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REVIEW

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# Vascular hyporesponsiveness to vasopressors in septic shock: from bench to bedside

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**Abstract** *Purpose:* To delineate some of the characteristics of septic vascular hypotension, to assess the most commonly cited and reported underlying mechanisms of vascular hyporesponsiveness to vasoconstrictors in sepsis, and to briefly outline current therapeutic strategies and possible future approaches. *Methods:* Source data were obtained from a PubMed search of the medical literature with the following MeSH terms: Muscle, smooth, vascular/physiopathology; hypotension/etiology; shock/physiopathology; vasodilation/physiology; shock/therapy; vasoconstrictor agents. *Results:* Nitric oxide (NO) and peroxynitrite are crucial components implicated in vasoplegia and vascular hyporeactivity. Vascular ATP-sensitive and calcium-activated potassium channels are activated during shock and participate in hypotension. In addition, shock state is characterized by inappropriately low plasma glucocorticoid and vasopressin concentrations, a dysfunction and desensitization of alpha-receptors, and an inactivation of catecholamines by oxidation. Numerous other mechanisms have been individualized in animal models, the great majority of which involve NO: MEK1/2–ERK1/2 pathway, $H_2S$, hyperglycemia, and cytoskeleton dysregulation associated with decreased actin expression. *Conclusions:* Many therapeutic approaches have proven their efficiency in animal models, especially therapies directed against one particular compound, but have otherwise failed when used in human shock. Nevertheless, high doses of catecholamines, vasopressin and terlipressin, hydrocortisone, activated protein C, and non-specific shock treatment have demonstrated a partial efficiency in reversing sepsis-induced hypotension.

**Keywords** Septic shock · Vasopressor · Nitric oxide · Potassium channels · Catecholamine

## Introduction

Septic shock is the primary cause of death in critical care units [1]. Shock states are primarily characterized by acute circulatory failure leading to tissue hypoperfusion, and potentially resulting in multi-organ failure. Observed hypotension can be the consequence of three major hemodynamic disorders: hypovolemia, vascular failure, and heart failure [2]. Vascular dysfunction [3] is characterized by: (1) microvascular dysfunction, (2) endothelial dysfunction, and (3) a decrease in vasoconstrictor tone as well as vascular hyporesponsiveness along with a lesser sensitivity to vasopressor agents such as catecholamine but also vasopressin, angiotensin II,

and serotonin [4]. The outcome of the last of these characteristics is vasopressor-refractory arterial hypotension which can ultimately lead to patient death. The purpose of the present review is to assess the most commonly cited and reported underlying mechanisms of decreased responsiveness to vasoconstrictors in sepsis, to summarize their relevance and clinical applicability, and to briefly outline current therapeutic strategies and possible future approaches. This review is not intended to be all-inclusive.

## Definition(s) of vascular hyporesponsiveness to vasopressor agents

Vascular hyporeactivity to vasopressor agents is defined by a decreased effect of a vasopressor agent when compared to the normal response due to failure of vascular smooth muscle to constrict [4]. Vascular hyporeactivity can most often be observed either experimentally in organ chambers by exposing segments of isolated vessels to vasopressor agents, or in clinical practice by establishing dose–response curves to a pure alpha-adrenergic agonist such as phenylephrine. In this case, vascular hyporesponsiveness is defined by a smaller increase in arterial blood pressure (in patients) for a similar dose of vasopressor agent (healthy volunteers) [5]. This latter technique also incorporates other regulatory mechanisms, such as cardiac adaptation and baroreflex.

Hypotension associated with vascular hyporeactivity is clearly related, both significantly and independently, to mortality [6]. The extent of this vascular hyporesponsiveness can be assessed clinically by the measure of vasopressor dosage necessary to maintain mean arterial blood pressure [7] and by the drop in diastolic blood pressure reflecting vasoplegia [8, 9].

## Physiology

Vasoconstriction is the result of increased intracellular calcium in vascular smooth muscle cells (VSMCs) and involves two mutually dependent and synergistic processes. On the one hand, the increase in intracytoplasmic calcium can result from the action of neural or hormonal ligands such as angiotensin II or norepinephrine via their specific membrane receptors on the VSMC (G protein-coupled receptors). Alternatively, the increase in intracytoplasmic calcium can also be generated by a change in membrane potential. The normal membrane potential of smooth muscle cells varies between −45 and −70 mV. A depolarization of the membrane (to a potential approaching 0 mV) induces the opening of voltage-gated calcium channels and thus the influx of extracellular calcium into the VSMC.

Relaxation of the VSMC results from the decrease in the concentration of cytoplasmic calcium, either by expulsion of calcium to the extracellular space or by its reuptake into the sarcoplasmic reticulum. Again, several mechanisms may be involved.

