Association of objective measures of volume status with blood pressure, cardiac structure, and cardiac function among patients receiving maintenance hemodialysis

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By

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Area of Concentration: **Nephrology/ Hemodialysis and cardiovascular disease**

I have reviewed this thesis. It represents work done by the author under my guidance/supervision.

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Association of objective measures of volume status with blood pressure, cardiac structure, and cardiac function among patients receiving maintenance hemodialysis

TABLE OF CONTENTS

LIST OF FIGURES

Association of objective measures of volume status with blood pressure, cardiac structure, and cardiac function among patients receiving maintenance hemodialysis

LIST OF TABLES

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OVERVIEW OF THESIS PAPERS

Cardiovascular disease is the leading cause of mortality among patients with kidney failure receiving maintenance hemodialysis (HD), accounting for around 40% of deaths in the United States.[1] These patients are subject to both traditional and non-traditional cardiovascular risk factors,[2] with unique features including the episodic nature of intermittent HD, where blood pressure and volume status can rapidly change over relatively short periods.[3] For example, both intra-dialytic hypotension and intra-dialytic hypertension are each associated with adverse outcomes among patients receiving HD.[4,5]

Over time, patients receiving maintenance HD experience progressive loss of residual kidney function,[6] which results in increasing dependence on HD to achieve adequate volume and blood pressure control. However, despite widespread acceptance of a direct link between hypervolemia and hypertension in patients with kidney failure, the physical exam has major limitations in the accurate diagnosis of volume status,[7] which may adversely influence clinical management decisions related to volume and blood pressure control. In this respect, bioimpedance has been widely investigated as a tool to provide more objective measures of volume status among patients receiving maintenance HD. Indeed, bioimpedance proxies of hypervolemia (such as shorter vector length) were observed to be independently associated with adverse cardiovascular outcomes.[8] However, on the patient and per-session clinical practice level, there is a paucity of data regarding the association of vector length with intra-dialytic blood pressure parameters. Similarly, whether changes in vector length are associated with changes in metrics of cardiac structure and function among patients receiving maintenance HD is unclear.

The Frequent Hemodialysis Network (FHN) Daily Trial, a randomized trial of 6/week versus 3/week HD,[9] measured vector length and cardiac magnetic resonance imaging (cMRI) at multiple time points during the trial protocol, providing a unique opportunity to explore these research questions. Therefore, using data from FHN, in Paper 1 we explored the association of vector length with intra-dialytic blood pressure parameters; in Paper 2, we explored the association of changes in vector length with changes in cMRI measures of cardiac structure and function.

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Association of Bioimpedance Parameters with Increases in Blood Pressure during Hemodialysis

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Abstract

Background Intradialytic hypertension, defined as an increase in BP from pre- to post-hemodialysis (HD), affects 5%–15% of patients receiving maintenance HD and is associated with cardiovascular and all-cause mortality. Hypervolemia is believed to be a major etiological factor, yet the association of more objective biomarkers of volume status with intradialytic hypertension is not well described.

Methods In a *post hoc* analysis of the Frequent Hemodialysis Network Daily Trial (*n*=238), using data from baseline, 1-, 4-, and 12-month visits (*n*=800), we used random-effects regression to assess the association of bioimpedance estimates of volume (vector length) with post-HD systolic BP (continuous) and any increase in systolic BP (categorical) from pre- to post-HD. We adjusted models for randomized group, age, sex, self-reported race, Quetelet (body mass) index, vascular access, HD vintage, hypertension, history of heart failure, diabetes, residual kidney function (urea clearance), pre-HD systolic BP, ultrafiltration rate, serum-dialysate sodium gradient, and baseline values of hemoglobin, phosphate, and equilibrated Kt/V urea.

Results The mean age of participants was 50±14 years, 39% were female, and 43% were Black. In adjusted models, shorter vector length (per 50 Ω/m) was associated with higher post-HD systolic BP (2.9 mm Hg; 95% confidence interval [CI], 1.6 to 4.2) and higher odds of intradialytic hypertension (odds ratio 1.56; 95% CI, 1.07 to 2.33). Similar patterns of association were noted with a more stringent definition of intradialytic hypertension (≥10 mm Hg increase from pre- to post-HD systolic BP), where shorter vector length (per 50 Ω/m) was associated with a higher odds of intradialytic hypertension (odds ratio 2.17; 95% CI, 0.88 to 5.36).

Conclusions Shorter vector length, a bioimpedance-derived proxy of hypervolemia, was independently associated with higher post-HD systolic BP and risk of intradialytic hypertension.

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Introduction

Cardiovascular disease remains the leading cause of mortality among patients with kidney failure receiving maintenance hemodialysis (HD), accounting for around 50% of deaths.[1] As patients with kidney failure experience progressive loss of residual kidney function,[2] they become increasingly reliant on HD for volume removal and BP control, with the goal of achieving or at least approaching euvolemia and normal or near-normal BP at the end of each HD treatment.

While most patients experience a decline in BP during HD as ultrafiltration progresses, some patients develop intradialytic hypertension, where BP increases from pre- to post-HD, which is also associated with adverse outcomes.[3,4] Because hypervolemia is believed to be a major contributor to intradialytic hypertension,[5–9] accurate assessment of volume status is required to inform ultrafiltration prescriptions and target (estimated dry) weight.

Recognizing the limitations of the physical examination,[10] numerous studies have explored alternative methods of volume assessment in patients receiving HD.[11–15] Among these, bioimpedance has received much attention, in part because of its relatively low cost and portability.[16,17] Although studies have not consistently demonstrated a benefit of bioimpedance in guiding ultrafiltration,[18,19] there are fewer data exploring the association of bioimpedance with changes in BP during HD, with prior studies mostly of a cross-sectional nature.[20] In a secondary analysis of the Frequent Hemodialysis Network (FHN) Daily Trial using repeated measures of bioimpedance[28] and HD-related BP, we tested the hypothesis that vector length, a bioimpedance-derived proxy of volume status, is associated with post-HD BP and the development of intradialytic hypertension. In addition, we tested whether the association differed according to the randomized treatment arm (six-times-per-week or three-times-per-week HD).

Methods

Study Design and Population

The study design and protocol,[21,22] primary results,[23] and results of several secondary analyses of

the FHN Daily Trial have been published.[20–24] The FHN Daily Trial protocol was approved by institutional review boards at each participating center, and written informed consent was obtained from all study participants. We obtained data for these analyses from the National Institute of Diabetes and Digestive and Kidney Diseases data repository.

In brief, the FHN Daily Trial was a multicenter, randomized, parallel-group trial comparing frequent (six times per week) with conventional (three times per week) in-center HD, performed in the United States and Canada. Patients receiving maintenance HD were eligible for inclusion if they were 13 years or older, achieved mean equilibrated Kt/V urea >1.0 for the past two baseline HD sessions, and weighed >30 kg. Notable exclusion criteria included poor adherence, contraindication to heparin, residual urea clearance >3 ml/min per 35 L, HD vintage <3 months, and inability to have cardiac magnetic resonance imaging. The trial was designed to examine two co-primary composite outcomes: (*1*) death or change (from baseline to 12 months) in left ventricular mass and (*2*) death or change (from baseline to 12 months) in the physical health composite score of the RAND 36-item health survey.

Exposure Variables

We considered vector length, measured by single-frequency bioelectrical impedance analysis, as the primary exposure of interest. We calculated vector length indexed to height in meters (Z/H) from the raw measurements of resistance (R) and reactance (Xc), where R represents the opposition to the flow of an alternating current through ionic solutions and Xc is the capacitance produced by interfaces across tissues (*e.g.*, cell membranes), according to the following formula: $|Z/H| = \sqrt{(R/H)^2 + (Xc/H)^2}$.[20,25] A shorter vector length reflects a higher degree of soft-tissue hydration. Bioimpedance measurements were obtained at baseline (month 0) and follow-up visits (months 1, 4, and 12), with the patient in a recumbent position before a midweek HD treatment. We considered vector length as continuous and categorical (tertiles) variables. In companion analyses, we considered derived extracellular and intracellular water compartments (in L) and the ratio of extracellular water/total body water as exposures of interest.

Outcome Variables

The primary outcome for this analysis was post-HD systolic BP. Other outcomes of interest included development of intradialytic hypertension, defined as any increase >0 mm Hg from pre- to post-HD[26]; nadir intradialysis BP; and development of intradialytic *hypo*tension, defined as any occurrence of a minimum intradialytic systolic BP <90 mm Hg if pre-HD systolic BP was <160 mm Hg or minimum intradialytic systolic BP <100 mm Hg if pre-HD systolic BP was ≥160 mm Hg.[27,28] In a sensitivity analysis, we considered an alternate definition of intradialytic hypertension (any increase >10 mm Hg in systolic BP from pre- to post-HD).

Statistical Analyses

We examined continuous variables graphically and recorded data as means (±SDs) for normally distributed variables or medians (with 25th–75th percentiles) for non-normally distributed variables. We examined categorical variables by frequency distribution and recorded data as proportions. We compared baseline characteristics across tertiles of the vector length using tests for trend on the basis of linear regression, χ^2 trend test, and Cuzick nonparametric trend test, as appropriate for data distribution.

We assessed the association between vector length and post-HD and nadir intradialytic systolic BP using unadjusted and adjusted random-effects linear regression to account for repeated measures within patients. We used analogous approaches using random-effects logistic regression to assess the association with binary outcomes of intradialytic hypertension and intradialytic hypotension. Model 1 was adjusted for randomized treatment assignment and the pre-HD systolic BP. Model 2 was additionally adjusted for age, sex, self-reported race (collected per original study protocol), Quételet (body mass) index, and access type. Model 3 was additionally adjusted for vintage (<2, 2–5, >5 years); history of hypertension, heart failure, and diabetes; and baseline residual urea clearance (0, ≤1, >1–3, >3 ml/min), hemoglobin, serum phosphate, equilibrated Kt/V_{urea}, serum-dialysate sodium gradient, and ultrafiltration rate (ml/kg per h). All variables were time-updated as appropriate for each visit. We examined for potential effect modification by randomized treatment arm by inclusion of the corresponding cross-product term in the fully adjusted model. We used restricted cubic splines to model the association of mean vector length (as a continuous variable) with mean post-HD systolic BP.

