Staying on Target with Continuous Dialysis

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"It was through the evolution of this filtration-reabsorption system that the kidney came to be almost entirely responsible for the composition of the internal environment of the body, manufacturing it, as we have said, in reverse, by saving some things from the glomerular filtrate and rejecting others. Among the substances known to be reabsorbed by the tubules in man, for example, are water, sodium, potassium, calcium, chloride, bicarbonate, phosphate, sulfate, glucose, fructose, a large variety of amino acids, and several vitamins and hormones. There are certainly many others on which no quantitative observations are available." (1)

As the proverbial primitive man and woman ventured on to dry land, their kidneys continued to excrete wastes, but now with extreme frugality of water and salt. Kidneys had to accomplish high-volume filtration, as in their previous marine habitat, so they could excrete novel toxins and filter and secrete metabolic wastes, but now they had to also perpetually reabsorb salt and water in the tubule. Some additional solutes are reabsorbed so completely that their clearance approaches zero, whereas others are actively secreted so that their clearance approaches renal plasma flow. Inasmuch as filtration has become synonymous with renal function in the context of RRT, it is easy to overlook the robust and dynamic contribution of the renal tubule to homeostasis.

Almost four decades have passed since Kramer *et al.* (2) and Paganini *et al.* (3) introduced and popularized an ingeniously simple modality of dialysis. Continuous dialysis capitalized on advances of membrane technology and promised more physiologic and continuous renal support in the bed-bound critically ill patient. The opportunity to provide continuous small solute clearance raised the question of dose targeting: when compared with a healthy glomerular filtration rate of 120–140 ml/min, what is the best dose of continuous renal replacement to prescribe? Two large well-conducted studies failed to demonstrate improved survival with increased dialysis dose in the critically ill patient (4,5). We have conclusively exhausted that line of inquiry. As we increased dialysis duration in pursuit of the very high standard set by glomerular filtration, we perhaps once more underestimated the contribution of the renal tubule to homeostasis. Our bedside gadgets are incomplete mimics of the organs refined by millions of years of ceaseless tinkering by Mother Nature, and continuous RRT (CRRT) removes small solutes, including amino acids, vitamins, trace elements, hormones, minerals, antibiotics and vasopressors, and wastes and water. As the CRRT dose increases, so do the off-target effects of therapy (6–9).

It is established that phosphate removal during intermittent dialysis does not follow the same linear two-compartment kinetics of urea (10,11). Phosphate is effectively removed with increased frequency or duration of dialysis treatments (12). In this issue of the journal, Sharma *et al.* report measureable reductions in red blood cell concentration of 2,3 diphosphoglycerate contemporaneous with CRRT-induced phosphate depletion (13). Although the study based its conclusions on a relatively small sample size, it highlights the significant cumulative phosphate drain with time and its putative downstream mediator effect on tissue oxygen delivery in the critically ill patient (14). Moreover, CRRT-induced alkalemia, another dose-dependent side effect that follows a similar temporal pattern, will also shift the oxygen-hemoglobin curve further to the left because of the Bohr effect (reduces oxygen release in peripheral tissues) (15). This is especially disconcerting in this patient population where compromised oxygenation in the setting of renal failure, further compounded by volume burden, is the main determinant of mortality (16).

Continuous renal support saves lives by correcting electrolyte and acid-base derangements and controlling extracellular fluid volume in the critically ill. Nephrologists aspire to improve the disappointing survival rates in severe AKI, and the results of the VA/NIH Acute Renal Failure Trial Network Study and the Randomized Evaluation of Normal versus Augmented Level Replacement Therapy Study trials have redirected us from a focus on urea clearance to considering middle molecules and protein-bound solutes. Clearance of middle molecules and protein-bound uremic solutes will require increases in blood and dialysate flow rates (17–22). In an ideal scenario, we would know the identities of the molecular mediators of uremia and adjust dialysis settings to optimize their clearance. It is becoming more apparent that the off-target effects of CRRT, particularly depletion of needed metabolites and removal of essential drugs, are an underexplored opportunity to improve outcomes in severe AKI. Sharma and colleagues have added an important and novel mechanism by which unanticipated off-target effects of CRRT could undermine our efforts to support the critically ill patient.

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Disclosures

None.

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See related article, "Reductions in Red Blood Cell 2,3-Diphosphoglycerate Concentration during Continuous Renal Replacment Therapy," on pages 74–79.