Physiological Responses of Local Areas of the Cerebral Circulation in Experimental Primates Determined by the Method of Hydrogen Clearance

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Abstract: Physiological Responses of Local Areas of the Cerebral Circulation in Experimental Primates Determined by the Method of Hydrogen Clearance

The reactivity of cortex, putamen and white matter to changes in arterial CO₂ tension has been assessed. There was no significant difference between the CO₂ reactivity obtained for the three tissues which were in the region of 2% to 3.5% increase over basal blood flow per mm Hg PₐCO₂ increase. The data suggested a somewhat greater reactivity for white matter than for gray matter, though differences were not significant.

Excellent autoregulation to altered perfusion pressure, induced either by hemorrhage or by raising the intracranial pressure with cisternal infusion, was found in gray matter of cortex and putamen and in white matter. With reduction of perfusion pressure by both techniques, it appeared that zero blood flow could be more readily induced in white matter than in gray matter.

Autoregulatory curves to change in perfusion pressure obtained by either method seemed identical, suggesting that the mechanisms involved in the maintenance of cerebral blood flow in the face of reduced arterial pressure or rising intracranial pressure are the same.

Hyperemia was observed in all three areas of the cerebral circulation examined following the restoration of perfusion pressure after a period of reduction. No significant differences in the degree of hyperemia induced by similar stimuli were observed in these three sites.

Additional Key Words: CO₂ reactivity, perfusion pressure, autoregulation, reactive hyperemia, cortex, putamen, white matter.

Introduction

While the general behavior of the cerebral circulation in relation to change in blood pressure and to change in intracranial pressure has been clearly established, with constant blood flow well maintained within the brain in the face of reduced perfusion pressure, there have been few attempts to measure the responses of individual areas of the cerebral circulation either in autoregulation or to such common stimuli as raised arterial PₐCO₂. The highly focal recording made possible by the use of stereotactically placed polarographical needle electrodes measuring hydrogen clearance enables individual portions of the brain to be studied. Using this technique, we have assessed the autoregulatory characteristics of baboon cortex, putamen and white matter to changes in perfusion pressure induced either by hemorrhage or by raised intracranial pressure. We also have examined the reactivity of these tissues to changed CO₂ tension and have observed the phenomenon of hyperemia with the restoration of perfusion after a period of reduction.

Methods

The general methodology used in the 12 animals is described in a previous paper. In assessment of CO₂ reactivity, baseline hydrogen clearances were established at normal arterial PₐCO₂ levels between 35 and 45 mm Hg, and CO₂ in a concentration of between 7% and 10% used to raise the arterial PₐCO₂ to over 55 mm Hg. Levels between 70 and 80 mm Hg were commonly obtained. A steady state of blood PₐCO₂ having been
established and checked by serial blood gas analysis, a further hydrogen clearance was performed with a standard three to four minute inhalation, and the blood flows in cortex, putamen and white matter again were determined. Successful assessments of CO₂ reactivity were obtained on 51 occasions involving 102 clearances.

Assessment of autoregulation was made in two ways. In five animals, after preliminary determination of local blood flow in cortex, putamen and white matter, followed by an assessment of CO₂ reactivity, each animals was progressively exsanguinated by the withdrawal of aliquots of blood from the femoro-aortic catheter. Recurrent estimates of blood flow were made over periods of ten minutes at appropriate intervals, the blood pressure being held constant during each clearance. Continuous monitoring of epidural and cisternal pressures enabled calculation of perfusion pressure to be made in association with the exsanguination, perfusion pressure being calculated as the difference between mean extradural or cisternal pressure and the mean systemic arterial pressure. In four other animals, the intracranial pressure was progressively raised by cisternal infusion of Ringer's lactate solution at the animal's body temperature. By varying the speed of infusion, it was possible to maintain steady intracranial pressure during recurrent estimations of blood flow by hydrogen clearance over six to ten minutes up to very high levels of intracranial pressure. The cisternal recording was discontinued (cisternal pressure having been recorded at the start of such experiments for calibration purposes) and replaced by the infusion, and the intracranial pressure then was monitored by the extradural gauge.

