The heart and circulation in severe sepsis

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History and epidemiology

In the context of critical care, sepsis refers to the systemic response to an infection or to circulating bacterial products, rather than the presence of an infection per se. The ‘classic’ cardiovascular signs seen with severe sepsis due to Gram-negative bacteraemia were first described by Waisbren in 1951. He described the well known hyperdynamic state, with full bounding pulses, flushing, fever, oliguria and hypotension. He also described a second smaller group of patients who were pale, clammy, profoundly hypotensive with low volume pulses, and who appeared much more ill. This group may have been simply under-resuscitated, and as more detailed studies of the cardiovascular system in sepsis became possible, the importance of achieving an adequate circulating volume to maintain an adequate cardiac output became clear. However, it also became apparent that some patients did not significantly increase their cardiac output in response to expansion of their circulating volume, suggesting they had some element of myocardial dysfunction. In a study performed in fully resuscitated young patients with septic shock, Parker and colleagues demonstrated significant reductions in both stroke volume and ejection fraction compared with non-septic control patients from the intensive care unit (ICU), even when their total cardiac output was normal. A similar study showed both regional and global abnormalities of left ventricular function in patients with sepsis, in the absence of pre-existing ischaemic heart disease, and both confirmed earlier studies that had shown reduced inotropy in patients with severe sepsis.

This myocardial depression was not due to myocardial ischaemia, as coronary blood flow and coronary sinus lactate levels were normal in patients with septic shock, and the concept of a myocardial depressant factor that circulated in septic patients gained popularity. In spite of enormous advances in our understanding of the cellular and biochemical effects of severe sepsis, it remains unclear exactly what this myocardial depressant factor is, or even if it is a single entity. A small uncharacterized protein has recently been described in animal experiments, but other candidates include nitric oxide, cyclic guanosine monophosphate and tumour necrosis factor alpha (TNFα). Diastolic dysfunction due to myocardial oedema and reduced left ventricular compliance might also play a role.

In the peripheral circulation, a reduction in total peripheral vascular resistance (the ‘systemic vascular resistance’ or SVR) is the norm in sepsis, and it is the reflex response to the resulting hypertension that causes the increased cardiac output seen in the ‘classic’ picture of septic shock. Treatments aimed at increasing the SVR and hence arterial pressure remain one of the mainstays of ICU care of these patients.

Although most of the early case series of severe sepsis cited above used positive blood cultures (bacteraemia) as selection criteria, there are many patients who have all the features of severe sepsis but in whom no bacteraemia can be demonstrated. This has arguably become more common as antibiotic administration before ICU admission has increased, along with a shift towards less direct admissions. Using haemodynamic criteria to decide which patients have severe sepsis is cumbersome and impractical. In 1991, Bone suggested a set of definitions based on the combination of a clinically diagnosed infection and measures of organ dysfunction, which were largely endorsed by the American professional critical care organizations the next year. These ‘Bone criteria’ were of little practical value at the bedside but, crucially, provided a standardized set of diagnostic criteria that were used both in epidemiological surveys and as entry criteria for interventional studies. Though the definitions have been modified over the last 13 yr, the criteria used in recent large-scale epidemiological and interventional studies still retain the essential elements that Bone suggested.

In the UK, severe sepsis remains a major problem in ICUs. It has been estimated that in 1997, 10 016 deaths occurred in ICU admissions in England and Wales in
patients who met the current severe sepsis criteria in the first 24 h in the ICU, representing 24 deaths per 100 000 population per yr, or about 6% of all UK deaths. Patients with severe sepsis on admission to an ICU had a 46% hospital mortality. These figures represent the total number of patients who die having presented with severe sepsis. The number dying from severe sepsis (the attributable mortality of severe sepsis) is unknown but clearly is important as it represents the pool of patients who might benefit from treatment for severe sepsis per se (such as activated protein C) rather than treatments directed at the underlying cause of the sepsis.

