Original Paper

Association of Intradialytic Hypertension with Left Ventricular Mass in Hypertensive Hemodialysis Patients Enrolled in the Blood Pressure in Dialysis (BID) Study

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Key Words

Intradialytic hypertension • Hemodialysis • Left ventricular mass

Abstract

Background/Aims: Intradialytic hypertension (IDH), or paradoxical rise in blood pressure (BP) during hemodialysis (HD) is associated with increased morbidity and mortality. The association between IDH and increased left ventricular mass (LVM), a well-known risk factor for adverse cardiovascular outcomes in HD patients, has not been studied. The aim of our study is to evaluate the cross-sectional association of intradialytic change in BP with cardiac structure and function measured by cardiac MRI in hypertensive HD patients enrolled in the multi-center Blood Pressure in Dialysis (BID) clinical trial. **Methods:** Participants in the BID study were categorized into 3 groups based on average change (Δ) in systolic blood pressure (SBP) (post-HD SBP minus pre-HD SBP) during HD over a 1 month period: group 1 - patients with an increase in SBP ≥ 10 mm Hg during HD (IDH); group 2 - patients with SBP decrease of greater ≥ 10 mm Hg during HD; group 3 - patients with SBP increase or decrease by < 10 mm Hg during HD. LVM index (LVMI) was measured using cardiac MRI, which were centrally read.

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Baseline characteristics were compared in the 3 groups and multivariable regression models were fitted for the adjusted association of IDH with LVMI. **Results:** Among the 80 participants, 7 (8.8%) had IDH and had average Δ SBP 17.0 ± 10.1 mmHg during HD. Patients with IDH were less likely to be diabetic, had lower pre-dialysis SBP and lower percent interdialytic weight gain as compared to the other 2 groups ($p=0.02$, $p<0.001$ and $p=0.02$ respectively). In multivariable regression analyses, IDH was significantly associated with LVMI (adjusted mean difference relative to SBP decreased group [95% confidence interval (CI)] = 12.5 [3.6 , 21.5], $p=0.01$) after adjusting for age, sex, diabetes, IDWG%, pre-HD SBP and beta blocker use. Every 1 mm rise in Δ SBP during HD was associated with 0.2 g/m² increase in LVMI in adjusted models ($p=0.04$). **Conclusion:** IDH is independently associated with higher LVMI in hypertensive HD patients and may contribute to increased cardiovascular events.

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Introduction

The majority of hemodialysis (HD) patients experience a decline in blood pressure (BP) during HD treatment. However, there is a subset of patients that have a recurrent and paradoxical rise in BP during HD. This phenomenon of increase in BP from pre-post HD, known as intradialytic hypertension (IDH), occurs in approximately 10-15% of the patients [1-3]. No standard definition of IDH exists, but has most commonly been defined as ≥ 10 mmHg rise in systolic BP (SBP) during dialysis. IDH has been associated with poor clinical outcomes in HD patients including increased hospitalizations, higher ambulatory BP, cardiovascular morbidity, and mortality [4-6].

How IDH leads to adverse cardiovascular events is not known. Pathophysiological mechanisms underlying IDH such as extracellular volume overload, sympathetic overactivity, endothelial dysfunction, sodium loading from dialysate and/or clearance of anti-hypertensive medications during HD may contribute to increased cardiovascular risk in these patients [1, 7-11]. It is also plausible that IDH, directly or indirectly leads to increased left ventricular mass (LVM), a well-known risk factor for adverse cardiovascular outcomes in HD patients [12].

The aim of this study is to evaluate the cross-sectional association of intradialytic change in BP with cardiac structure and function measured by cardiac MRI in hypertensive HD patients enrolled in the Blood Pressure in Dialysis (BID) study [13]. We hypothesized that an increase in systolic blood pressure during dialysis (IDH) is associated with increased left ventricular mass index (LVMI) in HD patients.

