Is Fluid Overload as Measured by Bioimpedance Spectroscopy Harmful in CKD—If So, Why?

Lee A. Hebert and Samir Parikh

Clin J Am Soc Nephrol 10: 1–3, 2015. doi: 10.2215/CJN.11311114

Internal Medicine/ Nephrology, The Ohio State University Medical Center, Columbus, Ohio

Correspondence: Dr. Lee A. Hebert, Ohio State University, Wexner Medical Center, Division of Nephrology, 395 W. 12th Ave., Ground Floor, Columbus, OH 43210. Email: lee.herbert@osumc.edu

Bioimpedance spectroscopy (BIS) technology to assess clinical fluid status has been around for more than two decades. In patients with CKD, BIS has not created much of a splash until just recently (1,2). The most recent BIS splash is in this issue of *CJASN* (3). Here, Tsai *et al.* (3) report that, in patients with CKD stages 4 and 5, a relative hydration status (ΔHS) $\geq$7% is associated with a significant increase in all-cause mortality and cardiovascular (CV) events. Tsai *et al.* (3) postulate that ΔHS$\geq$7% is causally related to these adverse events. This work is well designed and executed (3). So, why are we skeptical?

First, the interpretation of this work is limited, because the exposure of interest (ΔHS) was measured at only a single point in time (at baseline) (3). In this respect, this work shares limitations with observational studies (3). Observational studies are ideal for hypothesis generation but cannot determine whether the exposure of interest (*e.g.*, ΔHS$\geq$7%) is in the causal pathway of the outcome of interest (*e.g.*, CV morbidity and all-cause mortality) or merely an epiphenomenon. Only a randomized trial that alters the exposure of interest and then follows the participants over time can be used to make such inferences.

In this work, 478 patients with CKD stages 4 and 5 were stratified according to whether ΔHS was abnormal ($\geq$7%) or normal ($<$7%) (3). Tsai *et al.* (3) found during follow-up that the fluid overload cohort (ΔHS$\geq$7%) had significantly increased numbers of CV events and deaths compared with the no fluid overload cohort (ΔHS$<$7%). Tsai *et al.* (3) concluded that ΔHS$\geq$7% may be causally related to the increased CV events and deaths. We are skeptical of this interpretation. The ΔHS$\geq$7% cohort at baseline already had a significantly greater prevalence of hypertension, heart disease, cerebral vascular disease, diabetes mellitus, blood lipid abnormalities, proteinuria, and hyperuricemia and a significantly lower eGFR than the cohort with ΔHS$<$7% (3). Unlike ΔHS$\geq$7%, each of these risk factors has been associated with an increased risk of CV events and mortality. Given that the ΔHS$\geq$7% cohort is already facing a formidable array of risk factors, it is difficult to believe that ΔHS$\geq$7% added to that risk, although that is conceivable as discussed later (3). Note also that ΔHS$\geq$7% is a value for fluid overload that is just above the normal limit. Considering all of the evidence, it seems more likely that the potent risk factors associated with ΔHS$\geq$7% cohort at baseline caused the increase in CV events and deaths during follow-up (3). Indeed, it is plausible that ΔHS$\geq$7% is an epiphenomenon and not in any important way in the causal pathway of the CV events and deaths noted during follow-up.

Second, the interpretation that ΔHS$\geq$7% is risky runs counter to the Law of Parsimony (3). This law has several corollaries. One of them is that, if there are multiple competing credible mechanisms that can explain an outcome, the mechanisms most likely to be explanatory are those involving the simplest possible means to a given end. Certainly, greater hypertension, heart disease, CKD, etc. (see above) qualify as simple explanations for the CV events and deaths observed during follow-up. By contrast, to explain how ΔHS$\geq$7% might cause these outcomes, one needs to use explanations with a much higher level of complexity. Note that ΔHS$\geq$7% is not associated with increased plasma volume (presumably increased blood volume as well). Rather, ΔHS$\geq$7% involves an isolated increase in interstitial fluid volume and not very much at that. To account for risk, Tsai *et al.* (3) speculate that ΔHS$\geq$7% might cause bowel edema, which would cause increased gut permeability, causing systemic exposure to bacteria and their toxins. Tsai *et al.* (3) also suggest that increased brain natriuretic peptides could influence the innate immune system by diminishing circulating monocytes, B cells, and NK cells, thereby increasing the risk of infection. Not discussed is how isolated interstitial fluid overload would increase brain natriuretic peptide.

Regardless of these theoretical concerns, it is conceivable that, in patients with CKD stages 4 and 5, relatively mild isolated interstitial fluid expansion is mechanistically related to CV events and mortality. Tsai *et al.* (3) note that this hypothesis is testable in a prospective randomized trial. Below, we provide a few suggestions for such a trial.