Certain mediators such as nitric oxide, the atrial natriuretic peptide, as well as acetylcholine, serotonin, and histamine are known vasorelaxant agents. These mediators bring about an increase in cyclic guanosine monophosphate and cyclic adenosine monophosphate (cGMP and cAMP) through the action of guanylate cyclase and adenylyl cyclase respectively.

## Clinical evidence of vascular hyporesponsiveness in septic shock

Clinical evidence has confirmed vascular hyporesponsiveness in septic shock, since volume-resuscitated septic shock patients remain hypotensive despite elevated levels of endogenous and exogenous catecholamines [10] and a maximum activation of the renin-angiotensin system. Administration of large doses of catecholamines is hence necessary to increase arterial pressure. In an experimental study, Bellissant and Annane [5] compared 20 patients with septic shock with 12 healthy subjects. Dose–response curves to phenylephrine, a pure alpha-adrenergic agonist, were established and ultimately showed a decreased response to alpha-adrenergic stimulation in the septic shock patients.

## Mechanisms involved

Vascular hyporesponsiveness to vasopressor during sepsis is probably multifactorial. Nevertheless, it is important to identify individual contributing factors and mechanisms in order to select meaningful therapeutic targets. As a consequence, a vast array of mechanisms, pathways, and disruptions in cellular homeostasis have been examined in septic vessels [11] (Figs. 1, 2, 3).

### Nitric oxide

Nitric oxide (NO) is an omnipresent intercellular messenger found in all vertebrates, notably regulating blood flow, coagulation, and neural activity. Physiologically, NO is produced in picomolar concentrations from L-arginine by nitric oxide synthase (NOS), an enzyme constitutively present in endothelial cells and termed endothelial constitutive NOS (cNOS). According to a few recent studies, a mitochondrial isoform of NOS (mtNOS) may also represent a significant source of NO during

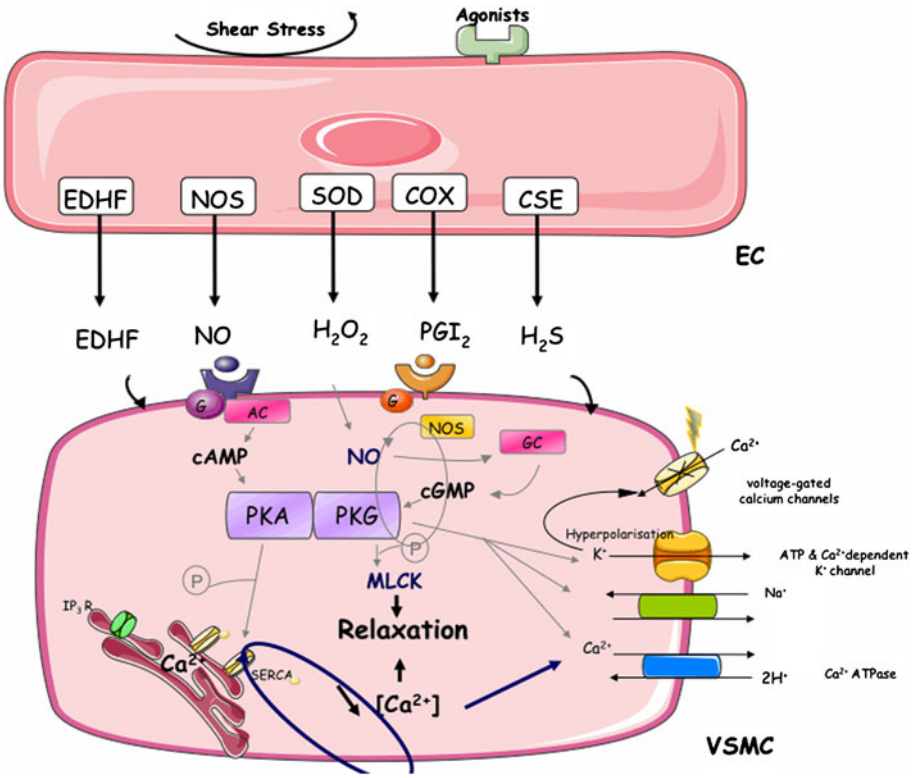


**Fig. 1** Endothelium-dependent relaxation. Multiplicity of mechanisms leading to endothelium relaxation such as shear stress and vasorelaxant agonists; ECs synthesize and release various vasorelaxation factors that can diffuse towards the VSMCs and produce relaxation. *EC* endothelial cell, *VSMC* vascular smooth muscle cell, *EDHF* endothelium-derived hyperpolarizing factor, *NOS* nitric oxide synthase, *SOD* superoxide dismutases, *COX* cyclooxygenase, *CSE* cystathionine $\gamma$-lyase, *NO* nitric oxide, $H_2O_2$ hydrogen peroxide, $PGI_2$ prostacyclin, $H_2S$ hydrogen sulfide; *G* protein G, *AC* adenylyl cyclase, *NO* nitric oxide, *GC* guanylate cyclase, *cAMP* cyclic adenosine monophosphate, *cGMP* cyclic guanosine monophosphate, *PKA* protein kinase A, *PKG* protein kinase G, *MLCK* myosin light-chain kinase, *SERCA* sarcoplasmic/endoplasmic reticulum $Ca^{2+}$-ATPases, *ATP* adenosine triphosphate, *IP3R* inositol-1,4,5-trisphosphate-receptor, *P* phosphate

