Blood pressure variability as an adverse prognostic risk factor in end-stage renal disease

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Abstract

Background. Prospective and case-control studies show that blood-pressure variability is an independent risk factor for severe organ damage and cardiovascular events in hypertensives. We prospectively studied the association between systolic blood pressure variability and cardiovascular mortality and mortality from all causes in end-stage renal disease patients.

Methods and results. The subjects were 144 patients (86 men, 58 women; mean age ±SD, 52 ± 13 years) who underwent dialysis in the same dialysis centre and were examined for blood-pressure variability. The study period was 38 months beginning in January 1995, during which six cardiovascular and seven non-cardiovascular fatalities occurred. Coefficient of variation in systolic blood pressure in 1994, as an indicator of systolic blood pressure variability, ranged from 7.8 to 14.6%. Cumulative incidence of death from all causes was related to coefficient of variation in systolic blood pressure. The difference between the maximum and minimum systolic blood pressure (ΔSBP) in 1994 ranged from 44 to 146 mmHg (mean ± SD, 78 ± 13 mmHg) and correlated significantly with coefficient of variation in systolic blood pressure (r = 0.65, P < 0.0001). Cox regression analysis was used to identify the independent predictors for mortality. The hazard ratio for death from all causes increased 1.63 times per 1% increase in coefficient of variation in systolic blood pressure (hazard ratio: 95% confidence interval: 1.63; 1.05–2.53) and 1.03 times per 1 mmHg increase in ΔSBP (1.08; 1.03–1.14).

Conclusion. These results suggest that systolic blood pressure variability may be a significant prognostic factor in end-stage renal disease.

Key words: blood pressure; haemodialysis; kidney; risk factor; variability

Introduction

The 1-year mortality rate for patients on dialysis in Okinawa, Japan between 1971 and 1990 was 11.6%, which was higher than that for the general population (0.45%). Cardiovascular and cerebrovascular diseases accounted for 45.1% of dialysis patient deaths [1]. Recent work suggest that blood pressure variability is a risk factor for cardiovascular complications in essential hypertension [2], and hypertension in the elderly [3] and a risk factor for complications in pregnant women [4]. The relation between blood pressure variability and prognosis of dialysis patients, however, has not been clarified. This study prospectively examines the association between systolic blood pressure variability and fatal events in patients with end-stage renal disease (ESRD).

Subjects and methods

Subjects

At the start of 1995, 144 patients who were undergoing regular dialysis three times per week in a single dialysis unit of Okinawa, Japan were selected. The subjects were 86 men (60%) and 58 women (40%) with a mean age of 52 ± 13 years (range 22–83). This dialysis unit is one of those included in the Okinawa Dialysis Study (OKIDS) [1]. Some patients received dialysis in the morning and others received it in the evening; however, each patient always underwent dialysis in the same manner at the same time (morning or evening). The patients underwent dialysis three times a week in 4-h sessions. Haemodialysis was performed with a cellulose membrane (surface area 1.0–2.0 m²) and a dialysate containing 140 mEq/l sodium, 100 mg/dl glucose, 30 mEq/l bicarbonate, and 8 mEq/l acetate. During the follow-up period, the regimen was changed when a patient suffered from heart failure, pulmonary oedema or insufficient dialysis. The number of these cases were small and were usually associated with the end of life. The coefficient of variation in systolic blood pressure was calculated from complete patient records of 1994 (January to December) and all patients selected had been introduced to chronic haemodialysis therapy by the end of 1993.

Some patients were given antihypertensive medicines. The
time of their administration varied from patient to patient and several types of drug were used over the study period in different patients; however, the patients were encouraged to take their medicine at a set recommended time every day.

Patients in this cross-sectional study were evaluated from 1 January 1995 to 28 February 1998 (38 months). We reviewed all medical records and registered the cases in the OKIDS. Baseline demographic data other than blood pressure were obtained in January 1994.

Systolic blood pressure variability

Immediately before each routine haemodialysis session, blood pressure was taken in the right or left arm with the patient assuming the supine position 5 min prior to measurement. These readings were performed by trained nurses or paramedical staff using a standard mercury sphygmomanometer. We previously verified the correlation between a single BP measurement and the 1-month average BP in the dialysis unit; the coefficient of correlation was 0.81 for one-point SBP and 1-month average SBP and 0.72 for 1-point DBP and 1-month average DBP [5]. We used the coefficient of variation (CV: standard deviation/mean × 100%) in systolic blood pressure as an indicator of systolic blood pressure variability. Coefficients of variation in SBP measured before the dialysis session were analysed from complete 1994 records which included 156 records per person. The difference between the maximum and minimum systolic blood pressure in 1994 (ΔSBP) was calculated in each patient and also used as an index of systolic-blood-pressure variability.

