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Severely impaired cerebrovascular reactivity predicts stroke and TIA risk in patients with carotid artery stenosis and occlusion

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Summary

Cross-sectional studies suggest that impaired cerebral haemodynamics is associated with symptomatic status in patients with carotid stenosis and occlusion, but there is relatively little prospective data confirming this association. Transcranial Doppler ultrasonography was used to determine the reactivity of the middle cerebral artery to 8% carbon dioxide in air in 107 patients with either carotid occlusion (n = 48) or asymptomatic carotid stenosis (n = 59). Subjects were followed prospectively until stroke, transient ischaemic attack (TIA), death or study end. Mean duration of follow-up was 635 days. No patients dropped out due to operation before an end-point was reached, or were lost to follow-up. There were 11 ipsilateral ischaemic events during follow-up (six strokes, five TIAs). Exhausted ipsilateral middle cerebral artery reactivity (>20% increase in ipsilateral middle cerebral flow velocity in response to 8% carbon dioxide) predicted ipsilateral stroke and TIA risk in the whole group (P < 0.00001) and in the carotid occlusion (P = 0.019) and carotid stenosis (P = 0.015) groups alone. It also predicted the risk of ipsilateral stroke alone in all three groups. Cox regression was performed, controlling for age, gender, hypertension, diabetes, smoking, ipsilateral CT infarct, degree of contralateral stenosis and the presence of ipsilateral stenosis versus occlusion. Exhausted reactivity remained an independent predictor of ipsilateral stroke and TIA (odds ratio 14.4, 95% confidence interval 2.63–78.74, P = 0.0021). In contrast, the pulsatility index of the middle cerebral artery was a poor predictor of the risk of stroke. Reactivity to 6% carbon dioxide also predicted the risk of stroke and TIA, but slightly less effectively than reactivity to 8% carbon dioxide. Severely reduced cerebrovascular reactivity predicts the risk of ipsilateral stroke and TIA in patients with carotid occlusion, and to a lesser extent in asymptomatic carotid stenosis. Particularly in the former group, a study is required to determine whether revascularization reduces the risk of stroke in patients with exhausted reactivity.

Keywords: carotid artery disease; transcranial Doppler ultrasonography; cerebrovascular disease; cerebral haemodynamics

Abbreviations: CBF = cerebral blood flow; CBV = cerebral blood volume; MCA = middle cerebral artery; SPECT = single photon emission tomography; TCD = transcranial Doppler ultrasonography; TIA = transient ischaemic attack

Introduction

Two large randomized trials have demonstrated that carotid endarterectomy prevents stroke in patients with tight symptomatic carotid stenosis (North American Symptomatic Carotid Endarterectomy Trial Collaborators, 1991; European Carotid Surgery Trialists' Collaborative group, 1991). In contrast, the benefit of surgery in patients with asymptomatic carotid stenosis and with carotid occlusion is less clear. The largest trial of carotid endarterectomy in patients with tight asymptomatic stenosis did show a significant reduction in the risk of ipsilateral stroke in the surgical group, but the overall benefit was small (Executive Committee for the Asymptomatic Carotid Atherosclerosis Study, 1995). The risk of ipsilateral stroke is also increased in patients with carotid occlusion. In contrast to carotid stenosis, in which stroke is believed to be of primary embolic origin, in patients with carotid occlusion the mechanism is usually thought to be haemodynamic. The Extracranial–Intracranial Bypass Study found no benefit of extracranial over intracranial revascularization in patients with carotid occlusion (EC/IC Bypass Study Group, 1985). However, an unselected group of patients with carotid occlusion were operated on, and no screening method of identifying patients at particular risk of

haemodynamic compromise was used. It remains possible that a subgroup of individuals with carotid occlusion, and possibly also with asymptomatic carotid stenosis, who have haemodynamic compromise, might benefit from revascularization. Before testing this hypothesis in intervention studies, it needs be proven in prospective studies that such a high-risk subgroup can be identified reliably.

Collateral supply, most importantly via the circle of Willis, but also by extracranial-to-intracranial collaterals, maintains normal perfusion pressure in many patients with carotid stenosis and occlusion. However, in a proportion of patients collateral supply is insufficient, leading to haemodynamic compromise. This state can be identified either by detecting brain tissue at risk or by demonstrating an impaired vasodilatory reserve (Derdeyn *et al*., 1999). PET methods allow the identification of haemodynamically compromised brain tissue, as evidenced by an increased oxygen extraction fraction (Gibbs *et al*., 1984; Derdeyn *et al*., 1999). However, such methods are expensive and time-consuming, and involve radiation. A simpler approach is to determine vasodilatory reserve or reactivity (Ringelstein *et al*., 1992; Derdeyn *et al*., 1999). In the presence of haemodynamic compromise, the intracranial arterial circulation vasodilates, and therefore its ability to vasodilate further in response to an administered vasodilator is reduced. Increased inspired carbon dioxide in air, or acetazolamide, are used most commonly as the vasodilator (Ringelstein *et al*., 1992). PET- and xenon-based methods (Bishop *et al*., 1987; Derdeyn *et al*., 1999), and, more recently, MRI techniques (Ostergaard *et al*., 1998; Lythgoe *et al*., 1999) can be used to measure cerebral blood flow (CBF) before and after administration of the vasodilator. A simpler method of assessing the change in CBF is the use of transcranial Doppler ultrasonography (TCD) (Ringelstein *et al*., 1988). This measures middle cerebral artery (MCA) blood flow velocity rather than flow itself. Assuming that the vessel diameter remains constant during administration of the vasodilator, the change in blood flow velocity will reflect accurately any change in CBF.

