Role of vascular smooth muscle cell pathobiology in sepsis-induced vasoplegia (Review)

HANG RUAN[1,2*], XIAO-YAN SHEN[3*], SHI-YAN LIU[1,2] and SHU-SHENG LI[1,2]

[1]Department of Critical-Care Medicine, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei 430030, P.R. China; [2]Department of Emergency Medicine, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei 430030, P.R. China; [3]Department of Anesthesiology, Renmin Hospital of Wuhan University, Wuhan, Hubei 430060, P.R. China

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Abstract. Sepsis-induced vasoplegia, a life-threatening complication of sepsis, has become a focal point of research endeavors aimed at determining its complex mechanisms. However, existing investigations predominantly focus on the role of endothelial cells (ECs) in sepsis, inadvertently dismissing the pivotal contribution of vascular smooth muscle cells (VSMCs). The present review highlights the frequently underappreciated role of VSMCs in sepsis-induced vasodilation, and provides a comprehensive and systematic elucidation of the associated pathophysiological mechanisms. The current review examines the structural characteristics, localization, phenotypic transitions and heterogeneity of VSMCs, emphasizing their critical role in maintaining vascular homeostasis and regulating blood pressure. Subsequently, the review delves into the multifaceted effects of sepsis on VSMCs. Direct injury to VSMCs in sepsis occurs through pathogens. Additionally, the sepsis-associated cytokine storm can activate key signaling pathways, such as the NF-κB and p38 MAPK pathways, leading to a phenotypic shift in VSMCs from a contractile state to a synthetic state, thus enhancing their proliferative and migratory abilities. Concurrently, sepsis disrupts the intricate interaction between ECs and VSMCs, and interferes with calcium homeostasis, ultimately resulting in reduced vascular reactivity and abnormal vascular remodeling. Together, these mechanisms contribute to sepsis-related vascular dysfunction and multiorgan failure. The in-depth analysis of these processes in the present review offers novel insights into the pathological mechanisms of sepsis-induced vasoplegia. The current study also provides a theoretical foundation for the development of clinical intervention strategies targeting VSMCs, with the potential to advance sepsis treatment strategies.

Correspondence to: Dr Shu-Sheng Li, Department of Critical-Care Medicine, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, 1095 Jiefang Avenue, Wuhan, Hubei 430030, P.R. China
E-mail: shushengli16@sina.com

*Contributed equally

Abbreviations: ASMCs, aortic smooth muscle cells; AVP, arginine vasopressin; CLP, cecal ligation and puncture; cGMP, cyclic guanosine monophosphate; ECs, endothelial cells; eNOS, endothelial nitric oxide synthase; ECM, extracellular matrix; HASMCs, human ASMCs; HCASMCs, human coronary ASMCs; HCMV, human cytomegalovirus; iNOS, inducible nitric oxide synthase; LDHA, lactate dehydrogenase A; LPS, lipopolysaccharide; LTA, lipoteichoic acid; M-CSF, macrophage colony-stimulating factor; PVAT, perivascular adipose tissue; RCT, randomized controlled trial; RNS, reactive nitrogen species; ROS, reactive oxygen species; TRPV, transient receptor potential vanilloid; VSMCs, vascular smooth muscle cells

Key words: vascular dysfunction, VSMC, EC, sepsis, vasoplegia

Contents

1. Introduction

Vasoplegia is a key driver of poor prognosis in sepsis, a severe complication characterized by persistent vasomotor dysfunction and catecholamine-resistant hypotension (1). Sepsis-induced vasoplegia contributes directly to multiple organ dysfunction syndrome, and associated mortality through circulatory failure and impaired oxygen utilization (1,2). According to the Global Burden of Diseases, Injuries, and Risk Factors Study, it was estimated that in 2021 there were 166 million (95% uncertainty interval: 135-201 million) sepsis cases worldwide, with 21.4 million (20.3-22.5 million) all-cause sepsis-related deaths, accounting for 31.5% of total global mortality (3). Consequently, elucidating the pathogenesis and regulatory

pathways of vasoplegia in sepsis, and developing effective management and targeted therapeutic strategies specifically addressing this complication, are imperative for improving sepsis management and patient survival.

Conventional paradigms in sepsis research focus predominantly on endothelial dysfunction, encompassing barrier disruption, glycocalyx degradation and dysregulated nitric oxide (NO)/cyclic guanosine monophosphate (cGMP) signaling, as the primary mediator of vasoplegia (4-6). However, a growing body of evidence from translational investigations challenges this endothelial-centric model, highlighting vascular smooth muscle cells (VSMCs), the ultimate effectors of vascular tone regulation, as equally important contributors. In rodent models of cecal ligation and puncture (CLP), the contractile impairment of VSMCs exhibits biphasic kinetics (7,8): Early impairment is influenced by endothelial-derived factors associated with sepsis, whereas late-phase dysfunction results from direct injury to VSMCs (7). Recent metabolomic profiling has further identified sepsis-associated lactic acidosis as a key driver of the phenotypic plasticity of VSMCs, facilitating transitions towards senescent, osteogenic and proinflammatory phenotypes that accelerate vascular stiffening (8). Therefore, understanding the role of VSMCs in vasoplegia during sepsis is crucial for elucidating the pathogenesis of sepsis-induced circulatory insufficiency and identifying novel targets for therapeutic intervention.

Notably, despite increasing recognition of the pivotal role of VSMCs, previous reviews in this field remain limited in several crucial aspects. Most reviews have concentrated on isolated mechanisms of VSMC dysfunction without sufficiently integrating upstream triggers, including endothelial injury and the cytokine storm, or examining intercellular crosstalk (7-9). Others have retained an endothelial-centric viewpoint, relegating VSMCs to a subordinate 'effector' role rather than recognizing them as central regulatory elements (4-6). Furthermore, few reviews successfully summarize preclinical data with clinical translational challenges, such as the disparity between promising VSMC-targeted therapies in animal models and their lack of efficacy in human trials, or engage with unresolved controversies, for example, the reversibility of septic VSMC dedifferentiation, which is critical for informing therapeutic strategies (1,6). These shortcomings have hindered the development of a comprehensive, translation-oriented understanding of VSMC-driven vasoplegia.

The present review advances the field by addressing these crucial limitations and building upon the existing literature. Specifically, it moves beyond fragmented, mechanism-focused accounts to develop an integrated framework linking upstream sepsis-related stimuli, such as inflammatory mediators, metabolic disturbances and endothelial crosstalk, to downstream VSMC dysfunction. Furthermore, it explicitly engages with fundamental scientific controversies and bridges preclinical insights with clinical translational challenges, a perspective rarely emphasized in prior reviews. By thoroughly examining the complex role of VSMCs in the pathogenesis of sepsis-induced vasoplegia, including their signaling pathways, inflammatory responses and regulatory interactions, the current review aims to provide a comprehensive, controversy-conscious and translationally oriented understanding of vascular dysfunction in this context. Ultimately, it not only consolidates current knowledge but also delineates critical gaps, thereby guiding future preclinical and clinical investigations, and addressing the limitations of the narrow or fragmented perspectives of previous literature.

2. Anatomical localization and functional properties of VSMCs

Within the pathological context of sepsis, VSMCs serve as crucial hubs for signal integration, processing cues from inflammatory mediators, alterations in mechanical stress, patterns of injury and fragments of extracellular matrix (ECM) degradation (10).

Cellular localization of VSMCs: Anatomical distribution and structural context. Anatomically, the vascular wall (excluding capillaries and lymphatic capillaries) is organized into three concentric layers from the lumen outwards: The intima, media and adventitia (11). Functionally, the media acts as the central hub for vascular tension regulation, housing circumferentially arranged VSMCs intertwined with elastic/collagen fiber networks. This arrangement endows vessels with both active contractility and passive elastic recoil (12). Ultrastructurally, VSMCs exhibit an elongated spindle-shaped morphology, containing cytoplasmic contractile units, force-transducing dense bodies and calcium-regulating sarcoplasmic reticulum (13). However, in sepsis, this structural organization is disrupted: VSMC detachment from the ECM and degradation of elastic fibers impair vascular compliance, exacerbating hypotension. The changes in VSMCs from physiological conditions to septic conditions are shown in Fig. 1.

Cellular heterogeneity of VSMCs: Lineage origins and phenotypic diversity. Studies employing single-cell transcriptomics and lineage tracing techniques have revealed the distinct origins of VSMCs: hindlimb/inguinal-axillary venous VSMCs predominantly stem from the lateral plate mesenchyme (14); SMCs in the proximal thoracic aorta are derived from the second heart field and cardiac neural crest (15); and coronary artery SMCs partly originate from epicardial cells that migrate into the heart during development (16). These differences in embryonic origins, combined with varied responses to local microenvironmental signals, confer upon VSMCs tissue-specific molecular profiles and functional characteristics.

Cellular contractility of VSMCs: Mechanisms and regulatory pathways. Under physiological conditions, VSMCs maintain a robust contractile capacity, which is crucial for the dynamic regulation of blood flow and pressure (17). This contractile ability is regulated by the phosphorylation of myosin light chain (MLC) through two primary pathways: The calcium-dependent MLC kinase (MLCK)/MLC signaling pathway and the calcium-sensitized Rho/Rho-associated protein kinase (ROCK) signaling pathway.

Regarding the MLCK/MLC signaling pathway, an increase in the intracellular calcium ion concentration ($[Ca^{2+}]i$) occurs via the opening of voltage-gated or receptor-gated calcium channels, or release from intracellular stores (18). Free calcium ions bind to calmodulin, activating MLCK; MLCK catalyzes the phosphorylation of the 19th serine residue on regulatory

