Myocardial dysfunction in sepsis: no role for NO?

E Belcher, J Mitchell, T Evans

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The effects of nitric oxide on myocardial function in clinical sepsis are unclear, with studies in experimental models suggesting both beneficial and deleterious effects

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Sepsis and its sequelae[1] represent an important cause of mortality among the critically ill, particularly if cardiovascular dysfunction ensues. In these circumstances, refractory hypotension develops leading to multiple organ failure, and some 50% of such cases fail to survive.[2] Although sepsis is defined as the systemic response to infection, less than 50% of patients with septic shock have positive blood cultures.[3] Indeed, the clinical manifestations of sepsis may be seen in association with a variety of non-infective insults including major trauma, burns, pancreatitis, rhabdomyolysis, and surgery necessitating cardiopulmonary bypass, and are then termed the systemic inflammatory response syndrome (SIRS).

MYOCARDIAL DYSFUNCTION IN SEPSIS

Traditionally, descriptions of septic shock defined an early, hyperdynamic phase, with warm peripheries, low systemic vascular resistance (SVR), and high cardiac output. In non-survivors the "warm" phase was thought to progress to a hypodynamic or "cold" phase in which cool peripheries, increased SVR, and low cardiac output were the dominant clinical features. However, traditional indices of myocardial function, including cardiac and stroke volume index and ejection fraction, may be inaccurate as a significant depression in contractility can be masked by changes in heart rate, preload, and afterload. To quantify intrinsic myocardial depression, an assessment of left ventricular performance using load independent techniques is therefore required. The end systolic pressure–volume relationship (ESPVR) is unaffected by changes in afterload and preload over a wide range. The slope is maximal at end systole (E_{max}) and has the units of elastance $E = \Delta P/\Delta V$. The linear relationship between these parameters is shifted to the left under conditions of increased contractility and to the right with reduced contractility.

Such techniques have revealed that patients with septic shock have severely depressed ejection fraction with ventricular dilatation, as measured by an increase in mean systolic and end diastolic ventricular volumes. In survivors, these changes reverse over a period of some 7–10 days,[4] suggesting that they form part of a compensatory mechanism in which acute dilatation of the left ventricle, without changes in pressure, leads to an increase in left ventricular compliance. Conceivably, this may enable patients to maintain a normal stroke volume and cardiac indices, despite a profound loss of myocardial contractility, via the Frank-Starling mechanism (fig 1).[5] By contrast, non-survivors develop diastolic dysfunction with a reduced left ventricular end diastolic volume (LVEDV) despite evidence of increased left atrial pressure. This stiffness impairs diastolic filling and therefore stroke volume. Similar changes in right ventricular performance have been detected.[6]

ROLE OF NITRIC OXIDE

The pathogenesis of depressed myocardial dysfunction in sepsis is incompletely understood, but recent clinical studies have provided insight into the potential role of the endogenous vasodilator nitric oxide (NO) in this process. NO is synthesised from the semi-essential amino acid L-arginine by three isoforms of NO synthase (NOS). Under physiological conditions, NO is produced by constitutive (cNOS) enzymes expressed predominantly in endothelial cells (eNOS) and neurons (nNOS) respectively. However, other cell types, including myocytes and endocardial cells, have also been shown to express NOS constitutively.[7][8] Under conditions of stress, including sepsis, induction of inducible NOS (iNOS) leads to the production of large amounts of NO. Since NO is the principal mediator of vascular smooth muscle tone, its role in causing profound systemic vasodilatation in septic shock seems logical.

By contrast, the role of NO in the pathogenesis of myocardial dysfunction in sepsis is less clear cut, although potential mechanisms exist. NO stimulates the enzyme soluble guanylate cyclase that converts guanosine triphosphate (GTP) to 3′,5′-cyclic guanosine monophosphate (cGMP). In the cardiac myocyte cGMP inhibits the β adrenergic stimulated increase in the slow inward calcium current and reduces the calcium affinity of the contractile apparatus.[9] NO also reduces cAMP via phosphodiesterase[10] and alters protein kinase activity and L type calcium channels.[11] Besides these direct adverse effects on myocardial contractility, NO inhibits mitochondrial respiration and therefore adenosine triphosphate production within the myocardium. Cellular damage may also occur following binding with reactive oxygen species to form the toxic radical peroxynitrite. At high concentrations NO also leads to apoptosis of cardiomyocytes.[12] Moreover, molecular studies using immunohistochemistry, reverse transcription polymerase chain reaction, and in situ

See end of article for authors' affiliations

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Correspondence to:
Professor TW Evans, Royal Brompton Hospital, Sydney Street, London SW3 6NP, UK; t.evans @rbh.nthames.nhs.uk

