Original Paper

Association of Age and BP Variability with Long-term Mortality in Hemodialysis Patients

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Key Words

Age • Blood pressure variability • Dialysis

Abstract

Background/Aims: Blood pressure (BP) variability is known as a poor prognostic factor for cardiovascular outcomes. This study assessed the prognostic significance of BP variability in association with increasing age in hemodialysis patients. **Methods:** We retrospectively analyzed 2,174 patients on hemodialysis from March 2005 to December 2012. The impact of intradialytic and interdialytic BP variability on all-cause mortality according to age groups was analyzed. **Results:** Kaplan-Meier survival curves for 5-year cumulative mortality showed higher mortality in patients with higher intradialytic systolic and diastolic BP variability as well as interdialytic systolic and diastolic BP variability (log-rank $p=0.006$, <0.001 , 0.018 and <0.001) in patients aged <55 years, but not in older age groups. Cox proportional analysis revealed that 5-year mortality was associated with intradialytic diastolic BP variability in patients aged <55 years (HR, 2.03 CI, 1.24–3.32). **Conclusion:** The overall mortality was associated with BP variability in patients aged <55 years, but not in older ages. This result suggests that younger hemodialysis patients with BP variability require further medical attention and intervention to reduce BP variability.

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Introduction

In patients on maintenance hemodialysis, hypertension is a well-documented risk factor for unfavorable cardiovascular outcomes, such as development of left ventricular hypertrophy, left ventricular dilation, stroke, heart failure, and mortality [1-3]. Clinical practice guidelines focus on recommended BP targets [4]; however, the impact of BP on

clinical outcomes may vary based on age [5]. An observational cohort study showed that there is a U-shaped association between BP and mortality among patients who are older than 85 years in general population. Very old patients may be at an increased risk from aggressive BP lowering therapy [6]. Together, these findings suggest the clinical impact of high BP varies with age.

BP variability and hypertension are proposed to be cardiovascular risk factors. A recent, large retrospective cohort study observed that first-year mortality was higher in hemodialysis patients with variability in BP compared with those with stable BP, independent of absolute BP level, suggesting that BP variability is associated with worse outcomes at all levels of BP [7]. It has been demonstrated that there is an association between BP variability and end-organ damage and clinical outcomes. Studies in the general population have shown an association between greater BP variability and cardiovascular events [8-11]. Systolic BP variability is a potent predictor for intima to media wall thickness of the common carotid artery [9] and for increased left ventricular mass [12]. In addition, BP variability has been linked with micro-albuminuria in hypertensive individuals [13, 14]. Because of the unique BP patterns that occur during hemodialysis, it is difficult to extrapolate these results to hemodialysis patients. Further, most studies focus on patients' average BP level as a prognostic risk factor; however, there has been comparatively little work examining the effects of BP variability in hemodialysis patients at different ages. Herein, we explored the hypothesis that the association between BP variability and all-cause mortality among hemodialysis patients varies at different ages.

Patients and Methods

Study population

This study was approved by the institutional review board of Chonnam National University Hospital, Gwangju, Korea (CNUH-2012-108). The institutional review board waived the need for consent given the retrospective design of the project. The mortality data were determined from government death records from Statistics Korea.

We conducted a retrospective evaluation of 2561 patients who had started hemodialysis at Chonnam National University Hospital between March 2005 and December 2012. Of these patients, 387 acute kidney injury patients, who died during hospitalization at the initiation of hemodialysis, were excluded from the study. A total of 2174 patients were included in the analysis.

Demographic, clinical, laboratory, and treatment data were obtained from the hospital's computerized database. We recorded laboratory findings at the initiation of hemodialysis, systolic blood pressure (SBP), diastolic blood pressure (DBP), and pulse pressure. Laboratory measurements included hemoglobin, sodium, albumin, total calcium, inorganic phosphate, and parathyroid hormone (PTH) levels. Other recorded variables included age, gender, and body mass index (BMI). To investigate whether an underlying condition may affect mortality, the presence of pre-existing diabetes, hypertension, and heart failure was identified. The use of therapeutic agents that may alter blood pressure, including angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARB), β -adrenergic blockers, and calcium channel blockers, was identified.

