Significance of Increased Oxygen Extraction Fraction in Five-Year Prognosis of Major Cerebral Arterial Occlusive Diseases

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In major cerebral arterial occlusive diseases, patients with increased oxygen extraction fraction (OEF), which is measured with PET, may be at increased risk for cerebral ischemia. However, the clinical significance of increased OEF remains unclear. This study investigated whether increased OEF is an independent predictor of 5-y risk of subsequent stroke. **Methods:** We prospectively evaluated the relationship between the regional hemodynamic status of cerebral circulation and the subsequent risk of stroke in 40 patients with symptomatic internal carotid or middle cerebral arterial occlusive diseases who underwent PET. Patients were divided into two hemodynamic categories according to the mean hemispheric value of OEF in the hemisphere supplied by the artery with symptomatic disease: one group with increased OEF and one with normal OEF. All patients were followed for 5 y with medical treatment until the recurrence of stroke or death. **Results:** During 5 y, 11 total and 9 ipsilateral ischemic strokes occurred. The incidences of all ischemic strokes in patients with increased OEF and in those with normal OEF were 5 of 7 and 6 of 33 patients, respectively. There were 4 ipsilateral ischemic strokes in patients with increased OEF and 5 in those with normal OEF. Kaplan-Meier analysis revealed that the risks of all stroke and ipsilateral ischemic stroke in patients with increased OEF were significantly higher than in those with normal OEF (log-rank test; $P < 0.0002$ and $P < 0.0018$, respectively). Multivariate analysis with the Cox proportional hazards model showed that increased OEF significantly increased stroke recurrence: the relative risk was 7.2 (95% confidence interval [CI], 2.0–25.5; $P < 0.005$) for all stroke and 6.4 (95% CI, 1.6–26.1; $P < 0.01$) for ipsilateral stroke. An increase in the absolute OEF value was a better predictor of recurrent ischemic stroke than was OEF asymmetry. **Conclusion:** These findings suggest that an increased OEF is an independent predictor of 5-y risk of subsequent stroke. Identification of patients with increased OEF may have clinical significance in preventing recurrent stroke.

Key Words: cerebrovascular disease; PET; hemodynamics; oxygen extraction fraction; stroke risk

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In patients with major cerebral arterial occlusive disease, an inadequate blood supply relative to metabolic demand (misery perfusion) (*1*) may increase the risk of cerebral ischemia (*2*), suggesting that identification and optimal treatment of patients with misery perfusion could help prevent stroke. Several studies have shown the existence of a hemodynamically compromised subgroup at increased risk of stroke and that this group may be identified by a reduced vasodilatory capacity or increased oxygen extraction fraction (OEF) (*3–5*). However, the importance of hemodynamic factors in the prognosis of major cerebral arterial occlusive disease remains controversial (*6,7*). The reported methods of evaluating chronic hemodynamic compromise are varied, and data are scarce on stroke occurrence in the subgroup of patients categorized by hemodynamic parameters. Thus, more information is needed for a well-designed, prospective randomized study to determine the clinical significance of chronic hemodynamic compromise in stroke occurrence and the optimal treatment strategies based on hemodynamic status.

PET is one of the most reliable tools for the quantitative evaluation of cerebral hemodynamic status. However, only a few studies have investigated systematically the relationship between cerebral hemodynamics determined by PET and the subsequent risk of stroke. Our previous study in symptomatic major cerebral arterial occlusive disease showed that patients with increased OEF (misery perfusion) have a high risk of 1-y recurrence of ischemic stroke (*8*). A recent masked, prospective study with PET also showed that patients with increased OEF had a high risk of subsequent ischemic stroke during an average follow-up of 31.5 mo (*4*). However, because increased OEF was defined as having an OEF asymmetry in the study, it is unclear whether the two methodologies (an increase in absolute OEF value and an OEF asymmetry) identify the same patients as having misery perfusion and a high risk of recurrent stroke.

