Paulo Benigno Pena Batista[1,2,3],Rogério da Hora Passos[1,2]

The new frontiers of acute kidney injury

As novas fronteiras da lesão renal aguda

1. Hospital São Rafael - Salvador (BA), Brazil.
2. Instituto Nacional de Ciência, Inovação e Tecnologia em Saúde - CITECS - Salvador (BA), Brazil.
3. Escola Bahiana de Medicina e Saúde Pública - Salvador (BA), Brazil.

Acute kidney injury (AKI) is a poorly understood syndrome. AKI has definitions and concepts that are changeable, and it can not rely on the possibility of histological examination for diagnosis, either because of the difficulty in performing a kidney biopsy in critical patients or for its focal nature and its preference for the external layer of the medulla that comprises most of the juxtamedullary glomeruli, which are not frequently obtained.[1]

The pathophysiology of AKI has many aspects and depends on many mechanisms involving the endothelium, glycocalyx, cytoskeleton, integrins, lymphokines and chemokines among others. In the most studied experimental animal models of ischemia and reperfusion[1] and even in recent studies of human kidneys from organ donors whose glycocalyces were analyzed *in vivo*, AKI has inflammatory components and involves neutrophils and macrophages/monocytes.[2]

Experimental studies have helped to clarify many aspects of AKI, but it is only possible to evaluate one etiological agent and a small number of mechanisms and outcomes in each study. This limitation is the exact opposite of what happens to patients in which multiple known factors (ischemic or toxic) act in synchrony or chaotically and in which multiple interactions between organs take place.[3]

It is possible that the phases of AKI, which are described as prerenal, initiation, extension, maintenance and recovery, do not occur homogeneously in all nephrons. Over times, this syndrome has had multiple definitions (over 30 according to certain reviews) based on serum creatinine levels.[4] Recently, new AKI classification methods[5,6] have been proposed that also use the serum creatinine levels and diuresis but in a manner that is dynamic and standardized.

Several drugs have been tested with the objective of preventing and treating AKI, but the promising results obtained in animal studies were not achieved in studies with humans. Is shall be asked if it is possible that the problem with those studies was the diagnosis and severity of disease instead of the treatment tested?

It has only recently become understood that that very small increases in serum creatinine (0.3 mg/dL) have an impact on mortality[7], that the cost associated with these increases is high[8] and that AKI patients can progress to stage 5 chronic kidney disease and become dialysis-dependent[9]. However, the implications of the elevated costs implied in treating severe patients by dialysis have been known for a long time and are thoroughly characterized and quantified, suggesting that the quality of life of the survivors is reasonably acceptable, despite the high mortality and cost.[10]

Conflicts of interest: None.

Corresponding author:
Paulo Benigno Pena Batista
Rua Sócrates Guanaes Gomes, 73, apto. 1.203
Zip Code: 40296-720 - Salvador (BA), Brasil
E-mail: paulobenigno@gmail.com

AKI prevention and decreasing the number of AKI patients who require dialysis are, therefore, essential goals.

The tests to identify biomarkers in urine are not new in AKI, and recently, significant knowledge about biomarkers has become available. A number of the biomarkers are already available for use in critical medicine. These are clearly capable of predicting which critical patients are at most risk for acquiring AKI, which AKI patients are at most risk of progressing to the need for dialysis and which patients are at most risk of death.[11]

The monitoring of urine electrolytes has always been studied in AKI patients. More recently, the use of a quantitative approach involving acidosis provided a new research perspective. The kidney is the main regulator of strong ion difference (SID). A broader analysis of this physiology aspect is beyond the scope of this paper, but in summary, the most relevant anion in urine is the sulfate (SO_4^{2-}) ion, which is derived from sulfuric acid metabolism, and the most relevant cation is ammonium (NH_4^+). When a strong ion, such as lactate, is combined with plasma, the plasma SID decreases. A type of counter-regulation is the increase of urine chlorine excretion, which leads to a decrease in urine SID.[12] To save sodium, chlorine excretion is accompanied by NH_4^+. Most patients with severe metabolic acidosis under intensive care have AKI at a certain level; thus, renal compensation for acidosis does not occur, and, as a consequence, positive urine SID and a high chlorine plasma concentration can be observed. However, patients with adequate renal response present with negative urine SID and $\Delta[AG] - \Delta[HCO^{3-}]$. These findings, which are often related to metabolic alkalosis, can be interpreted as a renal response to metabolic acidosis.[13]

In AKI patients, urea and urine electrolyte analysis often reveals dysregulation of free water clearance/natriuresis and a dysregulation of urea transport.[14] In AKI patients with metabolic acidosis, there is an elevated urine SID (strong ion difference in the urine).[15] A study published in this edition of the RBTI[16] confirms this finding. It is an interesting possibility that daily monitoring of simple parameters, such as phosphorus levels, non-measurable anions and urine potassium, along with decreased urine sodium and chlorine and urine SID can facilitate the early diagnosis of AKI, even before the decrease in urinary output and creatinine. This hypothesis is being tested by the same group in a prospective study and has already been exemplified in a case report.[17] It is important to note that the disproportionate relationship between the resorption of sodium and anions is the critical factor in the determination of urinary pH and the excretion of acid. Several anions affect both urinary pH and acid excretion through their influence on the electrical gradient that is established by active sodium transport in renal tubular cells. According to this hypothesis, the magnitude of this gradient is determined by the relative potential for transepithelial movement by available anions. Those anions that are more easily transported epithelially have a greater tendency to be transported along with sodium, thereby decreasing this difference in potential. Thus, the changes in urinary pH can be related to passive movement of hydrogen in response to changes in the transtubular gradient. This explanation does not exclude the possibility of active transport of hydrogen in the acidification process.[18] The chemical nature of these so-called non-measurable anions is mostly unknown; a small portion consists of amino acids, uric acid and organic acids.[19] Adding more complexity, these anions can also be urinary bicarbonate, as in the case of renal tubular acidosis. Finally, changes in urine SID, NH_4^+, carbon dioxide partial pressure ($PaCO_2$) or phosphate (PO_4^{3-}) lead independently and directly to a common final result, which is a change in urinary pH. Thus, the serial observation of urinary pH can provide an accurate evaluation of acid excretion.[20]

In this context, a study published in this edition of the Brazilian Journal of Intensive Care[16] demonstrates for the first time the association of laboratory markers, the costs of which are not high, with mortality and possibly the early diagnosis of AKI.

