Cerebrovascular CO₂ Reactivity of the Fast and Slow Clearing Compartments


Abstract:
Regional cerebral blood flow measurements have been made at two levels of Paco₂ using the clearance of ¹³³Xenon injected into the internal carotid artery. Specific and percent changes in blood flow per mm Hg change in Paco₂ (CO₂ reactivity) have been calculated for the fast and slow clearing tissue (Ff and Fs) and F initial. Mean hemisphere CO₂ reactivity was marginally greater in the fast clearing tissue than in the slow clearing tissue (P = 0.05). On a regional basis the greater CO₂ reactivity of Ff over Fs was significant in five areas (P < 0.05). A strong positive linear correlation between mean specific reactivity and conductance (the reciprocal of resistance) has been demonstrated for Ff and Fs and confirmed in the F initial.

Additional Key Words
regional cerebral blood flow
¹³³Xenon
internal carotid artery

It is well known that cerebral blood flow (CBF) can be altered by changes in the arterial carbon dioxide tension (Paco₂).¹⁻⁴ Cerebrovascular resistance is increased by the vasoconstrictor effect of hypocapnia resulting in a fall in CBF in proportion to the fall in CO₂ tension; hypercapnia has the opposite effect. This phenomenon is generally described as cerebrovascular CO₂ reactivity; it has been measured by calculating the change in slope of the first two minutes of isotope clearance curves (F initial). As the F initial is biased toward the flow of the fast clearing compartment of cerebral tissue or gray matter, so is the resultant CO₂ reactivity value. It seemed to be of interest to measure the CO₂ reactivity of the fast and slow clearing compartments separately to see if any difference exists in the way the vessels in gray and white matter react to changing arterial CO₂ tensions.

Technically all that is involved is the two-compartmental analysis of a 15-minute isotope clearance curve at two different levels of Paco₂ and the calculation of the reactivity for Ff and Fs separately. The interpretation of the results, however, may be complicated by growing evidence⁵⁻⁶ that the fast and slow clearing compartments are dynamic entities which change with the overall hemisphere flow, so that absolute values of flow as well as compartment size depend on the amount of overlap between the two compartments. Bearing this in mind we have examined the CO₂ reactivity of fast and slow clearing tissue and the implications of the results on two-compartmental analysis of isotope clearance curves.

The second aspect of CO₂ reactivity that we have considered is its relationship with conductance. In a previous publication from this group⁷ we showed a significant correlation between the CO₂ reactivity of cerebral vessels and conductance which is the reciprocal of resistance. The magnitude of change in the initial flow (F initial) parameter of blood flow for a given change in Paco₂ depended on the resting levels of flow and mean blood pressure. We have investigated whether this relationship between CO₂ reactivity, resting flow and conductance holds for both the fast and slow clearing tissue compartments.

Methods
The nine male and seven female patients between the ages of 23 and 66 years were all referred for evaluation of ischemic cerebrovascular lesions (table 1). They were studied under general anesthesia using a short-acting barbiturate for induction, anesthesia being maintained by nitrous oxide and oxygen supplemented by neuroleptanalgesia.⁸ Fifteen-minute isotope clearance curves were recorded at two levels of Paco₂; the starting level was between 39 to 46 mm Hg (normocapnia) and a difference of at least 10 mm Hg was obtained between the normocapnic and following hypocapnic measurement. The intracarotid injection method of CBF measurement was used as previously described⁹ and each paired study was followed immediately by angiography.

A fine polyethylene catheter placed in the internal carotid artery was used for the injections of approximately 10 mC ¹³³Xenon in 5 ml of saline. Injections were made on the R wave of the electrocardiogram by an automatic injector so that timing, pressure and volume were the same on every occasion. Before and during the CBF studies arterial CO₂ tensions were obtained using a microelectrode system (Radiometer). Arterial blood pressure was measured at...
three-minute intervals by a transducer connected to the catheter in the internal carotid artery. The clearance of isotope from the hemisphere was monitored by 15 highly collimated detectors. Falling count rates from each counter were recorded on a 16-channel digital magnetic tape and the data processed by computer to give regional results for the five CBF variables:

1. Ff is the perfusion rate of the fast clearing tissue which is mainly flow through gray matter, in ml/100 gm per minute.

2. Fs is the perfusion rate of the slow clearing tissue which is mainly flow through white matter, in ml/100 gm per minute.

3. Wf is the relative weight of tissue clearing at the fast rate (gray matter) as a percentage of the total weight of tissue being monitored by the detector.

4. F is the weighted mean flow rate in ml/100 gm per minute which is the average flow rate taking into account both the perfusion rates and relative weights of the fast and slow clearing tissue.

5. F initial is the "initial log slope" flow index estimated from the gradient of the first two minutes of the clearance curve.

