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Is misery perfusion still a predictor of stroke in symptomatic major cerebral artery disease?

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Studies in the 1990s demonstrated that misery perfusion is a predictor of subsequent stroke in medically treated patients with symptomatic major cerebral artery disease. A recent randomized controlled trial demonstrated no benefit of bypass surgery for such patients. In this light, outcome in patients with misery perfusion has regained interest. The purpose of this study was to determine whether misery perfusion is still a predictor of subsequent stroke despite recent improvements in medical treatment for secondary prevention of stroke, and if so, whether the predictive value of misery perfusion has changed in recent years. We prospectively studied 165 non-disabled patients with symptomatic atherosclerotic internal carotid artery or middle cerebral artery occlusive diseases who underwent positron emission tomography from 1999 to 2008. Misery perfusion was defined as decreased cerebral blood flow, increased oxygen extraction fraction and decreased ratio of cerebral blood flow to blood volume in the hemisphere supplied by the diseased artery. All patients were followed up for 2 years until stroke recurrence or death. Bypass surgery was performed in 19 of 35 patients with and 16 of 130 patients without misery perfusion. The 2-year incidence of ipsilateral ischaemic stroke was six and four patients with and without misery perfusion, including two and one after surgery, respectively ($P < 0.002$). Total strokes occurred in nine patients with misery perfusion and 12 patients without ($P < 0.01$). The relative risk conferred by misery perfusion in whole sample was 6.3 (95% confidence interval 1.7–22.4, $P < 0.005$) for ipsilateral ischaemic stroke and 3.5 (95% confidence interval 1.4–8.9, $P < 0.01$) for all strokes, while the respective values in medically treated patients were 12.6 (95% confidence interval 2.7–57.8, $P < 0.005$) and 4.7 (95% confidence interval 1.3–16.3, $P < 0.02$). The all-stroke incidence in patients entering the study from 2004 to 2008 (4/72) was significantly lower than in those entering from 1999 to 2003 (17/93; $P < 0.02$), although the prevalence of misery perfusion or bypass surgery did not differ. Between these periods, patients without misery perfusion demonstrated a decrease in stroke rate (from 16.2% to 0%), but patients with misery perfusion did not (26.3 and 25.0%). In symptomatic major cerebral artery disease, misery perfusion remains a predictor of subsequent stroke, although the recurrence rate was lower than the previous study. In patients without misery

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perfusion, the risk of stroke was reduced over time. Thus, identification and stricter management of patients with misery perfusion are essential to further improve prognosis.

Keywords: cerebrovascular disease; positron emission tomography; misery perfusion; prognosis

Abbreviations: EC/IC = extracranial to intracranial; ICA = internal carotid artery; MCA = middle cerebral artery; OEF = oxygen extraction fraction

Introduction

In patients with atherosclerotic internal carotid artery (ICA) or middle cerebral artery (MCA) occlusive disease, chronic reduction in cerebral perfusion pressure (chronic haemodynamic compromise) increases the risk of cerebral ischaemic damage (Baron *et al*., 1981; Powers, 1991; Klijn and Kappelle, 2010). Previous studies have shown that chronic haemodynamic compromise, as indicated by increased oxygen extraction fraction (OEF; misery perfusion; Baron *et al*., 1981) on PET or severely decreased vasodilatory capacity, is a risk factor for subsequent ischaemic stroke in atherosclerotic ICA or MCA occlusive disease (Yamauchi *et al*., 1996, 1999*a*; Grubb *et al*., 1998; Derdeyn *et al*., 1999; Vernieri *et al*., 1999; Kuroda *et al*., 2001; Markus and Cullinane, 2001; Ogasawara *et al*., 2002). Thus, correct evaluations of haemodynamic status are essential to determine patient prognosis, and therapeutic strategies to prevent recurrent strokes should differ between patients with and without haemodynamic compromise. However, strategies for selecting treatments based on haemodynamic measurements have not been clearly established.

Extracranial to intracranial (EC/IC) bypass surgery, which has no benefit in patients with ICA or MCA occlusive disease, in general (The EC/IC Bypass Study Group, 1985), may prevent recurrent strokes in select patients with haemodynamic compromise. To test this hypothesis, two randomized clinical trials have used haemodynamic criteria for patient selection (JET Study Group, 2002; Powers, 2011; Powers *et al*., 2011). One study using PET (Carotid Occlusion Surgery Study 2002–2010) reported a lack of benefit from bypass surgery in patients with symptomatic carotid occlusion and misery perfusion (hemispheric OEF ratio >1.13; Powers *et al*., 2011). The 2-year ipsilateral stroke rate was 23% in the medical group and 21% in the surgical group. The stroke rate in the medical group was much lower than the rate of 40% projected from a previous study carried out from 1992–7 (Grubb *et al*., 1998), which presumably reflects the overall increased efficacy of recent medical treatment for secondary stroke prevention (Abbott, 2009; Chimowitz *et al*., 2011). Thus, in addition to the issue of the hemispheric OEF ratio method to detect high risk patients (Carlson *et al*., 2011), outcome in patients with misery perfusion *per se* has regained interest.

After demonstrating in the 1990s at Kyoto University that patients with atherosclerotic ICA or MCA occlusive disease and misery perfusion on PET have high risk for recurrent stroke (Yamauchi *et al*., 1996, 1999*a*), we incorporated PET haemodynamic evaluation into routine clinical practice at Shiga Medical Centre. PET findings, specifically the presence of misery perfusion, were used to inform attending physicians, but the treatment of risk factors and use of drugs or EC/IC bypass were left to individual clinical judgement. Although the benefit from EC/IC bypass in patients with misery perfusion has not been proven yet, the operation is nevertheless performed in some patients in Japan and elsewhere. EC/IC bypass may reduce the recurrent stroke rate in patients with misery perfusion, which may in turn decrease the difference in stroke risk between patients with and without misery perfusion. In contrast, the improvement of medical treatments in recent years may reduce the recurrent stroke rate in general (Abbott, 2009; Chimowitz *et al*., 2011), which may also affect the predictive value of misery perfusion for stroke risk. Distinguishing between these two effects may be useful to further improve patient prognosis.

The purpose of this observational study conducted from 1999 to 2010 was to determine whether misery perfusion on PET is still a predictor of subsequent stroke in patients with symptomatic ICA or MCA occlusive disease under the use of EC/IC bypass and standard current medical treatments as therapeutic options in routine clinical practice, and if so, whether the predictive value of misery perfusion for stroke risk has changed in recent years.