Risk factors for vascular disease

Diabetes mellitus defined in one of our previous reports [6]. Total cholesterol and other biochemical data were determined in January 1994.

Stroke events

Newly developed cerebrovascular disease was diagnosed by both clinical symptoms and brain CT scan. Brain CT scan was performed in all patients who were at risk for stroke.

Causes of death

Cause of death was confirmed from medical records. Classification of cause of death in dialysis patients was defined previously [7]. In this paper, we modified this classification as shown in Table 1.

Statistical analysis

Descriptive statistics are reported as frequency and percent for categorical data and as mean and SD or range for continuous data. Percentages were compared by χ² test. Student’s t-test was used to compare continuous variables. Cumulative incidence curves were compared with the log-rank test. Cox regression analysis was used to evaluate the significance of risk factors for mortality due to cardiovascular events and to all causes. Significant risk factors for the model were chosen from a set of variables that included a coefficient of variation in systolic blood pressure, gender, age, smoking, diabetes, duration of haemodialysis, antihypertensive medication, systolic blood pressure, diastolic blood pressure, body weight gain between dialysis sessions, total cholesterol, serum albumin, and serum creatinine. Hazard ratio and 95% confidence interval are reported. Statistical test results having a probability of <0.05 were considered statistically significant.

Results

The mean duration of follow-up was 35.2 ± 8.1 months. Mean duration of haemodialysis was 87.5 ± 60.0 months. Twenty-five (17%) patients were diabetic. Forty-five patients (32%) had a history of smoking (current or past) and 36 patients (26%) had a history of moderate to excessive alcohol consumption (current or past). Mean systolic and diastolic pressures were 144 ± 15 mmHg and 77 ± 7 mmHg respectively. Mean cholesterol concentration was 174 ± 41 mg/dl. Mean albumin and creatinine concentrations were 3.8 ± 0.3 g/dl and 14.1 ± 2.9 mg/dl respectively. The coefficient of variation in systolic blood pressure, the mean was 10.2 ± 1.5%, median was 10.1%, and range was 7.8–14.6%. The demographic data for patients in each half of the coefficient of variation in systolic blood pressure range are shown in Table 2. We subdivided the study population into two equal subgroups on either side of the median coefficient of variation in systolic blood pressure value. The demographic data of the two groups were compared univariately (Table 2) and non-parametrically (Figure 1).

No significant differences in the prevalence of antihypertensive medication and erythropoietin therapy were found between the groups (Table 2). In addition, there was no difference between the two groups with respect to the types of antihypertensive medication used (Table 3).

Systolic blood pressure variability and clinical outcomes

Three (2%) of the 144 patients underwent renal transplantation during the follow-up period. By Cox hazards model, the hazard ratio can be analysed even when subjects are withdrawn for various reasons during the course of the study [8]. Therefore, we
Table 2. Demographic and clinical characteristics of patients divided into two groups based on the coefficient of variation in systolic blood pressure

<table>
<thead>
<tr>
<th></th>
<th>Smaller SBPCV</th>
<th>Larger SBPCV</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>9.0% (7.8–10.1%)</td>
<td>11.1% (10.2–14.6%)</td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>72</td>
<td>72</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>49 ± 12b</td>
<td>55 ± 13</td>
<td>0.013</td>
</tr>
<tr>
<td>Female (%)</td>
<td>32</td>
<td>49</td>
<td>0.061</td>
</tr>
<tr>
<td>Duration of dialysis (months)</td>
<td>93 ± 61</td>
<td>82 ± 59</td>
<td>0.291</td>
</tr>
<tr>
<td>Causes of renal failure (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic glomerulonephritis</td>
<td>81</td>
<td>62</td>
<td>0.016</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>10</td>
<td>25</td>
<td>0.028</td>
</tr>
<tr>
<td>Polycystic kidney disease</td>
<td>0</td>
<td>3</td>
<td>0.476</td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
<td>3</td>
<td>0</td>
<td>0.476</td>
</tr>
<tr>
<td>Nephrosclerotic</td>
<td>3</td>
<td>4</td>
<td>0.999</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>3</td>
<td>6</td>
<td>0.677</td>
</tr>
<tr>
<td>Smoker (%)</td>
<td>39</td>
<td>25</td>
<td>0.082</td>
</tr>
<tr>
<td>Alcohol consumer (%)</td>
<td>26</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>Antihypertensive medication (%)</td>
<td>67</td>
<td>63</td>
<td>0.727</td>
</tr>
<tr>
<td>Erythropoietin therapy (%)</td>
<td>71</td>
<td>78</td>
<td>0.445</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>22 ± 3</td>
<td>22 ± 4</td>
<td>0.827</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>146 ± 12</td>
<td>142 ± 17</td>
<td>0.101</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>78 ± 6</td>
<td>75 ± 8</td>
<td>0.023</td>
</tr>
<tr>
<td>ABW (kg)</td>
<td>2.1 ± 0.7</td>
<td>2.0 ± 0.7</td>
<td>0.198</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>172 ± 44</td>
<td>177 ± 38</td>
<td>0.524</td>
</tr>
<tr>
<td>Albumin (g/dl)</td>
<td>3.8 ± 0.2</td>
<td>3.7 ± 0.3</td>
<td>0.106</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>14.6 ± 2.8</td>
<td>13.4 ± 2.7</td>
<td>0.001</td>
</tr>
</tbody>
</table>

