ORIGINAL ARTICLE doi: 10.2176/nmc.oa.2014-0424

Neurol Med Chir (Tokyo) 55, 460–468, 2015 Online June 2, 2015

Results of Prospective Cohort Study on Symptomatic Cerebrovascular Occlusive Disease Showing Mild Hemodynamic Compromise [Japanese Extracranial-Intracranial Bypass Trial (JET)-2 Study]

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Abstract

The purpose of this study is to determine the true threshold of cerebral blood flow (CBF) and cerebrovascular reactivity (CVR) for subsequent ischemic stroke without extracranial-intracranial (EC-IC) bypass surgery in patients with hemodynamic ischemia due to symptomatic major cerebral arterial occlusive diseases. Patients were categorized based on rest CBF and CVR into four subgroups as follows: Group A, 80% < CBF < 90% and CVR < 10%; Group B, CBF < 80% and 10% < CVR < 20%; Group C, 80% < CBF < 90% and 10% < CVR < 20%; and Group D, CBF < 90% and 20% < CVR < 30%. Patients were followed up for 2 years under best medical treatment by the stroke neurologists. Primary and secondary end points were defined as all adverse events and ipsilateral stroke recurrence respectively. A total of 132 patients were enrolled. All adverse events were observed in 9 patients (3.5%/year) and ipsilateral stroke recurrence was observed only in 2 patients (0.8%/year). There was no significant difference among the four subgroups in terms of the rate of both primary and secondary end points. Compared with the medical arm of the Japanese EC-IC bypass trial (JET) study including patients with CBF < 80% and CVR < 10% as a historical control, the incidence of ipsilateral stroke recurrence was significantly lower in the present study. Patients with symptomatic major cerebral arterial occlusive diseases and mild hemodynamic compromise have a good prognosis under medical treatment. EC-IC bypass surgery is unlikely to benefit patients with CBF > 80% or CVR > 10%.

Key words: hemodynamic cerebral ischemia, stroke, recurrence, cerebral blood flow, cerebrovascular reactivity

Introduction

Patients with symptomatic major cerebral arterial occlusion or stenosis have a substantial risk of recurrent ischemic stroke.[1–3] A growing body of evidence is accumulating to show that patients with a compromised cerebral blood flow (CBF) have a high risk of ischemic stroke.[4–8] Single photon emission computed tomography (SPECT) combined with acetazolamide challenge enables us to measure CBF and cerebrovascular reactivity (CVR), which represent the degree of hemodynamic failure.

Received December 10, 2014; Accepted January 29, 2015

Decreased CBF and CVR are proven predictors of increased risk for subsequent stroke in patients with symptomatic major cerebral arterial occlusive diseases when treated medically.[6–10] On the other hand, extracranial-intracranial (EC-IC) bypass surgery improves impaired cerebral hemodynamics.[11,12] On the assumption that EC-IC bypass surgery prevents further ischemic stroke in high risk subgroups of patients with symptomatic major cerebral arterial occlusive diseases, Japanese EC-IC bypass trial (JET study) was conducted as a prospective randomized multicenter study, and demonstrated the effect of EC-IC bypass surgery in preventing subsequent cerebral ischemia in highly selected patients.[13] In the JET study, the recurrence rate of ipsilateral stroke in medically treated patients was not different between the moderate ischemia subgroup (0% < CVR < 10%) and the severe ischemia subgroup (CVR < 0%), suggesting that the threshold of hemodynamic compromise beneath which the risk of stroke recurrence increases when treated medically may be milder than initially assumed threshold (CBF < 80% and CVR < 10%). To determine the true threshold of CBF and CVR for subsequent ischemic stroke without EC-IC bypass surgery, JET-2 study was planned. In the JET-2 study, patients with symptomatic major cerebral arterial occlusive diseases in the anterior circulation and mild compromised cerebral hemodynamics were enrolled, divided into four groups, treated medically and prospectively followed up for 2 years.

