Does Changing the Volume Matter? The Relationship of Urine Volume and Dialysis Intensity

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Clin J Am Soc Nephrol 11: 1321–1323, 2016. doi: 10.2215/CJN.06420616

Despite many recent studies focused on novel biomarkers, urine volume remains one of the most important factors associated with renal prognosis. In patients with ESRD on either peritoneal dialysis or hemodialysis, urine output is often considered a marker of residual renal function, and preservation of residual renal function has shown contribute significantly to the overall health of patients on RRT (1–4). Along the same lines, AKI is typically defined by either increases in serum creatinine or decreases in urine output (5), and nonoliguric AKI is well known to be associated with better prognosis than oliguric AKI (6–8). However, it does not seem that the use of diuretics to convert oliguric (≤400 ml urine output daily) to nonoliguric AKI affects patient outcomes (9–11), and the clinical use of diuretics in patients with AKI remains controversial (12–14).

In fact, at present, our only therapy for severe AKI is supportive care, including RRT. Consequently, there has been significant interest in the optimal provision of RRT, including the timing, modality, and intensity of therapy. The Veterans Affairs (VA)/National Institutes of Health Acute Renal Failure Trials Network (ATN) Study and the Australian and New Zealand Intensive Care Society Randomized Evaluation of Normal Versus Augmented Level (RENAL) Study were large randomized clinical trials that evaluated the potential benefit of higher intensity RRT (15,16). The ATN Study enrolled 1124 patients at 27 VA and university–affiliated medical centers across the United States; patients were randomly assigned to receive either more intensive RRT (hemodialysis/sustained low–efficiency dialysis six times per week or continuous venovenous hemodiafiltration [CVVHDF] at 35 ml/kg per hour, with selection of modality on the basis of hemodynamic stability) or less intensive RRT (hemodialysis/sustained low–efficiency dialysis three times per week or CVVHDF at 20 ml/kg per hour). The RENAL Study randomized 1508 patients in Australia and New Zealand to receive CVVHDF at a dose of 40 or 25 ml/kg per hour. Both studies showed that more intensive RRT did not have any beneficial effects on mortality, renal recovery, or nonrenal organ failure compared with less intensive RRT. Subsequently, there has been a tremendous interest in the potentially deleterious effects of higher intensity dialysis, including the potential effect on antibiotic levels and the increased incidence of intradialytic hypotension reported in the ATN Study in the more intensive therapy arm (a similar effect was not observed in the RENAL Study, likely because patients received almost exclusively CVVHDF).

Given the prior studies suggesting a potential relationship between lower urine volumes and adverse outcomes, McCausland *et al.* (17) sought to explore the relationship of more intensive RRT with urine volume in the ATN Study. They hypothesized that more intensive RRT would be associated with lower urine volumes (17). To avoid the competing risk of death, they focused on only those patients who survived to day 7 (n=871) (17). In line with the original study findings, there were no differences in the baseline characteristics of the two treatment arms in this subgroup.

In the primary analysis, linear regression models were used to evaluate the effect of RRT intensity on change in urine output over the first 7 study days. In the unadjusted analysis, urine output increased by 23.2 ml/d with less intensive RRT and decreased by 8.5 ml/d with more intensive RRT, resulting in an overall difference of 31.7 ml/d. Similar trends were observed in subsequent analyses that adjusted for sex, age, race, oliguria, weight, height, heart disease, congestive heart failure, peripheral vascular disease, hypertension, stroke, liver disease, diabetes, malignancy, and the cardiovascular component of the Sequential Organ Failure Score (SOFA) score. Interestingly, a much smaller effect was observed when the same analysis was restricted to those who survived to day 28.

There was no evidence of effect modification by RRT modality but marginal evidence for effect modification by baseline urine output. Consequently, in an analysis stratified by baseline urine output, those who were oliguric (defined as the 25th percentile of urine output; 110 ml) and randomized to the lower intensity RRT arm had a more modest increase in urine volume compared with those who were nonoliguric and randomized to the lower intensity RRT arm (11.4 ml/d; 95% confidence interval [95% CI], −17.0 to 39.8 versus 45.7 ml/d; 95% CI, 14.2 to 77.2).

