ORIGINAL ARTICLE

Home systolic blood pressure on the morning of dialysis days has prognostic impact for hypertensive hemodialysis patients

Makoto Ogura · Yukiko Yamada · Hiroyuki Terawaki · Akihiko Hamaguchi · Yasuo Kimura · Tatsuo Hosoya

Abstract

Background Hypertension is a leading cause of cardiovascular (CV) disease in the general population. Although hypertension is very common in maintenance hemodialysis (HD) patients, adequate blood pressure (BP) values and measurement timing have not been defined.

Methods A total of 49 hypertensive HD patients were recruited. Average age was 63 ± 11 years, and duration of dialysis therapy was 6.2 ± 4.2 years. Dialysis unit BPs and various types of home BPs were separately measured, and which BPs were the most critical markers in evaluating the effect of hypertension on left ventricular hypertrophy and CV events was investigated.

Results Predialysis systolic BPs were not correlated with any home BPs. Left ventricular mass index (LVMI) had a significant positive correlation with home BPs, especially morning systolic BPs on HD days ($P < 0.01$) and non-HD days ($P < 0.05$), on univariate and multivariate analysis. In contrast, predialysis BPs did not correlate with LVMI. During the follow-up period (47 ± 18 months), it was demonstrated that diabetes and home BPs, especially systolic BPs on the morning of HD days, were significant predictors of CV events on multivariate Cox regression analysis. A 10 mmHg increase in BP had a significantly elevated relative risk for CV events.

Conclusions Home BP, especially systolic BPs in the morning on HD days, can provide pivotal information for management of HD patients.

Keywords Hemodialysis · Hypertension · Home blood pressure · Left ventricular hypertrophy · Cardiovascular events

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Introduction

Hypertension is very common in patients undergoing regular hemodialysis (HD) treatment. Using various definitions of hypertension, the prevalence of hypertension in HD patients is estimated to be 60–90% [1–6]; for example, in a study of 2,535 clinically stable adult HD patients, 86% were found to be hypertensive [6]. In that study, hypertension was controlled adequately in only 30% of hypertensive patients. In the remaining patients, hypertension was either untreated (12%) or was poorly controlled (58%). Cardiovascular (CV) disease is the leading cause of death in patients receiving maintenance HD. Hypertension of HD patients is a risk factor for development and progression of left ventricular hypertrophy (LVH), CV, and total mortality [7]. Although Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines suggest that pre-HD and post-HD blood pressure (BP) should be <140/90 and <130/80 mmHg, respectively [8], the optimum BP goals for HD patients have not yet been defined. A meta-analysis showed that dialysis unit BP (pre- and post-HD) have poor agreement with interdialytic ambulatory BP [9]. BP obtained outside the dialysis unit, whether by interdialytic ambulatory BP measurement or self-measurement of BP at home,

is useful in diagnosing LVH [10]. More recently, home BP and ambulatory BP have been found to provide superior prognostic value for all-cause mortality compared with dialysis unit BP among HD patients [11].

In this study, dialysis unit BP and various types of home BPs were separately measured, and which BPs were the most critical markers in evaluating the effect of hypertension on LVH and CV events in hypertensive HD patients was investigated.

Subjects and methods

Protocol

The protocol was in conformity with the ethical guidelines of our institutions, and informed consent was obtained from each participant.

Subjects

Forty-nine patients with end-stage renal disease (ESRD) (28 men and 21 women) who had been on regular dialysis treatment for at least 6 months at The Jikei University Kashiwa Hospital and Shin-Kashiwa Clinic were eligible for the study. All patients had been prescribed antihypertensive agents with diagnosis of hypertension. Patients with significant cardiac valvular disease, congestive heart failure with ventricular ejection fraction below 40%, or malignant disorders were excluded. No patients had experienced previous CV diseases. All patients underwent standard 3-times-a-week bicarbonate dialysis. All patients were on antihypertensive treatment [49 on calcium channel blockers (CCBs), 28 on angiotensin II receptor blockers (ARBs), 15 on alpha blockers, and 3 on beta blockers] with various combinations.

