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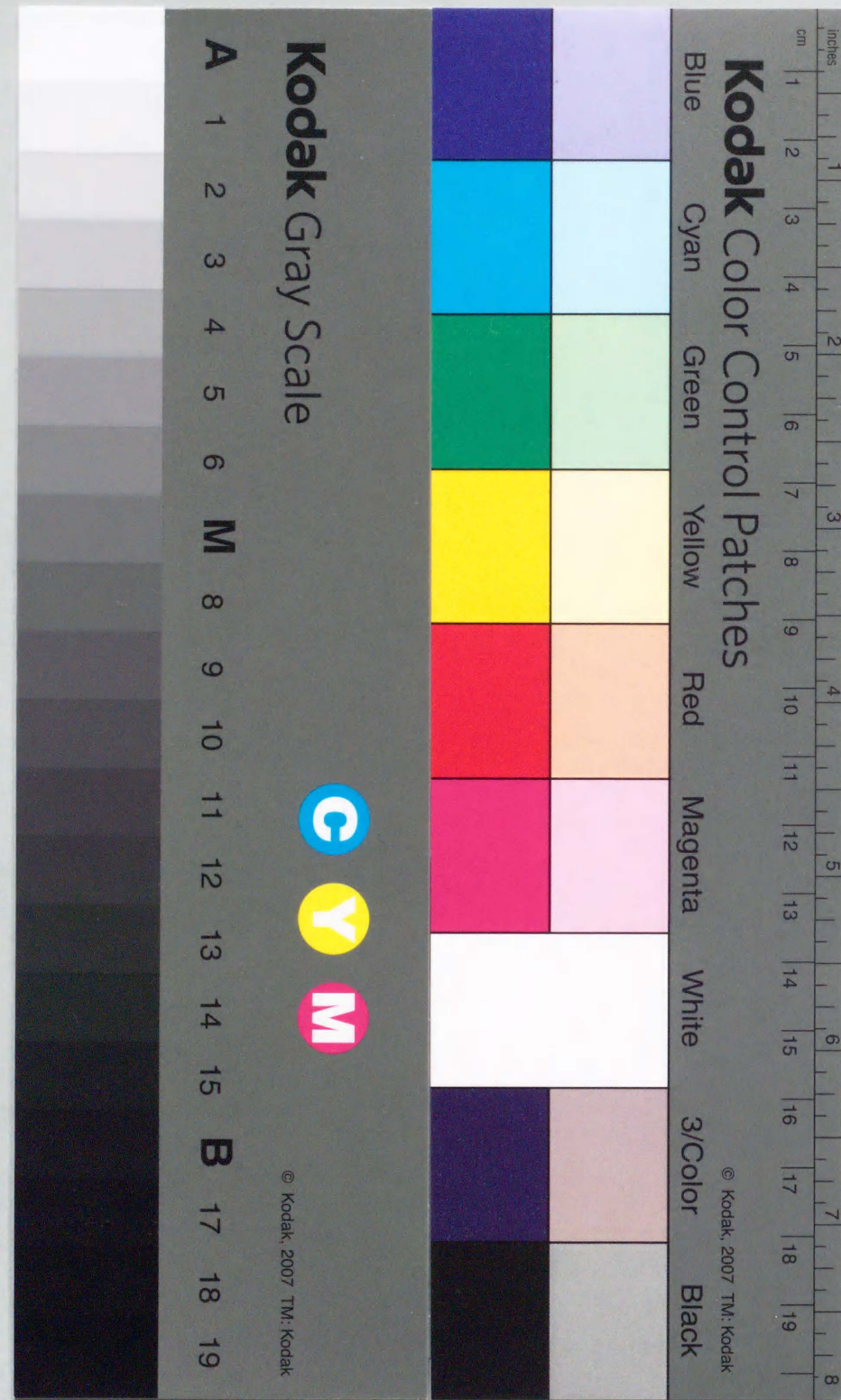
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## Hemodialysis Causes Severe Orthostatic Reduction in Cerebral Blood Flow Velocity in Diabetic Patients

