Dry-Weight Reduction in Hypertensive Hemodialysis Patients (DRIP)

A Randomized, Controlled Trial

Rajiv Agarwal, Pooneh Alborzi, Sangeetha Satyan, Robert P. Light

Abstract—Volume excess is thought to be important in the pathogenesis of hypertension among hemodialysis patients. To determine whether additional volume reduction will result in improvement in blood pressure (BP) among hypertensive patients on hemodialysis and to evaluate the time course of this response, we randomly assigned long-term hypertensive hemodialysis patients to ultrafiltration or control groups. The additional ultrafiltration group (n=100) had the dry weight probed without increasing time or duration of dialysis, whereas the control group (n=50) only had physician visits. The primary outcome was change in systolic interdialytic ambulatory BP. Postdialysis weight was reduced by 0.9 kg at 4 weeks and resulted in −6.9 mm Hg (95% CI: −12.4 to −1.3 mm Hg; P=0.016) change in systolic BP and −3.1 mm Hg (95% CI: −6.2 to −0.02 mm Hg; P=0.048) change in diastolic BP. At 8 weeks, dry weight was reduced 1 kg, systolic BP changed −6.6 mm Hg (95% CI: −12.2 to −1.0 mm Hg; P=0.021), and diastolic BP changed −3.3 mm Hg (95% CI: −6.4 to −0.2 mm Hg; P=0.037) from baseline. The Mantel-Hanzel combined odds ratio for systolic BP reduction of ≥10 mm Hg was 2.24 (95% CI: 1.32 to 3.81; P=0.003). There was no deterioration seen in any domain of the kidney disease quality of life health survey despite an increase in intradialytic signs and symptoms of hypotension. The reduction of dry weight is a simple, efficacious, and well-tolerated maneuver to improve BP control in hypertensive hemodialysis patients. Long-term control of BP will depend on continued assessment and maintenance of dry weight. **(*Hypertension*. 2009;53:500-507.)**

Key Words: hemodialysis ■ hypertension ■ ultrafiltration ■ ambulatory blood pressure ■ volume overload

Chronic kidney disease is common in the general population and is associated with increased cardiovascular risk.[1] Cardiovascular mortality is exceedingly high, especially in patients with more advanced chronic kidney disease. Hypertension is a cardiovascular risk factor common in patients with chronic kidney disease.[2] Despite drug treatment, hypertension is difficult to control, especially in patients who have end-stage renal disease.[3] Unlike office blood pressure (BP) measurement, which forms the basis of most hypertension management, BPs obtained in dialysis centers poorly represent the usual level of BP in hemodialysis patients, which makes the management of hypertension particularly challenging.[4]

Among factors causing hypertension in patients on hemodialysis,[5,6] excess volume is thought to be most important.[7–12] However, few data exist to confirm the role of excess volume in causing hypertension in these patients. Observational studies show that volume reduction is associated with improvement in BP in 70% to 90% of the patients,[13–17] that this reduction could be delayed for many months,[18] and that hypertension control without medication is the best single marker of survival in hemodialysis patients.[19] These studies were performed by measuring BP in the dialysis unit, which may not represent the true level of BP in hemodialysis patients.[20] Whether similar results would be obtained in patients who are now older and have a greater prevalence of vascular disease and diabetes mellitus is also unknown.

Accordingly, we hypothesized that additional volume reduction will result in rapid improvement in BP among hypertensive patients on hemodialysis. To test this hypothesis, we designed this 8-week, prospective, randomized trial to assess the efficacy, safety, and tolerability of augmented ultrafiltration therapy in controlling systolic hypertension assessed by interdialytic ambulatory BP monitoring in a prevalent hemodialysis cohort.

Methods

We recruited patients ≥18 years of age on long-term hemodialysis for ≥3 months, who were hypertensive based on a mean interdialytic ambulatory BP of ≥135/85 mm Hg. Patients found to have well-controlled hypertension had antihypertensive medications withdrawn until they became hypertensive. Patients with stroke, myocardial infarction, or limb ischemia in the previous 6 months; ambulatory BP of >170/100 mm Hg; who missed >1 dialysis in the previous month; and had chronic atrial fibrillation or morbid obesity (body

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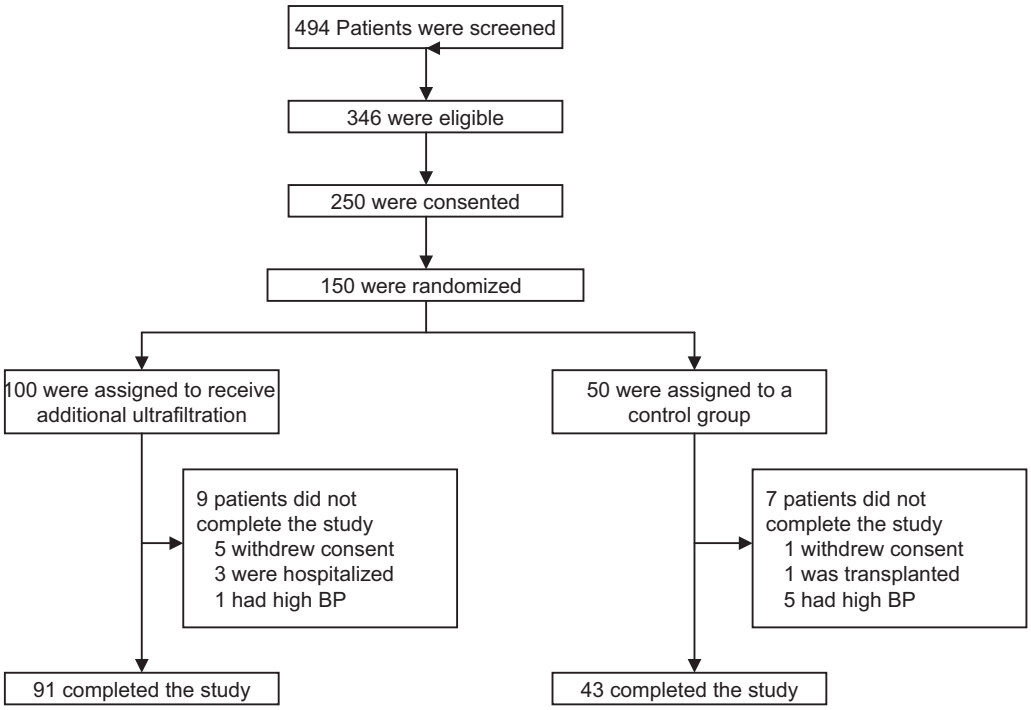

