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ORIGINAL ARTICLE

The effects of extracellular volume and intradialytic peripheral resistance changes on ambulatory blood pressure in hemodialysis patients with and without recurrent intradialytic hypertension

Meredith McAdams[1], L. Parker Gregg[1,2], Rong Lu[3], Michael Concepcion[1,2], Swati Lederer[1,2], Jeff Penfield[1,2] and Peter Noel Van Buren[1,2]

[1]Division of Nephrology, Department of Internal Medicine, University of Texas Southwestern Medical Center, Dallas, TX, USA, [2]Renal Section, Medical Service, Veterans Affairs North Texas Health Care System, Dallas, TX, USA and [3]Quantitative Sciences Unit, Stanford University School of Medicine, Palo Alto, CA, USA

Correspondence to: Peter Noel Van Buren; E-mail: peter.vanburen@utsouthwestern.edu

ABSTRACT

Background. Hypertension and extracellular volume (ECV) overload are interrelated mortality risk factors in hemodialysis (HD) patients, but confounding related to changes in ECV and vasoconstriction during and between treatments obfuscate their relationship. We sought to clarify independent contributions of post-HD ECV and intradialytic changes in vasoconstriction on ambulatory blood pressure (BP) in patients with and without recurrent intradialytic hypertension (IH).

Methods. In this prospective observational study, we obtained measurements of pre- and post-HD ECV with bioimpedance spectroscopy (BIS), pre- and post-HD total peripheral resistance index and 44-h ambulatory BP. Linear regression determined associations between post-HD ECV/weight and intradialytic change in total peripheral resistance index (TPRI) with interdialytic BP and slope.

Results. In fully-adjusted models for participants with complete data, post-HD ECV/weight associated with mean ambulatory BP ($\beta = 133$, $P = 0.01$; $n = 52$) and ambulatory BP slope ($\beta = -4.28$, $P = 0.03$; $n = 42$). ECV/weight was associated with mean ambulatory BP in those with recurrent IH ($\beta = 314$, $P = 0.0005$; $n = 16$) and with ambulatory BP slope in those without recurrent IH ($\beta = -4.56$, $P = 0.04$; $n = 28$). Interdialytic weight gain percentage and intradialytic TPRI change were not associated with ambulatory BP or slope in any analyses.

Conclusion. Ambulatory BP in HD patients is more strongly associated with post-HD ECV assessed with BIS than with intradialytic TPRI changes or interdialytic ECV increases. These findings highlight the essential role of

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recognizing and managing chronic ECV overload to improve ambulatory BP in HD patients, particularly so for those with IH.

Keywords: ambulatory blood pressure, bioimpedance, extracellular volume, hemodialysis, intradialytic hypertension

INTRODUCTION

Hypertension and extracellular volume (ECV) overload are two interrelated risk factors for mortality in end-stage renal disease (ESRD) patients on hemodialysis (HD). While time-averaged interdialytic blood pressure (BP) measurements provide the best information to assess end-organ damage and mortality from hypertension [1], ongoing changes in ECV, vasoconstriction and BP itself during and between HD treatments make it difficult to recognize the independent impact chronic ECV overload has on interdialytic BP. Certain intradialytic BP patterns can characterize both the degree of post-HD ECV overload [2–5] and the dynamic balance of vasoconstriction/vasodilation [3, 6–8] during HD. However, the understanding of how post-HD ECV impacts interdialytic BP while also accounting for other mechanisms that influence BP remains incomplete.

Patients that repeatedly experience BP increases from pre- to post-HD, known as intradialytic hypertension (IH), have increased morbidity and mortality compared with those with BP decreases [9–11]. Our research has shown that compared with patients whose BP decreases during HD, those with recurrent IH have higher mean ambulatory BP and have ambulatory BP 'patterns' that deviate from the expected gradual increase in BP between HD treatments [12, 13]. We also recently showed that recurrent IH is associated with high post-HD ECV and acute intradialytic increases in total peripheral resistance index (TPRI) compared with hypertensive control HD patients [3]. In the current study, we sought to characterize the independent associations of these 'peri-dialytic' factors with 'interdialytic' BP in hypertensive HD patients.

We hypothesized that the post-HD ECV and intradialytic changes in vasoconstriction would both have independent associations with ambulatory BP in ESRD patients. We conducted a comprehensive study inclusive of bioimpedance measurements, noninvasive cardiac output monitoring and ambulatory BP measurements in a cohort of hypertensive HD patients. We then evaluated the independent associations between interdialytic BP and interdialytic BP slopes with post-HD ECV/weight and intradialytic change in TPRI in the whole group and subgroup analyses based on presence of recurrent IH.