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• Orthostatic hypotension is a serious problem in patients with diabetes mellitus (DM) undergoing hemodialysis (HD). To evaluate cerebral circulation during orthostasis in patients with DM, we examined changes in mean blood flow velocity in the middle cerebral artery (VMCA) during 60° head-up tilt for 5 minutes in patients with DM (six men, two women; age,  $57 \pm 3$  years [mean  $\pm$  SEM]; HD duration,  $47 \pm 27$  months) before and after bicarbonate HD by using transcranial Doppler sonography. The findings were compared with those in HD patients without diabetes (non-DM; 12 men, 5 women; age,  $47 \pm 3$  years; HD duration,  $82 \pm 23$  months). Mean blood pressure (MBP) in the supine position, hematocrit (Hct), plasma fibrinogen, and volume of fluid removed by HD were not significantly different between the two groups (MBP,  $106 \pm 6$  versus  $103 \pm 4$  mm Hg; Hct,  $26\% \pm 1\%$  versus  $28\% \pm 1\%$ ; fibrinogen,  $355 \pm 37$  versus  $357 \pm 27$  mg/dL; fluid,  $2.5 \pm 0.2$  versus  $2.3 \pm 0.2$  L). Percentage of change in VMCA (%VMCA) during tilt was compared between the groups before and after HD. Before HD, MBP decreased significantly to  $93 \pm 5$  mm Hg during tilt only in patients with DM. The degree of MBP reduction was  $-13 \pm 2$  mm Hg in DM and  $-2 \pm 2$  mm Hg in non-DM patients ( $P < 0.01$ ). %VMCA equally decreased during tilt; DM,  $-12\% \pm 3\%$ , and non-DM,  $-12\% \pm 2\%$ . After HD; MBP decreased by  $36 \pm 7$  mm Hg in patients with DM, which was significantly greater than before HD. VMCA also decreased in both groups after HD, and %VMCA in DM ( $-32\% \pm 5\%$ ) was significantly greater than before HD ( $P < 0.01$ ) and in non-DM patients ( $-13\% \pm 2\%$ ;  $P < 0.01$ ). %VMCA positively correlated with the percentage of change ratio of MBP during tilt in both groups after HD (DM,  $r = 0.87$ ,  $P < 0.01$ ; non-DM,  $r = 0.61$ ,  $P < 0.01$ ). Our results showed a significant decrease in cerebral blood flow velocity during tilt of equal magnitude in both groups before HD despite differences in the level of hypotension, whereas reduction in cerebral blood flow velocity and decrease in MBP were more marked in DM after HD. Orthostasis could thus cause hemodynamically mediated brain damage after HD, especially in patients with DM.

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**INDEX WORDS:** Cerebral blood flow; hemodialysis (HD); transcranial Doppler (TCD); orthostasis; diabetes mellitus (DM).

**P**ATIENTS WITH diabetes mellitus (DM) undergoing chronic hemodialysis (HD) often develop severe orthostatic hypotension,<sup>1</sup> which results in poor control of overhydration, various forms of cardiovascular accidents, and even sudden death.<sup>2</sup> Dysfunction of the autonomic nervous system and vascular damage are the major

contributing factors to these cardiovascular instabilities.<sup>3</sup> DM is a well-known risk factor for atherosclerosis, and patients with DM are at greater risk for ischemic brain lesions compared with the general population.<sup>4</sup> Hemodynamic instability, especially frequent decreases in arterial blood pressure during HD, together with severe orthostatic hypotension, might predispose to these abnormalities. Cerebral blood flow or cerebral blood flow velocities have been reported to decrease after HD.<sup>5-10</sup> Therefore, it is important to investigate the effect of HD on cerebral blood flow during tilt in patients with DM with autonomic nervous system dysfunction.

Aaslid et al<sup>11</sup> first reported the usefulness of transcranial Doppler (TCD) sonography for investigating intracranial circulation. TCD allows real-time recording and measurement of cerebral hemodynamics. In this regard, Sugimori et al<sup>12</sup> previously reported a good correlation between the mean blood flow velocity in the middle cerebral artery (VMCA) recorded by TCD, with the values of cerebral blood flow of the ipsilateral hemisphere measured with positron emis-

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sion tomography. TCD has also been used to evaluate orthostatic responses of cerebral circulation during the head-up tilt-table test.<sup>13-18</sup>

In the current study, we examined the response of cerebral blood flow velocity to tilt using TCD technique in patients undergoing regular dialysis both before and after HD. Our aim was to identify differences in the response of cerebral blood flow velocity to tilt between patients with and without DM.

PATIENTS AND METHODS

Patients

Eight patients with DM undergoing HD (six men, two women; age, 57 ± 3 years [mean ± SEM]; HD duration, 47 ± 27 months) were recruited for this study. We also studied 17 patients without DM undergoing HD (non-DM; 12 men, 5 women; mean age, 47 ± 3 years; HD duration, 82 ± 23 months) as a control group. Of the total 25 patients from both groups, 21 were selected from inpatients at Kyushu University Hospital (Fukuoka City, Japan), whereas the remaining 4 patients were selected from 134 HD patients visiting the outpatient clinic at Fukuoka Ichō-Shinzo Clinic (Fukuoka, Japan). Informed consent was obtained from all patients before the study. The HD program included dialysis for 4 to 6 hours three times weekly. Table 1A lists the clinical profile of patients with DM, and Table 1B lists the clinical profile and original kidney diseases that progressed to end-stage renal failure in non-DM patients. Patients who had clinically overt congestive heart failure, cardiac arrhythmia, severe stenosis of the carotid artery (>70%, assessed by carotid duplex ultrasonography), or a history of symptomatic cerebrovascular disease were excluded from the study. Physical examination showed the presence of neuropathy in all patients with DM and orthostatic hypotension (defined as

a decrease in systolic pressure > 20 mm Hg with a change from supine to upright position) in all but one patient with DM (patient 2). No neurological deficits were detected on neurological examination. The Wechsler Adult Intelligence Scale was examined to five DM and 10 non-DM patients. Brain magnetic resonance imaging (MRI) was performed in six DM and eight non-DM patients.

