

# Two minute slope inhalation technique for cerebral blood flow measurement in man

## 2. Clinical appraisal

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**SYNOPSIS** The two minute slope technique for measuring CBF was devised primarily to study the response of the cerebral circulation to physiological stimuli. In this paper, measurements of the precision of the technique when applied to various groups of people are described, and measurements on normal subjects of the global and regional CBF changes in response to hyperventilation and hypercapnia are presented. It is shown that CBF measured using this technique during percutaneous carotid compression may prove useful in the prediction of cerebral ischaemia in patients who are candidates for carotid ligation.

A cerebral blood flow (CBF) inhalation technique—the two minute slope technique—has been developed (Wyper *et al.*, 1975) for clinical use. It gives a measure of mean CBF based on the clearance rate over a two minute period after inhalation of  $^{133}\text{Xe}$ , and has been shown to give a value for CBF which correlates well with results from other measurement methods, as described in the previous paper. This paper describes some clinical applications of the technique.

In many clinical situations the change in CBF in response to a physiological stimulus may provide more information than the absolute flow. It is therefore of fundamental importance to study the precision of the technique to determine if changes in CBF are statistically significant.

### METHODS

**PRECISION** The precision can best be assessed by performing a number of measurements of CBF under constant physiological conditions for each patient. If two such measurements are made on a group of patients, then the mean difference between measurements one and two gives a measure of any systematic trend in the measurement technique. Statistically, the

distribution of these differences is presented in terms of their standard deviation. If any two consecutive measurements of CBF differ by greater than twice this standard deviation, then there is a 95% probability that they are significantly different.

Using the mean and standard deviation in this way assumes that the distribution of CBF values in the population studied is normal. In a previous study (Rowan *et al.*, 1975) on patients having carotid angiography and CBF measurements by the carotid

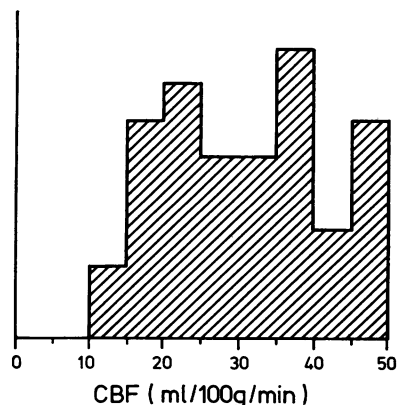


FIG. 1 Histogram of CBF values (run 1: patients N42).

injection technique this distribution was found to be closer to being log normal than normal. However, a histogram of the resting CBF values of 42 patients with a wide variety of pathological conditions studied using the two minute slope inhalation technique is closer to normal (Fig. 1). This group contained more patients with CBF in the 35–50 ml/100 g/min range than the previous series.

The distribution is important because it determines the nature of the statistical analysis used. If CBF values occur in a log-normal distribution in the population being studied, then logarithms of flow values should be taken before making comparisons, but for a linear distribution, the original flow values are used. One result of this is that significant differences are expressed in terms of a percentage change with a log-normal distribution, and an absolute change (in ml/100 g/min) with a normal distribution.

The precision of a technique depends both on the

TABLE 1  
PRECISION IN VARIOUS GROUPS

Group	N	$\overline{CBF}$	$\overline{\Delta CBF} \pm SD$	Precision
Geriatric patients	23	35.0	-1.0 3.5	7.0 (20%)
Normal subjects	20	49.4	-1.8 8.3	16.6 (33%)
Institute patients	17	48.3	-1.7 5.9	11.8 (24%)
Institute patients	42	31.4	+0.4 4.8	9.8 (30%)

$\overline{CBF}$ : average CBF in ml/100 g/min taking the first measurement in each subject.

$\overline{\Delta CBF}$ : average of second minus first CBF measurements in each group.

Precision: change in CBF necessary for significance of  $P < 0.05$  expressed in ml/100 g/min. The values as a percentage of CBF are shown in parentheses.

