BIC and Harrell's C) were almost identical between the eGFR$_{CKDEPI}$ and eGFR$_{MDRD}$ models. This suggests that no superiority existed in prediction of events either in the eGFR$_{CKDEPI}$ model or the eGFR$_{MDRD}$ model on multivariate-adjusted Cox regression analysis.

Table 5 lists detailed cross-tabulated classifications (CKD stage based on eGFR$_{CKDEPI}$ and on eGFR$_{MDRD}$) for calculating NRI separately by endpoint. For predicting all-cause death, NRI was estimated to be 6.7% and Z statistic was estimated to be 4.78 ($P<0.001$). The eGFR$_{CKDEPI}$ model reclassified risk categories better than the eGFR$_{MDRD}$ model. For predicting incident AMI, NRI was –9.1% and Z statistic was estimated to be –1.89 ($P=0.029$). Use of eGFR$_{CKDEPI}$ made reclassification worse than using eGFR$_{MDRD}$. For predicting incident stroke, NRI was –0.3% and Z statistic was estimated to be –0.20 ($P=0.421$) and no improvement was observed by using eGFR$_{CKDEPI}$ instead of eGFR$_{MDRD}$.

Discussion

We compared risk predictabilities of mortality and cardiovascular morbidity between 2 models using GFR based on eGFR$_{CKDEPI}$ and that based on eGFR$_{MDRD}$. In univariate analysis, discriminating ability using eGFR$_{CKDEPI}$ was significantly higher than that using eGFR$_{MDRD}$ to predict future death, AMI and stroke events (Figure 3; $P<0.01$). To compare discrimination abilities of the 2 models using eGFR$_{CKDEPI}$ and eGFR$_{MDRD}$ in multivariate-adjusted analysis, we compared model parameters including Harrell's C, AIC and BIC between the Cox regression model for CKD stage based on eGFR$_{CKDEPI}$ and that based on eGFR$_{MDRD}$. We could not identify better discriminating ability in the eGFR$_{CKDEPI}$ model than that in the eGFR$_{MDRD}$ model. NRI analysis indicated that the CKD-EPI equation was associated with a significantly positive NRI for predicting all-cause death, while it was not associated with a positive NRI for predicting AMI or stroke.

To capture discrimination, AUROC is the most common popular metric.[13] A larger AUROC indicates a more appropriate predictor for separating subjects into a diseased group and non-diseased group.[13] Harrell et al extended the concept of discrimination from the logistic regression setting to survival analysis and developed concordance C statistics.[14] To quantitatively estimate fitness of the model, information-theoretic methods, such as AIC and BIC, have been developed.[29,30] Lower AIC and BIC indicate more appropriate goodness of fit for predicting the endpoint in a multivariate-adjusted model. The c statistic (AUROC and Harrell's C, etc), however, may not be optimal in assessing models that predict future risk or stratify individuals into risk categories.[18]

The question of whether novel risk factors can contribute to overall risk prediction independent of traditional risk factors and the question of whether a new model can more accurately stratify individuals into higher or lower risk categories of clinical importance have been challenging us to developing new ways for assessing adequate model predictability.[15,16,18] Several studies have offered new methods of assessment of risk prediction regarding reclassification tables.[17–19] Pencina et al proposed a new method of statistical analysis named "the net reclassification improvement" (NRI).[20] Assessment of NRI enables determination of new risk factors that contribute to improvement of risk prediction. Although we failed to show superiority of the eGFR$_{CKDEPI}$ model in discrimination ability, we managed to identify statistically significantly better performance of the eGFR$_{CKDEPI}$ model compared to the eGFR$_{MDRD}$ model on NRI analysis.

Superiority in discriminating ability in the eGFR$_{CKDEPI}$ model disappeared after multivariate adjustment and we found similar predictability in the 2 models. Several confounding factors may attenuate superiority in predictive ability in the eGFR$_{CKDEPI}$ model. Poisson regression analysis showed that age adjustment drastically converted a positive and steep linear relationship between mortality and CKD stage into a U-shaped relationship in the eGFR$_{CKDEPI}$ model. We also showed that age distribution was different for corresponding CKD stage between the 2 models in the baseline characteristics on cross-sectional analysis. The age-adjusted model suggested that the contribution of age to prediction of death was greater in the eGFR$_{CKDEPI}$ model, and the difference in predictive ability between the 2 models was attenuated after age adjustment. Moreover, age adjustment made the risk for death higher in CKD stage 1, especially in the eGFR$_{CKDEPI}$ model.

