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Cerebral hemodynamics as a predictor of stroke in adult patients with moyamoya disease: a prospective observational study

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Abstract

Moyamoya disease is an obliterative vasculopathy of the large arteries at the base of the brain. In the US, it most commonly affects women in their 3rd and 4th decades of life, frequently causing ischemic stroke. The natural history of this disorder is not well described. It is very likely that hemodynamic factors play an important role in the risk of future stroke, as has been established in atherosclerotic carotid occlusive disease.

The authors describe an ongoing, prospective observational study designed to test the hypothesis that increased oxygen extraction in the cerebral hemisphere beyond the occlusive lesion is a predictor of subsequent risk of ipsilateral stroke in medically treated patients with moyamoya phenomenon. On enrollment, all patients undergo regional measurements of cerebral oxygen extraction fraction (OEF) with PET. Information on baseline clinical, laboratory, epidemiological, and angiographic risk factors are obtained at the time of the PET study. Decisions regarding surgery are made by the treating physicians based on clinical information while being blinded to PET data. Patients undergo follow-up at 6-month intervals to determine the subsequent risk of ipsilateral stroke. All patients will return at 1 and 3 years for repeat PET studies. Secondary, exploratory, aims of this longitudinal and blinded study are to determine other predictive factors for stroke in this population; to determine preliminary estimates of the effects of different medical treatment regimens in this population; to determine the temporal changes in hemodynamic impairment in medically treated patients; to determine the effects of surgery on hemodynamic impairment in the subset of patients who undergo surgical revascularization; and to obtain estimates of surgical complication rates for patients with and without hemodynamic impairment.

Keywords

moyamoya disease; cerebral hemodynamics; natural history; clinical trial

North American moyamoya disease is poorly understood in many regards. The etiology is unknown, and the natural history is not prospectively defined. As a consequence, the optimal treatment of patients with this disorder remains unclear. The disease is characterized by the angiographic appearance of non-atherosclerotic bilateral stenosis or occlusion of the distal

internal carotid arteries, often accompanied by characteristic enlargement of small lenticulostriate arteries that serve as collateral channels to bypass the occlusions.²⁴

North American and European moyamoya disease most commonly affects women in their 3rd and 4th decades of life, and the most frequent presentation is ischemic stroke or transient ischemic attack.^{1,3,4,10,16,25,30} Within this age group, this disorder accounts for up to 5–10% of ischemic strokes.²³ The risk of secondary stroke in these patients may be as high as 10% per year.³ In a retrospective study at our own institution, we found a 5-year risk of recurrent ipsilateral stroke of 65% after the first ischemic symptom and 27% after angiographic diagnosis.⁹ Nevertheless, the prognosis with this disorder is not universally poor.

Asymptomatic patients and those with unilateral disease have much lower risks of stroke than those with bilateral involvement, both in North America and Asia.^{10,14,18,21} In addition, there appears to be a time window of stroke risk, similar to the data reported for medically treated patients with symptomatic extracranial stenosis,²⁰ complete CA occlusion,⁸ and intracranial atherosclerotic disease.² The period of maximal risk in all these studies is during the 1st or 2nd year after diagnosis. After 2 years, risks fall to rates similar to those with little or no stenosis. In patients with atherosclerotic CA occlusion, this time course is associated with an increase in blood flow from collateral channels, with a concomitant reduction in OEF.⁶ We observed a similar pattern of time dependence in our retrospective analysis of adult patients with moyamoya disease at our institution.¹⁰ The duration from first ischemic event to last event was less than 2 years in the majority of patients.

It is very likely that hemodynamic factors play an important role in the risk of subsequent stroke in patients with moyamoya disease, as in patients with complete CA occlusion from other causes, such as atherosclerotic disease.^{9,15,29} The presence of severe hemodynamic impairment—identified as increased OEF by PET—is a powerful and independent predictor of subsequent stroke in patients with atherosclerotic CA occlusion.^{9,29}

The goal of this study is to determine if patients with moyamoya disease can be separated into high- and low-risk groups based on OEF measurements. For example, more than half of patients with atherosclerotic CA occlusion presenting with stroke or transient ischemic attacks have normal OEF and have a low risk for subsequent stroke.⁹ This information is of critical importance in the design of future trials of therapy. Trials of revascularization are more likely to show a benefit when targeted at a population with severe hemodynamic impairment. At present, we have little data on which to base reasonable estimates of sample size. Other important missing data that are necessary for proper trial design include the effects of surgery on reversing the hemodynamic abnormality and the complication rates of surgery. Follow-up data will also provide an estimate of the effect of increased OEF on stroke risk in medically treated patients and the effect of surgery on stroke risk in patients with normal and increased OEF.

