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Abstract

Ten adult cats were anesthetized and ventilated by respirator. After the basilar artery was exposed transclivally and visualized with an operative microscope, mean arterial blood pressure (MABP) was raised gradually by intravenous drip infusion of norepinephrine (5-20 micrograms/kg) or angiotensin-II-amide (0.3-1.0 micrograms/kg). At various blood pressures, microphotographs were taken. There was no appreciable change in vessel diameter at a MABP ranging from 78 to 191 mmHg. The blood pressure was allowed to return to the initial baseline level. Arterial spasm was produced by the topical application of 0.2 M calcium gluconate, which decreased the arterial diameter by 13 to 58 percent for more than 60 min. Blood pressure was increased again after the production of the arterial spasm. Significant increases in the diameter of the arteries were produced by the drug-induced hypertension at levels of MABP ranging from 82 to 192 mmHg. The maximum arterial dilations ranged from 123 to 208 percent of the untreated control. The degree of dilation of the arteries almost paralleled the rise in MABP. Norepinephrine and angiotensin-II had a similar effect on both the blood pressure and the arterial diameter. Induced hypertension would be expected to improve blood flow parameters in the case of spastic cerebral arteries.

KEYWORDS: cerebral arterial spasm, induced hypertension, norepinephrine, angiotensin-?-amide

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EFFECT OF INDUCED HYPERTENSION ON EXPERIMENTALLY-INDUCED CEREBRAL ARTERIAL SPASM

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Abstract. Ten adult cats were anesthetized and ventilated by respirator. After the basilar artery was exposed transclivally and visualized with an operative microscope, mean arterial blood pressure (MABP) was raised gradually by intravenous drip infusion of norepinephrine (5-20 μg/kg) or angiotensin-II-amide (0.3-1.0 μg/kg). At various blood pressures, microphotographs were taken. There was no appreciable change in vessel diameter at a MABP ranging from 78 to 191 mmHg. The blood pressure was allowed to return to the initial baseline level. Arterial spasm was produced by the topical application of 0.2 M calcium gluconate, which decreased the arterial diameter by 13 to 58 percent for more than 60 min. Blood pressure was increased again after the production of the arterial spasm. Significant increases in the diameter of the arteries were produced by the drug-induced hypertension at levels of MABP ranging from 82 to 192 mmHg. The maximum arterial dilations ranged from 123 to 208 percent of the untreated control. The degree of dilation of the arteries almost paralleled the rise in MABP. Norepinephrine and angiotensin-II had a similar effect on both the blood pressure and the arterial diameter. Induced hypertension would be expected to improve blood flow parameters in the case of spastic cerebral arteries.

Key words : cerebral arterial spasm, induced hypertension, norepinephrine, angiotensin-II-amide.

Cerebral ischemia due to cerebral arterial spasm is a leading cause of morbidity and mortality following rupture of intracranial aneurysms (2, 15, 36). Numerous investigators have attempted to clarify this phenomenon, but the pathogenesis and treatment remain obscure.

The combination of induced hypertension and hypervolemic therapy, which may improve an intravascular rheological factor, is currently employed to counteract the ischemic effect of cerebral arterial spasm following aneurysmal subarachnoid hemorrhage (SAH). The results demonstrate that this treatment can reverse the ischemic deficits (10). However, the pathophysiological changes brought about by this treatment have not been fully elucidated either clinically or experimentally. There is little information about the changes in the diameter of spastic cerebral arteries under increased blood pressure. Since cerebral arterial

spasm is defined clinically as the narrowing of major cerebral arteries (1), it is important, to study changes of arterial diameter in the circle of Willis or vertebro-basilar arteries to elucidate the changes brought about by hypertensive-hypervolemic therapy. The present study was designed to determine the reactivity of the cerebral arteries to increasing blood pressure under both untreated and spastic conditions, and the reason for the efficacy of induced hypertensive therapy.

MATERIALS AND METHODS

Ten adult cats were anesthetized with intramuscular ketamine hydrochloride (20 mg/kg). A volume-controlled respirator was attached by tracheostomy, and $PaCO_2$ was maintained between 35 and 45 mmHg. A polyethylene catheter was introduced into the femoral artery and attached to a Statham transducer to monitor the mean arterial blood pressure (MABP). A second catheter was inserted into the femoral vein for the administration of drugs. The head was immobilized in a stereotaxic apparatus.

