The Doppler CO₂ test to exclude patients not in need of extracranial/intracranial bypass surgery

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SUMMARY In patients with an internal carotid artery (ICA) occlusion who suffer from ipsilateral transient ischaemic attacks or minor stroke extra/intracranial (EC/IC) bypass surgery may be useful only where there is insufficient collateral supply. The transcranial Doppler CO₂ test offers a simple method of investigating the residual autoregulatory capacity which gives quantitative information about the efficiency of the collaterals. In 155 patients with 162 ICA occlusions there was a significant correlation between a markedly decreased or exhausted autoregulatory capacity and a recent ipsilateral ischaemic event ($p < 0.001$). The Doppler CO₂ test may enable the exclusion of patients not in need of EC/IC bypass surgery. In the reported series this affected more than 80% of all ICA occlusions.

Extra/intracranial (EC/IC) bypass surgery does not benefit patients with an occluded internal carotid artery (ICA) who are selected for surgery on the basis of clinical symptoms.¹ From the pathophysiological point of view this is not surprising: the establishment of an additional collateral pathway from the superficial temporal artery to branches of the middle cerebral artery (MCA) will help only if the circle of Willis is insufficiently developed.² In this case, the cerebral blood flow (CBF) may be partially maintained by a compensatory autoregulatory dilatation of the intracerebral arterioles; the brain, however, is then more vulnerable to ischaemia during periods of a decrease in systemic blood pressure. Therefore the degree of dilatation of the cerebral arterioles is a more sensitive index than the degree of stenosis, whether or not an ICA stenosis or occlusion is haemodynamically critical.³⁻⁶

Twenty years ago, Bloor *et al*⁷ proposed that patients at risk of haemodynamic ischaemia could be detected by measuring CBF during vasodilatation caused by CO₂ inhalation. The increase in CBF during hypercapnia ("CO₂ reactivity") gives a measure of the capability of the intracerebral arterioles to dilate further. This test has been revived during recent years, but it is expensive and few patients have been repor-

ted.⁸⁻¹³ The Doppler CO₂ test is noninvasive, inexpensive and much less time consuming than radionuclide CBF measurements.¹⁴ The present study reports our experience with this new method in a large series of patients with ICA occlusion.

Material and methods

The Doppler CO₂ test is based on transcranial Doppler sonography which enables the detection of blood flow velocity in the MCA and other basal cerebral arteries by ultrasound insonation through the temporal bone by a hand held probe.¹⁵ Time averaged MCA blood flow velocity is monitored continuously together with endtidal pCO₂ measured by an infrared analyser during normocapnia (moderate hypercapnia is induced by breathing a mixture of 5% CO₂ in 95% O₂), and hypocapnia induced by voluntary hyperventilation (fig 1a). A steady state of MCA velocity is usually reached about 1 minute after changing the pCO₂ and can be plotted offline against corresponding pCO₂ values (fig 1b).

Normally the CBF-pCO₂ curve is S-shaped with a linear relation between MCA flow velocity and pCO₂ in the physiological pCO₂ range of 30 to 50 mm Hg. In pathological cases, with decreased autoregulatory reserve, the curve is shifted to the left, and its upper bend can be reached within physiological pCO₂ values.¹⁶ To assess these changes in a standardised form we took a blood pCO₂ of 40 mm Hg as a reference point and defined a "Normalised Autoregulatory Response" (NAR) which can be calculated as the relative increase of MCA flow at hypercapnia of 46.5 mm Hg (= +1 vol % CO₂). Details of the method have been described previously.¹⁷

During a 26 month period, 155 patients with 162 total ICA

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Fig 1a Simultaneous recording of time averaged MCA flow velocity and pCO₂ in a 52 year old patient with left hemispheric minor stroke 2 months previously and ipsilateral ICA occlusion. On the right side marked increase in MCA flow during hypercapnia with prompt decrease within 30 seconds during hyperventilation. On the left no change in MCA flow for different pCO₂ values indicating an exhausted autoregulatory capacity.

Fig 1b The same patient as fig 1a. Graphs showing the relations between MCA flow velocities and pCO₂ values. The "Normalised Autoregulatory Response" (NAR) is calculated as the relative increase in MCA flow velocity between 40 and 46.5 mm Hg endtidal pCO₂.

occlusions were investigated by the Doppler CO₂ test. In general, the diagnosis of carotid occlusive disease was based on a combination of continuous wave-Doppler sonography, duplex scanning and intravenous digital subtraction angiography. Intra-arterial angiography was performed in

only a few unclear cases. The patients' ages ranged from 35 to 81 with an average of 61 years. Seventy two ICA occlusions were not associated with ipsilateral symptoms; 90 patients had suffered at least one ipsilateral transient ischaemic attack (TIA) and/or stroke. Sixty one patients had a concomitant stenosis of the contralateral ICA, with reduction in local diameter of 50% or more. Patients with an additional high grade stenosis or occlusion of an intracranial artery were not included in this study.