Protocol

Within 60 minutes before HD, patients underwent steady-state baseline TCD examination in the supine position in a quiet room. This was followed by a 60° head-up tilt, during which measurements of cerebral circulation (determined by TCD technique and carotid duplex sonography) and blood pressure were made. The patient was then moved to a dialysis room and underwent a single HD session. Blood samples were drawn before and after HD. The cardiac index (CI) was determined by the dye-dilution technique before and after HD. Within 60 minutes after HD, TCD was repeated to determine cerebral blood flow velocity in the supine position and at head-up tilt, in a manner similar to that before HD.

TCD Measurements

TCD technique was performed by a single examiner (H.S.) in a quiet room on a comfortable bed, with the temperature set at 25°C. The method has been described in detail elsewhere.<sup>19</sup> After 5 minutes in the supine position, a map of the circle of Willis and major intracranial arteries was generated by transtemporal TCD mapping technique with a 2-MHz Trans-scan (EME Co, Überlingen, Germany). Sample volumes were fixed at 6 mm in diameter. The M1 portion of the MCA was identified according to the map, usually at a depth of 45 to 60 mm. Maps and sonograms were stored on the hard disc of the computer for later analysis.

The VMCA was obtained from the time mean of the waveform envelope and corrected according to the insonated

Table 1A. Clinical Characteristics of HD Patients With DM

Patient No.	Sex	Age (y)	HD Duration (mo)	BP (mm Hg)	CTR (%)	IMT		Cardiac Disease	Brain MRI	Neuropathy	Orthostatic Hypotension
						Right (mm)	Left (mm)				
1	M	60	1	128/78	46.5	0.9	0.6		Normal study	+	+
2	M	58	1	142/71	44.5	0.9	0.7		ND	+	
3	F	48	2	150/95	49.8	0.6	0.8	HHD	ND	+	+
4	M	67	4	119/58	44.9	1.3	1.4	IHD	Multiple small infarcts	+	+
5	F	46	15	201/99	47.4	0.5	0.5		Normal study	+	+
6	M	65	16	174/93	40.9	0.9	0.7		Small white matter lesions	+	+
7	M	57	156	160/78	50.4	0.7	1.0		Normal study	+	+
8	M	56	180	165/83	49.3	0.9	0.8		Normal study	+	+
Mean		57	47	155 82	47.0	0.8	0.8				
SEM		3	27	9 5	1.0	0.1	0.1				

Abbreviations: BP, blood pressure; CTR, cardiothoracic ratio; IMT, intima media thickness of carotid artery; ND, not done; HHD, hypertensive heart disease; IHD, ischemic heart disease; HD, hemodialysis; MRI, magnetic resonance imaging.

Table 1B. Clinical Characteristics of HD Patients Without DM

Patient No.	Original Disease	Sex	Age (y)	HD Duration (mo)	BP (mm Hg)	CTR (%)	IMT		Cardiac Disease	Brain MRI
							Right (mm)	Left (mm)		
9	SA	M	49	0	158/90	50.4	0.6	0.6		ND
10	CGN	M	44	1	146/86	44.6	0.7	0.6	AR II	Small white matter lesions
11	CGN	M	23	1	148/80	38.4	0.5	0.5	HHD	ND
12	Unknown	M	65	1	181/90	45.1	0.7	0.7		ND
13	PCKD	F	53	3	124/85	53.5	0.7	0.5	p/s PDA	Normal study
14	CGN	M	53	1	135/85	49.7	0.5	0.5		ND
15	Unknown	M	58	1	128/85	52.5	0.5	0.5		Small white matter lesions
16	CGN	F	31	0	161/108	45.8	0.4	0.5		Small white matter lesions
17	CGN	F	31	32	117/76	46.2	0.5	0.5	HHD	ND
18	CGN	M	36	36	129/71	42.9	0.8	0.8		ND
19	CGN	M	67	203	138/77	47.4	0.7	0.7		Small white matter lesions
20	CGN	M	45	175	177/108	53.4	0.8	0.8		ND
21	PCKD	F	53	127	167/95	52.2	0.6	0.7		ND
22	CGN	M	47	266	102/52	52.0	0.6	0.5		Normal study
23	CGN	M	67	176	135/59	47.8	0.9	1.1		ND
24		As for patient 23			142/66	51.9				
25	CGN	F	41	148	134/84	41.9	0.6	0.6		Normal study
26	CGN	M	43	218	162/99	48.2	0.6	0.7		Normal study
Mean			47	82	144 83	48.0	0.6	0.6		
SEM			3	23	5 4	1.0	0.0	0.0		