Reactive hyperemia was assessed after marked reduction of blood flow from reduction of perfusion pressure, either by exsanguination or by raising the intracranial pressure. In each instance, the final saturation was succeeded by very slow or arrested blood flow, interrupted either by sudden release of intracranial pressure by allowing the cisternal needle to drain, or by rapid retransfusion of the withdrawn blood. There was an immediate increase in blood flow with a sharp inflexion in the hydrogen clearance curve recorded from the various electrodes, and this steepened clearance was used to determine blood flow during the early phase of hyperemia.

**Results**

**CO₂ response determined in cortex, putamen and white matter**

CO₂ responses were obtained in all 12 animals, but in only the six later experiments were completely satisfactory paired responses from gray and white matter obtained together. The modification of electronic control necessary to maintain a constant baseline at vastly different gains was adopted only about halfway through the series, and in the initial group, the extreme increase in blood flow under conditions of raised CO₂ tension tended to send pens off scale so that detail, particularly of higher flows, was lost. Satisfactory recordings from 14 putamen electrodes showed an increase in flow from baseline figures of 83.1 ml/100 gm per minute (SD ± 14.8) to between 95 and 173 ml/100 gm per minute to a CO₂ change of 26 to 60 mm Hg. Satisfactory recordings in 13 cortical electrodes showed changes from basal levels of 83.3 ml/100 gm per minute (SD ± 17.9) to between 86 and 173 ml/100 gm per minute to a similar P CO₂ change, and 24 white matter electrodes showed a change from a basal level of 19.7 ml/100 gm per minute (SD ± 4.2) to levels of 30 to 60 ml/100 gm per minute, and again to a similar P CO₂ change. The typical alteration in primary hydrogen curves obtained is shown in figure 1. In figure 1A P CO₂ was raised from levels of 34 to 56 mm Hg with an increase in right putamen flow from 101.9 ml/100 gm per minute to 150 ml/100 gm per minute. Left putamen flow increased similarly from 96.2 ml/100 gm per minute to 138.6 ml/100 gm per minute, and white matter flow increased from 17.3 ml/100 gm per minute to 36.5 ml/100 gm per min. Figure 1B shows a further CO₂ response with cortical, putamen and white matter electrodes recording together. Quantitation of CO₂ responses gave a 2.02% increase over basal flow per mm Hg P CO₂ increase (SD ± 0.8) for 14 putamen electrodes. For the cortical electrodes, the figure was 2.31% (SD ± 1.3), and for the 24 white matter electrodes the figure was somewhat higher, 3.44% (SD ± 1.7). Although the white matter responses appeared somewhat greater, the differences between gray and white matter probably are not significant (p = 0.05); using paired responses the differences were not significant (p > 0.05).

**Autoregulatory responses to alteration in systemic blood pressure**

Progressive exsanguination was performed in five experiments, and satisfactory recordings were obtained in 26 clearances in the cortex, 44 from the putamen, and 63 from white matter. When blood flow was expressed as a percentage of the basal level taken at normal blood pressure (which in the baboons was a mean systemic blood pressure of between 120 and 140 mm Hg) and plotted against the levels of blood pressure during clearance in all three tissues from which recordings were made, the blood flow remained reasonably constant down to levels of between 60 and 70 mm Hg. There was then a definite inflexion in the curves plotted by eye as shown in figure 2, so that the typical autoregulatory response appears to be characteristic of these tissues individually as well as of total CBF. It is noteworthy that zero flows to diminished systemic blood pressure of the levels employed were obtained only in the white matter. Thus, on four occasions zero flow was recorded in white matter at systemic blood pressures between 15 and 30 mm Hg, but on each of these occasions cortex and putamen still showed flow.
of not less than 15% of basal flow, that is, not less than 10 ml/100 gm per minute.

**Autoregulation to Change in Intracranial Pressure**

In four experiments, autoregulation was assessed during the progressive elevation of intracranial pressure by infusion of Ringer's lactate solution cisternally. Fifty-five satisfactory clearances from cortex, 39 from putamen, and 41 from white matter were obtained in this group. The results were expressed by plotting percentages of basal flow at normal intracranial pressure against the absolute intracranial pressure in mm Hg, and again against the perfusion pressure determined by subtraction of the intracranial pressure from the mean systemic pressure.