After the initial assessment, patients were followed for 56 months. During the follow-up period, CV events (fatal and nonfatal coronary heart disease diagnosed by coronary angiography, fatal arrhythmia, peripheral artery disease, transient ischemic attacks, stroke, and aortic dissection) and death were evaluated. To assess CV events and death accurately, two physicians checked the patients' medical records. Coronary heart diseases were suspected by chest symptoms and electrocardiographic findings, and diagnosed by coronary angiography. Arrhythmias were diagnosed based on a standard 12-lead electrocardiogram. Cerebral stroke and transient ischemic attacks were diagnosed by neurological signs and symptoms together with computed tomography (CT) or magnetic resonance imaging. Peripheral artery disease and aortic dissection were diagnosed by clinical symptoms and enhanced CT findings.

Measurement of left ventricular mass

Echocardiographic measurements were performed with a digital cardiac ultrasound machine on a midweek nondialysis day. M-mode echocardiogram measurements of interventricular septal thickness (IVSTd), posterior wall thickness (PWTd), and left ventricular internal diameter (LVIDd) were performed at end diastole according to established standards of the American Society of Echocardiography (ASE). Left ventricular mass (LVM) was calculated using the formula by Devereux et al. [12] according to the ASE guidelines:

$$LV \text{ mass (g)} = 0.8(1.04([IVSTd + PWTd + LVIDd]^3 - [LVIDd]^3)) + 0.06.$$

Echocardiography was performed by the same technician, and all measurements were performed in duplicate by the same cardiologist, who was unaware of the subject's BP. Left ventricular mass index (LVMI) was derived by dividing LVM in grams by the body surface area.

Predialysis BPs

A single predialysis BP measurement was taken by a dialysis unit staff member with patients in sitting position, within 30 min prior to the dialysis session using an automated sphygmometer on the nonfistula arm. Predialysis BP was calculated as the average value of 9 recordings over 3 weeks.

Home BPs

Home BP monitoring was performed 2 times daily for 3 weeks. Patients were asked to record their BP on waking up and before going to bed in sitting position using a validated self-inflating automatic oscillometric device. Four home BP values (morning BP and night BP on HD and non-HD days) were separately evaluated.

Statistical analysis

Subject characteristics are presented as mean ± standard deviation (SD) or median and interquartile range for continuous variables as appropriate, and number (percent) for categorical data. All BP measurements are reported as mean ± SD. Univariate and multivariate analyses were performed to evaluate the correlations between LVMI and several factors. The prognostic value for CV event of predialytic and home BPs was analyzed by multivariate Cox regression analysis. As potential confounders, a set of well-established risk factors in dialysis patients was considered: age, gender, HD duration, diabetes, antihypertensive (especially ARB) therapy, and clinical data. Hazard ratios

Table 1 Clinical characteristics and antihypertensive agents of study subjects

Clinical characteristic	$n = 49$
Male (%)	28 (57.1)
Age (years)	63 ± 11 (37–84)
HD duration (years)	6.2 ± 4.2 (1–16)
Diabetes mellitus (%)	16 (32.6)
Post-HD CTR (%)	48.4 ± 4.2 (41.3–59.8)
Interdialytic body weight gain	
/dry weight (%)	3.99 ± 0.99
BUN (mg/dl)	65.9 ± 14.7
Cr (mg/dl)	11.6 ± 2.5
Alb (g/dl)	3.9 ± 0.3
Ca (mg/dl)	8.9 ± 0.8
P (mg/dl)	4.4 ± 1.1
Hb (g/dl)	10.0 ± 0.9
Antihypertensive agents	
CCB (%)	49 (100)
ARB (%)	28 (57.1)
α Blocker (%)	15 (30.6)
β Blocker (%)	3 (6.1)

CTR cardiothoracic ratio, *BUN* blood urea nitrogen, *Cr* creatinine, *Alb* albumin, *Ca* calcium, *P* phosphate, *Hb* hemoglobin, *CCB* calcium channel blockers, *ARB* angiotensin receptor blockers

Table 2 Predialysis and home BP measurements

BPs	mmHg
Clinic	
Predialysis	
Systolic	152.8 ± 19.0
Diastolic	80.2 ± 13.4
Home	
Mornings on HD days	
Systolic	155.8 ± 17.8[a]
Diastolic	80.9 ± 14.5
Nights on HD days	
Systolic	152.3 ± 19.6
Diastolic	81.7 ± 14.4
Mornings on non-HD days	
Systolic	150.9 ± 18.4[a]
Diastolic	80.6 ± 12.4
Nights on non-HD days	
Systolic	156.1 ± 17.1
Diastolic	81.1 ± 12.9

[a] BP in the morning on HD days versus BP in the morning on non-HD days, $P < 0.05$

(HR) and their 95% confidence intervals (CI) were calculated with the use of the estimated regression coefficients and their standard errors in the Cox regression analysis. All analyses were conducted using SPSS software version 17.0 (SPSS, Chicago, IL, USA) for Windows. The *P* values reported are two sided and taken to be significant at <0.05.