Abbreviations: BP, blood pressure; CTR, cardiothoracic ratio; SA, secondary amyloidosis; ND, not done; IMT, intima media thickness of carotid artery; CGN, chronic glomerulonephritis; AR, aortic regurgitation; HHD, hypertensive heart disease; PCKD, polycystic kidney disease; p/s, postsurgery; PDA, patent ductus arteriosus; HD, hemodialysis; MRI, magnetic resonance imaging.

angle obtained from the previously described map. The Gosling pulsatility index (PI), representing an estimate of peripheral vascular resistance in the MCA territory, was calculated from the Doppler spectrum as follows:

PI = (peak systolic velocity – end-diastolic velocity)/VMCA

Arterial blood pressure and pulse rate were simultaneously recorded with an automatic monitoring device (BP-2031; Nippon Colin Co, Komaki, Japan). The mean blood pressure (MBP) was calculated as the sum of diastolic blood pressure and one third of the pulse pressure.

Tilt Test

The 60° head-up tilt test was performed on an automatic tilting table. After 10 minutes of rest, the TCD probe was fixed on the temporal bone above the zygomatic arch with a probe holder (IMP-2; EME Co), and the M1 portion of the MCA was insonated at the depth and direction determined by the previously described map. The blood flow velocity waveform in the MCA was recorded before and after 5 minutes of head-up tilt. Percentage of change ratio of VMCA (%VMCA) was used to analyze the obtained data to neglect

insonated angle. %VMCA was calculated using the following formula:

%VMCA = (VMCA during tilt – VMCA in supine position)/VMCA in supine × 100(%)

The same procedure was repeated after HD.

Carotid Duplex Ultrasonography

The thickness of the intima media layer of the common carotid arteries was measured by duplex ultrasonography (7.5-MHz, SSH-160GH; Toshiba, Tokyo, Japan). Blood flow velocities and cross-sectional areas of the common carotid arteries were measured simultaneously before and after 60° head-up tilt. For estimation of blood flow in the common carotid arteries, we multiplied the time-averaged maximum flow velocity by the cross-sectional area of the common carotid artery.

Cardiac Output Measurement

Cardiac output was measured using the dye-dilution technique (indocyanine green dye, 1 mg) with the cuvette



method (MLC4100&TL-430S, Nihon Kodens, Tokyo, Japan) before and after HD in a dialysis room. Measurement was made through an arteriovenous fistula after 10 minutes of bed rest.<sup>20</sup> Cardiac output was measured at least twice and expressed as CI after correction for body surface area (in liters per minute per square meter).

HD Conditions

All patients underwent a single bicarbonate HD for 4 to 6 hours with cuprophane hollow-fiber dialyzers. The dialysate solution contained sodium, 137 mEq/L; potassium, 2 mEq/L; calcium, 1.31 mmol/L; chloride, 107 mEq/L; and bicarbonate, 29.5 mEq/L. Ultrafiltration was discontinued when blood pressure decreased during HD. In such patients, isotonic saline (100 to 200 mL) was infused until blood pressure returned to the baseline level.

Smoking was prohibited, and antihypertensive medications were withheld on the examination day. Chest radiographs were performed before the dialysis session, and cardiothoracic ratio was calculated.

Blood Sampling

Arterial blood samples were obtained before and after HD for various measurements. These included arterial blood gas analysis (ABL 520; Radiometer, Copenhagen, Denmark); hematocrit (Hct) and hemoglobin (Hb; K-4500; Sysmex Co, Kobe, Japan); fibrinogen (MDA-180 hemostasis system; Organon Teknika, Boxtel, The Netherlands); ionized calcium (EML-100; Radiometer); serum osmolality by the freezing-point depression method (Fiske Os Osmometer; Fiske Associates, Burlington, MA); and whole-blood viscosity of 10, 20, and 50 rpm at 37°C (Biorheolizer; Tokyo Keiki, Tokyo, Japan). Serum chemistry was measured using an autoanalyzer (TBA-80S; Toshiba). Plasma lipoprotein(a) (turbidimetric immunoassay), midportion parathyroid hormone (radioimmunoassay; Yamasu, Choshi, Japan; normal range < 500 pg/mL), and aluminum (atomic absorption analysis; normal range < 10 µg/L) levels were measured before HD.

