

# Increasing Severity of Cardiovascular Risk Factors With Increasing Middle Cerebral Artery Stenotic Involvement in Type 2 Diabetic Chinese Patients With Asymptomatic Cerebrovascular Disease

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**OBJECTIVE** — To identify determinants associated with increasing severity of middle cerebral artery (MCA) stenosis in asymptomatic Chinese type 2 diabetic patients with and without MCA stenosis determined using transcranial Doppler. Conventional risk factors contribute to the pathogenesis of ischemic stroke, and differences in the pattern of these may explain the heterogeneity of disease presentation in different populations. In Chinese patients, MCA stenosis is the most commonly identified intracranial vascular lesion.

**RESEARCH DESIGN AND METHODS** — Anthropometric and fasting biochemical parameters were compared between type 2 diabetic patients with MCA stenosis in one ( $n = 185$ ) or both ( $n = 200$ ) vessels and 1,492 type 2 diabetic patients without evidence of stenosis.

**RESULTS** — Increasing MCA stenotic vascular involvement was associated with significantly increasing age, duration of diabetes, systolic blood pressure, and LDL cholesterol, but with lower glucose levels. There was also an increased prevalence of hypertension, dyslipidemia, and use of blood pressure- and glucose-lowering agents in the patients with MCA stenosis. Concomitant significant increases in the prevalence of peripheral vascular disease and retinopathy were also observed in the patients with MCA stenosis.

**CONCLUSIONS** — Transcranial Doppler examination identified stenosis in one or both MCAs in over one-fifth of the Chinese type 2 diabetic subjects without symptoms of cerebrovascular disease. A number of conventional cardiovascular risk factors were closely associated with MCA stenosis. This technique may allow the identification of a particularly high-risk group, and further studies are required to determine whether asymptomatic MCA stenosis is predictive of primary cerebrovascular events and whether intensive treatment of risk factors would reduce the risk.

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**Abbreviations:** MCA, middle cerebral artery.

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Stroke is a major cause of mortality and morbidity in Oriental populations, with the World Health Organization estimating 1.6 million stroke-related deaths in China alone in 2000, and rates are predicted to increase as the population ages (1). In China in 1999, mortality resulting from stroke (137.7 per 100,000 people) was second only to that due to malignancy (2). Improved control of risk factors has led to a reduction in age-adjusted stroke mortality rates, but as the population ages, absolute rates are rising.

In Oriental populations, apart from that in Singapore, higher mortality is attributed to stroke compared with Caucasian populations, where coronary heart disease generally predominates (3,4). However, even within China there is a great variability in stroke rates, which are generally higher in urban than in rural populations and in the North relative to the South. For instance, in 1986 the annual age-standardized incidence of stroke was 234.4 in Jilin Province in the Northeast vs. 53.2 per 100,000 people in Guangdong Province in southern China (5). The north-south differences were caused in part by the increased prevalence of hypertension in the North, with a 10% increase in prevalence of hypertension being associated with a 2.7-fold higher incidence of stroke (5). These studies support the importance of environmental and lifestyle factors in the etiology of stroke.

Stroke is a heterogeneous disorder, with marked ethnic differences in the distribution of arterial lesions. Intracerebral hemorrhage has been reported to be two to three times more frequent in Chinese than in Caucasian populations, accounting for 20–30% of strokes (6). In 114 nonselected autopsy subjects from Hong Kong, intracranial stenosis was found to be more severe than extracranial stenosis (7). In Hong Kong, of 705 consecutively