All-cause mortality and cardiovascular morbidity rates were high in subjects with normal eGFR (eGFR $\geq 90\,ml \cdot min^{-1} \cdot 1.73\,m^{-2}$) compared to subjects in stage 2 ($60–89\,ml \cdot min^{-1} \cdot 1.73\,m^{-2}$) in the present study. Although most previous studies identified a linear relationship between cardiovascular morbidity and mortality risk and CKD stage, recent studies have shown that there is a U-shaped relationship between death risk and CKD stage based on eGFR.[12,33–36] The ARIC study found elevated risk for death and cardiovascular disease in subjects with elevated eGFR. Risk elevation started at eGFR=$120\,ml \cdot min^{-1} \cdot 1.73\,m^{-2}$, and the lowest risk for death was observed for eGFR 90–$119\,ml \cdot min^{-1} \cdot 1.73\,m^{-2}$.[12] Tonelli et al reported that risk elevation started at eGFR=$75\,ml \cdot min^{-1} \cdot 1.73\,m^{-2}$ and that the lowest risk for death was observed for eGFR $60–74\,ml \cdot min^{-1} \cdot 1.73\,m^{-2}$.[33] Although reduced GFR has been shown to contribute to higher risks for all-cause death and cardiovascular mortality and morbidity in previous studies, whether elevated GFR contributes to high risks for all-cause death and cardiovascular mortality and morbidity has not been elucidated.

Serum creatinine level is affected not only by GFR but also by other factors such as muscle metabolism. Persons with muscle wasting secondary to an illness such as malignancy, malnutrition or inflammatory disease and other deconditioning situations have a low serum creatinine level with apparently overestimated eGFR. They possibly have high risks for all-cause death and cardiovascular morbidity and mortality. The association between high eGFR and poor prognosis might be attributable to overestimation of eGFR due to low serum creatinine level in persons with muscle wasting.

Aside from the possible contribution of difference in muscle mass to eGFR, increased GFR might have contributed to elevated risks for death and cardiovascular morbidity and mortality. Hostetter et al reported that reduced mass of nephrons by artificial ablation yielded a marked increase in GFR and contributed to structural hypertrophy in an animal study.[37] This suggested that early-stage kidney failure was accompanied by hyperfiltration. A cross-sectional study showed that higher eGFR correlated with presence of hyperfiltration among diabetic patients with microalbumimnuria,[38] and hyperfiltration status observed in diabetic children was thought to be associated with subsequent development of kidney dysfunction expressed as microalbuminuria.[39]

Whether higher eGFR is associated with early-stage renal failure in non-diabetic subjects has not been fully elucidated and whether higher eGFR is associated with elevated risks for cardiovascular morbidity and mortality has also not been elucidated until now. We have shown only that higher GFR based on eGFR$_{CKDEPI}$ was associated with higher risk for all-cause death in a general population. Whether the association be-

tween higher eGFR and an elevated risk for death reflects the true relationship between elevated actual measured GFR and an elevated risk for death due to cardiovascular disease should be examined.

Several limitations to the present study should be noted. We could not measure GFR directly, and we therefore compared risk predictability of CKD stage based on estimation using $eGFR_{CKDEPI}$ and estimation using $eGFR_{MDRD}$. Participants <40 years of age accounted for only 3.4% of the total subjects, and the number of persons diagnosed in K/DOQI CKD stage 1 category (GFR $\geq 90\,ml \cdot min^{-1} \cdot 1.73\,m^{-2}$) was only 747 (8.9% of the total subjects). Subject age was biased to middle-aged to elderly, and most of these participants had mildly reduced kidney function (K/DOQI CKD stage 2), therefore this might have contributed to uncertainty in risk predictability in persons in K/DOQI CKD stage 1. The subject group consisted of persons who underwent annual health check-ups and were in relatively good condition, and we could not perform accurate examination in persons who were diagnosed as having K/DOQI CKD stage 4+ because of the small sample size. The considerably low incidence rate of AMI in this cohort study, which was also observed in a previous study in Japan,[40] also contributed to uncertainty in risk predictability for AMI.

In conclusion, better discrimination was obtained using the $eGFR_{CKDEPI}$ model than the $eGFR_{MDRD}$ model in univariate analysis. NRI analysis indicated that the use of $eGFR_{CKDEPI}$ instead of $eGFR_{MDRD}$ offered a statistically significant improvement in prediction of death. The use of the new equation for eGFR instead of the old equation may contribute to accurate risk assessment.

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Disclosures

Conflict of Interest: None declared.

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Supplementary Files

Supplementary File 1

Figure S1. The study area.

Table S1. Formulas for Calculating eGFR Based on CKD-EPI Equation and MDRD Equation

Table S2. Cross-Tables of CKD Stage Based on eGFRCKDEPI and eGFRMDRD

Please find supplementary file(s);
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Original Research Paper

Combination of blood flow asymmetry in the cerebral and cerebellar hemispheres on brain perfusion SPECT predicts 5-year outcome in patients with symptomatic unilateral major cerebral artery occlusion

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Background and objective: Misery perfusion increases the risk of stroke recurrence in patients with symptomatic major cerebral artery occlusion. The ratio of brain perfusion contralateral-to-affected asymmetry in the cerebellar hemisphere to brain perfusion affected-to-contralateral asymmetry in the cerebral hemisphere (CblPR/CbrPR) indicates affected-to-contralateral asymmetry of oxygen extraction fraction (OEF) in the cerebral hemisphere. The purpose of the present study was to determine whether the CblPR/CbrPR on brain perfusion single-photon emission computed tomography (SPECT) predicts 5-year outcomes in patients with symptomatic unilateral occlusion of the middle cerebral artery (MCA) or internal carotid artery (ICA).

