Intradialytic hypertension is a marker of volume excess

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Abstract

Background. Intradialytic blood pressure (BP) profiles have been associated with all-cause mortality, but its pathophysiology remains unknown. We tested the hypothesis that intradialytic changes in BP reflect excess volume.

Methods. The dry weight reduction in hypertensive haemodialysis patients (DRIP) trial probed dry weight in 100 prevalent haemodialysis patients; 50 patients who did not have their dry weight probed served as time controls. In this post hoc analysis, intradialytic BP was recorded at each of the 30 dialysis treatments during the trial. The slope of intradialytic BP over dialysis was calculated by the log of BP regressed over time. Using a linear mixed model, we compared these slopes between control and ultrafiltration groups at baseline and over time, tested the effect of dry weight reduction on these slopes and finally tested the ability of change in intradialytic slopes to predict change in interdialytic systolic BP.

Results. At baseline, intradialytic systolic and diastolic BP dropped at a rate of ∼3%/h (P < 0.0001). Over the course of the trial, compared to the control group, the slopes steepened in the ultrafiltration group for systolic but not diastolic BP. Those who lost the most post-dialysis weight from baseline to 4 weeks and baseline to 8 weeks also ex-
performed the greatest steepening of slopes. Each percent per hour steepening of the intradialytic systolic BP slope was associated with 0.71 mmHg [95% confidence interval (CI) 0.01–1.42, P = 0.048] reduction in interdialytic ambulatory systolic pressure.

Conclusions. Intradialytic BP changes appear to be associated with change in dry weight among haemodialysis patients. Among long-term haemodialysis patients, intradialytic hypertension may, thus, be a sign of volume overload.

Keywords: ambulatory BP; dry weight; haemodialysis; hypertension; sodium

Introduction

Blood pressure usually declines with ultrafiltration dialysis in the majority of patients. However, in ~10–15% of the patients, blood pressure (BP) can increase during dialysis [1]. Emerging data suggest that intradialytic hypertension is associated with poor outcomes [2]. However, the mechanisms of these poor outcomes are poorly understood.

There are several possibilities that can relate intradialytic hypertension to increase in mortality rate. These possibilities include the following: (i) a rising BP may be a manifestation of endothelin excess [3]; endothelin excess is associated with endothelial dysfunction and atherosclerosis which may manifest in the observed increased mortality [4]. (ii) Patients with a rising peridialytic systolic BP have decreased oral intake, more wasting, and have significantly lower serum albumin, all of which by themselves portend poor outcomes [5]. (iii) Intradialytic hypertension may be due to activation of either sympathetic nervous system or the renin–angiotensin system, but as reviewed by Inrig, the direct evidence implicating either of these two pathways is preliminary [6]. (iv) Intradialytic BP can rise due to high calcium dialysate that increased myocardial contractility and peripheral resistance or low potassium dialysate which can lead to vasoconstriction or stimulate the sympathetic nervous system [7–9]. (v) Finally, the rise in BP may be due to inadequate volume removal coupled with higher dialysate sodium use [10]. We offered the latter possibility in a recent editorial to explain the high mortality associated with intradialytic hypertension, but the experimental evidence to support this hypothesis is lacking [11].

In a scholarly review of intradialytic hypertension, Inrig concluded, ‘further work is necessary to elucidate the pathophysiologic mechanisms of intradialytic hypertension and its appropriate management and determine whether treatment of intradialytic hypertension can improve clinical outcomes.’ [6]. Accordingly, in this study, we asked the following questions: (i) Is the relationship between intradialytic systolic BP and volume removal modified by the intent to reduce dry weight?; (ii) Does the change in post dialysis weight track with change in intradialytic BP?; and (iii) Does the slope of systolic BP with volume removal predict the subsequent change in ambulatory BP?

Affirmative answers to these three questions would suggest that intradialytic hypertension is a marker of volume overload.

Materials and methods

Study cohort

The analyses reported are post hoc results from a previously published dry weight reduction in hypertensive haemodialysis patients (DRIP) trial [12]. Briefly, we recruited patients 18 years of age or older on long-term haemodialysis for at least 3 months, who had hypertension defined as mean intradialytic ambulatory BP of 135/85 mmHg or more. After a six haemodialysis run-in phase, during which baseline data were collected, patients were randomized in 1:2 proportion into control group vs. ultrafiltration trial group for 8 weeks. During this 24 dialysis treatments phase, patients were seen at each dialysis visit and had dry weight probed as assessed by symptoms and signs related to hypovolaemia [13,14]. Among all participants, ambulatory BP was recorded at baseline, 4 weeks and 8 weeks, and dialysis unit BP was recorded at each treatment. The protocol specified that antihypertensive drugs not be changed during the trial. Thus, for maintaining patient safety, participants were excluded if intradialytic ambulatory BP reached 175/105 mmHg or more at any point in the trial. If the patients experienced symptomatic hypotension, no further reduction in dry weight was made. 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.