circulatory shock [12]. A non-enzymatic source of NO has also been described related to the reduction of nitrites under acidic and reducing conditions, as can occur in ischemic tissues [13]. NO diffuses into the underlying vascular smooth muscle and induces vasorelaxation via stimulation of soluble guanylate cyclase and resulting increase in cGMP concentration [14].

In the mid-1980s, it became apparent that inhibitors of NOS were able to restore, to a large extent, this contractile response to vasoconstrictor agents [15]. These effects were maintained in vessel models ex vivo, even in the absence of endothelium, thereby suggesting that inflammation and sepsis lead to the expression of an inducible NOS (iNOS) in vessel wall smooth muscle. Excessive production of NO (nanomolar concentrations) by iNOS hence resulted in an altered contractile response. Authors thus concluded that the results (1) were consistent with the pathophysiology observed, both experimental and clinical, during sepsis, and (2) may explain the profound vasoplegia and limited response to stimuli that normally regulate blood flow and tissue perfusion. High circulating levels of nitrites/nitrates (stable molecules generated from NO) found in patients with septic shock and associated with decreased vascular tone suggested that NO was clearly implicated in the pathophysiology of septic shock [16].

The above observations led to the initial use of non-selective inhibitors of NOS such as $N^G$-nitro-L-arginine methyl ester (L-NAME) in LPS models [17]. L-NAME increases blood pressure and vascular resistance along with a decrease in cardiac output. It is important to note, however, that these treatments did not improve survival in an animal model of endotoxemia [18]. Unfortunately, a phase III study was halted due to the emergence of a significant over-mortality in the treated group [19]. It was proposed that the use of a more selective inhibitor of iNOS would provide greater benefit to the patients. Some positive experimental results have since been reported with specific molecules such as *S*-methylisothiourea, L-canavanine [20], and aminoguanidine, but none have been tested to date in clinical trials. However, blocking the production of NO may cause other deleterious effects [21] such as:

