Cortical Ischemia: Effect Upon Direct Cortical Response

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SUMMARY Correlation of cortical blood flow as measured by a thermal diffusion flow probe (CBFp) with the direct cortical response (DCR) was studied in 48 lightly anesthetized cats with global ischemia. Thresholds for attenuation and loss of DCR were 21.3 ± 4.7 and 8.7 ± 3.4 ml/100 g/min respectively.

In abrupt ischemia, CBFp of 0–3 ml/100 g/min produced absence of DCR in 6 min or less; however, at CBFp of 5–10 ml/100 g/min, the time to obliteration of DCR varied from 5 to 180 min. DCR was unlikely to recover after 13 min of 0–2 ml/100 g/min and after 35 min of 4–5 ml/100 g/min. At higher flows, DCR could recover after 60 min or more of ischemia.

With gradual production of ischemia, flows less than 20 ml/100 g/min for over 60 min had a detrimental effect upon recovery of DCR if DCR was lost for 7.5 min or more. Some evidence that implied adaptability of the cortex to ischemia was found.

How low and for how long can cortical blood flow be reduced and still get return of function?

Cerebral blood flow is linked to neuronal function. With reduction of flow to ischemic levels, electrical activity of the cortex as evaluated by EEG² and evoked potentials³ is lost. Astrup, Symon, Branston, and Lassey demonstrated that K⁺ eflux from the cells was at a lower level of flow, thus demonstrating that a margin does exist when electrical function is altered before cell damage occurs.

The actual time limits for the reversibility of the effects of cerebral ischemia has remained in question. Hossman and Kleihues found that in animals anesthetized with barbiturates, some return in electrical activity could be obtained after one hour of total ischemia. More recently Jones et al., in awake primates, have demonstrated that severe ischemia (10–12 ml/100 g/min) for 2 to 5 hours caused infarction, but 15 to 30 min of ischemia could be tolerated without infarction. However, Traupe, Hess, and Umbach demonstrated no recovery of a single neuron after 13 minutes of flow reduction below 8 ml/100 g/min. In a preliminary study, we did not find return of cortical function as evaluated by the direct cortical response (DCR) when cortical blood flow as determined by a thermal flow probe (CBFp) was < 1 ml/100 g/min for 13 min or 5–8 ml/100 g/min for > 20 minutes.

The reasons for this disparity is probably related to heterogeneity of flow in both geographic and temporal parameters. Additionally, as pointed out by Mitchem et al., the hydrogen clearance technique for measuring cerebral blood flow is insensitive below about 8 ml/100 g/min since intercompartmental diffusion occurs at these levels.

Collateral circulation with focal ischemia models is so variable that it is impossible to assess how long and how low flow is reduced in a given area unless continuous recording of blood flow is done. White and Atkinson monitored CBFp while occluding the MCA of the cat and found a marked temporal variation of flow. The occlusion of the middle cerebral artery of subhuman primates produces a variable degree of cerebral ischemia. Techniques such as somatosensory evoked response recording depend on the integrity of other structures whose blood flows are not known. Pathological changes only demonstrate the end stage of the infarcted tissue.

Our experimental model was designed to study the blood flow and physiological function of an isolated segment of cortex. The cortex is highly sensitive to ischemia and is of paramount importance to the functional human brain. We measured cerebral ischemia with a thermal diffusion flow probe (CBFp) and determined the electrical responsiveness of the cortex by direct cortical response (DCR). A global ischemia model was used to reduce artifact created by collateral circulation.

Methods

Forty-eight mongrel cats of either sex weighing 2.5 to 4.5 kg were studied. All cats had halothane (1-2%) and nitrous oxide anesthesia. The right femoral vein and artery were cannulated for administration of fluids and medications, and for measurement of systemic arterial blood pressure. The animals were then intubated, paralyzed with pancuronium bromide (0.2 mg/kg) and placed on a Harvard respirator (Model 607). Body temperature was kept between 36.5°C and 38.0°C by heating pads and lamps. The left subclavian and the innominate arteries were dissected in the thorax for the induction of ischemia. The animals were then placed in the prone position and a right parietal craniectomy (2 cm in diameter) was performed. After dural incision, a previously calibrated thermal diffusion flow probe was placed on the cortex and CBFp was continuously measured. This method has been fully described by Carter et al.,