The purpose of this study was to investigate whether increased OEF is an independent predictor of 5-y risk of subsequent stroke in patients with symptomatic major

cerebral arterial occlusive disease and, if so, whether an increase in absolute OEF value is a better predictor of subsequent stroke than an OEF asymmetry. We followed 40 medically treated patients, for whom we have already reported 1-y prognoses (8), for 5 y until the recurrence of stroke or death and analyzed the relationship between the subsequent risk of stroke and several clinical variables, including an increase in the absolute OEF value and OEF asymmetry determined by PET.

MATERIALS AND METHODS

Patients

We followed 40 patients under medical treatment for symptomatic internal carotid artery (ICA) or middle cerebral artery (MCA) occlusive disease. The characteristics of the patients were described previously (8). All subjects were selected prospectively from 52 patients with symptomatic ICA or MCA occlusive disease, in whom regional cerebral blood flow (CBF), cerebral metabolic rate of oxygen ($CMRO_2$), OEF and cerebral blood volume (CBV) were measured using PET at our university hospital between 1985 and 1994. These were patients who had been referred consecutively to the Department of Neurology from related hospitals for pathophysiologic study of major cerebral arterial occlusive diseases using PET. Inclusion criteria for the PET studies were angiographically documented occlusion or stenosis (>70% diameter reduction) of the ICA or MCA and transient ischemic attacks (TIAs) or minor stroke with mild disability in the arterial distribution distal to the lesion. Exclusion criteria for the follow-up study were patients'

being scheduled for vascular reconstruction surgery and technical difficulties with PET scans. Seven patients underwent superficial temporal artery-MCA anastomosis between 1985 and March 1988. During this period, the surgical indications were controversial, and these 7 patients underwent surgery after providing informed consent to evaluate the hemodynamic and metabolic effects of this treatment, irrespective of the cerebral hemodynamics. After March 1988, all patients except those with extracranial ICA stenosis were treated medically. Five patients with unilateral extracranial ICA stenosis underwent carotid endarterectomy between 1988 and 1994, irrespective of the cerebral hemodynamics. The characteristics of these 12 patients did not markedly differ from those of other patients. All patients showed technically reliable PET measurements. Thus, no patient was excluded without neurovascular surgery. All patients and their relatives gave informed consent for the PET study but were not informed about the follow-up study.

The patients included 30 men and 10 women (age range 41–80 y; mean age 62 ± 8 y) (Table 1). Six patients had TIAs, and 34 had minor stroke. All except 1 patient had symptoms of cerebral hemispheric rather than retinal ischemia. Eleven patients had recurrent episodes of ischemic attack (recurrent symptoms) before PET. The intervals between the most recent ischemic event and PET studies ranged from 1 to 55 mo (mean 8 ± 11 mo). In all patients, CT scanning disclosed only minor abnormalities in the MCA territory or watershed areas of the hemisphere with major arterial disease. Only 1 patient also had symptoms related to posterior cerebral artery distribution, and CT scanning also disclosed a low-density area in the posterior cerebral artery territory ipsilateral to major arterial disease. Conventional angiography at

TABLE 1
Characteristics of Patients at Entry into Study

| | Oxygen extraction fraction | | | |
| | Absolute value | | Asymmetry | |
Characteristics	Increased	Normal	Positive	Negative
No. of patients	7	33	14	26
Age (y)	63 ± 9	62 ± 9	65 ± 9	60 ± 8
Sex				
Male	4	26	10	20
Female	3	7	4	6
Diagnosis				
TIA (amaurosis/hemispheric)	0	6 (1/5)	0	6 (1/5)
Minor stroke	7	27	14	20
Recurrent symptoms	3	8	3	8
No. of months between last symptom and PET, mean ± SD	10.6 ± 15.2	8.0 ± 11.2	10.7 ± 12.0	7.2 ± 11.7
Angiography*				
ICA (occlusion/stenosis)	6 (4/2)	30 (25/5)	12 (10/2)	24 (19/5)
MCA (occlusion/stenosis)	1 (1/0)	3 (2/1)	2 (1/1)	2 (2/0)
Contralateral carotid stenosis > 50%	1	7	3	5
Other medical illness				
Hypertension	4	16	5	15
Diabetes mellitus	3	5	3	5
Prior MI	0	3	0	3
Hypercholesterolemia	1	0	0	1
Smoking	4	24	10	18
Hemoglobin level, mean ± SD (g/dL)	12.6 ± 1.6	13.5 ± 1.2	13.2 ± 1.2	13.4 ± 1.3