Methods: Brain perfusion was assessed using *N*-isopropyl-*p*-[^{123}I]-iodoamphetamine (^{123}I-IMP) SPECT in 70 patients. A region of interest (ROI) was manually placed in the bilateral MCA territories and in the bilateral cerebellar hemispheres, and the CblPR/CbrPR was calculated. All patients were prospectively followed for 5 years. The primary end points were stroke recurrence or death.

Results: A total of 17 patients exhibited the primary end points, 11 of whom experienced subsequent ipsilateral strokes. Multivariate analysis revealed that only high CblPR/CbrPR was significantly associated with the development of the primary end point or subsequent ipsilateral strokes (95% confidential limits [CIs], 1.130–3.145; $P = 0.0114$ or 95% CIs, 2.558–5.140; $P = 0.0045$, respectively). The CblPR/CbrPR provided 65% (11/17) or 91% (10/11) sensitivity and 88% (47/53) or 88% (52/59) specificity in predicting the primary end point or subsequent ipsilateral strokes, respectively.

Conclusions: The CblPR/CbrPR on brain perfusion SPECT predicts 5-year outcomes in patients with symptomatic unilateral occlusion of the MCA or ICA.

Keywords: Crossed cerebellar hypoperfusion, Brain perfusion SPECT, Subsequent stroke

Introduction

When cerebral perfusion pressure is reduced, cerebral blood flow (CBF) is initially maintained by dilation of precapillary resistance vessels in a process known as cerebrovascular autoregulation.[1,2] With more severe reductions in cerebral perfusion pressure, the capacity for compensatory vasodilation exceeds, autoregulation fails, and CBF begins to decline. In this context, a progressive increase in oxygen extraction fraction (OEF) can act to maintain cerebral oxygen metabolism and brain function.[1,3] This form of cerebral hemodynamic failure has been termed 'misery perfusion'.[4] In patients with symptomatic major cerebral arterial occlusive disease, misery perfusion increases the risk of stroke recurrence.[5–7] Therefore, identification and optimal treatment of patients with misery perfusion may help to prevent

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stroke recurrence. However, direct detection OEF-related misery perfusion can only be accomplished using positron emission tomography (PET).

Brain perfusion single-photon emission computed tomography (SPECT) with an acetazolamide challenge is another reliable method for identifying patients with cerebral hemodynamic impairment[8,9] and for identifying those who are at high risk for stroke recurrence.[10,11] We previously demonstrated that reduced cerebrovascular reactivity to acetazolamide on brain perfusion SPECT is associated with a high 5-year risk of recurrence of ischemic stroke in patients with symptomatic occlusion of the middle cerebral artery (MCA) or internal carotid artery (ICA).[12] However, acetazolamide is associated with a variety of adverse side effects, including headache, nausea, dizziness, tinnitus, numbness of the extremities, and Stevens-Johnson syndrome.[13,14] In fact, 63% of patients who underwent SPECT study with acetazolamide challenge developed adverse effects after administration of acetazolamide, and these symptoms resulted in some impairment of the ability of patients to engage in their normal activities of daily living or work activities.[13] Thus, it would be beneficial to develop a SPECT method of detecting misery perfusion that does not require administration of acetazolamide.

Crossed cerebellar hypoperfusion (CCH) is defined as a reduction in blood flow in the cerebellar hemisphere contralateral to a supratentorial lesion.[15] This phenomenon can be demonstrated on brain perfusion images obtained by SPECT or by PET.[15–18] The mechanism underlying CCH reportedly consists of disruption of the corticopontocerebellar pathway that causes functional deafferentation and transneural metabolic depression of the contralateral cerebellar hemisphere.[17,18] A reduction in the blood flow in the cerebellar hemisphere corresponds with the degree of metabolic depression, resulting in CCH. The disruption of the corticopontocerebellar pathway also leads to metabolic depression of the ipsilateral cerebral hemisphere. Thus, the degree of CCH may reflect cerebral metabolism in the affected cerebral hemisphere relative to that in the contralateral cerebral hemisphere. A previous study demonstrated a correlation between the degree of CCH and affected-to-contralateral asymmetry of cerebral metabolic rate of oxygen ($CMRO_2$) in the cerebral hemispheres on PET in patients with unilateral carotid artery occlusive disease.[19] Oxygen extraction fraction is a function of the ratio of $CMRO_2$ to CBF, and we have demonstrated that the ratio of blood flow asymmetry in the cerebellar hemisphere (i.e. the degree of CCH) to blood flow asymmetry in the cerebral hemisphere on brain perfusion SPECT correlates with PET–OEF asymmetry in the cerebral hemisphere. Further, this blood flow ratio can detect misery perfusion in the affected cerebral hemisphere in patients with unilateral occlusion of the MCA or ICA.[20]

