Angiotensin in Critical Care

Anna Hall, *Guy's & St Thomas' NHS Foundation Hospital*
Laurence W. Busse, *Emory University*
Marlies Ostermann, *Guy's & St Thomas' NHS Foundation Hospital*

Copyright information:

Critical Care

REVIEW

Open Access

Angiotensin in Critical Care

CrossMark

Anna Hall[1], Laurence W. Busse[2] and Marlies Ostermann[3*]

Abstract

This article is one of ten reviews selected from the Annual Update in Intensive Care and Emergency Medicine 2018. Other selected articles can be found online at https://www.biomedcentral.com/collections/annualupdate2018. Further information about the Annual Update in Intensive Care and Emergency Medicine is available from http://www.springer.com/series/8901.

Background

Hypotension is a key feature of shock and strongly correlated with the development of multisystem organ failure. Multiple studies have highlighted that even short durations of hypotension are harmful [1, 2]. In a retrospective analysis of 33,000 non-cardiac surgical patients, Walsh et al. showed that short periods of intraoperative hypotension were associated with a significant increase in the risk of acute kidney injury (AKI), myocardial injury or cardiac complications and mortality [1]. The risk of renal and cardiac injury increased with duration of hypotension and was significant for periods as short as 1–5 min. Similarly, using data from over 57,000 patients undergoing non-cardiac surgery, Salmasi et al. showed that patients with a mean arterial pressure (MAP) less than 65 mmHg during the intraoperative period had a significantly higher risk of myocardial injury and AKI, confirming that hypotension does not need to be severe to affect organ function [2]. On the basis of these and other studies, European and international guidelines for the treatment of shock recommend that a minimum MAP should be maintained at all times and that the target should be at least 65 mmHg [3, 4]. Heretofore, the restoration and maintenance of MAP has been accomplished through the judicious use of fluids as well as vasopressors, namely catecholamines and vasopressin analogs. However, patients with sepsis

in particular often show marked hyporeactivity to traditionally administered therapies. To date, no vasopressor has consistently been proven to be superior to the others in terms of clinical outcomes [5–7]. In 2015, a meta-analysis concluded that in terms of survival, with the exception of noted superiority of norepinephrine over dobutamine, there was insufficient evidence to recommend any vasopressor agent or combination over another [8].

Angiotensin II (Ang II) has emerged as an effective therapy to raise blood pressure in patients with vasodilatory shock [9]. The first reports of Ang II administration in patients with shock date back 50 years, but interest was re-ignited following several small studies and a recent larger randomized controlled trial (RCT) confirming that Ang II was effective at maintaining MAP at target and reducing norepinephrine requirements without an increase in adverse effects [9–11]. The following review provides an overview of the physiological effects of angiotensin and summarizes existing data in the literature.
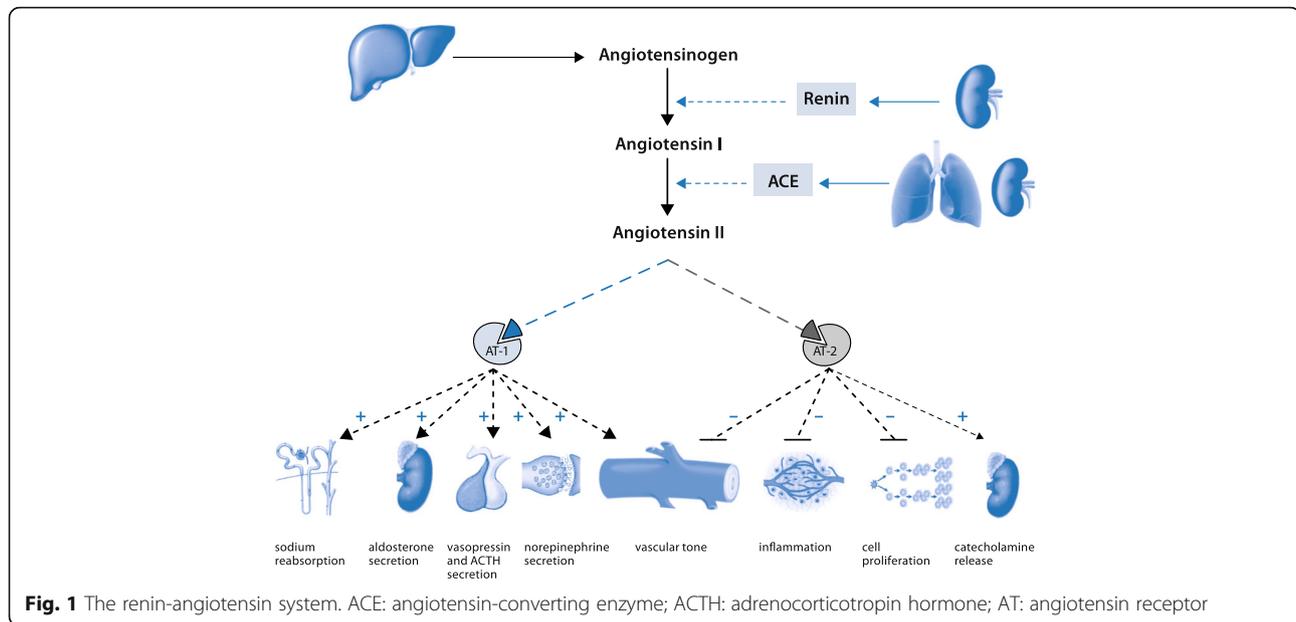
Role of Renin-Angiotensin System

