Original Articles

Shorter delivered dialysis times associate with a higher and more difficult to treat blood pressure

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ABSTRACT

Background. Shorter delivered dialysis times are associated with increased all-cause mortality. Whether shorter delivered dialysis times also associate with an increase in blood pressure (BP) and reduce the ability of probing dry weight to lower BP is unclear.

Methods. Among patients participating in the Dry-Weight Reduction in Hypertensive Hemodialysis Patients (DRIP) trial, interdialytic ambulatory BP was recorded at baseline, 4 weeks and 8 weeks. Median intradialytic BP was also calculated at each dialysis treatment and associated with the delivered daily dialysis time.

Results. The median time on dialysis at baseline was 3.6 h per treatment (range 2.5–4.5 h). At baseline, modeled median intradialytic systolic BP were higher among those who received fewer hours of dialysis. Among subjects who did not have their dry weight probed (control group), the median intradialytic systolic BP continued to be elevated. Probing dry weight (ultrafiltration group) provoked a drop in median intradialytic systolic BP regardless of the delivered dialysis time. However, the reduction in BP was achieved after fewer sessions of dialysis when delivered dialysis was longer in duration. The pattern of change was confirmed using interdialytic ambulatory BP monitoring.

Conclusions. Fewer hours of delivered dialysis are associated with a higher systolic BP. Upon probing dry weight, compared with shorter dialysis treatment times, 4 h of delivered dialysis per session provokes reductions in systolic BP over fewer dialysis treatment sessions. Reduction of BP may lag dry-weight reduction when shorter dialysis is delivered.

INTRODUCTION

According to the European Best Practice Guidelines, 4 h of dialysis delivered 3 times a week is the minimum recommended for dialysis to be considered adequate [1]. A recent report revealed that only about one quarter of the patients were receiving this recommended amount of dialysis across the USA [2]. Besides inadequate solute clearance, several adverse consequences are associated with shorter times on dialysis. Hemodynamic instability, intradialytic hypotension and inadequate dose of delivered dialysis are some of the correlates of shorter dialysis times [3, 4].

Shorter dialysis times can be due to either low prescribed time or nonadherence with dialysis treatment; the latter can be due to cutting short dialysis sessions or skipping treatments altogether. It has been known for a long time now that shorter delivered times on dialysis are associated with an increased risk of mortality. Compared with those dialyzing 3.5 h or more, those dialyzing less have a 17–118% higher risk of dying [5]. Shortening treatments or missing treatments altogether are also associated with increased all-cause mortality. For example, analysis of 6251 US patients found that each skipped hemodialysis (HD) session was associated with a 10% higher risk of mortality [6]; shortening of three of more sessions in 1 month was associated with an even higher mortality (20%) [6]. Compared with patients in Europe and Japan, nonadherence with dialysis treatments is much more common in the USA [7]. But skipping dialysis is associated with death worldwide. For example, the Dialysis Outcomes and Practice Patterns Study (DOPPS), a worldwide study, reported that skipping one or more dialysis sessions in a month...
is associated with a 30% increased mortality (risk ratio 1.30, P = 0.01) [7].

None of the studies noted above have explored the mechanistic basis underlying the association of increased mortality with reduced dialysis. Low hours of delivered dialysis can fail to remove the desired amount of fluid. Over time, subclinical hypervolemia may become more persistent; this may provoke an increase in systemic vascular resistance that may manifest as hypertension. If hypertensive subjects have their dry weight probed and they continue to low dialysis delivery times, it may cause uncomfortable intradialytic symptoms and this may not allow the achievement of dry weight and thus a lowering of BP. If so, the relationships between delivered dialysis time and subsequent BP can provide a mechanistic explanation to the high mortality rates seen with lowered dialysis delivery times.

In this study, which was an analysis of a prospectively designed, randomized controlled trial to explore dry-weight reduction versus conventional treatment among hypertensive hemodialysis patients, we asked the question whether a cross-sectional and longitudinal relationship exists between the delivered time on dialysis and blood pressure (BP).

MATERIALS AND METHODS

Study cohort

The analyses reported are post hoc results from the previously published Dry-Weight Reduction in Hypertensive Hemodialysis Patients (DRIP) trial [8]. Briefly, we recruited patients 18 years of age or older on long-term hemodialysis for at least 3 months who had hypertension defined as a mean interdialytic ambulatory BP of 135/85 mmHg or more. After a six hemodialysis run-in phase, during which baseline data were collected, patients were randomized in 1:2 proportion into the control group versus ultrafiltration trial group for 8 weeks. During this 24-dialysis treatment phase, patients were seen at each dialysis visit and had dry weight probed as assessed by symptoms and signs related to hypovolemia [9, 10]. Ambulatory BP recordings were made at baseline, 4 weeks and 8 weeks, and dialysis unit BP was recorded at each treatment. The trial was registered at ClinicalTrials.gov (NCT00067665). The Institutional Review Board of Indiana University and the Research and Development Committee of the VA Medical Center approved this study, and all patients gave their written informed consent.

