Is the Renin-Angiotensin-Aldosterone System Good for the Kidney in Acute Settings?

Emmanuel Dudoignon^{a, b} François Dépret^{a–c} Matthieu Legrand^{a–c}

^aDepartment of Anaesthesiology, Critical Care Medicine and Burn unit, AP-HP, Saint Louis University Hospitals, Paris, France; ^bINSERM UMR-S942, Institut National de la Santé et de la Recherche Médicale (INSERM), Lariboisière Hospital and INI-CRCT Network, Paris, France; ^cUniversité Paris Diderot, Paris, France

Keywords

Renin-angiotensin-aldosterone system · Acute kidney injury · Renal fibrosis · Antagonists · Chronic conditions · Acute conditions

Abstract

The renin-angiotensin-aldosterone system (RAAS) plays a major role in the regulation of blood pressure, renal hemodynamic, myocardial contractility via an enzymatic cascade leading to the synthesis of angiotensin 2. The activation of the RAAS system after acute kidney injury triggers renal inflammation and fibrotic process with long-term damaging consequences. To date, there is still a debate on the benefits of RAAS for the kidney in acute settings. Effects of RAAS antagonists are variable in chronic or acute conditions. The aim of this review is to discuss the renal and systemic effects of the RAAS, and its modulation, in acute situations.

© 2019 S. Karger AG, Basel

Introduction

The renin-angiotensin-aldosterone system (RAAS) plays a major role in the regulation of blood pressure vascular tone, renal hemodynamic, myocardial contractility via an enzymatic cascade leading to the synthesis of angiotensin 2 (ang-2). Ang-2, synthesized from ang-1 by the angiotensin converting enzyme (ACE), exerts its actions via 2 receptors (AT1 and AT2) present on the surface of many cells (cardiomyocytes, smooth muscle cells, fibroblasts, endothelial cells and immune cells). In chronic condition, the activation of the RAAS has been associated with morbidity and mortality related to cardiovascular

Contribution from the AKI and CRRT 2019 Symposium at the 24th International Conference on Advances in Critical Care Nephrology, Manchester Grand Hyatt, San Diego, CA, USA, February 26 – March 1, 2019. This symposium was supported in part by the NIDDK funded University of Alabama at Birmingham–University of California San Diego O'Brien Center for Acute Kidney Injury Research (P30DK079337).

Fig. 1. Schematic representation of the role of the RAAS modulation in kidney disease. TGF- β , transforming growth factor-beta.

damage secondary to structural changes in the myocardium [1] and the development of chronic kidney disease. The RAAS has long been considered a key adaptive mechanism to hypovolemia and shock in acute setting. In this line, RAAS antagonists have long been considered nephrotoxic, preventing the renal autoregulation of renal blood flow and glomerular filtration. However, accumulative data suggest that activation of the RAAS system after acute kidney injury (AKI) triggers renal inflammation and fibrotic process with long-term damaging consequences. Recently, ang-2 has been proposed for hemodynamic support in distributive shock [2]. The aim of this review is to discuss the renal and systemic effects of the RAAS, and its modulation, in acute situations.

Major Renal Effects of the RAAS

Angiotensinogen is synthesized by hepatocytes and released into the plasma (Fig. 1). Renin – a protease produced by the myoepithelioid cells of the afferent arteriole of the renal glomerulus – cleaves the angiotensinogen to ang-1. Renin is rapidly secreted in response to a decrease in blood pressure as detected by baroreceptors, a decrease

in the sodium concentration delivered to the distal tubules, and activation of the sympathetic nervous system (β 1 adrenergic receptors) [3]. The conversion enzyme is a carboxy-peptidase that cleaves plasma ang-1 to ang-2. Ang-2 stimulates the AT-1 and AT-2 receptors [4].

The AT-1 receptors are expressed over the entire length of the nephron but predominantly on the proximal circumvoluted tubules. Ang-2 essentially exerts a vasoconstrictive action on the efferent arteriole of the glomerular capillaries, increasing the glomerular capillary hydraulic pressure. Ang-2 is the key mediator in the renal blood flow and glomerular filtration rate autoregulation. In the event of a decrease in systemic arterial pressure, renal blood flow and glomerular filtration are aimed to be maintained by the vasodilation of the afferent arteriole and vasoconstriction of the efferent arteriole through ang-2 production [4].