recruited stroke patients, 49% (349) had occlusive arteries, 37% had only intracranial stenosis, 10% had tandem lesions, and 2.3% had only extracranial lesions (8). In Caucasian patients referred for the evaluation of asymptomatic carotid bruits, 39.2% were found to have extracranial carotid stenosis, whereas 12.9% were found to have intracranial stenosis, of whom 28.8% also had diabetes (9). In Chinese stroke patients, stenosis of the middle cerebral artery (MCA) was the most common lesion, found in 35.9% of the patients (8). The cerebrovascular lesions tended to be more diffuse rather than discrete, as generally observed in Caucasian populations, with over half having two or more (up to nine) lesions. In a population-based study of 590 rural Chinese subjects screened by transcranial Doppler, 7% of those aged >40 years were found to have intracranial stenosis (2). We have previously shown that the presence and extent of intracranial vascular lesions independently predicted the risk of secondary stroke or death at 6 months (8). Hypertension, diabetes, a family history of stroke, and a history of heart disease were independent predictors of intracranial stenosis, with risk increasing substantially with increasing coexisting factors (2). In a clinic-based study of >3,000 asymptomatic Chinese individuals, similar risk factors were identified. Furthermore, the prevalence of intracranial stenosis was up to 25% in those subjects with multiple risk factors (2). In Chinese patients with acute stroke screened for diabetes or impaired glucose tolerance, over half were found to have these conditions, which were previously undiagnosed in many of the patients, and nearly all had ischemic stroke (10). Interventions that target the modifiable risk factors, such as diabetes and hypertension, have been shown to reduce the development of stroke in Chinese subjects (11).

In this study in type 2 diabetic Chinese subjects asymptomatic for cerebrovascular disease, we determined the factors contributing to MCA stenotic vascular involvement, the most common form of cerebrovascular ischemia in this population.

## RESEARCH DESIGN AND METHODS

The study protocol was approved by the clinical research ethics committee of the Chinese University of

Hong Kong. All 2,165 type 2 diabetic patients, recruited from the diabetes clinic at the Prince of Wales Hospital, were unrelated and gave written informed consent. They were of Han Chinese origin, without any known ancestors of other ethnic origin, and they were living in the Hong Kong Special Administrative Region of the People's Republic of China at the time of the study. Patients were considered diabetic if the fasting plasma glucose was  $\geq 7.8$  mmol/l or the 2-h post-75-g oral glucose tolerance test plasma glucose level was  $\geq 11.1$  mmol/l (12). Type 1 diabetic patients (1.7% from an initial 2,202 patients recruited) were defined on the basis of acute symptoms, with heavy ketonuria ( $>3+$ ) or ketoacidosis at diagnosis or requirement for continuous insulin treatment within 1 year of diagnosis, and they were excluded from the study (12). None of the type 2 diabetic patients screened had previously suffered from a stroke.

