Early Systolic Blood Pressure Changes in Incident Hemodialysis Patients Are Associated with Mortality in the First Year

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Key Words

Hemodialysis • Mortality • Systolic blood pressure

Abstract

Background: In incident hemodialysis (HD) patients, the relationship between early systolic blood pressure (SBP) dynamics and mortality is unknown. **Methods:** Baseline SBP levels were stratified into 5 categories ranging from <120 and ≥180 mm Hg. Early pre-HD SBP change was defined as the slope of pre-HD SBP from week 1 to 12 and categorized in quartiles (Q1, lowest slope). SBP slopes were computed for each patient by simple linear regression. **Results:** In 3,446 incident HD patients (42% females, 44% black, age 62 ± 15 years), the median pre-HD SBP slope was −1.7 (Q1) to +2.3 (Q4) mm Hg/week. In an adjusted multivariate Cox regression analysis, patients with declining SBP (slope Q1) had higher mortality compared to patients with increasing pre-HD SBP (slope Q4) at 12 months (hazard ratio 2.01, 95% confidence interval 1.35–3.01). In addition, patients with baseline pre-HD SBP <120 mm Hg showed higher mortality compared to the reference group (SBP ≥180 mm Hg) at 12 months (hazard ratio 1.89, 95% confidence interval 1.03–3.45). **Conclusion:** Baseline pre-HD SBP and early SBP dynamics are associated with mortality in the first year of dialy-

sis. Patients who had low (pre-HD SBP <120 mm Hg) or declining SBP had the highest mortality rates. Particular attention is warranted in incident HD patients with low or declining SBP.

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Introduction

Renal regulation of body fluid volume and of blood pressure (BP) is impaired in patients with chronic kidney disease (CKD), making hypertension (HTN) highly prevalent. HTN is present in approximately 80–85% of patients with CKD [1]. HTN plays a major role in development of left ventricular hypertrophy, congestive heart failure, coronary artery disease and cerebrovascular disease and results in increased cardiovascular morbidity and mortality [2]. The majority of CKD patients are hypertensive prior to the start of dialysis. However, hemodialysis (HD) does not result in an appreciably lower frequency of HTN, and a prevalence of up to 80% is reported [3]. In addition to pre-existing HTN, non-adherence to salt restriction, intradialytic sodium gain due to dialysate sodium concentration exceeding serum levels, inappropriate sodium profiling, and intradialytic adminis-

tration of saline are associated with the high prevalence of HTN in HD patients. High BP may be further aggravated by increased sympathetic activity, the cause of which is multifactorial [4]. There is no generally accepted definition of HTN in HD patients [5]. In non-dialysis adults, HTN was defined by the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC VII) as systolic BP (SBP) ≥ 140 mm Hg and/or diastolic BP ≥ 90 mm Hg [6]. The National Kidney Foundation Kidney Disease Outcomes Quality Initiative recommended in-center predialysis BP targets for HD patients $<140/90$ mm Hg [7]. The evidence level for this recommendation is low since it was based on studies performed in pre-HD CKD patients. Survival analysis in HD patients revealed a U-shaped relationship between SBP and mortality with excess mortality risk in patients at the extremes, i.e. those in the lowest and highest strata of SBP [8–10] and those with declining SBP [11]. The impairment of left ventricular function by the effect of prior long-standing high SBP could explain to an extent the association between low SBP and mortality.

In the present study, we were particularly interested in SBP dynamics in the early time period after HD initiation. More specifically, we aimed to test the hypothesis that a low and/or declining SBP in the first 12 weeks on HD is related to increased mortality in the first year of treatment.

Methods

In this retrospective study, we investigated a large cohort of incident HD patients treated in Renal Research Institute facilities between 1 January 2001 and 30 July 2008. All incident patients >18 years and surviving beyond day 90 were included. All patients were followed until discharge from Renal Research Institute facilities, death or at the end of year 1.

