Original Investigation

Kidney360

Dynamics of Plasma Refill Rate and Intradialytic Hypotension During Hemodialysis: Retrospective Cohort Study With Causal Methodology

Christina H. Wang[1,2] *Dan Negoianu*,[1] *Hanjie Zhang*,[3] *Sabrina Casper*,[4] *Jesse Y. Hsu*,[2,5] *Peter Kotanko*,[3,6] *Jochen Raimann*,[3] *and Laura M. Dember*[1,2,5]

Key Points

- Directly studying plasma refill rate (PRR) during hemodialysis (HD) can offer insight into physiologic mechanisms that change throughout HD.
- PRR at the start and during HD is associated with intradialytic hypotension, independent of ultrafiltration rate.
- A rising PRR during HD may be an early indicator of compensatory mechanisms for impending circulatory instability.

Abstract

Background Attaining the optimal balance between achieving adequate volume removal while preserving organ perfusion is a challenge for patients receiving maintenance hemodialysis (HD). Current strategies to guide ultrafiltration are inadequate.

Methods We developed an approach to calculate the plasma refill rate (PRR) throughout HD using hematocrit and ultrafiltration data in a retrospective cohort of patients receiving maintenance HD at 17 dialysis units from January 2017 to October 2019. We studied whether (*1*) PRR is associated with traditional risk factors for hemodynamic instability using logistic regression, (*2*) low starting PRR is associated with intradialytic hypotension (IDH) using Cox proportional hazard regression, and (*3*) time-varying PRR throughout HD is associated with hypotension using marginal structural modeling.

Results During 180,319 HD sessions among 2554 patients, PRR had high within-patient and between-patient variability. Female sex and hypoalbuminemia were associated with low PRR at multiple time points during the first hour of HD. Low starting PRR has a higher hazard of IDH, whereas high starting PRR was protective (hazard ratio [HR], 1.26, 95% confidence interval [CI], 1.18 to 1.35 versus HR, 0.79, 95% CI, 0.73 to 0.85, respectively). However, when accounting for time-varying PRR and time-varying confounders, compared with a moderate PRR, while a consistently low PRR was associated with increased risk of hypotension (odds ratio [OR], 1.09, 95% CI, 1.02 to 1.16), a consistently high PRR had a stronger association with hypotension within the next 15 minutes (OR, 1.38, 95% CI, 1.30 to 1.45).

Conclusions We present a straightforward technique to quantify plasma refill that could easily integrate with devices that monitor hematocrit during HD. Our study highlights how examining patterns of plasma refill may enhance our understanding of circulatory changes during HD, an important step to understand how current technology might be used to improve hemodynamic instability.

KIDNEY360 4: 505–514, 2023. doi: https://doi.org/10.34067/KID.0000000000000082

Introduction

Intradialytic hypotension (IDH) occurs during 20%–50% of hemodialysis (HD) sessions and is associated with increased morbidity, mortality, and health care utilization.[1–4] Although lower ultrafiltration volumes and rates may decrease the incidence of IDH, these

[1]Renal, Electrolyte and Hypertension Division, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania
[2]Center for Clinical Epidemiology and Biostatistics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania
[3]Renal Research Institute, New York, New York
[4]Fresenius Medical Care Deutschland GmbH, Bad Homburg, Germany
[5]Department of Biostatistics, Epidemiology and Informatics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania
[6]Icahn School of Medicine at Mount Sinai, New York, New York

Correspondence: Dr. Christina H. Wang, University of Pennsylvania, Department of Medicine, Renal, Electrolyte and Hypertension Division, Founders 1, 3400 Spruce Street, Philadelphia, PA 19104. Email: hao.wang2@pennmedicine.upenn.edu

strategies may also contribute to persistent volume overload.[5,6] Other strategies to improve tolerability of ultrafiltration, such as lowering dialysate temperature or using sodium profiling, aim to enhance central vascular refilling.[7–10] However, responses to these interventions are variable, and a more tailored approach is desired.[11–13]

Although the pathophysiology of IDH is complex, a central driver of circulatory instability during HD is a rate of fluid removal (ultrafiltration rate [UFR]) that exceeds the rate of refill of the vascular space (plasma refill rate [PRR]) with fluid from extracellular compartments.[7, 14–16] PRR can be inferred from changes in relative blood volume (RBV), derived from continuous hematocrit monitoring devices integrated into the dialysis circuitry. Studies evaluating the clinical benefit of RBV monitoring have had mixed results,[17–24] potentially because RBV alone does not account for differences in UFR. In addition, contemporary devices display the RBV over time, but clinicians must make visual inferences about plasma refill, either (*1*) by examining the rate of change in RBV while accounting for the current UFR or (*2*) by pausing ultrafiltration to visually assess the rise in RBV, both of which can be burdensome and extend treatment time.[25–27] Few studies have directly examined PRR continuously across a large dialysis cohort.

We leveraged continuous hematocrit monitoring technology and ultrafiltration data to directly calculate PRR throughout HD sessions and determined whether (*1*) PRR is associated with traditional risk factors for hemodynamic instability, (*2*) PRR at the start of each session is associated with IDH, and (*3*) PRR throughout the session is associated with subsequent IDH. Because PRR fluctuates with hydrostatic pressure, oncotic pressure, and vascular tone,[9,28,29] we used causal inference methodology to adjust for time-varying confounding and better assess the relationship between PRR and IDH. Understanding the patterns of PRR throughout HD should generate insight into how current monitoring technology could be modified to guide ultrafiltration.

Methods

Study Population

We obtained deidentified data from 17 HD units in the United States operated by the Renal Research Institute from January 1, 2017, to October 31, 2019. Continuous hematocrit monitoring was implemented on a rolling basis and became the standard of care by 2012 at all units. Study entry was defined by the date of the first monitored HD session. Patients aged 18 years or older with >3 months of dialysis dependence were included. We excluded sessions with concurrent blood transfusions or incomplete data (total 2% of all sessions). Patients were censored for death, recovery of kidney function, transfer to a facility not operated by the Renal Research Institute, or end of follow-up time. This study was deemed exempt by the University of Pennsylvania Institutional Review Board (Protocol #832006).

