

Review Article

*Mechanisms of Disease*FRANKLIN H. EPSTEIN, M.D., *Editor***THE PATHOGENESIS OF
VASODILATORY SHOCK**DONALD W. LANDRY, M.D., PH.D.,
AND JUAN A. OLIVER, M.D.

PROFOUND vasoconstriction in the peripheral circulation is the normal response to conditions in which the arterial pressure is too low for adequate tissue perfusion, such as acute hemorrhagic or cardiogenic shock. In other conditions, the most frequent of which is septic shock,^{1,2} hypotension occurs as a result of failure of the vascular smooth muscle to constrict. Such so-called vasodilatory shock is characterized not only by hypotension due to peripheral vasodilatation but also by a poor response to therapy with vasopressor drugs. This syndrome has long attracted interest and defied understanding, but recent work on the function of vascular smooth muscle and on different types of vasodilatory shock has clarified its pathogenesis.

CAUSES OF VASODILATORY SHOCK

Sepsis is the most frequent cause of vasodilatory shock,^{1,2} accounting for more than 200,000 cases per year in the United States alone. Other causes include conditions in which adequate tissue oxygenation is compromised, such as nitrogen intoxication^{3,4} and carbon monoxide intoxication⁴ (Table 1). Of greater clinical importance is the fact that vasodilatory shock can be the final common pathway for long-lasting and severe shock of any cause. In patients with marked hypotension and decreased tissue perfusion due to hypovolemic or cardiogenic shock, correction of the initial problem may not cure the hypotension, because peripheral vasodilatation has supervened. For example, vasodilatory shock can follow volume resuscitation in patients who have prolonged and severe hypotension due to hemorrhage, known as “irreversible” or late-phase hemorrhagic shock.⁵⁻⁷ It can

From the Department of Medicine, Columbia University College of Physicians and Surgeons, New York. Address reprint requests to Dr. Landry at the Department of Medicine, Columbia University, Physicians and Surgeons Bldg., 10-445, 630 W. 168th St., New York, NY 10032, or at jao7@columbia.edu.

TABLE 1. CAUSES OF VASODILATORY SHOCK.*

Sepsis
Inadequate tissue oxygenation
Nitrogen intoxication (hypoxic lactic acidosis)
Carbon monoxide intoxication
Prolonged and severe hypotension
Hemorrhagic shock
Cardiogenic shock
Cardiopulmonary bypass
Shock with probable vasodilatation
Metformin intoxication
Some mitochondrial diseases
Cyanide poisoning
Cardiac arrest with pulseless electrical activity

*Anaphylaxis, liver failure, and glucocorticoid deficiency are sometimes listed among the causes of vasodilatory shock, but the data are inconclusive.

also occur in patients with severe heart failure who are treated with a mechanical assist device⁸ and undergo prolonged cardiopulmonary bypass.⁹ In addition, patients with less severe but prolonged hemorrhagic⁵ or cardiogenic¹⁰ shock often have less than maximal systemic vascular resistance. Other conditions that are characterized by cardiovascular collapse and that are likely to be associated with vasodilatation include lactic acidosis due to metformin intoxication,¹¹ certain mitochondrial diseases,¹² cyanide poisoning,¹³ and in some cases, cardiac arrest with pulseless electrical activity.¹⁴

**MECHANISMS PROMOTING
VASODILATION IN VASODILATORY
SHOCK**

In all the forms of vasodilatory shock that have been examined, plasma catecholamine concentrations are markedly increased^{4,15} and the renin-angiotensin system is activated.¹⁶ Thus, it is apparent that the vasodilatation and hypotension are due to failure of the vascular smooth muscle to constrict. Several mechanisms have been proposed to account for this failure, including the death of vascular cells due to prolonged hypotension,¹⁷ inadequate oxygen extraction by the tissues,¹⁸ and increased activity of prostaglandins with vasodilator activity.¹⁹ Some of these hypotheses have been experimentally or clinically tested — for example by increasing oxygen delivery²⁰ or inhibiting prostaglandin synthesis¹⁹ — with little evidence of benefit.

