Effect of Recirculation on Exacerbation of Ischemic Vascular Lesions in Rat Brain

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Using electron microscopy, we investigated the small arteries and veins in ischemic lesions induced by occlusion of the ostium of the middle cerebral artery in 42 rats. We observed endothelial denudation in the small arteries of rats receiving occlusion for >6 hours. When the occluding cylinder was removed to allow for reperfusion, however, 2 hours of occlusion was sufficient for endothelial denudation to occur. Medial smooth muscle cells seemed to be more vulnerable to ischemia than endothelial cells because ultrastructural changes in the former cells preceded endothelial denudation. Moreover, endothelial denudation definitely exacerbated vascular changes so that medial necrosis appeared to be complete beneath the denuded areas, allowing erythrocytes, platelets, and exogenous tracers to penetrate into the cytoplasm of smooth muscle cells. These arterial lesions seemed to be repaired 10 days after removal of the occluding cylinder following 2 hours of occlusion. On the other hand, small veins in the ischemic lesion did not show endothelial denudation or medial necrosis. Our study suggests that arterial changes in ischemic lesions play a role in exacerbating the brain edema caused by recirculation after ischemia. (*Stroke* 1991;22:635–642)

Restoration of blood flow during the early stage of cerebral embolism, when ischemic damage to the tissue has been minimal, would be an ideal treatment for this disease if recirculation did not often exacerbate brain edema and hemorrhage. Accordingly, there is no radical therapy available for cerebral embolism to date since restoration of blood flow during the acute stage of brain ischemia is regarded as a risk to life. It is thus essential to resolve the pathogenesis of these complications for the treatment of cerebral embolism during the acute stage.

We have established a new experimental model of cerebral embolism in rats in which recirculation can be easily introduced into ischemic areas.[1] We have previously shown that the brain water content increased according to the duration of ischemia and the degree of recirculation following >2 hours of ischemia.[1,2] However, we did not detail the intracerebral vascular changes causing brain edema in our model. Although there have been many morphological studies concerning cerebrovascular changes or increased vascular permeability caused by brain ischemia, these studies looked mainly at the microvessels.[3–11] Few reports exist describing ultrastructural changes of the intracerebral small arteries and veins in ischemic lesions.

We report the ultrastructural changes of small arteries and veins in ischemic lesions after specific periods of ischemia and recirculation. We also discuss the effect of recirculation on ischemic vascular lesions with regard to the exacerbation of brain edema by recirculation.

Materials and Methods

We anesthetized 62 male Wistar rats weighing 220–300 g with 40 mg/kg i.p. pentobarbital sodium. The terminal 5 mm of a 4-0 nylon surgical thread 16 mm long was coated with silicone (Xantopren light body, Bayer Dental, Leverkusen, F.R.G.) to a thickness of 0.3 mm.[1] The ostium of the right middle cerebral artery was occluded by the silicone cylinder inserted from the origin of the right internal common carotid artery.[1] After the cylinder was inserted, the right internal carotid artery was ligated with a tip of the thread at the origin. Recirculation could be achieved via the circle of Willis after positioning the cylinder at the origin of the right internal carotid artery.[1] We used 47 rats for ultrastructural studies

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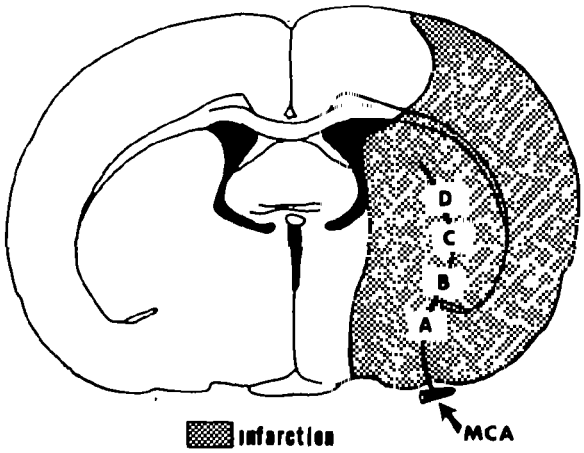

FIGURE 1. *Schematic representation of four sampling sites (A–D) in coronal section of rat brain. MCA, middle cerebral artery.*

and 15 for regional cerebral blood flow (rCBF) studies.

For the rCBF studies, an electrochemically generated hydrogen gas method[12] was used to measure rCBF in the lateral part of the caudate putamen in six rats receiving 2 hours of recirculation after 6 hours of occlusion and nine sham-operated (control) rats. The head of the rat, anesthetized with 40 mg/kg i.p. pentobarbital sodium, was fixed in a stereotactic frame to permit the opening of a burr hole 4 mm lateral and 0.5 mm posterior from the bregma in the right parietal bone. An electrode wire 3 cm long (urethane-coated platinum-iridium wire 80 μm in diameter, Biomedical Science Co., Kanazawa, Japan) was inserted to a depth of 4 mm through the burr hole and fixed at the burr hole with cyanoacrylate

TABLE 1. **Summary of Experimental Groups and Subgroups of Rats**

Subgroup	*n*	Occlusion (hr)	Recirculation
Group 1. Persistent ischemia			
2H	7	2	...
6H	7	6	...
8H	8	8	...
Group 2. Recirculation			
1+2H	6	1	2 H
2+2H	6	2	2 H
6+2H	6	6	2 H
2H+10D	2	2	10 D

H, hour; D, day.

monomer. Another electrode was introduced into the nuchal region. When the rat awoke, rCBF was measured with an electrolytic tissue rheometer (RBF-2, Biomedical Science Co.). The current and duration were 5 μA and 100 seconds, respectively. In our method, the rats did not need to be fixed or anesthetized and could be maintained in the physiological standing position during rCBF measurement. The rCBF was measured every hour for 8 hours. Data were analyzed by Student's *t* test. Differences were considered significant when $p<0.05$.

