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

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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 (β = 133, P = 0.01; n = 52) and ambulatory BP slope (β = -4.28, P = 0.03; n = 42). ECV/weight was associated with mean ambulatory BP in those with recurrent IH (β = 314, P = 0.0005; n = 16) and with ambulatory BP slope in those without recurrent IH (β = -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
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 intradialytic 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 intradialytic 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 prior 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).
Extracellular volume and ambulatory blood pressure in hemodialysis patients

**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 (Quintiglo) 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. In a more comprehensive analysis, 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). When interdialytic weight gain was removed from Model 2 (but ultrafiltration rate was left in), the regression coefficient for post-HD ECV/weight was associated with ambulatory systolic BP in participants with 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).

**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).

**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 the remaining variables in Model 2. In Model 2, the independent association of post-HD ECV/weight with ambulatory systolic BP persisted (β = 133, P = 0.01, Table 2). This also persisted in a separate analysis controlling for post-HD TPRI (β = 114, P = 0.03).

**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 the slope in Model 1 (β = −0.002, P = 0.006), but it was attenuated in with either post-HD TPRI or the intradialytic change in ADMA and ET-1.
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).
DISCUSSION

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

| Variable                        | 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) |
|---------------------------------|-----------------------------------------------|----------------------------------------------------------|-------------------------------------------------------|
| Post-HD ECV/weight (L/kg)       | −3.91 0.04                                    | −4.22 0.04                                               | −3.29 0.02                                            |
| Delta TPRI (dynes/s/cm²/m²)     | −0.00006 0.5                                  | −0.0001 0.4                                             | −0.0001 0.4                                          |
| 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                                            |

*All analyses adjusted for age, sex and presence of diabetes mellitus.
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 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.
REFERENCES

1. Alborzi P, Patel N, Agarwal R. Home blood pressures are of greater prognostic value than hemodialysis unit recordings. Clin J Am Soc Nephrol 2007; 2: 1228–1234
2. Nongnuch A, Campbell N, Stern E et al. Increased postdialysis systolic blood pressure is associated with extracellular overhydration in hemodialysis outpatients. Kidney Int 2015; 87: 452–457
3. Van Buren P, Zhou Y, Neyra J et al. Extracellular volume overload and increased vasoconstriction in patients with recurrent intradialytic hypertension. Kidney Blood Press Res 2016; 41: 802–814
4. Liu H, Lu R, Shastri S et al. Assessing extracellular volume in hemodialysis patients using intradialytic blood pressure slopes. Nephron Clin Pract 2018; 139: 120–130
5. Sebastian S, Filmalter C, Harvey J et al. Intradialytic hypertension during chronic hemodialysis and subclinical fluid overload assessed by bioimpedance spectroscopy. Clin Kidney J 2016; 9: 636–643
6. Inrig J, Van Buren P, Kim C et al. Intradialytic hypertension and its association with endothelial cell dysfunction. Clin J Am Soc Nephrol 2011; 6: 2016–2024
7. El-Shafey E, El-Nagar G, Selim M et al. Is there a role for endothelin-1 in the hemodynamic changes during hemodialysis? Clin Exp Nephrol 2008; 12: 370–375
8. Chou K, Lee P, Chen C et al. Physiologic changes during hemodialysis in patients with intradialytic hypertension. Kidney Int 2006; 69: 1833–1838
9. Inrig J, Oddone EH, Gillespie BV et al. Association of intradialytic blood pressure changes with hospitalization and mortality rates in prevalent ESKD patients. Kidney Int 2007; 71: 454–461
10. Inrig J, Patel U, Toto R et al. Association of blood pressure increases during hemodialysis with 2-year mortality in incident hemodialysis patients: a secondary analysis of the Dialysis Morbidity and Mortality Wave 2 Study. Am J Kidney Dis 2009; 54: 881–890
11. Park J, Rhee C, Sim J et al. A comparative effectiveness research study of the change in blood pressure during hemodialysis treatment and survival. Kidney Int 2013; 84: 795–802
12. Van Buren P, Kim C, Toto R et al. Intradialytic hypertension and the association with interdialytic ambulatory blood pressure. Clin J Am Soc Nephrol 2011; 6: 1684–1691
13. Hompesch C, Ma T, Neyra J et al. Comparison of ambulatory blood pressure patterns in patients with intradialytic hypertension and hemodialysis controls. Kidney Blood Press Res 2016; 41: 240–249
14. National Kidney Foundation. KDOQI Clinical Practice Guidelines for cardiovascular disease in dialysis patients. Am J Kidney Dis 2005; 45: S1–S154
15. Mechanisms of Increased Ambulatory Blood Pressure in Patients With Intradialytic Hypertension. ClinicalTrials.gov [Internet]. Bethesda, MD: National Library of Medicine (US), 2000 (cited 16 January 2016) NLM identifier: NCT01862497 NIDoDaDaKDNTUoTSMCaDAmToIABPiP. https://www.clinicaltrials.gov/ct2/show/NCT01862497?term=–van+buren&rank=2 (1 May 2018, date last accessed)
16. Davies S, Davenport A. The role of impedance and biomarkers in helping to aid clinical decision-making of volume assessments in dialysis patients. Kidney Int 2014; 86: 489–496
17. van de Kerkhof J, Hermans M, Beerenhout C et al. Reference values for multifrequency bioimpedance analysis in dialysis patients. Blood Purif 2004; 22: 301–306
18. Squara P, Denjean D, Estagnasie P et al. Noninvasive cardiac output monitoring (NICOM): a clinical validation. Intensive Care Med 2007; 33: 1191–1194
19. Fagugli R, Pasini P, Quintaliani G et al. Association between extracellular water, left ventricular mass and hypertension in haemodialysis patients. Nephrol Dial Transplant 2003; 18: 2332–2338
20. Agarwal R, Alborzi P, Satyan S et al. Dry-weight reduction in hypertensive hemodialysis patients (DRIP): a randomized, controlled trial. Hypertension 2009; 53: 500–507
21. Agarwal R. Volume-associated ambulatory blood pressure patterns in hemodialysis patients. Hypertension 2009; 54: 241–247
22. Agarwal R, Light R. Arterial stiffness and interdialytic weight gain influence ambulatory blood pressure patterns in hemodialysis patients. Am J Physiol Renal Physiol 2008; 294: F303–F308
23. Van Buren P, Kim C, Toto R et al. The prevalence of persistent intradialytic hypertension in a hemodialysis population with extended follow-up. Int J Artif Organs 2012; 35: 1031–1038