Original Article

Influence of Different Measurement Time Points on Brachial-Ankle Pulse Wave Velocity and Ankle-Brachial Index in Hemodialysis Patients

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In order to ensure that they are reliable markers of atherosclerosis and suitable for repetitive follow-up of disease progression and management responses in hemodialysis (HD) patients, brachial-ankle pulse wave velocity (baPWV) and ankle-brachial index (ABI) should be tested to see whether they change with different measurement time points. The aim of this study was to assess whether baPWV and ABI vary according to whether they are measured before HD, after HD, or on the next dialysis-free day. Eighty-nine patients undergoing regular HD were enrolled. The baPWV and ABI were measured 10–30 min before and after HD, and if patients agreed, on the next dialysis-free day. The third measurement of baPWV and ABI, performed 22±2 h after HD, was taken in 72 patients (81%). The body weight reduction after HD was 2.5±0.9 kg ($p<0.001$). The brachial and ankle systolic and diastolic blood pressures before HD were significantly higher than those after HD and on the next dialysis-free day ($p\leq0.038$). Right and left baPWV increased significantly after HD ($p\leq0.006$), but returned to the pre-dialysis level on the next dialysis-free day. However, the right and left ABI remained constant before and after HD, or on the next dialysis-free day ($p\geq0.498$). In conclusion, despite the significant decrease in body weight and blood pressures, baPWV increased significantly after HD. In addition, baPWV, but not ABI, may vary at different measurement time points. Therefore, baPWV, but not ABI, should be assessed in a timely manner in HD patients. (*Hypertens Res* 2007; 30: 965–970)

***Key Words*: pulse wave velocity, ankle-brachial index, hemodialysis**

Introduction

Patients with end-stage renal disease (ESRD) undergoing hemodialysis (HD) therapy have increased morbidity and mortality as compared with the general population. Cardiovascular disease is the leading cause of death in this population, presumably because of advanced atherosclerosis (*1*, *2*). Identification of patients at high risk for cardiovascular disease and requiring aggressive preventive and interventional strategies is an initial and essential step in managing patients with ESRD. The ankle-brachial index (ABI) was initially developed to assist in the diagnosis of peripheral artery occlusive disease, and an ABI <0.9 has been used to identify this condition in clinical practice and epidemiologic studies (*3–6*). Pulse wave velocity (PWV) has been reported as another good marker for atherosclerosis or arterial stiffness (*7–9*). Both are important factors of vascular damage. A clinical device, ABI-form (VP1000, Colin, Komaki, Japan), has recently been developed to simultaneously measure the four

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Received March 20, 2007; Accepted in revised form June 7, 2007.

limb blood pressures (BPs) by an automated oscillometric method. Using this device, we can easily obtain the values of brachial-ankle PWV (baPWV) and ABI (*10*). Ono *et al*. (*11*) showed that ABI is a powerful and independent predictor of all-cause and cardiovascular mortality in HD patients, and Kitahara *et al*. (*12*) demonstrated that baPWV is useful to identify a high-risk population in HD patients with an ABI greater than 0.9. In HD patients, several parameters, such as BP, heart rate, and fluid status, may vary with time. BP is a major determinant of baPWV (*13–15*) and heart rate is reported to have a significant impact on baPWV and ABI (*16*, *17*). Before they can be considered reliable markers of atherosclerosis and suitable for repetitive follow up of disease progression and management responses in HD patients, baPWV and ABI should be tested to see whether they change with different measurement time points. The aim of this study was to assess the acute effect of HD on baPWV and ABI by testing for differences in these parameters among three time points: before HD, after HD, and on the next dialysis-free day.

Methods

Study Patients

One hundred patients undergoing regular HD were initially screened for this study. Exclusion criteria were the presence of atrial fibrillation, high-degree atrioventricular block, and waveform images inadequate for the calculation of baPWV and ABI. Eleven patients were excluded, 8 with inadequate waveform images and 3 with atrial fibrillation. The final study population consisted of 89 patients (53 women, 36 men) with a mean age of 56±13 years. The protocol was approved by our Institutional Review Board and all enrolled patients gave written, informed consent.

Hemodialysis

All patients underwent their routine HD 3 times a week using a Toray 321 machine (Toray Medical Company, Tokyo, Japan). Each HD session was performed for 3–4 h using a dialyzer with a blood flow rate of 250 to 300 mL/min and dialysate flow of 500 mL/min. The composition of dialysate was as follows (in mEq/L): Na^+ 140, K^+ 2.00, Ca^{2+} 3.0, and HCO_3^- 39.00. The aim of fluid removal was to achieve a clinically determined dry weight, which was considered optimal when patients remained without symptoms of dyspnea, orthopnea, or edema during the interdialytic period.

