Stiffness of Cerebral Arteries—Its Role in the Pathogenesis of Cerebral Aneurysms

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Summary

Distensibility of human cerebral arteries was compared quantitatively with extracranial arteries using a parameter which was obtained from the pressure-radius data. It was found that cerebral arteries were much stiffer than the extracranial arteries of comparative sizes. The stiffness of cerebral arteries reached nearly maximum at the middle age and did not progress thereafter. Effect of arterial stiffness on blood flow was also examined using pulsatile flow in polymer tubes with different distensibility under the influence of sinusoidally oscillating pressure. The stiffer the tube was, the higher was pulsatile pressure. It is concluded that much larger fluctuation of pressure may occur in the cerebral arteries compared with extracranial arteries and induce the degenerative change or structural weakness in the wall, especially at the apex of bifurcation, which may play important roles in the pathogenesis of cerebral aneurysms and the mechanism of their growth and rupture.

Key words: Cerebral aneurysms, Vascular distensibility, Pathogenesis

Introduction

Saccular aneurysms are common in the cerebral arteries and rather rare elsewhere in the body. There are many theories[5,6,7,10,12,13,27,28] concerning the etiology of cerebral saccular aneurysms. These are congenital, acquired and of a combination of both lesions. From the biomechanical point of view, the formation of aneurysms seems to be related to a breakdown of strength and cohesion of the arterial wall at the site of aneurysms. Some unique morphological features of the cerebral arteries, especially at the apex of bifurcation where aneurysms usually develop, have been stressed[5,6,10,12,15]. However, there are few studies with regard to mechanical properties of the cerebral arteries related to these structural characteristics[4,26].

In the present study, a quantitative evaluation of the distensibility of cerebral arteries was made in comparison with extracranial arteries of comparable size. Then the effect of arterial stiffness on blood flow was examined. Based on these results as well as the morphological characteristics of cerebral aneurysms, the pathogenesis of cerebral aneurysms was discussed.

Mechanical Properties of Human Cerebral Arteries

1. *Materials and Methods*

Tubular segments approximately 3 cm in length of the common carotid, basilar, renal and mesenteric arteries, were obtained from four necropsies. They were stored at around 4 °C in physiological saline solution mixed with 1/10,000 merthiolate[2,23]. The following mechanical testing was carried out within 48 hours after isolation of the arterial segments.

First, a glass cannula whose external diameter was nearly equal to the internal diameter of the specimen was inserted into the each end of an excised arterial segment. The segment was fastened to the glass cannula by tying a ligature. The apparatus used for the measurement of vascular distensibility is schematically shown in Fig. 1. Each specimen was set to the apparatus in its in vivo length by adjusting the cannula. Intraluminal pressure of the arterial segment was raised by a one-way rubber hand pressure bulb through an 18-liter air reservoir bottle with physiological saline solution of 37 °C. The

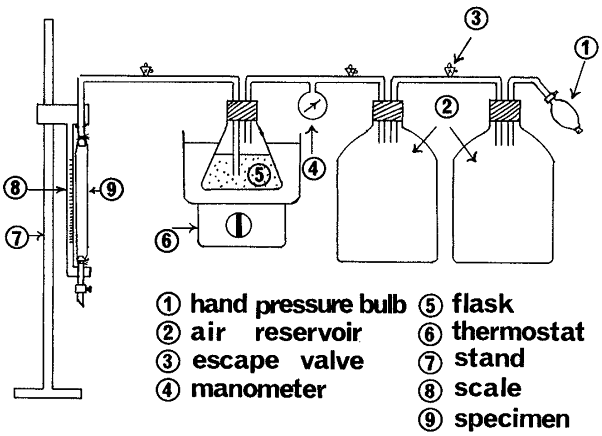

Fig. 1. Schematic diagram of testing apparatus.

external diameter of the specimen was measured using a photographic camera.

Before the measurement, gradual pressurizing and depressurizing maneuvers between 20 to 200 mmHg were repeated four to five times so that a stable pressure-diameter relationship was obtained. After effects of initial stress relaxation had disappeared, the internal pressure was raised up to 200 mmHg and then lowered down to 20 mmHg, step by step at the intervals of 10 mmHg. The external diameter was measured at each pressure level after loading the pressure for about 5 seconds.

The distension ratio, $(\lambda_0)_s$, was defined as the ratio of external radius, R_0, at each pressure, P, to that at 100 mmHg, $(R_0)_s$, and was used to represent the deformation due to the pressure change. The pressure of 100 mmHg, P_s, was adopted as the standard physiological pressure. The ratio of P to P_s was named the relative pressure.

