Detection of Postural Cerebral Hypoperfusion with Technetium-99m-HMPAO Brain SPECT in Patients with Cerebrovascular Disease

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Seventeen of 19 patients (67 ± 8 yr, 17 males and 2 females) had more than 75% unilateral stenosis or occlusion of the internal carotid or middle cerebral artery and two patients had carotid endarterectomy that previously had 90% stenosis of the internal carotid artery. They were studied during upright ^{99m}Tc-HMPAO brain SPECT. HMPA was injected immediately after arising from a supine position. Patients were classified into Group A (n = 10) with occlusion of the internal carotid or the middle cerebral artery or Group B (n = 9) with more than 75% unilateral stenosis of the internal carotid or the middle cerebral artery and with carotid endarterectomy. Additional cerebral blood flow perfusion abnormalities between upright and supine ^{99m}Tc-HMPAO brain SPECT were detected in seven patients in Group A and in only one patient in Group B. Semiquantitative analysis showed that the asymmetric ratios between upright and supine positions changed significantly in Group A from 0.82 ± 0.15 to 0.89 ± 0.10 ($p < 0.01$), but not in Group B, from 0.89 ± 0.11 to 0.92 ± 0.12 (ns). Additional perfusion abnormalities were relevant to occlusion of the internal carotid or middle cerebral artery indicated postural cerebral hypoperfusion. We conclude that upright ^{99m}Tc-HMPAO brain SPECT visualizes postural cerebral hypoperfusion possibly related to silent cerebral ischemia.

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Postural cerebral hypoperfusion is defined as a phenomenon that can lead to transient neurologic deficits during postural change (*1*) with or without significant postural hypotension (*2*). This phenomenon might precede cerebral infarction but would be silent, thus rendering it difficult to detect since there could be local vasodilation distal to the vascular compromise. Thus, stressed rather than resting cerebral blood flow (CBF) measurements have been recommended to visualize vascular flow abnormalities using acetazolamide or carbon dioxide reactivity in patients with cerebrovascular disease (*3*).

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Rapid conversion from the lipophilic to the hypolipophilic form (*4*) that deposits technetium-99m-hexamethylpropyleneamine oxime (^{99m}Tc-HMPAO) in the brain (*5,6*) reveals a "snapshot" of the cerebral perfusion image at the moment of radiopharmaceutical administration. The stress test using ^{99m}Tc-HMPAO is appropriate as a decreased CBF test to avoid ischemic brain damage because it induces only a short CBF change such as that of the Wada test (*7*), vasospasm detection (*8*) and posture-dependent CBF determination in a patient with aortitits (*9*). The upright test induces decreased cerebral perfusion pressure within a physiological range probably resulting from the upgrading of autoregulation in CBF. We applied the upright stress test with ^{99m}Tc-HMPAO brain SPECT on patients with cerebrovascular disease to detect postural cerebral hypoperfusion possibly related to silent cerebral ischemia.

METHOD AND MATERIALS

Upright Test with ^{99m}Tc-HMPAO Brain SPECT

After inserting a flexible plastic needle into the antecubital vein, the patients lay on a couch in a quiet and dimly lit room with their legs elevated (Fig. 1). Systolic blood pressure was measured in the supine position just before the upright test. At labeling of ^{99m}Tc-HMPAO, ^{99m}Tc-pertechnetate was added to a nonradioactive kit (Ceretec, Amersham, Tokyo) and gently stirred using a long needle and a three-way stopcock in order to minimize the loss in lipophilic fraction over time from labeling just before the upright test. After being recumbent for 15–30 min, the patient was instructed to move from the supine to a standing position in about 3 sec, with assistance if necessary. At initiation of the upright test, the patient was injected with 370 MBq of ^{99m}Tc-HMPAO in a bolus and flushed with 20 ml of saline. The patient remained standing for 2 min to complete ^{99m}Tc-HMPAO fixation in the brain during the injection. Systolic blood pressure in the standing position was also measured; the difference in the systolic blood pressure between the upright and supine positions was then recorded. The patient was then moved to the SPECT room to initiate the first SPECT scan. Thereafter, another 481 MBq of ^{99m}Tc-HMPAO was administered while the patient remained on the SPECT bed. Systolic blood pressure in the supine position was also measured. Technetium-99m-HMPAO brain SPECT scans were obtained with a conventional rotating gamma camera