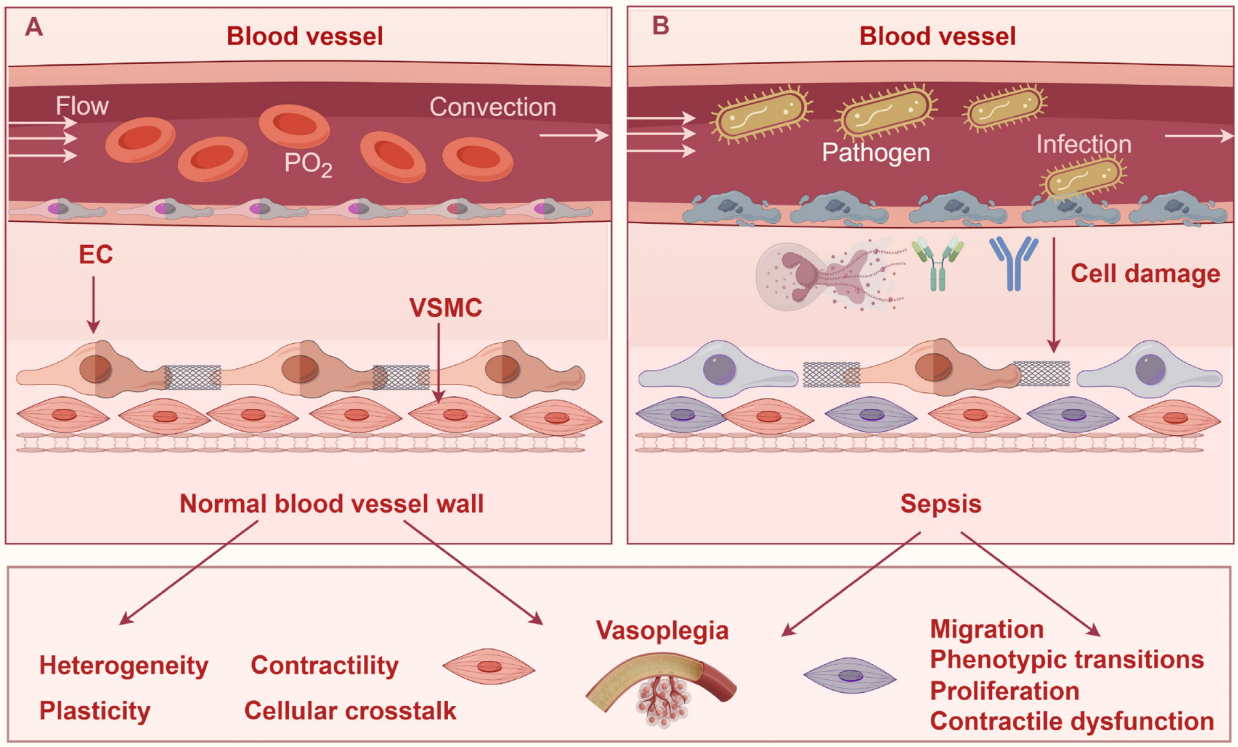

Figure 1. VSMCs in physiological and septic conditions. (A) VSMCs exhibit a quiescent, contractile phenotype characterized by organized cytoskeletal architecture and intact regulatory pathways. Key features include: i) Stable anatomical distribution within the vascular media, maintaining vascular wall integrity; ii) homogeneous lineage-specific phenotype with minimal heterogeneity; iii) robust contractility driven by intact calcium homeostasis and myofilament calcium sensitivity; iv) limited phenotypic plasticity, with minimal switching from contractile to synthetic states; v) balanced cellular crosstalk: Intricate bidirectional interactions with neighboring cells, primarily ECs. EC-VSMC communication relies on core pathways to maintain vascular homeostasis, enabling adaptation to mechanical injury, shear stress and chemical stimuli. (B) Sepsis induces profound structural and functional perturbations in VSMCs, characterized by five core changes: i) Altered cellular localization: Disrupted anatomical distribution within the vascular media due to sepsis-induced cell injury, compromising vascular wall stability; ii) enhanced cellular heterogeneity: Expanded phenotypic diversity with an increased proportion of synthetic VSMCs (arising from lineage switching or progenitor cell recruitment), contributing to vascular dysfunction; iii) impaired cellular contractility: Diminished contractile capacity driven by dysregulated calcium homeostasis and downregulated contractile proteins; iv) exaggerated cellular plasticity: Prominent phenotypic switching from contractile to synthetic states, associated with increased proliferation, migration and secretion of proinflammatory mediators; v) dysregulated cellular crosstalk: Collapse of bidirectional EC-VSMC communication, cytokine secretion becomes proinflammatory (increased release of proinflammatory cytokines), preventing adaptation to stressors. The figure was constructed using Figdraw 2.0 tool (https://www.figdraw.com/#/), with official authorization obtained by the authors (authorization no.: PTSIYbe897).VSMCs, vascular smooth muscle cells; ECs, endothelial cells; PO_2, partial pressure of oxygen.

MLC, activating the Mg^{2+}-ATPase activity of myosin heads. This induces a conformational change in myosin, enhancing its binding to actin (19). MLC phosphatase (MLCP)-mediated dephosphorylation of MLC reduces myosin-actin binding, inhibiting contraction. Regarding the Rho/ROCK signaling pathway (20), activation of RhoA leads to ROCK activation, which inhibits MLCP activity, thereby maintaining or increasing MLC phosphorylation levels by preventing dephosphorylation (21). ROCK can also directly phosphorylate MLC to promote myosin contraction (22). Additionally, the calcium-sensitized pathway is associated with actin cytoskeleton remodeling, such as via cofilin phosphorylation, which inhibits actin filament depolymerization, further enhancing contraction (23). In summary, these two signaling pathways work together to regulate VSMC contractility: The calcium-dependent pathway facilitates acute responses to fluctuations in $[Ca^{2+}]i$, whereas the calcium-sensitized pathway prolongs contraction.

Cellular plasticity of VSMCs: Phenotypic switching and functional adaptation. Upon encountering injury or stimulation by growth factors, VSMCs undergo a response characterized by enhanced proliferation, migration and synthesis of extracellular components, a phenomenon known as phenotypic switching (24). The main subtypes of VSMCs are as follows: i) Contractile VSMCs are characterized by a high concentration of myofilaments, a slender spindle-shaped morphology and robust contractility. ii) Synthetic VSMCs are characterized by an abundance of rough endoplasmic reticulum and Golgi apparatus, downregulation of contractile proteins, and upregulation of ECM components and inflammatory factors. Other identified phenotypes include osteogenic, macrophage-like, mesenchymal-like and fibroblast-like VSMCs (24). Under physiological conditions, VSMCs typically exhibit a quiescent state characterized by low proliferative and migratory activity. However, in response to pathological stimuli, such as vascular injury, diabetes or hypertension, VSMCs undergo phenotypic plasticity, transitioning from a contractile state to secretory/inflammatory phenotypes with increased proliferative, migratory and matrix-synthetic functions (25).

Cellular crosstalk involving VSMCs: Interactions with neighboring cells. Effective communication between endothelial cells (ECs) and VSMCs is a complex physiological process

essential for maintaining vascular structure and function, allowing cells to adapt to mechanical injury, shear stress and chemical stimuli through pathways such as Notch signaling, cytokine secretion and exosomal trafficking (12,24). The conserved Notch signaling pathway facilitates interactions between adjacent cells: ECs express Jagged1 ligands that bind to Notch3 receptors on VSMCs, inhibiting their transition from contractile to synthetic phenotypes (24). Additionally, ECs regulate VSMC metabolism, influencing phenotypic plasticity. In coculture models, hypoxic ECs increase lactate production, whereas the knockout of lactate dehydrogenase A (LDHA) reduces osteogenic marker expression and VSMC apoptosis (26). Cytokine secretion serves as another crucial regulatory mechanism. Factors such as prostanoids, arachidonic acid, acid metabolites and NO, which are released by ECs, have distinct effects on VSMC function (12). Furthermore, exosomes serve a notable role in vascular remodeling; in atherosclerosis models, endothelial autophagy facilitates the transfer of microRNA (miRNA/miR)-204-5p via exosomes to VSMCs, inhibiting endothelial apoptosis and VSMC calcification (27). This multidimensional crosstalk highlights the interconnection of ECs and VSMCs in preserving vascular health or contributing to pathological processes.

3. Multifactorial impairment of VSMCs in septic vasoplegia

Metabolic disturbances in VSMCs during sepsis-induced vasoplegia. Sepsis induces marked metabolic reprogramming in VSMCs, disrupting their function and contributing to disease pathogenesis. Systemic circulatory failure and microcirculatory dysfunction collectively impair cellular oxygen uptake and utilization, triggering metabolic remodeling (5). Under septic conditions, the energy metabolism of VSMCs transitions from oxidative phosphorylation (OXPHOS) to aerobic glycolysis, a metabolic reprogramming observed across various cell types. This glycolytic switch, characterized by increased glucose uptake and upregulation of hexokinase 2, supports the migratory activity of VSMCs (28).

Upregulated glycolysis results in excess lactate production, leading to lactic acidosis. This metabolic disturbance inhibits mitochondrial respiration (OXPHOS) and glutamine catabolism, decreasing cellular ATP levels and altering the NAD^+/NADH ratio (8). These sequential effects contribute to the phenotypic transition and functional decline of VSMCs, exacerbating sepsis-induced vascular dysfunction. Notably, glycolysis and lactate directly promote VSMC migration and proliferation. In sepsis-induced systemic cellular injury, elevated plasma LDH levels are indicative of tissue injury, a common feature observed in severe sepsis (29,30). At the mechanistic level, lysine 5 crotonylation enhances the tetramer formation of LDHA, increasing lactate production to drive the migration and proliferation of VSMCs (31). These combined metabolic disturbances impair VSMCs contractility and provoke phenotypic alterations, worsening the vascular pathophysiology induced by sepsis.

Shear stress and VSMCs dysfunction in sepsis-induced vasoplegia. Shear stress is the fluid dynamic force exerted by blood flow on the vascular wall, and is influenced by factors such as vessel diameter, flow pulsatility, blood viscosity and velocity (32). Physiological shear stress is crucial for vascular homeostasis, whereas abnormal shear stress serves as a notable mechanical trigger for vascular pathology. Abnormal shear stress in sepsis arises from two mutually reinforcing mechanisms: Hemodynamic disturbances and vascular structural damage.

First, sepsis-induced hyperdynamic circulation creates a paradoxical hemodynamic state: Inflammatory vasodilation and hypovolemia drive hypotension, whereas compensatory cardiac responses attempt to maintain tissue perfusion (33). This imbalance is exacerbated by microcirculatory dysfunction, characterized by vasoregulatory failure, capillary shunting and microthrombosis, which further disrupts blood flow patterns and amplifies tissue hypoperfusion (34). Collectively, these changes alter flow velocity, pulsatility and distribution, laying the foundation for abnormal shear stress.

Second, sepsis-mediated vascular structural damage compromises the ability of the vascular wall to buffer shear stress. Pathological alterations include glycocalyx degradation, reduced red blood cell deformability, redistribution of membrane phospholipids, and endothelial injury driven by platelet and neutrophil extracellular trap formation (35,36). When the endothelial barrier is disrupted, VSMCs are directly exposed to pulsatile shear stress, an insult that is normally attenuated by the endothelial layer, directly triggering functional dysregulation of VSMCs (37). This structural breakdown forms the anatomical basis for abnormal shear stress in sepsis.

Notably, invasive therapies for sepsis can further perturb hemodynamics by altering flow velocity and patterns, thereby modifying intravascular shear stress (38-40). These treatment-related changes may either mitigate or exacerbate the phenotypic plasticity of VSMCs, highlighting the need for tailored clinical management to minimize iatrogenic vascular damage.

Cellular crosstalk involving VSMCs in sepsis-associated vasoplegia. Sepsis-induced vascular dysfunction arises from a marked disruption of the EC-VSMC interaction network. In a physiological state, the close crosstalk between ECs and VSMCs serves a crucial role in maintaining vascular tone, structure and functional equilibrium (41). The presence of physiological laminar shear stress acting on ECs helps preserve the contractile phenotype of VSMCs, characterized by high α-smooth muscle actin (α-SMA) expression (42). Key paracrine pathways, such as endothelial NO synthase (eNOS)/NO, have a role in regulating platelet-derived growth factor signaling to facilitate flow-dependent vasodilation and adaptive remodeling processes (43,44). The ECM, which offers structural support, influences cellular signaling through its compositional and mechanical attributes (12,45).

Sepsis disrupts this balance through several mechanisms: i) Mechanical force-sensing dysregulation: Hemodynamic disturbances (such as hypotension and microcirculatory failure) alter physiological shear stress, compromising its role in preserving VSMCs contractility (46). ii) Aberrations in signaling pathways: Sepsis-induced inflammation, oxidative stress and endotoxemia disrupt communication between ECs and VSMCs. In acute kidney injury induced by lipopolysaccharide (LPS), endothelial calpain activation leads to p38 phosphorylation and upregulation of inducible NO synthase

(iNOS), resulting in excessive production of NO and reactive oxygen species (ROS) that leads to EC apoptosis (47). Multiple signaling factors involved in EC-VSMC crosstalk exhibit altered expression or activity in response to sepsis. iii) ECM remodeling dysfunction: Inflammatory mediators trigger excessive ECM deposition (48), imbalanced degradation (for example, altered metalloproteinase activity) and abnormal cross-linking, disrupting vascular mechanics and intercellular chemical/mechanical signaling. iv) Altered vesicle-mediated communication: Extracellular vesicles (EVs) serve a crucial role in EC-VSMC communication (49). Sepsis alters the release and contents (proteins, mRNAs and miRNAs) of EVs: EVs derived from ECs containing miR-539 promote VSMC proliferation (49), potentially contributing to vascular repair or pathological remodeling. Other sepsis-regulated miRNAs similarly modulate EC-VSMC interactions through EVs.

