

Ageing Population

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Nathan S. Cutler

Commander
Medical Corps
United States Navy
Department of Pulmonary and
Critical Care Medicine
Naval Medical Center
Portsmouth, Virginia

Nate.cutler@outlook.com


Jason W. Signorelli

Critical Care Medicine Fellow
Department of Anesthesiology
Section on Critical Care
Medicine
Wake Forest School of Medicine
Wake Forest Baptist Medical
Center
Winston-Salem, North Carolina

Jsignore@wakehealth.edu


Patrick M. Wieruszewski

Pharmacist
Cardiothoracic Surgery/Anes-
thesia ICU
Department of Pharmacy
Mayo Clinic
Rochester, MN

Multidisciplinary Epidemiology
and Translational Research
in Intensive Care (METRIC)
Laboratory
Mayo Clinic
Rochester, MN

wieruszewski.patrick@mayo.edu


Marc Reichert

Clinical Manager
Critical Care, Transplant, Emer-
gency Department
Department of Pharmacy
Wake Forest Baptist Medical
Center
Winston-Salem, North Carolina

mreichert@wakehealth.edu


Ashish K. Khanna

Associate Professor
Section Head for Research
Department of Anesthesiology
Section on Critical Care
Medicine
Wake Forest School of Medicine
Wake Forest Baptist Medical
Center
Winston-Salem, North Carolina
Outcomes Research Consortium
Cleveland, OH

akhanna@wakehealth.edu

Angiotensin II in Post Cardio- pulmonary Bypass Vasoplegia – The Experience So Far

Post cardiopulmonary bypass vasoplegia is common, and associated with poor outcomes. Traditional management strategies involving escalating doses of catecholamines, vasopressin and adjuncts such as methylene blue and hydroxycobalamin or ascorbic acid have not shown promising results. Since ACE enzyme dysfunction, high serum renin and low endogenous angiotensin II may be a common problem in these patients, synthetic Angiotensin II is a physiologically viable option. Both post hoc results from the ATHOS-3 trial and prospective outcomes from the real world use of Angiotensin II has shown encouraging results. More data is needed to map the renin angiotensin cascade in post cardiac surgery patients with vasoplegia and large prospective randomised trials should be done to validate these findings.

Introduction

Postoperative vasoplegia is a form of distributive shock, physiologically similar to the shock caused by sepsis. It is diagnosed when hypotension after surgery is due to low systemic vascular resistance (SVR), with cardiac output either preserved or adequately augmented, and adequate circulatory volume. The distinction is important since postoperative shock may be multifactorial, especially after cardiac surgery. Though estimates of prevalence vary, the condition affects 20% or more of patients who have undergone operations requiring cardiopulmonary bypass (CPB), particularly those with predisposing factors such as longer bypass times and higher comorbid disease burden (Shaefi et al. 2018). Patients with vasoplegia after CPB are at increased risk of death and other major complications (Busse et al. 2020).

Pathophysiology

The mechanism for vasoplegia due to CPB is not precisely known, but is thought to be multifactorial. This begins with an inflammatory response to the bypass circuit

and involves ischaemia-reperfusion injury, cytokine release, and excess production of vasodilatory molecules such as nitric oxide (NO), with eventual depletion of endogenous vasopressors including angiotensin II (ANG-2) (Shaefi et al. 2018). Further, prolonged exposure to the bypass circuit is known to impair angiotensin-converting enzyme (ACE) activity in pulmonary epithelia resulting in a relative endogenous ANG-2 deficiency, and potentially diverting the renin-angiotensin-aldosterone system (RAAS) to pathways which produce vasodilatory metabolites including angiotensin 1-7. Lastly, hydrogen sulfide, an additional vasodilatory mediator, is upregulated during CPB and may inhibit residual ACE activity (and thereby ANG-2 generation) as well as further activate NO generating pathways (Lambden et al. 2018). Treatment of the condition can be challenging and is fraught with potential adverse effects, particularly in the immediate postoperative period when the myocardium is already under significant stress. The most common interventions, similar to those for other distributive shock states, are volume

