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Using Intradialytic Systolic Blood Pressure Slopes to Guide Ultrafiltration in Hemodialysis Patients: A Validation Study and Clinical Trial

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PROTOCOL

1. AIMS 1-3 COMMON APPROACH ELEMENTS

This project's *overall objective* is to develop a broadly applicable method to assess extracellular volume (ECV) and guide precise ultrafiltration to minimize mortality risk factors in maintenance hemodialysis (HD) patients. *Our* *central hypothesis* is that prospectively prescribing ultrafiltration based on intradialytic blood pressure slopes (IBPS) from recent treatments will be superior to standard care at reducing ambulatory blood pressure and ECV without increasing risk for intradialytic hypotension.

To test this, we will conduct an un-blinded randomized clinical trial with an embedded cross sectional study in the baseline period of the trial:

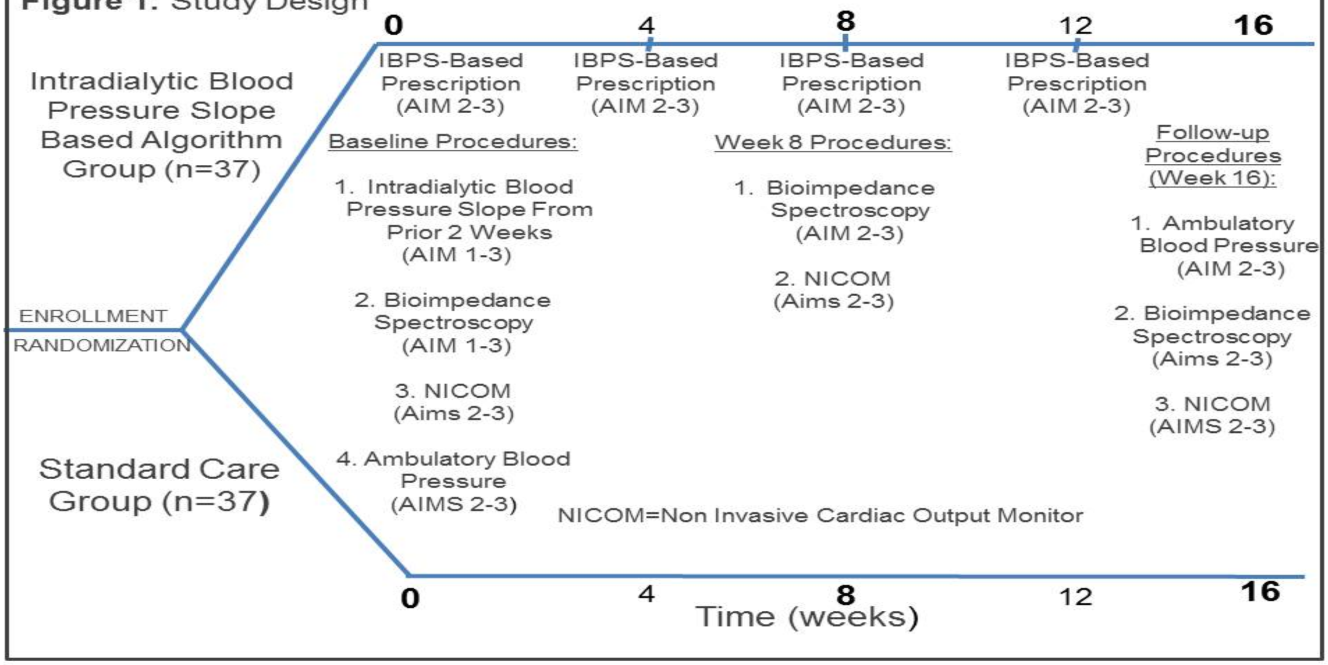
In **Aim 1**, we will implement a cross sectional study using baseline measurements from our clinical trial. We aim to establish the mean IBPS from the prior 2 weeks as a validated clinical metric for assessing ECV compared to bioimpedance spectroscopy analysis (BIA) that can be used in nearly all HD patients.

In **Aim 2**, we will conduct a randomized clinical trial comparing ultrafiltration prescriptions based on IBPS to standard care prescriptions driven by clinical determination of the individual treating nephrologist. We will establish that the IBPS guided approach more effectively modifies two primary mortality risk factors in HD patients: ambulatory blood pressure and ECV excess. We will also assess the mechanistic effect of our intervention by simultaneously measuring total peripheral resistance and cardiac index at baseline and end.

In **Aim 3**, we will analyze data from the trial in Aim 2 to determine if IBPS guided therapy is as safe as standard care by comparing the incidence of intradialytic hypotension and the intradialytic systolic blood pressure nadir.

1. A ***RESEARCH DESIGN:*** The overall design is a randomized clinical trial (**Figure 1**). An initial analysis of baseline measurements for this trial will comprise the data for Aim 1. Additional subjects who are eligible, but not interested in participating in the whole duration of the clinical trial, may participate in Aim 1 only by getting one set of measurements. Aims 2 and 3 will involve the comparison of outcomes between two assigned groups from beginning to end of the trial.