Cerebral Hemodynamics as a Predictor of Stroke

Hemodynamic impairment, as identified by a compensatory increase in oxygen extraction or an impaired vasodilatory response to breath holding, has been prospectively proven to be an independent risk factor for future stroke in atherosclerotic CA occlusive disease.^{5,22,26} The former technique may not be feasible in some patients with moyamoya disease due to the obliteration of the distal internal carotid artery and M₁ segments, where transcranial Doppler ultrasound velocity measurements are generally made. Grubb et al.⁹ have reported outcomes in 81 patients with symptomatic CA occlusion, the results of the STLCOS. This was a blinded, prospective study of 81 patients with symptomatic CA occlusion that also specifically assessed the impact of other risk factors. The risk of all stroke and ipsilateral ischemic stroke in symptomatic patients with increased OEF was significantly higher than in those with normal

OEF ($p = 0.005$ and $p = 0.004$, respectively, log-rank test). Univariate and multivariate analysis of 17 baseline stroke risk factors confirmed the independence of this relationship. The age-adjusted relative risk conferred by increased OEF was 6.0 (95% CI 1.7–21.6) for all stroke and 7.3 (95% CI 1.6–33.4) for ipsilateral ischemic stroke. An increased OEF was identified by a hemispheric ratio above the normal range. These data were confirmed in a subsequent study by Yamauchi et al.²⁹ who reported on 52 patients with high-grade atherosclerotic stenoses and occlusions of the internal carotid and middle cerebral arteries. The OEF was measured on study entry. Twelve cases were censored due to interval surgical revascularization. The presence of increased OEF, defined by absolute regional OEF above the 95th percentile from the mean in normal controls (53.3%), was strongly associated with a stroke during study follow-up.

Improvements in Collateral Flow Over Time

Collateral sources of blood flow may improve over time in some patients with atherosclerotic CA occlusion.^{6,11,27} In addition, it appears that stroke risk may improve over time in this patient population.⁸ A similar phenomenon may be present in some patients with moyamoya disease. Chiu et al.³ reported an initially high risk of stroke for patients with moyamoya disease in the 1st year (18%) after presentation, with a subsequent drop off in annual rates of ischemic stroke (5%). In our review of 34 patients with unilateral (12 cases) or bilateral (22 cases) moyamoya disease, there were only 6 cases in which the duration between first and last ischemic symptom was greater than 2 years.¹⁰

Measurements of OEF in Moyamoya Disease

Hemodynamic impairment is likely an important risk factor for ischemic stroke in this population, as in patients with atherosclerotic occlusive disease. Furthermore, it is likely that the degree of hemodynamic impairment, and consequently the risk of subsequent stroke, is variable between patients with this disease. The frequency of increased OEF and the relationship with stroke risk remains to be defined in North American moyamoya disease. Currently, some patients undergo surgical procedures designed to improve blood flow to the brain. The benefit of these procedures and their effect on cerebral hemodynamic status is unproven. Some of these patients may have normal hemodynamics and little to benefit from a revascularization procedure. The data from the present study will provide much of this information and allow us to determine if a randomized clinical trial of surgical revascularization in a subgroup of patients with moyamoya disease is indicated or feasible.

There is a wealth of data from Japanese studies documenting the severe hemodynamic impairment with childhood moyamoya disease, less severe impairment in adults, and improvement after surgical revascularization.^{13,17,19,28} Kuwabara and colleagues¹⁹ have reported PET measurements of CBF, cerebral blood volume (an indicator of autoregulatory vasodilation), and OEF in five children and four Japanese adults with moyamoya disease. Cerebral blood volume and OEF were consistently elevated over controls in the children, but not in adults, despite regions of low blood flow in both groups. This pattern of hemodynamic impairment is consistent with the theory that moyamoya disease in Asia likely begins in childhood with ischemic symptoms and that later presentations in adults who are generally hemorrhagic due to long-standing collateral flow through fragile arterial collaterals. Unfortunately, there is very little hemodynamic data on North American patients with moyamoya disease. Horowitz and colleagues¹² have reported variable CBF responses to acetazolamide challenge in 4 patients. No longitudinal studies of medically treated patients have been reported in the Japanese or North American literature.

