

Weekly Averaged Blood Pressure Is More Important than a Single-Point Blood Pressure Measurement in the Risk Stratification of Dialysis Patients

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Background and objectives: With regard to monitoring blood pressure in hemodialysis patients, it is important to define clearly the time point at which the blood pressure is measured, because the blood pressure of hemodialysis patients varies with each hemodialysis session as a result of loss of excess fluid.

Design, setting, participants, & measurements: Using weekly averaged blood pressure, 96 hemodialysis patients were studied prospectively for 35 mo. All patients were followed up for cardiovascular events or death from all causes.

Results: Pulse weekly averaged blood pressure and age at enrollment were significantly higher and parathyroid hormone level was significantly lower in patients with cardiovascular events compared with those without cardiovascular events; however, none of the components of pre- or postdialysis blood pressure was significantly different between patients with and without cardiovascular events. Pulse weekly averaged blood pressure, prepulse pressure, age, and human atrial natriuretic peptide were significantly higher in patients who died than in survivors. Kaplan-Meier method with a log-rank test demonstrated that survival free rate from cardiovascular events and that of all-cause mortality in patients with pulse weekly averaged blood pressure ≥ 70 mmHg were significantly lower than those in the remaining patients.

Conclusions: One-point measurement of blood pressure is insufficient to evaluate hypertension and prognosis of hemodialysis patients, and weekly averaged blood pressure is a useful marker because of averaging fluctuations of blood pressure during 1 wk. Among components of weekly averaged blood pressure, pulse weekly averaged blood pressure could be a good prognostic marker of the incidence of both cardiovascular events and all-cause mortality in hemodialysis patients.

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Hypertension plays an important role in the development of cardiovascular disorders in hemodialysis (HD) patients as well as patients with essential hypertensive (1,2). A number of observational cohort studies have reported U-shaped or reverse-J relationships between conventional BP measures (systolic [SBP], diastolic [DBP], and mean arterial) and mortality in patients who undergo HD (3–6); however, it has also been reported that no significant difference has been found between the survival rates of 168 normotensive and 202 hypertensive HD patients (7).

The difference of results among reports of the effect of hypertension in HD patients may be partly due to the timing and method of measuring BP and the component of BP. With respect to monitoring BP, it is important to define clearly the time point at which the BP is measured. Moreover, because the BP of HD patients varies with each HD session as a result of loss of

excess fluid, BP fluctuation should also be considered. Recently, we reported that weekly averaged BP (WAB) is a useful marker that reflects BP variability during 1 wk and correlates with target organ damage such as left ventricular mass index (LVMI) and brachial-ankle pulse wave velocity (PWV) (8). Furthermore, of importance to note is that the systolic and diastolic WAB are almost completely consistent with the wake-up BP on the next day after the middle dialysis session ($R^2 = 0.709$, $P < 0.0001$; $R^2 = 0.775$, $P < 0.0001$, respectively). In other words, we may be able to use this measurement instead of using the WAB. Agarwal *et al.* (9) reported the significance of self-recorded home BP three times a day during 1 wk in HD patients and showed that home BP correspond to ambulatory BP and left ventricular hypertrophy in HD patients (10,11). Thus, BP should not be evaluated by one-point measurement before or after dialysis or after waking up but should be evaluated by the average of sequential monitoring during 1 wk.

With respect to components of BP, London *et al.* (12) described the importance of pulse pressure in considering BP control in end-stage renal failure. Indeed, several studies have reported the relationship between pulse pressure and mortality or cardiovascular events in HD patients (13–17). In this study, we studied in a prospective cohort whether WAB was a more useful prognostic marker in HD patients than one-point BP

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measurement and investigated which components of WAB were the most potent marker in evaluating the effect of hypertension on cardiovascular events (CVE) or all-cause mortality in HD patients.