Materials and methods

Patients

We studied 165 consecutive symptomatic patients with atherosclerotic occlusive disease of the major cerebral artery. Patients were first referred to our PET unit at Shiga Medical Centre from 1999 to 2008 to evaluate the haemodynamic effect of artery disease as part of clinical evaluations to determine the necessity of EC/IC bypass. Inclusion criteria were as follows: (i) occlusion of the extracranial ICA, or occlusion or stenosis ($>50\%$ diameter reduction) of the intracranial ICA or MCA as documented by conventional or magnetic resonance angiography (Samuels *et al*., 2000); (ii) ability to independently carry out daily life activities (score on modified Rankin scale <3) and (iii) history of transient ischaemic attack or complete stroke involving the relevant ICA or MCA territory. Transient ischaemic attack was defined as the development of focal symptoms of presumed ischaemic cerebrovascular origin lasting <24 h. The exclusion criteria were: (i) history of vascular reconstruction surgery or (ii) presence of potential sources of cardiogenic embolism, including recent myocardial infarction (<3 weeks previous), known atrial fibrillation, mitral stenosis, mitral valve prosthesis, dilated cardiomyopathy, sick sinus syndrome or subacute bacterial endocarditis.

Patients included 126 males and 39 females aged 44–90 years (mean $\pm$ SD: 63 $\pm$ 8 years; Table 1). Twenty-seven patients had transient ischaemic attack and 138 had minor stroke. All but two patients had symptoms of cerebral hemispheric rather than retinal ischaemia.

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Table 1 Characteristics of patients with and without misery perfusion

Characteristics	Categorizations Misery perfusion	
	Present	Absent
No. of patients	35	130
Study period (1999–2003/2004–08), *n*	16/19	59/71
Age, mean ± SD, years	63 ± 8	63 ± 8
Sex, male/female, *n*	26/9	100/30
Diagnosis, *n*		
Transient ischaemic attack (amaurosis/hemispheric)	5(0/5)	22 (2/20)
Minor stroke	30	108
Recurrent symptoms, *n*	20	50
After demonstration of arterial disease	6	24
Number of months between last symptom and PET, mean ± SD	12 ± 19	7 ± 14
Asymptomatic bilateral lacunar infarcts, *n*	7	29
Symptomatic qualifying artery, *n*		
Occlusion/stenosis	30/5	81/49
Extracranial ICA occlusion	23	54
Intracranial ICA (occlusion/stenosis)	5 (2/3)	17 (2/15)
MCA (occlusion/stenosis)	7 (5/2)	59 (25/34)
Other asymptomatic arterial stenosis >50%, *n*	15	35
Other medical illness, *n*		
Hypertension	22	81
Diabetes mellitus	17	43
Ischaemic heart disease	11	26
Hypercholesterolaemia	10	39
Smoking habit (current and former), *n*	13	47
Bypass surgery, *n*	19	16

The interval between the latest ischaemic event and PET evaluations was 8 ± 15 months (range: 4 days to 72 months). Recurrent symptoms prior to PET were identified in 70 patients, including 30 after angiographic demonstration of arterial disease.

In 9 of 27 patients with transient ischaemic attack, MRI was normal. In 156 patients, MRI disclosed only minor abnormalities in the MCA territory or watershed areas of the hemisphere with symptomatic arterial disease. Thirty-six patients demonstrated asymptomatic lacunar infarcts in the bilateral basal ganglia (putamen, globus pallidus and caudate nucleus) on MRI, which were identified as increased signal intensity on FLAIR images with decreased signal intensity on T_1-weighted images. Symptomatic qualifying artery included extracranial ICA occlusion in 77 cases, intracranial ICA occlusion in four cases, intracranial ICA stenosis in 18 cases, MCA occlusion in 30 cases and MCA stenosis in 36 cases. Other asymptomatic arterial stenosis (>50% diameter reduction; North American Symptomatic Carotid Endarterectomy Trial Collaborators, 1991; Samuels *et al*., 2000) was found in 50 cases (53 arteries), including contralateral ICA disease in 28 cases, contralateral MCA disease in 14 cases and vertebral artery disease in 11 cases. Among vascular risk factors, hypertension, diabetes mellitus, ischaemic heart disease, hypercholesterolaemia and smoking status were evaluated from patient history recorded at PET examination (Table 1). Hypertension, diabetes mellitus, ischaemic heart disease and hypercholesterolaemia were judged as present based on treatment history. The ethics committee of our centre approved the protocol of this study. Each patient provided written informed consent for this study.

Positron emission tomography measurements

All patients underwent PET scans with a whole-body Advance PET scanner (General Electric Medical System), which permits simultaneous acquisition of 35 image slices with interslice spacing of 4.25 mm (Okazawa *et al*., 2001). Intrinsic scanner resolution was 4.6–5.7 mm in the transaxial direction and 4.0–5.3 mm in the axial direction. As part of the scanning procedure but before tracer administration, $^{68}Ge/^{68}Ga$ transmission scanning was performed for 10 min for attenuation correction. To reconstruct the PET data, images were blurred to 6.0 mm full-width at half-maximum in the transaxial direction using a Hanning filter. Functional images were reconstructed as 128 × 128 pixels, with each pixel representing an area of 2.0 × 2.0 mm.

A series of ^{15}O gas studies was performed. $C^{15}O_2$ and $^{15}O_2$ were inhaled continuously through a mask (Okazawa *et al*., 2001). The scan time was 5 min, and arterial blood was sampled manually from the brachial artery three times during each scan. The radiotracer radioactivity in whole blood and plasma was measured using a well counter. Bolus inhalation of $C^{15}O$ with 3-min scanning was used to measure cerebral blood volume. Arterial samples were manually obtained twice during scanning, and radiotracer radioactivity was measured in whole blood. Cerebral blood flow, cerebral metabolic rate of oxygen and OEF were calculated based on the steady-state method (Frackowiak *et al*., 1980). Cerebral metabolic rate of oxygen and OEF were corrected by cerebral blood volume (Lammertsma and Jones, 1983). The ratio of cerebral blood flow to cerebral blood volume was calculated pixel-by-pixel as an indicator of cerebral perfusion pressure (Schumann *et al*., 1998).

Data analysis

We analysed 10 tomographic planes from 46.25 mm to 84.5 mm above and parallel to the orbitomeatal line, which corresponded to the levels from the basal ganglia and thalamus to the centrum semiovale. The region of interest was placed on the cerebral blood flow images. Each image was examined by placing 10–12 circular regions of interest 16 mm in diameter compactly over the grey matter of the outer cortex in each hemisphere. According to the atlas (Kretschmann and Weinrich, 1986), the regions of interest in all 10 images covered the distribution of the MCA as well as the watershed areas between the anterior cerebral artery and MCA and between the MCA and posterior cerebral artery (Yamauchi *et al*., 1990*b*). The same regions of interest were transferred to the other images. The mean hemispheric values in each hemisphere were calculated as the average of the values of all circular regions of interest. In patients with infarction in the cerebral cortex, the circular regions of interest that overlapped low-intensity areas on T_1-weighted magnetic resonance images were excluded from analysis using a simple method correlating PET images with magnetic resonance images (Yamauchi *et al*., 1990*a*).