We have used PET scanning for cerebral hemodynamic assessment in 12 patients with moyamoya disease prior to the initiation of the present prospective study (Fig. 1). In all 12 patients, we found considerable variability in the degree of hemodynamic impairment, despite

similar angiographic appearances in both CA territories. All 12 patients were women, and all presented with ischemic events (4 transient ischemic attacks, 8 strokes). Their mean age was 36.5 years. Ten women were white and 2 were black. Seven had typical bilateral moyamoya disease (Suzuki Stage 3 or 4). Of these 7 patients, 2 had normal OEF, 3 had bilateral increases in OEF, and 2 had unilateral increases in OEF. Two patients had atypical bilateral moyamoya disease and both had focal unilateral increases in OEF. Two patients had typical unilateral disease (Suzuki Stage 3 or 4) and a normal OEF study, as did the final patient with atypical unilateral disease. Two patients have undergone a unilateral EDAS procedure and follow-up PET scanning (Fig. 1).

We have studied 2 patients 12 months after a unilateral EDAS (Fig. 1). The PET images in Fig. 1, obtained in a 31-year-old woman, demonstrated reduced absolute values of OEF and normalization of the initial asymmetry, compared with the baseline study. The patient had no further ischemic symptoms. On angiography, the internal carotid artery had progressed from severe stenosis to complete occlusion. Interval development of extensive external CA–pial arterial anastomoses had occurred. The second patient, with bilateral moyamoya disease (Suzuki Stage 2) and unilateral ischemic symptoms, underwent EDAS therapy on the symptomatic hemisphere. Positron emission tomography measurements of OEF were normal preoperatively and remained normal.

Prospective Observational Study Design and Analysis Plan

The goal of our present study is to determine if patients with moyamoya disease can be separated into high- and low-risk groups based on OEF measurements. Secondary objectives include the determination of other predictive factors for stroke in this population, to identify the temporal changes in hemodynamic impairment in medically treated patients, to obtain preliminary estimates of the effects of different medical treatment regimens in this population, and to determine the effects of surgery on hemodynamic impairment in the subset of patients undergoing surgical revascularization. Estimates of surgical complication rates for patients with and without hemodynamic impairment will also be established.

Patients with moyamoya disease will be recruited without restriction with regard to sex, race, age, and socioeconomic status. Exclusion criteria include the presence of any other disease that might be responsible for the vasculopathy, including atherosclerosis, neurofibromatosis, meningitis, sickle cell disease, skull base radiation therapy, and pregnancy. See Appendix 1 for inclusion and exclusion criteria. The experimental design consists of a prospective, nonrandomized, blinded study. Participating sites are listed in Appendix 2.

On enrollment, all patients will undergo regional measurements of cerebral OEF with PET. Noncontrast MR imaging of the brain will be performed for research purposes to permit accurate definition of infarct location and for the purposes of coregistration for future analysis. Information on baseline clinical, laboratory, epidemiological, and angiographic risk factors will be obtained at the time of the PET study through a detailed history, physical examination, and laboratory/radiological analysis. Vascular imaging studies will be centrally reviewed. Functional status will be measured using modified Barthel and Rankin scales.

Patients will be followed at 6-month intervals to determine the subsequent risk of ipsilateral stroke. All patients will return at 1 and 3 years for repeat PET studies. Fifty patients will be enrolled over the next 5 years (10 per year). Each involved hemisphere will be treated separately, for a total of 100 cerebral hemispheres at risk. Treating physicians and patients will be blinded to the results of the PET study. The primary endpoint is the occurrence of ipsilateral ischemic stroke in the territory of the affected vessels. Secondary endpoints are death and any stroke.

Patients with medically treated hemispheres will be followed over the 5-year study for the occurrence of stroke. The primary endpoint is the “survival” time from study baseline to the occurrence of ipsilateral stroke, which will be statistically censored for those patients without an occurrence of ipsilateral stroke during the entire study period. The survival time for any hemisphere that dies or undergoes surgical revascularization before the occurrence of ipsilateral stroke will also be considered statistically censored. Endpoint assessment will be made blind to PET data.