*Most severe angiographic lesion in MCA or ICA ipsilateral to symptoms.
TIA = transient ischemic attack; ICA = internal carotid artery; MCA = middle cerebral artery; MI = myocardial infarction.

the most recent ischemic event before the PET studies revealed unilateral ICA occlusion in 23 patients, unilateral extracranial ICA stenosis (70% and 90%) in 2 patients, unilateral intracranial ICA stenosis (80%, 90%, 95% and 95%) in 4 patients, unilateral MCA occlusion in 2 patients, unilateral MCA stenosis (90%) in 1 patient, ICA occlusion with contralateral extracranial ICA stenosis (50% and 80%) in 2 patients, ICA occlusion with contralateral intracranial ICA stenosis (65% and 70%) in 2 patients, MCA occlusion with contralateral extracranial ICA stenosis (60%) in 1 patient and bilateral ICA occlusions in 3 patients. In 8 patients with bilateral disease, only one side of the vascular lesions was symptomatic. Of 5 patients with ICA or MCA occlusion and contralateral ICA stenosis, the symptomatic vascular lesion involved ICA or MCA occlusion in 4 patients and intracranial ICA stenosis in 1 patient. The vertebrobasilar system was angiographically normal in all but 2 patients. Recurrent symptoms before PET after angiographic demonstration of ICA or MCA disease were identified in only 1 patient, who had intracranial ICA stenosis and orthostatic TIAs despite antiplatelet therapy. Thus, the intervals between the conventional angiography and PET studies also ranged from 1 to 55 mo (mean 8 ± 11 mo). All patients with an interval > 1 y underwent MR angiography within 3 mo before PET. The severity of vascular lesions was unchanged in all these patients.

Patients were followed up at our university hospital or at related hospitals. All patients were treated with antiplatelet therapy (aspirin or ticlopidine HCl), but the treatment of risk factors and use of other drugs were left to individual clinical judgment. Although the attending physicians were not unaware of the findings of the PET studies, the treatment did not markedly differ among the patients. All patients were examined at 1-mo intervals after the PET studies for 1 y, and then at 3-mo intervals or more frequently. At each visit, an interim history was obtained, and a neurologic examination was performed. Endpoints were defined as the occurrence of stroke or death. In patients with recurrent stroke, MR images or CT scans were obtained and compared with initial studies to confirm recurrent stroke. Stroke in the previously symptomatic arterial territory without evidence of primary intracranial hemorrhage was classified as an ipsilateral ischemic stroke.

PET

Regional CBF, CMRO$_2$, OEF and CBV were measured using PET at the beginning of the observation period. In the 24 patients studied between 1985 and 1989, PET was performed using the Positologica III PET Scanner (Hitachi Medical Co., Tokyo, Japan), and the remaining examinations between 1990 and 1994 were performed using the PCT3600W (Hitachi). Technical data regarding these two scanners are described elsewhere (9,10). With four and seven rings, respectively, the devices can obtain 7 and 15 tomographic slices, respectively, in a single scanning process. The best spatial resolutions are 7.6 and 6.5 mm, at full width at half maximum at the center of the scanning fields, and the axial resolutions are 12 and 7 mm, respectively, at the center. Before the study, ^{68}Ge-^{68}Ga transmission scanning was performed for 20 min to allow attenuation correction. CBF was determined while the subject continuously inhaled C^{15}O$_2$ through a mask. Measurements of CMRO$_2$ and OEF were obtained during continuous inhalation of ^{15}O$_2$. Data were collected for 5 min. A single breath of C^{15}O was used to measure CBV. We calculated CBF, CMRO$_2$ and OEF by the steady state method (11), and CMRO$_2$ and OEF were corrected by CBV (12).