Many cross-sectional studies have used transcranial Doppler to show that reactivity is impaired in a proportion of patients with carotid artery stenosis and occlusion (Ringelstein *et al*., 1988; Kleiser *et al*., 1991; Levine *et al*., 1991; Markus and Harrison, 1992; Hartl and Furst, 1995; Muller and Schimrigk, 1996; Silvestrini *et al*., 1996; Sorteberg *et al*., 1996; Matteis *et al*., 1999). However, few prospective studies have determined whether impaired reactivity predicts the risk of subsequent stroke and transient ischaemic attack (TIA) (Kleiser *et al*., 1992; Gur *et al*., 1996; Vernieri *et al*., 1999; Silvestrini *et al*., 2000). Previous studies have been small and many have not determined whether any relationship is independent of other cardiovascular risk factors and other markers of increased risk, such as the degree of contralateral stenosis (Derdeyn *et al*., 1999).

In this study, we recruited individuals with carotid occlusion or asymptomatic carotid stenosis and followed them prospectively to determine whether impaired cerebrovascular reactivity predicted the risk of subsequent stroke and TIA.

Methods and subjects

Subjects

One hundred and seventeen patients presenting to a neurology cerebrovascular out-patient service were recruited prospectively. Patients were referred from three sources. All patients referred to the carotid endarterectomy service, via the Department of Vascular Surgery or the Department of Neurology, were seen in this clinic. Additional patients were referred directly from family doctors or other physicians. In 10 patients the absence of an acoustic window prevented transcranial Doppler recordings being performed. Of the 107 patients with an acoustic window, 48 had carotid occlusion and 59 had $\geqslant$70% carotid stenosis. All patients with carotid stenosis had been asymptomatic in both carotid artery territories for at least 2 years. Patients with carotid occlusion were asymptomatic or, if the occlusion had been identified at the time of presentation with stroke, they were not recruited until at least 3 months after stroke. In 24 patients there was $\geqslant$70% contralateral carotid disease (16 patients had $\geqslant$70% stenosis and eight had occlusion). For the purpose of the study, carotid stenosis or occlusion was determined using carotid duplex performed in one laboratory, by one of three vascular technicians, the accuracy of which had been validated previously against angiography by the use of recognized criteria (Bluth *et al*., 1988).

Patient history

A detailed history of cardiovascular risk factors was taken from all individuals. Hypertension was defined as occurring when systolic blood pressure exceeded 160 mmHg or diastolic pressure exceeded 95 mmHg, or in the presence of anti-hypertensive drugs. Diabetes was defined as previously diagnosed insulin-dependent or non-insulin-dependent diabetes mellitus. At entry, CT or MRI of the brain was performed in all individuals. Scans were reviewed blind to the results of the reactivity, to determine the presence or absence of an ipsilateral cerebral infarct. Patients were followed until death, ipsilateral disabling stroke or study end. Stroke was defined as occurring when symptoms lasted $>$24 h. In patients who experienced ipsilateral TIA or minor disabling stroke, follow-up was continued. All patients were seen yearly or more frequently in an out-patient clinic. No patients were lost to follow-up. In cases of stroke, patients were reviewed in person, or the original notes and scans were reviewed to confirm the diagnosis and determine the arterial territory involved. In cases of death, the original notes were reviewed to determine the cause of death. This was not possible in two cases, and in these cases the cause of death was determined from death certificates obtained from the UK General Register Office.

Table 1 *Mean (standard deviation) values of haemodynamic variables ipsilateral to the stenosis or occlusion in patients who did and did not experience ipsilateral ischaemic events during follow-up*

	Ipsilateral event during follow-up		
	None	TIA	Stroke
All cases			
8% reactivity (%)	46.28 (31.63)	36.54 (27.58)	10.70 (7.44)
6% reactivity (%/kPa)	16.80 (11.55)	11.38 (7.63)	3.76 (5.27)
Pulsatility index	0.965 (0.229)	0.860 (0.331)	0.830 (0.314)
Carotid occlusion only (n = 48)			
8% reactivity (%)	34.09 (34.44)	16.30 (8.63)	9.90 (8.02)
6% reactivity (%/kPa)	12.69 (10.14)	4.20 (–)	1.70 (2.96)
Pulsatility index	0.869 (0.260)	0.920 (0.509)	0.752 (0.279)
Carotid stenosis only (n = 59)			
8% reactivity (%)	55.53 (26.01)	50.03 (28.30)	14.70 (–)
6% reactivity (%/kPa)	20.08 (11.65)	13.77 (7.29)	12.00 (–)
Pulsatility index	1.035 (0.176)	0.820 (0.288)	1.22 (–)

The absence of standard deviation (–) indicates that there was only one subject in that group.