MATERIALS AND METHODS

Study design and participants

We previously conducted a case–control study in 18 participants with recurrent IH in comparison with 18 HD patients with recurrent decreases in systolic BP >10 mmHg from pre- to post-HD [3]. We combined unpublished data from these individuals with data from an additional 39 hypertensive HD patients who were consecutively enrolled regardless of any intradialytic BP pattern [4]. Study inclusion criteria were (i) age >18 years, (ii) HD vintage >1 month and (iii) peri-dialytic hypertension defined as pre-HD systolic BP >140 mmHg or post-HD systolic BP >130 mmHg based on the most recent formal Kidney Disease Outcome Quality Initiatives recommendations [14]. Exclusion criteria were cardiac defibrillator or pacemaker, amputation of arm or leg, coronary artery stent, implanted metallic prosthesis, pregnancy or inability to achieve dry weight defined by the nephrologist providing the clinical care. For this study, we maintained the definition of recurrent IH to include all participants who had increases in systolic BP from pre- to post-HD ≥10 mmHg in four or more out of six screening treatments.

We obtained written informed consent from all participants prior to any study procedures. The University of Texas Southwestern Medical Center Institutional Review Board approved the protocol, and all procedures were in accordance with the Declaration of Helsinki. The study was part of a registered clinical trial, NCT01862497 [15].

Study procedures

Bioimpedance spectroscopy. Before and 30 min after a mid-week HD treatment, we obtained measurements of ECV and total body water (TBW) in liters (L) using whole-body multifrequency bioimpedance spectroscopy (BIS) (Impedimed SFB7, Carlsbad, CA, USA). Participants were supine, and electrodes were placed on the wrist, hand, foot and ankle contralateral to the HD access. Body weight was obtained using the HD unit standing scale before and after HD. We used the ratio of ECV/weight as our primary bioimpedance metric for the following reasons: (i) this standardizes for body size compared with ECV alone, (ii) this is a recognized metric for determination of ECV excess [16] and (iii) compared with the ratio of ECV/TBW, this metric eliminates a potential source of error from the intracellular volume measurement used along with ECV to calculate TBW and can be more sensitive for identifying ECV excess compared with ECV/TBW [17].

Impedance cardiography. Before and 30 min after the same mid-week treatment, we also obtained measurements of cardiac output and mean arterial pressure using impedance cardiography (Non-Invasive Cardiac Output Monitor, Cheetah Medical Inc., Newton Center, MA, USA), a device shown to demonstrate agreement with thermodilution measurements of cardiac output in critically ill patients [18]. We placed electrodes on the anterior and posterior of the trunk. TPRI was calculated from the measured cardiac index (CI) and mean arterial pressure. The change in TPRI (delta TPRI) was calculated from post-HD TPRI – pre-HD TPRI.

Ambulatory blood pressure. Following the mid-week treatment post-HD study measurements, we initiated ambulatory BP monitoring (Spacelabs 90207). The device measured BP every 30 min from 6 a.m. to 10 p.m., and hourly at night, and the mean ambulatory BP was calculated for 71 participants with available data. The average BP for each hour was calculated. We used linear regression modeling to calculate the systolic BP slope during Hours 1–24 and the whole interdialytic time period (Hours 1–44) among the participants with data available for at least 50% successful readings during these specific time periods ($n = 61$ and 54, respectively).

Intradialytic BP measurements. BP was measured using sphygmomanometers attached to the HD machine before, after and every 30 min during HD (more often as clinically indicated for hemodynamic instability). We used Gaussian regression to calculate the intradialytic BP slope (IBPS) [4].

Laboratory data. Blood was collected from the participant's HD access before and after the same mid-week treatment that we obtained the physiologic measurements. After centrifuging and storing in a −80°C freezer, we measured endothelin-1 (ET-1) with a quantitative sandwich enzyme immunoassay technique with Human Endothelin-1 Immunoassay (Quantiglo) and asymmetric dimethylarginine (ADMA) using competitive enzyme-linked immunosorbent assay (Biovendor) with a microtiter plate format. All other laboratory data were obtained from the medical record reflecting the most recent pre-HD labs drawn within the past 1–4 weeks.

Statistics

All variables are reported as mean and standard deviation for continuous variables and percentage for categorical variables. We compared differences in continuous variables using unpaired *t*-test and in categorical variables using Chi-square analysis. Continuous variables that did not have a normal distribution were analyzed with Wilcoxon rank-sum tests and reported as median and interquartile range (IQR).

We used linear regression models to analyze associations between various peri-dialytic variables (independent variables) and the following dependent variables: mean ambulatory systolic BP, ambulatory systolic BP slope for Hours 1–24 of the interdialytic period and ambulatory systolic BP slope during Hours 1–44 of the interdialytic period. Participants with data in <50% of the available hours of each interval were excluded from analysis. For each dependent variable, we conducted a separate analysis for each of the following normally distributed independent variables: pre-HD systolic BP, post-HD systolic BP, change in systolic BP from pre- to post-HD, IBPS, post-HD ECV/weight, delta TPRI, post-HD CI, delta CI, percentage of interdialytic weight gain (for the period after the mid-week treatment when ambulatory BP was being measured) and ultrafiltration rate (mL/kg/h). In each of these analyses, we controlled for age, sex and the presence of diabetes mellitus. We conducted analyses for the whole group of participants, as well as separate subgroup analyses among individuals with or without recurrent IH.