BP Measurement and BP Categories

BP was measured before each HD in the sitting position using the standard BP module (Colin Medical Technology, M2600; Japan) integrated in the HD machines.

Weekly pre-HD SBP was obtained by averaging the three pre-HD SBP values of any given week. Week 0 was defined as the week of in-center HD initiation. Baseline pre-HD SBP was defined as the average pre-HD SBP of weeks 1–3 of HD and was stratified into 5 categories: category 1, SBP <120 mm Hg; category 2, $120 \leq$ SBP <140 mm Hg; category 3, $140 \leq$ SBP <160 mm Hg; category 4, $160 \leq$ SBP <180 mm Hg; category 5, SBP ≥ 180 mm Hg.

Early pre-HD SBP change was defined as the slope of pre-HD SBP between weeks 1 and 12. SBP slopes (in mm Hg/week) were computed for each patient by simple linear regression and categorized into quartiles (Q), with Q1 as the lowest and Q4 as the highest slope. The analysis in categories of SBP and SBP slopes was prespecified and motivated by our a priori reasoning that differ-

Fig. 1. Study flow diagram. PD = Peritoneal dialysis.

ent slopes may be associated with outcomes in a non-linear fashion.

Statistical Methods

Data are expressed as the mean $\pm$ standard deviation or as crude numbers and percentages. Continuous variables were compared between categories by analysis of variance, and categorical variables were compared by the χ^2 test. Survival curves were calculated by the Kaplan-Meier method for SBP groups and SBP slope quartiles, and differences in survival times in the groups were compared by the log-rank test. The associations between the 5 categories of pre-HD SBP, quartiles of SBP slope and all-cause mortality at months 6 and 12 were evaluated with a Cox proportional hazards model. SBP category 5 (SBP ≥ 180 mm Hg) and SBP slope Q4 served as reference groups. Age at the start of HD, sex, race (white/black/other), diabetic status, cardiovascular comorbidities (congestive heart failure, coronary artery disease, peripheral vascular disease), 12-week averages of laboratory values (serum albumin, creatinine, blood urea nitrogen, hemoglobin), interdialytic weight gain, dialysis adequacy (eKt/V) and normalized protein catabolic rate, as determined by formal urea kinetic modeling, were included as covariates in the Cox survival analyses.

Results

Of 16,792 screened incident HD patients, 3,446 comprised the final study cohort (fig. 1). In the final cohort, 42% were female, 44% were black, 47% were white, and the mean age was 62 ± 15 years. Diabetes mellitus was

Table 1. Baseline characteristics**a** Stratified per SBP groups (n = 3,446)