TCD recordings

Bilateral simultaneous TCD recordings were made from both MCAs via the transtemporal route. All recordings were made with a commercially available TCD machine (Multidop X4; DWL Sipplingen, Germany) with the probe held in position by an external fixation device. Air or an air/carbon dioxide mixture was administered via a mask and a Douglas bag. The concentrations of all gases were determined and certified by BOC Crawley United Kingdom Ltd. Patients breathed through the mask until MCA velocity became stable. A further 30 s of recording was made at this stage. Six per cent carbon dioxide in air was then administered. Once MCA velocity had again stabilized, a further 30 s of recording was made. The gas mixture was then increased to 8% carbon dioxide in air, and once again after MCA velocities had stabilized a further 30 s of recording was made. End-expiratory carbon dioxide was measured as an estimate of blood carbon dioxide concentration using a Normocap 200 (Datex, Helsinki, Finland). Blood pressure was measured non-invasively throughout the procedure using a Finapress 2300 (Datex, Ohmeda, Louisville, Ky, USA). In addition, during baseline recordings when MCA had stabilized, the pulsatility index was measured for both MCAs from the average readings from a 5 s spectral display. Mean MCA velocity while the patient was breathing air, and 6 and 8% carbon dioxide in air, were determined by averaging readings over the 30 s periods once equilibrium had been reached, with proprietary software provided by the TCD manufacturer. The full vasodilatory range, or reactivity to 8% carbon dioxide in air, was determined by the percentage increase in MCA velocity that occurred during administration of 8% carbon dioxide. This results in a maximal vasodilatory response, and therefore the increase was not divided by the change in end-tidal carbon dioxide. Reactivity to 6% carbon dioxide was calculated in the same way, but the result was then divided by the absolute increase in end-tidal carbon dioxide (in kilopascals) occurring while the patient was breathing 6% carbon dioxide in air. A predetermined cut-off for exhausted reactivity to 8% carbon dioxide of 20% was used. This had been determined prior to this study in a control population of individuals in whom carotid stenosis had been excluded. The patients' consent was obtained and ethical permission for performing research reactivity studies was obtained from the King's College Hospital Ethics Committee.

Analysis of results

The relationship between impaired reactivity and subsequent ipsilateral TIA and stroke was determined using Kaplan–Meier analysis with log rank comparisons. Separate analyses were performed for ipsilateral stroke alone, ipsilateral stroke and TIA, and any stroke or TIA. Data were also analysed using a Cox regression model to allow us to control for other risk factors. All statistics was performed using SPSS for Windows version 10.

Results

Patient follow-up

The mean duration of follow-up of the patients was 635 days (SD = 332.92). In individuals not suffering stroke or TIA during follow-up, the minimum and maximum durations of follow-up were 112 and 1458 days, respectively. There were 11 ipsilateral events during the follow-up period, of which six were stroke and five hemispheric TIA or amaurosis fugax. Of the strokes, two were fatal during the acute period, three were disabling and one resulted in minor but permanent hand weakness. In addition, there were four TIAs and four strokes in other vascular territories. All of the four TIAs were