The purpose of the present study was to reanalyze the same patient cohort used in our previous studies[11,12] and to determine whether the ratio of blood flow asymmetry in the cerebellar hemisphere to blood flow asymmetry in the cerebral hemisphere on brain perfusion SPECT predicts 5-year outcomes in patients with symptomatic unilateral occlusion of the MCA or ICA.

Subjects and Methods

Patients

In all, 70 consecutive patients (53 men, 17 women) meeting the inclusion criteria and who were admitted from January 1993 to March 1996 prospectively entered into the study.[11,12] The mean age was 57 years (range, 38–69 years), and the population characteristics were described previously.[11] Inclusion criteria for the present study were as follows: (1) age younger than 70 years, (2) unilateral complete occlusion of the ICA or the horizontal portion of the MCA confirmed by angiography with arterial catheterization, (3) evidence of ischemic cerebrovascular events in the arterial distribution distal to the lesion within 3 months prior to study entry, (4) useful residual function (modified Rankin disability scale [RS] 0, 1, or 2), (5) no or border zone infarction on computed tomography (CT) or magnetic resonance (MR) imaging, and (6) informed consent obtained from the patient or relatives. Patients were excluded from the study if they had (1) cardioembolic infarction, based on the onset pattern, angiographic findings, and results of electrocardiography and echocardiography; (2) vascular lesions caused by other systemic diseases, such as aortitis syndrome, moyamoya disease, or fibromuscular dysplasia; (3) an occlusion, or moderate to severe stenosis (>50%) of major cerebral arteries in the contralateral carotid or vertebrobasilar system; or (4) systemic conditions such as cardiac failure, renal failure, hepatic failure, respiratory failure, severe diabetes mellitus (fasting blood sugar ≥ 300 mg/dl), and severe hypertension (diastolic blood pressure ≥ 110 mmHg).

All study protocols were reviewed and approved by the institutional ethics committee.

Patient Management and Outcome Measures

All patients were treated with antiplatelet therapy (81 mg/day aspirin or 200 mg/day ticlopidine HCl), and treatment of other risk factors and medical therapy were based on the individual case. Although the attending physicians were unaware of the findings of the SPECT studies, treatment did not differ among the patients. No patients underwent bypass surgery. Patients were examined at 1-month intervals and followed for 60 months after study entry. An interim

history was obtained, and a neurologic examination was performed at each visit.

The study terminated on 31 March 2001.[12] The primary end point was stroke recurrence or death, and observation was terminated if stroke recurred or if death occurred. Magnetic resonance imaging was obtained and was 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.

Single-Photon Emission Computed Tomography Methodology

Brain perfusion was assessed using *N*-isopropyl-*p*-[^{123}I]-iodoamphetamine (IMP) and SPECT. All patients underwent SPECT study 1 month or more after the last ischemic event and within 2 weeks before study entry. Single-photon emission computed tomography images were obtained using a multidetector ring-type scanner (Headtome-SET031, Shimadzu Corp., Kyoto, Japan), consisting of 64 NaI crystals in a 38-cm diameter circle. After tomographic reconstruction, the spatial resolution and slice thickness in the center of the plane were 9 and 16 mm full width at half maximum (FWHM), respectively. The device can obtain six tomographic slices in a single scanning process. The energy window in this study was 140 keV (±15%). Projection data were processed with Ramachandran's filtered backprojection after introduction of a Butterworth prefilter. A 64×64 image matrix was used.

An intravenous injection of 111 MBq, ^{123}I-IMP was administered. After 15 minutes, SPECT imaging with a high resolution collimator was performed, and tomographic data were continuously obtained over a 30-minute period.

Two tomographic planes, located 50–66 mm above (plane of the cerebrum) and 2–18 mm below (plane of the cerebellum) and parallel to the orbitomeatal line, were analyzed for each patient, and the region of interest (ROI) was placed directly on each selected SPECT image. Magnetic resonance-single-photon emission computed tomography imaging coregistration was not used. Following the atlas developed by Kretschmann and Weinrich,[21] one investigator, who was blinded to patient data, manually drew a large irregular ROI in the cerebral cortex perfused by the ipsilateral MCA on the plane of the cerebrum. On the same plane, a mirror-image ROI was also placed in the corresponding region on the contralateral side. Further, an irregular ROI was symmetrically placed in the bilateral cerebellar hemispheres on the plane of the cerebellum. Next, the mean count was determined in each ROI. The determination was accomplished at the time of study entry in all patients. Before the initiation of patient entry, the same SPECT studies were performed in 10 normal subjects (8 men and 2 women; age range, 35–65 years; mean age, 52.3 years) for whom informed consent was obtained.