Recent work has clarified the mechanisms responsible for the normal function of vascular smooth muscle and has provided a variety of pharmacologic tools

with which to elucidate the derangement of vascular smooth muscle in vasodilatory shock. Because of its clinical importance, septic shock is the most studied form of vasodilatory shock. However, generalizations must be made cautiously, because it is likely that different pathogenetic mechanisms are activated in different types of vasodilatory shock. For example, the vasodilatation associated with carbon monoxide intoxication may be partially mediated not only by tissue hypoxia but also by the activation of guanylate cyclase.²¹ Nonetheless, there may be common mechanisms for the vasodilatation and resistance to vasopressors that occur in most types of vasodilatory shock. Three such mechanisms have thus far been implicated in this syndrome: activation of ATP-sensitive potassium channels (K_{ATP} channels) in the plasma membrane of vascular smooth muscle, activation of the inducible form of nitric oxide synthase, and deficiency of the hormone vasopressin.

Activation of ATP-Sensitive Potassium Channels in Vascular Smooth Muscle

Adequate vasoconstriction requires that hormonal or neuronal ligands such as angiotensin II and norepinephrine bind to and activate receptors on the surface of vascular smooth-muscle cells and, by way of second messengers, increase the concentration of cal-

cium in the cytosol (Fig. 1). This increase results from the release of calcium from intracellular stores and the entry of extracellular calcium into the cell through voltage-gated calcium channels. At high cytosolic concentrations, calcium forms a complex with calmodulin, and this complex activates a kinase that phosphorylates the regulatory light chain of myosin. The phosphorylation of myosin allows the activation of myosin ATPase by actin and the cycling of myosin cross-bridges along actin filaments, a process that contracts the muscle. Conversely, vasodilators such as atrial natriuretic peptide and nitric oxide activate a kinase that, by interacting with myosin phosphatase, dephosphorylates myosin and thus prevents muscle contraction.²²

In addition to these well-known mechanisms that modulate vascular tone, recent work has indicated that the membrane potential of vascular smooth-muscle cells may have a critical role in this process. Indeed, the pathologic vasodilatation and resistance to vasopressors that characterize vasodilatory shock cannot be understood without a detailed appreciation of the role of membrane potential in the regulation of vascular tone (Fig. 2). The resting membrane potential of vascular smooth muscle ranges from -30 to -60 mV, depending on the cell type. A more positive potential (depolarization) opens the voltage-gated calcium channels, increases the cytosolic calcium con-

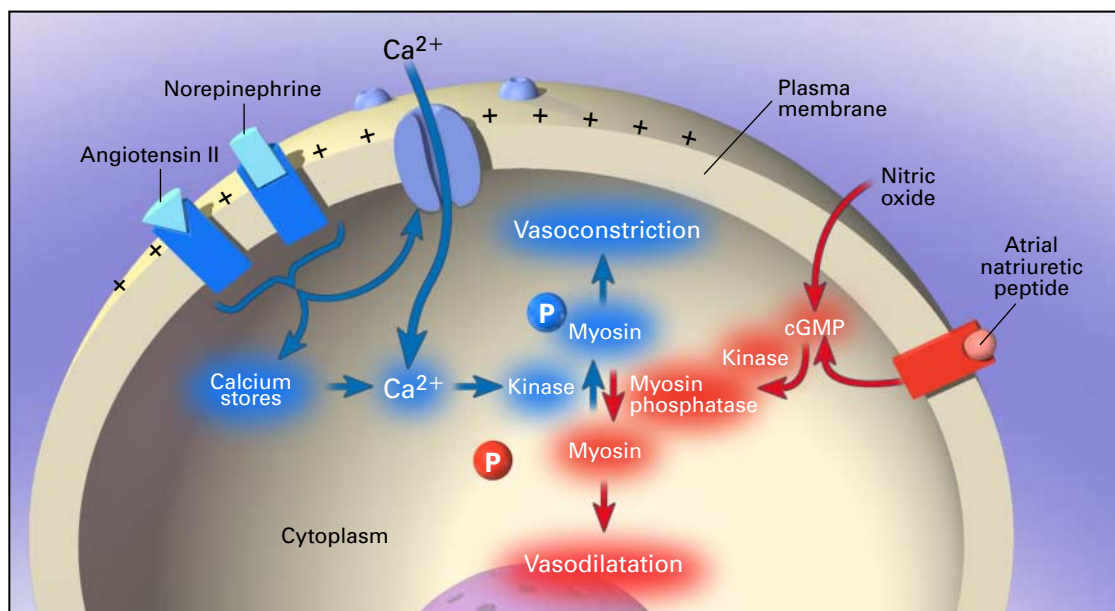


Figure 1. Regulation of Vascular Smooth-Muscle Tone.

