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

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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 ± 3 years [mean ± SEM]; HD duration, 47 ± 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 ± 3 years; HD duration, 82 ± 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 ± 6 versus 102 ± 4 mm Hg; Hct, 28% ± 1% versus 28% ± 1%; fibrinogen, 355 ± 27 versus 357 ± 27 mg/dL; fluid, 2.5 ± 0.2 versus 2.3 ± 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 ± 3 mm Hg during tilt only in patients with DM. The degree of MBP reduction was -13 ± 2 mm Hg in DM and -2 ± 2 mm Hg in non-DM patients (P < 0.01). VMCA equally decreased during tilt; DM, -13% ± 2%; and non-DM, -12% ± 2%. After HD, MBP decreased by 36 ± 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% ± 5%) was significantly greater than before HD (P < 0.01) and in non-DM patients (-13% ± 2%; P < 0.01). %VMCA positively correlated with the percentage of change ratio of MBP during tilt in both groups after HD, especially in patients with DM.

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.

INDEX WORDS: Cerebral blood flow; hemodialysis (HD); transcranial Doppler (TCD); orthostasis; diabetes mellitus (DM)
Patients and Methods

Patients

Eight patients with DM undergoing HD (six men, two women; age, 57 ± 3 years [mean ± SD]) were recruited for this study. We also studied 11 patients without DM undergoing HD (seven men, four women; 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 four patients were selected from 114 HD patients visiting the outpatient clinic at Fukuoka Kyousi Shoin 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.

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 neurologic deficits were detected on neurological examination. The Wechsler Adult Intelligence Scale was examined to rule 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 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 simple HD session.

Samples were drawn before and after HD. The cardiac index (CI) was determined by the dye-dilution technique before and after HD. Within 15 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. After 5 minutes in the supine position, a map of the circle of Willis and major intracranial arteries was produced by transcranial TCD mapping technique with a 2-MHz transducer (EMCO Co., Überlingen, Germany). Sample volumes were fixed at 6 mm in diameter. The MI portion of the MCA was identified according to the map, usually at a depth of 45 to 55 mm. Mean- and end-diastolic velocities were stored on the hard disk of the computer for later analysis. The VMC(%) was obtained from the time mean of the waveform envelope and corrected according to the insonated angle obtained from the previously described map. The Casting-Chandley index (PCI) representing an estimate of perpendicular vascular resistance in the MCA territory, was calculated from the Doppler spectrum as follows:

\[ PCI = \left( \frac{1}{4} \times \text{peak systolic velocity} \right) \times \left( \frac{1}{4} \times \text{end-diastolic velocity} \right) \times \text{VMCA} \]

VMCA was calculated using the following formula:

\[ \text{VMCA} = \text{VMCA during tilt} \times \left( \frac{1}{\text{VMCA in supine position}} \right) \]

The same procedure was repeated after HD.

Cardiac Doppler Ultrasonography

The thickness of the intima media layer of the common carotid arteries was measured by duplex ultrasonography (7.5-MHz, SLE-10: Hodol, Tokyo, Japan). Blood flow velocities and cross-sectional areas of the common carotid arteries were measured simultaneously before and after HD.

Tilt Test

The tilt head-up 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, Tokyo, Japan). The MI portion of the MCA was monitored 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 (SVMCA) was used to analyze the obtained data to neglect

<table>
<thead>
<tr>
<th>Patient</th>
<th>Original Disease</th>
<th>Sex</th>
<th>Age (y)</th>
<th>HD Duration (mo)</th>
<th>BP (mm Hg)</th>
<th>CI (%)</th>
<th>Right (mm)</th>
<th>Left (mm)</th>
<th>Cardiac Disease</th>
<th>Brain MRI</th>
<th>Neuraphy</th>
<th>Orthostatic Hypertension</th>
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<td>165/83</td>
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<td>155/82</td>
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</table>

