Evaluating the evidence for angiotensin II for the treatment of vasoplegia in critically ill cardiothoracic surgery patients

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Feature Editor Note—Vasoplegia, also known as vasodilatory, distributive, or high-output shock, is a dilemma that is often encountered in the cardiothoracic surgical patient. Compared with the different types of shock, vasoplegia is the most common, complex, and ubiquitous, as it can be present at a late stage of any of the other shock types, or at any stage, in intrinsically vasodilatory shock, as seen in sepsis, anaphylaxis, adrenal insufficiency, and primary vasoplegia after cardiac surgery.

There has been ongoing interest in the pathophysiology of vasoplegia that has helped develop new therapeutic strategies beyond the catecholamine and arginine-vasopressin based approaches. Despite the relative common use of rescue agents such as methylene blue, high-dose hydroxycobalamin, and steroids without much scientific rigor, angiotensin II (Ang-2) has been recently introduced as a treatment for catecholamine resistant vasodilatory shock with a more comprehensive study approach.

In this invited expert opinion, a multi-institutional team lead by Dr Khanna describes eloquently the unique aspects of vasoplegia in the cardiothoracic surgery patient and the reasons why Ang-2 may be considered the rescue therapeutic choice for catecholamine-resistant vasoplegia in these patients. The article starts describing the role of the renin–angiotensin cascade in vasoplegia, including the unique aspects affecting the cardiothoracic surgical patient, the multicenter randomized controlled ATHOS-3 trial, which studied the role of Ang-2 in the treatment of high-output shock, and novel concepts such as high renin shock and its potential implications for shock management. The manuscript then glances over current published data on Ang-2 and the cardiothoracic surgery patient population, including a full section on extracorporeal membrane oxygenation. Finally, the authors describe current recommendations and dosing protocols, including a brief comment on value and cost. This article brings light to a new agent that appears promising as a complement to our current management strategies of vasoplegia and opens the door for more research in this important area of perioperative care.

Juan N. Pulido MD

THE ANGIOTENSIN II FOR THE TREATMENT OF HIGH-OUTPUT SHOCK (ATHOS-3) TRIAL AND THE ROLE OF THE RENIN-ANGIOTENSIN CASCADE IN VASOPLEGIA

Shock is frequently encountered during cardiothoracic surgery and in the cardiothoracic surgical intensive care unit and can result from a number of etiologies, including cardiogenic, hypovolemic, hemorrhagic, obstructive, and distributive. Vasoplegia, also clinically referred to as
vasodilatory shock, distributive shock, or high-output shock, occurs in 5% to 25% of patients undergoing cardiac surgery and is a form of shock characterized by decreased systemic vascular resistance and normal-to-high cardiac output. The pharmacologic treatment of vasoplegic shock in the postcardiectomy state has traditionally focused on interventions that modulate the sympathetic nervous and arginine–vasopressin systems. Norepinephrine (NEpi) and epinephrine are medications that target the sympathetic nervous system by binding to α1-receptors, whereas vasopressin targets the arginine–vasopressin system by binding to V1α receptors. The Vasopressin versus Norepinephrine in Patients With Vasoplegic Shock after Cardiac Surgery (VANCS) trial is the only randomized control trial examining the use of NEpi and vasopressin strategies in cardiac surgery. Although there was no difference in mortality between the groups (30-day mortality 15.9% NEpi vs 15.4% vasopressin, P = .98), there was significantly less development of atrial fibrillation in those receiving vasopressin (63.8% vasopressin vs 82.1% NEpi, P = .0014), which is appealing in the postcardiectomy state. Alternative therapies such as methylene blue and hydroxycobalamin, which inhibit the production of potent vasodilatory nitric oxide, have been applied in severe vasoplegia. These agents are not vasoconstrictors, have sparse supporting evidence, and are limited by increased risk for serotonin syndrome and interference with oximetry readings (methylene blue) and false blood leak alarm and interference with laboratory assays using colorimetry (hydroxycobalamin).