The steps involved in vasoconstriction are shown in blue, and the steps involved in vasodilatation are shown in red. The phosphorylation (P) of myosin is the critical step in the contraction of vascular smooth muscle. By way of second messengers, vasoconstrictors such as angiotensin II and norepinephrine induce an increase in the cytosolic calcium concentration, which activates myosin kinase. Vasodilators such as atrial natriuretic peptide and nitric oxide activate myosin phosphatase and, by dephosphorylating myosin, cause vasorelaxation. The plasma membrane is shown at a resting potential (plus signs). The abbreviation cGMP denotes cyclic guanosine monophosphate.

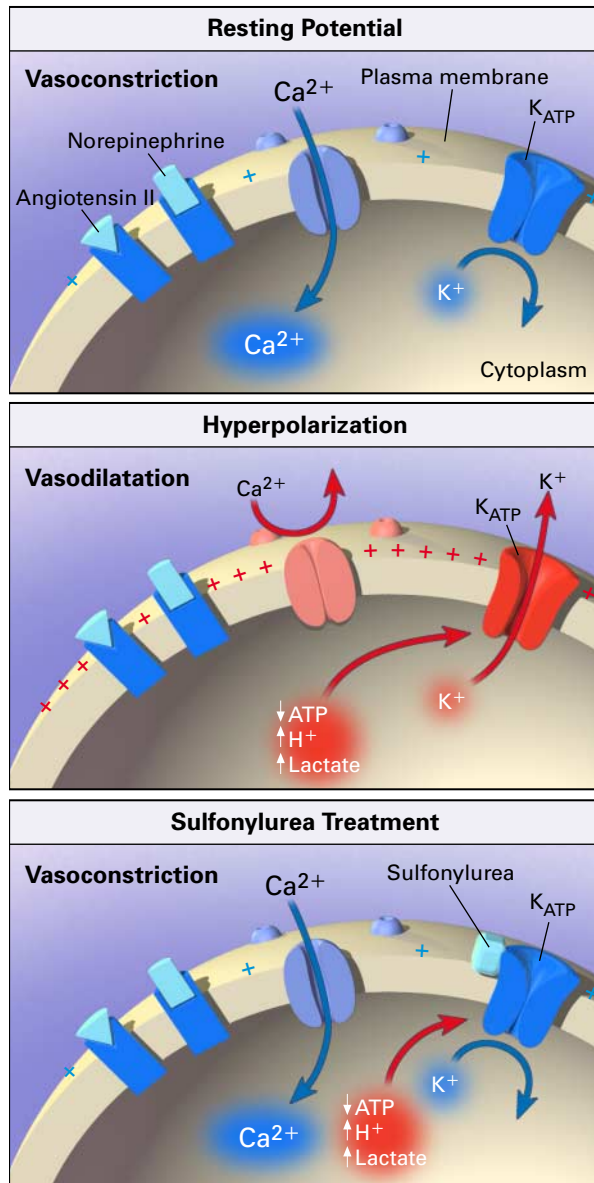


Figure 2. Effect of Membrane Potential on the Regulation of Vascular Tone.

