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Letters to the Editor

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Increased tubular creatinine secretion by remnant nephrons—unexplained but informative?

Sir,

It is well known that declining kidney function is accompanied by an increasing contribution of tubular creatinine secretion to the total creatinine clearance; secretion may account for as much as 50% of creatinine clearance in the later stages of chronic kidney disease (CKD). The implications of this phenomenon for creatinine-based

estimation of glomerular filtration rate are well recognized, but the mechanism responsible is not understood.

Increasing tubular creatinine secretion is often considered simply to reflect the greater interstitial creatinine concentration to which tubular cells are exposed as CKD progresses [1]. This is not, however, an adequate explanation for the greater relative contribution of secretion; the increase in plasma creatinine accompanying declining kidney function will also lead to a proportional increase in the rate of creatinine filtration across each intact functioning glomerulus. Therefore, if the functional integrity of glomeruli and tubules is conserved equally (consistent with Bricker's intact nephron hypothesis [2]), an increase in fractional contribution of secretion must require a mechanism whereby creatinine secretion per tubule increases disproportionately to the serum concentration.

Since tubular fluid creatinine concentration rises with ultrafiltrate reabsorption, increased concentration of plasma (and therefore filtered) creatinine will actually lead to a greater absolute concentration difference between tubular fluid and interstitium, opposing secretion at the proximal tubule. Furthermore, if there is hyperfiltration at remaining glomeruli (a 'remnant nephron' effect), then it is apparent that tubular creatinine hypersecretion must be even greater to achieve the observed increased proportional contribution.

What then is the basis for this increase in proportional tubular creatinine secretion? Possibilities include:

(1) Non-linear kinetics of the creatinine secretion apparatus: this is not supported by *in vitro* studies of the relevant organic cation transporters. Creatinine infusions also do not produce disproportionate increments in creatinine secretion, which is saturated when serum creatinine concentration approaches 700 μM [3].

(2) Increased tubular flow: the reduction in tubular sodium and water reabsorption required to maintain fluid homeostasis through a dwindling nephron number limits the distal tubular creatinine concentration, so could reduce tubular creatinine reabsorption. This effect may be important for other secreted organic ions, but tubular creatinine reabsorption is generally considered to be minimal in most circumstances.

(3) Disproportionate loss of glomerular function relative to tubular function: this would contradict both the 'intact nephron' and remnant nephron hypotheses.

(4) Up-regulation of the creatinine (organic cation) secretion apparatus: substrate stimulation regulating transcription of organic ion transporters is recognized mainly for its impact on anionic drug excretion, though it may also regulate cation transport [4]. Whether accumulation of organic ions in uraemia up-regulates transcription of their transporters is unknown. Similarly, the effect of the uraemic environment on organic ion secretion is unknown.

Laboratory assessment of residual kidney function is currently based largely on glomerular filtration rate estimation. The variable increase in tubular creatinine secretion accompanying declining kidney function suggests that tubular function, or at least secretion of some substrates, does not always parallel glomerular filtration. Therefore, the measurement of toxic compounds cleared by secretion might in future contribute to the assessment of a patient's uraemia burden. If organic ion transporters are up-regulated by their endogenous substrates or by the uraemic milieu, this could be an important mechanism by which the failing kidney defends against uraemic complications, contributing to the benefits of residual kidney function on dialysis; increased expression of an anion transporter protected against uraemic cardiovascular complications in an animal model [5]. Although most organic ions considered to be uraemic toxins are anionic, cationic compounds also accumulate in the setting of renal failure and may have adverse effects. Since organic ion transporters display wide substrate specificity, increased secretion of creatinine may indicate increased secretion of toxic cationic (and even anionic) compounds. Subjects with extremes of tubular creatinine secretion will also of course have inaccurate estimated glomerular filtration rates based on serum creatinine.

The unknown mechanism underlying the observed increased contribution of tubular secretion to creatinine clearance in CKD is thus of more than purely academic interest.

Conflict of interest statement. None declared.

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1. Rose BD, Post TW. *Clinical Physiology of Acid Base and Electrolyte Disorders*. Columbus, OH: McGraw-Hill; 2000; p.52
2. Bricker, N.S. On the meaning of the intact nephron hypothesis. *Am J Med* 1969; 46: 1–11
3. Rodriguez-Iturbe, B. *et al.* Tubular stress test detects subclinical reduction in renal functioning mass. *Kidney Int* 2001; 59: 1094–1102
4. Berkhin, EB. and MH. Humphreys Regulation of renal tubular secretion of organic compounds. *Kidney Int* 2001; 59: 17–30
5. Toyohara, T. *et al.* SLCO4C1 transporter eliminates uremic toxins and attenuates hypertension and renal inflammation. *J Am Soc Nephrol* 2009; 20: 2546–2555

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