Materials and Methods

I. Patient eligibility

This study is a multicenter prospective cohort study to examine the incidence of stroke recurrence, disability, and death of medically treated patients with symptomatic occlusive diseases of the anterior circulation. The target was patients with occlusion or severe stenosis of the middle cerebral artery (MCA) or the internal carotid artery (ICA) with mild-to-moderate hemodynamic failure who experienced transient ischemic attacks (TIAs) or non-disabling strokes within 6 months derived from the hemisphere ipsilateral to the lesion. Table 1 lists all the inclusion and exclusion criteria. The present study was approved by local ethics committees of all participant institutes. Written informed consent was obtained from all patients.

Table 1 Patient eligibility for the JET-2 study

Inclusion criteria
Clinical requirements
1. Age under 73 years at the time of registration
2. Independent of daily life (modified Rankin disability scale score of 0–2)
Radiological requirements
1. CT/MRI Lack of large infarction spread widely over the territory of a main arterial trunk Lack of contrast enhancement in the infarcted area
2. Angiography Occlusion or severe stenosis in the main trunk of the middle cerebral artery or the internal carotid artery (except for candidates for carotid endarterectomy)
3. SPECT/PET 80% of normal value < CBF < 90% of normal value or 10% < CVR < 30%
Exclusion criteria
1. Not independent in daily life (modified Rankin disability scale score of 3–5)
2. Major cerebral arterial occlusive lesions due to diseases other than atherosclerosis
3. Malignant tumors or organ failure of the heart, liver, kidney, or lung
4. Myocardial infarction within the past 6 months
5. Uncontrolled diabetes mellitus showing a serum fasting blood glucose level > 300 mg/dL, or requires insulin
6. Hypertension with a diastolic blood pressure of > 110 mmHg
7. Artery to artery embolism
8. Cardioembolism

CBF: cerebral blood flow, CT: computed tomography, CVR: cerebrovascular reactivity, JET: Japanese extracranial-intracranial bypass trial, MRI: magnetic resonance imaging, PET: positron emission tomography, SPECT: single photon emission computed tomography.

II. Measurements of CBF and CVR

Regional CBF was quantitatively measured more than 3 weeks after the last ischemic attacks using positron emission tomography (PET), ^{133}Xe inhalation method and SPECT, ^{133}Xe-enhanced computed tomography (Xe-CT), or N-isopropyl-p-[^{123}I]iodoamphetamine (^{123}I-IMP) SPECT. Regional CBF was measured with and without the injection of 17 mg/kg iv acetazolamide. In ^{123}I-IMP SPECT with acetazolamide challenge, ^{123}I-IMP was administered 7–10 min after injection of acetazolamide and SPECT acquisition was started 15–20 min after ^{123}I-IMP injection. ^{123}I-IMP SPECT with acetazolamide challenge was performed within a week of the measurement of rest CBF. In other methods, tracers were administered 15–20 min after injection of acetazolamide. The region of interest (ROI) was designated manually in the cerebral cortex in the territory of ipsilateral MCA at the level of the anterior horn of the lateral ventricle. ROIs were

also placed in bilateral cerebellar hemispheres and in the contralateral MCA territory as reference. Regional CBF was expressed as relative values (%) to normal control values of each institute obtained from volunteers free of cerebrovascular disease. CVR was calculated as follows: CVR (%) = [(acetazolamide challenge CBF − rest CBF)/rest CBF] × 100.

All patients were divided into four groups according to rest CBF (CBF) and CVR as follows: A: 80% < CBF < 90%, CVR < 10%; B: CBF < 80%, 10% < CVR < 20%; C: 80% < CBF < 90%, 10% < CVR < 20%; D: CBF < 90%, 20% < CVR < 30% (Fig. 1).

