https://doi.org/10.3329/cardio.v16i2.75079

Review Article

Understanding the Pathophysiology of Vasoplegia following Cardiopulmonary Bypass: A Comprehensive Narrative Review

Golam Mokthader Khan, Rehnuma Rashid Prima, Tawfiq Ahmed

Dept. of Cardiac Surgery, Sir Salimullah Medical College Mitford Hospital, Dhaka

Key Words : *Vasoplegia, Cardiopulmonary bypass.*

Abstract

During the realm of cardiovascular health, where disease remains strong, cardiopulmonary bypass (CPB) is a crucial tool in surgical interventions. Navigating through CPB and the turbulent waters of shock can unveil a difficult opponent called vasoplegia. Despite the heart's efforts to maintain its rhythm, the body may experience a state of low systemic vascular resistance, a key feature of vasoplegia. Physicians commonly resort to vasopressor medications to fight this condition, however, vasoplegia's subtle nature can resist these efforts, leading to catecholamines resistance and increased risks of mortality.

To tackle this issue, the medical field has introduced new treatment options such as angiotensin II, a non-catecholamine vasopressor, and nitric oxide scavengers, providing hope for vasoplegia management. Our investigation explores the characteristics, risk factors, and pathophysiology of vasoplegia. Vasoplegic syndrome typically occurs after cardiothoracic surgery, causing high-output shock with compromised systemic vascular resistance. The syndrome's core lies in the dysregulation of vasoconstriction and vasodilation in smooth muscle cells, influenced by various mechanical and patient-specific factors.

A promising advancement is the emergence of catecholamine-sparing agents, showing potential in managing vasoplegia. Recent accounts suggest new treatment strategies, highlighting the need for large-scale clinical trials to validate findings and establish optimal management approaches.

The ongoing fight against vasoplegia provides hope for improved outcomes in cardiovascular care as discoveries shape the field.

(Cardiovasc j 2024; 16(2): 92-97)

Introduction

Despite recent advancements resulting in lowered overall mortality rates in cardiovascular illness over the previous three decades, it remains the primary cause of fatalities in the Bangladesh. Though there has been a rise in minimally invasive cardiac procedures, the total count of open- heart surgeries have similarly grown. Subsequently, cardiopulmonary bypass (CPB) still maintains a critical function in the surgical handling of this fatal ailment. Vasoplegia, described by decreased systemic vascular resistance, is a relatively usual complication post-CPB, impacting about 5% to 25% of individuals.[1] The occurrence of vasoplegia after CPB has been tied to negative consequences such as kidney dysfunction, extended durations in the intensive care section and medical facility, and amplified fatality rates. Notably, catecholamine-resistant vasoplegia has demonstrated to be especially lethal, exhibiting fatality rates as high as 25%.[1] This narrative analysis seeks to delve into the fundamental mechanisms of vasoplegia subsequent to CPB and present an overview of fresh therapeutic strategies. Particularly, it will concentrate on two non-vasopressor-targeted treatments: methylene blue and hydroxocobalamin.

Pathophysiology

Vasoplegia, also known as vasoplegic shock or distributive shock, shows abnormally low systemic

Address of Correspondence: Dr. Golam Mokthader Khan, Dept. of Cardiac Surgery, Sir Salimullah Medical College Mitford Hospital, Dhaka, Bangladesh. Email-mokthaderkhan@gmail.com

vascular resistance (SVR) despite normal or elevated cardiac output. The diagnostic criteria for vasoplegia vary in the published literature. Generally, it involves a mean arterial pressure below 65 mmHg alongside a cardiac index exceeding 2.2 L/min/m^2 of BSA.[2] High doses of vasopressor drugs are often necessary to keep mean arterial blood pressure at an acceptable level. Though vasoplegia can be triggered by cardiopulmonary bypass (CPB), it can also arise in different medical situations like septic shock, end-stage liver disease, and glucocorticoid deficiency.

