Factors Contributing to Stroke in Patients with Atherosclerotic Disease of the Great Vessels: The Role of Diabetes

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SUMMARY The incidence of carotid artery disease and cerebrovascular symptoms were determined in 102 consecutive patients with peripheral arterial disease. Symptoms were correlated with risk factors of age, hypertension, smoking and diabetes and with the extent of disease at the carotid bifurcation. The incidence of stroke with permanent neurological deficit was twice as high in diabetics as in non-diabetics with equivalent atherosclerotic vascular disease ($p < .05$). In women, the incidence of stroke was three times higher in diabetics ($p < .02$). The number of transient ischemic attacks was significantly higher in non-diabetics ($p < .02$). The total number of ischemic episodes in diabetics and non-diabetics was equivalent. This indicates that diabetics are more prone to irreversible destruction of ischemic brain tissue regardless of the nature of the circulatory disturbance.

The Association of Atherosclerotic Disease at the carotid artery bifurcation with both transient ischemic attack and stroke is firmly established. However, a large proportion of patients with carotid disease remain asymptomatic. In addition, the majority of patients with transient ischemic attacks do not develop irreversible neurologic deficits. Therefore, it is imperative to determine what factors are responsible for permanent damage to neurons when the brain is subjected to disruption of circulatory perfusion.

In order to delineate the role of disease of the great vessels in stroke, we examined 102 consecutive patients with atherosclerotic peripheral arterial disease (PAD) who were referred to the vascular laboratory for non-invasive carotid artery testing. While this group of patients is not randomly selected, they all had a similar propensity to atherosclerotic arterial disease of the great vessels so that valid comparisons of other factors can be made.
Patients were referred to the laboratory both before and after peripheral arterial surgery. In addition, patients referred to the laboratory for neurologic complaints with an antecedent history of prior surgery or amputation for PAD were included. All patients were examined by a neurologist to categorize neurologic signs and symptoms of cerebrovascular disease.

All patients underwent a non-invasive carotid testing battery of pneuomooculopethysmography, supraorbital directional Doppler, Doppler carotid flow study and Real Time B-Mode Ultrasonography. The combination of these methods has been shown to correlate strongly with angiographic findings of hemodynamic obstruction to flow at the carotid bifurcation. Hemodynamic obstruction was defined as a reversal of flow on supraorbital Doppler examination, ophthalmic artery pressure less than 65% of brachial artery pressure and/or high frequency turbulence or decreased flow on carotid Doppler flow study. Real Time B-Mode Ultrasonography has also been successful in identifying small non-obstructive plaques which sometimes are not seen on angiography. Only patients in which there was adequate visualization of the carotid arteries were included in the analysis. Symptomatic stroke and transient ischemic attack were correlated with risk factors of age, sex, smoking, hypertension and diabetes.

A significantly higher incidence of completed stroke was observed in patients with diabetes (table 1). Non-diabetics had a significantly higher number of transient episodes of neurologic deficit. This indicates that diabetes predisposes the brain to irreversible damage during ischemia.

### Materials and Methods

### Patient Selection

One hundred two consecutive patients referred to the vascular laboratory with a history of peripheral arterial disease were included in the study. The incidence of neurologic symptoms was based on retrospective analysis at the time of the non-invasive vascular examination.

Transient ischemic attacks were defined as episodes of neurologic dysfunction lasting less than 24 hours with complete recovery and no evidence of structural or ictal etiology. All patients with irreversible neurologic deficits on an ischemic basis by history and CT scan were considered to have had a stroke. This included patients with mild deficits or partial resolution of symptoms. It is possible that some severe strokes may have been excluded by the selection process. However, several patients had severe deficits and were examined acutely to determine the etiology of their stroke. Patients with severe deficits who were about to undergo surgery for peripheral arterial disease were also included.