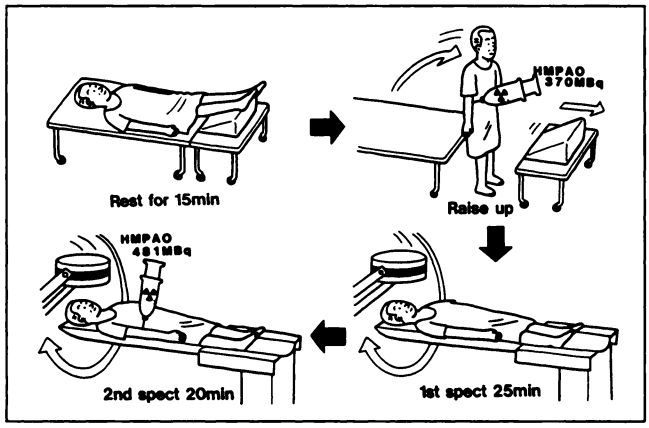

FIGURE 1. Procedure for upright stress test.

(STARCAM, 400AC/T, General Electric Co., Milwaukee, WI) with 12 mm full width at half-maximum (FWHM) obtained from 64 steps of 20-sec and 15-sec acquisitions in the first and second scans, respectively, onto a 64 × 64 matrix using a general, all-purpose collimator. Scans were also obtained using a ring-type gamma camera (Headtome SET 070, Shimadzu Co, Kyoto) with an 8-mm FWHM for a 20-min acquisition for both the first and second scan times. Images were acquired onto a 128 × 128 matrix using a general all-purpose collimator. During each acquisition, the patient was firmly secured to the headrest by a restraint and the head position was monitored by aligning with reference points to facilitate comparisons between upright and supine brain SPECT images. All data were corrected for an attenuation of 0.11 cm^{-1} and the tomographic data were reconstructed using a filtered backprojection algorithm. Hence, transaxial slices of 6 and 5 mm in thickness were obtained with the rotating and ring-type gamma cameras, respectively. Upon visual inspection, an additional perfusion abnormality (APA) of the CBF comparing the upright and supine ^{99m}Tc-HMPAO images was determined. For semiquantitative analysis, regions of interest (ROIs) were manually drawn on a transverse slice of the involved and contralateral areas at the matched contralateral side, and the mean count rate per voxel was estimated in each ROI. The asymmetric ratio was then calculated as the ratio of the counts in the involved area-to-the contralateral area (Fig. 2).

Informed consent was obtained from the 19 patients (age 67 ± 8 yr, 17 males and 2 females) participating in the study. Twelve patients had unilateral occlusion (ICO) or >75% unilateral stenosis of the internal carotid artery (ICS) (eight with ICO, two with 99% ICS, one with 90% ICS and one with 75% ICS). Five patients had unilateral occlusion (MCO) or >75% unilateral stenosis of the middle cerebral artery (MCS) (two with MCO, one with 90% MCS and two with 75% MCS) and two patients with carotid endarterectomy who previously had 90% ICS. Patients were classified into two groups: Group A (n = 10), with angiographic occlusion of the internal carotid or the middle cerebral artery and Group B (n = 9), with more than 75% stenosis of the internal carotid or the middle cerebral artery and carotid endarterectomy. The clinical profiles including symptoms and low density areas in x-ray computed tomography are listed in Table 1.

All results were expressed as mean ± s.d. The significance of differences was calculated using the paired t-test for comparison between upright and supine ^{99m}Tc-HMPAO brain SPECT and the unpaired t-test for comparison between Groups A and B. A significant difference between Groups A and B was the appearance of APA in low density areas on CT scans and transient ischemic attack (TIA) symptoms estimated by the chi-square test. A p value of <0.05 was considered to be significant.