Concise Methods

Patients

We included 125 patients in the prospective study from our HD center on February 2003. Patients were eligible for inclusion when (1) they had no clinical cardiovascular complication during a period of 6 mo before entry to the study, (2) they received HD for 3.5 to 4.0h during each HD session that occurred three times a week and for more than 6 mo at the time of enrollment in this study. Exclusion criteria were (1) congestive heart failure evidenced by symptoms and a chest x-ray, (2) uncontrolled dry weight, and (3) intradialytic hypotension. Congestive heart failure was diagnosed when a chest x-ray revealed infiltration in the lung with acute or chronic orthopnea. Hypotensive episode was defined as a fall in SBP below 100 mmHg or a reduction in SBP of ≥ 30 mmHg associated with hypotensive symptoms that required intervention, such as reducing the ultrafiltration rate, administering saline infusion, or ending the HD session early (when hypotension occurred near the end of the session). Chest x-rays were studied after dialysis of the first day of a week. Finally, we prospectively observed 96 eligible HD patients for 35 mo. Baseline data of laboratory and clinical variables were obtained before the first dialysis session in February 2003; only human atrial natriuretic peptide was measured after the HD session, and other laboratory data were measured before the first HD session in the week. All patients provided their informed consent, and the ethical committee of our institution approved this study.

Definition of CVE

CVE were defined as events including stroke, acute myocardial infarction, angina pectoris, and peripheral arterial disease evidenced by intermittent claudication and/or ulcer. All patients were followed up for 35 mo. Cause of death was determined by the criteria used in the study of Mailloux *et al.* (18).

BP Monitoring and Definition of WAB

Home BP of patients was monitored at their home twice a day for 1 wk. Recordings were carried out in a sitting position after taking at least a 5-min rest by using an automatic device that was based on the cuff-oscillometric method (19). The patients and their caregivers were taught by nurses how to measure the BP at home using this device. Validity of the device confirmed that the difference between the auscultatory method and the device should be within 5 mmHg in each individual (20). The two measurement time points were after waking up and before eating and taking medicines and before sleeping at night. During the same week, the BP was measured in the supine position before and after each dialysis session. The BP was measured with automated devices by the same method. The mean BP was calculated as follows: mean BP = DBP + [(SBP - DBP)/3]. The pulse pressure was calculated as follows: SBP - DBP.

We defined the WAB to be an average of 20 points of BP (data of BP recorded at home twice a day for 1 wk and that recorded in the hospital twice during each dialysis session that occurred three times a week). In patients using antihypertensive medications, the drugs were given as scheduled.

LVMI

Standard two-dimensional guided M-mode echocardiographies were performed on an inter-HD midweek day using a 3.75-MHz transducer

in a blinded manner by one operator. The LVMI was calculated according to the Penn convention (LVMI g/m²: LVMI = 1.04 × [(LVDD + IVStH + PWth)³ - (LVDD)³] - 13.6 g/m², where LVDD is the left ventricular end diastolic diameter, IVStH is the interventricular septal thickness, and PWth is the left ventricular posterior wall thickness) (21). The LVMI was also calculated by dividing the LVM by the body surface area.

Statistical Analyses

Values are expressed as means ± SD. The unpaired *t* test, the χ^2 test, and logistic regression analysis were used to compare values between patients with CVE and those without CVE and between patients who died and survived. Univariate analysis was used to reveal correlation between pulse WAB (pWAB) and several factors. We analyzed the data using multivariate logistic regression analysis when the presence of CVE was defined as one of the categorical variables. Survival curves were estimated with the Kaplan-Meier method, and a log-rank test was used to compare groups according to pWAB. StatView 5.0 (SAS Institute, Cary, NC) was used for data analysis. *P* < 0.05 was considered to be significant.

Results

Characteristics of the Patients

The clinical characteristics of the 96 eligible patients are presented in Table 1. The average age was 66.0 ± 11.2 yr, and duration of dialysis therapy was 71.4 ± 53.1 mo. Of the 96 patients, 63 patients were male, 63 patients had been treated with antihypertensive drugs, and 35 patients had diabetes.

