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Why Assistive Technology Is Needed for Probing of Dry Weight

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Key Words

Hypertension · Blood pressure · Dry weight · Volume status · Hemodialysis · Bioimpedance · Relative plasma volume · Physical exam · End-stage renal disease

Abstract

Despite advancements in dialysis therapy, the subjective clinical examination still remains the standard of care in managing volume removal in chronic dialysis. While there is no definitive trial establishing that dry weight management guided by an assistive technology is superior to the clinical method, there is ample evidence that there is a need for these technologies to be developed. Mortality, cardiovascular morbidity, and sequelae of volume overload remain far too common under the current paradigm. Recent studies indicate that the mortality associated with volume overload is independent of hypertension, suggesting that if mortality is to be improved, then a measure of volume independent of blood pressure must be developed. Even when considered as an integrated whole, the clinical method is inaccurate at setting dry weight when compared to the use of assistive technologies. A recent secondary analysis of a randomized trial showed that relative plasma volume (RPV) slope is responsive to change in volume status and may be useful in guiding therapy for hypertension. The only large randomized trial to investigate the ability of an assistive technology to manage volume removal in hemodialysis patients is the Crit-Line Intradialytic Monitoring Benefit Study, which found harm associated with RPV monitoring. However, the design of this trial did not require the RPV group to actually receive this intervention. Assistive technologies offer an opportunity to improve on the subjective clinical exam for the setting of dry weight, but well designed and adequately powered clinical trials are needed.

Introduction

The primary objective of chronic hemodialysis for patients with end-stage renal disease is to restore the extracellular environment. This entails two major processes: removal of uremic solutes primarily by diffusion and removal of excess sodium and water primarily by convection. The adequacy of uremic solute removal is objectively assessed by measuring the clearance of a uremic surrogate, urea, on dialysis. This clearance multiplied by time and normalized for volume comprises the Kt/V of urea, which is a widely accepted [1] and routinely used measure of dialysis adequacy. The state of the art for measuring adequacy of volume removal is far behind the Kt/V standard, for there is no validated objective method for assessing volume status or setting dry weight. Consisting of the physical exam, a review of the run records, and the patient interview, the integrated clinical exam still remains the standard of care when managing volume status in chronic hemodialysis patients [2].

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Now, 43 years since the first description of the clinical dry weight [3], it is natural to question whether the clinical method can be improved upon through the use of assistive technologies to objectively set the dry weight of dialysis patients, and whether such changes will ultimately improve outcomes. It is important to note that at this time it has not been proven that assistive technologies are necessary, as there exists no definitive trial demonstrating an improved clinical endpoint resulting from the use of such technologies. However, it is this author's opinion that the current subjective standard of care must be improved upon, and assistive technologies to aid the probing of dry weight in hemodialysis patients must be investigated and developed.

Current Standard of Care Is Inadequate

The current standard of care in hemodialysis therapy is not serving our patients well. Mortality remains unacceptably high with only one third of our patients alive 5 years after starting hemodialysis [4], which represents a worse prognosis than that of stage IIIC colon cancer [5]. The leading causes of death for dialysis patients are cardiovascular causes, and cardiovascular morbidity remains equally high [6]. This abysmal morbidity and mortality record persists despite assiduous attention to adequacy of dialysis, and despite prodigious spending totaling nearly USD 18 billion or 4.3% of the total Medicare budget in 2007 [4].

Volume overload plays a major role in hypertension in renal disease [7], and volume reduction has long been recognized to improve hypertension [8], which was recently shown definitively in a randomized clinical trial [9]. However, despite this widespread knowledge, hypertension remains commonly present and poorly controlled in the hemodialysis population [10, 11]. Similarly, other sequelae of volume overload remain common problems with a rate of 217 admissions per 1,000 patient-years for congestive heart failure [4] and a rate of 137 episodes of acute dialysis per 1,000 patient-years for volume overload, with the latter alone costing Medicare USD 266 million over a 2.5-year period [12].

To ask the question of whether the current standard of care for our chronic hemodialysis patients is adequate is to already have the answer. Hypertension, symptomatic volume overload, and cardiovascular morbidity and mortality all remain unacceptably common for our patients under the current paradigm. As a dialysis and healthcare delivery system, we have focused on addressing the adequacy of uremic solute removal, and we have found the limits of what dialysis dose can do to improve mortality in our patients [13]. To improve outcomes for our dialysis patients, it is incumbent on us to now devote a similar focus on that other cardinal goal of dialysis, the removal of excess volume. The current standard of care employing the subjective clinical exam to manage volume removal needs to be improved upon.

