WAIS-R performance IQ, 4.7 ± 6.1 on the WMS, 0.4 ± 1.1 in the Rey copy, and 2.9 ± 3.5 on the Rey recall.[22]

Data are expressed as the mean ± SD. Differences or incidences of each variable between older patients and younger patients were evaluated using the Mann-Whitney *U* test or the χ^2 test. To evaluate the inter-observer (neurosurgeon and patient's next of kin) agreement of the subjective assessment of postoperative changes in cognition of patients, the proportion of concordant assessments was calculated as the number of concordant assessments divided by the number of assessments by the neurosurgeon and/or the patient's next of kin. Differences or incidences of each variable among three groups with subjectively improved, unchanged, or impaired cognition were evaluated using the Scheffe's F test or the χ^2 test followed by Bonferroni's inequality correction. Changes between preoperative and postoperative neuropsychological scores were evaluated using the Wilcoxon signed-rank test. Differences were deemed significant for values of $p < 0.05$. The accuracy of the Δ score in each neuropsychological test for the detection of subjective improvement and impairment in cognition after surgery was assessed using receiver operating characteristic (ROC) curves. The ROC curve was calculated in increments and decrements of 0.5 SD from the mean value of the Δ score obtained in normal subjects.

Results

Of the 39 older patients who satisfied the inclusion criteria, 2 did not undergo postoperative neuropsychological testing and were excluded from the analysis. Thus, 37 patients were evaluated in the present study.

Table 1 compares the clinical characteristics of the older patients and the younger patients. The incidences of hyperlipidemia, symptomatic lesion, and infarction on preoperative MR imaging were significantly greater in older patients than in younger patients. Further, the incidence of modified Rankin disability scale of zero and duration of ICA clamping were significantly lower in older patients than in younger patients. The incidences of cerebral hyperperfusion or new ischemic lesions on diffusion-weighted imaging after surgery were similar in the two groups.

Table 2 shows the inter-observer agreement for the subjective assessment of postoperative change in cognition in older patients. Assessments by the neurosurgeon tended to be more favorable (i.e., better levels of cognition) compared with assessments by the patient's next of kin. The concordance rate for the subgroup of patients who were assessed as postoperatively improved, unchanged, or impaired cognition by the neurosurgeon and/or the patient's

Table 2 Inter-observer agreement of subjective assessment of postoperative change in cognition in older patients

Assessment by neurosurgeon		Assessment by patient's next of kin	
Postoperative change in cognition	Number of patients	Postoperative change in cognition	Number of patients
Improved	5	Improved	4
		Unchanged	1
		Impaired	0
Unchanged	27	Improved	0
		Unchanged	24
		Impaired	3
Impaired	5	Improved	0
		Unchanged	0
		Impaired	5

Table 1 Clinical characteristics of older and younger patients

	≥76 years old (n = 37)	<76 years old (n = 213)[22]	p Value
Age (mean ± SD), yrs	78.4±2.2	68.1±5.8	<0.0001
Male	89% (33/37)	93% (198/213)	NS
Hypertension	84% (31/37)	74% (157/213)	NS
Diabetes mellitus	24% (9/37)	33% (71/213)	NS
Hyperlipidemia	49% (18/37)	23% (50/213)	0.0025
Modified Rankin disability scale of zero	8% (3/37)	69% (146/213)	<0.0001
Symptomatic lesion	100% (37/37)	65% (138/213)	0.0005
Infarction on preoperative MR imaging	84% (31/37)	49% (105/213)	<0.0001
Duration of ICA clamping (mean ± SD), min	31.6±5.8	35.1±6.3	0.0111
Postoperative hyperperfusion	11% (4/37)	13% (28/213)	NS
New ischemic lesions on postoperative DWI	11% (4/37)	14% (30/213)	NS

ICA: internal carotid artery, DWI: diffusion-weighted imaging, MR: magnetic resonance, NS: not significant, SD: standard deviation.

Table 3 Comparison of clinical characteristics of older patients, stratified by changes in cognition

	Group			p Value		
	A: Improved cognition (n = 4)	B: Unchanged cognition (n = 28)	C: Impaired cognition (n = 5)	A vs. B	B vs. C	C vs. A
Age (mean ± SD), yrs	79.0±1.8	78.4±2.2	78.2±2.3	NS	NS	NS
Male	75% (3/4)	93% (26/28)	80% (4/5)	NS	NS	NS
Hypertension	100% (4/4)	82% (23/28)	80% (4/5)	NS	NS	NS
Diabetes mellitus	50% (2/4)	18% (5/28)	40% (2/5)	NS	NS	NS
Hyperlipidemia	25% (1/4)	50% (14/28)	60% (3/5)	NS	NS	NS
Modified Rankin disability scale of zero	25% (1/4)	4% (1/28)	20% (1/5)	NS	NS	NS
Symptomatic lesion	100% (4/4)	100% (28/28)	100% (5/5)	NS	NS	NS
Infarction on preoperative MR imaging	50% (2/4)	86% (24/28)	100% (5/5)	NS	NS	NS
Duration of ICA clamping (mean ± SD), min	31.8±7.0	31.9±6.0	29.8±5.1	NS	NS	NS
Postoperative hyperperfusion	0 (0%)	0 (0%)	4 (80%)	NS	0.0001	0.0147
New ischemic lesions on postoperative DWI	1 (25%)	3 (11%)	0 (0%)	NS	NS	NS

ICA: internal carotid artery, DWI: diffusion-weighted imaging, MR: magnetic resonance, NS: not significant, SD: standard deviation.

next of kin was 0.80 (4/5), 0.86 (24/28), or 0.63 (5/8), respectively. Thus, 4 (11%), 28 (75%), and 5 (14%) patients were defined as having subjectively improved, unchanged, and impaired cognition, respectively, after surgery. These incidences did not differ when comparing these older patients with the younger patients (subjectively improved cognition, 11%; subjectively unchanged cognition, 78%; subjectively impaired cognition, 11%).[22]

Table 3 shows clinical characteristics of older patients with subjectively improved, unchanged, or impaired cognition. The incidence of postoperative cerebral hyperperfusion was significantly greater in patients with subjectively impaired cognition after surgery than in those with subjectively improved or unchanged cognition. Other variables, including new ischemic lesions on postoperative diffusion-weighted imaging and duration of ICA clamping, did not differ between patients with subjectively improved, unchanged, or impaired cognition.

