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Estimation of Cerebrovascular Reactivity Using Transcranial Doppler, Including the Use of Breath-Holding as the Vasodilatory Stimulus

H.S. Markus, MRCP, and M.J.G. Harrison, FRCP

Background and Purpose: A proportion of individuals with carotid artery stenosis show a reduced cerebrovascular reserve as measured by a reduced cerebral arterial vasodilatory response to carbon dioxide. Two methods of quantifying this vasodilatory response, using transcranial Doppler ultrasonography, have been in general use: the total range of vasodilation between hypocapnia, induced by hyperventilation, and hypercapnia induced by breathing carbon dioxide, and the response to breathing a fixed concentration of 5% carbon dioxide. We studied whether it is possible to use the rise in carbon dioxide occurring during breath-holding as the vasodilatory stimulus.

Methods: Using transcranial Doppler, cerebral reactivity to carbon dioxide was measured in 23 subjects undergoing intravenous digital subtraction angiography of their carotid arteries for symptoms of cerebrovascular disease. A breath-holding method was compared with the two previous methods, which required administration of carbon dioxide.

Results: All three methods gave results that correlated highly significantly with the degree of carotid stenosis, although the correlation was highest when the full vasodilatory range was measured. This method was adopted as the gold standard, and the other methods were compared with it. The breath-holding method correlated at least as well ($\rho=0.67$) as the 5% CO_2 method ($\rho=0.64$). It identified a similar group of low reactors to our gold standard method, whereas the 5% CO_2 method gave some discrepant results.

Conclusions: The breath-holding method offers potential as a convenient, well-tolerated screening method of assessing carbon dioxide reactivity not requiring the administration of carbon dioxide, although further validation against more established methods of measuring cerebrovascular reserve is first required. (*Stroke* 1992;23:668–673)

KEY WORDS • carbon dioxide • carotid artery diseases • ultrasonics

Cerebral blood flow autoregulation in normal individuals ensures that a fall in perfusion pressure is counterbalanced by vasodilatation of cerebral arterioles, which, under normal conditions, maintains adequate cerebral blood flow. This cerebrovascular reserve can be estimated by measuring the change in cerebral blood flow that occurs in response to a vasodilatory stimulus; carbon dioxide or intravenous acetozolamide have been most extensively used. A proportion of individuals with occlusive carotid artery disease show reduced cerebrovascular reactivity as assessed by this technique.[1] It is believed that hemodynamically compromised tissue is supplied by maximally, or near maximally, dilated arterioles, that are therefore unable to dilate much further in response to additional vasodilator stimuli. This change in cerebral blood flow can be measured using xenon-133 clearance,[1] stable xenon CT blood flow,[2] positron emission tomography,[3] or, more recently, by using transcranial Doppler ultrasonography (TCD) to measure changes in middle cere-

bral artery blood flow velocity (V_{mca}).[4,5] Results obtained using TCD have been shown to correlate well with those obtained using xenon clearance.[4]

Workers using TCD to assess vasodilatory capacity have usually employed one of two measures of CO_2 reactivity. Ringelstein et al[5] assessed the full vasodilatory range by measuring the percentage change occurring in V_{mca} between hyperventilation and inspiration of increasing concentrations of CO_2 until no further increase in V_{mca} occurred. They found a mean vasodilatory range of 85% in normal individuals. This correlated well with previous studies in both animals and humans using continuous-wave Doppler ultrasonography of the extracranial cerebral arteries and regional cerebral blood flow measurements under CO_2 stimulation.[5] The method of Ringelstein et al appears to be reliable but is time consuming, and the high concentrations of inspired carbon dioxide required are uncomfortable for patients. Bishop et al[4] have advocated a simpler method in which the percentage change in V_{mca} that occurs on breathing 5% CO_2 is divided by the increase in end-tidal CO_2 occurring at the same time. End-tidal CO_2 measurement is used as a noninvasive estimate of the arterial partial pressure of carbon dioxide. This method is quicker but does require equipment for measuring CO_2 concentrations. Recently it has been suggested that the rise in

CO_2 that occurs during breath-holding could be used as the vasodilatory stimulus[6]; the rate of rise in V_{mca} during breath-holding was measured and was found to be markedly reduced in some patients above an occluded or severely stenosed common or internal carotid artery. As breath-holding after maximal inspiration is accompanied by a Valsalva effect that reduces V_{mca}, breath-holding after a normal inspiratory breath was used. This method is quick and does not require administration of CO_2 or measurement of CO_2 concentrations. Before becoming more widely used, however, it requires validation by comparison with other techniques.