Median intradialytic BP

Over a 2-week period at baseline and throughout the 24-dialysis trial (three treatments per week × 8 weeks of intervention), BPs obtained during dialysis were recorded by dialysis technicians or nurses using the oscillometric BP monitor equipped with dialysis machines. Dialysis machines used were Fresenius H 2008, Fresenius K 2008, Cobe Centry III and Cobe Plus and were maintained per protocol of the respective dialysis units. To reflect clinical practice, no technique was specified for these BP measurements. Typically, measurements were made every 30 min. These measurements were entered into a relational database. Accuracy of data entry into the database was verified by at least two technicians. Median intradialytic systolic BP was taken as the median of all BP recordings in the dialysis unit during a single hemodialysis treatment. We have previously shown that, among long-term hemodialysis patients, the median intradialytic BP can diagnose hypertension [11] and track changes in BP [12].

Ambulatory BP monitoring

Ambulatory BP monitoring was performed after the mid-week hemodialysis session for 44 h. Ambulatory BPs were recorded every 20 min during the day (6 AM to 10 PM) and every 30 min during the night (10 PM to 6 AM) using a SpaceLab 90207 ABP monitor (SpaceLabs Medical, Inc., Redmond, WA) in the nonaccess arm, as done previously [13]. Recordings began immediately after hemodialysis and were terminated immediately before the subsequent dialysis. Accuracy of ambulatory BP recordings was confirmed against auscultated BP at baseline. Data were analyzed using ABP Report Management System software, version 1.03.05 (SpaceLabs Medical, Inc., Redmond, WA). The mean interdialytic ambulatory BP was used to assess the similarity of change in BP pattern with the median intradialytic BP.

Statistical analysis

Baseline characteristics were compared between groups dichotomized by the median time of delivered dialysis using an unpaired t-test for continuous variables and a $\chi^2$-test for categorical variables. Baseline median intradialytic BP over 6 dialysis treatments was compared with the median intradialytic BP over 24 treatments during intervention using mixed models. Specifically, the mean difference between median intradialytic systolic BP was compared using a random coefficient model to account for repeated observations [14]. The dialysis treatment number was used as a continuous variable, whereas treatment (ultrafiltration or control) and phase (baseline or intervention) were specified as indicator variables. The outcome variable was the median intradialytic systolic BP. The fixed explanatory variables were treatment, phase, dialysis treatment number, square of the dialysis treatment number and all possible interactions. The square of the dialysis treatment number was added to model the lag phenomenon after confirming that the model with the squared term was statistically different from the one without. The random variables were subject and dialysis treatment number with an unstructured covariance matrix. To simplify the model, we assumed a fixed intercept during the baseline period for either group and dropped the quadratic term for the control group.

To evaluate the effect of delivered dialysis time, we calculated the actual time of delivered dialysis. These delivered dialysis times were interacted with the fixed factors noted above. We first tested the effect of delivered dialysis time by comparing the nested models using a likelihood ratio test. After rejecting the null hypothesis, we created the predicted median intradialytic systolic BP for the categories of 2, 3 and 4 h delivered dialysis. These times were arbitrarily chosen, but these allowed the comparison of extremes of delivered dialysis times.
The nominal level of significance was set at a two-sided P-value of <0.05, and all statistical analyses were performed with Stata version 11.2 (StataCorp LP, College Station, TX).

**RESULTS**

The baseline characteristics of groups that received less than median dialysis and median dialysis or more are shown in Table 1. Among the 150 patients who participated, the average age was 54 years, 69% were men, 87% were black, 55% had diabetes and the average vintage was 4.4 years. All patients were hemodialyzed three times weekly, at a blood flow rate of 400 mL/min and dialysate flow rate of 765 mL/min. The baseline characteristics were well matched except that those who received dialysis less than median time received more antihypertensive medications. The average number of antihypertensive medications was 2.5 in the group that received less than median hours of dialysis 1.9 in the group that received more than median hours on dialysis (P = 0.02). Those receiving fewer hours were also lighter by about 12 kg; therefore, the urea reduction ratios were matched.

Figure 1 shows the mean delivered times on dialysis at baseline and over 8 weeks of intervention. The times of delivered dialysis had an overall median of 3.6 h, and there was no statistically significant difference between the ultrafiltration and control groups over time. Thus, one group did not have more or less delivered treatment time compared with the other.