Figure 1. Enrollment and trial flow.

mass index >40 kg/m^2) were excluded. Baseline measurements included history and examination, signs and symptoms of hemodynamic instability, ambulatory BP monitoring, and the assessment of health-related quality of life via the Kidney Disease Quality of Life (KDQOL) questionnaire.

After a 6 hemodialysis treatment run-in phase, during which baseline data were collected, patients were randomly assigned in 1:2 proportion to control group or ultrafiltration intervention group for 8 weeks. During this 24-dialysis treatment phase, patients were seen at each dialysis visit and had evaluation of dry weight and symptoms and signs related to hypovolemia by study personnel.

The assessment of dry weight remains a clinical judgment,[21,22] which is what we used to determine the dry weight in each patient using the following protocol. In the ultrafiltration group, an initial additional weight loss of 0.1 kg/10-kg body weight was prescribed per dialysis without increasing the time or frequency of dialysis. This additional weight loss was combined with the ultrafiltration volume required to remove interdialytic weight gain to achieve the desired reduction in dry weight. If ultrafiltration was not tolerated based on symptoms and signs, such as muscle cramps, need for excessive saline, or symptomatic hypotension, the additional prescribed weight loss was reduced by 50%. If ultrafiltration was still not tolerated, the additional weight loss was further reduced by 50% until even 0.2-kg incremental weight loss per dialysis was not tolerated. At this point, the patient was said to be at his or her dry weight. Thus, by this protocol, each patient had to experience symptoms of volume depletion to be at dry weight. During the conduct of the trial, if the predialysis BP became 180 mm Hg systolic or 110 mm Hg diastolic or more over 2 consecutive treatments, the patient had interdialytic ambulatory BP measured and was excluded from further participation if the mean interdialytic BP was found to be ≥175/105 mm Hg. No changes in antihypertensive medication were permitted during the trial.

Ambulatory BP monitoring was performed after the midweek hemodialysis session for 44 hours. BPs were recorded every 20 minutes during the day (6 AM to 10 PM) and every 30 minutes during the night (10 PM to 6 AM) using a SpaceLabs 90207 ABP monitor (SpaceLabs Medical Inc) in the nonaccess arm. Recordings began immediately after hemodialysis and terminated immediately before the subsequent dialysis. Accuracy of ambulatory BP recordings was confirmed against auscultated BP at baseline. Hourly means were calculated. These means were then averaged over the entire course of recording to provide systolic and diastolic interdialytic ambulatory BPs.

Predialysis and postdialysis weights were recorded at each visit. The mean of the last 3 treatments in the baseline period, the 3 treatments in week 4, and the 3 treatments at week 8 were taken to represent the predialysis and postdialysis weights.

The KDQOL-Short Form questionnaire was self-administered before random assignment and at 8 weeks. The KDQOL-Short Form includes questions targeted at particular health-related concerns for individuals undergoing dialysis.[23] Scores on each KDQOL-Short Form dimension range from 0 through 100, with higher scores reflecting better health-related quality of life.

Random assignment to treatment or control groups was carried out in permuted blocks with 2:1 ultrafiltration:control ratio. Opaque sealed envelopes were used for treatment allocation by study personnel after assuring that the inclusion-exclusion criteria were met. The study protocol was approved by the institutional review boards and the Veterans' Affairs Research and Development Committee, and all of the patients provided written informed consent.

Statistical Analysis

The primary end point was the reduction in systolic ambulatory BP between groups at 8 weeks using an intent-to-treat analysis. A mixed model accounting for repeated measurements was fitted for ambulatory systolic BP at baseline, 4 weeks, and 8 weeks. The interaction effect of time and intervention was tested and 95% CIs calculated using maximal likelihood estimates. A similar analysis was performed for evaluating changes over time between randomized groups in postdialysis weights and the various domains of the KDQOL-Short Form questionnaire. We assessed the change in postdialysis weight with lowering of systolic BP in the ultrafiltration group at 4 and 8 weeks by least-squares linear regression.