Arterial oxygen content (CaO<sub>2</sub>) was calculated according to the following formula:

CaO<sub>2</sub>(mL/100mL) = 1.34 × Hb(g/dL) × SaO<sub>2</sub>(%) / 100 + 0.003 × t PaO<sub>2</sub>(mmHg) / 760

where SaO<sub>2</sub> is arterial oxyhemoglobin saturation (%) and PaO<sub>2</sub> is arterial oxygen tension (mm Hg).<sup>21</sup>

Statistical Analysis

Data are presented as mean ± SEM. Comparisons were analyzed using the StatView program (Abacus Concepts, Inc, Berkeley, CA). Student's *t*-test was used for comparison of either paired or unpaired data. Linear regression analysis was used to determine the relationship between two variables. *P* less than 0.05 is considered statistically significant.

RESULTS

Effect of HD

Age and HD duration were not significantly different between DM and non-DM patients by unpaired *t*-test (age, *P* = 0.059; HD duration, *P* = 0.38). The Wechsler Adult Intelligence Scale showed IQ scores of 107 ± 7 in DM and 111 ± 5 in non-DM patients. Brain MRI showed no abnormalities in all but five patients; one patient (no. 4) showed asymptomatic multiple small infarcts in the basal ganglia bilaterally and the white matter, and the other four patients (nos. 6, 10, 15, and 19) had silent small white matter lesions (Table 1A and B).

Blood pressure and cardiothoracic ratio were similar between the two groups, whereas intima media layer of carotid arteries in patients with DM (0.8 ± 0.1 mm) was significantly thicker than in non-DM patients (0.6 ± 0.0 mm; *P* < 0.05). Lipoprotein(a), midportion parathyroid hormone, and aluminum levels were not significantly different between the groups. Effects of HD on various clinical parameters are listed for both groups in Table 2. Reduction in body weight (DM, 1.6 ± 0.2 kg; non-DM, 1.4 ± 0.2 kg) and amount of fluid removed during HD (DM, 2.5 ± 0.2 L; non-DM, 2.3 ± 0.2 L) were similar in both groups. Changes in Hct and total protein values after HD were insignificant in both groups. Plasma fibrinogen levels significantly increased after HD in both groups. Arterial PCO<sub>2</sub> increased significantly after HD in non-DM, but not in DM, patients. Arterial oxygen content did not change after HD in both groups.

Hemodynamics in the Supine Position

Changes in CI, VMCA by three-dimensional mapping technique, and the calculated PI in the supine position are listed in Table 3. There were no significant differences in these parameters between the two groups either before or after HD, except for the value of PI, which was significantly greater in DM patients (*P* < 0.05). The index of blood flow distribution to the MCA territory expressed as the ratio of VMCA to CI (VMCA/CI) before HD was similar between the groups and did not change after HD.

There was no significant correlation between VMCA and Hct in either group before HD or in patients with DM after HD. There was a significant correlation between VMCA and Hct only in

Table 2. Changes in Clinical Parameters After HD in DM and Non-DM Patients

	Non-DM (n = 18)		DM (n = 8)	
	Before HD	After HD	Before HD	After HD
Body weight (kg)	53.8 ± 1.9	52.4 ± 1.8*	52.1 ± 2.3	50.5 ± 2.3*
Hematocrit (%)	28.3 ± 1.3	28.6 ± 1.2	26.4 ± 0.9	26.9 ± 3.2
Fibrinogen (mg/dL)	357 ± 27	378 ± 27†	355 ± 37	404 ± 49*
pH	7.41 ± 0.01	7.50 ± 0.01*	7.41 ± 0.01	7.51 ± 0.01*
PaCO <sub>2</sub> (mm Hg)	38.7 ± 0.8	40.0 ± 0.9†	37.6 ± 0.9	38.0 ± 0.8
CaO <sub>2</sub> (mL/100 mL)	11.1 ± 0.4	11.4 ± 0.4	10.8 ± 0.4	11.5 ± 0.4
Total protein (g/dL)	6.5 ± 0.1	6.7 ± 0.2	6.2 ± 0.2	6.4 ± 0.3
BUN (mg/dL)	57 ± 4	18 ± 1*	57 ± 6	20 ± 1*
Creatinine (mg/dL)	11.0 ± 0.7	3.9 ± 0.2*	9.0 ± 1.0	3.5 ± 0.3*
K (mEq/L)	4.5 ± 0.1	3.4 ± 0.1*	4.5 ± 0.2	3.4 ± 0.1*
Ca <sup>2+</sup> (mmol/L)	1.192 ± 0.036	1.239 ± 0.019	1.186 ± 0.041	1.197 ± 0.032

NOTE. Values expressed as mean ± SEM.  
Abbreviations: PaCO<sub>2</sub>, arterial carbon dioxide tension; CaO<sub>2</sub>, arterial oxygen content; BUN, blood urea nitrogen; Ca<sup>2+</sup>, ionized calcium concentration.  
\**P* < 0.01 versus before HD.  
†*P* < 0.05.

non-DM patients after HD. There was no significant correlation between VMCA and PaCO<sub>2</sub> before or after HD in either group.