Numerous risk factors are linked to post-CPB vasoplegia, including the use of angiotensin-converting enzyme inhibitors (ACEi) or beta-blockers before surgery, a higher burden of comorbidities, low preoperative ejection fraction, need for vasopressors before or during CPB, elevated core temperatures during bypass, and longer periods of aortic cross-clamping and CPB.

Concerning its pathophysiology at the cellular level, vasoplegia involves multiple interactions leading to impaired contraction of vascular smooth muscle, resulting in a vasoplegic state. These interactions include disturbances in receptor signaling, metabolic alterations, and depletion of endogenous substances.

Inducible nitric oxide synthase (iNOS), triggered by inflammatory cytokines, is potentially a significant contributor to the inappropriate widening of blood vessels in vasoplegia. Interestingly, CPB is linked to increased iNOS levels, which correspond to the duration of CPB. iNOS generates nitric oxide (NO), a substance that boosts cyclic guanosine monophosphate (cGMP) levels in blood vessels, resulting in vasodilation. Additionally, in smooth muscle cells, adenosine triphosphate-sensitive potassium (KATP) channels hinder calcium influx, thereby averting vasoconstriction. NO stimulates KATP channels, further impacting vasoplegia's pathophysiology.[3]

The repercussions of elevated NO levels in vasoplegia are worsened by reduced serum vasopressin levels, a common occurrence during prolonged shock periods. Remarkably, patients who experience vasoplegia post-CPB display even lower vasopressin levels than those in septic conditions. Vasopressin typically induces vasoconstriction by increasing intracellular calcium levels through vasopressin 1 (V1) and oxytocin receptors. Moreover, vasopressin adjusts KATP channels, lessening the NO-mediated cGMP surge and augmenting the vascular response to catecholamines.

Hydrogen sulfide (H2S), a byproduct of homocysteine metabolism via the vitamin B6-dependent route, serves as another trigger of vasoplegia. At higher concentrations, particularly in inflammatory scenarios, H2S directly activates and induces hyperpolarization in KATP channels, ultimately reducing vascular tension. This mechanism aligns with the NO-induced process mentioned earlier, suggesting a potential synergistic effect between H2S and NO in prompting vasodilation.[4]

Various specific mechanisms contributing to post-CPB vasoplegia are presumably linked to the pathological reaction following surgical trauma, ischemia-reperfusion injury, blood transfusions, and exposure to foreign surfaces during CPB. These procedures increase the generation of oxygen-free radicals, endothelins, NO, platelet-activating factors, thromboxane A2, prostaglandins, diverse cytokines, and other vasoactive agents. These elements contribute to a systemic inflammatory response, further disrupting vascular reactivity. Some theories propose that this inflammatory response may elucidate why pre-existing heart failure poses a risk for post-CPB vasoplegia, as patients with chronic heart failure often exhibit heightened levels of inflammatory agents.

Modifications in the endothelial glycocalyx, a stratum of molecules on endothelial cell surfaces, have been observed post-CPB. The glycocalyx is believed to manage vascular tension, making it a potential focus for therapeutic measures in post-CPB vasoplegia. Recent studies have displayed that reduced preoperative syndecan 1 levels, a specific proteoglycan, were linked to postoperative vasoplegia in CPB patients. Nonetheless, no pharmaceutical treatments are currently targeting the endothelial glycocalyx.[5]

Vasoplegia refractory to catacholemine

In vasoplegia, identified by vascular hypo-reactivity, vasopressors are commonly being used