After the discovery of renin in 1898, angiotensinogen and angiotensin-converting enzyme (ACE) were later identified as additional key components of the classical circulating renin-angiotensin system (RAS) [12, 13]. Angiotensinogen, the precursor of angiotensin, is an α-glycoprotein produced primarily by the liver and released into the systemic circulation where it is converted to angiotensin I (Ang I) under activity by renin (Fig. 1). Ang I is cleaved into Ang II, predominantly by endothelial-bound ACE in the lungs but also in plasma and the vascular bed of kidneys, heart and brain, and to some extent by chymases stored in secretory granules in mast cells [13, 14].

Renin is an enzyme produced by pericytes in the vicinity of the afferent arterioles and cells of the juxtaglomerular apparatus. It is stored in intracellular vesicles and rapidly secreted in response to three stimuli: a decrease in blood pressure as detected by baropressors, a decrease in the sodium concentration delivered to the

* Correspondence: Marlies.Ostermann@gstt.nhs.uk
[3]Department of Critical Care, King's College London, Guy's & St Thomas' NHS Foundation Hospital, London, UK
Full list of author information is available at the end of the article

Hall *et al. Critical Care* (2018) 22:69

Page 2 of 6

Fig. 1 The renin-angiotensin system. ACE: angiotensin-converting enzyme; ACTH: adrenocorticotropin hormone; AT: angiotensin receptor

distal tubules, and activation of the sympathetic nervous system (through β_1 adrenergic receptors). Renin itself has no peripheral receptors and no direct hemodynamic effects [14].

Ang II, an octapeptide, has strong vasopressor properties but its action is terminated by rapid degradation to angiotensin III by angiotensinases located in red blood cells and the vascular beds of most tissues. Ang II is also hydrolized into Ang (1–7) through the actions of ACE 2. It has a half-life in circulation of around 30 s, whereas, in tissue, this may be as long as 15–30 min [15].

In addition to the 'classic' systemic RAS, which regulates blood pressure, fluid and electrolyte homeostasis and preserves volume status and vascular tone, most organs contain a tissue RAS and an intracellular RAS. The tissue RAS is predominantly involved in local cardiovascular regulation and inflammatory processes, including vascular permeability, apoptosis, cellular growth, migration and cell differentiation, and the intracellular RAS participates in intracellular signaling pathways [16].

Physiologic Effects of Angiotensin II

Ang II exerts its effects by binding to specific angiotensin (AT) receptors based on the cell membrane of various cell types: AT-1, AT-2, AT-4 and Mas receptors. In humans, the major physiological effects are mediated by AT-1 receptors located in the kidneys, vascular smooth muscle, lung, heart, brain, adrenals, pituitary gland and liver, and relate to maintenance of hemodynamic stability and fluid and electrolyte regulation ([14, 16]; Fig. 1 and Table 1).

