Influence of Cerebral Vasoconstricting and Vasodilating Agents on Blood Flow in Regions of Focal Ischemia

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Abstract:
Regional cerebral blood flow (rCBF) measurements with krypton-85 (100 separate determinations) were compared in squirrel monkeys anesthetized with sodium pentobarbital (a cerebral vasoconstrictor) and halothane (a cerebral vasodilator) before, during, and after middle cerebral artery (MCA) occlusion. Prior to MCA occlusion, a normal physiological response to alterations in arterial carbon dioxide tensions (Paco2) was demonstrated in both groups of monkeys; the cerebral vascular resistance was significantly lower in those anesthetized with halothane. During ischemia, there was loss of autoregulation and a failure to respond to alterations in Paco2 in both groups. Flow in the ischemic region remained uniform in the barbiturate group but decreased progressively in the halothane group, suggesting a "paradoxical response" to the dilating agent. Reactive hyperemia (luxury perfusion) was demonstrated in both groups after restoration of flow. The use of a beta-emitting isotope ensured that measurements in regions of ischemia accurately reflected rCBF and were free of the artifacts ("look through" and Compton scatter) related to use of a gamma-emitting indicator.

Additional Key Words
"steal" autoregulation halothane
Compton scatter barbiturates "look through"
luxury perfusion

One marked characteristic of the literature dealing with the cerebral circulation is, we think, the contradictory nature of the results which have been obtained by different investigators." This statement by Roy and Sherrington in 1890 is still true. The introduction, by Lassen and Ingvar, of radioactive indicator techniques produced impressive gains in the field and permitted the clinical use of regional cerebral blood flow (rCBF) measurements. The application of these techniques has resulted in general agreement regarding the alterations of flow in normal brain that are produced by changes in systemic variables such as arterial carbon dioxide tension (Paco2). However, there also have been disagreement and confusion regarding the effects of vasoconstrictors and vasodilators in areas of ischemia. This controversy is related, in large measure, to a failure to recognize the limitations of methods that use a gamma-emitting indicator and specifically the artifacts caused by "look through" and Compton scatter.

In a recent review on the control of cerebral circulation, Lassen indicated the necessity of learning about the differences in the responses of normal brain vasculature and ischemic brain vasculature to various drugs, especially the vasoconstrictors and vasodilators. Often, drugs are used in disease states on the basis of information derived from studies in normal animals or normal man. The paradoxical rCBF changes in areas of ischemia that occur with a metabolic acidosis might not be unique to variations in Paco2. For accurate study of the variations of flow in regions of ischemia, it is necessary to use methods of measurement free of the artifacts of "look through" and Compton scatter.

The work described in this paper was undertaken to compare the effects of a vasodilator (halothane) and a vasoconstrictor (sodium pentobarbital) on variations in rCBF in a reliable preparation of focal ischemia by methods that produce accurate data.

Methods
LABORATORY PREPARATION
The surgical technique, method of rCBF measurement, injection of isotope into an isolated right internal carotid artery system, and recording of systemic variables in this laboratory preparation of focal, incomplete ischemia in the squirrel monkey (Saimiri sciureus) have been described in detail. One group of monkeys was anesthetized with sodium pentobarbital (20 mg per kilogram) by intraperitoneal injection and the other group with halothane (about 0.85%) added to the inspired gas mixture. The barbiturate group was a portion of a previous investigation reported from this laboratory.
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In those monkeys anesthetized with halothane, the inspiratory gas content of halothane was continuously monitored with a medical gas analyzer (Beckman LB-2) and maintained at approximately 0.85% by adjustment of the Fluotec vaporizer (overall mean: 0.847 ± 0.004%). In both groups, measurements of rCBF were made from identical right frontoparietal areas, and the protocol for each experiment was identical in the two groups except for the anesthetic used. The volume of injectate for each rCBF determination was 0.1 ml (85Kr, 1,000 ± 250 μCi per milliliter). The beta particle of 85Kr was recorded by an uncollimated, argon-quenched, Geiger-Müller tube with an end-window diameter of 6 mm.

