ISSN 2349-7823

International Journal of Recent Research in Life Sciences (IJRRLS)
Vol. 11, Issue 4, pp: (19-23), Month: October - December 2024, Available at: www.paperpublications.org

# Sepsis-induced vasoplegia; a short review

Osama Mohamed Abbas.[1], Alaweya Ali Ofash[2], Osama Sharafeldin Abbadi[3]

[1] Consultant physician and intensivist, Al Gmarik Hospital and Seaport corporation hospital, Sudan.

[2]ICU GP, Al Gmarik Hospital, Sudan.

[3]Assistant professor of Biochemistry, Faculty of Medicine, the National University, Sudan.

**DOI: https://doi.org/10.5281/zenodo.14028372**

**Published Date: 02-November-2024**

***Abstract:*** **Vasoplegia is a challenging condition to manage, particularly in intensive care unit (ICU) patients. It is a clinical condition that requires close monitoring and requiring continuous vasopressor support. This is a review highlighting the definition, etiology, and basic management protocol for vasoplegia occurring as a consequence of sepsis.**

***Keywords:*** **Vasoplegia, Sepsis, septic shock, ICU.**

## I. INTRODUCTION

Vasoplegia is a complex condition that often occurs in critically ill patients and poses significant risks if not promptly identified and treated. Vasoplegia, also known as vasodilatory shock, is a condition characterized by significant and uncontrollable widening of blood vessels due to persistently low systemic vascular resistance, despite having a normal or high cardiac index (1). This condition can be caused by various shock-inducing factors, including cardiac failure, sepsis, anaphylaxis, hemorrhage, and surgery (2). However, it most commonly occurs following the onset of septic shock and can be a complication of cardiac surgery in up to 25% of patients (3). Once vasoplegia has been identified and acknowledged, the priority in management should be the timely administration of fluids and vasopressors, including catecholamines (4).

Despite receiving treatment, the occurrence of vasoplegia is a concerning indication of deteriorating outcomes. It is linked to a substantial rise in mortality and morbidity rates, as well as complications like renal failure. Additionally, it is associated with prolonged stays in the intensive care unit (ICU) and hospital (5). In certain instances, there is a possibility for the development of catecholamine-resistant vasoplegia, which has been associated with a mortality rate of nearly 25% among patients (6).The severity of vasoplegia is correlated with a higher rate of multi-organ failure and complications, such as significant bleeding and respiratory failure (7).

Early identification and prompt treatment of sepsis, along with timely hemodynamic support, play a vital role in reducing the risk of vasodilatory shock and enhancing patient outcomes (8).

## II. AETIOLOGY OF SEPSIS-INDUCED VASOPLEGIA; FIG 1.

Sepsis and septic shock are responsible for a significant number of fatalities in intensive care units globally, resulting in around 1400 deaths each day (9). The prevalence of this condition is on the rise, with an annual growth rate of nearly 9%, and a global mortality rate of approximately 50% (10).

Hypotension plays a crucial role in the mortality risk of sepsis patients. There are several potential causes for hypotension, and one of them is the reduction of intravascular volume caused by capillary leakage. To address this issue, volume therapy is employed as a treatment approach (11), however, in cases where patients progress to septic shock, there is a significant 40% increase in mortality. Surprisingly, some patients in septic shock continue to experience persistent hypotension even after receiving appropriate volume therapy (12).

The impaired vascular smooth muscle contraction in vasoplegia can be attributed to dysregulation of signalling pathways involved in vasoconstriction, such as those mediated by adrenergic receptors and other vasoactive substances. Metabolic changes, such as alterations in intracellular calcium levels and energy metabolism, can also contribute to the dysfunction

of vascular smooth muscle (13). Furthermore, the depletion of endogenous vasoactive hormones, such as catecholamines and vasopressin, can further exacerbate the vasoplegic state (14). Alterations in the endothelial glycocalyx, which is involved in regulating vascular permeability and endothelial function, may also play a role in the pathophysiology of vasoplegia. Overall, the pathophysiology of vasoplegia involves a complex interplay of cellular and molecular mechanisms that result in impaired vascular smooth muscle contraction and the associated clinical manifestations of low systemic vascular resistance and hypotension (15).

