Management of Vasoplegic Shock in the Cardiovascular Intensive Care Unit after Cardiac Surgery

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KEYWORDS

• Vasodilatory shock • Vasoplegia • Vasopressors • Steroids

KEY POINTS

- Vasoplegic shock is common after cardiac operations that utilize cardiopulmonary bypass and contributes to organ failures and poor surgical outcomes.
- A systematic approach to diagnosing and maintaining perfusing pressures in vasoplegic shock is necessary.
- Vasopressors are the mainstay treatment of vasoplegic shock, and adjunctive agents such as corticosteroids or nitric oxide inhibitors may aid in a multimodal approach.
- Outcomes research geared toward identifying phenotypes of vasoplegic shock may help provide a more tailored approach to hypotension after cardiac operations.

INTRODUCTION

Shock is characterized by cellular and tissue hypoxia, caused by increased oxygen demand, insufficient oxygen delivery, impaired oxygen utilization, or a combination of these factors.[1,2] Vasoplegic shock is a form of vasodilatory/distributive shock that features a reduction in systemic vascular resistance (SVR) with further characterization by underlying mechanisms into septic, anaphylactic, neurogenic, endocrine, and drug or toxin-induced categories. In contrast to shock etiologies defined by a

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low cardiac output state, vasoplegic shock presents with a hyperdynamic, high output state. Septic shock, accounting for the majority of all ICU admissions for shock with a 40% to 50% mortality, has informed much of our understanding of all forms of vasodilatory shock.[3,4]

Clinical Presentation and Risk Factors

Vasoplegic shock–encountered post–cardiopulmonary bypass (CPB) is typically defined by a mean arterial pressure (MAP) less than 65 to 70 mm Hg, cardiac index (CI) greater than 2.2 to 2.5 L/min/m^2, and SVR less than 800 dyne s/cm^5, occurring after weaning from CPB. Because there is widespread heterogeneity in the literature and no consensus definition, the reported incidence of vasoplegic shock differs widely in reported series, ranging from 5% to 45%.[5,6] Risk factors associated with vasoplegic shock include preoperative renal failure, history of previous cardiac surgery, combined coronary artery bypass and valve surgery, increased duration of both cross-clamp time and CPB time, and intraoperative administration of red blood cells.[6]

Similar to other shock states, vasoplegic shock leads to end-organ malperfusion. Clinical and biochemical measures of tissue hypoperfusion include oliguria, defined as urine output less than 0.5 mL/kg/hour and often associated with an elevated serum creatinine due to acute kidney injury; altered mental status signaling cerebral hypoperfusion; and hyperlactatemia, frequently defined as a level greater than 2 mmol/L.[4] The development of vasoplegic shock is consistently associated with a significant increase in perioperative mortality.[6,7]

Pathophysiology

- Pathophysiology of vasoplegic shock after cardiac surgery resembles that of septic shock, sharing similarities in inflammatory reaction, macrophage activation, and cytokine release triggered by CPB.[8,9]
- Inflammatory-mediated vasodilation during CPB is multifactorial and is largely a result of hemodilution, blood exposure to nonendothelialized, nonbiologic surfaces of CPB equipment, and a reperfusion injury upon release of the clamped aorta.[8]
- Coagulopathy correction and transfusion with blood products is common during cardiac surgery and contributes to increased concentrations of circulating inflammatory mediators such as interleukin-6, interleukin-8, and bradykinin.[10] Preoperative optimization of anemia and meticulous surgical technique to reduce transfusions are important.

Hemodynamic assessment/monitoring

- Changes in hemodynamic parameters during vasoplegic shock consist of decrease in MAP, tachycardia, preserved or increased cardiac output/index, reduced central filling pressures, marked reduction in SVR, and oliguria.[9]
- In addition to hemodynamic monitoring data, clinical endpoints assessing organ function, such as liver function tests, serum creatinine, and lactate, should be measured to assess tissue hypoperfusion. Vasoplegic shock has been associated with higher degrees of renal failure and stroke after cardiac surgery.[11]

Standardization of Nomenclature

- The severity of vasoplegic shock should not be defined simply by the number of vasopressors; the need for 1 high-dose vasopressor may reflect a greater severity of shock than the use of 2 low-dose vasopressors. In an effort to

standardize the nomenclature and convert equivalent doses, the concept of NEE (norepinephrine equivalents) has been developed.[12]

- NEE normalizes norepinephrine, epinephrine, dopamine, phenylephrine, and vasopressin infusion dosages to facilitate comparisons at the bedside and outcomes research. More recent studies have proposed the addition of novel vasoconstrictor agents such as angiotensin II, methylene blue (MB), hydroxocobalamin, and midodrine, among others, to reflect current practice.[13]

Approach to treatment escalation

Patients at increased risk of vasoplegic shock benefit from multidisciplinary cooperation beginning preoperatively by withholding medications that may be implicated to cause or exacerbate vasoplegic shock, such as angiotensin-converting enzyme inhibitors/angiotensin receptor blockers.

