

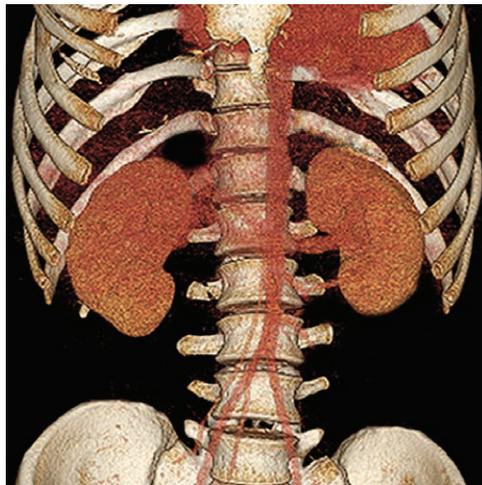
Natriuretic Peptides

A Role in Early Septic Acute Kidney Injury?

Nishkantha Arulkumaran, M.B.B.S., B.Sc., Ph.D., M.R.C.P., F.F.I.C.M.,
John R. Prowle, M.A., M.B., B.Chir., M.Sc., M.D., F.R.C.P., F.F.I.C.M.

ACUTE kidney injury is a common complication of critical illness and is associated with significant morbidity, mortality, and financial cost. Sepsis is the leading association of acute kidney injury in the intensive care unit and is implicated in more than half the cases.¹ Our understanding of the pathogenesis of sepsis-associated acute kidney injury continues to evolve. Current evidence suggests that pathways involving inflammatory injury to the renal tubules and microcirculation play a leading role in the development of the acute kidney injury syndrome, and these mechanisms may be dissociated from sepsis-induced changes in systemic hemodynamics.^{2,3} Reflecting our poor understanding of this complex syndrome, we lack any specific treatment for the prevention or resolution of septic acute kidney injury other than supportive care. In this issue of *ANESTHESIOLOGY*, Kitamura *et al.*⁴ present findings in an animal model of lipopolysaccharide administration that adds to our understanding of the pathogenesis of sepsis-associated acute kidney injury and the tubular cell dysfunction that is its pathologic hallmark. Furthermore, these findings support further investigation of natriuretic peptides in early sepsis as agents that could modify tubular function and ameliorate the wider effects of endotoxin on the microcirculation.

The hemodynamic instability associated with sepsis led to the dogma that sepsis-induced acute kidney injury is primarily a consequence of renal ischemia and ensuing acute tubular necrosis.⁵ However, clinical and animal studies have shown that acute kidney injury can arise in the context of preserved or even increased renal blood flow; thus, there is at least a disconnect between systemic hemodynamics and the development of renal injury.³ Furthermore, histopathologic



“...[A]trial natriuretic peptide may play a crucial role in maintaining normal function of the renal tubules and microcirculation in early sepsis...”

epiphenomenon. Furthermore, natriuretic peptides receptors (the guanylyl cyclase-A receptor), found on both endothelial cells and tubular cells, may play an important role in the regulation of renal function and urine output in acute kidney injury.

In their study, Kitamura *et al.*⁴ describe the role of renal proximal tubular and endothelial cell natriuretic peptide receptors on the regulation of urine output in a rodent model of endotoxemia. For these studies, they employed recombinant natriuretic peptides in rats and mice, or used mice that lacked renal or endothelial guanylyl cyclase-A receptor in either endothelial cells or proximal tubular cells (using “conditional knockout” transgenic mice with inducible tissue-specific genetic deletion). A particular strength of the study is the dynamic imaging of tubular function and flow in real time using intravital multiphoton microscopy to

studies have shown that in sepsis, the degree of frank tubular cell necrosis is disproportionately low compared to functional renal impairment.^{6,7} Thus, the pathophysiology of septic acute kidney injury is a more complex process that involves alterations in the renal microcirculation, bioenergetics, inflammation, and expression of tubular epithelial ion transporters.^{8,9} These insights into the pathophysiology underlying septic acute kidney injury have been made possible by animal models of sepsis.

The prohormone of atrial natriuretic peptide is acutely increased in sepsis, and may correlate with the incidence of acute kidney injury.¹⁰ Given the ability of atrial natriuretic peptide to modulate vascular and renal function,^{11,12} it seems plausible that increased atrial natriuretic peptide concentrations in sepsis reflect an adaptive response rather than simply an

Image: J. P. Rathbun.

Corresponding article on page 296.