Results from the five neuropsychological tests conducted before and after CEA in older patients are summarized in Table 4. All tests scores were unchanged after surgery. Table 5 shows the Δ score for each neuropsychological test in the older and the younger patients. The Δ scores in all neuropsychological tests were significantly less in the older patients than in the younger patients. Figure 1 shows the relationship between the subjective assessment of postoperative change in cognition and the Δ score for each neuropsychological test in the older patients. In all neuropsychological tests, the Δ score statistically differentiated patients with subjectively improved, unchanged, and impaired cognition after surgery.

Table 4 Neuropsychological test scores before and after surgery in older patients

Test	Before surgery	After surgery	p Value
WAIS-R verbal IQ	82.7±10.4	82.9±11.8	NS
WAIS-R performance IQ	85.9±11.4	86.8±12.1	NS
WMS	86.5±12.6	86.4±15.0	NS
Rey copy	32.3±3.8	31.9±4.4	NS
Rey recall	20.1±7.2	20.5±7.9	NS

Values are expressed as mean ± standard deviation. IQ: intelligence quotient, NS: not significant, Rey copy: Rey-Osterreith Complex Figure test (Rey test) copy, Rey recall: Rey test recall, WAIS-R: Wechsler Adult Intelligence Scale-Revised, WMS: Wechsler Memory Scale.

Table 5 Comparison of Δ scores for each neuropsychological test in older and younger patients

Test	≥76 years (n = 37)	<76 years (n = 213)[22]	p Value
WAIS-R verbal IQ	0.2±4.5	3.7±6.3	0.0005
WAIS-R performance IQ	0.9±5.3	4.6±7.2	0.0013
WMS	−0.1±6.5	3.7±8.1	0.0013
Rey copy	−0.5±1.6	0.7±2.1	0.0100
Rey recall	0.4±3.2	2.4±4.5	0.0043

Values are expressed as mean ± standard deviation. IQ: intelligence quotient, Rey copy: Rey-Osterreith Complex Figure test (Rey test) copy, Rey recall: Rey test recall, WAIS-R: Wechsler Adult Intelligence Scale-Revised, WMS: Wechsler Memory Scale.

Sensitivity, specificity, and positive- and negative-predictive values for the Δ score for each neuropsychological test at the cut-off point lying closest to the left upper corner of the ROC curve for the detection of subjective improvement and impairment in cogni-

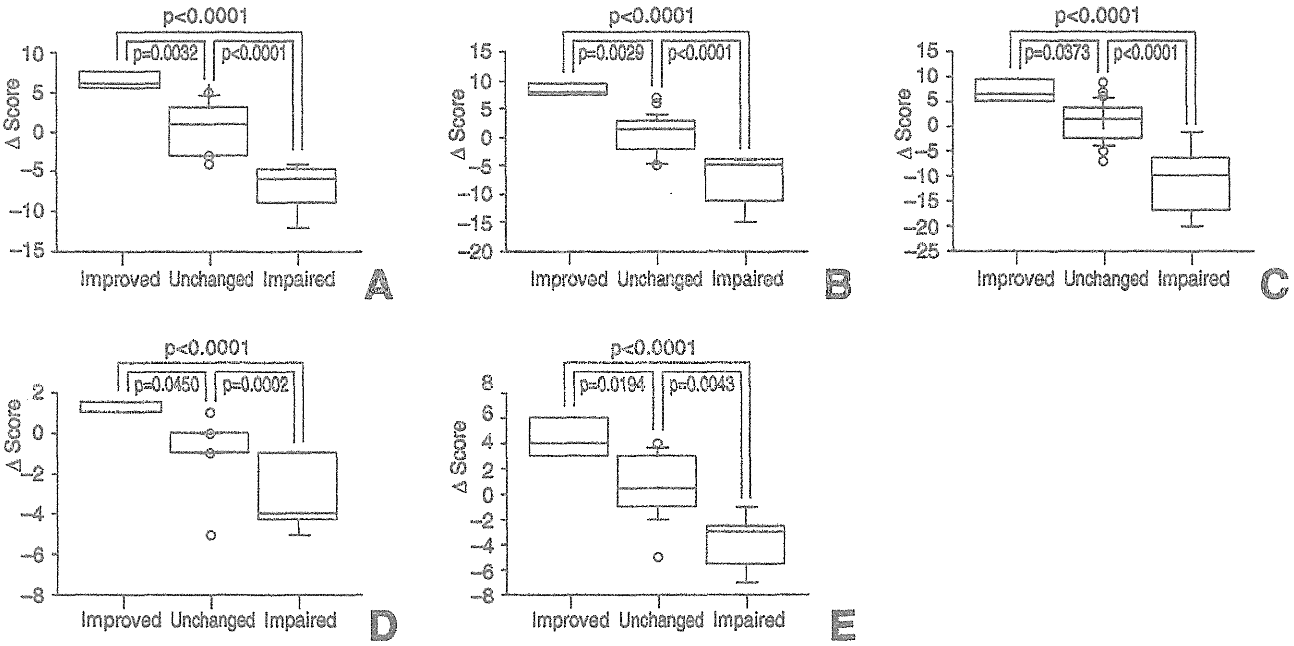

Fig. 1 Box plot showing the relationship between subjective assessment of postoperative change in cognition (improved, unchanged, and impaired) and the Δ score for each neuropsychological test in patients aged ≥76 years. A: Wechsler Adult Intelligence Scale-Revised (WAIS-R) verbal intelligence quotient (IQ), B: WAIS-R performance IQ, C: Wechsler Memory Scale, D: Rey-Osterreith Complex Figure test (Rey test) copy, E: Rey test recall.

