**laboratory and animal investigations**

**Inhibition of Nitric Oxide Synthesis Improves the Vasoconstrictive Effect of Noradrenaline in Sepsis**

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**Background:** Septic shock is characterized by systemic vasodilation and an impaired reactivity to vasoconstric- tor agents. It has been suggested that an excessive release of nitric oxide has a role in this hemodynamic derangement.

**Objective:** To investigate whether inhibition of nitric oxide synthesis by the administration of N\(^\text{N}\)-nitro-L-arginine (LNNA), improves the vasoconstrictor effects of catecholamines in sepsis.

**Material and Methods:** Mechanically ventilated and pentobarbital-anesthetized sheep received either no treatment (n=6) or LNNA (100 mg/kg IV bolus, n=4). Other sheep (septic group) received live *Escherichia coli* (*E coli*) (1.5\(\times\) 10\(^9\) micro-organisms/kg over 30 min) followed 1 hour later by either no treatment (n=5) or LNNA (100 mg/kg IV bolus, n=7). After these interventions, all sheep were given noradrenaline in a continuous IV infusion at three different doses (0.5, 1.5, and 4.5 \(\mu\)g, kg-1, min-1). Cardiovascular parameters were recorded at maximal blood pressure response achieved with each dose.

**Results:** The administration of live *E coli* to the septic group resulted in systemic hypotension, high cardiac output, and hyperlactatemia. The LNNA caused a significant systemic and pulmonary vasoconstriction in both septic and nonseptic sheep.

In nonseptic sheep, noradrenaline induced a significant increase in systemic vascular resistance (from 2,973 ± 637 to 4,561 ± 1,287 dyn/s/cm\(^{-5}\)/m\(^{-2}\)), whereas the increase caused in those that received LNNA was nonsignificant (5,562 ± 3,489 to 6,693 ± 2,571 dyn, s, cm\(^{-3}\), m\(^{-2}\)).

Septic sheep showed a nonsignificant vasoconstriction during the infusion of noradrenaline (from 1,438 ± 1,132 to 2,244 ± 1,391 dyn/s/cm\(^{-5}\)/m\(^{-2}\)). However, treatment with LNNA markedly improved the vasoconstrictor effect of noradrenaline (from 2,894 ± 2,317 to 4,894 ± 3,435 dyn/s/cm\(^{-5}\)/m\(^{-2}\)). The dose-response curve of systemic vascular resistance in these LNNA-pre- treated septic sheep became very similar to the corresponding curve obtained in nonseptic animals.

**Conclusions:** Inhibition of nitric oxide synthesis by the administration of LNNA significantly improves the vasoconstrictor effect of noradrenaline in septic sheep, allowing an increase in systemic vasmotor tone similar to that observed in nonseptic sheep. It is concluded that increased synthesis of nitric oxide contributes to the depressed vascular reactivity to vasoconstrictor agents characteristic of sepsis.

*(Chesl 1994; 106:250-56)*

CaO\(_2\)=arterial oxygen content; CVo\(_2\)=venous oxygen content; Do\(_2\)=oxygen delivery; *E coli*=*Escherichia coli*; E\(_2\)=oxygen extraction ratio; IL-1=interleukin-1; LNNA=N\(^\text{N}\)-nitro-L-arginine; P\(_{pa}\)=pulmonary artery pressure; PVR=pulmonary vascular resistance; S\(_{o}O_2\)=arterial oxygen saturation; Sv\(_{o}O_2\)=venous oxygen saturation; TNF=tumor necrotizing factor; VO\(_2\)=oxygen uptake

Septic shock is characterized by hypotension, decreased vascular reactivity to vasoconstrictor agents, and an abnormal tissue oxygen extraction leading to a pathologic supply-dependency of oxygen consumption.\(^1\)\(^,\)\(^2\) Persistent vasodilation is a frequent cause of death among these patients,\(^3\) when their condition evolves and blood pressure can no longer be maintained by increasing doses of sympathomimetic agents.