For the secondary analysis, Cox proportional hazards analysis was used to evaluate the time to decline in urine output by ≥50% to day 28. More intensive RRT was associated with an increased risk of a decline in urine output by ≥50% (hazard ratio, 1.29; 95% CI, 1.10 to 1.51; P=0.001). However, similar to the findings in

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the primary study, there was no difference in the rate of dialysis dependence to day 28 or 60 in this subcohort of survivors, and therefore, these changes in urine output with more intensive therapy could not be associated with poorer long–term outcomes. This is not incongruous with prior studies that have reported an increased risk of death in those with lower urine output, because all of these analyses were conducted after initiation of RRT, whereas many of the prior studies have examined urine output immediately before RRT initiation (6–8).

McCausland *et al.* (17) also conducted a number of analyses to examine factors that might mediate the relationship between more intensive RRT and lower urine output, including time–dependent SOFA score (as a measure of hemodynamic instability), BUN (as a measure of osmotic load), and overall fluid balance. However, by virtue of the treatment itself, time–dependent SOFA score may have been higher (because of more episodes of hypotension) and BUN was lower (by design) in the more intensive RRT arm; consequently, one might expect these factors to attenuate the association between more intensive RRT and urine volume, regardless of causality, and inferences about causality are difficult to make. In the case of fluid balance, fluid balance was, in fact, more negative in the less intensive RRT arm, suggesting that fluid overload was not responsible for the association of less intensive RRT with higher urine volume.

Although this is a well executed study, we believe that some caution needs to be applied to the statement that the findings of this study are "consistent with a potentially early adverse effect of more intensive RRT on residual renal function" (17). There is no doubt that urine output is lower in those receiving more intensive RRT, and there is no doubt that clinicians often use urine output as a surrogate for early renal recovery. In fact, even in the ATN Study, urine output of >30 ml/h (720 ml/d) was one of the clinical criteria used to identify patients who might have renal recovery; these patients subsequently underwent a timed creatinine clearance to assess renal function (15). However, in this subgroup analysis of the ATN Study by McCausland *et al.* (17), there were no reported differences in rates of dialysis dependence and presumably, no difference in time to renal recovery (although these data were not shown). Thus, it is not clear that the lower urine output observed here associates with less residual renal function. However, one of the other deleterious effects of more intensive RRT is presumably a failure to recognize and assess patients who may be in early renal recovery. For example, Figure 1 in the work by McCausland *et al.* (17) illustrates that, after day 1, more patients in the more intensive arm would meet the conventional definition of oliguria (*e.g.*, urine output <400 ml/d). Because recognition of early renal recovery often hinges on the dichotomy of conventional oliguria/nonoliguria, it is possible that clinicians might view patients in the less and more intensive arms differently on the basis of residual urine output.

This study also highlights the potential importance of secondary data analyses from large randomized clinical trials. Such *post hoc* analyses are an excellent economic, ethical, and resourceful way to conduct hypothesis-generating studies using robust and well organized data (in this case, creating a unique opportunity to test the effect of RRT intensity on changes in urine output, while minimizing the effect of confounding by the original randomized study design). The reader must (as McCausland *et al.* [17] highlight throughout) keep in mind that the initial study was designed to examine other outcomes as well as the selection and survivor bias that arise in subgroup analyses that only include study survivors to days 7 and 28. This is a major potential challenge of all studies of critically ill patients where mortality is high.

In sum, McCausland *et al.* (17) show yet another way in which more intensive RRT is not beneficial and may even be harmful: through a decline in urine output. Although this analysis does not show an association with longer-term outcomes, including dialysis dependence at day 28 or 60, there certainly seems to be no benefit with more intensive dialysis. With regards to recognition of renal recovery, there may be delay with the more intensive arm as well. It does not seem that this association is mediated by volume overload, because volume status was actually more negative in the less intensive arm—therefore, one cannot conclude that patients receiving less intensive therapy were more volume overloaded and consequently, had greater urine output. At present, the optimal volume status to allow for renal recovery is unknown and an area of great clinical interest. Consequently, in addition to studies to define other important characteristics of RRT for patients with AKI (such as timing of initiation), future studies should focus on optimal volume management for patient receiving RRT to reduce mortality and enhance renal recovery.

Acknowledgments

C.K.F. is funded by the Lundbeck Foundation Clinical Research Fellowship Program.

Disclosures

K.D.L. has no disclosures relevant to this editorial. She has consultancy agreements with Achaogen, Astute, Durect, Genentech, ZS Pharma, and Cheetah and holds stock in Amgen.

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Published online ahead of print. Publication date available at www.cjasn.org.

See related article, "Comparison of Urine Output among Patients Treated with More Intensive Versus Less Intensive RRT: Results from the Acute Renal Failure Trial Network Study," on pages 1335–1342.