Prognostic Value of 48-Hour Ambulatory Blood Pressure Measurement and Cardiovascular Mortality in Hemodialysis Patients

Robert Ekart^a Vojko Kanič^b Breda Pečovnik Balon^c Sebastjan Bevc^a
Radovan Hojs^c

Departments of ^aDialysis, ^bCardiology and ^cNephrology, Clinic for Internal Medicine, University Medical Centre Maribor, Maribor, Slovenia

Key Words

Ambulatory blood pressure monitoring • Cardiovascular mortality • Hemodialysis • Hypertension

Abstract

Background: Hypertension is common and contributes to high cardiovascular morbidity and mortality in hemodialysis (HD) patients. It is unknown which blood pressure (BP) better defines the influence on cardiovascular mortality. The purpose of our study was to analyze the relationship between various BP measurements, traditional risk factors, markers of asymptomatic atherosclerosis [left ventricular mass (LVM), carotid intima media thickness (IMT)], and cardiovascular mortality in HD patients. **Methods:** Seventy-three patients (44 males and 29 females; mean age: 54.2 years) were included. BP was measured before and after HD and 48-hour ambulatory blood pressure monitoring (ABPM) was performed. Using sonography, the LVM index and carotid IMT were measured. **Results:** During a follow-up period up to 3,664 days, 28 patients died – 16 of them from cardiovascular causes. In a Cox regression model, which included age, gender, smoking, diabetes, sensitive C-reactive protein, albumin, hemoglobin, troponin T, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, calcium, phosphorus, carotid IMT, and LVM index, only 48-hour systolic ABPM ($p = 0.037$) and 48-hour diastolic ABPM ($p = 0.006$)

turned out to be independent predictors of cardiovascular death. **Conclusion:** Only 48-hour ABPM and not single BP measurements before or after HD were associated with cardiovascular mortality in HD patients.

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Introduction

Cardiovascular disease is a leading cause of morbidity and mortality in chronic hemodialysis (HD) patients [1]. Cardiovascular risk markers include age, hypertension, carotid intima-media thickness (IMT), left ventricular mass (LVM), and aortic stiffness – pulse wave velocity. Hypertension is a common and difficult clinical problem in HD patients and its impact on cardiovascular prognosis is not as clear as in the general population. The diagnosis of hypertension in HD patients is difficult because of variability in blood pressure (BP) and different techniques of measuring BP. Hypertension in HD patients is often poorly controlled [2]. Routine dialysis unit BP agree poorly with ambulatory BP recordings that are obtained during an interdialytic interval [3–6]. Ambulatory blood pressure monitoring (ABPM) is a technique of BP measurement that may decrease measured BP variability and is an important tool for clarifying the mean level of BP, nocturnal hypertension, and the dipping phenomenon [7,

8]. ABPM has been shown to predict cardiovascular events better than conventional BP in patients with essential hypertension [7, 9].

In most studies of end-stage renal disease patients, dialysis unit BP measurements were used to explore the relationship between hypertension and cardiovascular events [10]. However, dialysis unit BP measurements fail to accurately characterize BP in HD patients, making it difficult to define the prognostic significance of hypertension in this population [10, 11]. It is not unexpected that in many studies a poor correlation was found between dialysis unit BP measurements and ABPM readings obtained in the interdialytic period [10, 11]. In the last decade, a few studies have assessed the prognostic power of ABPM and outcomes in HD patients [12–17]. The use of out-of-office BP measurement techniques, including self-measured BP and ABPM, in the management of HD patients is increasing.

Left ventricular hypertrophy (LVH) is a well-recognized cardiac manifestation of long-term hypertension-induced target organ damage [18]. In HD patients, LVH contributes substantially to high cardiovascular mortality [19]. The high prevalence of LVH among HD patients may be a consequence of inadequate diagnosis and treatment of hypertension. It is assumed that carotid IMT is a mirror for general atherosclerosis. IMT in the carotid arteries is a strong predictor for cardiovascular events in the general population and is an independent predictor of cardiovascular mortality in HD patients [20].

