Arterial stiffness and interdialytic weight gain influence ambulatory blood pressure patterns in hemodialysis patients

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Submitted 01 December 2007; accepted in final form 21 December 2007


Besides an overall increase in blood pressure, hemodialysis patients have marked disturbance in interdialytic ambulatory blood pressure pattern that is characterized by blunted circadian amplitude and a steady rise in blood pressure between dialysis treatments. The physiopathology of this abnormal blood pressure profile is poorly understood. We hypothesized that the circadian amplitude, the interdialytic increase (linear trend), and the average level of blood pressure (the intercept) are related to the degree of accumulation of salt and water between dialysis treatments. Using a generalized cosinor model, we simultaneously compared the impact of interdialytic weight gain and echo-Doppler-measured aortic pulse wave velocity on the mean level of blood pressure, linear changes over the interdialytic interval, and oscillatory changes in blood pressure. In a cross-sectional analysis of 11,833 blood pressure measurements from 125 long-term hemodialysis patients, we found that aortic pulse wave velocity and interdialytic weight gain had a substantial impact on interdialytic ambulatory blood pressure level, trends, and rhythms. Arterial stiffness was associated with an overall increase in the level (intercept) of systolic, diastolic, and pulse pressure. Interdialytic weight gain, on the other hand, was associated with interdialytic increase (linear trend) in blood pressure. The circadian amplitude was blunted by increments in either arterial stiffness or interdialytic weight gain. Since patterns of ambulatory arterial blood pressure are related to cardiovascular risk factors such as interdialytic weight gain and increased arterial stiffness, the pattern of ambulatory blood pressure recordings may also be of prognostic significance in hemodialysis patients.

In health, arterial blood pressure (BP) demonstrates a rhythmic variation. The short-term differences in BP can be seen in successive beats, and the longer-term variation is entrained in the more subtle changes from day to night. The causes of these variations are complex and incompletely understood, but it is clear that they occur because of physical activity and sleep, modulation of autonomic tone, and emotions among other reasons. Altered rhythms may reflect the health of the arterial tree and the processes that control them. For example, the lack of fall in BP during sleep—nondipping—is a well-recognized pattern seen in patients with chronic kidney disease (CKD) (3, 17, 18). However, even when patients with CKD progress to end-stage renal disease (ESRD), some degree of rhythmicity in arterial pressure is preserved. Patients with ESRD who receive hemodialysis differ strikingly from their counterparts without kidney disease, or even those with earlier stages of CKD, in that they exhibit a marked impairment in the excretion of salt and water load in the interdialytic period. Accordingly, a commensurate linear increase in BP is observed in the interdialytic period that is superimposed on the circadian rhythm of arterial BP (13).

Besides disturbances in arterial rhythms, patients with ESRD also have profound abnormalities in the structure of conduit blood vessels (1). Alteration in arterial structure can be clinically detected by increased arterial stiffness that is in part due to vascular calcification but also attributable to an increase in pulse wave reflection, which results in elevated systolic, lowered diastolic, and therefore amplified pulse pressure (1). The magnitude of arterial stiffness increment is related to mortality in patients with ESRD (8, 10).

In hemodialysis patients, the rhythm of arterial pressure changes can be described in mathematical terms with a combination of sine and cosine waves that is superimposed on a linear increase in arterial pressure between dialysis treatments (Fig. 1). These changes can be visualized as a gentle undulation of BP that has an upward trajectory. The magnitude of undulation, the increment between dialysis treatments, and the level of starting BP varies from patient to patient (13). We hypothesized that BP rhythms (the circadian amplitude), the interdialytic rise in arterial pressure (linear trend), and the average level of arterial pressure (the intercept) may relate to the degree of arterial stiffening and the degree of accumulation of salt and water between dialysis treatments. Exploring the provenance of impaired BP rhythms may offer insights into strategies to restore these rhythms. Furthermore, if established mortality risk factors also influence BP rhythms, it would lend credence to the hypothesis that simple examination of arterial rhythm patterns may predict mortal outcomes, much like the disturbance in hemodynamic predicts mortality, increasing the prognostic information obtained in ambulatory BP monitoring. Although several investigators have called attention to the relationship of interdialytic weight gain and predialysis...
and postdialysis BP (12, 16), measurement of predialysis and postdialysis BP is insufficient to analyze the pattern of BP changes. Also, the impact of arterial stiffness on interdialytic ambulatory BP level, trend, or rhythm has received scant attention. The purpose of this study was to evaluate the influence of interdialytic weight gain and arterial stiffness on the mean level of arterial pressure and interdialytic BP changes and circadian rhythms with the previously described trended cosinor change model (13).

