Journal of The Cardiovascular Thoracic Anaesthesia and Intensive Care Society

GKDA Derg 2024;30(4):125-131
Doi: 10.14744/GKDAD.2024.32659

REVIEW

Vasoplegia After Cardiopulmonary Bypass: Current Approaches

Elvin Kesimci

Department of Anesthesiology and Reanimation, Başkent University Faculty of Medicine, Ankara, Türkiye

ABSTRACT

Vasoplegia is a kind of distributive form of circulatory shock. It is commonly observed intraoperatively during cardiopulmonary bypass (CPB), after weaning from CPB or in the first postoperative 24 h follow-up in the intensive care unit (ICU). As CPB is still a cornerstone in surgical management of cardiovascular diseases, the incidence of vasoplegia increases up to 40% in cardiac surgical patients. The recognized characteristics are reduced blood pressure with profound peripheral vasodilation despite a preserved cardiac output. The pathophysiology is complex and mainly triggered by the systemic inflammatory response caused by CPB and surgical trauma. Early identification and prompt management of vasoplegia is crucial to prevent development of organ failure and longer hospital and ICU stay with increased morbidity and mortality. In this review, the risk factors, pathophysiology and current management approaches of vasoplegia after CPB are discussed.

Keywords: Cardiopulmonary bypass, management, pathophysiology, vasoplegia.

Please cite this article as: "Kesimci E. Vasoplegia After Cardiopulmonary Bypass: Current Approaches. GKDA Derg 2024;30(4):125-131".

Introduction

Cardiovascular diseases are one of the leading causes of death in the world.[1] Despite the improvements in interventional surgical techniques in cardiac procedures, open cardiac surgery is still the cornerstone in the treatment algorithm. A relatively common complication of this procedure is vasoplegia, with an estimated incidence of 5%–47%, depending on the predisposing factors in the population being investigated.[2] It is a distributive form of circulatory shock characterized by low systemic vascular resistance (<800 dynes·s/cm^5) in the presence of normal or high cardiac index (>2.2 l/min/m^2) with hypotension (MAP: mean arterial pressure <65 mmHg) resistant to fluid challenge and/or vasopressor treatment.[3]

Vasoplegic shock, indeed, can occur in any condition in which there is a profound inflammatory response that is unresponsive to vasopressors. Apart from CPB, it is common in ICU with sepsis, burns and trauma. Anyway, it is associated with organ failure, increased bleeding, length of intensive care unit (ICU) and hospital stay.[4] Thus, mortality following vasoplegia remains as high as 30%–50%, mainly due to inadequate cellular oxygen utilization and multiorgan failure, especially acute kidney injury.[5]

Pathophysiology and Potential Risk Factors

Vasoplegia after cardiopulmonary bypass is most likely related to an immunological-based response triggered by proinflammatory mediators release, complement activation secondary to surgical trauma, ischemia–reperfusion injury of heart and lungs, blood transfusion, and/or exposure of blood to the foreign surfaces of the CPB circuit. Actually, CPB-induced immunological response causes release of IL-1, IL-6 and TNF. By ischemic-reperfusion injury of heart and lungs, there is an endotoxin release and complement activation. All of these result in dysregulation of cytoplasmic Ca++ influx, leading to vasodilation. Besides, immunological response triggers increase in free O_2 radicals, endothelins, platelet-activating factor, thromboxane A_2, cytokines, prostaglandins, iNOS and NO. Vasopressin deficiency due to depletion of neurohypophyseal vasopressin stores and systemic inflammatory reaction commonly observed with congestive heart failure, low ejection fraction, and prolonged CPB altogether result in refractory vasoplegia.[6]

There is a myriad of biochemical interactions resulting in derangements in receptor signaling, metabolic changes, the depletion of endogenous vasoactive hormones, and the alteration of the endothelial glycocalyx.[7,8] These processes

Address for correspondence: Elvin Kesimci, MD. Başkent Üniversitesi Tıp Fakültesi, Anesteziyoloji ve Reanimasyon Anabilim Dalı, Ankara, Türkiye
Phone: +90 312 203 68 68 **E-mail:** elvinku@yahoo.com