We considered two-tailed *P* values < 0.05 as statistically significant. We conducted analyses using Stata MP (version 16.0, Stata Corp., College Station, TX).

Results

Baseline Characteristics

Data were available for 234 randomized patients (96%) and 800 study visits for this analysis (Figure 1). The median number of sessions with available bioimpedance measures was four (interquartile range, 3–4) per patient. The mean age of participants was 50±14 years, 39% were female, and

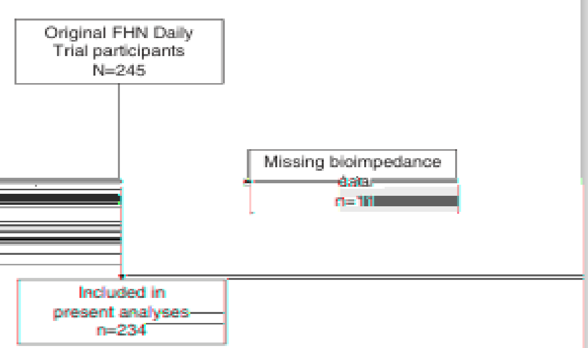

Figure 1. CONSORT diagram. FHN, Frequent Hemodialysis Network.

43% were Black. Differences in baseline characteristics of included and excluded participants are presented in Supplemental Table 1.

At baseline, patients in lower tertiles of vector length were more likely to be male; have a history of hypertension; and have a higher body mass index, lean body mass, phase angle, and residual kidney function. Patients in lower tertiles of vector length had a shorter HD vintage, were more likely to use a fistula, and had lower ultrafiltration rates and Kt/V_{urea} (Table 1).

Association of Vector Length with Post-Dialysis Systolic BP

During the follow-up period, the mean patient-level pre-dialysis vector length was 289±59 Ω/m. The median patient-level change (decrease) in systolic BP (pre-dialysis minus post-dialysis) was 13 (6–20) mm Hg; systolic BP increased from pre- to post-HD in 14% of participants.

In unadjusted analyses, shorter vector length (per 50 Ω/m) was associated with 3.7 mm Hg higher post-HD systolic BP (95% confidence interval [CI], 2.4 to 4.9). In the fully adjusted model, this association was attenuated such that shorter vector length (per 50 Ω/m) was associated with 2.9 mm Hg (95% CI, 1.6 to 4.3) higher post-HD systolic BP (Table 2). There was no evidence for effect modification according to the randomized treatment arm (P-interaction = 0.19). In fully adjusted categorical analyses, the lowest tertile of vector length was associated with 4.8 mm Hg (95% CI, 1.0 to 8.5) higher post-HD systolic BP compared with the highest tertile (Table 2). A monotonic association was also noted in spline analyses (Figure 2).

Association of Vector Length with Intradialytic Hypertension

During the follow-up period, the average patient-level frequency of intradialytic hypertension (defined as any increase >0 mm Hg from pre- to post-dialysis) was 19% of HD sessions. In unadjusted analyses, shorter vector

Table 1. Baseline characteristics according to categories of vector length

Characteristic[a]	Tertile 1, n=78	Tertile 2, n=78	Tertile 3, n=78
Vector length, Ω/m	223±20 226 (211–237)	276±15 273 (264–288)	356±48 342 (319–379)
Lean body mass, kg	53±8	45±7	35±5
Phase angle, °	5.9±1.7	5.5±1.4	4.8±1.2
Age, yr	49±12	51±14	51±16
Female, n (%)	8 (10)	27 (35)	55 (71)
Race or ethnic group, n (%)			
Asian	4 (5)	6 (8)	6 (8)
Black	35 (45)	31 (40)	34 (44)
Multiracial, unknown or not reported	7 (9)	6 (8)	10 (13)
Native American, Aboriginal Canadian, Alaskan Native, or First Nation	4 (5)	3 (4)	0 (0)
Native Hawaiian or another Pacific Islander	4 (5)	0 (0)	0 (0)
White	24 (31)	32 (41)	28 (36)
BMI, kg/m^2	29.4±6.1	28.2±6.5	25.3±6.9
Dialysis access, n (%)			
Fistula	56 (72)	52 (67)	40 (51)
Graft	10 (13)	11 (14)	20 (26)
Catheter	12 (15)	15 (19)	18 (23)
Duration of kidney failure, n (%)			
<2 yr	27 (35)	24 (31)	14 (18)
2–5 yr	28 (36)	22 (28)	26 (33)
>5 yr	23 (29)	32 (41)	38 (49)
Coexisting medical conditions, n (%)			
Hypertension	76 (97)	68 (87)	68 (87)
Heart failure	18 (23)	14 (18)	16 (21)
Diabetes mellitus	35 (45)	34 (44)	26 (33)
KrU ml/min, n (%)			
Anuria	44 (56)	51 (65)	58 (74)
>0–1	14 (18)	11 (14)	11 (14)
>1–3	17 (22)	15 (19)	9 (12)
>3	3 (4)	1 (1)	0 (0)
Pre-dialysis systolic BP, mm Hg	151±16	144±18	146±18
Pre-dialysis laboratory measurements			
Hemoglobin, g/dl	12.0±1.2	11.8±1.3	12.2±1.3
Phosphate, mg/dl	6.2±1.6	5.8±1.7	5.3±1.3
Equilibrated Kt/V urea	1.31±0.2	1.40±0.2	1.57±0.3
Ultrafiltration volume, L	3.6±0.9	3.1±0.9	2.8±0.9
Ultrafiltration rate, ml/kg per h	11±4	11±4	13±5
Sodium gradient, mmol/L	−2 (−4 to 1)	−1 (−4 to 1)	−2 (−4 to 1)
Randomized to 6/wk HD, n (%)	47 (60)	35 (45)	35 (45)

Sodium gradient calculated as pre-dialysis serum sodium minus prescribed dialysate sodium. BMI, body mass index; HD, hemodialysis; KrU, residual urea clearance.
[a]Results are presented as mean±SD or median (25th–75th percentiles) for continuous variables.

Table 2. Association of vector length with post-dialysis systolic BP

Model	Difference in Post-Dialysis Systolic BP (95% CI) in mm Hg			
	Per 50 Ω/m Lower Vector Length	Tertile 1	Tertile 2	Tertile 3
Unadjusted	3.7 (2.4 to 4.9)	7.2 (3.6 to 10.7)	3.1 (−0.1 to 6.3)	Ref
Model 1	1.9 (1.0 to 2.9)	4.5 (1.9 to 7.2)	2.2 (−0.2 to 4.7)	Ref
Model 2	3.2 (2.1 to 4.3)	6.7 (3.8 to 9.7)	3.7 (1.1 to 6.3)	Ref
Model 3	2.9 (1.6 to 4.3)	4.8 (1.0 to 8.5)	1.6 (−1.6 to 4.8)	Ref

Model 1 was adjusted for randomized treatment assignment and pre-dialysis systolic BP. Model 2 was additionally adjusted for age, sex, race, body mass index, and access type. Model 3 was additionally adjusted for vintage (<2, 2–5, >5 years), hypertension, heart failure, diabetes, residual urea clearance (0, ≤1, >1–3, >3 ml/min), hemoglobin, serum phosphate, equilibrated Kt/V, ultrafiltration rate, and serum-dialysate sodium gradient. Analyses include 800 visits from 234 patients. CI, confidence interval.

length (per 50 Ω/m) was not associated with odds of intradialytic hypertension (odds ratio [OR] 1.03; 95% CI, 0.81 to 1.32). In the fully adjusted model, shorter vector length was associated with 66% higher odds of development of intradialytic hypertension (OR 1.66; 95% CI, 1.07 to 2.55) (Table 3). There was no evidence of effect modification according to randomized treatment arm (*P*-interaction = 0.39). In fully adjusted categorical analyses, the lowest tertile of vector length was associated with 68% higher odds of intradialytic hypertension (OR 1.68; 95% CI, 0.56 to 5.03) compared with the highest tertile (Table 3).

A >10 mm Hg increase in pre- to post-dialysis systolic BP was observed in 7% of sessions. Using this more stringent definition, shorter vector length (per 50 Ω/m) was associated with a 2.2-fold higher odds of developing intradialytic hypertension (OR 2.17; 95% CI, 0.88 to 5.36; Supplemental Table 2).

Association of Vector Length with Nadir Systolic BP and Intradialytic Hypotension

During the follow-up period, the median patient-level change (decrease) in systolic BP (pre-HD minus nadir) was 27 (20–36) mm Hg, while the average patient-level frequency of intradialytic hypotension was 8% of sessions. Shorter vector length, both as a continuous and categorical variable, was associated with a higher nadir systolic BP. These effect estimates were accentuated with multivariable adjustment (Supplemental Table 3). Shorter vector length was not associated with the development of intradialytic hypotension (Supplemental Table 4).

Association of Intracellular Water and Extracellular Water with Outcomes

In companion analyses, derived intracellular and extracellular water and the ratio of extracellular water/total body water were considered separately as exposures of interest. In the fully adjusted models, extracellular water and the ratio of extracellular water/total body water were associated with a higher post-dialysis systolic BP, with a trend toward a higher risk of intradialytic hypertension. There was no association of intracellular water with any of the outcomes considered (Supplemental Table 5).