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Abbreviations: EDPVR, end diastolic pressure–volume relationship; ESPVR, end systolic pressure–volume relationship; LVEDV, left ventricular end diastolic volume; MLA, monophosphoryl lipid A; NO, nitric oxide; NOS, nitric oxide synthase; SIRS, systemic inflammatory response syndrome; SVR, systemic vascular resistance
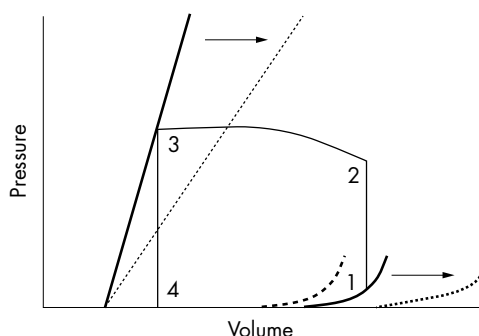
Figure 1 Left ventricular pressure-volume relationships.[5] The bold straight line shows the normal end systolic pressure–volume relationship (ESPVR), defining ventricular contraction. ESPVR is independent of changes in preload and afterload. The slope is maximal at end systole and has the units of elastance, $E=\Delta P/\Delta V$. It has therefore been designated E_{max}. The bold curved line shows normal end diastolic pressure–volume relationship (EDPVR). The straight section of the line represents addition of the initial volume. While ventricular volume increases from zero to approximately 50 ml, transmural pressure remains at zero. Left ventricular end diastolic pressure (LVEDP) then increases in a curvilinear manner during addition of further volume. The pressure–volume loop (1–4) represents one cardiac cycle (1–2, isovolumetric contraction; 2–3, stroke volume; 3–4, isovolumetric relaxation). The interrupted straight line represents E_{max} in sepsis, with depressed contractility indicated by a downward and right shift of the ESPVR. In survivors of septic shock this is accompanied by a right shift of the EDPVR (interrupted curved line) caused by ventricular dilatation, enabling an increase in stroke volume. In non-survivors diastolic stiffness develops represented by an upward and left shift of the EDPVR (bold interrupted curved line), leading to impaired diastolic filling and a reduction in stroke volume. Arrows represent possible contribution of nitric oxide (NO) to the pressure–volume relationships in sepsis. While NO may be responsible for the reduction in systolic contractility, the septic patient is able to maintain end systolic volume because of a reduction in systemic vascular resistance; therefore the overriding haemodynamic effect of NO in sepsis may be facilitation of ventricular dilatation, which acts to further stroke volume and maintain cardiac output. Potentially, NO blockade in sepsis may convert the EDPVR of a surviving septic patient to a non-survivor.

hybridisation have confirmed a sepsis induced release of NO in the microvasculature and cardiomyocytes in endotoxaemic rats.[13] 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,[14] in isolated papillary muscle preparation,[15] and in the isolated working heart.[16]

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 isoforms of NOS in patients with sepsis increased SVR with a concomitant reduction in the need for pressor agents.[17] 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.[18]

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[19] and (up to $1\,\mu M$) are known to support myocardial performance.[20] Furthermore, in human septic shock myocardial perfusion is normal or increased,[21] 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.[22] 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.[23] Similarly, in a porcine model, inhalation of NO prevented endotoxin induced left ventricular impairment.[24] 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.[25] Interestingly, monophosphoryl lipid A (MLA), a detoxified derivative of lipopolysaccharide

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

Potential cardiodepressant effects of NO
  (1) Alterations in protein kinase activity and then L type calcium channel
  (2) Decrease in the myofibril response to calcium
  (3) Decreased cAMP via phosphodiesterase
  (4) Direct inhibition of mitochondrial respiration and therefore adenosine triphosphate production within the myocardium
  (5) Stimulation of cellular damage following binding with reactive oxygen species to form peroxynitrite
  (6) Triggering of apoptosis in cardiomyocytes
Potential cardioprotective effects of NO
  (1) Increased myocardial perfusion due to vasodilatory effect
  (2) Free radical scavenger reducing ischaemia reperfusion injury via:
    –inhibition of platelet aggregation
    –inhibition of leucocyte adhesion to endothelial cells
    –stabilisation of cell membranes
  (3) Mediation of ventricular dilatation allowing utilisation of Frank-Starling mechanism
  (4) Antiarrhythmic properties of NO
  (5) Macrophage activation leading to bacterial lysis

from Gram negative bacteria, is able to produce delayed protection against myocardial infarction. NO has been implicated in the delayed preconditioning induced by ischaemia and by MLA.[26] 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 NOS 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, Unit of Critical Care, Imperial College School of Medicine, Royal Brompton Hospital, London SW3 6NP, UK

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STAMPS IN CARDIOLOGY

History of cardiac surgery
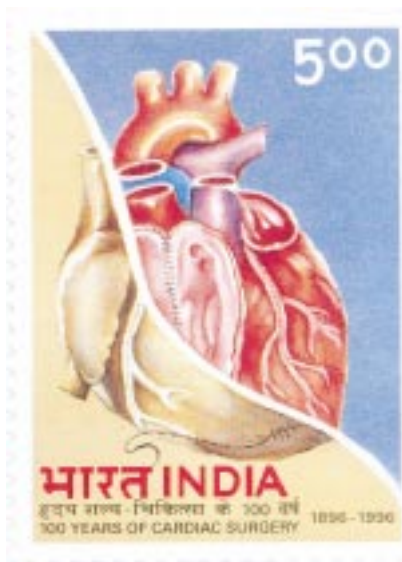
On 25 February 1996 India released this stamp to commemorate 100 years of cardiac surgery. The brochure issued by the Department of Posts contains the following comments: "Stephen Paget, a famous British surgeon, remarked in his textbook on surgery of the chest as late as in 1896, 'Surgery of the heart 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), systemic pulmonary shunt for blue babies (Alfred Blalock, Baltimore 1945), closure of atrial septal defect (John Lewis, Minnesota 1952), valve substitute implantation (Charles Hufnagel, Georgetown 1952), open heart operation (John Gibbon, Boston 1953), totally implantable pacemaker (Ake Senning, Sweden 1959), 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. On the left part of the design is depicted the first ever successful suturing of a heart wound and on the right cardiac transplantation in progress. A total of 600 000 stamps were printed by Calcutta Security Printers using the process of photo offset.

M K Davies
A Hollman