resuscitation, catecholamine vasopressors (typically norepinephrine [NE]), and arginine vasopressin (AVP). In severe cases, the vasculature becomes poorly responsive to NE (Hajjar et al. 2017). NE may also be limited by toxic potential when very high doses are required, specifically via end-organ injury from peripheral and mesenteric vasoconstriction and tachyarrhythmia due to excessive beta stimulation of the myocardium (Chawla et al. 2014). AVP also is not universally effective; in one single centre retrospective study, only 45% of 938 patients receiving catecholamines for septic shock who were given fixed-dose AVP were classified as AVP “responders,” defined as able to maintain MAP \geq 65 mmHg while permitting a reduction in catecholamine dose (Sacha et al. 2018).

Lastly, excessive fluids can also become problematic, as the extravasation of excess intravenous crystalloid leads to dysfunction in congested organs (Claire-Del Granado and Mehta 2016). When the therapeutic benefit of these traditional therapies is exceeded, adjunctive therapies such as methylene blue, hydroxocobalamin, high dose ascorbic acid, and hydrocortisone have been used in efforts to augment blood pressure or reduce the requirement for vasopressors. The data supporting adjuncts is minimal and the level of evidence is poor for most.

Methylene blue and hydroxocobalamin are thought to work by inhibiting excess synthesis of NO and to serve as NO scavengers (Weinberg et al. 2009; Hosseini et al. 2016). Use of methylene blue to improve haemodynamics during post-CPB vasoplegia is supported by several small prospective trials (Hosseini et al. 2016), but data regarding outcomes is contradictory. Its use has been retrospectively tied to worse outcomes (Weiner et al. 2013), and there are several case reports of serotonin syndrome due to methylene blue’s monoamine oxidase inhibitor (MAOI) activity (Schumacher et al. 2017). It is also a cause of haemolysis in patients with G6PD deficiency. Hydroxocobalamin is less proven

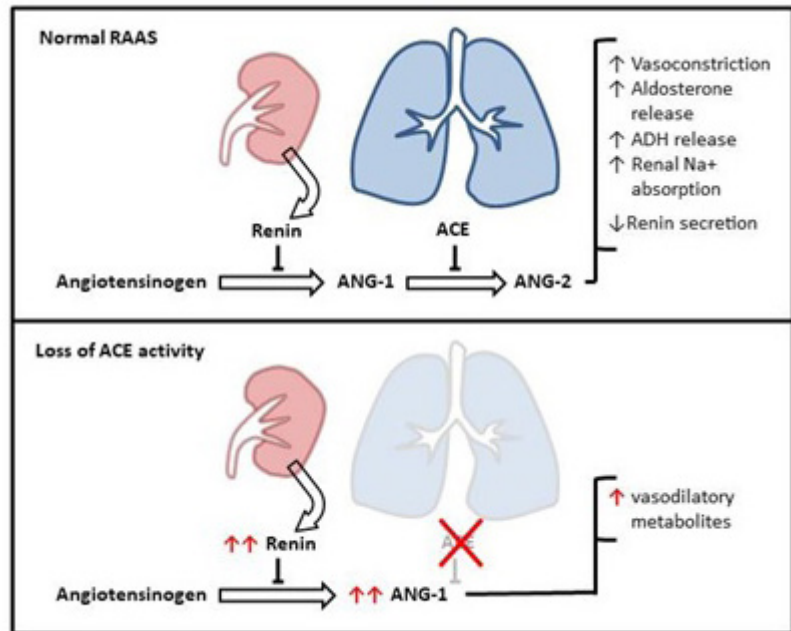


Figure 1. Normal RAAS versus loss of ACE activity. ACE= Angiotensin Converting Enzyme-1; ADH = Antidiuretic hormone; ANG-1=Angiotensin 1; ANG-2= Angiotensin II. RAAS= Renin-angiotensin-aldosterone system. Source: Santos et al. 2019; Bussard and Busse 2018.