Variability of BP and WAB

Figure 1 shows the average pattern of weekly variability of SBP and pulse pressure of the HD patients. SBP and pulse pressures upon waking were always higher than before HD. SBP before sleep was the lowest during a 24-h period. SBP upon waking on non-HD days was lower than that on HD days (Figure 1A). On the contrary, pulse pressure was the lowest after HD sessions

Table 1. Patient characteristics (*n* = 96)^a

| Characteristic | Value |
|-------------------------------|-------------|
| Age (yr; mean ± SD) | 66.0 ± 11.2 |
| Male (%) | 65.6 |
| HD duration (mo; mean ± SD) | 71.4 ± 53.1 |
| Kt/V urea | 1.28 ± 0.18 |
| Antihypertensive (%) | 65.6 |
| Diabetes (%) | 36.5 |
| Albumin (g/dl; mean ± SD) | 3.7 ± 0.3 |
| Hemoglobin (g/dl; mean ± SD) | 10.0 ± 1.0 |
| Hematocrit (%; mean ± SD) | 32.5 ± 3.4 |
| Calcium (mg/dl; mean ± SD) | 8.8 ± 1.0 |
| Phosphorus (mg/dl; mean ± SD) | 5.6 ± 1.3 |
| iPTH (pg/ml; mean ± SD) | 179 ± 128 |
| CTR (%; mean ± SD) | 48.8 ± 4.0 |
| hANP (pg/ml; mean ± SD) | 23.1 ± 19.3 |

^aHD, hemodialysis; iPTH, intact parathyroid hormone; CTR, cardio-thoracic ratio; hANP, human atrial natriuretic peptide.

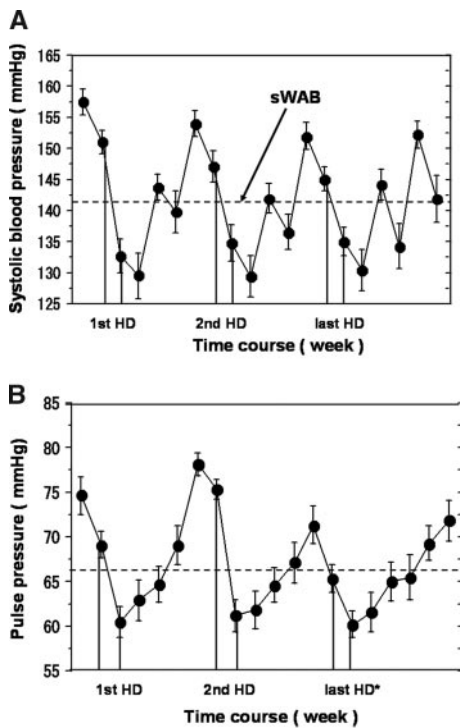


Figure 1. BP variability in hemodialysis (HD) patients during a period of 1 wk are shown. Average of systolic weekly averaged BP (WAB) in 96 patients was 141.6 ± 19.3 mmHg (A) and that of pulse WAB (pWAB) was 65.8 ± 14.9 mmHg. The highest systolic BP (SBP) was upon waking, and lowest SBP was before sleep (A). The highest pulse pressure was also upon waking, but the lowest pulse pressure was after HD (B).

during a 24-h period and then gradually increased before the next HD session (Figure 1B).

Average systolic WAB in 96 patients was 141.6 ± 19.3 mmHg and pWAB was 65.8 ± 14.9 mmHg. They approximately corresponded to BP at the next morning of the second HD session in a week, as has already been demonstrated by us (8).

Outcome during 35-Mo Follow-up Period

During a 35-mo follow-up period, 14 patients died (nine CVE, three malignancies, and two gastrointestinal bleedings) and 21 patients experienced CVE (four with acute myocardial infarction, four with coronary artery stenoses that needed angioplasty, seven with angina pectoris, and six with peripheral artery disease).

Factors Affecting Cardiovascular Events and All-Cause Mortality

As shown in Table 2, pWAB and age were significantly higher in patients with CVE than in patients without them and intact parathyroid hormone (iPTH) level was significantly lower in patients with them than in patients without them. Multivariate logistic regression analysis when significant variables by univariate regression analysis were entered demonstrated age (95% CI 0.984 to 0.999; $P < 0.01$) and iPTH (95% CI 1.017 to 1.154; $P < 0.01$) as independent variables. pWAB, however, did not reach statistical significance (95% CI 0.991 to 1.049; $P = 0.11$).

