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Rapid ultrafiltration rates and outcomes among hemodialysis patients: re-examining the evidence base

Magdalene M. Assimon, PharmD, MS[1,2] and **Jennifer E. Flythe, MD, MPH**[1,3]

[1]University of North Carolina Kidney Center, Division of Nephrology and Hypertension, Department of Medicine, UNC School of Medicine, Chapel Hill, NC

[2]Department of Epidemiology, UNC Gillings School of Global Public Health, Chapel Hill, NC

[3]Cecil G. Sheps Center for Health Services Research, University of North Carolina, Chapel Hill, NC

STRUCTURED ABSTRACT

Purpose of review—This review critically summarizes the evidence linking ultrafiltration (UF) rates to adverse outcomes among hemodialysis (HD) patients and provides research recommendations to address knowledge gaps.

Recent findings—Growing evidence suggests that fluid-related factors play important roles in HD patient outcomes. Ultrafiltration rate, the rate of fluid removal during HD, is one such factor. Existing observational data suggest a robust association between greater UF rates and adverse cardiovascular outcomes, and such findings are supported by plausible physiologic rationale. Potential mechanistic pathways include UF-related ischemia to the heart, brain, and gut and volume overload-precipitated cardiac stress from reactive measures to UF-induced hemodynamic instability. Inter-relationships among UF rates and other fluid measures such as interdialytic weight gain and chronic volume expansion render the specific role of UF rates in adverse outcomes difficult to study. Randomized trials must be conducted to confirm epidemiologic findings and examine the effect of UF rate reduction on clinical and patient-centered outcomes.

Summary—Compelling observational data demonstrate an association between more rapid UF rates and adverse clinical outcomes. Before translating these findings into clinical practice, randomized trials are needed to verify observational data results and to identify effective strategies to mitigate UF-related risk.

Keywords

ultrafiltration rate; hemodialysis; interdialytic weight gain; treatment time

Corresponding Author: Jennifer E. Flythe MD, MPH, University of North Carolina Kidney Center, 7024 Burnett-Womack CB #7155, Chapel Hill, NC 27599-7155, jflythe@med.unc.edu, (tel) 919-445-2656.

CONFLICTS OF INTEREST

Dr. Flythe has received speaking honoraria from Dialysis Clinic Incorporated.

INTRODUCTION

Mounting evidence linking fluid-related factors and outcomes among maintenance hemodialysis (HD) patients has stirred debate about optimal fluid management practices. Dialysis leaders have implored providers to consider fluid-related factors alongside clearance metrics and patient well-being in adequate HD determination.(1) Absence of objective volume status assessment tools and lack of fluid-related clinical trials have led to controversy regarding ideal fluid management standards. Ultrafiltration (UF) rate, the rate of fluid removal during HD, has been put forward as a potential actionable component of fluid management (Figure 1).(2, 3) Observational studies have demonstrated associations between more rapid fluid removal and greater morbidity and mortality, leading some experts to call for adoption of ceiling UF rate thresholds.(2) The objectives of this commentary are to: 1) critically review the UF rate and outcome evidence, 2) consider potential mechanistic pathways and mitigation strategies for UF-related harm and 3) identify knowledge gaps.

ULTRAFILTRATION RATE AND OUTCOME EVIDENCE

Three observational studies have demonstrated associations between greater UF rates and mortality. Using the Dialysis Outcomes and Practice Patterns Study cohort, Saran, *et al.* found an association between UF rates >10 mL/h/kg and higher all-cause mortality (adjusted HR 1.09, p=0.02).(4) Surprisingly, the authors found no association between higher UF rates and cardiovascular mortality. This analysis was followed by an Italian study in which Movilli *et al.* demonstrated that for every 1 mL/h/kg increase in UF rate, there was a 22% increase in mortality risk (p<0.01). In secondary analyses, authors identified a UF rate of 12.4 mL/h/kg as the most discriminatory cut-point for predicting two year mortality.(5) In a post-hoc analysis of the HEMO Study, Flythe *et al.* employed a UF rate threshold of 13 mL/h/kg, finding that patients with UF rates >13 mL/h/kg had a 59% increased risk of all-cause mortality and 71% increased risk of cardiovascular mortality (p<0.001 for both). UF rates 10–13 mL/h/kg were not associated with outcomes in the full cohort but were among patients with heart failure. When UF rate was considered as a spline, UF-associated risks were shown to rise markedly between 10 and 13 mL/h/kg.(6)