Ang-2 also acts on the systemic circulation: it triggers sodium reabsorption by the sodium-proton exchangers by stimulating aldosterone synthesis to regulate fluid balance and volemia. Finally, Ang-2 can potentially increase renal perfusion pressure through the systemic vasoconstrictive vascular effect and rise of systemic arterial pressure.

While potentially increasing the glomerular filtration rate, sustained increase in ang-2 production also however increases transforming growth factor-beta (TGF- β) expression and decreases lysosomal activity and protein fragmentation, causing proteinuria [5].

RAAS Promotes Renal Inflammation and Renal Fibrosis after AKI

Ang-2 has proinflammatory effects and promotes fibrosis. In response to ang-2 expression, tubular epithelial cells change their phenotype, migrate into the interstitium, and acquire a myofibroblastic phenotype (epithelial-mesenchymal transdifferentiation) [6]. Myofibroblasts then produce type 1 collagen involved in the fibrotic process. An indirect effect involves the activation of tyrosine kinase receptors (EGF-R, PDGF-R, FGF-R) that promotes fibrosis through the production of TGF- β . Ang-2 promotes a renal inflammatory response through the activation of the AT1 receptor in resident cells and the activation of NF-KB pathway with production of chemokines (Monocyte chemoattractant protein 1 and regulated on activation, normal T cell expressed and secreted recruiting inflammatory cells), cytokines (interleukin-1 [IL-1], tumor necrosis factor-alpha). Ang-2 dependent leukocyte recruitment has also been involved in the progression of glomerulosclerosis [6].

Ang-2 also binds to a 7-domain transmembrane receptor, AT1 activating a G protein, phospholipase C and inositol trisphosphate production responsible for an increase of intracellular calcium leading to intra renal vasoconstriction and vascular remodeling [6].

By reducing blood pressure, RAAS inhibitors limit the secondary immune activation in the kidney. Fimasartan has been shown to attenuate the upregulation of inflammatory cytokines (tumor necrosis factor-alpha, IL-1 and IL-6), decreased apoptosis of renal tubular cells (decrease caspase-3 activity), and finally preserves renal function and tubular architecture after ischemia-reperfusion injury in a mouse model. The upregulation of *Tgfb1* (encoding TGF- β 1), *Col3a1* and *Col1a1* in kidney was attenuated by administration of Losartan. It reduced renal fibrosis, mortality and ensuing CKD after severe AKI in mice [7]. One week after losartan administration in hypertensive mice, collagen I, collagen IV, and TGF- β gene and protein expressions were decreased and glomerulosclerosis less marked, whereas activities of metalloproteinases remain higher than those in controls. After 4 weeks of Losartan, the renal

functional and histologic parameters were completely normalized.

Animal studies have shown that the activation of RAAS during and after AKI would play a crucial role in the AKI to CKD transition [8]. The administration of Losartan before ischemia-reperfusion maintained renal blood flow, decreased inflammation, and prevented the development of chronic kidney disease [9]. Mineralocorticoid receptor antagonists given before and after ischemia-reperfusion were also shown to be protective, preventing the transition of AKI to CKD [10]. Interestingly, RAAS activation seems to persist long after AKI and treatment with Losartan may reduce the progression to CKD and mortality when given after AKI [11]. Altogether, these data suggest that RAAS blockers may prevent the progression of renal fibrosis after AKI (Fig. 1).

Importantly, worsening renal function detected with decrease in GFR is not necessarily associated with kidney damage. In patients with DM and CKD, dual RAS blockade using an ACEi and an ARB was associated with an increased risk of AKI compared to monotherapy. However, AKI in the setting of monotherapy was associated with poorer long-term outcomes [12]. Intensive blood pressure control in the SPRINT trial was accompanied by a decrease in levels of kidney damage biomarkers levels despite lower GFR. Not all declines in GFR may represent tissue damage, and automatic discontinuation of RAASi in the face of a decrease in GFR may not always be necessary [13].

Effect of RAAS Antagonists in Patients with Acute Conditions

Patients with AKI

The association between the use of ACEi or ARBs and 1-year mortality was studied in 1,551 patients discharged alive from an intensive care unit in a prospective observational cohort [14]. In patients with AKI during ICU stay, 1-year mortality was lower in patients treated with ACE or ARBs at ICU discharge hazard ratio (HR) of 0.55 (0.35–0.89), HR of 0.45 (0.27–0.75) and HR of 0.48 (0.27–0.85, $p < 0.001$). This association remained even after adjusted analysis and propensity score matching (including chronic heart failure, ACEi/ ARB on ICU admission, Charlson Comorbidity Index, age, diabetes mellitus, chronic kidney disease, estimated glomerular filtration rate and arterial blood pressure at ICU discharge vasopressors and renal replacement therapy). These results were confirmed in a recent observational study involving