In the healthy adult, the AT-2 receptor is expressed in certain cell types and tissues, such as vascular endothelial cells, distinct areas of the brain, adrenal glands, myometrium and ovaries and selected cutaneous, renal and cardiac structures [17, 18]. Although their expression level is often much lower than that of AT-1 receptors, AT-2 receptors have an important role in injury and repair mechanisms and, under conditions such as mechanical injury or ischemia, expression may be increased. There is also good evidence that AT-2 receptors are involved in the regulation of Ang II mediated adrenal catecholamine secretion, for example during sepsis [18]. The main biological effects of the AT-2 receptor are often opposite to the AT-1 receptors with focus on anti-proliferation, vasodilation and anti-inflammation. Stimulation of AT-2 receptors confers protection against an overstimulation of AT-1 receptors: for example, vasoconstriction mediated by the AT-1 receptors can be opposed by the vasodilatory effects of Ang II linked to the AT-2 receptor ([19]; Fig. 1). AT-2 receptors also play a role in pressure natriuresis, opposing the anti-natriuretic effects of AT-1 receptor activation, and in cardiovascular remodeling following myocardial infarction and hypertension, heart failure and stroke. Finally, in the fetus and neonate, AT-2 receptors are involved in fetal tissue development, neuronal regeneration and cellular differentiation.

The AT-4 receptor is activated by the Ang II metabolite Ang IV, and appears to contribute to the regulation of the extracellular matrix in the central nervous system, as well as modulation of oxytocin release.

Hall et al. Critical Care (2018) 22:69

Page 3 of 6

Table 1 Main physiological effects of angiotensin (Ang) II

Organ system	Physiological effects
Vascular	Vasoconstriction of venous and arterial vessels Increased vascular permeability by inducing VEGF
Renal	Stimulation of Na reabsorption and H^+ excretion in the proximal tubule via the Na/H$^+$ exchanger Stimulation of the release of aldosterone, which stimulates the distal tubule and collecting ducts of the kidneys to re-absorb sodium and water Variable effects on glomerular filtration and renal blood flow depending on the physiological and pharmacological setting: i) Constriction of the afferent and efferent glomerular arterioles; although this will tend to restrict renal blood flow, the effect on the efferent arteriole is markedly greater, and as a result, this tends to increase or maintain GFR ii) Constriction of the glomerular mesangium, thereby reducing the area for glomerular filtration iii) Enhanced sensitivity to tubuloglomerular feedback and thereby prevention of excessive rise in GFR iv) Stimulation of local release of prostaglandins, which oppose the effect of Ang II and antagonize renal vasoconstriction
Endocrine	Stimulation of the secretion of vasopressin from the posterior pituitary gland Secretion of ACTH in the anterior pituitary gland Enhancement of release of norepinephrine by direct action on postganglionic sympathetic fibers
Nervous	Enhancement of norepinephrine secretion
Cardiac	Mediation of cardiac remodeling through activated tissue RAS in cardiac myocytes
Coagulation	Prothrombotic potential through adhesion and aggregation of platelets and stimulation of PAI-1 and PAI-2
Immune	Promotion of cell growth and inflammation Increased expression of endothelium-derived adhesion molecules Synthesis of pro-inflammatory cytokines and chemokines Generation of reactive oxygen species

ACTH adrenocorticotropin hormone, *GFR* glomerular filtration rate, *RAS* renin-angiotensin system, *PAI* plasminogen activator inhibitor, *VEGF* vascular endothelial growth factor

Sepsis-Induced Dysregulation of the Renin-Angiotensin System

The natural role of the RAS is to preserve volume status and arterial blood pressure, thereby maintaining the systemic circulation and also the microcirculation. In sepsis, both over- and under-stimulation of the RAS have been reported in patients [20–25]. The capacity of ACE and the functionality of angiotensin receptors are key factors that determine whether hemodynamic stability can be achieved and maintained.

ACE is an ectoenzyme that is distributed primarily on the pulmonary capillary endothelium but can also be found in endothelial and renal epithelial cells. ACE molecules are uniformly distributed along the luminal pulmonary endothelial surface including the membrane caveolae [26]. As a result, ACE is directly accessible to blood-borne substrates and able to convert Ang I to Ang II rapidly, but also very susceptible to disease processes that affect the pulmonary vasculature [27].