Physical Findings Are Inaccurate

The clinical assessment of volume status includes a physical exam to detect findings consistent with either hypervolemia or hypovolemia. Large and rapid changes in volume status such as with acute volume overload are readily recognizable clinically; however, the management of volume status in end-stage renal disease also requires recognition of the more subtle changes of chronic volume overload. Most physical exam findings have not been rigorously validated, but of the findings that are frequently used to determine a dialysis patient's volume status [2], three have been studied: jugular venous distension, orthostatic hypotension, and pedal edema. Two systematic reviews from the late 1990s examined jugular venous distension [14] and orthostatic hypotension [15] for diagnosing volume status in patients who did not necessarily have renal disease. Neither jugular venous distension nor severe orthostatic hypotension performed well as diagnostic tests for hypervolemia or for moderate hypovolemia, respectively.

A recent cross-sectional study of 150 prevalent hemodialysis patients examined the relationship between pedal edema and objective markers of volume overload [16]. Pedal edema was not associated with any of the objective markers of volume studied, including N-terminal-pro-BNP, relative plasma volume (RPV) slope, or echocardiographic inferior vena cava diameter or collapsibility index [16]. However, pedal edema was independently associated with increased age, body mass index, and echocardiographic left ventricular mass. Therefore, of the three physical findings studied, none performs well as a diagnostic test for volume status.

Blood Pressure Is Not Equal to Volume Status

Consideration of blood pressure (BP) remains a critical component in the clinical evaluation of volume status [2, 17]. While volume overload is recognized as a major

cause of hypertension in end-stage renal disease [7], normotension is not synonymous with euvolemia, nor is hypertension synonymous with hypervolemia. This complex relationship is illustrated by three recent studies. The first was a cross-sectional multicenter study that measured predialysis systolic BP and volume as determined by bioimpedance analysis (BIA) in 500 hemodialysis patients [18]. The investigators reported that one third of patients were normotensive and euvolemic by their BIA definitions. In contrast, 10% of patients were normotensive but still hypervolemic, and 13% of patients were hypertensive but euvolemic. Therefore, using BP alone to classify volume status in these patients would result in nearly one quarter of patients being misclassified.

Additionally, two recent studies examined the relationship between volume overload, hypertension, and mortality. The first was a multicenter cohort study of 269 hemodialysis patients who had their volume status assessed by BIA and were subsequently followed for 3.5 years [19]. Volume overload as determined by BIA was an independent risk factor for mortality, even after adjustment for known mortality risk factors, including peridialytic BP averaged over 6 dialysis sessions. The second recent study was a single center cohort study of 308 hemodialysis patients who had RPV monitoring and were then followed up for a median of 30 months [20]. As shown in figure 1, volume overload as measured by RPV slope was an independent predictor of death, even when adjusted for known risk factors including interdialytic ambulatory BP. These results emphasize that BP and volume state are not synonymous, and they further suggest that achievement of normotension alone is unlikely to be sufficient to improve the mortality associated with volume overload. Therefore, if the mortality from volume overload is to be improved, then a measure of volume that is independent of BP must be developed and used to guide therapy.

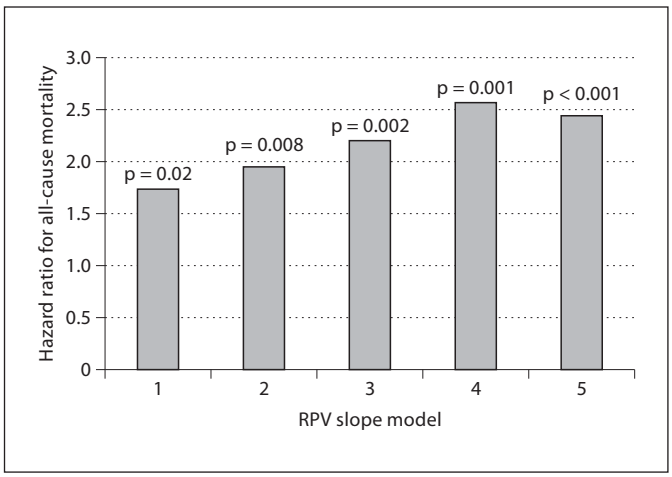

Fig. 1. Hazard ratios for all-cause mortality versus model of RPV slope. All models were adjusted for age, ethnicity, sex, serum albumin, hemoglobin, dialysis vintage, use of antihypertensive medications, and preexisting cardiovascular disease. Model 2 was additionally adjusted for ultrafiltration volume in liters. Model 3 was additionally adjusted for ultrafiltration volume per kilogram of body weight. Model 4 was additionally adjusted for ultrafiltration rate per kilogram of body weight. Model 5 was model 4 additionally adjusted for mean interdialytic ambulatory systolic BP. This figure is adapted from tabular data in Agarwal [20].