Table 6 Accuracy of the Δ score for each neuropsychological test for the detection of subjective improvement and impairment in cognition after surgery, analyzed using receiver operating characteristic curves in older patients

Subjective assessment	Δ Score for neuropsychological tests					
	Test	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Cut-off point
Improvement	WAIS-R verbal IQ	100% (4/4)	82% (27/33)	40% (4/10)	100% (27/27)	3.4
	WAIS-R performance IQ	100% (4/4)	82% (27/33)	40% (4/10)	100% (27/27)	4.9
	WMS	100% (4/4)	85% (28/33)	44% (4/9)	100% (28/28)	4.7
	Rey copy	100% (4/4)	94% (31/33)	67% (4/6)	100% (31/31)	0.9
	Rey recall	100% (4/4)	73% (24/33)	31% (4/13)	100% (24/24)	2.9
Impairment	WAIS-R verbal IQ	100% (5/5)	96% (31/32)	83% (5/6)	100% (31/31)	−3.4
	WAIS-R performance IQ	100% (5/5)	93% (30/32)	71% (5/7)	100% (30/30)	−2.6
	WMS	80% (4/5)	93% (30/32)	67% (4/6)	97% (30/31)	−4.5
	Rey copy	80% (4/5)	72% (23/32)	31% (4/13)	96% (23/24)	−0.6
	Rey recall	80% (4/5)	93% (30/32)	67% (4/6)	97% (30/31)	−2.4

IQ: intelligence quotient, Rey copy: Rey-Osterreith Complex Figure test (Rey test) copy, Rey recall: Rey test recall, WAIS-R: Wechsler Adult Intelligence Scale-Revised, WMS: Wechsler Memory Scale.

tion after surgery in older patients are summarized in Table 6. In all neuropsychological tests except for the Rey copy, the cut-off point of the Δ score for detection of subjective improvement (upper cut-off point) and impairment (lower cut-off point) in cognition after surgery was identical to the mean and the mean −1.5 SD respectively, of the control value obtained from normal subjects. In the Rey copy, the upper and lower cut-off points were identical to the mean +0.5 SD and the mean −1 SD, respectively. All four patients with a Δ score of more than each upper cut-off point in two or more neuropsychological tests exhibited subjectively improved cognition after surgery. Of the seven patients with a Δ score of less than each lower cut-off point in two or more neuropsychological tests, five (71%) and two (29%) patients exhibited subjectively impaired and unchanged cognition, respectively, after surgery. All 26 patients with a Δ score of more or less than each upper or lower cut-off point, respectively, in one neuropsychological test or a Δ score between the upper and lower cut-off points in all neuropsychological tests exhibited subjectively unchanged cognition after surgery.

Discussion

Neurosurgeons and/or patients' families often subjectively report postoperative improvements or impairments in cognition for patients undergoing CEA, so we defined these subjective assessments based on their feelings as significant postoperative changes in cognition. As a result, 11%, 75%, and 14% of patients were determined as having subjectively improved, unchanged, and impaired cognition, respectively, after surgery in older patients. These incidences did not differ when comparing with younger patients. Thus, regardless of age, some patients who underwent CEA may have subjectively improved or impaired cognition after surgery.

A recent study suggested that normalization of cerebral metabolism via improvements in cerebral hemodynamics after CEA may result in cognitive improvement as well as functional recovery of the neurotransmitter system.[5] Other investigators have hypothesized that cognitive impairment after CEA may result from three possible mechanisms[2,6–9,11–13,18]: cerebral hemispheric hypoperfusion during ICA clamping, intraoperative gaseous and particulate emboli from the surgical site, and postoperative cerebral hyperperfusion. The present study showed no relationship between duration of ICA clamping or new ischemic lesions on postoperative diffusion-weighted imaging and postoperative cognitive change. On the other hand, the incidence of postoperative cerebral hyperperfusion was significantly greater in patients with subjectively impaired cognition after surgery than in those with subjectively improved or unchanged cognition. Thus, postoperative cerebral hyperperfusion may be the main cause of impaired cognition after surgery in elderly patients.

In general, when healthy subjects repeatedly undergo neuropsychological testing, scores from the second testing session are usually higher than the first testing session (practice effect).[12,17] A recent study has reported that the practice effect occurs even during the neuropsychological testing of healthy elderly subjects, and that there was no correlation between the magnitude of the practice effect and age in such subjects.[15] While neuropsychological test scores reportedly increase after CEA in patients aged <76 years when analyzed as a group,[22] test scores did not change after surgery in those aged ≥ 76 years in the present group-rate analysis. Further, the degree of postoperative change in neuropsychological test scores was significantly lower in patients aged ≥ 76 years compared with those in patients aged <76 years. These findings suggest that the practice effect for neuropsychological testing may not occur in elderly patients undergoing CEA. Aging in addition to presence of carotid stenosis probably causes reduction in brain function, resulting in absence of the practice effect in such patients.

The present study demonstrated that the degree of postoperative increase or decrease in neuropsychological test scores could differentiate patients with subjectively improved, unchanged, and impaired cognition after surgery in older patients. These observations are consistent with those seen in younger patients.[22] However, the absolute values of the cut-off points of postoperative increase and decrease in neuropsychological test scores for detection of subjective improvement and impairment, respectively, in cognition after surgery were lower in older patients compared with the absolute value of the cut-off point for younger patients (mean +2 SD of the normal control value for detection of subjective improvement; mean −2 SD of the normal control value for detection of subjective impairment).[22] These data suggest that, although neuropsychological test scores reflect the subjective assessment of postoperative change in cognition even for older patients, the optimal cut-off points for the test scores for detection of subjective improvement and impairment in cognition after CEA are different from those in younger patients. The absence of a practice effect in older patients may result in a lower absolute value of the cut-off point of postoperative increase and decrease in neuropsychological test scores in such patients.

The present study suggests that although neuropsychological test scores reflect the subjective assessment of postoperative change in cognition in older patients, the optimal cut-off points for the test scores to detect subjective improvement and impairment in cognition after CEA are different in older patients compared with younger patients. This difference may be due to the absence of a practice effect in elderly patients.

Conflicts of Interest Disclosure

The authors have no personal financial or institutional interest in any of the drugs, materials, or devices in the article. All authors who are members of The Japan Neurosurgical Society (JNS) have registered online Self-reported COI Disclosure Statement Forms through the website for JNS members.

