Angiotensin II for the emergency physician

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INTRODUCTION
Humans have evolved multiple systems to autoregulate blood pressure under conditions of stress, and the regulation of blood pressure relies on several complex pathways. Two of these axes have been used regularly by clinicians for the past quarter century to treat the patient in shock: the catecholamine axis (eg, norepinephrine and epinephrine) and the arginine–vasopressin system axis (eg, vasopressin). A third axis, the renin–angiotensin–aldosterone system (RAAS), is intimately involved in blood pressure regulation, and one of its main components is angiotensin II (Ang-2). The hormone was first identified and clinically administered in the regulation of blood pressure relies on several complex pathways. Two of these axes have been used regularly by clinicians for the past quarter century to treat the patient in shock: the catecholamine axis (eg, norepinephrine and epinephrine) and the arginine–vasopressin system axis (eg, vasopressin). A third axis, the renin–angiotensin–aldosterone system (RAAS), is intimately involved in blood pressure regulation, and one of its main components is angiotensin II (Ang-2). The hormone was first identified and clinically administered in humans over 50 years ago, and a bovine formulation of Ang-2 was used in the management of hypotension for over 35 years. A human synthetic version of Ang-2 was approved by the US Food and Drug Administration (FDA) in 2017 and by the European Medicines Agency (EMA) in 2019 for the indication of distributive shock. It has not been widely used in the emergency department (ED), but in an environment where the ED has become so tightly integrated with other services, such as the operating room and intensive care unit (ICU), use of Ang-2 in the ED is foreseeable in the immediate future. Furthermore, especially in departments where critically ill patients must wait for a significant amount of time before being transferred to an ICU, an understanding of Ang-2’s mechanism of action, pharmacokinetics and adverse effects will be invaluable for the emergency medicine physician.

CURRENT CONVENTIONAL THERAPIES
Several vasopressors are available for use in the ED: phenylephrine, norepinephrine, epinephrine, vasopressin and dopamine. Based on clinical guidelines, norepinephrine is the first-line treatment for distributive shock and is one of the most commonly used vasopressors for this indication. Its mechanism of action is by agonism of α, receptors, which results in smooth muscle contraction. Vasopressin is also commonly used, particularly in profoundly hypotensive patients who require an adjunct to norepinephrine. As the second-line vasopressor for the treatment of septic shock, it acts on vasopressin type 1 and vasopressin type 2 receptors, leading to increased water reabsorption in the kidneys and smooth muscle contraction in the vasculature. Epinephrine also targets the catecholamine axis and is a potent α, agonist. Unlike norepinephrine, epinephrine also has agonistic effects on β, receptors that increase chronotropy, inotropy and lusitropy in a dose-dependent manner. Dopamine, which has extremely limited use in septic shock, also exhibits dose-dependent action on the catecholamine axis, where it acts on Dopamine type 1 receptors at low doses, on β, receptors at intermediate doses, and on α, and Dopamine type 2 receptors at high doses. The Surviving Sepsis Guidelines recommend that it be used as a tertiary agent only in highly selected patients with bradycardia and at low risk of developing tachydyssrhythmias. Many of these vasopressors share a quick onset of action, on the order of seconds to minutes, and short duration of action (table 1).

While there are physiological rationales for using one vasopressor over another in various types of shock, there is no evidence to show that one particular vasopressor is associated with better outcomes than another. While norepinephrine alone often adequately corrects hypotension, all conventional vasopressors at high doses and with prolonged use have a variety of clinically significant adverse effects (see table 2). Many clinicians commonly start vasopressin as a second-line agent following norepinephrine, but there is no consensus on the norepinephrine dose at which it should be initiated. In the Vasopressin versus Norepinephrine Infusion in Patients with Septic Shock trial, vasopressin did not significantly improve mortality when compared with norepinephrine (28-day mortality, 35.4% vasopressin vs 30.3% norepinephrine; p=0.26). Additionally, in 2016, the Effect of Early Vasopressin versus Norepinephrine on Kidney Failure in Patients with Septic Shock trial failed to demonstrate a difference in benefit between vasopressin and norepinephrine in preventing acute kidney injury (AKI) in patients with septic shock. Vasopressin use, unfortunately, does not eliminate, and may even potentiate, some of the negative ischemic effects of high-dose catecholamines.
of low renal perfusion, renin is secreted by the juxtaglomerular apparatus of the kidney and cleaves angiotensinogen to Ang-1. Endothelium-bound ACE, which is concentrated in the pulmonary capillary network, converts Ang-1 to its most active form, Ang-2. The pleiotropic effects of Ang-2 result from its multiple sites of action (figure 1). Among a number of activities, Ang-2 binds to angiotensin type 1 (AT1) receptors, causing release of calcium from the sarcoplasmic reticulum and activation of myosin light chain kinase, leading to smooth muscle contraction. In addition, agonism of AT2 receptors stimulates the release of the adrenocorticotropic hormone from the anterior pituitary gland; activates the sympathetic system, leading to the release of catecholamines; and promotes salt and water reabsorption in the kidneys through multiple mechanisms. The renal effects of Ang-2 include direct activation of sodium and chloride reabsorption in the proximal tubules, aldosterone release from the adrenal cortex to enhance sodium reabsorption in the convoluted tubules and secretion of vasopressin from the posterior pituitary gland to increase free water retention in the collecting ducts. All of these mechanisms work in concert to increase the mean arterial pressure (MAP) and the effective circulating volume during hypovolaemia and relative vasodilatation.

