

Alexandre Toledo Maciel^{1,2}, Marcelo Park¹,
Etienne Macedo³

Fractional excretion of potassium in the course of acute kidney injury in critically ill patients: potential monitoring tool?

Fração de excreção de potássio na evolução da lesão renal aguda em pacientes graves: um potencial marcador a ser monitorizado?

1. Intensive Care Unit, Department of Medical Emergencies, Hospital das Clínicas, Universidade de São Paulo - São Paulo (SP), Brazil.
2. Intensimed Research Group, Intensive Care Unit, Hospital São Camilo - São Paulo (SP), Brazil.
3. Department of Nephrology, Hospital das Clínicas, Universidade de São Paulo - São Paulo (SP), Brazil.

ABSTRACT

Objective: To evaluate the behavior of fractional excretion of potassium in the course of acute kidney injury in critically ill patients.

Methods: As part of a larger study in which we have evaluated blood and urinary parameters in the course of acute kidney injury, 168 patients were included. Blood and urine samples were collected daily until the removal of the urinary catheter or the initiation of renal replacement therapy. We describe the evolution of fractional excretion of potassium based on whether acute kidney injury was diagnosed, its duration (transient or persistent) and its severity (creatinine-based Acute Kidney Injury Network - AKIN stage). The diagnostic performance of fractional excretion of potassium in predicting the duration of acute kidney injury and the need for renal replacement therapy on the day of acute kidney injury diagnosis was also evaluated.

Results: Fractional excretion of potassium was significantly higher in persistent acute kidney injury compared

to transient acute kidney injury on the day of acute kidney injury diagnosis (24.8 vs. 13.8%, $p < 0.001$). Both groups had the median fractional excretion of potassium increasing in the two days preceding the acute kidney injury diagnosis. Patients without acute kidney injury had stable low fractional excretion of potassium values. The fractional excretion of potassium was fairly accurate in predicting persistent acute kidney injury (area under the curve: 0.712; 95% confidence interval: 0.614-0.811; $p < 0.001$) on the day of acute kidney injury diagnosis. The area under the curve was 0.663 (95% confidence interval: 0.523-0.803; $p = 0.03$) for renal replacement therapy. The fractional excretion of potassium increased with maximum AKIN stage reached, in both transient and persistent acute kidney injury.

Conclusion: Sequential fractional excretion of potassium assessment appears to be useful in critically ill patients at risk for acute kidney injury.

Keywords: Potassium/urine; Sodium/urine; Acute kidney injury; Critically illness; Urine/chemistry; Monitoring

Conflicts of interest: None.

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Corresponding author:

Alexandre Toledo Maciel
Intensimed Research Group, Intensive Care Unit,
Hospital São Camilo
Avenida Pompéia, 1.178
Zip code: 05024-000 - São Paulo (SP), Brazil
E-mail: alexandre.toledo@intensimed.com

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INTRODUCTION

Fractional excretions of sodium (FENa) and urea (FEUr) are well-known urinary indices and are frequently used for assessment of acute kidney injury (AKI).⁽¹⁻³⁾ For many years, these two variables were thought to help in distinguishing functional (pre-renal) and structural AKI (acute tubular necrosis - ATN). The physiological rationale for this was that low FENa (classically $< 1\%$) indicates preserved tubular function and an avid-sodium retaining state, which is normally attributed to low renal perfusion. As diuretics

may make the interpretation of FENa troublesome, FEUr emerged as a parameter for evaluating kidney perfusion in the presence of diuretics.⁽²⁾ However, many studies have questioned the utility of these two variables,⁽³⁻⁵⁾ mainly because low FENa and FEUr may be present in the absence of renal hypoperfusion⁽⁶⁾ and because they seem to have poor diagnostic accuracy in predicting transient AKI (tAKI) versus persistent AKI (pAKI).^(4,7) In addition, “pre-renal” and “ATN” paradigms have consistently been criticized.⁽⁸⁻¹¹⁾