References

1) Baracchini C, Mazzalai F, Gruppo M, Lorenzetti R, Ermani M, Ballotta E: Carotid endarterectomy protects elderly patients from cognitive decline: a prospective study. *Surgery* 151: 99–106, 2012
2) Brinkman SD, Braun P, Ganji S, Morrell RM, Jacobs LA: Neuropsychological performance one week after carotid endarterectomy reflects intra-operative ischemia. *Stroke* 15: 497–503, 1984
3) Brott TG, Hobson RW 2nd, Howard G, Roubin GS, Clark WM, Brooks W, Mackey A, Hill MD, Leimgruber PP, Sheffet AJ, Howard VJ, Moore WS, Voeks JH, Hopkins LN, Cutlip DE, Cohen DJ, Popma JJ, Ferguson RD, Cohen SN, Blackshear JL, Silver FL, Mohr JP, Lal BK, Meschia JF; CREST Investigators: Stenting versus endarterectomy for treatment of carotid-artery stenosis. *N Engl J Med* 363: 11–23, 2010
4) Chaturvedi S, Bruno A, Feasby T, Holloway R, Benavente O, Cohen SN, Cote R, Hess D, Saver J, Spence JD, Stern B, Wilterdink J; Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology: Carotid endarterectomy: an evidence-based review: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology* 65: 794–801, 2005
5) Chida K, Ogasawara K, Aso K, Suga Y, Kobayashi M, Yoshida K, Terasaki K, Tsushina E, Ogawa A: Postcarotid endarterectomy improvement in cognition is associated with resolution of crossed cerebellar hypoperfusion and increase in ^{123}I-iomazenil uptake in the cerebral cortex: a SPECT study. *Cerebrovasc Dis* 29: 343–351, 2010
6) Chida K, Ogasawara K, Suga Y, Saito H, Kobayashi M, Yoshida K, Otawara Y, Ogawa A: Postoperative cortical neural loss associated with cerebral hyperperfusion and cognitive impairment following carotid endarterectomy: ^{123}I-iomazenil SPECT study. *Stroke* 40: 448–453, 2009
7) Crawley F, Stygall J, Lunn S, Harrison M, Brown MM, Newman S: Comparison of microembolism detected by transcranial Doppler and neuropsychological sequelae of carotid surgery and percutaneous transluminal angioplasty. *Stroke* 31: 1329–1334, 2000
8) Cushman L, Brinkman SD, Ganji S, Jacobs LA: Neuropsychological impairment after carotid endarterectomy correlates with intraoperative ischemia. *Cortex* 20: 403–412, 1984
9) De Rango P, Caso V, Leys D, Paciaroni M, Lenti M, Cao P: The role of carotid artery stenting and carotid endarterectomy in cognitive performance: a systematic review. *Stroke* 39: 3116–3127, 2008
10) Feliziani FT, Polidori MC, De Rango P, Mangialasche F, Monastero R, Ercolani S, Raichi T, Cornacchiola V, Nelles G, Cao P, Mecocci P: Cognitive performance in elderly patients undergoing carotid endarterectomy or carotid artery stenting: a twelve-month follow-up study. *Cerebrovasc Dis* 30: 244–251, 2010
11) Gaunt ME, Martin PJ, Smith JL, Rimmer T, Cherryman G, Ratliff DA, Bell PR, Naylor AR: Clinical relevance of intraoperative embolization detected by transcranial Doppler ultrasonography during carotid endarterectomy: a prospective study of 100 patients. *Br J Surg* 81: 1435–1439, 1994
12) Heyer EJ, Adams DC, Solomon RA, Todd GJ, Quest DO, McMahon DJ, Steneck SD, Choudhri TF, Connolly ES: Neuropsychometric changes in patients after carotid endarterectomy. *Stroke* 29: 1110–1115, 1998
13) Heyer EJ, Sharma R, Rampersad A, Winfree CJ, Mack WJ, Solomon RA, Todd GJ, McCormick PC, McMurtry JG, Quest DO, Stern Y, Lazar RM, Connolly ES: A controlled prospective study of neuropsychological dysfunction following carotid endarterectomy. *Arch Neurol* 59: 217–222, 2002
14) Koyama M: [*Clinical Psychology of Brain Damage*]. Tokyo, Gakuen Sha, 1985, pp 48–54 (Japanese)
15) Krenk L, Rasmussen LS, Siersma VD, Kehlet H: Short-term practice effects and variability in cognitive testing in a healthy elderly population. *Exp Gerontol* 47: 432–436, 2012
16) Lezak MD: *Neuropsychological Assessment, ed 3.* New York, Oxford University Press, 1995
17) Lunn S, Crawley F, Harrison MJ, Brown MM, Newman SP: Impact of carotid endarterectomy upon cognitive functioning: a systematic review of the literature. *Cerebrovasc Dis* 9: 74–81, 1999
18) Ogasawara K, Yamadate K, Kobayashi M, Endo H, Fukuda T, Yoshida K, Terasaki K, Inoue T, Ogawa A: Postoperative cerebral hyperperfusion associated with impaired cognitive function in patients undergoing carotid endarterectomy. *J Neurosurg* 102: 38–44, 2005
19) Ogasawara K, Yukawa H, Kobayashi M, Mikami C, Konno H, Terasaki K, Inoue T, Ogawa A: Prediction and monitoring of cerebral hyperperfusion after carotid endarterectomy by using single-photon emission computerized tomography scanning. *J Neurosurg* 99: 504–510, 2003
20) Rao R: The role of carotid stenosis in vascular cognitive impairment. *Eur Neurol* 46: 63–69, 2001
21) Shinagawa F, Kobayashi S, Fujita K: [*Japanese Wechsler Adult Intelligence Scale-Revised*]. Tokyo, Nihon Bunka Kagakusha, 1990 (Japanese)
22) Yoshida K, Ogasawara K, Kobayashi M, Yoshida K, Kubo Y, Otawara Y, Ogawa A: Improvement and impairment in cognitive function after carotid endarterectomy: comparison of objective and subjective assessments. *Neurol Med Chir (Tokyo)* 52: 154–160, 2012

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Eur J Nucl Med Mol Imaging (2013) 40:1573–1581
DOI 10.1007/s00259-013-2463-2