Intradialytic BP

Over a 2-week period at baseline and throughout the 24 dialysis interventions period, BP was recorded during dialysis 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 the protocol of the respective dialysis units. To reflect clinical practice, no technique was specified for measurement of 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 people.

Ambulatory BP monitoring

Ambulatory BP monitoring was performed after the mid-week haemodialysis 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, USA) in the non-access arm, as done previously [15]. Recordings began immediately after haemodialysis and were terminated immediately before the subsequent dialysis. Accuracy of ambulatory BP recordings was confirmed against auscultated BP at baseline. Data were analysed using ABP Report Management System software, version 1.03.05 (SpaceLabs Medical Inc, Redmond, WA, USA). The mean intradialytic ambulatory BP served as the reference standard.

Statistical analysis

There are no standardized definitions of intradialytic hypertension. It is quite likely that intradialytic hypertension represents a continuum and that any definition based on a discrete cutoff is prone to error. Therefore, we defined the relationship of each of the two BP intradialytic systolic and diastolic BPs over the course of dialysis by linear regression. As would be expected, the relationship had negative slopes and followed an exponential relationship. Thus, systolic and pulse pressures were naturally log transformed prior to analysis. Using a linear mixed model, we compared these slopes between control and ultrafiltration groups at baseline and over time [16]. Six dialysis treatments prior to the 24 dialysis interventions phase served to define the baseline. The changes in slopes were compared to the intradialytic ambulatory BP response at 4 and 8 weeks. Indicator variables were used for each of the two groups (control and ul-
trafiltration) as well as for each of the three dialysis treatment periods.

Treatment periods constituted the baseline (6 dialysis treatments), Week 4 (12 dialysis treatments from post-baseline to Week 4) and Week 8 (12 dialysis treatments from post-Week 4 to Week 8). The terms used in the fixed part of mixed model were the following: period, group × period, hours of dialysis treatment, period × hours of dialysis treatment and group × period × hours of dialysis treatment. The terms used in the random component of the model were subject and hours of dialysis treatment nested within each dialysis visit. An unstructured covariance matrix was used to model the random component.

After fitting the mixed model, the slopes were computed for baseline, from post-baseline to 4 weeks and from 4 to 8 weeks by using the formula, \(100 \times [1 - \exp (\beta)]\), where \(\beta\) was the regression coefficient associated with the period and group.

Next, we computed the change in post-dialysis weight from baseline to 4 weeks and from baseline to 8 weeks. These changes were divided into quartiles. The relationship of the quartiles of change in post-dialysis weight was evaluated for its ability to detect changes in intradialytic systolic BP slope from baseline to 4 weeks and from baseline to 8 weeks. A mixed effects linear intercept model was used, one each for modelling the intradialytic systolic BP slope from baseline to 4 weeks and another from baseline to 8 weeks. The terms used in the fixed part of mixed model were the following: period, quartile, quartile × period, hours of dialysis, period × hours of dialysis treatment, quartile × hours of dialysis treatment, period × hours of dialysis treatment and quartile × period × hours of dialysis treatment. The terms used in the random component of the model were subject and hours of dialysis treatment nested within each dialysis visit. An unstructured covariance matrix was used to model the random component.

We finally calculated the change in intradialytic systolic BP slopes from baseline to 4 weeks and from baseline to 8 weeks. A negative change in slopes denoted steepening of slopes. Using a mixed effects model similar to above, the relationship of these changes in intradialytic systolic BP slopes was compared to ambulatory BP change observed in the corresponding weeks in the trial.

### Table 1

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<thead>
<tr>
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<th>Control</th>
<th>Ultrafiltration</th>
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<tbody>
<tr>
<td>Average slope of systolic BP (%/hr)</td>
<td>0.60, p=0.012</td>
<td>0.75, p=0.003</td>
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<td>0.21, p&gt;0.2</td>
<td>-0.09, p&gt;0.2</td>
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**Fig. 1.** Mean slopes of systolic BP (and SEM) over dialysis treatments are shown. The numbers and their P-value reflect the changes from baseline in the corresponding periods. In the control group, the slopes of systolic BP did not change over the course of the trial. In the ultrafiltration group, the slopes of systolic BP change became steeper. The difference in slopes at both 4 and 8 weeks from baseline was statistically significant. When compared to the corresponding change from baseline in the control group, the change from baseline in the ultrafiltration group was 0.38, P = 0.20 at 4 weeks and 0.84, P = 0.035 at 8 weeks.