III. Patient follow-up

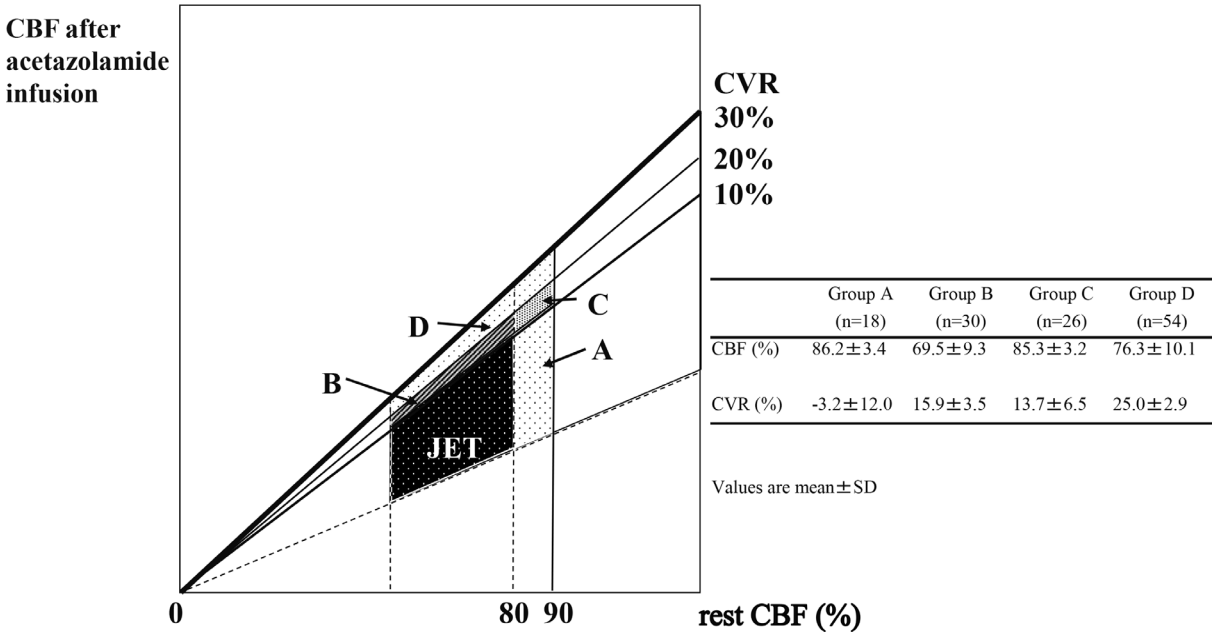
Each patient was followed up for 2 years after enrollment by a pair of a neurologist and a neurosurgeon in each participating institute. Neurological findings, computed tomography (CT)/magnetic resonance imaging (MRI), and CBF/CVR measurements were examined and reported at the time of enrollment and 6 months, 1 year, and 2 years after enrollment. Evaluation of the cognitive function and angiography were performed at the time of enrollment and 2 years after enrollment.

IV. End points

The following items constitute primary end points: (1) completed stroke causing significant morbidity (modified Rankin disability scale score of 3–5), (2) vascular death, (3) significant morbidity and mortality from other causes, and (4) requirement of EC-IC bypass as determined by a registered neurologist. The following items constitute secondary end points: (1) ipsilateral completed stroke causing significant morbidity (modified Rankin disability scale score of 3–5) and (2) death associated with ipsilateral completed stroke.

V. Comparison with data of the medical arm of the JET study as a historical control

JET study is a prospective multicenter trial to determine that EC-IC bypass surgery can prevent stroke recurrence of patients with major cerebral artery occlusive diseases and severe hemodynamic ischemia.[13] The medical arm of JET study consists of patients enrolled according to the same inclusion and exclusion criteria except for the values of CBF and CVR, and randomized to the medically treated group. The inclusion criteria for hemodynamic compromise of the JET study was CBF < 80% and CVR < 10%. The rate of patients reaching the end points and length of time without end points were compared between the medical arm of the JET study and the JET-2 study. Primary end points were the same between the two studies. But the secondary



	Group A (n=18)	Group B (n=30)	Group C (n=26)	Group D (n=54)
CBF (%)	86.2±3.4	69.5±9.3	85.3±3.2	76.3±10.1
CVR (%)	-3.2±12.0	15.9±3.5	13.7±6.5	25.0±2.9

