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Burgdorff, Anna-Maria; Bucher, Michael; Schumann, Julia .

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journals.sagepub.com/home/imr**A.-M. Burgdorff, M. Bucher and J. Schumann**

Abstract

Sepsis is one of the most frequent causes of death among patients in intensive care units. Many therapeutic strategies have been assessed without the desired success rates. A key risk factor for death is hypotension due to vasodilatation with vascular hyposensitivity. However, the pathways underlying this process remain unclear. Endotoxemia induces inflammatory mediators, and this is followed by vasoplegia and decreased cardiac contractility. Although inhibition of these mediators diminishes mortality rates in animal models, this phenomenon has not been confirmed in humans. Downregulation of vasoconstrictive receptors such as angiotensin receptors, adrenergic and vasopressin receptors is seen in sepsis, which is associated with a hyporesponsiveness to vasoconstrictive mediators. Animal studies have verified that receptor downregulation is linked to the above-mentioned inflammatory mediators. Anti-inflammatory therapy with glucocorticoids reportedly improves responsiveness to catecholamines with higher survival in rats, although this has not been shown to be clinically significant in humans. Hence, there is an urgent need for in-depth studies investigating the underlying mechanisms of vasoplegia to allow for development of effective therapeutic strategies for the treatment of sepsis.

Keywords

Vasoplegia, sepsis, cytokines, vasoactive receptors, hypotension, endotoxemia

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Background

Sepsis and septic shock are two of the main causes of death at intensive care units worldwide, accounting for approximately 1400 deaths daily.¹ This incidence is increasing by nearly 9% per year, with a worldwide mortality rate of approximately 50%.^{1–4} **This considerable death rate is**

Department of Anesthesiology and Surgical Intensive Care, University Hospital Halle (Saale), Halle (Saale), Germany

Corresponding author:

J. Schumann, Department of Anesthesiology and Surgical Intensive Care, University Hospital Halle (Saale), Franzosenweg 1a, Halle (Saale) 06112, Germany. Email: julia.schumann@uk-halle.de



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attributable to the inadequacy of current treatment options, which are limited and unsatisfactory. The most important therapeutic steps in sepsis are to treat the focus of inflammation with antibiotics or a surgical procedure and stabilize the cardiac and respiratory systems.^{5,6}

Hypotension is a key risk factor for death in patients with sepsis. Hypotension may be initiated by various causes. One is a decrease in the intravascular volume secondary to capillary leakage, which is treated by volume therapy. Nevertheless, patients who develop septic shock, which is associated with a 40% increase in mortality,⁷ show persistent hypotension despite adequate volume therapy. This suggests that hypotension has another root cause that might be high-risk and difficult to manage. The physiologically normal reaction to a low mean arterial pressure (MAP) is vasoconstriction in the peripheral circulation based on activation of the renin-angiotensin system and an increase in the catecholamine concentration.⁸ In patients with sepsis, the common vasoconstrictors do not act sufficiently. Patients develop vasodilatory shock; i.e., therapy-resistant vasodilatation with vascular hyporesponsiveness and hyporesponsiveness to vasoconstrictors.

This review article summarizes and discusses the most important pathomechanisms of vasoplegia in patients with sepsis to provide a basis for progress in treatment approaches. **To this end, a systematic literature search of Medline and Entrez PubMed was performed. No database search filters were applied. The search strategy encompassed the query terms “vasodilation,” “vasoplegia,” “vasopressins,” “NFκB,” “cytokines,” “interferons,” “interleukins,” “tumor necrosis factor,” “angiotensin,” “angiotensin II receptor blockers,” “methylene blue,” “nitric oxide,” “prostaglandins,” “endotoxemia,” and “septic shock.”**

Inflammatory mediators

The physiological and molecular background of vasodilatory shock has been extensively studied. A dominant proinflammatory milieu prevails in patients with sepsis and is driven by the activation of inflammation-associated transcription factors such as nuclear factor kappa B (NFκB) and the release of endogenous mediators such as nitric oxide (NO) as well as proinflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-1 beta (IL-1β).⁹ The presence of these mediators has been associated with cardiac and vascular dysfunction. Direct central myocardial depression and regional failure of vascular smooth muscle cells with ineffective vasoconstriction have been described.^{8,10} However, strategies by which to resolve mediator imbalances using inhibitors of NO, TNF-α, IL-1β, or prostaglandins/prostacyclins have not improved the survival of patients with sepsis.