To first address our primary question of whether post-HD ECV overload or changes in TPRI during HD were more strongly associated with ambulatory BP and ambulatory BP slope, we conducted multivariate linear regression analysis where post-HD ECV/weight, delta TPRI, age, sex and diabetes were independent variables (Model 1). This resulted in 57 participants that had mean ambulatory BP data analyzed, 49 with data for Hours 1–24 and 45 for Hours 1–44. In a more comprehensive analysis (Model 2), we conducted multivariate analyses using all of the following independent variables, which were considered clinically relevant to interdialytic BP: age, sex, diabetes mellitus, post-HD systolic BP, post-HD ECV/weight, delta TPRI, percentage of interdialytic weight gain, ultrafiltration rate and IBPS. Again, we conducted analyses for the whole group of participants, as well as separate subgroup analyses among individuals with and without recurrent IH. We only analyzed the data for the participants that had complete data for all the variables in each model ($n = 52$, 46 and 42). We finally conducted several exploratory analyses where post-HD ECV/weight was included in models with either post-HD TPRI or the intradialytic change in ADMA and ET-1.

RESULTS

Patient characteristics

There were 18 participants with recurrent IH and 57 without recurrent IH. Baseline demographics and clinical characteristics of the whole group and a comparison of those with and without recurrent IH are in Table 1. Participants with recurrent IH had lower estimated dry weight, blood urea nitrogen, serum phosphorus and protein catabolic rate. Participants with recurrent IH had lower pre-HD systolic BP, which increased by 7 (25) mmHg compared with a decrease of 20 (28) mmHg in those without recurrent IH (P = 0.0004). Participants with recurrent IH also had higher ECV/weight before and after HD as well as higher post-HD TPRI related to an increase (compared with decrease in those without recurrent IH) from pre- to post-HD (Table 1). Figure 1 shows a detailed flow of participants with data available for the ambulatory blood pressure analyses.

Mean ambulatory BP

There were 71 participants with sufficient ambulatory BP data. Pre- and post-HD systolic BP and post-HD ECV/weight were associated with mean ambulatory BP while controlling for age, sex and presence of diabetes mellitus (Supplementary data, Table S1). Of the 71 participants, there were 57 that had complete data for age, presence of diabetes, delta TPRI and post-HD ECV/weight. In Model 1, post-HD ECV/weight was associated with mean ambulatory BP ($\beta = 143$, P = 0.004), but delta TPRI was not ($\beta = 0.002$, P = 0.4) (Table 2). There were 52 participants that had complete data for the remaining variables in Model 2. In Model 2, the independent association of post-HD ECV/weight with ambulatory systolic BP persisted ($\beta = 133$, P = 0.01; Table 2). This also persisted in a separate analysis controlling for post-HD TPRI ($\beta = 114$; P = 0.03).

Mean ambulatory systolic and diastolic BP were 147 (13) and 79 (11) mmHg in participants with recurrent IH and 142 (14) and 80 (12) mmHg in participants without (P = 0.1, 0.9 for systolic and diastolic BP, respectively). In Model 1 (Table 2), post-HD ECV/weight was associated with ambulatory BP in participants with recurrent IH ($\beta = 324$, P = 0.00005), but the association was not as strong in those without IH ($\beta = 100$, P = 0.1). This association persisted in participants with recurrent IH in Model 2 (Table 2), as well as in an analysis controlling for post-HD TPRI ($\beta = 296$, P = 0.0004). Delta TPRI was not associated with mean ambulatory systolic BP in any analysis (Table 2).

When interdialytic weight gain was removed from Model 2 (but ultrafiltration rate was left in), the regression coefficient for post-HD ECV/weight was 144 (P = 0.005), 81.4 (P = 0.2) and 284 (P < 0.0001) for the whole group analysis, the analysis of those without recurrent IH and the analysis of those with IH, respectively.

Ambulatory BP slope Hours 1–24

The systolic BP slope during the first 24 h after HD was 0.23 (IQR −0.30 to 0.69) mmHg/h for the whole group ($n = 61$). Associations of individual variables with this slope are in Supplementary data, Table S2. There were 49 participants that had sufficient data for BP slopes during Hours 1–24 and complete data for the other variables in Model 1. In multivariable analysis, there was a negative association of delta TPRI with slope in Model 1 ($\beta = -0.002$, P = 0.006), but it was attenuated in