ORIGINAL ARTICLE

Detection of misery perfusion in the cerebral hemisphere with chronic unilateral major cerebral artery steno-occlusive disease using crossed cerebellar hypoperfusion: comparison of brain SPECT and PET imaging

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Received: 13 February 2013 / Accepted: 9 May 2013 / Published online: 6 June 2013

Abstract

Purpose In patients with unilateral internal carotid or middle cerebral artery (ICA or MCA) occlusive disease, the degree of crossed cerebellar hypoperfusion that is evident within a few months after the onset of stroke may reflect cerebral metabolic rate of oxygen in the affected cerebral hemisphere relative to that in the contralateral cerebral hemisphere. The aim of the present study was to determine whether the ratio of blood flow asymmetry in the cerebellar hemisphere to blood flow asymmetry in the cerebral hemisphere on positron emission tomography (PET) and single photon emission computed tomography (SPECT) correlates with oxygen extraction fraction (OEF) asymmetry in the cerebral hemisphere on PET in patients with chronic unilateral ICA or MCA occlusive disease and whether this blood flow ratio on SPECT detects misery perfusion in the affected cerebral hemisphere in such patients.

Methods Brain blood flow and OEF were assessed using ^{15}O-PET and *N*-isopropyl-*p*-[^{123}I]iodoamphetamine (^{123}I-IMP) SPECT, respectively. All images were anatomically standardized using SPM2. A region of interest (ROI) was automatically placed in the bilateral MCA territories and in the bilateral cerebellar hemispheres using a three-dimensional stereotaxic ROI template, and affected-to-contralateral asymmetry in the MCA territory or contralateral-to-affected asymmetry in the cerebellar hemisphere was calculated. Sixty-three patients with reduced blood flow in the affected cerebral hemisphere on ^{123}I-IMP SPECT were enrolled in this study.

Results A significant correlation was observed between MCA ROI asymmetry of PET OEF and the ratio of cerebellar hemisphere asymmetry of blood flow to MCA ROI asymmetry of blood flow on PET (r=0.381, p= 0.0019) or SPECT (r=0.459, p=0.0001). The correlation coefficient was higher when reanalyzed in a subgroup of 43 patients undergoing a PET study within 3 months after the last ischemic event (r=0.541, p= 0.0001 for PET; r=0.609, p<0.0001 for SPECT). The blood flow ratio on brain perfusion SPECT in all patients provided 100 % sensitivity and 58 % specificity, with 43 % positive and 100 % negative predictive values for detecting abnormally elevated MCA ROI asymmetry of PET OEF.

Conclusion The ratio of blood flow asymmetry in the cerebellar hemisphere to blood flow asymmetry in the cerebral hemisphere on PET and SPECT correlates with PET OEF asymmetry in the cerebral hemisphere, and this blood flow ratio on SPECT detects misery perfusion in the affected cerebral hemisphere.

Keywords Crossed cerebellar hypoperfusion · Misery perfusion · Oxygen extraction fraction · PET · SPECT

Introduction

In patients with major cerebral arterial occlusive disease, a marginally adequate blood supply relative to metabolic demand (misery perfusion) in the affected hemisphere [1] may

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increase the risk of cerebral infarction [2]. Misery perfusion can be identified by demonstrating an increased oxygen extraction fraction (OEF), which is directly measured only through positron emission tomography (PET). Several studies have identified increased OEF as a powerful and independent predictor of subsequent stroke in patients with symptomatic major cerebral arterial occlusive disease [3–5].

In clinical practice, the cerebral blood flow (CBF) response to acetazolamide can be used as an alternative parameter for detecting impaired cerebral hemodynamics [2]. Several investigators have demonstrated that cerebrovascular reactivity (CVR) to acetazolamide is inversely correlated with OEF [6–10]. Further, a subgroup of patients with symptomatic major cerebral arterial occlusive disease with reductions in both CVR to acetazolamide and CBF measured by single photon emission computed tomography (SPECT) has an increased risk of a subsequent stroke [11, 12]. However, more than half of patients who underwent SPECT with acetazolamide challenge developed adverse effects, such as headache, nausea, dizziness, tinnitus, numbness of the extremities, and Stevens-Johnson syndrome, after administration of the acetazolamide [13, 14]. These adverse events can have a significant effect on activities of daily living and/or ability to engage in routine employment [14].

Crossed cerebellar hypoperfusion (CCH) is defined as a reduction in blood flow in the cerebellar hemisphere contralateral to a supratentorial lesion [15]. This phenomenon can be demonstrated on brain perfusion images obtained by SPECT or by PET [15–18]. The mechanism underlying CCH reportedly consists of disruption of the corticopontocerebellar pathway that causes functional deafferentation and transneuronal metabolic depression of the contralateral cerebellar hemisphere [17, 18]. In patients with unilateral carotid artery occlusive disease, contralateral-to-affected side blood flow asymmetry in the cerebellar hemisphere reflects cerebral metabolic rate of oxygen ($CMRO_2$) in the affected cerebral hemisphere relative to that in the contralateral cerebral hemisphere [19]. Because OEF is a function of $CMRO_2$/CBF, the ratio of contralateral-to-affected side blood flow asymmetry in the cerebellar hemisphere to affected-to-contralateral side blood flow asymmetry in the cerebral hemisphere may reflect affected-to-contralateral side OEF asymmetry in the cerebral hemisphere. If this hypothesis is correct, then misery perfusion could be detected using only one brain blood flow imaging study without an acetazolamide challenge.

The aim of the present study was to determine whether the ratio of contralateral-to-affected side blood flow asymmetry in the cerebellar hemisphere to affected-to-contralateral side blood flow asymmetry in the cerebral hemisphere on PET and SPECT correlates with affected-to-contralateral side OEF asymmetry in the cerebral hemisphere on PET in patients with chronic unilateral middle cerebral or internal carotid artery (MCA or ICA) occlusive disease. Further, this study investigated whether this blood flow ratio on SPECT detects misery perfusion in the cerebral hemisphere ipsilateral to the affected artery in such patients.

