Residual renal function: a paradigm shift

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Residual renal function (RRF) in patients undergoing dialysis treatments is currently viewed as glomerular filtrate that has escaped tubular reabsorption. RRF has been quantified as a clearance of urea or creatinine, or urea + creatinine. A major paradigm shift has followed the recognition that a substantial number of organic anion retention solutes (possible "uremic toxins") are protein-bound and therefore are not readily filtered. These protein-bound aryl compounds are secreted by renal tubular organic anion transporters (OATs). This has led to the recognition that RRF in dialysis patients probably represents not only unreabsorbed glomerular filtrate but also a contribution of renal tubular transporters that secrete organic anions. Tubular secretion of hippurate, indoxyl sulfate, and p-cresol sulfate, protein-bound organic anions retained in the plasma of end-stage renal disease patients, can be quantified and used to evaluate the integrity of a function dependent on active solute transport. Here we propose a shift away from the exclusive "glomerulocentric" view of RRF as unreabsorbed glomerular filtrate and of the progression of renal disease as progressive glomerular loss. We expand the definition of RRF to include the combined renal and tubule functions remaining after a disease begins to destroy nephrons and proceeds to anuria. We propose renewed application of the first principles of renal physiology, articulated in the last century by Homer Smith, to the understanding and monitoring of RRF and progression of renal injury in patients during the sometimes long course of and at the end stage of chronic renal disease.

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Most patients reaching the end stage of renal disease excrete 100 to 250 ml of urine daily for many months after hemodialysis or peritoneal dialysis treatments are begun. This volume of urine has been attributed to residual renal function (RRF).[1] RRF is generally viewed as unreabsorbed glomerular filtrate and is quantified as a "clearance" by measurement of urea, creatinine, or urea + creatinine clearances in urine voided in the interval between dialysis sessions.[1] Alternatively, measuring plasma concentrations of cystatin C, beta-2 microglobulin, and beta-trace proteins, solutes too large to be removed by dialysis, as surrogate markers for impaired glomerular filtration that might not require urine collection has assumed that RRF represents unreabsorbed filtrate.[1]

The importance of RRF, as defined above, is that it is inversely associated with death related to cardiovascular disease, despite what would be considered adequate dialysis.[2,3] Viewed as the clearance of urea or creatinine, RRF is estimated to contribute only 3000 to 4000 ml/24 hours, roughly equivalent to what might be achieved by increasing the duration of hemodialysis by 10 to 15 minutes. Viewed together with the HEMO study,[4] it seems unlikely that an increase in the clearance of uremic toxins of a few liters per day could account for the improved outcome and better quality of life seen in patients with RRF.

Definition of RRF challenged

The assumption that RRF represents fluid and solute derived solely from glomerular filtration has changed since Vanholder *et al.*[5] identified roughly 100 solutes that were present in greater concentrations in the sera of patients with reduced renal function. Of these, about 25% were familiar small solutes including urea and creatinine, and another 25% were small (<250 Da) uremic solutes partially bound to plasma proteins, rendering them poorly dialyzable.[5,6] Organic anions, most notably hippurate (HIP), indoxyl sulfate (IS), and p-cresol sulfate (PCS), represent potential uremic toxins that are normally maintained at vanishingly low plasma levels owing to their secretion by powerful organic anion transporters (OATs) in the basolateral membranes of renal proximal tubules.[7,8]

Although we identify the renal tubular excretion of protein-bound organic anions as major contributors to a "paradigm shift," mechanisms for eliminating these solutes were already in the mainstream of thinking of classically trained nephrologists in the mid-20th century. Then, renal physiologists and physician-scientist–trained clinical nephrologists were students of renal tubular transport.[9]

Para-aminohippurate (PAH), a small aryl amine, was taken as the prototype of a protein-bound small solute transported by renal tubules. Despite being protein-bound, approximately 87% of PAH is extracted by proximal renal tubules in a single pass of blood through the kidney, evidence that the anion rapidly dissociates from plasma proteins and is transported into the tubular lumen.

A host of studies have now identified proximal tubule transport mechanisms that secrete aryl anions, elevating concentrations in final urine to many-fold greater than that in plasma, a powerful means of eliminating potential uremic toxins from the body.[10] Among the small protein-bound uremic solutes identified by Vanholder *et al.*,[5] IS and PCS have received the most attention as poorly dialyzed uremic toxins eliminated from body fluids via the OAT mechanism in renal proximal tubules.[7,8] James Shannon wrote in 1939,[11] "It would be possible in man, through the intervention of tubular excretion, to maintain at very low concentrations in the body substances, which being continuously formed, had a deleterious effect upon the organism …." Shannon's vision was dead on!