The peripheral circulation in sepsis

Vasodilation of the peripheral (systemic) resistance vessels occurs in severe sepsis, to the extent that the SVR may be reduced to a quarter of the normal value. The vasodilatation is not uniform across tissue beds nor is it simply an increase in the baseline vessel calibre. In severe sepsis, the term ‘vasoplegia’ is often applied to the vasculature, suggesting that rhythmic vasomotion is paralysed. This is not the case however: small vessels in septic patients do exhibit vasomotion, although the pattern of frequency and amplitude is altered. Altered responses to the hypoxaemia and acidosis caused by a tourniquet (reactive hyperaemia) are also found: the circulation exhibits less reflow during the hyperaemic period in septic patients. The vasculature of septic patients becomes progressively less responsive to sympathomimetic pressor agents. Yet the exact cause of this vasodilatation and pressor resistance remains to be determined.

It has been known for over a century that bacterial cell wall products can cause the cardiovascular signs of severe sepsis. In 1899, Romberg and colleagues reproduced the vascular collapse seen in severe infections by injecting extracts derived from Gram-negative organisms, which we now know consisted largely of endotoxin (lipopolysaccharide; LPS). Although purified (organism-free) endotoxin can reproduce many of the features of Gram-negative shock, significant interspecies differences exist, hinting at different host responses depending on the activity of intermediate pathways. The importance of the host response was confirmed by an experiment in which genetically endotoxin-resistant mice were rendered sensitive following engraftment of lymphoid tissue from sensitive strains.

In humans, circulating endotoxin binds to the LPS binding protein, and the complex is recognised by CD14 receptors on the surface of immune cells. This in turn triggers an inflammatory cascade, with the release of both pro- and anti-inflammatory mediators and cytokines. This complex network of mediators is responsible for the clinical manifestations of severe sepsis, including the peripheral vasodilatation. The mediator that has received most attention as the ‘culprit’ vasodilator in sepsis is nitric oxide.

Nitric oxide is produced from the cationic amino acid L-arginine by nitric oxide synthases (NOS). Three main isoforms of this enzyme are recognized: a neuronal form which synthesizes nitric oxide as a neurotransmitter; a constitutive (endothelial) form which is responsible for basal nitric oxide production, and an inducible form (iNOS), which is expressed after cytokine stimulation and sepsis. Constitutive NOS (cNOS) is found in vascular endothelium, platelets, some renal cells, myocardium, endocardium and other sites. In health, cNOS is generally involved only in low-output nitric oxide pathways concerned with homeostasis, especially matching blood vessel calibre to blood flow. The cNOS activity may be controlled by a negative-feedback mechanism. The iNOS is not normally present in significant quantities in the vessels. It is expressed after stimulation with pro-inflammatory cytokines such as TNFα, interleukin (IL)-1, IL-2, IL-6 and interferon-gamma, which are all part of the inflammatory cascade triggered by endotoxin. The iNOS is a high-output pathway, producing large quantities of nitric oxide, and is insensitive to feedback control.

Nitric oxide is a powerful vasodilator, and so this excess nitric oxide production might be the cause of the vasodilatation seen in septic shock. Excess nitric oxide might also explain some of the other features of severe sepsis. Most patients with severe sepsis develop a lactic acidosis even in the presence of a high cardiac output and other indicators of adequate tissue perfusion, such as a high mixed venous oxygen saturation or content. Although there are several mechanisms by which this could occur, one possible cause could be partial failure of oxidative metabolism in mitochondria. Excess nitric oxide (which binds avidly to a range of metalloproteins) might be inactivating the haem-containing cytochrome enzymes involved in oxidative metabolism. There is a body of laboratory evidence to support this theory, but more importantly, a recent clinical study using serial muscle biopsies from patients with severe sepsis showed both a reduction in mitochondrial function and a relationship between nitric oxide metabolite concentrations, mitochondrial function and pressor requirements. Excess nitric oxide production in the myocardium may also be the cause of the myocardial dysfunction seen in severe sepsis, as mentioned above.

