Vasoplegia after cardiopulmonary bypass: A narrative review of pathophysiology and emerging targeted therapies

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Abstract

Cardiovascular disease remains the leading cause of death in the United States, and cardiopulmonary bypass is a cornerstone in the surgical management of many related disease states. Pathophysiologic changes associated both with extracorporeal circulation and shock can beget a syndrome of low systemic vascular resistance paired with relatively preserved cardiac output, termed vasoplegia. While increased vasopressor requirements accompany vasoplegia, related pathophysiologic mechanisms may also lead to true catecholamine resistance, which is associated with further heightened mortality. The introduction of a second non-catecholamine vasopressor, angiotensin II, and non-specific nitric oxide scavengers offers potential means by which to manage this challenging phenomenon. This narrative review addresses both the definition, risk factors, and pathophysiology of vasoplegia and potential therapeutic interventions.

Introduction

Despite improvements in the overall mortality from cardiovascular disease over the past 35 years, it remains the leading cause of death in the United States.[1] While the volume of minimally invasive cardiac procedures has recently increased, the overall volume of open heart surgeries has also increased.[2] As such, cardiopulmonary bypass (CPB) remains a cornerstone in the surgical management for our country's deadliest disease. A relatively common complication of CPB is vasoplegia with an estimated incidence of 5%–25%.[3] Outcomes associated with vasoplegia after CPB include renal failure, prolonged intensive care unit and hospital length of stay, and increased mortality.[3–5] Catecholamine-resistant vasoplegia is particularly lethal with mortality rates as high as 25%.[6]

This narrative review will address the pathophysiology of post-CPB vasoplegia and summarize emerging treatment modalities with a focus on two non-vasopressor-targeted therapies: methylene blue and hydroxocobalamin.

Post-CPB vasoplegia: definition, risk factors, and pathophysiology

Vasoplegia, also known as vasoplegic shock or distributive shock, is the syndrome of low systemic vascular resistance (SVR) in the presence of normal or high cardiac output.

Criteria in the published literature have been variable, but broadly a mean arterial pressure of less than 65 mmHg with a cardiac index of greater than 2.2 L/min/m² is consistent with vasoplegia.[7] High-dose vasopressor drugs are typically necessary to maintain adequate mean arterial blood pressure. Beyond the effects of CPB, vasoplegia may occur in many disease states, such as septic shock, end-stage liver disease, and glucocorticoid deficiency. Risk factors for post-CPB vasoplegia include the use of preoperative angiotensin-converting enzyme inhibitors (ACE$_i$) or beta-blockers, higher comorbid disease burden, low preoperative ejection fraction, need for vasopressors before or during CPB, warmer core temperatures while on bypass, and relatively longer durations of aortic cross-clamping and CPB.[8,9]

The pathophysiology of vasoplegia has been relatively well elucidated at the cellular level. A myriad of interactions cause the associated impaired vascular smooth muscle contraction resulting in vasoplegia: derangements in receptor signaling, metabolic changes, the depletion of endogenous

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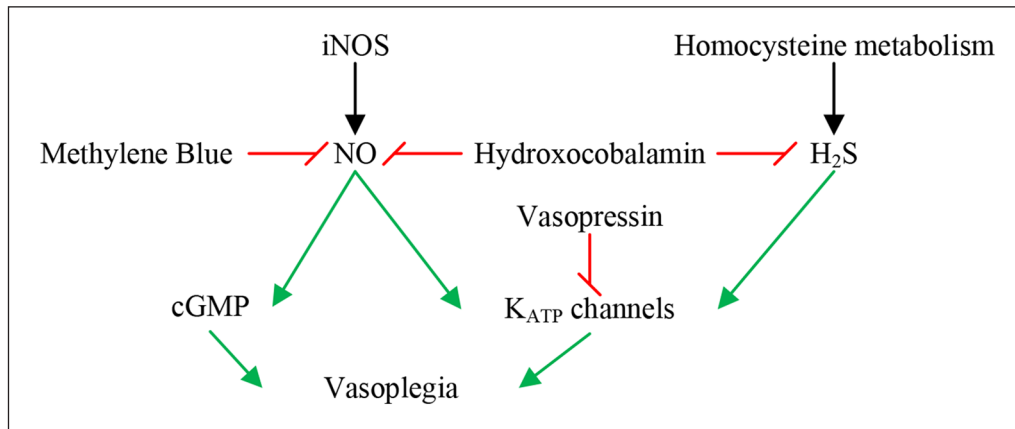Email: Theresa.J.Barnes@emory.edu