These collective disruptions force VSMCs to switch from a normal contractile phenotype to a pathological, proinflammatory, proliferative, migratory or synthetic state. This phenotypic transition serves as the fundamental cellular mechanism contributing to sepsis-associated vasoplegia, increased permeability, abnormal remodeling and organ hypoperfusion.

Calcium homeostasis dysregulation in VSMCs in sepsis-associated vasoplegia. Alterations in [Ca^{2+}]i are crucial events for initiating vascular contraction, and calcium levels and the sensitivity of contractile proteins collectively determine the strength of contraction. Bacterial LPS, a prominent pathogen-associated molecular pattern (PAMP), serves a central role in sepsis and septic shock. In a rat model of endotoxemia, the administration of LPS has been shown to result in systolic hypotension, tachycardia, peritoneal neutrophil migration and elevated alanine aminotransferase levels at 24 h. Concurrently, VSMCs displayed disturbances in calcium homeostasis, such as reduced calcium influx, depletion of sarcoplasmic reticulum calcium, inactivation of Orai1 channels, and ultimately, sepsis-associated vasoplegia (50).

The precise mechanisms through which LPS mediates intracellular calcium dysregulation have not been fully elucidated. In microglia, LPS-induced mitochondrial fragmentation hinders the capacity for and rate of calcium uptake, leading to disruption of calcium homeostasis (51). In cardiomyocytes, the interaction between pyruvate kinase M2 (PKM2) and sarcoplasmic/endoplasmic reticulum calcium ATPase 2a is crucial for maintaining calcium balance; PKM2 deficiency exacerbates the LPS-induced disruption of calcium homeostasis and cardiac contractile dysfunction (52).

Another crucial mechanism is the reduced sensitivity of contractile proteins to calcium: Intravenous LPS administration in adult rabbits has been reported to result in a depression of the force-calcium relationship in cardiac tissue despite an increase in [$Ca2^{+}$]i, indicating endotoxemia-induced ineffective calcium cycling and desensitization of myofibrils (53). Additionally, sepsis-associated vasoplegia is associated with a decrease in the expression of contractile proteins: LPS inhibits TGF-β control elements on the α-SMA promoter, leading to reduced α-SMA transcription and protein levels in human aortic and coronary VSMCs, and in rat aortic VSMCs (54).

The potential regulatory mechanisms of calcium homeostasis in VSMCs are illustrated in Fig. 2. Physiologically, Ca^{2+} enters VSMCs via voltage-dependent calcium channel, receptor-operated calcium channel, transient receptor potential channel and store-operated calcium channel, and intracellular calcium handling is regulated by plasmalemmal calcium ATPase, sodium-calcium exchanger and organelles (mitochondria and endoplasmic reticulum). GPCR activation triggers a signaling cascade via phospholipase Cβ/γ, which hydrolyze phosphatidylinositol 4,5-bisphosphate into inositol 1,4,5-trisphosphate (IP3); IP3 binds to endoplasmic reticulum receptors to release Ca^{2+} and elevate cytoplasmic Ca^{2+} levels. In sepsis and septic shock, LPS disrupts this finely balanced regulatory network by impairing calcium homeostasis through interference with calcium channels, intracellular calcium stores and calcium transporters. It also reduces myofibrillar calcium sensitivity and suppresses α-actinin expression (54). This decrease in α-actinin further undermines the structural integrity of the actin cytoskeleton, synergistically weakening myosin-actin interactions and VSMC contractility.

4. Mechanisms underlying VSMC injury in sepsis

The pathophysiology of VSMC injury encompasses a complex interplay of direct and indirect injury. These mechanisms intersect to disrupt vascular structure and function, leading to implications for sepsis-induced vasoplegia. Fig. 3 delineates the mechanisms by which pathogens, endothelial injury, cytokine storms and calcium/NO imbalances collectively contribute to VSMC dysfunction.

Direct VSMC injury caused by pathogens. The injury to VSMCs induced by sepsis results from a complex interaction of factors, including direct invasion by pathogens and injury caused by virulence factors. Pathogens disrupt cellular structures through their metabolic activities or through the action of secreted virulence factors, such as pore-forming toxins, exfoliative toxins and superantigens, leading to inflammatory processes that ultimately result in tissue necrosis (6). For example, bacterial sepsis, the predominant form of sepsis (55), has been shown to induce injury to VSMCs and impair their contractile function in a rat model of CLP (56). Different pathogens have unique effects: *Chlamydia pneumoniae* infection triggers an increase in mitochondrial ROS (mtROS) via Toll-like receptor (TLR)2, activating the JunB-Fra-1/matrix metalloproteinase-2 pathway to facilitate VSMC migration (57). By contrast, human cytomegalovirus enhances the expression of a disintegrin and metalloproteinase domain 9, promoting VSMC proliferation, migration and transition from a contractile to a synthetic phenotype (58). Notably, COVID-19 infection also induces a shift in the phenotype of VSMCs, worsening vascular dysfunction (59). These mechanisms underscore the direct involvement of pathogens and their virulence factors in inducing injury to VSMCs.

Moreover, pathogens indirectly damage VSMCs through the release of virulence factors, such as endotoxins and exotoxins. These molecules, which are essential for pathogen-induced tissue injury or immune response evasion, include LPS, exotoxins (such as cytotoxins, neurotoxins and enterotoxins), secretory systems and catalases (6). For example, LPS, a crucial component of gram-negative bacteria, serves a pivotal role in the pathogenesis of sepsis.

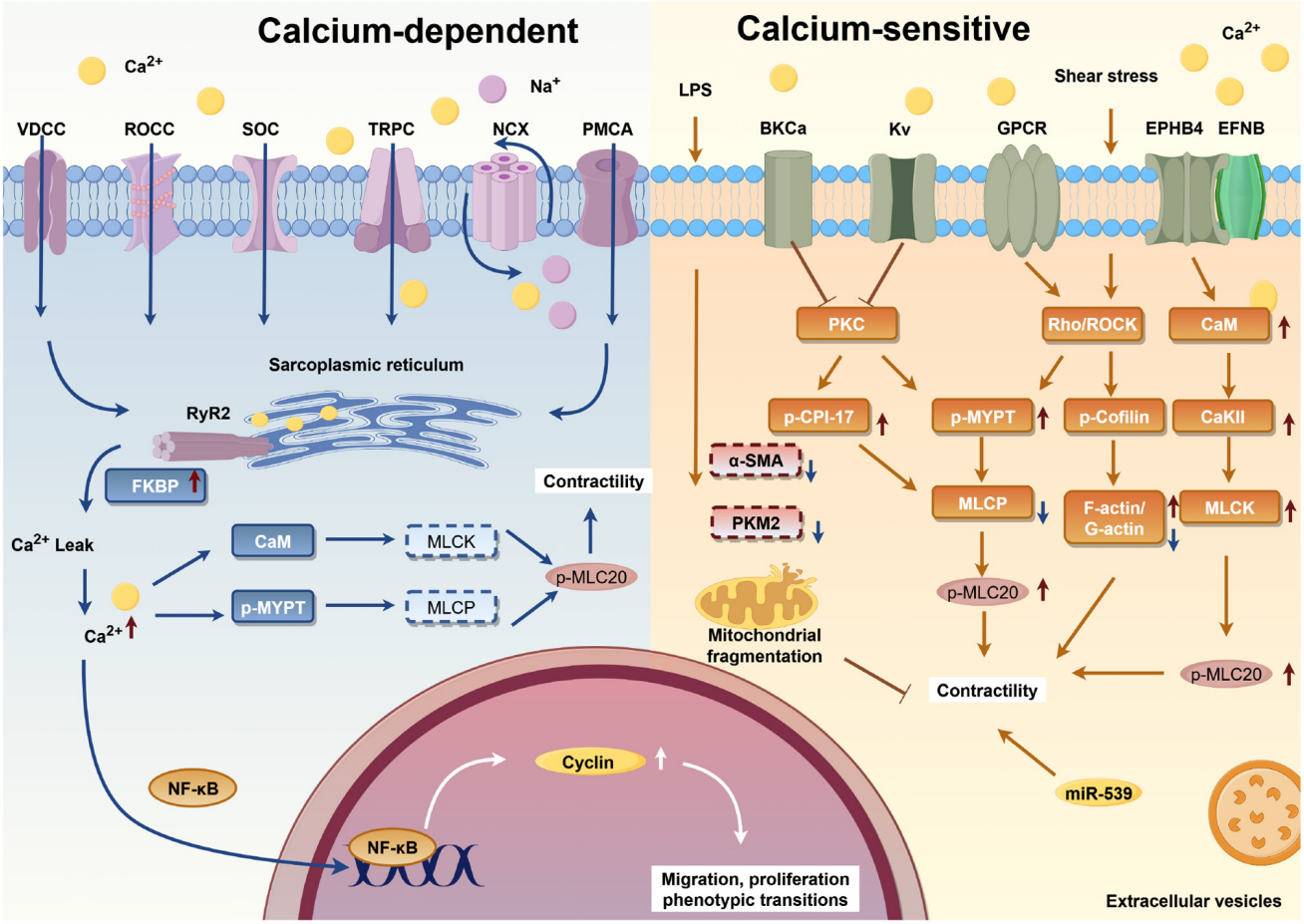

Figure 2. Regulation of Ca^{2+} and signal transduction in VSMCs. Ca^{2+} enters VSMCs via multiple pathways, including VDCC, ROCC, TRPC and SOC. Intracellular calcium handling relies on the PMCA and NCX at the cell membrane, as well as organelle-mediated transport in mitochondria and the endoplasmic reticulum. VSMC contraction is regulated by two primary mechanisms: Calcium-dependent and calcium-sensitive pathways. In the calcium-dependent pathway, increased intracellular Ca^{2+} forms a complex with CaM, activating MLCK. This activation enhances Mg^{2+}-ATPase activity, driving myosin-actin interaction and subsequent cell contraction. The calcium-sensitive pathway, mainly the Rho/ROCK pathway, is activated by sepsis-associated stimuli, including angiotensin II, leptin and mechanical stretch. PKC also modulates calcium influx by regulating the activity of calcium and potassium ion channels at the cell membrane. Additionally, miRNAs fine-tune these regulatory processes, adding another layer of complexity to calcium homeostasis and smooth muscle function. The figure was constructed using Figdraw 2.0 tool (https://www.figdraw.com/#/), with official authorization obtained by the authors (authorization no.: PPTAA80b0b).α-SMA, α-smooth muscle actin; BKCa, big-conductance calcium-activated potassium channel; Ca^{2+}, calcium ions; CaKII, calcium/calmodulin-dependent protein kinase II; CaM, calmodulin; EPHB4, Eph receptor B4; EFNB, ephrin B; FKBP, FK506 binding proteins; GPCR, G-protein coupled receptors; Kv, voltage-gated potassium channel; LPS, lipopolysaccharide; MLCK, myosin light chain kinase; MLCP, MLC phosphatase; miRNA/miR, microRNA; NCX, sodium-calcium exchanger; p-CPI-17, phosphorylated protein kinase C-potentiated inhibitor protein-17; p-MLC20, phosphorylated myosin light chain 20; p-MYPT, phosphorylated myosin phosphatase target subunit; PKC, protein kinase C; PKM2, pyruvate kinase M2; PLC, phospholipase C; PMCA, plasmalemmal calcium ATPase; ROCC, receptor-operated calcium channel; ROCK, Rho-associated protein kinase; RyR2, ryanodine receptor 2; SOC, store-operated calcium channel; TRPC, transient receptor potential channel; VDCC, voltage-dependent calcium channel.