Clinical Data

Comorbid conditions were derived from International Classification of Diseases, Ninth Revision codes, in the electronic health records at study entry. Medications and monthly laboratory data were derived from dialysis unit records. Predialysis and postdialysis weights, blood pressures, and heart rates were available from each HD session. Within individual sessions, blood pressures were measured using an automated oscillometric cuff at 30-minute intervals. Hematocrit was measured by using the CritLine-IV monitor (Fresenius Medical Care North America, Waltham, MA) 9000 times/min and averaged each minute. Nonphysiologic hematocrit values (<15% and >75%) were excluded, consistent with previous studies.[30] In addition, periods of rapid hematocrit drops of RBV>2% in 5 minutes were considered noise due to dilution from medication or fluids administered and excluded from the analysis.[30]

PRR

We leveraged hematocrit and ultrafiltration data to calculate PRR throughout each HD session. We built on the established relationship between RBV and the ratio of the starting hematocrit (hct_0) to the hematocrit at any time during each session (hct_1).[23,31,32] RBV was converted into an absolute volume through the Nadler method,[33,34] which uses height, weight, and sex to estimate the starting blood volume. Plasma refill volume was calculated as the sum of the changes in blood volume and ultrafiltration volume; plasma refill volume was then divided by time and by estimated postdialysis dry weight to calculate the PRR in units of ml/kg per hour. Owing to the presence of outliers from optical signal fluctuations, PRR was not calculated during periods of fluid administration and was winsorized at the 1st and 99th percentiles.

Starting PRR was defined as the average PRR during the first 10 minutes of each session; in sensitivity analyses, we varied the intervals for the first 15, 30, and 60 minutes. PRR was also calculated throughout the full session across each 15-minute interval. To account for differences in prescribed UFR, we used the ratio of the PRR:UFR across each time interval (PRR index [PRRi]) in all analysis between PRR and IDH. Because PRR was not normally distributed, PRRi was categorized as low (<0.3), moderate (0.3–0.9), and high (>0.9), representing the bottom 25%, middle 50%, and top 75%, respectively. The starting value of PRR was defined using hematocrit values after the tenth minute during each session to eliminate the optical noise attributed to the dilutional effect of the saline priming of the dialysis circuit[31,35] and mitigate the effects of varying timing of the automated baseline RBV reported from the CritLine-IV monitor.

IDH

We defined IDH as a systolic blood pressure (SBP) <90 mm Hg, which has been associated with increased mortality.[36] Given the lack of a consensus definition for IDH,[36] in sensitivity analyses, we used alternative definitions that incorporate symptoms, diastolic blood pressure, and chronic hypotension (summarized in Supplemental Table 1). Symptoms and interventions were identified through an algorithm that analyzed over 650,000 provider notes, presented in Supplemental Figure 1.

Statistical Analyses

Statistical analyses were performed using STATA (version 15.1).[37] Baseline demographics were summarized as

means and standard deviations for continuous variables and as proportions for categorical variables. Continuous variables that violated the linearity assumption in univariate analyses were converted into categories on the basis of clinically relevant cutoffs. Variables with <1% missingness were analyzed using complete case analysis. Variables with 1%–20% missingness were analyzed using a subcategory for "unknown." Variables with >20% missingness were excluded from analysis. Covariates were chosen from a pool of 72 potential demographic, laboratory, vital sign, and medication variables (Supplemental Table 2). For variables within the same category (*e.g.*, systolic and diastolic blood pressure), the variable with the best Akaike Information Criterion was selected. Variables associated with IDH and PRR in univariate regression with $\alpha<0.1$ were tested in the multivariable model.

The statistical models used for each analysis are summarized in Supplemental Table 3. Mixed effects regression was used to model the population average trajectories of PRRi. Logistic regression was used to evaluate clinical characteristics associated with low starting PRRi. We used three different models to evaluate the association between PRRi and IDH. To examine the relationship between starting PRRi and IDH, we used Cox proportional hazard regression with baseline covariates (model 1). To examine the relationship between PRRi during HD and IDH, we added PRRi as a time-dependent exposure (model 2); however, this model was created for comparison and adjusts for baseline confounders but not time-varying confounding. To adjust for time-varying confounding, we used marginal structural analysis (model 3),[38,39] presented in Supplemental Figure 2. In brief, each session was divided into 15-minute intervals. For each interval, PRRi was defined as the moving average at the end of the exposure interval and IDH was assessed across the next interval. A censorship model was created to estimate the probability of early session termination for reasons other than IDH. Stabilized inverse probability weighting was applied to each interval to account for (*1*) the history of PRRi in prior intervals, (*2*) the time-varying confounding by changes in UFR and SBP at each interval, and (*3*) the probability of censorship. The reweighted intervals were included with pooled logistic regression, forming a discrete time model whose odds ratios (ORs) approximate hazard ratios.

Table 1. Baseline demographic characteristics of the study population (2554 patients)

Characteristic	Mean±SD or Proportion
Age, yr	62.33±15.87
Sex, *n* (%)	
Male	1487 (58.20)
Female	1068 (41.80)
Race, *n* (%)	
White	1183 (46.30)
Black	764 (29.90)
Other	106 (4.15)
Unknown	502 (19.65)
Ethnicity, *n* (%)	
Hispanic	353 (13.82)
Not Hispanic	1622 (63.48)
Unknown	580 (22.70)
Diabetes	1439 (56.32)
Hypertension	2005 (78.47)
Vascular access type, *n* (%)	
Fistula	1319 (51.62)
Graft	342 (13.39)
Catheter	894 (34.99)
HD vintage, yr	3.19±4.32
BMI, kg/m^2	28.59±7.46
Serum creatinine, mg/dl	7.98±3.10
Serum albumin, g/dL	3.70±0.47
Serum sodium, mEq/L	137.69±3.34
SBP, mm Hg	
Pre-HD	147.18±26.99
Post-HD	138.70±25.25
Change pre–post-HD	8.49±25.78
IDWG, kg	1.81±1.53
Estimated dry weight, kg	80.87±23.02
Single-pool Kt/V	15.50±3.91
UFR, ml/kg per hour	8.33±4.52
HD treatment time, min	218.04±35.17

Dialysis treatment characteristics were defined as the average value within the first 3 months of study entry. HD, hemodialysis; BMI, body mass index; SBP, systolic blood pressure; IDWG, interdialytic weight gain; UFR, ultrafiltration rate.

Results

Baseline Characteristics

We analyzed 180,319 HD sessions across 2554 patients over the study period (total follow-up 2952.2 person-years). The demographic characteristics, summarized in Table 1, are similar to those of the overall US HD population.[40] The mean age was 62.3 years, 58% were male, 46% were White, and 30% were Black. Across all sessions, the mean interdialytic weight gain was 1.8±1.5 kg, single-pool Kt/V was 1.6±0.4, and UFR was 8.3±4.5 ml/kg per hour. The median treatment time was 223.0 (interquartile range, 199.0–242.0) minutes. IDH occurred in 12% of all sessions (range 7%–39% depending on the IDH definition used in Supplemental Table 1).