Results

Clinical characteristics of the patients are presented in Table 1. Average age was 63 ± 11 years (range 37–84 years), and duration of dialysis therapy was 6.2 ± 4.2 years (range 1–16 years). Interdialytic body weight (BW) gain was 3.9% per dry weight, and post-HD cardiothoracic ratio (CTR) was 48.4%. Intradialytic hypotension episodes were not found in any patient during the week in which the measurements were performed. All of the patients had been treated with antihypertensive drugs: 49 (100%) were on CCBs, 28 (57.1%) were on ARBs, 15 (30.6%) were on alpha blockers, and 3 (6.1%) were on beta blockers, with various combinations.

Table 2 presents the values of predialysis BPs and each home BP. Predialysis mean systolic BP was 152.8 ± 19.0 mmHg. Each mean systolic home BP was as follows: mornings on HD days 155.8 ± 17.8 mmHg, nights on HD days 152.3 ± 19.6 mmHg, mornings on non-HD days 150.9 ± 18.4 mmHg, and nights on non-HD days 156.1 ± 17.1 mmHg. The value of BP in the morning on HD days was significantly higher than BP in the morning on non-HD days ($P < 0.05$). There were no differences between diastolic BPs. Predialysis systolic BPs were not correlated with any home BPs. The difference between HD morning and non-HD morning BPs was weakly correlated with % interdialytic BW gain ($P = 0.05$, data not shown).

Predialysis and home BPs and LVMI

As shown in Fig. 1, home BPs, especially morning systolic BPs on HD and non-HD days, had a significant positive correlation with LVMI ($r = 0.50$, $P < 0.01$ and $r = 0.41$, $P < 0.01$, respectively). On the other hand, predialysis BP did not correlate with LVMI ($r = 0.27$, NS). Multivariate analysis including various factors (HD vintage, age, gender, diabetes, ARB, and BPs) demonstrated that only morning systolic BPs on HD and non-HD days had significant correlation with LVMI (Table 3).

Predialysis and home BPs and cardiovascular events

During the follow-up period (47 ± 18 months), 11 (22%) patients had CV events (4 with angina, 4 with stroke, 2 with idiopathic ventricular tachycardia, and 1 with aortic dissection). Among these patients, 3 patients died with stroke. Table 4 presents the relative risks (RR) of CV
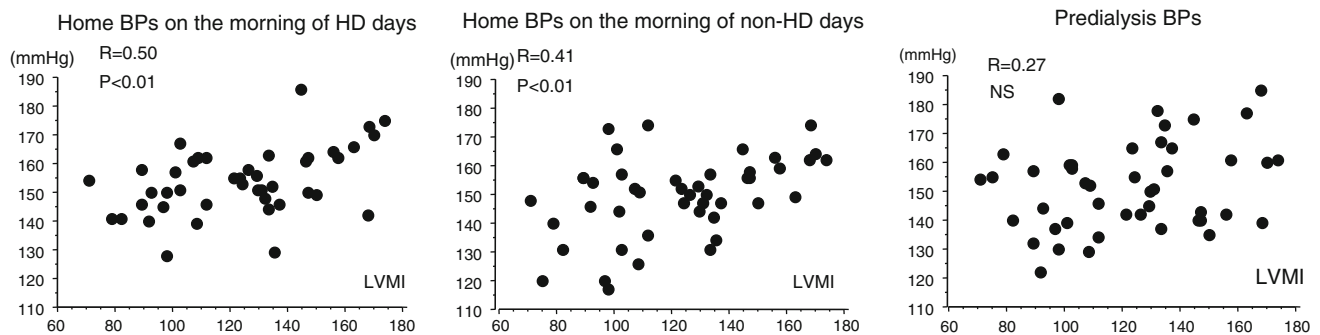
Fig. 1 Correlation with left ventricular mass index (LVMI) and various types of blood pressures (BPs). LVMI demonstrated significant correlation with morning BPs on hemodialysis (HD) ($R = 0.50$, $P < 0.01$) and non-HD ($R = 0.41$, $P < 0.01$) days. In contrast, LVMI did not have a correlation with predialysis BPs ($R = 0.27$, NS)