to combat the problem, and several of these vasopressors are catecholamines. But, a few patients with vasoplegia face genuine catecholamine resistance, which is linked to substantial mortality post cardiopulmonary bypass (CPB). Catecholamine-resistant vasoplegia can be defined as a state of low systemic vascular resistance (SVR) with a normal or increased cardiac output (CO), where maintaining the mean arterial pressure at 60 mmHg cannot be done despite high doses of vasopressors, generally 0.5 mcg/kg/min of norepinephrine or higher. During shock, oxidative stress may overwhelm the normal physiological process of reducing superoxide anions to hydrogen peroxide by superoxide dismutase. This causes an accumulation of superoxide, which has been demonstrated to deactivate norepinephrine introduced externally. Synthetic analogs of superoxide dismutase capable of reversing this deactivation may potentially enhance the response to catecholamines. In animal models of septic shock, alterations in the expression of alpha-1 adrenergic receptors have been noted, and it is feasible that comparable receptor changes may contribute to catecholamine resistance in vasoplegia.[6] The intricate and multifaceted mechanisms underlying true catecholamine resistance in vasoplegia entail interactions involving the modulation of vasopressors, oxidative stress, and receptor expression. More research is required to comprehensively comprehend and formulate efficient therapies for this condition.[7]

Vasopressors

Vasopressors are medications commonly used to treat vasoplegia, a condition characterized by severe hypotension and low systemic vascular resistance. When a fluid challenge fails to improve the condition, vasopressors are typically employed as the first-line treatment.

Sympathomimetic agents, such as norepinephrine, epinephrine, and phenylephrine, are commonly used vasopressors in this context. Norepinephrine acts on alpha-1 and beta-1 adrenergic receptors, while epinephrine acts on alpha-1, beta-1, and beta-2 adrenergic receptors. Phenylephrine primarily stimulates alpha-1 adrenergic receptors. These medications can have unwanted side effects at high doses, including dysrhythmias, increased myocardial oxygen demand, hyperglycemia, and lactic acidosis.

Table-I
Vasopressors for treatment of post CPB vasoplegia.

Agent	MOA
Norepinephrine	Significant α1, α2 agonism Moderate β1 agonism
Epinephrine	Significant α1, α2 agonism Significant β1 agonism
Phenylephrine	Significant α1, α2 agonism No effect on α1
Dopamine	Dose dependent adrenergic agonism α1 agonism as dose increases
Vasopressin	Repletion of vasopressin in ADH depleted state V1 agonism
Vitamin C	Cofactor for catecholamine synthesis
Thiamine	Cofactor of lactate dehydrogenase (increase in lactate clearance)
Hydrocortisone	Aids in vitamin C metabolism Repletion of glucocorticoid and mineralocorticoid activity in cortisol depleted state Inhibition of pro-inflammatory cytokines
Methylene blue	Inhibition of guanylyl cyclase and inducible endothelial NO synthase
Hydroxocobalamin	Inhibition of NO directly and inducible endothelial NO synthase Inhibition of hydrogen sulfide
Angiotensin II	AT1 agonism Stimulation of aldosterone release Increase in ADH synthesis

However, in cases where there is catecholamine resistance or an inadequate response to up-

titration of vasopressors, non-catecholamine vasopressors may be considered. One such vasopressor is vasopressin, which has a well-established role in managing catecholamine-resistant shock. Vasopressin is normally released in response to increased plasma osmolality or hypotension. It acts on V1a, V1b, and V2 receptors, leading to vasoconstriction, water reabsorption at the renal collecting ducts, and increased secretion of cortisol and insulin. Vasopressin infusions can be effective in the setting of depleted endogenous sympathetic activity, which may occur in post-cardiopulmonary bypass (CPB) patients experiencing vasoplegia. However, higher doses of vasopressin may have unwanted side effects, including renal and gastrointestinal malperfusion.[8]

Another vasopressor that has emerged for the treatment of vasodilatory shock is angiotensin II. Angiotensin II is a component of the renin-angiotensin-aldosterone system and acts on angiotensin type I receptors to cause vasoconstriction, activation of the sympathetic nervous system, secretion of aldosterone, and renal sodium and water retention. It has been shown to be useful in cases of persistent hypotension unresponsive to high-dose vasopressors. However, its effectiveness in improving mortality has been demonstrated only in specific subgroups of patients. Some concerns exist regarding potential side effects of angiotensin II, including reduced glomerular filtration rate, increased pulmonary vascular resistance, asthma exacerbations, and potential prothrombotic effects. Further research and clinical experience are needed to fully establish its safety, particularly in patients exposed to extracorporeal circulation during cardiac surgery.