We analyzed three (with the Positologica III) or six (with the

PCT3600W) tomographic planes located 43–82 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 (ROI) was placed on the CBF images. Each image was examined by placing a total of 18–20 circular ROIs 10 mm in diameter compactly over the gray matter of the cortex. According to the atlas developed by Kretschmann and Weinrich (13), the ROIs in all images included the distribution of the anterior cerebral artery (ACA), the MCA and the posterior cerebral artery (PCA), as well as the watershed areas between the ACA and MCA (anterior watershed [AWS]) and MCA and PCA (posterior watershed [PWS]) (14). In 5 patients with infarction in the cerebral cortex, the ROIs corresponding to the infarcted area were excluded from analysis. We used a method correlating PET images with CT or MR images described elsewhere (15). The ROIs including low-density areas on CT images or low-intensity areas on T1-weighted MR images were excluded. The mean hemispheric value was calculated as the average of the ROIs in the distribution of the MCA, AWS and PWS.

The hemodynamic status of cerebral circulation in the hemisphere ipsilateral to symptomatic ICA or MCA lesions was determined on the basis of the absolute value of OEF or the asymmetry of OEF. Using PET, we studied 10 healthy volunteers (8 men, 2 women; age range 35–78 y, mean age 52 ± 13 y). They had no history of medical or psychiatric disorders, including hypertension or diabetes mellitus. They underwent routine neurologic examination. No one showed any cerebral symptoms, abnormal neurologic findings or specific neurologic disease. None exhibited any abnormal CT or MRI findings, except for a few high-intensity spots in the subcortical white matter depicted on T2-weighted MR images. In 5 healthy volunteers (4 men and 1 woman), PET was performed using the Positologica III scanner, and the remaining 5 examinations were performed using the PCT3600W. Although no significant differences were found in age or mean hemispheric CBF, CMRO$_2$, OEF, CBV or CBF/CBV values between these two populations (Student t test), the values of PET data obtained by the camera with higher spatial resolution had a tendency to be higher. To determine the normal range of OEF, the use of two healthy control groups examined by PET is preferable. However, we treated these 10 healthy volunteers as one control group, as we assessed only small samples of healthy individuals with similar ages. According to the OEF data, the 40 patients were divided by two different methodologies into two hemodynamic categories. The first group included patients with increased or normal OEF. The OEF values in 20 hemispheres of the healthy volunteers ranged from 36.1% to 51.7% (42.6% ± 5.1%). No significant difference among the individual ROIs (MCA, AWS and PWS) existed in this subgroup (analysis of variance with post hoc Scheffé test). Absolute hemispheric values beyond the upper 95% confidence limits defined in healthy volunteers (>53.3%) were considered abnormal. The second group included patients with OEF asymmetry and those without OEF asymmetry, as indicated by the left-to-right OEF ratio. The normal values in 10 healthy volunteers ranged from 0.961 to 1.071 (1.016 ± 0.033). Patients with left-to-right OEF ratios outside the 95% confidence limits defined in healthy volunteers (0.941–1.091) were categorized as having OEF asymmetry. No subject showed a significant change in PaCO$_2$ during PET scanning. Categorization of the patients was performed by one investigator who was unaware of the clinical status of the patients.

Statistical Analysis

We compared the clinical background between the two groups using the Student t test or the χ^2 test, as appropriate. We also compared the incidence of recurrent stroke and death between the two groups using the Cox-Mantel test and Kaplan-Meier method (16). Multivariate analysis with the Cox proportional hazards model tested the effect of multiple variables on the recurrence of stroke (17). Age, sex, prior infarction, recurrent symptoms (recurrent episodes of ischemic attack before PET), time between the last symptoms and PET, contralateral arterial stenosis > 50%, complications (hypertension, diabetes mellitus, prior myocardial infarction, hypercholesterolemia), smoking status, hemoglobin level and abnormalities of OEF (an increase in absolute value and an abnormal hemispheric ratio) were considered covariates (Table 1). Significance was established at $P < 0.05$.