In one of our recent studies,⁽¹²⁾ we described the behavior of blood and urinary physicochemical parameters in the course of AKI. In that study, the diagnosis of AKI was made according to acute kidney injury network (AKIN) creatinine-based criterion.⁽¹³⁾ We evaluated these variables two days before (D-2) to two days after (D2) AKI diagnosis. Neither FENa nor FEUr were different between or within groups (non-AKI, tAKI, pAKI) during the days of observation. Herein, we present our data regarding the sequential evolution of fractional excretion of potassium (FEK) in the course of AKI and the diagnostic performance of FENa, FEUr and FEK at the day of AKI diagnosis in predicting AKI evolution (tAKI or pAKI and need of renal replacement therapy (RRT)). To our knowledge, no previous study has evaluated FEK sequentially in critically ill patients.

METHODS

The *Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo* ethics committee approved the study (protocol 0093/11), and the need for informed written consent was waived by the same committee. Briefly, we included 168 consecutive patients who were admitted to our intensive care unit (ICU) from October 2009 to November 2011 and who had an indwelling urinary catheter for at least two days after ICU admission and did not require RRT during the observation period. The observation period stopped when RRT was required or the urinary catheter was removed. tAKI was defined as resolution of AKI within 48 hours. pAKI was defined as AKI that did not resolve within 48 hours after diagnosis. A more detailed description of AKI diagnosis and the reversal criteria has previously been reported.⁽¹²⁾ D0 was the day of AKI diagnosis or the day of ICU admission for non-AKI patients. The AKIN creatinine-based criterion was used for AKI diagnosis.⁽¹³⁾ AKINmax refers to the maximum AKIN stage reached by the patient during the observation period. FEK was calculated as follows:

$FEK (\%) = [(KU \text{ (mEq/L)}/K^+ \text{ (mEq/L)}) / (CrU \text{ (mg/dL)}/SCr \text{ (mg/dL)})] \times 100$ (KU: urine potassium; CrU: urine creatinine; SCr: serum creatinine)

Analogous formulas were used to calculate FENa and FEUr. All blood and urinary variables needed in these formulas were measured simultaneously once daily from patients with an indwelling urinary catheter (a spot urine sample was used).

Statistical analysis

FEK was expressed as the median and 25-75 percentiles. Whisker plots represented the 10th-90th percentiles. Mann Whitney and Kruskal-Wallis tests were used to compare non-AKI, tAKI and pAKI, as appropriate. The area under the curve and 95% confidence interval were calculated based on receiver operating characteristic analysis. All statistical tests were two-sided, and $p < 0.05$ was considered significant. Statistical analyses were conducted using SPSS 19.0 (Chicago, Illinois, USA).

RESULTS

General characteristics of the patients

As previously mentioned, this is a complementary analysis that used the same patients included in another recent study by our group.⁽¹²⁾ In summary, there were no differences between the non-AKI, tAKI and pAKI patients in terms of age, gender and ideal body weight, but the pAKI patients were more severely ill at admission (higher SAPS 3 and SOFA score). There was a greater prevalence of severe sepsis and septic shock in the pAKI group. ICU and hospital mortality were also higher in the pAKI group.

Fractional excretion of potassium in the course of acute kidney injury

FEK was significantly different between the groups at D0. The pAKI patients had significantly higher FEK from D0 to D2 (Table 1). The tAKI patients had higher FEK values than the non-AKI patients only at D1. FEK increased during the two days preceding the AKI diagnosis in both tAKI and pAKI patients, decreasing thereafter in the tAKI patients but remaining high in the pAKI patients. The patterns of FEK were also not significantly altered by diuretic use (Figure 1).