The renin–angiotensin–aldosterone system (RAAS) is a third system that has been recently studied and can be modulated with the administration of angiotensin II (Ang-2), which primarily binds to AT1 receptors to achieve vasoconstriction. Evidence for the use of Ang-2 in shock is primarily based on the ATHOS-3 randomized controlled trial, which studied patients in distributive shock who required vasopressors for more than 6 hours. The primary outcome of the study was the achievement of a target mean arterial pressure (MAP) by hour 3 of the study, which was defined as an increase by 10 mm Hg from baseline, or an increase to 75 mm Hg. Although much criticism has surrounded this MAP target, this target was set deliberately in conjunction with a special protocol assessment agreement by the US Food and Drug Administration to study Ang-2 efficacy as a vasopressor (and not as a catecholamine-sparing agent) without compromising patient safety and introducing confounding variables from the de-escalation of other vasoconstrictive agents. ATHOS-3 found that, compared with placebo, patients receiving Ang-2 had a decreased NEpi-equivalent dosing requirement for background vasopressors (Table 1) (−0.03 ng/kg/min Ang-2 vs 0.03 standard of care [SOC], P < .001) and achieved the target MAP at a greater rate than those receiving SOC (69.9% Ang-2 vs 23.4% SOC, P < .001). Post-hoc analyses of ATHOS-3 found that those patients with acute kidney injury requiring renalreplacement therapy (RRT) had significantly improved 28-day mortality (51.8% Ang-2 vs 70.8% SOC, P = .037) and greater rates of liberation from RRT (38% Ang-2 vs 15% SOC, P = .007) than those receiving SOC. Patients who are Ang-2 deficient, as indicated by a high ratio of angiotensin I (Ang-1) to Ang-2, have a significantly greater risk of mortality (hazard ratio, 0.54; P = .011). In addition, high levels of renin may indicate deficiencies in the RAAS, whereby the inability of angiotensin-converting enzyme (ACE) to convert Ang-1 into Ang-2 may lead to the production of vasodilatory substances such as angiotensin-(1-9) and angiotensin-(1-7). The production of these byproducts leads to further decreases in MAP, which stimulates the juxtaplomerular cells of the kidney to produce additional renin. Normal plasma renin concentration ranges from 3 to 33 pg/mL. A prespecified subanalysis of ATHOS-3 reported that high-renin shock (defined as renin levels greater than the study population median of 172.7 pg/mL) was associated with significantly greater 28-day mortality when it was treated with SOC vasopressors versus SOC vasopressors plus Ang-2 (69.9% SOC vs 50.9% Ang-2 + SOC, P = .01). Because of the adverse implications associated with shock in the cardiothoracic population, we aimed to examine and summarize the evidence for the use of Ang-2 in this unique population. Many of the studies on Ang-2 have focused on the general population of patients, and only 16 of the 344 patients in the ATHOS-3 study underwent cardiac surgery (this specific subset was examined in a separate post-hoc analysis). The incidence of shock in the perioperative period for patients undergoing cardiothoracic surgery is not infrequent, and longer cardiopulmonary bypass (CPB) time is consistently associated with vasoplegia. Here, the role of the RAAS deserves special mention. ACE, responsible for the conversion of Ang-1 to Ang-2, is primarily a pulmonary capillary endothelial ectoenzyme that is compromised by lung injury. This clinical corollary matches the bypass of the pulmonary circulation that is a key component of cardiopulmonary bypass in cardiothoracic surgery procedures. Postcardiopulmonary bypass vasoplegia may therefore be caused by a dysfunctional ACE and a consequent low