Recently there has been renewed interest in the role of hemodynamic factors in the pathogenesis of stroke, fueled by the improved prognosis found after carotid endarterectomy for tight, and, hence, probably hemodynamically significant, carotid artery stenoses.[7,8] The measures of hemodynamic reserve discussed above may represent ways of separating out those individuals who will benefit most from interventional procedures, and they may prove useful in further study of the pathogenesis of stroke. Despite their widespread use, there has been little comparison between different methods. We performed this study to compare the different methods of estimating CO_2 reactivity using TCD; we compared the method advocated by Bishop et al[4] and a breath-holding method with the method advocated by Ringelstein et al.[5] In addition, the reproducibility of the breath-holding method was examined. As a further test of the validity of the breath-holding method, cerebrovascular reserve was measured before and after carotid endarterectomy in a subgroup of the patients; it has been shown, using other methods of measuring cerebrovascular reserve, that in the majority of patients in whom it is impaired preoperatively, cerebrovascular reserve improves after carotid endarterectomy.[9]

Subjects and Methods

We considered for the study 25 individuals undergoing intravenous digital subtraction angiography of the carotid arteries. In one subject neither middle cerebral artery could be insonated adequately, and one subject could not tolerate breathing increased CO_2; these two were excluded. Of the remaining 23 individuals, three were women, and mean age was 63.7 (range 48–77) years. The indications for angiography were amaurosis fugax in five, transient hemiparesis or transient hemisensory symptoms in five, stroke with nondisabling residual hemiparesis in nine, stroke and transient hemiparesis in one, amaurosis fugax and hemisensory symptoms in one, and noises in the head with a carotid bruit in two. In two cases inadequate views of the carotid arteries were obtained on intravenous angiography, and, therefore, intra-arterial carotid angiography was performed. In one patient one middle cerebral artery could not be adequately insonated; therefore, we studied 45 middle cerebral arteries. In these 45, angiography revealed the following degree of stenosis in the ipsilateral common and internal carotid arteries: no stenosis in 17, 10–30% stenosis in 10, 31–69% stenosis in 10, 70–99% stenosis in four, and complete occlusion in seven.

The V_{mca} was measured with a transcranial Doppler velocimeter (model TC2-64B, EME-Uberlingen) with a

2-MHz probe. The position of the probe was adjusted until a maximal signal was obtained; this was at a depth of 50 mm in all but two patients, in whom a depth of 55 mm was used bilaterally. The probe was held in position with a head strap. The subject breathed air through a close-fitting mask, and carbon dioxide could be added to the inspired air. Ports in both the inspiratory and expiratory circuits allowed air to be drawn off into a CO_2 analyzer (Instrumentation Laboratory End-tidIL 200 CO_2 monitor). The CO_2 concentrations were recorded on a chart recorder.

Subjects first breathed room air through the apparatus until a steady expiratory end-tidal CO_2 concentration was obtained. The mean middle cerebral velocity (V_{mca}), a mean of V_{mca} recorded over 4 seconds, was displayed on the TCD display. The mean of this reading over 60 seconds was recorded as the resting V_{mca}. Subjects then hyperventilated for 2 minutes, and the V_{mca} and end-tidal CO_2 were recorded. Subjects then breathed room air normally for 4 minutes, as we have found that changes in middle cerebral velocity due to hyperventilation may persist for up to 3 minutes after hyperventilation stops (M.J.G. Harrison, unpublished observations). Subjects were then instructed to hold their breath after a normal inspiratory breath; the rise in V_{mca}, calculated using the mean V_{mca} immediately after the end of the period of breath-holding, and the time of breath-holding were recorded. This was repeated after a rest period of 2 minutes, and the mean of the two values was taken. After an additional 2 minutes' rest, carbon dioxide was added to the inspired gas until the inspired CO_2 concentration was 5%. Subjects breathed this mixture for 2 minutes, after which V_{mca} and end-tidal CO_2 were recorded. Inspired CO_2 was then progressively increased in increments of approximately 1%; at each level the subject breathed the gas mixture for 2 minutes before V_{mca} and end-tidal CO_2 were recorded. This was continued until further increases in inspired CO_2 resulted in no further increase in V_{mca}. In a subgroup of seven patients, reproducibility of breath-holding was assessed by repeating the breath-holding test five times for each of the 14 middle cerebral arteries, with each test separated by 2 minutes.