than methylene blue, but has shown some promise in observational studies (Shapeton et al. 2019). High dose ascorbic acid, of recent interest in the treatment of septic shock, has demonstrated a potential vasopressor sparing effect for post-CPB vasoplegia in a case series (Wieruszewski et al. 2018), but was not associated with faster resolution of shock in a small prospective study (Yanase et al. 2020). Intravenous hydrocortisone is often added during treatment for severe refractory vasoplegia, with supporting data largely extracted from the use of corticosteroids in septic shock, but has not been prospectively studied for vasoplegia due to CPB. The success of these adjunctive therapies is variable. Often, multiple are used concurrently, and in some cases postoperative hypotension is refractory even to high doses of vasopressors and adjunctive therapies.

Role of the Renin-Angiotensin-Aldosterone System

The renin-angiotensin-aldosterone system (RAAS) plays a key role in blood pressure

homeostasis, and is of increasing interest as an additional potential target in the treatment of shock. ANG-2, a naturally occurring hormone in this system, has activity throughout the cardiovascular, renal, endocrine, and nervous systems. In addition to the regulatory role in aldosterone production, ANG-2 has direct arterial and venous vasoconstriction activity via Type 1 ANG-2 receptors in the vascular smooth muscle (Chawla et al. 2014). Use of ANG-2 in the treatment of shock has increased following the Angiotensin II for the Treatment of High Output Shock (ATHOS) trials, which found the addition of ANG-2 effective in patients with vasodilatory shock, for increasing mean arterial pressure (MAP) and allowing the reduction in doses of other vasopressor agents (Khanna et al. 2017). Endogenous ANG-2 begins as angiotensinogen, a precursor protein produced and constitutively released by the liver, which is catalysed into ANG-1 by renin, which is primarily secreted from the kidneys. ANG-1 is then converted to ANG-2 by angiotensin

converting enzyme-1 (ACE), an membrane-bound enzyme predominantly found on lung endothelium (**Figure 1**) (Santos et al. 2019). In the setting of profound inflammation, relative ANG-2 deficiency is thought to occur through decreased ACE activity, either by signaling mechanisms or due to pulmonary endothelial injury, furthering the state of shock (Bellomo et al. 2020a). While decreased ACE activity is difficult to measure directly due to the enzyme being membrane-bound, increased ANG-1 to ANG-2 ratio has been proposed as a surrogate test, and in recent studies has been linked to catecholamine-resistant vasodilatory shock and poor outcomes (Bellomo et al. 2020a).

Renin release, the rate limiting step in the RAAS cascade, receives negative feedback from ANG-2 (Bussard and Busse 2018), so that renin levels would be expected to increase in the setting of ANG-2 deficiency. Renin levels may be easier and more practical to check than an ANG-1/ANG-2 ratios, and these have been found to correlate (Bellomo et al. 2020b). In a recent prospective observational study, renin levels were found to be useful as a marker of tissue perfusion, and elevated renin levels were prognostic for increased ICU mortality (Gleeson et al. 2019). While it is unclear to what extent refractory shock is due directly to decreased ANG-2 activity or to increased ANG-2 precursors and their metabolites, both renin and ANG-1 appear to be suppressible by exogenous ANG-2 (Bellomo et al. 2020b). Further, in a post hoc analysis of the ATHOS-3 trial, treatment with ANG-2 was associated with reduced 28-day mortality among patients with renin levels above the study population median (Bellomo et al. 2020b).