Research has demonstrated that LPS enhances the expression of regulator of G-protein signaling 1, activates the JNK-p38 signaling pathway, and induces a shift in VSMCs from a contractile to a synthetic phenotype, thereby promoting proliferation, and contributing to the development and rupture of infectious intracranial aneurysms (60). *In vitro* studies have revealed that lipoteichoic acid from *Staphylococcus aureus* or *Streptococcal* Streptolysin O stimulates the expression of iNOS in rat VSMCs, leading to excessive NO production and subsequent vascular dysfunction, mechanisms closely associated with vasoplegia in gram-positive septic shock (61,62). Additionally, staphylococcal α-toxin directly causes coronary vasoconstriction and impairs myocardial contractility, a process mediated by the production of thromboxane A2 (63). In conclusion, sepsis-induced VSMC injury involves a variety of mechanisms, including direct invasion by pathogens, the release of virulence factors and the activation of inflammatory cascades. These insults disrupt the contractility of VSMCs and promote phenotypic transition, thereby contributing to the development of vasoplegia. Table I presents a summary of the pathogenic effects and molecular mediators of common pathogens on VSMCs (57-67).

VSMC injury mediated by cytokines in sepsis. PAMPs released by invading microorganisms are recognized by the host immune system, initiating innate immunity and the subsequent cytokine storm, a characteristic feature of sepsis (6,68). Cytokine release syndrome involves the extensive secretion of ILs, interferons (IFNs), TNF and colony-stimulating factors, driving systemic inflammation (69,70). These cytokines serve crucial roles not only in regulating immunity and tissue repair, but also in influencing the physiology of VSMCs and the progression

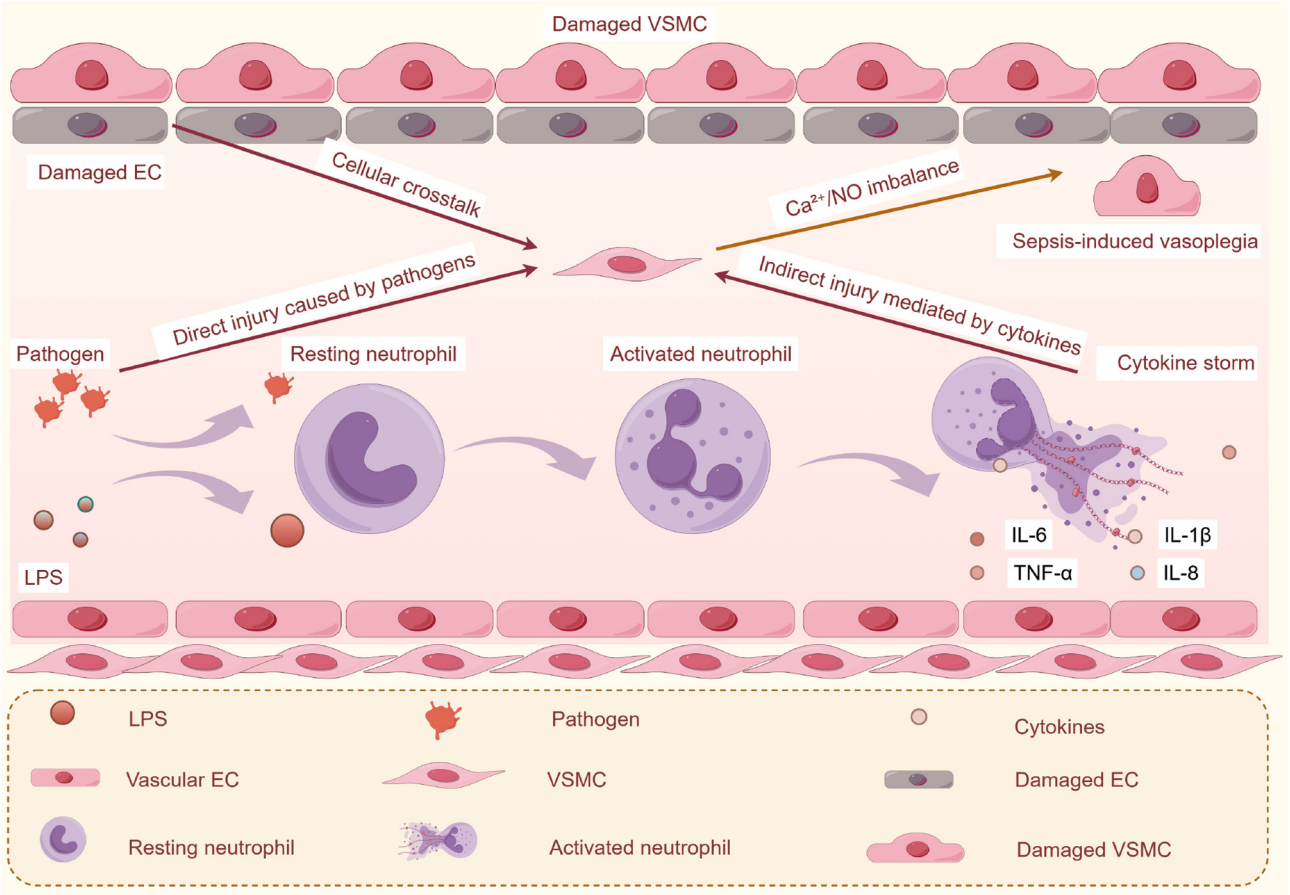

Figure 3. Conceptual overview of the convergence of endothelial injury, cytokine storm and Ca^{2+}/NO imbalance in sepsis-induced VSMC dysfunction. Sepsis (LPS or polymicrobial infection) initiates three interconnected pathological processes: Endothelial injury, cytokine storm and Ca^{2+}/NO imbalance, which synergistically drive VSMC dysfunction and subsequent sepsis-induced vasoplegia. Collectively, these events result in VSMC hypocontractility, phenotypic switching and apoptosis, ultimately causing vascular hyporeactivity and catecholamine resistance in septic vasoplegia. The figure was constructed using Figdraw 2.0 tool (https://www.figdraw.com/#/), with official authorization obtained by the authors (authorization no.: PWSOU68e36).Ca^{2+}, calcium ions; EC, endothelial cell; eNOS, endothelial NO synthase; iNOS, inducible NO synthase; LPS, lipopolysaccharide; NO, nitric oxide; ROS, reactive oxygen species; VSMC, vascular smooth muscle cell.

of diseases. Numerous studies have shown that inflammatory factors modulate the phenotype and function of VSMCs through distinct mechanisms. For example, the constitutive expression of the IL-1α precursor stimulates proliferation in human saphenous vein VSMCs (71), whereas IL-1β enhances the migration and invasion of human aortic SMCs through the p38 MAPK/angiopoietin-2 signaling pathway (72). TNF-α rapidly alters the expression of contractile and synthetic markers *in vitro*, promoting VSMC proliferation and migration at low concentrations (73). In sepsis, immune cells, including macrophages, neutrophils, T cells and natural killer cells, secrete substantial amounts of pro-inflammatory cytokines, with IFN-γ serving as a central mediator in regulating VSMC function (69). A previous study in a non-septic setting has demonstrated that IFN-γ secreted by decidual natural killer cells induces long non-coding RNA MEG3, thereby modulating VSMC migration and apoptosis, suggesting a conserved role for IFN-γ-regulated pathways in VSMC function (74). Furthermore, various other cytokines also participate in this regulatory network. Table II provides a summary of representative inflammatory factors, their regulatory effects on VSMCs and the underlying signaling pathways (71-101). These mechanisms collectively contribute to sepsis-induced vasoplegia.

VSMC injury-related signaling pathways in sepsis. The immunopathogenesis of sepsis is characterized by dysregulated immune responses, involving both hyperinflammation and immunosuppression (102). In sepsis, PAMPs and damage-associated molecular patterns (DAMPs) activate the host immune system, leading to cytokine storms and the aberrant activation of signaling pathways; events that compromise the function of VSMCs. These dysregulated signaling cascades are closely associated with VSMC inflammation, phenotypic switching and functional impairment. In addition to classical inflammatory pathways, emerging mechanisms, including NLRP3 inflammasome activation, mtROS release and the dysregulation of mechanosensitive ion channels, have recently been identified as critical regulators of VSMCs pathobiology in sepsis.

Notch signaling: A regulator of VSMC phenotypic stability. The Notch signaling pathway is a highly conserved intercellular communication system that includes receptors, ligands and effector molecules. In mammals, this pathway comprises four Notch receptors (Notch1-4) and five ligands (Jagged1, Jagged2, Delta1, Delta3 and Delta4) (103). Under normal physiological conditions, Notch signaling serves a role in regulating VSMC

Table I. Effects of common pathogens on VSMCs and their mechanisms of action.

First author, year	Pathogenic mechanisms	Model	Effector molecule	Molecular effects on cells	(Refs.)
A, Virulence factors					
Hu, 2024	Gram-negative bacteria LPS	HASMCs	RGS-1 upregulation	Phenotypic switching	(60)
Hattori, 1998	*Staphylococcus aureus* LTA	Rat VSMCs	iNOS upregulation	Vasodilation	(61)
Sibelius, 2000	*Staphylococcus* α-toxin	Rat CA	Thromboxane upregulation	Vasoconstriction	(63)
Seki, 2025	*Streptococcus* SLO	Rat ASMCs	iNOS upregulation	Vasodilation	(62)
Kook, 1999	*Vibrio vulnificus* hemolysin	Rat ASMCs	cGMP upregulation	Vasodilation	(64)
DelVechio, 2023	*Candida* CAWS	Rat ASMCs	COX2 upregulation	Vascular injury	(65)
B, Direct injury					
Zhao, 2022	*Chlamydia*	Rat VSMCs	JunB-Fra-1 upregulation	Migration	(57)
Zhang, 2013	*Porphyromonas gingivalis*	HASMCs	Notch and TGF-β upregulation	Promotes proliferation	(66)
He, 2023	HCMV	Human VSMCs	ADAM9 upregulation	Phenotypic switching	(58)
Oseghale, 2022	Influenza A virus	Pregnant mice ASMCs	CD69 upregulation	Vasodilation	(67)
Richards, 2024	COVID-19	hPSC-derived SMCs	IFN-α/IFN-γ upregulation	Phenotypic switching	(59)

ADAM9, a disintegrin and metalloproteinase domain 9; ASMC, aortic smooth muscle cell; CA, coronary artery; CAWS, *Candida albicans* water soluble; cGMP, cyclic guanosine monophosphate; HASMC, human ASMC; HCMV, human cytomegalovirus; hPSC, human pluripotent stem cell; IFN, interferon; iNOS, inducible nitric oxide synthase; LPS, lipopolysaccharide; LTA, lipoteichoic Acid; RGS-1, regulator of G-protein signaling 1; SLO, streptolysin O; SMC, smooth muscle cell; VSMC, vascular SMC.

differentiation and phenotype maintenance (24). However, under septic conditions, such as in a mouse model of CLP, the activity of the Notch pathway, particularly that of Notch3, is markedly reduced. This reduction is associated with the downregulation of the expression of Notch3 and its ligands Jagged1 and Delta4, resulting in impaired VSMC contractility (104). Moreover, in a mouse model of LPS-induced sepsis, Notch3 expression has been reported to be notably decreased in lung tissue, highlighting the essential role of Notch signaling in modulating VSMC function during sepsis (105).

AMPK/FOXO axis: Metabolic stress sensors in VSMC senescence. The AMPK/FOXO pathway serves a critical role in cellular energy balance and the response to oxidative stress. AMPK, a key energy sensor, is activated under metabolic stress conditions, whereas FOXO transcription factors act as important downstream effectors of stress signaling. Upon activation, AMPK phosphorylates FOXO proteins, augmenting their transcriptional activity and consequently upregulating the expression of antioxidant and cytoprotective genes, such as *SOD1* and SOD2, which facilitate peroxide degradation and mitigate the accumulation of ROS (106). In sepsis, tissue damage results in the release of extracellular histones, which serve as DAMPs. These external histones induce an inflammatory response and senescence in VSMCs in a dose-dependent manner through activation of AMPK/FOXO4 signaling (107). This signaling cascade connects the sensing of metabolic stress to the regulation of VSMC dysfunction during septic conditions, highlighting its role in integrating energy metabolism with inflammatory signaling networks.