Figure 1. Biochemical pathways and therapies for vasoplegia.
Red lines denote inhibition; green arrows denote stimulation. iNOS: inducible nitric oxide synthase; NO: nitric oxide; cGMP: cyclic guanosine monophosphate; K_{ATP}: potassium-adenosine triphosphate; H_2S: hydrogen sulfide.

vasoactive hormones, and the alteration of the endothelial glycocalyx (Figure 1).

Inducible nitric oxide synthase (iNOS), triggered by inflammatory cytokines, is likely a major contributor to inappropriate vasodilation in vasoplegia. Notably, CPB is associated with increased iNOS levels proportional to the total time on CPB.[5] iNOS produces nitric oxide (NO), which increases vascular levels of cyclic guanosine monophosphate (cGMP), resulting in vasodilation.[10] In addition, in vascular smooth muscle cells, adenosine triphosphate-sensitive potassium (K_{ATP}) channels prevent calcium entry, thus preventing vasoconstriction. NO is an activator of K_{ATP} channels thereby providing another pathophysiologic role in vasoplegia.[5]

The downstream effects of increased NO concentrations in vasoplegia are exacerbated by low levels of serum vasopressin, typical of prolonged shock. Of interest, in post-CPB patients that develop vasoplegia, vasopressin levels have been found to be even more depressed than in septic states.[5] Vasopressin normally induces vasoconstriction through vasopressin 1 (V1) and oxytocin receptors by way of increased intracellular calcium levels.[11] In addition, vasopressin also modulates K_{ATP} channels, blunting the NO-induced increase in cGMP[5] and enhancing the vascular response to catecholamines.[12]

Another pathophysiologic mediator of vasoplegia is hydrogen sulfide (H_2S), a by-product of the vitamin B6-dependent pathway of homocysteine metabolism. At high concentrations, such as in inflammatory states, H_2S directly activates and hyperpolarizes K_{ATP} channels, therefore reducing the vascular tone.[13,14] This mechanism is similar to the NO-mediated pathway of vasoplegia, as mentioned above. A small proportion of its vasodilatory effects may also be attributed to its synergistic effect with NO.[14]

Other specific mechanisms of post-CPB vasoplegia are likely related to the pathologic response secondary to surgical trauma, ischemia-reperfusion injury, transfusion, and/or exposure of blood to the foreign surfaces of CPB circuitry.[15]

All of these processes result in increased oxygen-free radicals, endothelins, NO, platelet-activating factors, thromboxane A_2, prostaglandins, a variety of cytokines, and other vasoactive substances. These factors likely lead to a systemic inflammatory response syndrome, further contributing to the derangement of vascular reactivity. It has been posited that this inflammatory response might explain why pre-existing heart failure is a risk factor for post-CPB vasoplegia, as chronic heart failure patients have high levels of inflammatory mediators.[5]

Endothelial glycocalyx alterations after CPB have been reported after CPB.[16] It is postulated that elements of the glycocalyx regulate vascular tone, making the glycocalyx a potential target for therapy in the setting of post-CPB vasoplegia. A recent study revealed that lower preoperative levels of a proteoglycan, syndecan 1, were associated with postoperative vasoplegia for patients exposed to CPB.[17] Currently, there are no commercially available therapeutic interventions which target the endothelial glycocalyx.