Figure 1: Study Design



<u>Patient Population:</u> We will utilize consecutive sampling to identify patients that are eligible for our study. There are approximately 500 prevalent patients in the 3 UT-Southwestern affiliated hemodialysis units at any point in time. We have contacted each individual UTSW nephrologist and obtained permission to review medical records to identify patients that meet the inclusion and exclusion criteria. Inclusion criteria are age >18 years and the presence of hypertension. We will define hypertension as a mean systolic blood pressure greater than 140 mmHg pre-dialysis or greater than 130 mmHg post-dialysis over a 2-week screening period. The pre dialysis blood pressures, post dialysis blood pressures, the lowest blood pressures, and all intradialytic blood pressure measurements are typically obtained every 30 minutes during treatment are electronically stored in the patients DaVita medical records. Exclusion criteria are in **Table 1.**

Table 1: Exclusion Criteria for Aims 1-3	
Exclusion Criteria	**Justification**
For Aims 1-3	
1. Hemodialysis Vintage <1 month	Patients that are newly started on hemodialysis do not have a dry weight that is firmly established.
2. Pregnancy	The patient will need specialized fluid removal goals beyond the parameters of our study to optimize outcome of the pregnancy
3. Nadir Systolic Blood Pressure <95 mmHg during screening	This defines patients at increased risk for mortality and highest risk for complications with additional fluid removal during dialysis. This is frequently associated with ECV-independent blood pressure during dialysis including related to advanced heart failure or autonomic neuropathy
4. Pre or Post Dialysis Systolic Blood Pressure >180 mmHg	This threshold identifies high risk patients who may need more aggressive pharmacologic therapy which will be left to the discretion of the patient's nephrologist.
5. Decrease in Systolic Blood pressure >60 mmHg from pre to post dialysis	Further increases in ultrafiltration would be increase further risk for hemodynamic instability
6. Ultrafiltration Rate >13 mL/hr/kg	In observational studies, this rate is associated with increased mortality; faster ultrafiltration may put patient at risk for increased morbidity or mortality
7. Peridialytic Midodrine Use	This can acutely influence intradialytic blood pressure in an ECV-independent way. Midodrine is used to treat intradialytic hypotension and is frequently used in patients with autonomic neuropathy
8. Intradialytic Clonidine Use	This can acutely influence intradialytic blood pressure in an ECV-independent way. This is used to treat severe hypertension during dialysis, and these patients frequently have ECV-independent etiology of hypertension, including possible medication non-adherence
9. Documented Antihypertensive Medication Non-adherence	This can acutely influence intradialytic blood pressure in an ECV-independent way.
Aim 1 Only	
10. Amputated Extremity (excluding fingers, toes, hands, or feet)	Bioimpedance measurements of extracellular water are less accurate if all 4 major limbs are not present.
11. Presence of cardiac defibrillator, pacemaker	The current from the bioimpedance electrodes may interfere with the function of these devices
12. Presence of metal prostheses	Bioimpedance measurements are less accurate if implanted metal is present

Eligible subjects agreeing to participate in all aims will be assigned to one of two study groups based on computer-generated randomization stratified by gender: IBPS-based management or Standard of Care (detailed in Aim 2). The presence of contraindications to BIA (see Table 1, #10-12) would not exclude a subject from participating in Aims 2 and 3. Such subjects would complete all study procedures except the BIA and NICOM. The outcomes of Aims 2 and 3 (ambulatory blood pressure and intradialytic hypotension) would still be ascertained. Eligible subjects not willing to undergo randomization into a 16 week trial (Aims 2-3) may participate in the BIA and measurements in Aim 1 only.

In short subjects may participate in Aim 1 only, Aims 2 and 3 only, or all Aims based on individual exclusion criteria and preference. We have successfully recruited more than 125 HD patients over the past several years for various prospective research studies and continue to maintain support from DaVita dialysis units (see Letters of Support).

<u>Study Procedures:</u> All procedures will be conducted by authorized personnel from the UT Southwestern research team consisting of the principal investigator and research nurses/coordinators.

<u>Baseline Information:</u>
Demographics and Data: Study personnel will conduct in-person interviews to ascertain medical comorbidities. Laboratory data (obtained every 1-4 weeks as part of HD unit protocol) will be obtained from the medical chart.

Intradialytic Blood Pressure Measurements: Subjects will have blood pressure measurements obtained during HD using the HD machine built-in sphygmomanometer. Measurements will be obtained every 30 minutes and more frequently in the event of hemodynamic instability. Measurements will be obtained in the non-access arm and electronically stored in patient records. We will obtain all measurements from the 6 prior treatments and use linear regression to calculate the IBPS.

Ambulatory Blood Pressure Measurement: Immediately after a mid-week HD treatment, a Spacelabs 90207 cuff will be placed on the patient's non-access arm. The first cuff inflation will occur in the HD unit, and the subject will be instructed to wear the cuff for 44 hours until the next HD treatment. The cuff will inflate every 30 minutes from 6 a.m. to 10 p.m. and every hour during the night.