The steps involved in vasoconstriction are shown in blue, and the steps involved in vasodilatation are shown in red. Vasoconstrictors such as angiotensin II and norepinephrine induce the entry of calcium into vascular smooth muscle through voltage-gated calcium channels, because under normal resting conditions, the ATP-sensitive potassium channels (K_{ATP}) remain closed, and the membrane potential is not too high (top panel). Lactic acidosis promotes vasodilatation by activating the K_{ATP} channels. When potassium exits the cell by way of the K_{ATP} channels, the plasma membrane becomes hyperpolarized, and inactivation of the voltage-gated calcium channels prevents an increase in the cytoplasmic calcium concentration in response to vasoconstrictors (middle panel). By inhibiting K_{ATP} channels, sulfonylureas allow the entry of calcium into the cell and restore the action of vasoconstrictors (bottom panel).

centration, and induces vasoconstriction.²³ Conversely, hyperpolarization closes these channels, decreases the cytosolic calcium concentration, and induces relaxation. In addition, because sustained vasoconstriction requires that extracellular calcium enter the cell, membrane hyperpolarization prevents vasoconstriction even in the presence of vasoconstrictor ligands.²³ A variety of ion transporters and channels, particularly potassium channels, contribute to the membrane potential of vascular smooth-muscle cells. Of the four known types of potassium channels in the plasma membrane of vascular smooth-muscle cells,^{23,24} the K_{ATP} channel is the best understood and has a critical role in the pathogenesis of vasodilatory shock.

The opening of K_{ATP} channels allows an efflux of potassium, thus hyperpolarizing the plasma membrane and preventing the entry of calcium into the cell (Fig. 2, middle panel). This is why pharmacologic activation of K_{ATP} channels (with diazoxide, for example) inhibits catecholamine-induced or angiotensin II-induced vasoconstriction.²⁴ K_{ATP} channels are physiologically activated by decreases in the cellular ATP concentration and by increases in the cellular concentrations of hydrogen ion and lactate,^{25,26} a mechanism that links cellular metabolism with vascular tone and blood flow.²⁴ It appears that under most normal resting conditions, K_{ATP} channels are closed and their inhibitors, such as the hypoglycemic sulfonylurea drugs, do not cause vasoconstriction. Under conditions of increased tissue metabolism or tissue hypoxia, however, activation of these channels causes vasodilatation, which can then be reversed with a sulfonylurea drug (Fig. 2, bottom panel).²⁴

The activation of K_{ATP} channels in arterioles is a critical mechanism in the hypotension and vasodilatation characteristic of vasodilatory shock. It is for this reason that the administration of sulfonylureas increases arterial pressure and vascular resistance in vasodilatory shock due to hypoxia,³ in septic shock due to lipopolysaccharide administration,^{3,27,28} and during the late, vasodilatory phase of severe hemorrhagic shock.²⁹ K_{ATP} channels are probably also activated in moderate hemorrhagic shock and cardiogenic shock and thereby contribute to the lower-than-expected peripheral vascular resistance often present in these conditions.^{5,10}

Neurohormonal activators of K_{ATP} channels may also be involved in some forms of vasodilatory shock. For example, atrial natriuretic peptide, calcitonin gene-related peptide, and adenosine can activate K_{ATP} channels.²⁴ Plasma concentrations of these substances are markedly increased in septic shock,³⁰⁻³² and plasma concentrations of atrial natriuretic peptide are increased in the late, vasodilatory phase of hemorrhagic shock.³³ The K_{ATP} channel may also be activated by increased nitric oxide through a cyclic guanosine monophosphate (cGMP)-dependent mechanism.³⁴

In summary, several conditions that compromise

tissue oxygenation and result in lactic acidosis probably activate K_{ATP} channels in vascular smooth muscle and thereby cause vasodilatory shock.

Increased Synthesis of Nitric Oxide

Increased synthesis of nitric oxide contributes to the hypotension and resistance to vasopressor drugs that occur in vasodilatory shock. Shortly after the discovery that nitric oxide is a potent endogenous vasodilator, the plasma concentrations of its metabolites were found to be markedly increased in patients with septic shock.³⁵ In both septic shock and decompensated hemorrhagic shock,⁷ nitric oxide production is increased as a result of increased expression of the inducible form of nitric oxide synthase. This increase occurs in many types of cells, including vascular smooth-muscle cells and endothelial cells.^{7,36} Moreover, nitric oxide synthesis does not increase during septic shock in knockout mice without the gene encoding the inducible synthase.³⁷⁻³⁹ The mechanisms responsible for the increased expression of inducible nitric oxide synthase have not been fully identified, but several cytokines (such as interleukin- 1β , interleukin-6, tumor necrosis factor α , interferon- γ ,^{36,40} and adenosine⁴¹) are probably involved. Regardless of the mechanism, increased nitric oxide synthesis contributes to vasodilatation in shock; inhibitors of nitric oxide synthase increase arterial pressure and vascular resistance in septic and late-phase hemorrhagic shock.^{7,42,43} Finally, knockout mice without the gene encoding inducible nitric oxide synthase have little hypotension in response to the administration of endotoxin.³⁸

