American Journal of Emergency Medicine 37 (2019) 1169–1174

Contents lists available at ScienceDirect

American Journal of Emergency Medicine

journal homepage: www.elsevier.com/locate/ajem

Review

Angiotensin II in septic shock☆

Amar P. Jadhav, MD [a,*], Farid G. Sadaka, MD [b]

[a] Intensivist, SSM St. Mary's Hospital, Richmond Heights, St. Louis, United States of America.
[b] Clinical Associate Professor, Critical care/Neurocritical care, Mercy Hospital St.Louis, St. Louis University School of Medicine Program, United States of America

ARTICLE INFO

Article history:
Received 26 October 2018
Received in revised form 13 March 2019
Accepted 18 March 2019

Keywords:
Septic shock
Vasopressors
Angiotensin II
Vasodilation
Circulatory failure
Organ dysfunction

ABSTRACT

Septic shock is a life threatening condition and a medical emergency. It is associated with organ dysfunction and hypotension despite optimal volume resuscitation. Refractory septic shock carries a very high rate of mortality and is associated with ischemic and arrhythmogenic complications from high dose vasopressors. Angiotensin II (AT-II) is a product of the renin-angiotensin-aldosterone system. It is a vasopressor agent that has been recently approved by FDA to be used in conjunction with other vasopressors (catecholamines) in refractory shock and to reduce catecholamine requirements. We have reviewed the physiology and current literature on AT-II in refractory septic/vasodilatory shock. Larger trials with longer duration of follow-up are warranted to address the questions which are unanswered by the ATHOS-3 trial, especially pertaining to its effects on lungs, brain, microcirculation, inflammation, and venous thromboembolism risk.

1. Introduction

Sepsis is a condition where life-threatening organ dysfunction is caused by a dysregulated host response to infection [1-3]. Septic shock is defined as a subset of sepsis in which profound circulatory, cellular, and metabolic abnormalities are associated with a greater risk of mortality than with sepsis alone. Patients with septic shock can be clinically identified by a vasopressor requirement to maintain a mean arterial pressure (MAP) of 65 mm Hg or greater and have serum lactate level >2 mmol/L (>18 mg/dL) in the absence of hypovolemia. When fluid resuscitation fails to improve arterial blood pressure, vasopressors are necessary. Sepsis with septic shock is associated with a high mortality rate upto 40% [1]. Refractory septic shock is the persistence of circulatory failure despite optimized therapy (fluid resuscitation, vasopressors, inotropes) [4].The pathophysiology of septic shock is marked by an imbalance between vasodilators like nitric oxide, tumor necrosis factor (TNF)-alpha, histamine, kinins and prostaglandins, angiotensin II (AT-II) and catecholamines (epinephrine and norepinephrine) [4].Norepinephrine (NE) is the standard vasopressor used in hypotension due to septic shock [5].Excessive use of cathecholamines is associated with several risks like splanchnic ischemia, arrhythmias, hyperglycemia and peripheral ischemia and is an independent risk factor for ICU mortality [6].Use of an additional vasopressor which acts via a different mechanism of action will help achieve desired mean arterial pressure goal in septic shock and will help reduce complications from excessive catecholamines. AT-II has various effects from potentiating sympathetic activity, direct vasoconstriction and fluid retention via the release of aldosterone and vasopressin/anti diuretic hormone.

2. Overview of renin-angiotensin – aldosterone system (RAAS)

AT-II is an endogenous vasopressor that is produced by the body in response to shock through the RAAS. It is synthesized in the interstitial space. The tissue RAAS utilizes enzymes such as cathepsins and chymase to synthesize AT-II and acts locally [7-9]. AT II is also synthesized inside the cell in secretory vescicles [7].Intracellular RAAS is localized in the cytoplasm, mitochondria and nuclei [9]. Intravascular volume depletion and decreased mean arterial pressure (MAP) leads to release of renin from the juxtaglomerular cells in the afferent arteriole in the kidney [10]. Angiotensinogen which is produced by the liver is converted by renin to angiotensin I (AT-I) in the plasma. AT-I is converted to AT-II by angiotensin converting enzyme (ACE). ACE is found in the pulmonary microcirculation and endothelium of systemic circulation [11].

Angiotensin converting enzyme II (ACE-2) breaks down AT I to angiotensin 1–9 (AT 1–9) and AT II to angiotensin 1–7 (AT 1–7) [11-13]. AT1–7 interacts with the bradykinin –nitric oxide prostaglandin system and produces vasodilatation [13]. AT 1–9 inhibits AT II induced vascular smooth muscle cell migration and proliferation and reduces the neointimal formation via AT2 receptor [14]. This effect helps in cardiac remodeling. The balance between ACE and ACE-2 plays an important role in hemodynamics by controlling

☆ None of the authors have financial or ethical conflicts of interest regarding the contents.

