Appropriateness of Antihypertensive Drug Therapy in Hemodialysis Patients

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The prevalence and treatment of hypertension in hemodialysis (HD) patients exceeds 85% in the United States. Because of uncertainties in the evaluation of BP, it is unclear whether the HD patients who are being treated with medications are truly hypertensive. For ascertainment of the appropriateness of antihypertensive therapy, a prospective study in which antihypertensive drugs were discontinued in HD patients and 44-h interdialytic ambulatory BP monitoring was performed and left ventricular mass and inferior vena cava were measured by echocardiography was conducted. Home BP was monitored weekly during washout. An average of 2.3 medications were tapered and discontinued in 41 black participants (age 56 yr, 46% men, 54% diabetes, duration of dialysis 5.3 yr). Thirty-three (80%) of 41 patients became hypertensive, but eight (20%) remained normotensive at 3 to 5 wk. Patients who remained normotensive had a higher body mass index (31 *versus* 25.7 kg/m^2) and diabetes (78 *versus* 45%), were less likely to smoke (13 *versus* 52%), had lower home BP at baseline (135/76 *versus* 147/85 mmHg), and had a lower left ventricular mass index (115 *versus* 146 g/m^2). The rate of rise of home BP was more rapid in patients who became hypertensive. None of the normotensive patients were volume overloaded in contrast to 12% of the hypertensive patients. It is concluded that a majority of the treated black hypertensive patients are appropriately receiving therapy for hypertension. Those who have well-controlled home BP and no left ventricular hypertrophy may have a cautious withdrawal of their antihypertensive drugs.

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In a cross-sectional study of chronic stable hemodialysis (HD) patients in the United States, hypertension was detected in 2173 (86%) of 2353 patients, and among those with hypertension, 88% were treated with antihypertensive drugs (1). Thus, the prevalence, recognition, and treatment rate of hypertension is high in the HD population.

Patients who are on chronic HD have large changes in BP from predialysis to postdialysis. What is a "normal" dialysis BP is not defined (2), but hypertension likely is associated with substantial morbidity in HD patients (2). Whereas it is widely believed that most patients who are on HD are being treated appropriately for hypertension, it also is possible that some chronic HD patients, such as those with nondialysis chronic kidney disease, have misdiagnosed hypertension that results in misdirected treatment for hypertension (3). In controlled trials of withdrawal of antihypertensive therapy, 15% of the patients with essential hypertension remain normotensive at 18 mo (4). In cohort studies of spontaneous discontinuation of antihypertensive agents in patients with treated essential hypertension, 23% are reported to be normotensive (5). The proportion of HD patients who remain normotensive on discontinuation of antihypertensive therapy is unknown.

To ascertain the appropriateness of antihypertensive therapy in HD patients, we conducted a prospective study in which we asked the following questions: What proportion of chronic HD patients remain normotensive when antihypertensive medications are withdrawn? Are there certain clinical characteristics that distinguish normotensive from hypertensive patients on drug withdrawal? Can home BP monitoring assist in the detection of normotensive patients? Is echocardiographic left ventricular hypertrophy (LVH) less common in treated normotensive patients compared with treated hypertensive patients? Is volume overload more common in treated hypertensive patients compared with normotensive patients?

Materials and Methods

Participants

Between January 2005 and October 2005, we screened men and women (age >18 yr) who had ESRD, were treated with chronic HD for at least 3 mo, and were treated for hypertension. Patients were excluded when they had atrial fibrillation, body mass index of ≥40 kg/m^2, history of missing one or more HD treatments in the previous month, known drug abuse, severe chronic obstructive airway disease, and stroke or myocardial infarction within the previous 6 mo. The institutional review board approved the protocol for the study. Every participant gave written informed consent.