The basilar artery was exposed transclivally using an operating microscope, as described elsewhere (12, 16, 24). The arachnoid membrane was removed from a portion of the exposed artery. Vascular spasm resulting from the operation was observed often, but disappeared in approximately 15 min. A 35 mm camera was mounted on the microscope, and serial photographs of the basilar artery were taken at 5-fold magnification, using Kodak High Speed Ektachrome film.

Blood pressure was raised gradually by the intravenous drip infusion of either norepinephrine hydrochloride (5-20 μg/kg) or angiotensin-II-amide (Hypertensin® CIBA, 0.3-1.0 μg/kg). When MABP greater than 50 percent above the pretreatment pressure was achieved, administration of the drug was terminated, and MABP gradually fell to the initial baseline level. Microphotographs were taken during both the increasing and decreasing blood pressure phases. The change in the basilar artery diameter was measured by comparison of the photograph.

After MABP returned to the initial control level, an arterial spasm was produced in the same basilar artery. The topical application of 2 ml of 0.2 M calcium gluconate reduced the basilar arterial diameter by 13 to 58 percent. Blood pressure was increased again, as above, 10 to 20 min after initiation of the arterial spasm. Serial photographs were taken again to measure the change in the arterial diameter. The changes in the vessel diameters were calculated by measurement of transverse breadth at three fixed positions of the basilar artery using the projected photographs. The diameter at a given pressure was expressed as the percent increase above the baseline values obtained prior to induction of hypertension. In the case of calcium gluconate-treated arteries, alterations in MABP were expressed as percentage change from the initial values.

RESULTS

Increased mean arterial blood pressure in basilar arteries (without spasm). Basilar arterial diameter was measured prior to and during induction and reduction of hypertension. Baseline MABP varied between 78 and 130 mmHg (104.6 ± 15.3 mmHg). Individual MABP before administration of hypertension-inducing drugs were stable. The blood pressure was increased in five cats by slow (over a 10 min) infusion of norepinephrine hydrochloride (Cats 1-5), and in the other five cats by

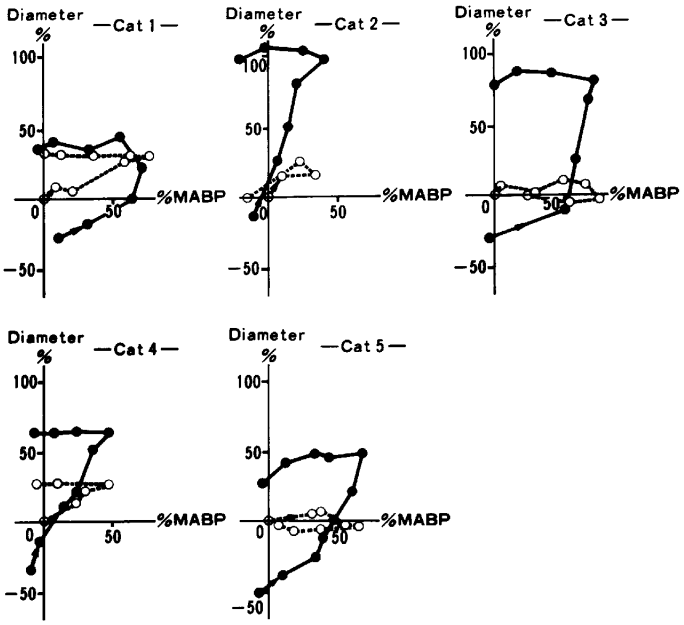


Fig. 1. Percent change in basilar artery diameter during norepinephrine-induced hypertension. Broken lines represent the changes in the diameter of the untreated arteries (prior to induced spasm), while solid lines show the changes of spastic arteries (following induced spasm).