* Corresponding author.
E-mail address: ajadhav@soundphysicians.com (A.P. Jadhav).

https://doi.org/10.1016/j.ajem.2019.03.026
0735-6757/

AT- II concentrations. AT-II regulates the renin angiotensin system by the negative feedback on renin production by the juxtaglomerular cells in the kidney [15].

3. Effects of angiotensin II (AT-2) receptors

AT-II binds to G-protein coupled receptors. Human cells express AT-1a receptors (AT-R1a) which are located in vascular smooth muscle, heart, brain, kidneys, adrenals, pituitary gland, liver and other tissues [16]. The majority of AT-II actions are mediated through AT-R1 which stimulates aldosterone release from the adrenal cortex, causing sodium and water reabsorption along with stimulation of vasopressin release and thus subsequently increasing the blood pressure (Fig. 1) [11]. The function of the AT-2 receptor has not been completely understood and it is believed that their stimulation may counteract the effects of AT-1 on cell growth, blood pressure and inflammation [16]. AT-II binding to AT-II receptors causes vasodilatation and decreased vascular resistance [15]. Through AT-I receptors, AT-II stimulates the production of endothelial adhesion molecules like P-selectin, E-selectin, vascular cell adhesion molecule 1 (VCAM-1) which induces pro-inflammatory mediators like vascular endothelial growth factor (VEGF) resulting in an increased vascular permeability through expression of PV-1 on endothelial cells [17]. While AT-II exerts it pro-inflammatory effects through AT-1 receptors, it also binds to AT-II receptors producing vasodilatation and decreased systemic vascular resistance. In addition, AT-II binds to AT-IV receptors and stimulates vasodilatatory, pro-inflammatory and procoagulant effects [11].

4. RAAS in septic shock

Clinical studies have shown activation of RAAS during sepsis [18-20]. Septic shock is a type of distributive shock characterized by reduced peripheral vascular resistance, increased capillary permeability, relative hypovolemia, increased cardiac output, and microcirculatory dysfunction leading to increased mixed venous oxygen saturations [4]. Nitric oxide causes vasodilatation resulting in reduced preload and afterload. Inflammatory markers like alpha-TNF, interleukin-1, interleukin- 6 causes myocardial depression in sepsis [4]. To counteract this, different physiological processes try to restore circulating volume, vascular resistance, mean arterial pressure by activation of sympathetic nervous system, vasopressin release, inhibition of atrial and cerebral natriuretic peptide; increased renin secretion results in RAAS activation and elevation AT-II levels [21]. As a result of reduced effective circulating volume and reduced mean arterial pressure in septic shock, activation of RAAS is increased due to renal hypoperfusion. Decreased stretch of the afferent arteriole and decreased delivery of chloride to distal tubules stimulates renin release from juxtaglomerular cells [22]. Hypovolemia also stimulates sympatho-adrenal and hypothalamo-pituitary-adrenal axis resulting in AT-II and renin release [22]. Angiotensin acts on the efferent renal arteriole causing vasoconstriction, thus preserving mean arterial pressure during hypotension and increasing glomerular filtration pressure.

5. Angiotensin II and shock

In vitro experimental models of sepsis have shown downregulation of AT-R1 and AT-R2 receptors in many organs like lung, liver, heart and

