

# Relation of stiffness parameter $\beta$ to carotid arteriosclerosis and silent cerebral infarction in patients on chronic hemodialysis

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## Abstract

**Objective** Aortic stiffness measured by pulse wave velocity (PWV) predicts all-cause and cardiovascular mortality in hemodialysis (HD) patients. However, there is a lack of information on stiffness parameter  $\beta$ , another index of arterial stiffness, in HD patients. The aim of the present study was to investigate the clinical usefulness of stiffness parameter  $\beta$  in HD patients.

**Materials and methods** We compared the relation of stiffness parameter  $\beta$  to carotid intima-media thickness (IMT) and plaque score estimated by carotid ultrasound and investigated the relationship between stiffness parameter  $\beta$  and silent cerebral infarction (SCI) in 64 HD patients.

**Results** Stiffness parameter  $\beta$  was positively correlated with mean IMT ( $r = 0.318$ ,  $P = 0.0113$ ) and plaque score ( $r = 0.672$ ,  $P < 0.0001$ ). Stepwise regression analysis revealed that pulse pressure and age were found to be independent determinants of stiffness parameter  $\beta$  (partial correlation coefficients:

$\beta = 0.501$  and  $P < 0.0001$  for pulse pressure,  $\beta = 0.488$  and  $P < 0.0001$  for age). In addition, stiffness parameter  $\beta$  in patients with SCI ( $12.2 \pm 3.9$ ) was significantly higher than those ( $8.0 \pm 2.4$ ) in patients without SCI. However, there was no significant difference in mean IMT and plaque score in both groups.

**Conclusion** These results suggest that arteriosclerosis assessed by stiffness parameter  $\beta$  is associated with atherosclerotic changes of carotid arteries and with the presence of SCI in HD patients.

**Keywords** Stiffness parameter  $\beta$  · Intima-media thickness · Plaque score · Silent cerebral infarction · Hemodialysis · End-stage renal disease

## Introduction

Arterial stiffness is an independent predictor of all-cause and cardiovascular mortality in patients on chronic hemodialysis (HD) [1, 2]. Arterial stiffness can be evaluated by measuring pulse wave velocity (PWV) between two sites in the arterial tree [3]. However, aortic PWV measurement is technically difficult and has low reproducibility [4]. Brachial-ankle PWV (baPWV), which provides a more convenient assessment of arterial stiffness, has been developed in Japan [5–7]. However, the problem with the clinical use of baPWV is that the index is

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significantly dependent on blood pressure levels [8]. On the other hand, stiffness parameter  $\beta$  was reported to be independent of blood pressure [9]. The stiffness parameter  $\beta$  has been used to evaluate arterial stiffness in patients with type 2 diabetes [10] and patients with chronic renal failure [11]. However, its clinical usefulness has not yet been fully clarified in HD patients.

An alternative method for evaluating arterial stiffness is the relative change in lumen diameter during the cardiac cycle adjusted for driving pulse pressure, expressed as arterial distensibility. Carotid distensibility is measured by ultrasound imaging. An ultrasound imaging of the common carotid artery (CCA) has been developed for the evaluation of early atherosclerotic lesions [12–14]. HD patients exhibit markedly increased intima-media thickness (IMT), a higher prevalence of plaques in the CCA compared to control subjects [15–17].

The aim of the present study was to measure stiffness parameter  $\beta$  and examine the relation of stiffness parameter  $\beta$  to IMT, plaque score or biochemical parameters in patients on chronic HD. In addition, we assessed the correlation between stiffness parameter  $\beta$  and silent cerebral infarction (SCI) estimated by magnetic resonance imaging (MRI).

## Methods

### Study subjects

The study subjects were 64 maintenance HD patients (31 men and 33 women) treated at the Dialysis Unit of Hidaka Hospital. HD was performed three times weekly (4 h/day). The dialysis potassium concentration was 2.0 mEq/l, and the calcium concentration was 3.0 mEq/l. Blood pressure was recorded three times with a brachial sphygmomanometer, after the subject had rested in the supine position for at least 10 min and the average value of the three measurements was adopted. Hypertension was defined as systolic blood pressure (SBP)  $\geq 140$  mmHg and/or diastolic blood pressure (DBP)  $\geq 90$  mmHg, or use of antihypertensive medication. Pulse pressure was calculated by the formula  $PP = SBP - DBP$ . Diabetes mellitus (DM) was defined by World Health Organization (WHO) criteria [18]. Patients with

congestive heart failure, atrial fibrillation, malignant tumor or autoimmune diseases were excluded. All measurements as listed below were performed after dialysis session except blood sampling. Information about antihypertensive medications was obtained from medical charts and analyzed. This study was in compliance with the Declaration of Helsinki and was in agreement with the guidelines approved by the ethics committee of our institution; informed consent was obtained from each patient.