Procedures

Patients were asked to monitor their home BP after a midweek dialysis for 4 d. Three consecutive BP were obtained on waking up and

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before going to bed using an oscillometric home BP monitor (HEM 705 CP; Omron Healthcare, Vernon Hills, IL). Antihypertensive medications were tapered, and home BP was obtained every week for 4 d as stated above. The washout period lasted a maximum of 5 wk. A placebo was dispensed to be taken three times a week after dialysis during this time. Interdialytic ambulatory BP monitoring (ABPM) was performed in all patients at the end of antihypertensive drug withdrawal. However, when home BP increased to 150/90 mmHg or more during washout, 44-h interdialytic ABPM was performed earlier. When found to be hypertensive by ABPM, patients were treated with antihypertensive medications.

Echocardiograms

Two-dimensional guided M-mode echocardiograms were performed with a digital cardiac ultrasound machine (Cypress Acuson, Siemens Medical, Malvern, PA) by one technician immediately after an HD session at the end of antihypertensive drug withdrawal. The postdialysis period was selected for echocardiography as it allows control over volume state of the patient because it is associated with the least intravascular volume. The protocol specified recording of at least 12 cycles of two-dimensional parasternal long- and short-axis LV views with optimal orientation of the cursor beam used to derive additional M-mode recordings. Each patient underwent six M-mode measurements of interventricular septal thickness (IVSTd), LV internal diameter (LVIDd), and LV posterior wall thickness (LVPWd) all in diastole using standards of the American Society of Echocardiography (6). LV mass was calculated with a previously validated formula (7): LV mass (g) = $0.832 \times [(\text{IVSTd} + \text{LVIDd} + \text{LVPWd})^3 - (\text{LVIDd})^3] + 0.60$. LV mass ≥ 104 g/m^2 in women and ≥ 116 g/m^2 in men was taken as evidence of LVH.

Inferior vena cava (IVC) diameter was measured at the end of dialysis at the time of echocardiography at the level just below the diaphragm in the hepatic segment by two-dimensional guided, M-mode echocardiography. IVC diameter was measured just before the P wave of the electrocardiogram during end expiration and end inspiration, while avoiding Valsalva-like maneuvers. Collapsibility index was defined as (maximal diameter on expiration − minimal diameter on deep inspiration)/maximal diameter on expiration × 100. Cheriex *et al.* (8) reported an IVC diameter of >11.5 mm/m^2 body surface area as a state of volume overload and <8 mm/m^2 as a state of volume depletion. These thresholds were used for the present analysis. All measurements were made over six cardiac cycles by a highly skilled echocardiographer and confirmed by an experienced cardiologist.

Interdialytic ABPM

ABPM was performed after the midweek HD session for 44 h at the end of antihypertensive drug withdrawal. ABP were recorded every 20 min during the day (6 a.m. to 10 p.m.) and every 30 min during the night (10 p.m. to 6 a.m.) using a Spacelab 90207 ABP monitor (SpaceLabs Medical Inc., Redmond, WA) in the nonaccess arm, as done previously (9). Recordings began immediately after HD and terminated immediately before the subsequent dialysis. Accuracy of ABP recordings was confirmed against auscultated BP at baseline. Data were analyzed using ABP Report Management System software, version 1.03.05 (SpaceLabs Medical Inc.). ABP and heart rates were averaged over the entire course of recording. We defined hypertension as interdialytic 44-h ABP as ≥135/85 mmHg.

Outcome

The primary outcome was to determine the proportion of patients who remained normotensive, defined by interdialytic 44-h ABPM, and to compare the distinguishing characteristics of normotensive patients.

Statistical Analyses

To contrast the characteristics of normotensive with hypertensive patients, we used a χ^2 test or Fisher exact test for comparing the proportions and an unpaired t test to compare means. When the variances were unequal, we used a t test without assuming equal variances and confirmed the results with the Mann-Whitney U test. To examine the time course of change in home BP after discontinuation of the drugs, we examined the weekly averages of home BP, with a repeated measures ANOVA model. All analyses were performed with the SPSS software (version 13.0, SPSS, Inc., Chicago, IL).