A general approach to vasoactive medications can be seen in **Fig. 1**.[14] Three classes of interventions should be considered as follows: (1) vasoactive medications to achieve an adequate blood pressure; (2) pharmacologic adjuncts that can mitigate the inflammatory process driving the vasoplegic shock; and (3) a thorough review of preoperative medications that may result in vasoplegia to identify potential medications to be stopped prior to surgery, and avoiding or limiting the use of postoperative agents that have a propensity to cause vasodilation (eg, milrinone, propofol).

The cornerstone of treatment for hypotension are vasopressors. Here we discuss the most common vasoactive medications utilized and their clinical management.

Catecholamines. Catecholamines, specifically norepinephrine, are considered the primary first-line therapy for vasoplegic shock because of its well-established role in septic shock. Norepinephrine is both a central neurotransmitter and a hormone produced in the adrenal medulla. Norepinephrine activates the alpha-1 receptor on vascular smooth muscle, resulting in muscle contraction.[2,12] Of note, endogenous vasodilators

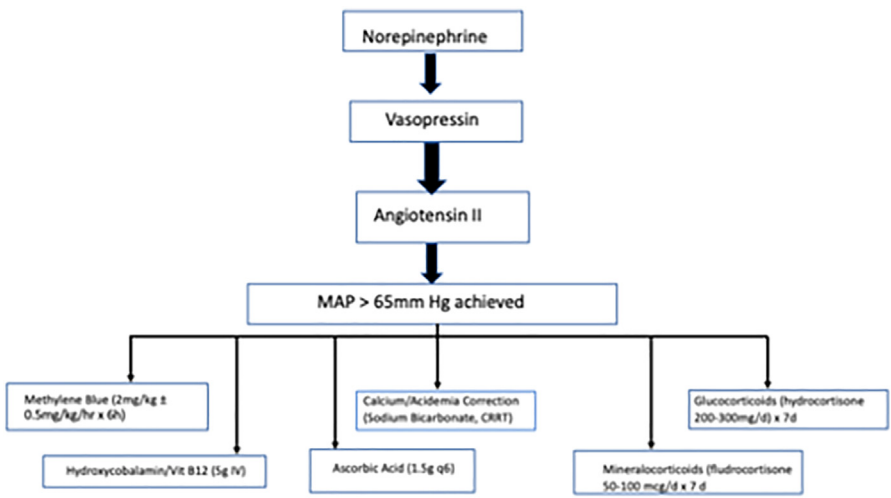

Fig. 1. Management algorithm for vasoplegic shock with vasoactive medications and pharmacologic adjuncts. (*From* Chatterjee, Subhasis (2022) "Profound Vasoplegia after Coronary Artery Bypass Grafting," Journal of Shock and Hemodynamics: Vol. 1(2) :E2022129. Available at: https://digitalcommons.library.tmc.edu/josh/vol1/iss2/9; with permission.)

such as atrial natriuretic peptide and nitric oxide cause vasodilatation and reduced sensitivity to catecholamine vasoconstriction.

It is worth recognizing that because few randomized, controlled, trials exist comparing different vasopressors for the treatment of post-CPB vasoplegic shock, management relies on data extrapolated from patients with septic shock. In the Sepsis Occurrence in Acutely Ill Patients (SOAP II) trial (Fig. 2), norepinephrine was shown to cause less tachycardia and arrhythmias than dopamine in the treatment of circulatory shock.[3] While no significant difference in mortality was found at 28 days, a subgroup analysis showed dopamine had increased mortality in patients with cardiogenic shock but not septic or hypovolemic shock.