### TABLE 1. NEpi equivalency of commonly used vasopressors

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>NEpi-equivalent</th>
</tr>
</thead>
<tbody>
<tr>
<td>NEpi</td>
<td>0.1 μg/kg/min</td>
<td>0.1 μg/kg/min</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>0.1 μg/kg/min</td>
<td>0.1 μg/kg/min</td>
</tr>
<tr>
<td>Phenylephrine</td>
<td>1.0 μg/kg/min</td>
<td>0.1 μg/kg/min</td>
</tr>
<tr>
<td>Dopamine</td>
<td>15 μg/kg/min</td>
<td>0.1 μg/kg/min</td>
</tr>
<tr>
<td>Vasopressin</td>
<td>0.04 units/min</td>
<td>0.1 μg/kg/min</td>
</tr>
</tbody>
</table>

This conversion scale of NEpi equivalent dosing was developed based on the values used in the ATHOS-3 trial. NEpi, Norepinephrine.
endogenous Ang-2, with an increased renin and Ang-1 and a diversion to the ACE 2 pathway, leading to an increased production of angiotensin-(1-9) and angiotensin-(1-7), which further the vasodilatory effect via the MAS and AT2 receptors and increased nitric oxide production (Figure 1). Poor clinical outcomes of high renin shock have been previously confirmed in a series of investigations, and recently a change in renin has been further strongly correlated with postcardiac surgery acute kidney injury.13-16

**CASE REPORTS OF ANG-2 IN VASOPLEGIC SHOCK AFTER CARDIOTHORACIC SURGERY**

Outside of organized clinical trials, Ang-2 has been used in vasoplegic shock associated with CPB in a number of instances (Table 2).17-28 These case reports have included a wide variety of cardiothoracic surgical procedures, including coronary revascularization with and without valve intervention, isolated valve intervention, heart transplantations, combined heart/liver transplantation, lung transplantation, pneumonectomy, left ventricular assist device insertion, and thoracoabdominal aortic aneurysm repair.18 In many of the cases, methylene blue or hydroxycobalamin were administered before Ang-2, with resulting persistent vasoplegia leading to the decision to initiate Ang-2.18,21,22,25 In a couple of cases, methylene blue and/or hydroxycobalamin were administered at some point after Ang-2 for reportedly additional MAP stabilization and vasopressor-sparing effects.19,26 All published case reports reported similar hemodynamic effects, with rapid restoration of the MAP and reduction of catecholamines and other concomitant vasocostricting interventions. Despite many cases having a high catecholamine requirement—which is known to be associated with worse outcome—only a few deaths were reported, neither of which were deemed to be due to Ang-2 administration. Interestingly, 3 patients required extreme dosages of NEpi (3 μg/kg/min) during CPB and had Ang-2 initiated during CPB.21,22 In all 3 of these cases, Ang-2 was continued into the postoperative setting. No postoperative hypotensive events were reported, and all patients were separated from vasoconstrictors quickly. Although 1 patient died from sepsis, the other 2 were discharged from the intensive care unit by postoperative day 3 despite having high catecholamine requirements and profound hypotension intraoperatively.

Of course, the quality of evidence for therapeutic efficacy to be extrapolated from such studies relative to clinical trials is low. Despite this, many important details regarding drug

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**FIGURE 1.** Effect of lung injury on the RAAS. *Left*, Renin converts angiotensinogen to angiotensin I. ACE hydrolyzes angiotensin I into angiotensin II, which then acts on AT1 receptors to increase mean arterial pressure. *Right*, Lung injury may prevent the conversion of angiotensin I to angiotensin II by causing ACE, which is synthesized in the pulmonary endothelium, to become dysfunctional. This leads to an excess of renin and angiotensin I, which is then metabolized into angiotensin-(1-9) and angiotensin-(1-7) via ACE2. Angiotensin-(1-7) leads to agonism of MAS and AT2 receptors, which leads to vasodilatation. It also activates nitric oxide synthase, which leads to the production of nitric oxide, a potent vasodilator. ACE, Angiotensin-converting enzyme; AT1, angiotensin type 1; AT2, angiotensin type 2; MAS, MAS1 oncogene; MAP, mean arterial pressure.
ADULT OLT real membrane oxygenation; and ultrasound. With stimulation of AT1 receptor in the fresh hepatic graft, verified by serial liver function tests in the recipient, Ang-2 was used without clinical compromise of hepatic stellate cells promoting hepatic inflammation and fibrosis. In a combined heart and liver transplantation procedure, Ang-2 was more consistent with atheroemboli from an intra-aortic counter-pulsation device rather than arterial thrombi. Lastly, thrombotic events in published case reports are scarce and limited to 1 patient report of ischemic digits, although the authors report the presentation was more consistent with athereoemboli from an intra-aortic counter-pulsation device rather than arterial thrombi.