Tilt-Induced Changes in Hemodynamic Parameters

Tilt-induced changes in hemodynamic parameters are listed in Table 4.

*Before HD.* The tilt test did not result in clinically evident neurological changes in all subjects. Tilting caused a significant reduction in MBP in patients with DM (decrease of 13 ± 2 mmHg; *P* < 0.01). This was more marked than the effect of tilting in non-DM patients (2 ± 2 mmHg; *P* < 0.01). VMCA decreased significantly in both groups, and %VMCA did not differ significantly between the groups (DM, -12% ± 3% versus non-DM, -12% ± 2%). PI of

the MCA did not change significantly during tilt in either group. The estimated carotid arterial blood flow decreased significantly during tilt in both groups. Percentage of change ratio of the estimated carotid arterial blood flow during tilt did not differ significantly between the groups (DM, -15% ± 6% versus non-DM, -12% ± 5%).

*After HD.* HD did not change MBP, CI, Hct, VMCA, or PI in either group when measured in the supine position. One patient with DM developed syncope during tilt, whereas others did not show clinically evident neurological changes during tilt. In patients with DM, however, MBP during tilt decreased by 36 ± 7 mm Hg, which was significantly greater than that before HD (*P* < 0.05). Tilt also significantly increased the PI of the MCA in patients with DM. In non-DM patients, MBP also significantly decreased by

Table 3. Changes in Hemodynamic Variables in the Supine Position

	Non-DM		DM	
	Before HD	After HD	Before HD	After HD
Cardiac index (L/min/m <sup>2</sup> )	3.69 ± 0.20	3.68 ± 0.12	3.31 ± 0.21	3.46 ± 0.31
VMCA (cm/s)	78 ± 6	77 ± 6	78 ± 5	66 ± 5
PI	0.79 ± 0.05*	0.80 ± 0.06*	1.06 ± 0.06	1.06 ± 0.10
VMCA/CI	22.7 ± 2.2	21.5 ± 1.5	24.3 ± 1.9	20.7 ± 1.6

NOTE. Values expressed as mean ± SEM.  
Abbreviations: VMCA, mean blood flow velocity in middle cerebral artery (MCA); PI, pulsatility index of MCA; VMCA/CI, mean blood flow velocity in the MCA divided by cardiac index as an index of blood distribution to the territory of the middle cerebral artery.  
\**P* < 0.05 versus DM.



Table 4. Tilt-Induced Changes in Blood Pressure, Pulse Rate, and %VMCA

	Non-DM		DM	
	Supine	Tilted	Supine	Tilted
Before HD				
SBP (mm Hg)	144 ± 5	140 ± 5	155 ± 9	129 ± 10*
DBP (mm Hg)	83 ± 4	81 ± 4	82 ± 5	75 ± 3*
MBP (mm Hg)	103 ± 4	101 ± 4	106 ± 6	93 ± 5*
PR	72 ± 2	80 ± 3*	74 ± 2	78 ± 3
ΔMBP		-2 ± 2		-13 ± 2
%VMCA		-12 ± 2		-12 ± 3
After HD				
SBP (mm Hg)	145 ± 6	130 ± 5*	152 ± 5	97 ± 10*
DBP (mm Hg)	85 ± 4	81 ± 4	83 ± 4	56 ± 6*†
MBP (mm Hg)	105 ± 5	97 ± 5*	106 ± 4	70 ± 7*†
PR	74 ± 2	89 ± 4*	76 ± 4	85 ± 6
ΔMBP		-8 ± 3		-36 ± 7
%VMCA		-13 ± 2		-32 ± 5†‡

NOTE. Values expressed as mean ± SEM.

Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure; PR, pulse pressure; %VMCA, percentage of change ratio in VMCA from supine to tilt position.

\* $P < 0.05$  versus supine.

† $P < 0.01$  versus non-DM.

‡ $P < 0.01$  versus before HD.

8 ± 3 mm Hg ( $P < 0.05$ ), but the PI of the MCA did not change during the test. Carotid duplex ultrasonography could not be performed in one patient with DM (no. 4) because of fainting. Percentage of change ratio of the estimated carotid arterial blood flow during tilt did not differ significantly between the groups (DM, -13% ± 15%; [n = 7]; versus non-DM, -11% ± 4%). %VMCA during tilt in patients with DM (-32% ± 5%) was significantly greater than that before HD ( $P < 0.01$ ), and also that in non-DM patients (-13% ± 2%;  $P < 0.01$ ), shown in Fig 1. There was a significant correlation between percentage of change ratio of MBP and %VMCA during tilt after HD in both groups, shown in Fig 2 (DM,  $r = 0.87$ ,  $P < 0.01$ ; non-DM,  $r = 0.61$ ;  $P < 0.01$ ).