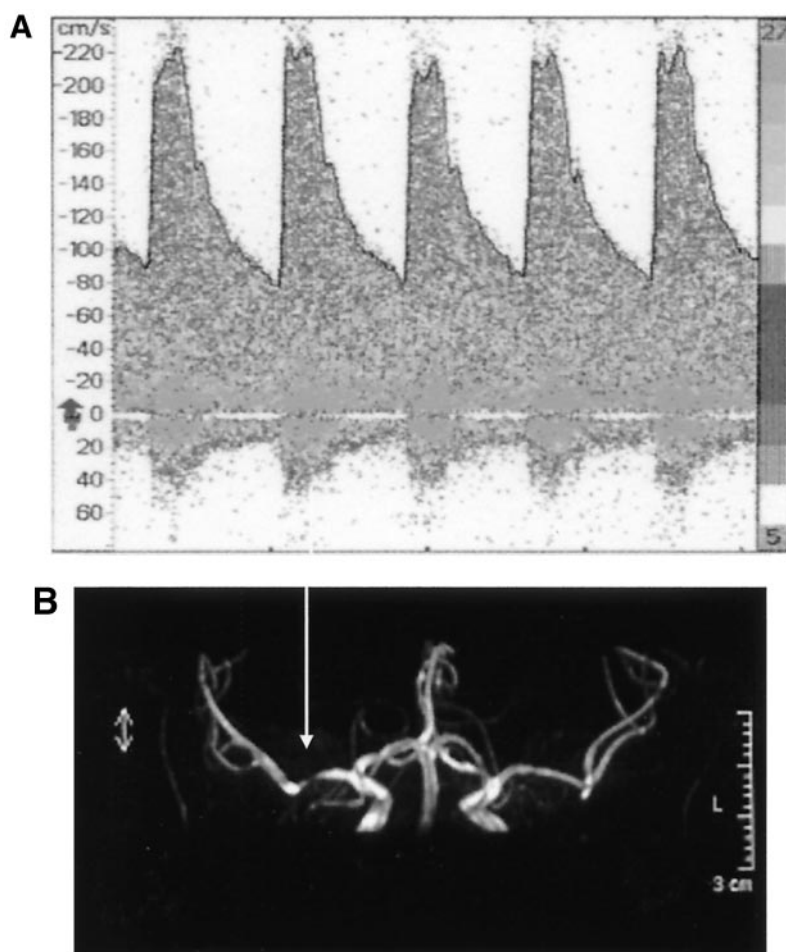
The patients were examined by transcranial Doppler (EME TC-2000). A single experienced operator (R.L.) performed all of the transcranial Doppler evaluations (Fig. 1). We studied the MCA using a standardized protocol, examining the artery with 4-cm increments through the temporal window at 52–64 mm. The criteria for occlusive arteries were defined by an abnormally high peak systolic flow velocity of  $\geq 140$  cm/s for the MCA (8). Apart from the above velocity criteria, we took into account the age of the patients, the presence of turbulence or musical sound, and whether the abnormal velocity was segmental. When it was not possible for insonation of the cerebral arteries through the temporal window, the patients (13.3% of the total group) were excluded from the analyses. The subjects who were excluded for technical reasons were slightly older ( $59.8 \pm 10.4$  vs.  $54.9 \pm 11.3$  years), with slightly higher systolic blood pressure ( $142 \pm 22$  vs.  $138 \pm 22$  mmHg) and with a lower proportion of men (28.7 vs. 40.8%, all  $P < 0.05$ ) than the subjects included in the study, but otherwise the remaining conventional cardiovascular risk factors and clinical details did not differ significantly between the groups. The above diagnostic criteria in our neurovascular laboratory were based on our laboratory references, which had a quality assurance program with supplementary angiographic studies. At our laboratory, we perform >1,200

transcranial Doppler examinations each year and had validated our criteria with magnetic resonance angiography (13) and clinical outcome (8).

Measurement of seated blood pressure and anthropometric (waist circumference and BMI) and plasma biochemical (lipid and glycemic profiles) parameters taken after an overnight fast were performed as described in detail previously (14). The patients' medications were suspended for the morning of the examination, providing assessment of trough levels, and therefore assessment of the hemodynamic parameters as continuous variables is not appropriate because some patients were on hypertension treatment. Subjects were defined as hypertensive if, after a 5-min rest, their seated systolic blood pressure was  $\geq 140$  mmHg and/or diastolic blood pressure  $\geq 90$  mmHg on at least two occasions or they were receiving blood pressure-lowering medication. Patients were assessed to rule out secondary causes of hypertension and renal disease.

Retinopathy was assessed by an ophthalmologist in all the patients. The fundi were examined through dilated pupils, and retinopathy was considered to be present if there was one or more areas of hemorrhages, microaneurysms, cotton wool spots, and/or laser coagulation scars related to diabetic retinopathy. Symptomatic peripheral vascular disease was diagnosed if claudication, gangrene, or ischemia-related amputation were present. Foot pulses were examined in each patient, and the ankle-brachial systolic arterial pressure ratio was determined by Doppler examination in those with abnormal pulses. An ankle-brachial ratio  $<0.9$  in either leg was considered suggestive and  $<0.7$  confirmatory of peripheral vascular disease (15). Histories of coronary and cerebrovascular disease were recorded, and patients with the latter were excluded.