Vasopressin. The rationale for the use of arginine vasopressin (AVP) in the management of vasoplegic shock, similar to that for other forms of distributive shock, is rooted in a presumptive deficiency of AVP in shock states. Water retention, the main homeostatic role of vasopressin, is achieved via V2-receptor-mediated regulation of renal collecting duct permeability, promoting water reabsorption. AVP synthesis occurs in the hypothalamus, stored in the posterior pituitary gland, with release into the circulation in response to hypertonicity.[2] In addition, hypovolemia sensed by baroreceptors in the left atrium, carotid, and aortic arch stimulates vagal-mediated AVP secretion, inducing renal water reabsorption. AVP binding to V1 receptors on vascular smooth muscle directly leads to increased vasoconstriction.

As shock worsens, the initial high AVP concentrations present in the initial shock phase fall as the endogenous stores deplete, leading to subsequent hypotension.[15] Correction of low AVP via exogenous infusion increases the arterial blood pressure in different shock states not responsive to escalating catecholamines.[16] Of note, AVP has also been shown to inhibit nitric oxide–mediated vasodilatory shock states.[15,17] Patients developing vasoplegic shock after cardiac surgery have lower levels of AVP than those who do not.[18]

What Are the Randomized Trials Supporting Vasopressin Use?

Previous trials have explored the utility of vasopressin as an adjunct to norepinephrine in septic shock (see Fig. 2). The Vasopressin and Septic Shock Trial (VASST),[19] a randomized control trial comparing norepinephrine alone to norepinephrine plus vasopressin, found no difference in 28-day all-cause mortality. The subsequent Vasopressin versus Norepinephrine as Initial Therapy in Septic Shock (VANISH) trial[20]

TRIAL NAME	INTERVENTION ARMS	SURVIVAL OUTCOMES	MAJOR FINDING(S)	TAKE HOME MESSAGE
SOAP II Trial (n=1679) (Ref 3. DeBacker NEJM 2010)	Norepinephrine vs. Dopamine	No mortality difference (Dopamine 53% vs. Norepinephrine 49%)	Two-fold higher risk of arrhythmias in Dopamine group (24% vs. 12%)	Survival advantage to Norepinephrine in cardiogenic shock cohort
VASST Trial (n=778) (Ref 19. Russell. NEJM. 2008)	Low dose Norepinephrine + Vasopressin vs. Higher Dose Norepinephrine	No mortality difference (Vasopressin 35% vs. Norepinephrine 39%)	No other differences in secondary outcomes	Vasopressin survival advantage in less severe shock
VANISH Trial (n=409) (Ref 20. Gordon, JAMA 2016.)	Norepinephrine ± Hydrocortisone vs. Vasopressin ± Hydrocortisone	No mortality difference (Vasopressin 57% vs. Norepinephrine 59%)	Early vasopressin had less norepinephrine need and renal replacement therapy but no difference in renal-failure free days.	Early vasopressin had similar survival and renal failure outcomes.
VANCS Trial (n-300) (Ref 7. Hajjar. ANESTHESIOL 2017) Cardiac Surgery only	Norepinephrine vs. Vasopressin	No mortality difference (Vasopressin 15% vs. Norepinephrine 16%)	Primary composite outcome favored Vasopressin	Vasopressin less atrial fibrillation (NNT=4) and renal replacement therapy (NNT=6)

Fig. 2. Summary of 4 major vasopressor trials comparing interventions and outcomes.

was designed to see if early use of vasopressin reduced the risk of renal failure in septic shock compared to norepinephrine. This 2 × 2 randomized trial also assigned patients to concomitant hydrocortisone (200 mg daily) or placebo and found no difference in mortality or renal failure-free days comparing norepinephrine alone or with vasopressin.

The only cardiac surgery–specific trial, the Vasopressin versus Norepinephrine in Patients with Vasoplegic Shock after Cardiac Surgery (VANCS), a single-center, randomized, double-blinded, control trial, evaluated the use of monotherapy norepinephrine or vasopressin as first-line therapy for post-CPB vasoplegic shock.[7] The vasopressin group had a lower composite outcome of mortality and severe complications, driven largely by lower atrial fibrillation and renal failure in the vasopressin group. Importantly, AVP was titrated up to 0.06 unit/min in this trial without adverse events.[7]

A large systematic review of norepinephrine monotherapy compared to combination of norepinephrine and vasopressin demonstrated reduced mortality and atrial fibrillation with the use of combination therapy.[21] In addition, patients with right ventricular failure may benefit more from vasopressin with no effect on pulmonary vascular resistance (PVR) compared to norepinephrine which does increase PVR.[22] Nevertheless, due to limited data comparing the use of vasopressin with other vasopressors, the consensus for vasoplegic shock remains norepinephrine as first-line treatment, with the addition of vasopressin with escalating doses of norepinephrine, although the precise threshold for initiation of vasopressin remains unknown.[4] However, earlier utilization of concomitant norepinephrine and vasopressin appears justified.