In seven patients who underwent carotid endarterectomy, ipsilateral cerebrovascular reserve estimated by the breath-holding method was measured in the week before and 4 weeks after surgery.

To compare the effect of deep breath-holding and breath-holding after a normal inspiratory breath on V_{mca} and arterial blood pressure, four subjects with indwelling arterial cannulas for measurement of arterial pressure were studied. None had signs or symptoms attributable to cerebrovascular disease; all were receiving treatment for coronary artery disease. In each subject, arterial blood pressure and V_{mca} (in one middle cerebral artery) were monitored during breath-holding after both deep inspiration and a normal inspiration.

Data Analysis

The following measures of cerebrovascular reactivity were calculated.

Full range of vasodilation (after Ringelstein et al[5]). The percentage change in V_{mca} from hyperventilation to hyper-

capnia, calculated from $100 \times (V_{mca}[\text{hypercapnia}] - V_{mca}[\text{hyperventilation}])/V_{mca}(\text{rest})$.

Change in V_{mca} per incremental increase in end-tidal CO_2 (after Bishop et al[10]). The percentage increase in V_{mca} occurring during inspiration of 5% CO_2 was divided by the absolute increase in end-tidal CO_2 (measured in kilopascals) occurring during the same time.

Breath-holding index. The percentage increase in V_{mca} occurring during breath-holding was divided by the time (seconds) for which the subjects held their breath.

The data were treated as nonparametric, and the different tests were compared using Spearman's correlation coefficient corrected for ties.

Results

The results of the different measures of cerebrovascular reactivity in the 45 middle cerebral arteries and the degree of ipsilateral internal or common carotid stenosis are given in Table 1. The correlation between the degree of carotid stenosis and cerebrovascular reactivity as measured by the different methods was calculated. Although there was no significant correlation between resting middle cerebral artery velocity while breathing room air and degree of stenosis ($\rho=0.02$, $p=0.87$ [NS]), there was a highly significant correlation between each method of measuring cerebrovascular reactivity and degree of carotid stenosis. This was strongest using the full range of vasodilation ($\rho=0.62$, $p<0.0001$) but was also highly significant for the breath-holding method ($\rho=0.47, p<0.0018$) and the 5% CO_2 method ($\rho=0.40$, $p<0.002$). It was stronger using our revised breath-holding index incorporating percentage rise in V_{mca} than using the original breath-holding index ($\rho=0.47$ vs. 0.37).

The measurement of the full range of vasodilation was adopted as the gold standard, and the two newer methods were compared with it. Both the breath-holding method ($\rho=0.67$, $p<0.0001$) and the 5% CO_2 method ($\rho=0.64, p<0.0001$) were highly correlated with it. Again, the correlation was higher with our revised breath-holding index than with the original breath-holding index ($\rho=0.67$ vs. 0.53). To determine whether the different methods identified the same cases as having impaired reactivity, the quartile ($n=12$) with lowest reactivity as determined by the method of Ringelstein et al[5] was identified. Of these 12 low reactors, 10 were also in the lowest 12 reactors as identified by the breath-holding method, but only six were also in the lowest 12 reactors as assessed by the 5% CO_2 method.

As mentioned above, one patient was unable to tolerate breathing increased inspired CO_2 concentrations. An additional 11 patients found breathing higher concentrations of CO_2 uncomfortable, and in one case this was accompanied by an episode of angina. All patients were able to hold their breath, and none found it uncomfortable, although some required practice holding their breath without taking a deep inspiration. Subjects held their breath for a mean time of 30.8 (range 14–75) seconds; individual times are given in Table 1 as the mean of the two breath-holding tests performed for each middle cerebral artery.

Reproducibility of the breath-holding index was calculated for 14 middle cerebral arteries by repeating the measurement five times for each artery. The mean and standard deviation of the breath-holding index was calculated for each artery. Taking the average of these values across all 14 arteries gave a mean±SD breath-holding index of 1.42±0.13.

In seven cases the breath-holding index was measured before and after carotid endarterectomy. The results are shown in Table 2. In all cases in which cerebrovascular reserve, as estimated by the breath-holding index, was reduced preoperatively, it returned to normal postoperatively. (The normal mean±SD range for the breath-holding index calculated from the index of those middle cerebral arteries from patients who have ≤30% carotid stenosis on either side (20 arteries) is 1.30±0.60. It should be noted that both the patients with moderate stenoses, and yet markedly reduced breath-holding index, had contralateral internal carotid occlusions.