### Table 2

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<th>Control</th>
<th>Ultrafiltration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average slope of diastolic BP (%/hr)</td>
<td>0.36, P = 0.11</td>
<td>0.41, P = 0.08</td>
</tr>
<tr>
<td></td>
<td>0.18, P &gt; 0.2</td>
<td>-0.11, P &gt; 0.2</td>
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**Fig. 2.** Mean slopes of diastolic BP (and SEM) over dialysis treatments are shown. The numbers and their P-values reflect the changes from baseline in the corresponding periods. In the control group, slopes of diastolic BP did not change over the course of the trial. In the ultrafiltration group, the slopes of diastolic BP change became steeper. The change in slopes from baseline at neither 4 nor 8 weeks was statistically significant. When compared to the corresponding change from baseline in the control group, the change from baseline in the ultrafiltration group was 0.17 at 4 weeks and 0.53 at 8 weeks.
The nominal level of significance was set at a two-sided P of <0.05, and all statistical analyses were performed with Stata version 11 (Stata-Corp LP, College Station, TX, USA).

Results

Among the 150 patients (50 controls, 100 ultrafiltration) who participated, the average age was 54 years, 69% were men, 87% were black, 39% had diabetes and the average vintage was 4.1 years. The average number of antihypertensive medications was 2.7, and 84% of the participants were using antihypertensive drugs. The types of antihypertensive drugs used in the ultrafiltration/control group were well balanced and were as follows: beta-blockers 71%/64%, dihydropyridine calcium channel blockers 48%/40%, centrally acting agents 26%/20%, angiotensin-converting enzyme (ACE) inhibitors 52%/50%, angiotensin receptor blockers 19%/8%. Other antihypertensive drugs were used in <10% of the participants. During the 2-day interdialytic period, median weight gain was 2.35 kg, 10th percentile weight gain was 1.05 kg, and 90th percentile weight gain was 4.03 kg and was similar between groups. Urea reduction ratio was 74.1% in the ultrafiltration group and 73.4% in the controls. Dialysate sodium averaged 141.7 ± 3.0 in the control group and 141.9 ± 2.8 in the ultrafiltration group with 46% in each of the two groups receiving a modelled sodium prescription. Dialysate calcium was 2.5 mEq/L in 92% of the controls and 86% of the ultrafiltered patients. Dialysate sodium or calcium prescription was left unchanged throughout the trial. All patients were haemodialysed three times weekly for an average of 235 min, at a blood flow rate of 400 mL/min and dialysate flow rate of 765 mL/min. The baseline characteristics were well matched between groups.

As reported earlier, post-dialysis weight was reduced by 0.9 kg at 4 weeks and resulted in −6.9 mmHg [95% confidence interval (CI) −12.4 to −1.3 mmHg; P = 0.016] change 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 [12]. At 8 weeks, dry weight was reduced by 1 kg. From baseline, systolic ambulatory BP changed −6.6 mmHg (95% CI: −12.2 to −1.0 mmHg; P = 0.021), and diastolic ambulatory BP changed −3.3 mmHg (95% CI: −6.4 to −0.2 mmHg; P = 0.037).

Systolic BP slopes

Slopes of systolic BP over dialysis treatments calculated from 32 894 BP readings in 150 patients are shown in Figure 1. The mean slope in the control group at baseline was 3.07%/h (95% CI 2.47–3.66, P < 0.0001). Among patients in the control group, slopes of systolic BP did not change over the course of the trial. However, among patients in the ultrafiltration group, the slopes of systolic BP change became steeper. The change from baseline at both 4 weeks (0.60%/h, P = 0.012) and 8 weeks (0.75%/h, P = 0.003) was statistically significant. When compared to the corresponding change from baseline in the control group, the change from baseline in the ultrafiltration group was 0.38, P = 0.20 at 4 weeks and 0.84, P = 0.035 at 8 weeks.

Diastolic BP slopes

Slopes of diastolic BP over dialysis treatments are shown in Figure 2. The mean slope in the control group at baseline was 2.93%/h (95% CI 2.28–3.59, P = 0.0001). Among patients in the control group, slopes of diastolic BP did not change over the course of the trial. Among patients in the ultrafiltration group, although the slopes of diastolic BP change became steeper, they did not achieve the nominal level of significance (0.36, P = 0.11 at 4 weeks and 0.41, P = 0.08 at 8 weeks).

Given that only the systolic BP slopes were significant over the duration of this trial, further analyses are reported.
only for changes with respect to changes in systolic BP slopes.