In sepsis, the characteristic proinflammatory milieu results from activation of basal immune-related transcription factors. As mentioned above, the most important transcription factor in sepsis is NFκB. Activation of NFκB occurs by recognition of typical surface molecules of gram-positive and gram-negative bacteria via the Toll-like receptor (TLR)-mediated signaling pathway.^{11,12} Furthermore, NFκB is triggered by proinflammatory cytokines such as TNF-α and IL-1β.^{11,12} A positive feedback loop is established as proinflammatory cytokines are released by enabled (i.e., NFκB-activated) immune cells.¹² Additionally, NFκB induces the increased expression of chemokines, adhesion molecules, and enzymes such as induced NO synthase (iNOS) and cyclooxygenase-2 (COX-2) through regulation of gene expression.^{9,11-13} The influence of NFκB on TNF-α release and iNOS and COX-2 expression is cited as one reason for systemic hypotension secondary to vasodilatation, decreased

vascular responsiveness to vasoconstrictors, and reduced cardiac contractility.¹² In this context, the inhibition of NF κ B has been assumed to reduce cardiac dysfunction.⁹ In lipopolysaccharide (LPS)-stimulated mice, the specific NF κ B inhibitor SUN C8079 was shown to result in diminished gene expression of TNF- α and iNOS, and this decrease was accompanied by a dose-dependent reduction in mortality.¹⁴ Similar results were obtained with another specific NF κ B inhibitor, IRFI-042, which reduced TNF- α release and lethality in endotoxin-treated rats.⁹ The antioxidant pyrrolidine dithiocarbamate, another selective inhibitor, dose-dependently attenuates NF κ B/DNA complexes and impairs the LPS-induced decrease in MAP in rats.¹⁵ Nevertheless, inhibition of NF κ B also has some detrimental effects. In one study, mice without a working NF κ B subunit p50 were unable to successfully defend against *Streptococcus pneumoniae* infection.^{11,12} The use of NF κ B inhibitors as a therapeutic strategy is therefore limited due to interaction with its host-defense function, which is important to eliminate sepsis-causing pathogens.¹²

Sepsis-mediated induction of iNOS leads to increased production of NO.¹⁶ NO itself activates soluble guanylate cyclase,¹⁷ which increases cyclic guanosine monophosphate (cGMP) and thereby triggers relaxation of myocardial and vascular smooth muscle.¹⁸ Treatment of mice with LPS reportedly results in expression of iNOS mRNA, which is accompanied by reduced contraction of the carotid rings compared with nonseptic mice and mice deficient in iNOS.¹⁷ Likewise, reactivity of aortic smooth muscle to the catecholamine norepinephrine is decreased in septic mice.¹⁹ LPS-treated rat hearts have been verified to develop increased iNOS and NO levels with decreased cardiac work and efficiency.²⁰ In humans, the responsiveness to catecholamines in LPS-pretreated failing and nonfailing hearts is reduced while iNOS

mRNA is highly expressed in all preparations, but without increased cGMP.²¹ Accordingly, different therapeutic approaches to iNOS and NO production have been evaluated. In LPS-based sepsis models of rats and rabbits, treatment with a specific iNOS inhibitor (1400W) reportedly reduced the NO blood level and hypotension in rats, but not in rabbits.²² In late but not early sepsis, 1400W improved cardiac contraction in rats.²³ Enhanced cardiac work and contractile function has also been shown in association with the iNOS inhibitors mercaptoethyl guanidine, aminoguanidine, or methylene blue in rat and mouse models.^{17,24,25} Human patients with sepsis who received methylene blue developed an increase in MAP and systemic vascular resistance, while changes in the cardiac index were dose-dependent and adverse events such as methemoglobinemia, hemolytic anemia, and changes in pulmonary function occurred.^{18,26,27} Overall, there is no survival advantage.²⁶ Treatment of human patients with sepsis using nonselective NOS inhibitors (L-arginine competitive analogs) has yielded both beneficial and detrimental results. The nonselective NOS inhibitor L-NMMA reportedly prevents an LPS-induced decrease in cardiac contractility²¹ and left ventricular function.¹⁷ Another nonselective NOS inhibitor, 546C88, was associated with higher mortality (59%) compared with placebo (49%) on day 28 in patients with sepsis, and an increased number of adverse events such as cardiac failure, diminished cardiac output, and pulmonary hypertension occurred with the use of this inhibitor.^{1,28} Collectively, study findings widely differ among different animal species as well as between animal models and humans; this is problematic in terms of developing new therapies. Moreover, the therapeutic success of iNOS inhibition might depend on the dose, time of administration, and phase of sepsis. More studies are clearly

necessary to evaluate the potential benefits of iNOS inhibitors for patients with sepsis.

Other therapeutic options that have been evaluated for sepsis include inhibition of inflammation-driving mediators such as prostaglandins (e.g., PG_2), prostacyclins (e.g., PGI_2), $\text{TNF-}\alpha$ and $\text{IL-1}\beta$. Nevertheless, no resounding improvement in survival of human patients with sepsis has been found based on such treatments.^{29,30} Multicenter randomized trials have only shown a small mortality reduction of 3.5% when various anti- $\text{TNF-}\alpha$ antibodies are administered to patients with sepsis.^{29,31} Therefore, these approaches are without practical relevance in everyday medical care of patients with sepsis.

Vasoconstrictive receptors

Patients with sepsis develop diminished plasma vasopressin levels^{8,32} and downregulation of vasoconstrictive receptors (angiotensin receptors, adrenergic receptors, and vasopressin receptors).³³ Consequently, treatment with common vasoconstrictors after volume resuscitation does not reduce mortality or result in any differences in organ dysfunction.^{34,35} A new therapeutic option could be to interfere with pathways affecting the expression and action of vasoconstrictive receptors. Few studies have investigated downregulation of vasoconstrictive receptors as a cause of vasoplegia in patients with sepsis.