To assess the frequency of hypovolemia-related signs and symptoms during dialysis treatments, we calculated the proportion of treatments complicated by a priori end points, such as cramps and dizziness. We first calculated the baseline frequency of these symptoms during a 2-week run in and then calculated the proportions of treatments complicated by these events within patients. Data were

Table. Clinical Characteristics of the Study Population

Clinical Characteristic	Ultrafiltration (n=100)	Control (n=50)
Age, y	54.1±12.9	54.7±11.5
Men	66 (66)	38 (76)
Race		
White	12 (12)	3 (6)
Black	85 (85)	46 (92)
Other	3 (3)	1 (2)
Predialysis BP	159.6±16.3/86.2±10.4	159.1±15.1/87.5±12.0
Postdialysis BP	143.3±17.5/77.8±10.3	142.7±19.4/78.3±12.8
Predialysis weight, kg	84.2±20.2	84.8±19.8
Postdialysis weight, kg	81.3±19.6	82.0±19.2
Body mass index, kg/m^2	27.3±5.9	27.3±6.5
Years of dialysis	3.8±4.7	4.5±5.7
Etiology of end-stage renal disease		
Diabetes mellitus	40 (40)	19 (38)
Hypertension	47 (47)	24 (48)
Glomerulonephritis	4 (4)	2 (4)
Obstruction	0 (0)	0 (0)
Polycystic kidney disease	3 (3)	0 (0)
Other	6 (6)	5 (10)
Current smoker	32 (32)	19 (38)
History of		
Congestive heart failure	18 (18)	4 (8)
Myocardial infarction	14 (14)	6 (12)
Stroke	10 (10)	5 (10)
Urea reduction ratio	74.1±7.0	73.4±6.2
Albumin, g/dL	3.7±0.5	3.7±0.4
Hemoglobin, g/dL	12.2±1.1	12.0±1.3
Presence of edema*	19 (20)	8 (16)
No. receiving antihypertensive drugs	87 (87)	38 (76)
No. of antihypertensives in users	2.7±1.4	2.6±1.3
Nature of antihypertensive agent		
Dihydropyridine calcium channel blockers	48 (48)	20 (40)
Nondihydropyridine calcium channel blockers	4 (4)	2 (4)
β-Blockers	71 (71)	32 (64)
α-Blockers	8 (8)	4 (8)
Centrally acting agents	26 (26)	10 (20)
Vasodilators	17 (17)	9 (18)
Angiotensin-converting enzyme inhibitors	52 (52)	25 (50)
Angiotensin receptor blockers	19 (19)	4 (8)

± indicates SD. Parentheses show the percentage of patients.
*Data are missing in 3 patients in the ultrafiltration group.

analyzed using a mixed model noted above. An exploratory subgroup analysis was performed to detect any interaction effect of demographic and clinical characteristics on treatment effect.

We expected the systolic BP to increase by 2.5 mm Hg in the control group. In the intervention group, we expected the BP to reduce by a mean of 5 mm Hg. When the sample sizes in the 2 groups were 45 (control) and 73 (intervention), respectively (a total sample size of 118), we calculated 80% power to detect the difference between group means of 7.5 mm Hg. We expected 1 of 4 patients to drop from the trial in the intervention group because of discomfort of ultrafiltration and inconvenience of ambulatory BP monitoring. We expected a 10% dropout rate in the control group. Thus, 50 patients in the control group and 100 in the intervention group were required to have 80% power to demonstrate 7.5 mm Hg difference between the 2 groups. The nominal level of significance was set at 2 sided P of <0.05, and all of the statistical analyses were performed with Stata 10.1 (Stata Corp LP).

Results

Between March 2004 and April 2008, we screened 494 patients in 4 dialysis units affiliated with Indiana University

School of Medicine (Figure 1). Of these 494 patients, 346 patients met eligibility criteria, and 250 consented. One hundred patients failed to randomize: 44 because of lack of hypertension, 4 because of extreme hypertension, 31 withdrawing consent, and 21 because of other reasons. Among 100 patients randomly assigned to the ultrafiltration group, 91 completed the study. Of the 9 patients who did not complete the study, 5 withdrew consent, 3 were hospitalized, and 1 had ambulatory BP above safety cutoff after random assignment. Among 50 patients allocated to the control group, 43 completed the study. Of the 7 patients who did not complete the trial, 1 withdrew consent, 1 underwent kidney transplantation, 4 were removed for ambulatory BP above safety cutoff, and 1 was removed for experiencing accelerated hypertension and pulmonary edema. A total of 87 participants (87%) in the ultrafiltration group and 45 (90%) in the control group provided paired ambulatory BPs at baseline and at 4 weeks, and 88 participants (88%) in the ultrafiltration group and 43 (86%) in the control group provided paired ambulatory BPs at baseline and at 8 weeks.

All of the patients were hemodialyzed 3 times weekly for an average of 235 minutes (SD: 21 minutes), at a blood flow rate of 400 mL/min (SD: 34 mL/min) and dialysate flow rate of 765 mL/min (SD: 77 mL/min). The 2 treatment groups were well balanced with respect to the baseline characteristics of the patients (Table).

Baseline postdialysis weight in the control group was 82.0 kg and was 1.1 kg lower in the ultrafiltration group (95% CI: −7.6 to +5.3 kg; $P=0.73$). In the ultrafiltration group, the change from baseline postdialysis weight was −0.9 kg (95% CI: −1.2 to −0.6; $P<0.001$) at 4 weeks and −1.0 kg at 8 weeks (95% CI: −1.3 to −0.7; $P<0.001$). In the control group, the change from baseline in postdialysis weight was 0.0 at 4 weeks (95% CI: −0.4 to +0.4; $P=0.99$) and 0.0 kg at 8 weeks (95% CI: −0.4 to 0.5; $P=0.90$). Accounting for the baseline difference in postdialysis weight and decline in the control group, ultrafiltration resulted in −0.9 kg change (95% CI: −1.4 to −0.4 kg; $P=0.001$) at 4 weeks and −1.0 kg change at 8 weeks (95% CI: −1.6 to −0.5 kg; $P<0.001$). Interdialytic weight gain averaged 2.9 kg in the ultrafiltration group and 2.8 kg in the control group at baseline and did not change significantly within or between groups over time.