Normal control values of the PET variables were obtained from seven normal volunteers (four males and three females), mean age (±SD) 47 (±7) years who underwent normal routine neurological examinations and MRI scans. The mean ± SD OEF value in the 14 control hemispheres was 44.5 ± 3.8%. Hemispheric OEF values beyond the upper 95% limit defined in normal subjects (>52.9%) were considered to represent increased OEF. Comparative values for

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cerebral blood flow and cerebral blood flow/cerebral blood volume ratio in normal volunteers were 44.6 ± 4.5 and 11.4 ± 1.8, respectively. Hemispheric cerebral blood flow and cerebral blood flow/cerebral blood volume values <35.0 ml/100 g/min and 7.6/min, respectively, were considered abnormal. Patients with increased OEF, decreased cerebral blood flow and decreased cerebral blood flow/cerebral blood volume ratio in hemispheres with arterial disease were categorized as having misery perfusion. This definition was adopted because increased OEF alone may not indicate misery perfusion if without decreased perfusion pressure (Schumann *et al*., 1998). One investigator unaware of patients' clinical status categorized the patients.

Follow-up and outcome

Attending physicians were informed of PET findings, but treatment of risk factors and use of drugs or EC/IC bypass was left to individual clinical judgement. All patients were examined at 1- or 2-month intervals after PET studies in the outpatient clinic in our centre or related hospitals in Shiga prefecture. At each visit, an interim history was obtained, and a neurological examination was performed. In patients with recurrent stroke, MRI or CT scan was obtained and compared with initial studies to confirm recurrent stroke, and magnetic resonance angiography was performed to study changes in arterial disease. The primary endpoint was ipsilateral recurrent ischaemic stroke defined as the acute onset of new focal neurological deficit of cerebral origin persisting for >24 h in a previously symptomatic arterial territory without primary intracranial haemorrhage on CT or MRI scan. The secondary endpoint was any ischaemic or haemorrhagic stroke.

Statistical analysis

Clinical backgrounds were compared between groups using Student's *t*-test or the chi-squared test, as appropriate. The incidence of recurrent stroke was compared between groups using the Mantel–Cox log-rank statistics and Kaplan–Meier survival curves. Survival analysis of subsequent endpoints began on the day of PET examination, which was considered the date of entry into the study. Multivariate analysis with the Cox proportional hazards model was used to test the effect of multiple variables on stroke recurrence. Age, sex, recurrent symptoms (recurrent episodes of ischaemic attack prior to PET or after angiographic demonstration of arterial disease), time between the last symptoms and PET, bypass surgery, symptomatic arterial occlusion, extracranial ICA occlusion, other asymptomatic major cerebral arterial stenosis (North American Symptomatic Carotid Endarterectomy Trial Collaborators, 1991; Samuels *et al*., 2000), bilateral asymptomatic lacunar infarcts, complications (hypertension, diabetes mellitus, prior ischaemic heart disease, hypercholesterolaemia), smoking habit, time of enrolment and misery perfusion or increased OEF were considered covariates. A forward stepwise selection was performed and variables demonstrating a significant relationship ($P < 0.05$) with an outcome event were included in the final model.

Results

Patient categorization

Based on OEF, cerebral blood flow and cerebral blood flow/cerebral blood volume values in the hemisphere supplied by the previously symptomatic artery, 35 patients (21%) had misery perfusion and 130 did not (Table 1). No patient characteristics significantly differed between the two groups. Thirty-five patients (21%), including 19 with misery perfusion and 16 without (Fisher's exact test, $P < 0.001$), underwent EC/IC bypass a median of 2.2 months after PET examinations (range: 0.2–15.0 months). All but two patients were treated with anti-platelet therapy. Twenty-two of 57 patients with increased OEF values did not show decreased cerebral blood flow or decreased cerebral blood flow/cerebral blood volume ratio.

Comparison of stroke risk in patients with and without misery perfusion

All patients were followed for 2 years until stroke recurrence or death. During this period, recurrent stroke occurred in 21 patients (12.7%). Ten of these 21 patients had ipsilateral ischaemic stroke (primary endpoint), while one ipsilateral haemorrhage and 10 strokes in another vascular territory were observed (secondary endpoint). Six patients (3.6%) died during follow-up.

In patients with and without misery perfusion, the 2-year incidence of ipsilateral ischaemic stroke was 6/35 (17.1%) and 4/135 (3.1%), respectively (Table 2), and the all-stroke incidence was 9 (25.7%) and 12 (9.2%), respectively. Death occurred in one patient with misery perfusion and five patients without. Using Kaplan–Meier survival curves, the risk of ipsilateral ischaemic stroke and all strokes was significantly higher in patients with misery perfusion than those without ($P = 0.0018$ and $P = 0.0074$, respectively; Fig. 1).

Analysis of 130 patients with medical treatments demonstrated similar results (Table 2 and Fig. 1). In patients with and without misery perfusion, the 2-year incidence of ipsilateral ischaemic stroke was 4/16 (25%) and 3/114 (2.6%), respectively (Table 2), and the all-stroke incidence was 4 (25%) and 9 (7.9%), respectively. The risk of ipsilateral ischaemic stroke and all strokes was significantly higher in medically treated patients with misery perfusion than in those without ($P = 0.0002$ and $P = 0.03$, respectively).

In 22 patients with increased OEF who did not have decreased cerebral blood flow or decreased cerebral blood flow/cerebral blood volume ratio, only one stroke (ipsilateral ischaemic stroke) occurred after bypass surgery in combination with aneurysm treatment. In patients with and without increased OEF, the 2-year incidence of ipsilateral ischaemic stroke was 7/57 (12.3%) and 3/108 (2.8%), respectively, and the all-stroke incidence was 10 (17.5%) and 11 (10.2%), respectively (Table 2). The risk of ipsilateral ischaemic stroke was significantly higher in patients with increased OEF than those without ($P = 0.016$) but that of all strokes was not ($P = 0.18$). Analysis of 130 patients with medical treatments demonstrated similar results ($P = 0.043$ and $P = 0.61$, respectively; Table 2).

In 35 surgically treated patients with and without misery perfusion, the 2-year incidence of ipsilateral ischaemic stroke was 2/19 (10.5%) and 1/16 (6.3%), respectively (log rank test, $P = 0.63$; Table 2), and the all-stroke incidence was five (26.3%) and three (18.8%), respectively ($P = 0.59$).