One important player in MAP regulation is the renin-angiotensin system. Activation of the renin-angiotensin system ultimately results in the release of physiologically active angiotensin II (AG II). Increased levels of renin and AG II have been found in animal models of sepsis.^{33,36} However, despite the high concentrations of AG II in the circulation, sepsis is associated with a decrease in MAP in these animals.^{33,36} AG II acts in association with angiotensin II type 1 (AT_1) and angiotensin II type 2

(AT_2) receptors. *In vivo* experiments utilizing mice or rats have verified downregulation of both the AT_1 and AT_2 receptor under septic conditions (cecal ligation and puncture model, endotoxemia, cytokine treatment) in various organs and tissues such as the heart, smooth muscle, liver, kidney, and lung.^{33,36-38} The inflammation-induced downregulation of AT_1 and AT_2 receptors could be reproduced *in vitro* via treatment of cells with a combination of the cytokines $\text{IL-1}\beta$, $\text{TNF-}\alpha$, and $\text{IFN-}\gamma$.^{33,36,38} Notably, siRNA-mediated inhibition of the cytokines $\text{IL-1}\beta$, $\text{TNF-}\alpha$ and $\text{IFN-}\gamma$ or of the transcription factor $\text{NF}\kappa\text{B}$ prevented the downregulation of AT_1 receptors, underlining the role of inflammatory signaling in sepsis-associated vasoplegia.³⁹ A further important player seems to be the AT_1 receptor-associated protein 1 (Arap 1). Expression of Arap 1 is reduced under conditions of septic shock.⁴⁰ In an Arap 1-deficient mouse model, sepsis-induced hypotension was found to be markedly increased compared with wild-type mice despite a similar baseline MAP.⁴⁰ This was associated with a reduced sensitivity to AG II in the vasculature of Arap 1-deficient animals.⁴⁰

Catecholamine-dependent blood pressure regulation is primarily mediated by the family of α_1 -adrenergic receptors. The three subtypes of these receptors are α_{1A} , α_{1B} , and α_{1D} . The α_{1A} - and α_{1D} -receptors are located in larger vessels, while the α_{1B} -receptor can be found in smaller vessels.³³ Treatment of human vascular cells with $\text{TNF-}\alpha$ results in downregulation of α_1 -adrenergic receptors.³⁷ Likewise, in septic mice, a cytokine- and time-dependent reduction in α_1 -adrenergic receptor expression has been shown.^{33,41} This was accompanied by a diminished binding capacity of the main α_1 -adrenergic receptor ligand, norepinephrine, which is one of the first vasopressors used in the treatment of sepsis.^{33,41} Interestingly, treatment of mice with dexamethasone and aldosterone

respectively attenuated the cytokine-mediated downregulation of α_1 -adrenergic receptors, which might be due to lower levels of proinflammatory cytokines.⁴² Therapy with aldosterone was accompanied by a higher response to catecholamines and higher survival rates.⁴¹

Vasopressin, also known as antidiuretic hormone, induces contraction of vascular smooth muscle cells following binding to its receptor. It mediates low vasoconstrictor effects; thus, high doses of vasopressin are necessary to induce an increase in blood pressure during sepsis. These high doses are accompanied by considerable adverse effects.^{43,44} Besides being a weak vasopressor, vasopressin has the ability to potentiate the vasoconstrictor effects of other vasopressors such as AG II or norepinephrine.⁸ However, in line with AT₁-, AT₂-, and α_1 -receptors, sepsis-mediated downregulation of the vasopressin receptor (subtype V_{1A}) has been reported and is due to increased levels of the cytokines IL-1 β , TNF- α , and IFN- γ .^{33,45} A decrease in the vasopressin binding capacity subsequently occurs.^{33,45} Treatment of septic animals with methylprednisolone reduces proinflammatory cytokine levels, thereby attenuating receptor downregulation.^{45,46} **However, despite the fact that anti-inflammatory therapy with glucocorticoids in animal models of sepsis diminishes the cytokine-mediated downregulation of vasoconstrictive receptors, such as α_1 -adrenergic receptors or the V_{1A} receptor, the clinical significance of this phenomenon in humans remains low. No clear survival advantage has been found in patients with sepsis treated with glucocorticoids.**^{29,30}

Conclusions

The pathomechanisms of sepsis-induced vascular dysfunction and vascular hyporesponsiveness to vasoconstrictors (vasoplegia) remain incompletely understood. One key factor seems to be endotoxemia-mediated

impairment of vasoconstrictive receptors. Existing data support the concept of sepsis-associated cytokines as the driving force in the inhibition of vasoconstrictive components. Therefore, future research should aim to elucidate the molecular mechanisms through which sepsis-relevant cytokines modulate receptor expression patterns of endothelial and smooth muscle cells. The identification of involved signaling pathways might be a decisive step toward the development of new therapeutic strategies for the treatment of sepsis-associated vasoplegia.

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Declaration of conflicting interests

The authors declare that there is no conflict of interest.

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