	All patients (n = 3,446)	SBP, mm Hg					p value
		<120 (n = 264)	120–139.9 (n = 952)	140–159.9 (n = 1,301)	160–179.9 (n = 709)	≥180 (n = 220)	
Age, years							
Mean ± SD	61.5 ± 15.1	66.7 ± 14.6	63.1 ± 16.0	60.1 ± 14.9	60.4 ± 14.3	59.8 ± 13.4	<0.001
Median	62.5	69.8	64.6	60.8	61.2	60.8	
Range	18.4–97.6	20.6–90.2	20.2–97.6	18.4–94.4	19.2–94.3	22.3–89.1	
Male	2,000 (58.0)	173 (65.5)	585 (61.4)	765 (58.8)	381 (53.7)	96 (43.6)	<0.001
Race							<0.001
Black	1,504 (43.6)	84 (31.8)	384 (40.3)	578 (44.4)	355 (50.1)	103 (46.8)	
White	1,635 (47.4)	165 (62.5)	494 (51.9)	589 (45.3)	285 (40.2)	102 (46.4)	
Other	307 (8.9)	15 (5.7)	74 (7.8)	134 (10.3)	69 (9.7)	15 (6.8)	
Body mass index	27.6 ± 7.1	25.8 ± 6.3	27.3 ± 6.8	27.7 ± 7.0	27.9 ± 7.3	28.9 ± 8.3	<0.001
Diabetes	1,740 (50.5)	108 (40.9)	384 (40.3)	679 (52.2)	408 (57.5)	161 (73.2)	<0.001
Laboratory results							
Albumin, g/dl	3.6 ± 0.4	3.5 ± 0.4	3.6 ± 0.5	3.6 ± 0.4	3.5 ± 0.4	3.6 ± 0.4	<0.001
Creatinine, mg/dl	6.9 ± 2.6	5.4 ± 1.8	6.9 ± 2.7	7.2 ± 2.7	7.2 ± 2.6	7.1 ± 2.5	<0.001
Hemoglobin, g/dl	11.0 ± 1.2	10.9 ± 1.1	11.1 ± 1.2	11.2 ± 1.1	11.0 ± 1.2	11.1 ± 1.2	0.096
Serum sodium, mEq/l	138.5 ± 2.7	138 ± 2.7	138 ± 2.7	138 ± 2.8	138 ± 2.7	138 ± 2.7	0.162
Residual renal urea clearance, ml/min	0.55 ± 1.33	0.48 ± 1.17	0.59 ± 1.34	0.59 ± 1.36	0.61 ± 1.82	0.54 ± 1.36	0.441
SBP change, mm Hg/month	0.31 ± 1.83	1.28 ± 1.79	0.85 ± 1.56	0.37 ± 1.68	−0.34 ± 1.78	−1.46 ± 2.02	<0.001

b Stratified per SBP slope quartiles (n = 3,446)

	Slope quartile				p value
	Q1 (n = 862)	Q2 (n = 861)	Q3 (n = 861)	Q4 (n = 862)	
Age, years					
Mean ± SD	61.7 ± 15.4	60.4 ± 15.3	61.4 ± 15.3	62.3 ± 14.3	0.061
Median	63.0	61.3	62.2	62.9	
Range	20.8–96.5	18.4–92.8	19.2–97.6	21.3–95.9	
Male	497 (57.7)	504 (58.5)	512 (59.5)	487 (56.5)	0.637
Race					0.422
Black	382 (44.3)	374 (43.4)	362 (42)	386 (44.8)	
White	415 (48.1)	397 (46.1)	421 (48.9)	402 (46.6)	
Other	65 (7.5)	90 (10.5)	78 (9.1)	74 (8.6)	
Body mass index	27.6 ± 7.2	27.3 ± 6.9	27.7 ± 7.1	27.7 ± 7.1	0.571
Diabetes	436 (50.6)	420 (48.8)	405 (47.0)	479 (55.6)	0.003
Laboratory results					
Albumin, g/dl	3.6 ± 0.4	3.6 ± 0.4	3.6 ± 0.4	3.5 ± 0.5	<0.001
Creatinine, mg/dl	7.3 ± 2.8	6.9 ± 2.6	6.8 ± 2.6	7.0 ± 2.6	0.925
Hemoglobin, g/dl	11.3 ± 1.2	11.2 ± 1.1	11.1 ± 1.2	11.0 ± 1.1	<0.001
Serum sodium, mEq/l	138.4 ± 2.6	138.3 ± 2.7	138.5 ± 2.8	138.5 ± 2.8	0.060
Residual renal urea clearance, ml/min	0.50 ± 1.20	0.58 ± 1.40	0.52 ± 1.61	0.70 ± 1.51	0.902
SBP, mm Hg	159.5 ± 20.0	147.6 ± 19.0	144.8 ± 18.5	140.9 ± 17.4	<0.001

Figures in parentheses are percentages.

Fig. 2. Distribution of baseline pre-HD SBP (average of weeks 1–3).

the most common cause of renal failure (50.5%). Detailed demographical data stratified by baseline SBP and predialysis SBP slope are shown in table 1a and b, respectively. Total follow-up time was 8,243 patient-years, with a median (25–75 percentile) follow-up time of 1.96 (0.94–3.45) years.