**METHODS**

The characteristics of this cohort and the development of the trended cosinor change model have been reported previously (13). **Subjects.** Patients 18 yr or older who had been on chronic hemodialysis at one of the four dialysis units in Indianapolis affiliated with Indiana University for >3 mo and were free of vascular, infectious, or bleeding complication within 1 mo were enrolled in the study. Those who missed two or more hemodialysis treatments over 1 mo, used illicit drugs, or had chronic atrial fibrillation or body mass index of 40 kg/m² or more were excluded. Patients who had a change in dry weight or a change in antihypertensive drugs within 2 wk were also excluded. Presence or absence of hypertension was not a selection criterion. All patients underwent standard dialysis three times a week.

**Anthropometric and demographic characteristics and antihypertensive medications actually taken by the patient were recorded.** The study was approved by the Institutional Review Board of Indiana University, Indianapolis, and Research and Development Committee of the Roudebush VA Medical Center, and all subjects gave written informed consent.

**Ambulatory BP monitoring.** Ambulatory BP monitoring was generally performed after the midweek 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) with a Spacelab 90207 ABP monitor (SpaceLabs Medical, Redmond, WA) in the nonaccess arm, as done previously (2). Patients with 16 ambulatory BP recordings were excluded, because pattern recognition was not possible with a limited number of recordings. These data were exported to a relational database to allow for data management as well as centering the time to that elapsed after dialysis with standard programming tools.

**Arterial stiffness measurement.** Aortic pulse wave velocity was directly recorded by direct visualization of the descending aorta with an echo-Doppler technique (15). Flow pulse was recorded by continuous Doppler from the root of the left subclavian artery and just proximal to the bifurcation of the abdominal aorta with simultaneous ECG recording. The length of the descending aorta was approximated by measuring the distance between the suprasternal notch and the site.
of measurement of aortic signal (near umbilicus). Time elapsed from the peak of the R wave to the foot of the systolic impulse was recorded over six beats. The length of the descending aorta divided by the difference between the transit times was calculated to yield the aortic pulse wave velocity.

**Statistical methods.** The mean level, trend, and diurnal pattern in arterial pressure pattern in an interdialytic interval was modeled with the trended cosinor change model (13). This method entails fitting an oscillating curve to temporal hemodynamic variables with a 24-h periodicity. The trended cosinor model describes the rhythmic cycle as \( y = b_0 + b_1 \times \cos[(2\pi/24)t] + b_2 \times \sin[(2\pi/24)t] + b_3 t \), where \( y \) represents the observed systolic BP, diastolic BP, or pulse pressure; \( b_0, b_1, b_2, \) and \( b_3 \) are regression coefficients; and \( t \) represents time elapsed after dialysis. The constant 2\( \pi/24 \) represents the 24-h periodicity of BP. The coefficient \( b_0 \) represents the 24-h rhythm-adjusted average intercept value of arterial pressure. The regression coefficients \( b_1 \) and \( b_2 \) are the coefficients for the cosine and sine component, respectively, and collectively describe the amplitude of the cosine curve, which is defined as amplitude = \( \sqrt{b_1^2 + b_2^2} \). The amplitude represents half the extent of rhythmic change in a cycle approximated by the fitted curve, which implies that it can be interpreted as the mean deviation across the time span. The coefficient \( b_3 \) represents the linear trend in arterial pressure in the interdialytic period. Thus the model considers the intercept and two types of change in a unified manner: a change that has a systematic linear component and another change that oscillates.

Using the above trended cosinor model, we examined the fixed effects of interdialytic weight gain and pulse wave velocity on the intercept, slope, and amplitude of the variation in arterial pressure. The interaction effect of interdialytic weight gain and pulse wave velocity was also evaluated. Pulse wave velocity was log transformed since it described the best functional form.