Three platinum electrodes attached to a thin, flexible silastic leaflet were employed for the measurement of DCR. The distance between the two stimulus electrodes was 1.0 mm, and that between the stimulus electrodes and the recording electrode was 5.0 mm. The silastic leaflet containing the three electrodes was inserted between the dura mater and the cortex under the skull. The leaflet was adjusted so that all three...
electrodes made contact with the same gyrus (suprasylvian gyrus). A reference electrode was attached to the right temporal muscle and a ground electrode was connected to the operating table. Stimuli of 50 μsec were given at frequencies ranging from 1 per sec and 1 per 5 sec. The stimulus intensity was set 2–3 times greater than that which produced threshold responses. This intensity was considered to be over the minimal current necessary to create a maximum initial negative response. In most cases, stimulus intensities ranged from 1.0 to 4.0 mA. The amplitudes of initial negative response of the DCR were between 0.8 and 1.0 mV. The responses were fed into a Tektronix Model 3A3 Differential Amplifier, displayed on an oscilloscope (Tektronix Type RM 564) and photographed with a Tektronix C-27 oscilloscope camera.

Arterial blood gas studies were periodically obtained. In all cases, PCO₂ was adjusted between 20 and 40 mm Hg and PO₂ was controlled within the range of 90–150 mm Hg, preceding the ischemic insult. The ischemic insult was produced by clamping the left subclavian and the innominate arteries in the chest. In cases where the CBFp was not reduced sufficiently enough to cause ischemia after clamping, the concentration of halothane was gradually increased up to 2.5% to reduce the systemic blood pressure.

The clamps were released after 5 min in 6 cases, 7.5 min in 4, 10 min in 11, 15 min in 12, and 20 min in 12 cases of complete loss of DCR. The clamps were released in 3 cases before the DCR was completely abolished.

Each animal was observed for six hours following the ischemic insult for the evaluation of recovery of DCR, as well as for changes of CBFp and for brain edema. The recovery of the DCR was evaluated by the recovery of DCR amplitude after six hours following restoration of blood flow, and divided into three grades. In complete recovery cases, the DCR amplitude recovered to 90% or more of preischemic levels, in moderate recovery cases it recovered to 50-89% of preischemic levels, and the DCR recovered less than 50% of preischemic levels in poor recovery cases. Brain edema was said to be present if edema was of such magnitude that herniation of the cortex occurred through the craniotomy. At the end of each experiment the cats were sacrificed by an intravenous injection of saturated potassium chloride to determine the zero flow value for the thermal diffusion probe. Only cases that had initial CBFp over 30 ml/100 g/min and could be adequately studied for the full six hours were evaluated.

**Results**

CBFp tracings, following occlusion of the left subclavian and innominate arteries, were of two types as shown in figure 1. In Type I, CBFp recovered after a precipitous drop immediately following application of the clamps, and then decreased gradually. There was little or no recovery of CBFp after clamping in Type II. Type I could be converted to Type II by occluding the costocervical trunk and the internal mammary artery, thus obliterating some collateral circulation. In Type IA, the CBFp recovery after clamping surpassed 20 ml/100 g/min, and then gradually decreased. The recovery of CBFp after clamping in Type IB was 13–20 ml/100 g/min. The recovery of CBFp was to less than 13 ml/100 g/min in Type IC.

**Thresholds**

Occasionally, following clamping, the amplitude of the DCR increased briefly and then decayed (fig. 2). In most cases, due to abrupt changes in CBFp after clamping, thresholds for attenuation and abolition of DCR were difficult to determine. In Type IA, however, CBFp gradually decreased from over 20 ml/100 g/min. Ten of eighteen cats in this group with gradual loss of CBFp and DCR could be evaluated. The threshold for attenuation of DCR was 21.3 ± 4.7 ml/100 g/min. Figure 3 compares this threshold with preischemic CBFp and time from occlusion. It appears that the initial CBFp and the time to attenuation has no effect on the attenuation threshold. Since the initial CBFp was quite variable, depending upon cortical activation, it is more accurate to describe an absolute CBFp value of threshold than as a percentage of preischemic flow.