Submitted: November 04, 2024 **Accepted:** November 07, 2024 **Available Online:** December 31, 2024
The Cardiovascular Thoracic Anaesthesia and Intensive Care - Available online at www.gkdaybd.org

result in increased oxygen-free radicals, endothelins, NO, platelet-activating factors, thromboxane A_2, prostaglandins, a variety of cytokines, and other vasoactive substances.[9–11] The relative plasma concentrations of the above-mentioned substances determine vascular relaxation. In addition, these factors are also involved in the development of a systemic inflammatory response syndrome (SIRS), that further exaggerates the generalized vascular dilatation. Further mechanisms of vasodilation include the lowering of plasma vasopressin, the desensitization of adrenergic receptors, and the activation of ATP-dependent potassium (KATP) channels.[4]

The main clinical characteristics, pathophysiological mechanisms and outcomes are summarized in the table below (Table 1).

Patients at higher risk of developing vasoplegia include those who are male, older with increased body mass index (BMI), anemia, chronic kidney disease, hepatic dysfunction and thyroid disease. Besides, previous cardiac surgery, recent myocardial infarction, high perioperative EuroSCORE also increase the tendency to develop vasoplegia. Those undergoing longer and combined (coronary artery and valve) operations with prolonged aortic cross-clamp and cardiopulmonary bypass times (>180 minutes) and the need for multiple transfusions present with a higher incidence of vasoplegia.[12–15] Although there is some controversy regarding the role of angiotensin-converting enzyme inhibitors and angiotensin 2 receptor blockers, general practice has been to discontinue those and other antihypertensive agents or goal-directed heart failure medical therapy before surgery.[16] It is also important to recognize that in LVAD recipients and redo operations, hypovolemia, hemorrhage, right ventricular dysfunction, and low cardiac output trigger hypotension resistant to vasoactive substances.[13,17–21]

Current Management Strategies

Peri-operative Prevention

Early recognition of the problem and timely management are crucial for vasoplegia treatment. For this reason, preoperative risk stratification might help to improve perioperative hemodynamic status and renal function to reduce the risk of postoperative vasoplegia.[15]

It has been suggested that strategies such as the use of minimal extracorporeal circulation (MECC) and biocompatible, heparin-coated short circuits might limit inflammation by reducing the exposure to foreign surfaces.[19] Although several trials reported a reduction in inflammation, the overall clinical benefits are limited, and adequately powered randomized controlled trials are warranted to address their effectiveness.[4]

Volume Resuscitation

The main goal of resuscitation is to meet the tissue metabolic needs by ensuring adequate tissue perfusion and oxygen delivery. This is achieved by the maintenance of sufficient cardiac output and perfusion pressure.[20] The sufficiency of perfusion should be demonstrated either by the mottling score and the capillary refill time, and/or biologically by the value of arterial blood lactate and the venous-to-arterial difference in the partial pressure of carbon dioxide (VA-pCO_2 gap).[21,22]

Beyond an initial fluid loading of 20–30 mL/kg, additional fluids should be administered cautiously with guidance from dynamic indices, such as pulse pressure variation and echographic indices of stroke volume variation.[23,24] The "mini fluid challenge" (administration of 100–150 mL crystalloid fluid over 60–120 s) technique is another method for accurate fluid overload evaluation.[24]

With respect to patient blood management, current guidelines recommend a transfusion threshold of 7.5 g/dL in stable patients without evidence of tissue hypoxia.[25,26] It is clear that anemia can reduce systemic vascular resistance, both by reducing blood viscosity and decreasing Hb-dependent inhibition of NO, which could contribute to aggravating hypotension in these patients. Therefore, higher transfusion thresholds, like Hb ≥9 g/dL, are suggested in this setting.[4]

Vasoactive Drugs

A mean arterial pressure (MAP) of 65–70 mmHg is considered sufficient, as higher values have not been associated with improved survival.[27–29] Although it has long been considered that vasopressors should be initiated following adequate volume resuscitation, according to the guidelines, it is now recommended to start vasoactive drugs together with volume resuscitation, as this strategy has been associated with reduced short-term mortality in sepsis-associated vasoplegia.[30] Besides, multiple vasopressors are also started rapidly, as the physiologic response to maintaining blood pressure is proven to consist of the sympathetic (norepinephrine), the vasopressin, and the renin-angiotensin (angiotensin 2) systems.[27] The combined therapy with norepinephrine and vasopressin is associated with improved mortality and less atrial fibrillation compared with norepinephrine alone.[31–33]