Based on these SPECT data obtained at the time of patient entry, several analyses were retrospectively performed. First, the ratio of the mean count in the MCA territory on the occluded side to that on the contralateral side was calculated and was defined as the cerebral perfusion ratio (CbrPR). In the 10 normal subjects, the CbrPR was calculated when the left and right cerebral hemispheres were defined as the occluded side and the contralateral side, respectively. Second, the ratio of the mean count in the cerebellar hemisphere on the contralateral side to that on the occluded side was calculated and was defined as the cerebellar perfusion ratio (CblPR). In the 10 normal subjects,[12] the CblPR was calculated when the left and right cerebellar hemispheres were defined as the contralateral side and the occluded side, respectively. Finally, the value of CblPR/CbrPR was calculated for each patient and for each normal subject.

Statistical Analysis

Descriptive data are expressed as mean ± standard deviation (SD). The relationship between CblPR/CbrPR in patients and those in normal subjects was evaluated using the Mann–Whitney's *U*-test. The relationship between each variable and the development of the primary end point or subsequent ipsilateral strokes was evaluated by univariate analysis using the Mann–Whitney's *U*-test or chi^2-test. A multivariate statistical analysis of factors related to development of the primary end point or subsequent ipsilateral strokes was also performed using a logistic regression model. Variables with $P < 0.2$ in the univariate analyses were selected for analysis in the final model. Regardless of the *P* value, modified RS and border zone infarction were adopted as confounders of the baseline clinical status in the model. Differences were deemed statistically significant if $P < 0.05$. The accuracy of CblPR/CbrPR at entry to predict the development of the primary end point or subsequent ipsilateral strokes was determined by a receiver operating characteristic curve when the relationship between the two variables was significant. The curve was calculated in increments or decrements of 0.5 SD from the mean value of CblPR/CbrPR obtained in normal subjects.

Results

All 70 patients were followed for 5 years or until stroke recurrence or death.[12] A total of 13 strokes were identified, 11 of which were ipsilateral to the ICA or MCA occlusion; the other two patients suffered stroke in the contralateral cerebral hemisphere or in the contralateral brain stem, respectively.[12] One death

each was attributed to lung cancer, gastric cancer, myocardial infarction, and a motor vehicle accident.[12] Thus, 17 patients were defined as having the primary end point.

Cerebellar perfusion ratio (CblPR)/cerebral perfusion ratio (CbrPR) was higher in the 70 patients [0.801–1.468 (mean, 1.072; SD, 0.122)] than in the 10 normal subjects [0.942–1.066 (mean, 1.002; SD, 0.050)] ($P = 0.0432$).

Results of univariate analysis of factors related to the development of the primary end point or subsequent ipsilateral strokes are summarized in Table 1. The CblPR/CbrPR was significantly higher in patients with the primary end point or subsequent ipsilateral strokes than in those without (Fig. 1). Other variables were not significantly associated with the development of the primary end point or subsequent ipsilateral strokes. After eliminating closely related variables in the univariate analyses, the following confounders with $P < 0.2$ in addition to modified RS and border zone infarction were adopted in the logistic regression model for the multivariate analysis: hyperlipidemia and CblPR/CbrPR. The multivariate analysis revealed that only high CblPR/CbrPR was significantly associated with the development of the primary end point or subsequent ipsilateral strokes (95% confidential limits [CIs], 1.130–3.145; $P = 0.0114$ or 95% CIs, 2.558–5.140; $P = 0.0045$, respectively).

Sensitivity and specificity for the CblPR/CbrPR in the cut-off point lying closest to the left upper corner of the receiver operating characteristic curve were 65% (11/17) and 88% (47/53) (cut-off point = 1.102: the mean+2 SD of the control value obtained from normal subjects), respectively, for prediction of development of the primary end point and were 91% (10/11) and 88% (52/59) (cut-off point = 1.102: the mean+2 SD of the control value obtained from normal subjects), respectively, for prediction of the development of subsequent ipsilateral strokes (Figs. 1 and 2). With the same cut-off point, the positive- and negative-predictive values were 65% (11/17) and 88% (47/53), respectively, for prediction of the development of the primary end point or were 59% (10/17) and 98% (52/53), respectively, for prediction of the development of subsequent ipsilateral strokes.