46,253 patients with an episode of AKI during hospitalization: ACEi or ARB therapy after discharge was associated with a 15% decrease in all-cause mortality (HR 0.85; 95% CI 0.81–0.89) [15]. The protective effect of ACEi/ARB may be driven by a reduction in cardiovascular events including myocardial infarctions and heart failure. Nevertheless, mortality reduction was accompanied by higher risk of hospitalization for renal causes in this later study. Altogether, preclinical and clinical data suggest a protective effect of drug blockage in RAAS after an episode of AKI.

Patients with Shock

ACE, an endothelium-bound protein that is mainly expressed in pulmonary and renal capillaries, cleaves ang-1 into ang-2. Patients with vasoplegic shock or endotoxemia may have acquired ACE deficiency. ACE activity was associated with the prognosis of patients in shock [16]. Endothelial dysfunction as observed in vasoplegic shock may cause ACE deficiency and ang-2 deficiency [16]. Furthermore, ACE inhibition is associated with an increase in bradykinin and angiotensin 1–7, which have vasodilatory properties in hypertensive patients. These data suggest that patients with vasoplegic shock may have an excess of vasodilator mediators and a deficit in ang-2 production due to low ACE activity. In this line, the administration of exogenous ang-2 in patients with distributive shock has been proposed to restore blood pressure. In the ATHOS trial [2], patients were randomized to receive Ang-2 or placebo. Death by day 28 occurred in 75 of 163 patients (46%) in the angiotensin II group and in 85 of 158 patients (54%) in the placebo group (HR 0.78; 95% CI 0.57–1.07; $p = 0.12$). Ang-2 effectively increased blood pressure in patients with vasodilatory shock that did not respond to high doses of conventional vasopressors. Even though the results of the ATHOS trial suggest that the administration of exogenous Ang-2 might be an option to restore blood pressure in shock patients requiring high doses of vasopressors, the impact on mid and long-term outcome on such a strategy remains unknown. The administration of exogenous Ang-2 raises concerns on the risk of organs fibrosis, long-term organ damage, and outcome in light of above-mentioned data.

Perioperative Period

The impact of blocking the RAAS in the perioperative period is largely unknown. Hollmann et al. [17] have in a recent meta-analysis included 25 studies including 6,022 perioperative noncardiac surgical patients treated with

ACEi or ARB. Of these 6,022 patients, 1,816 patients had stopped treatment on the morning of surgery and 4,206 had continued their treatment. Continuation of treatment was not associated with an increase in overall mortality, but there was more intraoperative hypotension. A multicenter, prospective, randomized trial is currently underway to evaluate the effect of discontinuation or continuation of RAAS inhibitors prior to major surgery on mortality and major postoperative complications at day 28 (NCT 03374449) [18].

Conclusion

The RAAS promotes the development of fibrosis. Blocking the RAAS has long been recognized as a protective strategy to prevent progression of chronic kidney. More recent data seem to show a benefit of blocking the RAAS after an episode of AKI in the post-acute setting. The inhibition of the RAAS may be therefore considered a strategy to improve long-term outcome in patients recovering from AKI. On the other hand, the administration of ang-2 has been proposed to restore blood pressure in distributive shock receiving high doses of vasopressors. The long-term consequences of ang-2 infusion in this setting are unknown. Well-designed prospective observational and interventional trials to explore the RAAS modulation are now rapidly needed in the acute setting.

Disclosure Statement

Matthieu Legrand reports research support from The French Ministry of Health, Shingotec and personal fees from Baxter, Fresenius and Novartis. The other authors have no disclosure to declare.

References

- 1 Go AS, Hsu CY, Yang J, Tan TC, Zheng S, Ordonez JD, et al. Acute Kidney Injury and Risk of Heart Failure and Atherosclerotic Events. *Clin J Am Soc Nephrol*. 2018 Jun;13(6):833–41.
- 2 Khanna A, English SW, Wang XS, Ham K, Tumlin J, Szerlip H, et al.; ATHOS-3 Investigators. Angiotensin II for the Treatment of Vasodilatory Shock. *N Engl J Med*. 2017 Aug; 377(5):419–30.
- 3 Paul M, Poyan Mehr A, Kreutz R. Physiology of local renin-angiotensin systems. *Physiol Rev*. 2006 Jul;86(3):747–803.
- 4 Kobori H, Nangaku M, Navar LG, Nishiyama A. The intrarenal renin-angiotensin system: from physiology to the pathobiology of hypertension and kidney disease. *Pharmacol Rev*. 2007 Sep;59(3):251–87.