**ANG-2 IN EXTRACORPOREAL MEMBRANE OXYGENATION (ECMO)**

With the efficacy Ang-2 demonstrated in the general distribution shock population, interest has increased in the use of Ang-2 in ECMO patients. Safety may be gained from these reports relevant to perioperative cardiothoracic care and specific use scenarios that were excluded from clinical trials. First, in animal models, Ang-2 may increase portal venous pressures and activate hepatic stellate cells promoting hepatic inflammation and fibrosis. In a combined heart and liver transplantation recipient, Ang-2 was used without clinical compromise of the fresh hepatic graft, verified by serial liver function tests and ultrasound. With stimulation of AT1 receptor in the pulmonary vascular bed, there is theoretical concern of worsening the pulmonary vascular resistance with Ang-2. This may be troublesome in certain cardiothoracic surgical patients in whom minimizing exacerbations of elevated pulmonary pressures is of upmost importance. In a patient with vasoplegia after on-pump pneumonectomy with pulmonary artery systolic pressures in the 80-mm Hg range and mild right ventricular failure, there was no report of worsening after application of Ang-2. Similarly, in a fresh bilateral lung transplantation recipient, right atrial pressures did not meaningfully change with Ang-2, and graft function was preserved. Lastly, thrombotic events in published case reports are scarce and limited to 1 patient report of ischemic digits, although the authors report the presentation was more consistent with atheroemboli from an intra-aortic counter-pulsation device rather than arterial thrombi.