Measurement of Brachial-Ankle PWV and ABI

The values of baPWV and ABI were measured 10–30 min before and after HD, and if patients agreed, on the next dialysis-free day. The third measurement of baPWV and ABI, performed 22±2 h after HD, was taken in 72 patients (81%). The baPWV and ABI were measured by using an ABI-form device (VP1000, Colin), which automatically and simultaneously measures BPs in both arms and ankles and records pulse waves of the brachial and posterior tibial arteries using an oscillometric method, respectively (*10*, *18–20*). Occlusion and monitoring cuffs were placed tightly around the upper arm without blood access and both sides of the lower extremities in the supine position. ABI was calculated as the ratio of ankle systolic BP divided by arm systolic BP. For measuring baPWV, pulse waves obtained from the brachial and tibial arteries were recorded simultaneously, and the transmission time, which was defined as the time interval between the initial increase in brachial and tibial waveforms, was determined. The transmission distance from the arm to each ankle was calculated according to body height. The baPWV value was automatically computed as the transmission distance divided by the transmission time.

Table 1. Baseline Characteristics of Study Patients

Number of patients	89
Age (years)	56±13
Sex (male:female)	36:53
Hematocrit (%)	31.6±3.7
Creatinine (mg/dL)	10.5±2.1
Albumin (g/dL)	3.92±0.26
Fasting blood sugar (mg/dL)	126±64
Total cholesterol (mg/dL)	198±41
Triglyceride (mg/dL)	190±116
Uric acid (mg/dL)	8.1±1.7
Calcium (mg/dL)	9.7±1.1
Phosphorous (mg/dL)	5.0±1.2
Cause of renal failure (*n* (%))	
Chronic glomerulonephritis	31 (35)
Diabetes mellitus	35 (39)
Hypertension	16 (18)
Polycystic kidney disease	2 (2)
Systemic lupus erythematosus	5 (6)
Dialysis membrane (*n* (%))	
Polymethylmethacrylate membrane	53 (60)
Polyamide membrane	26 (29)
Polysulfone membrane	10 (11)
Time on dialysis (month)	50±46
Diabetes mellitus (*n* (%))	36 (40)
Hypertension (*n* (%))	57 (64)
Vasoactive medications (*n* (%))	
β-Blockers	17 (19)
Calcium channel blockers	27 (30)
Angiotension-converting enzyme inhibitors	3 (3)
Angiotension II receptor blockers	28 (32)

Statistical Analysis

All data were expressed as the mean (±standard deviation). The Statistical Package for the Social Sciences (SPSS) 11.0

Table 2. Comparison of Blood Pressures, Heart Rate, and Body Weight before and after Hemodialysis, and on the Next Dialysis-Free Day

Parameter	Before HD	After HD	Next dialysis-free day
Number of patients	89	89	72
Body weight (kg)	62±11	60±11*	—
Heart rate (bpm)	80±13	83±13*	81±12
Brachial SBP (mmHg)	145±27	133±27*	138±27*
Brachial DBP (mmHg)	81±16	75±17*	77±16*
Right ankle SBP (mmHg)	158±38	144±40*	149±39*
Right ankle DBP (mmHg)	78±17	72±22*	75±17*
Left ankle SBP (mmHg)	161±37	148±39*	154±39*
Left ankle DBP (mmHg)	77±17	73±20*	75±18†

bpm, beats per minute; DBP, diastolic blood pressure; HD, hemodialysis; SBP, systolic blood pressure. *$p<0.01$ *vs*. before HD; †$p<0.05$ *vs*. before HD.

for Windows (SPSS Inc., Chicago, USA) was used for statistical analysis. The baPWV, ABI, body weight, BPs, and heart rate before and after HD and on the next dialysis-free day were compared by means of paired *t*-test. Comparisons of continuous variables between groups were made with the independent-samples *t*-test. The relationship between two continuous variables was assessed by a bivariate correlation method (Pearson's correlation). All tests were 2-sided, and the level of significance was established as $p<0.05$.

Results

The baseline characteristics of study patients are shown in Table 1. Causes of renal failure were chronic glomerulonephritis in 31 patients, diabetes mellitus in 35 patients, hypertension in 16 patients, polycystic kidney disease in 2 patients, and lupus nephritis in 5 patients. Dialysis membranes, including polymethylmethacrylate membrane (B_1-2.1 H, B_1-1.6 H, or BG-1.8 U, Toray) in 53 patients, polyamide membrane (polyflux 17 L, 21 L, or 170 H, Gambro, Hechingen, Germany) in 26 patients, and polysulfone membrane (F8 HPS, Fresenius, Wendel, Germany; or APS-18 MD, Asahi, Tokyo, Japan) in 10 patients, were used as usual. There were 36 patients with diabetes mellitus and 57 patients with hypertension. Vasoactive medications, including β-blockers (17 patients), calcium channel blockers (27 patients), angiotensin-converting enzyme inhibitors (3 patients), and angiotensin II receptor blockers (28 patients), were continued without interruption. However, there was no drug intake during HD. The time on dialysis was 50±46 months.

