Effects of Changes in Carbon Dioxide Pressure and Arterial Pressure on Blood Flow in Ischemic Regions of the Brain in Dogs

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ABSTRACT

The effect of locally induced cerebral ischemia on regional cerebral blood flow before and during elevation of Paco$_2$ was measured qualitatively in anesthetized dogs by a thermistor probe technique and a photographic method involving cerebral angiography. The flow response to changes in systemic arterial pressure was also noted in the ischemic zone. Increased Paco$_2$ resulted in increased flow to the ischemic zone and shrinkage of the area of ischemia, by virtue of collateral circulation from other arterial trunks. In no instance was "intracerebral steal," as previously reported, noted in response to increased Paco$_2$, though there was no means of determining if the quantitative response in the ischemic area was similar to that in normal brain. Arteries and arterioles in the ischemic zone were seen to be constricted and irregular, rather than maximally dilated, as has been proposed. The percent decrease in pressure in the occluded arterial segment was much greater than in the patent cerebral arteries. Response to increased Paco$_2$ occurred even though intraarterial pressures were less than 40 mm Hg. There was preservation of the response to norepinephrine in the ischemic zone, despite reduction in flow; response to changes in Paco$_2$ persisted even after this had been lost.

ADDITIONAL KEY WORDS intracerebral steal syndrome vasomotor paralysis collateral circulation tissue metabolites cerebral vasodilatation luxury perfusion syndrome heated thermistor transducer infrared absorption angiography

The variability and fluctuation of clinical symptoms in patients with occlusive cerebral vascular disease are thought to be related primarily to the extent of compensatory blood flow from the vascular beds surrounding the ischemic area, which eventually determines whether ischemia will be followed by infarction or recovery. It would, therefore, appear reasonable that cerebral vasodilating agents would diminish the area of ischemia by promoting collateral circulation, and this assumption has been the basis for a number of clinical therapeutic efforts (1-7). The lack of conclusive results from these studies is partially due to lack of appropriate controls and to the intrinsic variability of the disease process. The physiologic events occurring in ischemic tissue have not been extensively measured, but occlusion of a major cortical artery has been shown to be followed by decreased flow in the ischemic area by several observers (8-10). Meyer and Denny-Brown (8) showed that the decrease in tissue flow was associated with high Pco$_2$, low pH, and low Po$_2$ in the brain parenchyma, factors which should promote more profound local vasodilatation than could be produced by systemic administration of vasodilating agents. Despite conditions presumed ideal for local vasodilatation, observation of ischemic brain tissue has revealed a great variability in the caliber of the vessels, with vascular spasm often being noted (11-13).
The concept of "intracerebral steal" of blood flow from an ischemic to an intact area of the brain during increase of systemic PaCO₂ was suggested independently by Brawley (10) and Hoedt-Rasmussen et al. (14) in 1967. Brawley's experimentally produced ischemia in dogs was accompanied by decreased tissue flow. In Hoedt-Rasmussen's study of patients with acute apoplexy, there was increased regional flow adjacent to the presumed area of ischemia; local ischemia was thought to have produced "luxury perfusion" of the brain tissue due to local tissue acidosis with resultant vasomotor paralysis. Both groups of workers concluded that vasomotor paralysis was the result of ischemia and that blood was then "stolen" by the more reactive neighboring cerebral vessels following increase in PaCO₂, although in one instance the vasomotor paralysis was accompanied by low flow and in the other by abnormally high flow.

This study was designed to help clarify some of the hemodynamic responses which occur in local cerebral ischemia by measuring the changes in local cerebral thermal conductance and intraarterial pressure following changes in systemic PaCO₂ and systemic arterial pressure in areas of experimentally produced ischemia in brains of dogs. Qualitative changes in local cerebral blood flow were deduced from the thermal conductance traces.