Determinations of rCBF were obtained at 20-minute intervals at various Paco2 values during the 90 minutes prior to occlusion of the right middle cerebral artery (MCA), during 70 minutes of occlusion, and 30 minutes after release of occlusion. Paco2 was varied by altering the concentration of inspired CO2. Pao2 was maintained constant at 100 to 120 torr. Only monkeys that demonstrated normal variations in rCBF in response to changes in Paco2 prior to right MCA occlusion were included in the final analysis of data from the ischemia period (five in the barbiturate group and five in the halothane group; three were excluded).

REGIONAL CBF DETERMINATIONS

Regional CBF was determined by a simplification of the initial slope technique during the experiment and by the kinetic analysis of Zierler (H/A) after the experiment. The former method primarily measures flow in gray matter, whereas the latter also includes the small contribution of beta activity originating from white matter, even when 85Kr is used. The similarity of the changes was excellent between the two techniques (initial slope values were higher than H/A values). Only rCBF values computed by the H/A technique are reported here (± standard error), and the conclusions are based on the data obtained by this analysis, reflecting our confidence in the reliability of this technique. The more complex calculations involved in exponential analysis were not performed for two reasons: (1) rCBF values calculated by the initial slope formula correlate very closely with those values for gray matter flow obtained by exponential analysis (r = 0.98),28,29 and (2) the relative contributions of the two components (gray matter and white matter), derived from exponential analysis, vary as much as 30% during successive injections, despite relatively constant systemic blood pressure and Paco2.

Paco2-CBF RESPONSE CURVE

The physiological response of rCBF to variations in Paco2 was determined with each anesthetic agent before MCA occlusion and the pathophysiological response was obtained during the occlusion. The Paco2-rCBF response curve was plotted for each preparation in both groups of monkeys to ensure that normal physiological responsivity existed in each monkey prior to the onset of ischemia. These curves prior to occlusion (figs. 1 and 2) were created from the mean values of rCBF determinations at Paco2 values of 22, 33, 41, and 60 torr in the barbiturate group and 25, 39, 42, and 60 torr in the halothane group; they represent 20 separate rCBF determinations in each group. Regional CBF values in spontaneously breathing monkeys in either group were not included in the curves. During ischemia, alterations of Paco2,
(40, 24, 57, and 40 torr for the barbiturate group and 40, 24, 61, and 41 for the halothane group) rather than variable levels of anesthesia were used to alter cerebral vascular tone.

Results

STABILITY AND RELIABILITY OF LABORATORY PREPARATION

Throughout the entire procedure, blood loss never exceeded 3 ml and none of the monkeys ever received a transfusion. It was never necessary to supplement the original dose of sodium pentobarbital in the barbiturate group. The halothane concentration, 0.85% in the inspired gas mixture, provided a satisfactory level of anesthesia and only caused a moderate decrease of MABP. Serial hematocrit measurements throughout the experiment demonstrated no hemodilution or evidence of significant loss of blood. Core body temperature was maintained at 36.5°C throughout the experiment by the use of heating blankets.

Monkeys in which a physiological response to alterations of Paco, could not be demonstrated prior to occlusion of the MCA were excluded from the study. The cause of an impaired response to a change in Paco, was not always apparent. In one monkey it was considered to be a secondary effect of the craniectomy without gross evidence of cortical damage; in another, transient hypotension and hypoxia occurred with curarization and institution of mechanical ventilation; and in a third, a minute amount of air entered the injecting system used to deliver the radioactive indicator.

CEREBRAL VASCULAR RESISTANCE

As determined by the ratio, mean arterial blood pressure/cerebral blood flow (MABP/CBF), cerebral vascular resistance was lower in the halothane group than in the barbiturate group. This difference was most apparent during hypocarbia, and it became less marked at higher Paco, (fig. 3).

Comparison of cerebrovascular resistance (ml/100 gm per minute per mm Hg) curves for Na pentobarbital – – – – and halothane o- - - - in normal brain.

Comparison of rCBF, Paco, and MABP before, during, and following MCA occlusion in Na pentobarbital group – – – – and halothane group o- - - -.