The Integrated Clinical Exam Is Inaccurate

Individual physical findings may be unreliable, but the assessment of volume status does not rely on any single finding. Ultimately, the treating nephrologist's clinical judgment integrates the physical findings, the dialysis run record information, the patient's case history, and the patient's report of symptoms to arrive at an assessment of volume status and dry weight. It stands to reason that the integrated clinical exam would perform better as a whole, compared to individual physical findings considered in isolation. However, the integrated clinical exam still performs poorly at setting dry weight when compared to a variety of objective methods.

Several cross-sectional studies have found the clinical dry weight to be inappropriately set in a large proportion of patients when assistive technologies are used as the criterion standard, including early studies of inferior vena cava echocardiography [21] and RPV monitoring [22]. Two recent large multicenter cross-sectional studies utilizing BIA have found similar results. The first study examined 500 randomly selected hemodialysis patients and found 5% of patients to be hypovolemic, while 25% of patients met the authors' definition for gross volume overload [18]. The second study examined 370 randomly selected hemodialysis patients and similarly found 5% of patients to be hypovolemic, while 21% of patients were determined to be hypervolemic at the end of dialysis [23].

While cross-sectional trials illustrate the inadequacy of the integrated clinical exam in setting dry weight, interventional trials that start with patients at clinical dry weight and then use assistive technologies to further investigate the dry weight provide even stronger evidence. A recent trial used postdialysis BIA of the calf to refine the dry weights of 117 stable hemodialysis patients, and

42 patients were found to be hypervolemic by the authors' definitions [24]. The investigators then probed the dry weight of the hypervolemic patients under BIA guidance and achieved BIA-defined euvolemia in 27 patients. These patients had their weight reduced an average of 0.96 kg and had associated reductions in home BP and antihypertensive medication use.

Continuous BIA is a new application of BIA principles that is being studied as an assistive technology for the probing of dry weight. In a trial pioneering the technique, 15 hemodialysis patients had continuous intradialytic calf BIA to investigate their dry weight, and 13 of the patients were found to be hypervolemic by the authors' definitions [25]. The investigators then probed the dry weight of these hypervolemic patients under BIA guidance, and they achieved an average weight reduction of 0.66 kg, which was associated with an improvement in predialysis systolic BP but also with a higher incidence of hypovolemic symptoms [25]. Whole body continuous BIA has also recently been studied in 19 stable hemodialysis patients, all of whom had their dry weight changed as a result of the use of the assistive technology [26]. The 7 patients assessed as hypovolemic had their dry weight raised by an average of 0.8 kg with a subsequent amelioration of symptoms of hypovolemia, and with no increase in home BP or in number of antihypertensives prescribed. The 12 patients assessed as hypervolemic had their dry weight lowered by an average of 0.6 kg with a subsequent improvement in home BP and a decrease in antihypertensive medications prescribed.

Two trials using RPV monitoring to assess and alter dry weight had similar results. The first enrolled all 56 patients from a single dialysis unit and found 18% of patients to have a flat RPV slope, consistent with volume overload. These volume overloaded patients had their dry weight reduced by an average of 0.8 kg, which they tolerated well, though peridialytic BP was unchanged [27]. The second study enrolled 28 hemodialysis patients at clinical dry weight and used RPV monitoring to reassess dry weight [28]. All patients had their dry weight changed as a result of the use of the assistive technology, with the 6 patients with the flattest RPV slope having an average reduction in dry weight of 5.4 kg.

Lastly, the recent Dry Weight Reduction in Hypertensive Hemodialysis Patients (DRIP) Trial enrolled 150 hypertensive hemodialysis patients at clinical dry weight, and randomized 100 patients to probing of dry weight until hypovolemic symptoms resulted versus the control of having dry weight kept unchanged during the 8-week trial [9]. The patients randomized to probing of dry weight had an average reduction of 1.0 kg in their dry weight and a corresponding 7 mm Hg control-corrected improvement in ambulatory systolic BP. While this last trial did not utilize an assistive technology to guide probing of dry weight, it does illustrate that even hypertensive patients at clinical dry weight can have volume-responsive hypertension, and that this was only discovered by applying a clinical trial protocol.