Before and after a dialysis session, SBP, DBP, mean BP, and pulse pressure did not show any difference (Table 2). As shown in Table 3, pWAB, prepulse pressure, age, and hANP were significantly higher in patients who died than in survivors.

Table 2. Comparison between patients with CVE and those without CVE^a

| Parameter | No CVE (n = 75) | CVE (n = 21) | P |
|------------------------------------|--------------------|------------------|--------|
| Systolic WAB (mmHg) | 140.2 ± 18.0 | 146.8 ± 23.6 | 0.1675 |
| Diastolic WAB (mmHg) | 79.5 ± 9.5 | 76.5 ± 9.6 | 0.2066 |
| Mean WAB (mmHg) | 100.0 ± 10.9 | 100.1 ± 11.7 | 0.9764 |
| pWAB (mmHg) | 63.9 ± 13.1 | 72.8 ± 18.6 | 0.0144 |
| Predialysis SBP (mmHg) | 154.9 ± 20.0 | 163.1 ± 24.5 | 0.1137 |
| Predialysis DBP (mmHg) | 82.8 ± 9.2 | 81.0 ± 8.9 | 0.2893 |
| Predialysis mean BP (mmHg) | 102.4 ± 11.3 | 102.0 ± 11.5 | 0.5396 |
| Predialysis pulse pressure (mmHg) | 66.2 ± 11.6 | 72.1 ± 14.5 | 0.0576 |
| Postdialysis SBP (mmHg) | 132.1 ± 26.4 | 134.9 ± 26.7 | 0.6618 |
| Postdialysis DBP (mmHg) | 77.7 ± 14.1 | 77.3 ± 12.0 | 0.9141 |
| Postdialysis mean BP (mmHg) | 94.3 ± 18.1 | 95.0 ± 14.4 | 0.8804 |
| Postdialysis pulse pressure (mmHg) | 59.7 ± 15.5 | 62.7 ± 20.3 | 0.4774 |
| Age (yr) | 64.2 ± 11.0 | 72.6 ± 9.7 | 0.0021 |
| LVMI (g/m^2) | 117.8 ± 40.9 | 120.1 ± 38.4 | 0.8227 |
| hANP (pg/ml) | 21.6 ± 17.8 | 28.2 ± 23.7 | 0.1693 |
| iPTH (pg/ml) | 194.1 ± 134.9 | 125.8 ± 77.4 | 0.0293 |
| Hematocrit (%) | 32.8 ± 3.3 | 31.5 ± 3.6 | 0.1278 |
| Albumin (g/dl) | 3.7 ± 0.4 | 3.6 ± 0.2 | 0.3492 |

^aData are means \pm SD. CVE, cardiovascular events; DBP, diastolic BP; LVMI, left ventricular mass index; SBP, systolic BP; pWAB, pulse weekly averaged BP; WAB, weekly averaged BP.