Table 1. Participant characteristics

Variable, mean (SD), median (IQR) or *n* (%) (*n* for whole group, without recurrent IH, with recurrent IH; *n* = 75, 57, 18 unless otherwise specified)	Whole group (*n* = 75)	Without recurrent IH (*n* = 57)	With recurrent IH (*n* = 18)	P-value (comparison of with and without recurrent IH)
Demographic characteristics				
Age (years, *n* = 73, 55, 18)	49.4 (12)	48.3 (12)	53.2 (12)	0.1
Male (%)	46 (61)	34 (60)	12 (67)	0.6
African American (%)	44 (59)	37 (66)	7 (39)	0.05
Hispanic (%)	22 (30)	15 (27)	7 (39)	0.3
Diabetes mellitus (%) (*n* = 66, 48, 18)	44 (57)	31 (55)	11 (61)	0.6
Laboratory measurements				
Blood urea nitrogen (mmol/L, *n* = 72, 54, 18)	19.9 (5.7)	20.9 (5.7)	16.8 (4.6)	0.004
Serum creatinine (μmol/L, *n* = 70, 53, 17)	911 (240)	928 (120)	871 (230)	0.4
Serum potassium (mmol/L, *n* = 73, 55, 18)	4.80 (0.6)	4.81 (0.6)	4.76 (0.6)	0.7
Serum calcium (mmol/L, *n* = 74, 56, 18)	2.31 (0.2)	2.29 (0.2)	2.35 (0.2)	0.2
Serum phosphorus (mmol/L, *n* = 74, 56, 18)	1.95 (0.7)	2.06 (0.7)	1.61 (0.4)	0.001
Serum albumin (g/L, *n* = 74, 56, 18)	38.2 (3.0)	38.0 (3.0)	39.1 (3.0)	0.2
Protein catabolic rate (g/kg/day) (*n* = 74, 56, 18)	1.07 (0.4)	1.12 (0.4)	0.92 (0.2)	0.005
Pre-HD ET-1 (pg/mL, *n* = 68, 52, 16)	2.35 (1.5)	2.33 (1.5)	2.41 (1.5)	0.9
Post-HD ET-1 (pg/mL, *n* = 67, 52, 15)	2.37 (1.1)	2.38 (1.1)	2.31 (1.2)	0.8
Intradialytic change in ET-1 (pg/mL, *n* = 65, 50, 15)	0.02 (0.6)	0.07 (-0.2, 0.4)	0.009 (–0.2, 0.3)	0.6
Pre-HD ADMA (μmol/L, *n* = 70, 54, 16)	0.77 (0.2)	0.78 (0.2)	0.71 (0.1)	0.1
Post-HD ADMA (μmol/L (*n* = 67, 52, 15)	0.49 (0.2)	0.52 (0.2)	0.40 (0.07)	0.0004
Intradialytic change in ADMA (μmol/L, *n* = 67, 52, 15)	−0.28 (0.2)	−0.27 (0.2)	−0.30 (0.2)	0.5
Dialysis prescription				
Treatment time (min, *n* = 74, 56, 18)	233 (19)	234 (19)	232 (19)	0.6
Blood flow (mL/min, *n* = 74, 56, 18)	414 (89)	425 (97)	378 (43)	0.005
Dialysate flow (mL/min, *n* = 74, 56, 18)	682 (113)	684 (120)	672 (89)	0.6
Dialysate sodium (mmol/L, *n* = 74, 56, 18)	138 (0.9)	138 (0.9)	139 (0.9)	0.4
Dialysate potassium (mmol/L, *n* = 74, 56, 18)	2.12 (0.3)	2.14 (0.4)	2.06 (0.2)	0.2
Dialysate calcium (mmol/L, *n* = 74, 56, 18)	2.51 (0.1)	2.51 (0.1)	2.5 (0)	0.5
Dialysate bicarbonate (mmol/L, *n* = 74, 56, 18)	35.6 (3.4)	35.5 (3.5)	36.1 (3.1)	0.5
Estimated dry weight (kg)	86.3 (19)	90.2 (19)	74.2 (16)	0.001
Volume and hemodynamic measurements				
Pre-HD systolic BP (mmHg, *n* = 72, 54, 18)	155 (20)	159 (19)	142 (19)	0.002
Post-HD systolic BP (mmHg, *n* = 73, 55, 18)	142 (22)	139 (23)	149 (20)	0.09
Intradialytic systolic BP nadir (mmHg, *n* = 72, 54, 18)	117 (20)	115 (21)	123 (15)	0.1
Pre-HD ECV/weight (L/kg, *n* = 73, 55, 18)	0.25 (0.22–0.30)	0.23 (0.22–0.27)	0.30 (0.26–0.32)	0.0005
Post-HD ECV/weight (L/kg, *n* = 71, 54, 17)	0.24 (0.05)	0.23 (0.04)	0.27 (0.05)	0.002
Pre-HD TPRI (dynes/s/cm^5/m^2, *n* = 74, 56, 18)	3190 (770)	3250 (780)	2980 (750)	0.9
Post-HD TPRI (dynes/s/cm^5/m^2, *n* = 73, 56, 17)	2813 (2418–3180)	2720 (2350–3089)	2990 (2810–3920)	0.01
Delta TPRI (dynes/s/cm^5/m^2, *n* = 73, 56, 17)	−277 (820)	−478 (700)	385 (840)	0.001
Mean ambulatory systolic BP (mmHg, *n* = 71, 54, 17)	143 (14)	142 (14)	147 (13)	0.1
Percentage of weight gain prior to mid-week treatment (%, *n* = 74, 56, 18)	2.98 (1.8)	2.92 (1.7)	3.19 (2.0)	0.6
Ultrafiltration rate (mL/kg/h, *n* = 73, 55, 18)	8.00 (3.7)	7.86 (3.6)	8.42 (4.2)	0.6
Percentage of interdialytic weight gain after mid-week treatment (%,*n* = 72, 55, 17)	2.91 (1.8)	2.89 (1.8)	2.96 (1.8)	0.9
Antihypertensive drug use (*n* = 73, 55, 18 for all medications)				
Angiotensin-converting enzyme inhibitors (%)	27 (36)	18 (32)	9 (50)	0.2
Angiotensin receptor blockers (%)	15 (20)	12 (21)	3 (17)	0.7
Beta adrenergic receptor antagonists (%)	57 (76)	42 (74)	15 (83)	0.4
Alpha adrenergic receptor antagonists (%)	44 (59)	32 (56)	12 (67)	0.4
Calcium channel blocker (%)	47 (62)	33 (58)	14 (78)	0.1
Hydralazine (%)	9 (12)	7 (12)	2 (11)	0.9
Clonidine (%)	9 (12)	8 (14)	1 (6)	0.7