OBSERVATIONS DURING ISCHEMIA

During ischemia (fig. 4), rCBF initially decreased to nearly identical levels in both groups (0.487 ± 0.097 ml per gram per minute in the barbiturate group; 0.513 ± 0.081 ml per gram per minute in the halothane group). Concomitant mean Paco, levels also were nearly identical (39.6 ± 1.0 torr in the barbiturate group; 40.5 ± 1.2 torr in the halothane group) at this time, but MABP was higher in the monkeys anesthetized with sodium pentobarbital (113.1 ± 8.4 mm Hg in the barbiturate group; 96.0 ± 4.4 mm Hg in the halothane group).

Later during the period of ischemia rCBF remained constant in the barbiturate group, but in the halothane group there was a progressive deterioration of rCBF throughout the period of ischemia (fig. 4) with no significant decrease in perfusion pressure.

Statistical analysis was by the Student t test. During ischemia with hypocarbia the decrease in rCBF in the halothane group was statistically significant (P < 0.035) compared to the stable rCBF in the barbiturate group. Although the MABP was slightly lower in the halothane group, the change in MABP with hypocarbia was parallel in both groups (fig. 4) and of equal magnitude. Further decrease in rCBF
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during hypercapnia in the two groups was minimal and not statistically significant. However, the decrease in rCBF continued in the halothane group and the final difference in rCBF prior to restitution of flow, when Paco,
and MABP were equal in the two groups, was of borderline statistical significance (P < 0.054).

In the monkeys anesthetized with sodium pentobarbital, examination of individual Paco,-rCBF response curves during ischemia revealed the following: in one monkey there was an increase in rCBF during hypercapnia (0.63 to 0.82 ml per gram per minute; Paco,, 25 to 56 torr; MABP, 107 to 119 mm Hg), and in another there was an increase in rCBF in response to hypocarbia (0.65 to 0.90 ml per gram per minute; Paco,, 36 to 24 torr; MABP, 105 to 99 mm Hg). While the former probably represents simply an increase of rCBF in response to increased cerebral perfusion pressure, the latter is possibly secondary to an “inverse steal” induced in cortical communicating arterioles in response to hypocapnia. In a third monkey, rCBF during ischemia decreased in response to hypercapnia (0.27 to 0.13 ml per gram per minute; Paco,, 24 to 60 torr; MABP, 110 to 112 mm Hg) but failed to increase significantly when normocapnia was restored (0.15 ml per gram per minute; Paco,, 37 torr; MABP, 97 mm Hg). In the remaining two monkeys, rCBF remained relatively constant throughout the period of ischemia despite significant changes in Paco,.

In the halothane group there was a variable response to alterations in Paco, during the period of ischemia. In four monkeys, rCBF deteriorated progressively throughout the period of ischemia, and an increase of rCBF during the period of ischemia was observed only twice (0.29 to 0.40 ml per gram per minute; Paco,, 63 to 40 torr; MABP, 89 to 112 mm Hg; and 0.36 to 0.44 ml per gram per minute; Paco,, 26 to 60 torr; MABP, 89 to 105 mm Hg). Thus, the increased rCBF measured in these animals is correlated with increased MABP, not with alterations of Paco,. One monkey showed definite evidence of an intracerebral steal in response to hypercapnia (0.60 to 0.42 to 0.50 ml per gram per minute; Paco,, 23 to 62 to 42 torr; MABP, 77 to 100 to 107 mm Hg). Of specific interest is the fact that, during ischemia, rCBF failed to increase when Paco, was increased and there was concomitant secondary increase of MABP (0.37 ± 0.06 to 0.33 ± 0.06 ml per gram per minute; Paco,, 23.8 ± 0.8 to 61.1 ± 0.6 torr; MABP, 83.0 ± 2.3 to 96.2 ± 3.1 mm Hg) (see Discussion).

With restitution of flow, there was a dramatic increase in mean rCBF in both groups (0.51 ± 0.12 to 1.33 ± 0.36 ml per gram per minute in the barbiturate group; 0.30 ± 0.07 to 1.47 ± 0.24 ml per gram per minute in the halothane group). Reactive hyperemia (defined as a postocclusion rCBF 15% greater than the preocclusion rCBF at approximately the same Paco,) was found in four of the five monkeys anesthetized with halothane. Three of the five animals anesthetized with sodium pentobarbital exhibited this phenomenon.

