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ORIGINAL ARTICLE

Noninvasive indices of arterial stiffness in hemodialysis patients

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The purpose of this study was to evaluate the validity of brachial–ankle pulse wave velocity (baPWV) and the cardio–ankle vascular index (CAVI) as measures of arterial stiffness in hemodialysis (HD) patients. We studied 160 consecutively enrolled HD patients (mean age: 59 ± 13 years; 91 male patients). We measured baPWV and CAVI using a VaSera VS-1000, maximum intima-media thickness (max IMT) of the carotid artery by ultrasonography and blood renal and lipid parameters. As a control, baPWV and CAVI were also measured in age- and gender-matched healthy volunteers. Both baPWV and CAVI were significantly higher in HD patients than in controls (baPWV: 1698 ± 355 vs. 1454 ± 263 cm s^{-1}, $P<0.0001$; CAVI: 9.3 ± 1.4 vs. 8.9 ± 1.2, $P<0.01$). BaPWV correlated positively with age ($r=0.549$, $P<0.0001$), systolic blood pressure (SBP) ($r=0.510$, $P<0.0001$), diastolic blood pressure ($r=0.203$, $P<0.0001$), pulse pressure (PP) ($r=0.499$, $P<0.0001$), Kt V^{-1} ($r=0.221$, $P<0.01$), Brinkman index ($r=0.186$, $P<0.05$) and max IMT ($r=0.285$, $P<0.001$). CAVI also correlated positively with age ($r=0.562$, $P<0.0001$), SBP ($r=0.395$, $P<0.0001$), PP ($r=0.490$, $P<0.0001$), Kt V^{-1} ($r=0.216$, $P<0.01$), Brinkman index ($r=0.238$, $P<0.01$) and max IMT ($r=0.280$, $P<0.001$). Multiple regression analysis demonstrated baPWV and CAVI correlated independently with age and SBP. Receiver operating characteristics (ROC) curve analysis demonstrated that baPWV and CAVI had similar power to predict increases in max IMT. We also measured baPWV and CAVI immediately before and after HD, and showed CAVI was influenced by changes in water volume. Both baPWV and CAVI are therefore useful indices of arterial stiffness in HD patients.
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Keywords: arterial stiffness; baPWV; CAVI; hemodialysis

INTRODUCTION

Chronic kidney disease is a worldwide public health problem and is a risk factor for the development of cardiovascular disease.[1] The incidence and associated costs of treatment of end-stage renal disease are increasing in Japan similar to that occurring in Western countries.[2,3] Accelerated atherosclerosis in end-stage renal disease patients is a serious problem and the resulting poor prognosis in hemodialysis (HD) patients is an important issue.[4,5]

Brachial–ankle pulse wave velocity (baPWV) is used as a noninvasive clinical index of arterial stiffness[6,7] and has been shown to predict the presence of coronary artery disease[8] and also correlate with abdominal aortic calcification[9] and carotid intima-media thickness.[10] Although baPWV is a useful index for measuring arterial stiffness in HD patients,[11–14] it has the limitation of being influenced by changes in blood pressure (BP) during measurements.

Recently, an atherosclerotic index, the cardio-ankle vascular index (CAVI), has been developed that involves measuring pulse wave velocity (PWV) and BP. CAVI is adjusted for BP based on the stiffness parameter β and therefore measures arterial stiffness independent of BP.[15–17] We have reported previously that CAVI showed a weaker correlation with systolic BP (SBP) than baPWV and was not affected by changes in BP during measurement.[9] There is also evidence that CAVI reflects histological arterial fibrosis and is a useful clinical marker for evaluating arterial stiffness in HD patients.[18] The purpose of the study was therefore to evaluate the validity of the noninvasive indices of arterial stiffness, baPWV and CAVI, in HD patients.