**Figure 1**

Alteration in hydrogen clearance curves induced by raised arterial P\(_{CO_2}\). The direction of recording is from right to left. \(P_{CO_2}\) inhalation was begun between the records A and B, and continued until the end of the clearance at B.
Autoregulation to reduced systemic blood pressure. The relationship between percentage baseline local blood flow and mean systemic blood pressure in experiments in which the blood pressure was successively lowered by the withdrawal of aliquots of blood is shown for cortex, putamen and white matter. The curves are plotted by eye.

Combined data showing autoregulation to perfusion pressure change

The close similarity between the autoregulatory curves obtained from raised intracranial pressure and diminished systemic blood pressure led us to combine the data, plotting the maintenance of blood flow, again expressed as a percentage of basal flow, at the same time. A portion of the record showing typical data from which such measurements were made is shown in figure 3. Figure 4 shows that reduction of cerebral blood flow begins between 60 and 70 mm Hg intracranial pressure, and once again absolute zero flow was recorded frequently from electrodes in white matter, but from gray matter only rarely, and then only at very high intracranial pressures. Thus, absolute zero flows were seen on two occasions at levels of intracranial pressure as low as 100 mm Hg, but zero flow was not recorded in gray matter (in either putamen or cortex) at intracranial pressures below 150 mm Hg.

Recording of extradural pressure (EDP), systemic blood pressure (SBP), and end-tidal CO₂ (ETCO₂) during elevation of intracranial pressure by cisternal infusion. The stepwise increments were produced by infusion with a constant flow infusion pump. Varying the speed of the pump enabled constant intracranial pressure to be maintained during the determination of blood flow.

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Autoregulation to raised Intracranial Pressure.

Autoregulation of local blood flow to raised intracranial pressure. The percentage baseline local cerebral blood flow is plotted against the intracranial pressure in mm Hg recorded by the extradural transducer, the relationship being determined in cortex, putamen and white matter.

Against perfusion pressure. It is clear, as shown in figure 5, that there is no systematic difference between autoregulatory responses obtained to diminished perfusion pressure from exsanguination (open circles) and those obtained to diminished perfusion pressure from raised intracranial pressure (filled circles). In each instance, the break point occurs around 70 mm Hg in cortex, putamen and white matter. Once more, expression of the data in this way shows that zero flow is obtained in the white matter on occasion with perfusion as high as 40 mm Hg, but much lower levels of perfusion pressure are sustained in gray matter and putamen without the occurrence of zero flow. Only in one instance was zero flow recorded from gray matter at a perfusion pressure of over 20 mm Hg.

The details of two typical experiments involving exsanguination or raised intracranial pressure are shown in figures 6 and 7. Figure 6 displays the increase in local blood flow in cortex, putamen and white matter to a Pco2 change from 43 mm Hg to 78 mm Hg. There is then a period of a steady state followed by exsanguination with progressive reduction in the systemic blood pressure and the perfusion pressure. There is a sudden drop in perfusion values for the three tissues examined as the systemic blood and perfusion pressures reach the region of 65 mm Hg. Following a period of low flow in all tissues and white matter flow reaching almost zero, the restoration of the blood deficit leads to a rapid increase in flow (the phenomenon of reactive hyperemia). Figure 7 shows an almost identical picture where the perfusion pressure has been restricted by increasing the intracranial pressure with cisternal infusion of Ringer's lactate. Once again, the cortex, putamen and white matter perfusion remains steady until the perfusion pressure has fallen to the region of 60 mm Hg when there is a rapid fall. In this instance, the production of an intracranial pressure of over 250 mm Hg has resulted in almost zero flow levels in cortex, putamen and white matter. The release of raised pressure, by allowing drainage from the cisterna, results in extensive hyperemia in all three tissues.
**Physiological Responses of Cerebral Circulation**

Autoregulation of local blood flow in the face of diminished perfusion pressure. In this figure, the percentage of baseline local CBF in cortex, putamen and white matter has been plotted against the perfusion pressure in mm Hg in the experiments of figures 2 and 4 combined. Filled circles represent data from raised ICP, and open circles data from exsanguination.

