ANGIOGRAPHIC CHANGES ASSOCIATED WITH RECURRENT REDUCTION OF CAROTID AND CEREBRAL BLOOD FLOW IN DOGS, WITH SPECIAL REFERENCE TO TRANSIENT FOCAL CEREBRAL ISCHEMIC ATTACKS

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Morphological changes associated with recurrent reduction of blood flow in the partially constricted common carotid artery and that in the ipsilateral cerebrum were examined angiographically in anesthetized beagle dogs. During the recurrent reductions of carotid flow, spasm and small and multiple defects indicating platelet aggregates or thrombi in the constricted carotid segment were observed in 8 and 5 of 20 preparations, respectively. Also, large defects indicating thrombi were observed at the outlet of the constricted segment in the other 2 preparations. During the reduction of cerebral flow, spasm was observed in the internal carotid artery and cerebral arteries in 9 and 8 preparations, respectively. Also, obstruction of the cerebral arteries with “cut-off” sign indicating emboli was observed in the other 2 preparations. The changes appeared singly or in combination. It is suggested that spasm, platelet aggregates, thrombi and/or emboli were responsible for the recurrent reduction of carotid and cerebral blood flow.

TRANSIENT focal cerebral ischemic attack (TIA) is one of the important prodromal symptom of cerebral softening. In a certain group of patients with TIA, the attacks occur recurrently, and therefore, they were previously called recurrent cerebrovascular episodes or intermittent cerebral insufficiency. There are at least three hypotheses on the mechanism(s) of TIA: vasospasm, embolism of the cerebral arteries with platelet aggregates or thrombi flowed down from the atherosclerotic carotid artery or the heart, and hemodynamic crisis such as atrioventricular block.

During search for an experimental model of TIA, we found spontaneous and recurrent reduction of minute range in carotid and/or cerebral blood flow during partial constriction of the common carotid artery in dogs. This phenomenon resembles TIA in that reduction of cerebral blood flow occur spontaneously and recurrently in both. This study was undertaken to examine morphological changes associated with recurrent

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- Thrombus formation
- Embolism
- Thromboxane A
- Prostaglandin I

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METHODS

Experimental Preparations

Eighty-six beagle dogs were anesthetized with sodium pentobarbital (30–40 mg/kg, i.v.). The trachea was intubated for artificial positive pressure respiration with air. The left common carotid artery was dissected free of surrounding tissues and a magnetic flowmeter was placed on it for measurement of carotid blood flow. The superior thyroidal artery was cannulated for measurement of carotid blood pressure. A segment of the common carotid artery 2 to 3 cm proximal to the thyroidea artery but distal to the flowmeter was constricted with a cylindrical tube of 3 mm in length and with one of various internal diameters so as to reduce carotid blood flow below 70 and above 20 percent of the control value. The arterial segment was slipped into the tube through its longitudinal slit, and the tube was covered with another tube to prevent the segment to slip out. A pair of needle-type heated cross-thermocouples were introduced into the left anterior or lateral cerebral lobe for semiquantitative measurement of cerebral blood flow.

Fig. 2. Synchronous and recurrent reduction of carotid blood flow (CaBF), carotid blood pressure (CaBP) and cerebral blood flow (CBF) during partial constriction of the left common carotid artery. A: before carotid constriction. B: during constriction. AoBF = aortic blood flow. SBP = systemic blood pressure. HR = heart rate. CaBF was measured in the left frontal lobe.
The thermocouples could measure the blood flow within 0.1 ml of tissue in our previous study. After experiments, ventricular fibrillation was induced by electrical stimulation. The cerebral blood flow decreased gradually and attained a stable level. This level was called zero flow and the flow was expressed as \( \mu \text{V} \). The upper three ribs on the left side were removed and a magnetic flowmeter was placed on the aortic root for measurement of aortic blood flow. A catheter was introduced in retrograde fashion into the right femoral artery to monitor systemic blood pressure. Heart rate was obtained by a pulse-integrator triggered by femoral pressure pulse.
In sixty dogs, the right common carotid artery and the vertebral arteries were occluded in order to avoid the blood supply to the brain by these arteries. In nine dogs, these arteries were not occluded to observe whether recurrent reduction of carotid or cerebral blood flow could be induced without occlusion. In five dogs, the left common carotid artery was not constricted to examine whether the reduction could be induced without constriction.

In eleven of thirty dogs in which recurrent reduction with cycle length from one to 30 min occurred in either or both of carotid and cerebral blood flow, a catheter was introduced into the brachiocephalic artery through the right common carotid artery for the injections of contrast material (Conray H®), and angiography of the neck and head was performed at later projection. In another series of eight dogs, a segment of the common carotid artery between the superior thyroidal artery and the carotid bifurcation was constricted, and the contrast material was injected through the thyroidal artery. The angiograms were obtained during a decrease and an increase of carotid and/or cerebral blood flow (Fig. 1).