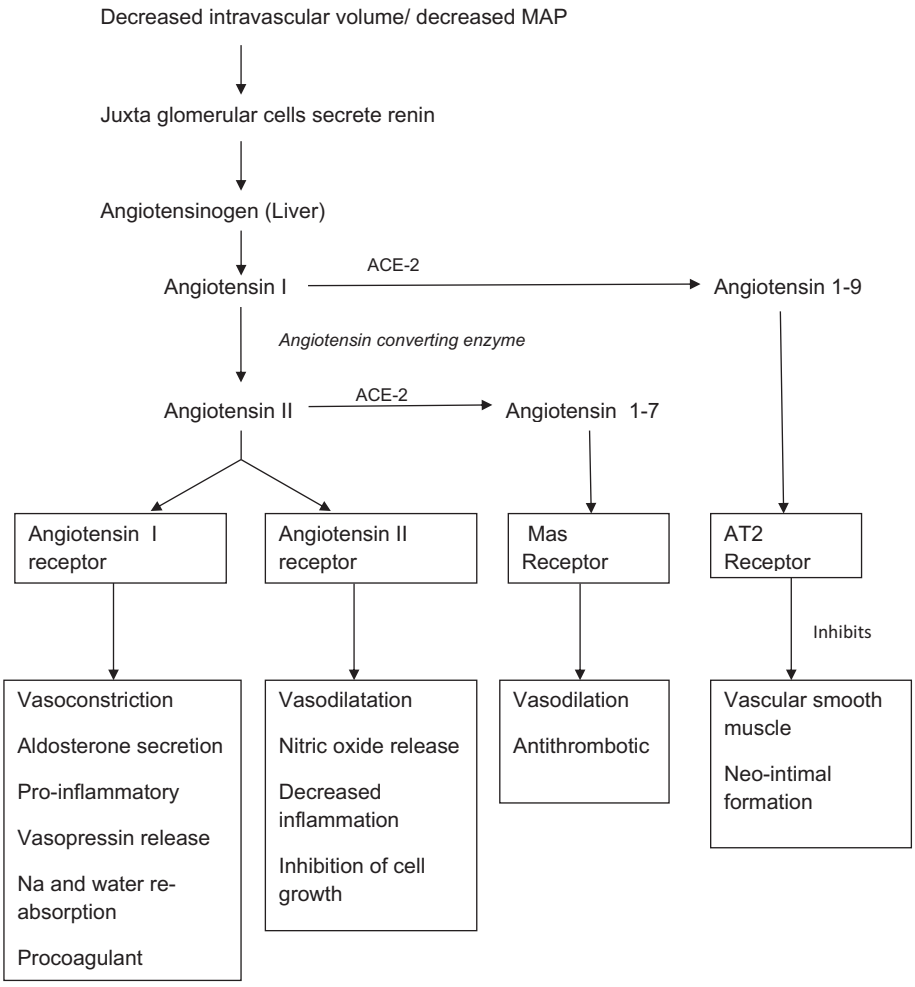

Fig. 1. Flowchart showing mechanism of activation of Angiotensin II and its effects on different receptors.

brain induced by Nitric Oxide (NO) and pro-inflammatory markers like IL-1B, TNF-alpha and INF-gamma [23,24]. Ikedia et al. and Sasamura et al. revealed that NO and pro-inflammatory cytokines down regulate AT-R1 expression in in-vitro models of vascular smooth muscle cells [25,26]. Mederle et al. showed that ARAP-1 (AT-R1 associated protein) could increase the expression of AT-R1 on the cell surface. Elevated AT-II levels could induce a marked down regulation of ARAP-1, thus in an auto regulatory fashion reducing the vasculature's sensitivity to AT-II as found in sepsis [27]. Mederle et al. confirmed this hypothesis in vivo as well in an experimental sepsis model. After lipopolysaccharide injection, they found a significant down-regulation of ARAP-1 expression in wild type mice and hemodynamic compromise in ARAP-1 knockout mice. ARAP-1 expression is dependent not only on AT-II levels but also on exposure to cytokines as noted in vascular smooth muscle cells [26,27]. In an animal model, Correˆa et al. found that AT-II can be used as a safe vasopressor without adverse effects on renal perfusion or mitochondrial respiration [28]. They randomized 21 pigs to a septic or control group. The septic group was further randomized to fluid resuscitation with NE or AT-II infusion. In the control group, the authors tested the effects of AT-II infusion in non-septic animals. In the septic group AT-II reversed sepsis-induced hypotension, while renal blood flow did not differ between AT-II and NE. In another study, exogenous AT-II did not worsen mitochondrial respiration, but was revealed to be having negative effects on mitochondrial function elsewhere [29].

6. Effect of angiotensin II on organs

AT II has a different effect on the lungs, brain, heart and the liver. Imai et al. reported that angiotensin converting enzyme- 2 (ACE-2) and the AT-R 2 protected mice from severe acute lung injury induced by acid aspiration or sepsis [30]. However ACE, AT-II and AT-R1a promote disease pathogenesis inducing lung edema thereby impairing lung function. Animal studies by Zambelli et al. and Supe et al. have revealed an increased amount and concentration of AT-II as compared to angiotensin 1–7 (AT 1–7) in broncho-alveolar fluid in ARDS [31,32]. Zambelli et al. found that high doses of angiotensin 1–7 reduced inflammatory cell numbers in bronchoalveolar lavage and reduced lung fibrosis [31]. Supe et al. found that infusion of angiotensin 1–7 protected against experimental lung injury [32]. A finding from these two studies suggests that lungs benefit from angiotensin 1–7 rather than AT-II. In the kidneys, AT-II produces efferent arteriolar constriction thus increasing filtration fraction [33]. In septic shock where kidneys are hypo-perfused due to distributive shock, AT-II produces efferent arteriolar constriction thus maintaining tubular perfusion and could potentially prevent renal ischemia and may even help improve renal functions. The liver plays an important role in the activation of the RAAS. Angiotensinogen is produced in the liver and its levels are reduced in cirrhotic patients [34]. In septic shock, cirrhotic livers are limited in being able to release angiotensinogen to activate the RAAS pathway. Hence patients with liver cirrhosis in septic shock could potentially benefit with exogenous administration of AT-II. RAAS may be implicated in neurodegenerative disorders like Alzheimer's disease [35], neuronal injury and cognitive disorder [36]. AT-R1 activation could promote reactive oxygen species and neuro-inflammation [37]. Villapol et al. tested AT-R2 antagonists (candisartan and telmisartan) on cognition and motor performance in traumatic brain injury patients. Both drugs improved cerebral blood flow and reduced neuronal injury, apoptosis and pro-inflammatory signaling [38]. These findings suggest a deleterious effect of AT-II on brain function. In a study reviewing clinical use of AT II, 31,281 participants have been exposed to IV ATII in the studies reviewed including healthy normotensive subjects, normotensive and preeclamptic pregnant women, subjects with hypertension, congestive heart failure, diabetes, solid tumors, and other co morbidities, critically ill patients, and children. This review was limited by the heterogeneity of study design, which precluded formal meta-analysis, reviewed studies differed in objectives; inclusion/exclusion criteria, co morbidities, and baseline characteristics, and only small proportion of patients had shock. This review concluded that adverse events associated with AT II were infrequent; exacerbation of asthma and congestive heart failure and one fatal cerebral hemorrhage were reported [39].