For the ultrastructural studies, 42 rats were divided into seven subgroups that incurred persistent ischemia or temporary ischemia followed by recirculation for an arbitrary duration according to the experimental design (Table 1). Carbon ink (Pelikan AG, Hannover, FRG) as a tracer for endothelial permeability was administered to the rats either just before surgery in group 1 or 1 hour after recirculation in group 2. After the operation, all rats were released

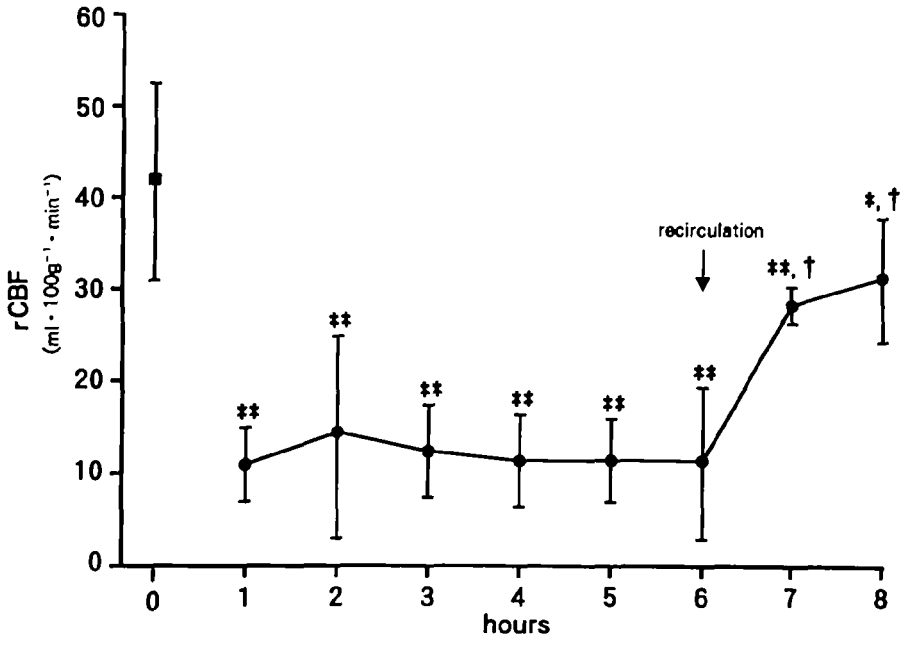

FIGURE 2. *Graph of mean±SD regional cerebral blood flow (rCBF) in lateral part of caudate putamen of controls (■, n=9) or rats exposed to 2 hours of recirculation after 6 hours of occlusion (●, n=6). **p<0.01 different from control; *p<0.05 different from control; †p<0.01 different from value after 6 hours of occlusion.*

TABLE 2. Endothelial Denudation Scores of Small Arteries in Semithin Sections From Caudate Putamen of Rats

	Sampling site							
	A		B		C		D	
Subgroup	No.	Mean±SD	No.	Mean±SD	No.	Mean±SD	No.	Mean±SD
Group 1. Persistent ischemia								
2H	35	0.000±0.000	37	0.000±0.000	28	0.000±0.000	24	0.000±0.000
6H	28	0.080±0.167	16	0.125±0.204	13	0.000±0.000	15	0.050±0.194
8H	29	0.086±0.214	24	0.021±0.102	26	0.048±0.123	18	0.000±0.000
Group 2. Recirculation								
1+2H	52	0.005±0.035	37	0.007±0.041	28	0.000±0.000	31	0.008±0.045
2+2H*†	25	0.080±0.213	20	0.225±0.343	17	0.324±0.350	16	0.172±0.350
6+2H‡§	25	0.190±0.282	22	0.193±0.327	17	0.162±0.196	17	0.279±0.432

Subgroups are defined in Table 1. Sampling sites are depicted in Figure 1.
*$p<0.01$ compared with 2H; †$p<0.01$ compared with 1+2H; ‡$p<0.01$ compared with 6H; §$p<0.01$ compared with 8H.

from the operating table until sacrifice. A sham operation was performed on the remaining five (control) rats.

At the end of the designated period of either persistent ischemia or recirculation, the rats were deeply anesthetized by inhaling diethyl ether and had catheters inserted into the abdominal aortae. All rats were perfused with 1,000 IU heparin in 20 ml physiological saline, followed by 100 ml of 2.5% glutaraldehyde in 0.1 M phosphate buffer (pH 7.4) at 150 mm Hg perfusion pressure. In group 2, the cylinder was removed immediately prior to fixation to perfuse the ischemic lesion.