2. *Results*

Relations between the internal pressure and the external radius of four kinds of arteries are shown in Fig. 2. When the distension ratio, $(\lambda_0)_s$, was plotted against the logarithm of relative pressure, $\ln(P/P_s)$, nearly linear relations were obtained in the physiological pressure range as shown in Fig. 3. These relations were described by the following equation,

$$\ln(P/P_s)=\beta((\lambda_0)_s-1).$$

In this equation, β is the slope of each line in Fig. 3 and proved to be a parameter representing the distensibility of human arteries. The larger the value of β is, the lower is the distensibility of arteries, that is, the parameter β

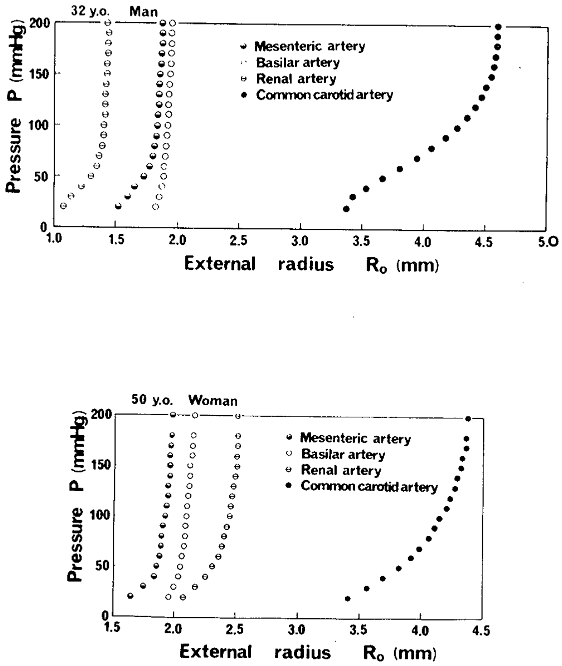

Fig. 2. Changes in external radius due to internal pressure in four kinds of human arteries.

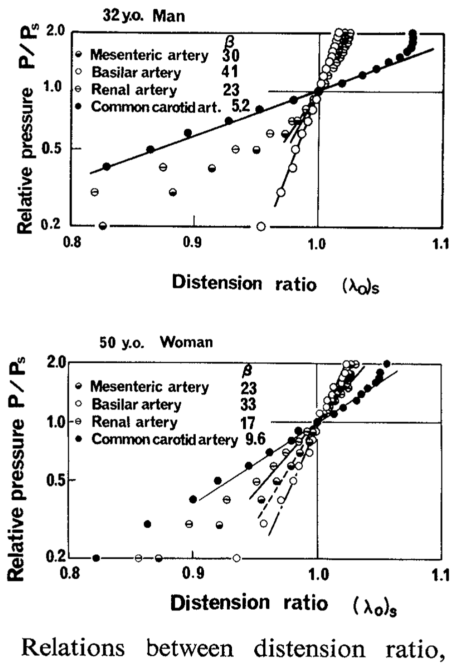

Fig. 3. Relations between distension ratio, $(\lambda_0)_s$, and logarithm of relative pressure, $\ln(P/P_s)$, in four kinds of human arteries. Nearly linear relations were observed between them.

corresponds with the stiffness of arteries. As shown in Fig. 3, the value of parameter β of the basilar artery, which stands for the large cerebral arteries, is much larger than that of the extracranial arteries of almost the same diameter. This result implies that cerebral arteries are generally much stiffer than extracranial arteries.