To date, there have been no clinical trials evaluating the effect of UF rates on outcomes. We are left to interpret and apply observational data, but in doing so, must be mindful of their limitations. Residual confounding is an inherent limitation of observational studies. Even the most optimally composed models cannot fully account for all confounding. Confounders are factors associated with both the exposure of interest and the outcome and are *not* factors recognized as intermediaries along the causal pathway between exposure and outcome.(7) All three UF rate studies included numerous potential confounders as covariates in multivariable analyses, but consideration of residual confounding from 1) unmeasured patient health status, 2) selective HD treatment prescription practices and 3) residual kidney function is warranted. All UF rate studies included markers of health such as albumin, blood pressure, and co-morbidities, but these variables fall short in fully capturing patient resiliency, leaving open the possibility of residual confounding from health status. Second, frailer patients may receive shorter treatments due to prior HD intolerance or a lower body weight-conferred ability to achieve clearance benchmarks in shorter time. Additionally,

shorter sessions may be selectively prescribed to non-adherent patients with histories of early HD termination. Thus, patients with longer treatment times (TTs) and associated lower UF rates may be healthier. Flythe *et al*. accounted for confounding from HD intolerance by employing prescribed rather than delivered TT, but this approach does not address confounding from selective HD prescriptions. In a separate analysis, Flythe *et al*. examined TT and outcomes among patients with adequate urea clearance matched on body weight, finding that patients with longer TTs had better survival than patients of the same weights with shorter TTs.(8) While this study did not directly address UF rates, it suggests that slower fluid removal facilitated by longer TTs may be advantageous independent of body weight.

Third, confounding from residual kidney function must be considered. Greater residual kidney function is associated with better clinical outcomes.(9) Patients requiring greater UF rates often have less native kidney function, rendering statistical control for urine output critical. Saran *et al*. did not consider residual kidney function in their analyses.(4) Flythe *et al*. included a binary variable (urine output ≤ versus >200 mL/day).(6) This is a coarse dichotomy. Patients with 2000mL urine/day may have better outcomes than patients with 250 mL urine/day, a difference not accounted for by Flythe *et al*. In contrast, Movilli *et al*. restricted study to patients with urine output ≤ 150 mL/day. This study provides the most compelling support for the UF rate—outcome association absent confounding from residual kidney function.(5)

Analytical decisions should also be considered when weighing observational data. All 3 studies considered UF rates as baseline mean values. Movilli *et al.* employed a mean UF rate over 30 days (approximately 13 treatments) and Flythe *et al*. used the mean UF rate in the HEMO Study pre-randomization period (1–4 treatments).(5, 6) Saran *et al*. also used a mean but did not report the number of treatments considered.(4) Arithmetic means are sensitive to extreme values. Outlier values for UF rate will have a greater influence in means derived from relatively few treatments, and thus may alter outcome associations. Additionally, when using a single, time-fixed mean UF rate as the exposure, the corresponding implicit assumption is that each individual's UF rate during follow-up is equivalent to the mean UF rate captured at baseline. In reality, UF rates are dynamic and fluctuate with TT and interdialytic weight gain (IDWG) changes, both factors altered by ambient health status. Related, none of the existing studies considered time-varying confounders. Studies employing UF rate as a time-varying exposure and considering time-varying confounders would enhance the evidence base.

Finally, Flythe *et al*. have been criticized for including IDWG in their multivariable models, as IDWG is highly correlated with UF rate. (2, 3, 6) Similar choices were made in the two other UF rate studies with Movilli *et al*. including IDWG and Saran *et al*. including intradialytic weight loss in models. Collinearity between UF rate and IDWG could lead to unreliable effect estimates from model imprecision. In repeat analyses of the HEMO Study without multivariable model inclusion of IDWG, Flythe *et al*. report similar magnitudes of association between UF rates and outcomes, providing reassurance that estimates were minimally affected by IDWG inclusion (*unpublished*).

POTENTIAL MECHANISTIC PATHWAYS

Although existing observational data have potential short-comings, the demonstrated UF rate—outcome association is supported by evidence from mechanistic studies. Such studies point to UF-induced hypo-perfusion of vital vascular beds as outcome mediators (Figure 2). UF-induced intravascular volume depletion diminishes coronary blood flow, leading to cardiac ischemia as evidenced by myocardial wall stunning on echocardiography and troponin elevation.(10–12) Repetitive cardiac ischemia leads to ventricular remodeling and downstream effects of heart failure and arrhythmia.(13, 14) Recurrent HD-induced myocardial stunning has been linked to greater ejection fraction declines.(11) Dialysis patients are especially vulnerable to reduced myocardial oxygen supply due to a high burden of small vessel disease and high oxygen-requiring, hypertrophied ventricles. Notably, more frequent HD, a schedule characterized by lower IDWG and UF rates, is associated with reduced myocardial stunning.(15) Collectively, this data support greater UF rates as a contributor to adverse cardiovascular outcomes.