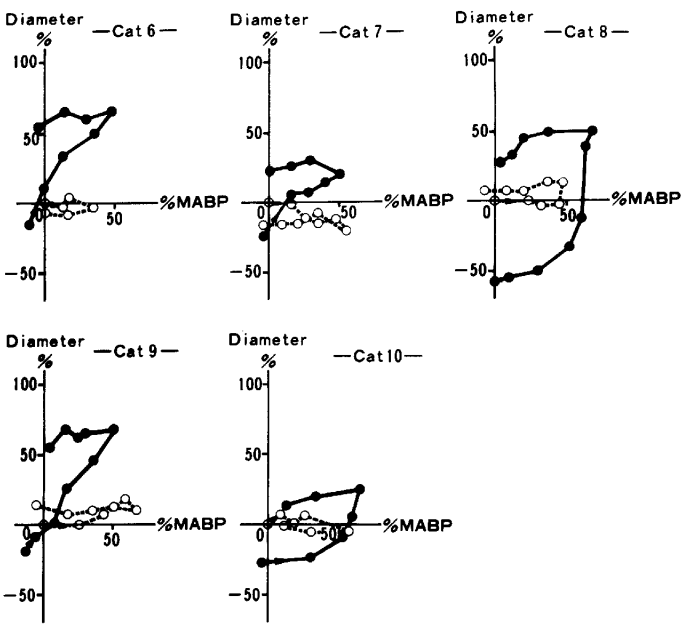
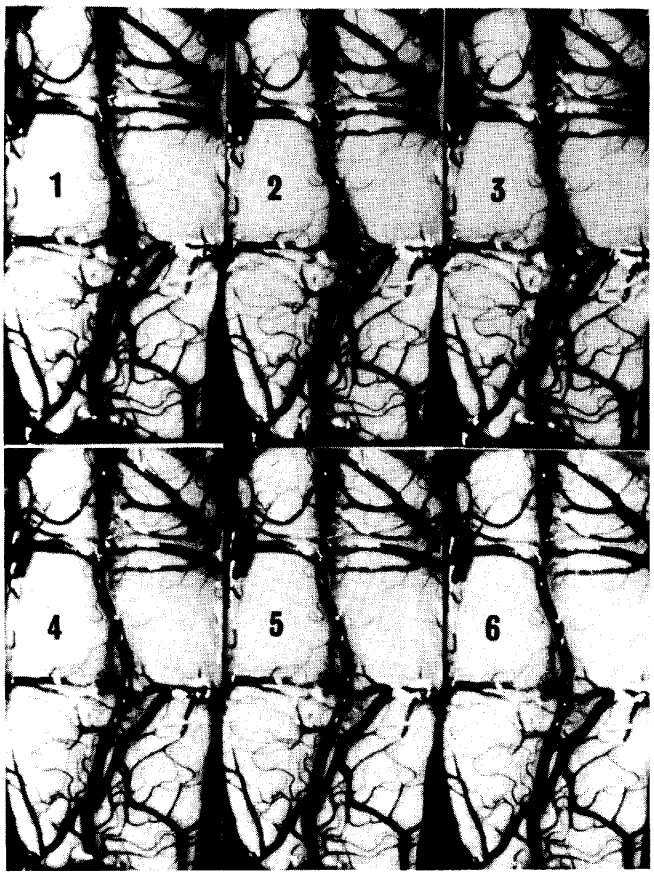


Fig. 2. Percent change in basilar artery diameter during angiotensin-induced hypertension. Broken lines, before spasm induction. Solid lines, after spasm induction.



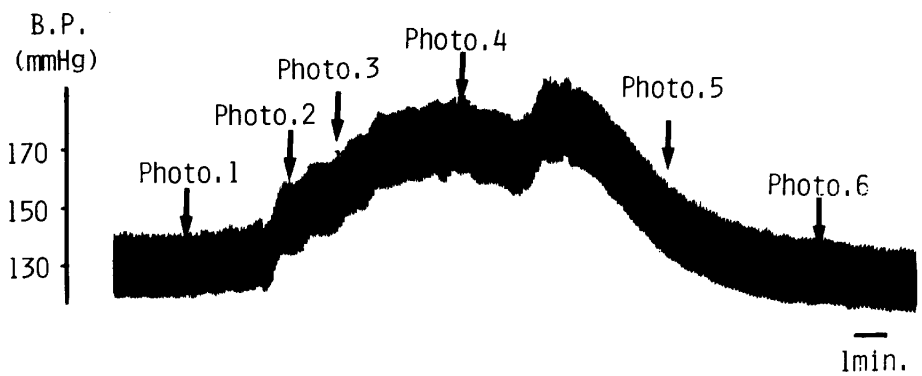


Fig. 3. Microphotographs of the untreated basilar artery in Cat 6 exposed transclivally during angiotensin-induced hypertension. Photograph 1 : MABP 130 mmHg ; 2 : 146.3 mmHg ; 3 : 153.1 mmHg ; 4 : 176 mmHg ; 5 : 150 mmHg ; 6 : 130 mmHg.