RESULTS

Categorization of Patients

In the symptomatic hemisphere, the mean hemispheric value of the OEF was significantly and negatively correlated with the mean hemispheric value of the CBF in the 40 patients studied ($r = -0.621$; $P < 0.0001$).

Based on the absolute OEF value in the hemisphere supplied by the symptomatic ICA or MCA (in the "ipsilateral" hemisphere), 7 patients had increased OEF values and 33 had normal OEF values (Table 1). There was no significant difference in the characteristics of patients between the two groups. The OEF values of the asymptomatic ("contralateral") hemispheres were normal in all 33 patients with normal ipsilateral OEF, whereas they were normal in 4 and increased in 3 of 7 patients with increased ipsilateral OEF.

Based on the left-to-right OEF ratio, 14 patients had abnormal hemispheric ratios of OEF (OEF asymmetry) and 26 patients had normal hemispheric ratios of the OEF values (Table 1). No significant difference in the characteristics of patients was found between the two groups. The hemisphere with the higher OEF was the symptomatic (ipsilateral) hemisphere in all patients. Of 14 patients with OEF asymmetry, 9 (64%) did not have increased OEF values. Two of 26 (8%) without OEF asymmetry had increased OEF values, with increased OEF in the contralateral hemisphere as well. OEF asymmetry had 71% sensitivity and 73% specificity for detecting patients with increased OEF values (Table 2).

TABLE 2
Relationship Between Increased Oxygen Extraction Fraction and Oxygen Extraction Fraction Asymmetry

| Asymmetry | Oxygen extraction fraction | | Total |
	Increased	Normal	
Positive	5	9	14
Negative	2	24	26
Total	7	33	40

Comparison of Risk of Stroke in Patients with Increased Oxygen Extraction Fraction and Patients with Normal Oxygen Extraction Fraction

All patients were followed up for 5 y or until stroke recurrence or death. During 5 y, 11 total and 9 ipsilateral ischemic strokes occurred. Ischemic strokes occurred in 5 of 7 patients with increased OEF and 6 of 33 patients, with normal OEF. There were 4 and 5 ipsilateral ischemic strokes in patients with increased OEF and in those with normal OEF, respectively. The Kaplan-Meier estimates for the risk of subsequent stroke at 1, 2 and 5 y are given in Table 3. The risks of all stroke and ipsilateral ischemic stroke in patients with increased OEF were significantly higher than in those with normal OEF ($P < 0.0002$ and $P < 0.0018$, respectively; Fig. 1). All stroke in patients with increased OEF occurred within 1 y. Death occurred in 1 patient with increased OEF and in 3 patients with normal OEF ($P = 0.78$).

Comparison of Risk of Stroke in Patients With and Without Oxygen Extraction Fraction Asymmetry

Ischemic strokes occurred in 6 of 14 patients with OEF asymmetry and 5 of 26 patients without OEF asymmetry. There were 5 and 4 ipsilateral ischemic strokes in patients with OEF asymmetry and in those without OEF asymmetry, respectively. The Kaplan-Meier estimates for the risk of subsequent stroke at 1, 2 and 5 y are given in Table 3. The risks of all stroke and ipsilateral ischemic stroke in patients with OEF asymmetry had a tendency to be higher than in those without OEF asymmetry but were not significantly higher ($P = 0.088$ and $P = 0.10$, respectively; Fig. 2). Death occurred in 3 patients with OEF asymmetry and 1 patient without OEF asymmetry ($P = 0.22$).