Baseline ambulatory systolic BPs were 146.4±10.6/83.4±10.9 mm Hg in the control group and 145.8±10.2/82.9±10.0 mm Hg in the ultrafiltration group and were similar between groups at baseline (Figure 2A). In the ultrafiltration group, the change from baseline in systolic ambulatory BP was −10.7 mm Hg at 4 weeks and −13.5 mm Hg at 8 weeks. In the control group, the change from baseline in systolic ambulatory BP was −3.8 at 4 weeks and −6.9 mm Hg at 8 weeks. The ultrafiltration-attributable change in systolic BP was −6.9 mm Hg (95% CI: −1.3 to −12.4 mm Hg; $P=0.016$) at 4 weeks and −6.6 mm Hg (95% CI: −1.0 to −12.2 mm Hg; $P=0.021$) at 8 weeks.

Each kilogram reduction in postdialysis weight in the ultrafiltration group resulted in 2.2-mm Hg (95% CI: −0.02 to 4.5; $P=0.052$) reduction in systolic BP at 4 weeks and 2.3-mm Hg (95% CI: 0.8 to 3.8; $P=0.003$) reduction at 8 weeks (Figure 3). No relationship was seen between weight

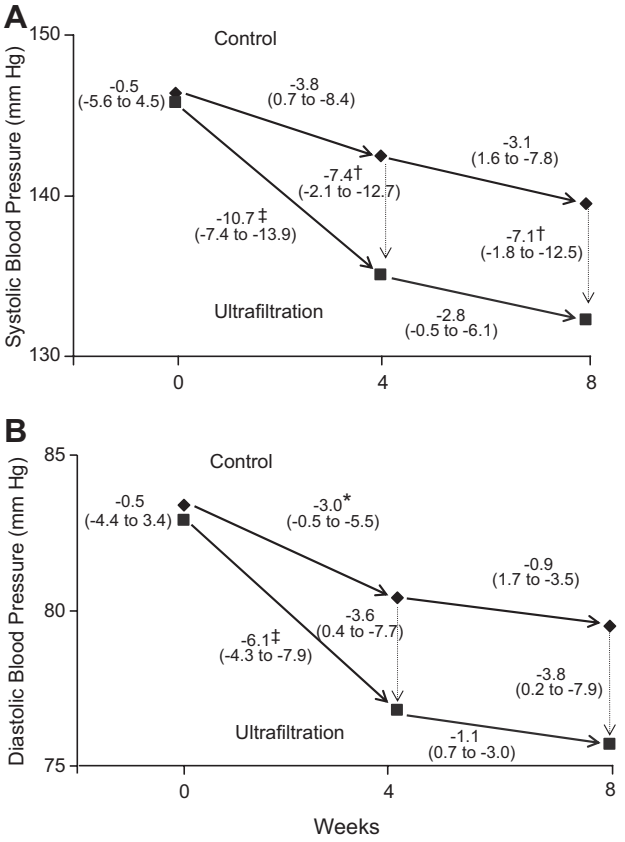

Figure 2. The effect of dry-weight reduction on interdialytic ambulatory systolic (A) and diastolic BP (B) in hypertensive hemodialysis patients. The mean systolic and diastolic BPs are shown for the control and ultrafiltration groups. The mean changes in BP are shown for weeks 4 and 8 after randomization (solid arrows), as well as the mean differences in BPs (dotted arrows) between the 2 groups at each 4 week interval. The numbers next to the dotted lines connecting the data points are the mean changes in BP between groups at 4 and 8 weeks after randomization. The 95% CIs are given in parentheses. *$P<0.05$, †$P<0.01$, and ‡$P<0.001$ indicate significant differences between groups or within groups. The ultrafiltration-attributable change in systolic BP was −6.9 mm Hg (95% CI: −12.4 to −1.3 mm Hg; $P=0.016$) at 4 weeks and −6.6 mm Hg (95% CI: −12.2 to −1.0 mm Hg; $P=0.021$) at 8 weeks. The ultrafiltration-attributable change in diastolic BP was −3.1 mm Hg (95% CI: −6.2 to −0.02 mm Hg; $P=0.048$) at 4 weeks and −3.3 mm Hg (95% CI: −6.4 to −0.2 mm Hg; $P=0.037$) at 8 weeks.

change in the control group from baseline to 4 weeks or baseline to 8 weeks and decline in systolic BP on these respective occasions.

At 4 weeks, 14 (31%) of 45 patients in the control group and 46 (53%) of 87 patients in the ultrafiltration group and, at 8 weeks, 16 (37%) of 43 patients in the control group and 48 (55%) of 88 in the ultrafiltration group had a ≥10-mm Hg drop in systolic BP. The Mantel-Hanzel combined odds ratio for systolic BP response was 2.24 (95% CI: 1.32 to 3.81; $P=0.003$).