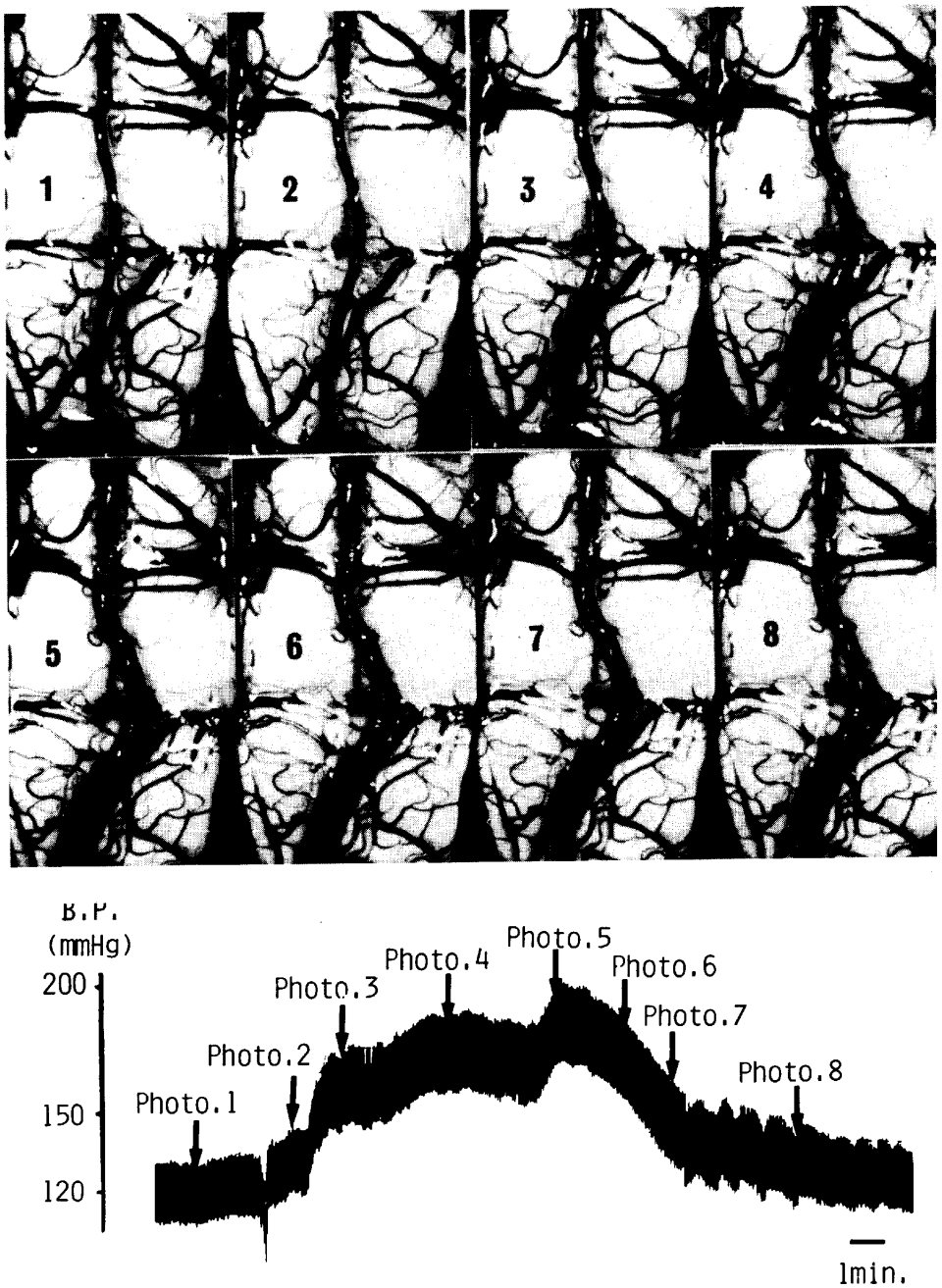


Fig. 4. Microphotographs of the spastic basilar artery in Cat 6 during angiotensin-induced hypertension. Photograph 1 : MABP 115.7 mmHg ; 2 : 130 mmHg ; 3 : 146.3 mmHg ; 4 : 176 mmHg ; 5 : 192.4 mmHg ; 6 : 171.6 mmHg ; 7 : 146.3 mmHg ; and 8 : 126.1 mmHg.