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Table 2 Two-year stroke occurrence and misery perfusion

	Total sample (n = 165)	With misery perfusion (n = 35)	Without misery perfusion (n = 130)	Increased OEF (n = 57)	Normal OEF (n = 108)
Ipsilateral ischaemic stroke					
Total	10 (6.1%)	6 (17.1%)	4 (3.1%)	7 (12.3%)	3 (2.8%)
Medical (n = 130)	7 (5.4%)	4/16 (25%)	3/114 (2.6%)	4/32 (12.5%)	3/98 (3.1%)
Surgical (n = 35)	3 (8.6%)	2/19 (10.5%)	1/16 (6.3%)	3/25 (12.0%)	0/10 (0%)
All stroke					
Total	21 (12.7%)	9 (25.7%)	12 (9.2%)	10 (17.5%)	11 (10.2%)
Medical	13 (10%)	4/16 (25%)	9/114 (7.9%)	4/32 (12.5%)	9/98 (9.2%)
Surgical	8 (22.9%)	5/19 (26.3%)	3/16 (18.8%)	6/25 (24.0%)	2/10 (20%)

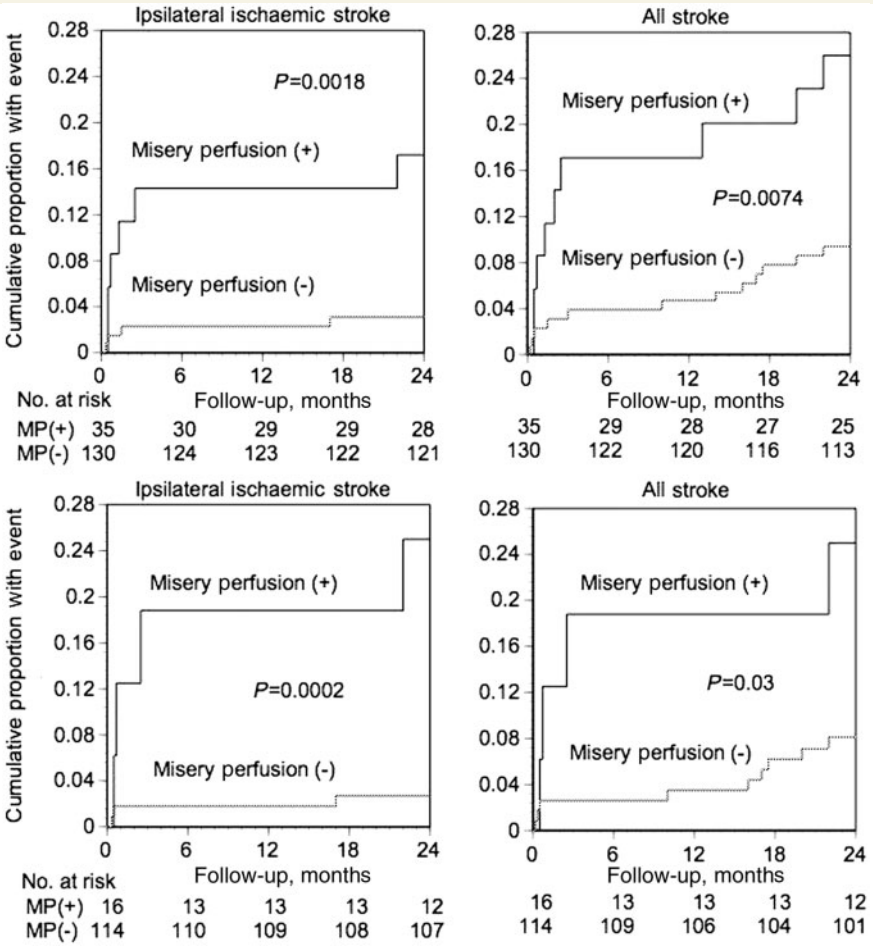

Figure 1 Kaplan–Meier cumulative failure curves for ipsilateral ischaemic stroke (*left*) and all strokes (*right*) in all patients (*top* panels) and in medically treated patients (*bottom* panels) with (solid lines) and without (dotted lines) misery perfusion. The number of patients who remained event free and available for follow-up evaluation during each 6-month interval is shown at the bottom of the graph.

Characteristics of recurrent stroke

Recurrent stroke under medical treatment occurred in 13 patients, including seven ipsilateral ischaemic strokes and six strokes in another vascular territory (Table 2). All but one recurrent stroke was located in the subcortical regions. In 16 medically treated patients with misery perfusion, four (25%) ipsilateral ischaemic strokes occurred, two within 30 days after PET examinations in patients with extracranial ICA occlusions that were enlargements of internal border zone infarcts at baseline, including one during catheter angiographic examination. After 1 month, one patient with MCA stenosis developed internal border zone infarction with

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progression of MCA stenosis at recurrence, and one with intracranial ICA stenosis developed lacunar infarction. The other three ipsilateral ischaemic strokes occurred in patients without misery perfusion. One patient with extracranial ICA occlusion developed an enlargement of internal border zone infarction at baseline with ischaemic heart attacks during catheter angiographic examination. One with intracranial ICA stenosis also developed an enlargement of internal border zone infarction at baseline. One lacunar infarction occurred in a patient with MCA stenosis.

All six strokes in another vascular territory occurred in patients without misery perfusion. Three ischaemic strokes in another vascular territory were associated with the presence of concomitant major arterial disease (a lacunar infarction with intracranial ICA stenosis emerged at recurrence, a corpus callosum infarction with anterior cerebral artery stenosis at baseline, and a cerebellar infarction with vertebro-basilar artery stenosis at baseline). One pontine lacunar infarction was associated with medication suicide (benzodiazepines and antihypertensive drugs), and one putaminal and one subcortical haemorrhage in another vascular territory were also observed.

Recurrent stroke after EC/IC bypass occurred in eight patients (Table 2). Three ipsilateral ischaemic strokes occurred within 30 days, one ipsilateral haemorrhage after 1.1 month, and four ischaemic strokes in another vascular territory after 1 month (1.7, 12.7, 13.4 and 18.2 months). In 19 surgically treated patients with misery perfusion, two ipsilateral ischaemic strokes occurred in the 30-day postoperative period in patients with extracranial ICA occlusion (perioperative stroke rate of 10.5%), and no additional patients experienced an ipsilateral ischaemic stroke during the 2-year follow-up period. One ipsilateral ischaemic stroke that occurred within 30 days in a patient without misery perfusion was associated with aneurysm treatment performed in combination with bypass surgery. This stroke was the only such event in a patient with increased OEF who did not have decreased cerebral blood flow or decreased cerebral blood flow/cerebral blood volume ratio. All four ischaemic strokes in another vascular territory were associated with the presence of concomitant major arterial diseases (multiple small cortical infarctions with extracranial ICA stenosis at baseline, a large MCA territory infarction with progression of extracranial ICA stenosis to occlusion at recurrence, a lacunar infarction with MCA stenosis emerged at recurrence and a brainstem infarction with vertebral artery occlusion at baseline).