The purpose of this study was to evaluate the relationship between various BP measurements (single BP measurements in dialysis unit on HD day, 48-hour ABPM), traditional risk factors (age, gender, smoking, cholesterol, triglycerides), sensitive C-reactive protein (s-CRP), troponin T, markers of asymptomatic atherosclerosis (LVM, carotid IMT), and cardiovascular mortality in HD patients.

Patients and Methods

Protocol

This prospective study was performed in the dialysis unit at the University Medical Centre Maribor, Slovenia. The protocol was in conformity with the ethical guidelines at our institution and before taking part in the study informed consent was obtained from all participants. The study was also approved by the Ethics Committee of the Republic Slovenia, ruling No. 130/12/03.

Patients

Patients who were stable on chronic HD in our dialysis unit for at least 1 month were invited to participate. Patients were includ-

ed between November 1999 and June 2005 and had to be cardiovascular event-free and without a history or clinical evidence of heart failure at the time of inclusion. Other exclusion criteria were: patients with malignant hypertension, patients with aortic valve stenosis, malignant disorders, alcoholism, and chronic inflammatory disease.

All patients were on regular HD three times a week for 3–5 h on polyamide, polysulfone, and cellulose triacetate hollow-fiber dialyzers with a surface of 1.4–2.2 m². All dialyzers were prescribed on an individual basis in an attempt to obtain a $Kt/V_{urea} \geq 1.2$. The blood flow rate was 200–300 ml/min and the dialysate flow rate was 500 ml/min. The ultrafiltration volume was adapted individually. During HD, all patients were ultrafiltrated to achieve their estimated dry weight.

Dialysis Unit BP Measurements

Pre-HD BP was measured by dialysis nurses after the patients had rested quietly for 15 min in the supine position, using a mercury sphygmomanometer on the upper portion of the nonfistula arm. Post-HD BP was measured using a similar technique. Hypertension was defined as systolic BP (SBP) ≥ 140 mm Hg, diastolic BP (DBP) ≥ 90 mm Hg, and/or lower levels if the patient was taking antihypertensive drugs.

Ambulatory Blood Pressure Measurements

ABPM was performed after the midweek HD session for 48 h. Ambulatory BPs were recorded every 20 min during the day (06.00–22.00 h) and every 60 min during the night (22.00–06.00 h) using a Spacelab 90207 ABP monitor (Spacelabs Medical Inc., Redmond, Wash., USA). The recordings started 20–30 min after a HD session and continued until the end of the next HD session. The ambulatory BP readings were considered adequate as recommended by the British Hypertension Society guidelines for ABP monitoring [21]. The patients were defined as ‘dippers’ when the nighttime SBP fall was $\geq 10\%$ and as ‘non-dippers’ when the nighttime SBP fall was $<10\%$. Hypertension was defined as a SBP ≥ 135 mm Hg, DBP ≥ 85 mm Hg, and/or even lower levels if the patient was taking antihypertensive drugs.

Ultrasonography

Ultrasonographic scanning of the carotid artery was performed with high-resolution echo color Doppler ultrasonography with a multifrequency of 5–10 MHz linear probe on a ATL HDI 3000 machine (Advanced Technology Laboratories, High Definition Imaging, Bothel, Wash., USA). All subjects were in the supine position with their necks slightly hyperextended and rotated away from the imaging transducer. Several images were captured in real time on the cine-loop frame grabber: the three most clearly visible ones were used for measurements. Images were displayed with a constant fourfold magnification. The carotid arteries were investigated bilaterally. We investigated IMT in the common carotid arteries. As in other studies, IMT was defined as the distance between the leading edge of the lumen-intimal interface and the leading edge of the media-adventitia interface of the far wall [22]. The measurement of IMT was done in a plaque-free section. Three still images from the same section of the artery were measured and the mean value was calculated. The mean value was also calculated from the left and right carotid artery. All the ultrasonic examinations were performed by the same operator.