Materials and Methods

Study Population

Blood Pressure in Dialysis (BID) is a multi-center pilot randomized clinical trial with the goal of assessing feasibility and safety of treating chronic HD patients to a standardized (155-165 mm Hg) versus intensive (110-140 mm Hg) pre-dialysis SBP target over 1 year period (Clinicaltrials.gov NCT01421771) [13]. Eligibility criteria included age ≥ 18 years, on maintenance HD ≥ 3 months, upper arm suitable for measuring blood pressure, and a predialysis SBP ≥ 155 mm Hg or anticipated to rise to ≥ 155 mm Hg after backtitration of antihypertensive drugs. Exclusion criteria included unscheduled dialysis treatments for congestive heart failure, intradialytic hypotension requiring hospitalization or contraindication for cardiac MRI. For this cross-sectional analysis, the subset of BID participants who had available baseline cardiac MRI data and dialysis unit BP data for at least 80% of treatments in 1 month prior to BID enrollment were included. All participants provided written, informed consent and the study was approved by each site's Institutional Review Board.

Intradialytic Hypertension (IDH)

Routine seated pre-HD and post-HD BP values were measured during every HD session by means of automatically inflated cuffs using a digital monitor attached to each HD machine according to standard dialysis unit protocols, and were captured electronically within the databases. All available pre- and post-HD BP measurements for 1 month prior to BID enrollment were included. We used pre-enrollment BPs rather than BPs during baseline period of BID study as the antihypertensive medications may have been adjusted during baseline period to achieve a 2-week average predialysis SBP ≥ 155 mm Hg as per the BID study protocol. Changes (Δ) in systolic BP, defined as post-HD SBP *minus* pre-HD SBP, were averaged for each patient. Patients were stratified into three groups; group 1 - patients with an increase in SBP ≥ 10 mm Hg during HD (IDH); group 2 - patients with SBP decrease of greater ≥ 10 mm Hg during HD; group 3 - patients with SBP increase or decrease by < 10 mm Hg during HD. Group 1 represents IDH based on existing definitions of increase in SBP ≥ 10 mm Hg [1].

Cardiac structural and functional measures

Cardiac MRI was done during the baseline period on a non-dialysis day using a standardized protocol. All MRIs were read centrally by the Core Lab in Brigham and Women's Hospital by a single cardiologist (RK). The main outcome of interest was left ventricular mass index (LVMI) at baseline. It was calculated as LVM/(height^{2.7}), where height is in meters [14]. Left ventricular hypertrophy (LVH) was defined as LVMI ≥ 45 g/m-height for women and ≥ 49 g/m-height for men based on established guidelines [15]. Other functional cardiac parameters such as left ventricular end-systolic volume (LVESV) and left-ventricular end-diastolic volume (LVEDV) were also obtained. Ejection fraction was calculated as (LVEDV-LVESV)/LVEDV $\times 100$. Given that, geometry of left ventricular hypertrophy, specifically increased left ventricular concentricity, is a reflection of diastolic dysfunction, we evaluated LV concentricity [16, 17]. LV concentricity was defined as LV mass/LVEDV^{0.67} and compared among the 3 groups [17]. Also, the percentage of patients with concentric hypertrophy in each group were calculated using predefined thresholds – concentricity ≥ 8.1 g/mL^{0.67} (women) and ≥ 9.1 g/mL^{0.67} (men) [17].

Socio-demographic, Disease, and Treatment Specific Factors

Socio-demographic data including patients' age, gender, race, ethnicity, comorbidity data, medication data, and laboratory values were gathered from the patients' medical record. Antihypertensive medications were classified as dialyzable or non-dialyzable based on published literature [11]. Dialysis treatment specific data including prescribed dialysate sodium, dialysate calcium, estimated dry weight (EDW) and interdialytic weight gain (IDWG) were obtained from dialysis records. Interdialytic weight gain (averaged for dialysis sessions over 1 month) was calculated as the average change in weight between dialysis sessions. Percent interdialytic weight gain (IDWG%) was calculated as the average interdialytic weight gain divided by the postdialysis weight averaged over 1 month. Dialysate serum sodium gradient was calculated as the prescribed dialysate sodium minus predialysis serum sodium. Dialysate serum calcium gradient was calculated as dialysate calcium minus predialysis serum calcium. For these calculations, average of all dialysate and serum electrolyte values over 1 month were used.