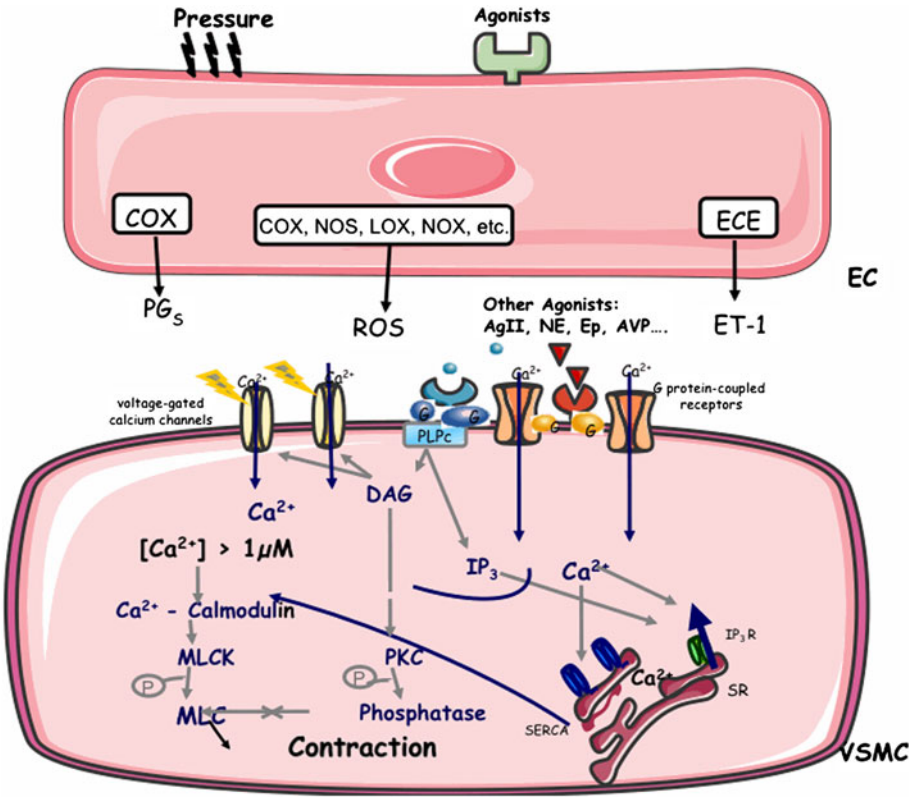


**Fig. 2** Mechanisms of contractions. Under certain conditions, the endothelial cells, when activated by neurohumoral mediators or subjected to pressure, release a vasoconstrictor substance(s), which diffuses to the underlying vascular smooth muscle and initiates its contraction. *EC* endothelial cell, *VSMC* vascular smooth muscle cell, *COX* cyclooxygenase, *LOX* lipoxygenase, *NOX* NADPH oxidase, *NOS* nitric oxide synthase, *ECE* endothelin-converting enzyme, *PGs* prostaglandins, *ROS* reactive oxygen species, *ET-1* endothelin-1, *AgII* angiotensin II, *NE* norepinephrine, *Ep* epinephrine, *PLPc* phospholipase C, *DAG* diacylglycerol, *IP3* inositol trisphosphate, *PKC* protein kinase C, *IP3R* inositol-1,4,5-trisphosphate-receptor, *PKC* protein kinase C, *MLCK* myosin light-chain kinase, *SERCA* sarcoplasmic/endoplasmic reticulum $Ca^{2+}$-ATPases

- Altered microcirculatory flow
- A decrease in NO-dependent bactericidal activity
- A decrease in neutralizing activity of oxygen-derived species
- A decrease in the modulation of blood coagulation
- An increase in oxygen demand by improving mitochondrial respiration in tissues in which perfusion, and hence oxygen delivery, remains precarious, thereby exacerbating the oxygen supply/demand balance

Thus, the current paradigm that NO and soluble guanylate cyclase (sGC) contribute to organ damage and death associated with septic shock may be challenged. For example, Cauwels et al. [22] recently demonstrated that nitrite treatment protects against morbidity and mortality in lipopolysaccharide (LPS)-induced shock in a soluble guanylate cyclase-dependent manner.

To summarize, excess production of NO seems to be a major and central actor in sepsis-induced vascular hyporeactivity. Nevertheless, inhibition through non-selective iNOS inhibitor increased mortality in septic shock.

## Prostacyclin and COX-2 pathways

Prostacyclin ($PGI_2$) is a major product of arachidonic acid metabolism formed in the vascular endothelium by the action of the enzymes cyclooxygenase (COX) and prostacyclin synthase (PGIS). $PGI_2$ mediates its effects through a $G_s$ protein-coupled receptor (IP), which is located on VSMCs. Stimulation of IP by $PGI_2$ leads to an increase in cAMP, which likely mediates relaxation of VSMCs. Increased levels of $PGI_2$ have been reported to occur in patients under septic shock and in animals treated with LPS or proinflammatory cytokines [23]. Recent evidence suggests that the inducible isoform of COX, COX-2, is the enzyme mainly responsible for the increased production of $PGI_2$ in VSMCs [24]. In keeping with this observation, it has been shown that inhibition of COX-2 attenuates the fall in blood pressure or improves vascular endothelial dysfunction in endotoxemic animals. Recently, Höcherl et al. [25] demonstrated that the selective inhibition of the receptor for prostacyclin attenuated the cardiovascular dysfunction induced by LPS without altering cytokine levels or NOx products, thus evoking a specific role for prostacyclin and/or the receptor for prostacyclin in the development of LPS-induced vascular failure.

Similarly to iNOS inhibitors, the non-selective inhibition of prostaglandin synthesis with ibuprofen failed to improve mortality in septic shock [26].

## Free radicals: the peroxynitrite ion and superoxide anion

Free radicals are molecules or portions thereof which possess one or more unpaired electrons in their outer orbital, a state