Table 1. Baseline clinical and biochemical characteristics of HD patients (n = 73)

Variable	
Age, years	54.2 ± 13.3
Sex, males/female	44/29 (60.3/39.7)
HD duration before inclusion, months	43.2 ± 42.1
HD session, h	4.23 ± 0.4
Smokers	32 (43.8)
Diabetes mellitus	11 (15.06)
BMI	24.7 ± 5.6
Interdialytic weight gain, kg	2.6 ± 0.9
Kt/V	1.4 ± 0.2
Ca, mmol/l	2.3 ± 0.2
P, mmol/l	1.7 ± 0.5
LDL cholesterol, mmol/l	2.5 ± 0.9
HDL cholesterol, mmol/l	1.2 ± 0.3
Triglycerides, mmol/l	1.8 ± 1.1
CRP, mg/l	10.7 ± 17.4
Troponin T, µg/l	0.05 ± 0.05
Albumin, g/l	39.6 ± 3.8
Hemoglobin, g/l	114.7 ± 15.1
Carotid IMT, mm	0.78 ± 0.20
LVMI, g/m ²	148.9 ± 49.4
Treatment with erythropoietin	55 (75.3)

Values are means ± SD or n (%).

Echocardiography

Standard two-dimensional and two-dimensional M-mode echocardiography was performed in all patients on the interdialytic day with an ATL HDI 3000 machine, using 3.5-MHz transducer. All patients were examined in the left lateral decubitus position by a single experienced echocardiographer who was blind to the results of the BP measurements. All measurements were made according to the American Society of Echocardiography guidelines [23]. LVM was calculated from the Devereux and Reichek formula [24]. LVM index (LVMI) was calculated by dividing LVM by body surface area. The presence of LVH was defined on the basis of a LVMI >131 g/m² for males and >100 g/m² for females (Framingham criteria) [25].

Laboratory Variables

Blood samples for hemoglobin, s-CRP, troponin T, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, calcium, phosphorus, and albumin were drawn from the arterial site of the arteriovenous fistula at the beginning of HD.

Follow-Up

Follow-up duration was calculated from the date of ABPM to the end of study or to the date on which an outcome of death occurred or the patient was transplanted or went to another dialysis center. Causes of death were classified as cardiovascular death

(ischemic heart disease, cardiac arrhythmias, congestive heart failure, stroke, and sudden death) and death not related to cardiovascular disease.

Statistical Analysis

All data are presented as means ± SD. Student's t and Mann-Whitney tests were used for comparison of patients who survived or died in the follow-up period. Cox proportional hazards regression was used to assess the influence of variables that possibly had an effect on cardiovascular outcomes. All of the analyses were performed using SPSS software (SPSS for Windows, version 12.0.; SPSS Inc., Chicago, Ill., USA), and p < 0.05 was considered indicative of statistically significant differences.

Results

We performed a study with a follow-up period up to 3,664 days (mean: 1,795 days; ± SD 1,063.5) on a population of 73 HD patients (44 males and 29 females) aged 54.2 ± 13.3 years (range: 19–78). At the beginning of the study they were treated with maintenance HD for a mean of 43.2 ± 42.1 months (range: 2–205). Thirty-two patients (43.8%) were habitual smokers and 11 patients (15.1%) had diabetes mellitus. The baseline characteristics of patients included in the study are shown in table 1.

In table 2, the results of different BP measurements (pre-HD, post-HD, and ABPM values) are presented. Twenty-three patients (31.5%) were dippers.