NF-κB: The central inflammatory hub in VSMCs. The NF-κB pathway serves as a central transcriptional regulatory hub that controls cell proliferation, apoptosis, inflammatory responses and immune homeostasis (108). In sepsis, stimuli from pathogens and proinflammatory cytokines activate NF-κB, promoting its translocation to the nucleus and subsequently inducing downstream inflammatory genes, including HIF-1α (6). Preclinical studies have shown that the pharmacological inhibition of NF-κB signaling effectively reduces VSMC proliferation and activation, leading to the mitigation of pathological vascular remodeling (80,81). These findings underscore the crucial role of NF-κB in linking septic inflammation to VSMC dysfunction, positioning it as a potential

Table II. Pathogen-induced direct injury and virulence factors on VSMCs.

First author, year	Cytokine	Model	Key molecular/signaling pathway	Molecular effects on cells	(Refs.)
A, ILs					
Beasley, 1999	IL-1α	HSVSMCs	Not given	Promotes proliferation	(71)
Xu, 2022	IL-1β	HASMCs	p38 MAPK/Angpt-2	Migration and invasion	(72)
Arumugam, 2019	IL-2	Human iliac artery	PI3K/Akt/mTOR	Migration and proliferation	(75)
Brizzi, 2001	IL-3	Human umbilical cord	ERK1/2	Migration and proliferation	(76)
Hofbauer, 2006	IL-4	HCASMCs	Osteoprotegerin	Calcification	(77)
Cimmino, 2021	IL-6	Rat ASMCs	Bcl-xL and p53	Reduces apoptosis	(78)
Yue, 1994	IL-8	Rat ASMCs	MAPK	Promotes proliferation	(79)
Mazighi, 2004	IL-10	Rat ASMCs	NF-κB/IκB	Inhibits activation	(80)
Zimmerman, 2002	IL-11	Human VSMCs	NF-κB	Inhibits proliferation	(81)
Cho, 2013	IL-13	HPASMCs	IL-13Rα2-Arg2	Phenotypic switching	(82)
Iwasaki, 2007	IL-15	Rat ductus arteriosus	PDGF	Inhibits proliferation	(83)
Park, 2015	IL-16	Rat ASMCs	p38 MAPK/Sp-1/ MMP-9	Enhanced migration and invasion	(84)
Duncan, 2020	IL-17	Rat ASMCs	MAPK/βENaC	Inhibits proliferation	(85)
Zhang, 2017	IL-18	HASMCs	TRPM7 channel	Calcification	(86)
Cuneo, 2010	IL-19	Human VSMCs	HuR	Reduces activation	(87)
Dale, 2019	IL-21	Mice ASMCs	Angiotensin II	Inhibits proliferation	(88)
Rattik, 2015	IL-22	Mice ASMCs	α-actin and caldesmon	Phenotypic switching	(89)
Conway, 2018	IL-23	Human temporal artery	Not given	Promotes proliferation	(90)
Lee, 2012	IL-24	Rat ASMCs	Wnt/β-catenin	Inhibits calcification	(91)
Hao, 2023	IL-29	Rat ASMCs	JAK2/STAT3/BMP2	Calcification	(92)
Son, 2017	IL-32	Mice ASMCs	MicroRNA-205	Reduces activation	(93)
DeVallance, 2014	IL-33	Rat ASMCs	ERK1/2	Increases vascular tone	(94)
Skowron, 2015	IL-35	HASMCs	ICAM-1	Immune homeostasis	(95)
Ding, 2022	IL-37	HASMCs	RIPK3	Phenotypic switching	(96)
B, IFNs					
Niessner, 2007	IFN-α	Human carotid artery	STAT	Enhances apoptosis	(97)
Sano, 2015	IFN-β	HCASMCs	Caspase-3	Enhances apoptosis	(98)
Liu, 2017	IFN-γ	VSMCs	Long non-coding RNA MEG3	Enhances both migration and apoptosis	(74)
C, TNF superfamily					
Sun, 2024	TNF-α	Calf ASMCs	Not given	Phenotypic switching	(73)
D, CSFs					
Vasudevan, 2003	M-CSF	VSMCs	ICAM-1	Enhances apoptosis	(99)
Plenz, 1999	GM-CSF	HASMCs	Collagen VIII	Modulates collagen	(100)
Rinaldi, 2016	G-CSF	Rat CCA	Foxo3a mRNA	Promotes differentiation	(101)

βENaC, β epithelial sodium channel; Angpt-2, angiopoietin 2; Arg2, arginine 2; ASMC, aortic SMC; BMP2, bone morphogenetic protein 2; CCA, common carotid artery; CSF, colony-stimulating factor; G-CSF, granulocyte CSF; GM-CSF, granulocyte-macrophage CSF; HASMC, human ASMC; HCASMC, human coronary artery SMC; HPASMC, primary hepatic pulmonary artery SMC; HSVSMC, human saphenous vein VSMC; HuR, human antigen R; ICAM-1, intercellular adhesion molecule-1; IFN, interferon; IL-13Rα2, IL-13 receptor α2; KLF4, Krüppel-like factor 4; M-CSF, macrophage CSF; MMP-9, matrix metalloproteinase-9; PDGF, platelet-derived growth factor; RIPK3, receptor-interacting serine/threonine-protein kinase 3; SMC, smooth muscle cell; Sp-1, specificity protein 1; TRPM7, transient receptor potential melastatin 7; VSMC, vascular SMC.

Table III. Summary of the principal signaling pathways implicated in VSMC injury in sepsis.

Pathway	Primary function in VSMCs	Key dysregulation in sepsis	Functional outcome in vasoplegia
Notch3	Maintains contractile phenotype (24).	Downregulation of Notch3/ Jagged 1/Delta 4 (104,105).	Reduced vasoconstriction, phenotypic switching (104,105).
AMPK/FOXO4	Energy sensing, stress response (106).	Activation by extracellular histones (107).	Senescence, SASP secretion (107).
NF-κB	Inflammatory gene transcription (108).	IKK-mediated nuclear translocation (80,81).	Cytokine production, vascular leak (80,81).
p38 MAPK	Inflammatory signaling (109-111).	Activation by IL-1β/ IL-16 (72,84).	Enhanced migration, amplified NF-κB activity (72,84).
PI3K/Akt/mTOR	Proliferation, survival (112).	Hyperactivation via IL-2/IL-2R (75).	Neointimal thickening, paracrine NO elevation (75).

IKK, IκB kinase; IL-2R, IL-2 receptor; NO, nitric oxide; SASP, senescence-associated secretory phenotype; VSMC, vascular smooth muscle cell.

therapeutic target for vascular complications associated with sepsis.

p38 MAPK: Mediating inflammatory VSMC migration. p38 MAPK is a crucial member of the MAPK family, which regulates cellular responses to environmental stressors and inflammatory stimuli (109). Consisting of four isoforms (α, β, γ and δ), p38 MAPK acts as a central transducer of signals from cell surface receptors to nuclear effectors, and is activated by various stressors and proinflammatory cytokines (110,111). In the context of sepsis, inflammatory factors such as IL-1β and IL-16 stimulate p38 MAPK activation, facilitating VSMC migration and invasion, processes that are fundamental to pathological vascular remodeling and dysfunction (72,84). This pathway links inflammatory signaling to alterations in VSMCs behavior, emphasizing its role in mediating sepsis-induced vascular pathology.

PI3K/Akt/mTOR: Regulating VSMC proliferation in sepsis. The PI3K/Akt signaling pathway serves as a central regulator of cell survival, proliferation and metabolic homeostasis (112). In sepsis, this pathway modulates inflammatory responses and vascular cell behavior. Research has indicated that the IL-2/IL-2 receptor system promotes VSMC proliferation and migration via the PI3K/Akt/mTOR axis, exacerbating vascular injury (75). Table III summarizes the key signaling pathways involved in VSMC injury during sepsis (24,72,75,80,81, 84,104-112).

Emerging mechanisms of VSMC regulation in sepsis-induced vasoplegia. Sepsis-induced vasoplegia is closely associated with dysregulated VSMC function, with emerging evidence highlighting three nonclassical regulatory mechanisms: NLRP3 inflammasome activation, mtROS overproduction and mechanosensitive ion channel dysfunction, which complement classical inflammatory pathways.

The NLRP3 inflammasome, which comprises the sensor NLRP3, adaptor ASC and effector pro-caspase-1, is activated through a two-stage pathway in sepsis: NF-κB-driven upregulation of NLRP3/pro-IL-1β (initiation) and assembly triggered by PAMPs or DAMPs (activation) (113,114). Direct evidence for its role in septic VSMC dysfunction remains scarce, with most data derived from indirect observations. For example, histones released as DAMPs by severely damaged cells in sepsis promote ASC-NLRP3 interactions in VSMCs, mediating VSMC inflammation and senescence (107), processes implicated in impaired VSMC contractility. Although characterized in the context of chronic kidney disease-related vascular calcification, *Prevotella copri*-derived LPS (a PAMP) has been shown to induce VSMC osteogenic differentiation *in vitro* via activation of the TLR4-NF-κB-NLRP3 inflammasome axis (115); notably, NF-κB blockade can abolish both inflammasome activation and the resulting VSMC phenotypic shift in a rat model of chronic kidney disease. Extrapolating from this mechanistic framework, these findings suggest that PAMP-mediated VSMC phenotypic perturbation in sepsis may also occur via inflammasome signaling pathways. Notably, NLRP3 is transcriptionally regulated by Runx2, which coordinates vascular matrix stiffness and VSMC inflammatory phenotypes (116). Although direct evidence in sepsis is lacking, matrix stiffness-induced VSMC dysfunction is a recognized contributor to decreased vascular compliance, a feature that overlaps with sepsis-induced vasoplegia (25,116). Given the critical role of NLRP3 inflammasome signaling in IL-1β production in VSMCs (117), crosstalk with the classical NF-κB pathway may be a possibility; for example, IL-1β released by activated VSMCs may further activate NF-κB, resulting in the formation of a feed-forward loop that amplifies VSMC inflammation and functional impairment.

Oxidative stress serves a pivotal role in the pathogenesis of sepsis. When the body is subjected to severe external insults, such as burns, shock or serious infections, cellular structural alterations lead to mitochondrial injury and a sudden surge in ROS and reactive nitrogen species (RNS) levels. An imbalance between oxidant and antioxidant systems allows oxidative stress products, including ROS and RNS, to inflict mitochondrial damage and compromise vital cellular components, such as lipids, proteins and nucleic acids (118). Sepsis-induced inflammatory stress triggers the production of excessive amounts of mtROS (119), a critical upstream regulator of VSMC dysfunction and NLRP3 inflammasome

activation (120). Mechanistically, mtROS upregulate NLRP3 at the translational level rather than directly activating the assembled inflammasome (121), although the specific molecular events involved in sepsis remain unclear. Beyond NLRP3 modulation, mtROS enhance MAPK activity and promote DNA synthesis, stimulating VSMC proliferation (122,123). This may perturb vascular wall integrity and exacerbate sepsis-induced decreases in vascular compliance, but direct evidence linking mtROS-driven proliferation to vasoplegia is lacking.