As reported earlier, postdialysis weight was reduced by 0.9 kg at 4 weeks and culminated in change from baseline between the groups of −6.9 mmHg [95% confidence interval (95% CI) −12.4 to −1.3 mmHg; P = 0.016] in systolic interdialytic ambulatory BP and −3.1 mmHg (95% CI −6.2 to −0.02 mmHg; P = 0.048) change in diastolic ambulatory BP [8]. At 8 weeks, dry weight was reduced 1 kg in the ultrafiltration group. From baseline, systolic ambulatory BP changed −6.6 mmHg (95% CI −12.2 to −1.0 mmHg; P = 0.021) between the groups, and diastolic ambulatory BP changed −3.3 mmHg (95% CI −6.4 to −0.2 mmHg; P = 0.037).

**Median intradialytic systolic BP**

The pattern of change in median intradialytic systolic BP is shown in Figure 2. BP levels were similar at baseline. In the control group, median intradialytic systolic BP remained elevated. In the intervention group, the median intradialytic systolic BP fell over 4 weeks (12 treatments) and remained low thereafter. Thus, a quadratic relationship was seen. A good agreement can be seen between observed and modeled median recordings per patient, there were only three ambulatory BP readings per participant. Thus, the ambulatory BP recordings were less precise in depicting the time course of BP change.

**DISCUSSION**

Earlier reports from this cohort have demonstrated that interdialytic ambulatory BP measurements improve with probing dry weight [8]. Furthermore, the median systolic BP measured on single occasions at baseline, 4 weeks and 8 weeks was able to detect the change observed with ambulatory BP [12]. The results of this study extend our earlier reports in several ways. (i) BP is higher and the need for antihypertensive agents greater among long-term hemodialysis recipients who dialyze for fewer hours. (ii) Among these patients, if dry weight is not probed, BP continues to be elevated. (iii) BP declines regardless of the delivered dialysis times upon probing dry weight and mostly in the first 4 weeks of probing dry weight. (iv) However, upon probing dry-weight BP declines more rapidly, i.e. BP decline occurs over fewer dialysis treatments when more hours of dialysis are delivered. (v) These changes in median intradialytic BP are recapitulated by interdialytic ambulatory BP.

Hypertension is prevalent in 60–90% of maintenance dialysis patients, and volume excess plays a central role in its pathogenesis [15, 16]. Experience from Tassin, France showed that long HD, 8 h three times a week was associated with excellent survival and low morbidity results mainly due to drug-free BP control and low incidence of interdialytic hypotension [3, 4]. Longitudinal studies including Frequent Hemodialysis Network trials have demonstrated the need for fewer antihypertensive drugs and better BP with longer dialysis [17, 18]. However, these studies were on different forms of dialysis modality than what is traditionally practiced in the USA. Our study results are directly applicable to hemodialysis care among patients getting thrice weekly dialysis without changing the dialysis modality.

For long-term hemodialysis patients, the minimum recommended treatment time that is considered adequate is 4 h [1]. Four hours enable adequate delivery of dialysis through the removal of toxins. More important, together with a sensible dietary sodium intake, 4 hours of dialysis allow an adequate time over which excess fluid volume can be removed without provoking uncomfortable dialysis symptoms. Inadequate prescription or shortened delivery of dialysis times necessitates the rapid removal of fluid, thus provoking hemodynamic instability and its downstream consequences [19]. Furthermore, hypervolemia among hemodialysis patients is associated with increased mortality [20]. European Best Practice guidelines suggest that dialysis treatment time or frequency should be increased if BP remains uncontrolled despite adequate volume removal [1]. Our study demonstrates that, among conventional three times a week dialysis patients, shortened dialysis times...
are associated with a higher BP. Among people who have their dry weight challenged, a shorter dialysis increases the time before which reduction in BP is seen.

Earlier studies have shown a strong and consistent association with lower dialysis delivery times with increased all-cause mortality. Our study provides one mechanism of why this may be so. Reduced dialysis delivery times increases the likelihood that the patient leaves the dialysis unit in a volume overloaded state and with repetitive missed treatments, patients may never achieve euvoeemia. Even when dry weight is probed, reduction in volume may produce reduction of BP over a much longer period. Volume excess and elevated BP both can cause myocardial dysfunction and culminate in increased mortality. Rahman et al. [21] showed that among 5369 long-term dialysis patients who received less dialysis as a consequence of missing or shortening one or more dialysis treatments had a higher BP. Our study supports their cross-sectional predialysis and postdialysis BP data with the median and interdialytic ambulatory BP recordings. We are not aware of any longitudinal studies that have explored the relationship between low hours of delivered dialysis and achieved BP. Furthermore, no study, to our knowledge, either longitudinal or cross-sectional, has explored this relationship using ambulatory BP monitoring.