Norepinephrine

Norepinephrine (NE) targets the vascular α-1 adrenoreceptor to increase intracellular Ca++ and promote vascular smooth muscle contraction. NE remains the first-line vasopressor agent and is thus still considered the standard of care, though no mortality benefit from its use in post-CPB vasoplegia has been demonstrated.[31–33] However, NE may

Table 1. Vasoplegia after cardiopulmonary bypass-main characteristics

Definition	Distributive form of circulatory Shock ≤ 24 h after CPB Initiation, characterized by: 1. MAP <65 mmHg resistant to fluid challenge 2. SVR <800 dynes s/cm^5 3. CI>2.2 L/min/m^2
Predisposing factors	
Patient-related factors	Advanced age; anemia, low LVEF, renal failure
Pre-/peri-operative drugs	Diüretics, sympatho-adrenergic inotropes, ACEI (controversial)
Operative factors	CPB/aortic cross clamping time, redo surgery, combined surgery, LVAD surgery, HTx
Pathophysiology	Systemic Inflammatory response triggered by; 1. Exposure of blood to the artificial surfaces of the extra-corporeal circuit 2. Surgical trauma 3. Ischemia/reperfusion injury
Initiating events	4. Oxidative stress 5. Release of endotoxin from the gut 6. Hemolysis 7. Reinfusion of cell saver blood
Mechanisms of pathological vasodilation	1. Desensitization of adrenergic receptors 2. Increased NO biosynthesis 3. Low plasma vasopressin 4. VSMC hyperpolarization due to opening of K_{ATP} channels 5. RAS dysfunction with low Ang2(?) 6. Excess H_2S generation (?) 7. Endothelial glycocalyx alteration (?)
Outcome	1. More frequent postoperative bleeding 2. Increased incidence of organ dysfunction, renal, liver, respiratory failure 3. Prolonged mechanical ventilation and length of ICU/hospital stay 4. Higher mortality

CPB: Cardiopulmonary bypass; MAP: Mean arterial pressure, SVR: Systemic vascular resistance; CI: Confindence interval; LVEF: Left ventricular ejection fraction; ACEI: Angiotensin converting enzyme inhibitor; LVAD: Left ventricular assist device; HTx: Heart transplantation; NO: Nitric oxide; VSMC: Vascular smooth muscle cell; K_{ATP}: ATP-dependent potassium; RAS: Renin angiotensin system; ICU: Intensive care unit.

trigger important side effects such as tachycardia, atrial fibrillation, increased myocardial oxygen consumption, and hyperlactatemia due to its beta-adrenergic actions. Even epinephrine and dopamine cause these side effects more commonly; thus, they are not preferred or recommended in the therapy of vasoplegia.[31,32]

There is currently no recommendation with respect to the threshold dose of NE (0.1–0.7 µg/kg/min) before vasopressin start, as higher doses may result in immunosuppression, predisposing to secondary infections and side effects. Therefore, a non-catecholaminergic vasopressor (vasopressin) should be added early if MAP cannot be rapidly restored with NE.

Vasopressin

Vasopressin (VP) provides vasoconstriction via vascular V1-receptor-dependent increase in cytosolic Ca++, modulation of NO signaling, and improvement of catecholamine sensitivity. Argenziano et al.[34] reported a significant increase in MAP in vasoplegic hypotensive LVAD surgery patients who received VP (0.1 U/min) after treatment with NE, in comparison to saline placebo. This was attributed to the reduced circulating levels of VP reported in patients with vasoplegia after CPB, so that the therapeutic use of exogenous VP was recommended.

Additionally, in other studies, the authors reported that the systemic vasopressor effect of VP didn't influence pulmonary vascular resistance and didn't increase right ventricular afterload while increasing right ventricular perfusion pressure.[34] A large randomized, controlled trial (VANCS trial), including 300 patients with VS after cardiac surgery, directly compared NE (10–60 µg/min) with VP (0.01–0.06 U/min) as first-line vasopressor to maintain a MAP of 65 mmHg.[35] Patients in the VP arm had a significant reduction (32% vs. 49%, p=0.0014) of the primary outcome (a composite of 30-day mortality or severe complications), mostly due to a marked reduction in acute renal failure (10% vs. 36%, p<0.0001).