UF-induced ischemia is not limited to the heart and likely impacts both the brain and gut. Chronic cerebral hypo-perfusion among HD patients has been linked to white matter changes, dementia, and depression.(16) Cooled dialysate may improve white matter changes via vasoconstriction.(17) Additionally, UF-induced gut ischemia may lead to bacterial translocation from the gut to the bloodstream. Increased blood endotoxin has been associated with cardiac stunning, and more frequent HD regimens are associated with lower endotoxin levels.(18, 19) HD-induced endotoxemia represents a plausible link between intradialytic hemodynamics and chronic inflammation.(18, 20)

Beyond its direct end-organ effects, UF-induced hypotension and cramping (UF-related or not) may result in interventions with unintended, deleterious consequences. Such events often leads to early UF termination, halting fluid removal before the target weight can be achieved, thereby introducing harm from volume overload. Over time, target weights may be adjusted upward to match post-dialysis weights, leaving patients chronically volume expanded. Chronic volume expansion has been linked to adverse cardiovascular outcomes through ventricular hypertrophy and fibrosis and eventual heart failure and arrhythmias.(13, 21–23) Not surprisingly, recent data link more frequent missed target weights to adverse cardiovascular outcomes.(24, 25) In addition to HD truncation, hypotension or patient cramping may lead to normal or hypertonic saline administration. These interventions put patients at risk for failed target weight achievement, greater IDWG from positive sodium balance, and exacerbated hypervolemia.(26, 27)

ULTRAFILTRATION RATE: RISK MARKER OR INDEPENDENT RISK FACTOR?

While the proposed physiologic link between rapid UF rates and outcomes is compelling, UF rate is a composite metric, dependent on two factors: IDWG and TT. Both factors have been independently associated with greater mortality, and both are plausible drivers of the UF rate—outcome association. Prior studies have shown that greater amounts of IDWG associate with adverse outcomes in a dose-response pattern.(28–30) Volume overload from

frequent high IDWG can lead to maladaptive cardiac structural changes. Additionally, intradialytic hypotension is more prevalent among patients with greater IDWG.(31) More frequent intradialytic hypotension is associated with all-cause and cardiovascular mortality.(31, 32) Thus, it is plausible that either volume overload or end-organ damage from intradialytic ischemia drive the observed UF rate—outcome association. Similarly, shorter TT has been linked to greater mortality in observational studies across various cohorts using a variety of methodologies.(4, 8, 33, 34) Shorter TT may impact mortality through both clearance and volume pathways, making TT a plausible mediator of the UF rate—outcome association.

Flythe *et al*. explored the roles of TT and IDWG in the UF rate—outcome association by matching patients with identical IDWGs and examining the TT and mortality association, and then, separately, matching patients with identical TTs and examining the IDWG and mortality association. The authors excluded patients not meeting Kt/V standards to limit confounding from clearance. Findings demonstrated that both TT and IDWG play significant roles in the UF rate—mortality association, independent of one another.(35) Finally, the role of chronic volume expansion in UF-related outcomes must be considered. Rapid UF rates indirectly contribute to chronic volume expansion when HD is terminated early, UF rates decreased, or target weights adjusted upward due to cramping or hypotension.

It is certainly physiologically plausible that greater UF rates are independent risk factors for morbidity and mortality, but, it is also conceivable that their harm stems from hypervolemia, rendering them surrogate risk markers. Existing data do not allow us to fully distinguish the individual influences of UF rate, IDWG, TT, and chronic hypervolemia on outcomes. Evidence supporting these fluid-related factors as critical contributors to adverse outcomes is strong, but the optimal approach to reducing their risks is less obvious due to measure inter-relationships.

INTERVENTIONS TO REDUCE ULTRAFILTRATION RISK

Ultrafiltration rate reduction is achieved by IDWG decrease or TT extension. Dietary restrictions, with salt restriction of greater import than fluid restriction, are physiologically sound approaches to IDWG reduction; however, patients are poorly adherent. In a survey of over 400 patients prescribed fluid restrictions, >40% reported non-adherence on a near-daily basis.(36) Psychological and behavioral interventions may improve adherence, but sustainability of these efforts has not been studied.(37–39) Use of lower dialysate sodium is an additional method for curbing IDWG. However, this intervention remains controversial as observational studies of the dialysate sodium--mortality association have yielded mixed results.(40–42) Diuretics may lessen IDWG among patients with residual kidney function, but this approach has not been evaluated. Dialysis prescription changes such as increased HD frequency to reduce IDWG and TT extension to allow for more gradual fluid removal are other options, but patients are generally averse to more frequent and longer HD. Flythe *et al*. surveyed 600 HD patients and found that only 12% were willing to add a 4th weekly treatment and 21% were willing to increase TT by 30 minutes in exchange for liberalized fluid intake.(36)

