Volume Overload in Dialysis: The Elephant in the Room, No One Can See

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Volume overload is the invisible threat to the health of dialysis patients. Currently, Medicare incentivizes the measurement of the dose of dialysis (urea reduction ratio) but has no measure of volume. Perhaps this is because the few who can recognize the epidemic nature of volume excess cannot agree on how to define it. Whereas, some have proposed interdialytic weight gain (IDWG) as a marker of volume, the in-depth review of Hecking et al. [1] quite clearly and importantly makes the distinction that IDWG should not be confused with hypervolemia. One has to wonder how IDWG got confused with dry weight in the first place. It appears that epidemiologists decided to use IDWG as a proxy of dry weight because of its ready availability in large databases. IDWG is a marker that is convenient; it can be measured easily and it can be related to outcomes such as all-cause mortality. This analysis was performed and a relationship emerged between IDWG and all-cause mortality. But establishing a relationship between IDWG and mortality does not establish causality. It could be numerous other factors, measured and unmeasured, associated with IDWG which may be causally related to mortality. Factors such as missing or cutting short dialysis, not taking medications as prescribed, and consuming a diet rich in phosphorus and potassium are some confounding factors that may also be associated with IDWG but may be more plausibly related to mortality.

The authors discuss several markers of volume excess. Although several exist, one marker, bioimpedance analysis (BIA), is discussed in great detail. This is understandable given both the academic and intellectual property

interests of the authors. However, considering the totality of the evidence, I am less convinced that this marker is superior to other volume markers. First, there are few head-to-head studies comparing BIA to other established markers of volume. Second, there is no range that defines 'normal'. Unlike blood pressure (BP) or cholesterol, there is no target that has been established. The normal values are obtained from healthy subjects whose body composition differs substantially from those on dialysis. Extrapolating from healthy subjects to those with ESRD on hemodialysis does not appear scientifically valid. Third, there is no study to my knowledge that demonstrates convincingly that compared to probing dry weight without BIA, BIA-guided dry weight reduction results in improved outcomes. Most data provided to support the use of BIA are associative and observational. A large amount of observational data does not prove causation. We therefore have to be cautious in interpreting these data as 'strongly indicative of fluid overload'.

Nearly all markers of volemia suffer from the same shortcomings. These shortcomings include lack of normative data, and data being largely observational and associative in nature. As an example, several observational studies suggest that B-type natriuretic peptide (BNP), NT-proBNP or other natriuretic peptides are associated with volume state among people with ESRD on dialysis [2–10]. However, only one study has been reported to date that relates the change in BNP to an intervention of probing dry weight [11]. In this study, a direct relationship existed at baseline between BNP and interdialytic ambulatory BP. Since interdialytic ambulatory BP is re-

lated to left ventricular mass, the relationship of cardiac natriuretic peptides and BP is likely confounded by left ventricular mass and function [11]. However, probing dry weight was not necessary for BNP to decline. This study found no relationship between probing dry weight with change in BNP [11]. Thus, reduction in volume was not related to reduction in BNP, calling into question our ability to predict changes in BP based on baseline BNP concentrations. These data illustrate the inconsistency of the results between observational and interventional studies. Aside from this limitation, there is nearly no information on whether marker-directed therapies will result in improvement in outcomes, with one notable exception that will be discussed further. This exception was a clinical trial that attempted to validate the use of relative plasma volume (RPV) monitoring to assess volume.

A multicenter randomized trial, the Crit-Line Intradialytic Monitoring Benefit (CLIMB) study, tested the notion whether RPV-guided therapy can improve outcomes [12]. The trial randomized 227 hemodialysis patients to RPV monitoring and 216 to conventional monitoring for 6 months to test the hypothesis that RPV-guided monitoring would mitigate hospitalization rates. Contrary to expectations, the trial demonstrated that RPV-guided therapy was associated with worse outcomes. Hospitalization occurred 1.53 times per year in the RPV-guided monitoring group and 1.03 times per year in the conventional group. Surprisingly, mortality was 8.7% in the RPV-guided monitoring, but only 3.3% in the conventional monitoring group ($p = 0.021$). Despite being a randomized trial, the authors did not follow their protocol. They state 'algorithm use was encouraged but not mandated, in contrast to earlier studies. This design was intended to assess the therapeutic efficacy of Crit-Line in a trial that permitted voluntary nonuse of the information from the device... Therefore, Crit-Line was studied as a voluntary adjunct to care.' Furthermore, 'highly variable implementation of the monitoring and interventional algorithm occurred within and across dialysis units; the causes were not collected.' Uncertain adherence to the protocol by the investigators makes it difficult to conclude that RPV-guided monitoring was a cause of higher complication rates. In fact, at baseline, as determined by RPV slope patterns, patients in the conventional group were more volume overloaded compared to the RPV-guided group. At 6 months, both groups had similar RPV slopes. In sum, the conventional group appeared to have had greater volume challenge than the intervention group. Since this study appears to be more observational than interventional because of uncertain ad-