TABLE 2  
CBF RESPONSE TO HYPERVENTILATION AND HYPERCAPNIA

	Hyper-ventilation N = 13	Normocapnia	Hypercapnia N = 10
CBF (ml/100 g/min)	28.3	50.1	67.5
Mean SD	4.6	6.9	12.9
PCO <sub>2</sub> (mmHg)	18.4	37.0	51.9
Mean SD	2.2	3.7	4.1
$\frac{\Delta CBF}{\Delta PCO_2}$	1.20		1.21
Mean SD	0.09		0.21

group of patients being studied and on the technique itself. It is therefore important to assess the precision on the particular group being investigated, or, if this is not possible, on a closely matched group. The precision of the two minute slope technique has been assessed by performing pairs of measurements on a group of geriatric subjects, a group of volunteers from the hospital staff, and a wide variety of patients in this Institute.

The PCO<sub>2</sub>, which is measured in the expired air by an infrared CO<sub>2</sub> analyser (Capnograph), is maintained as constant as possible. In most cases the PCO<sub>2</sub> tended to be constant from one measurement to the next, but, when it did vary, it could generally be corrected by instructing the patient to control his respiratory pattern. If the end-tidal PCO<sub>2</sub> varied by greater than 5.0 mmHg between one measurement and the next, these CBF results were excluded from this study.

The precision of the technique is different for the different groups, the geriatric group having the smallest standard deviation (Table 1). The larger spread in the other groups is attributable to a few

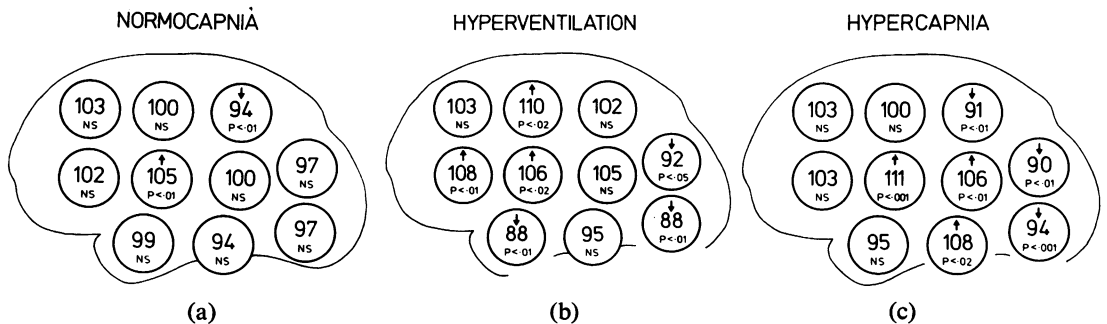


FIG. 2 The distribution of clearance rates at (a) normocapnia ( $n = 29 \cdot PCO_2: 37 \pm 3$  mmHg. CBF:  $50 \pm 7$  ml/100 g/min), (b) hyperventilation ( $n = 13 \cdot PCO_2: 18 \pm 2$  mmHg. CBF:  $28 \pm 5$  ml/100 g/min), and (c) hypercapnia ( $n = 12 \cdot PCO_2: 51 \pm 4$  mmHg. CBF:  $68 \pm 12$  ml/100 g/min). The upper figure in each circle represents rates as percentages of hemisphere mean; below is the significance of deviation from mean.

subjects in whom the variability of CBF measurements was appreciably greater than normal. These subjects were noticeably more anxious than the rest, but their end-tidal  $\text{PCO}_2$  values did not vary by more than 5.0 mmHg between the measurements.

These results indicate that the two minute slope technique can have a precision of 20%, but it is important that this be assessed for each group of patients investigated.

**RESPONSE TO HYPERVENTILATION AND HYPERCAPNIA**  
It is often important to study the reactivity of the cerebral circulation to an increase or decrease in  $\text{PCO}_2$ . The response to hyperventilation was studied in 13 normal subjects and to hypercapnia in 10 normal subjects. With hyperventilation the saturation phase was not started until the  $\text{PCO}_2$  was steady at a suitable value. Hyperventilation was then maintained for 4½ minutes. The CBF measurement relates to the final two minutes during which there were steady state conditions. To obtain hypercapnia a Douglas bag containing a mixture consisting of  $\text{O}_2$ -30%,  $\text{N}_2$ -63%, and  $\text{CO}_2$ -7% was attached to the air inlet tap.

