EDITORIAL REVIEW

Assessing the renal response in patients with potassium disorders: a shift in emphasis from the TTKG to the urine K+/creatinine ratio

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ABSTRACT

This article briefly reviews the reasons for replacing the transtubular K⁺ gradient (TTKG) with the urine K⁺/creatinine ratio as a tool for evaluating the response of the kidney in patients with potassium disorders. An appreciation of the magnitude and importance of the intrarenal recycling of urea led to the realization that a large amount of urea is reabsorbed daily in the terminal collecting duct and that this renders invalid the assumption, used by the TTKG, that there is minimal solute reabsorption downstream of the cortical collecting duct (CCD). The urine-to-plasma osmolality ratio cannot therefore be used to calculate the volume of fluid exiting the CCD or the concentration of K⁺ in luminal fluid in this nephron segment. We now recommend the use of the K⁺/creatinine ratio in random urine samples to estimate the rate of K⁺ excretion. A ratio of less than 1.5 mmol K⁺/mmol creatinine would be expected if the kidney is responding appropriately to hypokalaemia from a non-renal cause, and a ratio greater than 20 mmol K⁺/mmol creatinine would be appropriate as the renal response to hyperkalaemia.

Keywords: TTKG; transtubular K⁺ gradient; K⁺/creatinine ratio; urea recycling.

INTRODUCTION

In this editorial review, my purpose is to discuss the tools I now use to examine the renal excretion of potassium (K⁺) in patients with hypokalaemia or hyperkalaemia. One tool I formerly used was the transtubular concentration of K⁺ (transtubular K⁺ gradient, TTKG) [1]. I no longer use this tool after I realized the importance of the recycling of urea for the excretion of K⁺ [2] and it became evident that I had made a false assumption in my initial analysis [1]. The calculation of the TTKG was based on the false assumption that there would be substantial water reabsorption, but minimal solute reabsorption, down-stream to the cortical collecting duct (CCD) (summarized in reference [3]). However, in the process of the recycling of urea, a large quantity of urea is reabsorbed in the inner medullary collecting duct (MCD) [3]. Hence, I could not use the ratio of the urine-to-plasma osmolality (U/P Osom) to calculate the volume of fluid exiting the CCD or the concentration of K⁺ in the luminal fluid in this nephron segment.

INTRA-RENAL RECYCLING OF UREA

In an adult human with a glomerular filtration rate (GFR) of 180 L per day and a plasma urea concentration (P_urea) of 5 mmol/L, 900 mmol of urea are filtered daily. Close to 500 mmol of urea are reabsorbed in the proximal tubule, and 400 mmol of urea are ultimately excreted in the urine [4]. This reabsorption is driven by the higher luminal urea concentration resulting from the reabsorption of NaCl and water in the CCD.

We have calculated that close to 600 mmol of urea undergoes intrarenal recycling because approximately 1 000 mmol of urea is delivered to the early distal con-
vulated tubule (DCT) per day [5] and 400 mmol of urea are excreted in the urine [4,6] (see Figure 1). Based on the presence of urea transporters (UT) in the thin descending limbs of the loops of Henle in superficial nephrons that have their bends deeper in the outer medulla (summarised in references [3] and [7]), it is likely that much of this urea is reabsorbed in the inner MCD and added to the luminal fluid in the descending thin limbs of these nephrons via the A2 urea transporters (UT-A2) [8,9]. Since the CDN has the same osmolality as that of plasma when vasopressin acts, i.e. 300 mosmol/kg H2O, the recycling of 600 mmol of urea will add an additional 2 L of daily urine flow in this nephron segment (600 mosmol divided by the effective osmolality of plasma, which is its total osmolality minus the P_urea).

**Figure 1. Urea recycling in superficial nephrons.**
The diagram represents a superficial nephron. The circle on the left depicts its glomerulus where plasma is filtered. The open blue circles depict aquaporin 1 water channels (AQP1) in the proximal convoluted tubule (PCT) and the solid green circles represent aquaporin 2 channels (AQP2) in the late distal cortical nephron and the medullary collecting duct. Of note, some AQP1 are present in the pars recta (S3 segment of the PCT), which is distal to the last site accessible by micropuncture [5,8]. Micropuncture studies reveal that the ratio of the inulin concentration in tubular fluid to plasma (TF/P_inulin) is twice as high in the distal convoluted tubule (DCT) as it is in the PCT, reflecting the reabsorption of half of the tubular fluid volume. The urea concentration in the early DCT is 1.1 times that of plasma, reflecting the passage of around 1 000 mmol of urea through that nephron segment per day. Abbreviation: P_urea, the concentration of urea in plasma.

**Physiology of the excretion of K⁺**
Regulation of the excretion of K⁺ takes place in the late cortical distal nephron (CDN), which includes the late distal convoluted tubule (DCT), the connecting segment and the CCD (summarised in reference [3]). There are two components to examine in this context. First, one must consider the driving force – the negative intraluminal charge – that leads to a high concentration of K⁺ in the luminal fluid in the CDN. Second, one must understand why the flow rate is high in the CDN. For the latter, there must be a large number of effective osmoles in the late DCT. These luminal effective osmoles are urea, and the cations sodium (Na⁺), K⁺, ammonium (NH₄⁺) and their attending anions, which are usually chloride (Cl⁻) for the...
most part. Since urea is not reabsorbed in the CDN or the outer MCD, there is a large quantity of urea delivered to the inner MCD where it is reabsorbed with water.

Therefore, one should not use the ratio $U/P_{\text{Osm}}$ to calculate the volume of fluid traversing the terminal CCD, as we have done when calculating the TTKG. This overestimates the concentration of $K^+$ in the luminal fluid in the CDN making the TTKG approach inadequate, as it does not take account of the urea recycling which adds an extra 2 L of flow in this nephron segment each day.

**THE URINE $K^+$/CREATININE RATIO**

Instead of using the TTKG, we now rely on the ratio of $K^+$ in the urine to that of creatinine ($K^+/\text{creatinine}_{\text{urine}}$) in random urine samples as our initial step in calculating the rate of $K^+$ excretion because creatinine is excreted at a near-constant rate throughout the day. In patients who are $K^+$ depleted from non-renal causes, $K^+$ excretion would be expected to fall to 10–15 mmol/day [10] while in chronic $K^+$ loading with an appropriate renal response, excretion can exceed 200 mmol/day [3,11]. Considering that around 10 mmol of creatinine is excreted per day [12], the expected $K^+/\text{creatinine}_{\text{urine}}$ in hypokalaemia due to a non-renal cause (e.g., an intracellular shift) is less than 1.5 mmol $K^+/\text{mmol}$ creatinine, whereas the expected ratio in patients with hyperkalaemia due to a non-renal cause is greater than 20 mmol $K^+/\text{mmol}$ creatinine [13].

**Supplementary materials**

This is the version of record, with additional minor editorial changes. The first version (published 21 July 2017), and a PowerPoint slide of Figure 1, can be accessed via the supplementary materials.

**REFERENCES**