Although this theory is attractive, it is far from watertight. Many animal cells, especially those derived from rodents, can be made to express iNOS and produce large amounts of nitric oxide in vitro using appropriate cytokine mixtures, and in animal models of severe sepsis, nitric oxide metabolites (nitrates) increase 7–20 fold. In contrast, nitrate levels in patients with sepsis are usually modestly increased to 2–3 times control and although iNOS can be demonstrated in human tissues that are chronically inflamed, such as the colonic mucosa in inflammatory bowel disease or the synovium in rheumatoid arthritis, there is no clear evidence to date of iNOS expression in the vascular tissues of patients with sepsis. There is some evidence to...
suggest that even in animal models, the haemodynamic changes that occur with sepsis or endotoxaemia are not all due to induction of high-output NOS isoforms. Transgenic animals lacking the gene for iNOS do not increase their nitrate production in response to endotoxin stimulation but still die, and the haemodynamic effects are only mildly attenuated. \( ^{27,50} \)

The hypotension of septic shock has been reversed using analogues of L-arginine such as monomethylarginine (L-NMMA) and nitroarginine methyl ester (L-NAME) as competitive blockers of NOS in both animal studies\(^ {32} \) and human sepsis.\(^ {61,62} \) Although these studies all show an increase in arterial pressure with NOS inhibition, some animal studies have indicated an increased mortality. The phase III clinical trial of L-NMMA in septic shock\(^ {61} \) was stopped because of excess mortality in the treatment group, which occurred in spite of a reduction in pressor requirements. This increase in mortality seen in both human and animal studies may result from total blockade of nitric oxide synthesis, which inhibits not only the excessive nitric oxide production (from iNOS) but also the basal production (from cNOS), resulting in excessive vasoconstriction and a reduction in cardiac output. In the phase III clinical trial of L-NMMA, the excess mortality appeared to be due to cardiac failure. Whether this was a direct effect of nitric oxide inhibition in the myocardium or the combination of impaired cardiac function and suddenly increased afterload is uncertain. Certainly caution will be required if another highly effective vasoconstrictor with no inotropic actions is trialled in septic patients.

Nitric oxide is not the only diatomic gas that binds to metalloproteins. Carbon monoxide’s high affinity for haemoglobin is well known, but carbon monoxide also binds to cytochromes; this is thought to be the mechanism behind neurological changes in carbon monoxide poisoning. Endogenous carbon monoxide is produced by the heme oxygenase family of enzymes, which catalyse the first and rate-limiting step in haem degradation. The oxidation of haem generates iron, biliverdin and carbon monoxide. There are three known isoforms of heme oxygenase (HO-1, HO-2 and HO-3). HO-1 is the inducible form, and is upregulated by an increase in free haem in haemolytic diseases and other conditions. However, HO-1 is also an acute phase protein and responds by induction to a wide variety of stimuli, including sepsis, cytokines and nitric oxide. It has been suggested that the biliverdin produced by HO-1 acts as an inducible defence against oxidative stress.

The excess carbon monoxide produced by HO-1 induction can be detected in the exhaled breath (the only elimination pathway) and has been found to increase in critical illness.\(^ {22,47,67} \) As yet, no carbon monoxide measurements in a specific cohort of critically ill patients with sepsis have been reported, but carbon monoxide production does increase in pulmonary sepsis in ward patients.\(^ {55} \) Carbon monoxide activates soluble guanylate cyclase in the same way as nitric oxide, causing vascular relaxation. Carbon monoxide may also cause vascular relaxation by directly activating calcium-dependent potassium channels. That said, vasodilatation and hypotension are not the hallmarks of carbon monoxide poisoning, so these laboratory findings may not translate into clinically significant effects. At present it is unclear whether HO-1 and carbon monoxide are real culprits in sepsis, or minor players.\(^ {72} \)

Exogenous vasopressin has gradually gained popularity as a vasopressor drug in severe sepsis, usually in combination with norepinephrine or epinephrine. It is given in low doses to replace deficient endogenous production in severe sepsis, and at higher doses for additional vasoconstrictor effect. Normally, endogenous vasopressin is released from the axonal terminals of magnocellular neurones in the hypothalamus and mediates vasoconstriction via V1-receptor activation on vascular smooth muscle. The antidiuretic effect of vasopressin occurs via V2-receptor activation in the renal collecting duct system.