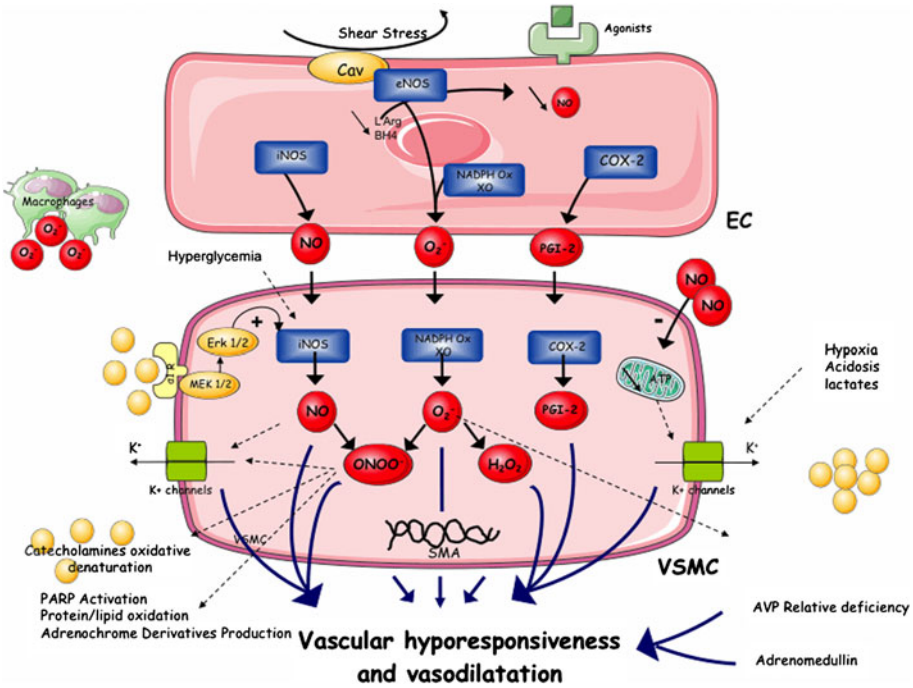


**Fig. 3** Mechanisms of vascular dysfunction in sepsis. When the infectious agent invades the bloodstream, systemic activation of inflammation leads to cytokine release and endothelial activation and dysfunction. Multiple cascades of intracellular signaling reactions are initiated and induce vascular hyporesponsiveness and vasodilatation. A functional impairment of ECs and VSMCs contributes to endothelial and vascular dysfunction. Both cells synthesize and release various factors of oxidative stress and vasodilatation, which subsequently react with many products, receptors, and channels to induce their oxidation. *EC* endothelial cell, *VSMC* vascular smooth muscle cell, *eNOS* endothelial nitric oxide synthase, *BH4* 5,6,7,8-tetrahydrobiopterine, *Cav* caveolin-1, *L-Arg* L-arginine, *iNOS* inducible nitric oxide synthase, *COX-2* cyclooxygenase-2, *NADPH Ox* oxy nicotinamide adenine dinucleotide phosphate, *XO* xanthine oxidase $O_2^-$ superoxide anions, *PGI-2* prostacyclin, *NO* nitric oxide, $ONOO^-$ peroxynitrite, $H_2O_2$ hydrogen peroxide, *Erk* extracellular signal-regulated kinases, *MEK 1/2* mitogen-activated protein kinase kinases 1/2, *Erk 1/2* extracellular signal-regulated kinases 1/2, *AVP* arginin vasopressin

that greatly increases their reactivity. The best-known reactive species generated from oxygen include superoxide anion, hydroxyl radical, and peroxynitrite.

It should be emphasized that every time NO and superoxide anion molecules collide, they spontaneously interact to form peroxynitrite [27]. This reaction does not require any enzymatic intervention. As a result, it is possible that the majority of the biological effects attributed to NO are rather due to peroxynitrite.

A state of shock constitutes a propitious environment for the production of peroxynitrite since NO and superoxide are both produced in large quantities and in the same tissues. The upregulated production of superoxide arises from the reactions catalyzed by NAPDH oxidase present in leukocytes and endothelial cells, by the conversion of xanthine dehydrogenase into xanthine oxidase, by the partial reduction of molecular oxygen within mitochondria, and finally by the uncoupling of NOS in conditions of L-arginine or tetrahydrobiopterin deficiency [27]. Formation of peroxynitrite has been demonstrated by using LPS as the inducer of shock with a time course similar to that of iNOS expression in muscle and aorta [28]. In endotoxic and hemorrhagic shock models, it has been shown that inhibitors of peroxynitrite formation and genetic suppression of nicotinamide adenine dinucleotide phosphate (NADPH) are able to reduce the amount of aortic peroxynitrite and reverse vascular hyporesponsiveness. Conversely, the increase in endogenous production of peroxynitrite by inducing a depletion of endogenous glutathione stores aggravates vascular hyporeactivity. Numerous studies have shown that the final effector of the deleterious effect of peroxynitrite on vascular responsiveness is linked to the activation of poly (ADP-ribose) polymerases (PARP), which are proteins involved in many cellular processes such as DNA repair and apoptosis [13].

Superoxide anion per se has also been implicated in vascular hyporeactivity. Superoxide is enzymatically reduced to hydrogen peroxide in the presence of superoxide dismutase (SOD). However, in many disease states such as shock, there is an imbalance between the amount of superoxide formed and the ability of SOD enzyme to remove the former, hence leading to superoxide-driven damage. Macarthur et al. [29] have published experimental evidence suggesting that hyporeactivity to exogenous norepinephrine results from its deactivation by

superoxide. Furthermore, these authors have also shown that endotoxin-induced hypotension is completely abolished by the administration of M40403, a synthetic and selective (for superoxide) low molecular weight mimic of SOD [30]. Nevertheless, despite these intriguing experimental results, there are currently no studies that have assessed the effects of neutralizing peroxynitrite or superoxide during human septic shock.