METHODS

Study subjects

We analyzed 160 consecutively enrolled patients with kidney failure who received HD therapy at Ueyama Hospital. The causes of kidney failure were nephritis in 120 patients, diabetes in 32 patients, collagen disease in seven patients and Fabry disease in one patient. Of these patients, 42 were treated with an angiotensin II receptor blocker (ARB), four with an angiotensin-converting enzyme inhibitor and 14 with a HMG-CoA reductase inhibitor. Exclusion criteria were diseases that affect baPWV and CAVI measurements including the presence of atrial fibrillation, a high frequency of ventricular and atrial premature beats, peripheral arterial disease with an ankle–brachial

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pressure index (ABI) of less than 0.9, heart failure (New York Heart Association class II and higher), pulmonary edema and cancer. To compare baPWV and CAVI between the HD patients and control subjects, 160 healthy volunteers matched with the HD patients for age and gender were enrolled in the study.

The protocol of this study was approved by the Institutional Review Board of Kagoshima University. Informed consent was given by all the patients and volunteers.

Measurements of baPWV and CAVI

Immediately before HD, baPWV and CAVI were measured using a Vasera VS-1000 (Fukuda Denshi, Tokyo, Japan). As reported previously, cuffs were placed on both ankles and the brachium, which were not used for blood access. Electrocardiographic electrodes were attached to the upper arm and a microphone was placed on the sternal angle for phonocardiography. The subjects rested in the supine position for 5 min. PWV was calculated by dividing the distance from the aortic valve to the ankle artery by the sum of the difference between the time the pulse waves were transmitted to the brachium and the time the same waves were transmitted to the ankle, and the time difference between the second heart sound on the phonocardiogram and the notch of the brachial pulse waves.[15–17] To minimize cuff inflation effects on blood flow dynamics, pulse waves were measured with the cuffs inflated to lower than diastolic pressure (50 mm Hg). The extremity blood pressure was then measured by oscillometry. SBP, diastolic BP (DBP) and pulse pressure (PP) were obtained by measuring the BP at the right brachial artery.

CAVI was calculated by the following equation: $\mathrm{CAVI}=a[\{2\rho\times 1/(\mathrm{SBP}-\mathrm{DBP})\}\times\{\ln(\mathrm{SBP}/\mathrm{DBP})\times \mathrm{PWV}^2\}]+b$ (ρ: density of blood, a and b: constants).[16,17,19]

Analysis of blood samples

Blood samples were obtained after an overnight fast on the morning of the day baPWV and CAVI were measured. The serum concentrations of creatinine (Cr), blood urea nitrogen (BUN), uric acid (UA), calcium (Ca), phosphoric acid (P), parathyroid hormone (PTH), total cholesterol, triglyceride (TG) and high-density lipoprotein cholesterol (HDL-C) were measured using standard laboratory procedures. Low-density lipoprotein cholesterol (LDL-C) was calculated by the Friedewald equation. $\mathrm{Kt\,V}^{-1}$ was determined according to the procedure of Shinzato *et al*.[20]

Measurement of maximum IMT

The maximum IMT (max IMT) of the carotid artery was evaluated by high-resolution ultrasonography (Fukuda Denshi) using a 7.5-MHz probe. The IMT was measured as the distance from the leading edge of the first echogenic line to the leading edge of the second echogenic line. In this study, the thickest point of the bilateral carotid artery was defined as the max IMT without plaque.

Statistical analysis

Data are expressed as the mean ± s.d. Differences between the mean values of the two groups were analyzed by unpaired *t*-tests, whereas differences between mean values of measurements at two points were analyzed using paired *t*-tests. The relationship between continuous variables was analyzed by linear regression analysis and independent associations between variables were examined by multiple regression analysis. The statistical analyses were performed with Statview version 5.0 (SAS Institute, Cary, NC, USA), whereas receiver operating characteristics (ROC) curve analysis was performed with JMP version 5.1.1 (SAS Institute). *P*-values less than 0.05 were considered statistically significant.

RESULTS

Comparison of baPWV and CAVI between HD patients and controls

The clinical characteristics of the HD patients and age- and gender-matched control subjects are summarized and compared in Table 1.