Severe sepsis was first thought to increase blood vasopressin concentrations\(^ {64} \) but later clinical studies showed this was just a transient effect and in septic shock vasopressin levels fall to very low levels compared with other causes of hypotension.\(^ {26,28,49} \) These low plasma levels of vasopressin are at least partly related to a depletion of vasopressin stores in the neurohypophysis.\(^ {50} \) Vasopressin infusion of 0.01–0.04 U min\(^ {-1} \) in patients with septic shock increases plasma vasopressin levels to those observed in patients with hypotension from other causes, such as cardiogenic shock, and reduces the need for other vasopressors.\(^ {56} \) In spite of the antidiuretic effects of vasopressin, the increased arterial pressure may increase urine output. Infusions in excess of these physiological levels may lead to adverse, likely vasoconstriction-mediated, events such as ischaemia of the extremities and gut hypoperfusion.\(^ {58} \) To date, clinical studies have been relatively small and have used surrogate outcomes, so a randomized controlled trial of vasopressin on clinical outcomes such as organ failure and mortality is needed.

As vasopressin levels are high in early sepsis at a point when vascular resistance is low, it is unlikely that vasopressin depletion is a primary cause of vasodilatation in sepsis, but it probably contributes in the later stages of the disease.

In 1988 the endothelin system was discovered. Endothelins are potent vasoconstrictors. Shortly after they were discovered, studies were started to determine if lack of endothelins caused the vasodilatation in severe sepsis. Paradoxically, a repeated finding was that endothelin plasma levels are increased in human sepsis\(^ {53,54,59,63} \) and this could be replicated in animal models.\(^ {34} \) Endothelin levels correlated with the severity of both the sepsis and the associated cardiac\(^ {43} \) and renal dysfunction. This release or overproduction of endothelin may occur as a consequence of endothelial injury by activated leucocytes and the infusion of catecholamines. As endothelins are important modulators of tissue blood flow, the excess release or
production might explain some of the inhomogeneity in the vasodilating effects of sepsis across different tissues. Thus, the drug bosentan, an endothelin blocker and hence a vasodilator, has shown some utility in maintaining splanchnic perfusion in animal studies of vasodilated sepsis.

Prostaglandins, leukotrienes and thromboxanes are metabolites of arachidonic acid, and are known to increase in concentration in the blood of patients with sepsis. They have a range of actions, including vasodilatation, leucocyte activation and damage to vascular endothelial cells, the specific effects depending on the specific prostaglandin. Prostaglandin and thromboxane concentrations correlate with the severity of organ failure in patients with severe sepsis. The production of prostaglandins depends on cyclo-oxygenase (COX) enzymes, the inducible form of which (COX-2) is upregulated in many inflammatory conditions, including sepsis. The wide availability of COX inhibitors and their clinical safety meant they were trialled early as possible modulators of the vascular disturbance in severe sepsis. Although early animal studies showed benefits with indomethacin, human studies of patients with severe sepsis failed to show any benefit with ibuprofen, and volunteer studies showed that the cardiovascular response to low-dose i.v. endotoxin administration was not ameliorated by ibuprofen. Again it seems unlikely that arachidonic acid metabolites are the culprit vasodilators. The cellular mechanism underlying the vasodilatation of severe sepsis still remains elusive.

**Treatment of the circulation in severe sepsis**

The core treatments for severe sepsis and the associated cardiovascular disturbances have changed little in the last 10–20 yr. Fluid, inotropes, pressors, targeted antibiotics and surgical drainage are still the mainstays of treatment. A detailed monologue on the evidence for various treatments, along with guidelines for haemodynamic support in sepsis has been published by the American professional critical care societies. The guidelines are useful but very general and reflect the lack of high-level rigorous research in these areas.