Nitric oxide (NO), a mediator that is causally involved in vasogenic shock- was originally described as an endothelium-derived relaxing factor of vascular smooth muscle (16).Since then, NO has been widely recognized as a vasodilator during sepsis (17). The nitric oxide synthases (NOS) are the enzymes that produce NO. Basal NO production is attributed to the endothelial isoform (eNOS) (18), which can briefly rise and produce trace levels of NO. The function of eNOS in sepsis is yet unclear. It appears that in a later stage, its activity rises and then falls. Conversely, the inducible version of NO synthases is significantly more when it is stimulated by pro-inflammatory agents such endotoxin, tumor necrosis factor alpha (TNF-α), interferon gamma (IFN-γ), and interleukins (IL)-1, IL-2, and IL-6, as long as L-arginine is present (19). The substrate for NO production is L-arginine, and endotoxins and cytokines can directly raise its availability, opening up a new route increasing NO synthesis during sepsis(9).

The most fascinating aspect concerning adenosine triphosphate-sensitive potassium (KATP) channels is that they are being blocked by micromolar intracellular concentrations of ATP, thus remaining mostly inactive under normal conditions. Channel opening results from a drop in ATP levels brought on by a reduced oxygen supply, which can occur in a number of shock conditions (20). Additional substances that can control channel opening or closure include kinases, phosphatases, G-proteins, phospholipids, intracellular calcium, and vasoactive hormones like CGRP (calcitonin gene-related peptide), adenosine, atrial natriuretic peptide, prostacyclin, vasopressin, endothelin, and angiotensin II. KATP channel activation during sepsis may be brought on by tissue dysoxia, an increase in CGRP, an actin cytoskeleton disruption, or an excess of NO (20).

Another remarkable finding is that rats given lipopolysaccharide (LPS) showed improved vascular hyporeactivity to catecholamines when administered with dexamethasone; this improvement is most likely the result of the steroid's reduction of KATP activity (21).This observation may suggest a potential mechanism beyond their anti-inflammatory effects that glucocorticoids may have when taken during sepsis or similar vasodilatory situations. Treatment with hydrocortisone is known to improve the response to infusion of an adrenergic agonist and to assist shock reversal (22).For this reason, the Surviving Sepsis Campaign recommends it for septic patients who fail to react well to vasopressor therapy and fluid resuscitation (15).

In some instances, the presence of an intracranial mass and the surgical intervention could have disrupted cerebral autoregulation, making blood pressure control more challenging. The compromised autoregulatory mechanisms may contribute to the patient's hypotension, as the brain's ability to regulate perfusion is compromised.

A portion of patients who recover from acute episodes of shock continue to experience hypotension that relies on vasopressors for support, despite the absence of obvious signs of reduced blood flow to vital organs. This ongoing vasoplegia, which probably has various underlying physiological causes, can lead to negative effects like arrhythmias, ischemia, and tissue necrosis. Furthermore, IV vasopressors require constant monitoring and adjustment, which can increase the workload and cost of ICU treatment, hinder the discharge of patients and may prolong their hospital stay (23).

## III. MANAGEMENT OF VASOPLEGIA

The management of vasoplegia requires a multifaceted approach. Initially, the patient received crystalloid fluids to optimize preload and maintain adequate cardiac output. However, vasopressor therapy with norepinephrine was initiated as hypotension persisted. In addition, the use of intravenous steroids helped mitigate the inflammatory response, promoting vasoconstriction. Vasodilatory shock states are unquestionably linked to excessive KATP channel activity, but more research is undoubtedly required to elucidate a number of questions regarding the physiologic and pathophysiologic role of these channels. Managing blood pressure in the presence of impaired cerebral autoregulation requires a cautious approach (24). It is crucial to balance the need to maintain adequate cerebral perfusion with the potential risks of increased intracranial pressure. Close monitoring of neurological status, cerebral perfusion pressure, and other relevant parameters is essential to guide blood pressure management.

ISSN 2349-7823

International Journal of Recent Research in Life Sciences (IJRRLS)
Vol. 11, Issue 4, pp: (19-23), Month: October - December 2024, Available at: www.paperpublications.org

Midodrine, an oral medication that activates alpha-1 adrenergic receptors in peripheral vascular smooth muscle cells, leads to increased arterial tone and blood pressure (25). It has been utilized to treat conditions such as orthostatic hypotension, neurogenic shock, and hepatorenal syndrome. Additionally, several studies have explored the use of midodrine as an adjunctive therapy to provide hemodynamic support and facilitate the discontinuation of IV vasopressors in patients experiencing persistent vasoplegia (26).