In summary, vasopressors are commonly used in the treatment of vasoplegia, and sympathomimetic agents are often the first-line choice. However, when there is catecholamine resistance or an inadequate response to these agents, non-catecholamine vasopressors such as vasopressin and angiotensin II may be considered. These medications have their own side effect profiles and should be used judiciously. Further research is needed to determine their optimal use and safety in specific patient(5) populations, including those undergoing cardiac surgery with CPB.

Non-vasopressor therapies

Corticosteroids have been used in the treatment of vasodilatory shock with the idea that they may supplement a depleted adrenal axis in critical illness. Some randomized controlled trials have shown that steroids can reduce the duration of vasoplegia in septic shock. Two of these studies even demonstrated a mortality benefit with steroid treatment. However, three other large studies failed to replicate this mortality benefit. Adverse events occurred similarly in the treatment groups, although hyperglycemia was more frequent in those who received steroids. The use of corticosteroids for the treatment of vasoplegia after CPB has not been specifically studied, but their potential adverse effects in this population should be carefully considered, including delayed wound healing, hyperglycemia, and an increased risk of gastrointestinal bleeding.

Ascorbic acid, also known as vitamin C, is a novel non-vasopressor agent that has been used in the treatment of vasodilatory shock and is currently being evaluated for its potential role in septic shock. Its use is based on its anti-inflammatory properties and its role as an electron donor in the synthesis of norepinephrine. Ascorbic acid also has some ability to metabolize superoxide. Small studies in septic patients have shown that it can decrease the duration and dose of norepinephrine infusion and improve mortality. However, it's important to note that the trial that initially sparked enthusiasm for vitamin C in septic shock was a retrospective study with a small number of patients, so the results should be interpreted with caution until larger clinical trials are conducted. A recent trial examining high-dose vitamin C in patients with sepsis and acute respiratory distress syndrome did not show significant improvements in scores or biomarkers. Another recent publication found that when combined with hydrocortisone and thiamine, vitamin C did not lead to a shorter time-to-shock-resolution compared to hydrocortisone alone. There are some case reports of successful use of vitamin C in cardiac surgery patients, but overall, there is a lack of conclusive evidence regarding its efficacy in all cases of vasoplegia.

In summary, corticosteroids have been used in vasodilatory shock, but their effectiveness in

improving mortality is still debated, and their potential adverse effects should be considered. Ascorbic acid has shown promise in some small studies, particularly in septic shock, but larger clinical trials are needed to establish its efficacy and safety in various vasoplegic states.[3]

Therapies targeted to NO

Limited research has been conducted on specific therapies for vasoplegia after CPB. Nitric oxide (NO) is believed to play a significant role in vasoplegia after CPB, and two potential treatments that target NO overproduction are methylene blue and hydroxocobalamin.

Methylene blue, a medication used for various purposes, including methemoglobinemia treatment, has inhibitory effects on NO synthase, the enzyme responsible for NO production. By inhibiting NO synthase, methylene blue may help reduce the excessive production of NO that contributes to vasoplegia. Studies have shown that methylene blue administration can improve hemodynamic stability and decrease the need for vasopressors in patients experiencing vasoplegia after CPB. Methylene blue may cause mild side effects such as nausea, vomiting, chest pain, hypertension, and interference with pulse oximetry readings. More serious adverse effects include impaired hypoxic pulmonary vasoconstriction and gas exchange, which may limit its use in patients with respiratory impairment. High doses of methylene blue can compromise splanchnic perfusion and may cause hemolysis, methemoglobinemia, and hyperbilirubinemia, particularly in patients with glucose-6-phosphate dehydrogenase deficiency. However additional research is needed to determine the optimal dosage, timing, and potential side effects of methylene blue in this specific population.