Mechanosensitive ion channels, which transduce mechanical stimuli into electrochemical signals, are potential regulators of septic VSMC dysfunction. Hemodynamic instability and inflammatory mediators induced by sepsis have been implicated in disrupting the function of key mechanosensitive channels in VSMCs, such as Piezo1, transient receptor potential vanilloid (TRPV) channels and two-pore domain potassium channels (124-126). Existing data primarily come from non-VSMC tissues or systemic models: Piezo1 has been shown to be upregulated in the intestinal tissues of CLP-induced septic mice (125), and its established role in VSMC Ca^{2+} influx suggests potential perturbation of Ca^{2+} homeostasis (127). In addition, TRPV1 has been reported to be upregulated in a rat model of endotoxemia (126), which may promote Ca^{2+}-dependent NO production and vasodilation in VSMCs. CLP-induced mice exhibit downregulation of TASK-1, TASK-2 and TREK-1 (124), with TREK 1 downregulation potentially altering VSMC membrane potential and inhibiting voltage-gated Ca^{2+} channel activation.

5. Targeting VSMC dysfunction in sepsis-induced vasoplegia

As aforementioned, exposure to stimuli such as metabolic disturbances, shear stress, cellular crosstalk and disruption of calcium homeostasis in sepsis triggers the transition of VSMCs from a differentiated contractile phenotype to a synthetic dedifferentiated phenotype (128). The core scientific controversy surrounding this process lies in whether VSMC dedifferentiation is irreversible. On one side, cellular dedifferentiation is traditionally regarded as irreversible due to stable epigenetic reprogramming and persistent alterations in gene expression profiles that lock VSMCs in a synthetic state. This perspective implicitly underpins early assumptions about septic VSMC dysfunction, where long-term phenotypic shifts were thought to preclude functional recovery without targeted intervention (25). On the other side, accumulating evidence challenges this irreversibility and supports the potential for redifferentiation. For example, VSMCs subjected to serum deprivation (a model of reduced pro-dedifferentiation stimuli) fully regain a spindle-like morphology, increased contractile filament density and restored expression of VSMC-specific contractile proteins (such as α-SMA, calponin), demonstrating functional redifferentiation (129). Preclinical studies have further identified agents that reverse septic VSMC dedifferentiation: Dehydrocorydaline sustains the contractile phenotype via Spta1 upregulation (130), and atorvastatin fully reverses morphological and functional abnormalities (including proliferation, medial layer rearrangement and impaired vasoreactivity) in a rat model of LPS-induced carotid artery inflammation (131), directly supporting the reversibility of VSMC dysfunction in inflammatory contexts relevant to sepsis. Notably, clinical observations of sepsis survivors have also documented partial recovery of vascular reactivity over time, indirectly suggesting that VSMC dedifferentiation may not be permanent (132). The current review focuses on pharmacological strategies targeting VSMC dysfunction in sepsis-induced vasoplegia (conventional drugs, calcium homeostasis modulators and NO-reducing therapies) precisely because of this unresolved controversy: If dedifferentiation were strictly irreversible, therapeutic efforts would focus solely on symptom relief, whereas evidence for potential reversibility justifies exploring mechanism-based interventions to restore intrinsic VSMC contractile function.

Conventional clinical drugs modulating VSMC function. Sepsis-induced vasoplegia is characterized by VSMC hypocontractility, impaired vasomotor tone and resistance to catecholamines, prompting clinical investigations into conventional agents targeting VSMC function. The current review presents a comprehensive analysis of four principal drug classes, vasopressin analogues, phosphodiesterase (PDE) inhibitors, antioxidants and calcium sensitizers, integrating preclinical mechanisms, clinical trial data and key translational challenges, with an emphasis on a critical and balanced appraisal of their therapeutic potential and limitations. Table IV summarizes the preclinical and clinical evidence, underlying mechanisms and translational challenges of conventional VSMC-targeted therapies for sepsis-induced vasoplegia (133-156).

Vasopressin and its analogues. As the most extensively studied agents for sepsis-induced vasoplegia, vasopressin analogues [including arginine vasopressin (AVP), terlipressin and selepressin] constitute a cornerstone in the clinical management of VSMC dysfunction. However, their therapeutic application is constrained by a delicate equilibrium between hemodynamic efficacy, off-target toxicity and patient heterogeneity; these are critical barriers that have limited translational success beyond symptomatic relief. Unlike catecholamines, which rely on intact adrenergic signaling (often compromised in sepsis due to receptor desensitization), vasopressin analogues directly restore vascular contractility via V1a receptors expressed on VSMCs (133). Activation of V1a receptors triggers downstream signaling of phospholipases A, C and D, promoting inositol triphosphate-mediated intracellular Ca^{2+} mobilization from the sarcoplasmic reticulum and increasing MLC phosphorylation (134). Moreover, in LPS-challenged rats, terlipressin suppresses aortic iNOS expression and activity by inhibiting NF-κB nuclear translocation, thereby disrupting the pathogenic calcium-NO feedback loop and ameliorating aortic vasoplegia in response to vasoconstrictors (135). This dual mechanism provides vasopressin analogues with a distinct advantage in targeting the fundamental pathophysiology of sepsis-induced vasoplegia rather than merely alleviating hemodynamic instability.

Clinically, evidence for vasopressin analogues remains mixed, reflecting the complexity of balancing efficacy and safety. A multicenter, randomized, double-blind trial (n=778) comparing low-dose AVP with norepinephrine in catecholamine-dependent septic shock showed no significant

Table IV. Subclass-specific comparison of preclinical and clinical evidence, mechanisms and translational barriers for VSMC-targeted conventional drugs in sepsis-induced vasoplegia.

Drug class	Representative agents	Mechanisms of action	Preclinical evidence[a]	Clinical evidence[b]	Core limitations[c]
Vasopressin and its analogues	Arginine vasopressin, terlipressin, selepressin	V1a receptor activation: Triggers PLC/IP3-mediated Ca^{2+}mobilization and MLC phosphorylation to restore VSMC contractility. Inhibits NF-κB nuclear translocation (133-134).	LPS/CLP models: Restored aortic vasoreactivity and reduced plasma NO metabolites (135).	VASST trial: No 28-day mortality reduction; post hoc analysis showed reduced AKI progression (136,137). TERLIVAP trial: Reduced catecholamine requirements and rebound hypotension (138). SEPSIS-ACT trial: Selepressin failed to reduce ventilator/ vasopressor-free days (139).	Ischemic off-target effects (digital gangrene, mesenteric ischemia).
PDE inhibitors	PDE3: Milrinone, enoximone. PDE4: Roflumilast; PDE5: Tadalafil, sildenafil	Inhibits cAMP/cGMP hydrolysis: Modulates VSMC Ca^{2+} sensitivity, suppresses inflammation and stabilizes micro-vascular barrier (140).	Roflumilast: Improved renal perfusion but worsened MAP/cardiac output in CLP rats (141,142). Tadalafil: Enhanced renal blood flow but not survival in CLP models (143). Milrinone: Restored mesenteric villus perfusion but exacerbated systemic hypo-tension in endotoxemia (144,145).	Scarce and inconclusive.	Context-dependent efficacy (beneficial in mild microvascular dysfunction, harmful in severe vasoplegia).
Antioxidants	Vitamin C, vitamin E, MitoQ	Vitamin C: Scavenges cytosolic ROS (146). Vitamin E: Preserves thiol-disulfide homeo-stasis to protect VSMC contractile proteins (147). MitoQ: TPP^{+}-mediated mitochondrial targeting; scavenges mtROS + activates Keap1/Nrf2 pathway (148).	Vitamin C: Mitigated cardio-myopathy and restored VSMC contractility in LPS-induced rats (146). Vitamin E: Reduced oxidative/inflammatory injury and preserved vasoreactivity in LPS-induced mice (147). MitoQ: Inhibited VSMC phenotypic switching and apoptosis (149).	Vitamin C: Meta-analysis (12 RCTs) indicated reduced vasopressor duration/SOFA scores (150); 1 RCT reported higher 28-day mortality (151). Vitamin E: Reduced 28-day mortality in a retrospective cohort study (152). MitoQ: No clinical data in sepsis-induced vasoplegia.	Poor bioavailability/ tissue penetration in sepsis. Conflicting clinicalevidence. Non-selective antioxidant effects mayblunt anti-infective immunity.

Table IV. Continued.

Drug class	Representative agents	Mechanisms of action	Preclinical evidence[a]	Clinical evidence[b]	Core limitations[c]
Calcium sensitizers	Levosimendan	Calcium sensitization and mitochondrial protection (153,154).	Relaxed thoracic aorta via PKC inhibition and Kir channel activation (153).	Meta-analysis: Improved hemodynamics and lactate clearance, and reduced in-hospital mortality in sepsis-induced cardiomyopathy (155). Prospective RCT: Increased sublingual micro-circulatory flow index (156). Dose-dependent hypotension reported in patients with septic shock (153).	Vasodilatory effects exacerbate hypotension in severe vasoplegia.

[a]Preclinical evidence primarily includes data from sepsis-related models unless otherwise specified; [b]Clinical evidence prioritizes RCTs and large-scale cohort studies, with retrospective analyses or case series noted for limitations. [c]Core limitations integrates species differences, model limitations, pharmacokinetic alterations and clinical application constraints. AKI, acute kidney injury; Ca^{2+}, calcium ions; cAMP, cyclin adenosine monophosphate; cGMP, cyclic guanosine monophosphate; CLP, cecal ligation and puncture; IP3, inositol triphosphate; LPS, lipopolysaccharide; MAP, mean arterial pressure; MitoQ, mitoquinone mesylate; MLC, myosin light chain; mtROS, mitochondrial ROS; NO, nitric oxide; PDE, phosphodiesterase; PKC, protein kinase C; PLC, phospholipase C; RCT, randomized controlled trial; ROS, reactive oxygen species; SOFA, Sequential Organ Failure Assessment; TPP, triphenylphosphonium; VSMC, vascular smooth muscle cell.

reduction in 28-day mortality (35.4% vs. 39.3%, P=0.26) (136), indicating that restoring vascular tone alone is insufficient to reverse sepsis-related multiorgan dysfunction. Nonetheless, post hoc analysis of the VASST trial revealed a promising renal protective effect of AVP: In high-risk patients (a ≥1.5-fold increase in serum creatinine from baseline or >25% glomerular filtration rate (GFR) reduction within 7 days, sustained for >24 h), AVP was associated with a significantly lower incidence of AKI progression to 'Failure' [serum creatinine >3-fold baseline; ≥4.0 mg/dl (353.6 μmol/l) with an acute ≥0.5 mg/dl rise; or >75% GFR reduction] or 'Loss' (permanent renal failure requiring dialysis for >4 weeks) than norepinephrine (20.8% vs. 39.6%, P=0.03) (137). This benefit may stem from reduced renal vasodilation and preserved glomerular filtration pressure (137). The phase II TERLIVAP trial (n=45) demonstrated that, compared with continuous infusion of 0.03 U/h vasopressin or 15 μg/min norepinephrine, administration of 1.3 μg/kg/h terlipressin, a longer-acting prodrug of vasopressin, significantly reduced catecholamine requirements needed to achieve hemodynamic stability within 48 h (0.8±1.3 vs. 1.2±1.4 vs. 0.2±0.4 μg/kg/min; each P≤0.05) (138). Moreover, terlipressin treatment was associated with a lower incidence of rebound hypotension compared with the two comparator groups (P<0.05) (138). Selepressin, a selective V1a agonist designed to mitigate off-target toxicity, failed to meet the primary endpoint of ventilator- and vasopressor-free day reduction in the SEPSIS-ACT trial (n=868) (139).

PDE inhibitors. PDE inhibitors modulate VSMC function by inhibiting the hydrolysis of cyclic nucleotides (cyclin adenosine monophosphate/cGMP), representing a mechanistically distinct approach to targeting sepsis-induced vasoplegia (140). However, their translational potential is constrained by context-dependent efficacy, off-target effects and a paucity of sepsis-specific clinical data, reflecting the gap between preclinical mechanistic insights and clinical reality. Mammalian PDEs are classified into 11 families, with PDE3, PDE4 and PDE5 being the most relevant to septic VSMC dysfunction because of their tissue distribution and cyclic nucleotide selectivity (157). Commonly used PDE inhibitors in clinical practice are classified based on their target PDE isoforms, as follows: PDE3 inhibitors, which target PDE3 (predominantly expressed in the heart and circulatory system), with milrinone as a prototypical agent; PDE4 inhibitors, which target PDE4 (primarily localized in the respiratory system, particularly the bronchial tissues), such as roflumilast; and PDE5 inhibitors, which target PDE5 (mainly expressed in the lungs and penile tissues), with sildenafil as a representative drug.