Catecholamine resistance in vasoplegia

Vasoplegia, by definition, involves vascular hyporeactivity, which is typically combatted clinically through the administration of vasopressors, many of which are catecholamines. Vasopressor needs are, therefore, typically elevated in vasoplegic states. However, a subset of patients develops true catecholamine resistance, which is associated with significant mortality after CPB.[6] Catecholamine-resistant vasoplegia may be defined as a low SVR state with normal or increased CO with an inability to maintain a mean arterial pressure of 60 mmHg despite high-dose vasopressors, typically 0.5 mcg/kg/min of norepinephrine (or equivalent) or greater.[10] Some underlying pathologic mechanisms are shared between vasoplegia and true catecholamine resistance.[18] For example, K_{ATP} under the influence of NO, vasopressin, and (indirectly) endotoxins modulates the endothelial

Table 1. Pharmacologic options for the treatment of post-CPB vasoplegia.

	Class	Drug	Cautions
Treatment	Vasopressor	Catecholamines	Well studied and familiar, however, clear risks (end-organ damage) exist with prolonged infusion.
		Vasopressin	Second line for vasoplegia. Risk for mesenteric malperfusion.
		Angiotensin II	Newest agent for high-output shock. Yet to be studied in the cardiac surgery population.
	Non-vasopressor	Corticosteroids	Extensively studied in septic shock, less so in cardiac surgery. May result in hyperglycemia, GI bleeding.
		Ascorbic acid	Dearth of high-quality evidence for its use both in septic shock and cardiac surgery.
		Methylene blue	May decrease norepinephrine requirement but can increase PVR. Monoamine oxidase inhibitory effects represent a contraindication in patients taking selective serotonin reuptake inhibitors or other serotonergic medications.
		Hydroxocobalamin	Under investigation for post-CPB vasoplegia. May cause dialysis alarms due to chromaturia.

GI: gastrointestinal; PVR: pulmonary vascular resistance.

response to catecholamines.[19,20] Oxidative stress during shock may be such that the typical physiologic reduction of superoxide anions to hydrogen peroxide by superoxide dismutase can be overwhelmed, leading to their proliferation. Superoxide has been shown to deactivate exogenous norepinephrine, which can be reversed by synthetic analogues of superoxide dismutase.[21] In extrapolating experimental evidence from animal models of septic shock, it is also conceivable that altered alpha-1 adrenergic receptor expression may contribute to catecholamine resistance.[22]

Therapies for post-CPB vasoplegia

Vasopressors

Vasopressors are typically the first-line treatment for vasoplegia after a fluid challenge has been performed without success (Table 1). At this time, there is no established first-line vasopressor for vasoplegia following CPB.[12,23–27] Sympathomimetic agents, such as norepinephrine, epinephrine, and phenylephrine, are commonly used. Norepinephrine is an alpha-1 and beta-1 adrenergic receptor agonist. Epinephrine is an alpha-1, beta-1, and beta-2 adrenergic receptor agonist. Phenylephrine is an alpha-1 adrenergic receptor agonist. These agents have variable but equally unwanted side effects at high doses, including dysrhythmias, increased myocardial oxygen demand, hyperglycemia, and lactic acidosis.[28,29] Regardless, these agents are very familiar to clinicians owing to their routine perioperative utilization for cardiothoracic procedures. As previously discussed, catecholamine resistance may accompany vasoplegia, and minimal or absent response to vasopressor up-titration is a common but alarming scenario for clinicians caring for patients after prolonged exposure to CPB.

