REVIEW

Circulatory failure in septic shock

Nitric oxide: too much of a good thing?

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Septicaemia and accompanying septic shock account for a substantial number of hospital deaths, despite appropriate antibiotic and supportive therapy. In the United States an estimated 100 000 patients die from sepsis in hospital each year.¹ One of the characteristic features of septic shock is profound hypotension caused by a decrease in peripheral vascular resistance. This hypotension is unusually resistant to both volume replacement and vasoconstrictor agents. In the earliest stages of septic shock stroke volume and cardiac output are maintained or even increased; later, ventricular dilatation develops with a reduction in ejection fraction.²⁻⁴ If patients survive, ventricular size and function return to normal as the infection is controlled and circulatory function restored. Recently, important advances have been made in our understanding of the pathophysiology and treatment of this frequently lethal condition.

Gram negative bacteria account for approximately 30% of cases of septic shock.⁵ Bloodborne infection liberates endotoxin, the lipopolysaccharide component of the bacterial cell wall, into the circulation. Endotoxin and the organisms themselves activate host defense and inflammatory systems, including the complement, kinin, and coagulation cascades; the interleukins; tumour necrosis factor (TNF) and other endogenous mediators of inflammation; leucocytes; and platelets. These together generate the acute inflammatory response to bacteraemia. Although many inflammatory mediators are themselves vasoactive, recent work has shown that the hypotension and cardiac depression of septic shock are mediated by important changes within the vascular and cardiac muscle cells themselves.

Nitric oxide biology

Endothelium-derived factors, predominantly nitric oxide, modulate blood flow within the vasculature (for review see Moncada *et al.*).⁶ Nitric oxide, synthesised from the amino acid L-arginine by a constitutive nitric oxide synthase enzyme, is present in endothelial cells. It is released tonically in small amounts to act on adjacent vascular smooth muscle, causing relaxation and vasodilatation. This mechanism exists in health to regulate blood flow within tissue.^{6,7} Endothelium-derived nitric oxide also inhibits platelet adhesion and

aggregation, maintaining an antithrombotic luminal surface.

Nitric oxide synthase is also constitutively expressed in other cell types. These include some neural tissues; circulating neutrophils, mast cells and platelets; pancreatic islet β cells; and renal macula densa cells.^{6,8} Production of nitric oxide seems to be a fundamental and important mechanism of intercellular signalling in these cell types. By its nature, nitric oxide is an unstable free radical with powerful oxidant properties when high local concentrations are achieved. Macrophages produce large amounts of nitric oxide when activated and this accounts for much of their cytotoxicity against micro-organisms and tumour cells.⁸⁻¹⁰ Nitric oxide also damages iron-containing enzymes, for example NADH, and can inhibit DNA synthesis in some tumour cells.⁸

Abnormalities of nitric oxide production in endotoxic shock

In endotoxic shock the presence of disseminated foreign antigen, together with the inflammatory response, causes an inducible nitric oxide synthase to be generated in many other cell types which do not normally express this enzyme, including hepatocytes, fibroblasts, and vascular smooth muscle.^{6,8} Subsequent production of large quantities of nitric oxide leads not only to haemodynamic instability but also to widespread production of nitric oxide-based free radicals which have the potential to cause considerable damage to tissues. Evidence from clinical studies supports this. Patients with endotoxic shock¹¹ and cancer patients receiving interleukin-2 (IL-2) chemotherapy, a cytokine which activates other endogenous cytokines to induce nitric oxide synthase,¹² excrete high concentrations of nitric oxide metabolites.

Vascular smooth muscle is itself not a source of nitric oxide in health. In endotoxic shock production of nitric oxide occurs within the muscle layer of the vessel wall and this causes excessive vasodilatation and hence a reduction in peripheral vascular resistance.⁶ Analogues of the substrate L-arginine have been developed that act as substrate inhibitors of nitric oxide synthase. These cause systemic vasoconstriction and a pressor response in healthy animals by inhibiting constitutive nitric oxide production by the

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endothelium. In animals with experimental endotoxic shock inhibitors of nitric oxide synthase reverse hypotension but also cause a sustained increase in systemic vascular resistance, and at higher doses a decrease in cardiac output.¹³⁻¹⁵ A reduction in cardiac output has also been seen with these agents in healthy animals.^{13 16 17} Whether this fall in cardiac output is secondary to the rise in vascular resistance or to a direct effect of nitric oxide synthase inhibitors on cardiac contractility was not established by these studies.

Cardiac failure in endotoxic shock

Global deterioration of myocardial contractile function in patients with endotoxic shock has been established by clinical and radionuclide studies.²⁻⁴ In healthy volunteers administration of purified endotoxin causes reversible depression of left ventricular function, in addition to the expected reduction in systemic vascular resistance.¹⁸ Until recently, the cause of myocardial depression in endotoxaemia was considered to be a direct effect of endotoxin or an inflammatory mediator on myocardial tissue. The existence of a specific circulating myocardial depressant substance in endotoxic shock has been postulated but not proven.⁴ Whereas coronary perfusion abnormalities in patients with coexisting cardiac or coronary disease and endotoxic shock may account for segmental abnormalities of left ventricular function, in patients with global myocardial impairment and endotoxic shock the loss of function cannot be wholly explained by changes in coronary flow.⁴ As in the peripheral vasculature, multiple factors exist which depress cardiac function in endotoxic shock. However, there may be a common pathway for such mediators to impair myocardial contraction.