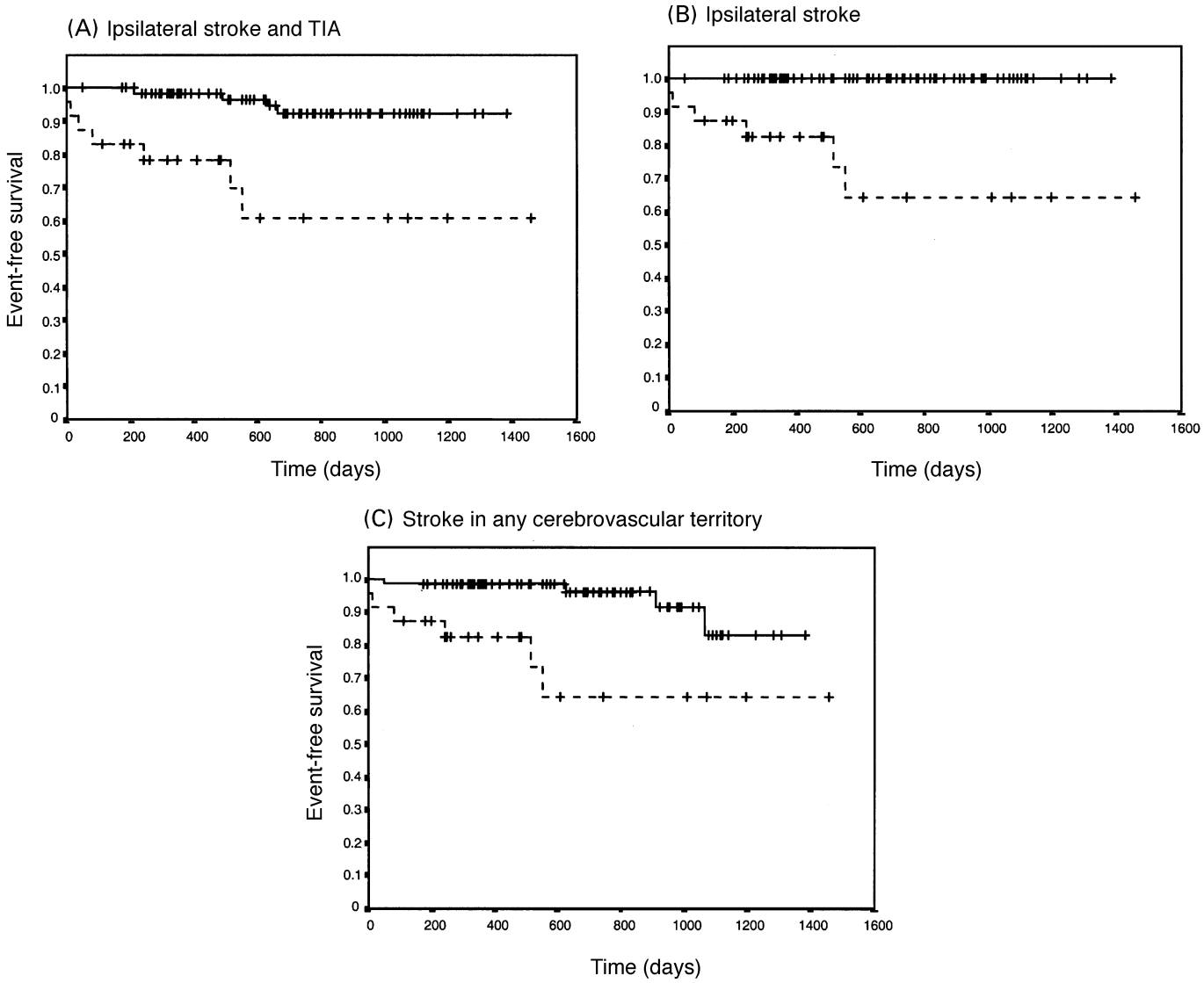

Fig. 1 Kaplan–Meier survival plots of the influence of impaired cerebral reactivity on the risk of (**A**) ipsilateral stroke and TIA event, (**B**) ipsilateral stroke only, (**C**) any stroke during the follow-up period. The broken line indicates the patient group with exhausted reactivity. The vertical cross-lines indicate patients whose data were censored due to study end, or a study end-point.

believed to result from posterior circulation ischaemia. The four strokes were all in the contralateral carotid hemisphere and three were disabling.

During the follow-up period, no subjects who remained asymptomatic underwent surgery. However, when patients became symptomatic, and had therefore reached a study end-point, they were offered surgical intervention if appropriate; three patients underwent carotid endarterectomy, one underwent extracranial–intracranial bypass, and subclavian angioplasty was performed to increase collateral supply in one patient with carotid occlusion and a subclavian steal on angiography.

TCD recording

Simultaneous TCD recordings made from both MCAs showed that mean (standard deviation) 8% carbon dioxide reactivity values were significantly lower in patients who suffered either any ipsilateral event [22.45 (22.67) versus 46.28 (31.63)%, $P = 0.007$] or ipsilateral stroke only [10.70 (7.44) versus 45.79 (31.39)%, $P = 0.0001$] during follow-up than in those who had no ipsilateral event. Similarly, mean 6% carbon dioxide reactivity values were significantly lower in patients who, during follow-up, suffered either any ipsilateral event [7.14 (7.20) versus 16.80 (11.55)%/kPa, $P = 0.003$], or ipsilateral stroke only [3.76 (5.27) versus 16.57 (11.43)%/kPa, $P = 0.003$]. In contrast, the mean pulsatility index was not significantly lower in patients experiencing any ipsilateral event [0.84 (0.31) versus 0.97 (0.23), $P = 0.226$] or ipsilateral stroke only [0.83 (0.31) versus 0.96 (0.23), $P = 0.361$] than in those who had no ipsilateral event. Mean 8 and 6% carbon dioxide reactivity values were lower in patients suffering ipsilateral stroke as opposed to TIA during follow-up (Table 1).

Table 2 *Relationship of exhausted reactivity to 8% carbon dioxide and other potential indicators of increased risk with the risk of any ipsilateral event during follow-up*

Variable	Odds ratio	95% CI of odds ratio	*P*
Exhausted 8% reactivity	14.40	2.63–78.74	0.0021
Male gender	0.102	0.023–0.447	0.0025
Age (years)	0.976	0.904–1.054	0.5444
Diabetes	0.154	0.013–1.718	0.1285
Hypertension	0.561	0.140–2.246	0.4139
Current smoking	3.378	0.828–13.776	0.0897
Ipsilateral CT infarct	2.428	0.510–11.562	0.2653
Ipsilateral carotid occlusion	0.136	0.0051–3.651	0.2347
Degree of ipsilateral stenosis (%)	1.071	0.947–1.211	0.2741
Degree of contralateral stenosis (%)	0.991	0.970–1.012	0.393

Cox's regression was performed. CI = confidence interval.

Exhausted reactivity to 8% carbon dioxide was detected in the ipsilateral MCA territory in 24 (22.2)% of all cases, 21 (42.9)% of carotid occlusion cases and 3 (5.1)% of carotid stenosis cases. Exhausted reactivity to 8% carbon dioxide was a highly significant predictor of both any ipsilateral event (Kaplan–Meier log rank statistic 15.96, $P < 0.00001$) and ipsilateral stroke alone (Kaplan–Meier log rank statistic 22.90, $P < 0.00001$). It was also a significant predictor of any cerebral ischaemic event (Kaplan–Meier log rank statistic 5.14, $P = 0.02$) and any stroke (Kaplan–Meier log rank statistic 12.01, $P = 0.0005$). Kaplan–Meier survival plots are shown in Fig. 1.

Cox's regression was performed to control for the effects of the following variables on the relationship between exhausted reactivity and ipsilateral stroke and TIA: age, gender, hypertension, current smoking, diabetes, the presence of an ipsilateral CT infarct, the degree of ipsilateral stenosis, the degree of contralateral stenosis, and whether the ipsilateral vessel was occluded. Exhausted reactivity remained a significant predictor, with an odds ratio of 14.4 (95% confidence interval 2.63–78.74, $P = 0.0021$). The only other independent predictor of stroke risk was female gender. The relative risks associated with the other variables are shown in Table 2.