In four subjects, arterial blood pressure (measured using indwelling arterial cannula) and V_{mca} were recorded during breath-holding after both a deep breath and a normal inspiratory breath. In all subjects, both arterial blood pressure and V_{mca} fell initially before rising during breath-holding after a deep breath. In all subjects, neither blood pressure or V_{mca} fell during breath-holding after a normal inspiratory breath (Figure 1).

Discussion

An analysis of the type undertaken in this study requires the adoption of one method as the gold standard against which the other methods can be compared. We adopted the measurement of the full vasodilatory range as the gold standard because most earlier physiological studies had used a similar method, and in our experience it is more reliable than the 5% CO_2 method. That it is the best choice is supported by the finding that of the three methods, it was most closely correlated with the degree of carotid stenosis. Although cerebrovascular reactivity depends on the patency of the circle of Willis and other collateral supply as well as the state of the ipsilateral carotid artery, one would expect, in a study of a number of individuals, a positive correlation with the degree of carotid artery stenosis. The breath-holding and 5% CO_2 method also correlated highly significantly with the degree of carotid stenosis.

Both the 5% CO_2 and the breath-holding methods were found to correlate to a similar extent with the full vasodilatory range method. This study suggests that, at least as a screening test for impaired cerebrovascular reactivity, the breath-holding method appears to be at least as effective as the 5% CO_2 method. Analysis of low reactors (those in the lowest quartile) identified by the three methods showed that the full-range method and the breath-holding method identified similar groups. All but two of the 12 lowest reactors identified by the full-range method were among the 12 lowest reactors identified by the breath-holding method. The two arteries identified in the lowest quartile by the full-range, but not the breath-holding, method, were only just outside the lowest quartile as assessed by breath-holding method. The correlation between poor reactors identified by the full-range method and the 5% CO_2 method was less good, with only six of the 12 lowest reactors, as assessed by the full-range method, also being identified

TABLE 1. Values of Resting Middle Cerebral Artery Flow Velocity and Cerebrovascular Reactivity Obtained With Three Methods in 45 Middle Cerebral Arteries

Middle cerebral artery	% Stenosis	V_{mca} rest	Cerebrovascular reactivity by method			BH time (sec)
			Full range	5% CO_2	BH index	
1	0	41.4	98.0	33.6	0.93	22.7
2	0	48.3	101.2	17.7	0.82	14.0
3	100	44.7	34.0	0	0.06	25.6
4	0	39.0	140.0	29.3	0.96	40.0
5	0	39.5	136.7	20.6	0.92	40.0
6	10	34.0	207.9	81.0	1.89	28.0
7	40	38.0	121.0	33.8	1.47	25.0
8	0	54.0	102.5	41.7	2.47	27.0
9	30	39.2	112.2	40.8	3.10	27.0
10	99	42.5	25.8	10.7	0.37	47.0
11	90	62.0	59.7	17.9	0.69	49.0
12	60	44.8	84.8	12.1	0.93	27.0
13	45	64.8	84.8	18.5	1.07	19.0
14	0	58.8	95.2	36.3	0.94	24.0
15	0	56.0	100.0	35.7	1.05	27.5
16	100	27.5	38.8	21.1	0.65	25.0
17	50	34.8	29.0	29.3	0.37	25.0
18	10	44.0	81.8	22.7	1.14	32.0
19	10	42.0	85.7	26.4	1.34	32.0
20	10	56.0	85.7	42.6	0.81	30.0
21	0	56.0	85.7	4.3	0.80	36.0
22	0	44.0	113.6	25.6	1.11	30.0
23	20	42.7	121.9	31.2	1.18	30.0
24	100	39.2	68.9	16.3	0.61	75.0
25	0	38.4	125.0	29.4	1.39	67.0
26	0	36.0	102.8	33.3	0.95	64.0
27	0	40.0	115.0	51.2	1.63	40.0
28	50	70.0	71.4	31.4	1.02	28.0
29	0	43.0	130.2	50.2	1.63	30.0
30	0	46.0	70.0	8.7	1.20	27.0
31	0	46.0	70.0	8.7	1.20	27.0
32	100	56.0	75.0	11.9	0.33	32.0
33	90	56.0	78.5	28.6	0.41	35.0
34	90	32.0	56.2	27.8	0.31	25.0
35	0	47.0	93.6	61.0	0.89	36.0
36	50	43.5	36.8	4.1	0.42	22.7
37	100	36.0	33.0	0	0.07	22.0
38	10	52.0	73.1	12.8	1.66	21.0
39	10	56.0	114.3	19.0	2.56	18.3
40	0	37.7	50.0	23.2	0.47	19.0
41	100	41.6	90.5	30.8	1.35	15.0
42	50	47.5	75.8	14.3	1.12	25.0
43	20	51.8	75.3	15.4	1.07	28.6
44	30	57.6	90.3	24.0	0.94	24.0
45	70	57.6	62.5	13.6	0.25	22.0