- 5 Russo LM, Brammar GC, Jerums G, Comper WD, Osicka TM. The effect of ramipril on albumin excretion in diabetes and hypertension: the role of increased lysosomal activity and decreased transforming growth factor-beta expression. *J Hypertens*. 2003 Feb;21(2): 419–28.
- 6 Ruiz-Ortega M, Esteban V, Rupérez M, Sánchez-López E, Rodríguez-Vita J, Carvajal G, et al. Renal and vascular hypertension-induced inflammation: role of angiotensin II. *Curr Opin Nephrol Hypertens*. 2006 Mar;15(2):159–66.
- 7 Chou YH, Huang TM, Pan SY, Chang CH, Lai CF, Wu VC, et al. Renin-Angiotensin System Inhibitor is Associated with Lower Risk of Ensuing Chronic Kidney Disease after Functional Recovery from Acute Kidney Injury. *Sci Rep*. 2017 Apr;7(1):46518.
- 8 Chou YH, Chu TS, Lin SL. Role of renin-angiotensin system in acute kidney injury-chronic kidney disease transition. *Nephrology (Carlton)*. 2018 Oct;23 Suppl 4:121–5.
- 9 Rodríguez-Romo R, Benítez K, Barrera-Chimal J, Pérez-Villalva R, Gómez A, Aguilar-León D, et al. AT1 receptor antagonism before ischemia prevents the transition of acute kidney injury to chronic kidney disease. *Kidney Int*. 2016 Feb;89(2):363–73.
- 10 Barrera-Chimal J, Pérez-Villalva R, Rodríguez-Romo R, Reyna J, Uribe N, Gamba G, et al. Spironolactone prevents chronic kidney disease caused by ischemic acute kidney injury. *Kidney Int*. 2013 Jan;83(1):93–103.
- 11 Cheng SY, Chou YH, Liao FL, Lin CC, Chang FC, Liu CH, et al. Losartan reduces ensuing chronic kidney disease and mortality after acute kidney injury. *Sci Rep*. 2016 Sep;6(1): 34265.
- 12 Palevsky PM, Zhang JH, Seliger SL, Emanuele N, Fried LF; VA NEPHRON-D Study. Incidence, Severity, and Outcomes of AKI Associated with Dual Renin-Angiotensin System Blockade. *Clin J Am Soc Nephrol*. 2016 Nov; 11(11):1944–53.
- 13 Zhang WR, Craven TE, Malhotra R, Cheung AK, Chonchol M, Drawz P, et al.; SPRINT Research Group. Kidney Damage Biomarkers and Incident Chronic Kidney Disease During Blood Pressure Reduction: A Case-Control Study. *Ann Intern Med*. 2018 Nov;169(9): 610–8.
- 14 Gayat E, Hollinger A, Cariou A, Deye N, Vieillard-Baron A, Jaber S, et al; FROG-ICU investigators. Impact of angiotensin-converting enzyme inhibitors or receptor blockers on post-ICU discharge outcome in patients with acute kidney injury. *Intensive Care Med*. 2018 May;44(5):598–605.
- 15 Brar S, Ye F, James MT, Hemmelgarn B, Klarenbach S, Pannu N; Interdisciplinary Chronic Disease Collaboration. Association of Angiotensin-Converting Enzyme Inhibitor or Angiotensin Receptor Blocker Use With Outcomes After Acute Kidney Injury. *JAMA Intern Med*. 2018 Dec;178(12):1681–90.
- 16 Chawla LS, Chen S, Bellomo R, Tidmarsh GF. Angiotensin converting enzyme defects in shock: implications for future therapy. *Crit Care*. 2018 Oct;22(1):274.
- 17 Hollmann C, Fernandes NL, Biccari BM. A Systematic Review of Outcomes Associated With Withholding or Continuing Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers Before Noncardiac Surgery. *Anesth Analg*. 2018 Sep;127(3): 678–87.
- 18 Legrand M, Futier E, Leone M, Deniau B, Mebazaa A, Plaud B, et al. Impact of renin-angiotensin system inhibitors continuation versus discontinuation on outcome after major surgery: protocol of a multicenter randomized, controlled trial (STOP-or-NOT trial). *Trials*. 2019 Mar 5;20(1):160.