Bioimpedance Spectroscopy Analysis (BIA): Bioimpedance analysis involves state of the art non-invasive measurements of extracellular water volumes in maintenance HD patients as demonstrated by comparison to bromide dilution, the gold standard ECV measurement in humans[1, 2]. Opposition to electrical current in the body is measured as reviewed in detail in Kuhlman[3]. Our device (Impedimed SFB7) calculates compartmental water volumes using Cole-Cole model plots of measured reactance and resistance at varying frequencies and using the Hanai equation[4, 5] accounting for height, weight, and sex. Our device is FDA approved to measure ECV in healthy individuals, and also measures intracellular water volumes which can then be used with ECV to provide measurements of total body water.

Impedance Cardiography: We will use bioreactance (Cheetah Non-Invasive Cardiac Output Monitor: NICOM) to obtain measurements of cardiac output (and index) and systolic blood pressure, from which total peripheral resistance (and index) will be calculated. This non-invasive procedure involves detection of intrabeat changes in voltage phase shifts following the application of electric current. The phase shift reflects the change in thoracic fluid volume with each heartbeat. Our device has been validated for measuring cardiac output in intensive care patients, patients with congestive heart failure and HD patients[6-8].

2. SPECIFIC APPROACH BY AIM

AIM 1: The premise for this aim is that there is a need to develop widely-available, easily-implementable method for accurate assessment of ECV in HD patients. The objective of this aim is to establish the association between ECV excess and IBPS from multiple treatments in hypertensive HD patients. We will test the *working hypothesis* that when measuring blood pressure every 30 minutes over 6 treatments, there will be a positive correlation between the mean systolic IBPS and the ECV/body weight measured with BIA in a cohort of 66 hypertensive HD patients. We have calculated the IBPS from a single treatment from 49 hypertensive HD patients in a more heterogeneous cohort who also have pre and post-HD BIA measurements. The median slope was -3.36 mmHg/hour (interquartile range -9 mmHg/hr, +3.5 mmHg/hour). There is a positive correlation between the IBPS and the ratio of ECV/body weight measured after HD (Pearson correlation coefficient 0.4, p=0.008). The post-HD correlation was 0.5 in men (n=32, p=0.01), but was 0.3 in the smaller group of women (n=17, p=0.2). It is necessary to demonstrate that the overall relationship between IBPS and ECV/body weight 1) persists when evaluating IBPS from multiple recent HD treatments and 2) is stronger in a more homogeneous cohort of HD patients without the extremely high or low intradialytic blood pressures that are more likely related to comorbid medical diseases than changes in ECV. It is also necessary to better define the association of this relationship with gender in a larger number of subjects with more equal distribution of men and women.

RESEARCH DESIGN AIM 1: We will use a cross sectional study design to determine the association between systolic IBPS and measurements of post-HD ECV/body weight using BIA in hypertensive HD patients. Limitations of BIA include that it cannot be used in patients with amputations or implanted metal prostheses due to inaccurate measurements. It cannot be used in pregnant individuals or those with cardiac defibrillators or pacemakers due to safety concerns. For this reason, additional exclusion criteria unique to this aim will be patients with 1) amputations of major extremity, 2) cardiac defibrillator or pacemaker, or 3) implanted metallic device (see Exclusion Criteria #10-12 above).

Study Procedures:

1. Intradialytic Blood Pressure Slope: We will obtain recorded blood pressure measurements from the prior 6 treatments. We will calculate the average systolic IBPS (mmHg/hour) using linear regression analysis. The slope will be our primary independent variable.
2. Extracellular Volume Excess: We will use whole body multifrequency BIA (Impedimed SFB7) to measure ECV, intracellular volume, and total body volume before and 20 minutes after a mid-week HD treatment. We will use the ratio of post-HD ECV/body weight (L/kg) as our primary dependent variable. This is a recognized metric for determination of ECV excess[9].

Statistical Analysis Plan and Power Calculation for Sample Size (Aim 1)

This aim's primary outcome is the correlation between mean IBPS and post-HD ECV/body weight. We will determine this with Pearson correlation analysis. In our preliminary data analysis of 49 HD patients, we demonstrated a significant association between ECV/body weight and systolic IBPS from one HD treatment ($r=0.4$, $p=0.008$). We aim to establish that an even stronger correlation exists in a more homogeneous population with less extremes of blood pressure and blood pressure changes (see Exclusion criteria 3-8 above). We also aim to establish associations within each gender. Assuming 80% power at a 0.05 significance level, we would need the following sample sizes to show the following correlations: 15 subjects for $r=0.6$, 23 subjects for $r=0.5$, 33 subjects for $r=0.4$ using Pearson correlation analysis. To confirm our assumption of normal distribution, we would need at least 30 subjects. We intend to recruit at least 66 subjects (33 of each gender) to ensure that we can demonstrate a strong correlation within each gender. Our expected Aim 2 sample size is 74 subjects (most of which will have BIA measurements), so we expect to have more than adequate sample size for Aim 1. Exploratory analyses will include correlation of ECV/body weight with diastolic blood pressure slope and overall change in blood pressure from pre to post dialysis as well as correlations involving ECV/total body volume with IBPS.