RESULTS

Between September 2003 and February 2005 we recruited 150 patients from four dialysis units staffed by the nephrology faculty of Indiana University, Indianapolis. Adequate ambulatory BP record was obtained in 136 hemodialysis patients, of which adequate pulse wave velocity measurement was obtained in 125. These 125 patients with 11,883 blood pressure measurements were the subject of further cross-sectional analyses. On average, 95 arterial pressure readings were recorded per patient (range 25–160). The demographic and clinical characteristics of these patients are shown in Table 1. Our cohort constituted predominantly of black patients; a third of these patients had diabetes mellitus as etiology of ESRD, and 82% received antihypertensive drugs—mostly beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, and calcium channel blockers.

Table 2 shows the intercept, slope, and amplitude of systolic, diastolic, and pulse pressures. The trended cosinor model (base model, model 1) showed an intercept BP of 124.6/71.0 mmHg with increase of 0.26/0.13 mmHg/h after dialysis and circadian amplitude of 1.01/1.81 mmHg. The modeled intercept pulse pressure was 53.5 mmHg with increase of 0.13 mmHg after dialysis and circadian amplitude of 0.93 mmHg.

<table>
<thead>
<tr>
<th>Clinical Characteristic</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>56±13</td>
</tr>
<tr>
<td>Men</td>
<td>83 (66%)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>8 (6%)</td>
</tr>
<tr>
<td>Black</td>
<td>115 (92%)</td>
</tr>
<tr>
<td>Other</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Predialysis weight, kg</td>
<td>81.7±19.9</td>
</tr>
<tr>
<td>Postdialysis weight, kg</td>
<td>79.1±19.3</td>
</tr>
<tr>
<td>Interdialytic weight gain, kg</td>
<td>2.6±1.6</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>26.7±6.3</td>
</tr>
<tr>
<td>Years of dialysis</td>
<td>4.1±3.1</td>
</tr>
<tr>
<td>Etiology of end-stage renal disease</td>
<td>Diabetes mellitus 40 (32%)</td>
</tr>
<tr>
<td>Nature of antihypertensive agent</td>
<td>Dihydropyridine calcium channel blockers 43 (34%)</td>
</tr>
</tbody>
</table>

The purpose of all subsequent analyses was to develop a model to uncover relationships of arterial stiffness, measured by pulse wave velocity, and volume excess, measured by interdialytic weight gain, with patterns of ambulatory BP. Adding log of the pulse wave velocity as a fixed effect to this base model (model 1) showed a significant effect on intercept, but not on slope or circadian amplitude (Table 2, model 2). For one log change in pulse wave velocity the intercept of systolic/diastolic BP increased 18.87/0.08 mmHg and that of pulse pressure by 11.7 mmHg. Increasing pulse wave velocity tended to blunt the circadian amplitude of systolic and pulse pressure. Although the model fit for systolic and pulse pressure was improved by adding pulse wave velocity to the model, it did not improve the model fit for diastolic pressure.

Interdialytic weight gain was associated with small increase in intercept and slope and blunting of circadian amplitude of systolic and diastolic BP, but none of these changes was significant (Table 2, model 3). The model fit was also not improved by inclusion of interdialytic weight gain in any of the BP models.
Table 2. Impact of pulse wave velocity and interdialytic weight gain on ambulatory blood pressure patterns