Under normal conditions, vascular tone is regulated by the interaction of neurogenic mechanisms and the release of nitric oxide by the endothelium.\(^4\) Contractile responses to electrical stimulation of perivascular nerves in arteries from several animal species are enhanced when the endothelium is removed.\(^5\) Also, removal of the endothelium or inhibition of nitric oxide synthase increased vascular reactivity to vasoconstrictor agents.\(^6\)

The mechanisms, however, involved in the decreased vascular reactivity in sepsis are not well understood. Several mediators have been implicated to explain this vascular hyporeactivity, such as endothelin, complement components, and several cyto-
More recently, an excessive vasodilation due to the release of the endogenous vasodilator nitric oxide has been invoked as an explanation for this phenomenon.\textsuperscript{10} This concept is based on several lines of evidence. Endotoxin stimulates the release of nitric oxide from several cell types.\textsuperscript{11} Tumor necrosis factor, a cytokine thought to play a pivotal role in the pathophysiology of sepsis, decreases the contractility of vascular rings to vasoconstrictor agents.\textsuperscript{12} It is also known that endotoxin\textsuperscript{13} and interleukin-1 (IL-1) stimulate the release of nitric oxide from vascular smooth muscle cells.\textsuperscript{14} Furthermore, several studies have shown that nitric oxide synthase inhibitors reverse the hypotension induced in dogs by the infusion of endotoxin\textsuperscript{15} or tumor necrosing factor (TNF),\textsuperscript{16} suggesting that nitric oxide release plays a fundamental role in the hypotension characteristic of septic shock. It has also been shown that the administration of several L-arginine analogues induces marked vasoconstriction in patients with septic shock.\textsuperscript{17,18} Therefore, nitric oxide seems to be an important mediator of hypotension in septic shock. Moreover, some in vitro evidence suggests that nitric oxide also mediates the vascular hypo responsiveness in septic shock.\textsuperscript{19} In the present study, we hypothesized that an increased nitric oxide release could account for the depressed vascular reactivity in a large animal model of sepsis. To test this hypothesis, we studied the influence of treatment with N\textsuperscript{\textordmasculine}-nitro-L-arginine (LNNA), an inhibitor of nitric oxide synthesis, on the vascular response to noradrenaline in sheep given live Escherichia coli (E. coli).

**MATERIAL AND METHODS**

Sheep weighing between 41 and 55 kg were anesthetized with pentobarbital (30 mg/kg IV bolus followed by 4 mg/min), intubated, and connected to a volume-cycled respirator with a respiratory rate of 10 per minute and a tidal volume of 15 ml/kg. Animals were monitored with a pulmonary artery catheter (Abbott Labs) introduced through the right internal jugular vein and an arterial catheter in one femoral artery. After instrumentation, sheep were allowed to stabilize before initiating other interventions as described below. Systemic and pulmonary artery pressure recordings were performed with two monitors (model 5557, General Electric). Cardiac output was measured in triplicate by the thermodilution technique. This value was indexed according to body surface area. Hemoglobin concentration was measured by an analyzer (Coulter S Plus Analyzer). Arterial (\(\text{CaO}_2\)) and venous (\(\text{CvO}_2\)) oxygen contents were calculated using the standard equation (\(\text{oxygen content} = 1.35 \times \text{hemoglobin concentration} \times \text{SaO}_2 + 0.003 \times \text{Pao}_2\)). Vascular resistance was calculated by a standard formula. Oxygen delivery (\(\text{Do}_2\)) was calculated as the product of cardiac index and \(\text{CaO}_2\) (\(\text{Do}_2 = 10 \times \text{CaO}_2 \times \text{cardiac index}\)). Oxygen uptake was calculated using the Fick equation (\(\text{Vo}_2 = 10 \times \text{cardiac index} \times \text{[CaO}_2 - \text{CvO}_2]\)).

Sepsis was induced by the administration of live E. coli (1.5\(\times\)10\(^6\) micro-organisms/kg over 30 min) serotype 5044552. This dose of the strain used in our study produced hypotension, decreased systemic vascular resistance, increased pulmonary vascular resistance, leukopenia, thrombocytopenia, hyperlactacidemia, and hypoxemia, as previously reported.\textsuperscript{20} Sepsis in sheep is accompanied by acute lung injury,\textsuperscript{21} and it has been reported that hypoxia impairs nitric oxide synthesis.\textsuperscript{22} Therefore, to avoid severe hypoxia that could alter nitric oxide synthesis by itself, we maintained FIO\(_2\) of 1 throughout the experiment. Normal saline solution (0.9 percent) was administered at a rate of 15 ml/kg/h during the experiment. The different interventions in the septic group were evaluated 1 h after the administration of E. coli was started.