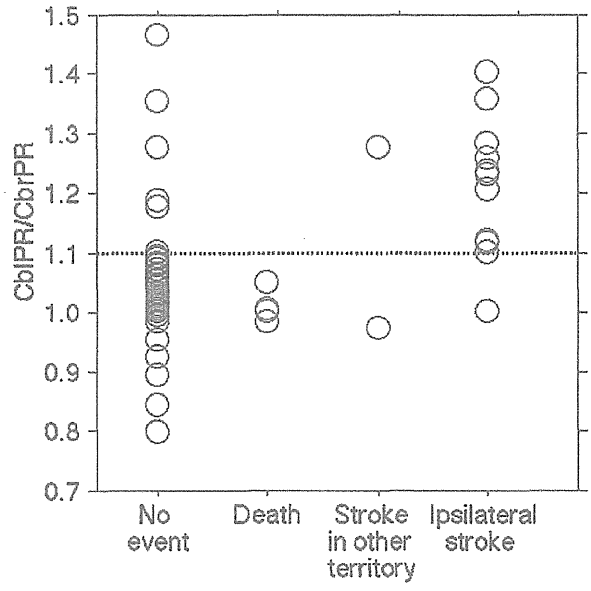

Figure 1 Relationship between cerebral perfusion ratio (CblPR)/cerebellar perfusion ratio (CbrPR) and the primary end point (death, stroke in the other vascular territory, and subsequent ipsilateral stroke). Dashed horizontal line denotes mean+2 SD (1.102) of CblP R/CbrPR obtained in healthy volunteers.

Single-photon emission computed tomography images at entry for a patient who developed a subsequent ipsilateral stroke are illustrated in Fig. 3.

Discussion

The present study demonstrated that the ratio of blood flow asymmetry in the cerebellar hemisphere to

Table 1 Univariate analysis of factors related to the development of the primary end point or subsequent ipsilateral stroke

	Primary end point			Subsequent ipsilateral stroke		
Variables	Yes (n = 17)	No (n = 53)	P value	Yes (n = 11)	No (n = 59)	P value
Age (years, mean±SD)	57.7±7.3	56.5±8.7	0.8477	58.6±6.1	56.4±8.7	0.6336
Male gender	12 (71%)	41 (77%)	0.7458	8 (73%)	45 (76%)	0.7215
Modified RS of zero	10 (59%)	22 (42%)	0.2678	7 (64%)	25 (42%)	0.3231
Border zone infarction	11 (65%)	29 (55%)	0.5778	8 (73%)	32 (54%)	0.3305
Site of lesion						
ICA	10 (59%)	31 (58%)	> 0.9999	7 (64%)	34 (58%)	0.7532
MCA	7 (41%)	22 (42%)		4 (36%)	25 (42%)	
Hypertension	10 (59%)	27 (51%)	0.5917	7 (64%)	30 (51%)	0.5219
Diabetes mellitus	4 (24%)	17 (32%)	0.5610	2 (18%)	19 (32%)	0.4852
Hyperlipidemia	3 (18%)	1 (2%)	0.0519	2 (18%)	2 (3%)	0.1136
Prior MI	1 (6%)	2 (4%)	0.5720	1 (9%)	2 (3%)	0.4061
Smoking	9 (53%)	38 (72%)	0.2344	64 (53%)	68 (72%)	> 0.9999
CblPR/CbrPR	1.155±0.138	1.045±0.104	0.0018	1.212±0.118	1.046±0.104	0.0001

SD: standard deviation; RS: Rankin disability scale; ICA: internal carotid artery; MCA: middle cerebral artery; MI: myocardial infarction; CblPR: cerebellar perfusion ratio; CbrPR: cerebral perfusion ratio.

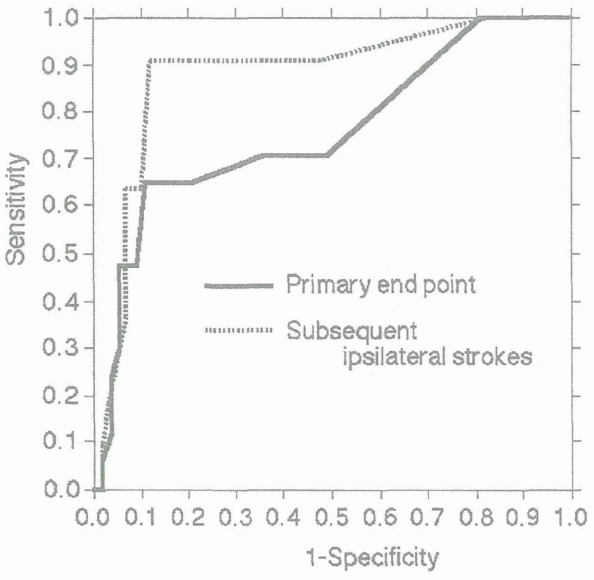

Figure 2 Receiver operating characteristics curves used to determine the accuracy of cerebellar perfusion ratio (CblPR)/ cerebral perfusion ratio (CbrPR) at entry to predict the development of the primary end point or subsequent ipsilateral strokes.