In the ultrafiltration group, the change from baseline in diastolic ambulatory BP was −6.1 mm Hg at 4 weeks and −7.3 mm Hg at 8 weeks (Figure 2B). In the control group, the change from baseline in diastolic ambulatory BP was −3.0 at 4 weeks and −3.9 mm Hg at 8 weeks. The ultrafiltration-

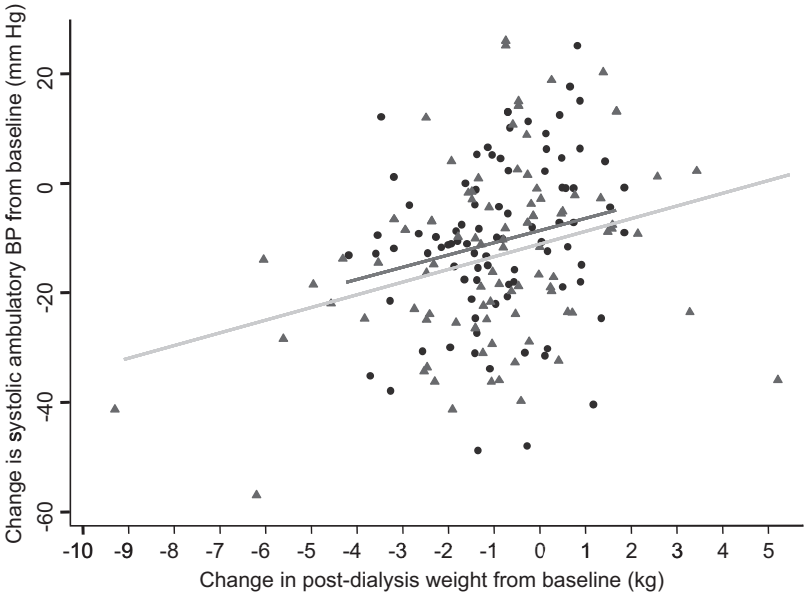

Figure 3. Relationship of change in systolic ambulatory BP with ultrafiltration vs the change in postdialysis weight. Changes depict the reduction in systolic BP at 4 weeks (circles) and 8 weeks (triangles) from baseline plotted against changes in postdialysis weight at 4 weeks and at 8 weeks. Regression lines reflect the linear relationships at 4 weeks (darker line) and at 8 weeks (lighter line).

attributable change in diastolic BP was −3.1 mm Hg (95% CI: −6.2 to −0.02 mm Hg; $P=0.048$) at 4 weeks and −3.3 mm Hg (95% CI: −6.4 to −0.2 mm Hg; $P=0.037$) at 8 weeks.

At 4 weeks, 6 (13%) of 45 patients in the control group and 24 (28%) of 87 patients in the ultrafiltration group and, at 8 weeks, 7 (16%) of 43 patients in the control group and 33 (38%) of 88 in the ultrafiltration group had a ≥5-mm Hg drop in diastolic BP. The Mantel-Hanzel combined odds ratio for diastolic BP response was 2.78 (95% CI: 1.43 to 5.44; $P=0.002$).

The end point of reducing weight in the intervention group was the appearance of symptoms that, in the opinion of the investigator, suggested that the goal was reached. The proportion of patients experiencing these symptoms is shown in Table S1 (please see http://hyper.ahajournals.org). Cramps, dizziness, intradialytic hypotension, need for saline, or reduction in ultrafiltration rates were more commonly seen among patients allocated to the ultrafiltration group, as expected. Dialysis treatments complicated by headache or nausea were similar between groups. Despite more symptoms, the various domains of the KDQOL, including energy, symptoms related to kidney disease, and physical functioning, were unchanged in our study from baseline to 8 weeks (Table S2).

Reductions in systolic BP were similar regardless of age, sex, diabetes mellitus, antihypertensive drug use, angiotensin-converting enzyme inhibitor or angiotensin receptor blocker use, β-blocker use, or pedal edema. Blacks had a more consistent antihypertensive response to ultrafiltration compared with nonblacks (Figure 4).

Adverse effects related to participation in the trial were as expected. One patient in the ultrafiltration group and 4 in the control group had to be withdrawn because of ambulatory BP that exceeded the limits of safety specified in our study. One patient in the control group developed accelerated hypertension, had pulmonary edema, and needed emergent ultrafiltration dialysis after 4 weeks of participation. One patient in the ultrafiltration group became hypotensive and seized but did not require hospitalization. Another developed chest pain, was given sublingual nitroglycerine, and developed hypotension, which resolved with intravenous saline administration. A third became very dizzy and required saline administration in the emergency department. In the ultrafiltration group, 3 patients had 1 episode each of clotted angioaccess, 2 patients had 2 episodes each of clotting, and 1 patient had 3 episodes of clotting, which is in contrast to 2 patients having 1 episode each of clotting in the control group.

Discussion

This trial yielded several key findings that will be useful in the management of long-term hemodialysis patients with hypertension. First, reduction in dry weight as defined by clinical signs and symptoms results in reduction in ambulatory BP. This improvement can be achieved without increasing the time or frequency of dialysis treatments. Although many observational studies suggest that this may be so, randomized trials are lacking to support the claim that dry-weight reduction is an effective strategy to control hypertension.[13–17] More than half of the patients in the intervention group had reduction in systolic BP by ≥10 mm Hg, suggesting that dry-weight reduction results in improved systolic BP equivalent to or greater than a single antihypertensive drug. Because most patients in our study were already taking antihypertensive drugs, it is quite likely that dry-weight reduction resulted in enhancement of the effect of other antihypertensive drugs. However, BP reduction in those on no antihypertensive agents was similar.

Second, the reduction in systolic BP is nearly twice as much as diastolic BP, which results in attenuation of pulse pressure. Pulse pressure is strongly and independently linked to all-cause mortality among hemodialysis patients.[24] Whether reducing dry weight will result in improvement in hard outcomes will depend on ongoing attention to dry weight and BP control, and these benefits remain to be demonstrated.