Patterns of Intradialytic Measures

Examining RBV alone, we did not find a consistent RBV threshold below which IDH occurred (an illustrative example of RBV trajectories between sessions of the same patient is shown in Supplemental Figure 3). The trajectories of four intradialytic measures (RBV, PRRi, SBP, and UFR) are presented Figure 1, with both an illustrative single HD session (Figure 1, A–D) and average across the study population (Figure 1, E–H). As RBV decreases, PRRi fluctuates throughout the session even during constant UFR. During the first hour of each session, the average PRRi was 0.44 after the priming period and stabilized at 0.80 by 60 minutes, corresponding to PRR of 4.15 and 7.21 ml/h per kilogram body weight, respectively. The intradialytic trajectories were also examined within subgroups of low, moderate, and high starting PRRi (see Supplemental Figure 4). On average, the low PRRi group had lower RBV values over time while the high PRRi group had higher RBV values and smaller changes in SBP, although there was substantial overlap in the standard deviations.

Clinical Factors and PRR

The associations between clinical factors and starting PRR are summarized in Table 2. Patients with low starting PRR were more likely to be 80 years or older (OR, 1.60, 95%

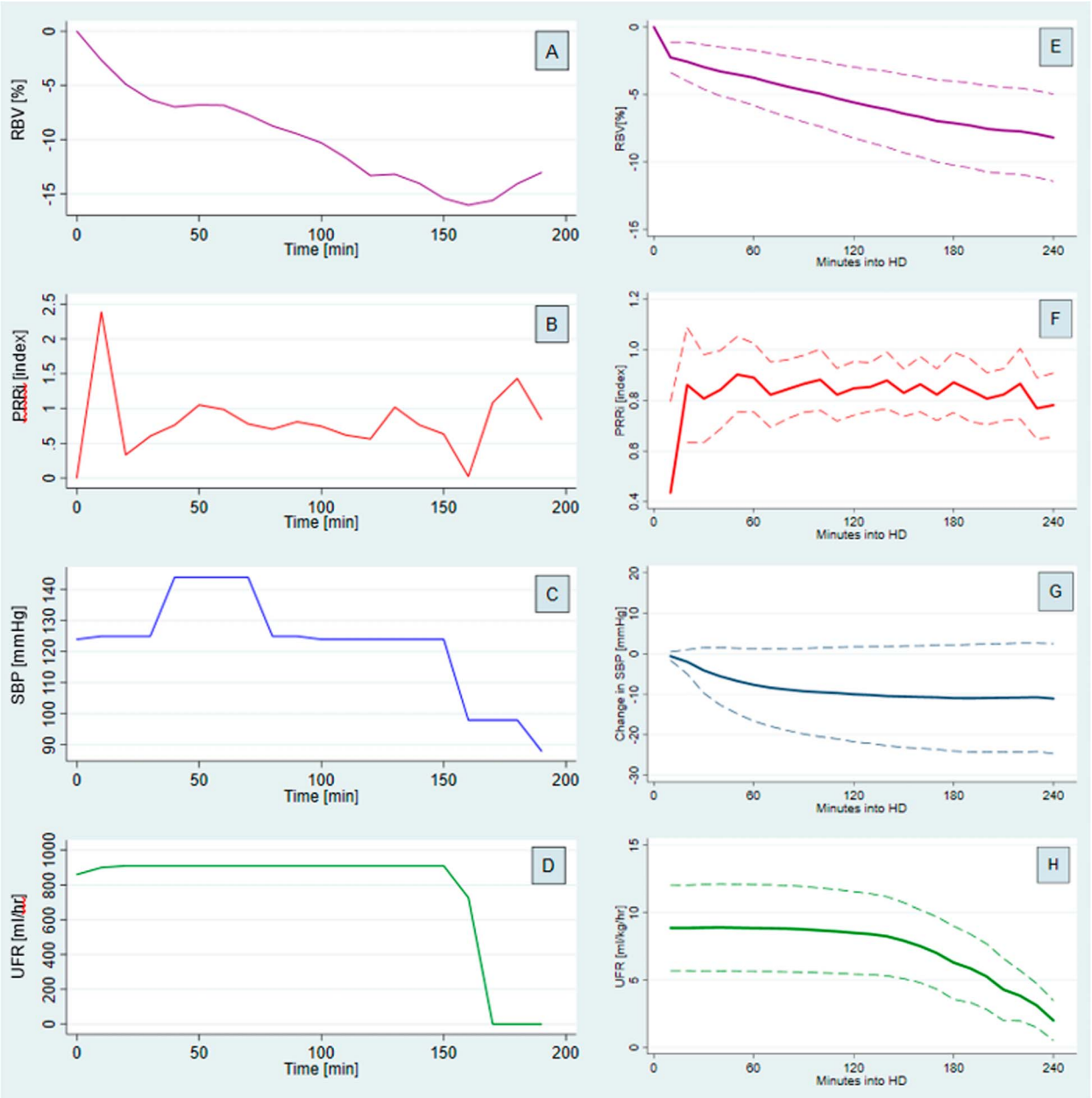

Figure 1. Summary of intradialytic metrics during HD across the study population. The left panels provide an illustrative example from a single HD session of four different intradialytic measures: (A) RBV, (B) PRRi, (C) change in SBP, and (D) UFR. The right panels summarize the population average (solid lines) and intrasubject random effects standard deviation (dashed lines) panels for (E) RBV, (F) PRR, (G) SBP, and (H) UFR throughout the entirety of treatment.

confidence interval [CI], 0.99 to 2.60), female (OR, 1.83, 95% CI, 1.38 to 2.41), and Black (OR, 1.55, 95% CI, 1.19 to 2.03). Owing to substantial missing data for cardiovascular conditions, we could not assess whether PRR was associated with preexisting heart failure, ischemic heart disease, or cerebrovascular disease. Many of the associations between clinical factors and PRR were enhanced within patients with diabetes. In sensitivity analysis, these associations were consistent for PRR defined at various time intervals during the first hour of HD (15, 30, and 60 minutes).

At the session level, low starting PRR was associated with low predialysis SBP and low serum albumin level, independent of UFR and interdialytic weight gain. While higher dialysate sodium and calcium were protective, due to the limited variability in dialysis prescriptions, the associations with dialysate composition were considered exploratory. PRR did not differ after 2-day versus 3-day interdialytic intervals ($P = 0.12$) or after hospitalizations ($P = 0.49$). PRR was correlated with UFR ($\rho = 0.72$), with an average increase of 0.58 ml/kg per hour in PRR per 1 ml/kg per hour increase in UFR with a slightly curvilinear relationship, while the ratio of PRR:UFR (PRRi) was relatively stable across different levels of UFR; thus, PRRi was used in subsequent analyses.