While vasoplegia is not a rare complication of sepsis, a persistent variant is not encountered commonly. In this case, the disturbance of cerebral autoregulation, added to the severity of sepsis, the prolonged ICU admission, and the evident reduction in immunity noted by the presence of fungal infection and assisted mechanical ventilation, might be the reasons behind the persistent vasoplegia.

To this date, only few cases have been reported regarding persistent vasoplegia (27,28). Unfortunately, no guidelines have been issued specifically addressing the complication of persistent vasoplegia in sepsis management, despite the existence of several guidelines in the broader field of sepsis management.

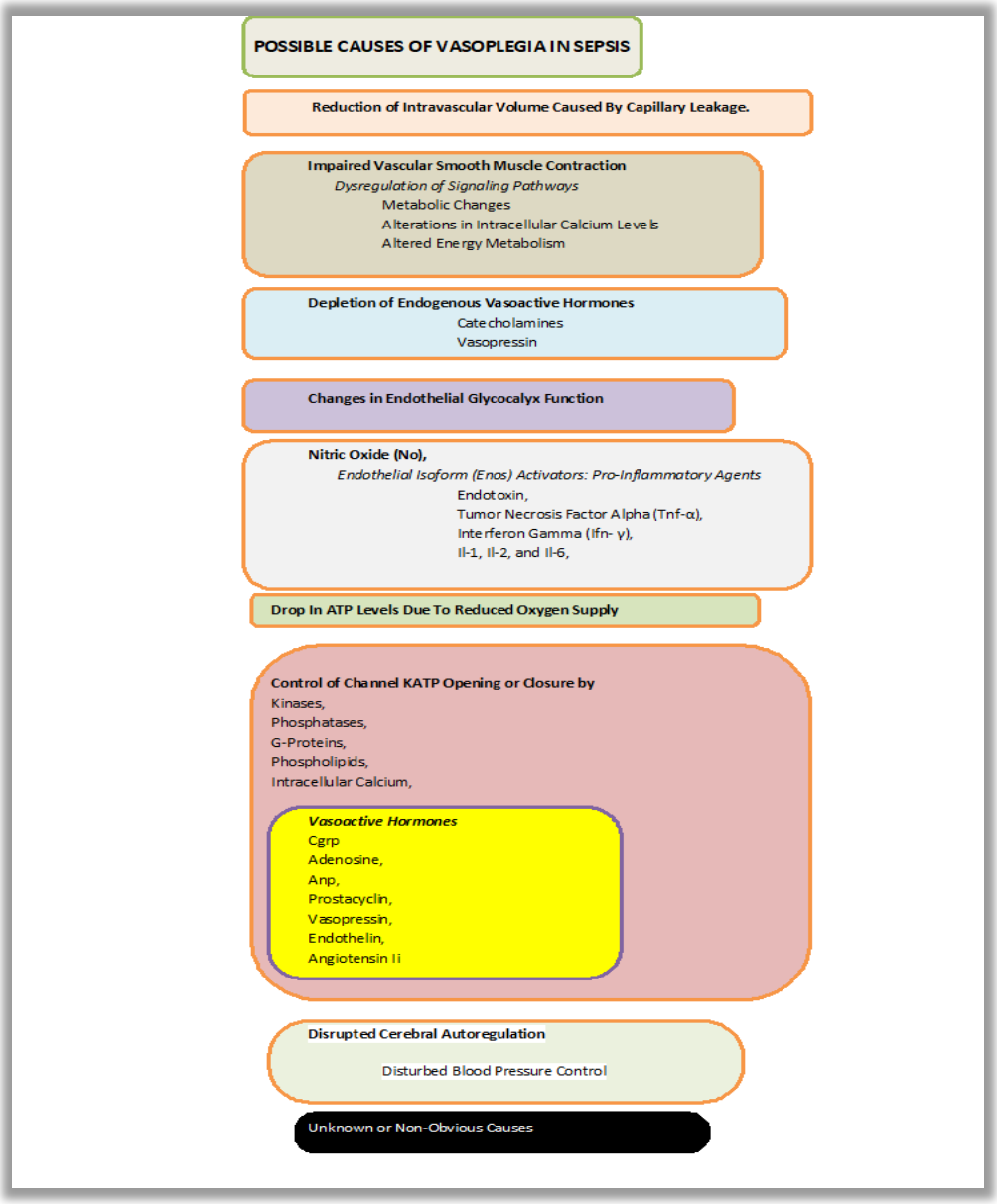


**Fig 1: Algorithm chart of the possible mechanisms that attribute to the development of vasoplegia in sepsis patients. More than one cause is usually coinciding in sepsis patients.**