**Figure 5**

Reactive Hyperemia

When the perfusion pressure was suddenly restored after a period at a low level and induced either by exsanguination or by grossly raising intracranial pressure, a sudden increase in clearance could be detected (the phenomenon of reactive hyperemia), as shown on figures 6 and 7. Eight recordings of hyperemia to lowered perfusion pressure were made, four to change in intracranial pressure, and four to change from induced exsanguination. There was no systematic difference between the level of reactive hyperemia in the two groups, although the numbers are too small to permit statistical analysis. Thus, the summed reactivity in cortical electrodes showed a mean increase of 205% of basal flow from very low levels of blood flow induced by hemorrhage, and of 175% from very low levels of blood flow induced by raising the intracranial pressure. The figures obtained in putamen were a 151% increase over basal flow in hyperemia from hemorrhage, and a 174% increase from hyperemia to raised intracranial pressure. In white matter, a hyperemia of 216% basal flow was seen in the restoration of perfusion pressure after hemorrhage, and a 175% increase in reactive hyperemia following grossly raised intracranial pressure. It seems, therefore, that to a significant degree of ischemia producing either no flow or very reduced flow of less than 20% of basal, reactive hyperemia of 150% to 200% basal flow increase is commonly observed.

**Discussion**

In these experiments, we have attempted to explore the reactivity to CO₂ and the autoregulation of various portions of the cerebral circulation within the cerebral hemisphere. In each instance, dissection of the brain following the experiment has confirmed the position of the electrodes. The flow data obtained are from the area of brain in immediate relation to the electrode placement and represent either deep gray matter, deep white matter or cortex. The findings in relation to CO₂ reactivity proved somewhat surprising. There was no clear evidence.
from our studies that CO₂ reactivity was significantly lower in the white matter, but rather the reverse. It appeared that the absolute levels of blood flow reached in hypercapnia were indeed much lower than those reached in the cortex, yet this represented a relatively greater increase in flow, so that the CO₂ reactivity of white matter vessels was no less and possibly somewhat higher than that in deep gray matter or in cortex, although the difference was scarcely significant. A possible explanation might be that during induced hypercapnia, vessels in gray matter are more capable than those in white matter of withstanding this metabolically and functionally useless stimulus, or perhaps that the inevitable hypertension induced by the levels of CO₂ involved in our present experiments was more readily buffered in gray matter than in white. For reasons not entirely connected with the present experiments, we prefer the latter explanation. Thus, the Queen Square (London, England) blood flow group has found that while CO₂ reactivity bears a linear relationship to conductance (the reciprocal of resistance) in relation to the fast components of ¹³³Xenon clearance, this relationship does not hold good if conductance is related to the slow components of ¹³³Xenon clearance. In other words, when vascular tone is high in the gray matter, CO₂ reactivity is low, but this relationship does not hold good in white
matter. Vasomotor tone as assessed by conductance in white matter has apparently a less definite relationship to CO₂ reactivity. One of the difficulties of two-compartmental analysis of isotope by external collimation in the human, however, is that when CO₂ alters clearance in brain tissue, the increase in flow is associated with an increase in the proportion of the fast-clearing components, suggesting that previously slow-clearing tissue is now being included in the fast-clearing portion, and therefore that CO₂ reactivity of white and gray matter cannot be independently assessed. It seems likely, however, that the slow components remaining on the tail of the xenon clearance curve are related to white matter blood flow, and from these data it also would appear that the modulating effect of conductance or cerebrovascular resistance on CO₂ reactivity is not as effective in white matter as in gray matter.

In the present experiments, the data obtained in relation to autoregulation also would suggest that the
circulation in the white matter possesses a less sensitive and effective regulatory mechanism than that in the gray matter. Thus, in stress of the autoregulatory mechanisms both by reduction of perfusion pressure with exsanguination and by increase of intracranial pressure, zero flow was more readily obtained in white than in gray matter. In our experiments, exsanguination was never pursued to levels in which zero flows were obtained in gray matter, but zero flows were frequently obtained in white matter while gray matter flows of over 10 ml/100 gm per minute remained. With grossly raised intracranial pressure, it was possible ultimately to abolish clearance in both white and gray matter, but invariably white clearance failed first. It seems that the regulatory mechanisms in cortex and deep gray matter are probably more effective than in white matter. It is likely therefore that during CO₂ inhalation, the more actively regulated vessels in gray matter are capable of buffering the induced hypertension and may to some extent reduce reactivity to CO₂ in consequence.