Statistical Analysis

Descriptive summaries for patient characteristics were presented using means and standard deviations (SD) for continuous variables; and frequencies and percentages for categorical variables. Bivariate associations with the 3 Δ SBP groups were assessed using ANOVA and Chi-square or Fisher exact test depending on the variable type. To examine crude correlations between continuous variables, scatter plots with LOWESS curve and Spearman correlation coefficients were used. Unadjusted and adjusted linear regression models were fitted to examine the relationship between Δ SBP and cardiac MRI measures (LVMI). Our primary analysis used LVMI as outcome and Δ SBP group as predictor. We also examined Δ SBP as a continuous variable. We adjusted for potential confounders selected based on clinical reasons rather than statistical and accounting for the limited sample size.

Sensitivity Analyses

Since IDH has also been defined as systolic BP increase ≥ 10 mmHg from pre- to post hemodialysis in at least four of six treatments [4], we used this definition to do sensitivity analysis in our study. Additionally, we also calculated the proportion of dialysis treatments for each individual patient with $\Delta\text{SBP} \geq 10$ mmHg. We evaluated whether the proportion of dialysis treatments with IDH were associated with LVMI. The proportion was examined both as continuous and categorical covariate. We categorized it using 25%, 50% and 75% as predetermined cut-offs.

Statistical analyses were carried out using R (version 3.3.3) using the packages dplyr for data manipulation, compareGroups for descriptive tables, rms for modeling, segmented for change-point estimation, and ggplot2 for plotting [18-20].

Results

The distribution of average ΔSBP during HD is shown in Fig. 1. Among the 80 hypertensive HD patients studied, 7 patients (8.8%) had IDH i.e. average $\Delta\text{SBP} \geq 10$ mmHg during HD (Group 1). Forty patients (50%) had an average $\Delta\text{SBP} \geq -10$ mmHg (Group 2) and 33 patients (41.3%) had $\Delta\text{SBP} < -10$ mmHg (Group 3). In the IDH group, the median of percentage of treatments in which ΔSBP during HD was ≥ 10 mmHg was 50% [interquartile range 44%, 62%].

Baseline characteristics

The baseline characteristics of the 3 groups are shown in Table 1. The 3 groups were similar in age, sex, race and dialysis vintage. Patients in IDH group were significantly less likely to be diabetic than the other groups ($p=0.02$) but there were no differences in other comorbidities including congestive heart failure, coronary artery disease or peripheral vascular disease. Interestingly, patients in IDH group had lower pre-dialysis systolic BP (SBP) and lower IDWG% as compared to the other 2 groups ($p<0.001$ and $p=0.02$ respectively). There was a significant moderate negative correlation between pre dialysis SBP and ΔSBP , such that those with higher pre dialysis SBP had lesser increase in ΔSBP during HD (spearman correlation $r = -0.59$, $p<0.001$).

There were no differences between the groups in terms of number or class of antihypertensive medications, except for beta-blocker use, which was much lower in the group 2. There was also no difference in dialyzable antihypertensive medications use among the 3 groups. There were no significant differences in laboratory parameters among the 3 groups. There were no significant differences in dialysate sodium, dialysate calcium and dialysate serum sodium or calcium gradients in the 3 groups. We did observe a weak positive correlation between dialysate serum calcium gradient and ΔSBP during HD (spearman correlation $r = 0.35$, $p=0.002$).

Fig. 1. Distribution of average change in systolic blood pressure during dialysis.

Table 1. Baseline Characteristics of HD patients according to average change in SBP during HD