After removal of the brains, small tissue blocks about 1.5×1.5×1.0 mm in volume including perforating branches were resected from four designated sites in the right caudate putamen involved with ischemia (Figure 1). These blocks were postfixed in 1% osmium tetroxide for 2 hours and then embedded in Epon 812 after dehydrating through graded ethanol. Semithin sections were stained with 1% toluidine blue and observed under a light microscope. Ultrathin sections

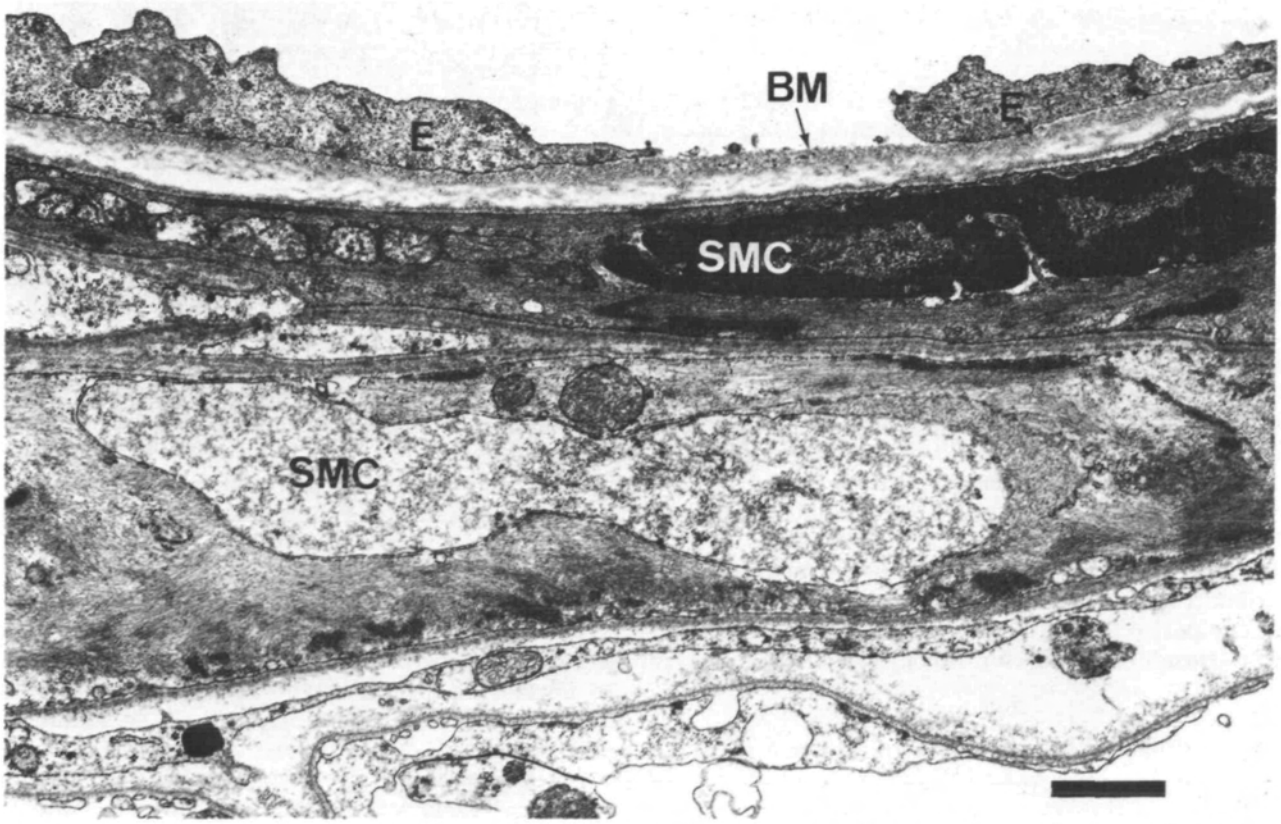

FIGURE 3. *Electron micrograph of small artery, 60 μm in diameter, of rat after persistent 8-hour occlusion. Endothelium is denuded, and subendothelial basement membrane (BM) is exposed. Endothelial cells (E) are swollen and decrease electron density. Chromatin of nucleus is condensed, and cytoplasm is edematously swollen in smooth muscle cells (SMC). Bar=1 μm.*