herence to protocol, a more valid evaluation of this technology would have been to compare the RPV slope data as an association. Unfortunately, no causal inference is possible even when the hypothesis was tested in the context of a randomized trial.

There is no gold-standard measure of volume excess. The volume markers discussed by Hecking et al. [1] are imperfect and not ready for 'prime-time' deployment. Although no measurement can show the presence of volume excess conclusively, volume excess can be measured at the bedside. This method is referred to as probing the dry weight. Before probing, two prerequisites need to be fulfilled. First, the patient should not cut time on dialysis or miss dialysis sessions [13]. Second, IDWG needs to be modest. This requires consuming a modest dietary sodium (ideally <1.5 g/day, but no more than 2 g/day). Sometimes the gain in weight is iatrogenic due to prescription of dialysate sodium that is higher than the predialysis sodium. de Paula et al. [14] have demonstrated in an interventional study that prescribing dialysate sodium that is 2–3% lower than the patient's predialysis sodium results in reduced thirst and reduced IDWG, as well as a fall in systolic BP among hypertensive patients. Once the IDWG is assured to be modest, the postdialysis weight is lowered gradually over weeks until the patient becomes symptomatic from hypovolemia [15]. Large reductions in postdialysis weight do not prove that dry weight has been reached unless the patient demonstrates some sign of hypovolemia. This method is of course tedious and requires the cooperation of the patient and the patient's nurse. For the dialysis nurses and technicians it requires increased vigilance and effort. Sudden and unexpected drops in BP with downstream consequences such as syncope may sensitize providers to not use this powerful tool at their disposal.

Besides the development of symptoms upon probing dry weight, there is one measure of efficacy that indicates achievement of dry weight that is practical and widely available, but often overlooked – BP [16]. BP self-measured at home by patients relates well to ambulatory BP recordings, target organ damage such as left ventricular hypertrophy [17], and all-cause mortality [18, 19]. This is also the only marker that in a randomized controlled trial designed to test the utility of this marker as a sign of volume excess was shown to be reduced by probing dry weight [20]. Another randomized controlled trial demonstrated that compared to predialysis BP-guided therapy, home BP-guided therapy can improve ambulatory BP [21]. Why then the reluctance to use this simple, easily understood, inexpensive technique that can be easily implemented [22]? I suspect that there are several factors at

play. Among these are a reluctance to accept this measure as a practical technique; there is also no reimbursement for equipment or interpretation. If some of these barriers were removed, assessment of home BP for a few days at monthly intervals would be a practical way to diagnose hypervolemia. To be sure, all hypertension is not hypervolemia, and all hypervolemia will not cause hypertension [23], but at least it will be a beginning of improved assessment of hypervolemia at the bedside.

To continue to gather observational data to support the use of one volume marker or the other is simple, inexpensive, and I am sure will continue to be done. However, time has come to move away from this temptation, and perform randomized controlled trials. The Lung Water by Ultra-Sound Guided Treatment to Prevent Death and Cardiovascular Complications in High Risk End-

Stage Renal Disease Patients with Cardiomyopathy (LUST) trial, currently being performed in several European countries under the leadership of Dr. Carmine Zoccali, is a step in the right direction [24]. It has been more than 4 decades since we started to dialyze people with ESRD. It is about time that we provide data beyond observational that show the utility of markers of volume in the care of the dialysis patients. Otherwise, like the blind men, we will continue to probe and try to incompletely recognize the elephant in the room.

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