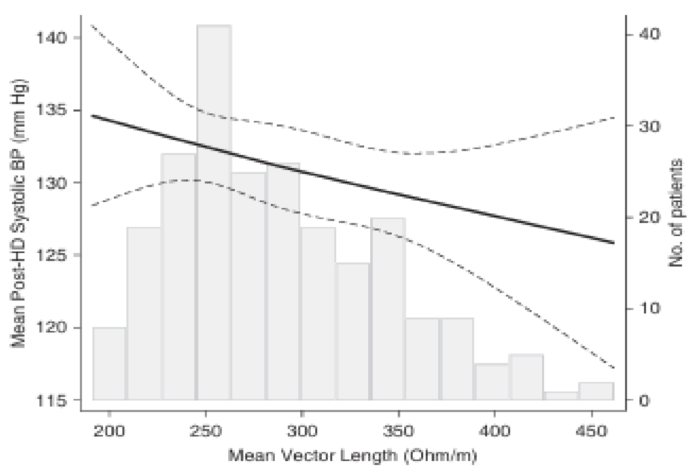

Figure 2. Association of mean vector length with mean post-dialysis systolic BP. The solid black line represents the association of mean vector length with mean post-dialysis systolic BP; the dashed lines are the 95% confidence intervals; the histogram in the background represents the frequency of patients with various mean vector lengths. HD, hemodialysis.

Table 3. Association of vector length with development of intradialytic hypertension (any increase >0 mm Hg from pre- to post-dialysis systolic BP)

Model	Odds of Intradialytic Hypertension (95% CI)			
	Per 50 Ω/m Lower Vector Length	Tertile 1	Tertile 2	Tertile 3
Unadjusted	1.03 (0.81 to 1.32)	0.98 (0.48 to 1.98)	0.85 (0.44 to 1.64)	Ref
Model 1	1.18 (0.90 to 1.55)	1.29 (0.61 to 2.73)	0.91 (0.46 to 1.82)	Ref
Model 2	1.65 (1.17 to 2.33)	2.35 (0.97 to 5.65)	1.32 (0.63 to 2.79)	Ref
Model 3	1.66 (1.07 to 2.55)	1.68 (0.56 to 5.03)	0.85 (0.34 to 2.12)	Ref

Model 1 was adjusted for randomized treatment assignment and pre-dialysis systolic BP. Model 2 was additionally adjusted for age, sex, race, body mass index, and access type. Model 3 was additionally adjusted for vintage (<2, 2–5, >5 years), hypertension, heart failure, diabetes, residual urea clearance (0, ≤1, >1–3, >3 ml/min), hemoglobin, serum phosphate, equilibrated Kt/V, ultrafiltration rate, and serum-dialysate sodium gradient. Analyses include 800 visits from 234 patients. CI, confidence interval.

Discussion

In this *post hoc* analysis of the FHN Daily Trial, we observed an association of shorter vector length (a proxy for increased tissue hydration) with higher post-HD systolic BP and higher odds of developing intradialytic hypertension.

Although there are several potential etiologies,[29,30] hypervolemia is hypothesized to be a major contributor to the development of intradialytic hypertension. In a *post hoc* analysis of the dry weight reduction in the hypertensive hemodialysis patient trial, patients whose dry weight decreased the most had the largest magnitude of intradialytic BP decline, which in turn was associated with a reduction in interdialytic ambulatory BP measurements.[31] Prior studies using bioimpedance have reported similar results. For example, Nongnuch *et al.* measured multifrequency bioelectrical impedance during a single mid-week HD session in 531 patients in the United Kingdom. They reported that patients who experienced a ≥10% rise in systolic BP had a higher ratio of bioimpedance-derived extracellular water/total body water at pre- and post-HD time points compared with those who did not.[7] Similar findings were noted in a smaller case–control study (n=18 in each group) where post-HD multifrequency bioimpedance measures of extracellular volume (at a single mid-week HD session) were higher among patients with intradialytic hypertension (defined as four of six screening sessions with an increase in systolic BP >10 mm Hg) compared with those without.[9] Consistent findings were also noted in a multicenter observational study (n=190) from South Africa.[8]

Our data extend the prior knowledge base by examining repeated measures of volume status over time and by exploring the association with changes in intradialytic BP measurements that were carefully collected as part of a randomized controlled trial. We observed that shorter vector length is associated with higher post-HD systolic BP and the development of intradialytic hypertension. Furthermore, this proxy of hypervolemia was also associated with higher nadir intradialytic BP and a lower risk of intradialytic hypotension. Prior reports using the FHN Daily Trial data have noted that extracellular water decreased to a greater degree from baseline to 12 months among the 6 times/week group (with corresponding increases in vector length) compared with the 3 times/week group,[20] suggesting that vector length may be a useful marker of extracellular water and a predictor of BP among patients receiving maintenance HD. Notably, vector length correlates directly with body cell mass, that is, shorter vector length correlates with higher body cell mass, necessitating some caution in reliance on vector length as a sole metric of volume status. However, in this respect, we also noted in companion analyses that only derived extracellular water and the ratio of derived extracellular/total body water were significantly associated with a higher post-dialysis systolic BP, providing some modicum of reassurance of the presence of the relationship of hypervolemia with postdialysis BP.

Objective measures of volume status have been promulgated as superior to clinical examination.[32] A systematic review and meta-analysis of randomized trials of technology-assisted target weight reductions (published in 2019) reported some benefit of technology-related interventions in relation to reduction in systolic BP, with a lower risk of hospitalization in subgroup analyses of bioimpedance studies. However, there was a large degree of heterogeneity and risk of bias with many of the studies, which were generally underpowered for hospitalization and mortality-related outcomes.[18] More recently, the open-label Lung Water by Ultrasound Guided Treatment in Hemodialysis Patients trial tested a lung ultrasound-guided treatment strategy versus usual care, reporting relief of lung congestion, but a nonsignificant reduction in the composite of all-cause death, nonfatal myocardial infarction, or decompensated heart failure (hazard ratio 0.88; 95% CI, 0.63 to 1.24). However, this trial under-recruited and overestimated the potential risk reduction in determining the original sample size calculations, necessitating caution in the interpretation of the primary results. Indeed, there were fewer intradialytic hypotensive events in the intervention arm compared with standard care, suggesting that data from objective volume assessment may lead to provider responses (*e.g.*, lengthening of HD sessions) that promote hemodynamic stability.[32] Some have commented on the variability of the relationship of BP and volume among patients receiving HD,[33] while others have reported that the association of extremes of pre-dialysis systolic BP with clinical outcomes may differ according to the concomitant volume status.[34,35] In the context of our current results, whether such objective volume assessments can be used to target patients at

risk of intradialytic hypertension with the goal of improving clinical outcomes remains to be seen.

There are several strengths to our study, including the availability of repeated measures of bioimpedance and BP, which were carefully collected in the setting of a randomized controlled trial, and the ability to adjust for several potential confounders that were also time-updated. However, our study has several important limitations. The FHN Daily Trial was not designed to test the association of bioimpedance measures with BP changes, and despite multivariable adjustment, the potential for residual confounding remains. Data regarding the exact timing of BP measurements and peri-HD medication use were lacking, as were post-HD bioimpedance measurements and changes in plasma osmolality, which limited our ability to assess the association of changes in these parameters with changes in BP. There are also limitations in the generalizability of our findings to non-North American patient populations and to those not represented within the inclusion/exclusion criteria of the FHN Daily Trial.

In conclusion, we observed that shorter pre-HD vector length was associated with higher post-HD systolic BP, a higher odds of intradialytic hypertension, and a lower risk of intradialytic hypotension among patients enrolled in the FHN Daily trial. Whether population-based or individualized vector lengths could be used to guide the volume and pace of ultrafiltration and associated outcomes will require prospective testing, preferably in an adequately powered randomized clinical trial.

Disclosures

G.M. Chertow reports consultancy for Akebia, Ardelyx, AstraZeneca, Calico, Gilead, Miromatrix, Reata, Sanifit, Unicycive, and Vertex; ownership interest in Ardelyx, CloudCath, Durect, DxNow, Eliaz Therapeutics, Outset, Physiowave, PuraCath, Renibus, and Unicycive; research funding from CSL Behring, NIAID, and NIDDK; advisory or leadership roles for Satellite Healthcare Board of Directors and as a Co-Editor of *Brenner & Rector's The Kidney* (Elsevier); and other interests or relationships with DSMB service: Bayer, Gilead, Mineralys, NIDDK, and ReCor. G.M. Chertow served as Chair or Co-Chair of Trial Steering Committees with Akebia, AstraZeneca, CSL Behring, Sanifit, and Vertex. He has served as an advisor to CloudCath, Durect, Eliaz Therapeutics, Miromatrix, Outset, Physiowave, Renibus, and Unicycive. He has served on Data Safety Monitoring Boards with Bayer, Mineralys, and ReCor. Y.M.K. Farag reports employment with Bayer US, LLC. F.R. Mc Causland reports consultancy for GlaxoSmithKline and Zydus Therapeutics Inc.; research funding paid to institution from Advanced Medical, Fifth Eye, Lexicon, NIH, Novartis, and Satellite Healthcare; and expert witness fees from Rubin Anders Scientific. K.S. Ravi reports research funding from the NIH (K23 DK127248). K.S. Ravi's spouse reports ownership interest in Halo LLC. The remaining author has nothing to disclose.

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Data Sharing Statement

Anonymized data created for the study are or will be available in a persistent repository upon publication.

Supplemental Material

This article contains the following supplemental material online at http://links.lww.com/CJN/B835.

Supplemental Table 1. Baseline characteristics of included study participants and those excluded for lack of bioelectrical impedance analysis (BIA) data.