Table 3 Correlation with LVMI and various factors assessed by multivariate analysis

	Model 1		Model 2	
	R	P	R	P
HD duration	0.03	0.83	0.03	0.84
Age	0.02	0.87	0.05	0.76
Gender	−0.22	0.19	−0.26	0.15
DM	−0.15	0.35	−0.05	0.77
ARB	0.12	0.45	0.18	0.30
BPs (mmHg)				
Predialysis	0.27	0.12	0.31	0.09
Home				
Mornings on HD days	0.57	0.008		
Nights on HD days	0.20	0.44	−0.12	0.67
Mornings on non-HD days			0.55	0.03
Nights on non-HD days	−0.32	0.27	−0.15	0.60

events in the study population. As assessed by multivariate Cox analysis, the significant predictors of CV events were diabetes and home BPs, especially systolic BPs on the morning of HD days. A 10 mmHg increase in BP had a significantly elevated RR for CV events (RR 2.00, 95% CI 1.07–3.74, $P = 0.03$).

Discussion

The results demonstrated that the median systolic values of predialysis and home BPs were around 150 mmHg, ranging from 151 to 156 mmHg, while the median diastolic values were around 80 mmHg. Predialysis systolic BPs were higher than the K/DOQI guideline (<140/90 mmHg) [8]. All patients in the present study had been diagnosed with hypertension before, and treated with at least one or more antihypertensive agents. Despite aggressive treatment, BP control was considered to be inadequate by the

K/DOQI guideline. The 12th annual report of the UK Renal Registry (UKRR) indicated that 43.1% of HD patients achieve predialytic BP of <140/90 mmHg [13]. Strict control of BPs is often difficult, considering the prevention of hypotension during HD. Davenport et al. [14] reported that intradialytic hypotension was significantly greater in centers that achieved better postdialysis BP targeting.

The present data showed that predialysis systolic BPs were not correlated with any home BPs. Agarwal et al. [15] reported that BPs obtained before and after dialysis, even if obtained using standardized methods, agree poorly with interdialytic ambulatory BP. In contrast, home BP served as a useful predictor of hypertension diagnosed by ambulatory BP monitoring. The difference between HD and non-HD morning BPs was weakly correlated with % interdialytic BW gain. This is reasonable because BPs in HD patients, in part, usually depend on an increase in fluid volume between dialysis.

The present study demonstrated that LVMI had a significant positive correlation on univariate analysis with home BP, especially morning systolic BPs on HD and non-HD days. In contrast, predialysis BP did not correlate with LVMI. Multivariate analysis including several factors which could affect LVMI demonstrated that only morning systolic BPs on HD and non-HD days were regarded as independent explanatory factors. LVMI has been reported as a critical indicator to predict mortality and CV outcomes in patients undergoing dialysis [16–19]. LVH regression in patients with ESRD has been shown to have a favorable and independent effect on patients' all-cause and CV survival [20]. Agarwal et al. [10] reported that dialysis unit BPs in 140 HD patients were weak correlates of LVH. On the other hand, systolic BPs outside the dialysis unit (1-week averaged home BP readings) were a stronger correlate of LVH. Diastolic BPs, regardless of the measurement technique, were of little use in detecting LVH. A more recent study reported that weekly averaged BP (WAB) was a useful marker that reflects BP variability

Table 4 Relative risk of cardiovascular events assessed by multivariate Cox proportional hazards models

	Relative risk	95% confidence limits	*P*
HD duration	1.19	0.93–1.52	0.17
Age	1.06	0.97–1.15	0.21
Gender	1.93	0.20–18.9	0.57
DM	8.76	1.30–58.9	0.03
ARB	1.16	0.18–7.50	0.88
Cr	1.20	0.77–1.87	0.41
Alb	1.69	0.09–33.7	0.73
Ca	1.14	0.34–3.79	0.83
P	0.44	0.17–1.18	0.10
Hb	1.10	0.45–2.66	0.84
BPs (10 mmHg)			
Mornings on HD days	2.00	1.07–3.74	0.03

during 1 week and correlates with target organ damage such as LVMI and brachial-ankle pulse wave velocity (PWV) [21]. Furthermore, systolic and diastolic WAB are almost completely consistent with BPs taken immediately after waking up on the next day after the middle dialysis session. The present data agree with these previous studies. It should be emphasized that home BPs, especially morning systolic BPs on HD days, play a pivotal role predicting LVMI. This phenomenon is considered to be reasonable because morning BPs on HD days can partly represent maximum volume overload to vasculature, thus affecting LVMI.