### Ultrasound evaluation

Ultrasound evaluation of the CCA was performed with an Aplio (Toshiba Co., Tokyo, Japan) using a 7.5-MHz probe equipped with a Doppler system. After the subjects had rested in the supine position for at least 10 min, their neck was placed in a slightly hyperextended position, and then optimal bilateral visualization of the CCA was performed. Based on multiple visualizations, plaque formation was identified as the presence of wall thickening at least 50% greater than the thickness of the surrounding wall. To evaluate the distribution of atherosclerosis in the CCA, we used a plaque scoring method as previously described [13]. The plaque score was computed by summing the maximum thickness of the intima-media complex, measured in millimeters, on the near and far walls of each of four divisions on both sides of the carotid arteries. The length of the individual plaques was not considered in determining the plaque score. The IMT of the far wall was measured in the CCA as sites 1 and 2 cm proximal to the bulb from the anterior, lateral, and posterior approaches, and the results were averaged in order to obtain the mean IMT values. No measurements were carried out at the level of discrete plaques.

Two-dimensional guide M-mode tracing of the right CCA 2 cm proximal to the bulb was recorded with simultaneous electrocardiogram and phonocardiogram. M-mode images were obtained in real time using a frame grabber. The axial resolution of the M-mode system was 0.1 mm. The internal diameters of the CCA at end diastole (Dd) and peak systole (Ds) were determined by continuous tracing of the intima-luminal interface of the near and far wall of the CCA during three cycles, and the results were then averaged. The stiffness parameter  $\beta$  was calculated by the following formulae:

Stiffness parameter  $\beta = \ln(\text{SBP}/\text{DBP}) \times [\text{Dd}/(\text{Ds} - \text{Dd})]$ .

Intraobserver intrasession variability was evaluated from three repeated measurements in one session. The coefficient of variation of the three measurements was calculated in each subject. Intraobserver intersession variability was studied by one observer by performing two sessions on different days. The intraobserver intrasession variability was less than 10%, and the intraobserver intersession variability was less than 15%. SBP and DBP were measured at the brachial artery in the arm without blood access by an automated sphygmomanometer (Omron-Colin Co., Tokyo, Japan) immediately after the evaluation of carotid ultrasound.

#### Magnetic resonance imaging (MRI)

All participating patients had a brain MRI (EXCEL-ART, Toshiba Co., Tokyo, Japan) and used a superconducting magnet at a field strength of 1.5 T on proton density, T1-, and T2-weighted images in axial planes at 10-min-thick slices. Infarction was defined as a focal area larger than 3 mm in diameter in both T1- and T2-weighted images that was visible as low-signal intensity areas on T1-weighted image and as high-signal intensity areas on T2-weighted image. The MR images were assessed independently by two neuroradiologists who had not been notified of any clinical information.

#### Laboratory data

Blood samples were drawn after an overnight fast of at least 12 h before dialysis session, and serum creatinine (automated enzymatic method), urea, glucose, total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), triglyceride (TG), albumin, calcium (Ca), phosphate (P), and C-reactive protein (CRP) levels were determined by using routine biochemical methods. With regard to the urea kinetics, we measured a blood-based dialysis parameter, Kt/V [19]. Serum intact parathyroid hormone (iPTH) was measured by commercially available radioimmunoassay.

#### Statistical analysis

Data are expressed as mean  $\pm$  standard deviation. Pearson's correlation coefficient was used to assess

the association between continuous variables. Student's unpaired *t*-test was used to analyze the comparisons between means. We used stepwise multiple regression analysis to evaluate the independent determinants of stiffness  $\beta$ . Differences with *P* less than 0.05 are considered statistically significant. Statistical analyses were performed using SPSS software, version 11.0 (SPSS Inc., Chicago, IL).