The vasoconstrictor response to catecholamines was evaluated by administering a continuous infusion of noradrenaline. After measuring baseline hemodynamic parameters, an infusion of noradrenaline at three different doses (0.5, 1.5, and 4.5 \(\mu\)g/kg-h) was administered. At each different dose, cardiovascular parameters were measured at the moment at which maximal blood pressure change was attained. The response to noradrenaline was studied in four different groups of sheep, as follows: (1) Group A (n=6), nonseptic sheep received noradrenaline as described above, 75 min after instrumentation; (2) Group B (n=4), nonseptic sheep received LNNA (100 mg/kg-h IV bolus) 50 min after instrumentation. Fifteen minutes after LNNA, an infusion of noradrenaline was started as in group A; (3) Group C (n=5), septic sheep were given noradrenaline 75 min after starting the infusion of E. coli; and (4) Group D (n=7), septic sheep received LNNA (100 mg/kg-h IV bolus) 1 h after starting the infusion of E. coli, and 15 min later the infusion of noradrenaline was started. This study was performed with our local Animal Care Committee approval. The LNNA was purchased from Sigma Chemical Co (St. Louis, Mo).

**RESULTS**

**Effects of LNNA**

Nonseptic sheep pretreated with LNNA presented a lower heart rate and a higher blood pressure, systemic vascular resistance, pulmonary artery pressure, and pulmonary vascular resistance as compared with those not receiving LNNA (Table 1, baseline values). Cardiac index, \(\text{Do}_2\) and \(\text{Vo}_2\) tended to be lower, but the difference did not reach statistical significance. The \(\text{Vo}_2\) did not change.

**Effects of Live E Coli Infusion**

In septic sheep, the administration of live E coli resulted in tachycardia, hypotension, increased cardiac index, and decreased systemic vascular resistance, as compared with nonseptic animals (Table 1, baseline values).

**Effects of Noradrenaline**

In nonseptic sheep, the administration of noradrenaline resulted in a significant increase in blood
Inhibition of Nitric Oxide Synthesis Improves Vasoconstrictive Effect (Landin et al)

pressure and systemic and pulmonary vascular resistance. There was also a decrease in oxygen consumption and oxygen extraction ratio (EO2), whereas oxygen delivery tended to increase but the change did not reach statistical significance (Table 1).

In nonseptic sheep pretreated with LNNA, noradrenaline induced an increase in blood pressure. Pulmonary artery pressure, systemic and pulmonary vascular resistance, cardiac index, and oxygen delivery did not change significantly. The EO2 decreased (Table 1).

The administration of noradrenaline to septic sheep resulted in a significant increase in blood pressure. Systemic vascular resistance, pulmonary artery pressure, and pulmonary vascular resistance, however, did not change significantly. Changes in VO2 and oxygen extraction ratio, and SvO2 were significantly different from those in nonseptic sheep (Table 1).

Septic sheep pretreated with LNNA showed an increase in blood pressure and SVR that was significantly more marked than that induced in septic sheep not receiving LNNA, and very similar to that observed in nonseptic sheep (Fig 1). However, pul-

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**Table 1. Hemodynamic Changes Induced by the Administration of Noradrenaline at 0.5, 1.5, and 4.5 μg/kg-1/min-1 in Normal and Septic Sheep Treated With Nο-nitro-Larginine**