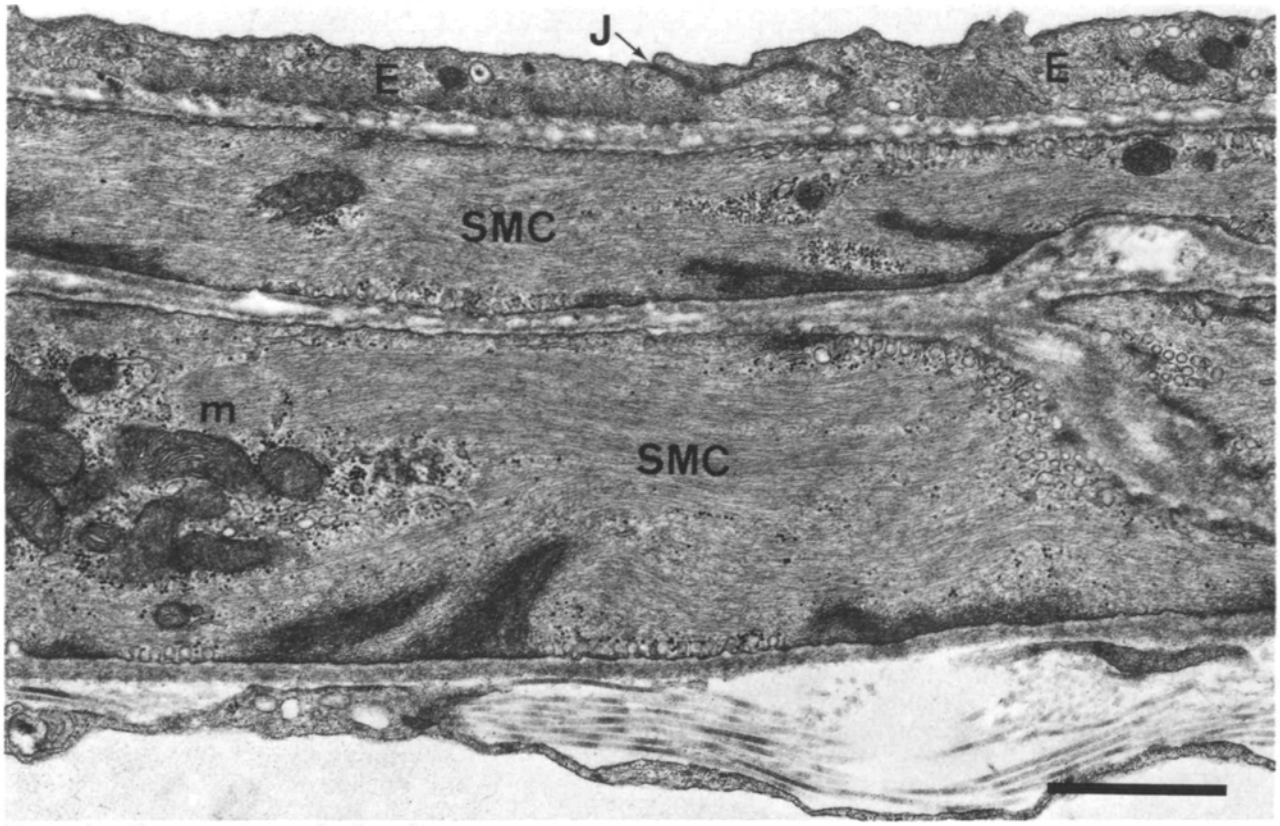

FIGURE 4. *Electron micrograph of small artery, 75 μm in diameter, in rat subjected to 2 hours of recirculation after 1 hour of occlusion. There is no striking change in endothelial cells (E) nor in smooth muscle cells (SMC). Tubular expansion and irregular arrangement of cristae are seen in SMC mitochondria (m). J, intercellular junction between E. Bar=1 μm.*

were cut and stained with uranyl acetate and lead citrate and examined under an electron microscope (JEM-100SX, JEOL Ltd., Tokyo, Japan).

Intracerebral arteries and veins >20 μm in diameter were selected in the semithin sections. The degree of endothelial denudation was quantified under a light microscope according to the ratio of the denuded area to the entire circumference of the vessels: no denudation was estimated as 0, denudation of less than one fourth of the circumference as 0.25, denudation of one fourth to a half as 0.5, denudation of a half to three fourths as 0.75, and denudation of three fourths to the whole circumference as 1. Data are presented as mean±SD. Differences among the three persistent ischemia and the three 2-hour recirculation subgroups and four sampling sites were evaluated by two-way analysis of variance. If there was a significant difference, multiple comparisons were made using a *t* test. Differences were considered significant when $p<0.01$.

Results

Mean±SD rCBF in the caudate putamen of the nine control rats was 41.8±10.7 ml/100 g/min (Figure 2). Middle cerebral artery occlusion reduced rCBF to approximately 12 ml/100 g/min, significantly less than the control value ($p<0.01$). Two hours of recirculation restored rCBF to approximately 30 ml/100 g/min, significantly greater than that after 6 hours of occlusion ($p<0.01$). However, this 30 ml/100 g/min value was significantly less than the control value ($p<0.05$).

In the light microscopic studies, we investigated 293 small arteries in group 1 and 307 in group 2. Endothelial denudation scores of the small arteries for each sampling site are displayed in Table 2. No significant difference was indicated among the four sampling sites ($p>0.05$); however, there was a significant difference among the six subgroups ($p<0.01$). By multiple comparisons, significant differences occurred between the 2H and 2+2H subgroups ($p<0.01$), between the 6H and 6+2H subgroups ($p<0.01$), and between the 8H and 6+2H subgroups ($p<0.01$). In group 2, endothelial denudation was significantly more intense in the 2+2H than in the 1+2H subgroup ($p<0.01$). Endothelial denudation also tended to be more severe in the 6+2H than in the 2+2H subgroup, but the difference was not significant. On the other hand, among the small veins (339 investigated in group 1 and 211 in group 2) endothelial denudation was hardly recognized.