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Model 1 (trended cosinor model)</th>
<th>Model 2 [model 1 + ln (pulse wave velocity)]</th>
<th>Model 3 (model 1 + interdialytic weight gain)</th>
<th>Model 4 (model 1 + ln (pulse wave velocity) + intercept)</th>
<th>Model 5 (model 4 + intercept)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept, mmHg</td>
<td>71.0 [68.5–73.5]</td>
<td>57.9 [46.8–69.0]</td>
<td>70.6 [65.8–75.3]</td>
<td>57.2 [47.0–67.5]</td>
<td>57.6 [47.3–67.9]</td>
</tr>
<tr>
<td>Slope, mmHg/h after dialysis</td>
<td>0.13 [0.08–0.18]</td>
<td>0.11 [–0.12 to 0.34]</td>
<td>0.11 [0.01–0.20]</td>
<td>0.13 [0.08–0.18]</td>
<td>0.08 [0.01–0.17]</td>
</tr>
<tr>
<td>Circadian amplitude, mmHg</td>
<td>1.81 [1.11–2.52]</td>
<td>0.82 [–2.01 to 3.65]</td>
<td>2.86 [1.34–4.37]</td>
<td>1.81 [1.11–2.52]</td>
<td>1.81 [1.11–2.52]</td>
</tr>
<tr>
<td>ΔIntercept</td>
<td>7.08 [1.22–12.93]</td>
<td>0.18 [–1.39 to 1.74]</td>
<td>7.44 [2.06–12.82]</td>
<td>7.22 [1.82–12.62]</td>
<td>0.22 [0.02–0.05]</td>
</tr>
<tr>
<td>ΔSlope</td>
<td>0.01 [–0.11 to 0.13]</td>
<td>0.01 [–0.02 to 0.04]</td>
<td>0.01 [–0.02 to 0.04]</td>
<td>0.07 [0.01–0.13]</td>
<td>0.02 [0.00–0.05]</td>
</tr>
<tr>
<td>ΔCircadian amplitude</td>
<td>0.47 [–1.45 to 2.39]</td>
<td>–0.46 [–1.00 to 0.08]</td>
<td>–0.46 [–1.00 to 0.08]</td>
<td>–0.46 [–1.00 to 0.08]</td>
<td>–0.46 [–1.00 to 0.08]</td>
</tr>
</tbody>
</table>

Model comparison (vs. model 1):

- Diastolic blood pressure:
P < 0.0001
P = 0.11
P < 0.0001
P < 0.0001

- Pulse pressure:
P < 0.0001
P = 0.13
P < 0.0001
P < 0.0001

Values are mean estimates with 95% confidence intervals in brackets. *P < 0.001, †P < 0.05, ‡P < 0.01.

Because slope and amplitude terms for pulse wave velocity were not significant, we dropped these terms from the model but retained the intercept term (Table 2, model 4). Dropping the redundant terms did not deteriorate the model fit of the parsimonious model 4 compared with model 2. Large effects were still evident for each log increment in pulse wave velocity on systolic, diastolic, and pulse pressures. Furthermore, model 4 was a better fit compared with the trended cosinor model (base model, model 1).

The final model (model 5) was obtained by adding a slope term for interdialytic weight gain to model 4. Each kilogram of weight gain was associated with 0.05/0.02 mmHg increase in systolic and diastolic BP and 0.03 mmHg increase in pulse pressure per hour elapsed after dialysis. Model 5 was superior to model 4 for systolic and pulse pressure models. The combined impact of the aortic pulse wave velocity and interdialytic weight gain on ambulatory systolic, diastolic, and pulse pressure is shown in Fig. 1.

Interaction effects of interdialytic weight gain and pulse wave velocity were not significant for either additive or multiplicative models (data not shown).

**DISCUSSION**

Arterial stiffness and interdialytic weight gain have a substantial impact on interdialytic ambulatory BP. The impact of weight gain and aortic pulse wave velocity appears to influence different components of ambulatory BP pattern. Arterial stiffness is associated with an overall increase in the level of systolic, diastolic, and pulse pressure. Interdialytic weight gain, on the other hand, is associated with increase in interdialytic slope. The circadian amplitude is somewhat blunted by increments in either arterial stiffness or interdialytic weight gain.

Rodby et al. (19) were the first to describe a circadian rhythm in systolic and diastolic BP in hemodialysis patients. The authors reported that despite interdialytic weight gain there was no apparent increase in BP from day 1 to day 2 in dialysis patients. The assumption of a flat midline estimating statistic of rhythm (MESOR), instead of a trend, may have obscured the linear trend in their data. The median weight gain in our patients was 2.4 kg over an interdialytic period that would result in ~5–mmHg increase in systolic, ~2-mmHg increase in diastolic, and ~3-mmHg increase in pulse pressure. This would be over and above an increase of 6.2 mmHg in systolic, 3.5 mmHg in diastolic, and 3.1 mmHg in pulse pressure if no weight gain was seen. Thus interdialytic weight gain plays a substantial role in interdialytic increments in BP (Fig. 1B). However, interdialytic weight gain had little influence on BP intercept.