Effects of Sepsis on Ang II Levels

During sepsis, renin, Ang I and Ang II are usually activated. However, variable and even low plasma levels of Ang II have been reported [20, 21]. The reasons are multifactorial. Pre-morbid treatment with an ACE-inhibitor will prevent conversion of Ang I to Ang II. There is also evidence that endotoxin associated with Gram-negative sepsis has potential to deactivate ACE [22]. Additionally, in diseases that affect the pulmonary capillary endothelium, such as acute respiratory distress syndrome (ARDS) and pneumonia, ACE activity is altered at an early stage, resulting in reduced capacity to convert Ang I to Ang II [23, 28–30].

Low levels of Ang II and ACE have clinical implications. Zhang et al. measured serial Ang II and ACE concentrations in 58 patients with severe sepsis and showed that the cohort with low levels exhibited more complications and had a greater risk of dying [20].

Sepsis-Induced Downregulation of Ang II Receptors

Ang II is antagonized by the endogenous vasodilator, nitric oxide (NO), and each has a role in influencing the production and functioning of the other. Several studies have shown that sepsis is associated with downregulation of AT-1 receptors, likely mediated by pro-inflammatory cytokines and NO [31, 32]. In addition, reduced activity of the AT-1 receptor associated protein 1 (Arap 1) has been reported [33]. The physiological role of Arap 1 is to support the

Hall *et al. Critical Care* (2018) 22:69

Page 4 of 6

trafficking of the AT-1 receptor to the cell membrane. As such, reduced activity of Arap 1 is associated with decreased sensitivity of the AT-1 receptor.

Downregulation of AT-2 receptors may also occur during septic shock [18]. The consequences of this process are reduced catecholamine release by the adrenal medulla and attenuation of the responsiveness of blood pressure and aldosterone formation.

Clinical Studies with Angiotensin

Ang II was discovered in the 1930s and has been used in clinical studies since the early 1960s. To date, over 31,000 subjects have been exposed to Ang II either as monotherapy or in combination with catecholamines and non-catecholamine vasopressors in various clinical settings [34].

Prevention of Hypotension During Obstetric Anesthesia

Hypotension is a frequently occurring adverse effect during spinal anesthesia. In the obstetric population where utero-placental blood flow depends directly on maternal blood pressure and where moderate maternal hypotension is associated with fetal hypoxemia and neurological morbidity, every attempt is made to prevent hypotension [35]. Phenylephrine and ephedrine are often used in clinical practice. Ephedrine was the vasoconstrictor agent of choice in obstetric anesthesia for many years because of its marked increase in utero-placental blood flow [36]. However, it has fallen out of favor because of its association with lower umbilical artery pH values, likely due to increased fetal metabolic activity [37].

Phenylephrine is a synthetic sympathicomimetic agent that is regarded to be safe in the treatment of regional anesthesia-induced maternal hypotension [35].

Ang II has been shown to cause less vasoconstriction of the utero-placental vascular bed compared with uterine or other systemic vessels [38, 39]. In 1994, Ramin et al. randomized 30 healthy pregnant women undergoing elective Cesarean section either to a control group or prophylactic Ang II infusion versus prophylactic ephedrine infusion in order to maintain a diastolic blood pressure 0–10 mmHg above the baseline [40]. In women randomized to Ang II infusion, the maternal Ang II levels were increased nearly fourfold but Ang II levels in the umbilical artery and vein were unchanged. Of note, no one in the Ang II cohort had a recorded umbilical artery blood pH < 7.20 in contrast to 40% of the ephedrine group. Vincent et al. reported similar results in 54 women randomized to Ang II versus ephedrine during spinal anesthesia for elective Cesarean delivery [41]. The umbilical arterial and venous pH and base excess were higher in the angiotensin group compared to women who had received ephedrine, and maternal heart rate

was higher in the ephedrine group. The authors concluded that Ang II maintained systolic blood pressure during anesthesia without causing fetal acidosis or increasing maternal heart rate.