Some experts have suggested imposing UF rate thresholds (such as 13 mL/h/kg) to reduce UF-related risk.(2, 3) Patients presenting with fluid gains requiring UF rates above the threshold would require TT extension or additional treatments. Patients declining TT extension would have UF rates capped, leaving them above their prescribed target weights at HD conclusion. While it is plausible that the mere mention of TT extension would motivate patients to limit IDWG, it is equally plausible that UF needs would remain unchanged and patients declining TT extension would become volume-expanded. Rigorous investigation of the effect of UF rate thresholds on volume status, fluid-related hospitalizations and other adverse outcomes including patient-centered outcomes are needed prior to threshold adoption. Other potential treatment changes to reduce rapid UF rate harm include chilled dialysate, UF profiling (decelerating UF rate to match declining plasma refill rate) and sequential dialysis (isolated UF followed by combined HD and UF). These methods have been incompletely studied and their effects on cardiac stunning, target weight achievement, and cardiovascular outcomes are unknown.

KNOWLEDGE GAPS

The relative importance of UF rate, IDWG, TT, and chronic volume expansion to clinical outcomes is unknown. In cases of high weight gain or chronic volume expansion, clinicians face the conundrum of choosing between rapid fluid removal and a “dry” patient and slower fluid removal and a “wet” patient. It is plausible, and in the authors’ opinions, likely, that exposure to high UF rates for isolated time periods in the name of target weight achievement or challenge is preferable to low UF rates and unchallenged, hypervolemic states. Existing data do not allow us to make these distinctions. Imposing UF rate thresholds without understanding their effect on other fluid measures is premature. Prospective study of these issues is needed before optimal fluid standards can be incorporated into quality programs.

Additionally, we lack prospective trial data confirming the effects of fluid-related factors on morbidity and mortality. Such studies should evaluate not only cardiovascular endpoints but also patient-reported outcomes including intradialytic symptoms, recovery time, and quality of life. We must place greater emphasis on identifying UF rate mitigation strategies that are acceptable to patients. Patient-dependent strategies like dietary restrictions and willingness to extend TT have proven unsuccessful. Increased focus on HD procedural alterations such as cooled dialysate and different fluid removal patterns may be prudent, but remain understudied. Finally, objective measures of volume status are needed. Improved accuracy in determining total-body euvolemia would obviate the need for target weight probing (with or without high UF rates) and would limit sub-clinical hypervolemia.

CONCLUSION

Observational data suggest an association between greater UF rates and mortality among HD patients. Recurrent end organ hypoperfusion and its downstream consequences of cardiac remodeling, brain white matter damage, and gut-related systemic endotoxemia are possible mechanisms underlying these associations. Despite the plausible and observational data-supported association between rapid UF rates and outcomes, we lack randomized trials confirming these findings. In conducting such trials, patient strategy acceptance must be

given high priority as clinical trials will be for naught, if patients are unwilling to adopt the identified, evidence-based intervention.

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Abbreviations

HD	hemodialysis
UF	ultrafiltration
IDWG	interdialytic weight gain
TT	treatment time

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KEY POINTS

- Existing data provide compelling evidence linking more rapid fluid removal and greater mortality, but these studies are limited by inherent shortcomings of observational data.
- Both overt and subclinical hypo-perfusion of vital organs including the heart, brain, and gut are plausible mediators of the observed association between greater ultrafiltration rates and adverse outcomes.
- Prior to establishing ultrafiltration-based quality metrics, clinical trials evaluating the effect of ultrafiltration rate thresholds on clinical outcomes is needed.

$$\text{Ultrafiltration rate (mL/h/kg)} = \frac{\text{Interdialytic weight gain (mL)}}{\text{Treatment time (h)}} \Big/ \text{Post-weight (kg)}$$

Figure 1.
Ultrafiltration rate calculation.

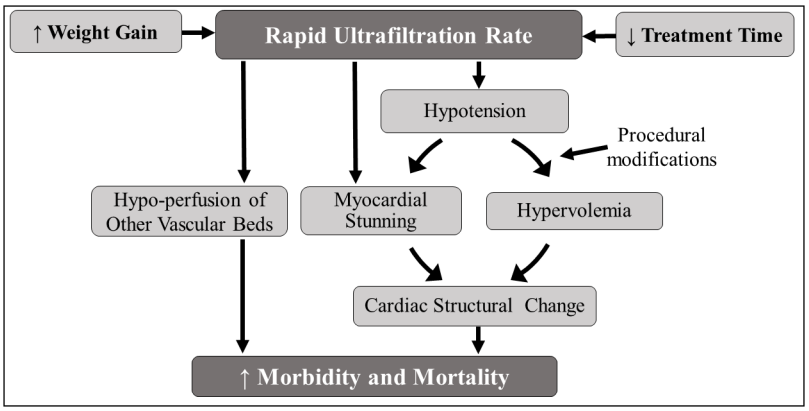

Figure 2.
Potential mechanisms underlying the ultrafiltration rate and adverse outcome associations.