The comparison of BPs, heart rate, and body weight before and after HD and on the next dialysis-free day is shown in Table 2. The mean body weight reduction after HD was 2.5±0.9 kg ($p<0.001$). The heart rate after HD was higher than that before HD ($p=0.002$). The brachial systolic (both $p<0.001$) and diastolic ($p<0.001$ and $p=0.001$, respectively) BPs, right ankle systolic ($p<0.001$ and $p=0.001$, respectively) and diastolic ($p<0.001$ and $p=0.002$, respectively) BPs, and left ankle systolic ($p<0.001$ and $p=0.002$, respectively) and diastolic ($p<0.001$ and $p=0.038$, respectively) BPs before HD were significantly higher than those after HD and on the next dialysis-free day.

The comparison of baPWV and ABI before and after HD and on the next dialysis-free day is shown in Table 3. The right baPWV after HD was significantly higher than that before HD ($p<0.001$) and on the next dialysis-free day ($p<0.001$). However, the right baPWV before HD did not differ from that on the next dialysis-free day ($p=0.075$). Similarly, the left baPWV after HD was significantly higher than those before HD ($p=0.006$) and on the next dialysis-free day ($p=0.015$). However, the left baPWV before HD did not differ from that on the next dialysis-free day ($p=0.826$). In contrast with the significant changes in baPWV, the right ABI remained constant between before and after HD ($p=0.734$), before HD and on the next dialysis-free day ($p=0.888$), and after HD and on the next dialysis-free day ($p=0.498$). Likewise, the left ABI remained constant between before and after HD ($p=0.679$), before HD and on the next dialysis-free day ($p=0.557$), and after HD and on the next dialysis-free day ($p=0.766$).

Diabetes mellitus and hypertension are traditional atherosclerotic risk factors. We further divided our study subjects into high and low atherosclerotic groups. The high atherosclerotic group included 68 patients with diabetes mellitus or hypertension and the low atherosclerotic group included the other 21 patients without diabetes mellitus or hypertension. All the values of right and left baPWV before and after HD or on the next dialysis-free day were higher in the high than in the low atherosclerotic group (all $p\leq0.005$). The right and left baPWV increased significantly after HD (all $p\leq0.040$), but returned to the pre-dialysis level on the next dialysis-free day, and the right and left ABI remained constant over the three time points both in the high and the low atherosclerotic group.

In addition, after HD, decrease in brachial systolic BP was negatively correlated with increases in right and left baPWV ($r=-0.307$, $p=0.006$ and $r=-0.358$, $p=0.001$, respectively).

Table 3. Comparison of Brachial-Ankle Pulse Wave Velocity and Ankle-Brachial Index before and after Hemodialysis, and on the Next Dialysis-Free Day

Parameter	Before HD	After HD	Next dialysis-free day
Number of patients	89	89	72
Right baPWV (cm/s)	1,801±456*	1,946±588	1,760±491*
Left baPWV (cm/s)	1,814±446*	1,923±554	1,794±573†
Right ABI	1.09±0.16	1.08±0.17	1.08±0.18
Left ABI	1.11±0.15	1.11±0.16	1.12±0.18

ABI, ankle-brachial index; baPWV, brachial-ankle pulse wave velocity; HD, hemodialysis. *$p<0.01$ *vs*. after HD; †$p<0.05$ *vs*. after HD.

However, the body weight reduction after HD had no correlation with increase in right or left baPWV ($r=-0.043$, $p=0.688$ and $r=-0.062$, $p=0.566$, respectively).

Discussion

The present study included clinically stable HD patients of a wide age range. Medications such as antihypertensive agents were not stopped and dialysis membranes were used as usual, not just for ethical reasons, but because the effects of dialysis should be evaluated in the routine clinical environment. Our results showed that HD resulted in a significant increase in baPWV, which disappeared on the next dialysis-free day. Therefore, when evaluating arterial stiffness in HD patients, the measurement time relative to HD is essential and should be mentioned. In contrast, ABI remained constant over the three measurement time points. Hence, when using ABI to survey peripheral artery occlusive disease in HD patients, it is not necessary to consider the measurement time relative to HD.