7. Angiotensin II in vasodilatory shock and renal replacement therapy

Sepsis is responsible for approximately 50% of Acute Renal Failure (AKI) cases in critically ill patients [40-42]. Patients who survive AKI are at risk for long term mortality that appears to be related to its severity [42,43]. Prognosis tends to be worse in patients requiring renal replacement therapy who have concurrent vasodilatory shock and AKI [44]. These patients have a mortality rate between 40 and 55% [45,46]. AKI in vasodilatory shock occurs due to hypotension which causes reduced renal perfusion. This vasodilatation and decreased blood flow potentiated by vasopressors leads to worsening AKI [47-49]. Lankedwa et al. revealed intra renal vasodilatation and shunting to be an important mechanism of AKI in sepsis [50]. In a prospective 6-month observational study in critically ill patients ($n = 180$), du Cheyron et al. found that patients with AKI had significantly higher mortality rates in the ICU and hospital overall compared with those without AKI [51]. In a post hoc analysis of the AT-II for the Treatment of High-Output Shock 3 trial (ATHOS-3 trial), Tumlin et al. showed that in patients with AKI requiring renal replacement therapy (RRT) at the beginning of the study drug, 28 day survival and MAP response were higher in the AT-II group v/s the placebo group [42]. The authors also found that the rate of RRT liberation was greater in the AT-II group than the placebo group. They concluded that patients with vasodilatory shock and AKI-RRT may benefit from AT-II. The potential beneficial effect of AT-II on AKI-RRT could be in part to the fact that the kidneys may be particular susceptible to the effects of perfusion pressure to maintain blood flow [40]. Vasodilatory shock caused by inflammation leads to increased capillary endothelial injury and increased leakiness, reduced organ perfusion and coagulation defects. Endothelial cell injury may also cause loss of ACE as it is a membrane bound endothelial enzyme [40,52]. ACE burden may be estimated by measuring the ratio of angiotensin I and angiotensin II levels with ratio. Healthy individuals have an angiotensin I to angiotensin II level ratio of 0.5. In the ATHOS-3 trial, patients had a median angiotensin I/angiotensin II ratio of 1.63 [53].This suggests angiotensin converting enzyme levels are reduced in vasodilatory shock likely due to endothelial dysfunction. Hence AT-II infusion will compensate for this reduction in levels and thus improve hypotension. Septic patients with less effective ACE activity as measured by increased angiotensin I/angiotensin II ratios were more likely to die compared to those with normal ACE activity [54]. Calzavacca et al. found that the use of catecholeamines is associated with unfavorable microcirculatory oxygenation profile (increased renal oxygen consumption with catecholamines as compared to AT-II) in an experimental sheep study model [55]. Data in vasodilatory shock models reveals that intravenous infusion of AT-II can restore GFR, increase urine output without decreasing renal oxygenation [40,50,53,56,57]. Unlike catecholamines, AT-II causes vasoconstriction of efferent arterioles [50,56,57]. This increases GFR by increasing glomerular capillary pressure [59]. Studies have demonstrated that septic shock creates a form of acute renal failure that is responsive to infusion of AT-II [50,56,58,60].

8. Angiotensin II in high output shock (ATHOS trial)

Patients with distributive shock who require high dose vasopressors have a high mortality. Chawla et al. [61] in 2014 first published the effects of AT-II in high output shock (ATHOS trial). This was a pilot study involving the use of AT-II. It was a prospective randomized double blind study in which 20 patients with distributive shock and a

cardiovascular Sequential Organ Failure Assessment (SOFA) score of 4 were randomized to either AT-II infusion ($N = 10$) or placebo plus standard of care (N = 10). AT-II was titrated for a goal MAP of 65 mmHg. The infusion (either AT-II or placebo) was continued for 6 h then titrated off. The primary endpoint was the effect of the AT-II infusion on the standing dose of NE that was required to maintain a MAP of 65 mmHg. The secondary endpoints evaluated the effect of the ATII infusion on urine output, serum lactate, cardiac output, and 30-day mortality. In this study, AT-II resulted in marked reduction in NE dosing in all patients. There was no statistically significant difference in 30 day mortality between AT-II group and placebo group. (50% versus 60% respectively, $p = 1.00$). Hypertension was the most common side effect noted in the AT-II group. The authors concluded the initial dose range of AT-II that appears to be appropriate for patients with distributive shock was 2 to 10 ng/kg/min.