Patients undergoing CPB may be particularly vulnerable to relative deficiency in ANG-2. In addition to the inflammatory cascade provoked by CPB, bypassing the pulmonary circulation effectively bypasses the primary site of ACE activity, which may result in less catalysis of ANG-1 to ANG-2,

at least temporarily (Busse et al. 2020). Elevation in plasma renin activity has been observed both during and after CPB (Lehot et al. 1992; Barta et al. 1980) though the precise relevance of this to vasoplegia is not clear. ATHOS-3, which primarily enrolled patients with septic shock, did include 19 patients with postoperative vasoplegia, of whom 9 received ANG-2 after CPB compared to 7 who received placebo after CPB. The remaining 3 of 19 did not undergo CPB. In a post hoc analysis, target MAP was achieved in the majority of the ANG-2 group (8 out of 9

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subjects), compared none in the placebo group (Klijian et al. 2020). Of note, the authors of that study confirmed circulating levels of ANG-1 and the median ANG-1/ANG-2 ratios in the group were elevated relative to healthy controls. Although ACE inhibitor use prior to CPB has been cited in some studies as a risk factor for vasoplegia, only 3 of the 19 had prior exposure to ACE inhibitors. Renin levels were not reported in this analysis.

Review of Literature

The United States Food and Drug Administration (U.S. FDA) approved synthetic human ANG-2 in December 2017. Prior to this, the agent had been approved for compassionate use in the summer of 2017. The European Medicines Agency (EMA) allowed use of the drug in summer 2019. Therefore, published data with this new vasopressor in the setting of post CPB vasoplegia is limited to the last two years. PubMed, Ovid, and Web of Science databases were searched for articles published

through Sept 2020, with the search terms “vasoplegia,” “cardiopulmonary bypass,” and “angiotensin.” Any articles were considered which addressed the use of synthetic human ANG-2 for the treatment of vasoplegia related to CPB. The authors identified a total of 15 articles, of which 4 were individual case reports, 2 were small case series, 5 were review articles on post-CPB vasoplegia which mentioned the potential of ANG-2 as an adjunctive therapy, one was a review article on ANG-2 that mentioned its potential use following CPB, one was a post hoc analysis of CPB patients enrolled in ATHOS-3, and one was a retrospective review of ANG-2 use which included one patient who received the drug after CPB. Additionally, a retrospective study was identified which included 270 patients who received ANG-2 for refractory shock, of which 55 occurred after cardiothoracic surgical procedures, though these were not analysed separately (Wieruszewski et al. 2020).

From the case reports, case series, and ATHOS-3 post hoc analysis, we assessed patient age, sex, type of surgery, start time and reported effect of ANG-2, and any postoperative events discussed (**Table 1**). Among these cases, use of ANG-2 to treat vasoplegia during or after CPB is reported in 22 patients, with some demonstrating dramatically improved haemodynamics or reduced need for other vasopressors, and some for whom the apparent effect was more subtle. This variable response is consistent with the findings of the retrospective study mentioned, which identified 181 of 270 total patients (67%) to be “responders” to ANG-2, meaning MAP \geq 65 mmHg was achieved and vasopressor doses were stabilised or reduced after initiating ANG-2; 159 (59%) of the total cases were able to reduce vasopressor doses once ANG-2 was initiated (Wieruszewski et al. 2020). Predicting which patients will most benefit is of great interest; in this study responders were significantly more likely to be receiving AVP, and to

have lower lactate levels, and those who responded were more likely to survive at 30 days (Wieruszewski et al. 2020)

Aside from the ATHOS-3 subgroup, components of the RAAS were not reported in the majority of cases identified. Among the case reports, however, one patient who suffered refractory vasoplegia after pneumonectomy had renin levels checked serially, including prior to initiation of ANG-2. While markedly elevated initially, renin levels trended downward during the ANG-2 infusion, closely mirroring the downward trend in catecholamine requirement (Trethowan et al. 2020). In a separate case series, one heart transplant patient was tested and found to have significantly elevated renin activity both during and after ANG-2 infusion, and this patient appeared to have a very favourable response to ANG-2 (Cutler et al. 2020). Finally, one patient was presumed to have abnormally low levels of renin after coronary artery