Effect of time of enrolment

Since the period of enrolment was long (~10 years) the predictive value of misery perfusion for stroke risk may have changed over time. To test this hypothesis, the 165 patients were divided into 93 patients enrolled during the first 5 years (1999–2003) and 72 enrolled during the second 5 years (2004–08; Table 3), and stroke incidence was compared between the two groups. Patient characteristics and the use of bypass surgery did not significantly differ between the two groups (Fisher's exact test, $P = 0.70$). However, patients were significantly more likely to take angiotensin receptor blockers after 2004 ($P < 0.02$), and an increased trend for statins was observed ($P = 0.054$). The risk of all-stroke in patients entering the study from 2004 to 2008 (4/72 patients) was significantly lower than that of patients from 1999 to 2003 (17/93; $P < 0.02$; Fig. 2). The stroke recurrence rate did not differ between patients with misery perfusion in the two groups (Fisher's exact test, $P > 0.99$; Table 4). Among patients without misery perfusion, patients from 1999 to 2003 had 12 strokes, while patients from 2004 to 2008 had no stroke recurrence ($P < 0.005$).

Analysis of 130 patients with medical treatments demonstrated similar results (Table 4 and Fig. 2). The risk of all-stroke in patients entering the study from 2004 to 2008 (2/58 patients) was significantly lower than that of patients from 1999 to 2003 (11/72, $P < 0.05$; Fig. 2). The stroke recurrence rate did not differ between patients with misery perfusion in the two groups (Fisher's exact test, $P = 0.61$; Table 4). Among patients without misery perfusion, patients from 1999 to 2003 had nine strokes, while patients from 2004 to 2008 had no stroke recurrence ($P < 0.005$).

Risk factors for recurrent stroke

Multivariate analysis with the Cox proportional hazards model demonstrated that only misery perfusion and bilateral asymptomatic lacunar infarcts were significant independent predictors for ipsilateral ischaemic stroke. Both variables, along with time of enrolment and the presence of other asymptomatic major cerebral arterial stenosis at baseline, were independent predictors for all strokes. The relative risk conferred by misery perfusion adjusted by other variables was 6.3 [95% confidence interval (CI), 1.7–22.4, $P < 0.005$] for ipsilateral ischaemic stroke and 3.5 (95% CI, 1.4–8.9, $P < 0.01$) for all strokes. The relative risk conferred by bilateral asymptomatic lacunar infarcts was 6.1 (95% CI, 1.7–21.8, $P < 0.01$) for ipsilateral ischaemic stroke and 5.5 (95% CI, 2.2–13.7, $P < 0.0005$) for all strokes. The relative risk for all strokes conferred by enrolment during the second 5 years and other asymptomatic major cerebral arterial stenosis was 0.25 (95% CI, 0.08–0.75, $P < 0.02$) and 2.9 (95% CI, 1.2–7.1, $P < 0.02$), respectively.

Analysis of 130 patients with medical treatments demonstrated that misery perfusion and bilateral asymptomatic lacunar infarcts were still significant independent predictors for both ipsilateral ischaemic stroke and all strokes. The relative risk conferred by misery perfusion was 12.6 (95% CI, 2.7–57.8, $P < 0.005$) for ipsilateral ischaemic stroke and 4.7 (95% CI, 1.3–16.3, $P < 0.02$) for all strokes.

Intracranial arterial disease and extracranial internal carotid artery occlusion

This study included 88 patients with intracranial arterial disease and 77 patients with extracranial ICA occlusion. Nineteen patients with intracranial arterial disease and 16 with extracranial ICA occlusion underwent EC/IC bypass. In 69 medically treated patients with intracranial arterial disease, four patients had misery perfusion and 65 did not. In patients with and without misery perfusion, the 2-year incidence of ipsilateral ischaemic stroke was 2/4 (50%) and 2/65 (3.0%), respectively. Using Kaplan–Meier survival curves, the

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Table 3 Characteristics of patients enrolled during the first and second 5 years of the study

Characteristics	Categorizations Time of enrolment	
	1999–2003	2004–08
No. of patients	93	72
Misery perfusion, *n*	19	16
Age, mean ± SD, years	64 ± 8	63 ± 8
Sex, male/female, *n*	72/21	54/18
Diagnosis, *n*		
Transient ischaemic attack (amaurosis/hemispheric)	16 (2/14)	11 (0/11)
Minor stroke	77	61
Recurrent symptoms, *n*	36	34
After demonstration of arterial disease	16	14
Number of months between last symptom and PET, mean ± SD	9 ± 16	8 ± 13
Asymptomatic bilateral lacunar infarcts, *n*	21	15
Symptomatic qualifying artery, *n*		
Occlusion/stenosis	59/34	52/20
Extracranial ICA occlusion	46	31
Intracranial ICA (occlusion/stenosis)	14 (0/14)	8 (4/4)
MCA (occlusion/stenosis)	33 (13/20)	33 (17/16)
Other asymptomatic arterial stenosis >50%, *n*	31	19
Other medical illness, *n*		
Hypertension	57	46
Angiotensin receptor blocker	7	16
Angiotensin converting enzyme inhibiter	16	7
Calcium channel blocker	35	22
Diabetes mellitus	31	29
Ischaemic heart disease	23	14
Hypercholesterolaemia	22	27
Statin	14	20
Smoking habit (current and former), *n*	29	31
Bypass surgery (misery perfusion), *n*	21 (9)	14 (10)

risk of ipsilateral ischaemic stroke was significantly higher in patients with misery perfusion than those without ($P < 0.0001$). Multivariate analysis with the Cox proportional hazards model demonstrated that only misery perfusion was a significant independent predictor for ipsilateral ischaemic stroke. The relative risk conferred by misery perfusion was 18.1 (95% CI, 2.5–129.6, $P < 0.005$) for ipsilateral ischaemic stroke.