Prediction in carotid occlusion patients

Among the 48 individuals with carotid occlusion, there were five ipsilateral strokes, two ipsilateral TIAs, and one further stroke and two further TIAs in other cerebral arterial territories. Mean duration of follow-up was 624 (SD = 379) days. Combined ipsilateral stroke and TIA risk was 8.53%/year, and the ipsilateral stroke rate was 6.09%/year. Exhausted 8% carbon dioxide reactivity was a highly significant predictor of any ipsilateral event (Kaplan–Meier log rank statistic 7.81, $P = 0.0052$) and ipsilateral stroke alone (Kaplan–Meier log rank statistic 8.70, $P = 0.0032$). It was also a significant predictor of any stroke (Kaplan–Meier log rank statistic 5.42, $P = 0.020$) but not of any stroke or TIA (Kaplan–Meier log rank statistic 2.42, $P = 0.12$). Kaplan–Meier survival plots are shown in Fig. 2A and B.

Prediction in carotid stenosis patients

Among the 59 individuals with 70–99% carotid stenosis, there was one ipsilateral stroke and three ipsilateral TIAs, and three further strokes and one further TIA in other vascular territories. Mean duration of follow-up was 644 (SD = 292) days. The combined risk of ipsilateral stroke and TIA was 3.84%/year, and the ipsilateral stroke rate was 0.96%/year. Exhausted 8% carbon dioxide reactivity was a highly significant predictor of any ipsilateral event (Kaplan–Meier, $P = 0.015$) and ipsilateral stroke alone (Kaplan–Meier log rank statistic 18.0, $P = 0.00001$). It was also a significant predictor of any stroke (Kaplan–Meier, $P < 0.0001$) but not of any cerebral ischaemic event (Kaplan–Meier, $P = 0.08$). Kaplan–Meier survival curves are shown in Fig. 2C.

Comparison of methods for determining haemodynamic impairment

In addition to 8% carbon dioxide reactivity measurements in all patients, pulsatility index measurements and 6% carbon dioxide reactivity measurements were available in 104 and 97 subjects, respectively. In 95 subjects, all three haemodynamic measurements were made on the same occasion. Kaplan–Meier analysis was performed to compare the predictive value of each haemodynamic parameter. Exhausted haemodynamic ranges for pulsatility index and 6% carbon dioxide reactivity were below the 20th centile of the ipsilateral MCA measurements in all subjects. This resulted in similar numbers of patients in the exhausted reactivity group for 6% carbon dioxide reactivity and pulsatility index, as for 8% carbon dioxide reactivity. Results are shown in Table 3. An impaired pulsatility index was a prediction of the risk of an ipsilateral event but not of the risk of ipsilateral stroke alone. Impaired 6 or 8% carbon dioxide reactivity was a prediction of the