9. Limitations of ATHOS

There were several limitations of the ATHOS trial. The study had a small sample size ($N = 20$). The study was inadequately powered to establish a difference in mortality between AT-II and placebo groups. The placebo group had younger but sicker patients. This may have potentially influenced a difference in response to AT-II between the two populations. Based on the pressor titration protocol used specifically in this study, results may not be applicable for lesser sick patients. The authors were unable to make a conclusion about effects of AT-II on urine output and renal functions due to the high incidence of oliguria and renal replacement therapy in both AT-II group and placebo group. The authors concluded the need for further larger randomized placebo controlled trials to more completely elucidate the role of AT-II as a pressor in the treatment of shock. This study laid the foundation for the ATHOS-3 trial.

10. Angiotensin II in vasodilatory shock/ATHOS-3 trial

Khanna et al. in the ATHOS-3 trial revealed AT-II effectively increased blood pressure in patients with vasodilatory shock that did not respond to high doses of conventional vasopressors [62]. This was a multinational, double blind, randomized, controlled trial. The authors randomly assigned patients with vasodilatory shock who were receiving >0.2 micrograms/kg/min of NE or the equivalent dose of another vasopressor to receive either angiotensin II or placebo. The primary end point was a response in MAP at hour 3 after the start of infusion. Response was defined as an increase from baseline of at least 10 mmHg or an increase to at least 75 mmHg, without an increase in the dose of background vasopressors. In this study 344 patients underwent randomization. 163 patients received AT-II and 158 received placebo (321 received a study intervention). At 48 h, the mean improvement in the cardiovascular Sequential Organ Failure Assessment score (SOFA) was greater in the AT-II group than the placebo group. Patient who received AT-II had a lower requirement for catecholamine use. Also the MAP at 3 h was significantly greater in the AT-II group than the placebo group. There was no statistically significant difference in mortality between the two groups. This is the first and only large study of AT-II in humans.

11. Critique of ATHOS 3 trial

ATHOS 3 had several issues that need to be addressed. Pertinent data such as central venous pressure, central venous oxygen saturation, and cardiac index were missing in 72 of 321 patients (22%), 84 of 321 (26%), and 179 of 321 (56%), respectively. Fluid balance difference between the two groups was not reported. Since AT-II may have deleterious effects on microcirculation, lactate and central venous oxygen saturation (which are frequently used as indirect measures of tissue perfusion and microcirculatory health) were not compared between the two groups. In addition, cardiovascular SOFA improved in the study group which is an expected finding since AT-II elevated blood pressure, but total SOFA was not different between the two groups. Does that mean that other organs included in total SOFA got worse in the study group compared to the control group? AT-II could have detrimental effects on lungs and brain. These two organs were not addressed specifically in ATHOS 3. The definition of refractory vasodilatory shock is arbitrary in the study and is different from other studies on septic shock and MAP >75 exceeds current recommendations. The authors acknowledged the study was not powered to detect mortality benefit. They also acknowledge that follow-up was limited to 28 days, thus the possibility of either beneficial or harmful long term effects of AT-II therapy could not be excluded. Though the study did not show significant difference in DVT between the 2 groups (1.8% group vs 0% in placebo group), the FDA package inserts report an increase in the combination of venous and arterial thrombotic events (13% vs 5%, $p = 0.02$). FDA recommends DVT chemoprophylaxis when using AT-II which is a standard of care while treating critically ill patients unless there is an active contra-indication to do so.

In a recent literature review on the effect of angiotensin II on blood pressure in patients with circulatory shock, 24 studies including 353 patients were identified that include ATHOS III trial. Shock was distributive ($n = 225$), cardiogenic ($n = 38$), or from other causes ($n = 90$). Patients with cardiogenic, septic, and other types of shock exhibited similar increases in BP. Only two of 24 studies analyzed were RCTs, with other studies being case-control and case-study formats. Of the 353 patients included in the analysis, 163 were from ATHOS III, however, this was a well-designed RCT, lending credibility to the results [63].

12. Conclusion

AT-II has been shown to increase the mean arterial pressure in vasodilatory shock refractory to catecholamines. AT - II is a molecule innate to human physiology and, along with catecholamines and vasopressin, helps maintain BP throughout a variety of conditions. Its widely described effects include direct vasoconstriction of peripheral vessels, potentiation of water reabsorption as part of the renin-angiotensin-aldosterone system, and interaction with other endogenous pressors (catecholamines and vasopressin). It also helps regulate and maintain glomerular filtration, especially during periods of reduced renal perfusion. AT-II is an available option approved by the FDA for its use in shock refractory to catecholamines provided patients have been adequately volume resuscitated. Larger trials with longer duration of follow-up are warranted to address the questions which are unanswered by the ATHOS-3 trial, especially pertaining to its effects on lungs, brain, microcirculation, inflammation, and venous thromboembolism risk.