Definition of blood pressure (BP) variability

BP data were collected three times at the initiation and completion of each hemodialysis session, and the highest and lowest measurements over the first month of dialysis were identified. Intradialytic BP variability was calculated as the difference between the highest and lowest BP measurements during each dialysis session. Intradialytic SBP variation over 20 mm Hg and DBP variation over 10 mm Hg were defined as intradialytic SBP and DBP variability, respectively. Interdialytic BP variability was calculated as difference between the BP at the start each dialysis session. Interdialytic SBP variations over 10 mm Hg and DBP variation over 5 mm Hg were defined as interdialytic SBP and DBP variability, respectively.

Table 1. Baseline characteristics and clinical features of patients divided by age

	<55 years (N=785)	55–74 years (N=1099)	≥75 years (N=290)	P-value
Mortality	105 (13.4%)	353 (32.1%)	136 (46.9%)	<0.001
Age (years)	42.7 ± 9.22	65.0 ± 5.50	79.1 ± 3.58	<0.001
Men (%)	477 (60.8%)	658 (59.9%)	162 (55.6%)	0.338
BMI (kg/m ²)	20.7 ± 12.14	21.3 ± 6.75	20.6 ± 7.09	0.056
Past Medical History				
Hypertension	531 (68.8%)	884 (80.9%)	231 (79.7%)	<0.001
Diabetes	298 (38.6%)	666 (60.9%)	123 (42.4%)	<0.001
Heart failure	17 (2.2%)	29 (2.7%)	18 (6.2%)	0.002
Medication				
ACE inhibitor or ARB	239 (30.4%)	347 (31.5%)	109 (37.5%)	0.210
β-adrenergic blocker	331 (43.1%)	532 (48.8%)	107 (36.9%)	0.001
Calcium channel blocker	478 (62.2%)	647 (59.4%)	145 (50.0%)	0.001
Blood Chemistry Profile				
Hemoglobin (g/dL)	9.6 ± 2.70	9.6 ± 2.16	9.5 ± 2.05	0.626
Sodium (mEq/L)	135.2 ± 4.99	134.8 ± 5.43	135.2 ± 5.40	0.084
Albumin (mg/dL)	3.4 ± 1.43	3.2 ± 0.67	3.2 ± 0.60	0.228
Total calcium (mg/dL)	6.8 ± 2.45	7.4 ± 3.78	8.0 ± 1.92	<0.001
Inorganic-Phosphate (mg/dL)	6.1 ± 6.04	5.0 ± 2.34	4.8 ± 1.84	0.044
PTH (pg/mL)	245.3 ± 284.82	189.8 ± 319.13	129.0 ± 134.93	<0.001
SBP (mmHg)	137.1 ± 42.35	144.1 ± 21.32	142.6 ± 21.86	0.074
DBP (mmHg)	82.2 ± 25.72	80.4 ± 16.51	75.6 ± 12.18	0.022
Pulse pressure (mmHg)	59.1 ± 22.31	63.5 ± 17.87	64.2 ± 16.56	0.001
Intradialytic SBPV (mmHg)	22.1 ± 14.02	24.3 ± 13.73	24.7 ± 12.52	0.001
Intradialytic DBPV (mmHg)	13.2 ± 7.96	13.9 ± 9.87	14.0 ± 7.23	0.225
Interdialytic SBPV (mmHg)	19.2 ± 10.93	19.8 ± 10.80	21.5 ± 10.76	0.011
Interdialytic DBPV (mmHg)	13.1 ± 9.92	12.7 ± 7.76	13.7 ± 8.42	0.392

Data are presented as number (%) or mean ± standard deviation. BMI = body mass index; ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker, PTH = parathyroid hormone; SBP = systolic blood pressure; DBP = diastolic blood pressure; SBPV = systolic blood pressure variability; DBPV = diastolic blood pressure variability

Statistical analysis

Patients were subdivided into three age groups: <55, 55–74, and ≥75 years. Continuous variables with normal distributions are presented as means ± standard deviation and were compared using one-way ANOVA. Pearson's chi-squared test was used to evaluate differences between categorical variables. Cox proportional hazards regression analysis was performed to evaluate the prognostic significance of BP variability for mortality in hemodialysis patients. The confounding factors analyzed in this study included age, gender, BMI, comorbidities (hypertension, diabetes, or heart failure), hemoglobin, sodium, albumin, total calcium, and medical treatments at the initiation of hemodialysis. All statistical tests were performed using the Statistical Package for Social Sciences software, version 18.0 (SPSS, an IBM Company, Armonk, NY). P-values < 0.05 were considered significant.