**Method**

Fourteen healthy mature mongrel dogs weighing 15 to 25 kg were studied. They were anesthetized with sodium pentobarbital, 25 to 30 mg per kg iv. Subsequent anesthesia was maintained with additional doses of sodium pentobarbital as required. The trachea was intubated and the dogs were artificially ventilated by a Harvard 607 respiratory pump to control PaCO₂ after paralysis of the animal by intravenous administration of 2 mg/kg of gallamine triethiodide. A wide bilateral craniotomy was performed after resection of the zygomatic arches and portions of the mandibles. The dura was reflected and the pyriform lobe lifted up to expose the main trunk of each middle cerebral artery. Doubled 5-0 arterial silk suture was passed under the middle cerebral artery of one side as near as possible to its origin with the aid of a Zeiss operating microscope. One of the small distal branches of the middle cerebral artery was cannulated in the upstream direction by sharpened PE-10 polyethylene tubing, and the tubing was connected to a Sanborn physiological pressure transducer (model 267A). This system was filled with heparinized saline to prevent blood coagulation. A similar tube was placed in a branch of a cerebral artery, usually the middle cerebral, on the opposite side; it did not occlude the artery and was used to measure pressure in a non-occluded cerebral artery. A cannula was placed in the common carotid artery (through the stump of the superior thyroid branch) in animals used for the photo-angiographic procedure.

Physiological saline or Ringer's solution was given intravenously to prevent dehydration during this procedure. The animal was covered with a canvas sheet and an electric heating lamp was used to keep rectal temperature above 35°C.

A heated thermistor flow transducer was applied gently to the surface of the exposed gyrus where preliminary angiographic studies located the center of the ischemic zone. The exposed surface of the brain was covered with very light wet cotton at body temperature and mantled by piled gauzes. The temperature of the brain surface was maintained at 34 to 35°C and monitored constantly by a Telethermometer (Yellow Springs Instrument Co., Inc.). Arterial PaCO₂, PaO₂, and pH were measured by a pH/gas analyzer model 113 (Instrumentation Laboratory). The percent of expired CO₂ was monitored continuously by a Beckman medical gas analyzer, Model LB-1. The electrocardiogram and bilateral electroencephalograms were constantly monitored.

The heated thermistor flow transducer contains a thin foil heater element supplied with a constant power of about 50 mw in the bevel of a 23-gauge needle. Some few thousandths of an inch behind the heater is a thermistor whose resistance reflects heater temperature. To compensate for environmental temperature and its changes, a second thermistor with only a 5 mm is placed in close proximity to the heater (High Temperature Instrument Corp.). Heater temperature variations are determined by measuring the heater resistance changes using a Wheatstone bridge circuit. In the bridge circuit there is a fixed resistor, a variable resistor for balancing, the heater thermistor, and the compensation thermistor. Very low power (about 10⁻⁶w) is applied to the bridge to avoid heating of the thermistors with the measuring circuit. The voltage due to temperature change is amplified, displayed on a panel meter, and connected to a Sanborn 560 panel meter.
series 8 channel oscillographic recorder, which was also used to record the other pertinent biological data.

Angiography was used to confirm the production and location of brain ischemia and to corroborate the data obtained by the flow transducer. For fluorescein angiography a technique originally described by Feindel et al. (15) was used with minor modification. Five milliliters of 2% fluorescein sodium solution was injected into the common carotid artery as rapidly as possible, and serial photographs were taken at the rate of 3/sec.

Infrared absorption angiography has been previously described in detail (16). A bolus of 1.5 ml of 1% indocyanine green was injected manually in about 2 seconds in the common carotid artery, and serial photographs were taken on infrared color film (Kodak Ektachrome Infrared-Aero). Since the dye is rapidly cleared by the liver, studies could be repeated frequently in the same animal.

After the animal had been prepared, cerebral vascular reactivity was tested by having the animal breathe a gas mixture of 5% CO₂ in air. The experiment was continued only if blood flow was increased as indicated by the thermistor flow transducer. The middle cerebral artery of one side was then ligated as close as possible to its origin without excessive surgical manipulation of the pyriform lobe. Pressure was measured distal to the ligature (pressure in occluded cerebral artery). After stabilization of regional flow and cortical arterial pressure, the effect on each animal using the 5% CO₂ and air mixture. Cortical flow in the ischemic area was also monitored after elevation of systemic arterial pressure by appropriate quantities of l-norepinephrine (17).

