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Time to Improve Fluid Management in Hemodialysis: Should We Abandon Clinical Assessment and Routinely Use Bioimpedance?

Adrian Covic and Mihai Onofriescu

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University of Medicine and Pharmacy "Gr.T.Popa", Nephrology Department, Iasi, Romania

Correspondence:
Dr. Mihai Onofriescu, "Dr. C.I. Parhon" University Hospital, Carol I Boulevard, Nr. 50, Iasi, Romania. Email: onomihai@yahoo.com

Underestimation of the dry weight of hemodialysis patients can result in unwelcome symptoms and intradialytic hypotension, which may be associated with adverse outcomes (1,2). Similarly, overestimation of dry weight can lead to chronic volume overload, which increases cardiovascular morbidity and mortality (3).

In reality, there are problems in detecting both hypovolemia and hypervolemia (4). Not all intradialytic hypotension is caused by hypovolemia or is ameliorated by increasing the dry weight. It is well recognized that an excessive rate of ultrafiltration can also lead to intradialytic hypotension in the absence of hypovolemia. In addition, physical findings other than intradialytic hypotension cannot be used as reliable markers of hypovolemia. In a systematic review of the physical diagnosis of hypovolemia in nondialysis patients with volume of blood loss as the gold standard, the findings best related to hypovolemia were severe postural dizziness or orthostatic increase in heart rate (5). These findings were highly specific (>96%) but unfortunately were also insensitive (22%).

On the other hand, hypertension and edema are most common in a hypervolemic patient. Volume overload is an important determinant of hypertension in dialysis patients, but sympathetic overactivity and arterial stiffness are other important causes of hypertension. Thus, the absence of hypertension does not necessarily denote euvolemia. In this context, one can easily argue the need of a better, more objective method of determining volume status in hemodialysis patients.

Several methods have been successfully used in determining the hydration status in dialysis patients, such as the measurement of inferior vena cava diameter, intradialytic blood volume monitoring, or the evaluation of N-terminal pro-brain natriuretic peptide levels. Last but not least, bioimpedance appears to be one of the most promising and increasingly used techniques to objectively determine fluid status. This technique has been introduced in different forms during the last 15 years (single/multiple frequency, segmental/whole-body bioimpedance) but recently gained momentum on the basis of new solid evidence from clinical studies on fluid status assessment. It has been validated in both healthy persons and patients with CKD by isotope dilution methods, by accepted reference body composition methods, and by techniques that measure relative changes in fluid volumes (6). Most important, a link has been made between hydration status measured by bioimpedance and both surrogate end points (BP, arterial stiffness) and hard endpoints (7–9). Indeed, in an observational study, overhydration, determined by single-frequency bioimpedance, was identified as an important and independent predictor of mortality in patients undergoing long-term hemodialysis, with a hazard ratio of 2.1 for all-cause mortality, second only to diabetes (8).

An increasing number of studies, both cross-sectional and prospective, have investigated bioimpedance as a fluid management tool. Wabel *et al.* used a bioimpedance device to explore a large number of mostly clinically asymptomatic patients. They found both hypertensive but underhydrated patients and hypotensive but overhydrated patients, who clearly need different management (10). At the same time, bioelectrical impedance analysis was also successfully used to actively guide hemodialysis patients toward normohydration and better BP control (11). In face of this strong body of evidence in favor of bioimpedance-driven volume management, the next logical step was to set and test a simple yet rigorous protocol for large scale use in dialysis patients.

In line with this approach, in this issue of *CJASN*, Moissl *et al.* (12) report the results of a study that optimized the fluid status of 56 hemodialysis patients using a bioimpedance device over the course of 3 months. Investigators used time-average fluid overload (TAFO) to adjust the dry weight of all patients and compared the fluid status at baseline and at the end of study. Taking into account the intermittent ultrafiltration therapy, TAFO is defined as the weekly average fluid overload, as measured before and after dialysis. In addition to volume status measures (fluid overload, TAFO), secondary outcomes included an evaluation of quality of life, the relationship of fluid overload with BP, intradialytic symptoms of volume depletion, and brain natriuretic peptide. The TAFO target in these patients was 0.5 L, and it was reached using a strict dry weight adjustment protocol. This is the median TAFO value of >17000 patients in Fresenius Centers, where bioimpedance is routinely used to

evaluate fluid status. Even though a timeframe of only 3 months seems short for a study on dry weight adjustment, the use of a rigorous protocol for such adjustments allowed the investigators to bring patients to normovolemia and maintain this status throughout the study. The analysis of baseline TAFO was stratified according to the three major categories of hydration: underhydrated, normovolemic, and overloaded.

The study also reconfirms the strong relationship between fluid overload and BP, with an average 9.9-mmHg systolic BP decrease for each 1-L reduction in TAFO.

Another strong point is the detailed description of both intradialytic (cramps and hypotension) and interdialytic adverse effects, with no significant changes from baseline to the end of study. Previous studies, using clinical methods of volume assessment (*i.e.*, predialysis BP), found that a strict dry-weight control may lead to vascular access problems and an increased number of hospitalizations (13).

On the other hand, quality of life may take more than 3 months to change, and there are still some problems with adherence to a more intensive dry weight adjustment because a weekly bioimpedance measurement may be difficult to implement on a large scale.

With a rigorous design, this study manages to touch key points regarding possible implementation of a dry weight adjustment protocol, exclusively using bioimpedance. It is easy to bring all hemodialysis patients, regardless of fluid status, to a state of normovolemia and maintain that status. This will have positive implications for BP values, without increasing the frequency of intra- and interdialytic adverse events. We strongly believe that this protocol is a good starting point for a truly randomized control trial in more patients.

The authors comment that a control group would have been unethical, but we disagree. The same was thought for phosphate control (by phosphate binders). More and more voices now support the need for an interventional prospective randomized controlled trial to demonstrate the impact of lowering phosphate in survival. Regarding bioimpedance, we already have some small randomized controlled trial suggesting that strict bioimpedance-driven volume control improves cardiovascular outcomes (14). Clinical methods of volume assessment must stand against a strict bioimpedance protocol in order to determine whether bioimpedance based dry-weight control is truly superior to current volume management in hemodialysis patients.

Disclosures

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