Overproduction of nitric oxide in the peripheral vasculature accounts for the vasodilatation and loss of vascular control in endotoxic shock. The hypothesis that overproduction of nitric oxide within cardiac muscle contributes to impaired function has now been tested. Studies of papillary muscles and individual cardiac myocytes isolated from healthy animals have shown that nitric-oxide-donating drugs^{19 20} or nitric oxide itself released from adjacent endocardium or endothelium^{19 21 22} can modulate the contractility of adjacent cardiac myocytes. In healthy cardiac myocytes do not produce appreciable amounts of nitric oxide.^{23 24} In experimental endotoxaemia, or after administration of inflammatory cytokines to isolated myocytes, nitric oxide synthase enzyme is induced within cardiac myocytes.²⁵ This activity and the subsequent generation of nitric oxide within the myocytes themselves²⁵ is accompanied by a substantial loss of contractile function, compared with myocytes from healthy animals.²⁴ Both the generation of nitric oxide by myocytes²⁵ and their depression of contractility²⁴ can be reversed by specific inhibitors of the nitric oxide synthase enzyme. Pretreatment of animals with high dose corticosteroids prevents the induction of this

enzyme and blocks completely the impairment of contraction.^{24 25} The cytokine TNF α and the interleukins IL-6 and IL-2 can cause marked depression of cardiac contraction in isolated papillary muscles.²⁶ This effect is mediated by nitric oxide generation within the cardiac muscle itself.²⁶ Furthermore, there is overproduction of nitric oxide within the coronary microcirculation in experimental endotoxic shock.²⁷ This may not only perturb coronary blood flow in the microvasculature but may also depress cardiac contraction, since current work has shown a moderating influence of nitric oxide derived from vascular endothelium on adjacent cardiac myocyte contraction.²²

Thus there seems to be a common mechanism in endotoxic shock contributing to both cardiac and vascular dysfunction. As in the peripheral vasculature, overproduction of nitric oxide within the myocardium, at least in experimental models, contributes importantly to the loss of contractility seen in patients with endotoxic shock.

Therapeutic strategies for the future

The cornerstones of treatment in septic shock are appropriately selected antibiotics and intensive support therapy. Molecular approaches to treatment accompanied by greater understanding of the pathophysiological mechanisms involved in endotoxic shock have generated important additions to existing therapy. Experimentally, pretreatment of animals with corticosteroids prevents the induction of the nitric oxide synthase enzyme within the heart and the vasculature.^{24 25 28} In the clinical setting patients present with established infection, too late for steroids to be of benefit. This may explain in part the results of previous clinical trials which showed no benefit from corticosteroids in this condition.^{5 29 30}

New developments in the treatment of endotoxic shock include a specific human monoclonal IgM antibody to the lipid A domain of endotoxin,³¹ although distribution of this agent has recently been suspended worldwide pending further clinical trials. Another new therapy is TNF antibody. In a pilot study inhibition of this mediator of inflammation was shown to improve left ventricular function in patients with septic shock.³² Whether there is also improvement in mortality has not been demonstrated.

Excess nitric oxide in the cardiovascular system seems to have a central role in endotoxic shock, but existing inhibitors of the nitric oxide synthase enzyme are not specific for the inducible form of the enzyme which accounts for this overproduction. In animal models of endotoxic shock a small dose of inhibitor blocked the excess production of nitric oxide but higher doses inhibited normal, endogenous nitric oxide production as well,¹³⁻¹⁵ causing intense vasoconstriction and cardiovascular collapse. The vasoconstriction can be modulated by coadministration of nitric-oxide-donating agents (drugs which act like sodium nitroprusside) to replace the

nitric oxide normally present in the vasculature. An inhibitor specific for the inducible nitric oxide synthase enzyme would be a potential treatment but is not available. Widespread inhibition of nitric oxide has potentially serious side effects, for example impairment of the normal anticoagulant status of endothelium, and alteration of neurotransmission. Moreover, a degree of vasodilatation may in fact be valuable, allowing washout of toxic oxides of nitrogen from tissues.⁶

Encouraging results have been described in two recent clinical reports in which the non-specific inhibitors were used.^{33,34} In two patients with septic shock, administration of L-arginine analogues (drugs which compete with L-arginine for the nitric oxide synthase enzyme) caused short-term increases in blood pressure. Cardiac output was increased in one patient and decreased in the other.³³ A further intriguing report described short-lived improvement in a patient with hepatic failure after administration of methylene blue, an agent that inhibits the effects of nitric oxide on vascular tone.³⁴ Methylene blue does not inhibit the cytotoxic effects of nitric oxide. Placebo controlled studies of nitric oxide synthase inhibitors in patients with septic shock are underway.

Conclusion

One of the principal mechanisms causing cardiovascular depression in endotoxin shock is an excessive production of nitric oxide both in the heart and in the vasculature. Research into the basic mechanisms of disease, in this case endotoxin shock, has led the way to potentially major advances in clinical practice. Results from current trials are awaited.

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