Table 3. Comparison between survivors and patients with all-cause mortality^a

| Parameter | Survivors (n = 82) | Fatalities (n = 14) | P |
|------------------------------------|-----------------------|------------------------|--------|
| Systolic WAB (mmHg) | 140.5 ± 18.4 | 148.1 ± 23.5 | 0.1702 |
| Diastolic WAB (mmHg) | 79.5 ± 9.6 | 75.4 ± 8.6 | 0.1355 |
| Mean WAB (mmHg) | 100.1 ± 11.0 | 99.9 ± 11.4 | 0.9643 |
| pWAB (mmHg) | 64.2 ± 13.5 | 75.1 ± 19.3 | 0.0110 |
| Predialysis SBP (mmHg) | 155.4 ± 19.8 | 164.1 ± 27.6 | 0.1577 |
| Predialysis DBP (mmHg) | 83.2 ± 10.8 | 81.0 ± 9.9 | 0.3412 |
| Predialysis mean BP (mmHg) | 102.5 ± 11.0 | 102.0 ± 10.8 | 0.6832 |
| Predialysis pulse pressure (mmHg) | 66.4 ± 12.1 | 73.7 ± 14.5 | 0.0462 |
| Postdialysis SBP (mmHg) | 131.1 ± 26.5 | 142.0 ± 24.6 | 0.1538 |
| Postdialysis DBP (mmHg) | 77.7 ± 13.5 | 77.4 ± 14.4 | 0.9386 |
| Postdialysis mean BP (mmHg) | 93.7 ± 17.7 | 98.3 ± 14.3 | 0.3645 |
| Postdialysis pulse pressure (mmHg) | 59.5 ± 15.8 | 65.6 ± 20.7 | 0.2177 |
| Age (yr) | 64.8 ± 11.2 | 73.2 ± 8.3 | 0.0088 |
| LVMI (g/m ²) | 115.4 ± 37.7 | 133.8 ± 50.1 | 0.1167 |
| hANP (pg/ml) | 20.9 ± 17.4 | 35.2 ± 25.3 | 0.0101 |
| iPTH (pg/ml) | 183.3 ± 132.4 | 154.9 ± 94.2 | 0.4430 |
| Hematocrit (%) | 32.6 ± 3.3 | 31.6 ± 3.9 | 0.2825 |
| Albumin (g/dl) | 3.7 ± 0.4 | 3.6 ± 0.4 | 0.5642 |

^aData are means ± SD.

Factors Affecting pWAB

Figure 2 shows the relationship among pWAB, age, and LVMI. pWAB was significantly correlated with age ($r = 0.310$, $P = 0.0020$; Figure 2A) and with LVMI ($r = 0.363$, $P = 0.0004$; Figure 2B). A stepwise forward regression analysis showed that age and LVMI were independent variables with respect to pWAB.

Prognosis and pWAB

Patients were divided into three groups depending on the pWAB value: First group pWAB <60.0 mmHg ($n = 35$), second group pWAB ≥60.0 and <70.0 mmHg ($n = 26$), and third group pWAB ≥70.0 mmHg ($n = 35$). The survival curves estimated with the Kaplan-Meier method and a log-rank test showed the patients in the third group were significantly lower than those in the other groups in both CVE and all-cause mortality ($P = 0.011$ and 0.002 , respectively; Figure 3); however, regarding the difference of outcome estimated with pulse pressure before dialysis, there was no statistically significant difference among these tertile groups (CVE $P = 0.142$, all-cause-mortality $P = 0.442$).

Discussion

We demonstrated the relationship between higher pWAB and CVE or all-cause mortality. The patients with pWAB >70 mmHg had a higher incidence of all-cause mortality and CVE. As a result of the comparison with various kinds of BP regarding at what point measurements were taken—predialysis, postdialysis, or WAB—and what kind of BP—SBP, DBP, mean, or pulse pressure—only pWAB was found to be an important pressure with respect to the incidence of CVE. Multivariate regression analysis, however, did not choose pWAB as an independent variable when age and iPTH were adjusted. It is

conceivable that pWAB might be correlated with age because it is known that aortic stiffness is associated with age. Indeed, in our study, age was correlated with pWAB. That there was no