Abbreviations

AT-I	Angiotensin I
AT-II	Angiotensin II
AT 1–7	Angiotensin 1-7
AT 1–9	Angiotensin 1-9
ACE	Angiotensin converting enzyme
ACE-2	Angiotensin converting enzyme -2
AT-R1	Angiotensin receptor 1
AT-R2	Angiotensin receptor 2
RAAS	Renin Angiotensin Aldosterone System
AKI	Acute kidney injury
RRT	Renal replacement therapy
NE	Norepinephrine
VCAM	vascular cell adhesion molecule
VEGF	Vascular endothelial growth factor
IL-1B	Interleukin-1B
TNF-alpha	Tumor necrosis factor- alpha

INF-gamma	Interferron-gamma
Arap	Angiotensin receptor associated protein
ATHOS	Angiotensin II in high output shock
GFR	Glomerular filtration rate
SOFA	Sequential Organ Failure Assessment
MAP	Mean arterial pressure

References

[1] Singer M, Deutschman CS, Seymour CW, et al. The third international consensus definitions for sepsis and septic shock (sepsis-3). JAMA 2016;315(8):801–10. https://doi.org/10.1001/jama.2016.0287.

[2] Shankar-Hari M, Phillips GS, Levy M, et al. Developing a new definition and assessing new clinical criteria for septic shock: for the third international consensus definitions for sepsis and septic shock (sepsis-3). JAMA 2016;315(8):775–87.

[3] Seymour CW, Liu VX, Iwashyna TJ, et al. Assessment of clinical criteria for sepsis: for the third international consensus definitions for sepsis and septic shock (sepsis-3). JAMA 2016;315(8):762–74. https://doi.org/10.1001/jama.2016.0288.

[4] Antonucci E, Fiaccadori E, Donadello K, et al. Myocardial depression in sepsis: from pathogenisis to clinical manifestations and treatment. J Crit Care 2014;29(4):500–11. https://doi.org/10.1016/j.jcrc.2014.03.028.

[5] Dellinger RP, Levy MM, Rhodes A, et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock. Crit Care Med 2012;41(2):580–637. https://doi.org/10.1097/CCM.0b013e31827e83af.

[6] Asfar P, Meziani F, Hamel JF, et al. High vs low blood pressure target in patients with septic shock. N Engl J Med 2014;370(17):1583–93.

[7] Lavrentyev EN, Estes AM, Malik KU et al. Mechanism of high glucose induced angiotensin II production in rat vascular smooth muscle cells. Circ Res 2007; 101:455–464. [PubMed: 17626897].

[8] Kumar R, Boim MA, et al. Diversity of pathways for intracellular angiotensin II synthesis. Curr Opin Nephrol Hypertens 2009;18:33–9 [PubMed: 19077687].

[9] Kumar R, Thomas CM, Yong QC, et al. The intracrine rennin angiotensin system. Clin Sci (Lond) 2012;123(5):273–84.

[10] Paul M, Poyan Mehr A, Kreutz R, et al. Physiology of local renin-angiotensin systems. Physiol Rev 2006;86(3):747–803.

[11] Corre^a TD, Takala J, Jakob SM, et al. Angiotensin II in septic shock. Crit Care 2015;16(19):98.

[12] Donoghue M, Hsieh F, Baronas E, et al. A novel angiotensin-converting enzyme-related carboxypeptidase (ACE2) converts angiotensin I to angiotensin 1–9. Circ Res 2000;87:e1–9. https://doi.org/10.1161/01.RES.87.5.e1.

[13] Santos RA, Ferreira AJ. Angiotensin-(1–7) and the renin-angiotensin system. Curr Opin Nephrol Hypertens 2007;16(2):122–8.

[14] McKinney CA, Kennedy S, Ballie G, et al. 178 Angiotensin 1-9 inhibits vascular smooth muscle cell proliferation and migration in vitro and neointimal formation in vivo. Heart 2015;101:A101.

[15] Fyhrquist F, Saijonmaa O, et al. Renin-angiotensin system revisited. J Intern Med 2008;264:224–36. https://doi.org/10.1111/j.1365-2796.2008.01981.x.

[16] Zhuo JL, Li XC, et al. New insights and perspectives on intrarenal rennin angiotensin system: focus on intracrine/intracellular angiotensin II. Peptides 2011;32:1551–65. https://doi.org/10.1016/j.peptides.2011.05.012.

[17] Bodor C, Nagy J, Végh B, et al. Angiotensin II increases the permeability and PV-1 expression of endothelial cells. Am J Physiol Cell Physiol 2012;302:C267–76. https://doi.org/10.1152/ajpcell.00138.2011.

[18] Tamion F, Le Cam-Duchez V, Menard JF, et al. Erythropoietin and renin as biological markers in critically ill patients. Crit Care 2004;8(5):R328–35. https://doi.org/10.1186/cc2902.

[19] Doerschug KC, Delsing AS, Schmidt GA, et al. Renin-angiotensin system activation correlates with microvascular dysfunction in a prospective cohort study of clinical sepsis. Crit Care 2010;14:R24. https://doi.org/10.1186/cc8887.