Preclinical evidence for the role of PDE inhibitors in sepsis is conflicting, highlighting their model-dependent efficacy. In CLP-induced septic rats, the PDE4 inhibitor roflumilast reduced VSMC-derived inflammatory cytokine release (TNF-α and IL-6) and apoptosis, while stabilizing the microvascular barrier and improving renal perfusion (141,142). However, roflumilast worsened hemodynamic parameters [mean arterial pressure (MAP) and cardiac output] and failed to improve survival, likely because of its nonselective vasodilatory effects in the context of systemic inflammation (142). In the colon ascendens stent peritonitis model (a more clinically relevant polymicrobial sepsis model), PDE4 inhibition

has been shown to stabilize the microvascular barrier and improve microcirculatory flow, supporting its potential in targeting sepsis-induced microvascular dysfunction (158). Similarly, the PDE5 inhibitor tadalafil improved basal renal blood flow in CLP-induced rats by increasing VSMC calcium sensitivity, but did not increase survival, suggesting that the benefits of isolated organ perfusion do not translate to systemic hemodynamic stability (143). Preclinical data on PDE3 inhibitors (for example, milrinone) present inherent contradictions, reflecting their context-dependent pleiotropic effects: Although milrinone restored mesenteric intestinal villus perfusion in rat models of endotoxemia, it concurrently aggravated systemic hypotension. Notably, despite this systemic hemodynamic deterioration, milrinone ameliorated intestinal mucosal hypoperfusion, underscoring a dissociation between systemic vascular tone and regional microcirculatory function (144,145).

Clinical evidence for the use of PDE inhibitors in sepsis-induced vasoplegia remains limited and inconclusive. A multicenter cohort study of 229 patients with septic shock revealed that compared with standard care, PDE3 inhibitors (milrinone and enoximone) did not improve lactate clearance, organ failure, length of Intensive Care Unit (ICU) or hospital stay, or mortality (159). Notably, the effects of PDE3 inhibitors on cardiogenic shock have also been evaluated, with a systematic review showing no differences in outcomes (early death, cardiac arrest, renal replacement therapy initiation) when PDE3 inhibitors were combined with other inotropes, findings that may be extrapolated to sepsis-related cardiomyopathy but not specifically to VSMC-mediated vasoplegia (160). To date, no large-scale randomized controlled trials (RCTs) have evaluated PDE4 or PDE5 inhibitors for sepsis-induced vasoplegia.

Antioxidants. Antioxidants exist in various forms, each characterized by distinct mechanisms of action and clinical indications. They can broadly be categorized into those already in clinical use and others still under experimental investigation. As a water-soluble antioxidant, ascorbic acid (vitamin C) participates in numerous enzymatic and nonenzymatic reactions, and serves as a cofactor in multiple biological processes (161). The therapeutic potential of vitamin C in sepsis and critical illness has been studied for several decades; however, its clinical utility remains unclear. *In vitro* studies have demonstrated that vitamin C, when administered orally or added directly to cell cultures, promotes EC growth while inhibiting SMC proliferation (162,163). Preclinically, in LPS-induced septic rats, vitamin C has been shown to mitigate endotoxin-induced cardiomyopathy by inhibiting oxidative stress-related cytokine expression, thereby protecting myocardial tissue from damage (146). Clinical evidence remains contradictory: A meta-analysis of 12 RCTs revealed that intravenous vitamin C supplementation markedly reduced the duration of vasopressor therapy and improved Sequential Organ Failure Assessment scores in patients with septic shock, findings indirectly attributed to restored VSMC contractility, reducing catecholamine dependence (150). However, another randomized placebo-controlled trial reported that compared with placebo recipients, adults with sepsis receiving vasopressor therapy who were treated with intravenous vitamin C exhibited a greater risk of death at 28 days (risk ratio 1.17; 95% CI 0.98-1.40) (151). This contradiction is partly explained by sepsis-specific pharmacokinetic alterations: Critically ill patients have an increased volume of distribution and reduced renal clearance of vitamin C, leading to subtherapeutic concentrations in VSMCs despite high plasma levels.

Natural vitamin E (α-tocopherol), a lipid-soluble antioxidant, is selectively depleted in septic VSMCs because of increased oxidative consumption, with deficiency independently associated with severe septic shock (adjusted OR 6.75; 95% CI 2.45-18.60; P<0.001) (164). In an LPS-induced sepsis mouse model, vitamin E notably protected against sepsis-induced oxidative and inflammatory damage by preserving thiol-disulfide homeostasis and attenuating cytokine production (147). However, clinical evidence remains limited to retrospective analyses: a cohort study of 523 patients with sepsis in the ICU revealed that vitamin E supplementation was associated with reduced 28-day mortality (HR 0.75; 95% CI 0.59-0.95; P=0.019) (152). Given the current scarcity of robust clinical evidence, which is limited primarily to the results of retrospective cohort studies indicating possible benefits in vitamin E-deficient subpopulations, and persistent translational challenges, the therapeutic efficacy of vitamin E in patients with sepsis-induced vasoplegia requires substantiation through rigorously designed, prospective, multicenter RCT.

Mitoquinone mesylate (MitoQ) is a mitochondrion-targeted antioxidant characterized by a triphenyl phosphonium cation conjugated to ubiquinone, this structural design enables selective accumulation in mitochondria via membrane potential-dependent uptake, allowing it to specifically scavenge mtROS and protect cells from oxidative stress-induced mitochondrial dysfunction (148). MitoQ, a key regulator of VSMC homeostasis, has been validated in multiple preclinical models to mitigate vascular pathologies related to sepsis-induced VSMC dysfunction. In human aortic VSMCs, MitoQ has been reported to attenuate PM2.5-induced vascular fibrosis by modulating mitochondrial dynamics; specifically, it can suppress the transition of VSMCs from a contractile to a synthetic phenotype, and alleviate mitochondrial fragmentation and mitophagy (149). This phenotype-stabilizing effect is highly relevant to sepsis, in which VSMC phenotypic dedifferentiation is a key driver of vasoplegia. In an adenine-induced rat model of aortic calcification, MitoQ inhibited VSMC oxidative stress and apoptosis via activation of the Keap1/Nrf2 signaling pathway, downregulating the activity of oxidative factors and upregulating the activity of antioxidant enzymes, thereby attenuating vascular calcification and preserving VSMC contractile potential (165). Notably, in endotoxin-induced cardiac dysfunction models, Supinski *et al* (166) demonstrated that MitoQ may protect against cardiac mitochondrial damage by inhibiting mtROS overproduction, and suppressing the activation of caspase-9 and caspase-3. These preclinical findings underscore the multifaceted role of MitoQ in regulating VSMCs phenotype, mitochondrial function, and survival, supporting its potential as a targeted therapy for sepsis-induced vasoplegia.

Calcium sensitizers (levosimendan). Calcium sensitizers are a novel class of potential therapeutic agents for sepsis-induced vasoplegia that increase VSMC contractility without increasing intracellular calcium levels, thereby

avoiding the risk of calcium overload and arrhythmia linked to catecholamines and vasopressin analogues (153-156). Levosimendan, a prototypical agent initially designed as an inotrope, has shown promise for treating septic vasoplegia because of its combined effects on cardiac cells and VSMCs, although its clinical use is limited by context-dependent vasodilation (156).

At the molecular level, levosimendan exerts VSMC-specific effects via two core mechanisms: i) Calcium sensitization: It binds to the N-terminal domain of troponin C (TnC) in VSMCs with high affinity, increasing the sensitivity of TnC to $[Ca^{2+}]i$ and promoting actin-myosin cross-bridge formation, even at physiological $[Ca^{2+}]i$ levels, thereby restoring contractile function compromised by NO-mediated calcium desensitization in sepsis (164). ii) Mitochondrial protection: It activates ATP-sensitive potassium (K-ATP) channels in VSMC mitochondria, reducing mtROS production and inhibiting caspase-9/-3-dependent apoptosis, thus preserving VSMC viability and the contractile phenotype in the context of septic oxidative stress (165). Unlike catecholamines, which rely on intact adrenergic signaling (often desensitized in sepsis), the direct modulation of contractile proteins by levosimendan is effective in catecholamine-resistant states.

Clinically, the efficacy of levosimendan in sepsis-related cardiovascular dysfunction has been supported by accumulating evidence, although data specific to sepsis-induced vasoplegia remain nuanced ,reflecting a dual effect with context-dependent benefits. A systematic review and meta-analysis of 12 RCTs comparing levosimendan with dobutamine in patients with sepsis-induced cardiomyopathy revealed that levosimendan markedly improved hemodynamic parameters, tissue perfusion and biomarkers of myocardial injury, while reducing in-hospital mortality and ICU length of stay (155). With respect to the treatment of septic shock-related vasoplegia, a prospective, double-blind RCT demonstrated that compared with a placebo, levosimendan (0.2 μg/kg/min) improved sublingual microcirculatory blood flow, reflected by a 32% increase in the microcirculatory flow indices of small and medium vessels, which suggested that enhanced regional tissue perfusion was mediated by VSMC function restoration (156). Despite these benefits, the vasodilatory properties of levosimendan pose a notable constraint to its use in sepsis-induced vasoplegia. The activation of Kir channels and inhibition of protein kinase C by the drug in systemic VSMCs can induce dose-dependent vasodilation, leading to transient hypotension, an adverse effect that may exacerbate hemodynamic instability in patients with severe vasoplegia requiring high-dose vasopressors (153). This paradox highlights the context-dependent nature of the effects of levosimendan; while its effects on calcium sensitization and mitochondrial protection are beneficial for VSMC dysfunction, its vasodilatory actions may be detrimental in the context of notable hypotension.

Modulating calcium homeostasis. Calcium homeostasis is a pivotal regulator of VSMC contractile function, and its disruption represents a central mechanism underlying vascular hyporeactivity in sepsis-induced vasoplegia. Pharmacological agents targeting calcium-handling mechanisms have diverse modes of action, including receptor modulation and ion channel blockade, and interact within a complex regulatory network. Table V summarizes the emerging therapeutic agents targeting VSMCs in sepsis-induced vasoplegia, focusing on modulating calcium homeostasis and reducing NO production (154,167-174).

One critical node in calcium homeostasis regulation is the calcium-sensing receptor (CaSR), a key mediator of extracellular calcium sensing that is pathologically overactivated in sepsis. In a rat model of traumatic hemorrhagic shock, Calhex-231 inhibited mitochondrial fragmentation and preserved mitochondrial morphology (154). Mitochondria serve a dual role in calcium buffering and energy production, and their structural integrity is vital for maintaining calcium sequestration and release in VSMCs. Calhex-231 has the potential to improve vascular reactivity in sepsis-induced vasoplegia, but its systemic administration may trigger adverse off-target reactions, primarily because of nonselective binding to CaSR in diverse tissues and interference with tissue-specific calcium signaling. As demonstrated in a study on pregnant human myometrium, Calhex-231 partially inhibits oxytocin-induced uterine contractions (175).