bypass graft (CABG) due to history of bilateral nephrectomies, and this patient also appeared to have a very favourable response (Cutler and Khanna 2020). All three of these cases could be postulated to have a relative ANG-2 deficiency prior to treatment, two due to decreased ACE activity and one due to decreased renin activity. Of note, one additional article was identified which described a series of 7 patients who received ANG-2 for shock in conjunction with extracorporeal membrane oxygenation (ECMO), which shares some physiology with CPB (Ostermann et al. 2018). The authors found overall that ANG-2 permitted reduction in dose of catecholamine vasopressors, reporting one case of digital ischaemia and one case of bowel ischaemia and death among that cohort, none of which were attributed to ANG-2. Some of those patients received ANG-2 in the context of the ATHOS-3 trial, including one who had undergone CPB earlier in

their hospital course. However, CPB was apparently not associated with vasoplegia in that case, so it does not appear in Table 1 and was not included in the post hoc by Klijian et al. (2020).

The burden of organ injury is relatively high among available published cases of post CPB vasoplegia, which is likely a consequence of current ANG-2 use primarily as a rescue therapy in refractory shock. Reported complications were consistent with what might be expected in cases of severe shock, with none attributed to ANG-2 by the authors cited. In ATHOS-3, thrombotic events occurred more frequently overall in the ANG-2 group (12.9%) than the placebo group (5.1%), and Wieruszewski and colleagues identified venous thromboembolism in 4 of 270 patients during their retrospective study (Wieruszewski et al. 2020). Although ANG-2 may have a pro-thrombotic effect at receptors in certain cell types including the vascular endothelium (Bauer et al. 2018), no arterial or venous thromboses were reported among the group of cases reported in Table 1. The relevance of this in the context of cardiac surgical patients who may already be receiving antithrombotics for new grafts or devices, remains unclear.

Angiotensin II use protocol at the Wake Forest University Medical Center

The authors present the current protocol for the use of ANG-2 in the treatment of post CPB vasoplegia at our tertiary care 900 bedded university hospital. Eligible patients are adults who have undergone cardiac surgery and had vasoplegia intraoperatively or postoperatively, which was not responsive to traditional high dose vasopressors, and which in the past would lead to the administration of methylene blue as salvage therapy at our facility. Vasoplegia in our population is defined as an inability to maintain a MAP \geq 65 mmHg in the presence of high dose vasopressors, as measured via invasive arterial blood pres-

Authors	Year	Study type	Case Numbers (n)	Age, sex	Procedure	Start POD #	Effect	Postoperative events**
Evans et al.	2019	Case report	1	81, M	CABG	0	Improved MAP, reduced NE	-
Wieruszewski et al.	2019a	Case series	4	47, M 57, M 37, M 64, M	Heart transplant CABG/AVR Lung Transplant LVAD implant	0 0 8 0	Reduced NE Improved MAP, reduced NE Reduced NE Transiently reduced NE	- Digital ischaemia - Death
Wieruszewski et al.	2019b	Case report	1	34, F	Heart and Liver Transplant	14	Improved MAP, reduced NE	-
Wong et al.	2019	Retrospective review	1	76, M	MV replacement	0	Brief infusion, no apparent effect	-
Cutler and Khanna	2020	Case report	1	70, M	CABG	0	Improved MAP, reduced NE	Ischaemic bowel
Trethowan et al.	2020	Case Report	1	57, M	Pneumonectomy	0	Improved MAP, reduced NE	VAP
Cutler et al.	2020	Case series	4	62, M 61, M 69, M 60, M	Heart Transplant Heart Transplant Heart Transplant Heart Transplant	0 0* 0 0	Transiently stabilised NE Transiently stabilised NE Reduced NE Transiently stabilised NE	Optic neuropathy, wound complication Renal failure, VAP, wound complication Liver injury Liver injury
Klijian et al.	2020	Post-hoc ATHOS-3 subgroup	9 (vs. 7 placebo)	57, M 48, M 64, M 67, M 80, M 72, M 60, M 52, M 88, M	TV and MV repair MV replacement CABG CABG CABG and MV replacement AV replacement CABG AV replacement AV replacement	1 1 1 1 1 1 1 1 1	Transiently improved MAP Improved MAP, reduced NE Improved MAP, reduced NE Improved MAP, reduced NE Improved MAP, reduced NE Improved MAP, reduced NE Improved MAP, reduced NE Improved MAP, reduced NE Improved MAP, reduced NE	- - - - VF arrest Liver and kidney injury, septic shock Cardiogenic shock, death - -