angiotensin-II-amide (Cats 6-10). MABP was raised from 78 to 168 mmHg in norepinephrine-treated cats and from 90 to 191 mmHg during angiotensin-induced hypertension. For each cat a series of 18 photographs were taken prior to and during norepinephrine-induced hypertension, and 20 photographs were taken prior to and during angiotensin-induced hypertension. The change in the diameter of the arteries during the course of both rising and falling blood pressures are shown in Figs. 1 and 2. The change in the vessel diameter ranged from −6 to +35 percent of the control during norepinephrine-induced hypertension, and from −20 to +18 percent during angiotensin-induced hypertension. In the norepinephrine-induced hypertension group, the diameter of untreated basilar arteries appeared to increase in company with the blood pressure (Fig. 5). The diameter of the arteries remained relatively constant in the angiotensin-induced hypertension group. The photographs of the basilar artery of Cat 6, in which no change was observed in the arterial diameter during angiotensin treatment, are shown in Fig. 3.

Increasing mean arterial blood pressure on basilar arteries with spasm. Arterial spasm was produced by the topical application of 2 ml of 0.2 M calcium gluconate in the same basilar artery which was studied earlier. The basilar arterial diameter decreased 13-58 percent. Blood pressure was raised by administration of norepinephrine in five cats (Cats 1-5) (Fig. 1) and with angiotensin in the other five cats (Cats 6-10) (Fig. 2). The MABP ranged from 82 to 173 mmHg during norepinephrine-induced hypertension, and from 88 to 192 mmHg during angiotensin treatment. The diameters of the spastic basilar arteries were measured 28 times during norepinephrine- or angiotensin-induced hypertension (Fig. 6).

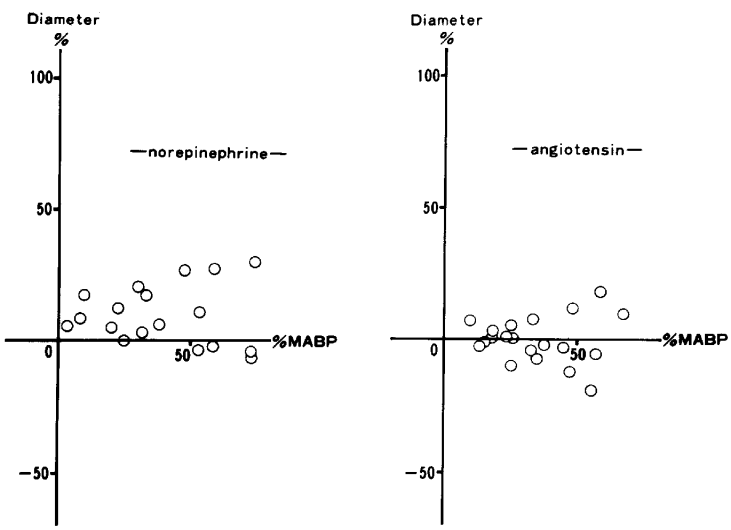


Fig. 5. Percent change in the diameter of untreated basilar arteries at various blood pressures. Left : Norepinephrine-induced hypertension. Right : Angiotensin-induced hypertension.