Statistical analysis: Patients were divided into categories on the basis of the results of the Doppler CO₂ test and by their clinical features. The Chi-square test was used to correlate the patients' clinical features and the results of the Doppler study, either from the side ipsilateral or contralateral to the ICA occlusion.

Results

Figure 2 shows the relation between the NAR and the clinical findings in the 162 cases. The neurological symptoms were subdivided into recent events and those where the time interval between the (last) onset of symptoms and the Doppler CO₂ test was more than 3 months. The 3 month interval was adopted from the inclusion criteria of the EC/IC Bypass Study.¹⁸ In all cases, the neurological events were due to ischaemia. Other causes such as cerebral haemorrhage were excluded by cranial computed tomography. Of 29 patients whose hemispheric autoregulatory response was nearly or completely absent (NAR < 5) 19 (66%) had suffered at least one stroke or TIA during the last 3 months. Of the 33 with a markedly diminished CO₂ reactivity (NAR = 5-9) 14 (42%) had recently suffered symptoms, whereas in 100 cases with higher NAR, acute cerebral ischaemia had occurred in only 29 (29%). The relation between low NAR and recent

Fig 2 Correlation between the "Normalised Autoregulatory Response" (NAR) and ipsilateral clinical findings in 162 ICA occlusions.

Fig 3 NAR in 162 ICA occlusions with respect to various degrees of stenosis of the contralateral ICA.

cerebral ischaemia was highly significant ($p < 0.001$). However, in patients who had suffered their (last) ischaemic event more than 3 months previously, there was no increased frequency of low NAR ($p > 0.05$).

A significant correlation between the NAR and the severity of the ischaemic event could not be found ($p > 0.05$). However, one cannot exclude the possibility that this was due to the small group in our study (12 patients) who had suffered a major stroke. From these, four had NAR values < 5 (33%). Of the 78 patients with TIA or minor non disabling stroke an exhausted autoregulatory reserve was present in 19 (24%).

The relationship between the NAR values and the patency of the contralateral ICA is shown in fig 3. A surprisingly high number of patients had a patent or only minimally diseased contralateral carotid artery (58%). There was no significant correlation between the ipsilateral NAR and the degree of stenosis of the contralateral ICA ($p > 0.05$). The patency of the vertebrobasilar system was not considered in this study.

Discussion

Cerebral ischaemia in ICA occlusion can be caused by a considerable number of non haemodynamic mechanisms such as pre, peri and postocclusive embolism.¹⁹⁻²⁵ Even haemodynamically induced events can occur only transiently until collateral supply is developed.²⁶ EC/IC bypass surgery, however, is likely to be helpful only when "collateralisation" is persistently insufficient. Such cases may be relatively rare. This view is supported by our results: compared with published normal values,¹⁷ only about one third of all ICA occlusions in our series produced a substantially decreased autoregulatory capacity. These patients had suffered more often from a recent ipsilateral TIA or

stroke, suggesting that an additional, probably haemodynamic mechanism could be responsible for this discrepancy. Additional subtotal stenoses or occlusions of the contralateral ICA were found more frequently in cases with low NAR, but in all the state of the contralateral carotid artery was not a reliable indicator of diminished or exhausted NAR. This may be due to the great variability of the circle of Willis,²⁷ and because the patency of the vertebrobasilar system could not be considered in this study.

Positron emission tomography (PET) offers the best method of identifying patients with impaired cerebral circulation because it assesses the autoregulatory capacity of the intracerebral arterioles as well as the oxygen extraction rate (OER) and the cerebral metabolic rate of oxygen (CMRO₂).^{4,5,28,29} These further features are of interest because an exhausted autoregulatory capacity does not necessarily lead to cerebral ischaemia: even marked drops in blood pressure can be compensated by increasing the OER from the blood. PET, however, is expensive and needs a cyclotron or a linear accelerator to provide positron emitting radionuclides. Therefore in 1986 Warlow concluded that "at the moment it is unrealistic to suggest that patients with a high OER can be identified in normal clinical practice".³⁰ The Doppler CO₂ test now offers a simple and reliable method of detecting ICA occlusions which are not haemodynamically significant and which will not result in an increased OER. This enables the identification of the vast majority of patients *not* in need of EC/IC bypass surgery (82% of our cases). In the remaining, PET studies may be justified for a more detailed analysis of the cerebral circulation.