Table 2. Demographic factors associated with low plasma rfill rate at the start of hemodialysis sessions

Demographic Characteristic	Univariate			Multivariable								
	All			All			Diabetic Subgroup			Nondiabetic Subgroup		
	OR	95% CI	Joint *P*	OR	95% CI	Joint *P*	OR	95% CI	Joint *P*	OR	95% CI	Joint *P*
Age, yr												
<50	Ref		$P < 0.01$	Ref		$P = 0.34$	Ref		$P = 0.01$	Ref		$P = 0.90$
50–69	1.18	0.89 to 1.56		1.18	0.82 to 1.70		1.36	0.80 to 2.32		1.03	0.61 to 1.75	
60–69	1.39	1.07 to 1.56		1.11	0.77 to 1.61		1.47	0.87 to 2.49		0.84	0.49 to 1.46	
70–79	1.84	1.42 to 2.38		1.29	0.85 to 1.94		1.87	1.06 to 3.31		0.89	0.47 to 1.67	
≥80	2.20	1.65 to 2.94		1.60	0.99 to 2.60		3.12	1.59 to 6.12		0.75	0.36 to 1.56	
Sex												
Male	Ref		$P < 0.01$	Ref		$P < 0.01$	Ref		$P < 0.01$	Ref		$P = 0.06$
Female	1.75	1.48 to 2.07		1.83	1.38 to 2.41		1.61	1.12 to 2.32		2.26	1.45 to 3.51	
Race												
White	Ref		$P = 0.28$	Ref		$P < 0.01$	Ref		$P = 0.03$	Ref		$P = 0.06$
Black	1.04	0.86 to 1.27		1.55	1.19 to 2.03		1.58	1.12 to 2.23		1.55	1.00 to 2.40	
Other/unknown	1.18	0.96 to 1.46		1.09	0.83 to 1.42		1.25	0.88 to 1.76		0.88	0.57 to 1.36	
Diabetes	0.85	0.72 to 1.01	$P = 0.06$	1.00	0.80 to 1.26	$P = 0.98$	—	—	—	—	—	—
BMI, per kg/m^2	0.93	0.92 to 0.94	$P < 0.01$	1.02	1.01 to 1.04]	$P < 0.01$	1.04	1.01 to 1.06	$P < 0.01$	1.01	0.98 to 1.04	$P = 0.59$
HD vintage, yr	0.98	0.96 to 1.00	$P = 0.03$	0.99	0.96 to 1.02	$P = 0.34$	0.99	0.95 to 1.04	$P = 0.72$	0.98	0.94 to 1.02	$P = 0.33$
Serum creatinine index, per mg/kg per day	0.89	0.87 to 0.92	$P < 0.01$	1.08	1.01 to 1.15	$P = 0.02$	1.13	1.03 to 1.24	$P = 0.01$	1.04	0.95 to 1.14	$P = 0.44$
Serum albumin, per 0.1 g/dl	0.96	0.94 to 0.98	$P < 0.01$	0.96	0.94 to 0.99	$P < 0.01$	0.94	0.91 to 0.98	$P < 0.01$	0.97	0.93 to 1.02	$P = 0.25$
Single-pool Kt/V	1.03	1.00 to 1.06	$P = 0.08$	0.99	0.94 to 1.04	$P = 0.61$	0.94	0.88 to 1.01	$P = 0.10$	1.03	0.95 to 1.11	$P = 0.48$
SBP, per 10 mm Hg	0.88	0.84 to 0.91	$P < 0.01$	0.87	0.82 to 0.92	$P < 0.01$	0.86	0.80 to 0.93	$P < 0.01$	0.90	0.82 to 0.99	$P < 0.01$
UFR, ml/kg per hour	0.82	0.80 to 0.85	$P < 0.01$	0.60	0.58 to 0.63	$P < 0.01$	0.63	0.59 to 0.67	$P < 0.01$	0.56	0.51 to 0.61	$P < 0.01$

Summary of patient demographic and dialysis treatment factors associated with low plasma refill rate, defined as the lowest 25th percentile of plasma refill rate across all treatments within the first 10 minutes of hemodialysis. Characteristics represent patient-averaged serum values within the first 3 months of study entry. Continuous variables with nonlinear log-odds relationships were converted to categorical variables with cutoffs chosen for clinical relevance with at least 20% of the population, and *P* values represent the joint test across all categories of each variable. Factors with $P > 0.2$ in univariate analysis were excluded from multivariable analysis. Factors with substantial collinearity were analyzed separately, and the factor with the strongest associated and best fit based on the Akaike Information Criterion was used in multivariable analysis. OR, odds ratio; CI, confidence interval; BMI, body mass index; HD, hemodialysis; SBP, systolic blood pressure; UFR, ultrafiltration rate.

Table 3. Comparison of baseline and time-varying models for plasma refill rate index and risk of intradialytic hypotension

Model	Unadjusted			Adjusted								
	All			All			Diabetes Subgroup			Nondiabetic Subgroup		
	HR[a]	95% CI	*P* Value	HR[a]	95% CI	*P* Value	HR[a]	95% CI	*P* Value	HR[a]	95% CI	*P* Value
Model 1: baseline model												
Low starting PRRi	1.41	1.30 to 1.53	$P < 0.001$	1.26	1.18 to 1.35	$P < 0.001$	1.36	1.25 to 1.47	$P < 0.001$	1.14	1.02 to 1.27	$P < 0.001$
High starting PRRi	0.74	0.68 to 0.80	$P < 0.001$	0.79	0.73 to 0.85	$P < 0.001$	0.74	0.67 to 0.82	$P < 0.001$	0.86	0.77 to 0.97	$P = 0.011$
Model 2: time-varying model												
Low time-updated PRRi	1.02	1.01 to 1.04	$P < 0.001$	1.04	1.02 to 1.05	$P < 0.001$	1.04	1.03 to 1.06	$P < 0.001$	1.02	1.01 to 1.04	$P = 0.003$
High time-updated PRRi	1.07	1.05 to 1.08	$P < 0.001$	1.07	1.06 to 1.08	$P < 0.001$	1.07	1.05 to 1.08	$P < 0.001$	1.07	1.05 to 1.09	$P < 0.001$
Model 3: marginal structural model												
Low time-updated PRRi	1.16	1.08 to 1.23	$P < 0.001$	1.09	1.02 to 1.16	$P = 0.008$	1.15	1.06 to 1.24	$P = 0.001$	1.01	0.92 to 1.12	$P = 0.791$
High time-updated PRRi	1.37	1.29 to 1.45	$P < 0.001$	1.38	1.30 to 1.45	$P < 0.001$	1.37	1.28 to 1.47	$P < 0.001$	1.38	1.27 to 1.51	$P < 0.001$

Summary of results from the models examining the relationship between plasma refill rate index and intradialytic hypotension. The baseline model (model 1) is a Cox proportional hazard regression using the starting plasma refill rate index and covariates defined at study entry and at the start of each hemodialysis session. The starting plasma refill rate index was defined as the ratio of plasma refill rate to ultrafiltration rate within the first 10-minute interval of each hemodialysis session, with low plasma refill rate index$<$0.3 (bottom 25th percentile) and high plasma refill rate index$>$0.9 (top 25th percentile) in reference to moderate plasma refill rate index (0.3$\leq$PRRi$\leq$0.9). The time-varying model (model 2) includes time-updated plasma refill rate index but only accounts for baseline confounding effects. Model 3 uses inverse probability weighting to account for the time-varying confounder-mediator effects from the time-updated changes in ultrafiltration rate and systolic blood pressure through marginal structural modeling. All effects are reported as hazard ratios with 95% confidence intervals and *P* values. HR, hazard ratio; CI, confidence interval; PRRi, plasma refill rate index.