Risk Factors for Recurrent Stroke

Multivariate analysis with the Cox proportional hazards model showed that only increased absolute OEF value and recurrent symptoms before PET were significant independent predictors of both all and ipsilateral strokes. OEF asymmetry was not a significant independent predictor. The relative risk conferred by the increased OEF value, which was adjusted by the recurrent symptom, was 7.2 (95% confidence interval [CI], 2.0–25.5) for all stroke and 6.4 (95% CI, 1.6–26.1) for ipsilateral ischemic stroke ($P < 0.005$ and $P < 0.01$, respectively). The relative risk conferred by the recurrent symptom was 4.4 (95% CI, 1.3–15.0) for all stroke and 4.0 (95% CI, 1.0–15.5) for ipsilateral ischemic stroke ($P < 0.02$ and $P < 0.05$, respectively).

Localization and Associated Conditions of Recurrent Stroke

Ischemic stroke developed in a total of 11 patients during the follow-up period: 9 with ipsilateral and 2 with contralateral strokes. Eight strokes were suggested to be of hemodynamic origin from the location of the infarct or the related conditions. All 8 infarcts occurred in the superficial or deep watershed region. Although no apparent associated conditions were identified in the 3 strokes in patients with

TABLE 3
Stroke Occurrence*

Strokes	Total sample (%) n = 40	Increased OEF (%) n = 7	Normal OEF (%) n = 33	Positive for OEF asymmetry (%) n = 14	Negative for OEF asymmetry (%) n = 26
All					
1 y	17.5	71.4	6.1	28.6	11.5
2 y	17.5	71.4	6.1	28.6	11.5
5 y	28.4	71.4	19.3	45.6	19.6
Ipsilateral					
1 y	15.0	57.1	6.1	21.4	11.5
2 y	15.0	57.1	6.1	21.4	11.5
5 y	23.2	57.1	16.0	40.1	15.6

*Event rates were derived from Kaplan-Meier estimates of survival (Figs. 1 and 2).
OEF = oxygen extraction fraction.

increased OEF, 1 contralateral stroke (in the hemisphere with increased OEF) in a patient with increased OEF and 4 strokes (3 ipsilateral and 1 contralateral) in patients with normal OEF were related to conditions leading to a deterioration of the hemodynamic status (a reduction in systemic blood pressure, hemoconcentration due to dehydration, progression of contralateral carotid diseases or deterioration of risk factors).

DISCUSSION

This study showed that increased OEF is an independent predictor of 5-y risk of subsequent strokes in patients with symptomatic major cerebral arterial occlusive disease. The high risk of ischemic stroke in patients with increased OEF, already shown at 1-y follow-up, was also shown at the 5-y follow-up. There were 4 ipsilateral strokes among 7 patients with increased OEF (57%) and 5 ipsilateral strokes among 33 patients with normal OEF (15%). Kaplan-Meier analysis revealed that the risk of recurrent ischemic strokes in patients with increased OEF was significantly higher than in those with normal OEF. All strokes in patients with increased OEF occurred within 1 y, suggesting the close relationship between increased OEF and recurrent strokes. Multivariate analysis with the Cox proportional hazards model showed that the increased absolute OEF value was a significant independent predictor of subsequent strokes.