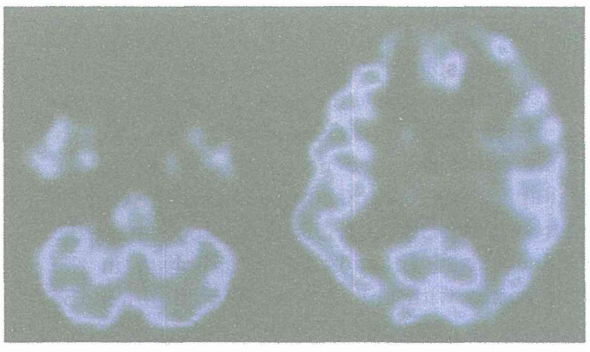

Figure 3 Single-photon emission computed tomography (SPECT) images of a 58-year-old woman with symptomatic occlusion of the left middle cerebral artery (MCA). While blood flow asymmetry in the cerebellar hemisphere is not observed, blood flow in the left MCA territory is reduced when compared with blood flow in the right MCA territory. This patient developed stroke recurrence in the left MCA territory 5 months after entry into the study.

blood flow asymmetry in the cerebral hemisphere on brain perfusion SPECT predicts 5-year outcomes in patients with symptomatic unilateral occlusion of the MCA or ICA.

We recently demonstrated that the CblPR/CbrPR on brain perfusion SPECT reflects OEF asymmetry in the MCA territory and that this blood flow ratio detects misery perfusion in the affected cerebral hemisphere with a sensitivity and negative-predictive value of 100% in patients with unilateral stenosis or occlusion of the MCA or ICA.[20] In that previous study, the misery perfusion in the affected MCA territory was defined as an affected-to-contralateral PET–OEF ratio greater than the mean+2 SDs (1.089) of the normal values. Grubb *et al.* categorized patients with the affected-to-contralateral PET–OEF ratio greater than 1.082 due to unilateral ICA steno-occlusive disease as having misery perfusion and reported that such patients are at high risk for subsequent stroke when treated medically.[6] The cut-off point for the affected-to-contralateral PET–OEF ratio in our recent study was similar to that defined by Grubb *et al.* Further, in the same study, the receiver operating characteristic analysis showed that the optimal cut-off point of the CblPR/CbrPR on brain perfusion SPECT for detection of the misery on OEF PET was the mean+2 SDs (1.101) of the control value obtained from normal subjects,[20] which is similar to the optimal cut-off point (the mean+2 SDs of the control value obtained from normal subjects, 1.102) of the CblPR/CbrPR in predicting development of the primary end point or subsequent ipsilateral strokes in the present study.

Although contralateral-to-affected side blood flow asymmetry in the cerebellar hemisphere essentially reflects $CMRO_2$ in the affected cerebral hemisphere relative to that in the contralateral cerebral hemisphere,[19,20] the degree of the blood flow asymmetry in the cerebellar hemisphere underestimates the degree of $CMRO_2$ asymmetry in the cerebral hemisphere when assessed at later than 3 months after the last ischemic event.[20] These findings are supported by previous reports in which CCH was not always seen in patients with decreased $CMRO_2$ in the cerebral hemisphere ipsilateral to a major cerebral artery occlusion.[22] In fact, CCH often disappeared 2–3 months after onset in patients with stroke.[23] As a result, while the CblPR/CbrPR overestimates the OEF asymmetry in patients who are assessed at later than 3 months after the last ischemic event, the specificity (83%) and positive-predictive value (72%) of the CblPR/CbrPR for detection of the misery perfusion are elevated when assessed in patients within 3 months after the last ischemic event.[20] The present study had included only the latter type of patients, and this inclusion criterion might explain why CblPR/CbrPR predicted subsequent stroke in this study.

The simplicity of requiring only the evaluation of asymmetry on blood flow images makes the present SPECT method practical. The present SPECT method also has the advantage of not requiring acetazolamide, which is otherwise associated with a significant risk of various adverse side effects.[13,14] In particular, this SPECT method is useful as a screening test to determine whether a PET study is needed to predict the development of subsequent strokes in patients within 3 months after the last ischemic event due to unilateral occlusion of the MCA or ICA.

Blood flow in the cerebral hemisphere ipsilateral to the arterial lesion and in the contralateral cerebellar hemisphere could be affected by stroke severity, as reflected by the infarct volume or the degree of neurological deficits. Border zone infarction may cause selective neuronal damage in the normal-appearing cerebral cortex beyond the regions of infarcts, resulting in reduced metabolism in the cerebral cortex.[24] In addition, metabolism in the cerebral cortex with border zone infarction may be reduced due to diaschisis from the infarction.[24] This reduction in metabolism in the affected cerebral hemisphere leads to CCH as well as hypoperfusion in the ipsilateral cerebral hemisphere.[17] Under such conditions, CblPR/CbrPR is not elevated, suggesting 'matched hypometabolism'[20] and a low risk of stroke recurrence. On the other hand, blood flow in the affected cerebral hemisphere is often reduced to a greater degree than its metabolism, even in patients with border zone infarction. In this condition, CblPR/CbrPR is elevated, suggesting 'misery perfusion'[20] and a high risk of stroke recurrence. These factors might account for why neither modified RS nor border zone infarction was associated with the development of the primary end point or subsequent ipsilateral strokes in the present study. These findings also suggest that when a patient with border zone infarction due to symptomatic unilateral chronic ICA or MCA occlusive disease exhibits a decrease in perfusion in the ipsilateral cerebral hemisphere on brain perfusion imaging, CblPR/CbrPR can distinguish 'misery perfusion' from 'matched hypometabolism'.[20]