## ATP-sensitive potassium channels

ATP-sensitive ($K_{ATP}$) potassium channels are distributed in a wide variety of tissues. Potassium ($K^+$) channels are membrane-spanning proteins that selectively allow movement of $K^+$ ions across cells through a water-filled permeation pathway (pore). A gating mechanism switches the channel between open and closed conformations. Normally, channel opening at the plasma membrane promotes $K^+$ loss from the cell, resulting in membrane hyperpolarization. These channels ensure the coupling between membrane excitability and energy metabolism of the cell, thus playing a primary role in both normal and pathological situations. Excessive activation of $K^+$ channels leads to membrane hyperpolarization and inhibition of voltage-sensitive calcium channels, inducing cell relaxation, vasodilation, and finally leading to hypotension and vascular hyporeactivity.

Various pathological situations such as increased NO and peroxynitrite production, ATP depletion, hypoxia, acidosis, and hyperlactatemia present during shock states can activate vascular $K_{ATP}$ channels and induce membrane hyperpolarization, thereby inducing cellular relaxation and vasorelaxation [11].

Experimental evidence for the involvement of $K_{ATP}$ channels was first established by Landry and Oliver [31] who demonstrated in an experimental model of endotoxic shock and hypoxic lactic acidosis that the injection of glibenclamide (a sulfonylurea inhibitor of $K_{ATP}$ channels) restored arterial pressure and responsiveness to catecholamines, both of which are largely reduced during these types of shock. Several experimental studies [32] of endotoxic shock have since confirmed these data, while subsequent studies have highlighted a decrease in contractile function in response to vasoconstrictors in rat arteries incubated in the presence of endotoxin. This hypocontractility is in turn partly restored in the presence of glibenclamide [32].

To date, two studies [33, 34] have studied the effects of glibenclamide versus placebo administration in patients with septic shock. Both studies showed no significant reduction in vasoconstrictor dose requirements or any significant improvement in arterial blood pressure in patients treated with glibenclamide. At the present time, the therapeutic perspectives for the use of potassium channel inhibitors in humans remain disappointing given the ubiquitous nature of these channels and their diverse pathophysiological implications.

## Involvement of $BK_{Ca}$ channels

The large-conductance calcium-activated potassium ($BK_{Ca}$) channels are by far the most abundant of the vascular potassium channels. Their role is to induce vascular relaxation when calcium levels are elevated and thus play a regulatory role in microvascular flow. These channels are activated in part by NO and by peroxynitrite and are therefore involved in vasoplegia observed during shock states. Experimentally, their inhibition enables one to improve vasoconstrictor response in both animal [35] and human sepsis [36]. There are currently no human data.

## Critical illness-related corticosteroid insufficiency

Critical illness-related corticosteroid insufficiency (CIRCI) is caused by adrenal insufficiency together with tissue corticosteroid resistance and is characterized by an exaggerated and protracted proinflammatory response [37]. CIRCI should be suspected in hypotensive patients who respond poorly to fluids and vasopressor agents, particularly in the setting of sepsis. In a study recently published by Annane et al. [38], the prevalence of adrenal insufficiency (as determined by metyrapone testing) in patients with severe sepsis and septic shock was reported to be 60%. Nevertheless, using an electrochemiluminescence immunoassay, data stemming from the Corticus Study [39, 40] demonstrated that there was a high inter-assay variation of total serum cortisol. Comparisons with a reference method revealed both over- and underestimations of true cortisol levels. These inter-assay variations in samples of patients with septic shock complicate the diagnosis of corticosteroid insufficiency.

The major effect of adrenal insufficiency in the critically ill patient is manifested through alterations in systemic inflammatory response and cardiovascular function. The use of glucocorticoids in septic shock is discussed in section "Therapeutics".

## Modifications of catecholamine signaling

The regulation of adrenergic receptors during sepsis has been studied at greater length for myocardial beta-receptors than for vascular alpha-receptors. At the heart level, Wu et al. [41] demonstrated that alpha-1 adrenergic receptors in the rat heart were externalized from light vesicles to the sarcolemma during the early hypercardiodynamic phase as opposed to being internalized from surface membranes to intracellular compartments during

the late hypocardiodynamic phase of sepsis. The liver is the most studied organ, albeit with the difficulty in correlating the observed modifications with those presumably occurring at the vessel level. For example, McMillan et al. [42] observed a reduction in the number of hepatic alpha-1 adrenergic receptors in a rat model of chronic sepsis. Conversely, Hwang et al. [43] noted that alpha-1 adrenergic receptors in human liver plasma membranes undergo dynamic changes during the development of sepsis; that is, receptor number increased in mild sepsis, returned to normal levels in moderate sepsis, and finally decreased in severe sepsis. This desensitization has no univocal explanation and involves a decrease in the number of receptors (downregulation) and/or an uncoupling of receptors and their intracellular messengers.

The use of beta-blockers in septic shock has been investigated in normotensive rodent models but not in human septic shock [44].