In this study, we also showed that an increase in absolute OEF value is a better predictor of recurrent ischemic stroke than is OEF asymmetry. The two methodologies did not predict the same patients as having misery perfusion in our patient samples. The Kaplan-Meier analysis revealed that the risk of all stroke and ipsilateral ischemic stroke in patients with OEF asymmetry had a tendency to be higher than in those without OEF asymmetry but was not significantly higher. A study by Grubb et al. (4) on 81 patients with symptomatic unilateral ICA occlusion showed that patients with OEF asymmetry have a high risk of ischemic stroke. The risk of subsequent strokes at 2 y in patients with and without OEF asymmetry in their study was comparable to
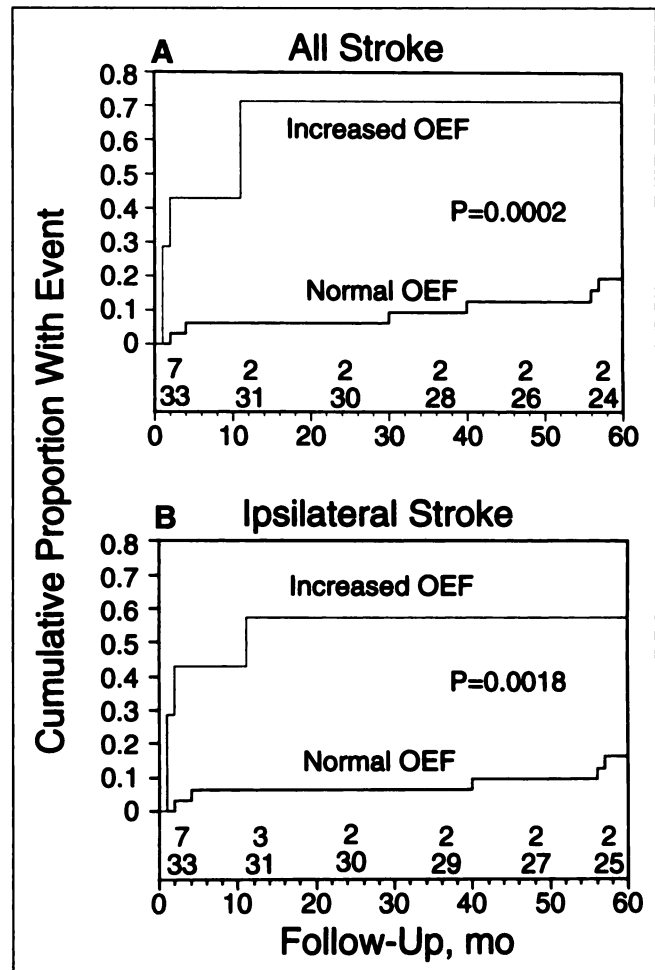

FIGURE 1. Kaplan-Meier cumulative failure curves for all stroke (A) and for ipsilateral stroke (B) in patients with increased oxygen extraction fraction (OEF) and patients with normal OEF. Number of patients who remained event free and available for follow-up evaluation during each 12-mo interval is shown at bottom of graph.
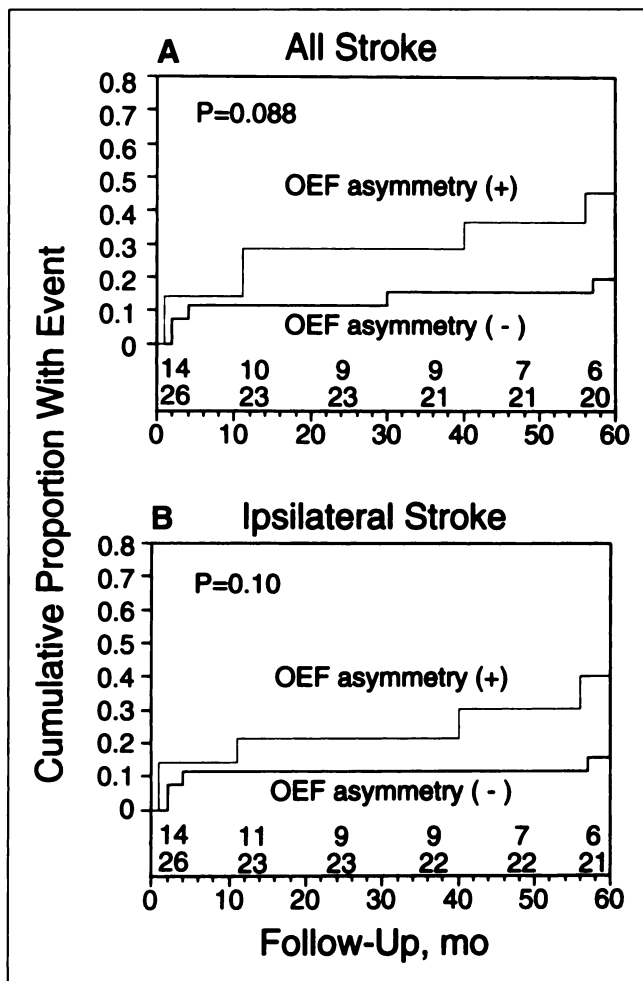
FIGURE 2. Kaplan-Meier cumulative failure curves for all stroke (A) and for ipsilateral stroke (B) in patients with oxygen extraction fraction (OEF) asymmetry and patients without OEF asymmetry. Number of patients who remained event free and available for follow-up evaluation during each 12-mo interval is shown at bottom of graph.