Forty-seven patients (64.4%) were on antihypertensive drugs at the time they were included in this study. Twenty-two patients (30.1%) were on monotherapy with angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists, calcium-channel blockers, β-blockers, α-blockers, or diuretics (furosemide); 16 patients (21.9%) were on 2 drugs; 6 patients (8.2%) were on 3 drugs; and 3 patients (4.1%) were on 4 antihypertensive drugs with different combinations of these drugs. After including the patient in the study, we did not change the doses of the antihypertensive drugs or suggest the patient should stop taking them.

We established the prevalence of hypertension in our patients using commonly used definitions (BP ≥140/90 mm Hg for measurements in the dialysis unit, ≥135/85 mm Hg for ambulatory values, and/or even lower values if the patient was taking antihypertensive drugs). Under such definitions, the prevalence of hypertension was 86.3% (63/73), 83.6% (61/73), and 79.4% (58/73) using pre- and post-HD BP and during 48-hour ABPM, respectively. Based on 48-hour ABPM, 36 patients (49.3%) had controlled hypertension, 14 (19.2%) had isolated systolic hy-

pertension, and 2 (2.7%) had isolated diastolic hypertension. In patients taking no antihypertensive drugs, 10 patients (38.5%) were dippers, 7 (26.9%) had isolated systolic hypertension, and nobody had diastolic hypertension. In patients taking antihypertensive drugs, 13 patients (27.7%) were dippers, 7 (14.9%) had isolated systolic hypertension, and 2 (4.2%) had isolated diastolic hypertension.

Echocardiography was performed in all patients; the mean LVMI was 148.9 ± 49.4 g/m² (range: 69–308). Regarding LVMI measurements, we found LVH in 52 patients (71.2%; 27 males and 25 females). Ultrasonographic scanning of the carotid artery was also performed in all patients; the mean carotid IMT value was 0.78 ± 0.20 mm (range: 0.4–1.3).

During the follow-up period, 28 patients (38.3%) died; of these, 16 (i.e. 57.1% of total deaths) were from cardiovascular causes (sudden cardiac death, myocardial infarction, heart failure, cerebrovascular insult). Twenty patients were transplanted and 3 patients went to another dialysis center. Among the patients who died, 5 (17.9%) were dippers and 23 (82.1%) were non-dippers. Among the patients who died of cardiovascular causes, 4 (25%) were dippers and 12 (75%) were non-dippers. Among patients who survived, 17 (37.8%) were dippers and 28 (62.2%) were non-dippers. The differences were not statistically significant.

Comparing patients who survived and died of cardiovascular causes, we found that patients who died of cardiovascular causes were statistically significantly older ($p < 0.001$), had increased carotid IMT ($p < 0.001$), lower HDL ($p = 0.039$), and higher s-CRP ($p = 0.016$). Both groups did not statistically differ according to different BP measurements, gender, presence of diabetes, smoking, LVMI, hemoglobin, LDL cholesterol, triglycerides, calcium, phosphorus, albumin, and Kt/V. Comparison of data of patients who survived or died of cardiovascular cause are presented in table 3.

In survival analysis we used multivariate Cox regression models. We constructed 6 models, each of which analyzed the possible impact of different BP measurements on cardiovascular mortality. In all models, we included known variables for cardiovascular morbidity and mortality: age, gender, smoking, diabetes, s-CRP, albumin, hemoglobin, troponin T, LDL cholesterol, HDL cholesterol, triglycerides, calcium, phosphorus, carotid IMT, and LVMI. In each model, different BP measurements (single SBP measurements before HD, single DBP measurements before HD, single SBP measurements after HD, single DBP measurements after HD, 48-hour systolic ABPM, and 48-hour diastolic ABPM) were added. We found that only 48-hour systolic ABPM ($p = 0.037$)

Table 2. Different BP measurements (n = 73)