**TABLE 2. Summary of Ang-2 use in cardiothoracic perioperative care**

<table>
<thead>
<tr>
<th>Citation</th>
<th>Study type</th>
<th>Procedures</th>
<th>CPB time, min</th>
<th>Pre-AngVP requirement, µg/kg/min</th>
<th>Effect</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bennett et al, 2001</td>
<td>RCT</td>
<td>CABG (6), valve (3), CABG/valve (1)</td>
<td>58.9 ± 17.4</td>
<td>0</td>
<td>↑MAP and SVRI</td>
<td>No significant change in renal function</td>
</tr>
<tr>
<td>Chatterjee et al, 2020</td>
<td>Case report</td>
<td>TAAA repair</td>
<td>0</td>
<td>0.70</td>
<td>↑MAP, VP-sparing, avoidance of spinal ischemia</td>
<td>Discharged alive without reported Ang-2 side effects</td>
</tr>
<tr>
<td>Cutler et al, 2020</td>
<td>Case report</td>
<td>CABG</td>
<td>118</td>
<td>0.40</td>
<td>↑MAP, VP-sparing</td>
<td>Ischemic bowel, discharged alive</td>
</tr>
<tr>
<td>Cutler et al, 2020</td>
<td>Case series</td>
<td>OHT</td>
<td>279-448</td>
<td></td>
<td>Stabilized VP escalation, VP-sparing</td>
<td>Optic neuropathy, subdural hematoma, renal failure, pneumonia, liver injury. All discharged alive</td>
</tr>
<tr>
<td>Evans et al, 2019</td>
<td>Case report</td>
<td>CABG</td>
<td>107</td>
<td>0.41</td>
<td>↑MAP, VP sparing</td>
<td>Discharged alive without reported Ang-2 side effects</td>
</tr>
<tr>
<td>Geary et al, 1990</td>
<td>Case report</td>
<td>AVR</td>
<td>134</td>
<td>3.0</td>
<td>Restoration of MAP</td>
<td>Discharged alive without reported Ang-2 side effects</td>
</tr>
<tr>
<td>Klijian et al, 2021</td>
<td>Post-hoc</td>
<td>NR</td>
<td>NR</td>
<td>0.28 (0.20-0.47)</td>
<td>↑MAP, VP-sparing</td>
<td>One death from cardiogenic shock</td>
</tr>
<tr>
<td>Ostermann et al, 2018</td>
<td>Case series</td>
<td>ECMO, aortic dissection (1)</td>
<td>NR</td>
<td>0.26-1.55</td>
<td>↑MAP, VP-sparing</td>
<td>Digital and bowel ischemia, 1 death</td>
</tr>
<tr>
<td>Thaker et al, 1990</td>
<td>Case series</td>
<td>CABG</td>
<td>NR</td>
<td>3.0</td>
<td>↑ perfusion pressure</td>
<td>Discharged alive without reported Ang-2 side effects. Death from sepsis</td>
</tr>
<tr>
<td>Troughton et al, 2020</td>
<td>Case report</td>
<td>Pneumonectomy</td>
<td>NR</td>
<td>0.75</td>
<td>↑MAP, VP-sparing</td>
<td>Discharged alive without reported Ang-2 side effects</td>
</tr>
<tr>
<td>Wieruszewski et al, 2019</td>
<td>Case report</td>
<td>OLT/OHT</td>
<td>166</td>
<td>0.22</td>
<td>↑MAP, VP-sparing</td>
<td>Discharged alive without reported Ang-2 side effects</td>
</tr>
<tr>
<td>Wieruszewski et al, 2019</td>
<td>Case series</td>
<td>OHT, CABG/AVR, BLT, LVAD/CABG</td>
<td>142-323</td>
<td>0.28-0.38</td>
<td>↑MAP, VP sparring</td>
<td>Ischemic digits. One death from withdrawal of care. Three discharged alive</td>
</tr>
</tbody>
</table>

* CPR, Cardiopulmonary bypass; Ang, angiotensin; VP, vasopressor; RCT, randomized controlled trial; CABG, coronary artery bypass grafting; MAP, mean arterial pressure; SVRI, systemic vascular resistance; TAAA, thoracoabdominal aortic aneurysm; OHT, orthotopic heart transplant; AVR, aortic valve replacement; NR, not reported; ECMO, extracorporeal membrane oxygenation; OLT, orthotopic liver transplant; BLT, bilateral lung transplant; LVAD, left ventricular assist device. *Started during CPB and continued postoperatively. (Patients were enrolled in the ATHOS-3 trial.)
potential for use in vasodilated patients undergoing mechanical circulatory support. Ostermann and colleagues used\(^2\) Ang-2 in the management of 7 patients undergoing ECMO, with 6 being discharged from the hospital and 1 death. Patients had a variety of etiologies for cardiogenic shock, including sepsis, cardiac arrest, myocardial infarction, drug overdose, pulmonary embolism, and type A aortic dissection. Five of the 7 patients were receiving venoarterial (VA) ECMO and 2 received venovenous (VV) ECMO. Before Ang-2 administration, NEpi equivalents ranged from 0.26 to 1.55 \(\mu g/kg/min\) and vasopressin was used in 6 of the 7 patients. Methylene blue and hydroxychloroquine have limited evidence for their use, as rescue agents and were not used.\(^3\) The authors noted a rapid decline in the need for vasopressor and catecholamine therapy after initiation of Ang-2. Two patients had adverse events during Ang-2 treatment including digital ischemia, which was reversible and bowel ischemia in the patient who ultimately died.