Results

Following ligation of the middle cerebral artery, the mean arterial pressure beyond the ligature dropped from an average value of 77 mm Hg to 32 mm Hg and gradually increased to an average value of 35 mm Hg within 10 minutes. The ligation did not alter the systemic pressure nor pressure in a nonobstructed cortical artery. Regional blood flow in the ischemic area was reduced promptly, requiring about 10 minutes to achieve a steady state. The pulsations of large pial arteries disappeared in the ischemic segment, and the large cortical arteries collapsed transiently, to be followed by rapid resumption of flow through the collateral arterial network. Cortical pallor appeared immediately after ligation but dis-
Experimental response in a typical animal. Trace 1 is response of the CO₂ analyzer in the outflow respiratory path (% scale). Trace 2 is the systemic (femoral) arterial pressure. Trace 3 is pressure in a nonoccluded cerebral artery; note absence of pressure pulsations during CO₂ inhalation. Trace 4 is the heat conductance, which varies directly with the regional cerebral blood flow. The magnitude of the change shown here is much less than the response to CO₂ in a nonischemic area but much greater than any spontaneous transient variations in the control period and, as shown here, clearly stimulus related. Trace 5 is the pressure in the occluded cerebral artery supplied only by collaterals. Traces 6 and 7 are the bifrontal leads of the EEG and ECG, respectively. The left panel was taken during inhalation of air, the middle panel, 5 minutes after inhalation of 5% CO₂ in air had been started, and the right panel, 10 minutes after inhalation of CO₂ had been discontinued. Straight lines mark omitted intervals of traces to maintain identity from panel to panel.

Repeatedly in the ischemic zone in early stages of the experiment. Inspection of Figure 4 shows that both regional cortical blood flow and systemic arterial pressure increased for 10 seconds, following which flow returned to normal although arterial pressure remained at its highest level. Although the cortical vessels in the area of measurement could have undergone some constriction during the initial rise in pressure, it was not sufficient to prevent the demonstrated increase in flow. The later fall in flow while systemic and occluded arterial pressure remained high suggest a mechanism of action slower than that associated with a direct norepinephrine effect. This suggests to us that the cortical vascular bed did not participate equally in the systemic vasoconstriction of norepinephrine-induced hypertension and that this increased flow was an initial passive response to systemic hypertension. The subsequent return of cortical blood flow to normal denotes that the vessels in the ischemic area retained their capacity to constrict. There is no way to be certain whether this was a delayed effect of norepinephrine on the vessels themselves, or whether it is a manifestation of intrinsic autoregulation to a pressure change. There are valid objections to utilizing vasoconstrictor drugs as a model for demonstrating autoregulation; yet
FIGURE 2

Angiographic demonstration with indocyanin green of the response of the cortical arteries to hypercapnia after ligation of the middle cerebral artery trunks. These are single, identically timed views selected from a series of 20 exposures taken 3/sec. Each was taken 3 seconds after the dye injection (the time of maximal filling for the ligated preparation in dogs breathing air). A. Control state, before arterial ligation, during air inhalation. B. After arterial ligation there is poor or no filling of the cortical vessels with the dye. C. The same cortical area after arterial ligation, but during hypercapnia. The dye now fills many vessels not filled in B, denoting the capacity of the ischemic area to increase its blood flow in response to hypercapnia.

FIGURE 3

Fluorescein angiography. Left: area of ischemia 3 seconds after fluorescein injection, with the animal breathing air. A considerable portion of the ectolateral gyrus is not stained with the dye. Right: the same area 3 seconds after fluorescein injection, during hypercapnia. The increased filling of vessels in the ectolateral gyrus is obvious. Sequential films not shown here established that this increase in vascular bed was accompanied by a more rapid circulation time. There was no significant change in blood pressure.

we feel that the data in these animals, as exemplified by Figure 4, clearly demonstrate that the reaction of the cerebral vessels was different from those of systemic vessels.

As shown in Figure 5, the capacity of the cortical vessels in the ischemic zone to constrict following norepinephrine-induced hypertension was lost toward the end of the experiment. There was no observable difference in the cerebral vessels at that time, and flow in the ischemic zone usually increased in response to increased systemic PaCO₂.

Discussion

Vasomotor paralysis in the ischemic zone is presumed to be the mechanism responsible for
Response to norepinephrine, 12 μg iv, given at the time shown by the arrow. The entire time span is 48 seconds. See text for explanation. The regional cerebral blood flow was measured in the area perfused by pressure from the occluded artery. This result was obtained within 1 hour of ligation of the middle cerebral artery.