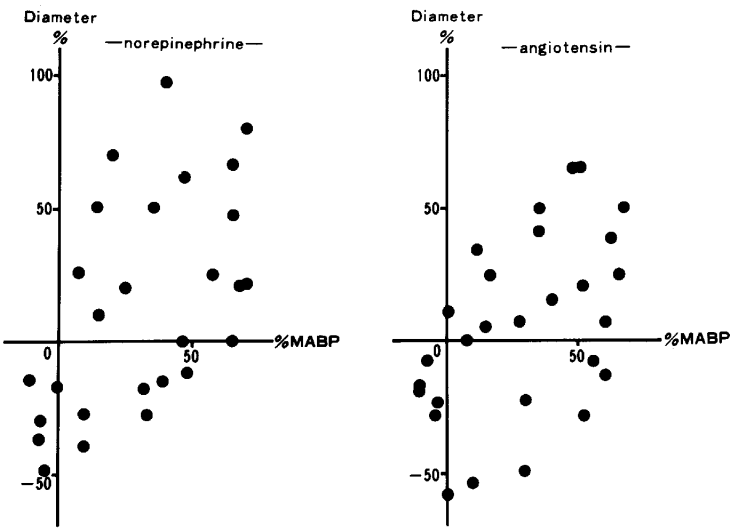


Fig. 6. Percent change in the diameter of spastic basilar arteries at various blood pressures. Left : Norepinephrine-induced hypertension. Right : Angiotensinin-duced hypertension.

The spastic arteries tended to remain constricted at lower blood pressures, while marked arterial dilations were observed with increased pressures. MABP and arterial diameter appeared to increase in parallel (Fig. 6). In all cats the arterial diameter at maximum MABP was greater than initially. The maximum increases ranged from 28 (Cat 7) to 108 (Cat 2) percent above the control level. Norepinephrine and angiotensin-II had similar effects on both the blood pressure and the spastic basilar arterial diameters.

The changes in the diameter of spastic arteries during both increasing and decreasing blood pressure are shown in Figs. 1 and 2. A remarkable dilation of the spastic arteries was noted at elevated blood pressures. Fig. 4 shows a series of photographs of the spastic basilar artery in Cat 6, which demonstrated a marked dilation with raised blood pressure. In all subjects the vessels remained dilated throughout the reduction of hypertension.

DISCUSSION

Fog (17) was the first to systematically study changes in normal pial vessel diameter in cats during changing perfusion pressures. Fog demonstrated that changes in intravascular pressure caused alterations in the physiologic state of the pial arteries, a fall in pressure caused relaxation of, and a rise in pressure constriction of the arteries. Lassen (27) established the concept of autoregulation of cerebral blood flow (CBF) in 1959, which proposes that a relatively constant blood flow is maintained over a wide range of cerebral perfusion pressures. It

has been generally accepted that cortical superficial arterioles and arteries constrict when blood pressure is raised. Thus under normal conditions, CBF autoregulation is thought to be a feature of the smaller resistance vessels, namely the arterioles and small arteries, although the exact size limit of the participating vessels remains unknown.

Gurdjian and Thomas (20) reported that mechanical manipulation of pial vessels over human or monkey brains did not result in contraction. However, the larger vessels of the circle of Willis were responsive to mechanical stimulation in the dog and the monkey. Their investigations indicate that the nature of the vascular wall differs between the arterioles or arteries of the cortical surface and the major cerebral basal arteries. Cerebral arterial spasm following SAH occurs mainly in the basal vessels of brain, namely the circle of Willis, the vertebro-basilar arteries, and their main branches (1).

Brawly and coworkers (6) first reported that CBF increased in parallel with a rising mean arterial blood pressure in the ischemic cortex of dogs. Recently many investigators have shown that the autoregulatory responses are impaired in various pathological conditions such as stroke (25, 31, 37, 47), head injury (34), the distressed newborn infant (28), and SAH (5, 14, 21, 35, 39). Impaired CO_2 response and autoregulation have been observed in patients with aneurysmal SAH suffering severe neurological deficits secondary to marked vasospasm and depression of mean CBF (23).

On the basis of poor or absent autoregulation in the ischemic brain, treatment of cerebral ischemia by increasing the blood pressure has often been much described since Denny-Brown first attempted it clinically (9, 13, 41). Kosnik and Hunt (26) first reported seven cases with ischemic syndrome attributable to cerebral arterial spasm following SAH, six of which were successfully treated by elevation of the systemic blood pressure. Subsequently several investigators have reported the efficacy of induced hypertension in treating cerebral arterial spasm (7, 8, 19). In these reports, induced hypertension was effective in alleviating the ischemic syndrome, although pathophysiological studies of the cerebral circulation, such as regional CBF, and angiographical findings of the spasm and its sequential time course, were not fully shown and discussed.