Results

Forty-seven chronic HD patients who were taking one or more antihypertensive drugs consented to participate. Six patients withdrew consent before home or ABPM could be performed. Thirty-nine of the 41 patients had complete removal of all antihypertensive medications. In the remaining two, only partial antihypertensive drug withdrawal was performed because their ABP were in the hypertensive range. Therefore, 41 (87%) of 47 patients were available for evaluation. The baseline characteristics of these 41 patients are shown in Table 1.

Table 1. Clinical characteristics of the study population ($n = 41$)[a]

Clinical Characteristic	Values
Age (yr; mean ± SD)	56.2 ± 14.1
Men (*n* [%])	19 (46)
Black race (*n* [%])	41 (100)
≤12 yr of education (*n* [%])	27 (66)
Income < $25,000/yr (*n* [%])	31 (76)
Predialysis weight (kg; mean ± SD)	79.1 ± 17.7
Postdialysis weight (kg; mean ± SD)	76.3 ± 16.5
BMI (kg/m^2; mean ± SD)	26.6 ± 5.2
Years of ESRD (mean ± SD)	5.3 ± 4.7
Current alcohol use (*n* [%])	11 (27)
Smoking (*n* [%])	
current	18 (44)
former	9 (22)
never	14 (34)
Diabetes (*n* [%])	22 (54)
Cardiovascular comorbidity (*n* [%])	11 (27)
Myocardial infarction (*n* [%])	4 (10)
Strokes (*n* [%])	6 (15)
Peripheral vascular disease (*n* [%])	3 (7)
Cause of ESRD (*n* [%])	
diabetes	18 (44)
hypertension	17 (42)
other	6 (14)
Kt/V (mean ± SD)	1.8 ± 0.35
Albumin (g/dl; mean ± SD)	3.6 ± 0.5
Hemoglobin (g/dl; mean ± SD)	12.0 ± 1.1
LVMI (g/m^2; mean ± SD)	139.4 ± 32.5
Prevalence of LVH (*n* [%])	34 (83)

[a]BMI, body mass index; LVH, left ventricular hypertrophy; LVMI, left ventricular mass index.

Table 2. Antihypertensive drug use and BP measurements[a]

No. of antihypertensives (mean ± SD)	2.3 ± 1.15
Nature of antihypertensive agent (*n* [%])	
dihydropyridine calcium channel blockers	14 (34)
nondihydropyridine calcium-channel blockers	1 (2.4)
β blockers	32 (78)
α blockers	3 (7)
centrally acting agents	8 (20)
vasodilators	7 (17)
ACE inhibitors	21 (51)
angiotensin receptor blockers	7 (17)
Home BP (mmHg; mean ± SD)	145.1 ± 14.9/ 83.6 ± 10.0
Home pulse (bpm; mean ± SD)	79 ± 10

[a]ACE, angiotensin-converting enzyme.

The average number of antihypertensive medication and the nature of antihypertensive drugs are shown in Table 2. β Blockers were the most commonly used medication class. Home BP averaged 146/84 mmHg in the week before withdrawal of the medications.

On withdrawal of antihypertensive drugs, 10 (24%) of the patients had normal systolic ABP and 13 (32%) had normal diastolic ABP. Eight (20%) patients had normal systolic and diastolic ABP (Table 3).

The unique characteristics that distinguished patients with normotension from those with hypertension are shown in Table 4. Patients who remained normotensive had more diabetes, were more obese, but smoked less often. In the eight patients who did not become hypertensive, the mean LV mas index (LVMI) was 115.1 ± 19.8 compared with 145.3 ± 32.4 g/m^2 in those who remained hypertensive ($P = 0.004$). In the eight normotensive patients, 50% had no LVH, compared with the presence of LVH in 91% of those with hypertension ($P = 0.018$).