Superficial temporal artery-MCA bypass for patients with recent symptomatic carotid artery occlusion and misery perfusion (as in the patients in the present study) was not effective in reducing recurrent, ipsilateral ischemic events in the Carotid Occlusion Surgery Study.[25] One of the factors that led to the negative outcome of that study was the high rate of ipsilateral strokes during the first 2 days after surgery.[26] The mechanism of these perioperative ischemic strokes was attributable to hemodynamic factors and the inability of patients with a symptomatic ICA occlusion and impaired hemodynamics in the cerebral hemisphere distal to the ICA occlusion to tolerate surgery in the majority of cases.[26] On the other hand, 2-year rates for the primary end point were 23% for patients who received current standard medical treatments in the Carotid Occlusion Surgery Study.[25] Thus, the optimal treatment strategy for patients with misery perfusion due to symptomatic ICA or MCA occlusive disease remains undetermined.

The present study possesses several limitations that require discussion. First, although misery perfusion is a predictor of subsequent stroke in medically treated patients with symptomatic major cerebral artery disease, this finding has been demonstrated in studies in the 1990s.[5,6] Advances in medical therapies over the last few decades, such as the use of angiotensin receptor blockers and statins, may reduce the recurrent stroke rate in general,[27–30] which may also affect the predictive value of misery perfusion for stroke risk. Yamauchi *et al.* prospectively studied patients with symptomatic ICA or MCA occlusive diseases who underwent PET from 1999 to 2008 and demonstrated that misery perfusion on PET is still a predictor of subsequent stroke in patients with symptomatic ICA or MCA occlusive disease who are receiving current standard medical treatments.[7] The present study was performed from 1993 to 2001, and the majority of patients who entered into the present study did not receive current standard medical treatments. Thus, even when considering the findings demonstrated by Yamauchi *et al.*, further investigation regarding the relationship between the blood flow ratio on brain perfusion SPECT used in the present study and the risk of stroke recurrence is needed in patients with symptomatic major cerebral artery occlusive disease who are receiving current standard medical treatments. Second, the study population included only patients with unilateral ICA or MCA occlusive disease and used blood flow asymmetry on SPECT images to detect misery perfusion in the affected cerebral hemisphere. However, impairments in cerebral hemodynamics are more severe in patients with bilateral major cerebral artery occlusive disease than in those with unilateral major cerebral artery occlusive disease,[31] and impairments in bilateral cerebral hemodynamics in patients with bilateral major cerebral arterial occlusive disease may not be detected by the present SPECT method. Third, irregular ROIs were manually drawn in the cerebral cortexes perfused by the bilateral MCAs and in the bilateral cerebellar hemispheres on SPECT images using the atlas developed by Kretschmann and Weinrich.[21] Because of the age of the scanner, a program for coregistration or anatomic standardization of SPECT data was not used. Furthermore, whether only one selected tomographic plane reliably reflects the hemodynamics on the entire territory perfused by the MCA is an important issue. The SPECT machine used in the present study can obtain only six tomographic slices for 123I-IMP SPECT in a single scanning process. In addition, the obtained SPECT tomographic slices are not sequential, and data are missing in every other slice. Therefore, we could not perform volumetric analysis of the SPECT data in the present study. Lastly, cerebral hemodynamic impairment can be identified using other less-invasive and lower cost methods, such as determination

of cerebrovascular reactivity to hypercapnia, as measured by transcranial Doppler ultrasonography and the breath-holding index values in the MCA flow velocity.[32] This method also identifies patients who are at high risk for stroke onset due to ICA occlusive disease.[33] However, transcranial Doppler ultrasonography with breath-holding often cannot be accomplished due to technical problems caused by poor insonation of the temporal bone window or subject problems caused by intolerance to breath-holding.[32,33] Although brain perfusion SPECT is more expensive than transcranial Doppler ultrasonography, it always displays left-to-right asymmetry of blood flow in the cerebral and cerebellar hemispheres, resulting in the prediction of patient outcomes.

In conclusion, the ratio of blood flow asymmetry in the cerebellar hemisphere to blood flow asymmetry in the cerebral hemisphere on brain perfusion SPECT predicts 5-year outcomes in patients with symptomatic unilateral occlusion of the MCA or ICA.

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