Our suggestions rest on the following two assumptions. (*1*) The ΔHS$\geq$7% cohort has both expanded intravascular volume and expanded interstitial volume. It seems unlikely that patients with CKD stages 4 and 5 with expanded interstitial volume (ΔHS$\geq$7%) would not also have expanded intravascular volume. We suggest that the method used to estimate plasma volume from BIS measurement is not sufficiently accurate to

detect this finding. However, it is possible that some of these patients have elevated cardiac filling pressures maintained by high venous tone and increased effective intravascular volume but not actual volume expansion. Either way, these patients would benefit from vascular volume reduction. (2) In some patients with ΔHS≥7%, capillary leak could account for isolated expansion of the interstitial fluid. This is a crucial issue. It would certainly do harm to reduce interstitial fluid volume if the underlying problem is capillary leak. To address this issue, we recommend that a pilot study of volume reduction in representative patients with ΔHS≥7% should be done first.

Assuming that the pilot study shows evidence that capillary leak is not the mechanism of ΔHS≥7%, we suggest that the patients with ΔHS≥7% be randomly assigned to either usual care or measures that intensify the reduction of intravascular (and interstitial) volume. These measures would include salt restriction and avoidance of high fluid intake.

The appropriate degree of salt restriction is not clear. However, we are concerned by the multiple lines of evidence that severe salt restriction (*e.g.*, 80 mM NaCl [about 2 g Na]) could actually be harmful (4–6). Also, recent studies of salt restriction in CKD do not provide compelling evidence that severe salt restriction is beneficial (7–11) but do indicate that patients with CKD can be salt sensitive. For example, diets containing 60–80 mM Na (1400–1800 mg Na and 3500–4000 mg NaCl) can result in large reductions in systolic BP (7).

Low-salt diet instructions should emphasize that dietary salt tastes best on the surface of food. Therefore, to make a salt-restricted diet more appealing (and likely improve compliance), the food should be prepared without addition of salt (*e.g.*, a 2.0–g Na diet). Salt can then be added to the food as it is being eaten. To provide the patients with a daily allotment of surface salt, we suggest adding to a salt shaker one third of a teaspoon of salt (about 1.5 g sodium chloride and about 25 mM Na). This greatly enhances the flavor of food for those who require some salt to make their food appealing (12,13).

Diuretic therapy can also achieve volume control. Indeed, in those with strong renal avidity for sodium, diuretic is the only effective therapy. Nevertheless, as a first approach to volume control, salt restriction is preferred over diuretic therapy because of the multiple lines of evidence that diuretic therapy increases CV and renal risk (14–16).

The patient should be advised to drink fluid if thirsty and to not drink fluid if not thirsty. This recommendation may seem controversial in light of recent reports that high fluid intake may protect kidney function (17,18). However, there is clear evidence from the Modification of Diet in Renal Disease Study that those with the highest urine volumes during follow-up had the fastest GFR declines during follow-up. The high urine volumes were almost certainly the result of the patients pushing fluids (19), perhaps because of the mistaken notion that drinking lots of fluid washes poisons from the body. This, of course, is not true. Waste product excretion is determined largely by GFR magnitude and not urine volume magnitude. Also, the beneficial effect of high fluid intake in patients with polycystic kidney disease has recently been challenged by a prospective randomized trial of increased fluid intake versus normal fluid intake. The study found harm and not benefit of high fluid intake (20,21).

We hope that Tsai *et al.* (3) or other investigators will carry out a randomized trial of fluid control in patients with stages 4 and 5 CKD. If Tsai *et al.* (3) find benefit, it would be another BIS splash.

Disclosures

None.