EXPECTED OUTCOMES (Aim 1)

We expect, for our primary outcome, that there will be a positive correlation between post-HD ECV/body weight and the mean IBPS of 0.6. We expect that the standard deviation in our cohort's IBPS will be smaller than that of our preliminary data cohort due to 1) a more homogenous population (see Exclusion criteria 3-8) excluding patients whose blood pressure changes are more likely to be related to ECV-independent comorbidities (autonomic neuropathy, medication non-adherence, advanced heart failure) and 2) calculation of the mean IBPS over 6 treatments, not a single treatment. We expect the ECV/body weight to be higher in men than women, but the correlations between ECV/body weight and IBPS will be similar. We expect that the association between IBPS and *pre*-HD ECV/body weight will not be as strong as with the slopes and *post*-HD ECV/body weight because pre-HD measurements are more reflective of acute, not chronic ECV excess. Based on our preliminary data, we do not expect as strong a correlation will exist with ECV/total body volume and IBPS.

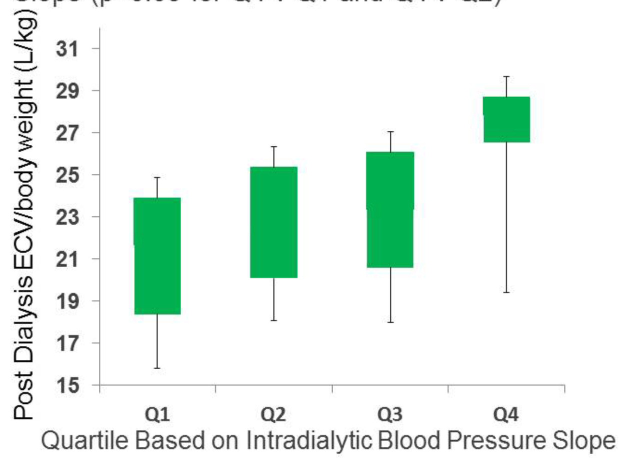
POTENTIAL PROBLEMS AND ALTERNATIVES (Aim 1)

Our hypothesis is strongly supported by our preliminary data. In the unlikely event that our experiment proves this invalid, we will have laboratory data and data on total body volume, dialysis prescription, antihypertensive medication use, and ultrafiltration rates to better understand which factors best associate with IBPS in various subgroups. There are some patients whose intradialytic blood pressure would likely be influenced by ECV-independent factors.

This includes 1) patients with very high amounts of acute and chronic ECV who have extremely high ultrafiltration rates (>13 mL/hr/kg) that may induce intravascular volume depletion in the absence of ECV depletion and 2) patients with large decreases in intradialytic blood pressure related to acute loss of total peripheral resistance (patients with diabetes for many years with autonomic neuropathy, patients with sympathetic nervous system dysfunction, patients taking antihypertensive medications during HD). Our exclusion criteria minimize the risk of these factors impacting our study.

3. **AIM 2: The premise for this aim is there is a need for individualized fluid management interventions that minimize mortality risk factors in HD patients. The objective of this aim is to demonstrate how IBPS-based ultrafiltration prescriptions affect ambulatory blood pressure and ECV in hypertensive HD patients. We will test the working hypothesis** that after 16-weeks, subjects randomized to our algorithm will have larger reductions in 1) ambulatory blood pressure during the interdialytic period, 2) post-HD ECV/body weight (measured with BIA), and 3) peripheral resistance compared to standard care.

Figure 2: Post Dialysis ECV/Body Weight Increases With Each Increasing Quartile of Intradialytic Blood Pressure Slope (p<0.05 for Q4 v Q1 and Q4 v Q2)



Based on our preliminary data showing a relationship between IBPS and ECV/body weight (**Figure 2)**, we have developed an algorithm that assigns ultrafiltration goals based on the IBSP demonstrated over the prior two weeks. With this algorithm detailed in **Table 2 (below)**, subjects with the most negative slopes will have the least aggressive fluid removal while those with positive slopes will have the most aggressive prescriptions.

RESEARCH DESIGN (Aim 2): Our design for Aim 2 will be an un-blinded, randomized clinical trial comparing IBPS based fluid management to standard care.

Patient Population: We will use consecutive sampling to identify eligible participants from our UT Southwestern-affiliated HD units. Inclusion and exclusion criteria are presented in the common approach section. Subjects agreeing to participate will be assigned to one of two study groups based on computer-generated randomization stratified by gender: IBPS-based management or Standard Care.

Study Procedures:
Baseline Information will be collected after subject enrollment (see Common Approach Elements above).