At baseline, more than one third of the patients (37.8%) had a pre-HD SBP between 140 and 160 mm Hg (category 3), and 27.6% of the patients were in SBP category 2 (120–140 mm Hg; fig. 2).

Between the start of HD (week 0) and week 1, mean pre-HD SBP dropped by 2.8 mm Hg [95% confidence interval (CI) –1.4 to –3.1] from 150.5 ± 24.1 to 147.7 ± 22.9 mm Hg ($p < 0.0001$). After week 1, SBP increased steadily and reached a plateau at week 12 (fig. 3). The dynamics of SBP differed between the 5 SBP categories: in the lower BP pressure categories (1 and 2), SBP decreased transiently followed by a rise. In contrast, in categories 4 and 5, SBP rose transiently followed by a decline; SBP in patients in category 3 remained stable throughout the first year (fig. 4).

Pre-HD weight decreased after initiation of HD from 80.7 ± 22.2 kg at baseline to 79.4 ± 21.4 kg at week 12. After 6 months, pre-HD weight gradually increased and reached $80.7 \text{ kg} \pm 21.8$ at the end of the first year (fig. 3).

The frequency distribution of SBP slopes is shown in fig. 5. Medians (range) of predialysis SBP slope quartiles (in mm Hg/week) were Q1: –1.7 (–7.0 to –0.8); Q2: –0.3 (–0.8 to 0.3); Q3: 0.8 (0.3–1.4), and Q4: 2.3 (1.4–9.4).

Survival Analysis

There were 76 and 244 deaths in the first 6 and 12 months, respectively. First-year Kaplan-Meier survival curves stratified by the SBP group are shown in figure 6a. Mortality in patients with baseline SBP <120 mm Hg was significantly higher compared to patients in other SBP groups ($p < 0.001$). Kaplan-Meier analysis of SBP slope quartiles showed that patients in the lowest quartile (Q1) had significantly poorer survival compared to those in the highest quartile (Q4) (fig. 6b).

Results of the Cox models for 6 and 12 months are shown in table 2. After adjustment, baseline SBP <120 mm Hg was associated with increased mortality at 6 months (hazard ratio 4.80, 95% CI 1.31–17.52; $p = 0.02$) and at 12 months (hazard ratio 1.89, 95% CI 1.03–3.45; $p = 0.04$). SBP changes in the first 12 weeks were related to survival in Cox analyses. Patients in Q4 had significantly better survival at both 6 and 12 months compared to patients in other slope quartiles ($p < 0.05$).

Discussion

A large number of risk factors for mortality have been identified in HD patients including age, race, cardiovascular diseases, HTN, infection, inflammation, diabetic status, hypoalbuminemia and dialysis adequacy [12–17]. In chronic HD patients, BP shows a time-dependent relationship with survival, and an excess mortality risk in patients at the extremes of BP has been noted (‘U-shaped relationship’) [8–10]. In this study, we tested the hypothesis that absolute SBP and SBP changes in the first 3 months on HD are predictors of outcome. This hypothesis is based on earlier observations that low and decreasing SBP is associated with increased mortality. In a study including 56,338 incident HD patients, Li et al. [10] reported that SBP <120 mm Hg, and between 120 to 140 mm Hg, is associated with a higher mortality risk in the first year of HD. In a recent study, Raimann et al. [11] estimated the slope of SBP change by linear regression using all SBP values in years 1 and 2 in 10,245 HD patients. Patients with an SBP decline had the highest risk of death in both years 1 and 2, irrespective of the absolute SBP at baseline [11]. The main finding of our study is that both low (baseline SBP <120 mm Hg) and declining SBP in the first weeks on HD are associated with increased mortality after 6 and 12 months, respectively. At 6 months, hazard ratios were 4.8 in patients with a baseline SBP <120 mm Hg, and 2.99 in patients with the steepest SBP decline (Q1). Because of the observational nature of our study, we

Fig. 3. SBP and pre-HD weight in the first year on HD (with 95% CI).