Angiotensin II

Angiotensin II is an endogenous peptide and one of the ultimate products of the renin-angiotensin cascade (see **Fig. 1**). Its primary mechanism in blood pressure regulation is the direct agonism of the angiotensin type 1 receptor present throughout the venous and arterial vascular smooth muscle.[23] This G-protein coupled receptor is responsible for angiotensin II's potent vasoconstricting effects. Angiotensin II also has downstream effects on vasopressin and aldosterone release and subsequent water and sodium homeostatic mechanisms in blood pressure regulation.[23]

The phase 3 registration clinical trial, ATHOS-3, demonstrated angiotensin II's efficacy in restoring MAP and sparing catecholamine vasopressor dosages in patients with refractory distributive shock.[24] In this trial, 16 patients had vasoplegic shock following cardiac surgery, of which the primary hemodynamic endpoint was achieved in 89% of those randomized to angiotensin II and 0% of those randomized to placebo ($P = .002$).[25] Similar findings have been identified in case anecdotes[26,27] as well as large postmarketing observational studies.[24,28]

The angiotensin-converting enzyme is produced mainly in the pulmonary capillary endothelium and is the rate-determining step for the conversion of angiotensin I to angiotensin II. In its absence (impaired function and synthetic deficiency), neprilysin and angiotensin-converting enzyme-2 metabolize angiotensin I, resulting in an excess of angiotensin-(1–7) and angiotensin-(1–9) (**Fig. 3**).[29] These angiotensin byproducts engage with the Mas receptor, angiotensin type 2 receptor, and nitric oxide pathways, and are profoundly vasodilatory.[29] This scenario is best characterized by hyperreninemia, which is predictive of angiotensin-converting enzyme insufficiency (state of high angiotensin I and low angiotensin II).[30] During CPB, circulatory cardiac output is effectively diverted away from the pulmonary vascular bed and may injure the pulmonary endothelium, impairing the synthetic capacity of the angiotensin-converting enzyme.[31] Indeed, plasma renin concentrations are elevated after CPB.[32] Interestingly, patients with high renin shock who are administered angiotensin II experience

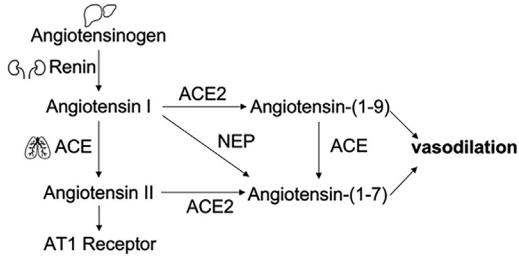

Fig. 3. Systemic pathway of conversion of renin to angiotensin II.

robust hemodynamic benefit and greater survival than those with low renin shock who did not receive angiotensin II.[30]

Concerns have been raised regarding angiotensin II's use in patients with cardiogenic shock.[33] However, in an observational report of vasoplegic shock in patients with profound cardiac shock requiring mechanical circulatory support (mostly ECMO), CI was unchanged and remained > 2.2 L/min/m^2, while the pulmonary artery pressures also did not meaningfully change in the first 12-hour observation period following angiotensin II initiation.[34] Importantly, in this context, angiotensin II increased MAP and spared catecholamine vasopressors,[34] an effect that was similar in another study of vasoplegic mechanical circulatory support patients.[35] While a concern was raised regarding arterial and venous thromboembolism in the ATHOS-3 trial, there were no reports of thromboembolism in patients receiving angiotensin II in the 16 patients in the study after cardiac surgery.[25] Furthermore, systematic reviews have not identified any major safety signals concerning angiotensin II use in cardiogenic shock.[36]

Pharmacologic adjuncts

Vasopressors target the 3 primary pathways of blood pressure regulation during shock: the adrenergic, vasopressin, and renin-angiotensin systems.[37] However, because there are multiple mechanisms for vasodilation during CPB, there are other nonvasopressor pharmacologic adjuncts (**Table 1**) that may contribute to improved blood pressure in vasoplegic shock management. Consequently, these adjuncts may be considered interventions that can mitigate the vasoplegic process.