Variable	SBP Increased ≥ 10 mmHg (N=7)	SBP Decreased ≥ 10 mmHg (N=40)	SBP Unchanged ± 10 mmHg (N=33)	P value
	Mean (SD) or n (%) or median [25 th , 75 th quartile]	Mean (SD) or n (%) or median [25 th , 75 th quartile]	Mean (SD) or n (%) or median [25 th , 75 th quartile]	
Age (yrs.)	50 (11.5)	56.2 (11.5)	57.5 (12.1)	0.32
Male (%)	6 (85.7%)	20 (50.0%)	20 (60.6%)	0.23
Race:				0.35
Black (%)	3 (42.9%)	14 (35.0%)	12 (36.4%)	
White (%)	2 (28.6%)	21 (52.5%)	15 (45.5%)	
Other (%)	2 (28.6%)	4 (10.0%)	6 (18.2%)	
Hispanic Ethnicity (%)	2 (28.6%)	18 (45.0%)	12 (36.4%)	0.70
Dialysis vintage (years)	2.4 [1.2, 5.2]	3.5 [1.8, 5.8]	2.4 [0.8, 3.8]	0.17
Diabetes	2 (28.6%)	32 (80.0%)	21 (63.6%)	0.02
Congestive Heart Failure	0 (0.0%)	5 (12.5%)	6 (18.2%)	0.63
Cardiovascular Disease	0 (0.0%)	3 (7.5%)	3 (9.1%)	1.00
Peripheral Vascular Disease	0 (0.0%)	5 (12.5%)	3 (9.1%)	0.60
EDW (Kg)	68.5 (11.8)	78.2 (18.1)	71.8 (17.6)	0.19
IDW gain (Kg)	2.0 (1.0)	3.0 (1.0)	2.2 (1.0)	0.001
IDWG%	3.0 (1.5)	3.9 (1.3)	3.1 (1.5)	0.02
Pre-dialysis SBP (mm Hg)	149 (7.7)	171 (15.3)	156 (14.5)	<0.001
Pre-dialysis DBP (mm Hg)	83.9 (9.4)	86.4 (12.1)	82.4 (13.3)	0.38
Post-dialysis SBP (mm Hg)	166 (7.9)	141 (15.7)	155 (14.2)	<0.001
Post-dialysis DBP (mm Hg)	88.9 (6.8)	73.8 (9.5)	81.3 (11.1)	<0.001
Average change in SBP during HD (mm Hg)	17.0 (10.1)	-29.4 (14.1)	-0.8 (5.1)	<0.001
No. of antihypertensive meds	2.7 (0.8)	2.5 (1.6)	3.1 (1.1)	0.26
RAAS Blockade (%)	3 (50.0%)	23 (57.5%)	19 (59.4%)	0.94
Beta-blocker	5 (83.3%)	24 (60.0%)	31 (96.9%)	<0.001
CCB	5 (83.3%)	25 (62.5%)	24 (75.0%)	0.45
Diuretic	1 (16.7%)	7 (17.5%)	12 (37.5%)	0.14
Vasodilator	0 (0.0%)	9 (22.5%)	6 (18.8%)	0.63
Dialyzable antihypertensive meds	4 (57.1%)	20 (54.1%)	20 (64.5%)	0.74
Erythropoietin Dose/week (units/wk)	2267 [1367, 4825]	2167 [821, 3425]	1500 [120, 3750]	0.66
Sodium (mEq/L)	140 (2.8)	139 (3.1)	139 (3.9)	0.64
Potassium (mEq/L)	4.5 (0.3)	4.7 (0.6)	4.6 (0.7)	0.57
Creatinine (mg/dl)	10.6 (3.3)	9.6 (2.6)	9.0 (3.4)	0.41
Calcium (mg/dl)	8.7 (0.5)	9.1 (0.6)	8.9 (0.8)	0.27
Phosphorus (mg/dl)	5.0 (1.9)	5.9 (2.0)	5.7 (2.0)	0.51
Albumin (mg/dl)	4.0 (0.4)	3.9 (0.4)	3.9 (0.3)	0.84
Hematocrit (%)	33.9 (6.9)	35.3 (2.8)	34.6 (2.9)	0.47
Single pool Kt/V	1.5 (0.2)	1.7 (0.2)	1.6 (0.4)	0.51
Dialysate sodium (mEq/L)	139 (1.5)	138 (1.8)	139 (2.1)	0.80
Dialysate Serum Sodium gradient (mEq/L)	-1.0 [-3.0; 0.0]	0.0 [-3.1; 2.3]	0.0 [-4.0; 2.0]	0.77
Dialysate calcium (mEq/L)	2.6 (0.5)	2.4 (0.3)	2.5 (0.3)	0.30
Dialysate serum Calcium gradient (meq/L)	-3.6 (1.0)	-4.2 (1.0)	-3.9 (0.9)	0.11

Table 2. Cardiac MRI characteristics among the 3 groups. *LVH defined as LVMI ≥ 45 g/m-height for women and ≥ 49 g/m-height for men. # LV concentricity defined as LV mass/LVEDV $^{0.67}$

