Myocardial dysfunction in sepsis: no role for NO?

E Belcher, J Mitchell, T Evans

The effects of nitric oxide on myocardial function in clinical sepsis are unclear, with studies in experimental models suggesting both beneficial and deleterious effects.
sion and the results of functional studies therefore make myocytes, in sepsis. NO decreased contractility in isolated cardiac microvasculature and cardiomyocytes in endotoxaemic rats. The hybridisation have confirmed a sepsis induced release of NO in the microvasculature and cardiomyocytes in endotoxaemic rats. Early animal studies also supported the concept of a causal relation between NO release and myocardial depression in sepsis. NO decreased contractility in isolated cardiac myocytes, in isolated papillary muscle preparation, and in the isolated working heart.

The existence of potential mechanisms for cardiac depression and the results of functional studies therefore make therapeutic NOS inhibition in sepsis theoretically attractive. Encouraging early clinical trials demonstrated that inhibition of both the constitutive and inducible isozymes of NOS in patients with sepsis increased SVR with a concomitant reduction in the need for pressor agents. Unfortunately, a subsequent investigation powered to show a mortality benefit in a similar patient population was stopped prematurely after NOS inhibition using the same agent administered for longer periods was associated with a significant increase in mortality, attributable to an excess of cardiovascular deaths.

Why this clinical trial demonstrated an apparently detrimental effect on cardiovascular function in these circumstances was not clear. However, it appears that the effect of NO on cardiac function in sepsis is more complex than the purely deleterious role first hypothesised. Evidence is emerging that NO derived from cNOS has beneficial effects in the heart. Physiological concentrations of NO do not have acute negative inotropic effects and (up to 1 µM) are known to support myocardial performance. Furthermore, in human septic shock myocardial perfusion is normal or increased, possibly because eNOS related biosynthesis of NO in the coronary vasculature exerts a beneficial effect by counteracting vasoconstriction induced by other vasomotor substances, such as the endothelins, which are also produced under inflammatory conditions. Indeed, in this and other animal models of sepsis, inhibition of constitutive derived NO has been associated with significant myocardial depression, although in this and other investigations the experimental techniques employed have not evaluated NO release, only protein transcription and expression.

If constitutive derived NO is beneficial, is selective iNOS inhibition the answer? Probably not, in that the concept of a detrimental effect of iNOS derived NO on myocardial function in sepsis is also questionable. Not only is direct evidence for a link between INOS expression and diminished contractility lacking, but inducible NO release may even have beneficial effects on myocardial performance. Should the ventricular dilatation seen in survivors of septic shock be NO mediated, a further mechanism for the detrimental effects of NO inhibition in sepsis would exist. Data from our own laboratory suggest that the myocardial hyporeactivity seen in endotoxin induced sepsis is reversed by the administration of L-arginine. In this model, NO is therefore cardioprotective. Similarly, in a porcine model, inhalation of NO prevented endotoxin induced left ventricular impairment. The idea that iNOS induction in sepsis may not be solely detrimental to myocardial function is paralleled by studies of late phase ischaemic preconditioning, which show that NO may play a pivotal role in myocardial protection as both a trigger and mediator of this phenomenon. Interestingly, monophosphoryl lipid A (MLA), a detoxified derivative of lipopolysaccharide

Table 1 Proposed beneficial and adverse effects of nitric oxide (NO) on myocardial function in sepsis

<table>
<thead>
<tr>
<th>Potential cardiodepressant effects of NO</th>
<th>Potential cardioprotective effects of NO</th>
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<tbody>
<tr>
<td>(1) Altered protein kinase activity and then L type calcium channel</td>
<td>(1) Increased myocardial perfusion due to vasodilatory effect</td>
</tr>
<tr>
<td>(2) Decrease in the myofilament response to calcium</td>
<td>(2) Free radical scavenger reducing ischaemia reperfusion injury via:</td>
</tr>
<tr>
<td>(3) Decreased cAMP via phosphodiesterase</td>
<td>–inhibition of platelet aggregation</td>
</tr>
<tr>
<td>(4) Direct inhibition of mitochondrial respiration and therefore adenosine triphosphate production within the myocardium</td>
<td>–inhibition of leucocyte adhesion to endothelial cells</td>
</tr>
<tr>
<td>(5) Stimulation of cellular damage following binding with reactive oxygen species to form peroxynitrite</td>
<td>–stabilisation of cell membranes</td>
</tr>
<tr>
<td>(6) Triggering of apoptosis in cardiomyocytes</td>
<td>(3) Mediation of ventricular dilatation allowing utilisation of Frank-Starling mechanism</td>
</tr>
<tr>
<td></td>
<td>(4) Antiarrhythmic properties of NO</td>
</tr>
<tr>
<td></td>
<td>(5) Macrophage activation leading to bacterial lysis</td>
</tr>
</tbody>
</table>
from Gram negative bacteria, is able to produce delayed protection against myocardial infarction. NO has been implicated in the delayed preconditioning induced by ischemia and by MLA. In this setting, iNOS induced NO is therefore not only cardioprotective, but may represent a protective mechanism for the protection evolved by an agent derived from lipopolysaccharide, a major mediator of septic shock.

NO WAY FORWARD FOR NO?
The effects of NO on myocardial function in clinical sepsis remain unclear. Studies in experimental models suggest both beneficial and deleterious effects (table 1). While inhibition of iNOS may improve systolic cardiac function and vasomotor tone, the beneficial effects of NO on diastolic function and myocardial perfusion would be lost. This knowledge alone is sufficient to justify further work to elucidate the possible therapeutic benefits of manipulation of NO production in sepsis.

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Authors’ affiliations
E Belcher, J Mitchell, T Evans, Royal Unit of Critical Care, Imperial College School of Medicine, Royal Brompton Hospital, London SW3 6NP, UK

REFERENCES

STAMPS IN CARDIOLOGY

History of cardiac surgery

On 25 February 1996 India released this stamp to commemorate 100 years of cardiac surgery. The brochure issued by the Department of Posts contains the following comments: “Stephen Paget, a famous British surgeon, remarked in his textbook on surgery of the chest as late as in 1896, ‘Surgery of the heart has probably reached the limit set by nature to all surgery; no new method and no new discovery can overcome the natural difficulties that attend a wound of the heart’. The same year however, Ludwig Rehn of Frankfurt performed the first successful repair of a stab wound of the heart. The era of cardiac surgery had begun”. The following cardiac surgical milestones over the next 100 years are quoted: surgery on the aortic valve (Theodore Tuffier, Paris 1912), surgery on the mitral valve (Elliot Cutter, Boston 1923), successful coronary artery bypass (Michael DeBakey, Houston 1964), and cardiac transplantation (Christiaan Barnard, Cape Town 1967).

The design of the stamp has been very carefully chosen to mark 100 years of cardiac surgery. The brochure issued by the Department of Posts contains the following comments: “Stephen Paget, a famous British surgeon, remarked in his textbook on surgery of the chest as late as in 1896, ‘Surgery of the heart has probably reached the limit set by nature to all surgery; no new method and no new discovery can overcome the natural difficulties that attend a wound of the heart’. The same year however, Ludwig Rehn of Frankfurt performed the first successful repair of a stab wound of the heart. The era of cardiac surgery had begun”. The following cardiac surgical milestones over the next 100 years are quoted: surgery on the aortic valve (Theodore Tuffier, Paris 1912), surgery on the mitral valve (Elliot Cutter, Boston 1923), successful coronary artery bypass (Michael DeBakey, Houston 1964), and cardiac transplantation (Christiaan Barnard, Cape Town 1967).

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M K Davies and A Hollman

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