## Results

### Characteristics of the study participants

The mean age of the participants was  $64.9 \pm 16.5$  years, and the mean duration of dialysis was  $8.7 \pm 5.8$  years. Underlying diseases of end-stage renal disease were 32 with chronic glomerulonephritis, 22 with DM, 5 with polycystic kidney disease, 3 with nephrosclerosis and 2 with unknown origin. All HD patients were treated with antihypertensive drugs, including calcium channel blockers (62 patients), angiotensin II receptor blockers/angiotensin-converting enzymes (51 patients),  $\alpha$ -blockers (17 patient) and  $\beta$ -blockers (10 patients). Three (4.7%) patients were treated with statins, and 45 (70.3%) were treated with anti-platelet drugs. The clinical characteristics and data of stiffness  $\beta$  and carotid parameters of the study subjects are summarized in Table 1. Twenty-eight (45.2%) had SCI as a lacunar infarction.

### Correlation between stiffness parameter $\beta$ and clinical variables

We examined the relationships between stiffness parameter  $\beta$  and pro-atherosclerotic factors, such as age, SBP and DBP, pulse pressure, Kt/V, TC, TG, HDL-C, Ca, P, iPTH, albumin, and CRP.

As shown in Table 2, the univariate linear regression analysis showed that the stiffness parameter  $\beta$  was strongly correlated with age and pulse pressure, weakly correlated with DBP and CRP, and not correlated at all with duration of dialysis, SBP, Kt/V, TC, TG, HDL-C, Ca, P, iPTH, or albumin. No significant difference in stiffness parameter  $\beta$  was noted in diabetic patients ( $10.4 \pm 3.7$ ) or non-diabetic patients ( $9.6 \pm 3.8$ ) ( $P = 0.1876$ ). Because these factors may be associated with each other, stepwise multiple regression analyses were

performed to evaluate the independent determinants of stiffness parameter  $\beta$  using age, DBP, pulse pressure, and CRP as covariates. Pulse pressure and

**Table 1** Characteristics of patients on chronic hemodialysis

<i>N</i> (male/female)	62 (31/31)
Age (years)	64.9 ± 11.5
BMI (kg/m <sup>2</sup> )	20.8 ± 2.9
Systolic blood pressure (mmHg)	140.5 ± 19.7
Diastolic blood pressure (mmHg)	77.0 ± 10.8
Pulse pressure (mmHg)	63.5 ± 15.0
Total cholesterol (mg/dl)	155.1 ± 31.2
Triglyceride (mg/dl)	109.6 ± 70.9
HDL-C (mg/dl)	45.1 ± 12.7
Kt/V	1.2 ± 0.2
Calcium (mg/dl)	8.9 ± 0.8
Phosphate (mg/dl)	5.3 ± 0.8
Intact PTH (pg/ml)	246.9 ± 180.3
Albumin (g/dl)	3.7 ± 0.3
C-reactive protein (mg/dl)	0.4 ± 0.5
Mean IMT (mm)	1.0 ± 0.3
Plaque score	13.8 ± 10.6
Stiffness $\beta$	9.9 ± 3.8
SCI (%)	28 (45.2)

*BMI* body mass index, *HDL-C* high-density lipoprotein-cholesterol, *PTH* parathyroid hormone, *IMT* intima-media thickness

**Table 2** Correlation between stiffness  $\beta$  and other clinical parameters in patients on chronic hemodialysis

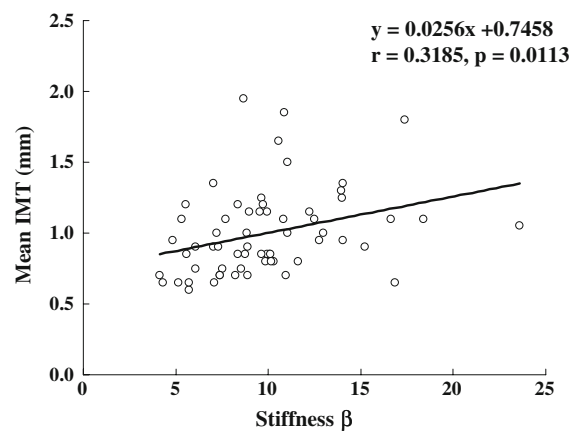
	<i>r</i>	<i>P</i> -value
Age	0.488	<0.0001
Duration of dialysis	−0.126	0.3310
Systolic blood pressure	0.243	0.0564
Diastolic blood pressure	−0.252	0.0480
Pulse pressure	0.501	<0.0001
Total cholesterol	0.063	0.6263
Triglyceride	−0.025	0.8475
HDL-C	−0.174	0.1781
Kt/V	0.030	0.8162
Calcium	−0.233	0.0688
Phosphate	−0.192	0.1363
Intact PTH	0.137	0.2906
Albumin	−0.199	0.2716
C-reactive protein	0.320	0.0108