Legend: BP = blood pressure; CI = cardiothoracic ratio; HHD = hypertension; HLD = hemodialysis; MRI = magnetic resonance imaging.
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 asymmetric 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 thickness 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 albumin 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, 2.2 ± 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 PCO2 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 VMCA(CA) 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 no significant correlation between VMCA and Hct only in non-DM patients after HD. There was no significant correlation between VMCA and Pco2 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. Tilt-induced changes were insignificant in both groups. MBP also significantly decreased by 0.019 ± 0.041 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, -0.15% ± 0.5% vs non-DM, -0.12% ± 0.5%). 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 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: MBP did not change significantly in either group. The tilt test did not result in clinically evident neurological changes in all subjects. There was no significant difference between the groups. MBP did not change significantly during tilt in both groups. There was no significant difference between the groups. MBP did not change significantly during tilt in both groups. There were no significant differences between the groups. MBP did not change significantly during tilt in both groups. There were no significant differences between the groups. MBP did not change significantly during tilt in both groups. There were no significant differences between the groups. MBP did not change significantly during tilt in both groups.
SEVERE DECREASE IN FLOW VELOCITY AT TILT AFTER HD IN DM

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

<table>
<thead>
<tr>
<th></th>
<th>SBP (mm Hg)</th>
<th>DBP (mm Hg)</th>
<th>MBP (mm Hg)</th>
<th>PR</th>
<th>%VMCA</th>
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<td>Non-DM</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before HD</td>
<td>144 ± 5</td>
<td>83 ± 4</td>
<td>103 ± 4</td>
<td>72 ± 2</td>
<td>8 ± 3</td>
</tr>
<tr>
<td>Tilted</td>
<td>140 ± 5</td>
<td>81 ± 4</td>
<td>101 ± 4</td>
<td>74 ± 2</td>
<td>-13 ± 2</td>
</tr>
<tr>
<td>DM</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before HD</td>
<td>145 ± 6</td>
<td>86 ± 4</td>
<td>106 ± 5</td>
<td>74 ± 2</td>
<td>13 ± 2</td>
</tr>
<tr>
<td>Tilted</td>
<td>130 ± 5</td>
<td>89 ± 4</td>
<td>97 ± 5</td>
<td>76 ± 4</td>
<td>-36 ± 7</td>
</tr>
</tbody>
</table>

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.

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 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.22-24 Autoregulatory vessel caliber changes are mediated by an interplay of myogenic mechanisms and chemically induced vasodilatation caused by CO2, hydrogen proton, potassium, and adenosine, in addition to neurogenic regulation.25 Grubb et al26 and Jorgensen et al27 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 less than the autoregulatory range of cerebral circulation because of the hydrostatic pressure difference between head and brain levels. This could explain the decrease in VMCA in non-DM patients before HD despite insignificant changes in MBP during tilt in this study. Levine et al28 showed that VMCA decreased in the absence of systemic hypotension during lower-body negative pressure, probably because of sympathetic activation and vasconstrictor. 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
severe decrease in flow velocity at tilt after HD in DM

Tilt before HD, despite the decrease in flow velocities, is not known at present. After HD, the decrease in VMCA, as well as in MBF, 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.19,20 and Grubh et al.14. MBF 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 patents 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 YMCA in either group before HD or in patients with DM after HD, or a correlation between PaCO2 and YMCA before or after HD. 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 osmolarity or arterial PCO2.21 Jørgensen et al.21 reported that TCD was useful for monitoring cerebral blood flow in the MCA in the current study. Thus, the use of TCD is acceptable for estimation of change in cerebral blood flow in the MCA in the current study.

Arterial CO2 or end-tidal CO2 was not measured during the tilt test. This was based on the assumption that only minimal changes in end-tidal CO2 would occur during tilt. This assumption was based on the results of Blaber et al.14 who showed that the decrease in CO2 from supine to 60° head-up tilt was not large enough to cause a significant change in VMCA. Thus, changes in end-tidal CO2 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.

Acknowledgment

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References