In this particular study we were concerned with Ff, Fs and F initial. Using the results from the paired CBF studies we have calculated specific reactivity (SR) and percent reactivity (PR) according to the formulas below which refer to reactivity of the fast clearing compartment:

\[
SR = \frac{F_f - F_{f'}}{\Delta Paco_2}
\]

\[
PR = \frac{\log F_f}{\log F_{f'}}
\]

Specific and percent reactivity of the slow clearing compartment and F initial are similarly calculated using the results for Fs and F initial. The numbers 1 and 2 refer to normocapnia and hypocapnia, respectively. We have calculated the conductance for Ff, Fs and F initial by dividing each resting value by the mean blood pressure. For example for the conductance (C) of the fast flow compartment:

\[
C_{f_f} = \frac{F_f}{MBP}
\]

Results

Table 2 shows the mean hemisphere Ff, Fs and F ini-
TABLE 3
Difference Between Percentage Change in Fast and Slow Clearing Compartments With Hypocapnia

<table>
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<tr>
<th>Area</th>
<th>No. of recordings</th>
<th>ΔFf%</th>
<th>ΔFs%</th>
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<th>P</th>
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</table>

Mean 6.4 3.0 0.05

For each patient at the two levels of Paco2. At normocapnia mean blood pressures varied between 60 and 120 mm Hg and did not change more than 15 mm Hg with hypocapnia. The mean fall in Paco2 with hyperventilation was 14 mm Hg and this was accompanied by a 45% fall in Ff, 39% fall in Fw and 51% fall in F initial, also shown in table 2. The reduction in F initial was significantly greater than that shown by both the Ff and Fs (P = 0.005 – 0.001 for both paired t tests). However, there was only a marginally significant difference between the changes in Ff and Fs (P = 0.05), the change in Ff always being the greater. Table 3 shows the differences between the reductions in Ff and Fs with hypocapnia on a regional basis. Only in area 7 does the difference reach the 2% level of significance. Regional CO2 reactivity calculated for Ff, Fs and F initial showed no significant differences from the hemisphere mean value; therefore, we have used the mean hemisphere reactivity to plot against conductance in each patient for Ff, Fs and F initial (figs. 1, 2 and 3). It can be seen in figures 1 and 3 that for Ff and F initial there is a strong positive linear correlation between specific reactivity and conductance as well as percent reactivity and conductance (P = 0.001). Fs (fig. 2) also showed a significant correlation (0.001) between specific reactivity and conductance but not between percent reactivity and conductance (> 0.1).

Discussion
It looks at first sight as if the CO2 reactivity of the fast clearing tissue is marginally higher than that of the slow clearing tissue (P = 0.05). This result is not in agreement with the findings of Symon et al.5 who showed that CO2 reactivity in the white matter was, if anything, higher than in the gray. Using electrodes placed directly in the gray and white matter of baboons, they showed an increase in flow through gray matter of 2.31% (SD ± 1.3) and in white matter 3.4% (SD ± 1.7) per millimeter rise in the arterial CO2 tension.

It is possible that the difference we found in the CO2 reactivity of fast and slow clearing tissue may be due to a change in compartment size with changes in hemisphere flow. In a previous publication6 we found that the amount of tissue clearing at the fast rate (Wf) falls with the fall in flow accompanying hypocapnia which suggests a shift in the fast clearing compartment at low flow rates. Thus, at hypocapnia some of the flow through the fast clearing compartment may
be sufficiently low to be included in the slow compartment flow. This would lead to an overestimation of Fs at hypocapnia and hence an underestimation of Fs reactivity. Similarly if the hemisphere flow at normocapnia is moderate or low, some of the slow flow compartment (namely the part at the upper end of the slow flow spectrum) could be included with the fast compartment. At hypocapnia the fall in flow might cause a return of this component to the slow flow compartment, again having the effect of reducing the apparent change in Fs. This overlap in clearance rates in the central portion of the curve is an inherent difficulty in the two-compartmental method of cerebral blood flow measurement and we are postulating it to be the cause of an apparent difference in CO₂ reactivity of the two tissue compartments.

If we assume that the Ff reactivity is indeed higher than the Fs, then one might expect the anatomical variation in gray and white matter to cause regional differences in F initial reactivity. The reason no such differences were found may be because F initial is largely biased toward the fast flow compartment so that it would need a very substantial difference in Ff and Fs reactivity for a difference to emerge above the experimental errors involved in the method of CBF measurement.

In this group of 16 patients we have shown an
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even stronger correlation between CO2 reactivity (calculated from F initial) and conductance than was previously shown by Ackerman et al. in 29 patients. This may be in part because the patients in the present group were all studied under the same conditions of general anesthesia, whereas most of the previous group were awake. The fact that all our present patients had mean blood pressures below 125 mm Hg also might account for the stronger correlation since Ackerman showed that the data from five hypertensive patients tended to deviate from the curve. The relationship between vascular reactivity to CO2 of the fast clearing tissue and conductance is as strong as that shown by the F initial (figs. 1 and 3). It is less strong, however, in the slow clearing compartment (fig. 2). The reason for this, as suggested by Symon et al.,5 may be that vessels in white matter autoregulate less well than vessels in gray matter and so are more susceptible to passive influences by the blood pressure. As conductance is a function of blood pressure, it might be expected that the relationship between Fs reactivity and conductance would be weak.

This study has emphasized some limitations of two-compartmental analysis of isotope clearance curves arising from the changing overlap in compartments with overall flow rate. This method of measurement of cerebral blood flow remains a valuable tool but its limitations must be taken into account when interpreting data.

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References

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