*BMI* body mass index, *HDL-C* high-density lipoprotein-cholesterol, *PTH* parathyroid hormone

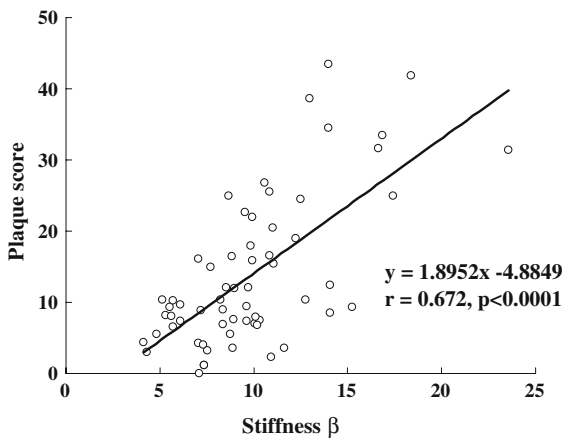
age were found to be independent determinants of stiffness parameter  $\beta$  (partial correlation coefficients:  $\beta = 0.501$  and  $P < 0.0001$  for pulse pressure,  $\beta = 0.488$  and  $P < 0.0001$  for age). In general, increased arterial stiffness is the cause of greater pulse pressure. However, it is likely that this statistical model included pulse pressure as a possible determinant of stiffness parameter  $\beta$ .

#### Correlation between stiffness parameter $\beta$ and carotid ultrasound parameters or SCI

In an attempt to investigate the relation of stiffness  $\beta$  to carotid atherosclerosis, univariate analysis was performed. There was a significant positive correlation between stiffness parameter  $\beta$  and mean IMT ( $r = 0.318$ ,  $P = 0.0113$ ) (Fig. 1) and plaque score ( $r = 0.672$ ,  $P < 0.0001$ ) (Fig. 2). The independent determinant factors of stiffness parameter  $\beta$  were mean IMT ( $\beta = 0.471$ ,  $P = 0.0116$ ) and plaque score ( $\beta = 0.672$ ,  $P < 0.0001$ ) estimated by a stepwise regression analysis using mean IMT and plaque score as covariates. Accordingly, we compared carotid atherosclerotic or arteriosclerotic parameters in HD patients with or without SCI. As shown in Table 3, stiffness  $\beta$  in patients with SCI ( $12.2 \pm 3.9$ ) was significantly higher than those ( $8.0 \pm 2.4$ ) in patients without SCI. However, there was no significant difference in mean IMT and plaque score in both groups. These findings suggest that stiffness parameter  $\beta$  is affected by mean IMT independent of plaque



**Fig. 1** Correlation between stiffness parameter  $\beta$  and mean intima-media thickness (IMT) in patients on chronic hemodialysis



**Fig. 2** Correlation between stiffness parameter  $\beta$  and plaque score in patients on chronic hemodialysis

**Table 3** Comparison of carotid atherosclerotic markers in HD patients in the presence or absence of silent cerebral infarction (SCI)

	SCI (+)	SCI (-)	P-value
Stiffness $\beta$	12.2 $\pm$ 3.9	8.0 $\pm$ 2.4	<0.0001
Mean IMT	1.1 $\pm$ 0.4	1.0 $\pm$ 0.3	0.2667
Plaque score	16.5 $\pm$ 13.2	11.6 $\pm$ 7.3	0.1162

Values are mean  $\pm$  SD. *IMT* intima-media thickness

score, and stiffness parameter  $\beta$  is affected by plaque score independent of mean IMT.

## Discussion

Although the usefulness of measuring stiffness parameter  $\beta$  has been shown in type 2 diabetes mellitus and other populations, no previous paper is available for HD patients. In the present study, we found a strong correlation between stiffness parameter  $\beta$  and IMT or plaque score. Thus, this study provides novel information on stiffness parameter  $\beta$  in HD patients.