There was no significant difference in %VMCA between patients who showed ischemic lesions in MRI and those with normal MRI results in non-DM and DM patients before or after HD. There was a significant correlation between %VMCA and percentage of change in MBP in patients with DM after HD, even in those with normal MRI results ( $r = 0.99$ ;  $P < 0.05$ ).

#### DISCUSSION

Our study showed that cerebral blood flow velocity decreased by passive orthostasis in both DM and non-DM patients by approximately 10%

before HD in the presence of a relative overhydration. However, %VMCA in patients with DM increased threefold after HD compared with both before HD and in non-DM patients. The magnitude of decrease in ratio of cerebral blood flow

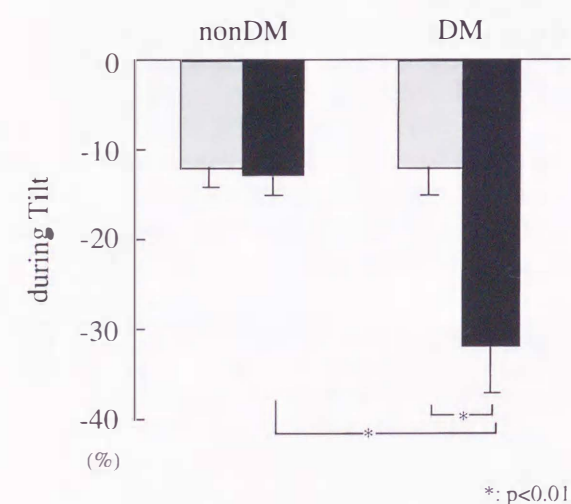


Fig 1. Percentage of change in mean blood flow velocity of the middle cerebral artery (%VMCA) during tilt before and after HD. There were no significant differences in %VMCA between DM and non-DM patients (□) before HD. (■) After HD, percent reduction of VMCA in patients with DM was greater (approximately threefold) than that before HD ( $P < 0.01$ ) and also greater than in non-DM patients after HD ( $P < 0.01$ ).

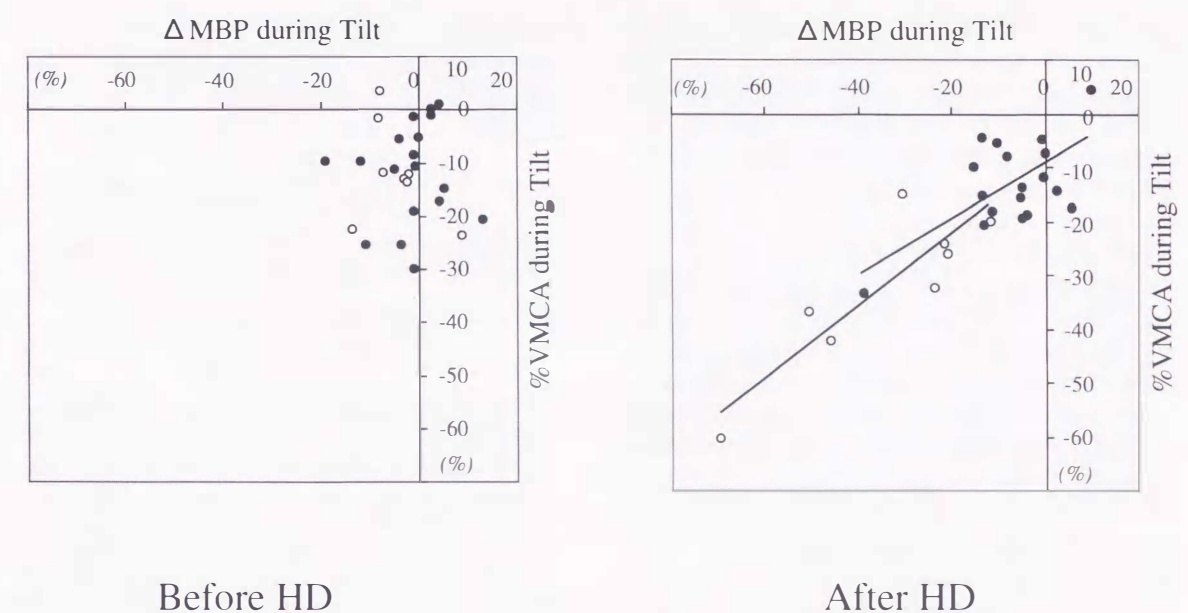


Fig 2. Correlation between percentage of change ratio of MBP (%ΔMBP) and %VMCA during tilt before HD and after HD. (○), DM; (●), non-DM. There was no correlation between %ΔMBP and %VMCA during tilt before HD in either group. There was a significant correlation between %ΔMBP and %VMCA during tilt after HD in both groups (DM,  $r = 0.87$ ,  $P < 0.01$ ; non-DM,  $r = 0.61$ ;  $P < 0.01$ ).