[a]Of note, model 3 (marginal structural model) forms a discrete time function which produces an odds ratio whose estimates approximate an hazard ratio. All models were adjusted for the following baseline confounders: age at dialysis initiation, sex, race, body mass index at dialysis initiation, dialysis vintage, diabetes status, serum albumin, serum creatinine index, predialysis systolic blood pressure, interdialytic interval, dialysate temperature, and average single-pool Kt/V.

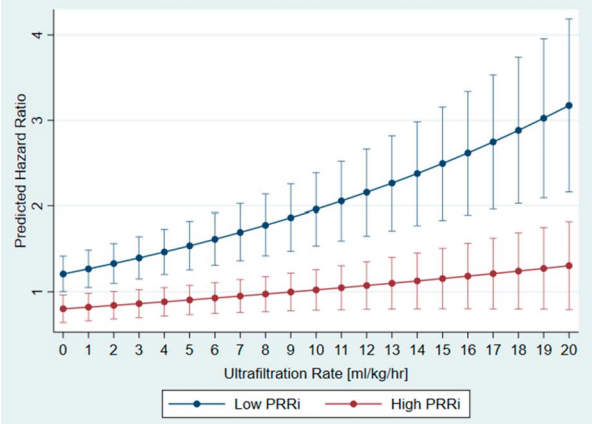

Figure 2. Interaction of PRRi and ultrafiltration on risk of IDH. The predicted HR for IDH across different levels of UFR is shown, stratified by low versus high PRRi within the first 10 minutes into the HD session. Models were based on Cox proportional hazard regression accounting for repeated HD sessions within the same patient, with an interaction between PRRi and UFR.

PRR and IDH

The relationships between starting PRRi and IDH and time-varying PRRi and risk of IDH are summarized in Table 3. Compared with treatments with a moderate starting PRRi (0.3–0.9), treatments with low starting PRRi (<0.3) had an increased hazard of IDH while treatments with high starting PRRi (>0.9) were protective. The effect of starting PRRi on risk of IDH was enhanced in patients with diabetes (P interaction = 0.007) and at higher UFR (P interaction = 0.04, illustrated in Figure 2).

In sessions with IDH, the average PRRi was progressively increasing during the 15 minutes before a drop in SBP (Figure 3). In sensitivity analysis, this pattern of rising PRRi was consistent preceding IDH across different definitions of IDH and preceding the nadir SBP during sessions without IDH. In the subset of sessions during which UFR was constant and no fluids were administered, RBV was observed to have a similar rising pattern before nadir SBP (not shown). Examining PRRi as a time-varying exposure, low PRRi at any time during the session was still associated with increased risk of IDH, but a high PRRi was also associated with risk of IDH. Adjusting for time-varying confounding using marginal structural analysis, the association between high PRRi throughout the session and risk of IDH is enhanced. These results were similar across different definitions of IDH and examining the change in PRRi between each interval (Supplemental Table 4).

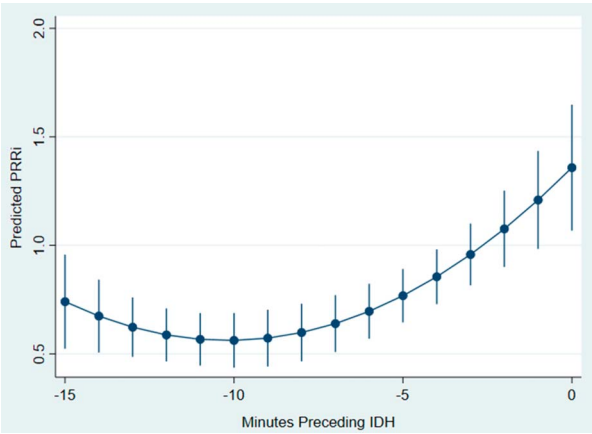

Figure 3. Population average PRRi before IDH. The average behavior or PRRi during the 15 minutes preceding an episode of IDH (defined as SBP <90 mm Hg) was modeled using mixed-effects linear regression with time as a quadratic term. Data from sessions with documented or suspected fluid administration before IDH were not included.

Discussion

Hemodynamic monitoring during HD typically relies on blood pressure and heart rate measurements, which are often inadequate to detect impending hypotension. Continuous hematocrit monitoring provides alternative indicators of hemodynamic status; however, its clinical adoption is not widespread, and previous trials evaluating this technology did not show benefit for hospitalization or mortality.[22] In its current application, continuous hematocrit monitoring does not directly quantify PRR; however, future devices could be modified to do so. Our study, intended as a first step in exploring the dynamics of PRR as an intradialytic metric, had three major findings: (*1*) we identified several clinical factors associated with low PRR near the start of each HD session; (*2*) low starting PRRi was associated with a greater hazard of IDH, independent of traditional risk factors for intradialytic events; and (*3*) both low and high PRRi throughout HD were associated with subsequent IDH.

The association of low PRRi with the risk of IDH was expected, as was the finding that the association is enhanced at higher UFR. One explanation for the interaction between PRRi and UFR is that PRR can rise to meet the demands of increased UFR up to a threshold UFR, after which the inability of PRR to match UFR may lead to hemodynamic instability. Interestingly, we found that while high starting PRRi was protective against IDH, high PRRi throughout dialysis was associated with increased risk of IDH. The association between high PRRi and IDH was unexpected given the leading theory that falling plasma refill causes hemodynamic instability.[26,41] However, when we examined the patterns of PRRi preceding IDH, we found that PRRi was increasing acutely before a detectable drop in SBP, a pattern which persisted after accounting for fluid administration and across different definitions of IDH. In addition, the rise in PRRi was largely attributed to changes in RBV and not UFR. This finding is likely capturing consequences of circulatory changes just before decompensation. As cardiac output decreases, intracapillary hydrostatic pressures in the peripheral tissue will drop, leading to transient net fluid uptake into the vascular space.[42] The observed acute rise in PRR before IDH may reflect transient fluid uptake during a period when cardiac output has dropped but blood pressure is still maintained through vasoconstriction. To further maintain cardiac output during HD, there is redistribution of blood from venous reserves (*e.g.*, peripheral, splenic, and splanchnic vasculature).[43] Fluid redistribution from other fluid compartments would be measured as increased plasma refill because of the lower hematocrit concentration in the periphery.[17] In addition, decreasing cardiac

output triggers vasoconstriction in the mesenteric vascular bed and emptying of the splanchnic reservoir, delivering an additional approximately 500 ml of blood to the central circulation,[44–46] which might be detected as increases in PRRi.[17] Impaired recruitment from these vascular reservoirs that occurs with autonomic dysfunction could lead to the development of IDH.[44–46] It is possible that there is a differential pattern between patients with intact splanchnic redistribution and those without. These hypotheses and the observed pattern of rising PRRi before IDH warrant further exploration.