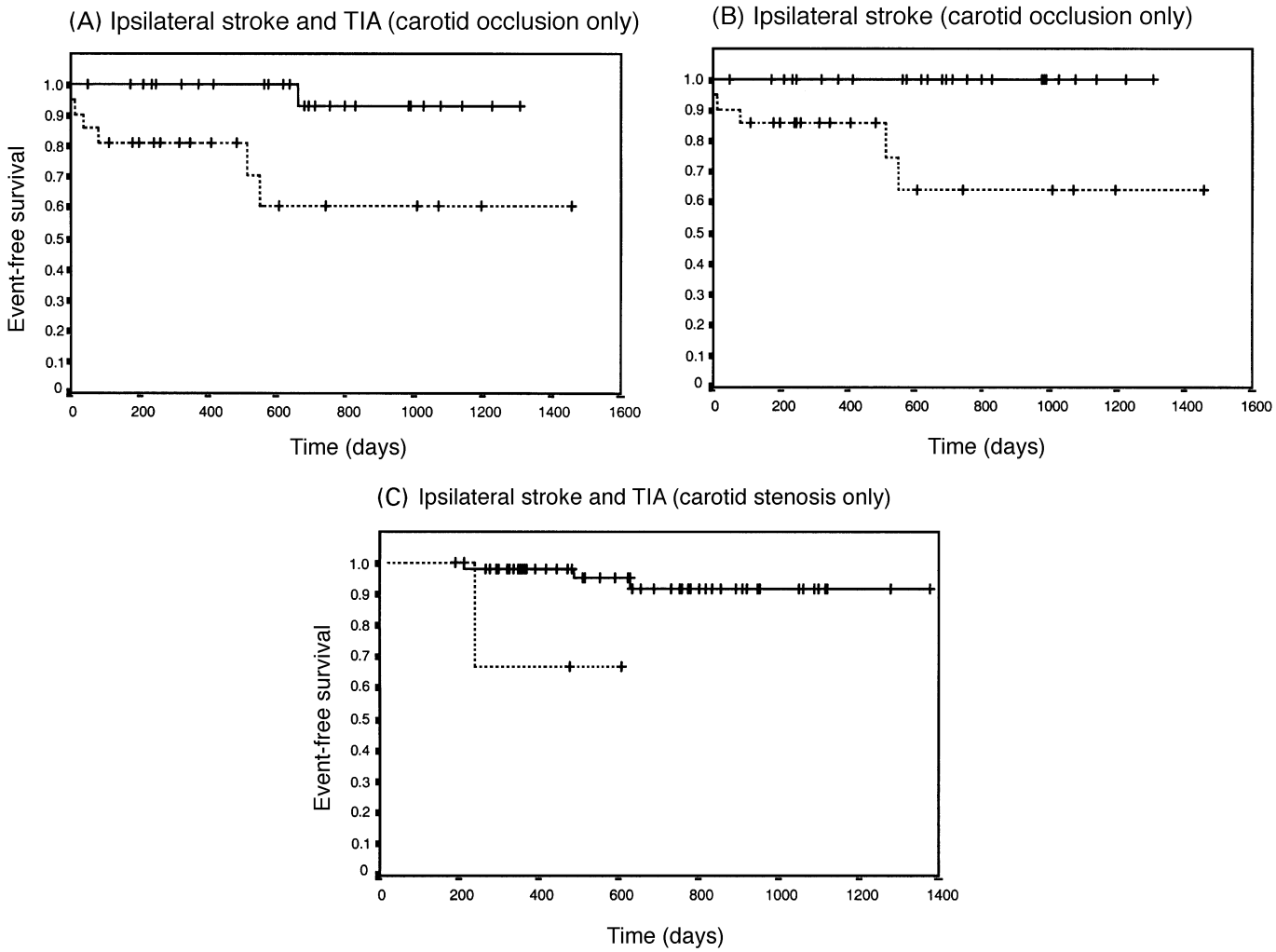

Fig. 2 Kaplan–Meier survival plots of the influence of impaired cerebral reactivity on the outcome in the two groups of patients (carotid occlusion and carotid stenosis). (**A**) Any ipsilateral event in the carotid occlusion group. (**B**) Ipsilateral stroke in the carotid occlusion group. (**C**) Any ipsilateral event in the carotid stenosis group. There is no plot for ipsilateral stroke in the carotid stenosis group as there was only one event during follow-up in this group. The broken line in each graph indicates the patient group with exhausted reactivity. The vertical cross-lines indicate patients whose data were censored due to study end, or a study end-point.

risk both of any ipsilateral event and of ipsilateral stroke. However, log rank values were higher for 8% than for 6% carbon dioxide reactivity, particularly in predicting the risk of ipsilateral stroke. Using different cut-off values to indicate exhausted reactivity did not significantly improve the predictive values of the pulsatility index and 6% carbon dioxide reactivity measurements.

Discussion

Our results demonstrate that severely impaired or exhausted cerebral haemodynamics, as determined by carbon dioxide reactivity using TCD, is an independent predictor of ipsilateral ischaemic events in patients with carotid artery disease. A significant relationship was seen in the two subgroups of patients, one with tight carotid stenosis and the other with carotid occlusion. We controlled for other possible markers of increased risk, including cardiovascular risk factors, ipsilateral brain infarction on neuroimaging, and the degree of contralateral stenosis. Exhausted reactivity remained an independent predictor of the risk of an ipsilateral ischaemic event.

A variety of different imaging techniques have been developed for the indirect or non-invasive assessment of cerebral haemodynamics in patients with carotid artery disease. These can be divided into techniques identifying tissue evidence of ischaemia and techniques detecting the autoregulatory vasodilatation that occurs in the presence of reduced perfusion pressure (Derdeyn *et al.*, 1999). The first category relies on direct measurements of the oxygen extraction fraction in the ipsilateral cerebral hemisphere (Gibbs *et al.*, 1984; Yamauchi *et al.*, 1996; Derdeyn *et al.*, 1999). Such regional measurements can only be made with PET. With this technique in a subgroup of patients with

carotid stenosis and occlusion, an increased oxygen extraction fraction was demonstrated that was consistent with haemodynamic compromise (Gibbs *et al*., 1984; Powers *et al*., 1989). However, this technique is expensive and is not widely available, and it requires exposure to radiation. The second group of techniques relies on the fact that as perfusion pressure drops, if collaterals are not adequate to maintain normal perfusion, reflex vasodilatation occurs to maintain CBF within normal limits. Evidence of this vasodilatation can be obtained using a variety of techniques. Regional cerebral blood volume (CBV), alone or in combination with measurements of CBF, can be measured to detect the presence of vasodilatation. The CBV : CBF ratio, mathematically equivalent to the vascular mean transit time, may be more sensitive than CBV alone for the identification of such haemodynamic compromise. Quantitative or semiquantitative measurements of regional CBV and CBF can be made using PET or single photon emission tomography (SPECT). MRI techniques for the quantitative measurement of CBV and CBF have also been developed recently (Ostergaard *et al*., 1998).

An alternative method to determine the presence of cerebral vasodilatation is to measure the vasodilatory reserve. Paired measurements of CBF are made at rest and after exposure to a vasodilator. Both carbon dioxide and acetazolamide have been used (Ringelstein *et al*., 1988, 1992; Dahl *et al*., 1994). In a normal individual a marked increase in CBF is found, but if compensatory vasodilatation has already occurred in response to haemodynamic compromise the degree of possible further vasodilatation is reduced. Impaired reactivity correlated well with the presence of an increased oxygen extraction fraction on PET (Herold *et al*., 1988). For such measurements, quantitative or relative measurements of CBF can be made using a variety of methods, including xenon inhalation, intravenous xenon methods, stable xenon-CT, SPECT, PET and MRI (Derdeyn *et al*., 1999). Many of these involve radiation and are relatively expensive. An alternative is to measure flow velocity in the MCA by TCD. It has been demonstrated that during carbon dioxide inhalation there is little change in MCA diameter (Huber and Handa, 1967), and therefore any change in velocity is directly proportional to the change in flow. TCD-based techniques are cheap and simple and are tolerated by almost all patients. Impaired reactivity determined using this method correlated with evidence of ischaemia on magnetic resonance spectroscopy, as determined by the presence of lactate and a reduction in the neuronal marker *N*-acetyl aspartate (Visser *et al*., 1999). It also correlated with vasodilatation, detected as an increased CBV : CBF ratio, estimated by PET (Sugimori *et al*., 1995). The disadvantages of TCD-based methods are that they lack the regional specificity of other methods of CBF measurement, and are not possible in individuals who lack an acoustic window. This latter problem prevented measurements being made in 8.5% of our patients.