In 61 medically treated patients with extracranial ICA occlusion, 12 patients had misery perfusion and 49 did not. In patients with and without misery perfusion, the 2-year incidence of ipsilateral ischaemic stroke was 2/12 (16.7%) and 1/49 (2.0%), respectively. The risk of ipsilateral ischaemic stroke was significantly higher in patients with misery perfusion than those without ($P < 0.05$). Multivariate analysis demonstrated that only misery perfusion and bilateral asymptomatic lacunar infarcts were significant independent predictors for ipsilateral ischaemic stroke. The relative risk conferred by misery perfusion adjusted by bilateral asymptomatic lacunar infarcts was 14.1 (95% CI, 1.2–163.3, $P < 0.05$) for ipsilateral ischaemic stroke.

Comparison of stroke risk in patients with and without oxygen extraction fraction asymmetry

The mean ± SD value of the right-to-left OEF ratio in the seven control subjects was 1.002 ± 0.015. The ipsilateral-to-contralateral OEF ratio beyond the upper 95% limit defined in normal subjects (above 1.039) was considered to represent increased OEF asymmetry. In 61 medically treated patients with extracranial ICA occlusion, 22 patients had increased OEF asymmetry and 39 patients did not. Among patients with increased OEF asymmetry, the incidence of misery perfusion and increased OEF was 7/22 and 9/22, respectively. In patients with and without increased OEF asymmetry, the 2-year incidence of ipsilateral ischaemic stroke was 2/22 (9.1%) and 1/39 (2.6%), respectively. Using Kaplan–Meier survival curves, the risk of ipsilateral ischaemic stroke was not significantly higher in patients with increased OEF asymmetry than those without ($P = 0.26$). When the ipsilateral-to-contralateral OEF ratio beyond the upper 99% limit (above 1.059) was used as a cut-off value, among patients with increased OEF asymmetry, the incidence of misery perfusion and increased OEF was 2/13 and 3/13, respectively. In patients with and without increased OEF asymmetry, the 2-year incidence of ipsilateral ischaemic stroke was 2/13 (15.4%) and 1/48 (2.1%), respectively. One stroke occurred in the patient with increased OEF asymmetry and misery perfusion. The risk of ipsilateral ischaemic stroke was significantly higher in patients with increased OEF asymmetry than those without ($P < 0.05$). Only three patients had the OEF ratio above 1.13 that is a cut-off value in the Carotid Occlusion Surgery Study trial. Among them, the incidence of misery perfusion and increased OEF was 2/3 and 2/3, respectively. In patients with and without the OEF ratio above 1.13, the 2-year incidence of ipsilateral ischaemic stroke was 1/3 (33%) and 2/58 (3.4%), respectively. The risk of ipsilateral ischaemic stroke was significantly higher in patients with the OEF ratio above 1.13 than those without ($P < 0.05$).

In 69 medically treated patients with intracranial arterial disease, 22 patients had increased OEF asymmetry (above 1.039) and 47 patients did not. Among patients with increased OEF asymmetry, the incidence of misery perfusion and increased OEF was 3/22 and 6/22, respectively. In patients with and without increased OEF asymmetry, the 2-year incidence of ipsilateral ischaemic stroke was 2/22 (9.1%) and 2/47 (4.3%), respectively. The risk of ipsilateral ischaemic stroke was not significantly higher in patients with increased OEF asymmetry than those without ($P = 0.42$). When the upper 99% limit (above 1.059) was used as a cut-off value, the results were similar. Among patients with increased OEF asymmetry, the incidence of misery perfusion and increased OEF was 0/11 and 1/11, respectively. In patients with and without increased OEF asymmetry, the 2-year incidence of ipsilateral ischaemic stroke was 0/11 (0%) and 4/58 (6.9%), respectively.

Discussion

This study conducted from 1999 to 2010 demonstrated that in patients with symptomatic major cerebral arterial occlusive disease,

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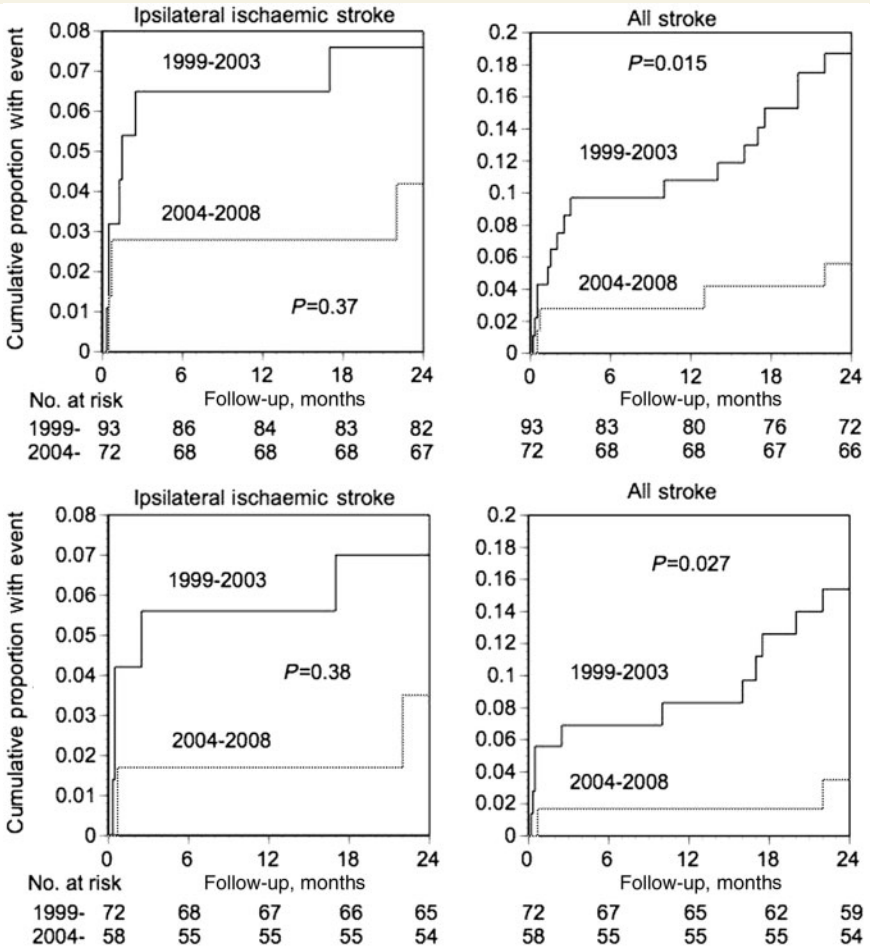

Figure 2 Kaplan–Meier cumulative failure curves for ipsilateral ischaemic stroke (*left*) and all strokes (*right*) in all patients (*top* panels) and in medically treated patients (*bottom* panels) in patients entering the study from 1999 to 2003 (solid lines) and 2004 to 2008 (dashed lines). The number of patients who remained event free and available for follow-up evaluation during each 6-month interval is shown at the bottom of the graph.