It is likely that the vasodilating action of nitric oxide in vasodilatory shock is mediated mainly by the activation of myosin light-chain phosphatase (Fig. 1). However, nitric oxide may also cause vasodilatation by activating potassium channels in the plasma membrane of vascular smooth-muscle cells.^{24,34,44,45} Of particular interest is the potassium channel that is sensitive to cytosolic calcium (the K_{Ca} channel), because, under normal conditions, one of the functions of this channel is to blunt the effect of vasoconstrictors,⁴⁶ and such blunting is characteristic of all types of vasodilatory shock. The increase in the cytosolic calcium concentration in vascular smooth-muscle cells that is induced by vasoconstrictors (such as norepinephrine) opens the K_{Ca} channels; the opened K_{Ca} channels, by hyperpolarizing the plasma membrane, prevent further vasoconstriction.⁴⁶ Nitric oxide can activate K_{Ca} channels by two mechanisms: direct nitrosylation of the channel⁴⁴ and activation of a cGMP-dependent protein kinase.⁴⁵ Regardless of the mechanism, activation of K_{Ca} channels by nitric oxide probably contributes to vasodilatation and vasopressor resistance in vasodilatory shock.

The vascular hyporeactivity to catecholamines and endothelin that occurs in septic shock and decom-

pensated hemorrhagic shock is markedly improved by the administration of inhibitors of nitric oxide synthesis.^{7,47,48} Vasopressor responses to catecholamines during sepsis are greater in knockout mice without the gene for inducible nitric oxide synthase than in wild-type mice.⁴⁹ In humans, as in animal models, administration of inhibitors of nitric oxide synthesis during septic shock increases arterial pressure and decreases the doses of vasoconstrictor catecholamines needed to maintain arterial pressure.⁴²

In summary, increased synthesis of nitric oxide is an important cause of the hypotension, vasodilatation, and vascular hyporesponsiveness that occur in septic shock and late-phase hemorrhagic shock. Although nitric oxide may exert these effects by several mechanisms, the resistance to vasopressor agents that is characteristic of these conditions is probably mediated, at least in part, by the ability of nitric oxide to activate potassium channels and hyperpolarize the plasma membrane of vascular smooth-muscle cells. Indeed, endotoxin-induced vascular hyporesponsiveness to norepinephrine can be partially reversed by K_{Ca} -channel inhibitors.⁵⁰

Deficiency of Vasopressin

Water conservation is the most notable action of vasopressin, a hormone secreted under osmotic control to regulate the permeability of the renal collecting ducts to water. However, vasopressin is also involved in cardiovascular homeostasis, and thus it is secreted under baroreflex control and constricts vascular smooth muscle. Whereas the regulation of collecting-duct permeability takes place at plasma vasopressin concentrations in the range of approximately 1 to 7 pg per milliliter (0.9 to 6.5 pmol per liter), its vasoconstrictor effects occur at much higher concentrations (approximately 10 to 200 pg per milliliter [9 to 187 pmol per liter]). Normally, vasopressin plays a minor part in arterial pressure regulation, but in response to hypotension, such as that due to hemorrhage⁵¹ or sepsis,⁵² it is released from the neurohypophysis, and its concentration in plasma markedly increases. During the initial phase of hemorrhagic or septic shock, vasopressin (along with other vasoconstrictors) contributes to the maintenance of arterial pressure. Thus, agents that block the vasopressin receptor in vascular smooth muscle lower arterial pressure in both acute hemorrhagic shock⁵³ and septic shock,⁵⁴ and animals with diabetes insipidus tolerate shock very poorly.⁵⁵