Effect of post-dialysis weight change on systolic BP slopes

The relationship between quartiles of weight loss and systolic BP slopes is shown in Figure 3. At 4 weeks, the 25, 50 and 75 percentiles of weight change were $-0.94$, $-0.36$ and 0.11 kg, respectively. At 8 weeks, the 25, 50 and 75 percentiles of weight change were $-1.25$, $-0.42$ and 0.40 kg, respectively. Quartile 1 had the least weight change (gained $>0.11$ kg weight at Week 4), and consequently, the change in slope of intradialytic BP was not significant. The lack of significance was true for both models: baseline to 4 weeks and from baseline to 8 weeks. Quartile 4 had the greatest weight change (lost $>0.94$ kg weight at Week 4) and also had the greatest change in slope for both models shown in the right and left panels of Figure 3. The relationship between the overall change in slopes and quartiles of weight change was highly significant ($P < 0.001$) for both models.

At the end of 4 weeks or at the end of 8 weeks, the slopes between quartiles were similar. However, at baseline, the slopes were flatter if the patients were in the top quartile of weight loss. At both 4 and 8 weeks, the baseline slope of the top quartile of weight loss (Quartile 4) was significantly different from baseline slope of the least quartile of weight loss. The difference from the mean change in slope in Quartile 4 (2.69%/h, $P < 0.001$) and the mean change in slope in Quartile 1 (0.35%/h, $P = 0.20$) was significantly different at Week 4 ($\Delta/\Delta 2.34\%$/h, $P = 0.013$). The difference from the mean change in slope in Quartile 4 (3.42%/h, $P < 0.001$) and the mean change in slope in Quartile 1 (0.62%/h, $P = 0.08$) was also significantly different at Week 8 ($\Delta/\Delta 2.79\%$/h, $P = 0.007$).

Systolic BP slopes and interdialytic ambulatory BP

The relationship between interdialytic ambulatory BP and systolic BP slopes is shown in Figure 4. Plotted on the $y$-axis, a negative change in mean interdialytic BP denotes a reduction in BP. Plotted on the $x$-axis, a negative change in intradialytic slope denotes a steepening of slopes. The intercept at zero change in the slope of intradialytic systolic BP was $-9.17$ mmHg ($P < 0.001$). The slope of the regression line was 0.71 mmHg (95% CI 0.01–1.42, $P = 0.048$) %/h. Thus, steepening of the slope of intradialytic BP was associated with mean reduction in overall interdialytic ambulatory systolic BP.

Discussion

The major findings of this study are the following: (i) during the dialysis session, both systolic and diastolic BP fall at a rate of $\sim3\%/h$ ($P < 0.0001$); (ii) at intent to reduce dry weight leads to steepening of the slopes for systolic but not for diastolic BP (Figures 1 and 2); (iii) this steepening of intradialytic systolic BP slopes is strongly related to the loss in post-dialysis weight (Figure 3); and (iv) each percent per hour steepening of the intradialytic systolic BP slope is associated with 0.71 mmHg (95% CI 0.01–1.42, $P = 0.048$) reduction in interdialytic ambulatory systolic BP.

The results of this study begin to explain some of the associations between intradialytic hypertension and poor outcomes. As shown in Figure 3, patients who subsequently had the greatest decline in weight (Quartile 4, solid line) had the flattest slopes at baseline. In fact, the mean slope was less than zero at baseline which implies that these patients experienced intradialytic systolic hypertension. At baseline, these patients had a significantly flatter slope compared to those who lost the least weight or even
gained weight (Quartile 1). However, after an ultrafiltration-induced fall in dry weight, these patients had slopes that were similar to the other quartiles. These data imply that intradialytic hypertension may be a sign of excessive extracellular fluid volume. This excess volume is not always manifested by over the signs of volume overload [17]. Excess dry weight over time may lead to worse hypertension, congestive heart failure, pneumonia and increased mortality.

Inrig et al. reported that patients who experience intradialytic hypertension are thinner, have lower muscle mass (lower serum creatinine) and take more antihypertensive medications [5]. Greater intake of antihypertensive medications may be necessitated by not being at dry weight, and those who have a lower weight and muscle mass are more likely to experience a rise in BP with minimal volume excess. Our data also extend the interventional cohort of Cirit et al. of seven hypertensive patients on haemodialysis with marked cardiac dilatation who experienced paradoxical hypertension during dialysis [18]. After probing dry weight, both BP and post-dialysis weight were reduced; BP reduction was 46/22 mmHg, and post-dialysis weight was reduced by 6.7 kg. They concluded, and we agree, that BP may paradoxically rise with ultrafiltration when patients are volume overloaded.