Through a separate mechanism, Ang-2 also plays an important role in the bradykinin pathway and regulates inflammatory states, particularly in the pulmonary system. Dysfunction in ACE results in excess Ang-1 accumulation, which then follows a pathway that generates bradykinin. Hypotension, therefore, results not only from diminished Ang-2-mediated vasoconstriction but also from excess bradykinin-induced vasodilatation.

### CLINICAL DATA AND RELEVANCE TO EMERGENCY MEDICINE

#### Preclinical and animal studies

Initially thought to be the primary explanation for malignant hypertension, the RAAS is a core component of the body’s physiological response to stress. In experiments performed by Goldblatt and colleagues as far back as the 1930s, investigators clamped the renal artery of canines and observed fluctuations in blood pressure. The induction of relative renal ischaemia resulted in hypertension and highlighted the kidney’s integral role in blood pressure regulation.

The first reported case series of Ang-2 in humans was published in 1961, and for over 35 years, a bovine version of Ang-2 was produced for the treatment of shock. One systematic review assessing 353 patients in 24 studies from 1960 to 2017 examined the blood pressure effects of Ang-2 in patients with hypotension. Uniformly, Ang-2 significantly raised blood pressure for cardiogenic, distributive and undifferentiated shock. Despite the literature documenting its effectiveness for the treatment of shock, bovine Ang-2 production was halted by its producer for financial reasons in 1996.

### Recent clinical data

Ang-2 was ‘rediscovered’ in Australia in 2009 when Wan and colleagues studied its effects in ewes experimentally infected with *Escherichia coli* septic shock. They found that those animals to whom Ang-2 was administered had increased urine output and increased creatinine clearance compared with those receiving placebo. This finding prompted researchers at George Washington University to create a synthetic human Ang-2 octapeptide identical to the human peptide and to study it more formally in humans.

The Intravenous Angiotensin for High-Output Shock (ATHOS) trial was a 2014 pilot study that examined 20 patients...
with distributive shock who were randomised to either Ang-2 or placebo. Those receiving Ang-2 required a lower mean norepinephrine dose at 1 hour (7.4±12.4 µg/min Ang-2 vs 27.6±29.3 µg/min control), although this did not reach statistical significance (p=0.06) (figure 2).

The ATHOS-3 study, the phase III multicentre follow-up to ATHOS, demonstrated the safety and efficacy of Ang-2 in patients with refractory hypotension. Patients in distributive shock requiring >0.2 µg/kg/min of norepinephrine equivalents were eligible for enrolment and were randomised to either Ang-2 plus standard-of-care vasopressors or to placebo plus standard of care vasopressors. The primary endpoint of the study was a MAP increase of ≥10 mm Hg or a MAP increase to ≥75 mm Hg by hour 3 of the intervention. As a phase III trial, the high MAP target of ≥75 mm Hg was deliberately used in the first 3 hours of the trial to demonstrate the utility of Ang-2 as a vasopressor rather than as a catecholamine-sparing agent. After this requirement was satisfied following the 3-hour mark, the MAP targets were decreased to the conventional level of 65 mm Hg. ATHOS-3 demonstrated that 69.9% of patients in the Ang-2 group achieved the primary endpoint, compared with 23.4% of those receiving only SOC vasopressors (p<0.001). Furthermore, a significant reduction in background NE dose was achieved in those patients receiving Ang-2 (−0.03 µg/kg/min Ang-2+SOC vs 0.03 µg/kg/min SOC only, p<0.001).