### Table 1. Baseline clinical characteristics of the study population

<table>
<thead>
<tr>
<th>Variable</th>
<th>Less than median hours on dialysis</th>
<th>More than median hours on dialysis</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delivered dialysis time (h/treatment)</td>
<td>3.25 ± 0.25</td>
<td>3.89 ± 0.21</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age (years)</td>
<td>54.4 ± 13.3</td>
<td>55.2 ± 11.5</td>
<td>0.68</td>
</tr>
<tr>
<td>Men, n (%)</td>
<td>47 (62.7%)</td>
<td>56 (74.7%)</td>
<td>0.11</td>
</tr>
<tr>
<td>Blacks, n (%)</td>
<td>63 (84%)</td>
<td>67 (89.3%)</td>
<td>0.34</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>39 (52%)</td>
<td>43 (57.3%)</td>
<td>0.57</td>
</tr>
<tr>
<td>Smokers, n (%)</td>
<td>27 (36%)</td>
<td>25 (33.3%)</td>
<td>0.29</td>
</tr>
<tr>
<td>Congestive heart failure, n (%)</td>
<td>7 (9.3%)</td>
<td>12 (16%)</td>
<td>0.19</td>
</tr>
<tr>
<td>Myocardial infarction, n (%)</td>
<td>12 (16%)</td>
<td>5 (6.7%)</td>
<td>0.07</td>
</tr>
<tr>
<td>Stroke, n (%)</td>
<td>4 (5.3%)</td>
<td>10 (13.3%)</td>
<td>0.1</td>
</tr>
<tr>
<td>End-stage renal disease duration (years)</td>
<td>5 ± 6.5</td>
<td>3.9 ± 5.1</td>
<td>0.28</td>
</tr>
<tr>
<td>44-h ambulatory systolic BP (mmHg)</td>
<td>145.9 ± 11.2</td>
<td>146.3 ± 9.5</td>
<td>0.79</td>
</tr>
<tr>
<td>44-h ambulatory diastolic BP (mmHg)</td>
<td>83.4 ± 9.7</td>
<td>82.9 ± 10.6</td>
<td>0.74</td>
</tr>
<tr>
<td>44-h ambulatory pulse rate (per min)</td>
<td>77.5 ± 10.2</td>
<td>77.6 ± 10.6</td>
<td>0.95</td>
</tr>
<tr>
<td>Antihypertensive drug use (n/patient)</td>
<td>2.5 ± 1.6</td>
<td>1.9 ± 1.5</td>
<td>0.02</td>
</tr>
<tr>
<td>Beta-blocker use, n (%)</td>
<td>50 (66.7%)</td>
<td>52 (69.3%)</td>
<td>0.73</td>
</tr>
<tr>
<td>Angiotensin-convertingenzyme inhibitor, n (%)</td>
<td>44 (58.7%)</td>
<td>32 (42.7%)</td>
<td>0.05</td>
</tr>
<tr>
<td>Angiotensin receptor blocker, n (%)</td>
<td>12 (16%)</td>
<td>11 (14.7%)</td>
<td>0.82</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>11.9 ± 1.4</td>
<td>12.2 ± 1.2</td>
<td>0.1</td>
</tr>
<tr>
<td>Serum albumin (g/dL)</td>
<td>3.6 ± 0.4</td>
<td>3.8 ± 0.5</td>
<td>0.07</td>
</tr>
<tr>
<td>Serum creatinine (mg/dL)</td>
<td>9.8 ± 3.3</td>
<td>10.3 ± 3</td>
<td>0.31</td>
</tr>
<tr>
<td>Serum calcium (mg/dL)</td>
<td>8.9 ± 0.7</td>
<td>9 ± 0.8</td>
<td>0.59</td>
</tr>
<tr>
<td>Serum phosphorus (mg/dL)</td>
<td>5.2 ± 1.5</td>
<td>5.5 ± 1.6</td>
<td>0.22</td>
</tr>
<tr>
<td>Predialysis blood urea nitrogen (mg/dL)</td>
<td>47 ± 15.6</td>
<td>48.9 ± 13.7</td>
<td>0.43</td>
</tr>
<tr>
<td>Postdialysis blood urea nitrogen (mg/dL)</td>
<td>12.5 ± 7.3</td>
<td>13.8 ± 7</td>
<td>0.26</td>
</tr>
<tr>
<td>Urea reduction ratio (%)</td>
<td>74.2 ± 7.8</td>
<td>73.1 ± 6.5</td>
<td>0.32</td>
</tr>
<tr>
<td>Predialysis weight (kg)</td>
<td>78.4 ± 18.7</td>
<td>90.4 ± 19.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Postdialysis weight (kg)</td>
<td>75.7 ± 18.1</td>
<td>87.2 ± 19</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Median delivered dialysis time at baseline 3.6 h/treatment ± represents standard deviation.
Our study has limitations. (i) The majority of the participants were black. Although race should not influence the measurement of BP or delivered dialysis times, whether these data are applicable to nonblacks requires further studies. (ii) We only looked at delivered time on dialysis and were not powered to tease out the differences in BP achieved between shorter prescribed dialysis time and nonadherence with prescribed dialysis treatments. (iii) There were differences in weight, and likely body composition, among those who received less or more dialysis. The protocol for reduction on dry weight may have influenced the BP response. A merit of our study is the large number of intradialytic BP measurements that were prospectively collected in the setting of a randomized controlled clinical trial allowing the determination of median BP and detection of the pattern of change. We used median intradialytic BP at each dialysis to describe the overall pattern of BP change since the median intradialytic BP was available at each treatment. We confirmed these results using interdialytic ambulatory BP recordings. We used ambulatory BP as a reference standard because ambulatory BP recording is an accurate estimate of arterial pressure and shares a stronger relationship with all-cause mortality compared with BPs obtained before.