Several lines of evidence suggest that the tubular secretion of solutes and the attendant fluid transport may contribute significantly to RRF. Immunohistochemistry has identified proximal renal tubule epithelium as the exclusive site of OAT expression in the kidney.[12] The capacity of OAT mechanisms in residual nephrons to secrete, with considerable power, the unwanted organic anions that accumulate in disease raises the possibility that as nephropathies progress, the urine produced in patients with residual renal function may represent, increasingly, the secretion of solutes and osmotically driven fluid secretion in proximal renal tubules.

The active secretion of small solutes provides the force for osmotically driven fluid transport in a direction counter to the usual reabsorption in the proximal renal tubule. Microperfusion studies proved that PAH, added to the bathing medium, was secreted into isolated rabbit proximal tubules sufficient to raise the transepithelial concentration difference ~39 mmoles/l in S2 and S3 segments[13] (Figure 1). The resultant osmotic force drove secretory fluid flows as high as 0.1 nl/mm/minute, overwhelming the usual reabsorptive flow of 0.2 nl/mm/minute. The rate of net fluid secretion was dependent upon the concentration of the anion in the extracellular fluid bathing the tubule segment.[14] As renal function declines, HIP, IS, and PCS accumulate progressively in the plasma, achieving concentrations sufficient to promote the secretion of fluid into proximal tubules.[14] We propose that a significant portion of the urine produced by dialysis patients may be the product of proximal tubular solute–driven fluid secretion, together with some unreabsorbed glomerular filtrate.

Further evidence that RRF reflects the activity of OAT secretory mechanisms has been reported by Marquez *et al.*[15]

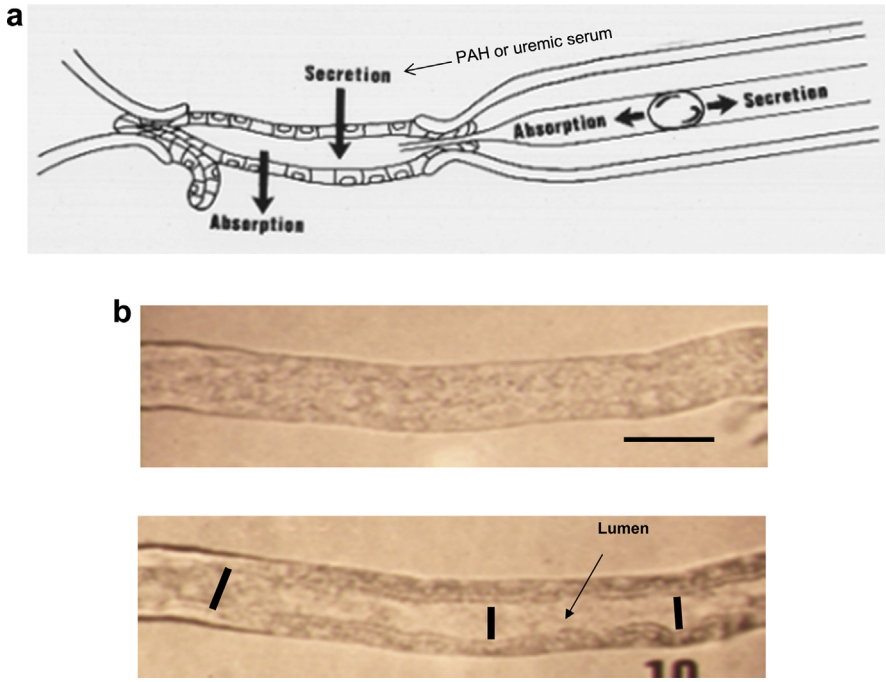

Figure 1 | Evidence that proximal tubules secrete organic anions with sufficient power to overcome sodium chloride absorption when glomerular filtration rate approaches zero.[13,14] (**a**) Scheme for measuring fluid absorption and secretion in isolated proximal tubules. Para-aminohippurate (PAH) or uremic serum added to the bath caused secreted fluid to be forced into the inner pipette on the right, causing the oil drop to move backward. (**b**) Isolated proximal tubule segments minus glomeruli. Upper panel: the lumen is completely collapsed as all fluid had been removed by net reabsorption. Horizontal bar = 50 μm. Lower panel: ten minutes after adding PAH or uremic serum, tubules form lumens indicated by the black vertical bars. (**b**) Reprinted with permission from Grantham JJ, Irwin RL, Qualizza PB, et al. Fluid secretion in isolated proximal straight renal tubules. Effect of human uremic serum. *J Clin Invest*. 1973;52:2441–2450.[14] Copyright © 1973 American Society for Clinical Investigation.