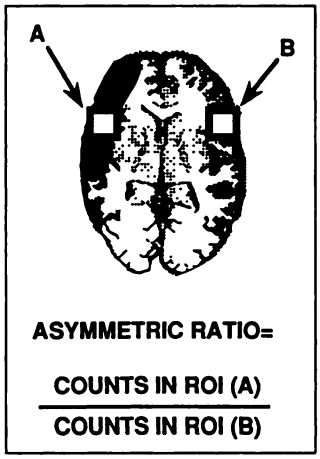

FIGURE 2. Calculation of asymmetric ratio between upright and supine ^{99m}Tc-HMPAO brain SPECT. (A = ROI in the involved area; B = ROI in the contralateral area.)

RESULTS

All upright tests with ^{99m}Tc-HMPAO brain SPECT were conducted with no complications. APA was visually determined in seven patients in Group A and in only one patient in Group B. Semiquantitatively, the asymmetric ratios between upright and supine positions changed significantly in Group A, from 0.82 ± 0.15 to 0.89 ± 0.10 ($p < 0.01$), but not in Group B, from 0.89 ± 0.11 to 0.92 ± 0.12 (ns) (Fig. 3). The appearance of APA on upright ^{99m}Tc-HMPAO brain SPECT differed between Groups A and B ($p < 0.001$). The systolic blood pressure also changed significantly during the upright test between Groups A and B ($p < 0.05$) being 15.8 ± 8.1 mmHg and 7.8 ± 5.9 mmHg, respectively. The systolic blood pressure measured at the time of the injection for the second SPECT returned to that of the supine level just before the upright test. However, there was no significance between Groups A and B in appearance of LDA in CT or TIA symptoms.

Patients 1, 6 and 11 (Table 1) are presented in detail. Patient 1 is a 60-yr-old male with no neurological deficit. However, 99% stenosis in the left internal carotid artery was found incidentally after follow-up angiography of a postcoronary artery bypass. CT revealed no LDA. The blood pressure fall during the upright test was 10 mmHg. Upright ^{99m}Tc-HMPAO brain SPECT showed decreased activity in the left fronto-parietal area, and subsequent supine ^{99m}Tc-HMPAO brain SPECT revealed filling in the left fronto-parietal area (Fig. 4). Patient 6 is a 62-yr-old male with mild left hemiparesis. Six months previously, he had undergone replacement of a syphilitic thoracic aortic aneurysm, during which the left subclavian artery was ligated because preoperative angiography revealed occlusion of the left common carotid artery. After surgery, he complained of mild hemiparesis and amaurosis fugax. CT revealed LDA in the right corona radiata but not in the frontal area. The blood pressure fall during the upright test was 10 mmHg. Upright ^{99m}Tc-HMPAO brain SPECT

TABLE 1
Patient Symptoms and Clinical Profiles

Patient no.	Age	Sex	Symptom	Lesion in CT	Stenosis	Upright*	Supine*	APA	Comments
1	62	M	L-mild hemiparesis	R-corona radiata	R-IC 100%	130	140	(+)	TAA p.o.
2	59	M	(−)	B-basal ganglia	R-IC 100%	158	164	(+)	AAA p.o.
3	85	M	orthostatic hypotension	R-parietal	R-IC 100%	98	132	(+)	
4	66	F	L-mild hemiparesis	R-corona radiata	R-IC 100%	112	130	(+)	
5	62	M	TIA	(−)	R-IC 100%	126	138	(+)	
6	77	M	dysarthria	L-frontal	L-IC 100%	150	160	(+)	subacute CI
7	66	M	dysarthria	R-occipital	L-IC 100%	128	138	(−)	HT
8	70	M	(−)	(−)	L-IC 100%	148	168	(−)	
9	48	M	(−)	R-corona radiata	R-MC 100%	106	124	(+)	
10	66	M	TIA	(−)	L-MC 100%	120	140	(−)	
11	60	M	(−)	(−)	L-IC 99%	122	132	(+)	CABG p.o.
12	77	M	TIA	L-corona radiata	L-IC 99%	130	140	(−)	
13	63	M	dysarthria	L-corona radiata	L-IC 99%	144	146	(−)	HT
14	64	M	(−)	L-thalamus	L-MC 90%	158	162	(−)	HT
15	74	F	(−)	R-parietal	L-IC 75%	114	124	(−)	AAA, HT
16	62	M	TIA	B-corona radiata	L-MC 75%	134	136	(−)	HT
17	73	M	TIA	L-frontal	L-MC 75%	136	140	(−)	HT
18	72	M	(−)	brain atrophy	0%	148	160	(−)	CEA p.o.
19	66	M	dysarthria	B-basal ganglia	0%	134	140	(−)	CEA p.o.