Table 1. Summary of Cases for use of ANG-2 after CPB since U.S. FDA approval
 ANG-2 = Angiotensin II. ATHOS-3 = ANG-2 for the Treatment of High Output Shock trial. AVR = Aortic valve replacement. CABG = Coronary artery bypass graft. CPB = Cardiopulmonary bypass. LVAD = Left ventricular assist device. MAP = Mean arterial pressure. MV = Mitral valve. NE = norepinephrine requirement. POD= postoperative day. TV = Tricuspid Valve. VF = Ventricular fibrillation. *Wieruszewski and colleagues recently report using ANG-2 in 55 patients post CPB, however the data published is part of a retrospective multi-institutional effort of all comers with vasodilatory shock of different etiologies. The reader is referred to [Wieruszewski et al. 2020] for complete details. *ANG-2 was initiated intraoperatively prior to wean from CPB. **None of these events are complications attributed to ANG-2 use.

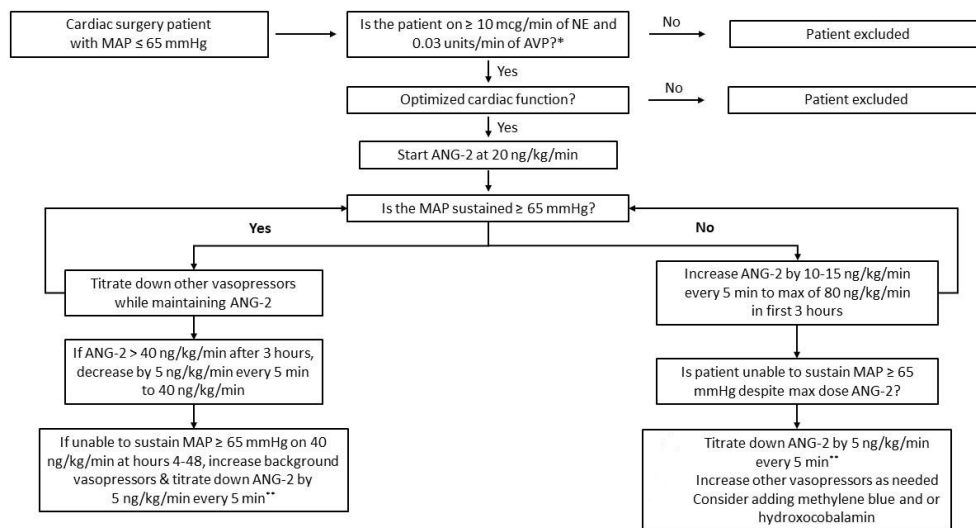


Figure 2. ANG-2 = Angiotensin II. AVP = Arginine vasopressin. NE = norepinephrine. *Total 0.2 mcg/kg/min NE equivalents for an 80kg patient.

**Leave ANG-2 at lowest dose 20ng/kg/min and let run out over 24 hours

sure monitoring, despite optimised cardiac function. The definition of optimised cardiac function has been loosely worded to allow for the clinical judgement of the cardiac intensivists and cardiac surgical teams. This would be a combination of the exclusion of low cardiac output and or hypovolaemic states, and the clinical background of a vasoplegic state (prolonged bypass run, pre-existing reduced ejection fraction, patients with infective endocarditis, or those with a mechanical circulatory support device, to name a few). High dose vasopressors are defined as NE ≥ 10 mcg/min plus AVP ≥ 0.03 unit/min (total NE equivalent ≥ 0.2 mcg/kg/min for an 80 kg patient). All clinical care providers were provided training regarding initiation and titration of ANG-2 (**Figure 2**). Upon meeting inclusion criteria ANG-2 is initiated at 20 ng/kg/min and up titrated to a maximum of 80 ng/kg/min, within the first three hours, with a target MAP of ≥ 65 mmHg. This dose is maintained for up to three hours as needed and then titrated downward to a maximum maintenance dose of 40 ng/kg/min for up to 48 hours total. In our previous experience and based on published literature most patients are able to sustain adequate blood pressures at a dose of ANG-2 between 20-40ng/kg/