Treatment of Hypotension Following ACE Inhibitor Overdose

ACE-inhibitor overdose may result in severe refractory hypotension. Several case reports have highlighted successful treatment with Ang II [42–44]. Although in all cases, Ang II was administered in combination with other therapies, including gut decontamination, intravenous fluids, vasopressors and naloxone, there was a profound effect on blood pressure immediately after starting Ang II infusion. Physiologically, it is logical to regard Ang II as a rational treatment for ACE-inhibitor induced hypotension.

Treatment of Vasodilatory Shock

The most immediate and critical need of patients with vasodilatory shock is the achievement of hemodynamic stability to prevent multiorgan dysfunction whilst allowing time to treat the underlying etiology. Multiple vasopressors and catecholamines are often needed [45]. Studies using Ang II as a vasopressor for management of shock were originally conducted in the 1960s. Ang II was compared to catecholamines in non-randomized designs and was shown to have comparable effects to norepinephrine [46, 47].

In the first RCT, Chawla et al. reported a catecholamine-sparing effect in patients with high output shock treated with Ang II administration [10]. The subsequent Angiotensin for the Treatment of High Output Shock (ATHOS)-3 trial was a phase 3, placebo-controlled, double-blind, multicenter RCT including 321 patients with refractory vasodilatory shock who were randomized to Ang II infusion or placebo [9]. Analysis of the primary efficacy endpoint (defined as the percentage of patients achieving the pre-specified target blood pressure response) was statistically significant ($p < 0.0001$). Twenty-three percent of the 158 placebo-treated patients had a desired blood pressure response compared to 70% of the 163 patients treated with Ang II. Treatment with Ang II also resulted in a significant decrease in the standard of care vasopressor use, as measured by a change in the cardiovascular Sequential Organ Failure Assessment (SOFA) score at 48 h (– 1.75 versus – 1.28, $p = 0.01$). No difference in mortality was noted but there were fewer adverse events with Ang II. In a recent systematic review including data from > 31,000 patients, Busse et al. also confirmed that Ang II was safe to be used in humans [34].

Hall *et al. Critical Care* (2018) 22:69

Page 5 of 6

Conclusion

The RAS plays a key role in maintaining hemodynamic stability, vascular tone and electrolyte homeostasis. Studies suggest that its physiological regulation is disturbed in sepsis and critical illness, which results in altered ACE functionality, reduced generation of Ang II and downregulation of Ang II receptors. Recent RCTs stipulate that Ang II is an effective and safe treatment for hypotension in patients with refractory vasodilatory shock, allowing for sparing of catecholamines. It may also have a role in cardiogenic, distributive and unclassified shock [48].

Innate to the human body are three molecules (catecholamines, vasopressin and angiotensin) that maintain and regulate BP. The addition of Ang II as a potential tool in the armamentarium against shock offers clinicians the opportunity to provide a 'balanced' approach to vasopressor therapy. The combination of different vasoactive drugs that mimic the natural response to severe vasodilatation and hypotension makes physiological sense [49]. With this approach, the likelihood of hemodynamic recovery is enhanced and toxicity from large doses of monotherapy can be minimized.

Authors' contributions
AH wrote the first draft of the manuscript. All authors revised the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

Publisher's Note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Author details
[1]Department of Critical Care, Guy's & St Thomas' NHS Foundation Hospital, London, UK. [2]Department of Medicine, Emory Saint Joseph's Hospital, Emory University School of Medicine, Atlanta, GA, USA. [3]Department of Critical Care, King's College London, Guy's & St Thomas' NHS Foundation Hospital, London, UK.