As such, there is an established role for non-catecholamine vasopressors in these scenarios. Vasopressin, one such agent, has an established track record for the management of catecholamine-resistant shock. Its release from the posterior pituitary gland normally occurs in humans in response to increased plasma osmolality or hypotension. It binds to V1a, V1b, and V2 receptors, which cause vasoconstriction, water reabsorption at the renal collecting ducts, and increased secretion of cortisol and insulin, respectively.[30] Agonism of V1 receptors also augments baroreflex inhibition of efferent sympathetic nerve activity, which explains the mild bradycardia and lack of blood pressure effect seen for healthy adults receiving a vasopressin infusion.[31] However, vasopressin infusions can be quite effective in the shock state with depletion of endogenous sympathetic activity. As discussed above, post-CPB patients may have low serum vasopressin levels, and therefore, vasopressin may be used with some success in the treatment of post-CPB vasoplegia.[12,25,27] However, it may also have unwanted side effects at higher doses, including renal and gastrointestinal malperfusion.[32–34]

Angiotensin II is a new vasopressor used for the treatment of vasodilatory shock. As a component of the renin–angiotensin–aldosterone system, angiotensin II acts on angiotensin type I receptors throughout the body to cause vasoconstriction, sympathetic nervous system activation, secretion of aldosterone, and renal sodium and water retention.[35] Its utility has been demonstrated with persistent hypotension unresponsive to high-dose vasopressors. It has been shown to decrease other vasopressor requirements but with a mortality improvement only in specific subgroups, including those with an Acute Physiology and Chronic Health Evaluation II (APACHE II) score greater than 30 and in those with kidney injury receiving renal replacement therapy.[36–38] It has not been exclusively studied in cardiac surgery patients, though case reports of successful use in this population exist.[39,40] Undesirable side effects may include its association with a reduction in glomerular filtration rate, increased pulmonary vascular resistance, and asthma exacerbations.[35] Although the underlying evidence

is inconclusive, some concern persists about the potential prothrombotic effects of angiotensin II.[41,42] Additional investigational and clinical experience is needed to establish its safety in this domain, namely in patients exposed to extracorporeal circulation.

Non-vasopressor therapies

Corticosteroids are often used to treat vasodilatory shock with the assumption that they may supplement a depleted adrenal axis in critical illness. Several randomized controlled trials have shown that steroids may reduce the duration of vasoplegia in septic shock. Two of these studies demonstrated a mortality benefit with steroids, but three other large studies failed to replicate that mortality benefit.[43–47] In all of these trials, adverse events occurred similarly in the treatment groups, though hyperglycemia was unsurprisingly more frequent in those that received steroids. There are some data that prophylactic dexamethasone administration to cardiac surgery patients may reduce the composite outcome of death and other major morbidities.[48] The use of corticosteroids for the treatment of vasoplegia after CPB has not been studied, but their adverse effects in this population should be closely considered, including delayed wound healing, hyperglycemia, and an increased risk of gastrointestinal bleeding.[5]

Ascorbic acid (i.e. vitamin C) is a novel non-vasopressor agent used in the treatment of vasodilatory shock, currently being evaluated for its role (if any) in septic shock. The rationale for its use stems from its anti-inflammatory properties and its role as an electron donor in the synthesis of norepinephrine from dopamine by dopamine-beta-hydroxylase.[49,50] Ascorbic acid also mediates non-enzymatic metabolism of superoxide, albeit modestly.[51] In small studies of septic patients, it has been shown to decrease the duration and dose of norepinephrine infusion and improve mortality.[49,52] The trial that prompted enthusiasm for using vitamin C in septic shock was a retrospective before-after study with 47 patients, and therefore, these original results should be interpreted with great caution pending the forthcoming results of large clinical trials. A recent trial examined the role of high-dose vitamin C in patients with sepsis and acute respiratory distress syndrome and found that it did not significantly improve SOFA scores or biomarkers at 1 week.[53] An additional recent publication revealed that in concert with hydrocortisone and thiamine, vitamin C did not lead to a shorter time-to-shock-resolution when compared to hydrocortisone alone.[54] Case reports exist of vitamin C's successful use in cardiac surgery patients,[55] but proof of its efficacy in all vasoplegic states is lacking.

Targeted therapies

While many of the above therapies have been studied in a variety of vasoplegic conditions, limited attention has been focused on targeted therapies for vasoplegia after CPB. As discussed, NO is likely a key modulator of vasoplegia after

CPB, and two therapies which target NO overproduction hold promise for cardiac surgery patients: methylene blue and hydroxocobalamin.