velocity during tilt correlated with the reduction ratio of MBP during tilt in both groups after HD. Cerebral blood flow velocity was apparently blood pressure-dependent after HD in both groups either because of the decrease in MBP to less than the lower limit of cerebral autoregulation or insufficient autoregulatory mechanisms of cerebral circulation. Our results also showed that the intima media layer of carotid arteries in patients with DM was thicker than that in non-DM patients, suggesting atherosclerosis was more advanced in DM than non-DM patients participating in this study.

In healthy subjects, cerebral blood flow is kept constant between an MBP of 50 to 60 and 140 to 150 mm Hg.<sup>22-24</sup> Autoregulatory vessel caliber changes are mediated by an interplay of myogenic mechanisms and chemically induced vasodilatation caused by CO<sub>2</sub>, hydrogen proton, potassium, and adenosine, in addition to neurogenic regulation.<sup>25</sup> Grubb et al<sup>26</sup> and Jørgensen et al<sup>18</sup> reported that the VMCA decreased in parallel with decreases in MBP to less than 83 mm Hg until 50 mm Hg during head-up tilt in healthy subjects. In the current study, however, VMCA decreased significantly in both DM and non-DM patients before HD, and %VMCA during tilt was

similar in the two groups. Although MBP during tilt was considered to be within the range of autoregulation, DM and non-DM patients could not preserve VMCA. Considering the difference between heart-level MBP and brain-level MBP during head-up tilt because of the hydrostatic pressure difference between heart-level and brain-level MBP, brain-level MBP could be less than heart-level MBP. In non-DM patients, MBP did not change during tilt before HD. However, brain-level MBP could have decreased to less than the autoregulatory range of cerebral circulation because of the hydrostatic pressure difference between head and heart levels. This could explain the decrease in VMCA in non-DM patients before HD despite insignificant changes in MBP during tilt. In this regard, Levine et al<sup>27</sup> showed that VMCA decreased in the absence of systemic hypotension during lower-body negative pressure, probably because of sympathetic activation and vasoconstriction. Sympathetic activation would be another explanation of the decrease in VMCA noted in our non-DM patients during tilt before HD. The lack of a significant change in PI during tilt in non-DM patients favors the former explanation. The exact reason for the lack of change in PI of the MCA during



tilt before HD, despite the decrease in flow velocities, is not known at present.

After HD, the decrease in VMCA, as well as in MBP, during tilt was markedly augmented in patients with DM. The profound decrease in VMCA could be caused by a marked increase in PI, shown by Jørgensen et al<sup>18</sup> and Grubb et al.<sup>26</sup> MBP should have decreased to less than the lower limit of the autoregulatory range during tilt, therefore VMCA decreased to a greater extent after HD. In this context, a passive orthostasis without special care might cause hemodynamically mediated ischemic neural damage in patients with DM even when the volume of removed fluid is small. In this study, all patients with DM showed autonomic neuropathy. It is likely that this abnormality might have a significant impact on our findings.

Our results failed to show a correlation between severity of hemodynamic changes and MRI findings. This is probably because of the small number of patients examined in this study.

Our results also failed to show a correlation between Hct and VMCA in either group before HD or in patients with DM after HD, or a correlation between PaCO<sub>2</sub> and VMCA before or after HD in either group. This could be caused by interindividual variability in the diameter of the MCA.

It is known that cerebral arteries with internal diameter greater than 2.5 mm do not significantly change in size by alteration of either blood osmolality or arterial PCO<sub>2</sub>.<sup>28</sup> Jørgensen et al<sup>18</sup> reported that TCD was useful for monitoring cerebral perfusion during tilt. Thus, the use of %VMCA is acceptable for estimation of change in cerebral blood flow in the MCA in the current study.

Arterial CO<sub>2</sub> or end-tidal CO<sub>2</sub> was not measured during the tilt test. This was based on the assumption that only minimal changes in end-tidal CO<sub>2</sub> would occur during tilt. This assumption was based on the results of Blaber et al,<sup>14</sup> who showed that the decrease in CO<sub>2</sub> from supine to 60° head-up tilt was not large enough to cause a significant change in VMCA. Thus, changes in end-tidal CO<sub>2</sub> during tilt are expected to be minimal in our study.

In conclusion, orthostatic hypotension affected brain circulation after HD in proportion to the decrease in MBP. Body position during and

after dialysis should be carefully controlled to reduce the degree of orthostatic hypotension and preserve brain circulation, especially in patients with DM.

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