In the five control rats, under an electron microscope the intima was seen to consist of one layer of endothelial cells and the intracellular junction consisted of the tight and gap junctions. A few pinocytotic vesicles could be observed in the endothelial

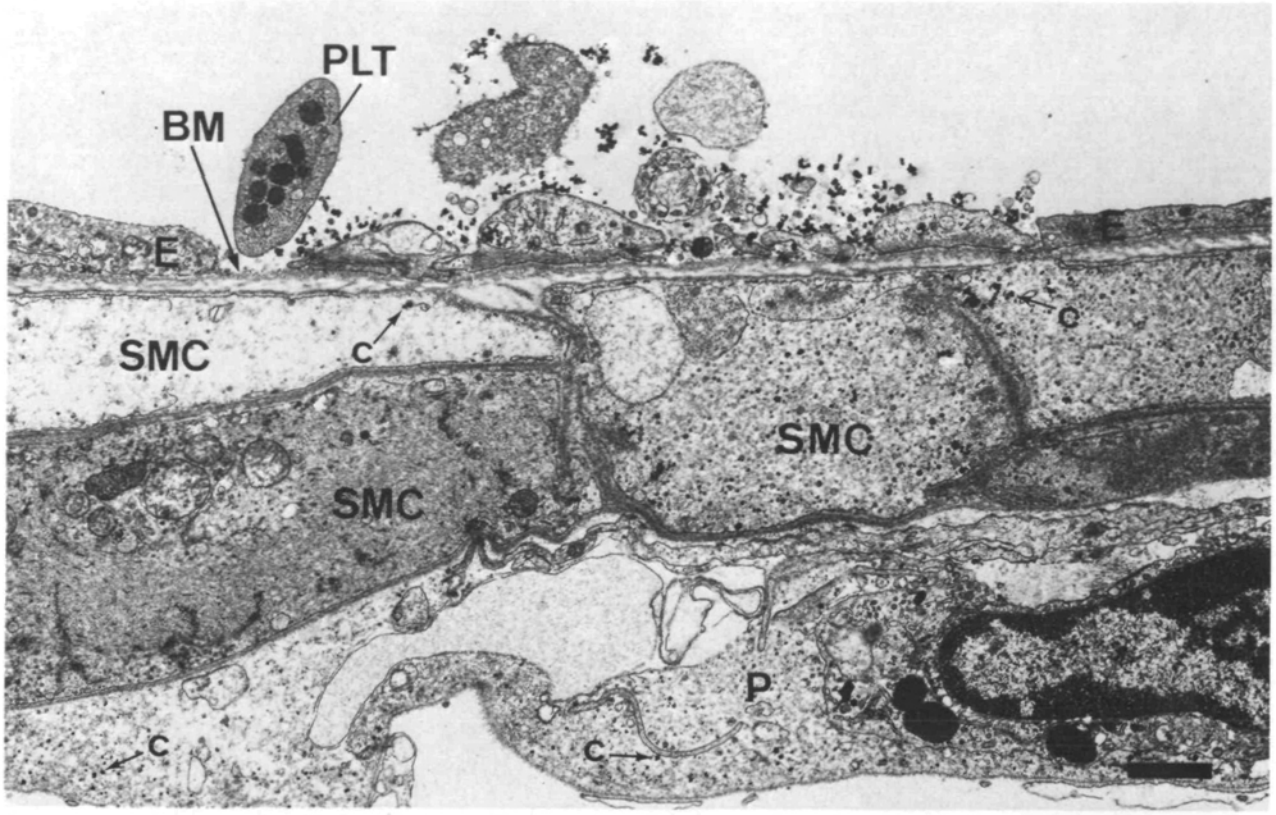

FIGURE 5. *Electron micrograph of small artery, 60 μm in diameter, in rat subjected to 2 hours of recirculation after 2 hours of occlusion. Endothelial denudation is observed in part of vascular wall, and adhesion and aggregation of platelets (PLT) are seen. Smooth muscle cell (SMC) beneath denuded endothelium becomes hydropic and is similar to ghost cell, in which only cell membrane remains. Carbon particles (c) are seen in SMCs and in pericytes (P). E, endothelial cell; BM, basement membrane. Bar=1 μm.*

cells. The media consisted of one to three layers of smooth muscle cells. Electron density of the mitochondrial matrices was high, and expansion of the cristae was rarely observed. No tracer penetrated the vascular wall.

In the 2H subgroup, no opening of the intercellular junctions, endothelial necrosis, nor denudation was recognized. The smooth muscle cells showed fragmentation of the myofilaments and an increase in the amount of transparent cytosol between the myofilaments. Decreased density of the matrices and tubular expansion and an irregular arrangement of the cristae were observed in smooth muscle cell mitochondria.

In the 6H subgroup, alterations were frequently found in the mitochondria of smooth muscle cells. Decreased density of the cytosol and partial resolution and disappearance of the myofilaments appeared even in the media without endothelial denudation. A portion of the cytoplasm in the smooth muscle cells was swollen and intruded into the endothelium through fenestrae of the internal elastic lamina and raised endothelial cells.

In the 8H subgroup, the change was essentially similar to that in the 6H subgroup, but the vascular change was more extensive. A few endothelial cells were denuded from the basement membrane (Figure 3), but the intercellular junctions of the remaining endothelial cells were not open. Chromatin of the medial muscle cell nuclei was condensed. Intensely degenerated muscle cells left only the cytoplasmic membranes holding flocculent or granular materials (Figure 3).