Standard Care Group: Subjects randomized to standard care will continue to be managed by their individual nephrologists. In our units, 10 different nephrologists manage patients. Each nephrologist evaluates individual patients in person once every 1-2 weeks to ascertain interval subjective events, physical examination, blood pressure, and laboratory data. There are no mandatory changes at any visit. The nephrologist has discretion to change blood pressure medications, target dry weight, and ultrafiltration goals based on his/her individual assessment of the patient's needs.

IBPS-Based Management: Subjects in this arm will have ultrafiltration prescriptions ordered by study personnel based on the IBPS from the prior 2 weeks. We will recalculate IBPS every month to as we expect IBPS to change with gradual ECV reduction throughout the course of the study. At each monthly visit, study personnel will modify the prescription based on the prior 2 weeks of intradialytic blood pressure data.

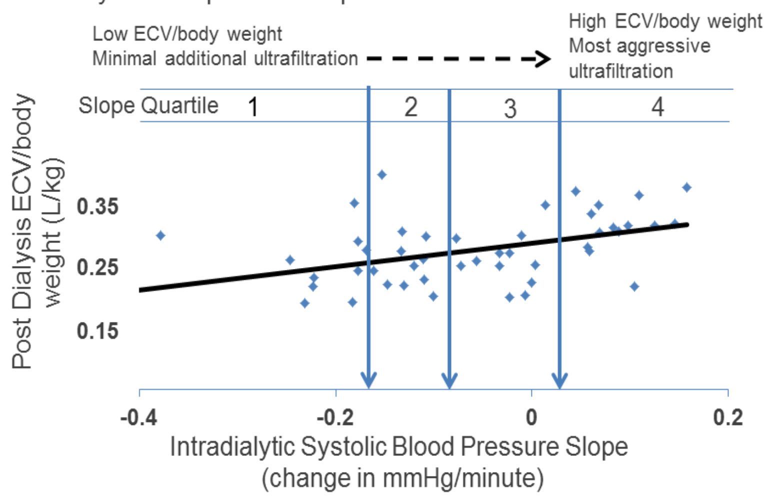
The specific algorithm used to prescribe the ultrafiltration is shown in **Table 2.** In addition to the ultrafiltration prescribed to achieve the patient's prior dry weight, we will assign an pre-specified percentage of dry weight to be removed each treatment for 3 consecutive treatments to establish a new dry weight. After these 3 treatments, we will use this new dry weight as the target weight for ultrafiltration each visit until the next monthly evaluation. In a given month, the minimal dry weight reduction would be 0% and the maximum would be 1.5% of the target weight. New orders will be placed each month for 4 months.

TABLE 2: Ultrafiltration Prescription Algorithm for Intervention Group

Slope	Intervention
<-9 mmHg/hr	Continue UF prescription. Extend dialysis treatment length
-9<x<-4 mmHg/hr	Target Weight Reduction of 0.3% each treatment x1 week
-4<x<+2 mmHg/hr	Target Weight Reduction of 0.4% each treatment x 1 week
>+2 mmHg/hr	Target Weight Reduction of 0.5% each treatment x 1 week

Our algorithm assigns a graded increase in additional ultrafiltration based on flat or positive IBPS compared to more negative slopes. Our determination of the slope cutoffs is based on the quartiles of IBPS in our preliminary data of 49 hypertensive HD patients (**Figure 3**). Each increasing quartile reflects increasing post-dialysis ECV excess, warranting a more aggressive ultrafiltration prescription. The assigned intervention is derived from parameters in prior HD trials. In the intensive ultrafiltration arm of the Dry Weight Reduction in Hypertensive Hemodialysis Patients (DRIP) trial[10], the assigned fluid removal was the amount needed to offset interdialytic weight gain with an additional 1% of the patient's body weight [10]. A separate trial using BIA to determine ultrafiltration goals used additional increments of 0.2 kg per treatment[11]. We believe our approach aiming for ultrafiltration goals within these parameters will be safe and efficacious.

Figure 3: A graded ultrafiltration algorithm will assign more aggressive ultrafiltration per weight with each increase in quartile of intradialytic blood pressure slope



Dialysis Unit Procedures: Intradialytic hypotension (systolic blood pressure >90 mmHg) or related symptoms will be managed per DaVita dialysis unit protocols including reduction of ultrafiltration and/or administration of saline (see Appendix attachment). In subjects with recurrent symptomatic intradialytic hypotension, we will recommend an increase in dialysis time to minimize the ultrafiltration rate. If intradialytic hypotension persists, dry weight will be increased back up. If the assigned ultrafiltration prescription exceeds a ultrafiltration rate 13 mL/hr/kg, we will adjust it to be no more than 13 mL/hr/kg. Slopes will be repeated after 2 weeks at the new weight.

In both groups, the treating nephrologist will have the liberty of adjusting blood pressure medications as deemed clinically necessary.

Outcomes During The Study:

Ambulatory Blood Pressure: The mean ambulatory systolic blood pressure will be the primary dependent variable. We selected this variable because it is the blood pressure metric that best predicts mortality in HD patients[12]. Unlike BIA or NICOM, no subjects that would be excluded from obtaining ambulatory blood pressure measurements in this study. All subjects will have baseline measurements of ambulatory blood pressure at week 0 following a mid-week treatment. It will be repeated at week 16 following a mid-week treatment.