There are, however, two trials which suggest that major improvements in mortality in patients with severe sepsis are possible. Rivers and colleagues published a study of 263 patients with severe sepsis and septic shock treated in one centre in the USA. The essential elements of their treatment were early intervention (in the emergency department) and a protocol-driven resuscitation technique that used target values for physiological variables as end-points for resuscitation. This style of patient management is referred to as ‘goal-directed’ therapy. The primary goal was a haemoglobin oxygen saturation in right atrial blood (measured via a central venous line) of greater than 70%. The control group was a ‘usual treatment’ group, treated according to the attending physician’s usual practice. Hospital mortality was 30.5% in the goal-directed therapy group, compared with 46.5% in the control group, an absolute reduction of 16% and a relative reduction of 34.4%. This is, by the standards of critical care trials, an enormous treatment benefit, and would normally raise the suspicion of unnoticed bias in the study. However, the authors clearly and diligently reported their results and no bias was apparent from the published data.

The study used central venous blood to determine mixed venous saturation, rather than true mixed venous blood from the pulmonary artery. There are theoretical problems with this: depending on where the tip of the catheter is, desaturated blood from the inferior vena cava or more highly saturated blood from the superior vena cava will be sampled, and so true mixed venous blood sample will not be obtained. Presumably the simplicity of the approach, which did not require a pulmonary artery catheter, allowed earlier decision making and the benefits of this outweighed the theoretical problems associated with right atrial sampling.

The underlying concept behind the study of Rivers and colleagues is that the haemoglobin oxygen saturation in central or mixed venous blood reflects the balance between oxygen consumption and delivery, and that by improving the balance in favour of delivery, better tissue oxygenation and improved survival will result. Two other large studies have tested this concept in the past. A 100 patient randomized controlled trial in the UK showed that patients were actually harmed by a goal-directed approach using mixed venous oxygen saturation as a target, and a 762 patient multicentre study in Italy showed no difference in outcome with treatment guided by mixed venous oxygen saturation. Both these studies enrolled a heterogeneous group of critically ill adults, rather than just a group with severe sepsis. Two smaller studies in septic patients, using oxygen delivery as a goal, failed to show any benefit. So why did the study of Rivers and colleagues show such a marked treatment effect when the others did not? The major difference between their study and the other studies seems to be timing: all patients were enrolled and treated within a mean time (from admission) of 1.3 h, they were not already inpatients in an ICU at the time of enrollment and randomization. Compared with other studies of goal-directed treatment in sepsis, there were more patients, treatments were more heterogeneous in the study and control groups, and the end-points were simpler to determine and monitored continuously.

It would seem that simple treatments done early and well can have a major effect on mortality. There was, however, a bias in the Rivers study that did not appear in the manuscript but emerged when the data were presented at meetings. The principal investigators attended and directed treatment for the treatment group, but not for the usual treatment (control) group. So a more correct assessment of the Rivers study might be that simple treatments done early and well can have a major effect on mortality when directed by senior staff.
Most recently, another approach to treatment of the circulation in severe sepsis has shown a treatment benefit. A phase III randomized clinical trial of drotrecogin alfa (recombinant human activated protein C) in severe sepsis—the Protein C Worldwide Evaluation of Severe Sepsis (PROWESS) trial—showed a 6.1% absolute and 19.8% relative increase in survival in the treatment group compared with ‘usual-treatment’ controls. The PROWESS trial was an international multicentre fully blinded study. The entry criteria for the study included a systemic inflammatory response to an infection and at least one associated acute organ dysfunction. The primary end-point was death from any cause and was assessed 28 days after entry into the study. Subjects in the treatment arm received a continuous 96 h infusion of activated protein C, with no dose titration and interruption only for invasive procedures. The study fulfilled predetermined stopping rules at the second planned interim analysis because of a significantly lower mortality in patients receiving activated protein C when compared with the patients on placebo. A total of 1728 patients were recruited and 1690 patients actually received the drug or placebo. When analysed by patients receiving drug or placebo, a 6.1% absolute (19.8% relative) reduction in mortality 28 days after starting the infusion was noted (30.8% to 24.7%) in the treatment group. This difference was also maintained when the results were evaluated on a true intention-to-treat basis.

