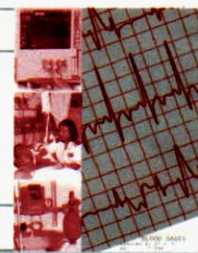


Goal directed resuscitation — the state of play in 2004



Department of Critical Care and Surgical ICU, Groote Schuur Hospital, and Department of Surgery, University of Cape Town
W L Michell, FFA (SA) (Critical Care)

Patients with septic shock have an improved survival if they are resuscitated within 6 hours of presentation to a central venous oxygen saturation of at least 70%. Oxygen delivery to tissues is determined by cardiac output, haemoglobin and arterial oxygen saturation. Strategies to improve oxygen delivery include intravenous fluids, blood transfusion and inotropic drugs; however, these therapies all carry inherent risks. Balancing these risks with the goal of achieving rapid restoration of tissue oxygenation is the key to successful therapy in shock.

More than 30 years ago Shoemaker *et al.* popularised the concept of 'optimal goals' in the resuscitation of haemodynamic shock. The concept was simple — shocked patients acquire an 'oxygen debt' that has to be repaid in order to ensure survival. Shoemaker and co-workers retrospectively found that survivors of haemorrhagic shock achieved greater than normal oxygen delivery and consumption while patients who died could not meet these oxygen flux requirements. In a prospective study² of surgical patients, he later showed that targeting 'supra-normal' goals of oxygen delivery (DO_2) and consumption (VO_2) resulted in dramatically improved survival.

Using a variety of endpoints of resuscitation, subsequent studies had less impressive outcomes. A large study by Gattinoni *et al.*³ including a mixed population of ICU patients showed no survival advantage, and in another study by Hayes *et al.*⁴ mainly of elderly patients with septic shock, those randomised to optimal goal therapy using fluids and dobutamine actually had an increased mortality. However, in both of these studies, goal-directed therapy was introduced fairly late in the course of the illness. While Shoemaker's hypothesis held true in trauma and surgical patients, septic shock seemed different.

Recently Rivers and colleagues⁵ showed convincingly that in septic shock, early goal-directed therapy, performed in the emergency room, dramatically reduced mortality. What was different about the Rivers study?

There are several possible explanations for the difference between positive and negative studies. In the first place, the therapies used to improve oxygen delivery, namely intravenous fluids, inotropes and blood

transfusion, all have known deleterious effects and it could be that in some population groups the disadvantages of these treatments outweigh the benefit of achieving a higher DO_2 . Secondly, the endpoints chosen to assess the adequacy of oxygen delivery may not be appropriate for all patients. Lastly the timing of the intervention may have an impact on the outcome.

Oxygen delivery (Table I)

The hallmark of shock is inadequate tissue perfusion. Cells become anoxic, cease to function and eventually begin to die off. The heart and brain are initially protected by the sympathetic nervous system which preferentially shunts blood to them and away from other organs.⁶ Death in shock occurs early when myocardial ischaemia causes a further decrease in cardiac output, leading to a rapid downward spiral and cardiac arrest. On the other hand, patients with prolonged, compensated shock can appear to be fully resuscitated and can eventually achieve normal homodynamic parameters but the hidden toll of

Table I. Oxygen delivery and consumption formulae⁷

$DO_2 = CaO_2 \times CO$
$CaO_2 = Hb \times 1.39 \times 10 \times SaO_2 + 0.021 \times PaO_2$
$VO_2 = CaO_2 - CvO_2$
$DO_2 =$ oxygen delivery (ml/min)
$VO_2 =$ oxygen consumption (ml/min)
CO = cardiac output (l/min)
$CaO_2 =$ arterial oxygen content (ml/100 ml)
$CvO_2 =$ mixed venous oxygen content (ml/100 ml)
Hb = haemoglobin concentration (g/dl)
$SaO_2 =$ arterial oxygen saturation (%)
$PaO_2 =$ arterial oxygen partial pressure (Kpa)

prolonged ischaemia to the kidneys, gut and liver sets the stage for a gradual decline into multiple organ failure.

Oxygen delivery can be manipulated by three variables: cardiac output (CO), haemoglobin (Hb) and oxygen saturation (SaO₂). (The amount of dissolved oxygen in blood is determined by the arterial oxygen partial pressure (PaO₂) but too small to be significant.)⁷

Oxygenation

An oxygen saturation of close to 100% is usually the easiest objective to achieve in early septic shock and also the least controversial therapeutic intervention. It is usually quite simple, but vitally important, to maintain adequate oxygenation with the aid of mechanical ventilation, positive end expiratory pressure (PEEP) or an increased inspired oxygen fraction (FiO₂). It should be borne in mind that high levels of PEEP can reduce cardiac output. There is no advantage in increasing the PaO₂ to more than that necessary to achieve an SaO₂ of 95 - 100%.