Data from normally distributed parameters are presented as the means  $\pm$  SD, whereas skewed data were logarithmically transformed and expressed as the geometric mean with 95% CIs. Differences in anthropometric and fasting plasma biochemical parameters between those patients with or without MCA stenosis were examined using ANOVA. A Bonferroni post hoc test was used to determine differences between the individual groups. Dichotomous variables were compared using the  $\chi^2$  test. Sex was



**Figure 1**—An example of MCA stenosis detected by transcranial Doppler ultrasound (A) with a peak systolic velocity up to 220 cm/s and turbulent flow. The stenosis was confirmed by a magnetic resonance angiography (B).

coded 0 and 1 for male and female, respectively. Those patients with and without MCA stenoses were coded 0 and 1, respectively. Those variables that correlated with MCA stenosis were included in the forward conditional linear regression analyses to determine independent predictors of this condition. These variables included age, sex, systolic blood pressure, diagnosis of hypertension, glucose, diagnosis of dyslipidemia, LDL cholesterol levels, and duration of diabetes. The variables included in the analyses were linearly related to the dependent variable. SPSS was used in the analyses (SPSS version 11.0.1, 2001; SPSS, Chicago, IL).

**RESULTS**—Of the 2,165 type 2 diabetic patients who had no symptoms of cerebrovascular disease, the presence or absence of stenosis in the MCA could be determined in 1,877 patients, in whom evidence of MCA stenosis was identified in 385 subjects (20.6%). This included 185 (48.1%) subjects with single-vessel

involvement and the remainder with stenoses in both vessels.

The demographic characteristics and prevalence rates of concomitant disorders of the type 2 diabetic Chinese patients with or without evidence of MCA stenosis are described in Table 1. Age, age of onset of diabetes, and duration of diabetes were significantly higher in those patients with an increasing number of stenotic vessels. Systolic blood pressure, prevalence and treatment of hypertension and total and LDL cholesterol, and prevalence of dyslipidemia were also significantly increased. HbA<sub>1c</sub> did not significantly differ between the three groups, but glucose surprisingly decreased with increasing vascular involvement. In contrast, the proportion of the patients receiving glucose-lowering therapy increased. A number of other concomitant vascular disorders were also associated with the MCA stenoses, including peripheral vascular disease and retinopathy (Table 1).

Using stepwise multiple regression,

the presence of hypertension ( $\beta = 0.11$ ,  $P = 0.003$ ), age ( $\beta = 0.07$ ,  $P = 0.013$ ), LDL cholesterol ( $\beta = 0.08$ ,  $P = 0.003$ ), glucose ( $\beta = 0.07$ ,  $P = 0.006$ ), and systolic blood pressure ( $\beta = 0.09$ ,  $P = 0.021$ ) were independent predictors of the presence of MCA stenosis in one or both vessels (MCA stenosis =  $[0.15 \times \text{hypertension}] + [0.004 \times \text{age}] + [0.06 \times \text{LDL cholesterol}] - [0.32 \times \text{glucose}] + [0.03 \times \text{systolic blood pressure}] - 0.28$ ;  $R^2 = 0.067$ ,  $F = 18.2$ ,  $P < 0.001$ ).

**CONCLUSIONS**—In Chinese subjects, MCA stenosis is the most commonly identified intracranial arterial lesion (8), and in the current study we investigated type 2 diabetic subjects, who are particularly prone to vascular disease (16). A total of 20.6% of the type 2 diabetic subjects assessed were found to have evidence of MCA stenosis in one or both vessels.