Although some variability existed, there were no
cases in which the DCR was abolished with CBFp over 13 ml/100 g/min. The threshold for loss of DCR was best evaluated from the Type IA and IB groups. An ischemic insult of over 40 min had a lower level for loss of DCR than shorter insults. If we consider ischemic insults of less than 40 min, then 16 cases in groups IA and IB had a mean threshold for loss of DCR of 8.7 ± 3.4 cc/100 g/min and a median of 10 cc/100 g/min. In Type II, as shown in figure 4, it was observed that at CBFp of 3 ml/100 g/min or less DCR was abolished within 6 min, and that from 5–10 ml/100 g/min loss of DCR varied from 5 to 180 minutes.

Recovery From the Ischemic Insult

Recovery from the ischemic insult may be affected by preceding ischemia or edema, in addition to the actual ischemic insult. In order to evaluate the actual ischemic insult in a relatively pure form, Type IC and II cases were analyzed. All cases without preceding ischemia in which the highest CBFp during occlusion was less than 10 ml/100 g/min are shown in figure 5. At very low CBFp, 0–2 ml/100 g/min, recovery occurred with less than 13 min of occlusion. At 13 min and over, 4 of 5 cases did not recover DCR completely. At 4–5 ml/100 g/min, 3 cases recovered completely.
with a total occlusion time of less than 33 min. Over 33 min, 2 cases did not recover DCR. Frequently, with the gradual induction of ischemia, a prolonged period of reduced CBFp existed before actual loss of DCR. As shown in figure 4, the interval from clamping to abolition of DCR was quite variable. The relationship between recovery and the two types of ischemia (before loss of DCR and after loss of DCR) is seen in figure 6. CBFp below 20 ml/100 g/min is defined as the preceding insult. In ischemic episodes with loss of DCR for 5 min or less, all cases recovered even though preceding ischemia occurred for up to three hours. One case developed edema. The cases, in which the clamps were released more than 7.5 min after the DCR was lost, showed that preceding ischemia appeared to have no influence on recovery as long as it did not exceed more than one hour. More than one hour of preceding ischemia was associated with poor recovery of DCR. Ten minutes of loss of DCR seemed to be well tolerated with only one animal out of ten not recovering DCR. This animal developed cerebral edema. At 15- and 20-min non-DCR insults, preceding ischemia episodes of less than one hour did not seem to influence recovery.

The relationship between recovery, non-DCR insult, and the mean CBF is shown in figure 7. Only cases in which the DCR was lost within one hour after clamping were employed so that the influence of the preceding ischemia during the insult would be minimized. The DCR amplitude recovered completely in all cases of the 5-min and 7.5 min non-DCR insult groups. An edematous brain was observed in two of the 7.5 min group. Of the ten cases in the 10-min non-DCR insult group, there was only one in which the DCR amplitude did not recover completely, and this animal had a low CBFp. In the 15-min non-DCR insult group, the DCR amplitude recovered completely in five of eleven cases. At low CBFp, three of five cases, and at CBFp between 7 and 10 ml/100 g/min three of six cases did not recover. The three cases that did not recover at higher flows had edematous brains. In the 20-min non-DCR insult group, four of eleven cases recovered completely. No correlation with recovery and CBFp was found.

In some of the nonrecovery cases in the 15-min and 20-min non-DCR groups, there was a tendency for the DCR amplitude to begin to recover initially and then to decay 2 or 3 hours after the release of the clamps. These results demonstrate that it is possible for the DCR to recover completely after it is abolished for 10 min unless brain edema occurs and suggest that the cortex may recover at 15 min if extremely low flow or edema has not occurred. At 20 min, the chances are that the cortex will not recover, although occasionally it can, even at very low flow. All animals developed a hyperemic response after release of the clamps. No correlation was found with magnitude of hyperemia and the ability to recover DCR.

The mean zero flow or dead brain value at the end of the experiments was 359 μV (SD ± 9.1, n = 48). In animals that made a complete recovery in the 5-min non-DCR insult group and in animals where the DCR was not abolished, mean zero flow value was 355.6 μV (SD ± 8.2, n = 9). In animals that made a poor recovery in the 15- and 20-min non-DCR groups, mean zero flow value was 358.1 μV (SD ± 3.8, n = 8). No significant difference in thermal conductivity was found between brains that recovered and those that were damaged by ischemia.