Results

Patient Characteristics

The demographic and clinical features of the patients, divided by age category, are shown in Table 1. A total of 2174 patients (60.2% male) were included in the study, with a mean age of 60.0 ± 14.72 years. In all, 594 (27.3%) patients died and overall mortality increased with age (13.4%, 32.1%, and 46.9% for patients aged <55 years, 55–74 years, and ≥75 years, respectively; P = 0.001). The prevalence of hypertension and diabetes was highest in the 55–74 year group, whereas the prevalence of heart failure, defined as an ejection fraction of less than 40 percent by echocardiogram [15] was highest in the ≥ 75 years group.

Fig. 1. Prevalence of intradialytic systolic blood pressure (SBP) and diastolic blood pressure (DBP) variability and interdialytic SBP and DBP variability according to age.

β -Adrenergic blocker use was highest in the 55–74 years group, and calcium channel blocker use was highest in the <55 years group. There were no differences in hemoglobin, sodium, and albumin levels between the groups. In contrast, inorganic phosphate levels increased and total calcium decreased with decreasing age. Parathyroid hormone also increased with decreasing age. In the <55 years group, the correlation between intradialytic SBP variability (22.1 ± 14.02 mm Hg) and interdialytic SBP variability (19.2 ± 10.93 mm Hg) was significant ($r = 0.107$, $P = 0.003$). The correlations between intradialytic SBP variability and intradialytic DBP variability (13.2 ± 7.96 mm Hg) and between interdialytic SBP variability and interdialytic DBP variability (13.1 ± 9.92 mm Hg) were also significant ($r = 0.679$, $P < 0.001$ and $r = 0.489$, $P < 0.001$; respectively).

Prevalence of BP variability by age category

The prevalence of intradialytic SBP and DBP variability and interdialytic SBP and DBP variability divided by age are shown in Figure 1. As age increased, the prevalence of intradialytic SBP variability increased (51%, 59%, and 60% for patients aged <55 years, 55–74 years, and ≥ 75 years, respectively; $P = 0.001$). Although the prevalence of intradialytic DBP variability did not differ significantly between the three groups, there was a trend of increasing prevalence of intradialytic DBP variability with increasing age (64%, 68%, and 70%, for patients aged <55 years, 55–74 years, and ≥ 75 year, respectively; $P = 0.064$). The prevalence of interdialytic SBP and DBP variability did not differ significantly between the groups (interdialytic SBP: 79%, 80%, and 83%, for patients aged <55 years, 55–74 years, and ≥ 75 years, respectively; $P = 0.367$; interdialytic DBP: 84%, 85%, and 87%, for patients aged <55 years, 55–74 years, and ≥ 75 years, respectively; $P = 0.429$).

BP variability as a risk factor for 5-year mortality

We investigated the impact of BP variability on 5-year mortality. Kaplan-Meier survival analysis showed that the survival rate in patients with intradialytic and interdialytic SBP and DBP variability aged <55 years was reduced (intradialytic SBP: $P = 0.006$; intradialytic DBP: $P < 0.001$; interdialytic SBP: $P = 0.018$; interdialytic DBP variability: $P < 0.001$; Figures 2 and 3).

To determine if intradialytic and interdialytic SBP and DBP were risk factors for 5-year mortality, Cox proportional analysis was performed (Table 2). In unadjusted Cox proportional analysis, the relative risk for death increased only in patients aged <55 years, not in patients aged 55–74 or in patients aged ≥ 75 years. In patients aged <55 years, intradialytic SBP variability, intradialytic DBP variability, and interdialytic SBP variability were associated

Fig. 2. Kaplan-Meier survival analysis of patients aged <55 years divided by intradialytic systolic blood pressure and diastolic blood pressure variability.

Fig. 3. Kaplan-Meier survival analysis of patients aged <55 years divided by interdialytic systolic blood pressure and diastolic blood pressure variability.