Concerns regarding the use of Ang-2 during ECMO were raised in a letter discussing a theoretical harmful impact of Ang-2 in patients with acute respiratory distress syndrome (ARDS), the potential reduction of cardiac output secondary to increased afterload, and the effect on coagulation status in patients requiring anticoagulation for the ECMO circuit.\(^2\) Ostermann and colleagues\(^2\) responded that human trials of a drug to reduce the concentration of Ang-2 in patients with ARDS not only failed to show any improvement in outcomes but also was terminated due to futility. Furthermore, 71% of patients in that trial had low baseline concentrations of Ang-2, which supports the hypothesis of Ang-2 deficiency in patients with pulmonary pathology such as ARDS. Finally, in patients undergoing VA ECMO, the majority of cardiac output bypasses the pulmonary circulation, where Ang-1 is converted to Ang-2 and may contribute further to Ang-2 deficiency.

Regardless of etiology that leads to initiation of ECMO, considerations regarding inotropic and vasopressor therapy and anticoagulation are universally important. Ang-2 stimulates tissue factor expression and can result in increased thrombosis.\(^31,32\) When examining the rate of venous thromboembolic events (VTE) in the ATHOS-3 trial, there was an increase in overall rate of VTEs in the Ang-2 group (12.9% Ang-2 vs 5.1% SOC), although the rate of clinically significant VTEs was not statistically different between the groups (1.8% Ang-2 vs 0% SOC, \(P > .05\)).\(^3\) In 2 multicenter studies examining outcomes in critically ill patients, one found a VTE rate of 3.1%, whereas the other reported a rate of 1.5%, which is consistent with the 5.1% VTE reported in the control arm of the ATHOS-3 trial, and less than the 12.7% baseline incidence found in a meta-analysis of critically ill patients.\(^33-35\)

Because of this, it is commonplace to initiate VTE prophylaxis in patients receiving Ang-2, and anticoagulation is already a key component in ECMO to prevent circuit thrombosis. Adequacy of anticoagulation is judged not only by laboratory parameters but also on inspection of the ECMO circuit and must be balanced with any bleeding complications. VV ECMO may be run with decreased or no anticoagulation, especially in the setting of robust flows; however, anticoagulation remains common.\(^36\) VA ECMO without anticoagulation has been reported, but the circumstances are often unique and secondary to bleeding concerns.\(^37\) Due to the use of systemic anticoagulation in ECMO support, these patients may be protected against thrombotic complications potentially associated with Ang-2. This question remains unanswered and warrants further investigation.

The appropriateness of vasopressor support in patients receiving ECMO is complex and associated with the underlying illness, complicating factors, and cannulation strategy. An underlying illness with vasodilation as a prominent feature, as in septic shock, would support the use of a vasopressor to treat the shock state. However, most ECMO cases are not straightforward and often a combination of cardiogenic and vasodilatory shock states exists. VV ECMO requires native cardiac function to support oxygenation and ventilation, whereas VA ECMO also provides cardiac support. Some of the most difficult scenarios to balance involve peripheral VA ECMO. Adequate perfusion is required to support organ function and avoid Harlequin (or North–South) syndrome; however, left ventricular ejection is desired to prevent left ventricular distention and stasis of blood in the heart. Using a pure vasoconstrictor in such a setting requires real time monitoring of perfusion and cardiac function.