Model 2 ($\beta = -0.0002$, P = 0.1, Table 3). Post-HD ECV/weight had no association with slope in either model.

The slopes were −0.35 (IQR −0.75 to 0.34) and 0.28 (IQR −0.06 to 0.75) mmHg/h in participants with and without recurrent IH (P = 0.02). In Model 1, slope had a marginal association with delta TPRI in participants with IH ($\beta = -0.0003$, P = 0.09), but no association with delta TPRI in those without IH (Table 3). In this model, ECV/weight had no association with slope in those with or without IH. Neither of these variables had an association with a slope in either group in Model 2 (Table 3).

Table 2. Multivariable linear regression associations of clinical and hemodynamic parameters with mean ambulatory systolic BP

	Whole group (Model 1, $n=57$; Model 2, $n=52$)		Without recurrent IH (Model 1, $n=41$; Model 2, $n=36$)		With recurrent IH (Model 1, $n=16$; Model 2, $n=16$)	
Variable	β	P-value	β	P-value	β	P-value
Model 1[a]						
Post-HD ECV/body weight (L/kg)	143	0.004	100	0.1	324	0.00005
Delta TPRI (dynes/s/cm^5/m^2)	0.002	0.4	0.004	0.3	0.0006	0.8
Model 2[b]						
Post-HD ECV/body weight (L/kg)	133	0.01	49.4	0.5	314	0.0005
Delta TPRI (dynes/s/cm^5/m^2)	0.003	0.2	0.004	0.3	−0.002	0.2
Post-HD systolic BP (mmHg)	0.28	0.004	0.30	0.02	0.24	0.002
Ultrafiltration rate (mL/kg/h)	0.15	0.8	−0.16	0.8	−0.04	0.9
Percentage of interdialytic weight gain after mid-week treatment (%)	−0.06	0.9	0.55	0.7	−1.30	0.07
Intradialytic BP slope (mmHg/min)	−53.2	0.003	−80.3	0.002	−2.33	0.8

[a]Each model also adjusted for age, sex and the presence of diabetes mellitus.

Table 3. Multivariable linear regression associations of clinical and hemodynamic parameters with ambulatory systolic BP slope during Hours 1–24

	Whole group (Model 1, $n=49$; Model 2, $n=46$)		Without recurrent IH (Model 1, $n=34$; Model 2, $n=31$)		With recurrent IH (Model 1, $n=15$; Model 2, $n=15$)	
Variable	β	P-value	β	P-value	β	P-value
Model 1[a]						
Post-HD ECV/body weight (L/kg)	−1.83	0.3	1.28	0.6	−4.77	0.2
Delta TPRI (dynes/s/cm^5/m^2)	−0.0002	0.006	−0.00008	0.5	−0.0003	0.09
Model 2[a]						
Post-HD ECV/body weight (L/kg)	−0.50	0.8	2.34	0.3	−2.08	0.7
Delta TPRI (dynes/s/cm^5/m^2)	−0.0002	0.1	0.00004	0.7	−0.0003	0.3
Post-HD systolic BP (mmHg)	−0.007	0.08	−0.01	0.03	−0.01	0.3
Ultrafiltration rate (mL/kg/h)	−0.01	0.6	0.004	0.9	−0.04	0.5
Percentage of interdialytic weight gain after mid-week treatment (%)	0.004	0.9	−0.02	0.8	0.06	0.7
Intradialytic BP slope (mmHg/min)	−0.45	0.5	−0.14	0.9	1.13	0.5

[a]All analyses adjusted for age, sex and presence of diabetes mellitus.