aValues are median (range).
bMean ± SD.

SBPCV: coefficient of variation in systolic blood pressure.

D_BW: body-weight gain between dialysis sessions.

The coefficient of variation in systolic blood pressure was calculated from 156 records per person in 1994.

Fig 1. Cumulative incidence of cardiovascular death (left panel) and death from all causes (right panel) during the follow-up period for patients in the two SBPCV groups: lower half of the range and upper half of the range. The follow-up period was from 1 January 1995 to 28 February 1998.

included the patients’ data when analysing the hazard ratio. Of the 144 patients, 13 (9%) died during the follow-up period. Causes of mortality in these patients are shown in Table 1 (6 cardiovascular and 7 non-cardiovascular deaths occurred). None of the patients suffered from myocardial infarction during the follow-up period. Patients in the group with the greater coefficient of variation in systolic blood pressure were more likely to develop a cardiovascular fatal event (5 of 72, 7%) than patients in the first half of the range (1 of 72, 1%; P = 0.211). Cox regression analysis failed to show that coefficient of variation in systolic blood pressure is a significant independent predictor for cardiovascular mortality (adjusted hazard ratio; 95% confidence interval: 1.76; 0.94–3.37), but revealed that it is an independent predictor for mortality from all causes (1.63; 1.05–2.53) (Table 4).

ΔSBP ranged from 44 to 146 mmHg (mean ± SD, 78 ± 13 mmHg) and correlated significantly with coefficient of variation in systolic blood pressure (see Figure 2). One outlier in ΔSBP was identified statistically by Grubbs–Smirnov test. We excluded the patient’s data when analysing the hazard ratio of ΔSBP. Cox regression analysis failed to show that ΔSBP is a
Table 3. Types of antihypertensive medications used by the patients

| Type of Antihypertensive Medication | Smaller SBPCV range 7.8–10.1% | Larger SBPCV range 10.2–14.6% | P  
|------------------------------------|---------------------------------|--------------------------------|  
| Calcium-channel blockers           | 38 (53)                         | 35 (49)                        | 0.738  
| Beta blockers                      | 22 (31)                         | 22 (31)                        | —       
| ACE inhibitors                     | 6 (8)                           | 10 (14)                        | 0.426  
| Central acting drugs               | 3 (4)                           | 1 (1)                          | 0.612  
| Alpha blockers                     | 2 (3)                           | 0 (0)                          | 0.476  

*Numbers of patients (percentage) are shown.

SBPCV: coefficient of variation in systolic blood pressure.

Table 4. Cox regression analysis of cardiovascular mortality and mortality from all causes

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Crude hazard ratio (95% CI)</th>
<th>Adjusted hazard ratio* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular mortality</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBPCV (%)</td>
<td>1.93 (1.16–3.21)</td>
<td>1.78 (0.94–3.37)</td>
</tr>
<tr>
<td>ΔSBP (mmHg)</td>
<td>1.10 (1.04–1.16)</td>
<td>1.75 (0.82–3.73)</td>
</tr>
<tr>
<td>Mortality from all causes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBPCV (%)</td>
<td>1.70 (1.20–2.41)</td>
<td>1.63 (1.05–2.53)</td>
</tr>
<tr>
<td>ΔSBP (mmHg)</td>
<td>1.07 (1.03–1.11)</td>
<td>1.08 (1.03–1.14)</td>
</tr>
</tbody>
</table>

*Adjustments were made for age, gender, duration of dialysis, diabetes, smoking habit, antihypertensive medication, systolic blood pressure, diastolic blood pressure, body weight gain between dialysis sessions, total cholesterol, serum albumin, and serum creatinine.

CI, confidence interval; SBPCV, coefficient of variation in systolic blood pressure; ΔSBP, the difference between the maximum and minimum systolic blood pressure in 1994.