V_{mca} rest, resting middle cerebral artery flow velocity; Full range, method after Ringelstein et al[5]; 5% CO_2, method after Bishop et al[4]; BH index, breath-holding method; BH time, mean duration of breath-holding for each cerebral artery.

in the lowest 12 by the 5% CO_2 method. Indeed, one of the worst reactors assessed by both the full-range and breath-holding methods was above the mean reactivity when the 5% CO_2 method was used.

The breath-holding method also has the advantage of not requiring a source of CO_2 or a method of measuring CO_2 concentration; therefore, as many transcranial Doppler ultrasound machines are portable, it can easily

| Patient No.	% stenosis	BH index	
		Pre	Post
10	99	0.37	1.00
11	90	0.69	1.43
17	50	0.37	1.40
28	50	1.02	1.12
33	90	0.41	1.35
36	50	0.42	1.24
42	50	1.12	0.82

Pre, values before ipsilateral carotid endarterectomy; Post, values after endarterectomy.

be performed at the bedside or in the outpatient clinic. Patient tolerance was excellent; this represents an advantage over the methods using increased inspired CO_2 concentrations, particularly at higher concentrations, which many subjects found uncomfortable. It is impor-

FIGURE 1.   *Graph of effect of breath-holding after a deep inspiratory breath* (panel a) *and normal inspiration* (panel b) *in four subjects. Only the former results in a fall in blood pressure and middle cerebral artery flow velocity (Vmca).*

tant that the breath is held after a normal inspiratory breath rather than a deep breath, as the latter will induce a Valsalva effect that will cause an initial fall in middle cerebral artery velocity. This may result in an underestimate of the reactivity. By measuring V_{mca} concurrently with arterial blood pressure, our results demonstrate that in contrast, breath-holding after a normal inspiratory breath does not result in a fall in arterial blood pressure, probably because it does not result in a Valsalva effect.

The initial study of the use of a breath-holding method[6] used the absolute rise in V_{mca} on breath-holding; we modified this to use the percentage rise instead to reduce the bias in favor of low or high resting levels of V_{mca} and to make the method more comparable with the 5% CO_2 method, which also uses the rise, rather than absolute change, in V_{mca}. The use of the percentage rise rather than the absolute rise in V_{mca} is supported by our results; percentage changes were found to correlate better with both the degree of stenosis and with the results using the full range of vasodilation method. During breath-holding, V_{mca} started to rise, usually after 8–14 seconds; therefore, there is a possibility that if the period of breath-holding is too short this method might underestimate reactivity. In our study, patients held their breath for a mean of 31.5 seconds; one patient was only able to hold for 15 seconds, but, nevertheless, a correlation was found with his reactivity measured by the method of Ringelstein et al.[5] Nevertheless, in patients who have impaired respiratory function the use of the breath-holding method may be limited.