Ambulatory BP slope Hours 1–44

The systolic BP slope during the entire interdialytic period was 0.26 (0.4) mmHg/h for the whole group ($n=54$). Associations of individual variables with this slope are shown in Supplementary data, Table S3. There were 45 participants that had sufficient data for BP slopes and complete data for the other variables in Model 1. In Model 1, post-HD ECV/weight had a significant association with slope ($\beta=-3.91$, P = 0.04), but delta TPRI did not (Table 4). The negative association between slope and ECV/weight persisted in Model 2 ($\beta=-4.28$, P = 0.03, Table 4).

The slopes were 0.17 (0.4) and 0.3 (0.4) mmHg/h in participants with and without recurrent IH, respectively. In Model 1, there was a trend for an association with post-HD ECV/weight ($\beta=-4.22$, P = 0.1) in those without recurrent IH that was statistically significant in Model 2 ($\beta=-4.56$, P = 0.04) (Table 4). There was no association with post-HD ECV/weight with BP slope in either model in those with recurrent IH. There was no association with delta TPRI with BP slope in either model for either subgroup (Table 4).

When interdialytic weight gain was removed from Model 2 (but ultrafiltration rate was left in), the regression coefficient for post-HD ECV/weight was −4.24 (P = 0.02), −4.08 (P = 0.06) and −2.1 (P = 0.5) for the whole group analysis, the analysis of those without recurrent IH and the analysis of those with IH, respectively.

Exploratory analyses of ET-1 and asymmetric dimethylarginine

There was no association between intradialytic change in ET-1 or ADMA with the mean ambulatory BP, ambulatory BP slope during Hours 1–24, or ambulatory BP during Hours 1–44 in models adjusting for age, sex, diabetes and post-HD ECV/weight in the whole group or either subgroup (Supplementary data, Table S4).

DISCUSSION

The primary finding of this study was that post-HD ECV/weight measured with BIS was a predominant independent factor

Table 4. Multivariable linear regression associations of clinical and hemodynamic parameters with ambulatory systolic BP slope during Hours 1–44

	Whole group (Model 1, $n = 45$; Model 2, $n = 42$)		Without recurrent IH (Model 1, $n = 31$; Model 2, $n = 28$)		With recurrent IH (Model 1, $n = 14$; Model 2, $n = 14$)	
Variable	β	P-value	β	P-value	β	P-value
Model 1[a]						
Post-HD ECV/body weight (L/kg)	−3.91	0.04	−4.22	0.1	−3.29	0.2
Delta TPRI (dynes/s/cm^5/m^2)	−0.00006	0.5	−0.0001	0.4	−0.0001	0.4
Model 2[a]						
Post-HD ECV/body weight (L/kg)	−4.28	0.03	−4.56	0.04	0.03	0.9
Delta TPRI (dynes/s/cm^5/m^2)	−0.000007	0.9	0.00002	0.9	−0.0002	0.2
Post-HD systolic BP (mmHg)	−0.01	0.002	−0.02	0.0001	−0.005	0.5
Ultrafiltration rate (mL/kg/h)	0.01	0.7	−0.05	0.1	0.01	0.8
Percentage of interdialytic weight gain after mid-week treatment (%)	0.007	0.9	0.09	0.1	−0.13	0.2
Intradialytic BP slope (mmHg/min)	1.01	0.1	2.01	0.005	−0.26	0.8

[a]All analyses adjusted for age, sex and presence of diabetes mellitus.

associated with elevated ambulatory BP and ambulatory BP slope in HD patients, even while controlling for dynamic changes in vasoconstriction during HD, post-HD BP, interdialytic weight gain and other clinically relevant variables. Post-HD ECV/weight had a much stronger association with mean ambulatory BP in participants with recurrent IH compared with those without, but it had a stronger association with ambulatory BP 'slope' in those without IH. This provides novel quantitative evidence of the independent association between an objective assessment of ECV excess and one of the BP metrics best associated with adverse outcomes in this population. Furthermore, it argues against acute changes in intradialytic vasoconstriction or interdialytic volume expansion as independent drivers of interdialytic BP in HD patients.