Figure 1A shows the time course of the weekly home systolic BP (SBP) changes in the normotensive and hypertensive groups. Patients who remained normotensive had baseline home SBP of 135 ± 18.4 compared with 147 ± 13.1 mmHg in those who became hypertensive ($P = 0.032$). There was a significant increase in SBP over time ($P = 0.020$) and a more rapid rise in SBP in hypertensive patients (time × group interaction, $P = 0.009$). Figure 1B shows the changes in home diastolic BP (DBP). Patients who remained normotensive had baseline home DBP of 76 ± 11.2 compared with 85 ± 8.8 mmHg in those who became hypertensive ($P = 0.012$). There was a significant increase in DBP over time ($P = 0.009$) and a more rapid rise in DBP in hypertensive patients (time × group interaction $P = 0.032$).

Table 3. Interdialytic ambulatory BP and LVH after washout

Clinical Characteristic	Values
44-h ambulatory BP (mmHg; mean ± SD)	147.3 ± 18.1/86.4 ± 13.9
Awake ambulatory BP (mmHg; mean ± SD)	147.5 ± 18.2/87.4 ± 14.4
Asleep ambulatory BP (mmHg; mean ± SD)	147.3 ± 20.1/84.3 ± 14.3
44-h ambulatory pulse rate (bpm; mean ± SD)	86 ± 10
Awake ambulatory pulse rate (bpm; mean ± SD)	88 ± 11
Asleep ambulatory pulse rate (bpm; mean ± SD)	82 ± 9
Normotensives (*n* [%])	8 (20)
Isolated systolic hypertension (*n* [%])	5 (12)
Isolated diastolic hypertension (*n* [%])	2 (5)
Systolic diastolic hypertension (*n* [%])	26 (63)
LVMI (g/m^2; mean ± SD)	139.4 ± 32.5
Prevalence of LVH	34 (83)

The median IVC diameter in expiration in the normotensive and hypertensive groups was 7.17 and 7.59 mm/m^2, respectively. The median IVC diameter in inspiration in the normotensive and hypertensive groups was 3.63 and 4.01 mm/m^2, respectively. The median collapse index in the normotensive patients was 35.9% and in the hypertensive patients was 38%. Among the normotensive group, no patient was volume overloaded and seven (88%) of eight were volume depleted. In the hypertensive group, four (12%) of 33 were volume overloaded and 19 (58%) of 33 were volume depleted. No statistical significance was seen between the two groups for any of the IVC medians or proportions.

Discussion

Although studies on discontinuation of antihypertensive drugs in patients with chronic kidney disease or those who are on HD are not available, the first double-blind, placebo-controlled trial in 86 male veterans who had essential hypertension and were treated for 2 yr showed 68% incidence of recurrence of hypertension at 23 wk and 85% recurrence at 18 mo (4). At baseline, these patients had well-established hypertension with DBP between 90 and 129 mmHg. In the Framingham Heart Study, 337 of 1138 patients who reported the use of antihypertensive medications at two consecutive examinations spontaneously discontinued the use at a subsequent examination (5). A total of 95 (28%) of 337 patients remained normotensive, but only 12% remained normotensive over the next 4 yr. The major finding of our prospective study is that 80% of the patients who were on antihypertensive therapy were noted to be hypertensive on withdrawal of their medications. However, one in every five patients who were on HD and thought to be hypertensive failed to become hypertensive over the short term (3 to 5 wk). These data suggest that the prevalence of recurrence of hypertension on discontinuation of antihypertensive drugs in HD patients is at least as high as that seen in patients with essential hypertension.