Supplemental Table 2. Association of vector length with development of intradialytic hypertension (any increase >10 mm Hg from pre- to post-dialysis systolic BP).

Supplemental Table 3. Association of vector length with nadir intradialytic systolic BP.

Supplemental Table 4. Association of vector length with development of intradialytic hypotension.

Supplemental Table 5. Association of intracellular water and extracellular water with outcomes on interest.

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Association of changes in vector length with changes in left ventricular mass among patients on maintenance hemodialysis: A secondary analysis of the Frequent Hemodialysis Network Daily Trial

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ABSTRACT

Background and hypothesis:
Hypervolemia is thought to be a major contributor to higher left ventricular mass (LVM), a potent predictor for cardiovascular mortality among patients on maintenance hemodialysis. We hypothesized that a decrease in vector length over time (a bioimpedance proxy of worsening hypervolemia) would be associated with an increase in LVM.

Methods:
Using data from the Frequent Hemodialysis Network Daily Trial (n=160) we used linear regression to assess the association of changes in vector length from baseline to month 12 with changes in magnetic resonance imaging (MRI) measures of LVM and other cardiac parameters. We adjusted models for the randomized group, baseline vector length, age, sex, race, body mass index, vascular access, dialysis vintage, hypertension, heart failure, diabetes, residual kidney function, pre-dialysis systolic blood pressure (BP), ultrafiltration rate, serum-dialysate sodium gradient, hemoglobin, phosphate, angiotensin-converting enzyme inhibitor or angiotensin receptor blocker use, log-transformed erythropoietin dose, and equilibrated Kt/V.

Results:
The mean age was 50 $\pm$13 years; 35% were female. In the fully adjusted models, a decline in vector length (per 50 Ω/m; i.e., increase in volume) was associated with a 6.8 g (95%CI -0.1, 13.7) and 2.6 g/m2 (95%CI -1.2, 6.3) increase in LVM and LVM index, respectively; and an increase of 15.0 mL (95%CI 7.5, 22.4), 7.3 mL (95%CI 3.0, 12.7), 7.8 mL (95%CI 3.0, 12.7), and -0.9 % (95%CI -3.1, 1.3) in left ventricular (LV) end-diastolic volume (LVEDV), end-systolic volume (LVESV), stroke volume (LVSV), and ejection fraction (LVEF), respectively. The lowest tertile of change in vector length (i.e., greater increase in volume) was associated with greater increases in LVEDV and LVSV, versus the highest tertile. There was no evidence of heterogeneity by randomized group.

Conclusions:
Change in vector length over 12 months, a bioimpedance-derived proxy of volume status, was inversely associated with indices of left ventricular mass and volume measured by cardiac MRI in patients randomized to conventional or frequent hemodialysis over 12 months.

INTRODUCTION

Cardiovascular disease remains the leading cause of mortality among patients with end-stage kidney disease (ESKD) receiving maintenance hemodialysis (HD), accounting for around 40% of deaths. [1]

Cardiac structural abnormalities tend to accumulate with the progression of chronic kidney disease, such that left ventricular hypertrophy (LVH) is estimated to affect 75% of patients initiating maintenance HD therapy.[2–4] LVH and higher left ventricular mass (LVM) are potent predictors of cardiovascular mortality among patients receiving maintenance HD,[5,6] while observational data suggests that regression of LVH is associated with lower mortality. [3] Similarly, higher left ventricular volume is a powerful independent predictor of death in patients with structural heart disease.[7,8]

Hypervolemia, estimated to affect 56-73% of patients receiving maintenance HD,[9] is thought to contribute to changes in left ventricular structure and function. [10] Clinical assessment of volume status has inherent limitations,[11] while data regarding the association of more objective measures of volume status (and changes over time) with sensitive measurements of cardiac indices (cardiac magnetic resonance imaging [MRI]) remain sparse.

Therefore, using detailed data from Frequent Hemodialysis Network (FHN) Daily Trial, we tested the hypothesis that changes in vector length, a bioimpedance-derived proxy of volume status, are associated with changes in left ventricular structure and function assessed by cardiac magnetic resonance imaging (MRI). Further, we tested if the associations differed according to the randomized treatment arm (6/week vs. 3/week hemodialysis).

METHODS

Study design and population

FHN Daily Trial was a multicenter, randomized, parallel-group trial comparing frequent (6/week), to conventional (3/week) in-center HD, conducted in the United States and Canada.

Patients undergoing maintenance HD were considered for enrollment if they were at least 13 years old, attained a mean equilibrated Kt/V urea value greater than 1.0 during their last two baseline HD sessions, and had a body weight exceeding 30 kg. Notable factors that led to exclusion from the trial were inadequate treatment adherence, an inability to use heparin, residual urea clearance >3 ml/min per 35 L, undergoing HD for fewer than three months, and being unable to undergo cardiac MRI.

The study design and protocol, [12,13] primary results,[14] and results of several secondary analyses of the FHN Daily Trial have been published.[15–17] The protocol was approved by Institutional Review Boards at each participating center and written informed consent was obtained from all study participants. We obtained data for the present analyses from the NIDDK data repository.

Two co-primary composite outcomes were assessed in the original trial: 1) death or change (from baseline to 12 months) in left ventricular mass; 2) death or change (from baseline to 12 months) in the physical health composite score of the RAND 36-item health survey.

Exposure variables

We considered changes in vector length from baseline to the end of the follow-up period (month 12 – month 0), as the primary exposure of interest. These measurements were obtained with single-frequency (50 Hz) bioelectrical impedance analysis, using the Hydra 4200 Bioimpedance Analyzer (San Diego, CA, USA) just before a mid-week HD session with the patient in a recumbent position for those with at least one intact leg and arm; however, a minority of BIA assessments were performed on other days or after HD. We calculated vector length indexed to height in meters (Z/H) from the raw measurements of resistance (R) and reactance (Xc), where R represents the opposition to the flow of an alternating current through ionic solutions and Xc is the capacitance produced by interfaces across tissues (e.g., cell membranes), according to the following formula: $|Z/H| = \sqrt{[(R/H)^2 + (Xc/H)^2]}$. [18,19]

We considered the change in vector length in both a continuous and categorical (tertiles) fashion. A positive value for the change in vector length reflects a decrease in soft tissue hydration from baseline to month 12; conversely, a negative value reflects an increase in soft tissue hydration from baseline to month 12. The highest tertile of change was chosen as the reference; the lowest tertile of change therefore reflects an increase in soft tissue hydration from baseline to month 12.

Outcomes

The primary outcome of interest was the change in left ventricular mass (LVM), as assessed by cardiac MRI from baseline to 12 months after randomization. Secondary outcomes included the changes from baseline to 12 months in left ventricular mass index (LVMI), left ventricular end-

diastolic volume (LEDV), left ventricular end-systolic volume (LVESV), left ventricular stroke volume (LSV), and left ventricular ejection fraction (LVEF).

Cardiac MRI was performed using the 1.5-Tesla MRI systems (minimum gradient performance: peak strength ≥12 mT/m, slew rate ≥40 mTm/s) with dedicated surface coils. Standardized protocols were utilized across centers, with central and blinded review of acquired images. [14,15] Myocardial volume (excluding papillary muscles) was measured on end-diastolic frames using validated software. The derived volume was multiplied by the specific density of the myocardium (1.05 g/cm^3) to calculate LVM,[15] and indexed to body surface area using the formula of DuBois and DuBois.[20]

Statistical analyses

We examined continuous variables graphically and reported values as means (± standard deviations) for normally distributed data, or medians [25th, 75th percentiles] for non-normally distributed data. We examined categorical variables by frequency distribution and reported values as proportions. We compared baseline characteristics across tertiles of the change in vector length using tests for trend based on linear regression, χ^2 trend test, and the Cuzick nonparametric trend test, as appropriate for data distribution.

We assessed the association of the change in the vector length with change in left ventricular indices from baseline to month 12 using unadjusted and adjusted linear regression models. The multivariable model adjusted for randomized treatment assignment, pre-dialysis systolic BP, baseline vector length, age, sex, self-reported race, Quételet (body mass) index (BMI),

vascular access type (arteriovenous fistula, graft, or tunneled catheter), dialysis vintage (<2, 2-5, >5 years), hypertension, heart failure, diabetes, residual kidney function (0, ≤1, >1 to 3, >3 ml/min), hemoglobin, serum phosphorus, ultrafiltration rate, angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) use, log-transformed erythropoietin dose, and equilibrated Kt/V. For each separate cardiac MRI parameter, the corresponding baseline measurement was included in the multivariable model. A further model was considered that additionally adjusted for serum sodium to dialysate gradient – this was considered as an exploratory sensitivity analysis, as data were missing from 27% of sessions. Other covariates had complete data, apart from one missing hemoglobin value. As all models considered the change from baseline to month 12 for the exposure and outcome and adjusted for baseline covariates, there was no violation of the assumption of independence of observations, allowing the use of linear regression models. Non-linearity was assessed via restricted cubic splines. Effect modification according to the randomized treatment arm was assessed by the inclusion of cross-product terms in the adjusted model.

We conducted all analyses at an alpha level of 0.05, without correction for multiple hypothesis testing, using Stata MP (version 16.0, Stata Corp., College Station, Texas).

RESULTS

Baseline characteristics

A total of 160 (65%) of the original 245 patients had cardiac MRI and bioimpedance data at baseline and 12 months and were included in the present analyses (Figure 1). A comparison of the baseline characteristics of included versus excluded patients is presented in Supplementary Table S1.

Of the patients included in the present analyses, at baseline, the mean age was 50 ±13 years, 35% were women, and 39% had diabetes mellitus. At baseline, those in the lowest tertile of change in vector length (i.e., largest increase in volume from baseline to 12 months) were more likely to be older, have higher hemoglobin, be randomized to 3/week HD, have lower ultrafiltration rates, and were less likely to have hypertension (Table 1). There were no major differences in the cardiac MRI parameters at baseline or 12 months across the tertiles of change in vector length (Table 2).