Fig. 4 shows the changes of the distensibility

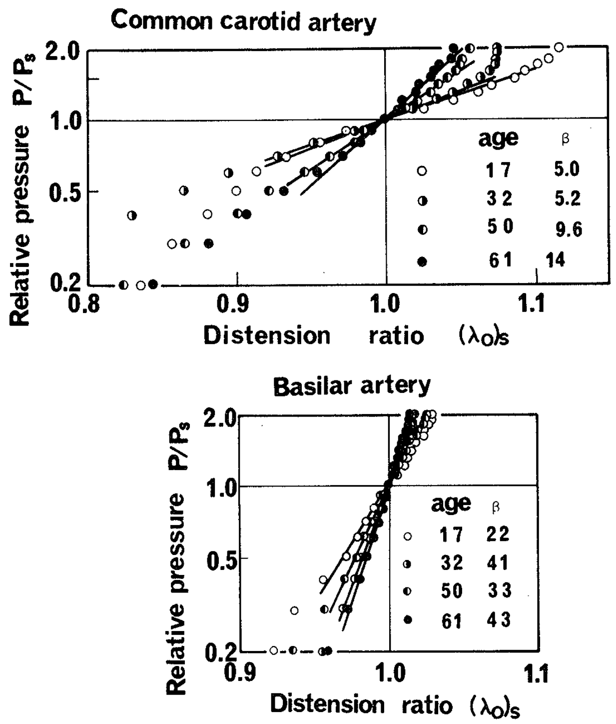

Fig. 4. Change in distensibility with age in two kinds of human arteries.

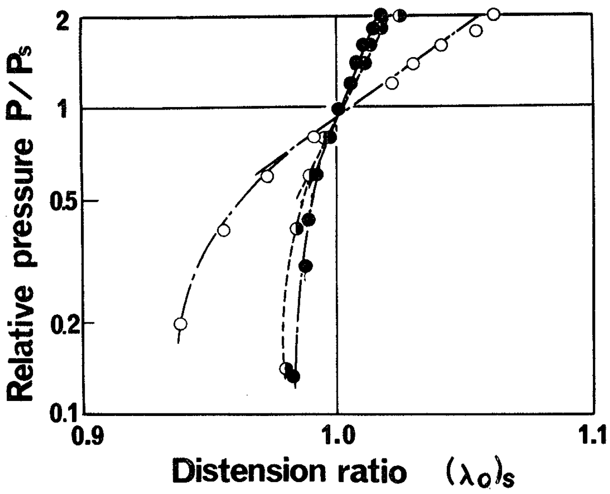

Fig. 5. Relations between distension ratio, $(\lambda_i)_s$, and logarithm of relative pressurem $\ln(P/P_s)$, of three kinds of elastic tubes.

Table 1. Dimensions and distensibilities of three kinds of tubes.

	Material	Internal diameter D_i (cm)	Wall thickness t (cm)	Distensibility (β)
Elastic tube	Rubber	0.47	0.117	15
Medium tube	Synthetic polymer	0.50	0.092	44
Stiff tube	Synthetic polymer	0.46	0.211	51

of the common carotid and basilar arteries with age. The value of β of the common carotid artery increases with increasing age, while the basilar artery does not change the value of β, being already a high value at the middle age.

Effects of Cerebral Arterial Distensibility on the Pulsatile Blood Flow

1. *Materials and Methods*

Three kinds of polymer tubes with almost the same internal diameter and length but with different distensibilities were used as the models of arteries. The distensibility of each tube was represented by a parameter β which was determined by the same method as for arteries. In this case, however, the distension ratio was calculated using the internal radius of tubes instead of the external radius and denoted by $(\lambda_i)_s$. Fig. 5 shows relationship between the distension ratio, $(\lambda_i)_s$, and the relative pressure, (P/P_s), from which the value of β was calculated for each tube. Dimensions and distensibilities of these three tubes are shown in Table 1.

Water was flowed through these three tubes. The pressure waves were made nearly sinusoidally by a pulsatile-flow generator. The set-up for the flow experiment is schematically shown in Fig. 6. Mean flow velocity, $\overline{V}$(cm/sec), was

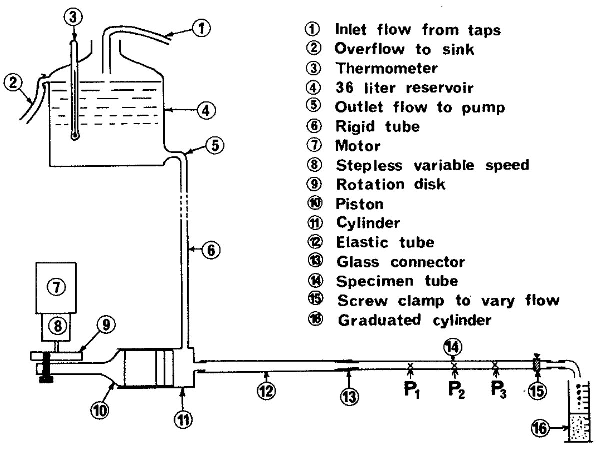

Fig. 6. Schematic diagram of pulsatile-flow generator.