Table 2. Cox proportional analysis for 5-year mortality by blood pressure variability in each age group

	<55 years		55–74 years		≥75 years	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Unadjusted model						
Intradialytic SBP variability	1.73 (1.16–2.57)	0.007	0.96 (0.77–1.19)	0.733	1.23 (0.79–1.59)	0.518
Intradialytic DBP variability	2.38 (1.50–3.79)	<0.001	1.03 (0.82–1.30)	0.764	0.83 (0.57–1.24)	0.333
Interdialytic SBP variability	1.98 (1.11–3.55)	0.021	0.85 (0.66–1.09)	0.202	0.68 (0.45–1.04)	0.078
Interdialytic DBP variability	1.90 (0.99–3.65)	0.053	0.85 (0.64–1.13)	0.284	0.63 (0.39–1.00)	0.053
Adjusted model						
Intradialytic SBP variability	1.08 (0.70–1.66)	0.714	0.90 (0.72–1.13)	0.383	1.20 (0.82–1.75)	0.335
Intradialytic DBP variability	2.03 (1.24–3.32)	0.005	1.02 (0.81–1.30)	0.828	0.79 (0.54–1.16)	0.246
Interdialytic SBP variability	1.67 (0.90–3.09)	0.100	0.95 (0.73–1.23)	0.708	0.77 (0.49–1.21)	0.272
Interdialytic DBP variability	1.92 (0.96–3.85)	0.064	0.93 (0.70–1.24)	0.642	0.61 (0.36–1.01)	0.059
Adjusted for age (year), gender, comorbid conditions (hypertension, diabetes, and heart failure), medication (ACE inhibitor or ARB, β-adrenergic blocker, and calcium channel blocker), blood chemistry profile (hemoglobin (<8 g/dL, 8–12 g/dL, and >12 g/dL), Sodium (<135 mEq/L and ≥135 mEq/L), Albumin (<3.5 mg/dL and ≥3.5 mg/dL), and total calcium (<8.5 mg/dL, 8.5–10.5 mg/dL, and >10.5 mg/dL))						

with 5-year mortality [HR (CI): 1.73 (1.16–2.57), 2.38 (1.50–3.79), and 1.98 (1.11–3.55), respectively]. In adjusted Cox proportional analysis, intradialytic DBP variability was a risk factor of 5-year mortality in patients aged <55 years [HR (CI): 2.03 (1.24–3.32)].

In order to determine if additional variables affected 5-year mortality in patients aged <55 years, Cox proportional analysis was performed (Table 3). Variables that showed an association of $p < 0.1$ in univariate analysis and/or were clinically plausible were included in this analysis. After adjusting for confounders, 5-year mortality was independently associated with age, diabetes, and hypoalbuminemia (albumin level <3.5 mg/dL).

Table 3. Cox proportional analysis for 5-year mortality in patients aged <55 years

Variables	HR (95% CI)	P-value
Age (year)	1.06 (1.03-1.10)	<0.001
Gender (female)	0.70 (0.46-1.08)	0.112
Comorbid conditions		
Hypertension	0.86 (0.52-1.43)	0.579
Diabetes	2.15 (1.37-3.36)	0.001
Heart failure	2.07 (0.63-6.75)	0.224
Medication		
ACE inhibitor or ARB	1.00 (0.61-1.62)	0.998
β -adrenergic blocker	1.15 (0.73-1.84)	0.532
Calcium channel blocker	0.96 (0.57-1.60)	0.886
Blood chemistry profile		
Hemoglobin level < 8 g/dL	2.22 (0.96-5.15)	0.062
Hemoglobin level 8-12 g/dL	1.51 (0.67-3.38)	0.311
Total calcium level < 8.5 mg/dL	0.99 (0.58-1.69)	0.981
Total calcium level $\geq$ 10.5 mg/dL	0.30 (0.04-2.27)	0.246
Sodium level <135 mEq/L	1.34 (0.89-2.03)	0.157
Albumin level <3.5 mg/dL	1.58 (1.03-2.45)	0.036

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker

Discussion

Hemodialysis is a stressful hemodynamic procedure that requires adequate cardiovascular compliance. The rapid change in blood volume, electrolyte levels, and osmolality may overwhelm the capacity of the cardiovascular system to respond adequately to stress. During hemodialysis, better cardiovascular compliance is expected in younger patients than in older patients, as younger patients have fewer atherosclerotic diseases and less degenerative changes of their cardiovascular structures. We demonstrated that as age increased, the prevalence of intradialytic SBP variability increased significantly. Similarly, there was a trend of increasing prevalence of intradialytic DBP variability with increasing age. It has been demonstrated by Flythe *et al.* [16], that intradialytic SBP variability is associated with greater dialytic fluid removal and with demographic characteristics such as older age. It is known that several factors contribute to intradialytic BP variability, including compromised autonomic nervous system and cardiovascular compensatory mechanisms [17]. Elderly patients have a lower tolerance for volume changes, which may be because of the higher morbidity from cardiac dysfunction and impaired vascular compliance. In contrast, we demonstrated that the prevalence of interdialytic BP variability did not differ among the age groups, suggesting that adjustments of cardiovascular compliance in response to acute volume reduction during hemodialysis and interdialytic weight gain vary depending on age.