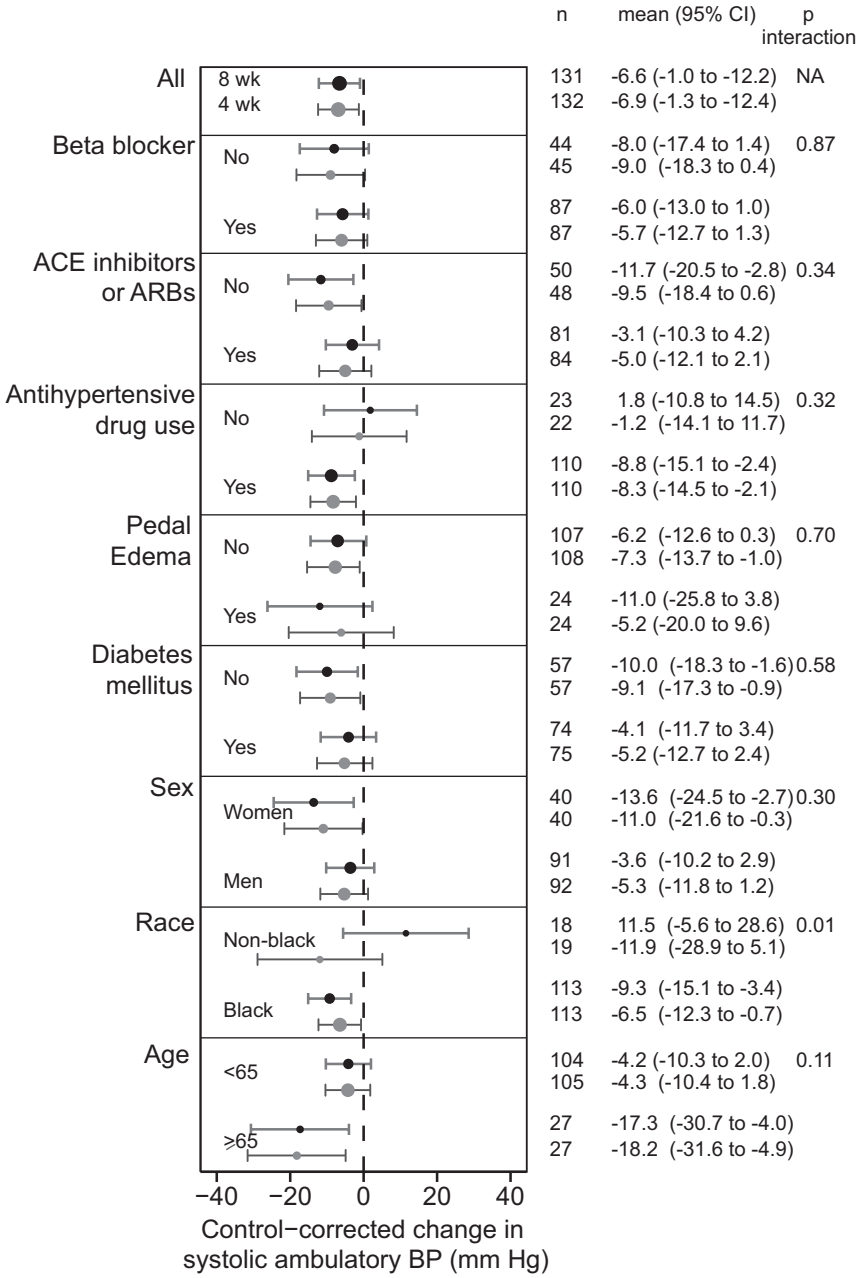

Figure 4. Reduction in systolic ambulatory BP with ultrafiltration vs the control group. Changes depict the reduction in systolic BP at 4 weeks (gray circles) and 8 weeks (black circles) and their 95% CIs. Only the interaction between ultrafiltration and race was significant ($P=0.01$). The size of the circles is proportional to the number of patients.

Third, reduction in BP was evident within 4 weeks of the beginning of intervention, and at 8 weeks no additional reduction in ambulatory BP attributable to reduction in dry weight was evident. The "lag phenomenon" refers to a fall in BP that occurs weeks to months after reducing dry weight. Renal hemodynamic changes with thiazides occur within a week,[25] and systemic hemodynamic changes are demonstrable within 3 days of diuretic administration.[26] In a trial of diuretics in hypertensive patients lasting 10 to 12 weeks, placebo-corrected fall in BP of 10/5 mm Hg is seen within 4 weeks, which is not statistically different from a 12/7-mm Hg fall in BP seen at 10 to 12 weeks.[27] Thus, our results are similar to those seen with the effect of thiazide diuretics on BP in patients with essential hypertension, and we found no support for the lag phenomenon among prevalent hypertensive hemodialysis patients.[18]

Fourth, only ≈2-mm Hg reduction in systolic BP was achieved per kilogram of weight loss with ultrafiltration. Because the observed systolic BP reduction was ≈3 times as much, this indicates that postdialysis weight is a poor proxy of expanded extracellular fluid volume among hemodialysis patients. Fifth, the lack of deterioration in the various components of kidney disease–related quality of life despite experiencing more symptoms related to hypovolemia during dialysis suggests that the therapy was well accepted.

Achieving strict dry-weight control in the prevalent dialysis population as a whole presents a challenge, as well as an opportunity. Dietary and dialysate sodium restrictions limit interdialytic weight gain and may facilitate the attainment of an appropriate dry weight,[15,28] and some studies suggest that frequent dialysis may evoke better BP control even when patients are not at dry weight.[29,30] We did not alter the

dialysate, dietary sodium, or the dialysis time or frequency. In our study, dialysis patients were evaluated at each dialysis treatment to evaluate safety and efficacy of a further reduction in dry weight. This strategy optimizes the determination of the effect of dry-weight reduction on BP. Probing for dry weight led to the predictable increase in muscle cramps, dizziness, and hypotensive episodes.[21] Even with careful supervision, we witnessed ≥3 serious adverse events that were likely related to intervention: hypotension and seizures, dizziness requiring saline administration after dialysis, and chest pain followed by hypotension. It is also possible that lower BPs achieved as a result of challenging dry weight may increase the risk of access thrombosis.