Using TCD-based methods, a large number of cross-sectional studies have been performed (Ringelstein *et al*., 1988; Kleiser *et al*., 1991; Levine *et al*., 1991; Markus and Harrison, 1992; Hartl and Furst, 1995; Muller and Schimrigk, 1996; Silvestrini *et al*., 1996; Sorteberg *et al*., 1996; Matteis *et al*., 1999) and demonstrate that, in a subgroup of patients with carotid occlusion and stenosis, there is severe impairment of cerebral haemodynamics. This is found primarily in individuals with poor collateral supply. Studies have shown a greater reduction in reactivity in patients with symptomatic, compared with asymptomatic, carotid stenosis (Ringelstein *et al*., 1988, 1992). However, despite the large number of cross-sectional studies, there have only been a few prospective studies using TCD to determine the predictive value of such measurements (Kleiser and Widder, 1992; Gur *et al*., 1996; Vernieri *et al*., 1999; Silvestrini *et al*., 2000). These have found that impaired reactivity predicts the risk of stroke and TIA.

A recent review critically assessed most of the prospective studies performed to date to examine the association between impaired haemodynamics and stroke risk in carotid artery disease. The studies reviewed used a variety of methods, including TCD, PET and SPECT. Methodological problems were found in many of these studies (Derdeyn *et al*., 1999). Particular problems included the inclusion, without distinction, of both recently symptomatic and asymptomatic patients; the inclusion of both extracranial carotid stenosis and occlusion and of intracranial stenosis and occlusion without distinction; the failure to determine at onset a cut-off value for impaired haemodynamics, leading to retrospective assignment to low- and high-risk groups; and large numbers of patients censored owing to surgical revascularization or lost to follow-up. In addition, a number of studies showing an association failed to include multivariate analysis and determine whether any relationship that was found was independent. Our method overcame these potential criticisms. Patients were recruited prospectively, and no patients were lost to follow-up or surgical revascularization unless they

Table 3 *Comparison of the predictive value of exhausted haemodynamics*

Method of assessing haemodynamics	Kaplan–Meier analysis	
	Log rank value	*P*
Any ipsilateral event (total 9 events)		
8% reactivity	15.96	0.0001
6% reactivity	14.88	0.0001
Pulsatility index	8.81	0.0042
Ipsilateral stroke (total 5 events)		
8% reactivity	22.90	0.0001
6% activity	12.32	0.0004
Pulsatility index	1.26	0.2617

The value was determined by measuring the effects of 6 and 8% carbon dioxide reactivity and pulsatility index on the risk of any ipsilateral event and ipsilateral stroke in the 95 subjects for whom all measurements were available.

had already reached a study-end-point, namely an ipsilateral ischaemic event. We used a predetermined cut-off value for 8% carbon dioxide reactivity of 20%, a value that had been derived previously from a normal population. All patients with carotid stenosis were asymptomatic, and patients with carotid occlusion had been free of symptoms for at least 3 months. This is important because follow-up studies have demonstrated that reactivity measurements can improve rapidly after an acute carotid occlusion (Widder *et al*., 1994). We did not include patients with evidence of intracranial stenosis or occlusion that was excluded on TCD, and we performed a second analysis in which the patients were divided into carotid stenosis and occlusion groups. We entered a variable that differentiated between the two groups in our multivariate analysis. Finally, we identified other potential risk factors at study onset, including the presence of cardiovascular risk factors, ipsilateral brain infarction on neuroimaging, and the anatomy of both the ipsilateral and the contralateral carotid system. These factors have been suggested as potential markers of increased risk and are simpler to measure than reactivity (Nicolaides *et al*., 1995). It is important to determine whether measuring reactivity provides any additional useful information. These potential risk markers were included in multivariate analysis, and this demonstrated that impaired reactivity was an independent predictor of ipsilateral ischaemic events. No other risk factor was found to be a similar independent predictor, apart from female gender. The cause of this remains unexplained and has not been found in previous studies.

Therefore, our results provide strong evidence for the importance of haemodynamic factors in determining the risk of stroke in patients with carotid occlusion and, to a lesser extent, patients with carotid stenosis. These results are consistent with the results of previous TCD studies in patients with either carotid occlusion (Kleiser and Widder, 1992; Vernieri *et al*., 1999) or asymptomatic carotid stenosis (Gur *et al*., 1996; Silvestrini *et al*., 2000). Two small studies from the same group in which reactivity was measured by using xenon CT techniques have also produced positive results (Yonas *et al*., 1993; Webster *et al*., 1995), but one study using SPECT failed to find an association (Yokota *et al*., 1998). Nevertheless, a number of unanswered questions remain. Despite our study being one of the largest to date, the 95% confidence intervals in multivariate analysis were wide; to produce tighter confidence intervals would require a sample size of a few hundred, necessitating a multicentre approach. Furthermore, to prove a causal relationship between impaired haemodynamics and the risk of stroke, it needs to be demonstrated that modification of this risk factor (i.e. by revascularization) alters the outcome. Separate studies will be required for asymptomatic carotid stenosis and carotid occlusion.

