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 endpoint 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 asymptomatic 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 revasculariza-
tion. 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 >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
>70% contralateral carotid disease (16 patients had >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

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

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
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).
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 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, 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 TIsAs, and one further stroke and two further TIsAs 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 TIsAs, 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

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**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

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

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

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

<table>
<thead>
<tr>
<th>Method of assessing haemodynamics</th>
<th>Kaplan–Meier analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any ipsilateral event (total 9 events)</td>
<td>Log rank value</td>
</tr>
<tr>
<td>8% reactivity</td>
<td>15.96</td>
</tr>
<tr>
<td>6% reactivity</td>
<td>14.88</td>
</tr>
<tr>
<td>Pulsatility index</td>
<td>8.81</td>
</tr>
<tr>
<td>Ipsilateral stroke (total 5 events)</td>
<td>Log rank value</td>
</tr>
<tr>
<td>8% reactivity</td>
<td>22.90</td>
</tr>
<tr>
<td>6% activity</td>
<td>12.32</td>
</tr>
<tr>
<td>Pulsatility index</td>
<td>1.26</td>
</tr>
</tbody>
</table>

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; Powars 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 asymomatic 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 relative importance was significantly 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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Exhausted reactivity and carotid disease


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