Blacks had a more consistent response in our study compared with nonblacks. Edema, on the other hand, was not predictive of a greater antihypertensive response to ultrafiltration. Although these results may suggest more volume-dependent hypertension among blacks[31] and overt signs of volume excess, such as edema, not necessary for BP lowering,[32] the results of subgroup analysis, especially with limited number of participants, should be interpreted with caution.[33] The variation in BP responses was probably caused in large part by variable tolerance to the prescribed regimen of dry-weight reduction, inadequate trial design, or small sample size. The change in BP in the control group was likely a result of participation in the study and numerous physician visits, which may have had a placebo effect. The intervention period in our trial was only 8 weeks, but the reduction in BP occurred within 4 weeks and persisted for an additional 4 weeks. It is likely that achievement of dry weight would result in long-term control of hypertension. Whether achievement of better BP control via improvement in dry weight will result in lower cardiovascular mortality and other "hard" outcomes among dialysis patients remains to be seen and should now be tested in randomized, controlled trials.

Perspectives

Our data provide support for the hypothesis that extracellular volume expansion, even in the absence of clinical signs of volume overload, may mediate hypertension.[34] Thus, challenging dry weight in long-term hemodialysis patients as first line therapy appears a reasonable strategy for controlling hypertension. However, given the risks of hypotension-related serious adverse effects, implementation of this strategy requires close clinical supervision. Although we did not find any evidence for the lag phenomenon, such an effect may exist in incident hemodialysis patients. Better markers to assess volume status are needed in hemodialysis patients.

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Disclosures

None.

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Online Supplement

Dry-weight reduction in hypertensive hemodialysis patients (DRIP): A randomized controlled trial

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Running Head: Dry-weight reduction in HD
Supplemental Tables

Table S1: Proportion of patients with intradialytic signs and symptoms of hypotension

Symptom/Sign	Baseline prevalence	Change from baseline			
Cramps	-2 to 0 weeks	0-2 weeks	2-4 weeks	4-6 weeks	6-8 weeks
Control	14.5 (8.6 to 20.3)	-1.5 (-7.7 to 4.7)	-4.2(-10.6 to 2.1)	-1.7 (-8.2 to 4.8)	-4.5 (-11.1 to 2.1)
Ultrafiltration	10.2 (6.0 to 14.3)	5.6 (1.2 to 10.1)*	11.8 (7.4 to 16.3)‡	8.3 (3.8 to 12.9)‡	6.0 (1.4 to 10.5)†
Difference	4.3 (-11.4 to 2.8)	7.1 (-0.5 to 14.8)	16.1 (8.3 to 23.9)‡	10.1 (2.2 to 18.0)*	10.1 (2.5 to 18.5)†
Dizziness					
Control	4.7 (1.0 to 8.3)	-2.3 (-6.7 to 2.0)	-2.7 (-7.0 to 1.7)	-2.1 (6.6 to 2.3)	-2.4 (-7.0 to 2.1)
Ultrafiltration	3.4 (0.8 to 6.0)	2.2 (-0.8 to 5.3)	5.1 (2.0 to 8.2)‡	6.7 (3.5 to 9.8)‡	6.0 (2.8 to 9.1)‡
Difference	-1.3 (-5.7 to 3.2)	4.6 (-0.6 to 9.9)	7.7 (2.4 to 13.1)†	8.8 (3.3 to 14.2)†	8.4 (2.9 to 13.9)†
Hypotension					
Control	12.1 (5.9 to 18.2)	-0.6 (-6.9 to 5.7)	-0.6 (-6.9 to 5.8)	4.0 (-2.4 to 10.5)	0.6 (-6.0 to 7.2)
Ultrafiltration	11.6 (7.2 to 16.0)	6.1 (1.6 to 10.5)†	9.6 (5.2 to 14.1)‡	13.2 (8.6 to 17.8)‡	13.2 (8.6 to 17.7)‡
Difference	-0.4 (-8.0 to 7.1)	6.7 (-1.0 to 14.4)	10.2 (2.5 to 18.0)†	9.2 (1.2 to 17.1)*	12.6 (4.6 to 20.6)†
Nausea					
Control	0.3 (-1.4 to 2.1)	1.3 (-0.8 to 3.4)	0 (-2.1 to 2.1)	0.4 (-1.7 to 2.6)	1.6 (-0.6 to 3.8)
Ultrafiltration	1.0 (-0.2 to 2.3)	1.5 (-0.02 to 3.0)	1.7 (0.2 to 3.2)	1.7 (0.1 to 3.2)	1.3 (-0.2 to 2.8)
Difference	0.7 (-1.4 to 2.8)	0.1 (-2.4 to 2.7)	1.7 (-0.9 to 4.3)	1.2 (-1.4 to 3.9)	-0.3 (-3.0 to 2.4)
Headache					
Control	0.3 (-1.3 to 2.0)	1.3 (-0.7 to 3.4)	2.8 (0.7 to 4.9)†	1.4 (-0.6 to 3.6)	1.1 (-1.1 to 3.2)
Ultrafiltration	0.9 (-0.3 to 2.1)	0.4 (-1.0 to 1.9)	0.5 (-0.9 to 2.0)	-0.5 (2.0 to 1.0)	0.4 (-1.1 to 1.8)
Difference	0.6 (-1.5 to 2.6)	-0.9 (-3.4 to 1.6)	2.2 (-4.8 to 0.3)	-1.9 (-4.5 to 0.7)	-0.7 (-3.3 to 1.9)
Trendelenberg					
Control	2.0 (-0.6 to 4.6)	-0.3 (-3.2 to 2.6)	-1.0 (-3.9 to 1.9)	0.8 (-2.1 to 3.8)	0.6 (-2.4 to 3.6)
Ultrafiltration	1.1 (-0.8 to 2.9)	2.5 (0.4 to 4.6)*	3.6 (1.5 to 5.6)‡	3.1 (1.0 to 5.2)†	3.2 (1.1 to 5.3)†
Difference	-0.9 (-4.2 to 2.3)	2.8 (-0.7 to 6.3)	4.6 (1.0 to 8.2)*	2.3 (-1.4 to 5.9)	2.6 (-1.1 to 6.3)
Ultrafiltration reduced					
Control	9.7 (5.3 to 14.2)	1.2 (-4.1 to 6.6)	-1.2 (-6.6 to 4.2)	-3.0 (-8.6 to 2.5)	-1.1 (-6.7 to 4.5)
Ultrafiltration	7.1 (3.9 to 10.3)	4.5 (0.7 to 8.3)*	7.8 (4.0 to 11.7)‡	5.5 (1.6 to 9.4)†	6.3 (2.4 to 10.2)‡
Difference	-2.6 (-8.1 to 2.8)	3.2 (-3.3 to 9.9)	9.1 (2.4 to 15.7)†	8.6 (1.8 to 15.3)*	7.4 (5.6 to 14.2)*
Ultrafiltration stopped					
Control	13.3 (7.5 to 19.1)	-2.5 (-9.0 to 4.0)	-2.7 (-9.3 to 3.9)	2.0 (-4.7 to 8.7)	1.8 (-5.0 to 8.6)
Ultrafiltration	14.1 (10.0 to 18.2)	5.8 (1.1 to 10.4)*	13.3 (8.7 to 18.0)‡	9.6 (4.8 to 14.3)‡	10.2 (5.5 to 14.9)‡
Difference	0.7 (-6.4 to 7.8)	8.3 (8.0 to 24.1)‡	16.1 (8.0 to 24.1)‡	7.6 (-0.6 to 15.8)	8.4 (0.1 to 16.7)*
Bolus saline					
Control	9.7 (5.1 to 14.3)	-0.3 (-5.6 to 5.1)	-3.7 (-9.1 to 1.7)	-0.8 (-4.7 to 6.2)	0.0 (-0.5 to 0.6)
Ultrafiltration	6.4 (3.2 to 9.7)	5.3 (1.6 to 9.2)†	7.3 (3.5 to 11.1)‡	9.3 (5.4 to 13.1)‡	8.4 (4.5 to 12.2)‡
Difference	-3.3 (-8.9 to 2.3)	5.6 (-0.9 to 12.1)	11.0 (4.4 to 17.6)‡	8.5 (1.8 to 15.2)*	8.4 (1.6 to 15.1)*