In addition, VP was associated with a lower incidence of atrial fibrillation (64% vs. 82%, p=0.0004), and did not result in a greater occurrence of digital, mesenteric,

or myocardial ischemia. Based on these data, and on meta-analyses confirming a reduced incidence of AF and possible decreased incidence of acute kidney injury with VP,[36,37] Guarracino et al.[38] proposed to start or add VP to increase MAP in case of adverse effects related to sympathoadrenergic drugs and to use VP as a first-line vasopressor therapy. Regarding the dose of VP, doses higher than 0.06 U/min are recommended to be avoided due to dose-dependent increased risk of ischemic complications.

Angiotensin 2

The possibility of a disturbed renin-angiotensin system leading to reduced Ang2 generation in vasoplegia after CPB suggests that exogenous Ang2 might be a therapeutic option in this setting. Several case reports and small case series reported safe and successful administration of Ang2.[39]

The ATHOS-3 trial evaluated the effectiveness of Ang2 (20–200 ng/kg/min) in refractory vasodilatory shock from various origins (primarily septic shock) unresponsive to high doses of vasopressors.[40] The pre-defined hemodynamic target was reached significantly more often with Ang2 than placebo.[41] However, current evidence remains insufficient to make any recommendation, implying the need for additional RCTs evaluating Ang2 in cardiac surgery patients.[38–42]

Methylene Blue

Methylene blue (MB) is a thiazine dye used as an antidote to treat methemoglobinemia.[43] Owing to several pharmacological actions, MB increases vascular tone. It acts by inhibiting NO-dependent vasodilation via either direct scavenging of NO, inhibition of NO synthase, or most significantly, inhibition of guanylyl cyclase. However, data on clinical outcomes with MB remain scarce and contrasted.

The results of randomized controlled trials are conflicting regarding hemodynamic status, in-hospital mortality, and postoperative complications.[44] Therefore, given the lack of high-quality data, uncertainties regarding clinical outcomes, the potential for severe side effects, and unresolved issues regarding the timing (pre-, peri-, or postoperatively), dose, and mode of administration (bolus vs. infusion), the use of MB to treat VS after CPB is presently not recommended, except as a rescue therapy in cases with hypotension refractory to usual vasopressors.[38]

Hydroxocobalamin

Hydroxocobalamin (vitamin B12), which is used for the therapy of pernicious anemia and in cyanide poisoning, has been evaluated for the treatment of refractory vasoplegia after CPB. It may increase vascular tone, including inhibition of NOS enzymes, direct NO inactivation, and reduction in H_2S toxicity through direct binding.[45,46]

A 5 g dose of hydroxocobalamin is administered by IV infusion over 15 min to increase MAP and reduce the doses of vasopressors. Hydroxocobalamin appears generally associated with hemodynamic improvement and decreased vasopressor requirements in the setting of VS after cardiac surgery, as reviewed recently by Shapeton et al.[46]

However, safety and mortality data are lacking, and both the timing (pre- or postoperative) and mode (bolus vs. continuous infusion) of administration remain to be established. Therefore, the use of hydroxocobalamin should only be considered as a rescue strategy in deteriorating patients refractory to usual vasopressors.

Vitamin C

Vitamin C (ascorbic acid) is a co-factor for several enzymes involved in the biosynthesis of endogenous catecholamines, and it also increases the sensitivity of adrenoreceptors.[47] It is also a free radical scavenger and might therefore reduce oxidant-mediated tissue injury, inflammation, and endothelial dysfunction.

An important reduction in plasma Vitamin C occurs following CPB, suggesting a potential therapeutic role from exogenous supplementation.[48] However, the data are both conflicting and are provided from either case reports or small series of cardiac surgery patients.[49] Therefore, it cannot yet be recommended in the treatment of vasoplegia.