**POST-HOC ANALYSIS OF CARDIAC SURGICAL PATIENTS**

Klijian and colleagues\(^2\) performed a post-hoc analysis of the ATHOS-3 data specifically examining the effect of Ang-2 on postcardiotomy vasoplegia. Sixteen patients met inclusion criteria, with 9 receiving Ang-2 plus SOC and 7 receiving placebo plus SOC. The 2 groups had similar baseline MAP values and were receiving similar NEpi equivalent doses before receiving Ang-2 or placebo. The Ang-2 group achieved the goal MAP response at hour 3 in 89%, whereas 0% in the placebo group achieved the target. The effect was rapid, and all responders in the Ang-2 group achieved the target MAP within 1 hour of initiating Ang-2. Interestingly, the majority of responsive patients required relatively low dose Ang-2 for vasopressor effect. All patients in the Ang-2 group started at a dose of 20 ng/kg/min, and 67% were receiving a dose of \(\leq 5\) ng/kg/min by 30 minutes after initiation with a median dose at hour 3 of 5 ng/kg/min. Ang-2 was found to have a significant vasopressor-sparing effect. Adverse events did not occur more frequently in the Ang-2 group compared with...
placebo; however, all patients in the Ang-2 group were on anticoagulation. This agrees with findings from an earlier study examining the use of Ang-2 in patients receiving ACE 1 who required cardiothoracic surgery by Bennet and colleagues. Patients were randomized to receive either Ang-2 (n = 10) or phenylephrine (n = 10) for low systemic vascular resistance index. All patients required vasoconstrictor support during the surgical procedure, and 1 patient who did not respond to phenylephrine received Ang-2 with good response. This study examined the impact of Ang-2 on creatinine clearance and found no reduction in the Ang-2 group compared with the phenylephrine group. Further data on the impact of Ang-2 on renal function in cardiac surgical patients will be quite interesting, but thus far, the data do not reveal harm.

CURRENT RECOMMENDATIONS AND DOSING PROTOCOLS FOR VASOPLEGIA

At Wake Forest University Health Sciences, Ang-2 is used on adult cardiothoracic surgery patients with evidence of vasoplegia intraoperatively or postoperatively. Vasoplegia in these cases is based on the diagnosis of hypotension (MAP < 65 mm Hg) while on high-dose vasopressors (total NEpi equivalent ≥ 0.2 µg/kg/min, which would, for example, translate into NE ≥ 10 µg/min plus vasopressin ≥ 0.03 units/min for an 80-kg patient [based on predefined NEpi-equivalent calculators, Table 1 and Figure 2]). In addition, appropriate clinical context for vasoplegia is taken into consideration, along with no evidence of hypovolemia or hemorrhage or coexistent significant cardiogenic shock based on a combination of filling pressures and bedside cardiac output numbers. All critical care clinicians are provided training regarding the initiation and titration of Ang-2 based on this standard dosing protocol (Figure 2). This protocol mandates initiation of Ang-2 at 20 ng/kg/min, up titration to a maximum of 80 ng/kg/min, within the first 3 hours, with a target MAP of ≥ 65 mm Hg. This dose is maintained for up to 3 hours as needed and then titrated downward to a maximum maintenance dose of 40 ng/kg/min for up to 48 hours total. Ang-2 failure is considered when there is sustained hypotension while on Ang-2 (at a maximum of 80 ng/kg/min) within 4 hours of initiation, and in these cases the dose of catecholamine vasopressors and vasopressin is increased. The use of methylene blue and/or hydroxocobalamin is also considered, although there is limited evidence for their use in vasoplegic shock. For Ang-2 responders, background vasopressors are titrated to minimal doses and Ang-2 is allowed to run up to 48 continuous hours. All patients under this dosing protocol have serial serum renin, renin metabolites, and lactate measured up to 48 hours after Ang-2 initiation. However, renin and renin metabolites cannot be used to guide further

FIGURE 2. Current dosing protocol for Ang-2 in postpump vasoplegia at the Wake Forest Baptist Medical Center Cardiovascular Intensive Care Unit. MAP, Mean arterial pressure; NE, norepinephrine; AVP, arginine vasopressin; Ang-2, angiotensin-II. *Total 0.2 µg/kg/min of NE equivalents for an 80-kg patient. **Leave Ang-2 at lowest dose 20 ng/kg/min and let run out over 24 hours.