Diagnostic performance of fractional excretion of potassium in predicting acute kidney injury duration and the need for renal replacement therapy

Of the fractional excretions, only FEK demonstrated fair accuracy in predicting pAKI (Figure 2): the area under the receiver operating characteristic curve (AUC)

Table 1 - Fractional excretion of potassium in the course of acute kidney injury

	Day -2 (N=13)	Day -1 (N=21)	Day 0 (N=168)	Day +1 (N=164)	Day +2 (N=117)
No AKI (n=55)	-	-	11.5 [5.7,16.9]	7.9 [5.5,12.9]	8.0 [4.3,14.1]
Transient (n=57)	7.2 [4.2,42.3]	12.7 [2.6,15.7]	13.8 [9.7,21.2]	12.7 [8.6,20.9]	10.1 [6.9,20.5]
Persistent (n=56)	13.8 [11.6,31.2]	16.8 [10.1,27.6]	24.8 [15.2,39.7]	30.1 [18.8,48.8]	31.3 [14.7,42.2]
p value			0.00*/0.00**/0.34***	0.00/ 0.00/ 0.00	0.00/0.00/0.23

Day 0 - day of AKI diagnosis or intensive care unit admission for non-AKI patients. * among the three groups; ** between transient and persistent AKI; *** between no AKI and transient AKI. FEK - fractional excretion of potassium. AKI - acute kidney injury.

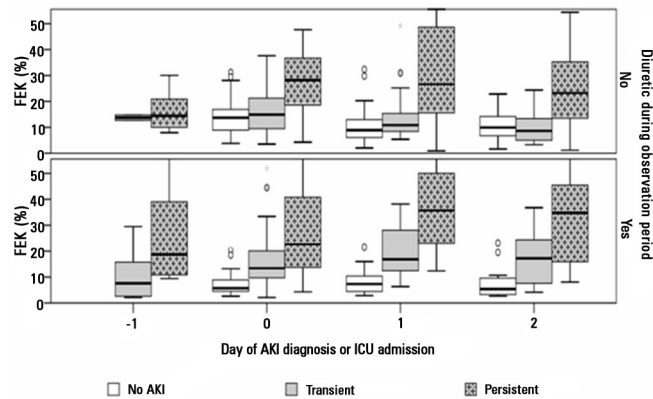


Figure 1 - Fractional excretion of potassium between 1 day before (-1) and 2 days after (2) diagnosis of acute kidney injury (0), according to AKI duration and diuretic use during the observation period. For non-AKI patients, D0 is the day of intensive care unit admission. FEK - fractional excretion of potassium; AKI - acute kidney injury; ICU - intensive care unit.

was 0.712 (95% CI 0.614-0.811, $p < 0.001$) for detecting pAKI at the day of AKI diagnosis. A FEK value of 18.3% was found to be the best discriminatory cut-off, with a sensitivity of 74.6%, a specificity of 67.3%, a positive predictive value of 69.5% and a negative predictive value of 72.6%. In addition, the AUC was 0.663 (95% CI 0.523-0.803, $p = 0.03$) for RRT in the course of AKI.

Fractional excretion of potassium evaluation according to acute kidney injury severity

To evaluate whether the variations in FEK were proportional to the degree of AKI severity, we compared these parameters among patients who reached AKINmax stages 1, 2 or 3 during the observation period (Figure 3). We compared the FEK values on the day that AKINmax was reached for each patient, and the non-AKI patients served as controls, with FEK values at the time of admission used for comparison. FEK increased progressively from non-AKI to AKINmax stage 3, in both the tAKI and pAKI patients (Figure 3).