Accepted for publication May 7, 2018. From the Bloomsbury Institute of Intensive Care Medicine, Division of Medicine, University College London, London, United Kingdom (N.A.); the Critical Care and Perioperative Medicine Research Group, William Harvey Research Institute, Queen Mary University of London, London, United Kingdom (J.R.P.); and the Adult Critical Care Unit and Department of Renal Medicine and Transplantation, The Royal London Hospital, Barts Health National Health Service Trust, London, United Kingdom (J.R.P.).

Copyright © 2018, the American Society of Anesthesiologists, Inc. Wolters Kluwer Health, Inc. All Rights Reserved. *Anesthesiology* 2018; 129:235-7

observe the working nephrons of live, anesthetized animals. Fluorescent dyes were injected intravenously, and the timing of their appearance in various nephron segments allowed estimation of glomerular filtration rate and flow along the nephron from the proximal to distal tubule as well as any changes that occurred in response to injection of lipopolysaccharide and administration of resuscitation fluids and/or recombinant human atrial natriuretic peptides.

As expected, lipopolysaccharide injection was associated with lower mean arterial pressure and urine output, and an increase in serum creatinine, accompanied by demonstration of decreased glomerular filtration and reduced tubular flow rates in imaged nephrons. Fluid resuscitation alone restored urine output and serum creatinine to normal values, and administration of human atrial natriuretic peptides increased urine output above the normal range. Early (2-h) fluid resuscitation alone partially restored glomerular filtration rate, but had no effect on downstream tubular flow, while early administration of human atrial natriuretic peptides increased improved flow along the tubule as well as the proportion of functional nephrons. In contrast, late (18-h) administration of human atrial natriuretic peptides and fluids had no beneficial effect on either glomerular filtration or tubular flow. The effect of human atrial natriuretic peptides on tubular flow, but not glomerular filtration, was mediated primarily by proximal tubular guanylyl cyclase-A, as demonstrated by no improvement in tubular flow rates in response to human atrial natriuretic peptides in mice that lacked functional proximal tubular guanylyl cyclase-A receptors. Conversely, the effect of human atrial natriuretic peptides on glomerular filtration was mediated primarily by endothelial tubular guanylyl cyclase-A, as demonstrated by the lack of improvement in glomerular filtration in response to human atrial natriuretic peptides in mice that lacked functional endothelial guanylyl cyclase-A receptors. Overall, these findings indicate that atrial natriuretic peptide may play a crucial role in maintaining normal function of the renal tubules and microcirculation in early sepsis and that loss of these responses could be associated with progression of acute kidney injury. Finally, in addition to these renal-specific roles, an important systemic role for guanylyl cyclase-A receptors in maintaining endothelial cell integrity in general was suggested by exaggerated leakage of albumin (ascites, lung) in mice that lacked functional endothelial guanylyl cyclase-A receptors.

What do these elegant but complex findings mean for the clinician in anesthesia and critical care? While pathologic mechanisms seen in this rodent model of endotoxin-induced acute kidney injury may not directly parallel human sepsis, this study provides us with a better understanding of mechanisms of early renal dysfunction in sepsis-associated acute kidney injury and how human atrial natriuretic peptides may be a candidate therapeutic agent. Importantly, other potential benefits of atrial natriuretic peptides, beyond renal protection (*e.g.*, reduced vascular leak), also warrant investigation.

However, while the improvement in glomerular filtration, tubular flow, and urine output seen with human atrial natriuretic peptides is promising, it cannot be assumed that this equates to improved organ function and survival. For example, increasing urine output (*e.g.*, by using diuretics) does not necessarily improve renal function or survival.¹³ In the current study, it was not possible to assess the independent effect of atrial natriuretic peptide administration on short- and longer-term renal function. The results of this study should also be interpreted in context of limitations. In particular, the model had a high mortality, and therefore any benefits of atrial natriuretic peptide might not be generalizable to clinical practice.

There are other more immediately applicable insights from this research. Crucially, the timing of intervention is vital. The early administration of fluids and human atrial natriuretic peptides may be of use in preventing sepsis-associated acute kidney injury, but the use of fluid or human atrial natriuretic peptides later in the disease process when acute kidney injury is established was not beneficial. This finding is consistent with evidence of lack of efficacy for use of natriuretic peptides in treatment of human perioperative acute kidney injury.¹⁴ Established acute kidney injury is associated with loss of polarized expression of tubular cell transmembrane proteins, and it is tempting to conclude that in established acute kidney injury, kidneys have effectively developed the knock-out phenotype and become atrial natriuretic peptide-unresponsive. This timing sensitivity of targeted interventions for acute kidney injury is also in line with our increasing recognition of the limited efficacy (and potential harm) associated with aggressive fluid resuscitation beyond the very earliest phases of sepsis.