Discussion

METHODOLOGY

In the present study, 85Kr was used as the isotope indicator for measurement of rCBF. The Geiger-Müller probe recorded beta particles originating from very superficial layers of the brain and did not detect significant activity from a depth greater than 2.5 mm. This is consistent with the characteristics of the indicator and is accepted for most workers in the field. Consequently, rCBF within the area of focal, incomplete ischemia is accurately measured and the errors of “look through” and Compton scatter are eliminated. The significance and magnitude of these errors have been documented in previous studies and may explain, in part, reports of increased rCBF within areas of incomplete, focal cerebral ischemia in response to increasing concentrations of halothane or hypercarbia.

Paco,-rCBF RESPONSE CURVES

The physiological integrity of each experimental preparation was validated by the Paco,-rCBF response prior to occlusion of the MCA. Animals not demonstrating this response were excluded from the study. This ensured that the experiments were performed on reliable laboratory preparations. The importance of such precautions in both laboratory and clinical studies has been stressed by numerous investigators.

PERFUSION PRESSURE

The MABP in both groups (fig. 4) had individual variations but followed an expected integrated vascular response to alterations in Paco, throughout the entire experiment. Hypotension was not present in any monkey accepted for analysis. The period of ischemia was not prolonged to the time after occlusion at which cerebral edema interferes with superficial collateral circulation. In this preparation, such interference occurs after one hour of ischemia and results from compression of the epicerebral anastomotic channels at the margins of the craniectomy.

CEREBRAL VASCULAR RESISTANCE

The modest differences in MABP during the control periods in the two groups were consistent with known properties of the anesthetic agents. The monkeys accepted for evaluation during the ischemic period exhibited the expected responses to alterations in Paco, during the control period. The cerebrovascular resistance during the control period (fig. 3) showed a marked difference in the vasoactive effects of the two drugs. These curves demonstrated the known cerebral vasodilator action of halothane.
RCBF DURING ISCHEMIA

Prior to the onset of ischemia, rCBF was comparable in the two groups despite the slightly lower MABP in the monkeys anesthetized with halothane. After MCA occlusion, rCBF initially decreased 65% in the barbiturate group and 57% in the halothane group. Throughout this interval, PaCO₂ and MABP remained relatively stable and this decrease in rCBF is attributed to MCA occlusion. Over the ensuing period of ischemia, however, rCBF continued to decrease in the halothane group and at the end of the period of occlusion, when systemic variables were the same as immediately after MCA occlusion, rCBF was only 59% of the immediate postocclusion value. This suggests a “steal” analogous to that produced by hypercapnia. In contrast, during the entire period of ischemia in the barbiturate group, rCBF remained essentially unchanged. In both groups, PaCO₂ changed over the same range.

The findings in the present study differ from those of Smith et al. concerning the effects of halothane on rCBF in regions of focal ischemia, and it is necessary to consider the possible causes of the discrepant results. Infarcts from MCA occlusion vary in size in different species and are less uniform and predictable in subprimates. It therefore is probable that the degree of ischemia in their preparation was less severe than that in our study. In less severe degrees of ischemia with marginal autoregulation, some reactivity to variations in PaCO₂ may be preserved. However, it was reported by Smith et al. that both increasing the concentration of halothane and hypercapnia caused an increase of rCBF of the same proportion in both normal and ischemic regions. This is improbable even with preservation of marginal autoregulation and is most unlikely in core areas of ischemia with a severe lactic acidosis and vasoparalysis. Rather, it would seem that the variation in results can be explained by differences in methods used for the determination of rCBF.