Table 1 Clinical characteristics of the control and HD groups

Variable	*Control (n=160)*	*HD (n=160)*	P-*value*
Age (years)	60 ± 10	60 ± 13	NS
Gender (M/F)	91/69	91/69	NS
BMI (kg m^{-2})	23.2 ± 2.8	21.6 ± 7.1	<0.05
SBP (mm Hg)	127 ± 14	148 ± 22	<0.0001
DBP (mm Hg)	83 ± 10	87 ± 13	<0.001
PP	45 ± 9	62 ± 17	<0.001
Cr (mg per 100 ml)	0.8 ± 0.2	11.0 ± 3.0	<0.0001
BUN (mg per 100 ml)	16 ± 4	71 ± 16	<0.0001
UA (mg per 100 ml)	5.2 ± 1.3	6.8 ± 1.4	<0.0001
HDL-C (mg per 100 ml)	57 ± 14	54 ± 17	NS
LDL-C (mg per 100 ml)	130 ± 31	80 ± 27	<0.0001
TG (mg per 100 ml)	112 ± 69	104 ± 62	NS
Duration of dialysis (days)	—	3138 ± 2498	ND
Medication			
ARB	0	42	ND
ACE-I	0	4	ND
Statin	0	14	ND

Abbreviations: ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; BUN, blood urea nitrogen; Cr, serum creatinine; DBP, diastolic blood pressure; HD, hemodialysis; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; ND, not done; NS, not significant; PP, pulse pressure; SBP, systolic blood pressure; statin, HMG-CoA reductase inhibitor; TG, triglyceride; UA, uric acid.

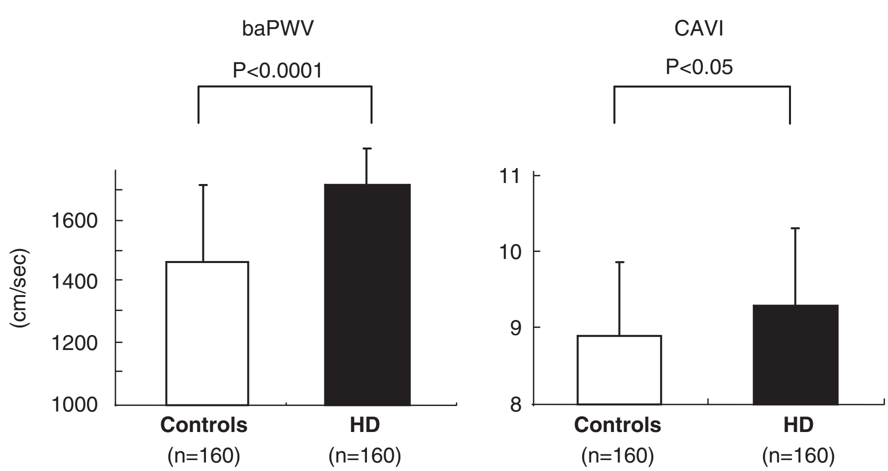

Figure 1 Comparison of baPWV and CAVI between HD patients and controls. baPWV, brachial–ankle pulse wave velocity; CAVI, cardio–ankle vascular index; HD, hemodialysis.

There was no significant difference in age, gender, HDL-C and TG between the two groups, whereas SBP, DBP and PP were significantly higher and BMI and LDL-C significantly lower in the HD patients compared with the control group. In addition, both baPWV and CAVI were significantly higher in the HD patients than in the control group (Figure 1).

Table 2 Correlation coefficients between baPWV or CAVI and other variables in HD patients calculated by linear regression analysis

	baPWV		*CAVI*	
Variables	R	P-*value*	R	P-*value*
Age (years)	0.549	<0.0001	0.562	<0.0001
SBP (mm Hg)	0.510	<0.0001	0.395	<0.0001
DBP (mm Hg)	0.203	<0.0001	0.018	NS
PP	0.499	<0.0001	0.490	<0.0001
Max IMT	0.285	<0.001	0.280	<0.001
$Kt V^{-1}$	0.221	<0.01	0.216	<0.01
Duration of dialysis	0.375	<0.0001	0.390	<0.0001
Brinkman index	0.186	<0.05	0.238	<0.01
BMI	0.020	NS	0.041	NS
LDL-C	0.051	NS	0.064	NS
HDL-C	0.155	NS	0.131	NS
TG	0.067	NS	0.001	NS
ip×Ca	0.101	NS	0.082	NS
i PTH	0.104	NS	0.126	NS

Abbreviations: baPWV, brachial–ankle pulse wave velocity; BMI, body mass index; CAVI, cardio–ankle vascular index; DBP, diastolic blood pressure; HDL-C, high–density lipoprotein cholesterol; i PTH, intact parathyroid hormone; LDL-C, low-density lipoprotein cholesterol; Max IMT, maximum intima-media thickness; NS, not significant; PP, pulse pressure; SBP, systolic blood pressure; TG, triglyceride.