*Upright systolic blood pressure during upright test (mmHg) and supine is systolic blood pressure during supine test (mmHg).

AAA = abdominal aortic aneurysm; APA = additional perfusion abnormality; B = bilateral; BP = systolic blood pressure; CABG = coronary arterial bypass graft; CEA = carotid endarterectomy; CI = cerebral infarction; CT = computed tomography; HT = hypertension; IC = internal carotid artery; L = left; MC = middle cerebral artery; TAA = thoracic aortic aneurysm; TIA = transient ischemic attack; p.o. = postoperative state; and R = right.

showed decreased activity in the left fronto-parietal area, and subsequent supine ^{99m}Tc-HMPAO brain SPECT showed filling of only the left frontal area (Fig. 5). Patient 11 is a 77-yr-old male with left cerebral infarction caused by left internal carotid arterial occlusion symptomatized by mild hemiparesis. The upright test was performed on Day 15, from a supine to a sitting position instead of standing, because of the subacute phase. The blood pressure drop during the upright test was 10 mmHg. Upright ^{99m}Tc-HMPAO brain SPECT revealed decreased activity in the bilateral frontal area and masked the normal activity in the left fronto-temporal area where CT had shown previous LDA. Subsequent supine ^{99m}Tc-HMPAO brain SPECT revealed filling in the right frontal area and excessively increased activity in the masked normal area in the left fronto-temporal region (Fig. 6). However, because of the

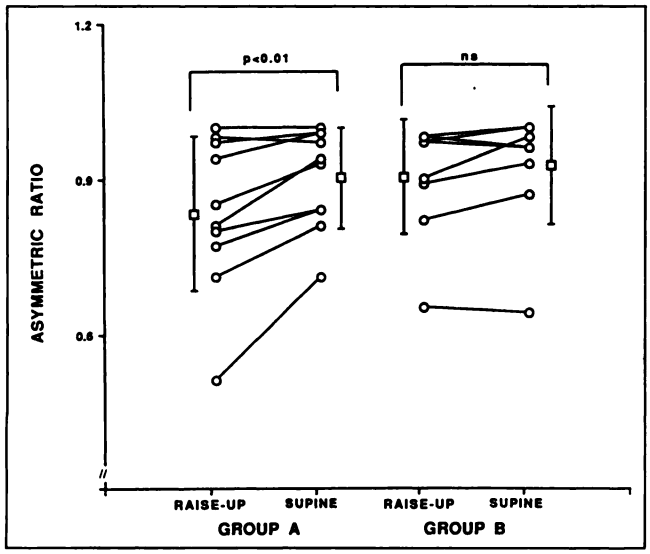

FIGURE 3. Asymmetric ratio between upright and supine ^{99m}Tc-HMPAO brain SPECT in Groups A and B. (Raise-Up = asymmetric ratio at upright ^{99m}Tc-HMPAO brain SPECT; Supine = asymmetric ratio at supine ^{99m}Tc-HMPAO brain SPECT; Group A = patients with occlusions and Group B = patients with more than 75% stenosis and those with carotid endarterectomy.

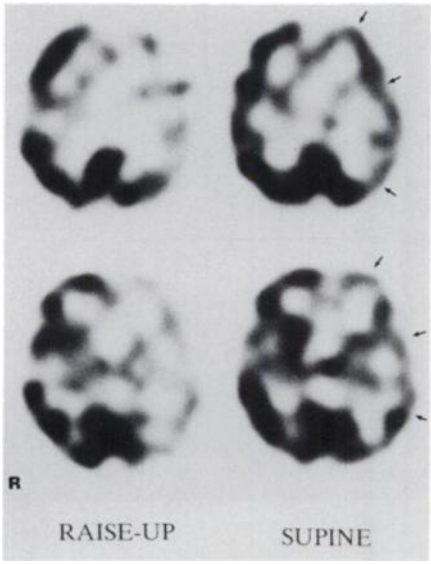

FIGURE 4. Patient 1 with 99% stenosis in the left internal carotid artery. Upright ^{99m}Tc-HMPAO brain SPECT shows decreased activity in the left fronto-parietal area. Subsequent supine ^{99m}Tc-HMPAO brain SPECT shows filling in the left fronto-parietal area (↑). The blood pressure drop during the upright test was 10 mmHg. (R = right, Raise-up = upright ^{99m}Tc-HMPAO brain SPECT, Supine = Supine ^{99m}Tc-HMPAO brain SPECT.)

