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The fallacy of low interdialytic weight gain and low ultrafiltration rate: lower is not always better

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Despite 50 years of experience, outcomes for patients on chronic hemodialysis (HD) remain poor. Annual mortality rate remains in excess of 20% and morbidity remains high with an average of 1.9 hospitalizations per HD patient per year (1). These outcomes persist despite Medicare spending over \$23 billion in 2010 for chronic HD alone, fully 4.5% of the entire Medicare budget (1). The leading causes of mortality in this population are cardiovascular, yet traditional risk factors don't explain the high cardiovascular risk in this population. There are numerous hypothesized causes for this excess cardiovascular risk; one modifiable but often overlooked factor is volume overload. Not only does volume overload play a major role in causing hypertension in this population, but it also contributes to cardiac remodeling manifest as chamber enlargement and left ventricular hypertrophy. Additionally, two recent cohort studies have shown volume overload measured by objective methods to be independently associated with subsequent all-cause mortality (2;3). The more direct sequelae of volume overload also remain common, with a 13.7% risk per patient-year of requiring hospital based acute dialysis for volume overload not of primary cardiac etiology (4).

Managing volume overload requires vigilant minimization of volume gain coupled with adequate volume removal. Volume removal is achieved by ultrafiltration on dialysis, guided by the dry weight method. The latter is an iterative technique and remains the gold-standard because of lack of validated objective measures of volume status. The dry-weight method allows for the extracellular fluid volume that is optimal for a given individual. On the other hand, volume gain is minimized by providers limiting the prescribed dialysate sodium concentration and by patients reducing their dietary sodium intake, both of which are associated with lower interdialytic weight gain (IDWG). Thus lower IDWG is a desirable goal for HD patients. However, is lower IDWG always preferable?

Multiple studies have shown an association between lower IDWG and outcomes. The largest is a retrospective cohort study of over 34,000 HD patients dialyzing at DaVita facilities over a 2 year period (5). After multivariate adjustment the authors found IDWG >1.5 kg to be significantly associated with increased risks both for all-cause and cardiovascular mortality compared to IDWG between 0.5 kg and 1.5 kg. Similarly, higher increments of IDWG conferred even greater risk of both all-cause and cardiovascular death. This association is plausible as having high IDWG may be akin to having episodes of heart failure 3 times per week between HD sessions, which may provoke similar maladaptive neurohumoral responses as seen in heart failure including increased sympathetic activity and renin-angiotensin-aldosterone system activation ultimately leading to cardiovascular morbidity and mortality.

High IDWG also necessitates a high ultrafiltration rate (UFR) to remove the volume gained since the last HD session during the prescribed HD time. Several studies have found an association between high UFR and adverse outcomes, exemplified by a secondary observational analysis of the over 1800 subjects who participated in the HEMO Study, a randomized controlled trial (6). The authors of the secondary analysis found a UFR of over 13 milliliters of ultrafiltration per hour of dialysis per kilogram of body weight (mL/h/kg) to be significantly associated with an increased risk of both all-cause and cardiovascular mortality when compared with UFR <10 mL/h/kg. Furthermore using restricted cubic spline analysis the authors found the mortality risk starts to increase above UFR of 10 mL/h/kg, which corresponds to the UFR for a 70 kg patient who dialyzes for 4 hours and has a UF goal of 2.8 kg total. This association between UFR and mortality is also plausible, as high UFR is associated with intradialytic hypotension and its downstream consequences which may contribute to mortality. However, it is additionally possible that high IDWG and UFR do not directly cause significant cardiovascular risk themselves, but rather that they are markers of another underlying cause. High IDWG leads to the scenario where patients can't achieve their prescribed post-HD dry weight, so the nephrologist will raise the dry weight administratively to reflect whatever weight the patient is actually achieving at the end of HD. Since this administrative raise in dry weight is not due to hypovolemia it will leave the patient with some degree of volume overload. Furthermore, even if the nephrologist assesses a patient as volume overloaded, a high IDWG will make it difficult for the nephrologist to successfully treat the volume overload through challenging of the dry weight. High UFR, whether from high IDWG or from a short prescribed time on dialysis, predisposes to intradialytic symptoms including hypotension, nausea, and cramping. Such symptoms will impair the ability for the patient to consistently reach an adequately low dry weight, and additionally such symptoms may prompt the nephrologist to raise the prescribed dry weight in the absence of true hypovolemia.

In these ways both high IDWG and high UFR will predispose patients toward chronic volume overload and the resulting adverse cardiovascular consequences. However, it is vital to note that high IDWG or high UFR are not synonymous with volume overload. It is possible for a patient to have a high IDWG with resulting high UFR and to still consistently reach an adequately low prescribed dry weight that achieves euvolemia. Conversely, it is possible for a patient to have both low IDWG and UFR, and to consistently reach a prescribed dry weight that is too high such that the patient remains volume overloaded.

We have observed that hypertensive volume overloaded patients often have low IDWG and that when dry weight is challenged to treat their hypertension, then their IDWG increases. This relationship is shown graphically in figure 1, with data from a subject who participated in an ongoing trial treating hypertension on HD. This figure shows that dry-weight could be successfully lowered and this was associated with an increase in IDWG. Additionally a secondary observational analysis of the Dry Weight Reduction in Hypertensive Hemodialysis Patients (DRIP) Trial examining the utility of relative plasma volume slopes in assessing volume status found that those hypertensive subjects who were measured to be most volume overloaded at baseline were those with the lowest IDWG (7). Conversely, those subjects least volume overloaded at baseline were those with the highest IDWG. Most importantly, when dry weight was challenged during the 8 week DRIP Trial it was the most volume overloaded group that achieved the largest lowering in both weight (1.5 kg) and in ambulatory BP (12.6 mmHg systolic). Lastly, a prospective cohort study found baseline volume overload assessed by relative plasma volume monitoring to be a significant independent risk factor for subsequent mortality, even after adjustment for ultrafiltration volume, UFR, and 44 hour ambulatory BP (3).

As there is yet no validated objective measure of volume status in chronic HD patients and in the absence of clinical trial evidence to guide the nuances of dry weight management, ensuring adequate volume removal on HD remains a subjective endeavor. Recent opinions from a large group of experts point out that high IDWG should not serve as a proxy of dry-weight (8). Based on the above observations it is our practice to strive for both low IDWG and UFR not as ends in themselves, but as means toward achieving euvolemia at an appropriately low dry weight. Low IDWG presents an opportunity to challenge dry weight in patients we judge to be volume overloaded, whereas high IDWG and UFR are frequent obstacles to achieving an appropriately low dry weight. Oftentimes higher UFR is necessary when challenging dry weight to achieve euvolemia, and a higher IDWG may result when the patient nears euvolemia but we tolerate these consequences for the benefit of reducing volume overload. We await future trials that may explicate the influences of hypertension, volume overload, IDWG, and UFR on outcomes in the chronic HD population. For now, slavishly adhering to a threshold of UFR (such as <12/mL/kg/hr) at the expense of leaving the patient hypervolemic is, in our opinion, short sighted.

Acknowledgments

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Figure 1.

Relationship of dry-weight to interdialytic weight gain. In a subject participating in a clinical trial who previously had well controlled BP measured at home was hospitalized for pneumonia. Upon discharge from hospital, BP was poorly controlled despite increasing the number of antihypertensive medications. Figure shows that dry weight was reduced gradually over time. Over a few weeks, BP was controlled to <140/90 mmHg (not shown). The modeled dotted line overlying the IDWG illustrates that reduction of dry-weight was accompanied by increasing interdialytic weight gain (IDWG).