Nitric oxide modulators

Suppression of nitric oxide–mediated vasodilation may serve as a beneficial additive strategy to vasoconstrictor pathways in the management of vasoplegic shock (**Fig. 4**). MB and hydroxocobalamin are 2 agents that have gained significant interest in this regard.

Methylene blue

The thiazine dye, MB, is an inhibitor of soluble guanylyl cyclase and nitric oxide synthase. Although studies of MB in septic shock have shown variable results,[38] the effects appear more favorable in vasoplegic shock.[39] In an early clinical trial of patients with refractory vasoplegic shock requiring approximately 0.7 mcg/kg/min norepinephrine, those randomized to receive 1.5 mg/kg MB bolus had rapid reversal of vasoplegic shock and all patients survived, whereas 21% of placebo recipients died (P = .01).[40] Interestingly, a study assessing timing of intervention found those receiving MB early post-CPB in the operating room had less acute kidney injury (10% vs 29%, P = .018) and greater 30-day survival (90% vs 71%, p = 0.018) compared to those receiving it later in the intensive care unit.[41]

Table 1
Nonvasopressor pharmacologic adjuncts in vasoplegic shock

Drug	Mechanism & Benefits	Typical Dosing	Adverse Effects & Limitations
Methylene blue	Inhibits guanylyl cyclase and nitric oxide synthase, suppresses nitric oxide–mediated vasodilation	1–2 mg/kg bolus, 1–2 mg/kg/h continuous infusion	Serotonin syndrome, methemoglobinemia, accumulates in and stains tissues, interferes with oximetry measurements, avoid in glucose-6-phosphate dehydrogenase deficiency, maximum cumulative dose of 7 mg/kg
Hydroxocobalamin	Direct nitric oxide scavenger, binds hydrogen sulfide, suppresses nitric oxide–mediated vasodilation	5 g iv bolus over 15 min or 6 h	Chromaturia, intermittent dialysis false-blood leak alarm, cobalt toxicity, interference with colorimetric assays
Thiamine	Cofactor for pyruvate dehydrogenase to produce acetyl-CoA, facilitate lactate clearance	200 mg iv q12h	Flushing, nausea, restlessness
Ascorbic acid	Cofactor for catecholamine synthesis, improve microcirculation	1500 mg iv q6h	Oxalate nephropathy, avoid in glucose-6-phosphate dehydrogenase deficiency

Following a MB bolus, a continuous infusion appears to provide more sustained MAP elevation and further reduced catecholamine requirements.[41] Even in ECMO patients with vasoplegic shock, MB has favorable hemodynamic effects in approximately half of recipients; importantly, nonresponse to MB appears to predict a poor

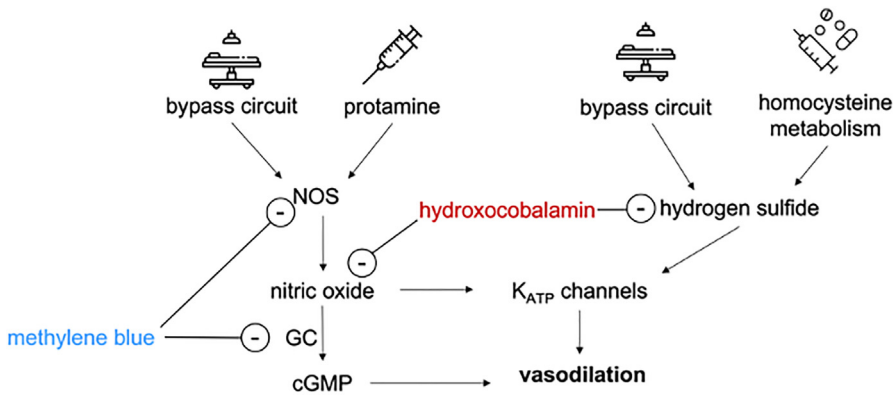

Fig. 4. Comparison of methylene blue and hydroxocobalamin and pathophysiology to vasodilation.

outcome.[42] In left ventricular assist device (LVAD) patients with vasoplegic shock, MB also allows for reductions in vasopressor dosages, but has not demonstrated improvement in clinical outcomes.[43]

MB is a potent inhibitor of monoamine oxidase and has been implicated in serotonin toxicity when co-administered with antidepressants and other drugs with serotonin activity used in the operating room and intensive care unit, such as fentanyl.[44] In addition, it is recommended not to exceed a maximum cumulative dosage of 7 mg/kg due to tissue deposits and potential for inducing methemoglobinemia.