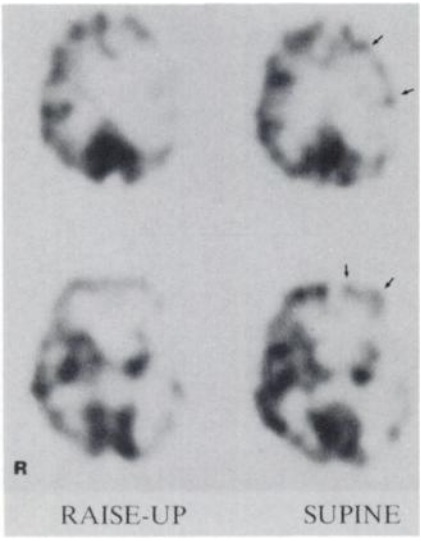

FIGURE 5. Patient 6 with left internal carotid arterial occlusion. Upright ^{99m}Tc-HMPAO brain SPECT shows decreased activity in the left fronto-parietal area. Subsequent supine ^{99m}Tc-HMPAO brain SPECT shows filling of the left frontal area (↑). The blood pressure fell during the upright test by 10 mmHg. (Abbreviations same as in Fig. 3.)

left frontal hypoperfusion, the asymmetric ratio of the right frontal-to-the right parietal area changed from 0.7 to 0.8 and the asymmetric ratio of the left fronto-temporal-to-the right parietal area increased from 1.0 to 1.3.

DISCUSSION

Nineteen patients with more than 75% unilateral stenosis or occlusion of the internal carotid artery (n = 12), or middle cerebral artery (n = 5) and carotid endarterectomy (n = 2) were studied. A comparison of upright and supine SPECT of images reveal, that seven patients in Group A (70%) with occlusion of the internal carotid or middle cerebral artery and one in Group B (11.1%) showed positive APA. This shows that postural cerebral hypoperfusion would be undetectable if CBF was assessed only in the supine position. We detected silent cerebral ischemia in Patient 1, silent cerebral ischemia around cerebral infarction in Patient 6 and silent cerebral ischemia that extended to the contralateral site in Patient 11 with upright ^{99m}Tc-HMPAO brain SPECT. Semiquantitatively, the asymmetric ratio also changed significantly between the upright and the supine test in Group A, but not in Group B. Sixty-three percent of arterial stenosis is said to initiate a decrease in blood flow (*10*). However, even in patients having 75%–90% arterial stenosis, upright ^{99m}Tc-HMPAO brain SPECT could not detect APA. This was perhaps due to the collateral intervention and the detection accuracy of the SPECT machines in distinguishing the hypoperfused areas from those perfused normally.

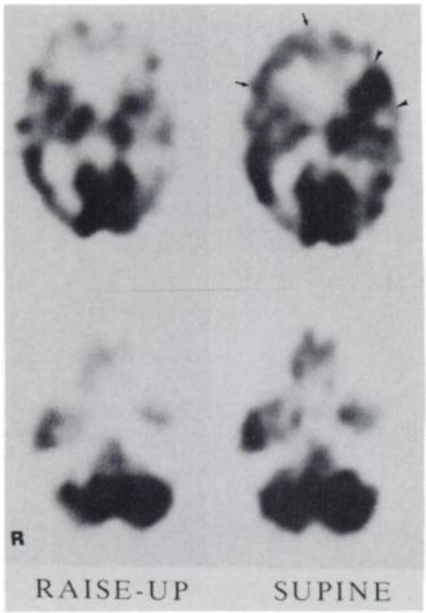

FIGURE 6. Patient 11: subacute left cerebral infarction with left internal carotid arterial occlusion. On Day 15, upright ^{99m}Tc-HMPAO brain SPECT shows decreased activity in the bilateral frontal area and apparently normal activity in the left fronto-temporal area. Subsequent supine ^{99m}Tc-HMPAO brain SPECT shows filling of the right frontal area (↑) and excessively increased activity in the apparently normal area of the left fronto-temporal region (→). The blood pressure drop during the test was 10 mmHg. (Abbreviations same as in Fig. 3.)