Materials and methods

Healthy volunteers

The healthy study population consisted of 20 normal men ages 30–52 years (mean 38 years) who underwent screening based on past history, physical examination, neurological and cognitive testing, and magnetic resonance imaging (MRI) findings. Exclusion criteria included any history of hypertension, diabetes mellitus, atrial fibrillation, or pulmonary disease or observation of organic brain lesions (including leukoaraiosis or asymptomatic lacunar infarction) on MRI.

Patient inclusion criteria

Patients who satisfied the following basic inclusion criteria were prospectively selected: age <75 years; presence of clinical symptoms suggesting ischemic episodes in the MCA or ICA territory within 6 months before visiting our institute; absence of clinical symptoms suggesting ischemic episodes in the vertebrobasilar territory; useful residual function (modified Rankin disability scale 0, 1, or 2); presence of unilateral MCA or ICA stenosis (greater than 70 % for the ICA; greater than 50 % for the MCA) or occlusion on cerebral angiography using arterial catheterization, CT, or MRI; absence of occlusion or stenosis of greater than 50 % in the contralateral ICA, the contralateral MCA, the basilar artery, and the vertebral arteries; no infarct or only subcortical abnormalities (excluding infarcts involving the posterior limb of the internal capsule) in the MCA territory of the affected cerebral hemisphere on T1-, T2- and diffusion-weighted MRI; absence of gross morphological alterations in the cerebellum and brain stem on T1-, T2- and diffusion-weighted MRI; and provision of written informed consent. Finally, according to the brain perfusion SPECT criteria as described below (see "Brain SPECT study" and "Data analysis" sections), patients who were defined as having reduced blood flow in the affected cerebral hemisphere entered into the present study.

The study protocol was approved by the local Ethics Committee. Written informed consent was obtained from all subjects prior to enrollment in the study.

Brain SPECT study

SPECT studies were performed using a ring-type SPECT scanner, a Headtome-SET080 (Shimadzu Corp., Kyoto, Japan), which provides 31 tomographic images simultaneously [20].

The spatial resolution of the scanner with a low-energy, all-purpose collimator was 13 mm full-width at half-maximum (FWHM) at the center of the field of view, and the slice thickness was 25 mm FWHM at the field of view center. Image slices were taken at 5 mm center-to-center spacing parallel to the orbitomeatal (OM) line. The images were reconstructed using the weighted filtered backprojection technique, in which the attenuation correction was made by detecting the edge of the object. An attenuation coefficient of 0.065 cm^{-1}, a Butterworth filter (cutoff=0.45 cycle/cm; order=3), and a ramp filter were used for image reconstruction.

The distribution of brain perfusion was assessed using *N*-isopropyl-*p*-[^{123}I]-iodoamphetamine (IMP) and SPECT. The IMP SPECT study was performed as described previously [20]. Briefly, after a 1-min intravenous infusion of 222 MBq of ^{123}I-IMP (5-ml volume) at a constant rate of 5 ml/min and a 1-min infusion of physiological saline at the same rate, data acquisition was performed at a midscan time of 30 min for a scan duration of 20 min. The IMP SPECT study was performed at least 3 weeks after the last ischemic attack.

Brain PET study

PET studies were performed using a SET-3000GCT/M scanner (PET/CT, Shimadzu Corp., Kyoto, Japan) [21]. This modality uses gadolinium silica oxide detectors and provides 59 slices with 2.6-mm slice thickness. The axial field of view was 156 mm, and the spatial resolution was 3.5 mm FWHM at 1 cm in-plane and 4.2 mm FWHM at the center axially. The scanner was operated in a static scan mode with dual-energy window acquisition for scatter correction. The coincidence time window was set to 10 ns. A shield module consisting of 7-mm-thick lead plates was attached to the gantry bed and was used to cover the breast and shoulder of the subject to reduce the counting rate of random coincidence and scatter coincidence attributable to radioactivity outside the field of view.

Before the emission scan, a transmission scan (3 min) with a ^{137}Cs point source was performed with a bismuth germanate transmission detector ring coaxially attached to the gadolinium silica oxide emission detector ring. Brain blood flow was determined while the subject continuously inhaled 1,480 MBq of $C^{15}O_2$ through a mask. Measurements of $CMRO_2$ and OEF were obtained during continuous inhalation of 1,480 MBq of $^{15}O_2$. Data were collected for 5 min. A single breath of 444 MBq of $C^{15}O$ was used to measure cerebral blood volume. Brain blood flow, $CMRO_2$, and OEF were calculated using the steady-state method [22], and $CMRO_2$ and OEF were corrected according to cerebral blood volume [23].

The PET study was performed between 2 and 6 days after SPECT study only for patients who were defined as having reduced blood flow in the affected cerebral hemisphere on SPECT imaging, as described below. Patients were also classified into subgroups of those undergoing a PET study within (defined as early PET study) or later than (defined as late PET study) 3 months after the last ischemic event.

Data analysis

All SPECT and PET images were transformed into the standard brain size and shape by linear and nonlinear transformation using SPM2 for anatomic standardization [24]. Thus, brain images from all subjects had the same anatomic format. Three hundred and eighteen constant regions of interest (ROIs) were automatically placed in both the cerebral and cerebellar hemispheres using a three-dimensional stereotaxic ROI template (3DSRT) with SPM2 (FUJIFILM RI Pharma Co., Ltd., Tokyo, Japan) [25]. The ROIs were grouped into ten segments (callosomarginal, pericallosal, precentral, central, parietal, angular, temporal, posterior, hippocampus, and cerebellar) in each hemisphere according to the arterial supply. Five (precentral, central, parietal, angular, and temporal) of these ten segments were combined and defined as an ROI perfused by the MCA (Fig. 1). While the MCA ROI included only the cerebral cortex, the cerebellar hemispheric ROI included the cerebellar cortex as well as the cerebellar while matter and the cerebellar ganglia. The mean value of radioactive counts on ^{123}I-IMP SPECT images and the mean value of blood flow on PET images were measured in the bilateral MCAs and in cerebellar hemispheric ROIs; the mean value of $CMRO_2$ and OEF on PET images was measured in the bilateral MCA ROIs. Then, the asymmetry ratio in the MCA ROI (AR_{MCA}) was calculated as: the value in the cerebral hemisphere ipsilateral to the side of the stenosed or occluded artery/the value in the contralateral cerebral hemisphere. The asymmetry ratio in the cerebellar hemispheric ROI (AR_{cbl}) was calculated as: the value in the cerebellar hemisphere contralateral to the side of the stenosed or occluded artery/the value in the ipsilateral cerebellar hemisphere.