Values are mean±SD

Fig. 1 Entry criteria and cerebral blood flow (CBF) classification of the JET-2 study. Patients were classified into four groups according to rest CBF and cerebrovascular reactivity (CVR) as follows: A: 80% < CBF < 90%, CVR < 10%; B: CBF < 80%, 10% < CVR < 20%; C: 80% < CBF < 90%, 10% < CVR < 20%; D: CBF < 90%, 20% < CVR < 30%. The mean ± standard deviation of CBF and CVR in each group are listed in the right panel. JET: Japanese extracranial-intracranial bypass trial.

end point of the JET study included requirement of EC-IC bypass as determined by a registered neurologist in addition to ipsilateral completed stroke causing significant morbidity (modified Rankin disability scale score of 3–5). Therefore, concerning the rate of the ipsilateral stroke recurrence, we compared these two studies according to the secondary end point of the JET study.

VI. Statistical analysis

One-way analysis of variance (ANOVA) and χ^2 for independence test were used to compare baseline characteristics of the four groups. The length of time without an adverse event was compared between groups with the Kaplan-Meier method and log-rank statistics. The data were analyzed using a univariate Cox regression model to determine which risk factors had significant associations with the adverse events. Age, sex, complications (hypertension, diabetes mellitus, hypercholesterolemia, prior myocardial infarction), entry event, side of the lesion, responsible lesion, and CBF classification were considered covariates. When some covariates were shown to be a significant predictor of end points, multivariate analysis was performed using stepwise selection with a P value of 0.10 for backward elimination to select the best predictive model. All analyses were performed with IBM SPSS software, version 22 (IBM Software Group, Chicago, Illinois, USA). A value of $P < 0.05$ was considered statistically significant.

Results

A total of 132 patients were enrolled in the JET-2 study between January 2002 and March 2007. Eighteen patients were classified into group A, 32 into group B, 26 into group C, and 56 into group D. The means of CBF and CVR in each group are listed in Fig. 1. Two patients of group B and 2 patients of group D were dropped out from the follow-up. Therefore, 128 patients were followed up until end points occurred or for 2 years after enrollment if no event occurred. Table 2 summarizes the baseline characteristics of patients. No variables at entry in the study differed significantly among the four groups.

The primary end point was observed in 3 (16.7%) in Group A, in 2 (6.7%) in Group B, in 3 (11.5%) in Group C, and 1 (1.9%) in Group D (Table 3). Of these, only 2 patients [1 (5.6%) in Group A and 1 (3.3%) in Group B] experienced recurrence of ipsilateral stroke (Table 3). Other primary end points observed were as follows: 3 patients died of cardiac diseases (1 in Group A, 1 in Group C, and 1 in Group D), 1 died of cancer (in Group C), and 3 patients underwent EC-IC bypass determined by neurologists (1 in Group A, 1 in Group B, and 1 in Group C). The rates of the primary end point and the secondary end point did not differ among the four groups ($P = 0.13$ for the primary end point, $P = 0.29$ for the secondary end point, χ^2 test). Cox regression analysis revealed that the hazard ratios

Table 2 Baseline characteristics

	Group A (n = 18)	Group B (n = 30)	Group C (n = 26)	Group D (n = 54)	P value
Age, yr (mean ± SD)	64.1 ± 6.7	62.4 ± 8.4	58.2 ± 11.5	60.9 ± 9.3	0.19
Male	14 (77.8%)	27 (90%)	22 (84.6%)	43 (79.6%)	0.6
Hypertension	9 (50%)	19 (63.3%)	10 (38.5%)	32 (59.3%)	0.23
Diabetes	6 (33.3%)	6 (20%)	5 (19.3%)	14 (25.9%)	0.67
Hypercholesterolemia	7 (38.9%)	8 (26.7%)	6 (23.1%)	10 (18.5%)	0.36
Prior MI	1 (5.6%)	2 (6.7%)	2 (7.7%)	5 (9.3%)	0.95
Prior stroke	1 (5.6%)	2 (6.7%)	1(3.9%)	2 (3.7%)	0.93
Entry event type					
transient ischemic attack	11 (61.1%)	16 (53.3%)	12 (46.2%)	26 (48.2%)	0.75
completed stroke	7 (38.9%)	14 (46.7%)	14 (53.9%)	28 (51.9%)	
Entry event side					
right	8 (44.4%)	15 (50%)	9 (34.6%)	28 (51.9%)	0.52
left	10 (55.6%)	15 (50%)	17 (65.4%)	26 (48.2%)	
Responsible lesion for entry event					
ICA	10 (55.6%)	17 (56.7%)	16 (61.5%)	36 (66.7%)	0.76
MCA	8 (44.4%)	13 (43.3%)	10 (38.5%)	18 (33.3%)	