Fig. 4. One-year SBP course in the 5 SBP groups (mean and 95% CI).

Table 2. Cox proportional hazard analysis

	6-month survival						12-month survival					
	B	SE	Sig.	HR	95.0% CI for HR		B	SE	Sig.	HR	95.0% CI for HR	
					lower	upper					lower	upper
SBP group												
SBP <120 mm/Hg	1.57	0.66	0.02	4.80	1.31	17.52	0.63	0.31	0.04	1.89	1.03	3.45
SBP 120–139.9 mm/Hg	0.67	0.64	0.30	1.95	0.55	6.88	0.16	0.28	0.58	1.17	0.67	2.03
SBP 140–159.9 mm/Hg	0.57	0.63	0.36	1.77	0.52	6.07	−0.13	0.28	0.65	0.88	0.51	1.51
SBP 160–179.9 mm/Hg	0.41	0.65	0.53	1.50	0.42	5.40	−0.16	0.29	0.57	0.85	0.48	1.50
SBP slope quartiles												
Q1	1.10	0.37	0.00	2.99	1.44	6.23	0.70	0.21	0.00	2.01	1.35	3.01
Q2	0.89	0.37	0.02	2.43	1.18	5.03	0.58	0.20	0.00	1.79	1.21	2.64
Q3	0.64	0.38	0.09	1.90	0.90	4.00	0.57	0.20	0.00	1.76	1.19	2.60

Adjustments were made for age (in years) at the start of HD, sex, race (white/black/other), diabetic status, cardiovascular comorbidities (congestive heart failure, coronary artery disease, peripheral vascular disease), 12-week averages of laboratory values [serum albumin (g/dl), creatinine (mg/dl), BUN (mg/dl), hemoglobin (g/dl)], interdialytic weight gain (kg), dialysis adequacy

(eKt/V, as determined by formal urea kinetic modeling), and normalized protein catabolic rate (g/kg body weight/day). SBP ≥ 180 mm Hg and SBP slope quartile Q4 were used as reference categories. B = Regression coefficient; SE = standard error; Sig. = Significance; HR = hazard ratio.

Fig. 5. Distribution of SBP slopes (in mm Hg/week) in the first 12 weeks on HD.

can only speculate about the underlying mechanisms. When SBP slope quartiles Q1 and Q4 were examined, it is obvious that these groups were heterogeneous in terms of baseline SBP; 47.8% of patients in SBP slope Q1 had a baseline SBP ≥ 160 mm Hg and 48% of patients in SBP slope Q4 had a baseline SBP < 140 mm Hg. Although the mean SBP of the study population fluctuated over the first year, it stabilized at an average of about 150 mm Hg (fig. 3). The evolution of SBP in the first year on HD stratified by the baseline SBP group is shown in figure 4. Given the observational nature of the study, it cannot be excluded that the declining SBP in patients with high baseline SBP and the rising SBP in patients with a low baseline SBP, respectively, may result to some extent from regression to the mean. However, the retrospective nature of this study prevents quantitative statements about the potential impact of regression to the mean.

The changing relationship of BP with mortality over time has been demonstrated in several studies. Mazzuchi et al. [18] reported that normal or low BP was related with increased mortality during the early years of dialysis, whereas high BP was related with increased mortality in later years. Similar findings were observed by Stidley et al. [9] in 17,000 patients. In their study baseline, pre-HD SBP < 120 mm Hg was associated with increased mortality in the first 2 years of HD, whereas SBP ≥ 150 mm Hg