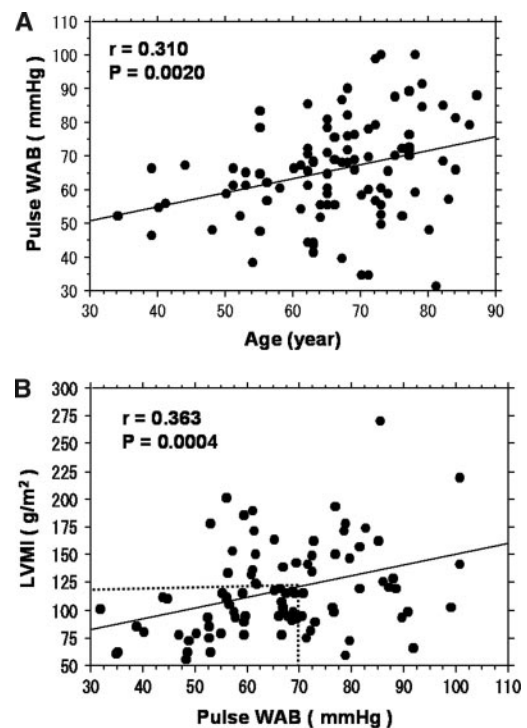


Figure 2. pWAB had a significant positive correlation with age ($r = 0.310$, $P = 0.0020$; A) and with left ventricular mass index (LVMI; $r = 0.363$, $P = 0.0004$; B). pWAB of 70 mmHg corresponded to LVMI of 122.1 g/m².

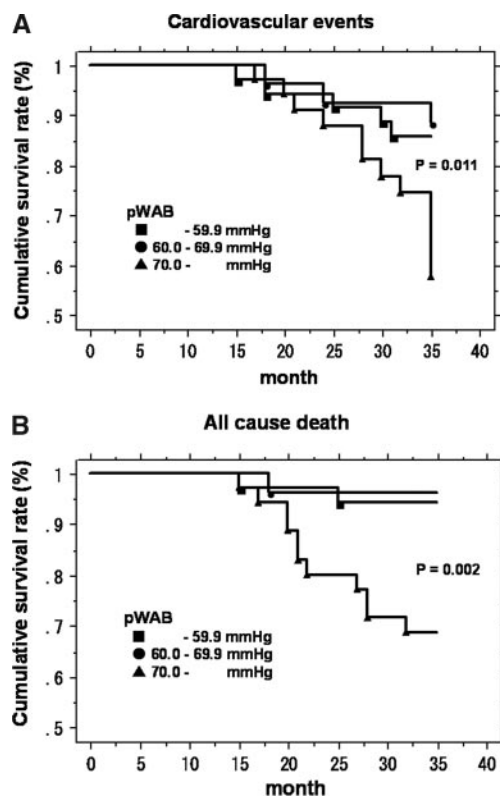


Figure 3. Cumulative survival curve in the three groups that were divided on the basis of the degree of pWAB. (A) Curve of cardiovascular events (CVE). (B) Curve of all-cause mortality. Both curves revealed that the group of pWAB >70 mmHg (\blacktriangle) showed significantly worse prognosis in comparison with other groups (pWAB <59.9 mmHg [\blacksquare]; pWAB 60.0 to 69.9 mmHg [\bullet]).

statistically significant difference with the Kaplan-Meier method regarding the difference of outcome estimated with pulse pressure before dialysis also demonstrates the importance of WAB.

Tomita *et al.* (2) revealed the prognostic role of SBP. Iseki *et al.* (22) and Blacher *et al.* (23) found that low DBP was associated with a higher death rate and cardiovascular mortality. Degoulet *et al.* (24) showed an association between both SBP and DBP and cardiovascular mortality in 1453 prospectively studied HD patients. Conversely, it was reported that no significant difference was found between the survival rates of 168 normotensive and 202 hypertensive patients (7).

With regard to monitoring BP, it is important to define clearly the time point at which the BP is measured. Moreover, because the BP of HD patients varies with each HD session as a result of loss of excess fluid, BP fluctuation should be considered. In this regard, we reported that WAB is a useful marker that reflects BP variability during 1 wk and correlates with target organ damage such as LVMI and brachial-ankle PWV (8); however, it has been unclear whether there is any causal relationship between higher WAB and these target organ damages.