ICA: internal carotid artery, MCA: middle cerebral artery, MI: myocardial infarction, SD: standard deviation, yr: year.

of Group A to Group D were 1.22 (95% confidence interval, 0.68–2.08) as to the primary end point and 1.07 (95% confidence interval, 0.60–1.83) as to the secondary end point. Kaplan-Meier analysis and the log-rank test also showed the cumulative event-free survival rate was not different among the four groups (P = 0.15 for the primary end point, P = 0.30 for the secondary end point) (data not shown). Univariate Cox regression analysis showed that no risk factors including CBF classification selected as covariates were significant (Table 4). Thus, multivariate analysis was not performed.

In the medical arm of the JET study, the primary end point was observed in 17 (16.6%) and secondary end point (including ipsilateral stroke recurrence and bypass surgery determined by neurologists) was observed in 11 (10.7%) (Table 5), which were significantly higher than those in patients enrolled in the JET-2 study (P = 0.02 for the primary end point, P = 0.04 for the secondary end point, χ^2 test). Fig. 2 shows the Kaplan-Meier survival curves for the primary and secondary end points of the medical arm of the JET study and the JET-2 study. The log-rank test revealed that the JET group was at significantly higher risk than the JET-2 group for both the primary end point (P = 0.02) and the secondary end point (P = 0.04).

Table 3 End point rate

	Group A (n = 18)	Group B (n = 30)	Group C (n = 26)	Group D (n = 54)	P value
Primary end point	3 (16.7%)	2 (6.7%)	3 (11.5%)	1 (1.9%)	0.13
stroke	1	1			
death	1		2	1	
EC-IC bypass	1	1	1		
Secondary end point	1 (5.6%)	1 (3.3%)	0	0	0.29

EC-IC: extracranial-intracranial.

Table 4 Univariate Cox regression analysis of risk factors for the primary end point

	Primary end point		P value
	Hazard ratio	95% CI	
Age > 65 yr	1.91	0.50 – 7.70	0.33
Male	1.68	0.31 – 31.2	0.6
Hypertension	0.64	0.16 – 2.43	0.51
Diabetes	1.56	0.33 – 5.91	0.54
Hypercholesterolemia	0.87	0.13 – 3.61	0.86
Prior MI	3.6	0.54 – 14.9	0.16
Entry event type			
TIA	1.22	0.32 – 4.92	0.77
Entry event side			
right	1.4	0.37 – 5.64	0.62
Responsible lesion for entry event			
ICA	2.17	0.52 – 14.6	0.3
CBF classification (to Group D)*			
Group A	9.29	0.97 – 89.3	0.054
Group B	3.73	0.67 – 61.5	0.28
Group C	6.39	0.68 – 1.81	0.11

*Group D was considered as a reference. CI: confidence interval, ICA: internal carotid artery, MI: myocardial infarction, TIA: transient ischemic attack.

Discussion

The present study demonstrated that patients with major cerebral arterial occlusive diseases showing mild hemodynamic compromise carry a relatively low risk of stroke recurrence. The overall rate of ipsilateral stroke recurrence was 0.8%/year and distinctly lower than that in the medical arm of the JET study. In the JET-2 study, patients were divided into four groups according to the severity of CBF in order to find the threshold of CBF and CVR for stroke recurrence. However, because of the low rate of vascular events in all groups, there was no significant difference among the groups in terms of end point rates and an event-free survival rate. Instead, the rates of both adverse events (primary end point) and recurrence of ipsilateral stroke including EC-IC bypass surgery determined by neurologists (secondary

Table 5 End point rate (JET vs. JET-2)

	JET-2 (n = 128)	Medical arm of JET (n = 103)	P value
Primary end point	9 (7.0%)	17 (16.6%)	0.02
any stroke	2	9	
death	4	2	
MI		2	
EC-IC bypass	3	4	
Secondary end point	5 (3.9%)	11 (10.3%)	0.04
ipsilateral stroke	2	7	
EC-IC bypass	3	4	

JET: Japanese extracranial-intracranial bypass trial, EC-IC: extracranial-intracranial, MI: myocardial infarction.