A general association between ECV overload and hypertension in HD patients has been demonstrated in various ways previously. Both high pre- and post-HD systolic BP have been associated with high ratios of extracellular water/TBW using bioimpedance [2, 19], but these studies did not examine the association of ECV with ambulatory BP. Agarwal demonstrated in a randomized trial that dry-weight lowering reduced ambulatory BP compared with standard care [20]. Dry-weight lowering also resulted in lower post-HD BP but steeper interdialytic BP rise, suggesting that relative ECV overload was associated with post-HD hypertension and blunted rise in BP between treatments [21]. Our findings provide additional novel information by (i) demonstrating the independent effect of ECV while controlling for post-HD systolic BP, percentage of interdialytic weight gain and intradialytic TPRI change and (ii) objectively demonstrating these associations using quantitative BIS measurements. A noteworthy difference we found compared with others is our lack of an association of percentage of interdialytic weight gain with ambulatory BP slope [22]. We can therefore establish that despite acute hemodynamic changes occurring during HD and the subsequent accumulation of fluid following, post-HD ECV overload remains the variable most strongly associated with overall BP burden. We further demonstrated an independent association of ECV with ambulatory BP while controlling for post-HD TPRI and intradialytic changes in ET-1 and ADMA. The overall clinical impact of these findings is that the limitation of interdialytic weight gain without concomitant dry-weight reduction would not be expected to significantly influence BP burden. Our finding that, among individuals with similar post-HD BP, ambulatory BP was higher based on higher post-HD ECV/weight reinforces the need for better tools to assess ECV in HD patients beyond the physical exam and peridialytic BP measurements.

Another novel aspect of this study was our determination of whether post-HD ECV overload or intradialytic TPRI change was more strongly associated with ambulatory BP burden and slope in participants with recurrent IH. We demonstrated the presence of a strong association between ambulatory BP and post-HD ECV/weight along with an absence of association between intradialytic change in TPRI and ambulatory BP in the participants with recurrent IH. As either of these variables could contribute to a high post-HD BP, it is notable that post-HD ECV/weight remained an independent predictor of ambulatory BP in the final model. This is further indirect evidence against the vasoconstrictive surge having a major contribution to the overall BP burden. While some groups have implicated acute increases in vasoconstrictors such as ET-1 as a mechanism responsible for IH [7, 8], we found no evidence that intradialytic changes in ET-1 or ADMA were independently associated with the ambulatory BP or ambulatory BP slope when evaluated with ECV/weight in participants with recurrent IH. This is consistent with prior findings of ours that endothelial cell dysfunction assessed with flow-mediated vasodilation did not predict ambulatory BP slope [13]. Altogether, our data suggest that ECV management should be the initial focus to lower ambulatory BP in patients with recurrent IH.

In the participants without recurrent IH, which is more reflective of the general hypertensive HD population, post-HD ECV/weight was associated with 44-h interdialytic systolic BP slope. There was a trend for post-HD ECV/weight to have an association with mean ambulatory BP in univariate analysis and when controlling for intradialytic change in TPRI, but this weakened when considering other factors. In the final model in these participants, mean ambulatory BP was associated with the post-HD BP and the IBPS. The discordance of the associations between post-HD ECV/weight with mean ambulatory BP in the different models may be related to findings observed in the DRIP (Dry-weight reduction in hypertensive hemodialysis patients) trial where ambulatory BP lowering occurred in the context of lower post-HD BP as dry weight is reduced over time