Linear regression analysis of baPWV or CAVI and other variables in HD patients

The results of the linear regression analysis of baPWV and the other variables in the HD patients are shown in Table 2. Positive correlations were found between baPWV and age, SBP, DBP, PP, $Kt V^{-1}$, Brinkman index and max IMT and between CAVI and age, SBP, PP, $Kt V^{-1}$, Brinkman index and max IMT. Although baPWV and CAVI showed a similar degree of correlation with age, CAVI was more weakly correlated with SBP than baPWV (Figure 2).

Multiple regression analysis between baPWV or CAVI and other variables in HD patients

Table 3 shows the results of a multiple regression analysis with baPWV or CAVI as the dependent variable, and age, SBP, PP, max IMT, $Kt V^{-1}$, duration of dialysis and diabetes mellitus as the independent variables. In HD patients, baPWV correlated independently with age, SBP and PP, whereas CAVI correlated independently with age, SBP, $Kt V^{-1}$ and diabetes mellitus.

ROC curve analysis between baPWV or CAVI and increased max IMT (⩾0.9 mm)

Figure 3 demonstrates the ROC curves of baPWV and CAVI to predict increased max IMT (⩾0.9 mm). The area under the ROC curve (AUC) for baPWV was 0.66, with the highest discriminating sensitivity and specificity being 0.76 and 0.59, respectively at baPWV=1563 $cm s^{-1}$. In contrast, the AUC for CAVI was 0.65 and the highest discriminating sensitivity and specificity were 0.57 and 0.70, respectively at CAVI=9.5. These results suggest that baPWV and CAVI have similar power to predict the increases in max IMT.

Effect of water volume changes on baPWV and CAVI

To analyze the effect of HD on baPWV and CAVI, we measured both indices immediately before and after HD in 101 patients (Table 4). In these patients, SBP, DBP and baPWV decreased significantly after HD,

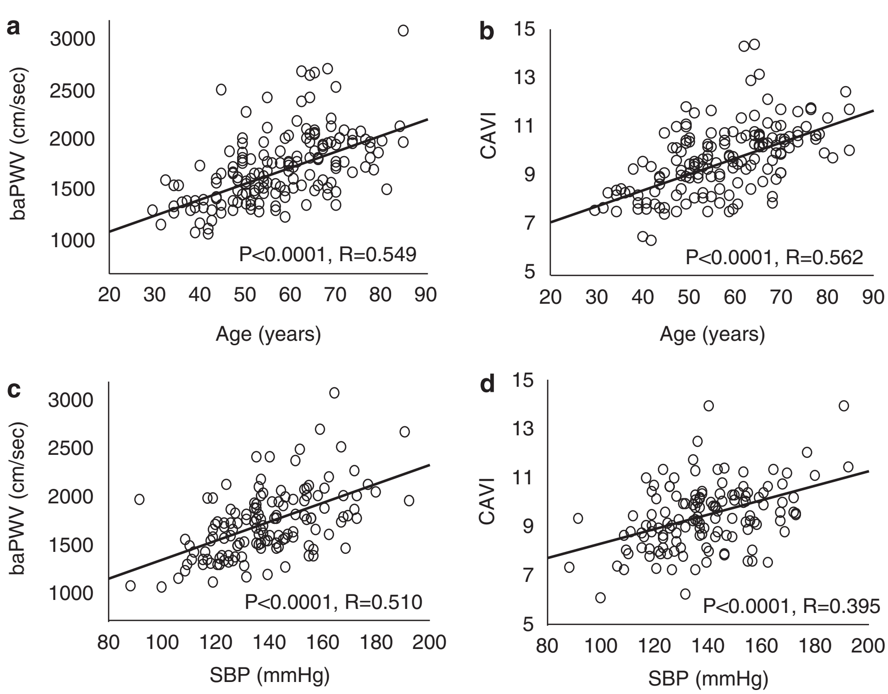

Figure 2 Relationship between baPWV and age (**a**), CAVI and age (**b**), baPWV and SBP (**c**) and CAVI and SBP (**d**). baPWV, brachial–ankle pulse wave velocity; CAVI, cardio–ankle vascular index; SBP, systolic blood pressure.