[20] Hilgenfeldt U, Kienapfel G, Kellermann W, et al. Renin angiotensin system in sepsis. Clin Exp Hypertens A 1987;9:1493–504. https://doi.org/10.3109/10641968709158998.

[21] Rolih CA, Ober KP, et al. The endocrine response to critical illness. Med Clin North Am 1995;79(1):211–24.

[22] du Cheyron D, Lesage A, Daubin C, et al. Hyperreninemic hypoaldosteronism: a possible etiological factor of septic shock induced acute renal failure. Intensive Care Med 2003;29(10):1703–9 2003 https://doi.org/10.1007/s00134-003-1986-6.

[23] Bucher M, Hobbhahn J, Kurtz A, et al. Nitric oxide-dependent down-regulation of angiotensin II type 2 receptors during experimental sepsis. Crit Care Med 2001;29(9):1750–5.

[24] Bucher M, Ittner KP, Hobbhahn J, et al. Downregulation of angiotensin II type 1 receptors during sepsis. Hypertension 2001;38(2):177–82.

[25] Ikeda Y, Takeuchi K, Kato T, et al. Transcriptional suppression of rat angiotensin AT1a receptor gene expression by interferon-gamma in vascular smooth muscle cells. Biochem Biophys Res Commun 1999;262(2):494–8.

[26] Sasamura H, Nakazato Y, Hayashida T, et al. Regulation of vascular type 1 angiotensin receptors by cytokines. Hypertension 1997;30(1):35–41.

[27] Mederle K, Schweda F, Kattler V, et al. The angiotensin II AT1 receptor-associated protein Arap1 is involved in sepsis-induced hypotension. Crit Care 2013;17(4):R130.

[28] Correâ TD, Jeger V, Pereira AJ et al. Angiotensin II in septic shock: effects on tissue perfusion, organ function, and mitochondrial respiration in a porcine model of fecal peritonitis. Crit Care Med 2014: 42(8): 550–559.doi:https://doi.org/10.1097/CCM.0000000000000039.

[29] Inoue N, Kinugawa S, Suga T, et al. Angiotensin II-induced reduction in exercise capacity is associated with increased oxidative stress in skeletal muscle. Am J Physiol Heart Circ Physiol 2012;302(5):1202–10. https://doi.org/10.1152/ajpheart.00534.2011.

[30] Imai Y, Kuba K, Rao S, et al. Angiotensin-converting enzyme 2 protects from severe acute lung failure. Nature 2005;436(7047):112–6. https://doi.org/10.1038/nature03712.

[31] Zambelli V, Bellani G, Borsa R, et al. Angiotensin-(1-7) improves oxygenation, while reducing cellular infiltrate and fibrosis in experimental acute respiratory distress syndrome. Intensive Care Med Exp 2015;3(1):44. https://doi.org/10.1186/s40635-015-0044-3.

[32] Supe S, Kohse F, Gembardt F, et al. Therapeutic time window for angiotensin-(1-7) in acute lung injury. Br J Pharmacol 2016;173(10):1618–28. https://doi.org/10.1111/bph.13462.

[33] Denton KM, Anderson WP, Sinniah R, et al. Effects of angiotensin II on regional afferent and efferent arteriole dimensions and the glomerular pole. Am J Physiol Regul Integr Comp Physiol 2000;279(2):629–38.

[34] Wernze H, Spech HJ, Muller G, et al. Studies on the activity of the renin-angiotensin-aldosterone system (RAAS) in patients with cirrhosis of the liver. Klin Wochenschr 1978;56(8):389–97.

[35] Zhuang S, Wang HF, Wang X et al. The association of renin angiotensin system blockade use with the risks of cognitive impairment of aging and Alzheimer's disease: a meta-analysis. J Clin Neurosci 2016: 33:32–38. DOI: doi:https://doi.org/10.1016/j.jocn.2016.02.036

[36] Wharton W, Goldstein FC, Zhao L, et al. Modulation of renin-angiotensin system may slow conversion from mild cognitive impairment to Alzheimer's disease. J Am Geriatr Soc 2015;63(9):1749–56. https://doi.org/10.1111/jgs.13627.

[37] Bali A, Jaggi AS et al. Angiotensin II-triggered kinase signaling cascade in the central nervous system. Rev Neurosci 2016: 27(3):301–315. doi: https://doi.org/10.1515/revneuro-2015-0041.

[38] Villapol S, Balarezo MG, Affram K, et al. Neurorestoration after traumatic brain injury through angiotensin II receptor blockage. Brain 2015;138(11):3299–315. https://doi.org/10.1093/brain/awv172.

[39] Busse LW, Wang XS, Chalikonda DM, et al. Clinical experience with IV angiotensin II administration: a systematic review of safety. Crit Care Med 2017 Aug;45(8):1285–94. https://doi.org/10.1097/CCM.0000000000002441.

[40] Zarjou A, Agarwal A, et al. Sepsis and acute kidney injury. J Am Soc Nephrol 2011;22:999–1006. https://doi.org/10.1681/ASN.2010050484.

