Reversibility of Experimental Cerebrovascular Obstruction Induced by Complete Ischemia*

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By perfusing rabbit brains with a suspension of carbon, it has been possible to demonstrate the development of vascular obstructions during complete ischemia. These are manifested as white areas in which the perfused carbon fails to displace entrapped red blood cells from portions of the microvasculature. The occlusive changes first appear after 5 to 7.5 minutes of ischemia and increase with time, about half the brain failing to reperfuse after 15 minutes and 60% after 30 minutes of ischemia. Light and electronmicroscopy have demonstrated that the obstruction is due to compression of vascular lumen by swollen endothelial cells and perivascular glia; \(^1\) and the protection against the vascular obstruction provided by prior administration of hypertonic Mannitol or glucose \(^2\) is consistent with this interpretation.

In some of the prior studies, carbon perfusion was performed immediately after the ischemia; in others, 30 minutes later. The results in the latter group were not appreciably different from the former, but no measures were taken to maintain normal blood pressure during the 30-minute post-ischemia period. Without such measures, marked and persistent hypotension is a regular sequela when cerebral ischemia lasts more than 7.5 minutes \(^3,4\) and there is little recovery of neurologic function. \(^3\)

The present study was undertaken to assess the reversibility of the occlusive changes in the cerebral vasculature. The experiments were designed to see whether the vascular obstruction that is present at the end of the ischemia lessens as the brain is reperfused for varying periods of time with well-oxygenated blood at normal arterial pressure.

**Methods**

Studies were performed on 27 New Zealand white rabbits. All of them were anesthetized with sodium pentobarbital and then subjected to 15 minutes of complete cerebral ischemia produced by ligating the ascending aorta. The details of this technique are described elsewhere. \(^3\) Following release of the aortic ligature, blood pressure was restored to, and maintained at, normotensive levels with an intravenous infusion of adrenalin. Arterial pressure was monitored continuously by means of a catheter in the femoral artery connected to a recording electromanometer (Sanborn).

The patency of the cerebral vasculature was assessed by carbon perfusion performed either immediately after the ischemia (9 animals) or after reestablishment of normal arterial pressure for periods of 7.5 minutes (6 animals), 15 minutes (6 animals), and 2 hours (6 animals). The carbon suspension was perfused into the cerebral vasculature for 30 seconds at a pressure of 110 mm Hg. The details of this procedure are described elsewhere. \(^2\) At the end of the carbon perfusion, the brain was removed; fixed in 10% formalin; and cut into six coronal sections located as follows: 1) mid-frontal lobe; 2) optic chiasm; 3) anterior edge of mammillary body; 4) posterior edge of mammillary body; 5) inferior colliculus; and 6) mid-cerebellum. The sections were scored under a dissecting microscope for the percentage of surface not perfused. An average was calculated from the six sections for the percentage of the total brain that had not been perfused. A second average was obtained from sections 1–4 for the percentage of cortex that had not been perfused.

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Results

In the nine animals in which carbon perfusion was performed immediately after the period of ischemia, the percentage of vascular obstruction was 44 ± 5 (mean ± standard error) for the total brain and 15 ± 3 for the cortex (Table 1). After reestablishment of cerebral blood flow at normal pressures for 7.5 minutes, the corresponding percentages were 21 ± 5 (total brain), 7 ± 2 (cortex). After reestablishment of blood flow for 15 minutes, the percentages of obstruction were 13 ± 3 (total brain), 10 ± 3 (cortex). After 2 hours of reflow, obstruction was only 5 ± 1 (total brain), and 2 ± 0.4 (cortex). The statistical significance of these decreases is shown in Table 1.

Discussion

The development of vascular obstruction following ischemia has been demonstrated in the kidney, heart, adrenal gland, and hind limb as well as in the brain. In these prior investigations, the perfusions to assess vascular patency were usually carried out immediately after the ischemia. Few, if any, systematic studies have been undertaken to assess the reversibility of the obstructive lesion.

The results of the present study indicate that much of the ischemia-induced vascular obstruction in brain is indeed reversible, provided that the brain is resupplied with well-oxygenated blood at normal pressures. Considerable time is required, however, to bring about this recovery, and, in the present experiments, there was significant further improvement in the period between 15 minutes and 2 hours after return of normal arterial pressure. This delay in reperfusion may be of critical importance in determining how much irreversible parenchymal damage results from a period of ischemia. The results of these experiments may explain why the many microscopic studies of post-ischemic brains, carried out days to weeks after the ischemic period have revealed parenchymal destruction but show no evidence of vascular changes that were probably a prominent feature of the acute response.

The extent of the reversibility of the vascular obstruction came as a considerable surprise. It had seemed unlikely, a priori, that vessels that could not be perfused because local obstructive lesions would be responsive to the reestablishment of normal pressures in the major arteries. In other words, we had anticipated that a lesion that was due to circulatory arrest and that, in itself, caused circulatory arrest, would constitute an irreversible vicious cycle. The mechanism responsible for the recovery can only be speculated on at this time. It is possible that a sustained pressure gradient serves to slowly dislodge red cells that are entrapped in the narrowed capillaries, or that it serves to force, past the trapped red cells, oxygen and glucose-containing plasma which can initiate restorative metabolic changes in the swollen perivascular cells. Another possibility is that spasm of the larger arteries plays an appreciable role in the obstructive phenomena, for this would be expected to be reversible when the blood pressure is reestablished.

The reversibility of the occlusive vascular changes, as demonstrated in the present experiments, must constitute a necessary condition for the recovery of neural function, which may be appreciable even after 15 minutes of complete ischemia, provided that normal blood pressures are reestablished in the post-ischemic period.

Summary

Total ischemia of 15 minutes duration was produced in 27 rabbit brains. The