Drotrecogin alfa is the first licensed cogn, one of a new class of biologically derived drugs that influence the coagulation/inflammation cascade. It is produced by a genetically modified mammalian cell line. The precursor molecule is secreted into the culture medium and is then enzymatically cleaved to produce the active compound. The recombinant drug has the same amino acid sequence as the native human compound (activated protein C) but a different glycosylation pattern. Physiologically, activated protein C is known to have several major mechanisms that limit the microvascular injury seen in severe sepsis. By inhibiting Factors Va and VIIIa, activated protein C exerts an antithrombotic effect. It also inhibits plasminogen activator inhibitor-1 and limits the production of thrombin activatable fibrinolysis inhibitor, thereby increasing thrombolysis. Finally, by blocking leucocyte adhesion to selectins, pro-inflammatory cytokine release is inhibited and vessel permeability maintained.

The exact pathway by which the actions of activated protein C lead ultimately to a mortality benefit are not clear. A lot of the justification for the trial rested on data that suggested protein C deficiency was related to poor outcome in overwhelming sepsis, rather than on a clear link between the drug’s actions and an immediate haemodynamic or other benefit likely to save lives directly. However, it is generally believed that the combination of antithrombotic and thrombolytic actions decreases the microvascular thrombosis that occurs in severe sepsis, and promotes lysis of any thrombi formed. This would, presumably, lead to improved organ blood flow and perfusion, and improve survival by reducing or preventing organ failure. In addition, by preventing the expression of selectins and adhesion molecules on the endothelial cells, neutrophil margination and migration would be reduced, decreasing both vessel permeability and the inflammatory burden. Certainly, infusion of activated protein C does not produce a clinically recognizable improvement in global haemodynamics or a rapid reduction in inotrope and pressor requirements.

In spite of the drug’s obvious potential to cause bleeding, haemorrhagic complications did not occur any more frequently in the treatment group, though the tight trial exclusion criteria prevented patients at risk of bleeding from being recruited. In addition, the dosing schedule chosen was based on a pilot dose-ranging study in which activated partial thromboplastin time (APTT), which is increased by activated protein C, was monitored. The dose selected for the phase III study was one that minimized major changes in the APTT.

There is, however, a practical problem with the widespread use of activated protein C. It is a very expensive treatment—the drug cost per patient will be over seven times the UK average, and the infusion will increase the average daily drug cost over eleven fold whilst the infusion is running. If an oft-quoted estimate of 15% of the patients in ICUs being eligible for activated protein C is correct, giving all these patients the product would theoretically double a unit’s drug budget. Several cost-effectiveness studies have been carried out in various countries though as yet none has been published for the UK. The published studies cannot be used to estimate cost-effectiveness in the UK because of the different health-care systems studied and different costs used in the calculation. The National Institute for Clinical Excellence (NICE) has undertaken a review of activated protein C and will publish a UK cost-effectiveness study in due course. It would be interesting to see a comparable cost-effectiveness analysis of goal-directed treatment; the cost per quality adjusted life-year would probably be a lot less than the figure NICE will compute for activated protein C.

Summary

Severe sepsis is a major cause of mortality in critically ill patients. Although the haemodynamic patterns caused by the disease have been extensively characterized using a range of measurement techniques, at the cellular level the final mediator in the vasodilatation, cardiac dysfunction and disordered oxygen utilization has yet to be identified. Treatments based on modulating the inflammatory process are at last beginning to show promise, but possibly the best hope for new treatments in the short term needs to be based round changing the process of delivery and monitoring of our current core therapies.
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