In elderly hemodialysis patients, the overall clinical status is poor, and renal replacement therapy may further compromise their condition. There is a high prevalence of comorbid conditions, including heart failure and myocardial infarction, which may be associated with poor clinical outcomes [18]. In our study, we found that all-cause mortality increased with increasing age. In addition, the prevalence of heart failure was increased in elderly patients. These findings suggest that age related cardiovascular dysfunctions contribute to poor clinical outcomes in elderly patients. Further, we showed that inorganic phosphate and parathyroid hormone levels increased, while total calcium levels decreased, with decreasing age. These findings are consistent with a previous study that demonstrated that calcium levels were decreased and inorganic phosphate and parathyroid hormone levels were increased in patients aged <65 when compared to patients aged $\geq$ 65 [19]. These findings

may be attributed to the lower daily phosphorus intake and the prevalence of a dynamic bone disease in elderly dialysis patients [20].

Increased pulse pressure, which is an indirect measurement of arterial stiffness, is an established risk factor for cardiovascular outcomes and a prognostic factor for mortality in hemodialysis patients [5]. In addition, endothelial dysfunction and arterial stiffness are independently associated with intradialytic hypotension and intradialytic hypertension [21], suggesting that intradialytic BP variability might be associated with distinct vascular changes. In our patients, we demonstrated that pulse pressure increases with age, suggesting that the prevalence of arterial stiffness is higher in older populations and may represent a high risk for BP variability.

It has been suggested that interdialytic BP variability [22] and intradialytic BP variability [23] are associated with increased all-cause and cardiovascular mortality. We demonstrated, using Kaplan-Meier survival curves, that higher mortality is associated with higher intradialytic SBP and DBP variability and higher interdialytic SBP and DBP variability in patients aged <55 years but not in the older age groups. The varied prognostic significance of BP variability depending on the age group, along with the high prevalence of BP variability in elderly patients, suggest that mortality risk stratification should not be based on the same BP variability and hemodynamic cut points in the elderly as in younger age groups. Consistent with this, age has been shown to have an impact on the association of mortality with several other common conditions. Higher BP is associated with favorable 5-year survival among subjects aged 75 years and over, whereas the reverse is true for younger patients [24]. Similarly, we have previously demonstrated a differential prognostic significance of renal dysfunction with myocardial infarction [25]. In addition, lower glomerular filtration rate is associated with decreases in mortality with increasing age. The lower relative risk for death attributable to BP variability in older populations may reflect the higher prevalence of comorbidities and other mortality risks, lessening the potential for the single comorbidity of BP variability to have an impact on mortality.

Using Cox proportional analysis with an adjustment for multiple factors revealed that 5-year mortality was associated with intradialytic DBP variability only in patients aged <55 years. In older patient groups, there was no significant association between 5-year mortality and intradialytic SBP and DBP variability or interdialytic SBP and DBP variability. This suggests that BP variability is a feasible and acceptable variable to use in predicting prognosis in hemodialysis. In addition, the significance of BP variability is more important in younger hemodialysis patients than in older hemodialysis patients.

The present study has several limitations. First, BP was measured at the time of dialysis initiation so the observed BP variability may not be representative of the BP variability present in stable maintenance hemodialysis patients. Second, it was not possible to exclude the possibility of residual confounding factors because of the presence of unmeasured confounders or measurement errors in the included factors. Finally, as this study was a retrospective, single-center, observational study, it was not possible to demonstrate a causal relationship between BP variability and all-cause mortality.

Conclusion

This study demonstrated that the association between BP variability and all-cause mortality in hemodialysis patients differs by age group. There is an association between 5-year mortality and BP variability, by Kaplan-Meier survival analysis and Cox proportional hazards regression analysis, only in patients aged <55 years. Thus, BP variability has a greater impact on mortality in younger patients. Younger hemodialysis patients with BP variability require further medical attention and intervention to reduce BP variability.

Conflict of Interests

All the authors have no conflicts of interest to declare.

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