In the present study, the diameter of untreated basilar arteries in the cat was not significantly affected by elevation of blood pressure. Meyer *et al.* (30), reported that the larger cerebral vessels of rhesus monkeys showed minimal change during induced hypertension, but the method of measuring vessel diameter and blood pressure was not delineated in detail. Olesen (33) noted that carotid angiograms revealed no remarkable changes in the diameter of the larger cerebral arteries before and during intracarotid infusion of norepinephrine in patients with brain tumors, although intracarotid norepinephrine infusion increased the blood pressure slightly. Such slight changes in arterial diameter are assumed to be a direct effect of the vasoconstrictive agent on the arterial wall and not secondary

to the induced hypertension. If so, it is curious that the diameter of normal basilar arteries remained relatively constant during induced hypertension in the present study. This situation may be explained on the grounds of an *in vitro* experimental study (3). It was shown that the basilar and internal carotid arteries response to several adrenergic agents was much less than that of the mesenteric, renal and femoral arteries in dogs. It is likely that administration of adrenergic agents induces hypertension by constriction of mesenteric, renal and femoral arteries without any effect on the major cerebral arteries.

The nature and action of various vasoactive substances have been discussed, and many agents, among them hemoglobin, prostaglandins, and serotonin, have been hypothesized as being responsible for cerebral arterial spasm. The actions of such putative regulators may be synchronous or sequential, but the final common pathway involves the cation calcium (10). The contraction of vascular smooth muscle is determined by the distribution, and flux of calcium ions (4). Hiraoka *et al.* (22) demonstrated that an increase in the extracellular Ca^{++} concentration could cause vasoconstriction. Persistent cerebral arterial constriction requires increased intracellular Ca^{++} concentration. Herein, basilar arterial spasm was produced by topical application of 0.2 M calcium gluconate. The basilar artery diameter was reduced 13 to 58 percent. This model mimics the situation following SAH, and is thus useful in the study of SAH.

Increasing blood pressure produced a characteristic change in the diameter of spastic basilar arteries in cats . The diameter of the arteries increased progressively, exceeding the initial, nonspastic, control values. The arteries appeared to dilate passively in response to increasing pressure. This suggests that there is a difference in the nature of vascular wall responsiveness to the increasing blood pressure between untreated and spastic basilar arteries.

The distensibility of spastic cerebral arteries has not been scrutinized. Nagasawa and coworkers (32) made biomechanical studies of segments of intracranial vertebral arteries obtained from autopsy of patients with subarachnoid hemorrhage. The pressure-diameter curves of the arteries were biphasic, having a sharp flexion point, beyond which the vascular wall become distensible. It was thus postulated that induced hypertension might dilate spastic cerebral arteries. The present results support this *in vitro* investigation. Pressure sensitive arterial dilation indicated a flexion point in half of the cats (#1, 3, 5, 8,and 10), while the arterial diameter increased linearly in the others.

In large spastic cerebral arteries of the baboon, DuBoulay *et al.* (11) observed that an elevation of blood pressure caused arterial dilation. When the blood pressure rose or was maintained at a high level, it resisted or partly overcame the vasoconstrictive actions. Thus, spastic cerebral arteries, both *in vitro* and *in vivo*, have been shown to be dilated more easily by increasing blood pressure than untreated vessels. However, the exact reason for this difference is still unknown.

Smooth muscle relaxation results from a series of complex reactions which require an adequate supply of high energy phosphate bonds. According to Sundt (38), the contracted state is likely to persist in ischemic vascular smooth muscle, because there is insufficient energy to maintain the membrane function, the 10,000-fold difference between extra- and intra-cellular calcium concentrations promotes inward Ca^{++} flux, and there is insufficient energy for the intracellular sequestration of the inflowing calcium. It is presumed that in spastic cerebral arteries an increased perfusion pressure enhances blood flow, which provides sufficient energy for muscle relaxation and subsequent vessel dilation. Although Folkow *et al.* (18), argued that vascular distension is roughly balanced by adaptive changes in smooth muscle tone under normal condition, spastic arteries may lack this ability to adapt.

The present study demonstrated that mechanical force generated by induced hypertension could dilate spastic cerebral arteries. This supports the clinical use of induced hypertension as a therapy for cerebral arterial spasm following SAH.

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