After 4 hours of occlusion of middle cerebral artery, regional cerebral blood flow follows the systemic blood pressure; there is no vasoconstrictive response to norepinephrine in the ischemic area.

“intracerebral steal.” An increase in systemic PaCO₂ would theoretically have no effect on vessels already maximally dilated by ischemia, and flow might be diverted into the nonischemic zone where vascular resistance had been reduced by CO₂ effect. The pressure beyond the occluded artery is certainly reduced to a level consistent with loss of responsiveness to CO₂ as shown by Harper and Glass (18). It is important to recall that these experiments involved reduction of systemic arterial pressure, which may well...
produce a different physiologic state in relation to vascular responsivity to CO₂ than local or segmental reduction of arterial pressure. It is obviously difficult to draw conclusions about flow from pressure changes. In this study the percent reduction in mean pressure (16%) in the artery beyond the occlusion was greater than in the nonoccluded cerebral artery (7%); yet both are reduced following CO₂. It is obviously incorrect, therefore, to infer a reduction in flow from a reduction in pressure, for in the nonoccluded artery flow was presumably increased by the CO₂, and the decrease in pressure represented a decrease in vascular resistance. One could reason that the enormous pressure difference between the intact and occluded cortical arterioles would always favor flow in the direction of lower pressure, so that the greater percent reduction in vascular resistance in the ischemic zone would encourage flow toward that region by way of the collaterals. There is clear evidence, as previously mentioned, that the state of the vessels in an ischemic zone is variable and that arterial spasm and collapse of vessels may be present, so that the assumption of maximal dilatation of these vessels cannot appropriately be made. Our own observations confirmed the narrowing of arteries in the ischemic zone, and there is no doubt that these vessels responded by some mechanism to increased Paco₂ in these experiments and not only improved the flow but also shrank the area of the ischemia. This is in agreement with a recent study of Meyer et al. (19).

The observation that the vessels in the ischemic area can constrict during the early part of the experiment is of interest, for it is contrary to many previous observations (20-26). It clearly establishes the principle that valid observations on cerebral circulatory physiology can be made in such experimental conditions if the tissues are carefully handled. Inspection of Figure 4 shows that the secondary vasoconstrictive response in the ischemic area following increase in systemic arterial pressure must have been mediated by vessels from the collateral circulation, since the pressure changes in the occluded arterial segment were insignificant. These data are quite different from those of Brawley et al. (10), for they reported that systemic pressor agents consistently increased both flow and pressure in the ischemic segment. Hoedt-Rasmussen et al. (14) mentioned the intracerebral steal syndrome in the context of a study which included studies of regional cerebral blood flow in six patients in the acute stage of "apoplexy," using the ¹³³Xe clearance method. They found that local hyperemia was present in four patients and that regional cerebral blood flow did not increase following CO₂ inhalation, but there was no reduction of regional cerebral blood flow under those circumstances. Vasoconstriction induced by l-norepinephrine was lost in the region of the injured cerebrum. There would be less reason to anticipate increased cerebral blood flow following CO₂ administration in a region where local flow was already increased by local acidosis causing the luxury perfusion syndrome than in an area of ischemia in which flow was reduced.

In our experiments, cerebral vascular reaction to changes in Paco₂ usually persisted even after the vasoconstrictive response following norepinephrine had been lost late in the experiment. A similar dissociation was noted by Fieschi (27). This finding suggests a difference in the physiologic mechanisms responsible for regulation of vascular tone.

The difficulties involved in quantifying local cerebral ischemia, whether experimentally induced in animals by arterial occlusion or the result of cerebral vascular disease in humans, pose problems for one who would transfer laboratory data to the bedside. One cannot infer from these data that administration of CO₂ by inhalation to unanesthetized patients with cerebral infarction and adjacent ischemia would necessarily improve circulation in the ischemic zone or enhance collateral circulation. It is probable that different responses to CO₂ would occur, depending upon the size of the infarct, the availability of collateral circulation, the location of the vascular occlusion, its duration, chemical substances

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released from emboli or thrombi, and various other unpredictable factors.

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References


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