Anti-Inflammatory Strategies

Corticosteroids

Corticosteroids may be a preferred option due to their anti-inflammatory effects and their ability to enhance the synthesis of catecholamines and the expression and sensitivity of adrenoreceptors.[50–53]

In cardiac surgery, two large trials (SIRS trial—7507 patients, and DECS trial—4494 patients) evaluated the effects of high-dose corticosteroids (intraoperative methylprednisolone or dexamethasone) on mortality and major complications. These studies did not report any significant effects of the interventions.[54] However, none of the studies specifically addressed the role of low-dose steroids in established VS after cardiac surgery.

Therefore, although low-dose steroids appear safe and may be associated with some beneficial effects, there is no evidence supporting their use to specifically treat CPB-induced vasoplegia.

Extracorporeal Cytokine Adsorption Therapy

Extracorporeal cytokine adsorption therapy (ECAT) is a technique of extracorporeal blood purification using

specifically designed filters capable of adsorbing and removing inflammatory mediators from circulation. This strategy has been applied to decrease inflammation in sepsis.[55]

In the field of cardiac surgery, the largest RCT to date was published by Diab et al.,[56] who compared ECAT using the CytoSorb® cytokine filter integrated into the CPB circuit (n=142 patients) with standard care (n=146 patients). Although patients in the intervention arm displayed significantly lower levels of IL-1β and IL-18 at the end of CPB, they did not differ from controls in terms of postoperative change from baseline in sequential organ failure assessment scores with respect to the use of vasopressors.

In a systematic review including 5 RCTs (n=163 patients) evaluating ECAT in cardiac surgery, Goetz et al.[57] reported no significant benefits from the technique in terms of mortality and postoperative complications. As a whole, these data indicate that the efficacy and safety of ECAT remain unestablished. Therefore, its application in cardiac surgical patients cannot currently be recommended.

Conclusion

The aim of the management of vasoplegia is to restore organ perfusion pressure and adequate oxygen delivery by ensuring appropriate preload and by the administration of vasoactive drugs to maintain a MAP of 65 mmHg. The present evidence indicates that conventional vasopressors are recommended as first-line therapy. In this respect, norepinephrine is generally considered the standard of care.

Vasopressin should be added to norepinephrine in case of adverse effects (tachycardia, atrial fibrillation) related to excessive sympathetic stimulation or could be used as the initial vasopressor, as supported by the recent VANCS clinical trial.[13] Non-conventional vasopressors, including methylene blue, angiotensin 2, and hydroxocobalamin, have been increasingly used in refractory cases, but evidence is not sufficient to make any recommendations. Low doses of hydrocortisone may be associated with vasopressors in order to potentiate their effects, due to their demonstrated role in shortening the duration of vasoplegia in sepsis. However, vitamin C and cytokine adsorption filters should not be used due to a lack of theoretical advantages. Thus, management strategies should focus on early recognition of the problem and awareness of the current treatment options.

Disclosures

Conflict of Interest: All authors declared no conflict of interest.

Use of AI for Writing Assistance: No AI technologies utilized.

Financial Disclosure: The authors declared that this study has received no financial support.

Peer-review: Externally peer-reviewed.