Published online: 20 March 2018

References
1. Walsh M, Devereaux PJ, Garg AX, et al. Relationship between intraoperative mean arterial pressure and clinical outcomes after noncardiac surgery: toward an empirical definition of hypotension. Anesthesiology. 2013;119:507–15.
2. Salmasi V, Maheshwari K, Yang D, et al. Relationship between intraoperative hypotension, defined by either reduction from baseline or absolute thresholds, and acute kidney and myocardial injury after noncardiac surgery. Anesthesiology. 2017;126:47–65.
3. Cecconi M, De Backer D, Antonelli M, et al. Consensus on circulatory shock and hemodynamic monitoring. Task force of the European Society of Intensive Care Medicine. Intensive Care Med. 2014;40:1795–815.
4. Rhodes A, Evans LE, Alhazzani W, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock: 2016. Intensive Care Med. 2017;43:304–77.
5. Sakr Y, Reinhart K, Vincent J-L, et al. Does dopamine administration in shock influence outcome? Results of the Sepsis Occurrence in Acutely Ill Patients (SOAP) Study. Crit Care Med. 2006;34:589–97.
6. Myburgh JA, Higgins A, Jovanovska A, et al. A comparison of epinephrine and norepinephrine in critically ill patients. Intensive Care Med. 2008;34:2226–34.
7. Russell JA, Walley KR, Singer J, et al. Vasopressin versus norepinephrine infusion in patients with septic shock. N Engl J Med. 2008;358:877–87.
8. Zhou F, Mao Z, Zeng X, et al. Vasopressors in septic shock: a systematic review and network meta-analysis. Ther Clin Risk Manag. 2015;11:1047–59.
9. Khanna A, English SW, Wang XS, et al. Angiotensin II for the treatment of vasodilatory shock. N Engl J Med. 2017;377:419–30.
10. 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.
11. Correa TD, Takala J, Jakob SM. Angiotensin II in septic shock. Crit Care. 2015;19:98.
12. Tigerstedt R, Bergman P. Niere und Kreislauf. Scand Arch Physiol. 1898; 8:223–71.
13. Correa TD, Takala J, Jakob S. Angiotensin II in septic shock. Crit Care. 2015;19:98.
14. Paul M, Mehr A, Kreutz R. Physiology of local renin-angiotensin systems. Physiol Rev. 2006;86:747–803.
15. Kopf P, Campbell W. Endothelial metabolism of angiotensin II to angiotensin III, not angiotensin (1–7), augments the vasorelaxation response in adrenal cortical arteries. Endocrinology. 2013;154:4768–76.
16. Fyhrquist F, Saijonmaa O. Renin-angiotensin system revisited. J Intern Med. 2008;264:224–36.
17. Steckelings UM, Kaschina E, Unger T. The AT2 receptor – a matter of love and hate. Peptides. 2005;26:1401–19.
18. Bucher M, Hobbhahn J, Kurtz A. Nitric oxide-dependent down-regulation of angiotensin II type 2 receptors during experimental sepsis. Crit Care Med. 2001;29:1750–5.
19. Carey RM, Wang ZQ, Siragy HM. Role of the angiotensin type 2 receptor in the regulation of blood pressure and renal function. Hypertension. 2000;35:155–63.
20. Zhang W, Chen X, Huang L, et al. Severe sepsis: Low expression of the renin-angiotensin system is associated with poor prognosis. Exp Ther Med. 2014;7:1342–8.
21. Dong LW, Chang YZ, Tong LJ, Tang J, Su JY, Tang CS. Role of regulatory peptide in pathogenesis of shock. Sci China B. 1994;37:162–9.
22. Dunn CW, Horton JW. Role of angiotensin II in neonatal sepsis. Circ Shock. 1993;40:144–50.
23. Chawla LS, Busse LW, Brasha-Mitchell E, Alotaibi Z. The use of angiotensin II in distributive shock. Crit Care. 2016;20:13.
24. Wray GM, Coakley JH. Severe septic shock unresponsive to noradrenaline. Lancet. 1995;346:1604.
25. Salgado DR, Rocco JR, Silva E, Vincent J-L. Modulation of the renin-angiotensin-aldosterone system in sepsis: a new therapeutic approach? Expert Opin Ther Targets. 2010;14:11–20.
26. Orfanos SE, Langleben D, Khoury J, et al. Pulmonary capillary endothelium-bound angiotensin-converting enzyme activity in humans. Circulation. 1999;99:1593–9.
27. 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.
28. Casey L, Krieger B, Kohler J, Rice C, Oparil S, Szidon P. Decreased serum angiotensin converting enzyme in adult respiratory distress syndrome associated with sepsis: a preliminary report. Crit Care Med. 1981;9:651–4.
29. Johnson AR, Coalson JJ, Ashton J, Larumbide M, Erdös EG. Neutral endopeptidase in serum samples from patients with adult respiratory

Hall *et al. Critical Care* (2018) 22:69

Page 6 of 6

distress syndrome. Comparison with angiotensin-converting enzyme. Am Rev Respir Dis. 1985;132:1262–7.