Variable	Mean $\pm$ SD
SBP before HD, mm Hg	146.9 $\pm$ 21
DBP before HD, mm Hg	84 $\pm$ 10.9
SBP after HD, mm Hg	138.4 $\pm$ 20.6
DBP after HD, mm Hg	81.2 $\pm$ 9.4
48-Hour ABPM, mm Hg	
SBP	135 $\pm$ 21.7
DBP	80.4 $\pm$ 12.1

Table 3. Comparison of age, mean carotid IMT, different BP measurements, LVMI, and laboratory values of patients who survived or died of cardiovascular cause

Variable	Survived	Cardiovascular death	p
Age	49.64 $\pm$ 13.79	61.44 $\pm$ 8.16	<0.001
Mean carotid IMT, mm	0.68 $\pm$ 0.15	0.95 $\pm$ 0.17	<0.001
SBP before HD, mm Hg	143.5 $\pm$ 20.6	146.9 $\pm$ 20.1	0.074
DBP before HD, mm Hg	83.6 $\pm$ 10.7	80.3 $\pm$ 8.3	0.069
SBP after HD, mm Hg	135.8 $\pm$ 21.3	139.7 $\pm$ 21.1	0.167
DBP after HD, mm Hg	80.7 $\pm$ 9.4	80.3 $\pm$ 10.4	0.519
48-Hour ABPM SBP, mm Hg	131.4 $\pm$ 22.2	140 $\pm$ 18.6	0.07
48-Hour ABPM DBP, mm Hg	80.6 $\pm$ 11.7	79.1 $\pm$ 10.9	0.808
LVMI, g/m ²	142.9 $\pm$ 47.7	158.7 $\pm$ 50.8	0.198
LDL cholesterol, mmol/l	2.6 $\pm$ 0.82	2.4 $\pm$ 0.96	0.49
HDL cholesterol, mmol/l	1.26 $\pm$ 0.35	1.11 $\pm$ 0.27	0.039
Triglycerides, mmol/l	1.6 $\pm$ 0.63	2.22 $\pm$ 1.45	0.057
s-CRP, g/l	6.01 $\pm$ 8.2	13.94 $\pm$ 14.8	0.016
Albumin, g/l	39.86 $\pm$ 3.91	39.72 $\pm$ 4.18	0.488
P, mmol/l	1.69 $\pm$ 0.55	1.65 $\pm$ 0.3	0.953
Ca, mmol/l	2.25 $\pm$ 0.22	2.36 $\pm$ 0.15	0.1

and 48-hour diastolic ABPM ($p = 0.006$) turned out to be an independent predictor of cardiovascular death in HD patients included in the study. Single BP measurements in the dialysis unit were not independent predictors of cardiovascular mortality in these patients.

Discussion

The results of our study demonstrated that only 48-hour ABPM is an important and independent determinant for cardiovascular mortality in HD patients. Individual dialysis unit BP measurements were not associated with cardiovascular mortality in these patients. We also confirmed that cardiovascular disease is the most common cause of death in HD patients. According to our

knowledge we performed the longest prospective study with a follow-up of up to 10 years as well as the longest (48-hour) ABPM in HD patients.

The results of our study are consistent with previously published studies using BP monitoring in HD patients [5, 12, 14, 17]. In these four studies, ABPM contained greater prognostic information compared to BP measurements in the dialysis unit. ABPM was performed for 24 h in two of the studies [12, 14] and for 44 h in the other two [5, 17]. In our study, we performed 48-hour ABPM, also during HD session, which is more than the above reports. There is a paucity of data in HD patients regarding which time length of ABPM should be achieved to properly assess BP and reduce cardiovascular events and peridialytic adverse effects in these patients.