determined from the water volume stored in a graduated cylinder in a unit time. In part of the experiments, a physiological saline solution was used instead of water to measure instantaneous flow velocity, V(cm/sec), by an electromagnetic flowmeter (Medicon, FM-6R). The Reynolds number (Re) was calculated from the.

following dimensionless expression,

$$\mathrm{Re} = \rho VD/\eta,$$

where ρ is the fluid density ($\mathrm{gm/cm^3}$), η the fluid viscosity (poise) and D the internal diameter of the tube (cm). This number is useful to obtain hydrodynamically analogous flow of different fluids in tubes of different sizes. For example, the mean blood flow velocity in a human internal carotid artery was estimated as about 50 cm/sec from the mean flow-volume and its internal diameter[10] or from the cerebral transit time[11]. This flow velocity corresponds to Reynolds number of about 750[10]. In the present experiments, the pulsatile flow with the Reynolds number of about 700 was used to model the blood flow in large cerebral arteries where aneurysms commonly occur. Mean pressure was adjusted by changing the level of water reservoir. Oscillating pressure was superimposed upon the mean pressure by reciprocating a piston with a stepless variable speed which regulated the pulse rate. Pulse pressure, ΔP, was adjusted by changing the stroke of piston. If the pump is regarded as the heart and the specimen tube as the peripheral artery, the tube put between them corresponds to the aorta. This tube played the role of making the pressure wave of pulsatile flow smooth and sinusoidal. Intraluminal pressure was measured by a pressure transducer (Nihon-Kohden) through a 19 gage stainless steel pipe inserted radially into the lumen of specimen tube at the middle point, P_2 (Fig. 6).

2. Results

Relations between the instantaneous flow velocity and the stroke volume ratio are shown in Fig. 7, where the stroke volume ratio represents the relative stroke of the piston. With the increase in the stroke volume ratio, n, the maximum flow velocity (peak velocity), max, V., increases, while the minimum flow velocity, min. V., decreases. Flow fluctuation, ΔV, which defines the difference between the maximum and the minimum velocities, is almost proportional to the stroke volume ratio, n.

Fig. 8 shows an example of pressure waves recorded in three kinds of tubes under almost the same flow conditions, namely, at the pulse rate of 70 cmp, Reynolds number of about 700, and the stroke volume ratio of 8. Fig. 9 shows the effects of the stroke volume ratio on the maximum pressure, the mean pressure, the minimum pressure and the pulse pressure. The stiffer the tube is, the higher are the maximum pressure and the pulse pressure. This tendency becomes more prominent as the stroke volume ratio increases. Fig. 10 shows the effects of pulse rate on the pulsatile pressure when stroke volume ratios were 4 and 8. As the pulse rate increases, the maximum pressure increases and

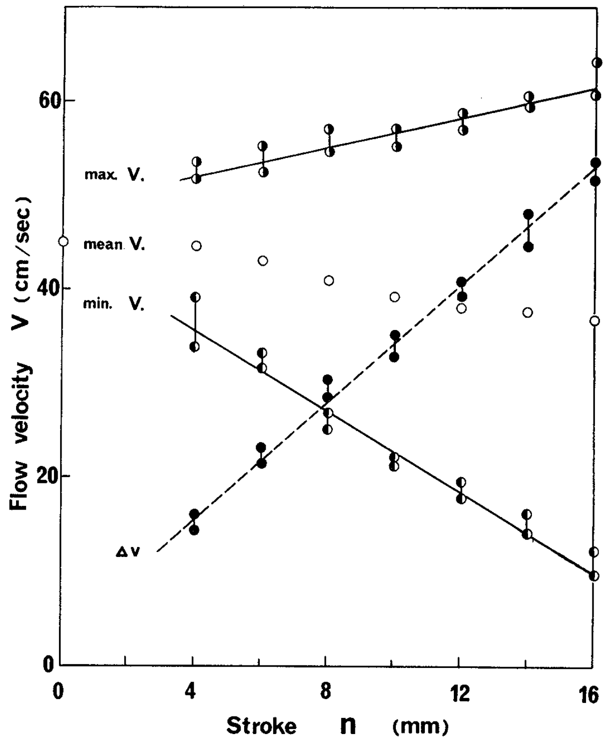

Fig. 7. Relations between the instantaneous flow velocity and the stroke volume ratio.