Hydroxocobalamin

The activated form of vitamin B12, hydroxocobalamin, is a cobalamin used in the treatment of inhalational cyanide toxicity. Hypertension was a notable side effect when hydroxocobalamin was used in this setting, leading to its first application for hypotension after cardiac surgery.[45] Unlike MB that indirectly suppresses nitric oxide production, hydroxocobalamin has direct inhibitory effects on nitric oxide itself (see **Fig. 2**). Additionally, hydroxocobalamin binds hydrogen sulfide, a product of homocysteine metabolism upregulated during CPB with potent vasodilatory effects.[46]

Evidence supporting the use of hydroxocobalamin in vasoplegic shock is limited to case reports and a few observational studies. In general, hydroxocobalamin appears to effectively increase MAP and spare catecholamine vasopressors in refractory vasoplegic shock.[47] Longer durations of CPB appear to reduce the likelihood of hemodynamic response to hydroxocobalamin; nonresponders exhibit numerically greater mortality.[48] Moreover, when compared to MB, hydroxocobalamin has similar hemodynamic effects.[49]

The typical 5-gram intravenous bolus dose is extrapolated from hydroxocobalamin's use in cyanide toxicity; although useful when rapid hemodynamic restoration is desired, it seems to provide transient blood pressure effects likely due to nitric oxide's very short half-life.[50] Extending the infusion and administering hydroxocobalamin over a longer period of 6 hours appears to prolong its blood pressure elevating and catecholamine-sparing effects.[51] Although hydroxocobalamin is generally well tolerated, an important consideration of its use, particularly in patients with refractory vasoplegic shock, where acute kidney injury and use of dialysis is frequent, is its propensity to stain serum. This phenomenon leads to a stained dialysis effluent, which is benign during continuous dialysis modes but has been shown to cause a false-blood leak alarm in intermittent hemodialyzers, precluding transition from continuous to intermittent hemodialysis.[52]

Metabolic resuscitators

The so-called metabolic resuscitators, thiamine (vitamin B1) and ascorbic acid (vitamin C), may provide complementary hypotension-correcting mechanisms to vasoconstrictors and nitric oxide inhibitors. Thiamine plays a critical role in cellular metabolism and is a coenzyme for pyruvate dehydrogenase conversion of pyruvate to acetyl-CoA.[53] In its absence and during anaerobic respiration, pyruvate is processed by lactate dehydrogenase to produce L-lactate. As such, thiamine deficiency has been associated with severe lactic acidosis.[54] Ascorbic acid is a cofactor for endogenous catecholamine synthesis, has antioxidant and anti-inflammatory properties, and plays a role in vascular endothelial function.[55] Specifically, ascorbic acid increases the density of capillary beds and improves perfusion in the microcirculatory system.[56] Thiamine and ascorbic acid have garnered interest for application to vasodilatory hypotension given initial beneficial signals of reduced mortality in patients with septic shock.[57,58]

Initial case reports suggested promising effects of ascorbic acid in vasoplegic shock by reducing vasopressor requirements.[59] However, a subsequent randomized trial failed to demonstrate any benefits of ascorbic acid in patients receiving norepinephrine for post–cardiac surgery vasoplegic shock.[60] As ascorbic acid is not a vasopressor, it is unclear whether deploying it when hypotension is already present is the optimal strategy. Indeed, CPB is known to effectively remove this water-soluble vitamin,[61] so perhaps future investigations can assess the utility of ascorbic acid in preventing or temporizing the severity of vasoplegic shock by administering it in closer proximity to the insult of CPB.

Thiamine, on the other hand, has not demonstrated signals of benefit in vasoplegic shock. In one randomized trial, thiamine did not produce any differences in lactate levels following cardiac surgery or duration of vasopressor requirement.[62] Additionally, in a pilot study, thiamine supplementation was deemed safe and feasible but did not result in any meaningful effects or outcomes.[63] These studies, however, did not restrict inclusion to or assess the effects of supplementation specifically in thiamine-deficient patients. Interestingly, in patients with septic shock, one randomized trial did not find any differences in 24-hour lactate concentrations; however, when dichotomized, patients with thiamine deficiency did experience lower lactate concentrations at 24 hours compared to those not deficient.[58]

Based on the available evidence, these agents may be best used when their vitamin deficiencies have been confirmed rather than routinely.