Fig. 6. a Kaplan-Meier curves of 1-year survival stratified by baseline SBP. log-rank test showed significant differences between category 1 (SBP < 120 mm Hg) and category 2 (SBP 120–139.9 mm Hg; $p < 0.001$), category 1 and category 3 (SBP 140–159.9 mm Hg; $p < 0.001$), category 1 and category 4 (160–179.9 mm Hg; $p <$

0.001), and between category 1 and category 5 (SBP ≥ 180 mm Hg; $p = 0.009$). **b** Kaplan-Meier analysis of survival between patients stratified by quartiles of SBP slope. log-rank test showed significant differences between the first and fourth quartile ($p = 0.01$) as well as between the third and fourth quartile ($p = 0.046$).

showed its adverse effect on survival after 3 years of HD, indicating that higher BP is associated with better survival in the early period of HD. Our findings in incident HD patients are in line with these reports, as the mortality risk in the early period (6–12 months) was increased in patients with a baseline SBP < 120 mm Hg.

In the present study, SBP changes early after initiation of HD were related to mortality in the first year, so that an increase in SBP in the first 3 months after HD initiation was associated with better survival at months 6 and 12 compared to an SBP decrease.

BP is determined by peripheral resistance and cardiac output and is thus related to cardiac function and volume status. While we have no direct measures of volume status, our data indicate that body weight decreased in the first 3 months most likely because of removal of excess fluid; other potential explanations (e.g. loss in muscle and/or fat mass) are less probable. A reduced fluid overload may improve cardiac function and consequently raise SBP. Hence, the increase in SBP in patients with SBP slope Q4 may be a reflection of improved cardiac function. On the other hand, the high mortality in patients within SBP slope Q1

may be related to a poor cardiac function at dialysis initiation and a failure to increase cardiac output and SBP. Patients with diastolic dysfunction may have experienced a reduction in cardiac output and SBP because of a decrease in filling pressure. In addition, HD itself may precipitate coronary ischemia, leading to myocardial stunning [19]. In a recent study, HD-induced myocardial stunning was assessed in 70 HD patients by serial intradialytic echocardiography. Myocardial stunning, manifested by the development and subsequent recovery of regional wall motion abnormalities, occurred in around two thirds of patients [20]. In the present study, patients with declining SBP (Q1) may have been affected by myocardial stunning to some degree. Above all, since objective means to determine dry weight (e.g. bioimpedance) were not used, ultrafiltration rates might have been too high or post-HD weight reduction might have been excessive resulting in myocardial hypoperfusion. Higher ultrafiltration volume, which is associated with dialysis-induced cardiac injury and myocardial stunning [20, 21], might have resulted in decreased SBP and possibly excess mortality.

In addition to the observational nature of our study, other limitations are evident. Several options exist to determine BP in HD patients, such as pre- or post-dialysis BP, ambulatory BP measurement, and interdialytic home BP. Reliance upon immediate predialysis and/or postdialysis BP measurements alone to detect HTN in patients undergoing HD may be misleading. A single-center cross-sectional study reported that home BP measured by the patients was better than pre-HD BP in predicting left ventricular hypertrophy [22]. Although ambulatory BP measurement and self-measured home BP are preferable, they are available only in a minority of HD patients and prone to bias by indication. For this reason, pre- and post-HD BP was used in this study. In our data system, no indicators of cardiac function (e.g. echocardiography) and dry weight (e.g. bioimpedance) were available. Markers of

cardiovascular autonomic nervous functions (e.g. heart rate variability) would have aided data interpretation. Another limitation is the lack of reliable information on antihypertensive drug use in most of the patients. Therefore, we cannot make statements about the relationship between SBP slope and changes in antihypertensive medication.

In conclusion, our data suggest that both baseline SBP and early SBP change are associated with mortality in the first year on HD. Particular attention is warranted in incident HD patients with low SBP and SBP decline in weeks 1–12. Since declining BP may reflect deteriorating cardiac function, echocardiography and early cardiology referral should be considered. Additional prospective studies are necessary to confirm these findings and identify pathophysiological mechanisms.

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