When AR_{MCA} in IMP SPECT was less than 0.933, a patient was defined as having reduced blood flow in the affected cerebral hemisphere [10] and was allowed to enter into the present study.

Healthy volunteers were assigned to one of two groups, each consisting of ten subjects who underwent PET or SPECT study, respectively. In each group, the AR_{MCA} on OEF PET or the AR_{cbl}/AR_{MCA} on blood flow PET and IMP SPECT was calculated when the left cerebral hemisphere was defined as the affected side. An abnormally elevated AR_{MCA} on OEF PET was defined as a value greater than the mean+2 standard deviations (SDs) obtained in the healthy volunteers.

Statistical analysis

Data are expressed as the mean±SD. Correlations between various parameters were determined using linear regression

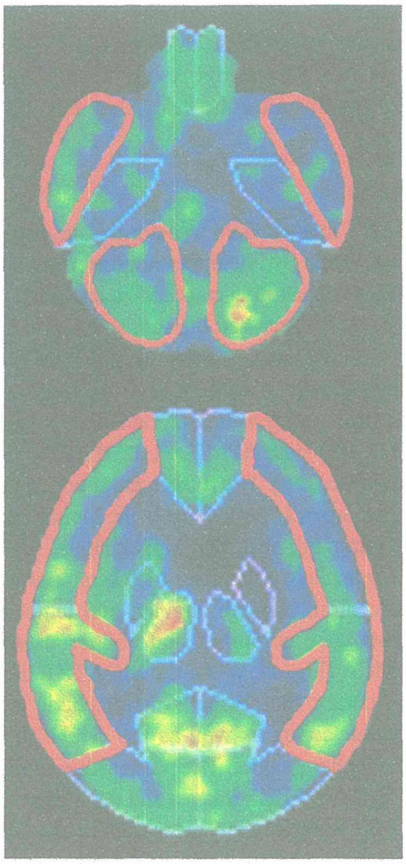

Fig. 1 Parts of the ROIs in a 3DSRT. ROIs surrounded by *red lines* indicate the bilateral cerebellar hemispheres and cortical territories perfused by the bilateral MCAs

analysis and by computing regression equations and correlation coefficients, and the function of better fit was determined. The analysis of covariance (ANCOVA), including Levene's test followed by pairwise comparisons, was also used to compare the intercepts of two regression lines to test the effect of the timing of PET study (early or late PET study) on a dependent variable (y-axis) while controlling for the effect of a continuous covariable (x-axis). Statistical significance was set at the $p<0.05$ level. The accuracy of AR_{cbl}/AR_{MCA} on blood flow SPECT to detect abnormally elevated AR_{MCA} on OEF PET in patients was determined by a receiver-operating characteristic curve. The curve was calculated in increments or decrements of 0.5 SD from the mean value of AR_{cbl}/AR_{MCA} on blood flow SPECT obtained in healthy volunteers.

Results

A total of 109 patients satisfied the basic inclusion criteria. Among these patients, 63 were defined as having reduced blood flow in the affected cerebral hemisphere on blood flow SPECT imaging and entered into the present study.

The mean age of the 63 patients (21 women and 42 men) was 59±11 years (range 34–74 years). Of the patients, 23 and 40 had experienced only transient ischemic attacks and minor complete strokes with or without transient ischemic attacks, respectively. Cerebral angiography demonstrated ICA stenosis in 15 patients, ICA occlusion in 27 patients, MCA stenosis in 12 patients, and MCA occlusion in 9 patients. Of the patients, 43 and 20 underwent early and late PET studies, respectively.

No significant correlation was observed between AR_{cbl} and AR_{MCA} on blood flow PET in patients (Fig. 2a). However, the AR_{cbl} correlated with AR_{MCA} on $CMRO_2$ PET [$r=0.305$, 95 % confidence interval (CI) 0.062–0.514, $p=0.0147$]; while the slopes of the regression lines between these two were statistically similar among equations of patients undergoing early and late PET studies, their intercepts were significantly lower in an equation of patients undergoing late PET study than in an equation of patients undergoing early PET study ($p=0.0002$, mean difference 0.106, 95 % CI 0.054–0.159) (Fig. 2b). The correlation coefficient was higher when reanalyzed in the 43 patients undergoing early PET study ($r=0.522$, 95 % CI 0.262–0.711, $p=0.0003$).

AR_{cbl}/AR_{MCA} on blood flow PET correlated with AR_{MCA} on OEF PET ($r=0.381$, 95 % CI 0.147–0.575, $p=0.0019$) in patients; while the slopes of the regression lines between these two were statistically similar among equations of patients undergoing early and late PET studies, their intercepts were significantly lower in an equation of patients undergoing late PET study than in an equation of patients undergoing early PET study ($p<0.0001$, mean difference 0.164, 95 % CI 0.092–0.237) (Fig. 3). The correlation coefficient was higher when reanalyzed in the 43 patients undergoing early PET study ($r=0.541$, 95 % CI 0.288–0.724, $p=0.0001$).