Fig 2. Correlation between the difference between minimum and maximum systolic blood pressure in 1994 (ΔSBP) and the coefficient of variation in systolic blood pressure (SBPCV).

Fig 2. Correlation between the difference between minimum and maximum systolic blood pressure in 1994 (ΔSBP) and the coefficient of variation in systolic blood pressure (SBPCV).

Discussion

This study extends previous analyses in case-control studies of hypertensives [2,3] and pregnant women [4] and shows prospectively that there is a relation between systolic blood pressure variability and mortality in patients with ESRD.

A large number of papers [13–18] have described seasonal variation of blood pressure. Therefore we calculated the coefficient of variation in SBP from the complete year records of SBP in this study. We analysed coefficient of variation in systolic blood pressure but not coefficient of variation in diastolic blood pressure.
pressure because SBP correlates better than DBP does with epidemiological end-points [19,20].

The incidence of acute myocardial infarction in dialysis patients in Okinawa, Japan was 1.1 per 1000 cases/year between April 1988 and March 1991 [21]; in other words, the rate was only 0.5 per 141 persons over 3 years. No myocardial infarction occurred in our study patients during the follow-up period, which was compatible with the statistics in Okinawa, Japan.

Our method of BP sampling was different from those used in previous studies. Frattola et al. [2] and Ayala et al. [4] took hour-to-hour circadian blood pressure, Hata et al. [3] used month-to-month measurements for a year, and we took three measurements per week for a year. Although the BP sampling methods differed, all these reports showed a positive association between BP variability and adverse events.

Determination of coefficient of variation in systolic blood pressure calculated from complete records of a full year of sessions may not be realistic for general use. Therefore, we introduced \( \Delta \text{SBP} \) as an index of the variability of SBP and as an alternative to coefficient of variation in systolic blood pressure. Although the adjusted hazard ratio of \( \Delta \text{SBP} \) is lower than that of coefficient of variation in systolic blood pressure for mortality from all causes, the hazard ratio is significant (Table 4). This suggests that \( \Delta \text{SBP} \) is a feasible, acceptable variable for predicting prognosis in end-stage renal disease.

Relative hypotension [22] and low diastolic blood pressure [23] are risk factors for mortality in dialysis patients. In our univariate and non-parametric analyses, patients whose coefficient of variation in systolic blood pressure was in the range above the median had lower DBP and a worse prognosis than those in the range below the median. Cox regression analysis with an adjustment for multiple factors, however, showed that DBP was not a significant risk factor. In previous studies with a short-term follow-up period, the effect of blood pressure on mortality was not found to be significant [9,24] which is agreement with our findings.

Although the pathogenesis is not clearly understood, increased risk of cardiovascular disease is associated with recombinant human erythropoietin therapy for renal anaemia in chronic dialysis patients. This has been demonstrated in both retrospective [25] and prospective studies [26]. In our study, the percentage of patients using erythropoietin was not significantly different between the two groups.

The mechanisms by which blood pressure variability increases the risk of mortality remains uncertain. One possible mechanism is that a change in the volume gain between dialysis sessions may affect blood pressure variability because the blood pressure of dialysis patients is largely volume dependent [27] and controlled by adequate dialysis [28]. In this study, body-weight gain between dialysis sessions was taken into account during statistical analysis. This factor, however, was not different between the two groups and was not an independent risk factor for mortality by Cox analysis. Disorders of the autonomic nervous system may also be a possible factor in this situation because sympathetic overactivity is a common finding in end-stage renal disease and it correlates with the increase in both vascular resistance and systemic blood pressure [29]. Afferent signals from the kidney may be the mechanism for this overactivity [29]. However, all 144 patients in this study had end-stage renal disease. If a disorder of the autonomic nervous system was involved, the degree of disorder suffered by the patients should be different between the two coefficient of variation in systolic blood pressure groups, and this was not the case. Finally, sodium sensitivity also may be a mechanism that contributes to this relation because sodium sensitivity is an independent risk factor for cardiovascular events in essential hypertension [30] and the daily variability of sodium intake may influence the variability of blood pressure.

Limitations of the present study include the relatively short duration of follow-up (38 months), the small patient numbers and the late stage in the entire course of dialysis treatment (average 80 months). An analysis of subsets such as elderly patients or patients in the early stages of dialysis could not be performed. All the patients survived while on haemodialysis through all of 1994 and, therefore, these patients may have a better prognosis than other ESRD patients.

In summary, the present study suggests that patients with increased systolic blood pressure variability are more likely to develop fatal events. Further study is needed to establish methods of risk reduction.

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BP Variability and prognosis of ESRD


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