min. Other vasopressors are maintained at their pre-ANG-2 initiation dose during this time. If the patient is unable to maintain MAP ≥ 65 mmHg while on ANG-2 (at a maximum of 80ng/kg/min) within 4 hours of initiation, they are considered to have treatment failure, and ANG-2 is titrated off to a low dose (with the aim of stopping at 24 hours) while other interventions continue. These could include the escalation of catecholamine vasopressors and AVP, and the use of methylene blue and or hydroxycobalamin. If patients are determined to respond to ANG-2, then other vasopressors are decreased as tolerated until the patient remains solely on ANG-2. If allowable, serum renin and lactate levels are drawn at initiation of ANG-2 and at regular intervals during the 48 hours afterwards.

Future work

Early data from the prospective utilisation of ANG-2 and post-hoc analysis of the ATHOS-3 population have shown very encouraging signals for use in post-CPB vasoplegia. There is a well-established pathophysiologic cascade of events that lead to dysfunctional ACE and low endogenous ANG-2 in post CPB patients. The data obtained from our protocol will be

reviewed annually for research and quality control purposes. The best evidence requires a large randomised double-blind placebo-controlled trial of ANG-2 versus standard of care in this population. However, we hope for a large dataset of prospective and protocolised ANG-2 use in established post CPB vasoplegia patients. By mapping biomarkers, we aim to establish the need for specific vasopressor therapies in these patients, and in conjunction with parallel work at other institutions, anticipate the ability to identify populations for whom the addition of ANG-2 will be most beneficial. Knowing the well-established utility of serum renin as a prognostic marker in shock, personalised use of vasopressors that target the RAAS should be the unstated rule in most critically ill patients. Herein, future research should focus on detailing all aspects of the RAAS, including angiotensin 1-7 and angiotensin 2-9, along with renin, ANG-1, and ANG-2 levels in several different clinical phenotypes of shock.

Conclusion

Vasoplegia is relatively common following cardiothoracic surgery, and is associated with significant morbidity. Treatment of severe cases can be challenging. ANG-2 is of increasing interest in this role for

improving blood pressure and reducing the requirement for catecholamine vasopressors, but its appropriate place in the hierarchy of adjunctive therapies is not yet clear. Some cases described in the literature have experienced dramatic improvement, and the limited prospective data from ATHOS-3 is promising. ANG-2 may be uniquely beneficial to patients following CPB, particularly in subgroups of patients with specific patterns of RAAS dysfunction. Potentially, markedly abnormal renin levels will indicate greatest need or benefit, but further data is needed to clarify this in the setting of CPB. Personalised vasopressor management is the need of the hour, and the one-size-fits-all approach to increasing blood pressure in the ICU may become a thing of the past.

Conflict of Interest

The views expressed in this article reflect the results of research conducted by the authors and do not necessarily reflect the official policy or position of the Department of the Navy, Department of Defense, nor the United States Government.

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Key Points

- Postoperative vasoplegia is a form of distributive shock, physiologically similar to the shock caused by sepsis.
- Though estimates of prevalence vary, the condition affects 20% or more of patients who have undergone operations requiring cardiopulmonary bypass (CPB).
- Treatment of the condition can be challenging and is fraught with potential adverse effects, particularly in the immediate postoperative period when the myocardium is already under significant stress.
- The most common interventions, similar to those for other distributive shock states, are volume resuscitation, catecholamine vasopressors (typically norepinephrine[NE]), and arginine vasopressin (AVP).
- The authors present the current protocol for the use of ANG-2 in the treatment of post CPB vasoplegia at our tertiary care 900 bedded university hospital.