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EDITORIAL REVIEW

Assessing the renal response in patients with potassium disorders: a shift 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 can therefore not be used to calculate the volume of fluid exiting the CCD nor the concentration of K^+ in the 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: TTGK; transtubular K^+ gradient; K^+/creatinine ratio; urea recycling.

INTRODUCTION

In this editorial review, my purpose is to discuss the tools I 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 since I realised 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 use of the TTKG was based on the assumption that there would be substantial water reabsorption, but minimal solute reabsorption, downstream to the cortical collecting duct (CCD). 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_{Osm}) to calculate the volume of fluid exiting the CCD nor 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 is filtered daily. Close to 500 mmol of urea is reabsorbed in the proximal tubule, and 400 mmol of urea is ultimately excreted in the urine [4]. This reabsorption is driven by the higher luminal urea concentration resulting from the reabsorption of NaCl and water.

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 convoluted tubule (DCT) per day [5] and only 400 mmol of

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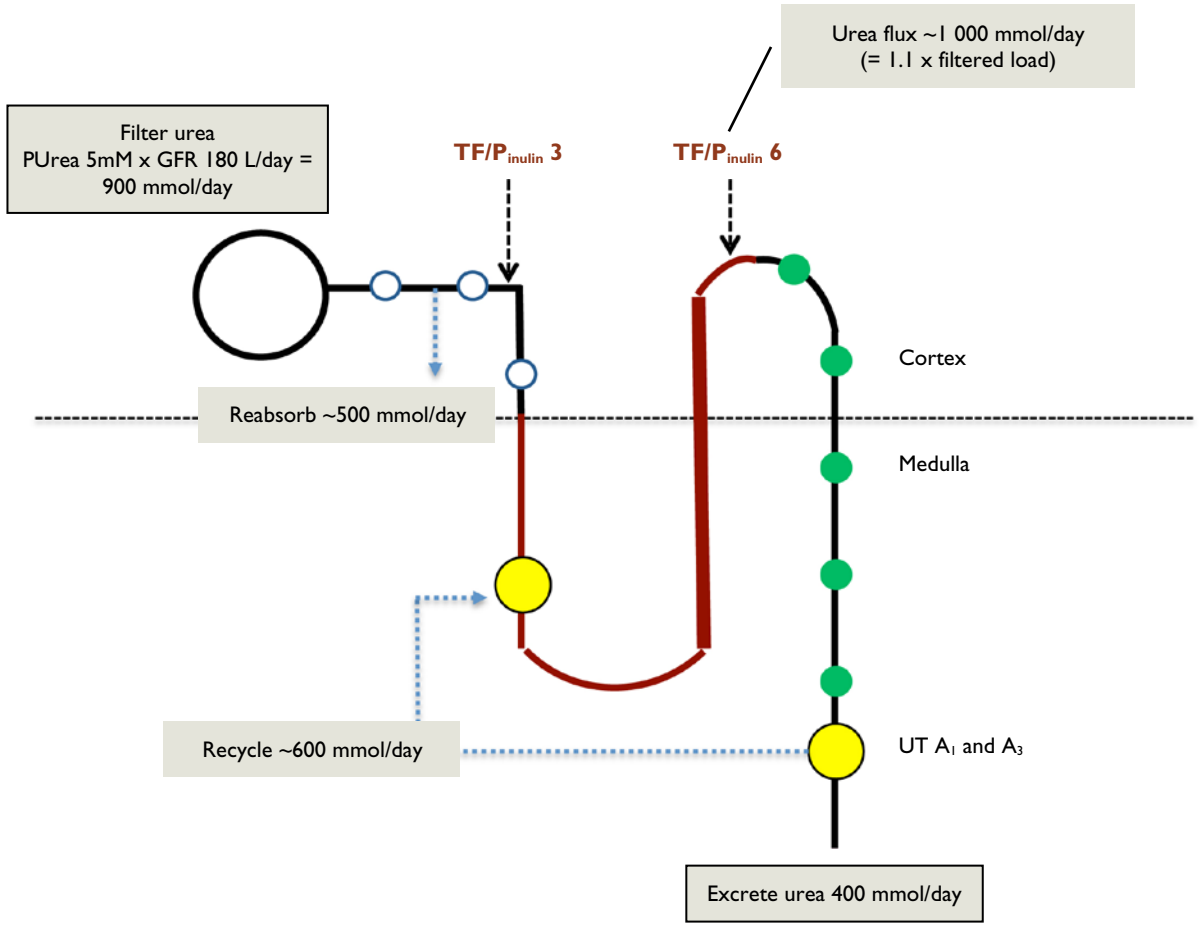

Figure 1. Urea recycling in superficial nephrons.
The diagram represents a superficial nephron. The circle on the left depicts its glomerulus where plasma is filtered. The open blue circles depict aquaporin 1 water channels (AQP1) in the proximal convoluted tubule (PCT) and the solid green circles represent 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 [5,12]. 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.

this is excreted in the urine [4,6]. 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 [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 A_2 urea transporters (UT-A_2) [8]. See Figure 1. Since the CDN has the same osmolality as that of plasma when vasopressin acts, i.e. 300 mosmol/kg H_2O, 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 300 mosmol/kg H_2O).

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. 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 attendant anions, which are usually chloride (Cl^-) for the most part. Since urea is not reabsorbed in the CDN nor the outer MCD, there is a large quantity delivered to the inner MCD where it is reabsorbed with water.

Therefore, one cannot use the U/P_{Osm} ratio to calculate the volume of fluid traversing the terminal CCD as we have done when calculating the TTKG. One overestimates the concentration of K^+ in the luminal fluid in the CDN because the TTKG approach 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 ($K^+/creatinine_{urine}$) 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 [9] while in chronic K^+ loading with an appropriate renal response, excretion can exceed 200 mmol/day [10]. Considering that around 10 mmol of creatinine is excreted per day [11], the expected $K^+/creatinine_{urine}$ in hypokalaemia due to a non-renal cause (e.g., an intracellular shift) is less than 1.5 mmol K^+/mmol creatinine, whereas the expected ratio in patients with hyperkalaemia due to a non-renal cause is greater than 20 mmol K^+/mmol creatinine.

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