Therefore, the study further broadens the frontiers of AKI by overcoming the well-known and inadequate limit of 2 mg/dL serum creatinine, as defined during the 1990s by the International Society of Nephrology, which was necessary for the diagnosis of this condition.

Rather than focusing on a reductive concept of renal function, we should study renal functions, as the characteristics of several renal roles that are not limited to the measurement of creatinine and diuresis and that are increasingly being recognized.

REFERENCES

1. Bonventre JV, Yang L. Cellular pathophysiology of ischemic acute kidney injury. J Clin Invest. 2011;121(11):4210-21.
2. Snoeijs MG, Vink H, Voesten N, Christiaans MH, Daemen JW, Peppelenbosch AG, et al. Acute ischemic injury to the renal microvasculature in human kidney transplantation. Am J Physiol Renal Physiol. 2010;299(5):F1134-40.
3. Scheel PJ, Liu M, Rabb H. Uremic lung: new insights into a forgotten condition. Kidney Int. 2008;74(7):849-51.
4. Mehta RL, Chertow GM. Acute renal failure definitions and classification: time for change? J Am Soc Nephrol. 2003;14(8):2178-87.
5. Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P; Acute Dialysis Quality Initiative workgroup. Acute renal failure - definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. Crit Care. 2004;8(4):R204-12.
6. Mehta RL, Kellum JA, Shah SV, Molitoris BA, Ronco C, Warnock DG, Levin A; Acute Kidney Injury Network. Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. Crit Care. 2007;11(2):R31.
7. Coca SG, Peixoto AJ, Garg AX, Krumholz HM, Parikh CR. The prognostic importance of a small acute decrement in kidney function in hospitalized patients: a systematic review and meta-analysis. Am J Kidney Dis. 2007;50(5):712-20.
8. Chertow GM, Burdick E, Honour M, Bonventre JV, Bates DW. Acute kidney injury, mortality, length of stay, and costs in hospitalized patients. J Am Soc Nephrol. 2005;16(11):3365-70.
9. Ishani A, Xue JL, Himmelfarb J, Eggers PW, Kimmel PL, Molitoris BA, et al. Acute kidney injury increases risk of ESRD among elderly. J Am Soc Nephrol. 2009;20(1):223-8.
10. Hamel MB, Phillips RS, Davis RB, Desbiens N, Connors AF Jr, Teno JM, et al. Outcomes and cost-effectiveness of initiating dialysis and continuing aggressive care in seriously ill hospitalized adults. SUPPORT Investigators. Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments. Ann Intern Med. 1997;127(3):195-202.
11. Coca SG, Yalavarthy R, Concato J, Parikh CR. Biomarkers for the diagnosis and risk stratification of acute kidney injury: a systematic review. Kidney Int. 2008;73(9):1008-16.
12. Gattinoni L, Carlesso E, Cadringher P, Caironi P. Strong ion difference in urine: new perspectives in acid-base assessment. Crit Care. 2006;10(2):137.
13. Masevicius FD, Tuhay G, Pein MC, Ventrice E, Dubin A. Alterations in urinary strong ion difference in critically ill patients with metabolic acidosis: a prospective observational study. Crit Care Resusc. 2010;12(4):248-54.
14. Han KH, Kim HY, Croker BP, Reungjui S, Lee SY, Kim J, et al. Effects of ischemia-reperfusion injury on renal ammonia metabolism and the collecting duct. Am J Physiol Renal Physiol. 2007;293(4):F1342-54.
15. Moviat M, Terpstra AM, van der Hoeven JG, Pickkers P. Impaired renal function is associated with greater urinary strong ion differences in critically ill patients with metabolic acidosis. J Crit Care. 2012;27(3):255-60.
16. Maciel AT, Park M, Macedo E. Monitorização de eletrólitos urinários em pacientes críticos: estudo preliminar observacional. Rev Bras Ter Intensiva. 2012;24(3):236-45.
17. Maciel AT, Park M. Early diagnosis of acute kidney injury in a critically ill patient using a combination of blood and urinary physicochemical parameters. Clinics (Sao Paulo). 2012;67(5):525-6.
18. Bank N, Schwartz WB. The influence of anion penetrating ability on urinary acidification and excretion of titratable acid. J Clin Invest. 1960;39(10):1516-25.
19. Moviat M, Terpstra AM, Ruitenbeek W, Kluijtmans LA, Pickkers P, van der Hoeven JG. Contribution of various metabolites to the "unmeasured" anions in critically ill patients with metabolic acidosis. Crit Care Med. 2008;36(3):752-8.
20. Constable PD, Gelfert CC, Fürll M, Staufenbiel R, Stämpfli HR. Application of strong ion difference theory to urine and the relationship between urine pH and net acid excretion in cattle. Am J Vet Res. 2009;70(7):915-25.