BIA and NICOM: At baseline (week 0), all eligible subjects will undergo BIA and NICOM for measurements of ECV/body weight (see Aim 1) and total peripheral resistance index before and after a mid-week treatments. The procedures will all be repeated at week 8 and week 16 following a mid-week treatment.

Statistical Analysis Plan and Power Calculation for Sample Size (Aim 2)

The primary outcome of this aim will be the ambulatory systolic blood pressure from baseline to 16 weeks. Secondary endpoints include ECV/body weight and total peripheral resistance, from baseline to 16 weeks. We will use the two-sample t test to perform the unconditional comparison of the difference in endpoints over time between treatment and control groups. For conditional comparison, we will use the linear mixed effect model to estimate the fixed effect of the treatment group indicator, while adjusting for the fixed effects from baseline variables and time and the random effect within the same patient. We determined our sample size based on known effects of intense ultrafiltration on ambulatory blood pressure reduction. In the DRIP trial[10], systolic blood pressure decreased by 13.9 mmHg in the intense ultrafiltration group and 6.9 mmHg in the standard group (95% CI -12.2 – 1 mmHg) after 8 weeks. We expect a more modest decrease in systolic blood pressure due to our less aggressive approach per treatment. Assuming a standard deviation for the ambulatory systolic blood pressure change of 6 mmHg (this was approximately 2.7 mmHg in DRIP and our study will have a smaller sample size), we will be able to show with 90% power and an alpha of 0.05, that a between group difference ≥2.7 mmHg will occur. If the normality assumption indeed holds in our observed data, this would require 14 subjects per arm, but we will recruit 30 subjects per arm to facilitate simple normality check such as the Q-Q plot. Assuming a 25% dropout rate, we will aim to recruit 74 subjects (37 in each group).

With our sample size (n=74), we will have 85% power to detect a 0.025 difference in the change between groups after 16 weeks in ECV/body weight. This clinically significant difference is consistent with the difference in post-HD ECV/body weight we found in patients with intradialytic hypertension and HD controls [13]. Based on our prior experiences recruiting HD patients for clinical research, we expect that we will be able to enroll 1-2 patients each month (18 patients each year including excluding dropouts).

EXPECTED OUTCOMES (Aim 2)

We expect the IBPS-based ultrafiltration group to have ≥3 mmHg greater reduction in mean ambulatory systolic blood pressure from baseline to 16 weeks than the standard care group. We expect that such differences could be as high as 7 mmHg based on the DRIP trial. Because our algorithm assigns fluid removal objectively and most hypertensive HD patients have ECV excess that is difficult to identify clinically, we expect that subjects assigned to our algorithm will be assigned more fluid removal over the course of the study than those in the standard care group. We expect the outcomes to include improvement in chronic ECV excess as shown by greater reduction in post-HD ECV and ECV/body weight. We expect to also see reduction in post-HD total peripheral resistance. We do expect ambulatory blood pressure to decrease in the standard care group due to patient motivated lifestyle changes while in a clinical trial. However, we expect that the decrease in blood pressure will be of greater magnitude in our IBPS-based ultrafiltration group as specified above. We expect our algorithm will optimize fluid removal and that the change in post-HD ECV/body weight will be ≥0.025 in the IBPS-based ultrafiltration group compared to standard care.

POTENTIAL PROBLEMS AND ALTERNATIVES (Aim 2)

In the unlikely event our Aim 1 hypothesis is proven invalid and fails to show as robust association between IBPS and ECV as hypothesized, the evidence remains strong that intensifying ultrafiltration lowers blood pressure. Aim 2 will provide an opportunity to determine if an algorithmic alternative to the arbitrary prescription approach in standard care is more effective at achieving that goal, and it will provide a mechanistic assessment of how gradual changes in ECV impact vascular resistance and cardiac output in HD patients.

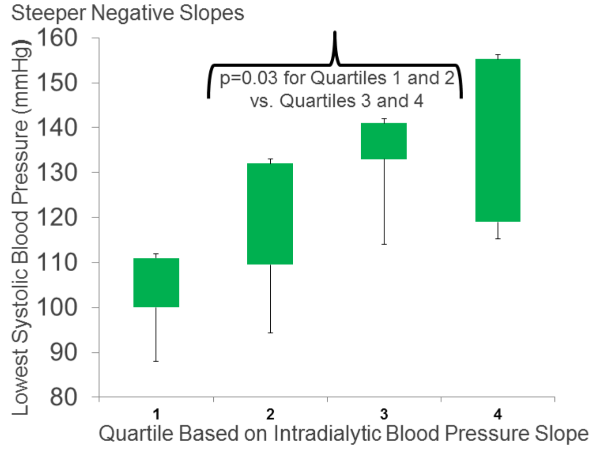
Potential problems in Aim 2 include the possibility that patients with severely uncontrolled BP will need major changes in antihypertensive medications during the study. In this case, blood pressure slopes may be modified despite no change to the patient's ECV. We will minimize this risk by excluding patients with poor control of blood pressure (pre or post HD systolic BP> 180 mmHg) and history of medication non-adherence. In the unlikely event that our intervention fails to improve blood pressure or ECV in the overall population, we will be able to explore which subgroups did appear to achieve benefit so that we can further refine our algorithm.