Our study has several strengths. First, we examined PRR and IDH across a large multicenter dialysis cohort. The analyses are based on what we believe to be the largest dataset containing continuous hematocrit and RBV data, allowing for both within-patient and between-patient analyses. Second, unlike previous studies which examined plasma refill cross-sectionally, we used causal inference methodology to examine the effect of PRR updated throughout HD and account for time-varying effects from UFR and SBP, which is an important step as conventional statistical methods often yield biased results in the setting of time-varying confounding.[38] Third, by incorporating an algorithm to adjudicate symptoms and interventions, we were able to demonstrate that our results were robust across four different definitions of IDH. In addition, we used an anthropometric method to calculate intradialytic PRR expressed in the same units as UFR. This approach provides direct quantification of a physiologic process. Although not directly measured, our calculated PRR values fall within the range of PRR reported from previous studies in which PRR was measured or modeled under constant and controlled UFRs.[47–50] Importantly, this method for calculating PRR is straightforward, uses routinely available clinical data, and could be readily integrated to quantify PRR in real time using current continuous hematocrit monitoring technology. Our method can also be adapted to allow use of other methods, such as hemodilution, to estimate the absolute blood volume.[51]

Our study also has limitations. Given the retrospective nature of the data, misclassification bias and unmeasured confounding are possible. However, dialysis data were collected systematically and were >95% complete, so missingness of data at the session level is likely random and would bias our results toward the null. Owing to substantial missingness, we were not able to evaluate the effects of cardiovascular disease on starting PRRi and the relationship between PRRi and UFR. Although our data came exclusively from dialysis units associated with a single dialysis provider, dialysis prescriptions and patient demographics were similar to those of the general population of patients receiving HD in the United States. Although the use of marginal structural modeling allowed us to compare consistently low or high values of PRRi throughout HD, we could not examine whether shifts across PRRi categories or whether the timing of changes in PRRi are associated with differential risk on subsequent IDH. Further studies into varying patterns of PRRi would help to elucidate how PRRi might be incorporated into automated monitoring systems for volume management during HD.

Although the concept of plasma refill is not new, our study indicates that PRRi varies substantially during HD and offers complementary information about circulatory stability. Since the initial development of continuous hematocrit monitoring, contemporary studies have shifted away from RBV alone, and many studies have suggested that the critical level of RBV may depend primarily on cardiovascular defense mechanisms and require consideration of the current UFR.[11,16,31] Some studies have proposed the use of RBV slope together with UFR as a clinical tool to probe the dry weight, but application of this across a dialysis shift can be burdensome. From Figure 1, one can appreciate how direct visualization of PRRi makes evident the dynamic changes that occur even during constant UFR and a seemingly steady decline in RBV. While further investigation is needed to better characterize the predictive applications of PRR and its implications for clinical management, PRR or PRRi could potentially provide an important additional "vital sign" to guide volume removal during dialysis therapy.

In summary, we found that PRR is a truly dynamic entity. Both low PRR early in treatment and a sudden increase in PRR later in therapy serve as markers of risk for circulatory collapse. This is a departure from the traditional approach that focuses on decreasing RBV alone to guide management. Initial trials of continuous hematocrit monitoring may have been hampered by incomplete tools to interpret this clinical parameter. Our results highlight opportunities for further investigation that could increase the utility of intradialytic technologies, such as continuous hematocrit monitoring in the management of volume status during HD therapy.

Disclosures

S. Casper reports the following: Employer: Fresenius Medical Care Deutschland GmbH and Patents or Royalties: Fresenius Medical Care. L.M. Dember reports the following: Consultancy: L. Dember: AstraZeneca, Cara Therapeutics, CSL Behring, GlaxoSmithKline, Merck, and Vertex; Spouse: Actelion, Alexion, Bristol Myers Squibb, ChemCentryx, Genentech/Roche, Genzyme/Sanofi, and GlaxoSmithKline; Ownership Interest: Spouse: stock options in Kyverna; Research Funding: Spouse: Actelion, Bristol Myers Squibb, Celgene, ChemoCentryx, Genentech/Roche, and GlaxoSmithKline; Honoraria: AstraZeneca, Cara Therapeutics, Merck, and Vertex; Advisory or Leadership Role: *American Journal of Kidney Diseases*, Deputy Editor, and Other Interests or Relationships: Spouse: compensation as author and section editor for UpToDate. J. Hsu reports the following: Advisory or Leadership Role: *American Journal of Kidney Diseases*, Statistics/Epidemiology Editor; American Medical Association, Statistical Reviewer; *PLOS One*, Statistical Advisory Board. P. Kotanko reports the following: Employer: Renal Research Institute; Ownership Interest: Fresenius Medical Care; Research Funding: Fresenius Medical Care, KidneyX, and NIH; Honoraria: HSTalks; Patents or Royalties: Multiple patents in the kidney space; and Advisory or Leadership Role: Editorial Board of *Blood Purification*, *Frontiers in Nephrology*, and *Kidney and Blood Pressure Research*. J. Raimann reports the following: Employer: Renal Research Institute, a wholly owned subsidiary of Fresenius Medical Care, and Other Interests or Relationships: Member of the Board of Directors "Easy Water for Everyone" (501c3). H. Zhang reports the following: Employer: Renal Research Institute and Patents or Royalties: Renal Research Institute. The remaining authors have nothing to disclose.

Funding

Research reported in this publication was supported by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) under award T32DK007006 and F32DK123948 (C.H.W.).

Acknowledgments

The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIDDK.

Author Contributions

Conceptualization: Dan Negoianu, Christina H. Wang.
Data curation: Christina H. Wang.
Formal analysis: Jesse Y. Hsu, Christina H. Wang.
Funding acquisition: Christina H. Wang.
Investigation: Christina H. Wang.
Methodology: Christina H. Wang.
Resources: Sabrina Casper, Laura M. Dember, Jochen Raimann.
Supervision: Laura M. Dember.
Visualization: Christina H. Wang.
Writing – original draft: Christina H. Wang.
Writing – review & editing: Sabrina Casper, Laura M. Dember, Jesse Y. Hsu, Peter Kotanko, Dan Negoianu, Jochen Raimann, Christina H. Wang, Hanjie Zhang.

Data Sharing Statement

Partial restrictions to the data and/or materials apply (please include a detailed explanation). Data owned by the Renal Research Institute used for this study under an agreed on Data Use Agreement Collaboration between the University of Pennsylvania and the Renal Research Institute.

Supplemental Material

This article contains the following supplemental material online at http://links.lww.com/KN9/A320.