whereas CAVI increased significantly after HD. We also determined the water removal rate as follows; (body weight before HD−body weight after HD)/dry weight. CAVI increased significantly after HD in patients with a water removal rate >5%, but did not change in patients with a water removal rate ⩽5%. In contrast, baPWV decreased significantly after HD with no influence of water removal rate being observed. These results suggest that CAVI is influenced by changes in water volume.

Table 3 Multiple regression analysis between baPWV or CAVI and other variables in HD patients

	baPWV		CAVI	
Variable	*Coefficient*	P-*value*	*Coefficient*	P-*value*
Age (years)	13.987	<0.0001	0.056	<0.0001
SBP (mm Hg)	9.689	<0.0001	0.017	<0.05
PP	−8.078	<0.05		NS
Max IMT		NS		NS
$Kt V^{-1}$		NS	−0.789	<0.05
Duration of dialysis		NS		NS
HDL-C		NS		NS
DM		NS	0.73	<0.05

Abbreviations: baPWV, brachial–ankle pulse wave velocity; CAVI, cardio–ankle vascular index; Cr, serum creatinine; DM, diabetic mellitus; HDL-C, high density lipoprotein cholesterol; Max IMT, maximum intima-media thickness; PP, pulse pressure; SBP, systolic blood pressure.

DISCUSSION

This study demonstrated that baPWV and CAVI were both significantly higher in HD patients than in age- and gender-matched controls. In HD patients, baPWV and CAVI showed positive correlations with age, SBP, PP, $Kt V^{-1}$, Brinkman index and max IMT. Multiple regression analysis revealed that baPWV and CAVI were correlated independently with age and SBP. ROC curve analyses demonstrated that baPWV and CAVI had similar power to predict increases in max IMT. Furthermore, we measured baPWV and CAVI immediately before and after HD and showed CAVI was influenced by changes in water volume.

The baPWV is a noninvasive clinical index of arterial stiffness in HD patients. It has been reported that glycated albumin, but not glycated hemoglobin or plasma glucose, is independently and positively associated with baPWV in HD patients with type 2 diabetes.[12] Kobayashi *et al.*[21] also reported a positive association between blood rheology and carotid IMT and baPWV in 118 HD patients. Furthermore, there is evidence to show that baPWV is useful for identifying a high-risk population of HD patients with an ABI greater than 0.9.[11] In addition, it has been reported that baPWV measurement shows variations at different time points in HD patients.[22] Su *et al.*[22] measured baPWV before and after HD and then on the next dialysis-free day and found baPWV increased significantly after HD, despite a significant decrease in body weight and BP.

CAVI is a useful index of arterial distensibility[16] and is not influenced by BP changes during measurement.[17] Several studies have shown the usefulness of CAVI for detecting atherosclerotic disease,[23,24] with one study in 67 HD patients using multiple regression analysis to reveal that the high-molecular weight adiponectin to