### Hyperglycemia and insulin

As part of the stress response, shock patients become hyperglycemic. Clearly, hyperglycemia is associated with adverse outcome and normalizing blood glucose by intensive insulin therapy improves mortality and morbidity. Pacheco et al. [45] demonstrated in healthy rats that high glucose increases iNOS induction and subsequent NO production by activating the protein kinase C-beta II. Glycemic control may affect regional NO bioavailability by changing NOS activity, NOS transcription, NOS substrate availability, or the endogenous NOS inhibitor asymmetric dimethylarginine (ADMA) levels [46].

Although promising in animal models [47], intensive insulin therapy did not improve in-hospital mortality in patients treated with hydrocortisone for septic shock [48].

## Vasodilation is heterogeneous

During shock state and especially in sepsis, there are marked differences in vasopressor responses according to the vessel under investigation. Resistance arteries such as those present in the mesenteric vascular bed play a major role in blood pressure maintenance. On the other hand, conductance arteries such as the aorta only make a small contribution to systemic vascular resistance. The majority of in vitro investigations into mechanisms of vascular hyporeactivity have used rodent aortic tissues [15]. In contrast, inducing hyporeactivity in smaller rodent blood vessels has proven to be difficult [49]. Moreover, in septic shock patients, Stoclet et al. [50] found that contractile responses of small omental arteries from septic patients were not significantly altered ex vivo. This observation is certainly intriguing since the arteries were removed from patients whose peripheral resistance and blood pressure were dramatically reduced. Moreover, contraction experiments performed in the presence of either L-NAME or indomethacin unmasked enhanced responses to low concentrations of NE in arteries from septic patients. The mechanisms of this hyperactivity are unknown but highlight the potential opposite behavior between resistive and conductive arteries during sepsis.

From a clinical standpoint, we must keep in mind that arterial pressure during shock is measured in a conductive artery. Thus, the titration of vasopressor may be inadequate in increasing arterial pressure more than is needed for the microcirculation. This latter point is illustrated by the fact that the use of an NO donor such as nitroglycerin in hemodynamically resuscitated septic patients can open the microcirculation and thereby perfuse weak microcirculatory units [51].

## Therapeutics

### Catecholamines

After volume resuscitation, the use of catecholamine is considered to be the cornerstone of septic shock hemodynamic treatment [52]. Currently, dopamine and above all norepinephrine are the most used agents without any differences in terms of mortality [53]. It is generally considered that vasopressor agents must be titrated to increase mean arterial pressure to about 65–70 mmHg [54]. The pharmacodynamic effects of catecholamines are characterized by the existence of a concentration threshold at which the expected effect is observable (in the order of 100 pg/ml for adrenalin and 1,000 pg/ml for norepinephrine), followed by a linear increase in effect as a function of the logarithm of concentrations [55]. The maximum effect is usually achieved at doses ranging from 100 to 1,000 times the threshold dose, which largely surpasses the standard dosage range used in clinical practice. This type of dose–response curve explains why for threshold doses that differ by only 1 μg/kg/min from one patient to another, an identical pharmacodynamic effect on the dose–response curve will require dosages that differ by 10 μg/kg/min [56]. The obvious conclusion is therefore not to hesitate in transiently increasing the dosage of catecholamines if the patient is vasoplegic and hyperkinetic (although this remains experimental) or to use alternative therapies [57]. In this particular case, which is associated with a dramatic prognosis, other agents such as vasopressin or terlipressin [58], methylene blue [59], high volume hemofiltration [60], or plasmapheresis [61] have demonstrated their efficiency in case report studies or small series.

## Vasopressin and terlipressin for catecholamine-resistant septic shock

Vasopressin (AVP), better known as antidiuretic hormone, is a nonapeptide produced by the supraoptic and paraventricular nuclei of the hypothalamus. AVP is synthesized in response to hyperosmolarity and arterial hypotension. As a result, its levels are extremely high in cardiogenic or hypovolemic shock. Paradoxically, in a study by Landry et al. [62] in which AVP levels in patients with cardiogenic shock were compared with that of patients with severe septic shock with both having similar arterial pressure values, sepsis was shown to induce a relative deficiency in AVP (22.7 vs. 3.1 pg/ml). Indeed, the neurohypophysis of a patient in septic shock is virtually depleted in AVP, as confirmed by the absence of T1-weighted hypersignal in magnetic resonance imaging [63]. AVP, by binding to its V1a or V1R receptor, located primarily on blood vessel smooth muscle cells, induces vasoconstriction. In clinical practice, vasopressin increases arterial blood pressure without any change in heart rate while generally decreasing cardiac index. However, some patients remain refractory to the doses of AVP used. It is probable that this lack of effectiveness is likely linked to a decreased vascular responsiveness to vasopressin as previously demonstrated [64]. Although effective in the weaning of vasopressors and for improving renal function, vasopressin treatment is potentially dangerous because of possible intense vasoconstriction if the obtained arterial pressure is too high. The VASST study [65], in which vasopressin was used in substitutive doses (less than 0.04 U/min), showed no overall improvement in mortality. However, in a post hoc study, patients with less severe septic shock (i.e., less than 15 μg/min of norepinephrine) at arginine vasopressin initiation had a lower 28-day mortality rate compared with norepinephrine-only infusion (26.5 vs. 35.7%; $P = 0.05$).