Various prespecified post hoc analyses of ATHOS-3 highlighted multiple groups of patients that may experience a survival benefit from Ang-2 administration. The rationale for the disproportionate Ang-2 responsiveness in these groups is largely based on the pathophysiological deficits of the RAAS (eg, ACE dysfunction resulting from severe capillary endothelial injury) within each particular subgroup. For example, severely ill patients with Acute Physiology and Chronic Health Evaluation (APACHE) II scores >30 were shown to have significant mortality benefit when administered Ang-2 and SOC vasopressors rather than SOC vasopressors alone (51.8% Ang-2 vs 70.8% SOC; HR 0.62, 95% CI 0.39 to 0.98, p=0.037). In another analysis, Wunderink and colleagues examined the effect of baseline Ang-1 and Ang-2 levels on mortality. A high ratio of
Ang-1:Ang-2 (＞1.63)，indicating a relative Ang-2 deficiency and ACE dysfunction, was significantly associated with an increased risk of death (HR 1.78, 95%CI 1.25 to 2.53, p=0.002). In patients with high ratios of Ang-1:Ang-2，mortality decreased when Ang-2 was exogenously administered (HR 0.64, 95%CI 0.41 to 1.00, p=0.047). Similarly, Ham et al found that patients only requiring ≤5 ng/kg/min of Ang-2 (ie, physiological repletion dose) within 30 min of its initiation benefited from lower mortality rates, suggesting a baseline endogenous Ang-2 deficiency.

Animal studies have identified an increase in both creatinine clearance and urine output when Ang-2 was administered. Because renal failure has been shown to predict mortality in patients with sepsis, another post hoc analysis of the ATHOS-3 data was performed in patients with AKI on renal replacement therapy (RRT). This analysis found that such patients were more likely to survive if they received Ang-2 in addition to SOC vasopressors (53% Ang-2+SOC vs 30% SOC only; HR 0.52, 95%CI 0.30 to 0.87, p=0.012). Additionally, those patients receiving Ang-2 had shorter durations of RRT (by day 7, 38% RRT-free Ang-2 vs 15% RRT-free SOC; p=0.012). The number needed to treat to prevent the need for dialysis after 7 days was 4.3.

While these analyses identify subgroups that may particularly benefit from Ang-2，they are limited by having been performed post hoc，although subgroups were designated before the trial，given their various physiological characteristics pertaining to the RAAS pathway. Additional prospective studies are necessary to corroborate these results. Furthermore，although ATHOS-3 was an international study involving 75 clinical sites，the total enrolment was only 321 patients. It was powered to detect a difference in the MAP response，its primary outcome，and not a difference in mortality. Furthermore，it was a placebo-controlled trial in which Ang-II was used in conjunction with other vasopressors，and there are no recent studies that have evaluated its use as a single agent. Additionally，the exclusion criteria included patients with a life expectancy of <12 hours，which is a somewhat subjective metric that may vary among clinicians and，thus，potentially introduce selection bias，resulting in the exclusion of some critically ill patients. Nevertheless，almost half of all patients at enrolment were on ≥3 vasopressors; 35.6% of patients had an APACHE II score >30; and the median APACHE II score was 27，indicating that，despite the possibility of selection bias，the trial’s patients were still extremely critically ill. Finally，ATHOS-3 used a MAP target of 75 mm Hg in the first 3 hours of the trial. While this target was established deliberately to satisfy the FDA requirement to demonstrate the efficacy of Ang-2 as a vasopressor，this is not a standard target in the ICU or in the ED. Despite this，the High versus Low Blood-Pressure Target in Patients with Septic Shock trial，which examined the effect of higher MAP targets ranging from 80 to 85 mm Hg in septic shock，did not find any evidence of harm or increased mortality when high MAP targets were used.

A thorough literature search was completed for this practice review using PubMed. MeSH terms included angiotensin 2, Ang-2 and shock. Interestingly，no published studies have demonstrated a lack of the ability of Ang-2 to increase blood pressure. Although registered clinical trials must be reported to either ClinicalTrials.gov or the EU Clinical Trials Registrar for the USA and Europe，respectively，their results are not required to be published. Therefore，as is the case with most approved therapies in the USA and Europe，publication bias may exist.

Pharmacokinetics and dosing
Ang-2 has a time of onset of 60s and a half-life of about 30s. Degradation of Ang-2 occurs quickly in the plasma，as it is metabolised by aminopeptidases that cleave it into angiotensin III and IV. Therefore，it can be rapidly titrated and quickly discontinued once no longer necessary to maintain blood pressure.