Supplemental Table 1. Alternative Definitions of Intradialytic Hypotension.

Supplemental Table 2. Summary of Baseline Covariates.

Supplemental Table 3. Summary of Statistical Models Used in Each Analysis.

Supplemental Table 4. Summary of Associations of Plasma Refill Rate Index and Intradialytic Hypotension.

Supplemental Figure 1. Details of Algorithm Used for Symptom Adjudication and Interventions.

Supplemental Figure 2. Conceptual Diagrams of the Marginal Structural Model.

Supplemental Figure 3. Illustrative Example of Relative Blood Volume Trajectories Between Different Hemodialysis Sessions Within the Same Patient.

Supplemental Figure 4. Summary of Intradialytic Metrics During Hemodialysis Across the Study Population, Stratified by Starting Plasma Refill Rate Index Category.

References

1. Chou JA, Kalantar-Zadeh K, Mathew AT. A brief review of intradialytic hypotension with a focus on survival. *Semin Dial.* 2017;30(6):473–480. doi:10.1111/sdi.12627
2. Shoji T, Tsubakihara Y, Fujii M, Imai E. Hemodialysis-associated hypotension as an independent risk factor for two-year mortality in hemodialysis patients. *Kidney Int.* 2004;66(3):1212–1220. doi:10.1111/j.1523-1755.2004.00812.x
3. Flythe JE, Kimmel SE, Brunelli SM. Rapid fluid removal during dialysis is associated with cardiovascular morbidity and mortality. *Kidney Int.* 2011;79(2):250–257. doi:10.1038/ki.2010.383
4. Kuipers J, Oosterhuis JK, Krijnen WP, et al. Prevalence of intradialytic hypotension, clinical symptoms and nursing interventions - a three-months, prospective study of 3818 haemodialysis sessions. *BMC Nephrol.* 2016;17(1):21–11. doi:10.1186/s12882-016-0231-9
5. Zoccali C, Moissl U, Chazot C, et al. Chronic fluid overload and mortality in ESRD. *J Am Soc Nephrol.* 2017;28(8):2491–2497. doi:10.1681/ASN.2016121341
6. Flythe JE, Assimon MM, Overman RA. Target weight achievement and ultrafiltration rate thresholds: potential patient implications. *BMC Nephrol.* 2017;18(1):185–213. doi:10.1186/s12882-017-0595-5
7. Agarwal R. How can we prevent intradialytic hypotension? *Curr Opin Nephrol Hypertens.* 2012;21(6):593–599. doi:10.1097/MNH.0b013e3283588f3c
8. Flythe JE, Chang TI, Gallagher MP, et al. Blood pressure and volume management in dialysis: conclusions from a kidney disease: improving global outcomes (KDIGO) controversies conference. *Kidney Int.* 2020;97(5):861–876. doi:10.1016/j.kint.2020.01.046
9. Brummelhuis WJ, Van Geest RJ, Van Schelven LJ, Boer WH. Sodium profiling, but not cool dialysate, increases the absolute plasma refill rate during hemodialysis. *ASAIO J.* 2009;55(6):575–580. doi:10.1097/MAT.0b013e3181bea710
10. van der Sande FM, Wystrychowski G, Kooman JP, et al. Control of core temperature and blood pressure stability during hemodialysis. *Clin J Am Soc Nephrol.* 2009;4(1):93–98. doi:10.2215/CJN.01800408
11. Krepel HP, Nette RW, Akçahüseyin E, Weimar W, Zietse R. Variability of relative blood volume during haemodialysis. *Nephrol Dial Transplant.* 2000;15(5):673–679. doi:10.1093/ndt/15.5.673
12. Abohtyra R, Chait Y, Germain MJ, Hollot CV, Horowitz J. Individualization of ultrafiltration in hemodialysis. *IEEE Trans Biomed Eng.* 2019;66(8):2174–2181. doi:10.1109/tbme.2018.2884931
13. Douvris A, Malhi G, Hiremath S, et al. Interventions to prevent hemodynamic instability during renal replacement therapy in critically ill patients: a systematic review. *Crit Care.* 2018;22(1):41. doi:10.1186/s13054-018-1965-5
14. Barth C, Boer W, Garzoni D, et al. Characteristics of hypertension-prone haemodialysis patients: is there a critical relative blood volume? *Nephrol Dial Transplant.* 2003;18(7):1353–1360. doi:10.1093/ndt/gfg171
15. Reeves PB, McCausland FR. Mechanisms, clinical implications, and treatment of intradialytic hypotension. *Clin J Am Soc Nephrol.* 2018;13(8):1297–1303. doi:10.2215/CJN.12141017
16. Anand S, Sinha AD, Agarwal R. Determinants and short-term reproducibility of relative plasma volume slopes during hemodialysis. *Clin J Am Soc Nephrol.* 2012;7(12):1996–2001. doi:10.2215/CJN.04190412
17. Dasselaar JJ, Van Der Sande FM, Franssen CFM. Critical evaluation of blood volume measurements during hemodialysis. *Blood Purif.* 2012;33(1-3):177–182. doi:10.1159/000334142
18. Davenport A. Using dialysis machine technology to reduce intradialytic hypotension. *Hemodial Int.* 2011;15(suppl 1):37–42. doi:10.1111/j.1542-4758.2011.00600.x
19. Gil HW, Bang K, Lee SY, et al. Efficacy of hemocontrol biofeedback system in intradialytic hypotension-prone hemodialysis patients. *J Korean Med Sci.* 2014;29(6):805–810. doi:10.3346/jkms.2014.29.6.805
20. Santoro A, Mancini E, Basile C, et al. Blood volume controlled hemodialysis in hypotension-prone patients: a randomized, multicenter controlled trial. *Kidney Int.* 2002;62(3):1034–1045. doi:10.1046/j.1523-1755.2002.00511.x
21. Basile C, Giordano R, Vernaglione L, et al. Efficacy and safety of haemodialysis treatment with the Hemocontrol™ biofeedback system: a prospective medium-term study. *Nephrol Dial Transplant.* 2001;16(2):328–334. doi:10.1093/ndt/16.2.328
22. Reddan DN, Szczech LA, Hasselblad V, et al. Intradialytic blood volume monitoring in ambulatory hemodialysis patients: a randomized trial. *J Am Soc Nephrol.* 2005;16(7):2162–2169. doi:10.1681/ASN.2004121053
23. Thijssen S, Kappel F, Kotanko P. Absolute blood volume in hemodialysis patients: why is it relevant, and how to measure it? *Blood Purif.* 2013;35(1-3):63–71. doi:10.1159/000345484
24. Martin M, Bansal A, Perez L, Stenson EK, Kendrick J. Use of relative blood volume monitoring to reduce intradialytic hypotension in hospitalized patients receiving dialysis. *Kidney Int Rep.* 2022;7(9):2105–2107. doi:10.1016/j.ekir.2022.06.018