Terlipressin (TP) is a synthetic analogue of AVP characterized by greater selectivity for the $V_1$ receptor than AVP [66]. The elimination half-life of TP is longer than that of AVP (50 vs. 6 min). Bolus administration of TP has been associated with several adverse effects in both preclinical and clinical studies such as reduction in cardiac index or coronary vasoconstriction [58]. The adverse effects after intermittent TP bolus injections are probably due to excessive systemic and regional vasoconstriction. Consequently, it has been suggested that administration of lower TP boluses at shorter intervals or continuous infusion of TP may be equally effective in restoring systemic blood pressure, thereby avoiding the risk of uncontrolled vasoconstriction [67]. TP use has been demonstrated to be efficient in cases of catecholamine-resistant septic shock [68]. Nevertheless, based on current knowledge, it remains unclear whether AVP or TP should be preferred in the treatment of vasodilatory shock states unresponsive to conventional vasopressor agents.

## Activated protein C

Recombinant human activated protein C (APC) has been demonstrated to reduce the mortality rate of adult patients with septic shock [69]. Initially, this effect was thought to be related to a reduction in coagulation and, to a lesser extent, to a reduction in inflammatory response to sepsis. Indeed, data from the PROWESS study demonstrated that the use of APC was associated with a quicker reduction in cardiovascular failure. Post-PROWESS investigative areas have been associated with a myriad of cellular studies [70] demonstrating that APC, through reactions mediated by the endothelial protein C receptor (EPCR) [71] and the effector receptor (protease activated receptor-1), acts directly on cells to exert multiple cytoprotective effects including: (a) downregulation of proinflammatory gene expression [72]; (b) anti-apoptotic activity [73]; (c) antioxidant properties; and (d) protection of endothelial barrier function [74]. Recent animal [75] and human [76] data have suggested that APC may improve both vascular and myocardial dysfunction and vascular reactivity to catecholamines during endotoxin and/or septic challenges. Nevertheless, despite a high recommendation level [52], the use of APC remains controversial. A multicenter study is currently investigating the effects of APC in a more severe (catecholamine dependent) and homogeneous group of septic shock patients.

## Hydrocortisone

Hydrocortisone is widely used in patients with septic shock. Annane et al. [77] found a survival benefit only in patients who remained hypotensive after fluid and vasopressor resuscitation and whose plasma cortisol levels did not rise appropriately after the administration of corticotropin. On the other hand, Sprung et al. [39] found that hydrocortisone did not improve survival or reversal of shock in patients with septic shock, either overall or in patients who did not respond to corticotropin, although hydrocortisone hastened the reversal of shock in patients in whom shock was ultimately reversed. Clearly, hydrocortisone [5] treatment allows for a more rapid weaning of catecholamines in patients with severe septic shock treated with high doses of catecholamine, by reducing among others the production of interleukin-6 [77]. Furthermore, by decreasing the expression of NF-$\kappa$B, corticoids also decrease the production of NO via iNOS. The detailed mechanisms of action of corticosteroids involve genomic as well as non-genomic effects after activation of their nuclear receptor [78]. Beneficial effects of glucocorticoids have also been found in non-infectious shock states such as vascular failure in post-cardiac surgical patients [79]. Currently, both the Surviving Sepsis Campaign [52] and the American College of Critical Care Medicine International Consensus [37] recommend

giving stress-dose steroid therapy only in septic shock after blood pressure is identified to be poorly responsive to fluid and vasopressor therapy (grade 2C).

## Conclusions

As previously described, the pathophysiology of shock-induced vascular hyporeactivity to vasopressor agents involves many mechanisms and a number of cellular pathways. Indeed, despite this vast amount of scientific knowledge, there is currently no "vascular-directed therapy" that has proven its efficiency in human septic shock. Indeed, many of the therapeutic approaches that have proved their efficiency in animal models and especially therapies directed against a particular compound have failed when used in human shock.

The most obvious conclusion is that preventing or decreasing the global cellular consequences of septic shock may prevent the overproduction of the involved mediators. For example, manipulating innate immunity with a peptide derived from the triggering receptor expressed on myeloid cells-1 (TREM-1) has been shown to improve hemodynamics and mortality in various forms of shock [80].

Another example stems from the Rivers study [81], in which patients who benefited from a goal-directed therapeutic approach required less vasopressor therapy after 24 h of treatment, hence demonstrating that early treatment of vascular failure accompanied by sound commonsense practices (antibiotic therapy, monitoring) enables one to reduce the impact of sepsis on vascular failure, likely by reducing the consequences of tissue hypoperfusion.

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