

## 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 ( $DO_2$ ) and oxygen consumption ( $VO_2$ ), decrease any oxygen debt present, and potentially improve survival. However, the tissue extraction of needed oxygen is maintained even at very low levels of  $DO_2$ . Furthermore,  $VO_2$  increases with increasing  $DO_2$  only up to a point. Thereafter, subsequent increases in  $DO_2$  do not result in any further increase in  $VO_2$  (Fig. 1). Attempts to increase the  $DO_2$  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?

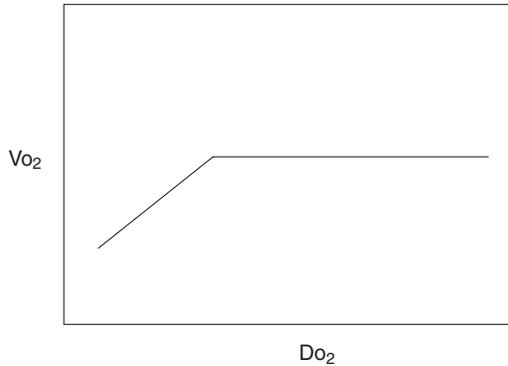
The rationale for maintaining high CO comes from studies that found higher levels of cardiac index (CI),  $DO_2$ , and  $VO_2$  in patients with septic shock who survived than in those who died [1,2]. However, other studies failed to find a statistically

significant difference in these parameters between survivors and nonsurvivors from septic shock [3–5], and one study found  $VO_2$  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,  $DO_2$ , and  $VO_2$  than do nonsurvivors, the question is whether the higher levels of CI,  $DO_2$ , and  $VO_2$  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  $DO_2$  is associated with an increase in  $VO_2$  (suggesting that a tissue oxygen debt exists), both  $DO_2$  and  $VO_2$  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  $DO_2$  and  $VO_2$ . To avoid mathematical coupling, it has been suggested that  $VO_2$  be calculated by a

**Figure 1**



Relationship between oxygen consumption ( $VO_2$ ) and oxygen delivery ( $DO_2$ ).

different method from that used for  $DO_2$ . Four subsequent studies in septic patients using independent methods to calculate the parameters found no correlation between  $DO_2$  and  $VO_2$  [11–14], although one study did show a correlation [15]. Thus, there is controversy regarding whether maintaining a high CO will result in the desired increase in  $VO_2$ .

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

The studies advocating treatment to achieve supranormal cardiorespiratory values have generally used increased  $DO_2$  as the goal of therapy. However, the calculated  $DO_2$  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  $DO_2$ . In an experimental model of endotoxic shock in

pigs [16], norepinephrine (noradrenaline) was used to increase mean arterial pressure (MAP) from 52 to 77 mmHg in stages. Despite a dose dependent increase in CI and  $DO_2$ , 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 CO and  $DO_2$  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 [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 [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 [22], despite significantly higher CI and  $DO_2$  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 [23]; overall mortality data were not given in the report.

A number of the studies [17–19], with no overall mortality benefit in the protocol groups, subsequently compared the subgroup of protocol patients who achieved high CI and  $DO_2$  with the subgroup of control patients with normal or low CI and  $DO_2$  (thus excluding protocol patients with low CI and  $DO_2$  and control patients with high CI and  $DO_2$ ); they found lower mortality in the former subgroup. Although the authors suggested that this adds to the evidence that a high  $DO_2$  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 (%)		P	Comments
					Protocol	Control		
[17]	1992	51	Septic shock	CI $\geq$ 6.0	72	50	0.14	
[18]	1993	67	Medical and surgical	$DO_2 > 600$	34	34	NS	52 patients with sepsis
[22]	1994	100	Medical and surgical	CI $> 4.5$ , $DO_2 > 600$ , $VO_2 > 170$	54	34	0.04	72 patients with sepsis
[21]	1995	762	Medical and surgical	Protocol group 1: CI $> 4.5$ Protocol group 2: $SvO_2 > 70\%$	48.4 48.6	52.1	0.64	No difference in mortality in the subgroup with sepsis
[19]	1995	89	Surgical patients	$DO_2 > 599$	NA	NA	NS	Majority with sepsis
[23]	1998	105	Surgical patients (99 with sepsis)	$DO_2 > 600$	9 12	12 11	0.01 0.99	Subgroup 50–75 years Subgroup $> 75$ years
[20]	1999	63	Severe sepsis or septic shock	$DO_2 > 600$	74	66	0.46	

CI, cardiac index;  $DO_2$ , oxygen delivery; NA, not available; NS, not significant;  $VO_2$ , oxygen consumption.

prediction of better survival in patients who have the ability to generate a higher  $DO_2$ . The fact that control patients who generated high CI and  $DO_2$  despite conservative treatment, also had lower mortality, supports the latter explanation.

Supporters of high CO also argue that many patients in the treatment arms of these trials did not achieve the target values. Rather than inadequate treatment, it is more likely that the patients who did not achieve target values had poorer cardiovascular reserves and prognosis, and were incapable of achieving the target values.

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  $\geq 8$  mmHg, MAP  $\geq 65$  mmHg, urine output  $\geq 0.5$  ml/kg per hour, and central venous oxygen saturation  $\geq 70\%$ . 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, DO<sub>2</sub>, or VO<sub>2</sub> outside of an approved, controlled clinical trial.

## Competing interests

None declared.

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