The findings in relation to raised intracranial pressure or to profoundly reduced perfusion pressure from hemorrhage are of significance in relation to some of the curious clinical phenomena associated with markedly reduced perfusion pressure. Thus, some years ago Strich¹⁰,¹¹ pointed out the curious occurrence of massive white matter dissolution in relation to severe head injury, and we have several times observed severely brain-damaged patients in whom the thickness of cortex appeared almost normal, while the white matter was grossly atrophic. If it is indeed the case that the white matter regulation is less efficient than that of gray, this would provide a possible explanation for the occurrence of selective white matter necrosis in states of either prolonged hypotension or severely raised intracranial pressure.

Although autoregulation has been extensively studied,¹²-¹⁶ it is interesting to note that few have attempted to fractionate the autoregulatory response in various portions of the cerebral circulation. Only Bozzao et al.¹⁷ have previously shown that subcortical white matter possesses autoregulatory capacity, although they were unable to demonstrate failure of autoregulation through an inability to lower sufficiently the blood pressure in the cat. Rosendorf¹⁸ demonstrated the autoregulatory capacity of hypothalamic gray matter in his experiments using the technique of locally injected ¹³³Xenon in microliter quantities. From seven experiments Rosendorf concluded that the hypothalamic circulation showed good autoregulation in the 41 to 140 mm Hg range and suggested that the autoregulatory capacity within this gray matter might even be effective to lower levels. The scatter of his data in these experiments was such, however, that differences in flow data at low levels could well have become significant with greater numbers of observations.

A fact of particular interest emerging from the current experiments has been the similarity of the point of inflexion of the autoregulatory curve, whether perfusion pressure has been reduced by hemorrhage or by raised intracranial pressure. Data in relation to raised intracranial pressure tend to be obscured by concomitant changes in systemic arterial pressure in the Cushing response. Only by the use of true perfusion pressure may the identity of the point of inflexion be reserved. It then emerges that in reduction of perfusion pressure by hemorrhage or by raising the intracranial pressure, autoregulation breaks down at a perfusion pressure between 60 and 70 mm Hg. It seems very likely, therefore, that the same mechanism is responsible for the autoregulatory response in both conditions. This mechanism is a probably direct stretch of the muscle cells in the vessel walls, this stretch being mediated by differential pressure across the vessel wall. Compression of the vessel from outside results in a lesser stretch upon the vessel wall, just as does reduction of intraluminal pressure. Both lead to dilatation and the autoregulatory process is set in train. It is not possible to exclude a local reflex, but it seems most likely that this is a direct myogenic response, as suggested by Symon, Held and Dorsch.¹⁹

Observations of hyperemia in the present experiments are among the few where the technique of tissue clearance of a tracer is employed, in which the early phases of hyperemia can be observed. As previously explained, this is possible because of the repeatability of hydrogen clearance and the capacity to detect changes of the slope during clearance, when perfusion conditions are suddenly changed. In the present experiments, the degree of hyperemia to the same stimulus appeared roughly identical in cortex, deep gray and white matter. This would support the view previously put forward²⁰ that the initial phase of hyperemia is dependent more upon the degree of reduction of perfusion pressure at the time of the ischemia insult than upon any metabolic factors resulting from deprivation of tissue blood supply during the period of occlusion. Reduction of perfusion pressure affecting all tissues in the brain roughly equally would result in hyperemia of approximately the same degree immediately following release of such ischemia, and indeed this has been found in the current experiments. This is not to suggest that a later phase of hyperemia more related to metabolic activity may not exist, but the present experiments were not prolonged in an endeavor to detect or fractionate this later phase.