30. Kuba K, Imai Y, Penninger JM. Angiotensin-converting enzyme 2 in lung disease. Curr Opin Pharmacol. 2006;6:271–6.

31. Bucher M, Ittner KP, Hobbhahn J, Taeger K, Kurtz A. Downregulation of angiotensin II type 1 receptors during sepsis. Hypertension. 2001;38:177–82.

32. Schmidt C, Höcherl K, Kurt B, Moritz S, Kurtz A, Bucher M. Blockade of multiple but not single cytokines abrogates downregulation of angiotensin II type-I receptors and anticipates septic shock. Cytokine. 2010;49:30–8.

33. 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:R130.

34. Busse LW, Wang XS, Chalikonda DM, et al. Clinical experience with IV angiotensin ii administration: a systematic review of safety. Crit Care Med. 2017;45:1285–94.

35. Chooi C, Cox JJ, Lumb RS et al (2017) Techniques for preventing hypotension during spinal anaesthesia for caesarean section. Cochrane Database Syst Rev CD002251.

36. McGrath J, Chestnut D, Vincent R, et al. Ephedrine remains the vasopressor of choice for treatment of hypotension during ritodrine infusion and epidural anesthesia. Anesthesiology. 1994;80:1073–81.

37. Shearer VE, Ramin SM, Wallace DH, Dax JS, Gilstrap LC 3rd. Fetal effects of prophylactic ephedrine and maternal hypotension during regional anesthesia for cesarean section. J Matern Fetal Med. 1996;5:79–84.

38. Naden RP, Rosenfeld CR. Effect of angiotensin II on uterine and systemic vasculature in pregnant sheep. J Clin Invest. 1981;68:468–74.

39. Rosenfeld CR, Naden RP. Uterine and nonuterine vascular responses to angiotensin II in ovine pregnancy. Am J Physiol. 1989;257:H17–24.

40. Ramin SM, Ramin KD, Cox K, Magness RR, Shearer VE, Gant NF. Comparison of prophylactic angiotensin II versus ephedrine infusion for prevention of maternal hypotension during spinal anesthesia. Am J Obstet Gynecol. 1994;171:734–9.

41. Vincent RD Jr, Werhan CF, Norman PF, et al. Prophylactic angiotensin II infusion during spinal anesthesia for elective cesarean delivery. Anesthesiology. 1998;88:1475–9.

42. Jackson T, Corke C, Agar J. Enalapril overdose treated with angiotensin infusion. Lancet. 1993;341:703.

43. Newby DE, Lee MR, Gray AJ, Boon NA. Enalapril overdose and the corrective effect of intravenous angiotensin II. Br J Clin Pharmacol. 1995;40:103–4.

44. Trilli LE, Johnson KA. Lisinopril overdose and management with intravenous angiotensin II. Ann Pharmacother. 1994;28:1165–7.

45. Brand DA, Patrick PA, Berger JT, et al. Intensity of vasopressor therapy for septic shock and the risk of in-hospital death. J Pain Symptom Manage. 2017;53:938–43.

46. John JN, Luria MH. Studies in clinical shock and hypotension. II. Hemodynamic effects of norepinephrine and angiotensin. J Clin Invest. 1965;44:1494–504.

47. Belle MS, Jaffee RJ. The use of large doses of angiotensin in acute myocardial infarction with shock. J Lancet. 1965;85:193–4.

48. Busse LW, McCurdy MT, Osman A, Hall A, Chen H, Ostermann M. The effect of angiotensin II on blood pressure in patients with circulatory shock: a structured review of the literature. Crit Care. 2017;21:34.

49. Bellomo R, Hilton A. The ATHOS-3 trial, angiotensin II and The Three Musketeers. Crit Care Resusc. 2017;19:3–4.