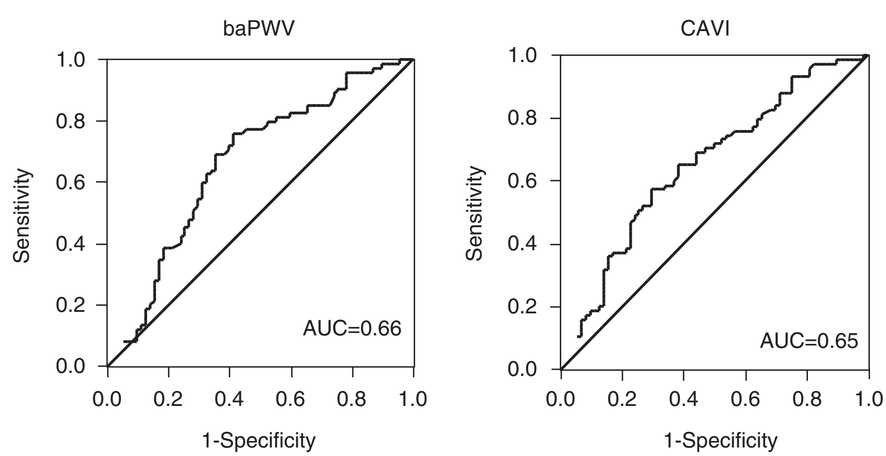

Figure 3 Receiver operating characteristic (ROC) curves of the ability of baPWV and CAVI to predict increases in IMT (⩾0.9 mm). AUC, area under ROC curve; baPWV, brachial–ankle pulse wave velocity; CAVI, cardio–ankle vascular index.

Table 4 Effect of changes in water volume on baPWV and CAVI

	Total (n=101)			Water removal rate ⩽5% (n=33)			Water removal rate >5% (n=68)		
	Before HD	*After HD*	P-*value*	*Before HD*	*After HD*	P-*value*	*Before HD*	*After HD*	P-*value*
Body weight (kg)	53.6±9.9	50.8±9.6	<0.0001	55.7±9.2	53.6±8.9	<0.0001	52.7±10.1	49.4±9.6	<0.0001
SBP (mm Hg)	155±23	125±20	<0.0001	144±21	125±22	<0.0001	159±23	125±20	<0.0001
DBP (mm Hg)	86±12	76±12	<0.0001	81±10	73±11	<0.001	89±11	78±12	<0.0001
baPWV ($cm s^{-1}$)	1794±394	1711±385	<0.05	1740±334	1656±320	<0.05	1820±419	1737±412	<0.05
CAVI	8.9±1.4	9.4±1.4	<0.0001	9.3±1.4	9.4±1.4	NS	8.7±1.3	9.4±1.4	<0.0001

Abbreviations: baPWV, brachial–ankle pulse wave velocity; CAVI, cardio–ankle vascular index; DBP, diastolic blood pressure; HD, hemodialysis; SBP, systolic blood pressure.

total adiponectin ratio was an independent determinant of PWV and CAVI.[25] Takaki *et al.*[26] compared baPWV and CAVI in 130 patients with chest pain syndrome and concluded that CAVI was superior to baPWV as a parameter of arterial stiffness. A further study in 103 HD patients used multiple regression analysis to show a significant association between histological arterial fibrosis and CAVI, but no such relationship with PWV.[18] Ichihara *et al.*[13,14] reported that several drugs including an angiotensin II receptor blocker (losartan), angiotensin-converting enzyme-I (tradolapril) and HMG-CoA reductase inhibitor (fluvastatin) improved arterial stiffness measured by PWV. However, in our study, there was no significant difference in baPWV or CAVI in patients either taking or not taking an angiotensin II receptor blocker, angiotensin-converting enzyme-I or HMG-CoA reductase inhibitor (data not shown). The previous studies by Ichihara *et al.*[13,14] were longitudinal studies, whereas the present study was a cross-sectional design.

We demonstrated that CAVI increased significantly after HD in patients with a removal rate $>5\%$. Large volume reduction after HD may increase the sympathetic nervous activity, which increases the vascular tone. The increase of vascular tone may result in the increase of CAVI. In addition, the hemoconcentration after HD may increase the CAVI, because the density of blood (ρ) is one of the determinants of CAVI.

There are several limitations in the measurement of CAVI as it cannot be determined accurately in patients with aortic stenosis, peripheral arterial disease or atrial fibrillation. An ABI <0.95 has been reported to be the cutoff value for diminished baPWV accuracy,[27] and therefore CAVI cannot be measured accurately if the ABI is less than 0.95. Further prospective studies are therefore needed to evaluate the validity of CAVI in the clinical assessment and prediction of mortality in HD patients.

In conclusion, baPWV and CAVI in HD patients were significantly higher than in age- and gender-matched control subjects, with both indices correlating independently with age and SBP in the HD patients. ROC curve analysis demonstrated that the power of baPWV and CAVI to predict increases in max IMT was similar. Furthermore, we measured baPWV and CAVI immediately before and after HD, and showed CAVI was influenced by changes in water volume. Therefore, both baPWV and CAVI are useful indices of arterial stiffness in HD patients.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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