Whereas interdialytic weight gain had a substantial impact in linear trends in BP, arterial stiffness had a large impact on BP intercept (Fig. 1A). The log of pulse wave velocity was related to BP in a linear relationship. Each log increment in pulse wave velocity was associated with 20.3-mmHg increase in systolic, 7.2-mmHg increase in diastolic, and 12.8-mmHg increase in pulse pressure. Arterial stiffness measurements had little impact on the slope of BP change. The circadian amplitude of systolic and pulse pressure was blunted with increasing arterial stiffness. This is consistent with a study in 42 hemodialysis patients that demonstrated that increased pulse wave velocity was associated with blunted nocturnal dipping (7). The relationship of blunted circadian BP amplitudes and increased
pulse wave velocity raises the hypothesis that in hemodialysis patients blunted circadian amplitude would be associated with worse outcomes.

Two studies have assessed the prognostic power of ambulatory BP monitoring and outcomes in hemodialysis patients. Amar et al. (6) followed 57 hypertensive hemodialysis patients in France for ~3 yr and demonstrated that nocturnal systolic BP and 24-h pulse pressure were independent risk factors for cardiovascular deaths. Tripepi et al. (21), in a much larger study of 168 Italian hemodialysis patients without diabetes mellitus, found that the ratio of night to day systolic BP was associated with all-cause and cardiovascular mortality in multivariable Cox models. We recently reported (5) that the average level of ambulatory BP is a powerful predictor of all-cause and cardiovascular mortality in hemodialysis patients. Although all studies assessed the prognostic significance of ambulatory BP monitoring, none evaluated the joint influence of BP level, trends, and circadian amplitudes on mortal outcomes. Dichotomizing a continuous variable such as circadian amplitude into dipping and nondipping BP categories sacrifices information contained in ambulatory BP recordings. Analyzing continuous circadian amplitudes may allow us to evaluate the functional form of this variable and the nature of the relationship between circadian amplitude and outcome such as a threshold effect.

Whether aortic stiffness is linked to interdialytic weight gain is better addressed by animal studies. These data draw attention to the endothelial effects of increased salt intake that are independent of BP (20). For example, Ying and Sanders (23) have shown that increased sodium chloride feeding leads to increased transforming growth factor-β production in aortic rings from Sprague-Dawley rats. To counter these effects, nitric oxide production is enhanced. However, aortic rings from Dahl salt-sensitive rats have impaired nitric oxide production, which because of unopposed transforming growth factor-β production may lead to conduit vessel stiffness. Thus habitual increase in dietary sodium intake may result in long-term increase in pulse wave velocity. Short-term changes in sodium balance are unlikely to influence aortic pulse wave velocity. Acute volume control fails to improve arterial stiffness in hemodialysis patients (14, 22).

It also stands to reason that interdialytic weight gain may evince greater interdialytic BP slopes in patients with increased arterial stiffness. To test this notion, we tested the three-way interaction effect of interdialytic weight gain, log pulse wave velocity, and time, but, somewhat surprisingly, the interaction effects were not found to be significant (P values >0.7 for systolic, diastolic, and pulse pressure models). It is possible that increased aortic stiffness has such a profound effect on intercept BP that comparatively smaller changes in BP trends are masked. Alternatively, in those with increased arterial stiffness, the accumulated salt and water may exude into the interstitial space instead of remaining in intravascular space, thereby causing no additional increase in BP.

Early evidence suggests that pulse wave velocity can be reduced with the use of agents that block the renin-angiotensin system in hemodialysis patients (11). It would follow that agents that block the renin-angiotensin system would have a large impact on ambulatory BP, which is also supported by small clinical trials (4). Since pulse wave velocity (8, 10) and interdialytic weight gain (9) are both adverse mortality risk factors and they also influence ambulatory BP patterns, future studies should examine the patterns of interdialytic BP such as the level, trend, and circadian amplitude in hemodialysis patients for prognostic significance. The assessment of prognostic significance of BP patterns may reveal pathophysiological insights into the processes that initiate and maintain hypertension in hemodialysis patients.

ACKNOWLEDGMENTS

We thank the staff of the dialysis units at Dialysis Clinics, Inc., Clarian Health, and the Roudebush VA Medical Center and the faculty of the Division of Nephrology, who graciously allowed us to the study their patients.

GRANTS

This work was supported by National Institute of Diabetes and Digestive and Kidney Diseases Grant 5RO1-DK-062030-05.

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