Our study provides an important link between change in intradialytic systolic BP profiles and change in interdialytic systolic BP (Figure 4). Although our study demonstrates an association of steepening of intradialytic systolic BP slopes with reduction in interdialytic ambulatory BP, the confidence intervals that surround this regression are wide. Accordingly, the strength of the relationship between intradialytic change in systolic BP and subsequent change in interdialytic systolic BP is weak. Thus, simply because the patient had steeper drop in intradialytic BP does not guarantee that interdialytic ambulatory BP will fall.

A shortcoming of our study is that the majority of the participants were black. Although race should not influence the slopes of BP change during dialysis, whether these data are applicable to non-blacks requires further studies. 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 and that each intradialysis BP recording was regressed against dialysis time to derive the intradialytic BP profile. It is now well recognized that peridialytic BP recordings themselves are prone to high variability [19]. Because we modelled over 30 000 intradialytic BP recordings, a random error despite using only 150 patients was likely mitigated.

There are two implications of our study. (i) For clinicians, our study shows that intradialytic hypertension should trigger an evaluation of dry weight. The ‘paradoxical’ rise in BP may not be such a paradox after all. Achieving dry weight may lead to a normal decline in BP over a dialysis treatment and achievement of a more normal interdialytic ambulatory BP. (ii) Since intradialytic BP recordings are readily available, epidemiologists may want to assess the prognostic significance of intradialytic BP profiles and its change over time on cardiovascular events and mortality; this may better clarify the prognostic significance of intradialytic hypertension instead of simply using pre- and post-dialysis measurements [20].

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Conflict of interest statement. None declared.

References

Geriatric Nutritional Risk Index in haemodialysis patients

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Abstract

Background. Malnutrition is a common complication in haemodialysis patients. Recently, the Geriatric Nutritional Risk Index (GNRI) has been reported as a simple and accurate tool to assess nutritional status of haemodialysis patients. Our objective was to examine the association between GNRI and mortality in chronic haemodialysis patients.

Methods. We examined the GNRI of 490 maintenance haemodialysis patients (60 ± 12 years, 293 males and 197 females) and followed up these patients for 60 months. Predictors for all-cause death were examined using Kaplan–Meier analysis and Cox proportional analyses.

Results. The GNRI was 98.0 ± 6.0, and was significantly and negatively correlated with age and haemodialysis duration. During the 60-month follow-up period, 129 patients died. According to the highest positive likelihood and risk ratios, the cutoff value of GNRI for mortality was set at 90. Kaplan–Meier analysis revealed that patients with a GNRI <90 (n = 50) had a significantly lower survival rate, compared to those with GNRI ≥90 (n = 440) (log-rank test, P < 0.0001). Multivariate Cox proportional hazards analyses demonstrated that GNRI was a significant predictor for mortality [hazard ratio (HR) 0.962, 95% confidence interval (CI) 0.931–0.995, P < 0.05], after adjustment for age, gender, C-reactive protein, presence of diabetes and haemodialysis duration.

Conclusions. These results demonstrated that GNRI is a significant predictor for mortality in haemodialysis patients. The simple method of GNRI is considered to be a clinically useful marker for the assessment of nutritional status in haemodialysis patients.

Keywords: Geriatric Nutritional Risk Index; haemodialysis; malnutrition; mortality

Introduction

Protein–energy wasting (PEW), or malnutrition, is highly prevalent in maintenance haemodialysis patients [1], and is associated with increasing risk of mortality [2]. Malnutrition and nutritional management is important for patients on maintenance haemodialysis, and regular nutritional assessment is recommended for all dialysis patients [1,2,3]. For the assessment of the nutritional status of haemodialysis patients, there are several methods, including subjective global assessment (SGA) [4,5] and malnutrition–inflammation score [6]. However, since these methods utilize several subjective assessments and judgements, assessment by a well-trained staff is necessary to obtain consistent results between different examiners and institutions. Furthermore, these methods are somewhat time-consuming and cumbersome.

Without the use of several subjective assessments, there are some simpler, more objective nutritional assessments that have been developed for use in various patients, such as hospitalized, post-operative and elderly patients. These methods include the Mini Nutritional Assessment-Short Form (MNA-SF) [7], Nutrition Risk Score (NRS) [8], Malnutrition Universal Screening Tool (MUST) [9], Malnutrition Screening Tool (MST) [10] and Geriatric Nutritional Risk Index (GNRI) [11]. The GNRI was developed as a simple method to assess nutritional condition, which utilizes only three objective parameters of body weight, height