25. Atallah R, Bauer F, Strohhöfer C, Haueisen J. A feedback system that combines monitoring of systolic blood pressure and relative blood volume in order to prevent hypotensive episodes during dialysis. *Med Eng Phys.* 2019;71:10–16. doi:10.1016/j.medengphy.2019.07.006
26. Brummelhuis WJ, Van Schelven LJ, Boer WH. Continuous, online measurement of the absolute plasma refill rate during hemodialysis using feedback regulated ultrafiltration: preliminary results. *ASAIO J.* 2008;54(1):95–99. doi:10.1097/MAT.0b013e3181609d91
27. Pietribiasi M, Katzarski K, Galach M, et al. Kinetics of plasma refilling during hemodialysis sessions with different initial fluid status. *ASAIO J.* 2015;61(3):350–356. doi:10.1097/MAT.0000000000000206
28. Casagrande G, Teatini U, Romei Longhena G, Miglietta F, Fumero R, Costantino ML. A new method to evaluate patient characteristic response to ultrafiltration during hemodialysis. *Int J Artif Organs.* 2007;30(5):377–384. doi:10.1177/039139880703000504
29. Pietribiasi M, Wójcik-Zaluska A, Zaluska W, Waniewski J. Does the plasma refilling coefficient change during hemodialysis sessions? *Int J Artif Organs.* 2018;41(11):706–713. doi:10.1177/0391398818803439
30. Zhang H, Chan L, Meyring-Wösten A, et al. Association between intradialytic central venous oxygen saturation and ultrafiltration volume in chronic hemodialysis patients. *Nephrol Dial Transplant.* 2018;33(9):1636–1642. doi:10.1093/ndt/gfx271
31. Pstras L, Waniewski J, Wojcik-Zaluska A, Zaluska W. Relative blood volume changes during haemodialysis estimated from haemoconcentration markers. *Sci Rep.* 2020;10(1):14809. doi:10.1038/s41598-020-71830-0
32. Preciado P, Zhang H, Thijssen S, Kooman JP, Van Der Sande FM, Kotanko P. All-cause mortality in relation to changes in relative blood volume during hemodialysis. *Nephrol Dial Transplant.* 2019;34(8):1401–1408. doi:10.1093/ndt/gfy286
33. Nadler SB, Hidalgo JHBT, Bloch T. Prediction of blood volume in normal human adults. *Surgery.* 1962;51(2):224–232.
34. Fuertinger DH, Malha L, Kotanko P, Goldfarb DS, Thijssen S. Blood volume estimation in hemodialysis patients (abstract SA-PO910). *J Am Soc Nephrol.* 2015;26:842A.
35. Kron S, Wenkel R, Leimbach T, Aign S, Kron J. Effects of osmotic changes on measuring relative blood volume: comparison of three hemodialysis devices. *ASAIO J.* 2016;62(2):214–215. doi:10.1097/MAT.0000000000000306
36. Flythe JE, Xue H, Lynch KE, Curhan GC, Brunelli SM. Association of mortality risk with various definitions of intradialytic hypotension. *J Am Soc Nephrol.* 2015;26(3):724–734. doi:10.1681/ASN.2014020222
37. StataCorp. 2021. Stata Statistical Software: Release 17. College Station, TX: StataCorp LLC.
38. Robins JM, Hernan MA, Brumback B. Marginal structural models and causal inference in epidemiology. *Epidemiology.* 2000;11(5):550–560. doi:10.1097/00001648-200009000-00011
39. Williamson T, Ravani P. Marginal structural models in clinical research: when and how to use them? *Nephrol Dial Transplant.* 2017;32(suppl_2):ii84–ii90. doi:10.1093/ndt/gfw341
40. Saran R, Robinson B, Abbott KC, et al. US renal data system 2019 annual data report: epidemiology of kidney disease in the United States. *Am J Kidney Dis.* 2020;75(1):A6–A7. doi:10.1053/j.ajkd.2019.09.003
41. Schroeder KL, Sallustio JE, Ross EA. Continuous haematocrit monitoring during intradialytic hypotension: precipitous decline in plasma refill rates. *Nephrol Dial Transplant.* 2004;19(3):652–656. doi:10.1093/ndt/gfg590
42. Woodcock TE, Woodcock TM. Revised Starling equation and the glycocalyx model of transvascular fluid exchange: an improved paradigm for prescribing intravenous fluid therapy. *Br J Anaesth.* 2012;108(3):384–394. doi:10.1093/bja/aer515
43. Magder S. Volume and its relationship to cardiac output and venous return. *Crit Care.* 2016;20(1):271–311. doi:10.1186/s13054-016-1438-7
44. Grant CJ, Huang SS, McIntyre CW. Hepato-splanchnic circulatory stress: an important effect of hemodialysis. *Semin Dial.* 2019;32(3):237–242. doi:10.1111/sdi.12782
45. Kanbay M, Ertuglu LA, Afsar B, et al. An update review of intradialytic hypotension: concept, risk factors, clinical implications and management. *Clin Kidney J.* 2020;13(6):981–993. doi:10.1093/CKJ/SFAA078
46. Daugirdas JT. Intradialytic hypotension and splanchnic shifting: integrating an overlooked mechanism with the detection of ischemia-related signals during hemodialysis. *Semin Dial.* 2019;32(3):243–247. doi:10.1111/sdi.12781
47. Santoro A, Mancini E, Zucchelli P. Ultrafiltration behaviour with different dialysis schedules. *Nephrol Dial Transplant.* 1998;13(suppl 6):55–61. doi:10.1093/ndt/13.suppl_6.55
48. Tonelli M, Astephen P, Andreou P, Beed S, Lundrigan P, Jindal K. Blood volume monitoring in intermittent hemodialysis for acute renal failure. *Kidney Int.* 2002;62(3):1075–1080. doi:10.1046/j.1523-1755.2002.00523.x
49. Kron S, Schneditz D, Leimbach T, Aign S, Kron J. Vascular refilling is independent of volume overload in hemodialysis with moderate ultrafiltration requirements. *Hemodialysis Int.* 2016;20(3):484–491. doi:10.1111/hdi.12417
50. Mitsides N, Pietribiasi M, Waniewski J, Brenchley P, Mitra S. Transcapillary refilling rate and its determinants during haemodialysis with standard and high ultrafiltration rates. *Am J Nephrol.* 2019;50(2):133–143. doi:10.1159/000501407
51. Samandari H, Schneditz D, Germain MJ, Horowitz J, Hollot CV, Chait Y. Variable-volume kinetic model to estimate absolute blood volume in patients on dialysis using dialysate dilution. *ASAIO J.* 2018;64(1):77–85. doi:10.1097/MAT.0000000000000608

Received: November 7, 2022 **Accepted:** January 18, 2023
Published Online Ahead of Print: February 14, 2023