Cardiac MRI variable	SBP Increased ≥ 10 mmHg (N=7)	SBP Decreased ≥ 10 mmHg (N=40)	SBP Unchanged ± 10 mmHg (N=33)	P value
	Mean (SD) or n (%)	Mean (SD) or n (%)	Mean (SD) or n (%)	
LV Mass (g)	188.4 (75.7)	143.6 (43.1)	154.8 (44.5)	0.07
LV Mass Index (g/m ²)	41.0 (12.6)	35.9 (10.2)	37.4 (8.7)	0.43
LV hypertrophy*	2 (28.6%)	5 (12.5%)	4 (12.1%)	0.43
LV concentricity (g/mL ^{0.67})#	4.8 (0.9)	4.4 (1.0)	4.5 (1.0)	0.68
LV End-Diastolic Volume (ml)	236 (97.0)	181 (52.0)	200 (60.0)	0.07
LV End-Systolic Volume (ml)	123 (74.6)	86.7 (45.4)	99.1 (40.6)	0.14
LV Ejection Fraction (%)	51.3 (11.9)	54.3 (12.6)	51.3 (8.8)	0.47

Cardiac structural and functional measures

The cardiac parameters in 3 groups are shown in Table 2. In unadjusted analyses, there was no significant difference in LVMI among the 3 groups (Fig. 2). Four (11.8%) of women and 7 (15.2%) of men had left ventricular hypertrophy (LVH). The distribution of LVH was/was not significantly different in the 3 groups ($p=0.43$). We did not find any difference in LV concentricity among the 3 groups. Moreover, none of the patients in our cohort had concentric hypertrophy suggestive of diastolic dysfunction, as defined by the cutoff thresholds by Khouri et al. [17].

In multivariable regression analyses, IDH was significantly associated with an increased LVMI relative to the SBP decreased group (β [95% confidence interval (CI)] = 12.5 [3.6, 21.5], $p=0.01$) after adjusting for age, sex, diabetes, IDWG%, pre-HD SBP and beta blocker use (Table 3 and Fig. 3). Also, a rise or drop in BP <10 mm Hg during HD was associated with increased LVMI (β [95% confidence interval (CI)] = 6.4 [0.9, 11.9], $p=0.03$). The regression model explained 20% of the variance in LVMI (adjusted $R^2=0.2$). Pre-HD SBP was also significantly associated with LVMI (β [95% confidence interval (CI)] = 0.3 [0.2, 0.5], $p<0.001$) in adjusted analysis. In adjusted models, when Δ SBP was modeled as a continuous variable, every 1 mm rise in Δ SBP during HD was associated with 0.2 g/m² increase in LVMI after adjusting for age, sex, diabetes, IDWG%, pre-HD SBP and beta blocker use ($p=0.04$) (Fig. 4). Since RAASi may have effect on cardiac remodeling, we conducted additional regression analysis adjusting for RAASi use, and this did not significantly alter our results (data not shown).

Sensitivity Analyses

Using the definition that has been used in some of the prior studies i.e. Δ SBP ≥ 10 mmHg during HD in at least 4 of 6 HD treatments, 6 (7.5%) of the patients had IDH. There was no association of IDH by this definition and LVMI ($p=0.44$).

We also categorized patients based on the proportion of dialysis treatments with Δ SBP ≥ 10 mmHg during HD in a 1 month period. Fifty-nine (74%) patients had Δ SBP ≥ 10 mm Hg in 0- 25% of HD treatments, 17 (21%) experienced this in $>25\%$ to 50% of HD treatments, 3 (4%) in $>50\%$ to 75% of HD treatments, and only 1 patient had this in $>75\%$ of HD treatments. There was no significant association between quartiles of proportion of HD treatments with Δ SBP ≥ 10 mm Hg and LVMI ($p=0.65$). Additional sensitivity analysis using Δ SBP cutoff of ± 5 mm Hg, instead of ± 10 mm Hg revealed no significant association between the 3 patient groups and any of the cardiac MRI characteristics.

Fig. 2. Unadjusted association of change in systolic blood pressure and left ventricular mass index in the 3 groups.