* represents $0.01<p<0.05$, † $0.001<p<0.01$ and ‡$p<0.001$

Table S2: Effect on Kidney Disease Quality of Life

Subdomains	Baseline Score	Change from baseline to 8 w
Symptom per problem list		
Control	76.6 (71.8 to 81.3)	0.3 (-3.1 to 3.6)
Ultrafiltration	73.2 (69.8 to 76.7)	-1.4 (-3.8 to 1.0)
Difference	-3.3 (-9.2 to 2.5)	-1.7 (-5.8 to 2.4)
Kidney Disease Effects		
Control	66.1 (59.9 to 72.3)	4.1 (-0.9 to 9.2)
Ultrafiltration	63.7 (59.3 to 68.2)	0.2 (-3.5 to 3.9)
Difference	-2.3 (-10.0 to 5.3)	-3.9 (-10.2 to 2.3)
Kidney Disease Burden		
Control	52.3 (44.7 to 59.8)	-1.3 (-7.5 to 4.8)
Ultrafiltration	45.5 (40.0 to 50.9)	2.1 (-2.3 to 6.5)
Difference	-6.8 (-16.2 to 2.5)	3.4 (-4.1 to 11.0)
Physical function		
Control	56.6 (48.8 to 64.4)	-0.3(-5.6 to 5.0)
Ultrafiltration	52.4 (46.9 to 57.9)	-2.3 (-6.1 to 1.6)
Difference	-4.2 (-13.8 to 5.3)	-2.0 (-8.5 to 4.6)
Energy/fatigue		
Control	51.5 (45.6 to 57.4)	-1.2 (-5.8 to 3.4)
Ultrafiltration	49.1 (44.9 to 53.3)	-0.1 (-3.5 to 3.2)
Difference	-2.4 (-9.7 to 4.8)	1.1 (-4.6 to 6.8)
Physical health composite		
Control	37.5 (34.5 to 40.4)	-0.7 (-2.9 to 1.6)
Ultrafiltration	37.4 (35.3 to 39.5)	-0.7 (-2.3 to 1.0)
Difference	-0.1 (-3.7 to 3.5)	-0.0(-2.8 to 2.7)
Mental health composite		
Control	49.8 (46.7 to 52.8)	-1.2 (-3.8 to 1.5)
Ultrafiltration	48.4 (46.2 to 50.7)	-1.0 (-2.9 to 1.0)
Difference	-1.3 (-5.1 to 2.5)	0.3 (-3.1 to 3.6)

Difference is ultrafiltration minus control

Dry-Weight Reduction in Hypertensive Hemodialysis Patients (DRIP): A Randomized, Controlled Trial

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