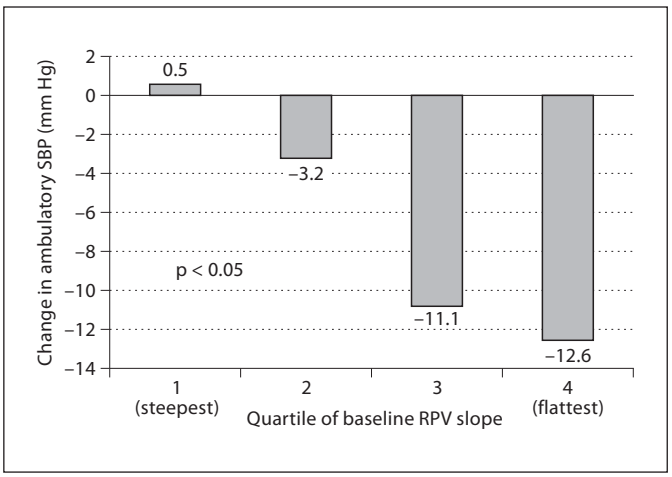

Fig. 2. Change in ambulatory systolic BP in ultrafiltration group corrected for control and versus quartile of baseline-RPV slope from steepest (least volume overloaded) to flattest (most volume overloaded). The quartile with the steepest slopes had an increase in BP despite attempted probing of dry weight, while the quartile with the flattest slopes had the largest decrease in BP with probing of dry weight. This figure was adapted from tabular data in an online data supplement to reference [29] available at http://hyper.ahajournals.org.

Developing a New Gold Standard

For an assistive technology to be accepted as the standard of care to assess volume status and to set dry weight, it is not sufficient to only show that these technologies arrive at different dry weights for dialysis patients compared to the clinical dry weights. How then can a new gold standard for assessing dry weight be developed when there is currently no gold standard? For an assistive technology to be a valid measure of volume status that guides the setting of dry weight, it must (1) be responsive to changes in volume status, (2) guide care in a meaningful way and (3) improve clinical outcomes.

My group has recently conducted a prespecified secondary analysis of the DRIP Trial that supports the use of RPV monitoring to assess volume status and to guide dry weight management based on points 1 and 2 above [29]. All patients in the DRIP Trial had RPV monitoring at baseline and again at the end of the 8-week trial. What we showed was that RPV slope significantly steepened in the intervention group randomized to probing of dry weight over 8 weeks, while RPV slope remained unchanged in the control group. Furthermore, we showed that baseline RPV slope predicted subsequent systolic ambulatory BP response to lowering of dry weight in these hypertensive patients. As shown in figure 2, the quartile of patients with the flattest slope at baseline, i.e. the most volume overloaded patients, had a statistically and clinically significant control-corrected improvement in systolic ambulatory BP of 11 mm Hg. Conversely, the quartile of patients with the steepest slope at baseline, i.e. the patients closest to euvolemia, actually had a control-corrected increase in systolic ambulatory BP despite attempted reduction in dry weight. Thus, RPV monitoring appears capable of identifying patients with volume responsive hypertension, guiding therapy in a meaningful way. However, the DRIP Trial did not use RPV monitoring to guide therapy, so it cannot be concluded that RPV-guided dry weight management will improve BP control – only a specifically designed interventional trial can answer that question.

The only large randomized clinical trial that has investigated the ability of an assistive technology to manage volume removal in hemodialysis patients is the Crit-Line Intradialytic Monitoring Benefit (CLIMB) Study, which randomized 443 hemodialysis patients to 6 months of RPV-guided ultrafiltration versus usual care [30]. The CLIMB Study found a significantly higher rate of hospitalization and mortality for the RPV group; however, the design of the trial did not require the RPV monitoring group to actually receive the intervention of RPV monitoring, and adherence to the study protocol was not measured [30]. Therefore, it is difficult to draw a conclusion about the harm of RPV monitoring when the level of exposure to the intervention is unknown.

Conclusion

The current standard of care for management of volume status in chronic hemodialysis patients is not achieving adequate outcomes for this population as sequelae of volume overload remain far too common. Assistive technologies offer an opportunity to improve on the inaccurate and subjective clinical method for the setting of dry weight, but well-designed and adequately powered randomized clinical trials are needed to determine the efficacy of these objective measures.

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