All patients bearing a diagnosis of diabetes were included in the diabetic group, irrespective of the method of treatment. This included patients diagnosed as having "chemical" diabetes. All patients being treated for hypertension or with a blood pressure greater than 150/100 mm Hg were considered to be hypertensive.

### Non-Invasive Test Battery

Ophthalmic artery pressure was measured with a pneuomo-oculopethysmograph (Life Sciences, PVR). The normal mean value is 75% of brachial artery systolic pressure with a standard deviation of 5%. Supraorbital Doppler was performed with a bidirectional Doppler (Parks, 806) at 9.5 MHz. Superficial temporal and facial artery compression were performed to determine if augmentation or suppression of supraorbital flow occurred. Augmentation indicates patency and suppression obstruction.

Direct carotid artery flow study was performed by the velocity waveform technique of Rutherford et al. with the same bidirectional Doppler. In addition, patterns of turbulence were identified either by Spectral Analysis of Doppler frequencies with an Angioscan (Unigon) or by auditory determination. The combination of these techniques have shown a high degree of correlation with hemodynamic lesions demonstrated on angiography. Real Time B-Mode Ultrasonography of the carotid bifurcation was performed with small parts scanner at a frequency of 7.5 MHz (High Stoy SP-100B). Statistical analysis was performed by the Chi-Square method.

### Results

### Cerebrovascular Disease

A total of 32 strokes occurred in the 102 patients. All but two of the strokes occurred within one month of entry into the study. One occurred 2 years prior to noninvasive evaluation. The other occurred one year before, with a high grade carotid stenosis on the appro...
prial side diagnosed by angiography. One patient had bilateral cerebral hemispheric stroke and one had a vertebrobasilar stroke. Eighteen patients had a history of transient ischemic attacks (TIA) with 2 having bilateral episodes and one a vertebrobasilar TIA. Four strokes occurred following peripheral arterial surgery and were included in the analysis. In addition, 4 strokes occurred following carotid endarterectomy. These patients were classified according to their symptoms prior to carotid endarterectomy. Only 2 patients had undergone carotid endarterectomy prior to entry into the study. One was evaluated for recurrent transient ischemic attacks on the operated side and a new stenosis was identified. The other was the previously mentioned patient with stroke, who underwent subsequent carotid endarterectomy.

The mean age for patients with stroke was 65.8 ± 10.3 (mean ± S.D.). The mean age of patients without stroke was 68.2 ± 9.5. Fifteen of the 31 (48.4%) stroke patients smoked, 33 of the remaining 71 (46.5%) did not. Hypertension was present in 48.4% of the stroke patients and 60.6% of the normal patients.

Carotid Artery Disease

A total of 204 carotid arteries were examined by non-invasive testing. 115 (56.4%) were found to have atherosclerotic disease at the carotid artery bifurcation. There was evidence of hemodynamically significant obstruction to flow at the bifurcation in 60 carotid arteries (29.4%). These figures are in agreement with the incidence of carotid artery disease in patients with PAD found in other studies. Stroke occurred ipsilateral to a diseased carotid artery in 17/115 cases and ipsilateral to a normal carotid artery in 14/89 cases.

Diabetes

Diabetes was the only risk factor associated with a significantly greater incidence of stroke in this group of patients with equivalent atherosclerotic disease of the great vessels. Twenty-two strokes occurred in 21 of 50 patients with diabetes while 10 strokes occurred in 52 patients with no diabetes (p < .05). In addition, 3 of the 4 strokes that occurred after carotid endarterectomy were in diabetics. The risk of stroke was even more significant for women with diabetes. Fourteen of 30 diabetic women had strokes while 3 of 21 non-diabetic women had strokes (p < .02).

There were no significant differences in other risk factors between diabetics and non-diabetics. The mean age for diabetics was 66.2 ± 8.9 and for non-diabetics was 67.8 ± 9.9. Twenty of the diabetics were male and 30 were female. Thirty-one of the non-diabetics were male and 21 were female. Twenty-four percent of the diabetics and 69.2% of the non-diabetics smoked. This reflects a greater incidence of smoking in non-diabetics with PAD, but there was no relation of smoking to stroke in non-diabetics. Fifty-four percent of the diabetics and 59.6% of the non-diabetics had hypertension, but again there was no relation of hypertension to stroke in the two groups.