Methylene blue: everything old is new again?

Methylene blue directly competes with guanylyl cyclase, thereby interrupting the production of cGMP, which leads to vasodilation. It also inhibits iNOS, therefore decreasing the production of NO.[56] The use of methylene blue in cardiac surgery patients was first described over 20 years ago.[57]

Several case reports have described the use of methylene blue in the postoperative period following cardiac surgery with vasoplegic syndrome, which resulted in decreased vasopressor requirements.[58–62] A retrospective review of methylene blue administration in vasoplegia after CPB found improved survival and a reduced rate of major adverse events (as defined by the Society of Thoracic Surgeons major morbidities) when administered early versus late in the course of vasoplegia.[63] Notably, this study is observational, and the decision for early versus late administration of methylene blue was made under the discretion of the physicians managing the case without any protocol or randomization.

Two randomized trials prophylactically administered methylene blue to patients undergoing surgery with CPB and found a decreased norepinephrine requirement post-CPB.[64,65] In one such study, the sample size was small ($N=30$) and only included patients currently taking ACE_i medications.[64] Similarly, another study used a small sample size ($N=100$) and only included patients taking ACE_i medications, calcium channel blockers, or heparin.[65] Another small ($N=56$) randomized trial showed a decrease in mortality and duration of vasoplegic syndrome in patients receiving methylene blue compared to placebo.[66]

In contrast, a retrospective analysis found that cardiac surgery patients who had received methylene blue had higher rates of mortality and a higher composite morbidity measure.[67] Of note, after propensity-matching, only the morbidity association remained significant, which may suggest that in this retrospective study, patients at risk for complications of vasoplegic syndrome may have been more likely to receive methylene blue.[68]

Mild side effects of methylene blue include nausea and vomiting, chest pain, hypertension, and interference with pulse oximetry readings.[69] A more serious adverse effect is impaired hypoxic pulmonary vasoconstriction and impaired gas exchange which may limit its use in patients with concomitant impaired respiratory function.[70] High doses of methylene blue may compromise splanchnic perfusion.[71] As methylene blue can paradoxically act as an oxidant, at high doses, it may cause hemolysis (particularly in patients with glucose-6-phosphate dehydrogenase deficiency), methemoglobinemia, and hyperbilirubinemia.[72] In patients also exposed to serotonergic medications (e.g. selective serotonin reuptake inhibitors (SSRIs), fentanyl), methylene blue's

monoamine oxidase inhibitory effect can precipitate serotonergic excess or serotonin syndrome.[73] As patients with heart failure may be on SSRIs for the treatment of depression, this is an important consideration.

While there is some evidence for the use of methylene blue in the treatment of post-CPB vasoplegia, more research is needed. Methylene blue offers another treatment option for this condition, particularly when patients have failed traditional vasopressor therapy and face high mortality risk. Serious side effects of the drug must be weighed with its potential benefits. Certain patient populations, such as those already taking serotonergic drugs and patients with glucose-6-phosphate dehydrogenase deficiency, should be thoughtfully considered before administering methylene blue. It should also be used with caution in patients with lung injury or those who cannot tolerate further increases in pulmonary vascular resistance.

Hydroxocobalamin: an emerging therapeutic option

Hydroxocobalamin, a precursor of vitamin B_{12}, is a novel compound increasingly utilized for the treatment of vasoplegia. It is worth noting that the use of hydroxocobalamin for vasoplegia is an off-label use of the medication. Hydroxocobalamin is approved in the United States for the treatment of cyanide poisoning under the trade name Cyanokit. Similar to methylene blue, B_{12} has the ability to inhibit guanylate cyclase and is a scavenger for NO (see Figure 1).[74,75] It binds H_2S attenuating its downstream effects leading to decreased vascular tone whereby leading to hypotension.[76]