AR_{MCA} on blood flow SPECT correlated with AR_{MCA} on blood flow PET in patients ($r=0.845$, 95 % CI 0.755–0.903, $p<0.0001$); both of the slopes and intercepts of the regression lines between these two were statistically similar among equations of patients undergoing the early and late PET studies (Fig. 4a). AR_{cbl} on blood flow SPECT correlated with AR_{cbl} on blood flow PET in patients ($r=0.801$, 95 % CI 0.710–0.858, $p<0.0001$); both of the slopes and intercepts of the regression lines between these two parameters were statistically similar when comparing equations of patients undergoing the early and late PET studies (Fig. 4b). In half of patients, AR_{MCA} and AR_{cbl} were higher on blood flow SPECT than on blood flow PET. AR_{cbl} on blood flow SPECT correlated with AR_{MCA} on $CMRO_2$ PET in patients ($r=0.515$, 95 % CI 0.307–0.677, $p<0.0001$); while the slopes of the regression lines between these two were statistically similar among equations of patients undergoing

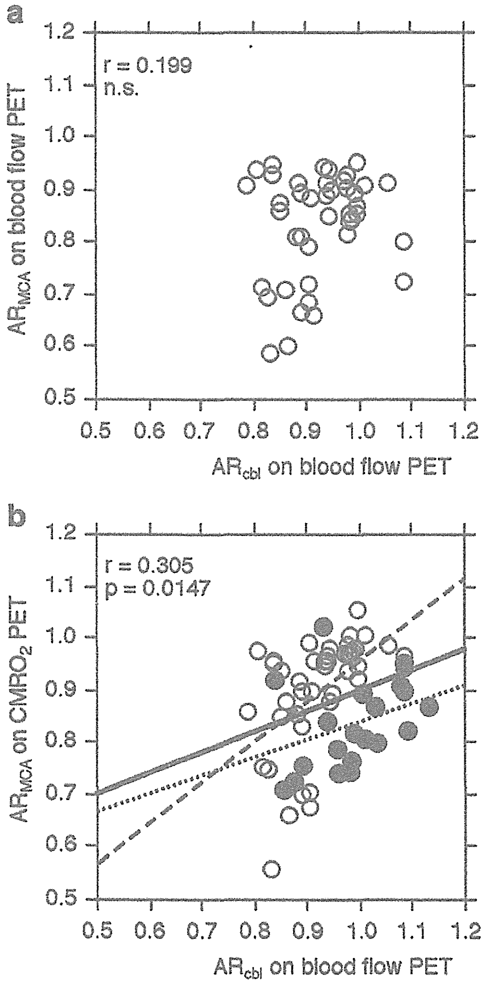

Fig. 2 Correlation between AR_{cbl} (asymmetry ratio in the cerebellar hemispheric ROI) on blood flow PET and AR_{MCA} (asymmetry ratio in the MCA ROI) on blood flow PET (**a**) or AR_{MCA} on $CMRO_2$ PET (**b**) in patients. In **b**, *open* and *closed circles* denote patients undergoing early and late PET studies, respectively; *solid line* (Y=0.399X+0.503), *dashed line* (Y=0.783X+0.177), and *dotted line* (Y=0.346X+0.492) denote the regression lines of all patients, those undergoing early PET study and those undergoing late PET study, respectively

early and late PET studies, their intercepts were significantly lower in an equation of patients undergoing late PET study than in an equation of patients undergoing early PET study (p=0.0001, mean difference 0.096, 95 % CI 0.051–0.140) (Fig. 4c). The correlation coefficient was higher when reanalyzed in the 43 patients undergoing early PET study (r=0.653, 95 % CI 0.439–0.797, p<0.0001).

AR_{cbl}/AR_{MCA} on blood flow SPECT correlated with AR_{MCA} on OEF PET (r=0.459, 95 % CI 0.239–0.635, p=0.0001) in patients; while the slopes of the regression lines between these two were statistically similar among equations of patients undergoing early and late PET studies, their intercepts were significantly lower in an equation of patients undergoing late PET study than in an equation of patients undergoing early PET study (p=0.0032, mean difference 0.094, 95 % CI 0.0328–0.155) (Fig. 5). The correlation coefficient was higher when reanalyzed in 43 patients undergoing early PET study (r=0.609, 95 % CI 0.363–0.762, p<0.0001).

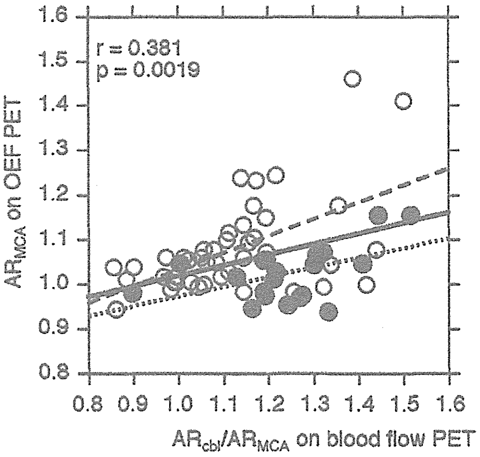

Fig. 3 Correlation between AR_{cbl}/AR_{MCA} on blood flow PET and AR_{MCA} on OEF PET in patients. *Open* and *closed circles* denote patients undergoing early and late PET studies, respectively; *solid line* (Y=0.234X+0.792), *dashed line* (Y=0.374X+0.661), and *dotted line* (Y=0.216X+0.757) denote the regression lines of all patients, those undergoing early PET study and those undergoing late PET study, respectively

The AR_{MCA} on OEF PET in healthy volunteers was 1.001±0.044, and an abnormally elevated AR_{MCA} on OEF PET was defined as a value greater than 1.089. As a result, 15 patients were classified as having an abnormally elevated AR_{MCA} on OEF PET. The AR_{cbl}/AR_{MCA} on blood flow SPECT in healthy volunteers was 0.999±0.051, and the receiver-operating characteristic curve was calculated in increments or decrements of 0.974 from 1.484 in AR_{cbl}/AR_{MCA} on blood flow SPECT. The sensitivity and specificity for the AR_{cbl}/AR_{MCA} on blood flow SPECT in the cutoff point lying closest to the left upper corner of the receiver-operating characteristic curve for detection of an abnormally elevated AR_{MCA} on OEF PET was 100 % (15/15) and 58 % (28/48) (cutoff point 1.101), respectively (Fig. 5). Using the same cutoff point, the positive and negative predictive values were 43 % (15/35) and 100 % (28/28), respectively. The cutoff point for AR_{cbl}/AR_{MCA} on blood flow SPECT was the mean+2 SDs of the control value obtained from normal subjects.

When reanalyzed in 43 patients undergoing early PET study using the same cutoff point, the sensitivity, specificity, and positive and negative predictive values for the AR_{cbl}/AR_{MCA} on blood flow SPECT for detection of an abnormally elevated AR_{MCA} on OEF PET were 100 % (13/13), 83 % (25/30), 72 % (13/18) and 100 % (25/25), respectively (Fig. 5).