Table 3. Multivariable regression analyses of Left ventricular mass index in HD patients. SBP decreased ≥ 10 mmHg is the reference group

Variable	Unadjusted analysis		Adjusted analysis*	
	Coefficient (95% CI)	P-value	Coefficient (95% CI)	P-value
Δ SBP ≥ 10 mm Hg	5.1 (-2.8, 13.0)	0.21	12.5 (3.4, 21.5)	0.01
Δ SBP unchanged (-10 to 10 mm Hg)	1.4 (-3.1, 6.0)	0.54	6.4 (0.9, 11.9)	0.03
Age (years)			-0.0 (-0.2, 0.2)	0.92
Sex (Female)			-0.8 (-5.0, 3.4)	0.71
IDWG%			0.3 (-1.3, 1.8)	0.74
Diabetes			0.2 (-4.6, 4.9)	0.95
Pre-HD SBP			0.3 (0.2, 0.5)	<0.001
Beta blocker use			0.4 (-4.9, 5.7)	0.88

Fig. 3. Multivariable adjusted association of change in systolic blood pressure during hemodialysis and left ventricular mass index in the 3 groups*. *Adjusted for age, sex, diabetes, IDWG%, pre-HD SBP and beta blocker use.

Fig. 4. Multivariable adjusted association of change in systolic blood pressure (as a continuous variable) during hemodialysis and left ventricular mass index*. *Adjusted for age, sex, diabetes, IDWG%, pre-HD SBP and beta blocker use.

Discussion

Intradialytic hypertension is a well-known but under recognized entity in HD patients [2, 3]. It is associated with poor clinical outcomes including increased morbidity and mortality, however the exact mechanisms are poorly understood [5, 6]. Our study identified a significant independent association of IDH with left ventricular mass index as measured by cardiac MRI in HD patients, providing insights into potential mechanism by which IDH may lead to adverse outcomes.

Association of IDH with adverse clinical outcomes is well established. Inrig et al. showed that among prevalent HD patients, those with Δ SBP ≥ 10 mm Hg during HD had a 2-times higher odds of hospitalization or death at 6 months compared to subjects whose SBP fell during HD [6]. They further demonstrated a similar finding in incident HD patients, in whom every 10mmHg increase in SBP during HD was independently associated with a 6% increased hazard of death at 2-year follow up (HR 1.06, CI 1.01-1.11) [5]. In fact, a recent observational

study of more than 100,000 HD patients showed that any rise in systolic BP over 0 mm Hg during HD was associated with higher mortality, thus emphasizing the importance of IDH [21]. Our study provides a plausible mechanistic explanation for increased mortality in these patients by showing an association of IDH with increased LVMI as LVMI has been shown to be a strong and independent predictor of survival and cardiovascular events in HD patients [12, 14]. However, it is important to note that we did not look at cardiovascular morbidity or mortality as an outcome in this study. Thus, although our findings demonstrate an association of IDH and a well-known cardiovascular risk factor, we cannot directly conclude that IDH is associated with poor outcomes because of LVH. Additionally, IDH and left ventricular hypertrophy may share common underlying pathophysiological mechanisms such as extracellular volume overload and increased peripheral vascular resistance due to endothelial dysfunction [1, 7-11]. IDH has also been associated with increased ambulatory blood pressure in HD patients, which may in turn accentuate LVH [4]. Recent studies show regression of LVM with intensive and frequent dialysis [22, 23]. It is plausible that aggressive management of IDH may also prevent increases in LVM.

Among the potential mechanisms for IDH, extracellular volume overload has been implicated as one of the most important ones [1]. Using bioimpedance spectroscopy, patients with IDH have been demonstrated to have higher volume overload [24]; and aggressive dry weight lowering has been shown to modify the intradialytic BP slope [9]. However surprisingly, consistent with prior studies, we found that patients with IDH had lower pre HD SBP and lower IDWG% as compared to those without IDH [6, 21]. This counterintuitive finding in multiple studies begs further exploration [5, 6, 21]. It may be that although these patients have lower IDWG%, they are still intravascularly volume overloaded. And lower IDWG and normal pre HD SBP may mislead towards lower ultrafiltration goals, thus contributing to volume overload. In fact, it has been shown that patients with recurrent IDH have higher post-dialysis extracellular volume as measured by bioimpedance analysis [25]. Additionally, in a study of more than 500 HD patients, the post HD extracellular water overhydration (in liters) was shown to be significantly greater in the IDH group [0.7 (0.17 to 1.1) liter] as compared to stable [0.39 (-0.2 to 0.95) liter] and fall in BP groups [0.38 (-0.19 to 0.86) liter] [26]. Additionally, inappropriate increase in renin-angiotensin or sympathetic nervous system activity or endothelial response triggered by small decrements in intravascular volume during ultrafiltration on HD in these patients may also play a role in IDH, as demonstrated by increased intradialytic total peripheral resistance in these patients [6, 8, 25, 27].

