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.
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 \( \mu \text{sec} \) 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, PCO\(_2\) was adjusted between 20 and 40 mm Hg and PO\(_2\) 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 CBF\(_p\) 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 recovery of DCR, as well as for changes of CBF\(_p\) 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 CBF\(_p\) over 30 ml/100 g/min and could be adequately studied for the full six hours were evaluated.

**Results**

CBF\(_p\) tracings, following occlusion of the left subclavian and innominate arteries, were of two types as shown in figure 1. In Type I, CBF\(_p\) recovered after a precipitous drop immediately following application of the clamps, and then decreased gradually. There was little or no recovery of CBF\(_p\) 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 CBF\(_p\) recovery after clamping surpassed 20 ml/100 g/min, and then gradually decreased. The recovery of CBF\(_p\) after clamping in Type IB was 13–20 ml/100 g/min. The recovery of CBF\(_p\) 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 CBF\(_p\) after clamping, thresholds for attenuation and abolition of DCR were difficult to determine. In Type IA, however, CBF\(_p\) gradually decreased from over 20 ml/100 g/min. Ten of eighteen cats in this group with gradual loss of CBF\(_p\) 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 CBF\(_p\) and time from occlusion. It appears that the initial CBF\(_p\) and the time to attenuation has no effect on the attenuation threshold. Since the initial CBF\(_p\) was quite variable, depending upon cortical activation, it is more accurate to describe an absolute CBF\(_p\) 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 CBFp 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 5-min non-DCR insult group, there was only one animal 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 insults, 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 cortex 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...
hydrogen clearance and SER in cats, found that SER became monophasic at 15–19 cc/100 g/min and disappeared at 12 cc/100 g/min. Bunegin et al.,20 using SER and flow, determined by microspheres in dogs, found that when flow falls to 22 ml/100 g/min, electrical activity is dramatically reduced. Jones et al.,6 described a threshold of 23 cc/100 g/min in awake monkeys for development of paralysis and 10–12 cc/100 g/min for two hours for infarction to occur. These results compare with our finding that the DCR was attenuated at 21.3 ± 4.7 ml/100 g/min and was lost at 8.7 ± 3.4 ml/100 g/min. It is reassuring to note that the thresholds of approximately 20 and 10 cc/100 g/min hold true in a variety of experimental conditions, despite the use of different species, physiologic function measurements, and techniques of measuring blood flow.

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 frequently 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 133Xe 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.26 employing SER in baboons. They associated the nonrecovery cases with lower CBF and tissue PO₂ 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 inferences from this study would be more comparable to ischemia occurring in the operating theater.

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