The aim of this study was to demonstrate whether the breath-holding method might provide an easier way of obtaining the information provided by the two previously used TCD methods. Our results suggest that it may have a potential use at least as a screening test. However, it must be recognized that although highly significant correlations were found between the results obtained by the three different methods of measurement, the correlation coefficient between the breath-holding method and Ringelstein method was only 0.65, implying that the two methods have only about 50% of the variance in common. There are a number of potential sources of error in the breath-holding method. Our reproducibility data showed a mean standard deviation of almost 10% of the mean breath-holding index. This is more important for low values of the breath-holding index, in which a small absolute variation may result in a much larger percentage variation. Our apparatus and protocol recorded the mean V_{mca} over 4 seconds. Because the V_{mca} is still rising at the end of breath-holding, increased accuracy may be provided by recording mean V_{mca} per cardiac cycle. Second, it is possible that the arterial PCO_2 may rise at different rates during breath-holding in different subjects. It is not possible to measure accurately and noninvasively changes in arterial PCO_2 concentrations occurring over seconds. An end-expiratory CO_2 measurement at the end of breath-holding does not give a measure of the arterial PCO_2 at that time because, unlike the estimation of the arterial PCO_2 from the end-tidal CO_2, steady state does not exist. Third, if the rise in arterial PCO_2 during breath-holding is not linear, the length of breath-holding may influence the value of the breath-holding index. To assess the
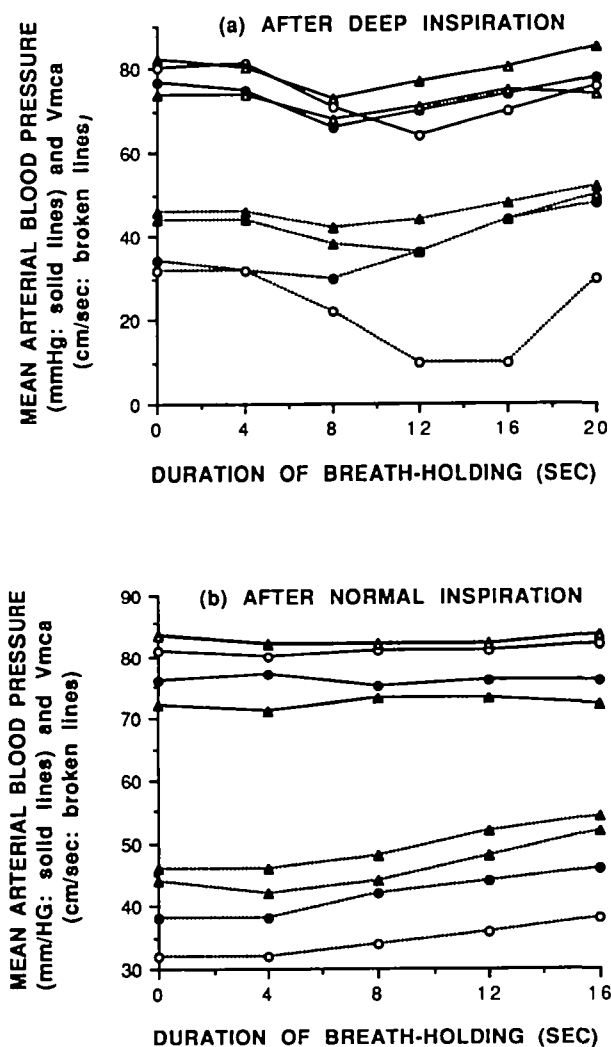
extent of any bias due to this problem, we compared the correlation between the breath-holding index and the Ringelstein method for those patients with a short breath-holding time (>27 seconds; $n=23$) and those with long breath-holding times (>27 seconds; $n=22$). There was no significant difference in the correlations found in the two groups ($\rho=0.77$ and 0.65, respectively).

When using any of the three methods of estimating cerebrovascular reserve using TCD, it should be remembered that there has been only been limited validation with other more established techniques of measuring cerebrovascular reserve. Bishop directly compared his method with ^{133}Xe techniques.[4] Ringelstein et al have shown appropriate reductions in reactivity above carotid stenoses and occlusions. In this study we have shown that impaired reactivity as assessed by the breath-holding index returns to within the normal range after carotid endarterectomy. Nevertheless, before these TCD methods are applied to clinical practice, further validation is required by comparison against more established techniques and examination of the effects of different vascular lesions on reactivity. It is only when such validation has been performed that we will know whether discrepancies among the three methods studied are due to errors in any one particular method.

The two large, recent studies of carotid endarterectomy in symptomatic patients have shown an improved prognosis in patients with carotid stenosis of $\geq 70\%$.[7,8] Preliminary results from these studies also suggest that, within this group of patients with tight carotid stenoses, the improvement in prognosis may be related to the degree of stenosis. Therefore, it is likely that an important determinant of the risk of stroke, and hence of the potential benefit of intervention, is the hemodynamic effect of the stenosis. Measurement of cerebrovascular reactivity may represent a better assessment of the hemodynamic effect of a carotid stenosis than of the anatomical degree of stenosis because it also takes into account the collateral supply. If this proves to be the case, selection of those patients who will benefit from

operation may need to take into account the effect of the stenosis on cerebrovascular reactivity. The breath-holding method described in this paper offers potential as a simple method of assessing cerebrovascular reactivity that could be used in this situation, although further validation is required before its widespread application.

Acknowledgments

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