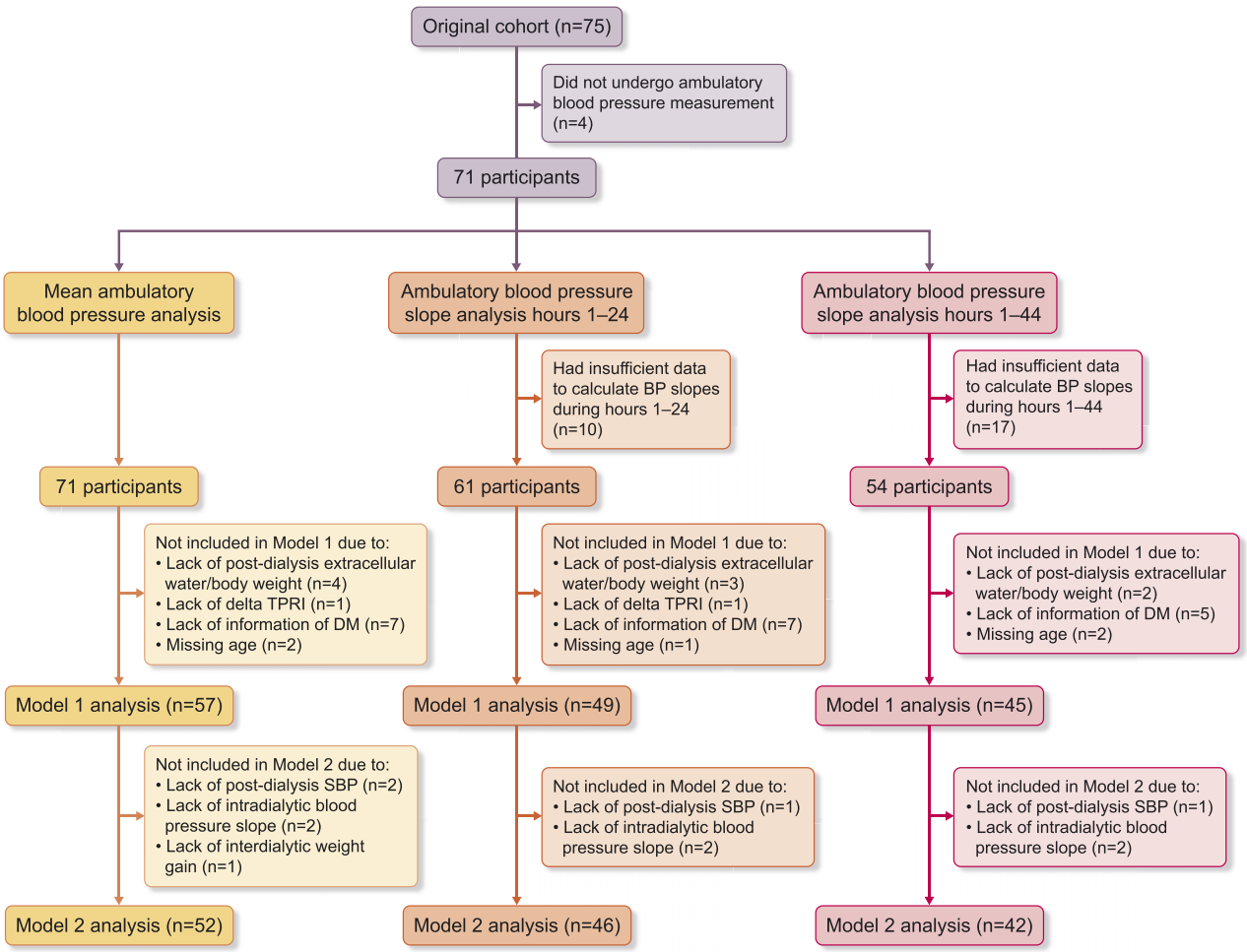

FIGURE 1: Our initial cohort included 75 participants, but 4 did not undergo ambulatory BP measurements. Of the 71 participants with data to calculate mean ambulatory BP, 14 were lacking the complete data to be included in the analysis for Model 1 ($n = 57$ analyzed). Of these 57, 5 were lacking the complete data to be included in analyses for Model 2 ($n = 52$ analyzed). Of the 71 participants with ambulatory BP data, 10 had insufficient data to calculate a slope during Hours 1–24. Of the remaining 61 participants, 12 were lacking the complete data to be included in analyses for Model 1 ($n = 49$ analyzed). Of these 49, 3 were lacking the complete data to be included in the analysis for Model 2 ($n = 46$ analyzed). Of the 71 partcipants with ambulatory BP data, 17 had insufficient data to calculate a slope during Hours 1–44. Of the remaining 54 participants, 9 were lacking complete data to be included in the analysis for Model 1 ($n = 45$ analyzed). Of these 45, 3 were lacking complete data to be included in the analysis for Model 2 ($n = 42$ analyzed).

[20]. We expect that a larger sample size might have established the association between post-HD ECV/weight and ambulatory BP in our study, but it remains unclear if this effect would be uncoupled from the association with post-HD BP. The findings of an association of chronic ECV overload with ambulatory BP slope might represent a novel method where ambulatory BP trajectories might ultimately be used to guide assessment of ECV in select patients, but this requires further research in a larger population.

Limitations to the study include its observational nature and inability to establish causality of the observed relationships. The number of patients with recurrent IH was small yet disproportionately larger than in an average HD cohort [23] such that inadequate power cannot be excluded as explanations for negative findings in this subgroup and some findings from the entire cohort may be over-influenced by this group. However, the positive findings from this group reinforce the overwhelming influence of ECV in patients with recurrent IH. Also, we did not account for antihypertensive medication use in our analyses due to the fact that lack of information on dosing, timing or adherence would limit the validity. Overall, there was a large portion of participants who were Hispanic and African American, so our results may not be entirely generalizable to populations with different demographics.

In conclusion, we used BIS to identify that post-HD ECV overload was a greater contributor to mean ambulatory BP in HD patients than were the intradialytic changes in TPRI or interdialytic weight gain. This effect was particularly pronounced in individuals with recurrent IH. Post-HD ECV overload was also associated with blunted interdialytic BP increases, and this effect was particularly pronounced in the majority of participants without recurrent IH. These findings were independent of post-HD BP and weight gain during the interdialytic period. This reinforces the critical need to optimize diagnosis and management of chronic ECV overload in HD patients to improve ambulatory BP, and particularly so for those with IH. Further research is needed to determine whether ascertainment of ambulatory BP slopes can be utilized as a novel method of identifying ECV overload in HD patients, in general.

SUPPLEMENTARY DATA

Supplementary data are available at ckj online.

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AUTHORS' CONTRIBUTIONS

All authors provided significant input into the design of the study, collection of data, interpretation of data, writing of the manuscript or revision of the manuscript.

CONFLICT OF INTEREST STATEMENT

None declared. Data from this manuscript were presented as a poster presentation at the American Society of Nephrology Kidney Week (November 2019, Washington, DC, USA). This manuscript has not otherwise been published otherwise in whole or part.

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