{CI} > 4.5 \) Protocol group 2: \( \text{SvO}_2 > 70\% \) | 48.4         | 52.1     | 0.64     |
|      |      |                 |                  |                | 48.6         |          |          |
| [19] | 1995 | 89              | Surgical patients | \( \text{DO}_2 > 599 \) | NA           | NA       | NS       |
| [23] | 1998 | 105             | Surgical patients (99 with sepsis) | \( \text{DO}_2 > 600 \) | 9            | 12       | 0.01     |
|      |      |                 |                  |                | 12           | 11       | 0.99     |
| [20] | 1999 | 63              | Severe sepsis or septic shock | \( \text{DO}_2 > 600 \) | 74           | 66       | 0.46     |

\( \text{CI} \), cardiac index; \( \text{DO}_2 \), oxygen delivery; NA, not available; NS, not significant; \( \text{VO}_2 \), oxygen consumption.
pathophysiology of septic patients in whom DO$_2$ is already the dependence of VO$_2$ on DO$_2$ may not be important in the estimates based on pooled data. These findings suggest that first time in individual patients) was much lower than previous

In a study conducted in humans with septic shock, norepinephrine infusion resulted in significant increases in renal blood flow without always affecting the CO. Endotoxemic dogs had significantly lower arterial pressure and renal blood flow than controls. Infusion of norepinephrine on the renal vasculature in endotoxemic dogs. Bellomo and coworkers [25] studied the effects of norepinephrine infusion resulted in significant increases in arterial pressure and renal blood flow without always affecting the CO.

Thus, the overwhelming evidence from randomized controlled trials does not support the hypothesis that maintaining high CO and DO$_2$ improves outcome, and at least one study suggests that this practice may even increase mortality.

**Do septic patients have higher critical oxygen delivery?**

Another reason for maintaining higher CO and DO$_2$ offered by proponents of this strategy is that patients with sepsis may have a higher critical DO$_2$ level (i.e. the level of DO$_2$ below which metabolism changes from aerobic to anaerobic). However, Ronco and coworkers [13] measured DO$_2$ (using the Fick equation) and VO$_2$ (by indirect calorimetry) in nine septic and nine nonseptic critically ill patients. Those investigators found no difference in critical DO$_2$ threshold, critical oxygen extraction ratio, and maximal oxygen extraction ratio between the septic and nonseptic patients. Furthermore, the critical DO$_2$ (determined for the first time in individual patients) was much lower than previous estimates based on pooled data. These findings suggest that the dependence of VO$_2$ on DO$_2$ may not be important in the pathophysiology of septic patients in whom DO$_2$ is already well above the critical DO$_2$.

**Adequate vascular pressure versus high cardiac output in septic patients**

MAP and systemic vascular resistance have been shown to be determinants of mortality in patients with septic shock. In a retrospective study [24], hemodynamic variables in septic shock patients who died were compared with those in patients who survived. Both MAP and systemic vascular resistance values were significantly lower in patients who died, but CI values were similar in both groups.

Bellomo and coworkers [25] studied the effects of norepinephrine on the renal vasculature in endotoxemic dogs. Endotoxemic dogs had significantly lower arterial pressure and renal blood flow than controls. Infusion of norepinephrine, in both control and endotoxemic dogs, resulted in significant increases in both arterial pressure and renal blood flow without always affecting the CO.

In a study conducted in humans with septic shock, norepinephrine infusion resulted in significant increases in MAP, urine output, and creatinine and osmolar clearance, without an associated increase in CI [26]. Martin and coworkers [27] found that norepinephrine significantly increased both MAP and DO$_2$ in septic shock patients. CI, however, did not increase significantly in these patients. Levy and coworkers [28] documented the hemodynamic effects of norepinephrine over time in patients with septic shock. Administration of norepinephrine was associated with a significant and persistent increase in both MAP and DO$_2$. The CI increased initially but then dropped to baseline without an accompanying reduction in DO$_2$.

Rivers and coworkers [29] randomized septic patients to 6 hours of early goal-directed therapy or standard therapy. The targets of goal-directed therapy were a central venous pressure ≥8 mmHg, MAP ≥65 mmHg, urine output ≥0.5 ml/kg per hour, and central venous oxygen saturation ≥70%. In the first 6 hours, patients in the treatment group received significantly higher volumes of fluids and a significantly higher number of patients received dobutamine and red blood cell transfusions. At the end of 6 hours, patients in the treatment arm had significantly higher central venous pressure, MAP, and central venous oxygen saturation. Both 28-day and 60-day mortality rates were significantly lower in the treatment arm. Because more than one intervention was involved and because hemodynamic data from pulmonary artery catheterization were not available, it is difficult to pinpoint what specific factor resulted in the improved outcome. One possible explanation is that achieving a higher MAP alone in the treated patients resulted in higher perfusion pressures and better perfusion, thus reducing tissue hypoxia.

Phenylephrine, a selective $\alpha_1$ agonist, has been shown to improve blood pressure, DO$_2$, and VO$_2$ in septic patients [30]. In a more recent study [31], increasing doses of phenylephrine in septic patients were shown to result in a linear increase in MAP without a significant increase in CI. Although overall there was no significant increase in DO$_2$ and VO$_2$, clinically significant increases (>15%) in VO$_2$ were seen in 8 out of 10 septic patients, with an average increase of 38%. Clinically significant increases in DO$_2$ were only seen in three patients (average increase 42%). Another study compared the effects of various doses of dopamine and dobutamine on renal function in critically ill patients [32]. Dopamine resulted in significant increases in MAP, diuresis, creatinine clearance, and fractional excretion of sodium. During dopamine infusion, there was a significant correlation between MAP and creatinine clearance. However, dobutamine infusion, despite resulting in a significantly higher increase in CI than with dopamine, had no effect on MAP or on any of the renal variables.

Thus, there is adequate evidence to support the opinion that maintaining an adequate vascular pressure may be more important than maintaining a higher than normal CO in patients with septic shock.
Conclusion
In conclusion, the available data do not support the targeting and maintenance of supranormal CO, DO2, or VO2 outside of an approved, controlled clinical trial.

Competing interests
None declared.

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