Carotid Artery Disease in Diabetes

Atherosclerotic disease was present in 57% of carotid arteries in diabetics and 55.8% in non-diabetics. Twelve of 21 strokes occurred ipsilateral to a diseased carotid in non-diabetic patients and 5 of 11 strokes (10 patients) occurred ipsilateral to a diseased carotid in non-diabetics. In diabetics, there were 29 hemodynamically significant lesions. Eight strokes occurred ipsilateral to one of these carotids. This association was not significant (table 1).

The total number of cerebrovascular events including TIA was 23 for non-diabetics and 27 for diabetics. Thirteen TIA's occurred in the non-diabetics and 5 in the diabetics. When the number of TIA's in each group was compared to the total number of cerebrovascular events, there were significantly more TIA's in the non-diabetic group (p < .02).

Discussion

The pathophysiology of cerebral infarction is multifactorial. It involves vascular pathology causing interruption of cerebral perfusion and the effect of ischemia on cerebral metabolism. The brain is provided with extensive collateral circulation, so that obstruction to flow in a great vessel supplying the brain need not result in a stroke. However, when a decrease in perfusion pressure to the brain occurs in the carotid circulation, the risk of stroke is increased. Furthermore, emboli from the heart or carotid bifurcation can produce stroke. The greatest risk appears to be in patients with both intracranial vascular disease and carotid disease.

The primary epidemiological risk factor for stroke is hypertension. This produces proliferative disease of intracranial vessels which can occlude to cause infarction or rupture to cause intracerebral hemorrhage. Diabetes is also a significant risk factor in stroke. The incidence of stroke is twice as high in diabetics compared to the non-diabetic population and three times as high in diabetic women. The same increased frequency of stroke was noted for diabetics in this study of patients with peripheral arterial disease. The prevalence of stroke in diabetics becomes apparent with increasing age and does not correlate with the type of diabetes. This is also true of peripheral arterial disease.

The reasons for the increased risk of stroke in diabetics have not been definitively determined. Whereas diabetes is associated with an increased incidence of atherosclerotic PAD, there is no evidence of increased atherosclerotic disease at the carotid bifurcation. The increased frequency of stroke is attributed to proliferative changes in intracranial vessels causing local thrombosis. However, Strandness has noted no difference in small distal arterial disease between diabetics and non-diabetics with PAD. In this series of patients with PAD, diabetics and non-diabetics had a similar number of episodes of cerebral ischemia, but there were significantly more irreversible strokes in the diabetic group. The ischemic events could have been related to disease in the carotid artery in some in-
stances, but many patients with a normal carotid artery suffered ischemic episodes. This suggests that intravascular or metabolic factors are responsible for the increased irreversible cerebral damage in diabetics rather than the type of circulatory disturbance.

Diabetics have been noted to have increased platelet adhesiveness.24 Therefore, when a vessel is temporarily occluded, an irreversible platelet plug may be more likely to form.

Laboratory studies of ischemia in experimental animals indicate that hyperglycemia has deleterious effects on recovery of cerebral function when circulatory factors are held constant.25-27 This may be due to increased production of toxic substances such as lactic acid or to an increase in cerebral edema.27 Stroke occurs to a significantly greater extent in diabetics with poor control of serum glucose levels.28 This suggests that strict control would be beneficial in the prevention of stroke in diabetics irrespective of the nature of the ischemic episode.

This study of patients with peripheral arterial disease confirms the finding of an increased incidence of stroke in diabetic patients. It also supports the concept of Thiele et al.19 that intracranial vascular and metabolic factors are the principal determinants in the pathophysiology of stroke.

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