Atherosclerosis involves a combination of fatty degeneration (atherosis) and vessel stiffening (sclerosis) of the arterial wall [20]. Arterial stiffness is usually assessed in the aorta by measuring carotid-femoral PWV, but it can also be assessed in the CCA by measuring the distensibility coefficient. Atherosclerosis is commonly assessed by IMT and the presence of plaques in the carotid artery [21]. A

significant relationship between PWV and IMT has been demonstrated, especially in the general population [21, 22]. Kawada et al. [23] reported that stiffness parameter  $\beta$  was higher in hypertensive HD patients than in non-hypertensive HD patients and was independently associated with age and hypertension. In the present study, stiffness parameter  $\beta$  was related to both IMT and plaque score in all HD patients treated with antihypertensive agents.

Makita et al. [24] reported that plaque score was reported to be more closely related to serum CRP level than to IMT in the general population. In the present study, stiffness parameter  $\beta$  was positively associated with CRP level ( $r = 0.320$ ,  $P = 0.0108$ ) in HD patients. It has been shown that baseline PWV as well as the changes of PWV during follow-up was independently associated with serum CRP level [25] in HD patients. They indicated that low-grade inflammation decreases the efficiency of cardiovascular therapeutic interventions and participates in the persistence of cardiovascular hemodynamic overload. These reports and our results suggest that the correlation between stiffness parameter  $\beta$  and plaque score may be stronger in HD patients with chronic inflammation in HD patients. Moreover, Tseke et al. [26] reported that stiffening and atherosclerosis are associated with chronic inflammation as well as DBP in HD patients.

SCI is thought to be an underlying or concomitant condition of clinical subcortical brain infarction or brain hemorrhage in the general population [27]. In most cases, SCI is found as a lacunar infarction, the most common form of subcortical infarction, defined by Fisher as a small, deep cerebral infarction caused by occlusion of small penetrating cerebral arteries [28]. Nakatani et al. [29] reported a higher incidence of SCI in HD patients compared with the control group using MRI studies (48.8% vs. 9.6%, respectively). They also showed that HD patients with SCI had a significantly higher cerebral and vascular morbidity than the group without SCI [30]. In the present study, stiffness parameter  $\beta$  in patients with SCI was significantly higher than those in patients without SCI, suggesting that carotid arteriosclerosis is associated with the presence of SCI in HD patients.

In order to overcome the problem that baPWV is significantly dependent on blood pressure levels, we used stiffness parameter  $\beta$  to evaluate the atherosclerotic burden in HD patients. Kanters et al. [31] reported

the reproducibility of measurement of distensibility in the CCA, and showed that the intraobserver intrasession variability and the intraobserver intersession variability of stiffness parameter  $\beta$  were 19.1% and 25.4%, respectively. In the present study, the intraobserver intrasession variability was less than 10%, and the intraobserver intersession variability was less than 15%, showing that our reproducibility of measurement of stiffness parameter  $\beta$  was higher than those in the previous study. The stiffness parameter  $\beta$  should give the better estimate without pressure dependence of the real deformation behavior of the vascular wall within the physiological pressure range. Further prospective studies are required to evaluate if stiffness parameter  $\beta$  is a useful tool for predicting atherosclerotic burden and SCI in HD patients.

There were several limitations in our study, namely that the study population was relatively small and that we could not eliminate the effect of medications on stiffness parameter  $\beta$  level. Another limitation of this study is that brachial SBP and DBP were used to calculate the carotid stiffness parameter  $\beta$  instead of carotid SBP and DBP. Physiologically, mean blood pressure and DBP are nearly identical in the carotid and brachial arteries, whereas SBP and pulse pressure are significantly higher in the brachial arteries than the carotid arteries, although the differences are minimized with aging [32]. This may be a reason that stiffness parameter  $\beta$  was associated with mean IMT, although this association was relatively weak. The pulsatility index and/or resistive index might be an additional indicator for carotid arteriosclerosis in HD patients [33].

In conclusion, we demonstrated that stiffness parameter  $\beta$  was associated with carotid IMT and plaque score in HD patients. Stiffness parameter  $\beta$  may serve as a useful clinical marker for arteriosclerosis in HD patients with SCI.

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