**Discussion**

There have been numerous reports concerning the relationship between CBF and the electrical responsiveness of the brain. Branston et al. suggested a threshold-type relationship between the amplitude of the somatosensory evoked response (SER) and CBF as measured by hydrogen clearance. They showed that the SER began to decay at CBF of 16 ml/100 g/min and abolished at less than 12 ml/100 g/min when the middle cerebral artery was occluded in baboons. More recently Umbach, Hess and Traupe, using

![Figure 4](image-url)  
**Figure 4.** Mean CBFp versus time from occlusion to loss of DCR in 12 Type II cases.

![Figure 5](image-url)  
**Figure 5.** Relationship between total occlusion time and mean CBFp in 13 Type II cases where CBFp during occlusion was less than 10 ml/100 g/min. 0 = DCR recovery ≥ 90%; □ = recovery 50–89%; △ = recovery < 50%; solid symbols = edematous brain.
Blood flow to the internuncial neurons in the SER is unknown so we elected to correlate CBFp with the DCR. This is local electrical activity and independent of what may be happening in other parts of the brain. Since Adrian’s first description of DCR in 1936, it has been concluded that the 15–20 msec surface negative wave evoked by direct stimulation of the cerebral cortex is a synaptic potential of apical dendrites of the pyramidal cells.21–23 The changes of DCR in cerebral ischemia induced by increased intracranial pressure was investigated by Grossman et al.,16 and in 1977 a linear relationship between the amplitude of DCR and CBF was reported by Teasdale et al.24 In our experiments, it was difficult to determine this relationship because of the rapid decrease of CBF. However, it was possible to measure the thresholds for attenuation and loss of DCR. Some interesting characteristics of the DCR occurred in these experiments. A small but reproducible increase in the wave form occurred with the induction of ischemia. This was followed by attenuation of the wave (see fig. 2). If CBFp remained constant while the DCR was attenuated, the DCR frequency gradually increased. These events imply some adaptation of DCR to ischemia.

CBF as measured by thermal conductivity and hydrogen clearance was reported to have a linear relationship by Cusick and Myklebust.25 They emphasized the need for intermittent recalibration because of a possible change of tissue thermal conductivity after prolonged cerebral ischemia. In our experiments, the flow probe was calibrated previously by $^{133}$Xe clearance15 and CBFp was based on the dead brain value for each animal at the end of the experiment. The dead brain value is the voltage related to the temperature differ-
ence, at zero flow. This value reflects the heat conductivity of the cortex. We observed no difference in comparing ischemic damaged and undamaged cortex. Cusick and Myklebust used an electrode which penetrated the pial membrane and cortex which was then fixed with acrylic to the skull. The pulsatile brain would naturally cause changes in the thermal contact, possibly accounting for their need to recalibrate the thermal probe.

The recovery of brain function from cerebral ischemia was reported by Branston et al. using SER in baboons. They associated the nonrecovery cases with lower CBF and tissue PO$_2$ during the ischemic insult, and with greater persisting tissue hypoxia after the occlusion than in the recovery cases. According to their results, none of 7 cases in which CBF was less than or equal to 11 ml/100 g/min with occlusion times of 15 min or longer recovered completely. However, contrary to Branston’s results, we found that in flows of 4–5 ml/100 g/min the cortex could recover after 33 min of ischemia. Occasionally very low flows were tolerated for over 20 minutes (see figure 7).

In cases with gradual ischemia, if the preceding ischemic event was longer than 60 min followed by loss of DCR for 7.5 min or longer, the electrical responsiveness of the cortex was less likely to recover (figure 6). Additionally, at 15 min or longer of non-DCR insult, the cortex was much less likely to recover (figure 7). This gradual reduction in CBFp is very difficult to analyze because of changing flow and emphasizes the importance of a continuous measurement of flow. If intermittent recording is used, it must be done frequently. With the production of severe ischemia taking more than 40 min, the loss of DCR occurred at lower CBFp levels. This may mean that with slow production of ischemia the electrical function of the cortex may adapt to ischemia.

Halothane anesthesia may have an effect on the ischemic brain, so any clinical influences from this study would be more comparable to ischemia occurring in the operating theater.

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