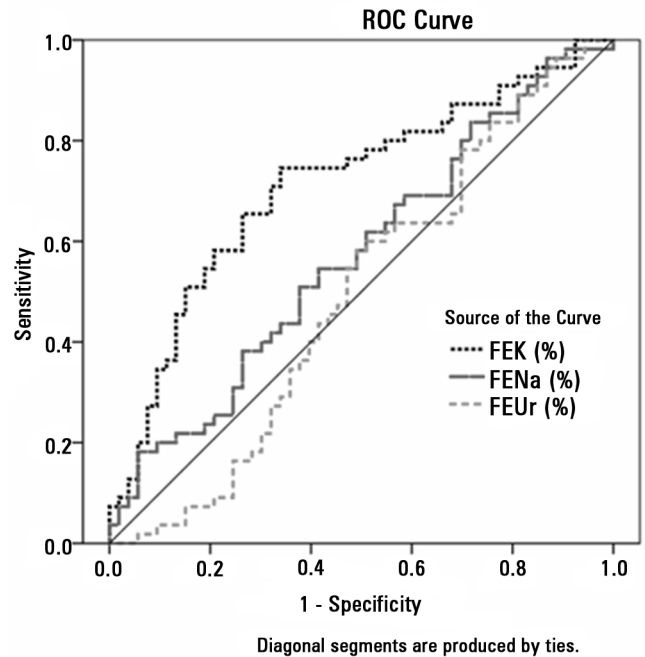


Figure 2 - Receiver operating characteristic curves of fractional excretions on the day of acute kidney injury diagnosis in predicting persistent acute kidney injury. FENa - fractional excretion of sodium; FEK - fractional excretion of potassium; FEUr - fractional excretion of urea.

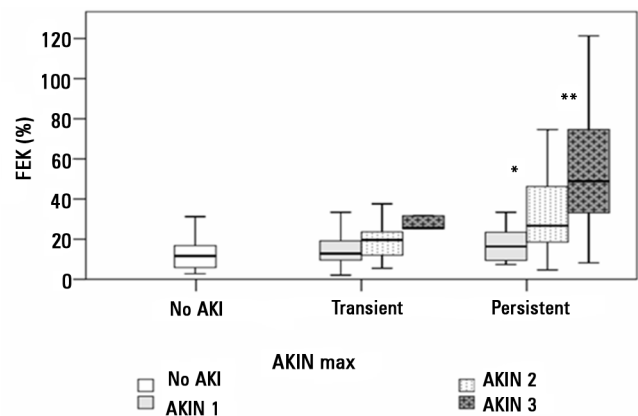


Figure 3 - Fractional excretion of potassium on the day of maximum Acute Kidney Injury Network stage of acute kidney injury (AKINmax), according to acute kidney injury duration. * $p = 0.04$; ** $p = 0.01$. FEK - fractional excretion of potassium; AKI - acute kidney injury; AKIN - Acute Kidney Injury Network.

DISCUSSION

Fractional excretion measurements (mainly FENa and FEUr) in AKI diagnosis and management are still a matter of controversy. In our previous article,⁽¹²⁾ we showed that no significant differences were found in FENa and FEUr between or within groups (non-AKI, tAKI, pAKI) on all days. As expected based on these previous findings, neither FENa nor FEUr demonstrated any diagnostic accuracy in predicting AKI duration (Figure 2). We decided to evaluate FEK. K⁺ handling in the tubules is distinct from the handling of Na⁺ and urea, and K⁺ is exchanged for Na⁺ in the distal tubules. Hence, K⁺ secretion is enhanced by Na⁺ reabsorption, which is stimulated by aldosterone. Activation of Na⁺-retaining mechanisms, including renin-angiotensin-aldosterone, is part of AKI development;⁽¹⁴⁾ therefore, we believe that although there is a progressive decrease in the glomerular filtration of K⁺ in AKI, FEK, which reflects tubular handling of K⁺, increases in parallel with enhanced K⁺ secretion. In our previous study,⁽¹²⁾ the median FENa was less than 1%, and the median FEUr was less than 35% in the AKI groups on the day of AKI diagnosis, suggesting preserved tubular capacity to retain sodium and urea. Other authors have also found low FENa^(4,7) in the majority of AKI patients.

The reasons why FEK values are different between the groups and with a more dynamic course in AKI development than FENa and FEUr are not clear. Perhaps the fact that K⁺ is secreted distally may lead to greater and more evident variations in FEK compared to FENa and FEUr. The fair accuracy of FEK on the day of AKI diagnosis in predicting pAKI (Figure 2) and the need for RRT may reflect the AKI severity, which is corroborated by the data shown in figure 3.