In some clinical studies, measurements obtained with BIA have been used to guide fluid removal. The inability to include subjects with amputations, cardiac defibrillators or pacemakers in the 16 week clinical trial would reduce our ability to achieve the necessary sample size and would limit our ability to generalize our findings to many other hypertensive HD patients. Subsequently, the measurements obtained with BIA in this aim will only be used as secondary outcomes among those subjects that have no exclusion criteria for its use. Another potential marker for ECV excess that has been considered is the slope of intradialytic hematocrit using relative blood volume monitoring as an estimate of intravascular volume. Our primary concern with this is that the device used for this application is currently on FDA recall. Furthermore, there is prior evidence from a randomized trial showed that mortality and hospitalization increased in patients who had blood volume monitoring[14].

4. **AIM 3: The premise for this aim is there is a need for fluid management approaches that minimize intradialytic hypotension. The objective of this aim is to demonstrate how IBPS-based ultrafiltration prescriptions affect intradialytic hypotension. We will test the working hypothesis that** in a randomized trial (Aim 2) using IBPS to guide ultrafiltration, the frequency of intradialytic hypotension, the intradialytic systolic blood pressure nadir, and the occurrence of intradialytic symptoms will be similar in subjects randomized to our algorithm and standard care.

Recurrent intradialytic hypotension, defined as systolic blood pressure <90 mmHg) is a mortality risk factor, such that blindly and aggressively removing large amounts of fluid to manage ECV excess may cause more harm than good in some patients with ECV excess. For HD patients that cannot adhere to the strict dietary sodium and fluid restriction recommendations, there is currently no standardized approach to remove sufficient fluid during dialysis to prevent ECV excess without inducing large decreases in blood pressure. In our preliminary data, the nadir systolic blood pressure is significantly lower in patients in lower quartiles of IBPS (more negative slopes) compared to the upper quartiles (positive slope) as shown in **Figure 4.** Our graded ultrafiltration algorithm assigns less ultrafiltration to those patients with steep negative slopes and therefore avoids overly aggressive fluid removal in patients that are least likely to tolerate it.

Figure 4: Patients With Positive or Flat Intradialytic Blood Pressure Slopes Have Higher Nadir Systolic Blood Pressure Than Patients With Steeper Negative Slopes



RESEARCH DESIGN (Aim 3):

We will use a randomized clinical trial comparing IBPS based fluid management to standard care comprised of the subjects participating in Aim 2 (see above).

<u>Study Procedures:</u> *<u>IBPS Based Fluid Management</u>*: See Aim 2.

<u>Intradialytic Hypotension Measurement:</u> A systolic blood pressure nadir <90 mmHg will be the definition of intradialytic hypotension. We are using this definition because it is the metric of intradialytic hypotension that has the strongest independent association with mortality[15]. Consistent with dialysis unit protocol, blood pressure will be measured with an automated sphygmomanometer attached to the dialysis machine every 30 minutes during the dialysis treatment and more frequently in the context of hemodynamic instability. We will obtain blood pressure records from each treatment, including the lowest blood pressure measured. An occurrence of intradialytic hypotension will not be counted more than once per treatment. Secondary outcomes will be the systolic blood pressure nadir.

<u>Intradialytic Interventions:</u> We will obtain HD records for each treatment to document the frequency of recorded intradialytic symptoms (cramping, dizziness, nausea/vomiting), as well as the frequency and type of intervention used to manage these symptoms (reduction/cessation of ultrafiltration; administration of intravenous fluid; transport to hospital).

Statistical Analysis Plan (Aim 3): This aim's primary outcome is the difference in intradialytic hypotension between subjects randomized to IBPS-based ultrafiltration or standard care. We will use a generalized mixed linear model with an event indicator for intradialytic hypotension as the response, controlling for within subject correlation. Based on our preliminary data, patients with lower than median IBPS had nadir blood pressure of 108.4 (15.7) mmHg compared to 126.8 (13.1) mmHg (p=0.003) in patients above the median. There were five subjects with nadir SBP less than 100 mmHg during HD, and two of these subjects had nadir SBP <90 compared to zero and zero in the steeper slope group. Our sample size is determined based on our calculations for the primary outcome in Aim 2. We will compare systolic blood pressure nadir throughout the study using mixed model repeated measures analysis similar to other continuous outcomes in Aim 2.