Since most patients with moyamoya have bilateral disease, an absolute measurement of OEF rather than a ratio compared with the contralateral hemisphere will be used. The threshold for abnormal OEF will be set prospectively as > 0.44 . In their study Yamauchi et al.²⁹ found absolute values of OEF to be predictive of stroke. The data from the STLCOS demonstrated similar performance of absolute OEF.⁷ Mean hemispheric ($\pm$ SD) absolute OEF in the 18 normal control individuals was 0.41 ± 0.09 (range 0.26–0.64). When the upper 95% confidence limit for absolute OEF (0.44) was used as a threshold value, 33 of the 68 patients in the STLCOS with complete quantitative studies were categorized as having increased OEF. Eight of the 9 strokes occurred in these patients ($p = 0.0042$). Absolute OEF was a significant predictor of stroke risk as a continuous variable. In multivariate analysis comparing the 2 methods, absolute hemispheric values performed better than ratios of absolute values (p to remove = 0.0043). The ROC (receiver operating characteristic) analysis demonstrated a greater area under the curve for the absolute OEF (0.769) than the ratio of absolute hemispheric values (0.737), an indicator of greater accuracy in predicting stroke risk.

The primary statistical analysis will be a comparison of the survival distribution of the time to stroke occurrence in hemispheres with increased OEF versus those with normal OEF on initial PET studies. This analysis will be done using a log-rank test. Using 2 hemispheres from each patient will increase the overall Type I error rate, as correlated multivariate survival times are observed from the same patients. Consequently, before performing the log-rank analysis, a multivariate Cox regression analysis will first be performed on OEF and other stroke risk factors to reject the null hypothesis that both regression coefficients associated with OEF from the two hemisphere-specific Cox proportional hazards models are simultaneously zero.

Cox proportional hazards models will be used to perform the comparison after adjusting the effect of other covariates. Repeat PET measurements of OEF in medically and surgically treated hemispheres will be compared with baseline measurements to determine if OEF improves over time in either group.

This study is ongoing, having been funded in April of 2006. To date, 24 patients have been enrolled. The study is on target to meet recruitment goals.

Conclusions

We have described our ongoing study, which is designed to test the hypothesis that increased OEF is an independent predictor of stroke risk in patients with moyamoya disease. In addition, the study will provide important prospective data regarding other potential predictors of stroke risk in this population, changes in hemodynamics over time, and improvement after cerebral revascularization procedures. This information will be useful in determining if a clinical trial of surgical revascularization in this population is necessary or feasible.

Abbreviations used in this paper

CA, carotid artery; CBF, cerebral blood flow; EDAS, encephaloduroarteriosynangiosis; OEF, oxygen extraction fraction; STLCOS, St. Louis Carotid Occlusion Study..

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Appendix

Appendix 1

Inclusion and Exclusion Criteria

Inclusion criteria:

- a. Adult ≥ 18 years of age
- b. Capable of giving informed consent
- c. Clinical: Both asymptomatic and symptomatic patients will be included. The large majority of patients referred to our institution have had recent symptoms of cerebral ischemia, leading to their diagnosis of moyamoya disease, but a few have been asymptomatic. It will be clinically relevant to determine the prevalence of increased OEF in asymptomatic patients, as well.
- d. Anatomical: Unilateral or bilateral imaging findings consistent with moyamoya disease on digital subtraction, CT, or MR angiography
 - i. narrowing or occlusion of the supraclinoid CA beyond the origin of the posterior communicating artery or
 - ii. narrowing or occlusion of the proximal anterior cerebral artery or
 - iii. narrowing or occlusion of the proximal middle cerebral artery and
 - iv. with moyamoya collaterals

Exclusion criteria:

- a. Any other disease that might be responsible for the vasculopathy, including atherosclerosis, neurofibromatosis, meningitis, sickle cell disease, and history of skull base radiation therapy
- b. Pregnancy

Appendix 2

Participants and Centers

Cristina S. Ivan, M.D., Indiana University

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Fig. 1.

Positron emission tomography scans demonstrating asymmetrical OEF abnormality and improvement following a unilateral EDAS procedure in a 31-year-old woman presenting with an episode of right-sided weakness. Angiography had demonstrated bilateral internal carotid artery disease with moyamoya collaterals. *Upper:* Preoperative images demonstrating a focal area of reduced CBF (*arrow*) in the left motor cortex with preserved oxygen metabolism ($CMRO_2$). A compensatory increase in OEF is present (*arrow*). Regional analysis of the middle cerebral artery territories bilaterally, using the same 7 spherical regions of interest as used in the STLCOs and proposed for the present study, demonstrated increased OEF by hemispheric ratio (1.10) and absolute values (0.470), when compared with values from 18 normal control patients. The patient underwent an uncomplicated unilateral EDAS procedure. *Lower:* Repeat PET images obtained at 12 months showing improvement in CBF and OEF (*arrows*). CBV = cerebral blood volume.