K⁺ secretion is partially dependent on the luminal tubular flow rate; therefore, the fact that urinary output was not different between the groups in our previous article⁽¹²⁾ and that urine volume is not included in FEK calculation argues against the idea that our results can be explained by differences in urine output. Importantly, our results regarding FEK are not representative of total, absolute K secretion/excretion rates, which are expected to be progressively lower as AKI develops, leading to

hyperkalemia. However, hyperkalemia usually occurs in the presence of a very significant decrease in the glomerular filtration rate (GFR), a phenomenon explained by the exponential increases in FEK with decreases in GFR until it reaches very low levels (15-20mL/min). Hence, our results regarding FEK may be in part an epiphenomenon of impaired GFR.

Although the K⁺ intake may theoretically interfere in the analysis, which is a limitation of our study, we do not believe that this substantially biases our results. Furosemide is capable of increasing FEK, but in general, its use did not seem to interfere much in the interpretation of the results (Figure 1). Diuretic use may be a cause of high FEK in the presence of low serum creatinine.

One may argue that spot urine samples provide random information due to the oscillations in urinary electrolyte concentrations over the course of the day; however, in clinical practice a daily, sequential evaluation of these parameters in spot urine samples together with routinely collected blood parameters seems quite useful.^(12,15-17)

Unfortunately, we have very limited data regarding FEK in the two days preceding AKI diagnosis, due to the fact that very few patients had these data available. Data on FEK during this period would be very useful in its evaluation as a predictive biomarker of AKI. The modest FEK accuracy in predicting pAKI suggests that this variable must be evaluated in conjunction with other variables to improve its usefulness in daily practice.

CONCLUSION

Fractional excretion of potassium is related to the severity and duration of acute kidney injury. Its increase as acute kidney injury progresses is possibly a result of decreases in glomerular filtration rate and aldosterone activation (an attempt to maintain K⁺ homeostasis). It seems to be more useful than classically measured fractional excretions of sodium and urea. Our preliminary data on fractional excretion of potassium indicate that increases in its value may be a sign of a decrease in the glomerular filtration rate, even before a rise in serum creatinine. This is an intriguing line of research that deserves prompt additional studies.

RESUMO

Objetivo: Avaliar o comportamento da fração de excreção de potássio durante a evolução da lesão renal aguda em pacientes graves.

Métodos: Foram incluídos 168 pacientes como parte de um estudo maior, no qual avaliamos parâmetros sanguíneos e urinários durante a evolução da lesão renal aguda. Foram coletadas diariamente amostras de sangue e urina até a remoção da sonda vesical ou a necessidade de terapia de substituição

renal. Descrevemos a evolução da fração de excreção de potássio conforme a presença ou não de lesão renal aguda, sua duração - transitória ou persistente - e gravidade (com base no estágio *Acute Kidney Injury Network* - AKIN). Foi também avaliado o desempenho diagnóstico da fração de excreção de potássio no dia do diagnóstico da lesão renal aguda, para prever a sua duração e a necessidade de terapia de substituição renal.

Resultados: A fração de excreção de potássio foi significativamente maior na lesão renal aguda persistente do que na transitória no dia do diagnóstico da lesão renal aguda (24,8 versus 13,8%; $p < 0,001$). Ambos os grupos tiveram aumento de sua fração de excreção de potássio mediana nos 2 dias que precederam o diagnóstico de lesão renal aguda. Pacientes que não desenvolveram mantiveram níveis baixos e estáveis de

fração de excreção de potássio. A fração de excreção de potássio, no dia do diagnóstico de lesão renal aguda, demonstrou razoável precisão em prever lesão renal aguda persistente (área sob a curva: 0,712; intervalo de confiança de 95%: 0,614-0,811; $p < 0,001$). A área sob a curva para terapia de substituição renal foi de 0,663 (intervalo de confiança de 95%: 0,523-0,803; $p = 0,03$). A fração de excreção de potássio aumentou com o estágio máximo atingido do AKIN, tanto para lesão renal aguda transitória quanto para persistente.

Conclusão: A avaliação sequencial da fração de excreção de potássio parece útil em pacientes graves em risco de lesão renal aguda.

Descritores: Potássio/urina; Sódio/urina; Lesão renal aguda; Estado terminal; Urina/química; Monitoramento

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