Association of change in vector length with changes in LVM and LVMI

The median change in vector length from baseline to month 12 was +5 [-20, +34] Ω/m. In unadjusted analysis, a more pronounced decline in vector length from baseline to month 12 (per 50 Ω/m; i.e., generally corresponding to an increase in volume) was associated with an increase in LVM (10.1; 95%CI 4.6, 15.6 g) and LVMI (5.1; 95%CI 2.1, 8.0 g/m^2). In fully adjusted models, these associations were attenuated: LVM (6.8; 95%CI -0.1, 13.7 g) and LVMI (2.6; 95%CI -1.2, 6.3 g/m^2) per 50 Ω/m decline in vector length from baseline to 12 months (Table 3). In additional

analyses adjusting for sodium gradient, effect estimates were accentuated: LVM (13.5; 95%CI 4.2, 22.7 g) and LVMI (5.5; 95%CI 0.6, 10.5 g/m^2) per 50 Ω/m decline in vector length from baseline to 12 months (Supplementary Table S2).

In the unadjusted categorical analyses, an inverse association was observed between change in vector length with change in LVM and LVMI from baseline to month 12 (Table 3). However, these associations only approached statistical significance for LVM in the fully adjusted models that included adjustment for serum-to-dialysate sodium gradient (Supplementary Table S2).

Association of change in vector length with the changes in LVEDV, LVESV, LVSV, and LVEF

In adjusted analyses, a more pronounced decline in vector length from baseline to month 12 (per 50 Ω/m; i.e., increase in volume) was associated with an increase from baseline to month 12 in LVEDV, LVESV, and LVSV, but not with changes in LVEF (Table 3). There was no evidence for a non-linear association of change in vector length with change in LVM, LVMI, LVEDV, LVESV, LVSV, or LVEF (P for non-linearity=0.18, 0.32, 0.19, 0.10, 0.85, and 0.73, respectively; Supplementary Figure 2). Similar patterns were noted in models where the change in vector length was considered as a categorical variable and in models that additionally adjusted for serum-to-dialysate sodium gradient (Table 3 and Supplementary Table S2).

Assessment for differential associations according to randomized treatment arm

In the fully adjusted model, there was no evidence for effect modification of the association of changes in vector length with LVM, LVMI, LVEDV, LVESV, LVSV, or LVEF (P-interaction=0.67, 0.39,

0.74, 0.63, 0.23, and 0.22, respectively). Sub-group analyses according to the randomized treatment arm are presented in Supplementary Table S3.

DISCUSSION

In this post hoc analysis of the FHN Daily Trial, we observed that decreases in vector length from baseline to 12 months, a proxy for volume expansion, were associated with increases in cardiac MRI determinations of LVM and indices of LV volume over the same period. These associations were not modified by the randomized treatment assignment of 6/week versus 3/week HD.

Cardiac structural abnormalities are common among patients initiating maintenance HD, with prior echocardiographic studies estimating that around 75% of patients meet the criteria for LVH, 36% had evidence for LV dilatation, and 15% had evidence of systolic dysfunction.[2] Somewhat similar estimates of LVH prevalence of 64% have been documented using cardiac MRI, [21] which is widely recognized to provide more accurate assessments of cardiac dimensions than echocardiography in this patient population.[22] Importantly, LVH and higher LVM are potent predictors of mortality among patients receiving maintenance HD.[23,24] As such, changes in LVM have sometimes been considered as potentially modifiable surrogate endpoints for clinical trials (including as a co-primary endpoint for the FHN Daily trial). [14]

Although there are many potential etiologies for the development of higher LVM and other cardiac structural changes among patients receiving HD, [25] unremitting hypervolemia is thought to play a major role, [10,26] and has itself been independently associated with hospitalization and cardiovascular-related mortality.[27] A prior study of prevalent patients (maintenance HD for >3 months; n=246) reported that higher end-diastolic volume, pre-HD systolic BP, and calcium-phosphate product were independent predictors of LVH and higher LVMI.[21] The observation that higher EDV was the strongest predictor of LVH and LVMI is

consistent with the contention that sustained hypervolemia results in maladaptive responses of the LV in the setting of kidney failure.

To date, few studies have examined the association of bioimpedance-proxies of volume status with echocardiographic or cardiac MRI assessments of cardiac structure and function among patients with kidney failure. One modest-sized cross-sectional study of Italian patients on maintenance HD (n=110) reported that higher extracellular water (derived from bioimpedance measurements) was independently and directly correlated with LVMI, assessed by echocardiography.[28] Other cross-sectional observational studies in patients with stage V CKD, but not yet on HD, have reported similar findings.[29,30] Our present findings therefore expand the knowledge base in this regard, supporting the notion that changes in vector length over a 12-month period are significantly associated with changes in cardiac MRI parameters of LV mass and volume.

The primary results of the FHN Daily trial demonstrated that frequent HD (compared with conventional, thrice-weekly HD) resulted in a relative reduction in LVM. [14] A post hoc analysis of FHN also reported that randomization to 6/week HD resulted in more profound reduction in LVEDV, compared with 3/week HD.[31] Further, they observed that these effects differed by residual urine volume and were most apparent among those with urine volume ≤100 mL/day vs >100 mL/day (-14.2 mL vs -3.25 mL, respectively; P-interaction=0.02). One of the hypotheses put forward to explain these observations was related to improved overall volume status, which was also suggested from a smaller randomized cross-over trial of daily versus thrice-weekly HD, where concomitant reductions in bioimpedance metrics of extracellular volume and LVM were noted.[32] Our present results support this hypothesis and, as evidenced by the lack of differential

associations according to the randomized treatment arm, additionally suggest that the modality by which optimization of volume is achieved may not be paramount. In this respect, given the association of higher dialysate sodium with inter-dialytic weight gain on one hand and a lower risk of intra-dialytic hypotension on the other hand, [33] it is notable that the effect estimates were more pronounced in models that adjusted for the serum-to-dialysate sodium gradient. However, a prior randomized controlled trial of conventional versus lower dialysate sodium (140 vs. 135 mmol/L) did not report any differences in cardiac MRI-assessed LVMI over 12 months, highlighting the need for further research in this area. [34]

The strengths of our study include the availability of repeated measures of bioimpedance and cardiac MRI performed in the setting of a randomized controlled trial. Further, we were able to perform multivariable-adjusted models to account for potential confounders, including ultrafiltration rates and the serum-to-dialysate sodium gradient. However, there were several limitations to consider. These include the potential for residual confounding and risk of false positive results from multiple testing in this post hoc observational analysis, lack of detailed information on dietary sodium intake and sodium balance, and lack of data on natriuretic peptides. Further limitations relate to the generalizability of our findings to patients beyond those included in the FHN Daily Trial, who by virtue of their willingness to be randomized into a trial potentially requiring a more burdensome and time-consuming therapy, were likely different from the general HD population. Lastly, despite several strengths, bioimpedance still requires a degree of technical and interpretative expertise and remains an imperfect biomarker of true volume status, necessitating some caution in the extrapolation of the present results to contemporary clinical practice.

In conclusion, among patients in the FHN Daily trial, we observed that decreases in vector length from baseline to 12 months were associated with increases in cardiac MRI parameters of LV mass and volume over the same period. These findings did not differ according to the randomized treatment arm, suggesting that improved volume control may be a potential mechanism for improvements in cardiac structure and function.

DATA AVAILABILITY STATEMENT

We obtained data for the present analyses from the NIDDK data repository.

AUTHORS' CONTRIBUTIONS

Research idea and study design: EE, FMC; Data acquisition: GC; Data analysis/interpretation: EE, YF, KSR, GC, FMC; Statistical analysis: EE, FMC; Supervision or mentorship: GC, FMC; and all authors revised the paper and approved the final version of the manuscript.

DISCLOSURES

Dr. Elsayed has nothing to disclose.

Dr. Farag reports employment at Bayer US, LLC which is not related to this study.

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Dr. Chertow has served on the Board of Directors of Satellite Healthcare, a non-profit dialysis provider. He has served as Chair or Co-Chair of Trial Steering Committees with Akebia, AstraZeneca, CSL Behring, Sanifit, and Vertex. He has served as an Advisor to CloudCath, Durect, Eliaz Therapeutics, Miromatrix, Outset, Physiowave, Renibus, and Unicycive. He has served on Data Safety Monitoring Boards with Bayer, Mineralys, and ReCor.