Corticosteroids

The beneficial effect of corticosteroids in reversing distributive shock can be attributed to the mitigation of the systemic inflammatory response. Moreover, patients after CPB have demonstrated increased levels of endotoxin, TNF-alpha activity, and increased expression of nitric oxide synthase in vascular endothelial cells.[64,65] Administration of corticosteroids, which inhibit TNF-alpha mRNA translation, has shown reduced levels of TNF-alpha, neutrophil CD11b surface glycoprotein, and other inflammatory markers.[64] Similarly, corticosteroids inhibition of inducible nitric oxide synthase mRNA transcription prevents de novo synthesis of the enzyme.[65]

What Are the Randomized Trials Supporting the Use of Corticosteroids?

Utilization of glucocorticoids in septic shock trials has demonstrated mixed survival results. Trials utilizing glucocorticoids alone—the 2008 CORTICUS (Corticosteroid Therapy of Septic Shock)[66] and the 2018 ADRENAL (Adjunctive Corticosteroid Treatment in Critically Ill Patients with Septic Shock) trial[67]—did not show a survival benefit. Meanwhile, trials utilizing combination of glucocorticoids and mineralocorticoids—the 2002 “Annane Trial” or “Ger-Inf-05”[68] and the 2018 APROCCHSS (Activated protein C and corticosteroids for human septic shock)[69]—did show a survival benefit. Each of those trials did demonstrate shock reversal and reduced vasopressor dependence with any corticosteroid use.[70] (**Fig. 5**).

Two randomized trials have evaluated the role of glucocorticoids in vasoplegic shock in patients prior to undergoing CPB, with neither demonstrating a difference in survival or major morbidity outcomes.[71,72] However, neither were designed to assess hemodynamic response or shock improvement parameters nor have postoperative corticosteroids been analyzed after cardiac surgery.

The current recommendation in septic shock includes hydrocortisone 200 to 300 mg total daily dose and fludrocortisone 100 mg daily for vasoplegic shock despite adequate resuscitation and use of vasopressors. Duration of corticosteroid use has not been shown to effect outcomes, and given concerns for hyperglycemia, impaired

	Ger-Inf-05	CORTICUS	ADRENAL	APROCCHSS
Sample size	299	499	3800	1241
Inclusion criteria	Septic shock	Septic shock	Septic shock + IPPV	Septic shock, SOFA score, and a pressor requirement (0.25 μg/kg/min of noradrenaline)
Predominantly medical sepsis cohort	Y	N	Y	Y
Proportion mechanically ventilated	90%	90%	100%	92%
Baseline plasma lactate (mmol/L)	4.4 ± 4.4	3.9 ± 3.6	3.8 ± 3.0	4.4 ± 4.9
Treatment				
Drugs	HC/FC	HC	HC	HC/FC
Dosage (mg/μg) per day	200/50	200	200	200/50
Duration (days)	7	11	7	7
Mode of administration of HC	Bolus	Bolus	Infusion	Bolus
Tapering	N	Y	N	N
Corticotropin test	Y	Y	Not performed	Y
Nonresponders (%)	77%	46%	N/A	54%
Etomidate usage	Y 24%	Y 19%	N	Unspecified
Mortality benefit with HC				
Intention to treat	—	—	—	—
In-hospital	N	N	N/A	Y
28 d	N	N	N	N
90 d	N	N/A	N	Y
6 mo	N/A	N/A	N	Y
Differential mortality effect in nonresponders to corticotropin	Y	N	N/A	N
Other outcomes				
Shock reversal	Y	Y	Y	Y
Weaning from mechanical ventilation	N/A	N/A	Y	Y
Length of ICU stay	N/A	N	Y	N
Length of hospital stay	N/A	N	N	N
Adverse effects with HC	N	Y (superinfections)	Y (metabolic)	Y (metabolic)

Fig. 5. Summary of major randomized trials comparing use of steroids in septic shock. (*From* Venkatesh B, Cohen J. Hydrocortisone in Vasodilatory Shock. Crit Care Clin. 2019;35(2):263-275; with permission.)

wound healing, and surgical site infection from corticosteroid use, the general practice is to discontinue steroids within 5 to 7 days.[4,73] In the absence of evidence demonstrating a clear benefit in vasoplegic shock after cardiac surgery, corticosteroid use should be individualized in appropriate patients.