Several explanations can be offered for lack of increase in BP in some HD patients. First, this may be because the clinical decisions regarding management of hypertension in HD patients are based largely on BP recordings that are made in the dialysis unit. The inaccuracies of these recordings are widely recognized, and treatment that is guided by these recordings may lead to inappropriate therapy in these patients (2). Second, patients who initially were recognized to be hypertensive and treated with drugs may have subsequently become normotensive. For example, Stamler *et al.* (10) randomly assigned 189 treated hypertensive patients to treatment withdrawal only; treatment withdrawal with nutritional recommendations such as weight loss, dietary sodium restriction, and limitation of

Table 4. Clinical characteristics that differed between hypertensive and normotensive patients[a]

Clinical Characteristic	Normotension	Hypertension	*P*
n	8	33	
Age (yr; mean ± SD)	54.8 ± 12.5	56.5 ± 14.6	NS
Men	3	16	NS
Predialysis weight (kg; mean ± SD)	88.4 ± 18.8	77.5 ± 17.3	NS
Postdialysis weight (kg; mean ± SD)	85.6 ± 18.3	74.6 ± 15.8	NS
BMI (kg/m^2; mean ± SD)	31 ± 2.8	25.7 ± 5.2	0.022
Years of ESRD (mean ± SD)	5 ± 2.6	5.4 ± 5.1	NS
Current alcohol use	2	9	NS
Smoking			0.024
current	1	17	
former	1	8	
never	6	8	
Diabetes	7	15	0.05
Cause of ESRD			NS
diabetes	6	12	
hypertension	2	15	
others	0	6	
Kt/V (mean ± SD)	1.8 ± 0.2	1.8 ± 0.4	NS
Albumin (g/dl; mean ± SD)	3.4 ± 0.5	3.7 ± 0.4	NS
Hemoglobin (g/dl; mean ± SD)	11.6 ± 1.5	12.1 ± 0.9	NS
No. of BP medications (mean ± SD)	2.4 ± 1.2	2.3 ± 1.1	NS
44-h ambulatory BP (mmHg; mean ± SD)	122.1 ± 10.7/68.0 ± 5.3	153.4 ± 13.7/90.8 ± 11.4	<0.0001
44-h ambulatory pulse rate (bpm; mean ± SD)	88 ± 7	85 ± 10	NS
Home systolic BP (mmHg; mean ± SD)	135 ± 18.4	147 ± 13.1	0.032
Home diastolic BP (mmHg; mean ± SD)	76 ± 11.2	85 ± 8.8	0.012
LVMI (g/m^2; mean ± SD)	115.1 ± 19.8	145.3 ± 32.4	0.004
Prevalence of LVH	4	30	0.018
IVC diameter in expiration (mm/m^2; mean ± SD)	6.9 ± 1.4	8.0 ± 2.8	NS
IVC diameter in inspiration (mm/m^2; mean ± SD)	4.3 ± 1.6	5.1 ± 2.6	NS
Collapse index (%; mean ± SD)	37.9 ± 16.6	36.0 ± 20.3	NS
Volume depleted	7	19	NS
Volume overloaded	0	4	NS

[a]IVC, inferior vena cava.

alcohol intake; and continuation of antihypertensive drugs. After 4 yr, 39% of the patients in the nutritional recommendation group remained normotensive, compared with 5% in the treatment withdrawal group alone. Although measurements of IVC diameter did not show statistical significance, this likely is due to the small sample size. It is notable that 12% of the hypertensive patients but none of the normotensive patients were volume overloaded. Taken together, these data are consistent with the hypothesis that at least some normotensive patients achieved remission of hypertension as a result of better volume control over time.

The prevalence of normotension is unlikely to be due to random error or inadequate follow-up for two reasons. First, there was little change in BP at home in normotensive patients despite removal of an identical number of antihypertensive agents. Second and perhaps most convincing, normotensive patients had a lower LVMI and a much lower prevalence of LVH compared with hypertensive patients. Therefore, lower prevalence of cardiovascular damage combined with lack of increase in BP on discontinuation of antihypertensive drugs suggests that the prevalence of normotension in treated patients is not due simply to statistical error.

Our study had several limitations. This study was limited to black patients. Whether the same prevalence of appropriate treatment for hypertension holds true for other ethnicities is not known. The sample size of our study was limited. A larger study may yield more precise estimates of the prevalence of misdirected treatment of hypertension in HD patients. The prognosis of lack of treatment in those without hypertension diagnosed by ABPM is unknown in HD patients. Therefore, firm recommendations on the treatment of such patients cannot be made.