References

1. Hansen LS, Hjortdal VE, Andreasen JJ, Mortensen PE, Jakobsen CJ. 30-day mortality after coronary artery bypass grafting and valve surgery has greatly improved over the last decade, but the 1-year mortality remains constant. Ann Card Anaesth 2015;18:138–42.
2. Omar S, Zedan A, Nugent K. Cardiac vasoplegia syndrome: Pathophysiology, risk factors and treatment. Am J Med Sci 2015;349:80–8.
3. Ortoleva J, Dalia AA, Pisano DV, Shapeton A. Diagnosis and management of vasoplegia in temporary mechanical circulatory support: A narrative review. J Cardiothorac Vasc Anesth 2024;38:1378–89.
4. Ltaief Z, Ben-Hamouda N, Rancati V, Gunga Z, Marcucci C, Kirsch M, et al. Vasoplegic syndrome after cardiopulmonary bypass in cardiovascular surgery: Pathophysiology and management in critical care. J Clin Med 2022;11:6407.
5. Tsiouris A, Wilson L, Haddadin AS, Yun JJ, Mangi AA. Risk assessment and outcomes of vasoplegia after cardiac surgery. Gen Thorac Cardiovasc Surg 2017;65:557–65.
6. Szeles TF, Almeida JP, Cruz JASD, Artifon ELA. Vasopressin in vasoplegic shock in surgical patients: Systematic review and meta-analysis. Acta Cir Bras 2023;38:e387523.
7. Papazisi O, Palmen M, Danser AHJ. The use of angiotensin II for the treatment of post-cardiopulmonary bypass vasoplegia. Cardiovasc Drugs Ther 2022;36:739–48.
8. Datt V, Wadhhwa R, Sharma V, Virmani S, Minhas HS, Malik S. Vasoplegic syndrome after cardiovascular surgery: A review of pathophysiology and outcome-oriented therapeutic management. J Card Surg 2021;36:3749–60.
9. Shaefi S, Mittel A, Klick J, Evans A, Ivascu NS, Gutsche J, et al. Vasoplegia after cardiovascular procedures-pathophysiology and targeted therapy. J Cardiothorac Vasc Anesth 2018;32:1013–22.
10. Jochberger S, Velik-Salchner C, Mayr VD, Luckner G, Wenzel V, Falkensammer G, et al. The vasopressin and copeptin response in patients with vasodilatory shock after cardiac surgery: A prospective, controlled study. Intensive Care Med 2009;35:489–97.
11. Barnes TJ, Hockstein MA, Jabaley CS. Vasoplegia after cardiopulmonary bypass: A narrative review of pathophysiology and emerging targeted therapies. SAGE Open Med 2020;8:2050312120935466.
12. Weis F, Kilger E, Beiras-Fernandez A, Nassau K, Reuter D, Goetz A, et al. Association between vasopressor dependence and early outcome in patients after cardiac surgery. Anaesthesia 2006;61:938–42.
13. Dayan V, Cal R, Giangrossi F. Risk factors for vasoplegia after cardiac surgery: A meta-analysis. Interact Cardiovasc Thorac Surg 2019;28:838–44.
14. van Vessem ME, Palmen M, Couperus LE, Mertens B, Berendsen RR, Tops LF, et al. Incidence and predictors of vasoplegia after heart failure surgery. Eur J Cardiothorac Surg 2017;51:532–8.
15. Chatterjee S. Management of vasoplegic shock in left ventricular assist device insertion procedures. Tex Heart Inst J 2023;50:e238172.