A contrasting approach to restoring calcium-dependent VSMC function involves the targeting of ion channels, with K-ATP channels emerging as key therapeutic nodes. Glibenclamide, a nonselective K-ATP channel blocker, has been shown to restore vascular tone in animal models of septic shock by preventing potassium ion efflux-induced VSMC hyperpolarization (176). In an *ex vivo* model of hypoxic human endotoxemia, its anti-inflammatory effect was attributed to reduced depolarization of hypoxic monocytes, which in turn decreased calcium influx (167). However, its nonselectivity poses critical off-target risks: K-ATP channels are highly expressed in pancreatic β cells and immune cells, and systemic glibenclamide administration may cause hypoglycemia and suppress monocyte phagocytic activity (139), both of which worsen outcomes in patients with sepsis. Additionally, a randomized, double-blind, placebo-controlled crossover pilot study (177) revealed a critical translational gap: The lack of efficacy of glibenclamide in reducing the dosage of norepinephrine compared with that of a placebo in patients with septic shock may be attributed to individual patient variations, such as the severity of the condition and the etiology, leading to diverse responses to and efficacy of the drug.

Whereas glibenclamide targets calcium influx via voltage-gated calcium channel, another agent, chloro-N6-(3-iodobenzyl) adenosine-5'-N-methyluronamide (IB-MECA), targets intracellular calcium release, highlighting the diversity of calcium handling defects in sepsis (168). IB-MECA blocks the overactivation of ryanodine receptor (RyR)-mediated Ca^{2+} release, a pathological feature of hypoxic VSMCs and hemorrhagic shock-associated vascular hyporeactivity (168). Compared with control cells, hypoxic VSMCs exhibit a marked increase in $[Ca^{2+}]i$ in response to RyR activation by caffeine, which is associated with the loss of vascular responsiveness to norepinephrine. The stimulation of A3 adenosine receptor (A_3AR, a G protein-coupled receptor subtype regulating calcium signaling) activity by IB-MECA directly counteracts this excessive RyR activity, thereby normalizing intracellular calcium dynamics. However, A_3AR is also expressed by immune cells (178), and the nonselective activation by IB-MECA may modulate cytokine production

Table V. Principal medications targeting VSMC for improved vascular hyporeactivity in sepsis-induced vasoplegia.

A, Calcium modulators

First author, year	Agent name	Core mechanism	Experimental model	Key efficacy outcomes	(Refs.)
Lei, 2020	Calhex-231	Inhibited mitochondrial fragmentation	Rat model of traumatic hemorrhagic shock	Sustained calcium sequestration and release in VSMC	(154)
Schmid, 2011	Glibenclamide	Reduction of calcium influx into VSMCs	*In ex vivo* endotoxemia model	Prevented calcium overload and desensitization of the contractile machinery	(167)
Zhou, 2010	IB-MECA	Blocked overactivation of ryanodine receptor-mediated calcium release	Rat model of hemorrhagic shock	Antagonized vascular hyporeactivity caused by aberrant calcium release	(168)
Li, 2008	Ang-II	Mediated calcium sensitivity	Rat model of hemorrhagic shock	Improved Vascular hyporeactivity	(169)

B, iNOS inhibitors

Gibraeil, 2000	4-ABH4	Inhibition of iNOS activity	Pig pulmonary/ coronary vasculature model	Reduced NO-mediated vasodilation	(170)
Squadrito, 2000	CsA	Inhibition of iNOS activity	Rat model of splanchnic artery occlusion shock	Decreased vascular NO levels	(171)
Luo, 2020	Tubeimoside I	Inhibition of iNOS activity	Septic mouse model	Suppressed NO-driven vasodilation and preserved vascular reactivity	(172)
Liu, 2013	Andrographolide	Downregulation of iNOS expression	LPS-induced rat endotoxemia model	Reversed LPS-induced upregulation of PVAT iNOS	(173)
Altavilla, 1999	U-74389G	Inhibition of iNOS activity	Septic models	Reduced NO-mediated vascular hyporeactivity	(174)

4-ABH4, 4-amino analogue of tetrahydrobiopterin; Ang-II, angiotensin II; CsA, cyclosporin-A; IB-MECA, chloro-N6-(3-iodobenzyl) adenosine-5'-N-methyluronamide; iNOS, inducible NO synthase; LPS, lipopolysaccharide; NO, nitric oxide; PVAT, perivascular adipose tissue; VSMC, vascular smooth muscle cell.

while impairing T-cell proliferation, a trade-off that could exacerbate immunosuppression in late-stage sepsis.

Complementing agents that target calcium flux or release are therapies that increase calcium sensitivity, a mechanism that is particularly critical in advanced sepsis where calcium-handling machinery is severely disrupted. AVP and angiotensin II (Ang-II), which have been evaluated in rat models of hemorrhagic shock, increase calcium sensitivity in VSMCs (169,179). Unlike agents targeting calcium flux, they increase the affinity of myofilaments for calcium, a mechanism particularly relevant in sepsis, where calcium sensitivity is often impaired. These findings position them as potentially more effective in advanced sepsis, where calcium-handling machinery is severely disrupted. However, their clinical use is limited by nonselective vasoconstriction in noncritical vascular beds (such as renal and splanchnic circulation) and potential off-target immunomodulatory effects. For example, in early experimental hypotensive hyperdynamic sepsis, the intravenous infusion of Ang-II has been shown to decrease renal blood flow (180).

Reducing NO production. Excessive NO production by iNOS in VSMCs and other vascular cells is a major driver of vasodilation and vascular hyporeactivity in sepsis. This pathological process is mediated by NO-cGMP-protein kinase G signaling, which reduces VSMC calcium sensitivity and enhances intracellular calcium leakage. To counteract this, four key pharmacological agents have been developed, each of which

target iNOS through distinct mechanisms and exhibit varying degrees of clinical translation potential. The present review has provided a summary for each of these agents, with a focus on how their mechanisms align with the pathophysiology of sepsis and where gaps persist in translating preclinical success to patient care.

Among iNOS-targeted therapies, selectivity for VSMC iNOS over eNOS is a critical criterion to avoid compromising endothelial barrier function, a common pitfall of nonspecific NOS inhibitors. Notably, 4-amino analogue of tetrahydrobiopterin (4-ABH4) addresses this need as a potent and selective inhibitor of SMC iNOS (170). Its mechanism relies on competing with BH4, a cofactor essential for iNOS catalytic activity, for binding to VSMC iNOS while sparing eNOS (due to the markedly greater affinity of eNOS for BH4). In an *in vitro* model of endotoxemia, this selectivity translated to tangible benefits: 4-ABH4 specifically inhibited VSMC iNOS activity, preventing excessive NO production without disrupting eNOS-mediated endothelial protection (170). As a result, it effectively blocked endotoxin-induced vascular hyporeactivity, making it a promising candidate for sepsis subtypes in which EC-VSMC crosstalk is preserved.

While 4-ABH4 directly targets iNOS catalytic activity, another agent, cyclosporin-A (CsA), takes an upstream approach by suppressing iNOS activation, highlighting the diversity of strategies for inhibiting iNOS. CsA reduces iNOS activation, decreases plasma nitrite/nitrate levels, increases blood pressure and markedly improves survival in rats with splanchnic artery occlusion shock (171). Despite these preclinical benefits, its clinical translation is hindered by two interconnected challenges: Nephrotoxicity, a condition that poses a marked risk in patients with sepsis and pre-existing renal impairment, and off-target immunosuppression. CsA induces distal renal tubular acidosis by inhibiting H pumps in the distal nephron (181). Furthermore, the primary mechanism through which CsA inhibits calcineurin-NFAT signaling is not restricted to VSMCs; it also suppresses T-cell proliferation and cytokine production, exacerbating the immunosuppressive phase of sepsis and increasing susceptibility to opportunistic infections (182).

Beyond direct or upstream iNOS inhibition, targeting the inflammatory signaling cascades that induce iNOS represents another viable strategy, one that aligns with the polymicrobial nature of clinical sepsis. Tubeimoside I (TBM), a triterpenoid saponin, reduces iNOS expression by inhibiting the TLR4-MyD88-NF-κB-iNOS signaling pathway (172). In a CLP-induced sepsis model, an intraperitoneal injection of 4 mg/kg TBM 1 h before surgery improved survival, ameliorated the MAP, and enhanced vascular responsiveness to norepinephrine and KCl in wild-type septic mice (172). Notably, iNOS gene knockout completely abrogated the protective effects of TBM, confirming that its therapeutic efficacy is mediated by reducing excessive NO production. Nevertheless, the translational applicability of TBM is hindered by nonspecific NF-κB inhibition. Off-target NF-κB inhibition in immune cells could attenuate the synthesis of proinflammatory cytokines during the hyperinflammatory stage, yet it might also impede macrophage phagocytosis.

Complementing single-mechanism iNOS inhibitors are agents that combine iNOS inhibition with adjunctive effects to address coexisting sepsis pathologies, such as oxidative stress, which amplifies VSMC dysfunction by modifying calcium-handling proteins (for example, RyRs). Andrographolide, evaluated in endotoxemia rats, restores vascular reactivity by downregulating iNOS in perivascular adipose tissue (173). U-74389G, which has been tested in septic models, combines iNOS inhibition with vascular protection (174); it reduces NO-mediated hyporeactivity via iNOS inhibition, reverses vascular failure and protects against endotoxin shock, addressing the broader pathological cascade of sepsis. However, andrographolide has poor bioavailability, and neither agent has validated biomarkers for iNOS activity or oxidative stress to enable precise patient stratification, hindering their clinical translation. Moreover, the nonselective tissue distribution of U-74389G increases the risk of off-target effects in organs with high metabolic activity, where it may disrupt normal NO signaling and exacerbate organ dysfunction.

Outstanding questions in VSMC-targeted therapy for sepsis-induced vasoplegia. The preceding assessment of calcium-modulating and iNOS-targeted strategies emphasizes the identification of promising VSMC-directed pathways for mitigating sepsis-induced vasoplegia in preclinical studies. However, the attainment of translational efficacy is consistently hindered by sepsis-specific obstacles in drug delivery and off-target effects. The following is a consolidation of the core challenges and actionable future directions to address them (25,34,70,150,178): i) Disrupted tissue distribution and bioavailability: Sepsis-induced increases in vascular permeability and organ dysfunction disrupt drug distribution, leading to reduced accumulation at VSMC sites and increased systemic exposure. ii) Lack of VSMC-specific targeting: Currently, agents demonstrate limited selectivity for VSMCs, resulting in off-target effects on immune cells and vital organs. iii) Formulation and dosing limitations: Challenges such as poor aqueous solubility, short half-lives and the need for parenteral administration present logistical barriers in critically ill patients with sepsis. Additionally, the lack of validated biomarkers hinders precise patient stratification, resulting in variable clinical responses. iv) Immunosuppressive paradox: A number of VSMC-targeted pathways serve vital roles in immune cell function. Nonspecific blockade of these pathways risks exacerbating sepsis-induced immunosuppression and increasing susceptibility to secondary infections, a notable unmet challenge in translating preclinical efficacy into clinical benefit.

6. Conclusion and prospects

The present review identifies VSMCs as a core driver of sepsis-induced vasoplegia, with dysfunction stemming from two linked cascades: Dysregulated calcium homeostasis and excessive iNOS-derived NO. These factors impair VSMC contractility and vascular tone, highlighting VSMCs as a key therapeutic target. In conclusion, VSMCs are critical for the management of sepsis-induced vasoplegia, and aligning mechanistic insights with translational approaches may drive progress in VSMC-focused therapies to improve outcomes in treating catecholamine-resistant sepsis.

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Authors' contributions

HR was responsible for literature collection and the initial draft of the manuscript. XYS and SYL contributed to the analysis and integration of data and table data extracted from published literatures collected in this review, focusing on vascular smooth muscle cell function in sepsis, and participated in the writing of this review; they were additionally responsible for image rendering and critically revised the manuscript for content accuracy. SSL contributed to revising the manuscript critically for intellectual content and approved the final version for publication. Data authentication is not applicable. All authors reviewed the manuscript critically for intellectual content, and read and approved the final manuscript.

Ethics approval and consent to participate

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Competing interests

The authors declare that they have no competing interests.

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