<table>
<thead>
<tr>
<th>Group</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
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<tbody>
<tr>
<td>Sepsis</td>
<td>no</td>
<td>no</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>LNNA</td>
<td>no</td>
<td>yes</td>
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<table>
<thead>
<tr>
<th>HR, beats*min⁻¹</th>
<th>baseline</th>
<th>0.5</th>
<th>1.5</th>
<th>4.5</th>
<th>baseline</th>
<th>0.5</th>
<th>1.5</th>
<th>4.5</th>
<th>baseline</th>
<th>0.5</th>
<th>1.5</th>
<th>4.5</th>
<th>baseline</th>
<th>0.5</th>
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<tr>
<td></td>
<td>98.8 ± 15.6</td>
<td>79.0 ± 8.2</td>
<td>102.6 ± 11.9</td>
<td>96.6 ± 13.0</td>
<td>120.0 ± 23.3</td>
<td>146.4 ± 43.0</td>
<td>65.1 ± 24.7</td>
<td>99.3 ± 32.0</td>
<td>202.8 ± 34.6</td>
<td>220.0 ± 57.0*</td>
<td>110.2 ± 56.2*</td>
<td>180.1 ± 56.8*</td>
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<tr>
<td>MBP, mm Hg</td>
<td>120.0 ± 22.3</td>
<td>145.6 ± 28.0</td>
<td>179.1 ± 31.2</td>
<td>202.8 ± 34.6</td>
<td>120.0 ± 22.3</td>
<td>145.6 ± 28.0</td>
<td>179.1 ± 31.2</td>
<td>202.8 ± 34.6</td>
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<tr>
<td>Ppa, mm Hg</td>
<td>14.0 ± 2.2</td>
<td>15.5 ± 2.4</td>
<td>17.8 ± 3.1</td>
<td>20.3 ± 4.8*</td>
<td>14.0 ± 2.2</td>
<td>15.5 ± 2.4</td>
<td>17.8 ± 3.1</td>
<td>20.3 ± 4.8*</td>
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<td>17.8 ± 3.1</td>
<td>20.3 ± 4.8*</td>
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<td>PVR, dyn/s/cm⁻²</td>
<td>143 ± 70</td>
<td>161 ± 68</td>
<td>225 ± 133</td>
<td>278 ± 180*</td>
<td>143 ± 70</td>
<td>161 ± 68</td>
<td>225 ± 133</td>
<td>278 ± 180*</td>
<td>143 ± 70</td>
<td>161 ± 68</td>
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<td>D0g, ml/min⁻¹</td>
<td>469 ± 112</td>
<td>519 ± 117</td>
<td>507 ± 122</td>
<td>541 ± 123</td>
<td>469 ± 112</td>
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<td>507 ± 122</td>
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<td>VO2, ml/min⁻¹</td>
<td>135 ± 46</td>
<td>134 ± 52</td>
<td>96 ± 36</td>
<td>76 ± 37*</td>
<td>135 ± 46</td>
<td>134 ± 52</td>
<td>96 ± 36</td>
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<td>76 ± 37*</td>
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<td>E02, %</td>
<td>0.283 ± 0.039</td>
<td>0.249 ± 0.049</td>
<td>0.183 ± 0.032</td>
<td>0.134 ± 0.055*</td>
<td>0.410 ± 0.011</td>
<td>0.346 ± 0.012</td>
<td>0.293 ± 0.012</td>
<td>0.240 ± 0.0145*</td>
<td>0.298 ± 0.014</td>
<td>0.284 ± 0.015</td>
<td>0.274 ± 0.016</td>
<td>0.252 ± 0.015†</td>
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*p<0.05 for the effects of the different doses of noradrenaline.  
†p<0.05 for the influence of sepsis on the effects of noradrenaline.  
‡p<0.05 for the influence of treatment with LNNA on the effects of noradrenaline in septic sheep.  
§HR=heart rate; MBP=mean blood pressure; CI=cardiac index.
monary artery pressure (Ppa) and pulmonary vascular resistance (PVR) did not change significantly. The DO$_2$ and oxygen extraction ratio did not change significantly during the infusion of noradrenaline (Table 1).

**Discussion**

**Effects of LNNA**

Although smaller doses of LNNA (20 mg/kg) have been shown to induce significant vasoconstriction in septic sheep, we have found that a 100 mg/kg dose induces a more marked vasoconstriction (Landin et al, 1993, unpublished data), indicating a more complete blockade of nitric oxide synthesis by the higher dose. Therefore, we chose to use the higher dose. The blockade of nitric oxide release by 20 mg/kg LNNA by serial acetylcholine injections has been proved in previous experiments. Since the effects of LNNA are long-standing, we did not find it necessary to administer a continuous IV infusion of LNNA. Under normal conditions, we found that inhibition of nitric oxide synthesis by LNNA resulted in systemic and pulmonary vasoconstriction. Oxygen consumption was not different in sheep receiving LNNA suggesting that the LNNA-elicited vasoconstriction does not limit VO$_2$ by the tissues.