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Table 1. Baseline characteristics according to categories of change in vector length

Characteristic	Categories of change in vector length (Ω/m) from baseline to month 12			
	Tertile 1 **-41 ±26 Ω/m** (n=54)	**Tertile 2** **4 ±10 Ω/m** (n=53)	**Tertile 3** **54 ±27 Ω/m** (n=53)	**P-trend**
Baseline vector length, Ω/m	315 ± 65	276 ± 63	261 ± 55	<0.001
Age, yrs	51 ± 14	53 ± 14	45 ± 9	0.03
Gender, n (%)				0.59
- **Female**	21 (39 %)	17 (32 %)	18 (34 %)	
Race or Ethnic group, n (%)				0.89
- **Native American, Aboriginal Canadian, Alaskan Native, or First Nation**	1 (1.9 %)	3 (5.7 %)	2 (3.8 %)	
- **Asian**	4 (7.4 %)	2 (3.8 %)	7 (13.2%)	
- **Native Hawaiian or another Pacific Islander**	0 (0.0 %)	1 (1.9 %)	2 (3.8 %)	
- **Black**	28 (51.9%)	26 (49.1%)	18 (34.0%)	
- **White**	14(25.9%)	18 (34.0%)	17 (32.1%)	
- **Multiracial, unknown or not reported**	7 (13.0%)	3 (5.7 %)	7 (13.2%)	
BMI, kg/m^2	27.3 ± 6.9	27.7 ± 6.6	26.5 ± 6.2	0.54
Dialysis Access, n (%)				0.02
- **Graft**	15 (28.3%)	5 (9.4 %)	6 (11.5%)	
- **Fistula**	31 (58.5%)	36 (67.9%)	34 (65.4%)	
- **Catheter**	7 (13.2%)	12 (22.6%)	12 (23.1%)	
Duration of ESKD, n (%)				0.86
- **< 2 years**	11 (20.4%)	23 (43.4%)	13 (24.5%)	
- **2-5 years**	23 (42.6%)	10 (18.9%)	17 (32.1%)	
- **> 5 years**	20 (37.0%)	20 (37.7%)	23 (43.4%)	

Coexisting Medical Conditions, n (%)				
- **Hypertension**	47 (87.0%)	48 (90.6%)	52 (98.1%)	0.04
- **Heart Failure**	11 (20%)	9 (17%)	11 (21%)	0.96
- **Diabetes Mellitus**	22 (40.7%)	20 (37.7%)	20 (37.7%)	0.75
KrU, n (%)				0.54
- **Anuria**	35 (64.8%)	30 (56.6%)	39 (73.6%)	
- **> 0- 1 ml/min**	11(20.4%)	7 (13.2%)	5 (9.4 %)	
- **> 1- 3 ml/min**	8 (14.8%)	15 (28.3%)	8 (15.1%)	
- **> 3 ml/min**	0 (0.0 %)	1 (1.9 %)	1 (1.9 %)	
Pre-dialysis systolic blood pressure, mmHg	146 ± 17	150 ± 20	147 ± 18	0.79
Pre-dialysis laboratory results:				
- Hemoglobin, mg/dL	12.3 ± 1.3	12.0 ± 1.2	11.8 ± 1.2	0.05
- Serum Phosphate, mg/dL	5.6 ± 1.6	5.6 ± 1.8	6.1 ± 1.4	0.11
Kt/V Equilibrated	1.43 ± 0.27	1.40 ± 0.28	1.44 ± 0.24	0.76
Ultrafiltration rate, mL/kg/hour	11.4 ± 3.4	11.9 ± 4.0	12.9 ± 4.5	0.05
Sodium gradient, mmol/L	-2 [-4, -0]	-1 [-4, 1]	-2 [-6, 1]	0.88
ACEi or ARB use, n(%)	25 (46.3%)	19 (35.8%)	34 (64.2%)	0.07
Erythropoietin dose, Units	9862 [4500, 21000]	6400 [2700, 18750]	8500 [3275, 12125]	0.26
Randomized to 6/week HD, n(%)	21(38.9%)	27(50.9%)	38 (71.7%)	<0.001

Results are presented as mean ± standard deviation, or median [25th-75th percentiles] for continuous variables.

Abbreviations: BMI, body mass index; ESKD, end-stage kidney disease; KrU, residual renal urea clearance; BP, blood pressure; HD, hemodialysis; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker

Table 2. Baseline and 12-month cardiac MRI parameters according to categories of change in vector length

Characteristic	Categories of change in vector length (Ω/m) from baseline to month 12			
	Tertile 1 **-41 ±26 Ω/m** (n=54)	**Tertile 2** **4 ±10 Ω/m** (n=53)	**Tertile 3** **54 ±27 Ω/m** (n=53)	**P-value**
LV Mass, g				
Baseline	137 ± 46	143 ± 57	149 ± 64	0.54
Month 12	132 ± 47	133 ± 57	129 ± 46	0.91
LV Mass Index, g/m^2				
Baseline	71 ± 23	73 ± 29	80 ± 32	0.28
Month 12	68 ± 24	68 ± 28	70 ± 25	0.92
LV End-Diastolic Volume, mL				
Baseline	173 ± 53	171 ± 60	184 ± 60	0.42
Month 12	171 ± 42	164 ± 58	155 ± 42	0.22
LV End-Systolic Volume, mL				
Baseline	78 ± 40	72 ± 32	81 ± 38	0.43
Month 12	75 ± 32	71 ± 35	64 ± 26	0.19
LV Stroke Volume, mL				
Baseline	94 ± 26	99 ± 35	103 ± 36	0.37
Month 12	96 ± 26	93 ± 31	91 ± 23	0.60
LV Ejection Fraction, %				
Baseline	56 ± 11	59 ± 9	57 ± 11	0.40
Month 12	57 ± 11	58 ± 10	60 ± 8	0.44

Abbreviations: LV, left ventricle

Table 3. Association of change in vector length with change in cardiac MRI parameters

		Change in outcome from baseline to month 12 according to change in vector length (95%CI)					
Outcomes	**Model**	**Per 50 Ohm/m decrease in vector length**	**P- value**	**Tertile 1**	**Tertile 2**	**Tertile 3**	**P-trend**
LVM, g	Unadjusted	10.1 (4.6, 15.6)	<0.001	15.0 (2.7, 27.3)	9.3 (-3.1, 21.6)	Ref	0.02
	Adjusted	6.8 (-0.1, 13.7)	0.05	6.5 (-8.2, 21.1)	7.0 (-6.3, 20.3)	Ref	0.37
LVMI, g/m^2	Unadjusted	5.1 (2.1, 8.0)	0.001	6.7 (0.2, 13.3)	4.3 (-2.3, 10.9)	Ref	0.04
	Adjusted	2.6 (-1.2, 6.3)	0.17	0.5 (-7.4, 8.4)	2.2 (-5.1, 9.4)	Ref	0.89
LVEDV, mL	Unadjusted	16.3 (9.2, 23.4)	<0.001	27.5 (11.6, 43.4)	23.3 (7.4, 39.3)	Ref	0.001
	Adjusted	15.0 (7.5, 22.4)	<0.001	25.4 (9.3, 41.6)	15.6 (0.9, 30.3)	Ref	0.002
LVESV, mL	Unadjusted	9.4 (4.7, 14.0)	<0.001	13.4 (2.9, 23.9)	15.8 (5.3, 26.3)	Ref	0.01
	Adjusted	7.3 (1.9, 12.7)	0.01	9.2 (-2.5, 20.8)	9.5 (-1.0, 20.0)	Ref	0.11
LVSV, mL	Unadjusted	6.9 (2.2, 11.6)	0.004	14.1 (3.7, 24.4)	7.5 (-2.9, 17.9)	Ref	0.01
	Adjusted	7.8 (3.0, 12.7)	0.002	15.8 (5.5, 26.1)	6.7 (-2.7, 16.0)	Ref	0.003
LVEF, %	Unadjusted	-1.7 (-3.4, 0.1)	0.06	-1.8 (-5.6, 2.0)	-3.1 (-6.9, 0.7)	Ref	0.36
	Adjusted	-0.9 (-3.1, 1.3)	0.41	-0.3 (-4.9, 4.3)	-0.9 (-5.1, 3.2)	Ref	0.89

The multivariable model adjusted for baseline vector length, baseline outcome, randomized treatment assignment, age, sex, race, body mass index, access type, vintage (<2, 2-5, >5 years), pre-dialysis systolic BP, hypertension, heart failure, diabetes, residual urea clearance (0, ≤1, >1 to 3, >3 ml/min), hemoglobin, phosphate, ultrafiltration rate, angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) use, log-transformed erythropoietin dose, and equilibrated Kt/V.

Abbreviations: LVMI, left ventricular mass index; LVM, left ventricular mass; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVSV, left ventricular stroke volume; LVEF, left ventricular ejection fraction.

Supplementary Table S1. Baseline characteristics of included and excluded participants

Characteristic	Included participants n=160	Excluded participants n=85	P-value
Age, yrs	50 ±13	51 ±15	0.52
Female, n(%)	56 (35.0%)	38 (44.7%)	0.14
Race or Ethnic group, n (%)			0.18
- **Native American, Aboriginal Canadian, Alaskan Native, or First Nation**	6 (3.8%)	2 (2.4%)	
- **Asian**	13 (8.1%)	3 (3.5%)	
- **Native Hawaiian or another Pacific Islander**	3 (1.9%)	1 (1.2%)	
- **Black**	72 (45.0%)	30 (35.3%)	
- **White**	49 (30.6%)	40 (47.1%)	
- **Multiracial, unknown or not reported**	17 (10.6%)	9 (10.6%)	
BMI, kg/m^2	27.2 ± 6.6	28.3± 7.0	0.19
Dialysis Access, n (%)			0.69
- **Graft**	26 (16.5%)	17 (21.0%)	
- **Fistula**	101 (63.9%)	49 (60.5%)	
- **Catheter**	31 (19.6%)	15 (18.5%)	
Duration of ESKD, n (%)			
- **< 2 years**	47 (29.4%)	18 (21.2%)	0.37
- **2-5 years**	50 (31.3%)	31 (36.5%)	
- **> 5 years**	63 (39.4%)	36 (42.4%)	
Coexisting Medical Conditions, n (%)			
- **Hypertension**	147 (91.9%)	72 (84.7%)	0.08
- **Heart Failure**	31 (19.4%)	18 (21.2%)	0.74
- **Diabetes Mellitus**	62 (38.8%)	38 (44.7%)	0.37
KrU, n (%)			0.57
- **Anuria**	104 (65.0%)	58 (68.2%)	
- **> 0- 1 ml/min**	23 (14.4%)	14 (16.5%)	

- **> 1- 3 ml/min**	31 (19.4%)	11 (12.9%)	
- **> 3 ml/min**	2 (1.3%)	2 (2.4%)	
Pre-dialysis Systolic BP, mmHg	148 ± 18	145 ± 17	0.22
Pre-dialysis laboratory measurements			
- **Hemoglobin, g/dL**	12.0 ±1.3	11.8 ± 1.3	0.10
- **Phosphorus, mg/dL**	5.8 ± 1.6	5.7 ± 1.7	0.76
Equilibrated Kt/V urea	1.4 ± 0.3	1.4 ± 0.3	0.69
Ultrafiltration rate, mL/kg/hour	12 ± 4	11 ± 4	0.07
Sodium gradient, mmol/L	-2 [-4, 1]	-1 [-4, 1]	0.52
ACEi or ARB use, n(%)	78 (48.8%)	40 (47.1%)	0.80
Erythropoietin dose, Units	8188 [3150, 17125]	11250 [5625, 19800]	0.08
Randomized to 6/week HD, n(%)	86 (53.8%)	39 (45.9%)	0.24

*Results are presented as mean ± standard deviation, or median [25th-75th percentiles] for continuous variables.