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**Fig.5.** Various types of the changes in CBF and their relations to those in CaBF and CaBP. A (a): synchronous reduction of CaBF, CaBP and CBF. A (b): changes of CBF opposite to those of CaBF and CaBP. A (c): reduction of CBF independent from those of CaBF. A (d): recurrent reduction of CaBF while gradual decrease of CBF. A (e): recurrent reduction of CaBF while no obvious change in CBF. B (a): recurrent reduction of CaBF and CBF while no obvious change in CaBP. B (b): changes of CBF opposite to those of CaBF, and no obvious change in CaBP. B (c): recurrent reduction of CBF independent from those of CaBF. B (d): gradual reduction of CBF and CaBF, and no obvious change in CaBP. C (a): recurrent reduction of CBF while no obvious change in CaBF and CaBP. C (b): gradual reduction of CBF while no obvious change in CaBF and CaBP. C (c): no obvious change in CBF, CaBF and CaBP.

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**Fig.6.** A: time course of the changes in cycle length of the reduction of CaBF and CBF. B: percent incidence of the cycle length. The first, third and fifth cycle from each preparation were used for comparison.

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Dec = decrease; Inc = increase; Sd = diffuse spasm suggestive; Ss = segmental spasm suggestive; P = platelet aggregates suggestive; T = thrombi suggestive; E = emboli suggestive; D = dilatation; — = almost unchanged; ? = not visualized.

RESULTS

1. Recurrent Reduction of Carotid and Cerebral Blood Flow

Recurrent reduction of carotid blood flow (CaBF) and that of cerebral blood flow (CBF) appeared in twenty-five and thirty of sixty preparations, respectively. The time required for appearance of the reduction of CaBF and CBF ranged from 9 to 60 (21.5 ± 8.4, mean ± SD) min and 5 to 51 (26.0 ± 9.0) min, respectively. The occurrence of the recurrent reduction was not related to the magnitude of initial flow reduction induced by constriction. Further flow reduction by replacing the constrictor failed to induce the recurrent reduction in the preparations in which the recurrent reduction did not appear within one hour after the initial constriction. As shown in Figs. 2 and 5, CaBF, carotid blood pressure (CaBP) and CBF decreased and then increased synchronously, and the changes were repeated in eight preparations. In these and in the other preparations, systemic blood pressure rose during the decrease of CaBF and fell during the increase of CaBF. However, no obvious change in aortic blood flow and heart rate was observed (Fig. 2). CaBF, CaBP and CBF changed recurrently but CBF changed opposite to CaBF in two preparations (Fig. 3 and A(b) in Fig. 5). CBF changed recurrently but independent to CaBF in six preparations (A(c) in Fig. 5), while CBF decreased gradually and was little influenced by the recurrent changes of CaBF in six preparations (A(d) in Fig. 5). CaBF changed recurrently but CBF remained almost unchanged in two preparations (A(e) in Fig. 5). In these
preparations, CaBF changed recurrently at relatively high levels. In thirteen preparations, CBF changed recurrently while CaBF remained almost unchanged (Fig. 4 and C(a) in Fig. 5).

The time course of the changes in cycle length of the flow reduction was examined in seven preparations in which both CaBF and CBF changed recurrently, however, no significant change (Student's test, P < 0.05) was observed at least from the first to the eleventh cycle. The cycle length of the reduction of CaBF and CBF ranged from one to 32 and from 2 to 40 min, respectively (Fig. 6).

The recurrent reduction of CaBF appeared in

four of nine preparations in which left common carotid artery was constricted but right common carotid and vertebral arteries were not occluded. In these preparations, however, no obvious change in CBF was observed. Recurrent reduction in CaBF and CBF did not occur in five preparations in which left common carotid artery was not constricted.

2. Angiographic Changes

Changes in the Constricted Carotid Segment

The magnitude of constriction of the left common carotid artery \( \left( \frac{\text{diameter of proximal non-constricted segment} - \text{diameter of constricted segment}}{\text{diameter of non-constricted proximal segment}} \right) \times 100 \) ranged from 55 to 80 in the preparations in which angiography was performed.

During reduction of CaBF, smooth and diffuse narrowing of the constricted segment (A in Fig. 7), smooth narrowing of the distal portion of the constricted segment, small and multiple defects in the constricted segment (B in Fig. 7), smooth narrowing of the constricted segment with small defects (C in Fig. 7) were observed respectively in five, one, three and two of twelve
preparations in which CaBF and CBF changed synchronously (Table I). On the other hand, large defects were observed at the outlet of the constricted segment in the remaining two preparations (Fig. 8). In one of these preparations, the common carotid artery was removed to examine macroscopically the nature of the defects. It was revealed that the defects were fresh thrombi. The constricted segment was stained by Carstairs's method in three preparations in which small defects were observed. It was revealed that the defects were platelet aggregates.

Fig. 13. Left: during an increase of CBF. Right: during a decrease of CBF. Diffuse narrowing in the distal segment of the internal carotid artery (arrow labelled with 1), middle cerebral artery (arrow labelled with 2) and in the anterior cerebral artery (arrow labelled with 3). Posterior communicating artery (arrow labelled with 4) was not visualized.

Fig. 14. Left: during an increase of CBF. Right: during a decrease of CBF. Obstruction with “cut-off” sign in the proximal segments of the anterior cerebral artery (arrows labelled with 1). The peripheral segments of the artery were not visualized (arrows labelled with 2).