Previous studies have reported that inhibition of nitric oxide synthesis induces an increase in blood pressure in rabbits, guinea pigs, and dogs. Those findings indicate a role for nitric oxide in the regulation of basal vasomotor tone. Nitric oxide has a regulatory role not only under normal conditions, but also in certain pathologic conditions such as sepsis. Endotoxin stimulates the synthesis of nitric oxide by several cell types. It is known that there is an inducible form of nitric oxide-synthase in vascular smooth muscle cells and macrophages stimulated by endotoxin and cytokines. We and others have reported the vasoconstrictor effects of nitric oxide synthesis inhibition in sepsis. Kilbourn et al found that the increase in blood pressure after N-monomethyl-L-arginine administration was relatively small in control dogs, whereas it was greatly potentiated in animals treated with endotoxin or TNF, suggesting that hypotension in sepsis is mediated by excessive nitric oxide synthesis. On the contrary, we reported that the vasoconstrictor effects of LNNA in septic sheep were significantly less marked as compared with that of nonseptic animals. Although these findings contrast with those previously reported, they are still compatible with an increased release of nitric oxide in sepsis. Differences in the models used (endotoxin or TNF-induced vs live E. coli-induced) could also account for some of the discrepancies. It could also be possible that there are other vasodilators that cannot be inhibited by L-arginine analogues, or that LNNA inhibits more efficiently the constitutive form of the enzyme nitric oxide synthase than the inducible form. In fact, recent reports suggest that other vasodilator mechanisms, such as those involving the ATP-sensitive potassium channels, could be more relevant for the hypotension of sepsis than nitric oxide itself.

**Responses to Noradrenaline**

In nonseptic sheep noradrenaline induced systemic and pulmonary vasoconstriction. The decrease in VO$_2$ and EO$_2$ suggests that this vasoconstriction limits systemic oxygen uptake. In nonseptic sheep pretreated with LNNA, noradrenaline induced increases in blood pressure, but systemic and pulmonary vascular resistance did not rise further, probably from the LNNA-induced vasoconstriction already present.

In septic sheep, noradrenaline evoked a significant increase in blood pressure, although systemic and pulmonary vascular resistance did not vary. These findings indicate a depressed reactivity to pressor agents in sepsis, as it has previously been reported in *in vitro* and *in vivo* experiments. The mechanisms of this sepsis-associated impaired vascular reactivity are not completely understood. A role for metabolites of the arachidonic acid has been suggested based on the finding that inhibition of cyclooxygenase improves the response to pressor agents in several preparations. However, others have found that indomethacin fails to improve vascular hypore-
responsiveness in septic tissues.\(^{37}\) Other mechanisms proposed include a decrease in the number of alpha receptors.\(^{38}\) The response to other nonreceptor-mediated agonists, such as potassium chloride, however, is also diminished.\(^{38,40}\) Recently, an increased synthesis of nitric oxide has been involved in the vascular hyporesponsiveness of sepsis.\(^{41}\)

Previous in \textit{vitro} studies have provided considerable experimental evidence supporting the concept that the endothelium exerts a breaking effect on the contractile response of normal vessels by releasing nitric oxide.\(^{42,43}\) There is also in \textit{vitro} evidence that nitric oxide may mediate the depressed vascular reactivity of endotoxin-treated vessels or vessels from septic animals. The contractile response of aortic rings from septic rats was partially restored by denuding the aortic rings of endothelium.\(^{44}\) Inhibition of nitric oxide synthesis also improved the responsiveness to noradrenaline of aorta from endotoxin-treated rats, and this effect was observed also in endothelium-denuded vessels, suggesting that depressed vascular reactivity is the result of the release of nitric oxide from a nonendothelial source.\(^{41}\) The reduction in the responsiveness to contractile agents is associated with an increase in cyclic GMP levels\(^{45}\) and is restored by inhibitors of nitric oxide synthesis.\(^{45,46}\) Furthermore, IL-1 inhibits contraction of rat aortic rings by an endothelium-independent mechanism mediated by nitric oxide.\(^{47-49}\) Recent evidence indicates that nitric oxide produced within the vessel wall of rat iliac arteries incubated with endotoxin inhibits arterial contractions induced by perivascular noradrenergic stimulation.\(^{50}\) In rats given endotoxin, it has been seen that nitric oxide inhibition restored their responsiveness to noradrenaline.\(^{51,52}\) All these findings indicate that endotoxin stimulates the synthesis of nitric oxide from a nonendothelial source, that is at least partially responsible for the decreased vascular responsiveness to pressor agents.