Another potential cause of IDH is thought to be dialysate serum sodium gradient, and a more positive gradient (i.e. net intradialytic sodium gain) has been associated with IDH [10, 28]. However, we did not find any significant differences in sodium gradient in the 3 groups in our study. The average sodium gradient was only 0.5 ± 3.5 meq/L as compared to previous studies which showed a positive association with IDH (3.5-5 meq/L) and thus may explain this negative finding [10, 28]. Antihypertensive medications may play a role in IDH. One possible mechanism is due to dialyzability of water soluble medications during HD [11]. However, in our study there was no difference in use of dialyzable antihypertensive medications among those with IDH as compared to those without. RAASi may mitigate effect of renin on HTN and prevent IDH, but their use was similar in the 3 groups in our study. There is also limited evidence supporting role of carvedilol in improving endothelial function and potentially decreasing the risk for IDH [8]. Although we did find that patients with IDH had less beta blocker use as compared to those with unchanged BP during HD, our conclusions are limited given the small sample size in our study. Lastly, calcium channel blockers (CCBs) may cause peripheral vasodilatation and thus volume overload and IDH. However, in contrast to Sebastian et al. we did not find any association of IDH with CCBs [24].

The prevalence of IDH in our study was 8.6% which is similar to that reported in other studies that have used multiple months BP data to define IDH [21, 29]. This is in contrast to 12-28% prevalence reported in some studies that have used BP data from only 3-6 HD

sessions [5, 6, 24]. This suggests that there may be wide variability in change in SBP during HD and regression to mean by using BP data over longer time periods may help to decrease false positive rates of IDH. Also, since patients with IDH tend to have lower pre-HD SBP, as shown in ours and prior studies [5, 21], they may have not met eligibility criteria for our study which only enrolled hypertensive patients. Interestingly, we found that patients with IDH were less likely to be diabetic as compared to the other two groups. However, we cannot be sure whether this is due to the small number of patients with IDH in our study or due to plausible role of underlying autonomic dysfunction and impaired peripheral vascular resistance in diabetes, leading to lack of rise of SBP during HD in patients without IDH.

Strengths of our study include use of averaged blood pressure data from 1 month period to identify IDH, detailed antihypertensive medication data, detailed dialysate prescription data, and evaluation of LVMI using centrally read cardiac MRIs. However, our findings should be considered in light of several limitations. Firstly, we used routine dialysis unit BP, which may not have been taken using standard BP measurement guidelines. However, we captured BP from all treatments over a 1 month period, instead of ≤ 2 weeks data as done in most prior studies, thus decreasing measurement error and the potential impact of outliers [4–6]. Moreover, routine dialysis BP measures are more practically applicable in the clinical setting. Secondly, since we used BP readings prior to BID enrollment, there was an average of 2.1 ± 0.8 months time lapse between the baseline BP readings and the cardiac MRI. During this baseline time period, BP management changes may have been implemented per the BID study protocol. However, given the short duration, it is unlikely that the BP changes in this time period had an effect on LVM. Thirdly, we did not have information on measured dialysate sodium in our study, which may be significantly different from prescribed dialysate sodium, as shown in a study of >300 hemodialysis patients [30]. Fourthly, since this is a cross-sectional, we cannot establish causality and may have not accounted for other unmeasured confounders. Fifth, only 7 (8.6%) patients in our cohort had IDH, and may not reflect characteristics of the larger HD population with IDH, thus limiting the generalizability of our findings. Lastly, the cohort utilized for this analysis was part of a randomized controlled trial, which excluded “sicker patients” such as those prone to intradialytic hypotension requiring hospitalizations or who had contraindications to MRI (cardiac pacemaker, etc.), or those who were not hypertensive based on pre dialysis SBP, which likely underestimated our results.

Conclusion

Intradialytic hypertension in HD patients is associated with increased left ventricular mass index, and may contribute to their increased cardiovascular morbidity and mortality. Identifying patients with IDH may help clinicians to risk stratify high risk patients, and aggressively target IDH lowering strategies such as aggressive volume control in this population.

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Disclosure Statement

The authors of this manuscript have no conflicts of interest to disclose.

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