Changes in the Internal Carotid Artery

During the reduction of CBF, smooth and diffuse narrowing, and smooth but segmental narrowing in the internal carotid artery were observed respectively in seven and two of nineteen preparations in which CBF changed singly or in combination with the changes of CaBF. The changes remained, although reduced in their magnitude, even during the increase of CBF in four preparations. The narrowing in the internal
carotid artery appeared when the narrowing of the constricted segment disappeared in two preparations in which CBF changed opposite to the changes of CaBF (Fig. 9), while the narrowing in the internal carotid artery appeared with that of the constricted segment in four in which CBF and CaBF changed toward the same direction (Fig. 10 and Table I).

**Changes in the External Carotid Artery**

During the reduction of CaBF, segmental or diffuse narrowing of one to 3 branches of the external carotid artery was observed in three preparations. The change appeared with those in the constricted segment in two and without obvious change in the constricted segment in the remaining one preparation (Fig. 11).

**Changes in the Cerebral Arteries**

During the reduction of CBF, smooth and diffuse narrowing was observed in the anterior cerebral artery in two (Fig. 12), and in both anterior and middle cerebral arteries in six preparations (Fig. 13). In addition, obstruction with "cut-off" sign was observed in the anterior and/or middle cerebral arteries in two preparations (Fig. 14).

**DISCUSSION**

In this study, segmental or diffuse narrowing of the constricted common carotid artery, internal carotid artery and cerebral arteries were frequently observed during recurrent reduction of CaBF and/or CBF. Usually, both sides of the wall protruded symmetrically inwards. Since such a change was unusual for platelet aggregates or thrombi, the changes were probably due to vasospasm. Less frequently, small defects which were usually multiple, were observed in the constricted segment. Since the defects were identified as platelet aggregates in a few preparations, the changes in the remaining preparations might also have been due to platelet aggregates. In addition to these changes, large defects were also observed at the outlet of the constricted segment. The defects were identified as thrombi in one preparation. Fox, et al. suggested that boundary layer separation of blood flow occurred in the distal segment close to the constricted portion and caused thrombus formation. The thrombi observed in this study may have been formed by this mechanism. Segmental obstruction with "cut-off" sign was also observed in the cerebral arteries. Since it is generally accepted that "cut-off" sign indicates embolization, the sign observed in this study may have been due to embolism with platelet aggregates or thrombi flowed down from the common carotid artery. These changes in the carotid and cerebral arteries always appeared singly or in combination during the flow reduction. Therefore, we considered that these changes were responsible for the recurrent flow reduction.

In a few preparations, CaBF changed recurrently while CBF did not. Since the changes of CaBF were small, the changes in CaBF had not been reflected on CBF. In several preparations, CBF changed recurrently but CaBF did not. In the preliminary study, the flow in the internal carotid artery was around fifteen percent of that in the common carotid artery. Therefore, the flow changes due to spasm or embolism of the internal carotid and cerebral arteries may have not been reflected on CaBF. In several other preparations, CBF changed recurrently but opposite to the changes in CaBF. There are at least two mechanisms for these changes: platelet aggregates or thrombi detached the common carotid artery and flowed down into the cerebral arteries causing embolism, and simultaneous occurrence of spasm in the internal carotid artery or cerebral arteries with disappearance of the changes in the common carotid artery. These two mechanisms were demonstrated angiographically in this study.

Exact mechanisms of recurrent vasospasm, platelet aggregation and thrombus formation during partial constriction of the common carotid artery are not well known. In the previous studies the recurrent reduction of CaBF and CBF was eliminated by acetylsalicylic acid and ketoprofen that inhibited synthesis of prostaglandin endoperoxides by prostaglandin I_2 that inhibited platelet aggregation and caused relaxation of vascular smooth muscles and by (E)-3-[3-pyridylmethyl) phenyl -2-methy-propanoic acid that inhibited synthesis of thromboxane A_2. On the other hand, the reductions were induced, although not always, by prostaglandin F_20 and E_2 that caused contraction of carotid and cerebral arteries by epinephrine that accelerated synthesis of prostaglandin endoperoxides by tranylcypromine that inhibited synthesis of prostaglandin I_2, and by thromboxane A_2 that accelerated platelet aggregation and contraction of vascular smooth muscles. The fact may suggest that the changes in production or wasting of prostaglandins I_2, F_20 and E_2 and thromboxane
A₂, or recurrent reduction of the ratio of prostaglandin I₂/thromboxane A₂ + prostaglandins E₂ and F₂α, caused recurrent vasospasm, platelet aggregation of thrombus formation, leading to recurrent reduction of CaBF and CBF.

Vasospasm and embolism with thrombi or platelet aggregates in the cerebral arteries have been suggested as the causative factors of TIA⁵, ¹⁷,¹⁸ All these changes were observed in this study. In TIA, duration of the attack is usually of minute range. The cycle length of flow reduction in this study was also of minute range. In addition, acetylsalicylic acid was effective for both TIA and this experiment phenomenon. Thus, this experimental phenomenon resembles TIA.

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