In this study, HD resulted in a significant decrease in body weight and BPs and a significant increase in heart rate. It has previously been reported that the decrease in body weight and BPs after HD may reduce baPWV (*13–15*). In the present study, however, both the right and left baPWV increased significantly after HD. Previous studies (*16*, *17*) have shown that baPWV can increase as heart rate increases. Hence, in our study, a compensatory increase in heart rate due to the acute volume reduction after HD may have played a role in the increase in baPWV. Nakao *et al*. (*21*) found that baPWV was closely associated with sympathetic nervous activity. In our study, heart rate increased significantly after HD, which implied that the sympathetic nervous activity of patients might be augmented after HD. This increased sympathetic tone after HD may have an effect on the increase in baPWV. In addition, HD may cause numerous changes, including abnormal complement activation with disordered leukocyte-endothelial interactions, and the release of plasma factors such as tumor necrosis factor-α and reactive oxygen species (*22*). Oxidative stress commonly contributes to the recurrent activation of polymorphonuclear neutrophils and monocytes during blood passage through dialysis circuits (*23*). HD can also result in an alteration in vascular tone *via* endothelial release of endothelin-1. These acute changes during HD may alter arterial stiffness and partially explain the increase in baPWV after HD. Furthermore, such acute effects by HD may be only temporary, which could have caused the baPWV to decrease significantly on the next dialysis-free day when compared with that after HD.

In the study by Kosch *et al*. (*24*), aortic PWV was measured before and after HD or on the next dialysis-free day in 25 HD patients. They found that aortic PWV remained constant over the three measurement time points. In their study, systolic and diastolic BPs and heart rate also remained constant during the study period. In contrast, in our study involving a relatively large number of patients ($n=89$), BPs and heart rate did not remain constant over the three time points. Therefore, the afterload and sympathetic tone of patients may have been constant in their study and variable in our study, which could explain the inconsistent results between the two reports. In a study by Mourad *et al*. involving 24 HD patients (*25*), HD with polysulfone but not polyamide membranes acutely increased arterial stiffness during HD, but this acute change disappeared 15 min after HD. This result was also inconsistent with ours. In their study, body weight and mean BP decreased, but heart rate remained constant 15 min after HD. Consequently, the sympathetic tone of patients may not have changed after HD in their study, which would explain why the PWV returned to the pre-dialysis level 15 min after HD in their patients.

In the subgroup analysis, the baPWV was higher in the high than in the low atherosclerotic group. Hence, the arterial stiffness was more severe in the high atherosclerotic group. In addition, the changes of baPWV and ABI at different measurement time points either in the high or low atherosclerotic group were similar with those in the entire group. Consequently, the results noted in the entire group can be extended to the subgroups of patients with high or low risk of atherosclerosis.

Many studies have demonstrated that systolic BP has a strong positive correlation with baPWV (*14–16*). Our study showed that the extent of brachial systolic BP decrease after HD had a negative correlation with the extent of right and left baPWV increase after HD ($r=-0.307$, $p=0.006$ and $r=-0.358$, $p=0.001$, respectively). This result suggests that the degree of baPWV increase after HD may be counteracted

by the extent of systolic BP decrease after HD.

Although subject body weight was not recorded on the next dialysis-free day, it is reasonable to suppose that body weight and thus fluid status were lower on the next dialysis-free day, as compared with those before HD. In addition, our results showed that brachial and ankle systolic and diastolic BPs were lower on the next dialysis-free day, when compared with those before HD. However, in spite of the lower levels of BPs and fluid status, the baPWV remained unchanged on the next dialysis-free day in comparison with that before HD. This finding may imply that the baPWV can remain constant during certain physiological alterations.

Our study showed that right and left ABI were not significantly different among the three measurement time points. This suggests that alterations of afterload and preload with time occurred frequently in HD patients and the abundant changes caused by HD may have a similar influence on the brachial and ankle systolic BPs. Thus, the derived ABI remained constant over the different measurement time points.

This study has several limitations. The changes of preload and afterload were determined indirectly by the changes in body weight and systolic BP, not by the changes in invasive data. However, it was not possible to perform invasive measurements in such study subjects. In addition, we did not check the values of atherosclerotic markers, so it is unknown which markers are responsible for the increase in baPWV after HD. Finally, an analysis of reproducibility was not performed in this study; however, the reproducibility of results obtained with this ABI-form device had been demonstrated by Yamashina *et al*. (*10*).

In summary, this study showed that in spite of the significant decrease in body weight and BPs, baPWV still increased significantly after HD, but returned to the pre-dialysis level on the next dialysis-free day. Therefore, when measuring arterial stiffness in HD patients, the measurement time relative to HD is important and should be taken into consideration. In contrast, ABI remained constant over the three time points. Hence, when using ABI to survey peripheral artery occlusive disease in HD patients, the measurement time relative to HD may not be a matter of concern.

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