Hydroxocobalamin, a form of vitamin B12, is another therapy that has been investigated for its potential in vasoplegia after CPB. Hydroxocobalamin can scavenge and neutralize NO, thereby reducing its vasodilatory effects. Some studies have demonstrated that hydroxocobalamin administration can improve blood pressure and decrease the requirement for vasopressors in patients with vasoplegia following CPB. However, further research is necessary to determine the ideal use, potential adverse effects, and long-term outcomes associated with hydroxocobalamin in this context. Adverse effects of hydroxocobalamin are generally mild and rare, including chromaturia, erythema, headache, and photosensitivity. Serious side effects such as allergic reactions

It is important to note that while methylene blue and hydroxocobalamin show promise in targeting NO overproduction, vasoplegia after CPB is a complex condition with multiple underlying factors. NO is just one component of the intricate pathophysiology, which also involves factors such as inflammation, endothelial dysfunction, and oxidative stress. Therefore, a comprehensive approach that addresses these various factors may be crucial for effective management of vasoplegia after CPB.

In summary, methylene blue and hydroxocobalamin are potential therapies that target NO overproduction in vasoplegia after CPB. However, further research is needed to determine their optimal use, safety, and efficacy in this specific patient population. A comprehensive approach that considers the multifactorial nature of vasoplegia after CPB may be necessary for successful management.

Conclusion

Vasoplegia after cardiac surgery with CPB is a significant and common problem. Patients who do not respond to traditional vasopressor therapy are at risk of complications and death. Targeted therapies that address the underlying causes of post-CPB vasoplegia are crucial for improving outcomes. Methylene blue and hydroxocobalamin are two treatment options for vasoplegia, but further research is needed to determine their effectiveness and safety.

The concept of tailored medicine, where specific cellular-level pathophysiology is targeted, holds promise for the treatment of vasoplegia. If future trials demonstrate success with targeted therapies, the findings may have implications beyond specific disease states, such as post-CPB vasoplegia and septic shock, which carry a significant mortality burden.

Conflict of Interest - None.

References:

1. Busse LW, Barker N, Petersen C. Vasoplegic syndrome following cardiothoracic surgery-review of pathophysiology and update of treatment options. *Crit Care*. 2020;24(1):36. Published 2020 Feb 4. doi:10.1186/s13054-020-2743-8

2. Byrne JG, Leacche M, Paul S, et al. Risk factors and outcomes for 'vasoplegia syndrome' following cardiac transplantation. *Eur J Cardiothorac Surg*. 2004;25(3):327-332. doi:10.1016/j.ejcts.2003.11.032

3. Omar S, Zedan A, Nugent K. Cardiac vasoplegia syndrome: pathophysiology, risk factors and treatment. *Am J Med Sci*. 2015;349(1):80-88. doi:10.1097/MAJ.0000000000000341

4. Leyh RG, Kofidis T, Strüber M, et al. Methylene blue: the drug of choice for catecholamine-refractory vasoplegia after cardiopulmonary bypass?. *J Thorac Cardiovasc Surg*. 2003;125(6):1426-1431. doi:10.1016/s0022-5223(02)73284-4

5. Landry DW, Oliver JA. The pathogenesis of vasodilatory shock. *N Engl J Med*. 2001;345(8):588-595. doi:10.1056/NEJMra002709

6. Gomes WJ, Carvalho AC, Palma JH, et al. Vasoplegic syndrome after open heart surgery. *J Cardiovasc Surg (Torino)*. 1998;39(5):619-623.

7. Weis F, Kilger E, Beiras-Fernandez A, et al. Association between vasopressor dependence and early outcome in patients after cardiac surgery. *Anaesthesia*. 2006;61(10):938-942. doi:10.1111/j.1365-2044.2006.04779.x

8. Mets B, Michler RE, Delphin ED, Oz MC, Landry DW. Refractory vasodilation after cardiopulmonary bypass for heart transplantation in recipients on combined amiodarone and angiotensin-converting enzyme inhibitor therapy: a role for vasopressin administration. *J Cardiothorac Vasc Anesth*. 1998;12(3):326-329. doi:10.1016/s1053-0770(98)90017-9