References

1. Tsai YC, Tsai JC, Chen SC, Chiu YW, Hwang SJ, Hung CC, Chen TH, Kuo MC, Chen HC: Association of fluid overload with kidney disease progression in advanced CKD: a prospective cohort study. *Am J Kidney Dis* 63: 68–75, 2014
2. Hung SC, Kuo KL, Peng CH, Wu CH, Lien YC, Wang YC, Tarng DC: Volume overload correlates with cardiovascular risk factors in patients with chronic kidney disease. *Kidney Int* 85: 703–709, 2014
3. Tsai Y-C, Chiu Y-W, Tsai J-C, Kuo H-T, Hung C-C, Hwang S-J, Chen T-H, Kuo M-C, Chen H-C: Association of fluid overload with cardiovascular morbidity and all-cause mortality in stages 4 and 5 CKD. *Clin J Am Soc Nephrol* 10: 39–46, 2015
4. O'Donnell M, Mente A, Rangarajan S, McQueen MJ, Wang X, Liu L, Yan H, Lee SF, Mony P, Devanath A, Rosengren A, Lopez-Jaramillo P, Diaz R, Avezum A, Lanas F, Yusoff K, Iqbal R, Ilow R, Mohammadifard N, Gulec S, Yusufali AH, Kruger L, Yusuf R, Chifamba J, Kabali C, Dagenais G, Lear SA, Teo K, Yusuf S; PURE Investigators: Urinary sodium and potassium excretion, mortality, and cardiovascular events. *N Engl J Med* 371: 612–623, 2014
5. Mozaffarian D, Fahimi S, Singh GM, Micha R, Khatibzadeh S, Engell RE, Lim S, Danaei G, Ezzati M, Powles J; Global Burden of Diseases Nutrition and Chronic Diseases Expert Group: Global sodium consumption and death from cardiovascular causes. *N Engl J Med* 371: 624–634, 2014
6. Oparil S: Low sodium intake—cardiovascular health benefit or risk? *N Engl J Med* 371: 677–679, 2014
7. McMahon EJ, Bauer JD, Hawley CM, Isbel NM, Stowasser M, Johnson DW, Campbell KL: A randomized trial of dietary sodium restriction in CKD. *J Am Soc Nephrol* 24: 2096–2103, 2013
8. Anderson CA, Ix JH: Sodium reduction in CKD: Suggestively hazardous or intuitively advantageous? *J Am Soc Nephrol* 24: 1931–1933, 2013
9. Sharma S, McFann K, Chonchol M, de Boer IH, Kendrick J: Association between dietary sodium and potassium intake with chronic kidney disease in US adults: A cross-sectional study. *Am J Nephrol* 37: 526–533, 2013
10. Fan L, Tighiouart H, Levey AS, Beck GJ, Sarnak MJ: Urinary sodium excretion and kidney failure in nondiabetic chronic kidney disease. *Kidney Int* 86: 582–588, 2014
11. Middleton JP, Lehrich RW: Prescriptions for dietary sodium in patients with chronic kidney disease: How will this shake out? *Kidney Int* 86: 457–459, 2014
12. Hebert LA: Optimizing ACE-inhibitor therapy for chronic kidney disease. *N Engl J Med* 354: 189–191, 2006
13. Haddad N, Shim R, Hebert LA: Nutritional management of water, sodium, potassium, chloride, and magnesium in kidney disease and kidney failure. *Nutr Manag Renal Dis Chapter* 22: 323–338, 2013
14. Hebert LA, Rovin BH, Hebert CJ: The design of ALLHAT may have biased the study's outcome in favor of the diuretic cohort. *Nat Clin Pract Nephrol* 3: 60–61, 2007
15. Rovin BH, Hebert LA: Thiazide diuretic monotherapy for hypertension: Diuretic's dark side just got darker. *Kidney Int* 72: 1423–1426, 2007
16. Jamerson K, Weber MA, Bakris GL, Dahlöf B, Pitt B, Shi V, Hester A, Gupte J, Gatlin M, Velazquez EJ; ACCOMPLISH Trial Investigators: Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high-risk patients. *N Engl J Med* 359: 2417–2428, 2008
17. Hebert LA, Parikh S: Chronic kidney disease: Fluid in chronic kidney disease-how much is too much? *Nat Rev Nephrol* 9: 630–631, 2013

18. Sontrop JM, Dixon SN, Garg AX, Buendia-Jimenez I, Dohein O, Huang SHS, Clark WF: Association between water intake, chronic kidney disease, and cardiovascular disease: A cross-sectional analysis of NHANES data. *Am J Nephrol* 37: 434–442, 2013
19. Hebert LA, Greene T, Levey A, Falkenhain ME, Klahr S: High urine volume and low urine osmolality are risk factors for faster progression of renal disease. *Am J Kidney Dis* 41: 962–971, 2003
20. Higashihara E, Nutahara K, Tanbo M, Hara H, Miyazaki I, Kobayashi K, Nitatori T: Does increased water intake prevent disease progression in autosomal dominant polycystic kidney disease? *Nephrol Dial Transplant* 29: 1710–1719, 2014
21. Meijer E, Casteleijn NF: Riding the waves: evidence for a beneficial effect of increased water intake in autosomal dominant polycystic kidney disease patients? *Nephrol Dial Transplant* 29: 1615–1617, 2014

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

See related article, "Association of Fluid Overload with Cardiovascular Morbidity and All-Cause Mortality in Stages 4 and 5 CKD," on pages 39–46.