The levels of a number of factors increased with increasing presence of the MCA stenosis, including age, female sex,

**Table 1**—Demographic features and prevalence rates of concomitant disorders in 1,877 Chinese type 2 diabetic patients with and without evidence of MCA stenosis

Parameters (%)	MCA stenosis			P
	None	One vessel	Two vessels	
n	1,492	185	200	—
Age (years)	54.0 ± 11.4	58.3 ± 10.5*	58.8 ± 10.3*	<0.001
Sex (male)	42.2	36.2	35.5	0.031
Duration of diabetes (years)	4.1 (3.8–4.3)	4.6 (3.7–5.8)	5.4 (4.4–6.6)*	0.030
Age of diabetes onset (years)	47.8 ± 11.2	49.6 ± 10.0	50.5 ± 10.8*	0.010
BMI (kg/m <sup>2</sup> )	24.8 ± 3.7	24.3 ± 3.6	24.4 ± 3.4	NS
Waist circumference (cm)	84.2 ± 9.6	84.7 ± 10.6	85.2 ± 8.2	NS
Systolic blood pressure (mmHg)	136 ± 21	143 ± 22*	149 ± 24*†	<0.001
Diastolic blood pressure (mmHg)	80 ± 16	80 ± 12	80 ± 15	NS
Mean arterial pressure (mmHg)	99 ± 15	101 ± 13	103 ± 14*	0.001
Pulse pressure (mmHg)	55 ± 20	63 ± 18*	69 ± 20*†	<0.001
Glucose (mmol/l)	8.66 (8.49–8.84)	8.45 (8.02–8.91)	8.06 (7.67–8.48)*	0.039
HbA <sub>1c</sub> (%)	7.8 ± 2.0	7.8 ± 1.7	7.6 ± 1.6	NS
Total cholesterol (mmol/l)	5.6 ± 1.1	5.7 ± 1.0	5.8 ± 0.9*	0.012
HDL cholesterol (mmol/l)	1.26 ± 0.32	1.27 ± 0.32	1.26 ± 0.35	NS
LDL cholesterol (mmol/l)	3.6 ± 0.9	3.8 ± 0.9*	3.8 ± 0.8*	<0.001
Triglyceride (mmol/l)	1.43 (1.28–1.48)	1.39 (1.28–1.51)	1.44 (1.34–1.56)	NS
Drug treatment of diabetes (%)	78.3	84.3	86.4	0.033
Prevalence of hypertension treatment (%) under treatment)	50.6 (29.8)	71.7* (51.7)*	79.0* (51.9)*	<0.001 (<0.001)
Prevalence of dyslipidemia treatment (%) under treatment)	48.0 (4.5)	54.1 (4.8)	56.4* (3.6)	0.021 (NS)
Peripheral vascular disease (%)	3.4	4.2	9.5*	0.006
History of myocardial infarction (%)	3.1	5.3	4.2	NS
Retinopathy (%)	24.1	27.8	39.6*	0.001
Smoking consumption (% ex/current)	13.5/13.4	11.9/12.6	13.8/12.0	NS
Alcohol consumption (% ex/current)	11.7/7.2	12.6/8.4	13.7/7.4	NS

Data are means ± SD, geometric mean (95% CI), or n (%). P values are for ANOVA among all three groups. \*P < 0.05 compared with the no-stenosis group; †P < 0.05 compared with the single-vessel group.

age at diabetic onset, duration of diabetes, systolic blood pressure, presence of hypertension, and LDL cholesterol, whereas glycemia levels decreased, although the prevalence of glucose-lowering treatment increased. Although the age at onset of diabetes increased by 2.7 years, this difference is unlikely to be clinically significant.

In the current study, despite a significant decrease in the proportion of male subjects with the number of stenotic MCAs, sex was not an independent risk factor after the other conventional risk factors were considered. Although men have a higher incidence of stroke, the longer life expectancy of women results in a greater proportion of women having strokes (4). This may also result from more men dying at younger ages from heart disease; although there was no evidence of survivor bias in the current study, selection bias in the older patients may have occurred.

Age further contributes to the development of hypertension and stroke (4,17), and it was an independent predictor of the number of affected vessels in the current study. Age acts as a composite factor associated with a clustering of a number of risk factors. Regression equations function to explain the largest proportion of the variance in the model, rather than identifying biologically relevant parameters involved in the disease pathogenesis. As such, composite variables are most likely to be strong independent predictors of the variable of interest. It is also important to remember that exclusion of a parameter does not exclude it from directly contributing to the pathogenesis of the disorder, merely that the variance attributed to the parameter is accounted for by other variables.