The subject breathed this mixture for one minute before the start of the saturation phase. As the  $^{133}\text{Xe}$  is mixed with air, a transient  $\text{CO}_2$  drop occurred at the beginning of the saturation phase, but the  $\text{CO}_2$  absorber was removed from the system, and so at the end of the two minute saturation phase the  $\text{PCO}_2$  had built up to about 7%. During the desaturation phase breathing was from the Douglas bag.

The mean CBF and  $\text{PCO}_2$  values at normocapnia, hypocapnia, and hypercapnia are shown in Table 2 together with the slopes of the CBF responses.

As these results were obtained using a gamma camera to view the head it was possible to study changes in the regional distribution of CBF under conditions of hypo- and hypercapnia. As the input function to the normal brain—that is, the arterial concentration of  $^{133}\text{Xe}$  A(t)—is the same for all areas, this has little effect on the relative values for different regions especially if these values are fairly close. Head clearance rates ( $K_H$  as described by Wyper *et al.*, 1975) can be used in place of CBF values. Figure 2a shows the distribution of clearance rates in the left hemisphere in 29 normal subjects with normocapnia (values are expressed as a percentage of the hemisphere mean). Clearance is significantly high in the region of the insula and low in the superior parietal region.

During hyperventilation in 13 subjects (Fig. 2b) the CBF fell to  $28 \pm 5$  ml/100 g/min but there was a significant increase in clearance rate relative to the hemisphere mean in the frontal region and a decrease in the temporal and occipital regions. The increase,

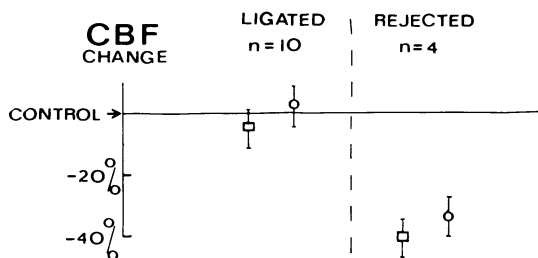


FIG. 3 The change in CBF between control measurements and during temporary compression of the carotid artery.  $\circ$ : percutaneous comp. (inhalation).  $\square$ : operative clamping (injection).

which affects the motor region, could be due to the physical activity involved in voluntary hyperventilation.

At hypercapnia (Fig. 2c) the mean CBF rose to  $68 \pm 12$  ml/100 g/min and the relative clearance was high in the region of the insula and low in the occipital region.

**CAROTID COMPRESSION** Percutaneous digital compression of the carotid artery at the neck may indicate intolerance to carotid ligation by providing clinical signs of hemisphere ischaemia. We have attempted to refine the procedure by measuring CBF during a carotid compression test on 16 patients who were candidates for carotid ligation, the result being compared with a control measurement. The carotid artery was compressed for 4½ minutes, which is the duration of the CBF measurement procedure. EEG was monitored continuously and the pulse in the ear lobe was monitored using a photosensitive peripheral pulse monitor to confirm the effectiveness of the compression.

In one case the patient could not tolerate the discomfort of the compression. In another case the compression had to be released early because of adverse clinical and EEG signs. There was good agreement between the changes in CBF obtained during percutaneous compression using the inhalation technique and that obtained in the operating theatre during clamping of the carotid artery in both the ligated and rejected groups (Fig. 3). There is also a clear distinction between the CBF change during percutaneous compression in the two groups.

The measurement of CBF during carotid compression may therefore prove useful in eliminating unsuitable patients without their going to theatre.

CBF measurement in conjunction with the carotid

compression test is useful in another respect. If the resting value of CBF is less than 20 ml/100 g/min then a compression would not even be attempted.

#### DISCUSSION

Flow maps consist of an array of numbers which are the clearance values ( $K_H$ ) superimposed on a varying grey shade map of the static distribution of  $^{133}\text{Xe}$  during one of the epochs of four seconds. A map in which the distribution was grossly abnormal was produced by a stroke patient who also had orthostatic hypotension. The measurement was made with the patient in the standing position—a position which she could not maintain for more than five minutes. An ischaemic area could be clearly seen in the frontal region, demonstrating loss of autoregulation in this region.