As shock worsens, the initially very high concentrations of vasopressin in plasma decrease.^{51,56,57} For example, in a recent study of hemorrhagic shock in dogs, the average plasma vasopressin concentrations were greater than 300 pg per milliliter (280 pmol per liter; normal, less than 5 pg per milliliter [4.6 pmol per liter]) during the acute phase of hypotensive hemorrhage but decreased to less than 30 pg per millili-

ter (28 pmol per liter) after approximately one hour of sustained hypotension.⁵⁷ Similarly, we found that patients with septic shock,⁵⁸ late-phase hemorrhagic shock,⁵⁷ or vasodilatory shock after cardiopulmonary bypass and placement of a left ventricular assist device⁸ had inappropriately low plasma vasopressin concentrations, given their degree of hypotension⁵⁹⁻⁶¹; that is, the concentrations of vasopressin were low for its vascular action but were well within the range of its antidiuretic effect. The exact mechanism responsible for these low concentrations remains to be determined, but it is known that neurohypophyseal stores of vasopressin may be depleted after profound osmotic stimulation^{62,63} and probably also after profound, sustained baroreflex stimulation. In support of this hypothesis, immunohistochemical analysis of the neurohypophysis in dogs revealed that vasopressin all but disappeared after one hour of severe hemorrhagic hypotension (Fig. 3).

Correction of the inappropriately low plasma vasopressin concentrations in vasodilatory shock by administration of the hormone at doses yielding concentrations similar to those found in acute hypotension significantly increases arterial pressure (by approximately 25 to 50 mm Hg).⁵⁹⁻⁶¹ Such vasopressor responses to vasopressin occur in patients with severe septic shock,⁵⁸ hemorrhagic shock that is unresponsive to volume replacement and catecholamine administration,⁵⁷ and vasodilatory shock after cardiopulmonary bypass and placement of a left ventricular assist device⁸ and in organ donors with hemodynamic instability.⁶⁴ In addition, vasopressin has a vasopressor action in patients with cardiac arrest that is refractory to cardiovascular resuscitation.⁶⁵ These clinical ob-

servations parallel findings in animals, in which the vasoconstrictor action of vasopressin increased by five orders of magnitude with septic shock.⁵⁴

The vasopressor action of vasopressin in patients with vasodilatory shock is remarkable not only because the doses given have no such effect in normal subjects,⁶⁶⁻⁶⁸ but also because one of the most prominent features of this type of shock is resistance to vasoconstrictors such as norepinephrine,⁷ angiotensin II,⁶⁹ and endothelin.⁴⁸ What, then, are the reasons for the marked sensitivity to exogenously administered vasopressin in vasodilatory shock? There are several likely possibilities. First, because plasma concentrations of vasopressin are relatively low, its vascular receptors are available for occupancy by exogenous hormone. In contrast, the administration of norepinephrine and angiotensin II may not increase receptor occupancy to the same extent, because endogenous concentrations of these substances are high; these high concentrations may also cause desensitization of receptors. Second, the vasopressor action of vasopressin is markedly increased in dogs with baroreceptor denervation⁷⁰ and in patients with autonomic failure,⁶⁶ and patients in vasodilatory shock are usually sedated or comatose. Furthermore, if sepsis is present, the function of the sympathetic nervous system in such patients may be impaired.⁷¹ Third, vasopressin potentiates the vasoconstrictor effect of norepinephrine,⁷² and plasma norepinephrine concentrations are markedly elevated in vasodilatory shock.^{4,15} Fourth, vasopressin directly inactivates K_{ATP} channels in vascular smooth muscle.⁷³ Finally, vasopressin blunts the increase in cGMP that is induced by nitric oxide⁷⁴ and atrial natriuretic peptide⁷⁵ and decreases the synthesis