Table 4 Two-year stroke occurrence and time of enrolment

	Ipsilateral ischaemic stroke		All stroke	
	1999–2003 (*n* = 93)	2004–08 (*n* = 72)	1999–2003	2004–08
Total (*n* = 165)	7 (7.5%)	3 (4.2%)	17 (18.3%)	4 (5.6%)
Medical (*n* = 130)	5/72 (6.9%)	2/58 (3.4%)	11/72 (15.3%)	2/58 (3.4%)
Surgical (*n* = 35)	2/21 (9.5%)	1/14 (7.1%)	6/21 (28.5%)	2/14 (14.2%)
With misery perfusion (*n* = 35)	3/19 (15.8%)	3/16 (18.8%)	5/19 (26.3%)	4/16 (25%)
Medical (*n* = 16)	2/10 (20%)	2/6 (33%)	2/10 (20%)	2/6 (33%)
Surgical (*n* = 19)	1/9 (11%)	1/10 (10%)	3/9 (33%)	2/10 (20%)
Without misery perfusion (*n* = 130)	4/74 (5.4%)	0/56	12/74 (16.2%)	0/56
Medical (*n* = 114)	3/62 (4.8%)	0/52	9/62 (14.5%)	0/52
Surgical (*n* = 16)	1/12 (8.3%)	0/4	3/12 (25%)	0/4

misery perfusion is still an independent predictor of subsequent stroke risk over a 2-year follow-up period under the use of EC/IC bypass and recent standard medical treatments as therapeutic options in routine clinical practice. The 2-year incidence of ipsilateral ischaemic stroke (17.1%) and all strokes (26%) was higher in patients with misery perfusion at baseline than in those without (3.1 and 9.2%, respectively). The predictive value of misery perfusion for stroke risk changed over time, because only patients without misery perfusion showed a decrease in stroke rate over this period.

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Definition of misery perfusion

We defined misery perfusion as increased OEF, decreased cerebral blood flow and decreased cerebral blood flow/cerebral blood volume ratio, which differed from our previous study, where only increased OEF was used. In our previous study, patients with increased OEF also had decreased cerebral blood flow and decreased cerebral blood flow/cerebral blood volume ratio (Yamauchi *et al*., 1996), which is consistent with misery perfusion. In this study, however, cerebral blood flow and cerebral blood flow/cerebral blood volume ratio did not decrease in some patients with increased OEF. Several aged patients had anaemia with decreased blood O_2 content. Compensatory increase in cerebral blood flow may not change OEF under normal conditions (Hino *et al*., 1992) but may be insufficient in patients with brain atherosclerosis or arteriolosclerosis, leading to increased OEF without decreased cerebral blood flow or cerebral blood flow/cerebral blood volume ratio. The recurrence rate in patients with increased OEF without decreased cerebral blood flow or cerebral blood flow/cerebral blood volume ratio was low. Only one stroke occurred after bypass surgery in combination with aneurysm treatment. Patients with increased OEF without decreased cerebral blood flow or cerebral blood flow/cerebral blood volume ratio may not have decreased perfusion pressure despite decreased oxygen delivery. Thus, they may be at lower risk for stroke, although they may be at risk for hypoxic damage of cortical neurons (Yamauchi *et al*., 2007). A previous study of ICA occlusion also suggested that patients with increased OEF without increased cerebral blood volume may be at lower risk for stroke than those with increased OEF and increased cerebral blood volume (Derdeyn *et al*., 2002). We emphasize that 'complete' misery perfusion is a better predictor of stroke risk than increased OEF alone in patients with symptomatic major cerebral arterial occlusive disease.

In the Carotid Occlusion Surgery Study trial, misery perfusion was defined by hemispheric OEF ratio > 1.13 which was calculated from a quotient image of $O^{15}O/ H_2{}^{15}O$ PET counts. In this study, increased OEF ratio beyond the upper 95% limit defined in normal subjects (above 1.039) was not a predictor of stroke risk in patients with extracranial ICA occlusion or those with intracranial arterial disease, as already shown in our previous study, where the OEF ratio was calculated from a quantitative OEF image (Yamauchi *et al*., 1999*a*). Increased OEF ratio and increased OEF value did not identify the same patients as having misery perfusion. However, the OEF ratio beyond the upper 99% limit (above 1.059) or >1.13 was a predictor of stroke only in patients with extracranial ICA occlusion. The increased OEF ratio may be a predictor of stroke risk only when an appropriate cut-off value is selected in ICA occlusion, but may not in intracranial major arterial disease. These findings suggest that the PET method used in the Carotid Occlusion Surgery Study trial was accurate in selecting patients at high risk for recurrent stroke (Carlson *et al*., 2011; Powers *et al*., 2011). However, the PET method used here allowed effective stratification of high-risk patients regardless of whether the arterial disease affected the extracranial or intracranial vasculature.

Risk factor managements based on haemodynamic measurements

Improvement of medical secondary prevention may progressively decrease the recurrent stroke risk in patients with ICA or MCA occlusive disease (Abbott, 2009; Chimowitz *et al*., 2011). The 2-year recurrence rate in medically treated patients with or without misery perfusion in this study (25 and 2.6% for ipsilateral ischaemic stroke, respectively; Table 2) was lower than that in our previous study in the 1990s (57 and 6%; Yamauchi *et al*., 1996, 1999a). PET studies in North America (St. Luis Carotid Occlusion Study and Carotid Occlusion Surgery Study) have also shown reduction of the recurrent ipsilateral ischaemic stroke rate in medically treated patients with misery perfusion from the 1990s to 2000s (from 50% to 22.7% in patients with hemispheric OEF ratio >1.14 and 1.13, respectively; Derdeyn *et al*., 2000; Powers *et al*., 2011). The combination of these four PET studies shows that the 2-year recurrence rate was significantly decreased from 13/25 in the 1990s to 24/114 in the 2000s (Fisher's exact test, $P = 0.003$). This finding is also true in patients with decreases in cerebral blood flow and vasodilatory capacity [11/25 in the 1990s (Kuroda *et al*., 2001; Ogasawara *et al*., 2002) and 3/20 in the 2000s (Hokari *et al*., 2009); $P = 0.056$]. In the St. Luis Carotid Occlusion Study, treating physicians were blinded to PET results (Grubb *et al*., 1998). Thus, the knowledge of haemodynamic status in each patient as well as improvement of medical secondary prevention may have contributed to reduction of the recurrent ipsilateral ischaemic stroke rate in medically treated patients with misery perfusion from the 1990s to 2000s.