We found that the depressed vascular responsiveness of septic sheep to noradrenaline improved by pretreatment with LNNA. This improvement is shown by a statistically significant increase in systemic vascular resistance in septic sheep pretreated with LNNA whereas the change was not significant in those that did not receive LNNA (Fig 1). Furthermore, there was a statistically significant influence of pretreatment with LNNA on the effects of noradrenaline for blood pressure and systemic vascular resistance. Therefore, the differences observed cannot be explained by a baseline shift in blood pressure and systemic vascular resistance due to the pressor effects of pretreatment with LNNA. The dose-response curve of systemic vascular resistance to noradrenaline was indistinguishable from that of control sheep. It can be argued that in our model of sepsis, 1 h after starting the administration of live \textit{E. coli}, the induction of nitric oxide synthase has not taken place. Certainly, the induction of nitric oxide synthase requires several hours, according to \textit{in vitro} experiments. Endothelial cells released nitric oxide only after 8 h of exposure to monokines in the presence of endotoxin.\(^{53}\) In cultured vascular smooth muscle cells, an L-arginine-dependent increase in cyclic GMP occurred after 6 h of exposure to IL-1.\(^{14}\) However, TNF-induced hypotension appeared only 20 min after its administration and was reversed by the administration of monomethyl-L-arginine,\(^{16}\) suggesting that TNF stimulates an early nitric oxide release. Furthermore, it has been shown that endotoxin-stimulated macrophages were able to inhibit phenylephrine-induced contractions in excised rabbit carotids after as little as 1 h of incubation.\(^{54}\) The presence of endothelium partially protected carotid contractility from depression by activated macrophages. Furthermore, addition of an inhibitor of nitric oxide synthesis prevented this depression in arteries with and without endothelium. Synergy between the different inflammatory mediators might account for the discrepancy found in \textit{in vitro} experiments. Moreover, it has been suggested that smooth muscle cells possess both the inducible and constitutive nitric oxide synthases, the latter being involved in the immediate formation of nitric oxide and the former induced subsequently.\(^{55}\)

In summary, our findings indicate that the depressed vascular reactivity in a large animal model of sepsis can be greatly restored by the administration of LNNA, an inhibitor of nitric oxide synthesis. This study expands previous \textit{in vitro} evidence supporting the concept that an excessive release of nitric oxide contributes to the vascular hyporesponsiveness of sepsis. The complex mechanisms that regulate the interaction between the sympathetic and nitric oxide systems in sepsis remain to be elucidated.

\begin{thebibliography}{10}
\item Sibbald WJ, Fox G, Martin C. Abnormalities of vascular reactivity in the sepsis syndrome. Chest 1991; 100(suppl):155-59
\item Rees DD, Palmer RMJ, Moncada S. Role of endothelium-derived relaxing factor in the regulation of blood pressure. Proc Natl Acad Sci USA 1989; 86:3573-78
\item Martin W, Furchgott RF, Villani GM, Jothishamadan D. Depression of contractile responses in rat aorta by spontaneously released endothelial-derived relaxing factor. J Pharmacol Exp Ther 1988; 245:417-24
\end{thebibliography}

27 Steuer DJ, Marletta MA. Mammalian nitrate biosynthesis: mouse macrophages produce nitrite and nitrate in response to E coli lipopolysaccharide. Proc Natl Acad Sci USA 1985; 82:7738-42


30 Landry DW, Oliver JA. The ATP-sensitive K+ channel mediates hypotension in endotoxemia and hypoxic lactic acidosis in dog. J Clin Invest 1992; 89:2071-74


45 Flemming I, Julou-Schaeffer G, Gray GA, Parratt JR, Stoclet JC.
Evidence that an L-arginine/nitric oxide dependent elevation of tissue cyclic GMP content is involved in depression of vascular reactivity by endotoxin. Br J Pharmacol 1991; 103:1947-52

3rd International Symposium on Advanced Physiological Monitoring

Dr. Ulrich J. Pfeiffer, Institut fur Experimentelle Chirurgie der Technischen Universitat Munchen, has announced that this congress will be held September 8-10 at the Gasteig Congress Center, Munich, Germany. For information, contact the MCN Medizinische Congressorganisation Nurnberg GmbH, Wielandstrasse 6, D-90419 Nurnberg, Germany (49-(0)911-37 40 12.)