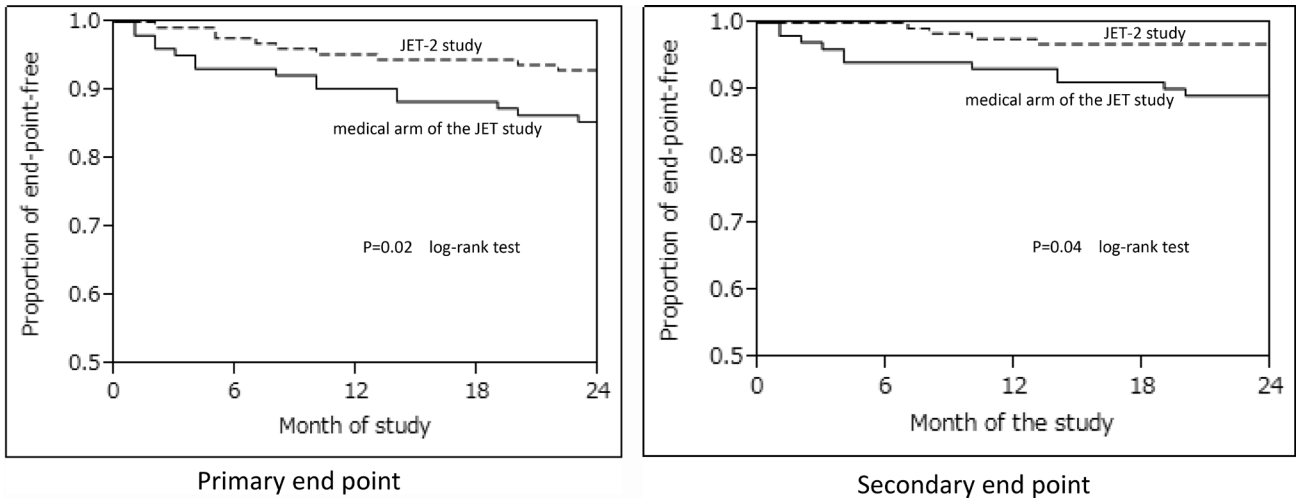


Fig. 2 Kaplan Meier survival curves for end points of the medical arm of the JET study and the JET-2 study. The curves of the two study groups differed significantly by log rank test (P = 0.02 for the primary end point, P = 0.04 for the secondary end point). JET: Japanese extracranial-intracranial bypass trial.

end point) were significantly higher in the medical arm of the JET study than those in patients enrolled in the JET-2 study. Inclusion criteria and exclusion criteria in these two groups were identical except for values of rest CBF and CVR at the entry, and patients in both groups were followed up for 2 years receiving medical treatment. Therefore, these results suggest that "rest CBF < 80% and CVR < 10%" is the threshold of hemodynamic compromise beneath which the risk of stroke recurrence increases in patients with symptomatic major arterial occlusive diseases, if treated medically.