that in our study. Thus, the nonsignificant results in our study may result mainly from our small sample size, and both categorizations may identify patients at high risk of recurrent stroke.

Several factors may contribute to the fact that the two methodologies (an increase in absolute OEF value and an OEF asymmetry) did not predict the same patients as having misery perfusion. First, patients with unilateral ICA occlusion, especially with collateral circulation through the anterior communicating artery, may show hemodynamic disturbance in both hemispheres, suggesting that the OEF in the contralateral hemisphere cannot be used as an internal control for each patient, even in strictly unilateral ICA occlusive disease (*14,18*). Second, a bilateral increase in the OEF in patients with bilateral major cerebral arterial occlusive disease may be detected only by evaluation of absolute OEF values. Third, diffuse arteriosclerosis may increase OEF in both hemispheres, leading to overestimation of the

effect of major cerebral arterial disease on hemodynamic status. The hemispheric OEF ratio may cancel out the effect of diffuse lesions. Lastly, the absolute OEF value may be affected by many variables, including CO_2 tension, O_2 content of blood, arousal level and measurement conditions. These factors causing discrepancy between absolute OEF values and OEF asymmetry need to be checked by referring to clinical, physiologic and angiographic findings for the correct detection of patients at risk.

In clinical practice, it is important to detect patients with compromised hemodynamics and high risk of stroke, such as those with increased OEF, using widely available and cost-effective modalities of modern imaging techniques other than PET. Although a close relationship has been shown between impaired cerebrovascular reactivity measured by intravenous injection of acetazolamide (ACZ) or CO_2 inhalation and increased OEF (*19–22*), it remains controversial whether patients with major cerebral arterial disease and impaired cerebrovascular reactivity have a high risk of stroke. A recent prospective study of large patient samples using SPECT and ACZ showed that reduced cerebrovascular reactivity evaluated by a qualitative method is not a significant predictor of stroke recurrence (*7*). However, quantitative studies using stable xenon CT or ^{133}Xe-SPECT and ACZ (*23,24*) or transcranial Doppler and CO_2 (*25*) have revealed that a small subgroup of patients with highly impaired cerebrovascular reactivity, especially those with steal phenomenon, had an increased risk of developing a stroke. It is unclear whether the data from different methodologies can be compared. Therefore, future studies should investigate the ideal methodology in clinical practice for identifying the subgroup at risk for stroke. Further examination is needed to determine whether extracranial-intracranial bypass surgery, which could normalize the increased OEF (*1,2*), reduces the risk of stroke in this subgroup. However, standardization of the method of evaluating chronic hemodynamic compromise in clinical practice must be established first. Then, choosing optimal treatment strategies based on the hemodynamic status of each patient may be essential for preventing recurrent stroke, and it may be appropriate to conduct a new trial of extracranial-intracranial bypass surgery.

CONCLUSION

In this small, selected patient sample, increased OEF is an independent predictor of 5-y risk of subsequent stroke in patients with symptomatic major cerebral arterial occlusive disease. All strokes in patients with increased OEF occurred within 1 y, indicating the close relationship between increased OEF and recurrence of stroke. A hemodynamically compromised subgroup at increased risk of stroke exists and can be identified by increased OEF.

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