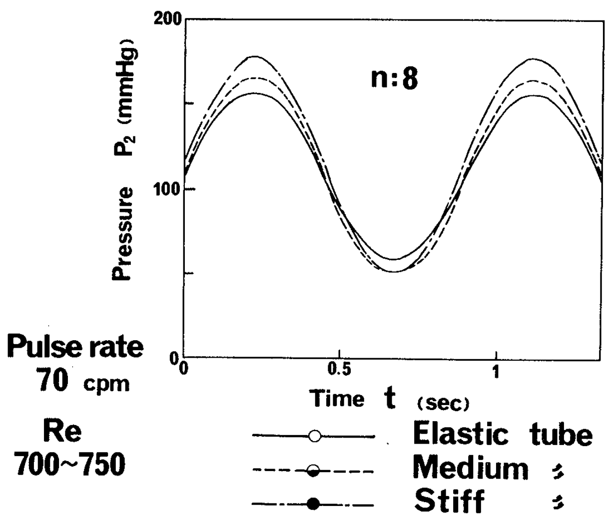

Fig. 8. An example of pressure waves recorded in three kinds of tubes under almost the same flow condition.

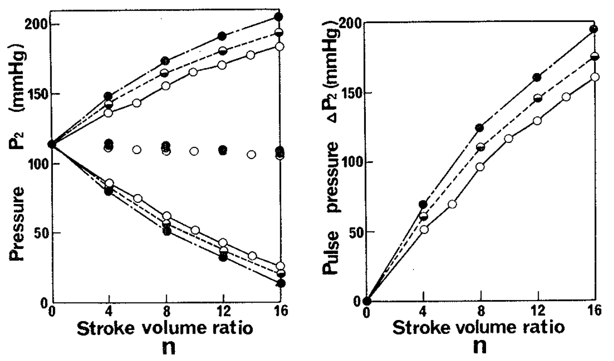

Fig. 9. The effects of the stroke volume ratio on the pressure components. The left shows the maximum pressure, the mean pressure and the minimum pressure, and the right shows the pulse pressure in three kinds of tubes.

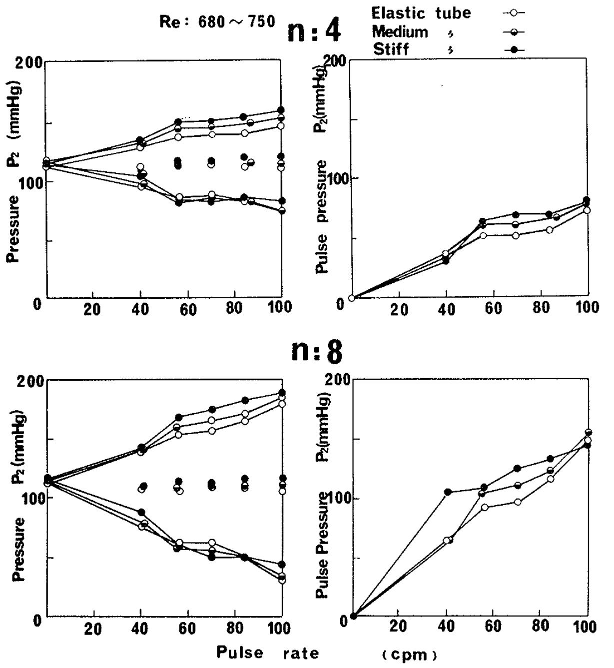

Fig. 10. The effects of pulse rate on the pulsatile pressure in the cases of the stroke volume ratios of 4 and 8. The left shows the maximum pressure, the mean pressure and the minimum pressure, and the right shows the pulse pressure in three kinds of tubes in each case.

the minimum pressure decreases so that the pulse pressure is raised. The pulse rate has the similar effects on the pressure components to the distensibility of tubes.

Discussion

Regarding the principal histological differences between larger arteries at the base of the brain and extracranial arteries with almost the same diameter, the following features have been pointed out[8]: (1) The much reduced adventitia of intracranial arteries, consisting of a thinner layer of collagen fibers with very poor development or virtual absence of elastic fibrils in the adventitial coat; (2) The relative pausity of elastic fibrils in the medial coat of the intracranial arteries; and (3) The relative prominence of the internal elastic lamina in the intracranial arteries. These structural transitions occur in the internal carotid[22] and vertebral arteries[29] as they enter the intracranial cavity. Some researchers[7,10,27] pointed out that the exceedingly frail adventitia, the concentration of elastin chiefly into the internal elastic lamina, the striking involvement of the media in established atheroma, and the absence of close investiment of arteries by stronger tissues with independent blood supply might play important roles in the formation of cerebral aneurysms. These peculiar morphological features of cerebral arteries must reflect their mechanical properties.