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resuscitation since they are not available as point of care testing.

Furthermore, in an effort to elucidate the effect of post-pump vasoplegia and exogenous Ang-2 on cerebral hemodynamics, serial cerebral blood flow measurements via transcranial Doppler are also being performed under a coexistent research protocol. Published data using this protocol have shown effective hemodynamic outcomes in a variety of postcardiothoracic surgery vasoplegia clinical situations and with the background of heart transplantation as well.18,19

The introduction of a new drug to any protocol must take into account the cost. Ang-2 is not generic and is not surprisingly more expensive than its generic counterparts NEpi and vasopressin. However, vasopressin was found to increase blood pressure in only 45% of patients in septic shock in 1 study, whereas in the ATHOS-3 trial, almost 70% of patients were responsive to Ang-2 within 3 hours.5,38 The greater rate of responsiveness and shorter duration of therapy of Ang-2, in addition to the mortality benefits of Ang-2 in the acute kidney injury on RRT and high-renin shocks groups, may make Ang-2 a more cost-effective drug when all of the beneficial outcomes are taken into account.6,13 In one economic analysis examining the life-years and quality-adjusted life-years (QALYs) gained, Ang-2 in addition to SOC led to 0.96 life-years and 0.66 QALYs gained.39 The probability analysis found that Ang-2 was 86% likely to be cost-effective at a threshold of $50,000 per QALY,39 although it is important to note these analyses were performed using a limited ATHOS-3 dataset and do not include the complexities and costs of perioperative cardiothoracic surgery, an area for future investigation. Using the dosing protocol provided in Figure 2, Ang-2 is being used in patients with known vasoplegic shock, meeting NEpi equivalence criteria (postcardiothoracic surgery and including those with mechanical circulatory support) on an average at 1 to 2 occurrences per week.

**FUTURE DIRECTIONS**

While the clinical benefit of synthetic Ang-2 in cardiothoracic patients has been established based on prospectively enrolled patients in several reported series, the biochemical mechanistic pathways for these outcomes remain unanswered. The hypothesis of significant ACE dysfunction with prolonged pump runs, leading to low endogenous Ang-2, and deviation of the pathway to vasodilatory Ang-2 metabolites such angiotensin-(1-7), angiotensin-(1-5), and angiotensin-(1-9) via increased ACE 2 needs to be investigated and established. Similarly, the role of an inhibited feedback mechanism leading to high serum renin, angiotensinogen, along with an altered Ang-1/Ang-2 ratio and the response of these to the use of synthetic exogenous Ang-2 is a critical question that deserves to be answered.

The best clinical evidence for this novel vasopressor also needs to be investigated via a large randomized double-blind placebo-controlled trial of Ang-2 versus SOC in post-CPB vasoplegia. The selection of patients could be narrowed to those at high risk for vasoplegia, which include those on ACE inhibitors, calcium channel blockers, amiodarone, heparin, as well as those with an ejection fraction <35%.20 Besides the typical end points of hemodynamic responsiveness and mortality, end points of particular interest in the cardiac surgery population should be also examined, such as the incidence of postoperative atrial fibrillation. However, protocolized use of Ang-2 and the collection of RAAS metabolites in established post-CPB patients with vasoplegia is an effective first step. A futuristic aim would be the development of a true point-of-care serum renin measurement that would allow clinicians at the bedside to establish the presence of an altered RAAS axis and treat this with an effective dose of synthetic Ang-2, with subsequent serial renin measurements to ensure that a true response and correction is seen as treatment progresses. Personalized management of shock states, in conjunction with biochemical estimates of the same that can be objectively quantified and used in these patients, is certainly a much-needed area of scientific exploration and translational research.

**Conflict of Interest Statement**

J.H.C. serves on the speaker’s bureau for La Jolla Pharmaceutical Company. All other authors reported no conflicts of interest.

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**References**


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