**Figure 1:** Mean delivered times on dialysis at baseline and over 8 weeks of intervention. The times of delivered dialysis had an overall median of 3.5 h, and there was no statistically significant difference between groups over time. Error bars represent one standard error of the mean.

**Figure 2:** Observed and modeled patterns of change in median intradialytic systolic BP. BP levels were similar at baseline. The vertical dashed line denotes the end of the baseline period and the start of the intervention period. In the control group, median intradialytic systolic BP remained elevated. Open circles represent the observed BP and the broken vertical lines one standard error of the mean. In the intervention group, median intradialytic systolic BP fell over 4 weeks (12 treatments) and remained low thereafter (subsequent 12 treatments). Solid squares represent the observed BP in the intervention group, and the solid line the modeled quadratic relationship. A good agreement can be seen between observed and modeled median intradialytic systolic BP recordings for both control and ultrafiltration (UF) groups.
or after dialysis [22]. These data suggest that, on average, there does not appear to be a lag between probing dry weight and reduction in BP. However, among those who have lower dialysis delivery times, a lag between attempts to lower dry weight and subsequent drop in BP can be observed.

There are several implications of our study. (i) The median intradialytic BP can track BP longitudinally and detect the patterns of change in BP rapidly. (ii) Longer treatment times may increase the time over which reduction of BP occurs. (iii) Since median BP is readily available and is responsive to change, consideration of intradialytic BP recordings may improve the diagnosis and management of hypertension among hemodialysis patients [23]. (iv) These data support future guidelines that emphasize the need to deliver at least 4 h of dialysis for all patients on dialysis. Our study challenges the notion of prescribing dialysis based on the clearance of small molecules and therefore target $K_t/V$ only. Our data support the concept of BP control as a surrogate for volume control; it supports the idea of prescribing dialysis treatment time that allows the achievement of euvolemia and therefore BP [3, 4, 24–26].

**FIGURE 3:** Modeled relationship between median intradialytic BP and the delivered time on dialysis. Relationships are modeled for delivered dialysis of 2, 3 and 4 h durations. At baseline, median intradialytic systolic BP was higher with fewer hours of delivered dialysis. Among subjects who did not have their dry weight probed (control group shown with dotted lines), median intradialytic systolic BP continued to be elevated. Probing dry weight (ultrafiltration group shown with solid lines) provoked a drop in median intradialytic systolic BP regardless of the delivered dialysis time. However, the reduction in BP was achieved after fewer sessions of dialysis when delivered dialysis was longer in duration.

**FIGURE 4:** Modeled relationship between interdialytic ambulatory systolic BP and the delivered time on dialysis. The pattern of change with ambulatory BP was similar to that seen with median intradialytic systolic BP. There were only three measurements of ambulatory BP; therefore, the patterns of change are more difficult to discern.
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CONFLICT OF INTEREST STATEMENT

R.A. is a consultant to Roche, Merck, Takeda, Daiichi Sankyo, Sigma Tau, serves on the speaker bureau of Merck and Abbott, steering committees of Abbott and Reata, and has received research support from National Institutes of Health, VA and Daiichi Sankyo.

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