Mortality is U-shaped or reversed J-shaped in large epidemiological studies with HD patients regardless of their level of cardiovascular illness [26, 27]. In our study we included only stable patients without signs of heart failure or acute coronary syndrome, similar to the study of Tripepi et al. [14] and Amar et al. [12]. In this way we excluded patients with low BP as a result of heart failure which is known to increase mortality [27]. Furthermore, our results probably show better interpretation of actual real BP influence on cardiovascular mortality in these patients. Agarwal [17] reported in the largest similar study to date, which included 326 HD patients with a mean follow-up of 32 months, that the effect of 44-hour ambulatory BP and home BP on survival persisted even after adjustments for cardiovascular disease as well as conventional and nonconventional cardiovascular risk factors for mortality. Similar to our study, Agarwal also excluded patients who were recently hospitalized or sick or more hypotensive. The mean follow-up in our study was almost 6 years, with the longest follow-up lasting 10 years, which is the longest follow-up in all similar studies reported to date. Only 5 patients had a follow-up less than 365 days: 3 were transplanted, 1 died after sepsis, and 1 died because of acute pancreatitis.

In our study there were 31.5% dippers, which is similar to the study by Liu et al. [13] in which 30% of 80 HD patients were dippers. Among those who died in our study, 82% were non-dippers. The non-dipping phenomenon was significantly associated with more cardiovascular events and higher cardiovascular mortality in HD patients in the studies by Liu et al. [13], Amar et al. [12] and Tripepi et al. [14]. In our study, we did not find any significant association between mortality and the non-dipping phenomenon.

BP is poorly controlled in the majority of HD patients. In our study on antihypertensive drugs, 72.3% were non-dippers suggesting the lack of efficacy of antihypertensive drugs to control BP during the night. In the cohort of 649 HD patients, only 28% had controlled BP [28]. In a study of 489 HD patients, Rahman et al. [29] found that 62% of patients exhibited uncontrolled hypertension, 91% of patients with uncontrolled hypertension were receiving submaximal antihypertensive drug therapy, and 59% withheld their medications before dialysis. In 53 hypertensive HD patients using 24-hour ABPM, Cheigh et al. [30] found that only 15% of patients had the target BP. In their study including 57 HD patients, Amar et al. [12] found that 33% of the patients had their hypertension controlled, and the pre-HD BP and ABPM measurements were at goal levels in 53 and 22% of patients, respectively. Based on 48-hour ABPM, in our study 49.3% of all patients and 46.8% of patients on antihypertensive drugs had target BP <135/85 mm Hg, which is more than in other studies [12, 30].

The results of our study also show that individual routine pre- and post-HD BP measurements in the dialysis unit does not have any influence on cardiovascular mortality in HD patients. Use of a single BP reading in the dialysis unit to characterize the long-term behavior of BP in HD patients is unrealistic – c.f. a single serum creatinine measurement in a course of acute or chronic renal failure. This is also in accordance with our findings – there is a need for analysis of multiple BP measurements. ABPM with multiple measurements during daily life and sleep cover many readings in different situations, and this is more close to realistic BP variability of every single patient. Such data have more predictive power.

There are some limitations of our study. The number of patients included in the study was relatively small, and because of the small number of cardiovascular events, the results of the present study must be interpreted cautiously. The small number of diabetics is also noteworthy; however, we have to emphasize that in our country the number of diabetics among the HD population is relatively small. We did not perform home BP monitoring, which is also useful and associated with all-cause and cardiovascular mortality in HD patients [5]. The time length of ABPM was 48 h, and BP recordings included those obtained in the dialysis unit. We wish to study the influence of all BP measurements over a period of 2 days, including those during the HD procedure.

In conclusion, we demonstrated the importance of 48-hour ABPM for prognostication of cardiovascular mortality in HD patients. For predicting cardiovascular mortality, ABPM is clearly superior to routine dialysis unit BP

measurements before and/or after HD, also after adjustment for known cardiovascular risk factors. In the near future, 48-hour ABPM may become an important tool and the gold standard to assess BP as an important risk factor for asymptomatic (target-organ damage) and symptomatic atherosclerosis (cardiovascular mortality) in the HD population and also as a starting point for therapeutic strategy.

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Disclosure Statement

We declare that we have no conflict of interest.

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