The hemodynamic status of an occlusive disease has been categorized into three stages.[14] Stage 0 represents normal cerebral hemodynamics. Stenosis or occlusion of major cerebral arteries can cause a reduction in the perfusion pressure in their vascular territories if collaterals are not adequate. At first, autoregulatory vasodilation maintains normal CBF (Stage 1 hemodynamic ischemia).[14] When perfusion pressure decreases further, CBF begins to decrease, and the brain tissue increases oxygen extraction fraction (OEF) to maintain cerebral oxygen metabolism and function (Stage 2 hemodynamic ischemia).[14] Previous prospective studies demonstrated that increased OEF on PET is predicative of recurrent ischemic stroke in symptomatic major cerebral arterial occlusive diseases.[4,5] Although PET has the advantage of being able to directly detect stage 2 hemodynamic ischemia, its clinical availability is limited by high cost and complexity. Diminished vascular reactivity in response to acetazolamide challenge with reduced rest CBF quantified by SPECT is also proven independent predictors of increased risk for stroke recurrence in patients with symptomatic major cerebral arterial occlusive diseases.[6–10] Several previous reports stated the correlation between compromised CVR and high OEF.[9,15,16] Pindzola et al. reported that CVR was able to identify all regions with elevated OEF at a CVR threshold of 10%,[17] showing significant agreement with the CVR threshold derived from the JET and JET-2 study.

EC-IC bypass surgery can restore the perfusion pressure in the area of stage 2 hemodynamic ischemia and has been expected to have the preventive effect on stroke recurrence in patients with cerebral arterial occlusive diseases. The JET study demonstrated, for the first time, the preventive effect of EC-IC bypass on stroke recurrence in selected patients (rest CBF < 80% and CVR < 10%). Based on the result of a subgroup analysis in the JET study showing that the recurrence rate of ipsilateral stroke in medically treated patients was not different between the moderate ischemia subgroup (0% < CVR < 10%) and the severe ischemia subgroup (CVR < 0%), the JET-2 study was planned to identify the true threshold of CBF and CVR for the selection of patients who are benefited from EC-IC bypass surgery. Initially, the threshold was assumed to exist in the range of hemodynamic ischemia milder than JET study inclusion criteria. However, results of the JET-2 study strongly suggested that the CBF threshold of inclusion criteria of the JET study was the true threshold of the surgical indication of EC-IC bypass surgery. The preventive effect of EC-IC bypass surgery on stroke recurrence is still controversial, because carotid surgery occlusion

study (COSS) failed to demonstrate the benefit of EC-IC bypass surgery over medical treatments for patients with symptomatic ICA occlusion and severe hemodynamic ischemia evaluated by PET.[18] High incidence of the early postoperative stroke prevented COSS from proving the effectiveness of EC-IC bypass. The failure of COSS is partly because of the semiquantitative OEF ratio used for the patient selection.[19] The results of the JET-2 study also warn that surgical indication for EC-IC bypass surgery should be decided based on the strict evaluation of hemodynamics by a quantitative method.

Some limitations exist in the JET-2 study. First, the JET-2 study is a multicenter study, thus the methods of CBF measurement includes various modalities. The normal values of rest CBF and CVR differs among participating institutes. To minimize the difference among institutes, we expressed rest CBF as the relative value to the normal control value of each institute. The dose and timing of the administration of acetazolamide was consolidated. However, the degree of hemodynamic impairment by one method does not necessarily correspond to that by another. Second, the number of cases in each CBF group was not large enough to show statistically significant difference. There is a possibility that the threshold of CBF exists between Group A and B in terms of all adverse events (the primary end point). However, given the extremely low rate of stroke recurrence in the whole JET-2 group, it is reasonable and proper to consider that the threshold of CBF for stroke recurrence lies between the criteria of the JET study and the JET-2 study (rest CBF < 80% and CVR < 10%).

Conclusion

The JET-2 study revealed a good prognosis of medically treated patients with symptomatic major cerebral arterial occlusive diseases showing mild hemodynamic compromise. The rate of stroke recurrence in medically treated patients increased if rest CBF was less than 80% of a normal value and CVR was less than 10%. EC-IC bypass surgery is unlikely to benefit patients with rest CBF > 80% or CVR > 10%.

Acknowledgments

This study was supported by research grants cardiovascular diseases (16C-13 and 18C-22) from the Ministry of Health, Labor, and Welfare of Japan.

Clinical trial registration: http://www.umin.ac.jp/ctr/index.htm. Unique identifier: C000000171

Conflicts of Interest Disclosure

The authors report no conflicts of interest relevant to the research. All authors who are members of The Japan Neurosurgical Society have registered online Self-reported COI Disclosure Statement Form.

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Appendix: Study Organization

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