There are several case reports on the use of hydroxocobalamin for postoperative vasoplegia in cardiac surgery, liver transplant surgery, and vascular surgery.[77–84] In these reports, hydroxocobalamin was used for refractory vasoplegia and authors reported increased mean arterial blood pressure and decreased vasopressor needs after infusion. The degree to which hydroxocobalamin affects mean arterial blood pressure is unclear as demonstrated in a retrospective case series of 33 patients. This series showed significant heterogeneity in response to hydroxocobalamin infusion for vasoplegic cardiac surgery patients. Of relevance, 27% of patients had no change in blood pressure or vasopressor requirements, and the remainder of the patients had variable positive responses to hydroxocobalamin.[85]

Another study retrospectively analyzed a small cohort of vasoplegic post-CPB patients who received treatment of only methylene blue ($N=14$) or treatment of methylene blue and hydroxocobalamin ($N=6$). The authors found that both groups had no significant difference in increased mean arterial blood pressure at 1 h after treatment; however, they did find that the dual therapy group required significantly less vasopressors at that same time point.[86] The retrospective nature of this study should be noted with variable-dosing regimens among patients and disparate, small sample sizes in the treatment groups.

As clinical experience with hydroxocobalamin grows, more rigorous studies are necessary to determine its utility and safety.[87] There are several pending clinical trials, including the comparison of methylene blue versus hydroxocobalamin in cardiac surgical patients.[88,89] Another study will randomize patients with septic shock to receive hydroxocobalamin versus placebo.[90] An additional trial will examine the use of hydroxocobalamin versus methylene blue for vasoplegic patients undergoing liver transplant.[91]

Adverse effects associated with hydroxocobalamin are generally mild and rare. These include chromaturia, erythema, headache, and photosensitivity. More serious side effects include allergic reactions and acute renal failure.[92] Other side effects include its ability to falsely activate the blood leak alarm during dialysis owing to chromaturia, transient hypokalemia if used in patients with anemia secondary to B_{12} deficiency, and interference with various laboratory values.[80,92,93] Elevated serum cobalt levels have also been reported after multiple doses of hydroxocobalamin, which can be associated with myocardial dysfunction, polyneuropathy, thyroid dysfunction, and cognitive dysfunction.[78]

Conclusion

Vasoplegia after cardiac surgery with CPB remains a serious and relatively frequent occurrence. Patients that do not respond to traditional vasopressor therapy are at risk for complications associated with high-dose vasopressors and death. Targeted therapies which address the multifaceted causes of post-CPB vasoplegia will be important for improving outcomes. Methylene blue and hydroxocobalamin are two options in the clinician's armamentarium for treating vasoplegia, however, further investigation of their utility and safety is unequivocally needed.

This review has limitations. While vasoplegia may affect numerous patient populations, such as those undergoing liver transplantation, we have focused on those requiring CPB. While the underlying pathophysiology may be similar, vasoplegia in other clinical settings may be best approached differently; care should be taken when extrapolating lessons from post-CPB vasoplegia. This narrative review was further intended to maximize clinical utility at the bedside. As discussed previously, scant evidence remains to guide clinicians when confronted with vasoplegia, and our conception of its underlying pathophysiology and management remains dynamic. Many of the therapeutic options reviewed herein are not grounded in firm investigational evidence, which highlights the need for continued research. This need for greater scrutiny cannot be understated, as previous targeted therapies, such as a nitric oxide synthase inhibitor for vasoplegia, showed promise until a randomized trial demonstrated harm.[94]

The era of tailored medicine with the ability to target specific cellular level pathophysiology, rather than broad treatments with unintended consequences, holds promise. Given the mortality burden conferred by various vasoplegic

etiologies, namely post-CPB and septic shock, if future trials show success with targeted therapies, perhaps findings can be applied across disease states.

Author contributions

T.J.B. helped to acquire and interpret the primary source information, drafted the work, and approved the final version to be published. M.H. helped to acquire and interpret the primary source information, revised the work critically for important intellectual content, and approved the final version to be published. C.S.J. helped conceive the work, helped interpret the primary source information, revised the work critically for important intellectual content, and approved the final version to be published.

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