Haemoglobin

The optimal Hb during resuscitation is controversial. *In vitro* studies suggest that oxygen delivery is maximal at an Hb of approximately 10 g/dl.⁸ Below this value the increased cardiac output due to decreased blood viscosity is outweighed by the reduced oxygen content of the blood. Presumably a normal Hb of about 15 g/dl has evolved to give a survival advantage in the event of haemorrhagic shock or hypoxia. One must bear in mind that transfused blood, as opposed to the patient's own blood, has distinct disadvantages. Apart from the well-known hazards of infection, transfused red blood cells (RBCs) have a storage lesion that makes them less deformable and also less able to give up oxygen to the tissues.⁹ This reduces both capillary perfusion and cellular oxygenation. Several studies have failed to show any increase in oxygen consumption shortly after blood transfusion.^{10,11} Furthermore, there is plenty of evidence that blood transfusion depresses cellular immunity and this could add to the already impaired immune state of critically ill patients.¹² The Canadian Trials Group showed that a transfusion trigger of 7 g/dl was at least as good as, and probably better than, 10 g/dl in stable, anaemic, critically ill patients.¹³ In patients with shock the situation may well be different. In their work Shoemaker *et al.*¹ suggest a minimum Hb of 12 g/dl for resuscitation. In the Rivers study⁵ patients in the treatment group received RBC to a haematocrit of at least 30% (equivalent to an Hb of 10 g/dl) if they did not achieve adequate tissue oxygenation.

Cardiac output

The cardiac output component of the oxygen delivery equation offers the most scope for manipulating oxygen delivery. Cardiac output can be maximised by ensuring an adequate preload, through the administration of

appropriate volumes of intravenous fluid, improving myocardial contractility with inotropic agents, and occasionally, reducing after-load using vasodilators if the blood pressure allows.

In severe sepsis increased permeability of the vascular endothelium leads to a rapid loss of albumin and fluid from the intravascular compartment.¹⁴ The first step in resuscitation is the restoration of an adequate intravascular volume. Traditionally the central venous pressure and pulmonary capillary wedge pressure have been used to gauge the adequacy of volume replacement. Recently more dynamic, and less invasive methods such as the pulse pressure variation¹⁵ and the haemodynamic response to leg raising¹⁶ have been shown to be more useful. Too much fluid however worsens pulmonary function and the consequent oedema may reduce tissue oxygenation.

Inotropic agents become necessary in septic shock when volume replacement alone is insufficient. It is important to remember that while a reasonable blood pressure is important for organ perfusion, improved cardiac output is the main object of the exercise. In Europe and North America a combination of the beta stimulant dobutamine and the predominantly alpha stimulant noradrenaline is the most widely used and most studied regimen.^{17,18} Unfortunately noradrenaline is not registered in South Africa and adrenaline is therefore used most frequently. Dopamine is virtually obsolete because it does not provide renal protection¹⁹ and also has neuro-endocrine side effects.²⁰

Unfortunately inotropes are a two-edged sword. They increase oxygen consumption of all tissues, especially the myocardium, potentially impairing the chief goal of restoring the cellular oxygen delivery-supply ratio. In addition, inotropes with vasoconstrictor properties can decrease gut, liver and renal perfusion.²¹

Recently, relatively low doses of corticosteroids have been shown to reduce mortality in patients with septic shock requiring inotropes. The benefit is most noticeable in patients with a poor endogenous adrenal response, although it is not always practical to test for this.²²

Which optimal goal?

The above measures for managing septic shock are well established and uncontroversial. The issue that remains to be debated is what parameter of oxygen delivery should be used to target the resuscitation endpoint. The logical approach would be to measure oxygen consumption — but this requires the use of either a metabolic cart or a pulmonary artery catheter.²³ The latter is notoriously inaccurate.²⁴ On reflection, Shoemaker's idea of a particular oxygen delivery and oxygen consumption goal may only represent the average survival values in a group of patients. Some patients would be under-resuscitated at this endpoint

and others over-resuscitated — possibly resulting in the increased mortality of the Hayes study.⁴

An endpoint that measures cellular hypoxia in an individual patient would seem to be more useful. The mixed venous oxygen saturation — taken from a pulmonary artery catheter — is a good index of global hypoxia and correlates well with cardiac output in both haemorrhagic and cardiogenic shock.⁷ In septic shock, mixed venous saturation can be normal or increased in the presence of tissue hypoxia because of peripheral microvascular shunting and impaired cellular oxygen uptake.²⁵ Other surrogates of global tissue hypoxia are base deficit and arterial lactate.^{26,27} While the response to therapy of these parameters and their trend towards normal are useful predictors of survival they have not been shown to improve outcome when used as resuscitation endpoints.

Of course, global tissue hypoxia only reflects the average hypoxic state of the body and with a normal mixed venous oxygen saturation or acid-base status it is still possible that some organs are under-resuscitated. Using gastric tonometry to assess the adequacy of gut perfusion was an attractive idea given the important role gut dysfunction may play in causing multiple organ failure.²⁸ Unfortunately, a prospective trial using tonometrically guided resuscitation failed to show an improvement in outcome.²⁹

The use of central venous oxygenation, as in the Rivers study,⁵ has the advantage of being a relatively easy value to obtain, as all patients with septic shock require a central line. This study used continuous monitoring of central venous saturation using a special fibre-optic catheter. In the absence of such a device, serial measurements using a blood gas analyser — available in any self-respecting ICU or emergency department — should be just as efficacious.

Conclusion

The most important point made by the Rivers study is that if goal-directed therapy is to benefit patients in septic shock, it should be used early, i.e. within the first 6 hours of presentation. The challenge is to develop patient management systems that enable patients with severe sepsis to be recognised early and for there to be no delay in resuscitation to an optimal endpoint.

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