Abbreviations: BMI, body mass index; ESKD, end-stage kidney disease; KrU, residual renal urea clearance; BP, blood pressure; HD, hemodialysis; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker

Supplementary Table 2. Association of the change in vector length with the changes in cardiac MRI indices parameters (models including adjustment for sodium gradient).

		Change in outcome from baseline to month 12 according to change in vector length (95%CI)					
Outcome	Model	Per 50 Ω/m decrease in vector length	P- value	Tertile 1	Tertile 2	Tertile 3	P-trend
LVM, g	Unadjusted	10.1 (4.6, 15.6)	<0.001	15.0 (2.7, 27.3)	9.3 (-3.1, 21.6)	Ref	0.02
	Adjusted	13.5 (4.2, 22.7)	0.01	17.6 (-1.5, 36.8)	10.3 (-5.9, 26.5)	Ref	0.06
LVMI, g/m^2	Unadjusted	5.1 (2.1, 8.0)	0.001	6.7 (0.2, 13.3)	4.3 (-2.3, 10.9)	Ref	0.04
	Adjusted	5.5 (0.6, 10.5)	0.03	5.9 (-4.3, 16.0)	4.2 (-4.4, 12.9)	Ref	0.22
LVEDV, mL	Unadjusted	16.3 (9.2, 23.4)	<0.001	27.5 (11.6, 43.4)	23.3 (7.4, 39.3)	Ref	0.001
	Adjusted	20.4 (11.2, 29.7)	<0.001	31.3 (11.7, 50.8)	15.4 (-1.2, 31.9)	Ref	0.002
LVESV, mL	Unadjusted	9.4 (4.7, 14.0)	<0.001	13.4 (2.9, 23.9)	15.8 (5.3, 26.3)	Ref	0.01
	Adjusted	10.6 (3.5, 17.8)	0.004	13.2 (-1.7, 28.0)	9.7 (-2.9, 22.2)	Ref	0.06
LVSV, mL	Unadjusted	6.9 (2.2, 11.6)	0.004	14.1 (3.7, 24.4)	7.5 (-2.9, 17.9)	Ref	0.01
	Adjusted	9.8 (3.4, 16.2)	0.003	16.9 (4.0, 29.9)	5.5 (-5.5, 16.5)	Ref	0.01
LVEF, %	Unadjusted	-1.7 (-3.4, 0.1)	0.06	-1.8 (-5.6, 2.0)	-3.1 (-6.9, 0.7)	Ref	0.36
	Adjusted	-1.1 (-4.1, 1.9)	0.48	-0.7 (-6.7, 5.4)	-1.3 (-6.4, 3.7)	Ref	0.77

The multivariable model adjusted for baseline vector length, baseline outcome, randomized treatment assignment, age, sex, race, body mass index, access type, vintage (<2, 2-5, >5 years), pre-dialysis systolic BP, hypertension, heart failure, diabetes, residual urea clearance (0, ≤1, >1 to 3, >3 ml/min), hemoglobin, phosphate, ultrafiltration rate, angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) use, log-transformed erythropoietin dose, equilibrated Kt/V, and sodium gradient.

Abbreviations: LVMI, left ventricular mass index; LVM, left ventricular mass; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVSV, left ventricular stroke volume; LVEF, left ventricular ejection fraction.

Supplementary Table 3. Association of the change in vector length with the changes in cardiac MRI indices parameters according to sub-groups of randomized treatment arm (3/week or 6/week hemodialysis).

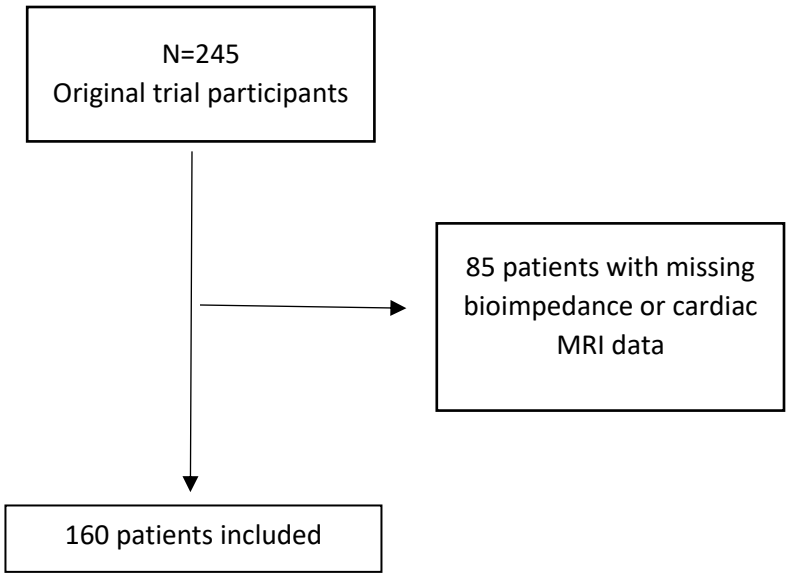
		Change in outcome from baseline to month 12 according to change in vector length (95%CI)					
Outcome	**Model**	**Per 50 Ω/m decrease in vector length**	**P-value**	**Tertile 1**	**Tertile 2**	**Tertile 3**	**P-trend**
Randomized to 3/week HD							
LVM, g	Unadjusted	7.6 (0.3, 14.9)	0.04	11.0 (-5.1, 27.2)	2.4 (-14.3, 19.2)	Ref	0.13
	Adjusted	11.3 (-2.6, 25.3)	0.11	13.8 (-13.9, 41.6)	4.3 (-22.6, 31.2)	Ref	0.30
LVMI, g/m²	Unadjusted	3.4 (-0.6, 7.5)	0.10	4.6 (-4.4, 13.5)	0.4 (-8.9, 9.7)	Ref	0.24
	Adjusted	4.9 (-2.8, 12.5)	0.21	5.5 (-9.5, 20.6)	2.0 (-12.7, 16.6)	Ref	0.44
LVEDV, mL	Unadjusted	16.0 (5.1, 26.9)	0.01	25.5 (1.2, 49.8)	7.3 (-18.0, 32.6)	Ref	0.03
	Adjusted	24.9 (9.3, 40.5)	0.003	35.9 (4.0, 67.7)	18.2 (-12.8, 49.2)	Ref	0.03
LVESV, mL	Unadjusted	8.8 (1.2, 16.4)	0.02	11.3 (-5.7, 28.3)	12.1 (-5.6, 29.8)	Ref	0.26
	Adjusted	10.6 (-1.2, 22.4)	0.08	15.4 (-7.5, 38.3)	17.3 (-4.9, 39.6)	Ref	0.21
LVSV, mL	Unadjusted	7.2 (-0.3, 14.8)	0.06	14.2 (-1.8, 30.3)	-4.8 (-21.5, 11.9)	Ref	0.03
	Adjusted	14.3 (2.6, 26.1)	0.02	20.0 (-3.3, 43.2)	1.6 (-21.2, 24.4)	Ref	0.07
LVEF, %	Unadjusted	-1.3 (-4.4, 1.7)	0.39	-1.4 (-8.0, 5.2)	-6.0 (-12.9, 0.8)	Ref	0.97
	Adjusted	0.4 (-4.4, 5.2)	0.87	-0.6 (-9.7, 8.5)	-4.5 (-13.5, 4.5)	Ref	0.98
Randomized to 6/week HD							
LVM, g	Unadjusted	9.7 (1.5, 18.0)	0.02	9.9 (-9.8, 29.7)	10.5 (-7.8, 28.7)	Ref	0.26
	Adjusted	-1.3 (-10.3, 7.7)	0.77	-8.5 (-28.2, 11.1)	-3.5 (-22.6, 15.6)	Ref	0.39
LVMI, g/m²	Unadjusted	5.2 (0.9, 9.5)	0.02	4.5 (-5.9, 14.8)	5.3 (-4.3, 14.9)	Ref	0.33
	Adjusted	-1.4 (-6.5, 3.7)	0.58	-8.1 (-19.1, 2.8)	-2.0 (-12.9, 8.9)	Ref	0.15
LVEDV, mL	Unadjusted	13.5 (3.7, 23.2)	0.01	14.3 (-8.5, 37.0)	30.9 (9.9, 52.0)	Ref	0.11
	Adjusted	7.5 (-2.0, 17.0)	0.12	13.9 (-7.7, 35.4)	12.4 (-7.8, 32.7)	Ref	0.17