16. Levin MA, Lin HM, Castillo JG, Adams DH, Reich DL, Fischer GW. Early on-cardiopulmonary bypass hypotension and other factors associated with vasoplegic syndrome. Circulation 2009;120:1664–71.
17. Sun X, Zhang L, Hill PC, Lowery R, Lee AT, Molyneaux RE, et al. Is incidence of postoperative vasoplegic syndrome different between off-pump and on-pump coronary artery bypass grafting surgery? Eur J Cardiothorac Surg 2008;34:820–5.
18. Sun X, Boyce SW, Herr DL, Hill PC, Zhang L, Corso PJ, et al. Is vasoplegic syndrome more prevalent with open-heart procedures compared with isolated on-pump CABG surgery? Cardiovasc Revasc Med 2011;12:203–9.
19. Anastasiadis K, Antonitsis P, Haidich AB, Argiriadou H, Deliopoulos A, Papakonstantinou C. Use of minimal extracorporeal circulation improves outcome after heart surgery; A systematic review and meta-analysis of randomized controlled trials. Int J Cardiol 2013;164:158–69.
20. Vincent JL, De Backer D. Circulatory shock. N Engl J Med 2013;369:1726–34.
21. Hernández G, Ospina-Tascón GA, Damiani LP, Estenssoro E, Dubin A, Hurtado J, et al. Effect of a resuscitation strategy targeting peripheral perfusion status vs serum lactate levels on 28-day mortality among patients with septic shock: The ANDROMEDA-SHOCK randomized clinical trial. JAMA 2019;321:654–64.
22. Ltaief Z, Schneider AG, Liaudet L. Pathophysiology and clinical implications of the veno-arterial PCO2 gap. Crit Care 2021;25:318. Erratum in: Crit Care 2024;28:110.
23. Lamontagne F, Meade MO, Hébert PC, Asfar P, Lauzier F, Seely AJE, et al. Higher versus lower blood pressure targets for vasopressor therapy in shock: A multicentre pilot randomized controlled trial. Intensive Care Med 2016;42:542–50.
24. Messina A, Lionetti G, Foti L, Bellotti E, Marcomini N, Cammarota G, Bennett V, et al. Mini fluid chAllenge aNd End-expiratory occlusion test to assess flUid responsiVEness in the opeRating room (MANEUVER study): A multicentre cohort study. Eur J Anaesthesiol 2021;38:422–31.
25. Mueller MM, Van Remoortel H, Meybohm P, Aranko K, Aubron C, Burger R, et al. Patient blood management: Recommendations from the 2018 Frankfurt Consensus Conference. JAMA 2019;321:983–97.
26. Tibi P, McClure RS, Huang J, Baker RA, Fitzgerald D, Mazer CD, et al. STS/SCA/AmSECT/SABM update to the clinical practice guidelines on patient blood management. Ann Thorac Surg 2021;112:981–1004.
27. Alamami A, Rahhal A, Alqudah B, Shebani A, Alammora A, Mohammad H, et al. Clinical outcomes of angiotensin II therapy in vasoplegic shock: A systematic review and meta-analysis. Life (Basel) 2024;14:1085.
28. Asfar P, Meziani F, Hamel JF, Grelon F, Megarbane B, Anguel N, et al. High versus low blood-pressure target in patients with septic shock. N Engl J Med 2014;370:1583–93.
29. Lamontagne F, Day AG, Meade MO, Cook DJ, Guyatt GH, Hylands M, et al. Pooled analysis of higher versus lower blood pressure targets for vasopressor therapy septic and vasodilatory shock. Intensive Care Med 2018;44:12–21.
30. Li Y, Li H, Zhang D. Timing of norepinephrine initiation in patients with septic shock: A systematic review and meta-analysis. Crit Care 2020;24:488.
31. Levy B, Bastien O, Karim B, Cariou A, Chouihed T, Combes A, et al. Experts' recommendations for the management of adult patients with cardiogenic shock. Ann Intensive Care 2015;5:52.
32. Levy B, Perez P, Perny J, Thivilier C, Gerard A. Comparison of norepinephrine-dobutamine to epinephrine for hemodynamics, lactate metabolism, and organ function variables in cardiogenic shock. A prospective, randomized pilot study. Crit Care Med 2011;39:450–5.
33. Sponholz C, Schelenz C, Reinhart K, Schirmer U, Stehr SN. Catecholamine and volume therapy for cardiac surgery in Germany--results from a postal survey. PLoS One 2014;9:e103996.
34. Argenziano M, Chen JM, Choudhri AF, Cullinane S, Garfein E, Weinberg AD, et al. Management of vasodilatory shock after cardiac surgery: identification of predisposing factors and use of a novel pressor agent. J Thorac Cardiovasc Surg 1998;116:973–80.
35. Hajjar LA, Vincent JL, Barbosa Gomes Galas FR, Rhodes A, Landoni G, Osawa EA, et al. Vasopressin versus norepinephrine in patients with vasoplegic shock after cardiac surgery: The VANCS randomized controlled trial. Anesthesiology 2017;126:85–93.
36. Dünser MW, Bouvet O, Knotzer H, Arulkumaran N, Hajjar LA, Ulmer H, et al. Vasopressin in cardiac surgery: A meta-analysis of randomized controlled trials. J Cardiothorac Vasc Anesth 2018;32:2225–32.
37. McIntyre WF, Um KJ, Alhazzani W, Lengyel AP, Hajjar L, Gordon AC, et al. Association of vasopressin plus catecholamine vasopressors vs catecholamines alone with atrial fibrillation in patients with distributive shock: A systematic review and meta-analysis. JAMA 2018;319:1889–900.
38. Guarracino F, Habicher M, Treskatsch S, Sander M, Szekely A, Paternoster G, et al. Vasopressor therapy in cardiac surgery-an experts' consensus statement. J Cardiothorac Vasc Anesth 2021;35:1018–29.
39. Roumpf SK, Hunter BR. Does the addition of vasopressin to catecholamine vasopressors affect outcomes in patients with distributive shock? Ann Emerg Med 2019;74:153–5.
40. Khanna A, English SW, Wang XS, Ham K, Tumlin J, Szerlip H, et al. Angiotensin II for the treatment of vasodilatory shock. N Engl J Med 2017;377:419–30.
41. Chow JH, Wittwer ED, Wieruszewski PM, Khanna AK. Evaluating the evidence for angiotensin II for the treatment of vasoplegia in critically ill cardiothoracic surgery patients. J Thorac Cardiovasc Surg 2022;163:1407–14.
42. Coulson TG, Miles LF, Serpa Neto A, Pilcher D, Weinberg L, Landoni G, et al. A double-blind randomised feasibility trial of angiotensin-2 in cardiac surgery. Anaesthesia 2022;77:999–1009.
43. Pushparajah Mak RS, Liebelt EL. Methylene blue: An antidote for methemoglobinemia and beyond. Pediatr Emerg Care 2021;37:474–7.
44. Perdhana F, Kloping NA, Witarto AP, Nugraha D, Yogiswara N, Luke K, et al. Methylene blue for vasoplegic syndrome in