## IV. CONCLUSION

This is a short report highlighting the challenges associated with managing hypotension and the significant consequences can have on patient outcomes. It underscores the importance of early recognition, prompt intervention, and close monitoring to prevent irreversible organ damage and adverse outcomes. The unfortunate outcome of the patient serves as a reminder of the critical need for further research and advancements in the understanding and management of hypotension to improve patient outcomes in similar clinical scenarios. Our recommendations are to establish guidelines in persistent vasoplegia assessment and management. Also early recognition of risk factors for sepsis patients prone to develop persistent vasoplegia, and creating a systematic risk factor algorithm for septic patients that might evolve into persistent vasoplegia, as compared to post cardiac surgery patients' risk factors assessment.

## REFERENCES

[1] Lambden S, Creagh-Brown BC, Hunt J, Summers C, Forni LG. Definitions and pathophysiology of vasoplegic shock. Crit Care. 2018; 22(1):174. doi: 10.1186/s13054-018-2102-1.

[2] Ltaief Z, Ben-Hamouda N, Rancati V, Gunga Z, Marcucci C, Kirsch M, Liaudet L. Vasoplegic Syndrome after Cardiopulmonary Bypass in Cardiovascular Surgery: Pathophysiology and Management in Critical Care. J Clin Med. 2022; 11(21):6407. doi: 10.3390/jcm11216407.

[3] Ratnani I, Ochani RK, Shaikh A, Jatoi HN. Vasoplegia: A Review. Methodist Debakey Cardiovasc J. 2023; 19(4):38-47. doi: 10.14797/mdcvj.1245.

[4] Omar S, Zedan A, Nugent K. Cardiac vasoplegia syndrome: pathophysiology, risk factors and treatment. Am J Med Sci. 2015; 349(1):80-8. doi: 10.1097/MAJ.0000000000000341

[5] Fischer GW, Levin MA. Vasoplegia during cardiac surgery: current concepts and management. Semin Thorac Cardiovasc Surg. 2010; 22(2):140-4. doi: 10.1053/j.semtcvs.2010.09.007

[6] Gomes WJ, Carvalho AC, Palma JH, et al. Vasoplegic syndrome after open heart surgery. J Cardiovasc Surg (Torino). 1998; 39(5):619-23.

[7] Cebula B, Musfeldt D. 1664: METHYLENE BLUE TO MANAGE MULTIFACTORIAL VASOPLEGIC SHOCK. Crit Care Med. 2016; 44(12):491. doi: 10.1097/01.ccm.0000510337.34856.e9

[8] Gyawali B, Ramakrishna K, Dhamoon AS. Sepsis: The evolution in definition, pathophysiology, and management. SAGE Open Med. 2019 Mar 21; 7:2050312119835043. doi: 10.1177/2050312119835043.

[9] Burgdorff AM, Bucher M, Schumann J. Vasoplegia in patients with sepsis and septic shock: pathways and mechanisms. J Int Med Res. 2018; 46(4):1303-1310. doi: 10.1177/0300060517743836

[10] Cauwels A and Brouckaert P.. Nitrite regulation of shock. Cardiovasc Res 2011; 89: 553–559. doi:10.1093/ cvr/cvq317.

[11] Martin GS, Mannino DM, Eaton S, et al.. The epidemiology of sepsis in the United States from 1979 through 2000. N Engl J Med 2003; 348: 1546–1554.

[12] Landry DW andOliver JA.. The pathogenesis of vasodilatory shock. N Engl J Med 2001; 345: 588–595. doi:10.1056/ NEJMra002709.

[13] Barnes TJ, Hockstein MA, Jabaley CS. Vasoplegia after cardiopulmonary bypass: A narrative review of pathophysiology and emerging targeted therapies. SAGE Open Med. 2020 Jun 25;8:2050312120935466. doi: 10.11 77/2050312120935466.