In the 1+2H subgroup, although there was no striking change in the endothelium or smooth muscle cells, the number of vesicles seemed to increase in the endothelial cells (Figure 4).

In the 2+2H subgroup, endothelial denudation was observed in about 32% (25) of 78 small arteries. Even though the areas of denudation were small, they allowed the adhesion and aggregation of platelets on the exposed subendothelial tissues. Some of the remaining endothelial cells held enlarged vacuoles containing carbon particles, swollen mitochondria, and an increased volume of cytosol with low electron density. Necrosis was recognized in almost all of the medial layer. Smooth muscle cells beneath the denuded endothelium became hydropic and were similar to ghost cells, which retained only the cell membranes and have few myofilaments and organelles. There were smooth muscle cells containing swollen mitochondria, enlarged vacuoles, and some carbon particles in their almost-empty cytoplasm. Conversely, in other smooth muscle cells, electron

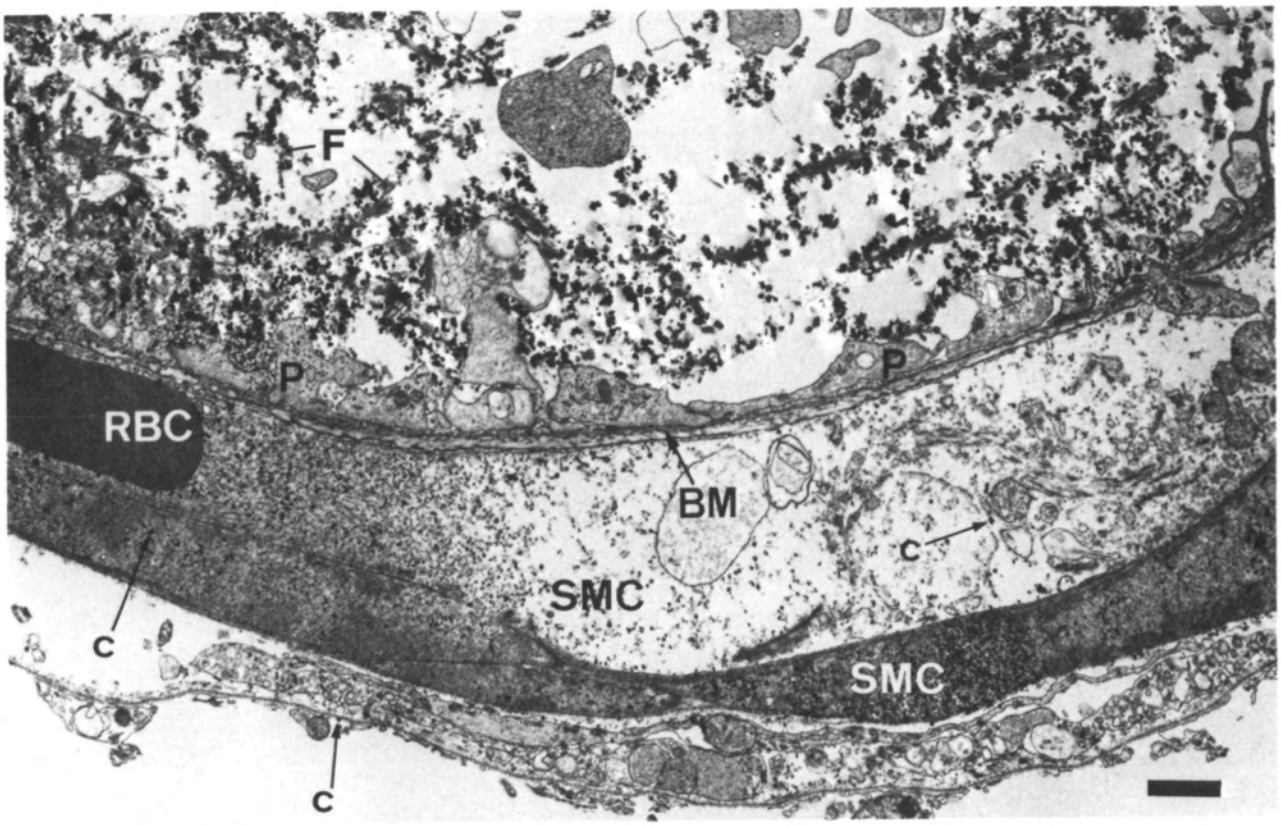

FIGURE 6. *Electron micrograph of small artery, 60 μm in diameter, in rat subjected to 2 hours of recirculation after 6 hours of occlusion. Platelets (P) adhere to basement membrane (BM), with deposition of fibrin (F). Erythrocytes (RBC), Ps, and carbon particles (c) are lodged in smooth muscle cells (SMC). Vascular wall is supported only by interstitial connective tissue. A few c particles are observed in perivascular space. Bar=1 μm.*

density increased due to the accumulation of carbon particles in their cytoplasm, despite a severe reduction in the numbers of myofilaments and organelles. In general, the electron density of smooth muscle cells increased in the outer layer of the media and decreased in the inner layer, depending on the amount of carbon deposited in the cytoplasm. This tendency was more apparent in areas beneath denuded endothelium (Figure 5). The pericytes also contained swollen mitochondria and an increased number of vacuoles.