We assumed that the hemodynamics, which determined the severity of cerebral ischemia, in cerebrovascular disease might differ according to posture change. We found that a patient with aortitis who complained of fainting and had occlusion of the carotid arteries showed a posture-dependent difference in CBF with ^{99m}Tc-HMPAO brain SPECT. The inhomogeneous distribution of CBF resulted from an altered response to the change in cerebral perfusion pressure, probably indicating inadequate autoregulatory function (*9*). Two patients with carotid endarterectomy did not show this phenomenon. CBF is autoregulated extremely well between pressure limits of 60 and 140 mmHg in the supine position (*11*). Because CBF decreases below the control of autoregulation, cerebral blood volume will increase to maintain metabolism (*12*). The upright test with ^{99m}Tc-HMPAO brain SPECT might contribute to shifting the lower threshold of autoregulation upward (*13*). Patient 11 with subacute cerebral infarction had a luxury perfused area, as shown later in a PET steady-state gas study. This area had excessively increased blood flow in the supine position compared with upright ^{99m}Tc-HMPAO brain SPECT. We determined that the cerebral perfusion pressure of the luxury perfused area, which had abundant cerebral flow in supine position, was low.

When an individual stands up, blood pressure drops due to a physiological response. After the baroreceptor system identifies this event, blood pressure will be resumed within minutes via nervous and humoral pathways such as noradrenalin excretion (*1*). The short-term circulatory adaptation to the upright position has been arbitrarily divided into an initial phase (first 30 sec) with marked changes in heart rate and blood pressure of as much as a 30-mmHg drop and an early steady-state response (after standing 1–2 min) of as much as a 10 mmHg drop (*14,15*). One problem with a single blood pressure measurement is that the beat-beat fluctuations cannot be recognized, especially during a shift to an upright posture. Nevertheless, a conventional sphygmomanometer is accurate enough for a routine clinical assessment of blood pressure adjustment to the standing position (*16*). The bolus injection of ^{99m}Tc-HMPAO reached the brain parenchyma within 30 sec of the initial phase of the short-term circulatory adaptation since the circulation time between the peripheral and cerebral veins via the parenchyma is less than 30 sec, during which radi-

onuclide angiography can cover the venous phase of cerebral circulation (*17*). This is based upon the assumption that the radiopharmaceutical reached the circulatory imbalance before the sympathetic or humoral reaction acted to restore the blood pressure. We found that the blood pressure drop in Group A was larger than that in Group B, but was rather low as an initial phase response. We may have been measuring blood pressure during the early steady-state rather than at the initial phase. However, a poor correlation has previously been reported between postural blood pressure decreases and symptoms, which illustrates the inability of blood pressure changes to reflect similar changes in cerebral perfusion (*2*). However, the blood pressure drop in the cerebral vessel might be more effective in severely stenotic areas because cerebral perfusion pressure should have the hydrostatic pressure subtracted from the blood pressure at the upper arm, where our measurements were taken.

Among our population of patients, there was no significant differences between Groups A and B in the appearance of low density areas in CT and TIA symptoms. Hemodynamic cerebral infarction is thought to cause cerebral derangement in patients who have a significantly stenotic area in their cerebral vasculature (*18*). APA in the upright ^{99m}Tc-HMPAO brain SPECT were represented as postural cerebral hypoperfusion which might be an initial stage of silent cerebral ischemia preceding structural imprinting or the onset of symptoms. The number of elderly patients who have orthostatic hypotension has increased (*19*), which may be derived from vascular stenosis or a delayed autonomic nervous response to restore the blood pressure according to postural changes. Upright ^{99m}Tc-HMPAO brain SPECT is a simple and safe physiological test which does not require drugs and can even be used for elderly patients with cerebrovascular disease caused by a decrease in blood pressure within physiological ranges. We conclude that upright ^{99m}Tc-HMPAO brain SPECT visualizes postural cerebral hypoperfusion which may be related to silent cerebral ischemia.

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