This study also demonstrated a further decrease of stroke recurrence rate in patients without misery perfusion over this study period (1999–2010). Ipsilateral ischaemic stroke incidence was lower in medically treated patients who entered the study during the second 5 years (4.2%) than in those who entered during the first 5 years of the study (7.5%; Table 4). During these periods, medically treated patients without misery perfusion showed a decreased ipsilateral ischaemic stroke rate (from 4.8% to 0%), but medically treated patients with misery perfusion did not (20 and 33%). In addition to misery perfusion, asymptomatic lacunar infarcts in the bilateral basal ganglia, which may be a marker of generalized arteriosclerosis, was found to be a risk factor for recurrent stroke. In this study, all but one recurrent stroke in medically treated patients were located in the subcortical regions. Arteriosclerosis of striatal or medullary penetrating arteries in itself causes subcortical infarction and could accentuate subcortical ischaemia due to ICA or MCA disease (Yamauchi *et al*., 1999*b*). Thus, changes to standard medical treatments including the frequent use of vascular protective drugs (angiotensin receptor blockers and statins; Powers, 2011; Yamauchi *et al*., 2011) may have reduced the incidence of subsequent stroke caused by the progression of small as well as large artery diseases in patients without misery perfusion. The thresholds used to treat hypertensive, diabetic and hyperlipidaemic patients were lowered over this study period. In patients with asymptomatic carotid stenosis, improvement of medical secondary prevention is reported to have decreased stroke risk in the 2000s as well (Marquardt *et al*.,

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2010), supporting our findings. The decrease in stroke rate over the study period in patients without misery perfusion confirms that medical treatment has considerably gained in efficiency, which in turn has implications for the management of patients as well as for the design of future clinical trials.

In contrast, the stroke recurrence rate in medically treated patients with misery perfusion did not decrease further over this period. In the Carotid Occlusion Surgery Study trial, it is unclear whether there was the time-related trend of decreasing stroke risk over time during the study period (2002–10; Powers *et al*., 2011). For patients with misery perfusion, more aggressive medical therapy may be needed to reduce stroke recurrence. However, blood pressure could have been strictly controlled only in patients without misery perfusion who had a low risk of low-flow infarcts due to reduction in systemic blood pressure (Klijn and Kappelle, 2010). On the other hand, if hypertension is untreated, stroke incidence may increase with progression of large or small cerebral artery diseases. Blood pressure control is also needed to prevent cerebral haemorrhage during anti-platelet therapy. Treatment with antihypertensive drugs may be safe and reduce stroke recurrence only when individual haemodynamic status is evaluated correctly, and aggressive hypotensive therapy should be avoided in haemodynamically compromised patients (Yokota *et al*., 1998). Randomized clinical trials including haemodynamic measurements are needed to test this hypothesis.

Extracranial to intracranial bypass

EC/IC bypass surgery may be a useful treatment to improve misery perfusion (Baron *et al*., 1981; Powers, 1991; Klijn and Kappelle, 2010). However, its benefit may depend on achieving low operative risk (JET Study Group, 2002; Powers *et al*., 2011). In this study, among 19 surgical patients with misery perfusion, two ipsilateral ischaemic strokes occurred during the 30-day postoperative period (10.5% perioperative stroke rate) and no additional patients experienced ipsilateral ischaemic stroke during 2-year follow-up. Although selection bias was present, among patients with misery perfusion, recurrent ipsilateral ischaemic stroke rate was lower in patients with bypass surgery (10.5%) than in patients with medical treatments only (25%). The risk of stroke in surgical patients with misery perfusion was not different from the risk in those without, supporting the finding of a high risk of stroke in medically treated patients with misery perfusion in this study. However, 2 of 16 patients who did not undergo EC/IC bypass surgery despite the finding of misery perfusion experienced recurrent ipsilateral ischaemic stroke (enlargement of internal border zone infarcts probably due to haemodynamic fluctuation) within 30 days after PET while considering the indications for EC/IC bypass. Stricter perioperative management may be required to further improve the prognosis of patients with misery perfusion using bypass surgery. Alternatively, a more preferred method for revascularization with lower perioperative risk may be identified (Chimowitz *et al*., 2011).

Importance of haemodynamic factor in intracranial arterial disease

As opposed to ICA occlusion (Grubb *et al*., 1998), little information is available on the relationship between haemodynamic compromise and stroke risk in patients with major intracranial arterial occlusive disease. The association of haemodynamic compromise and stroke risk in patients with intracranial arterial disease was suggested from the studies of a mix of ICA or MCA diseases (Yamauchi *et al*., 1996, 1999*a*; Kuroda *et al*., 2001; Ogasawara *et al*., 2002), as in this study, which might make it difficult to accurately compare patient groups. However, separate analysis of patients with intracranial arterial disease and those with extracranial ICA occlusion in this study showed that misery perfusion was a predictor of recurrent ipsilateral ischaemic stroke in medically treated patients in the both groups. Haemodynamic factor may be important in the prognosis of symptomatic major intracranial arterial occlusive disease as well.

Limitations

This study has several limitations. Twenty-five per cent of patients were diagnosed by magnetic resonance angiography, which could overestimate stenosis. The lack of co-registered MRI to define the regions of interest might limit correct stratification of the patient groups. In some patients, the severity of haemodynamic compromise might not be reflected by the PET variables in the whole hemisphere but by those in more regional areas. The selection of bypass surgery was left to individual clinical judgment by attending physicians, which may cause selection bias. Sixteen patients without misery perfusion underwent EC/IC bypass surgery due to regional increase in OEF in addition to other characteristics (poor collateral pathways or recurrent symptoms), among whom only one ipsilateral ischaemic stroke occurred after bypass surgery in combination with treatment for aneurysm. Whether this treatment strategy prevented ischaemic stroke in these patients remains unclear, although we suspect that bypass surgery may not modify their prognosis.

Conclusion

In symptomatic atherosclerotic major cerebral artery disease, misery perfusion remains an independent predictor of subsequent stroke risk under the use of EC/IC bypass and standard medical treatments as therapeutic options, although the recurrence rate was lower than in a previous study conducted in 1990s (Yamauchi *et al*., 1996, 1999*a*). In patients without misery perfusion, the risk of stroke significantly decreased over the study period (1999–2010). Thus, identification and stricter management of patients with misery perfusion are essential steps to further improve prognosis. Our study also shows that haemodynamic factors are still important in the pathogenesis of recurrent stroke in symptomatic major cerebral artery disease, which is consistent with the finding of the Carotid Occlusion Surgery Study that beyond the perioperative period where stroke risk was high, improved haemodynamics by bypass surgery was associated with

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very low residual risk of recurrent ipsilateral stroke (Powers *et al*., 2011).

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