This is, however, a fairly gross ischaemic area. A small ischaemic area is unlikely to be seen by a technique in which the whole brain is perfused with  $^{133}\text{Xe}$ . In such cases, the input function to the brain is not the same for all regions because of the slower arrival rate of arterial blood at the ischaemic area.

Although the flow map data which we have presented may be of interest in showing how the circulation in various regions of the brain responds to a state of hyper- or hypocapnia, it must be borne in mind that these are fairly gross regions and, although the variations recorded were less than 15%, there are, in all probability, much larger variations occurring within small regions.

Out of 264 lateral flow maps produced so far, very few have shown abnormality which is significant on an individual basis. Because of this, we are now using the gamma camera in only a few situations and, in general, we are using our four channel detector system. The chief advantage of the gamma camera is that regions can be selected retrospectively.

The  $\Delta\text{CBF}/\Delta\text{PCO}_2$  response is similar with hypercapnia and hyperventilation. This contrasts with the results of Olesen *et al.* (1971) who found an exponential response, with  $\Delta\log\text{CBF}/\Delta\log\text{PCO}_2$  approximately linear. This could reflect an inherent inaccuracy in the two minute slope inhalation technique. Wilkinson and Browne (1970) have shown that the CBF response

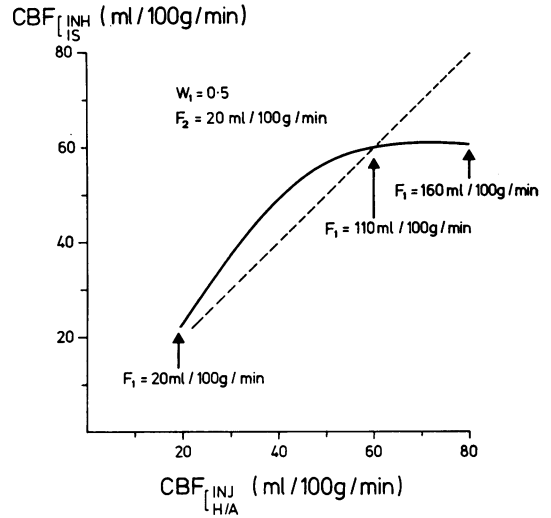


FIG. 4 An illustration of the poor response of the two minute slope method to an increase in flow in a hypothetical situation in which only the fast flow changes.

to hypocapnia is greater in grey matter than in white matter. If this is also the case at hypercapnia, which would be consistent with the regional responses presented here, where the CBF response to hypercapnia is greatest in the region of the insula, then this could account for a diminished CBF response. This is illustrated in an extreme case by considering a two compartment model and varying the fast compartment flow only. We have generated simulated clearance curves using a two compartment model and have processed these curves using the two minute slope analysis method (Fig. 4).

CBF measured by this technique increases as expected with mean CBF until high fast compartment flows are reached, when there is a discrepancy and the measured CBF is lower than mean flow. Such an extreme situation would not arise in practice and mean flows in excess of 100 ml/100 g/min have been recorded by the two minute slope method.

In a study on conscious subjects at normocapnia, Wilkinson *et al.* (1969) found an increased grey matter perfusion in the precentral region and a decrease in grey matter in the temporal region in 10 conscious normocapnic subjects. It has been shown by Risberg and Ingvar (1973) and by Brooks *et al.* (1975) that mental function

affects the distribution of CBF values at normocapnia, so perhaps our results, which were obtained using the short atraumatic inhalation technique and Wilkinson's, which were obtained using the injection technique, are not contradictory.

The studies presented here involve a physiological stimulus either in the form of hyperventilation, breathing 7% CO<sub>2</sub>, or carotid compression and could be undertaken only with a technique in which CBF is measured over a short time interval. The response of the cerebral circulation to a stimulus is generally of greater interest than a knowledge of resting CBF and so a technique of the type presented here is essential in the clinical study of CBF.

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