LVESV, mL	Unadjusted	8.9 (2.5, 15.2)	0.01	11.2 (-3.8, 26.2)	16.8 (2.9, 30.7)	Ref	0.08
	Adjusted	2.8 (-4.0, 9.6)	0.41	2.9 (-12.4, 18.2)	3.1 (-11.3, 17.5)	Ref	0.67
LVSV, mL	Unadjusted	4.6 (-1.6, 10.8)	0.14	3.1 (-11.2, 17.3)	14.1 (0.9, 27.4)	Ref	0.45
	Adjusted	4.6 (-1.3, 10.5)	0.13	12.1 (-0.9, 25.2)	8.3 (-4.0, 20.7)	Ref	0.06
LVEF, %	Unadjusted	-1.9 (-4.1, 0.2)	0.08	-3.3 (-8.4, 1.7)	-0.8 (-5.4, 3.9)	Ref	0.21
	Adjusted	-0.5 (-3.2, 2.3)	0.73	0.4 (-5.6, 6.5)	1.8 (-3.9, 7.5)	Ref	0.84

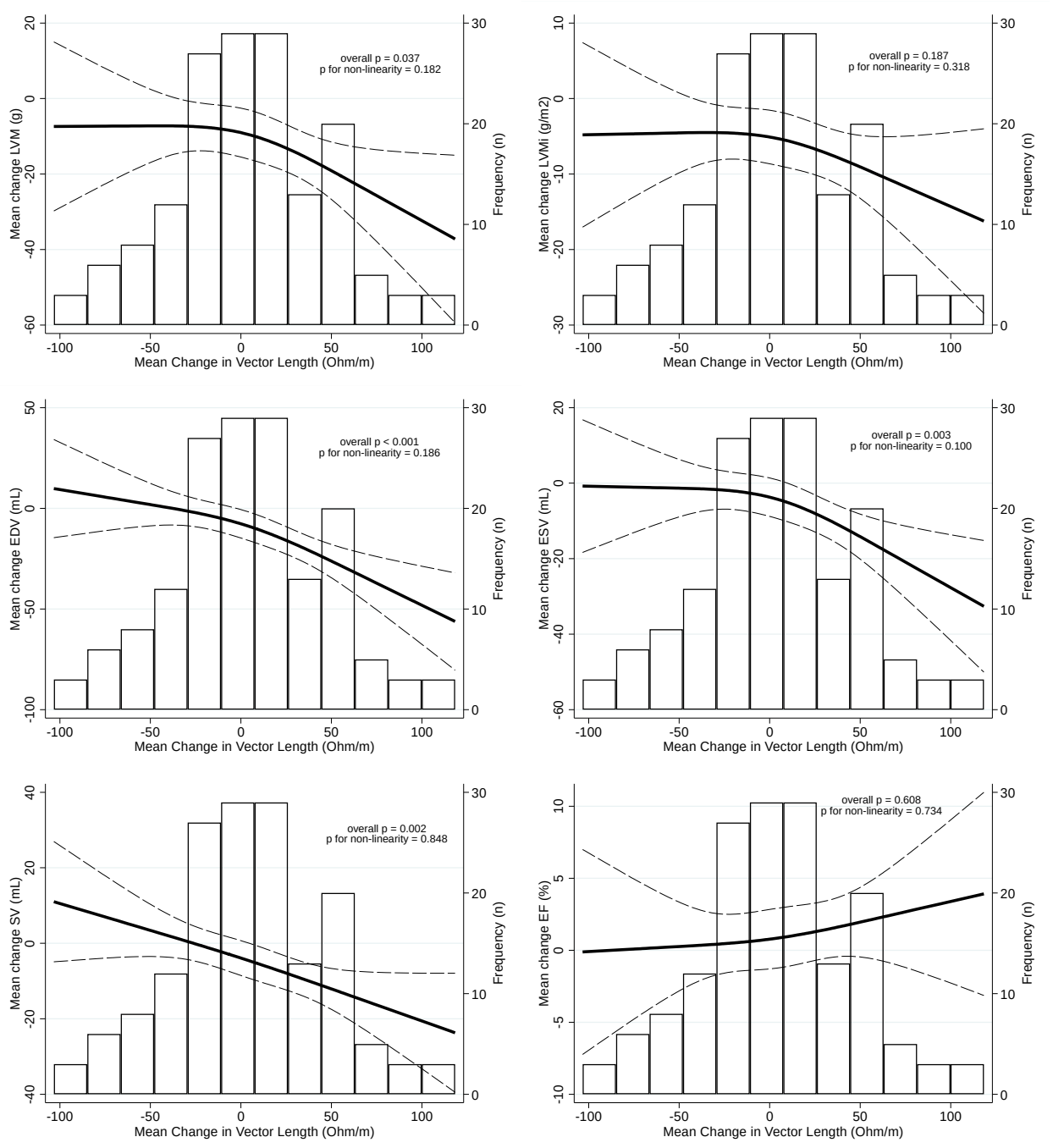
The multivariable model adjusted for baseline vector length, baseline outcome, randomized treatment assignment, age, sex, race, body mass index, access type, vintage (<2, 2-5, >5 years), pre-dialysis systolic BP, hypertension, heart failure, diabetes, residual urea clearance (0, ≤1, >1 to 3, >3 ml/min), hemoglobin, phosphate, ultrafiltration rate, angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) use, log-transformed erythropoietin dose, and equilibrated Kt/V.

Abbreviations: LVMI, left ventricular mass index; LVM, left ventricular mass; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVSV, left ventricular stroke volume; LVEF, left ventricular ejection fraction.

Figure 1. Consort diagram



Supplementary Figure 1. Restricted cubic splines showing the adjusted association of mean changes in vector length with the mean changes in cardiac MRI parameters.



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OVERALL SUMMARY

In the two papers comprising this Master's thesis, we analyzed the dataset from the FHN Daily Trial to test our hypotheses regarding the association of: 1) bioimpedance assessments of volume status (vector length) with peri-HD systolic blood pressure parameters; and 2) changes in vector length with changes in cardiac MRI indices of left ventricular mass and other metrics of cardiac structure and function.

In our first paper, we observed that shorter vector length (a proxy of hypervolemia) among patients on maintenance HD was independently associated with an increase in systolic blood pressure from pre to post-HD and with a higher risk of intradialytic hypertension, which is known to be a poor prognostic marker and associated with adverse cardiovascular outcomes in the HD population.

In our second paper, we observed that changes in pre-HD vector length were inversely associated with changes in left ventricular mass, left ventricular end-diastolic volume, left ventricular end-systolic volume, and left ventricular stroke volume, as assessed by cardiac MRI. In other words, worsening (increasing) volume status was associated with an increase in these cardiac parameters over time, suggesting the presence of a temporal association.

These findings provoke an important clinical question - could using more objective methods to assess volume status (and potentially guide the hemodialysis prescription) improve volume control and reduce maladaptive changes in cardiac structure and function? To test this, and whether this might translate into reducing cardiac morbidity and mortality among patients on maintenance hemodialysis, will require a prospective interventional study.

DISCUSSION AND PERSPECTIVES

In our study, we explored the association of hypervolemia with the occurrence of intradialytic hypertension, left ventricular hypertrophy, and other cardiac functional and structural changes among patients receiving maintenance HD. We used vector length, a bioimpedance proxy of volume status, as our exposure of interest and observed that shorter vector length was independently associated with the occurrence of intradialytic hypertension (an increase in systolic blood pressure from pre to post-HD). Furthermore, we observed that a decrease in vector length over 12 months (increasing volume overload) was associated with an increase in left ventricular mass and volume indices, which are known to be associated with cardiac morbidity and mortality among patients receiving maintenance HD.

One issue that arises is the challenge of interpreting vector length, as it is not a commonly used metric. To provide context, FHN Daily Trial participants have shorter vector length (261 Ohm/m in men, 323 Ohm/m in women) than values observed in healthy individuals (287 Ohm/m in men, 382 Ohm/m in women). These data highlight the differences in vector length and reflect increased pre-HD volume status among the HD population.[1] A second issue is the fact that vector length reflects primarily extravascular volume status, as opposed to intravascular (the latter probably having more immediate importance to the development of intra-dialytic hypotension). The Crit-Line monitor, which is a device used during hemodialysis to monitor hematocrit levels in the patient's blood continuously, can provide a surrogate of intravascular volume. Hematocrit is the proportion of red blood cells to the total blood volume and tends to increase with progressive ultrafiltration. An excessive rate of increase in hematocrit during the HD session can reflect inadequate plasma refilling, predisposing to hypotension. Despite these limitations, our data

support the hypothesis for a central role of hypervolemia with higher blood pressure and the development of intradialytic hypertension among this high-risk patient population. The temporal changes we observed highlight the possibility that intervening to optimize volume status may make a difference in clinical practice in terms of reducing the development of maladaptive changes in cardiac structure and function.

Our analyses had several strengths, which included the availability of repeated measures of bioimpedance, intra-HD blood pressure, and cardiac MRI measurements, which were carefully collected in the setting of a randomized controlled trial. Furthermore, we were able to perform several multivariable-adjusted models to account for potential confounders. However, these were all post hoc analyses and should be considered hypothesis-generating. As discussed in the papers, a major limitation relates to the possibility of residual confounding, particularly in relation to nutritional factors, and the generalizability to patients who would not have been eligible to participate in the FHN Daily Trial. Further limitations include the lack of availability of post-HD bioimpedance measurements, limiting our ability to examine pre-to-post HD changes in vector length with outcomes of interest. Furthermore, although peri-HD BP measurements were collected in the setting of a randomized controlled trial, there remains the potential for variability in such measurements. We only performed a complete case analysis – despite reasonable comparability of included and excluded patients, the potential for selection bias remains.

Despite the aforementioned limitations, our findings provide support for considering wider use of bioimpedance technology among HD patients, especially with improvements in the 'user-friendliness' of more contemporary platforms that are not as cumbersome to use and require less specialized training. Whether its use to guide blood pressure management will

translate into better cardiovascular clinical outcomes will require prospective testing in an adequately powered randomized controlled trial.

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