In the study by Smith et al., 133Xe was used as the indicator, and this is of questionable reliability because of “look through” and Compton scatter, the subject of recent reports from this laboratory. “Look through” occurs due to the impairment of delivery of isotope to the area of focal cerebral ischemia. Because of the linear absorption coefficient of the gamma photon radiation emitted from 133Xe, activity from tissue within the field of view of the NaI scintillation detector but outside the area of focal ischemia is recorded. Furthermore, because of Compton scatter, activity originating outside the theoretical field of view of the NaI scintillation probe also may be detected. This extraneous activity arises from tissue adjacent to the focal area of ischemia and may originate from areas of perifocal hyperemia. With a lower level discriminator at 75 keV, Compton scatter activity may be decreased to 12.5% but, if no discriminator is used, it may account for 35% to 55% of the total activity detected by the scintillation detector.

In the report by Smith et al., only the collimated diameter (18 mm) of their NaI scintillation detector was reported; no data were given regarding the isoresponse characteristics of the detectors used. It was stated that the discriminators were set to count the 81 keV peak of 133Xe but it was not specified if the discriminator was operating in the integral mode or whether or not a window discrimination was used in the counting of the activity detected by the probes. Therefore, it is possible that the measured increases of rCBF occurred outside the areas of focal cerebral ischemia in response to increasing concentrations of halothane or to hypercapnia. Comparison of flow data from the intact side and occluded side reveals comparatively modest differences and suggests an artifact related to “look through.” We suggest that the changes in rCBF following an alteration in PaCO₂ or anesthetic concentration actually occurred in adjacent vasoactive areas and, because of the lack of spatial resolution inherent in the technique, were interpreted as arising from the region of ischemia.

The hypotensive effects of halothane concentrations greater than 1% in the squirrel monkey model prevented evaluation of the influence of increased halothane concentrations per se before and during ischemia in our study. However, the effect of cerebral vasoconstriction and vasodilatation due to hypocapnia and hypercapnia could be assessed, and in neither group was there a significant change. The slight decrease in MABP that usually occurred with hypocapnia may have masked a “reverse steal,” but a beneficial effect from hypercapnia was excluded. These results agree with Symon and associates' careful work using hydrogen clearance to determine rCBF in a similar preparation. They are consistent with a lactic acidosis, vasoparalysis, and pressure-dependent flow in regions of focal ischemia.

CLINICAL IMPLICATIONS

Halothane Anesthesia

Halothane is a well-accepted and reliable general anesthetic agent widely used for neuroanesthesia. Its popularity has been based, in part, on its known vasodilating properties. In regions of ischemia less intense than produced in the laboratory preparation in this study, it is possible that some of these properties are preserved. However, it is clear that the combination of halothane and hypercapnia cannot be relied on to increase flow to regions of severe ischemia and may produce a “steal.” This is consistent with Boysen's excellent monograph on this subject and Lassen's recent review. One therefore must question the advisability of using a combination of halothane anesthesia and hypercapnia for carotid endarterectomy in an effort to exclude the need for a shunt.

We routinely use halothane anesthesia for carotid
endarterectomy at this institution. All patients are monitored with continuous electroencephalograms and rCBF measurements (133Xe) before, during, and after carotid occlusion. The critical blood flow, defined as that flow required to sustain a normal electroencephalographic pattern, has been found to be 18 ml/100 gm per minute under these conditions. It should be noted that these measurements are uniquely free of "look through" and Compton scatter artifact because the indicator is delivered to the area predestined for ischemia and only after counts are recorded is the internal carotid artery occluded. Routinely, during the period of occlusion the MABP is supported to 150/80 mm Hg with a phenylephrine drip. An internal shunt usually is used whenever rCBF decreases below 25 to 30 ml/100 gm per minute and always is used when there is a change in the electroencephalogram or when rCBF is less than 18 ml/100 gm per minute.

Hypercapnia has not been intentionally used in these patients, and on occasion we have encountered a "steal" when the Paco, has increased above the desired levels. This also has been reported by others. Barbiturate Anesthesia

A recent study by Smith et al. indicated a potential protective effect from barbiturate anesthesia in regions of focal cerebral ischemia, and current studies (Michenfelder, Milde and Sundt, unpublished data) at this institution apparently support this investigation. If a protective effect from barbiturates can be substantiated, it would appear from the results of our study that these would be on the basis of a direct metabolic protective effect from barbiturate anesthesia in ischemic regions of the brain. Communication Research 25:77-93, 1969

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