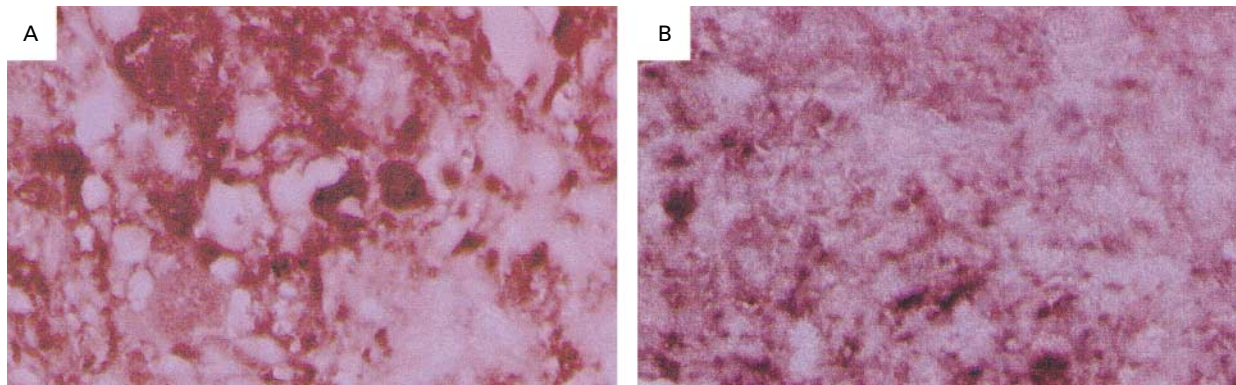


Figure 3. Vasopressin Immunoreactivity in the Neurohypophysis in Dogs.

Panel A shows a section of the neurohypophysis from a normal dog. There is staining of the macrovesicles with antivasopressin serum, a reaction indicative of replete stores of vasopressin. Panel B shows a section of the neurohypophysis from a dog after severe hemorrhagic hypotension (mean arterial pressure, ≤ 40 mm Hg) for one hour. There is minimal staining with antivasopressin serum. For both panels, paraformaldehyde-fixed pituitary glands were sequentially incubated with a vasopressin monoclonal mouse antibody, a horse antimouse IgG conjugated to biotin, and avidin-conjugated horseradish peroxidase and were stained with 3,3-diaminobenzidine in the presence of hydrogen peroxide ($\times 320$).

of inducible nitric oxide synthase that is stimulated by lipopolysaccharide.⁷⁴ The relative importance of these factors in explaining vasopressin sensitivity in vasodilatory shock remains to be elucidated.

The combination of inappropriately low concentrations of plasma vasopressin and a marked vasopressor response to exogenous hormone at doses that result in physiologic plasma concentrations indicates that vasopressin deficiency contributes to the vasodilatation and hypotension of vasodilatory shock. That is, with norepinephrine and angiotensin II both present at high concentrations in plasma, the defect in vasodilatory shock is at the level of vascular responsiveness to these ligands, probably as a result of the activation of K_{ATP} and K_{Ca} channels in vascular smooth muscle. In contrast, the plasma concentrations of vasopressin are inappropriately low for effective arteriolar constriction, probably because of depleted neurohypophyseal stores (i.e., a deficiency syndrome).

CONCLUSIONS

Vasodilatory shock is due to the inappropriate activation of vasodilator mechanisms and the failure of vasoconstrictor mechanisms (Fig. 4). Unregulated nitric oxide synthesis, by activating soluble guanylate cy-

clase and generating cGMP, causes dephosphorylation of myosin and hence vasorelaxation. In addition, nitric oxide synthesis and metabolic acidosis activate the potassium channels (K_{ATP} and K_{Ca}) in the plasma membrane of vascular smooth muscle. The resulting hyperpolarization of the membrane prevents the calcium that mediates norepinephrine- and angiotensin II-induced vasoconstriction from entering the cell. Hence, hypotension and vasodilatation persist, despite high plasma concentrations of these hormones. In marked contrast, the plasma concentrations of vasopressin are low, despite the presence of hypotension. This finding was unexpected, because plasma vasopressin concentrations are markedly elevated early in septic shock and hemorrhagic shock. However, the initial massive release of hormone may result in subsequent depletion, such that plasma concentrations of vasopressin are eventually too low to maintain arterial pressure. Although the pressor response to exogenous vasopressin in vasodilatory shock may be due to several different mechanisms, the ability of this hormone to block K_{ATP} channels in vascular smooth muscle and interfere with nitric oxide signaling are probably important contributors.