Existing clinical data on the therapeutic effect of human atrial natriuretic peptides in acute kidney injury have been limited to perioperative medicine and contrast nephropathy.¹⁴ We look forward to further preclinical and translational studies that will enable the design of clinical trials investigating the therapeutic benefit of human atrial natriuretic peptides in preventing or reversing sepsis-associated acute kidney injury. However, presentation with sepsis is often delayed, so in clinical practice, pharmacologic interventions may need to be developed in harmony with diagnostic approaches to identify patients within a window for benefit.

Competing Interests

The authors are not supported by, nor maintain any financial interest in, any commercial activity that may be associated with the topic of this article.

Correspondence

Address correspondence to Dr. Prowle: j.prowle@qmul.ac.uk

References

1. Bouchard J, Acharya A, Cerda J, Maccariello ER, Madarasu RC, Tolwani AJ, Liang X, Fu P, Liu ZH, Mehta RL: A prospective

- international multicenter study of AKI in the intensive care unit. *Clin J Am Soc Nephrol* 2015; 10:1324–31
2. Kellum JA, Prowle JR: Paradigms of acute kidney injury in the intensive care setting. *Nat Rev Nephrol* 2018; 307:2265
 3. Prowle JR, Bellomo R: Sepsis-associated acute kidney injury: Macrohemodynamic and microhemodynamic alterations in the renal circulation. *Semin Nephrol* 2015; 35:64–74
 4. Kitamura H, Nakano D, Sawanobori Y, Asaga T, Yokoi H, Yanagita M, Mukoyama M, Tokudome T, Kangawa K, Shirakami G, Nishiyama A: Guanylyl cyclase A in both renal proximal tubular and vascular endothelial cells protects the kidney against acute injury in rodent experimental endotoxemia models. *ANESTHESIOLOGY* 2018; 129:296–310
 5. Schrier RW, Wang W: Acute renal failure and sepsis. *N Engl J Med* 2004; 351:159–69
 6. Langenberg C, Gobe G, Hood S, May CN, Bellomo R: Renal histopathology during experimental septic acute kidney injury and recovery. *Crit Care Med* 2014; 42:e58–67
 7. Lerolle N, Nochy D, Guérot E, Bruneval P, Fagon JY, Diehl JL, Hill G: Histopathology of septic shock induced acute kidney injury: Apoptosis and leukocytic infiltration. *Intensive Care Med* 2010; 36:471–8
 8. Schmidt C, Höcherl K, Schweda F, Kurtz A, Bucher M: Regulation of renal sodium transporters during severe inflammation. *J Am Soc Nephrol* 2007; 18:1072–83
 9. Arulkumaran N, Pollen S, Greco E, Courtneidge H, Hall AM, Duchon MR, Tam FWK, Unwin RJ, Singer M: Renal tubular cell mitochondrial dysfunction occurs despite preserved renal oxygen delivery in experimental septic acute kidney injury. *Crit Care Med* 2018; 46:e318–25
 10. Mazul-Sunko B, Zarković N, Vrkić N, Antoljak N, Bekavac Beslin M, Nikolić Heitzler V, Siranović M, Krizmanić-Dekanić A, Klinger R: Proatrial natriuretic peptide (1-98), but not cystatin C, is predictive for occurrence of acute renal insufficiency in critically ill septic patients. *Nephron Clin Pract* 2004; 97:c103–7
 11. Sekino M, Makita T, Ureshino H, Sungsam C, Sumikawa K: Synthetic atrial natriuretic peptide improves systemic and splanchnic circulation and has a lung-protective effect during endotoxemia in pigs. *Anesth Analg* 2010; 110:141–7
 12. Aiura K, Ueda M, Endo M, Kitajima M: Circulating concentrations and physiologic role of atrial natriuretic peptide during endotoxic shock in the rat. *Crit Care Med* 1995; 23:1898–906
 13. Cantarovich F, Rangoonwala B, Lorenz H, Verho M, Esnault VL; High-Dose Furosemide in Acute Renal Failure Study Group: High-dose furosemide for established ARF: A prospective, randomized, double-blind, placebo-controlled, multicenter trial. *Am J Kidney Dis* 2004; 44:402–9
 14. Nigwekar SU, Navaneethan SD, Parikh CR, Hix JK: Atrial natriuretic peptide for preventing and treating acute kidney injury. *Cochrane Database Syst Rev* 2009; 80:CD006028