The extracranial–intracranial bypass study investigated the role of revascularization in recently symptomatic patients with stenosis or occlusion of the ipsilateral internal carotid or MCA (EC/IC Bypass Study Group, 1985). Rather than having a protective effect, revascularization was associated with earlier and more frequent fatal and non-fatal stroke than in the non-revascularized group. Separate analysis in patients with different angiographic lesions did not identify a subgroup with any benefit from surgery. However, all patients, irrespective of the degree of haemodynamic impairment, were included. Severe haemodynamic impairment occurs in only a minority of individuals with carotid occlusion (Gur and Yonas, 1986), but this does improve after extracranial–intracranial bypass, at least in some individuals (Baron *et al*., 1981; Powers *et al*., 1984; Gibbs *et al*., 1987). Furthermore, the inclusion of recently symptomatic patients may have reduced further the role of haemodynamic factors, because an impaired haemodynamic reserve may improve in the weeks following an acute event. Therefore, it remains uncertain whether a small subgroup of patients with carotid occlusion may benefit from extracranial–intracranial bypass (Gur and Yonas, 1986). The increasing evidence of the predictive value of impaired haemodynamics in identifying those at increased risk of stroke would justify such a study.

The risk of stroke in patients with asymptomatic carotid stenosis is relatively low, and most studies have given values of ~2% per year, or a combined risk of any ipsilateral event of 4% per year (Bornstein and Norris, 1993; Executive Committee for the Asymptomatic Carotid Atherosclerosis Study, 1995). This is similar to the incidence in our study. The benefit of performing carotid endarterectomy in such patients is marginal. Although the largest study to date did show a significant reduction in the risk of stroke in the surgical arm, the absolute benefit was small and 85 patients would have to be operated on to prevent one stroke over 1 year (Chambers *et al*., 2000). No haemodynamic assessment was performed in these patients, and the proportion of patients with impaired haemodynamics was lower than in patients with carotid occlusion. The mechanism of stroke in patients with carotid stenosis, in contrast to that in patients with carotid occlusion, is thought to be primarily embolic. This is supported by recent studies demonstrating that asymptomatic embolization in the ipsilateral MCA, detected by TCD, is an independent predictor of stroke risk in patients with both symptomatic and asymptomatic carotid stenosis (Siebler *et al*., 1995; Valton *et al*., 1998; Molloy and Markus, 1999). These studies suggest that the presence of asymptomatic embolic signals is likely to be a stronger predictor of stroke than exhausted reactivity in patients with asymptomatic carotid stenosis. In the present study, too few patients had microembolic signal recording to determine the additional benefit of this procedure, and any interaction with reactivity, on the risk of stroke. Despite this, our study suggests that haemodynamic factors are also important in this group of patients, which is consistent with the results of previous studies (Gur *et al*., 1996; Silvestrini *et al*., 2000). It has been suggested that hypoperfusion may lead to impaired clearance of emboli and therefore an increased risk of embolization, resulting in clinical stroke (Caplan and Hennerici, 1998). However, the number of ipsilateral ischaemic events in

patients with carotid stenosis, both in our study and in the previous studies to date, is small. Therefore, further studies are required to assess more accurately the contribution of impaired haemodynamics to the risk of stroke in this group. Such studies should include the recording of other potential markers of increased risk in this group, including ultrasonic plaque characterization and particularly the detection of asymptomatic cerebral embolic signals using TCD.

A number of different estimates of impaired vasodilatory reserve have been measured when using TCD in this context. No previous prospective studies have compared the relative predictive values of such methods. Carbon dioxide can be given at a higher concentration, such as 8%, which results in maximal vasodilatation, or concentrations that result in submaximal vasodilatation, such as 5 or 6% in air. If the latter concentrations are given, the magnitude of the rise in carbon dioxide concentration in the blood needs to be controlled for, and this is usually estimated by measuring the change in end-tidal carbon dioxide concentration. A simpler measure is to use the increase in carbon dioxide concentration that occurs when breath-holding is used as the stimulus (Markus and Harrison, 1992). This may provide a simple method of identifying potential patients with severely impaired haemodynamics, but absolute values have been shown to have poor reproducibility over the short term (Totaro *et al*., 1999). The use of both a maximal vasodilatory stimulus and a submaximal stimulus has potential advantages. The use of a maximal stimulus results in a larger and more robust increase in MCA velocity, but leads to greater systemic changes in haemodynamics. Carbon dioxide administration can result in an increase in systemic blood pressure, which may then result in a passive autoregulatory rise in blood flow velocity, and therefore produce a false-normal result in a patient who has exhausted reactivity (Dumville *et al*., 1998). In contrast, lower carbon dioxide concentrations, such as 5 and 6%, result in smaller increases in systemic blood pressure but also smaller increases in MCA flow velocity. No previous studies have examined the relative merits of the two methods in predicting the risk of stroke and TIA. We found that both independently predicted the risk of an ipsilateral ischaemic event, but the strength of the association was slightly stronger for reactivity to 8% carbon dioxide. It has also been suggested that a reduced pulsatility index may be a useful indicator of the degree of vasodilatation in the distal vascular bed. However, we found that, in contrast to carbon dioxide reactivity, a reduced pulsatility index was a poor predictive marker of the risk of ischaemic stroke.

In conclusion, our results support the role of haemodynamic factors in the pathogenesis of stroke in patients with carotid artery occlusion and, to a lesser degree, in patients with carotid stenosis. They suggest that the evaluation of cerebral haemodynamics using TCD may provide a method of identifying a subgroup of high-risk individuals who may benefit from revascularization. This hypothesis requires testing in randomized controlled intervention studies, particularly in the subgroup of patients with carotid occlusion who have exhausted reactivity.

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