Elucidation of key components of the pathogene-

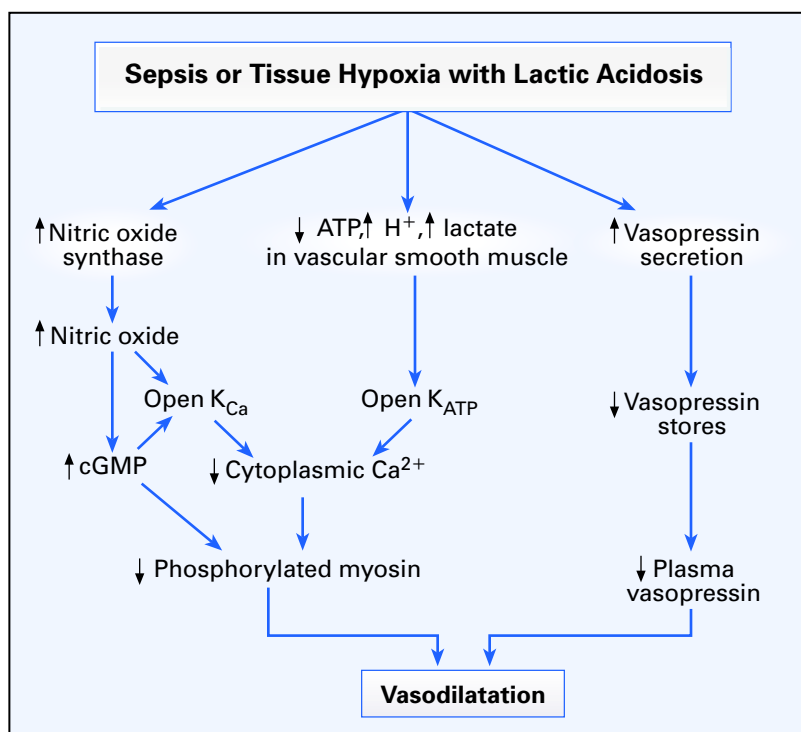


Figure 4. Mechanisms of Vasodilatory Shock.

Septic shock and states of prolonged shock causing tissue hypoxia with lactic acidosis increase nitric oxide synthesis, activate ATP-sensitive and calcium-regulated potassium channels (K_{ATP} and K_{Ca} , respectively) in vascular smooth muscle, and lead to depletion of vasopressin. The abbreviation cGMP denotes cyclic guanosine monophosphate.

sis of vasodilatory shock — K_{ATP} -channel activation, an increase in nitric oxide synthesis, and vasopressin deficiency — has suggested new possibilities for therapy. Although it is clear that excessive nitric oxide production is important in the pathogenesis of vasodilatory shock, the value of blockade remains to be clarified. Given the widespread actions of nitric oxide, it is not surprising that nonspecific inhibition of its synthesis in sepsis has been associated with a variety of deleterious effects and with increases in mortality. Indeed, a phase 3 trial of a nonselective inhibitor of nitric oxide synthase in patients with septic shock was recently halted because of side effects.⁷⁶ Although inhibitors with selectivity for inducible nitric oxide synthase are currently being developed, the risks entailed by interrupting the action of a pleiotropic substance (in this case, nitric oxide) in a complex homeostatic response remain. More intriguing is the possibility of specifically blocking the activation by nitric oxide of potassium channels in vascular smooth muscle, thereby restoring vasopressor responsiveness. Inhibitors of the K_{ATP} channel, such as sulfonylurea agents that specifically block the type of K_{ATP} channel found in vascular smooth muscle, provide another target for therapy. Finally, vasopressin — given its apparent function as an endogenous blocker of important potassium channels and cGMP-mediated signaling and its deficiency in vasodilatory shock — provides fertile ground for therapeutic development.

Effective treatment of vasodilatory shock is possible if the initiating event (such as infection) is controlled and if, over time, the metabolic derangements resolve. A new understanding of the pathophysiology of vasodilatory shock holds promise for a new generation of specific treatments.

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