In the 6+2H subgroup, the incidence of endothelial denudation increased to about 38% (31) of 81 small arteries. Changes of the endothelium were so extensive that the entire luminal surface was denuded, which permitted platelet adhesion and aggregation, with fibrin deposition onto the exposed subendothelial basement membrane. In addition, necrotic and lytic smooth muscle cells allowed the penetration of erythrocytes, platelets, and carbon particles into their cytoplasm (Figure 6). Some arteries were occluded by thrombi.

In the 2H+10D subgroup, no endothelial denudation or necrosis of the medial smooth muscle cells was seen. Junctions between endothelial cells were partially opened frequently, but no carbon was seen in the junctions because the junction apparatuses were observed on the luminal side from the opened areas. The number of mitochondria and rough endoplasmic reticuli increased in both the endothelial cells and the medial smooth muscle cells. Several layers of basement membrane–like substance accumulated to thicken the subendothelial spaces. The internal elastic lamina was sometimes fragmented, allowing the basement membrane–like substances to be mingled in both the subendothelium and the media. The interstitial connective tissue in the media, consisting mainly of basement membrane–like substances, became remarkably thickened in a nodular form, which was surrounded by smooth muscle cells. Cell debris and a few large aggregated carbon particles were scattered in the thickened interstitial connective tissue (Figure 7).

Endothelial denudation was rarely observed in the small veins, and the junctions between endothelial cells were not opened. Carbon particles were seen in neither the endothelial cells nor the intercellular junctions.

Discussion

In our model, mean rCBF in the caudate putamen was reduced to approximately 30% of the normal value by occlusion of the middle cerebral artery. In our investigated lesions rCBF recovered to 70% of the normal value ≤2 hours after recirculation following ischemia.

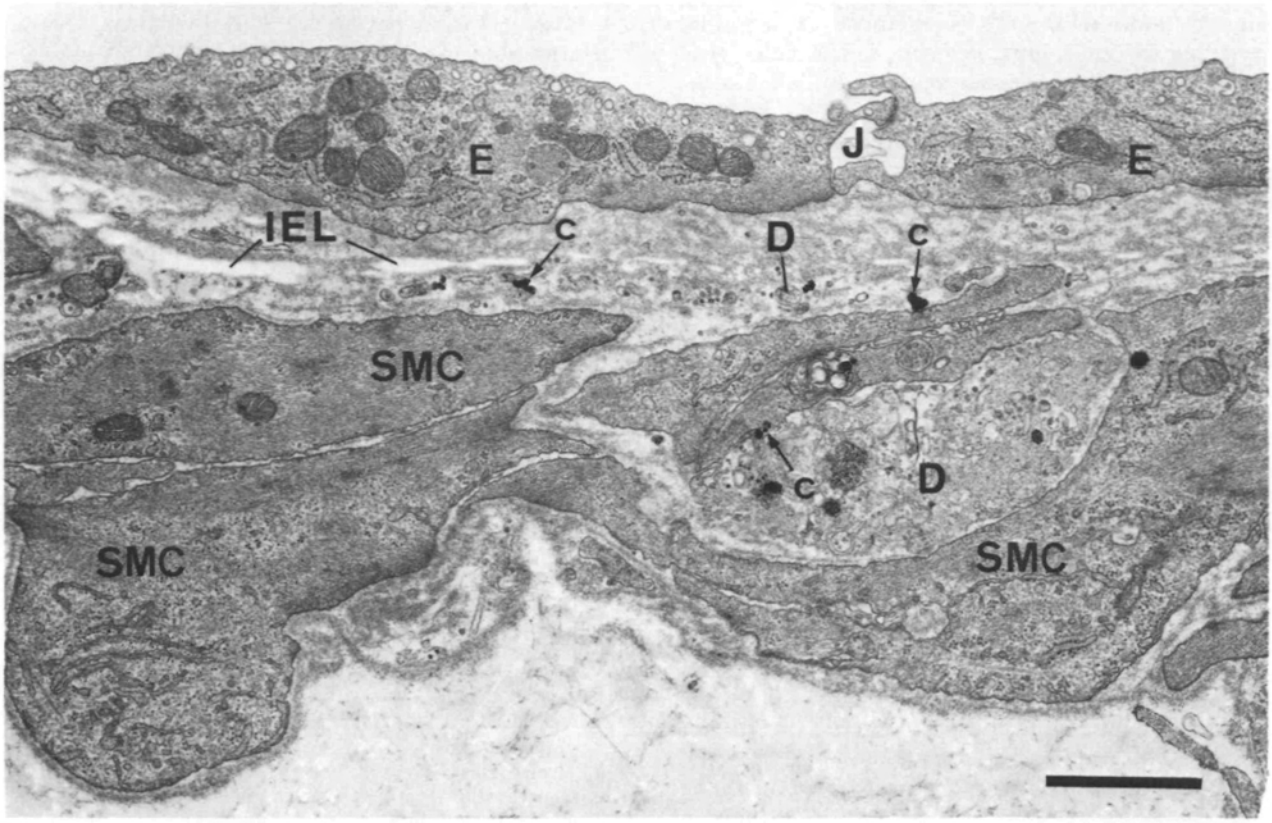

FIGURE 7. *Electron micrograph of small artery, 84 μm in diameter, in rat 10 days after 2 hours of occlusion. Damaged vessel is almost repaired. Intercellular junction (J) between endothelial cells (E) is partially opened. Activated E and modified smooth muscle cells (SMC) are seen in vascular wall. Cell debris (D) and carbon particles (c) remain in thickened interstitial connective tissue. Internal elastic lamina (IEL) is fragmented and dissolved. Bar=1 μm.*