With other endogenous hormones，Ang-2 exists under normal conditions. On average，the normal circulating level of Ang-2 in arterial blood is only 20 ng/L. Assuming a volume of distribution of 25 L in a patient weighing 100 kg，the rate of Ang-2 repletion to achieve normal physiological levels is approximately 5 ng/kg/min. The dosage used in the ATHOS-3 trial ranged from 5 to 80 ng/kg/min. Half of the group randomised to Ang-2 only required a dose of ≤5 ng/kg/min within 30 min from drug initiation，suggesting that repletion of an Ang-2 deficit during septic shock may effectively improve hemodynamics. Current prescribing guidelines suggest starting at an initial dose of 20 ng/kg/min and titrating every 5 min in increments of 15 ng/kg/min. The maximum dose is 80 ng/kg/min in the first 3 hours and 40 ng/kg/min after this time frame.

Adverse effects
The reported rate of adverse events in ATHOS-3 was not statistically different between the treatment and control arms (87.1% Ang-2+SOC vs 91.8% SOC only, p>0.05). There was an increase in the number of deep vein thromboses in those receiving Ang-2 (4.3% Ang-2+SOC vs 0% SOC only). However，when analysing only the DVTs deemed clinically relevant by blinded site investigators，the difference between the groups was not significant (1.8% Ang-2+SOC vs 0% SOC only, p>0.05). Nevertheless，based on its analysis of the raw data，the FDA suggests concurrent venous thromboembolism prophylaxis for all patients receiving Ang-2.

The original ATHOS pilot identified a subset of patients who exhibited marked variability in response to Ang-2. Specifically，two patients were exquisitely sensitive to Ang-2 and had unexpected hypertension at the time of initiation of the drug. Currently，it cannot be predicted who will have this hypertensive response，although it is hypothesised that hypersensitivity could result from concomitant pulmonary pathology.

Current use
In 2017，the FDA approved Ang-2 for use for distributive shock for use in the USA. Although the ATHOS-3 study addressed the use of Ang-2 concurrently with other vasopressors，the FDA does not comment on the use of Ang-2 as a single agent. In Europe，the EMA similarly approved Ang-2 in 2019 for use in distributive shock. It is currently in use throughout the USA and is expected to enter the European market in May 2020.

Further research
A clear need exists for a multimodal ‘broad-spectrum vasopressor’ approach to treating hypotension. While the ATHOS trials and subsequent analyses demonstrate the utility of Ang-2 in the treatment of vasodilatory shock，many questions remain. Patients with severe burns，myocardial infarction，liver failure，cardiac arrest and neutropaenia，and those on ECMO or receiving >500 mg/day of hydrocortisone equivalents were excluded from the trials.

This leaves the clinician with a number of patients for whom the benefit of Ang-2 is unclear，and further research in these populations is warranted. Moreover，the utility of Ang-2 outside the realm of distributive shock requires further investigation. While some case reports describe
the use of Ang-2 in cardiac arrest and cardiogenic shock, additional randomised controlled trials to rigorously examine the efficacy in these populations are needed.\cite{1,2} Finally, although the FDA does not comment on its use without other vasopressors, further studies addressing the use of Ang-2 as a single agent are also warranted, given the nature of the ATHOS-3 trial.

**CONCLUSION**

Refractory hypotension is a clinical problem that all emergency medicine physicians encounter in the treatment of critically ill patients. Vasopressors are among the most common medications used to treat life-threatening hypotension in the ED, but they also have significant dose-limiting side effects. Ang-2 is a naturally occurring hormone in the RAAS that is used for blood pressure regulation. Following the ATHOS-3 trial, a placebo-controlled study that evaluated Ang-2 use in conjunction with other vasopressors, synthetic Ang-2 was approved by the FDA in 2017 and by the EMA in 2019. As a result, the emergency physician should be familiar with this additional vasopressor for the treatment of refractory vasodilatory shock in the ED.

**Correction notice** This paper has been updated since first published. Third author name was incorrectly spelled as ‘Micheal E Winters’ and was amended to ‘Michael E Winters’.

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**Contributors** MCMC drafted the manuscript. JHC created all figures and assisted with edits. MTMcC served as an angiotensin II expert. MEW, along with all authors, contributed substantially to the revision. All authors approve of the final version of the submitted manuscript.

**Funding** The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

**Competing interests** MMT serves on the speaker’s bureau for La Jolla Pharmaceutical Company and was a site principle investigator in the Intravenous Angiotensin for High-Output Shock-3 study. JHC serves on the speaker’s bureau for La Jolla Pharmaceutical Company.

**Patient consent for publication** Not required.

**Provenance and peer review** Not commissioned; externally peer reviewed.

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