It is important that BP not be evaluated by one point of measurement, such as before dialysis or after dialysis, but

should be done by the average of multiple measurements of BP. In this study, the average of each point of SBP and pulse pressures fluctuated from 130 to 160 mmHg and from 60 to 78 mmHg, respectively. The average SBP and pWAB of all 96 patients was 141.6 ± 19.3 and 65.8 ± 14.9 mmHg, respectively. These data showed that BP vary dynamically during 1 wk, and more measurements of BP should be required to evaluate precisely hypertension of HD patients. In view of this, WAB may be a good surrogate index of fluctuating BP during 1 wk. Indeed, none of the components of predialysis BP (SBP, DBP, mean, and pulse) was significantly different between patients with and without CVE; therefore, it should be emphasized that measurement of one-point BP, such as before dialysis, would be misleading in evaluating hypertension and prognosis of HD patients.

In our previous cross-sectional study, the most potent marker of target organ damage was not SBP, DBP, or mean WAB but pWAB (8). Tozawa *et al.* (14) pointed out that the power of pulse pressure to predict total mortality was more accurate than that of SBP or DBP alone. London *et al.* (12) described the importance of pulse pressure in considering BP control, and several studies reported that pulse pressure was an independent risk factor for CVE in the general population (25–29) and an independent predictor of risk for mortality or CVE in long-term HD patients (13–17).

Pulse pressure is made up of two major components: One that is caused by ventricular ejection's interacting with the viscoelastic properties of the large arteries (direct) and the other that is caused by wave reflection (indirect). Elevated pulse pressure may be linked to high SBP, which favors left ventricular hypertrophy and consequently increases myocardial oxygen demand, whereas the decrease in DBP reduces the pressure on which coronary flow depends and together predispose the heart to ischemia and infarction. Lakka *et al.* (30) showed that elevated pulse pressure accelerates the progression of preclinical atherosclerosis. It was reported that elevated pulse pressure is both a cause and a consequence of atherosclerosis (31); therefore, pulse pressure could be considered a good surrogate marker of arterial stiffness and a prognostic factor of cardiovascular disease. Klassen *et al.* (13) reported that an incremental increase of 10 mmHg in postdialysis pulse pressure was associated with a 12% increase in hazard ratio for mortality.

In this study, pWAB was significantly higher in patients with CVE than in those without CVE and also in patients who died rather than in survivors. Klassen *et al.* (13) and Tozawa *et al.* (17) also elucidated the significant interaction between pulse pressure and age. Suzuki *et al.* (32) also reported that arterial PWV was positively correlated with age, SBP, and pulse pressure and that serum PTH concentration was not correlated with arterial stiffness. In this study, PTH was significantly lower in patients with CVE; therefore, further investigation is needed to demonstrate the relationship between PTH and CVE.

Cumulative survival curves revealed that HD patients with pWAB >70 mmHg showed significantly worse prognosis with respect to CVE and all-cause mortality. This study showed that pWAB of 70 mmHg nearly corresponded to LVMI of 120 g/m^2 , above which would be considered to represent left ventricular

hypertrophy; however, it is unclear that antihypertensive therapy should be aimed to control pWAB <70 mmHg in HD patients. Intervention studies could elucidate that pWAB <70 mmHg is a target index; however, we emphasize that this study is not intended to focus on the prognostic value of pWAB but rather to point out how useless single-point BP measurements are in the risk stratification of dialysis patients.

This study has some limitations. Numbers of patients and events were too small to conclude prognosis of HD patients with large variety and complexity. Prospective intervention studies with large numbers of patients will be needed to clarify the cause-and-effect relationship between pWAB and event rate. WAB has some problems with respect to its convenience of calculation and reliability of home BP; however, we consider that the evaluation of WAB only once or twice a year is not troublesome and that average of fluctuations of BP is more reliable than one-point measurement of BP. Moreover, we have already shown that instead of using the WAB, the wake-up BP on the next day after the middle dialysis session can be used because both measurements are almost completely consistent with each other ($R^2 = 0.709$ in systolic and $R^2 = 0.775$ in diastolic) (8).

Conclusions

One-point measurement of BP is insufficient to evaluate hypertension and prognosis of HD patients, and WAB is a useful marker in evaluating the BP of HD patients because it represents weekly average of BP. Moreover, pWAB could be a target index for controlling BP and a useful prognostic marker of cardiovascular events or all-cause mortality of HD patients.

Disclosures

None.

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