Conclusion

This is the first study in HD patients to demonstrate that among treated patients with hypertension, 80% remain hyper-

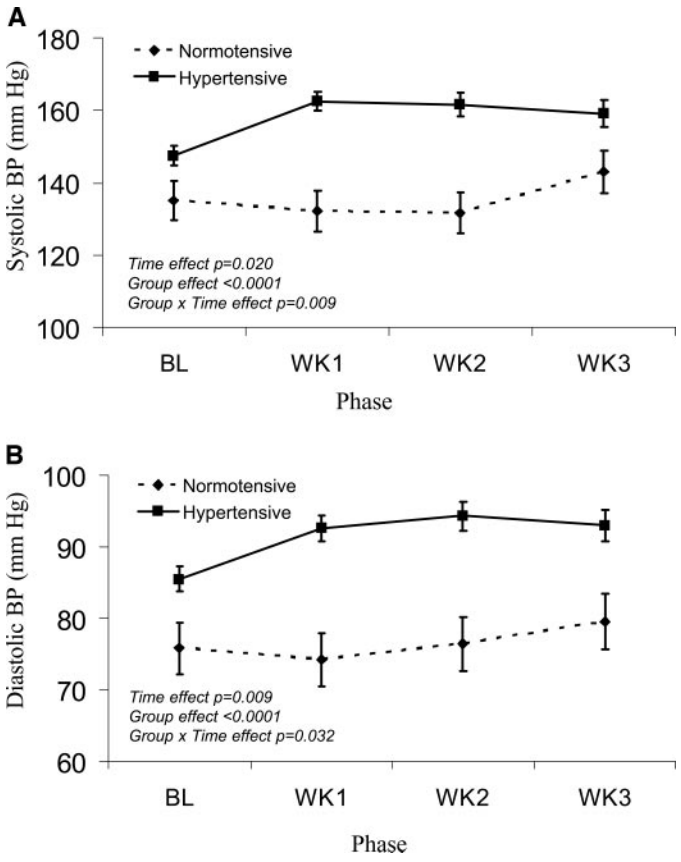

Figure 1. Time course of the weekly home systolic BP (A) and the time course of weekly diastolic home BP (B) changes in the normotensive and hypertensive groups. Error bars are SE. Patients who were hypertensive had a higher baseline BP and a steeper increase in BP over time.

tensive upon withdrawal of antihypertensive medications. In the remaining 20% who remain normotensive despite withdrawal of the medications, half have presence of LVH, a strong indicator for cardiovascular morbidity and mortality in HD patients. Patients who remain normotensive have 12/9 mmHg lower home BP compared with hypertensive patients. Therefore, only treated hypertensive HD patients who have well-controlled home BP are likely to remain normotensive on withdrawal of their antihypertensive drugs. The simple tools of home BP monitoring and echocardiograms may assist in the detection of true normotensive patients among those who are treated for hypertension. Therefore, patients who have well-controlled home BP and also have a normal LV mass may have a cautious withdrawal of their antihypertensive drugs.

In a population of dialysis patients, many of whom have diabetes and coronary artery disease, an argument can be made that even a "normal" BP should be lowered further to reduce the risk for future cardiovascular events. Whether this paradigm holds in the HD population has not been established. First, we lack randomized, controlled trials in this population to support the benefits of lowering of BP on cardiovascular morbidity or mortality. Second, it is uncertain whether treating "normotensive" HD patients with antihypertensive drugs makes the dialysis procedure unpleasant because of hypotension-related symptoms. Third, evidence is emerging wherein BP lowering, rather than BP-independent effect of antihypertensive drugs, may mediate the benefits of these drugs (11). If the latter hypothesis is correct, then lack of rise of BP on discontinuation of antihypertensive drugs may be taken as evidence of lack of protection.

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