cardiopulmonary bypass surgery: A systematic review and meta-analysis. Asian Cardiovasc Thorac Ann 2021;29:717–28.
45. Weinberg JB, Chen Y, Jiang N, Beasley BE, Salerno JC, Ghosh DK. Inhibition of nitric oxide synthase by cobalamins and cobinamides. Free Radic Biol Med 2009;46:1626–32.
46. Shapeton AD, Mahmood F, Ortoleva JP. Hydroxocobalamin for the treatment of vasoplegia: A review of current literature and considerations for use. J Cardiothorac Vasc Anesth 2019;33:894–901.
47. Carr AC, Shaw GM, Fowler AA, Natarajan R. Ascorbate-dependent vasopressor synthesis: A rationale for vitamin C administration in severe sepsis and septic shock? Crit Care 2015;19:418.
48. Rodemeister S, Duquesne M, Adolph M, Nohr D, Biesalski HK, Unertl K. Massive and long-lasting decrease in vitamin C plasma levels as a consequence of extracorporeal circulation. Nutrition 2014;30:673–8.
49. Lamontagne F, Masse MH, Menard J, Sprague S, Pinto R, Heyland DK, et al. Intravenous Vitamin C in adults with sepsis in the intensive care unit. N Engl J Med 2022;386:2387–98.
50. Annane D, Renault A, Brun-Buisson C, Megarbane B, Quenot JP, Siami S, et al. Hydrocortisone plus fludrocortisone for adults with septic shock. N Engl J Med 2018;378:809–18.
51. Annane D. Cortisol replacement for severe sepsis and septic shock: What should I do? Crit Care 2002;6:190–1.
52. Sprung CL, Annane D, Keh D, Moreno R, Singer M, Freivogel K, et al. Hydrocortisone therapy for patients with septic shock. N Engl J Med 2008;358:111–24.
53. Venkatesh B, Finfer S, Cohen J, Rajbhandari D, Arabi Y, Bellomo R, et al. Adjunctive glucocorticoid therapy in patients with septic shock. N Engl J Med 2018;378:797–808.
54. Whitlock RP, Devereaux PJ, Teoh KH, Lamy A, Vincent J, Pogue J, et al. Methylprednisolone in patients undergoing cardiopulmonary bypass (SIRS): A randomised, double-blind, placebo-controlled trial. Lancet 2015;386:1243–53.
55. Dieleman JM, Nierich AP, Rosseel PM, van der Maaten JM, Hofland J, Diephuis JC, et al. Intraoperative high-dose dexamethasone for cardiac surgery: A randomized controlled trial. JAMA 2012;308:1761–7.
56. Diab M, Lehmann T, Bothe W, Akhyari P, Platzer S, Wendt D, et al. Cytokine hemoadsorption during cardiac surgery versus standard surgical care foriınfective endocarditis (REMOVE): Results from a multicenter randomized controlled Trial. Circulation 2022;145:959–68.
57. Goetz G, Hawlik K, Wild C. Extracorporeal cytokine adsorption therapy as a preventive measure in cardiac surgery and as a therapeutic add-on treatment in sepsis: An updated systematic review of comparative efficacy and safety. Crit Care Med 2021;49:1347–57.