The present results also demonstrated that home BPs, especially systolic BPs on the morning of HD days, were the significant predictors of CV events during follow-up period. A 10 mmHg increase in BP had a significantly elevated RR for CV events (RR 2.00). Several studies using ambulatory or home BP monitoring in HD patients support the concepts that ambulatory BP and mortality are strongly related. Amar et al. [22] reported that nocturnal BP and 24-h pulse pressure were independent predictors of CV mortality in 57 treated hypertensive HD patients (34 ± 20 months). Tripepi et al. [23] analyzed the prognostic power of 24-h ambulatory BP monitoring for all-cause and CV mortality in 168 nondiabetic, event-free HD patients (38 ± 22 months). The ratio of the average systolic BP during the night and day (night/day systolic ratio) used to indicate the nocturnal fall in BP was associated with all-cause and CV mortality. Moriya et al. [24] reported that WAB could be a good prognostic marker of the incidence of both CV events and all-cause mortality in 96 HD patients (35 months). Recently, Agarwal [11] evaluated the presence, strength, and shape of the relationship between BP measured using different modalities (home, ambulatory, and dialysis unit) and all-cause mortality among 326 HD patients (32 ± 20 months).

Out-of-dialysis unit BP was reported as prognostically more informative than that recorded just before and after dialysis.

The role of hypertension as a risk factor for increased CV events in the general population is indisputable. However, a lot of studies have shown an association between low BP and increased mortality, or have shown a U-shaped relationship, with both low and high BP associated with increased RR of death [25–27]. These paradoxical observations have been referred to as "reverse epidemiology" [28]. As the etiology of this inverse association between conventional risk factors and clinical outcome is not clear, presence of malnutrition and inflammation may explain the existence of reverse epidemiology in dialysis patients. In the present study, patients who were recently hospitalized or sick were excluded. All of the patients in the present study had hypertension, nor pre- and postdialysis hypotension. Thus, this study differed in its recruitment criteria compared with previous studies which have analyzed all patients in the dialysis unit regardless of their level of illness.

In the present statistical evaluation, age did not contribute to the onset of CV events. Several reasons are considered to explain this phenomenon. First, the observation period was likely short to evaluate CV events. Second, patients in the present study had not experienced previous CV diseases. Third, few fatal events occurred, probably due to their healthy condition for dialysis patients.

All of the patients in the present study had been prescribed one or more antihypertensive agents: 49 (100%) were on CCBs, 28 (57.1%) were on ARBs, 15 (30.6%) were on alpha blockers, and 3 (6.1%) were on beta blockers. Recent data from the Dialysis Outcomes and Practice Patterns Study II (DOPPS II) showed that prescription of antihypertensive agent classes varied significantly by country, ranging for beta blockers from 9.7% in Japan to 52.7% in Sweden, for ARBs from 5.5% in Italy to 21.3% in Japan, and for CCBs from 19.5% in Belgium to 51.4% in Japan [29]. Therefore, the high proportion of prescribed CCBs and ARBs in the present study in Japan is not so surprising.

The ability to generalize the results of this study may be limited because of the number of patients and clinical characteristics. The number of patients was too small to conclude prognosis of a large variety and complexity of HD patients. Patients included in this study were all hypertensive and were treated with one or more antihypertensive agents. Furthermore, almost all patients were in good health. Recently, diurnal BP variation has been considered important [30]. In the present study, ambulatory BPs were not measured. Ambulatory BP monitoring provides not only static but also dynamic information about BP that should be considered to ensure effective management of hypertension and CV diseases.

In conclusion, the results of the present study are: (1) predialysis systolic BPs were not correlated with any home BPs; (2) LVMI had a significant positive correlation with home BPs, especially morning systolic BPs on HD and non-HD days; and (3) home BPs, especially systolic BPs in the morning on HD days, were significant predictors of CV events during the follow-up period. Prospective intervention studies with large numbers of patients will be needed to clarify the cause–effect relationship between various BPs and CV events.

Conflict of interest All the authors declare no competing interests.

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