[14] Muhammad R, Dharmadjati BB, Mulia EPB, Rachmi DA. Vasoplegia: Mechanism and Management Following Cardiopulmonary Bypass. Eurasian J Med. 2022;54(1):92-99. doi: 10.5152/eurasianjmed.2022.20394.

[15] Ignarro LJ, Buga GM, Wood KS, Byrns RE, Chaudhuri G. Endothelium-derived relaxing factor produced and released from arteries and veins is nitric oxide. Proc Natl Acad Sci U S A. 1987; 84:9265–9269.

[16] Hauser B, Bracht H, Matejovic M, Radermacher P, Venkatesh B. Nitric oxide synthase inhibition in sepsis? Lessons learned from large-animal studies. Anesth Analg. 2005;101:488–498.

[17] Chandra A, Enkhbaatar P, Nakano Y, Traber LD, Traber DL. Sepsis: emerging role of nitric oxide. Clinics. 2006; 61(1):71–76.

[18] Young JD. The heart and circulation in severe sepsis. Br J Anaesth. 2004;93:114–120.

[19] Estrada C, Gómez C, Martín C, Moncada S, González C. Nitric oxide mediates tumor necrosis factor-alpha cytotoxicity in endothelial cells. Biochem Biophys Res Commun. 1992; 186(1):475-82. doi: 10.1016/s0006-291x (05)80832-0.

[20] D'Emmanuele di Villa Bianca R, Lippolis L, Autore G, et al. Dexamethasone improves vascular hyporeactivity induced by LPS in vivo by modulating ATP-sensitive potassium channels activity. Br J Pharmacol. 2003; 140:91–96.

[21] Japiassu AM, Salluh JI, Bozza PT, Bozza FA, Castro-Faria-Neto HC. Revisiting steroid treatment for septic shock: molecular actions and clinical effects – a review. Mem Inst Oswaldo Cruz. 2009;104:531–548.

[22] Dellinger RP, Carlet JM, Masur H, Gerlach H, Calandra T, Cohen J, Gea-Banacloche J, Keh D, Marshall JC, Parker MM, Ramsay G, Zimmerman JL, Vincent JL, Levy MM; Surviving Sepsis Campaign Management Guidelines Committee. Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock. Crit Care Med. 2004 Mar;32(3):858-73. doi: 10.1097/01.ccm.0000117317.18092.e4. Erratum in: Crit Care Med. 2004 Jun;32(6): 1448. Dosage error in article text. Erratum in: Crit Care Med. 2004 Oct;32(10):2169-70.

[23] Lambden S, Creagh-Brown BC, Hunt J, Summers C, Forni LG (2018) Definitions and pathophysiology of vasoplegic shock. Crit Care 22 (1):174. doi: 10.1186/s13054-018-2102-1

[24] Levy B, Fritz C, Tahoe, Jacquot A, Auchet T, Kimmoun A. Vasoplegia treatments: the past, the present, and the future. Crit Care. 2018. Feb 27;22(1):52. doi: 10.1186/s13054-018-1967-3.

[25] Pittner H, Stormann H, Enzenhofer R. Pharmacodynamic actions of midodrine, a new alpha-adrenergic stimulating agent, and its main metabolite, ST 1059. Arzneimittelforschung. 1976; 26(12):2145-54.

[26] Hamed M, Elseidy SA, Elkheshen A, Maher J, Elmoghrabi A, Zaghloul A, Panakos A, Panaich S, Saad M, Elbadawi A. The Use of Midodrine as an Adjunctive Therapy to Liberate Patients from Intravenous Vasopressors: A Systematic Review and Meta-analysis of Randomized Controlled Studies. Cardiol Ther. 2023; 12(1):185-195. doi: 10.1007/ s40119-023-00301-0.

[27] Yan L, Bohorquez MA, Carr ZJ. Persistent Postoperative Vasoplegia After Ureteronephrectomy Due To Suspected Intravesical Gemcitabine Toxicity. A A Pract. 2021 ;15(10):e01537. doi: 10.1213/XAA.0000000000001537. PMID: 34695040.

[28] Clifford KM, Madhok J, Murray NM, Mohindra V. Rescue of Nimodipine-Induced Refractory Vasoplegia With Hydroxocobalamin in Subarachnoid Hemorrhage: A Case Report. Crit Care Explor. 2020; 2(10):e0205. doi: 10.1097/ CCE.0000000000000205.