Dietrich et al[13] reported endothelial alterations of a cortical arteriole in rats achieved with 1 hour of recirculation after 1 hour of occlusion of the middle cerebral artery. In our model, ultrastructural findings, such as an increase in the number of pinocytotic vesicles, were also observed in the endothelial cells of small arteries in rats subjected to 2 hours of recirculation after 1 hour of occlusion. Endothelial denudation is considered to be the most severe form of endothelial injury, bringing about the complete loss of blood–brain barrier function. We found that endothelial denudation developed in rats receiving ischemia for at least 2 hours followed by recirculation for another 2 hours. We thus conclude that at least 2 hours of occlusion with subsequent recirculation is the minimum requirement for denudation of endothelial cells in the small arteries.

Specimens were taken from four proximal to distal sites along the perforating branches of the middle cerebral artery in the infarcted basal ganglia, and the extent of endothelial denudation was studied. There was no significant difference in the frequency or extent of endothelial denudation of the perforating arteries among sites. The four sites investigated may have similar hemodynamic conditions because they have similar luminar diameters (63.4±14.3 μm at A and 52.8±16.2 μm at D, unpublished data).

Vascular damage may be exacerbated, as Kogure et al[14] stated, as a result of free radicals formed due to dysfunction of the respiratory chain in mitochondria when oxygen is resupplied to vascular walls that have been damaged by ischemia. Free radicals produced by the activation of xanthine oxidase in endothelial cells through an oxidative shock after ischemia are also conceivable injurious agents causing vascular damage. Allopurinol, a xanthine oxidase inhibitor, suppressed brain edema in rats receiving recirculation after ischemia.[15] If energy production in the vascular cells is impaired by the decreased supply of oxygen, then lactic acidosis, pooling of Ca^{2+} in the cells involved, and activation of lysosomal enzymes and phospholipase A_2 would result. In addition, consideration should be given to such vasoactive substances as arachidonic acid and thromboxane A_2 released by recirculated platelets, which could be activated by damaged endothelial cells. Turčáni et al[16] reported that platelets activated by cerebral ischemia might be involved in the development of ischemic brain edema in gerbils.

Changes were generally more apparent in the medial smooth muscle cells than in the endothelial cells of small arteries in the infarcted areas. Smooth muscle cell changes were more marked in group 2. Particularly, smooth muscle cell changes beneath

denuded endothelial cells were more remarkable. According to our results, smooth muscle cells were more vulnerable to hypoxia than endothelial cells. Smooth muscle cells may be in a higher metabolic state, which demands more oxygen, than endothelial cells. Endothelial denudation can enhance smooth muscle cell change.

Endothelial denudation was encountered more frequently in segments with medial necrosis after recirculation. Enlargement of the vascular lumen by medial necrosis seemed to be a causative factor for the enhancement of endothelial permeability.[17] Secretion of injurious agents, such as active oxygen and free radicals, from the damaged smooth muscle cells may be another contributing factor. Venous damage was rarely observed in this model. The reason for this remains obscure, but two possibilities are postulated. First, there are fewer smooth muscle cells in the venous wall than in the arterial wall. Second, venous endothelial cells may be more resistant to ischemia than arterial endothelial cells.

No-reflow has been suggested as a cause of microvessel damage after reperfusion.[18] Mural platelet thrombi were present in small arteries, and some small arteries appeared to be obstructed by platelet thrombi. Thus, no-reflow may play a role in the endothelial damage seen in our preparation. Chiang et al[3] have stated that blood clots and platelet thrombi do not contribute to the etiology of vascular obstruction.

After recirculation following 2 hours of occlusion, our rats survived for >7 days even though the brain water content increased after recirculation.[2] We investigated the subsequent changes in small arteries on the 10th day after recirculation. No endothelial denudation or medial necrosis was observed, but activated endothelial cells and modified medial smooth muscle cells were frequently seen. Both activated endothelial cells and modified smooth muscle cells are characterized morphologically by an increase in the number of mitochondria and rough endoplasmic reticuli and a reduction in the number of filamentous structures, particularly in the smooth muscle cells. Functionally, they are cells with an increased turnover rate. Accordingly, these cells might be regenerated during the repair of small arteries damaged by recirculation after occlusion. Nodular accumulations of basement membrane–like substances, cell debris, and tracer in the media may represent morphologic evidence for reorganization of damaged smooth muscle cells.

We were able to draw three conclusions. First, recirculation following ischemia exacerbated arterial changes and increased brain edema. Second, small arteries in ischemic lesions may be considered the major sites from which edema fluid was exuded during recirculation. Third, 2 hours seems to be the critical occlusion period for endothelial damage in arteries subjected to ischemia and reperfusion.

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