DISCUSSION: APPROACH TO TREATMENT DE-ESCALATION

In general, vasopressor utilization has typically followed a "last on, first off" approach since, at most institutions, cost increases from norepinephrine to vasopressin to angiotensin II. However, whether that is the most efficacious approach remains to be seen. It may be that a "broad spectrum" approach to vasopressors utilizing 2-3 initial vasopressors and then tailoring utilization based on response similar to empiric antibiotics in sepsis may be a better approach.[37] This is further supported by reports that about 45% of patients are vasopressin responders,[74] and 67% of patients are angiotensin

II responders.[28] Thus, if one vasopressor is not achieving a satisfactory MAP within a few minutes, it is important to swiftly move to another agent. It is likely that there are different phenotypes of vasoplegic shock with different degrees of relative adrenergic, vasopressin, and angiotensin II depletion. As our understanding of biomarkers improves, a more personalized approach to vasopressors may be more effective.

De-escalation follows not just the MAP but also markers of end-organ perfusion, especially serum lactate. The specific vasopressor combination or adjunct used is individualized with the general treatment algorithm (see **Fig. 1**). Vasoplegic shock and high-dose vasopressor therapy often result in limb ischemia, posing a difficult therapeutic dilemma since reducing vasopressors comes at the expense of an adequate MAP. It is important to recognize that limb ischemia is often multifactorial, and disseminated intravascular coagulation, ischemic hepatitis (shock liver), and high-dose vasopressors have been found to have similar contributions in that setting.[75]

SPECIAL POPULATIONS: HEART TRANSPLANT AND LEFT VENTRICULAR ASSIST DEVICE PROCEDURES

Overall, the incidence of vasoplegic shock post–heart transplantation ranges from 35% to 66%.[76,77] Furthermore, transplant recipients who had mechanical support (LVAD or ECMO) as a bridge to transplantation were at increased risk of developing vasoplegic shock.[78] In patients with LVADs, the presence of driveline infection at the time of transplantation was strongly associated with vasoplegic shock.[79] Some authors have speculated that exposure to donor antigens and prolonged CPB times are implicated in vasoplegic shock.[77] Strong predictors of vasoplegic shock after heart transplantation include preoperative and postoperative acute kidney injury, preexisting renal replacement therapy, and postoperative requirement for ECMO. Prolonged mechanical ventilation, increased need for renal replacement therapy, increased transfusion requirements, and increased hospital length of stay are also associated with vasoplegic shock after 1 year after transplantation.[80]

Vasoplegic shock can be problematic in patients with LVAD as lactic acidosis can cause increased PVR, leading to right ventricular dysfunction. Others have speculated that biochemical alterations in aortic wall integrity contribute to NO synthesis and cytokine release after LVAD implantation, resulting in vasoplegic shock.[81] Special consideration in patients with LVAD because of their afterload-sensitive nature and maintenance of MAP in the 70 to 80 mm Hg range is that hypotension and reduced afterload can result in increased LVAD flows and decreases pulsatility index. This may necessitate decreasing LVAD speed to offset this flow.[81] Vigilance should be incorporated when taking care of patients with LVAD as vasoplegic shock is reported in one-third of the patients with the newer generation of LVADS with continuous-flow configuration.[82]

SUMMARY

Vasoplegic shock is a common complication after cardiac surgery. Early recognition and an organized systematic approach to vasoactive medications and therapeutic adjuncts is necessary for optimal outcomes.

CLINICS CARE POINTS

- Achieving target blood pressure goals requires frequent assessment and evaluation of the adequacy of current vasopressor agents; escalation to additional agents should be utilized when targets are not being met.

- If glucocorticoids are administered for vasoplegic shock, concomitant mineralocorticoids should also be given for their demonstrated efficacy.

DISCLOSURE

P.M. Wieruszewski has served as a consultant for La Jolla Pharmaceutical Company. S. Chatterjee has served on advisory boards for Edwards Lifesciences, La Jolla Pharmaceutical Company, Eagle Pharmaceuticals, and Baxter Pharmaceuticals. The remaining authors have no conflicts to disclose.

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