Distensibility of extracranial arteries have been studied by a few researchers[2,21,23,24]. However, studies of the mechanical properties of cerebral arteries are rare[4,26].

In the present study, the distension ratio, $(\lambda_0)_s$, and the relative pressure (P/P_s) were defined in order to examine the distensibility of arterial walls. Linear relations were observed between $\ln P/P_s$ and $(\lambda_0)_s$ (Figs. 3 and 4), and they were described by an exponential function given in Eq. 1. The slope of the relation gives a parameter β, which represents the whole deformation behavior of vascular wall in the physiological pressure range. These figures show that cerebral arteries are much stiffer than extracranial arteries, which is quantitatively expressed by means of the parameter. This mechanical characteristic of cerebral arteries is ascribed to the paucity of elastic fibrils in the medial and adventitial coats, which is peculiar to cerebral arteries.

The reduction of distensibility of arteries with age had been observed in various kinds of human arteries[21,24]. Busby et al.[4] analized the pressure-volume data of major brain arteries aged 2 to 90 from autopsies. They observed that increase in the arterial length with distension was very small and negligible in vessels older than 30 years, and demonstrated quantitatively that the maximum stretches of cerebral arteries aged 30 to 90 were less than that of extracranial peripheral arteries. They considered that a decrease in the distensibility of arteries with age was due to the reduction of slackness of collagen fibers. In the present study, it was observed that the stiffening of basilar arteries with age reached nearly maximum by the middle age and does not progress thereafter, while the common carotid artery is stiffened significantly with age even after the middle age. This observation endorses the common occurrence of aneurysms after the middle age.

In general, relatively proximal large arteries which are rich in elastin are more distensible than distal arteries[17]. This fact may be one of the rational mechanisms in the cardiovascular system, for the pulsatile flow generated by the heart is gradually buffered during passing through aortas and large arteries with high distensibility, and moreover in peripheral blood vessels it becomes a steady flow which is advantageous for material exchanges between the blood and tissues. This effect of the arterial distensibility on pulsatile blood flow has been widely known as the "Windkessel effect". Luchsinger et al[16]. measured blood pressures at various points in the human aorta and observed that the pressure fluctuation increased with the distance from the heart. They attributed this phenomenon to the progressively increasing stiffness of the vessel wall along the aortas. The present study also substantiated it by model experiments. These experimental facts imply that the relatively stiffer cerebral arteries induce the increase in pressure fluctuation of the blood flow within the head. There have been few measurements of the blood pressure in the human cerebral artery because of the hazard and the nonfeasibility in measuring it[1,3,30,31]. Recently Ferguson[9] measured directly the intra-aneurysmal pressure during operative procedures and found out that the intra-aneurysmal mean pressure and pulse pressure were almost similar to those of the systemic pressure, respectively. This result suggests that the blood pressure in cerebral arteries is rather high and is one of the most important factors responsible for the development of intracranial aneurysms.

It has been shown that the apex of cerebral arterial bifurcation, where aneurysms commonly occur, is a weak point because of the muscular deficit in this area[5,6,10,12,15]. As the wall with this medial defect is mainly composed of internal elastic lamina, this site is considered to be extraordinarily flexible in contrast to the other greater parts of stiff cerebral artery. This singularity of structure at the apex cause repeated strains there locally. By model experiments Rodbard[25], and Hassler[13] demonstrated the possibility that high stress was induced at the apex of bifurcation by the impingement of central streams. Developed stress there thus has been taken as one of the important factors in the occurrence of cerebral aneurysms. The arterial wall within the head is relatively stiff as shown in Fig. 3, which induces relatively high fluctuation of pressure in cerebral arteries as shown in Fig. 9. On the other hand, as the wall at the apex is uniquely flexible due to having medial defect, large fluctuations of stress and strain are developed there. High fluctuation of pressure in the cerebral artery and high flexibility at the apex of bifurcation induce the degenerative changes in the wall at the apex similar to the fatigue process of metals and develop saccular aneurysms of the cerebral arteries.

However, if the medial defect at the apex of cerebral arterial bifurcation was covered with an intimal pad, apical defect may be protected from the development of aneurysm, for the intimal pad seems to possess high strength and will reinforce wall there[14,18]. These hypothesis also can be supported by our other experimental and pathological studies[17,18,19,20].

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