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Our data do not support the suggestion made by Johnston et al.21 that with rising intracranial pressure the Cushing response was always associated with marked hyperemia before the flow finally fell. The Cushing responses evoked by our animals were shortlived, characteristically, a peak in blood pressure associated with a high peak in intracranial pressure, during which the perfusion pressures measured could be observed to be appreciably reduced (table 1). These Cushing responses are superimposed upon a gradually increasing intracranial pressure induced by constant slow-speed infusion. Comparison of the two groups of experiments is difficult, but in our experiments intracranial pressure was raised from control levels of 10 mm Hg or under, which we have found to be normal in a baboon, while in the experiments of Johnston et al. control levels of intracranial pressure varied from 1 to 25 mm Hg (mean 13.6 mm Hg, SD ± 9.3). No less than three of the eight animals in the experiments of Johnston et al. had resting intracranial pressure levels of 20 mm Hg or more, which must be regarded as well above the normal range. It is possible that their technique of controlled infusion maintaining constant intracranial pressure by a reservoir system between steps of pressure increase encouraged the development of hyperemia through maintenance of constant intracranial pressure in the face of the rising arterial pressure of a transient Cushing response. In our experiments, this, of course, would have evoked a transient increase in the intracranial pressure. A rise in perfusion pressure would naturally be associated with an increase in cerebral blood flow if autoregulation were impaired. They further state that there was no clear relationship between perfusion pressure and cerebral blood flow under all circumstances of autoregulation. The data in figure 2 of their paper21 claim to show a random distribution. Recalculation of these data, however, using the method of least squares, shows that the relationship of cerebral blood flow to perfusion pressure at perfusion pressure levels of less than 70 mm Hg is a linear one (slope 0.82798, SD ± 0.1322, C.Y. 16.19, ±6.3, r 0.616, p < 0.001). This indicates that in their experiments there was no autoregulation below a perfusion pressure of 70 mm Hg. Above 70 mm Hg their data show no apparent relationship between perfusion pressure and cerebral blood flow (slope 0.11628, SD ± 0.246, C.Y. 60.5, ± 23.20, r 0.062, not significant). Calculation of the data of Johnston et al. over all ranges of perfusion pressure again shows a linear relationship between cerebral blood flow and perfusion pressure (slope 0.435, SD ± 0.07, C.Y. 30.98, ± 5.19, r 0.502, p < 0.001). It might be concluded, therefore, that there was no autoregulation in any of their experiments, but the comparison of the slope obtained with the entire group of data and that obtained with the data below 70 mm Hg shows a significant difference between the two slopes at just less than the 1% level. Our contention, therefore, is that their experiments suggest autoregulation above a perfusion pressure level of 70 mm Hg, although the data are so scattered that this fact is heavily obscured, and that below this level autoregulation was absent. This interpretation means that their experimental findings are closely comparable with our own.

It is difficult to understand the origin or possible significance of hyperemia occurring in an autoregulating vascular bed in the face of increasing intracranial pressure. Our experience would suggest that vasodilatation under these circumstances would further embarrass the circulation, giving rise as it would to further increased intracranial pressure. It seems more likely that this early hyperemia represents no more than a methodological artifact, and that the relationship between perfusion pressure and cerebral blood flow which holds good when the circulation is stressed by blood withdrawal in an adequate preparation also holds good in a similar preparation if the circulation is stressed by raised intracranial pressure.

TABLE 1
Blood Flow and ICP in Relation to Cushing Responses

<table>
<thead>
<tr>
<th>Basal pressures (mm Hg)</th>
<th>Basal flows (ml/100 gm per minute)</th>
<th>Pressures at peak Cushing response (mm Hg)</th>
<th>Flows at peak Cushing response (ml/100 gm per minute)</th>
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<tr>
<td>Basal pressures (mm Hg)</td>
<td>Basal flows (ml/100 gm per minute)</td>
<td>Perfusion pressures at peak Cushing response (mm Hg)</td>
<td>Perfusion pressures at peak Cushing response (ml/100 gm per minute)</td>
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<tr>
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<td>Perf P</td>
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</table>

Data from experiments in which intracranial pressure was raised by cisternal infusion. In no case was increased perfusion pressure visible at the height of a Cushing response. In no case was hyperemia evident during the phase of increasing intracranial pressure.
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References
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