Type 2 diabetes is closely associated with micro- and macrovascular disease, the major causes of morbidity and mortality in these patients (16). Interventions

to improve glycemic control, as seen in the U.K. Prospective Diabetes Study, were more effective in reducing micro- than macrovascular disease (18). This finding is consistent with the data from the current study, but it is not certain why the increasing vascular involvement was associated with slightly but significantly lower glucose levels. There was an increasing proportion of these patients who were receiving glucose-lowering therapy, which may have contributed to lower glucose levels through better glycemic control, and it is possible that these patients were being given more intensive hypoglycemic treatment because of the greater degree of additional risk factors.

It has been suggested that lipid parameters are more closely associated with extracranial and coronary atherosclerosis, and blood pressure is more closely associated with intracranial atherosclerosis (19). However, in the Oslo study, LDL cholesterol was an independent predictor



of the development of intracranial atherogenesis, as was seen in the current study. Lipid-lowering studies have clearly confirmed the importance of cholesterol in the pathogenesis of ischemic stroke. In the Heart Protection Study, treatment with simvastatin lowered the risk of ischemic stroke by 30% compared with placebo (20), and similar observations in the Eastern Stroke and Coronary Heart Disease Study support such findings (17).

Blood pressure is a major predictor of hemorrhagic and atherogenic forms of stroke (4,17). Hypertension has been reported to be associated with more severe atherosclerosis in the inter- but not the extracranial cerebral vessels, and this is supported by a number of studies (21,22). In the current study, both systolic blood pressure (despite confounding by treatment) and the proportion of subjects with hypertension were significantly elevated in subjects with MCA stenosis, and both were independent predictors for the increasing MCA stenotic vascular involvement. The inclusion of both blood pressure-related parameters suggests each contributed additional information in the regression analyses. Hypertension has also been reported as an independent predictor of stroke in other Chinese populations (5). The U.K. Prospective Diabetes Study highlighted the clear benefits of lowering blood pressure to reduce vascular disease in type 2 diabetic patients (23). Although the relationship between the MCA stenoses and systolic blood pressure was significant, it is likely that blood pressure-lowering treatment will have attenuated it. Therefore, the dichotomous classification of hypertension that combines blood pressure levels and treatment status, but which is generally less informative than a continuously distributed parameter, attributes an additional proportion of the variance to blood pressure. Treatment effects on diastolic blood pressure may have similarly limited any relationship, which contrasts with the Oslo study, in which, despite patients receiving blood pressure-lowering treatment, it was reported that diastolic blood pressure more strongly predicted fatal stroke than systolic blood pressure (24). Because systolic blood pressure increased, even though diastolic blood pressure levels were similar between the groups in our study, pulse pressure also increased and may have contributed to the development

of cerebrovascular disease in these patients.

In Chinese patients who had experienced acute cerebral ischemia, the presence of occlusive vessels was the strongest predictor of further vascular events or death within 6 months (8). The majority of the subsequent events were strokes rather than related to ischemic heart disease, as has been reported in other ischemic stroke series (8,25). The current data show the close relationship between modifiable cardiovascular risk factors and MCA stenoses and, by extrapolation, the increased risk of cardiovascular events, and they highlight the need for coordinated treatment of risk factors to minimize such events.

In summary, this simple noninvasive screening test identified that over one-fifth of this group of type 2 diabetic subjects had asymptomatic MCA stenosis, which was associated with a number of conventional cardiovascular risk factors, including age, LDL cholesterol, and, in particular, systolic blood pressure or hypertensive status. These patients with MCA stenosis might be assumed to be at higher risk of primary cerebrovascular events, and more aggressive treatment of risk factors in this group merits further evaluation.

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