EXPECTED OUTCOMES (Aim 3)

We expect that the risk of intradialytic hypotension will be similar in subjects randomized to IBPS-based ultrafiltration and standard care. Because of our exclusion criteria, we do not expect intradialytic hypotension to be common in our clinical trial subjects. We expect our graded algorithm to appropriately balance the intensity of ultrafiltration with the baseline intradialytic hypotension risk. This balanced approach will be reintroduced every month in the intervention group with reassessment of the IBPS. Therefore, we do not expect the incidence of intradialytic hypotension to increase much more than baseline in this same group. We also expect the nadir systolic blood pressure and number of treatments with cramps and dizziness to be similar in the two groups. If these outcomes are similar, we will interpret this as an indication that our algorithm does not introduce any new risk to patients compared to standard care and is a safe alternative that requires evaluation in a long term clinical trial.

POTENTIAL PROBLEMS AND ALTERNATIVES (Aim 3)

In the event that Aim 2's hypothesis is proven invalid, it is still necessary to known if our algorithmic approach to standard care ultrafiltration causes less intradialytic hypotension.

Because intradialytic hypotension and ultrafiltration rate are strongly associated, another approach to minimize the risk for intradialytic hypotension is to slow the ultrafiltration rate. While lowering the target ultrafiltration volume would achieve this, it would simultaneously increase the risk for ECV excess. Lengthening the dialysis treatment time is another strategy that enables similar (or more) absolute fluid removal at a slower rate. The major limitation of this approach is the logistic application to the population of nearly 500,000 ESRD patients on HD in the United States. Survey data has demonstrated a general unwillingness of HD patients to come in for extra treatments or have increased dialysis time on a regular basis[16]. It is critical to develop a novel approach that remains applicable to the present environment of dialysis care. Furthermore, our approach would remain relevant even in the context of an institutionalized increase in dialysis times.

REFRENCES

[1] Raimann J, Zhu F, Wang J *et al.* Comparison of fluid volume estimates in chronic hemodialysis patients by bioimpedance, direct isotopic, and dilution methods. Kidney International 2014; 85:898-908.
[2] Moissl U, Wabel P, Chamney P *et al.* Body fluid volume determination via body composition spectrscopy in health and disease. Physiologic Measurement 2006; 27:921-933.
[3] Kuhlmann M, ZHu F, Seibert E, Levin N. Bioimpedance, dry weight and blood pressure control: new methods and consequences. Current Opinion in Nephrology and Hypertension 2005; 14:543-549.
[4] Cole K. Dispersion and absorption in dielectrics-Alternating current characteristics. Journal of Chemical Physics 1941; 9:341-351.
[5] Kyle U, Bosaeus I, De Lorenzo AD, P *et al.* Bioelectrical impedance analysis-part I: review of principles and methods. Clinical Nutrition 2004; 23:1226-1243.
[6] Squara P, Denjean D, Estagnasie P *et al.* Noninvasive cardiac output monitoring (NICOM): a clinical validation. Intensive Care Medicine 2007; 33:1191-1194.
[7] Raval N, Squara P, Cleman M *et al.* Multicenter Evaluation of Noninvasive Cardiac Output Measurement By Bioreactance Technique. Journal of Clinical Monitoring and Computing 2008; 22:113-119.
[8] Karakitsos D, Patrianakos A, Paraskevopoulos A *et al.* Impedance cardiography derived cardiac output in hemodialysis patients: a study of reproducibility and comparison with echocardiography. International Journal of Artificial Organs 2006; 29:564-572.
[9] Davies S, Davenport A. The role of impedance and biomarkers in helping to aid clinical decision-making of volume assessments in dialysis patients. Kidney International 2014; 86:489-496.
[10] Agarwal R, Alborzi P, Satyan S, Light R. Dry-Weight Reduction in Hypertensive Hemodialysis Patients (DRIP): A Randomized, Controlled Trial. Hypertension 2009; 53:500-507.
[11] Onofriescu M, Hogas S, Voroneanu L *et al.* Bioimpedance-Guided Fluid Management in Maintenance Hemodialysis: A Pilot Randomized Controlled Trial. American Journal of Kidney Diseases 2014; 64:111-118.
[12] Alborzi P, Patel N, Agarwal R. Home blood pressures are of greater prognostic value than hemodialysis unit recordings. Clinical Journal of the American Society of Nephrology 2007; 2:1228-1234.
[13] Van Buren P, Zhou Y, Neyra J *et al.* Extracellular Volume Overload and Increased Vasoconstriction in Patients With Recurrent Intradialytic Hypertension. Kidney and Blood Pressure Research 2016; 41:802-814.
[14] Reddan D, Szczech L, Hasselbad V *et al.* Intradialytic blood volume monitoring in ambulatory hemodialysis patients: a randomized trial. Journal of the American Society of Nephrology 2005; 16:2162-2169.
[15] Flythe J, Xue H, Lynch K *et al.* Association of mortality risk with various definintions of intradialytic hypotension. Journal of the American Society of Nephrology 2015; 2015:724-734.
[16] Flythe J, Mangione T, Brunelli S, Curhan G. Patient-state preferences regarding volume-related risk mitigation strategies for hemodialysis. Clinical Journal of the American Society of Nephrology 2014; 9:1418-1425.