[41] Uchino S, Kellum JA, Bellomo R, et al. Acute renal failure in critically ill patients: a multinational, multicenter study. JAMA 2005;294(7):813–8. https://doi.org/10.1001/jama.294.7.813.

[42] Tumlin JA, Murugan R, Deane AM, et al. Outcomes in patients with vasodilatory shock and renal replacement therapy treated with intravenous angiotensin II. Crit Care Med 2018;46(6):949–57. https://doi.org/10.1097/CCM.0000000000003092.

[43] Chawla LS, Eggers PW, Star RA, et al. Acute kidney injury and chronic kidney disease as interconnected syndromes. N Engl J Med 2014;371:58–66. https://doi.org/10.1056/NEJMra1214243.

[44] Joannidis M, Druml W, Forni LG, et al. Prevention of acute kidney injury and protection of renal function in the intensive care unit: update 2017. Intensive Care Med 2017;43:730–49. https://doi.org/10.1007/s00134-017-4832-y.

[45] Gaudry S, Hajage D, Schortgen F, et al. AKIKI study group: initiation strategies for renal-replacement therapy in the intensive care unit. N Engl J Med 2016;375:122–33.

[46] Zarbock A, Kellum JA, Schmidt C, et al. Effect of early vs delayed initiation of renal replacement therapy on mortality in critically ill patients with acute kidney injury: the ELAIN randomized clinical trial. JAMA 2016;315:2190–9.

[47] Lim HA, Lee HH, Kim AJ, et al. Renin-angiotensin-aldosterone system blockade in critically ill patients is associated with increased risk for acute kidney injury. Tohoku J Exp Med 2016;238:17–23 12.

[48] Langenberg C, Bagshaw SM, May CN, et al. The histopathology of septic acute kidney injury: a systematic review. Crit Care 2008;12:R38. https://doi.org/10.1186/cc6823.

[49] Schrier RW, Wang W, Poole B, et al. Acute renal failure: definitions, diagnosis, pathogenesis, and therapy. J Clin Invest 2004;114:5–14.

[50] Lankadeva YR, Kosaka J, Evans RG, et al. Intrarenal and urinary oxygenation during norepinephrine resuscitation in ovine septic acute kidney injury. Kidney Int 2016;90:100–8.

[51] du Cheyron D, Fradin S, Ramakers M, et al. Angiotensin converting enzyme insertion/deletion genetic polymorphism: its impact on renal function in critically ill patients. Crit Care Med 2008;36:3178–83.

[52] Orfanos SE, Armaganidis A, Glynos C, et al. Pulmonary capillary endothelium-bound angiotensin-converting enzyme activity in acute lung injury. Circulation 2000;102:2011–8.

[53] Khanna A, English SW, Wang XS, et al. ATHOS-3 investigators: angiotensin II for the treatment of vasodilatory shock. N Engl J Med 2017;337:419–30.

[54] Wunderink RG, Alberton TE, Busse LW, et al. Baseline angiotensin levels and ACE effects in patients with vasodilatory shock treated with angiotensin II. Intensive Care Med Exp 2017;5:0703.

[55] Calzavacca P, Evans RG, Bailey M, et al. Variable responses of regional renal oxygenation and perfusion to vasoactive agents in awake sheep. Am J Physiol Regul Integr Comp Physiol 2015;309:R1226–33.

[56] Lankadeva YR, Kosaka J, Evans RG, et al. Urinary oxygenation as a surrogate measure of medullary oxygenation during angiotensin II therapy in septic acute kidney injury. Crit Care Med 2018;46:e41–8.

[57] Brenner M, Schaer GL, Mallory DL, et al. Detection of renal blood flow abnormalities in septic and critically ill patients using a newly designed indwelling thermodilution renal vein catheter. Chest 1990;98:170–9.

[58] Wan L, Langenberg C, Bellomo R, et al. Angiotensin II in experimental hyperdynamic sepsis. Crit Care 2009;13:R190.

[59] Prowle JR, Bellomo R, et al. Sepsis-associated acute kidney injury: macrohemodynamic and microhemodynamic alterations in the renal circulation. Semin Nephrol 2015;35:64–74.
[60] May CN, Ishikawa K, Wan L, et al. Renal bioenergetics during early gram-negative mammalian sepsis and angiotensin II infusion. Intensive Care Med 2012;38:886–93.
[61] Chawla LS, Busse L, Brasha-Mitchell E, et al. Intravenous angiotensin II for the treatment of high-output shock (ATHOS trial): a pilot study. Crit Care 2014;18:534. https://doi.org/10.1186/s13054-014-0534-9.
[62] Khanna A, English SE, Wang XS, et al. Angiotensin II for the treatment of vasodilatory shock. N Engl J Med 2017;377:419–30.
[63] Busse LW, McCurdy MT, Ali O, et al. The effect of angiotensin II on blood pressure in patients with circulatory shock: a structured review of the literature. Crit Care 2017;21(1):324.