Compared with the "Diamox test" used to assess CO₂ reactivity by Single photon emission computer tomography (SPECT) studies,¹¹⁻¹³ the Doppler CO₂ test has several practical advantages: the test procedure needs less time and transcranial Doppler sonography is far less expensive than SPECT. During the investigation blood pressure changes only minimally, within about $\pm 10\%$.¹⁷ This may be owing to the small amount of 5% CO₂ in 95% O₂ and the short duration of the CO₂ inhalation (about 1 minute). Therefore, in daily routine, we perform the Diamox test only in patients suspected of additional small vessel disease and in cases where the Doppler investigation is not feasible (see below).

The number of ICA occlusions regarded as haemodynamically critical can be reduced further by considering the actual blood pressure. It is obvious that in patients whose autoregulatory capacity is already exhausted the risk of cerebral ischaemia is increased if there is a severe drop in blood pressure. This is more likely in chronic hypertension. The study of Strandgaard³¹ gives some useful clues on the

Table Interpretation of the Doppler CO₂ test with respect to blood pressure

Doppler CO ₂ test	Autoregulatory capacity	Therapeutic approach
NAR > 10	Sufficient	No need for EC/IC bypass surgery
NAR ≈ 5	Markedly diminished	RR _{1,100} < 140 mm Hg: probably no need for EC/IC bypass surgery RR _{1,100} > 140 mm Hg: see NAR = 0
NAR = 0	Exhausted, compensatory OER increase	EC/IC bypass surgery could possibly be effective. Further PET (or AVO ₂) investigations required for detailed analysis

interpretation of this parameter: in each of 13 patients the mean blood pressure could be reduced to at least 40–45% below the lower limit of autoregulation before the first symptoms of cerebral ischaemia occurred. Applying these results to patients with ICA occlusion and an almost, but not completely, exhausted autoregulatory capacity means that a drop in blood pressure from about 140/90 to 80/50 mm Hg would in general still be tolerated without any symptoms. This ratio is supported by reports of haemodynamically induced cerebral events,^{32,33} and is the basis for practical recommendations on how to interpret the findings of the Doppler CO₂ test with respect to blood pressure (table). In cases with an NAR of 10 or more, there is no need for EC/IC bypass surgery because a sufficient collateral supply exists and even marked drops in blood pressure can be compensated. Also with an NAR of 5, an EC/IC bypass may not be justified if the systolic blood pressure does not exceed 140 mm Hg, indicating that normal variations in blood pressure can be compensated. In the remaining cases, PET or at least measurement of the cerebral arteriovenous O₂ difference (AVO₂)³¹ may give more detailed information about cerebral haemodynamics.

Some further studies in the literature report cerebral autoregulatory measurements by transcranial Doppler sonography but the authors performed only a few tests: Grosse and Ringelstein investigated 21 ICA occlusions and found a markedly decreased CO₂-reactivity in four cases (19%).³⁴ The study by Bishop *et al* included 11 ICA occlusions, of whom two showed an exhausted autoregulatory capacity.³⁵ A direct comparison of the results is not possible because the method of calculating the CO₂ reactivity is different.

Finally, several unavoidable limitations of the Doppler CO₂ test should be considered: (1) The test is not valid in acute stroke with disturbed autoregulation and in the case of large ischaemic areas (false positive results). In these instances cerebral haemodynamics are much more complicated and can only be investigated by PET scanning.⁴⁵ However, this does not

appear to be a major restriction since EC/IC bypass surgery is considered only in TIA or minor non-disabling strokes.¹⁸ (2) Transcranial Doppler measurement of the MCA blood flow velocity gives only a global overview of haemodynamics in the MCA distribution. Additional distal occlusions of intracranial arteries, however, can produce critical perfusion on a local basis (false negative results). Therefore, if angiography demonstrates additional occlusive disease of smaller arteries, or if there are typical cranial computed tomography findings,³⁶ the results of the Doppler CO₂ test must be interpreted sceptically. (3) Cardiac arrhythmia can cause unreliable results because steady states in MCA flow velocity cannot be reached. (4) Doppler recordings from the MCA are inadequate or absent in about 5% of all patients aged over 40 years because of poor ultrasound transmission through the skull.¹⁷

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