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Posterior Ciliary Artery Occlusion

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Abstract

Objective—To compare the severity of ischemic damage following posterior ciliary artery (PCA) occlusion in old, atherosclerotic, hypertensive monkeys to that in young monkeys.

Design—Experimental study.

Subjects—Seven eyes of normal, healthy rhesus monkeys and 8 of old, atherosclerotic, hypertensive monkeys.

Methods—By lateral orbitotomy, all PCAs were cut behind the eyeball in both groups of animals. The fundus and the optic disc were evaluated by repeated ophthalmoscopy, color fundus photography and fluorescein fundus angiography, before and immediately after cutting the PCAs and serially thereafter during the follow-up period.

Main Outcome Measures—Severity of acute ischemic damage to the choroidal, outer retinal and optic nerve head.

Results—Cutting all the PCAs resulted in the development of ischemic infarction of the choroid, retinal pigment epithelium, outer part of the retina and the optic nerve head within 24-hours, in both groups of animals. The severity of the various ischemic fundus and retinal lesions and of the optic disc during the acute phase showed no statistically significant differences between the two groups of animals. Fluorescein fundus angiography soon after cutting the PCAs showed no filling of the entire choroid and the optic disc in both groups of animals. On follow-up for up to about 3 months, in both groups, the white opacity of the infarct in the fundus seen during the acute phase gradually resolved in about 2–3 weeks, leaving greyish, granular, depigmented fundus, unmasking of the large choroidal vessels and optic atrophy; fluorescein angiography revealed gradual restoration of the choroidal blood flow and unmasking of the big choroidal vessels.

Conclusions—The study showed that the severity of ischemic damage following occlusion of all the PCAs was similar in both the young healthy and the old, atherosclerotic, hypertensive monkeys. This is in contrast to the findings of our similar study dealing with central retinal artery occlusion, where the young suffered much severe ischemic damage than the old.

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Our studies of central retinal artery occlusion in (a) young¹ and (b) old, atherosclerotic, hypertensive² rhesus monkeys showed that the severity of acute retinal ischemic damage following central retinal artery occlusion was much less in old, atherosclerotic, hypertensive monkeys than in the young healthy monkeys. This indicated that the retina of the old, atherosclerotic, hypertensive monkeys tolerated acute ischemia much better than that of the young monkeys. We discussed the reason for that disparity elsewhere.^{2,3} No information is available about the difference in severity of acute ischemic damage produced by the occlusion of the posterior ciliary artery (PCA) between the young and the old, atherosclerotic, hypertensive rhesus monkeys. I investigated that in the present study.

The PCA circulation is the most important component of the ocular and optic nerve head circulation. This is because it is the main source of blood supply to the optic nerve head (Fig. 1), the outer 130 μ of retina, the retinal pigment epithelium, the choroid up to the equator, and the medial and lateral segments of the ciliary body and iris.

Materials and Methods

In rhesus monkeys, by lateral orbitotomy, under intravenous pentobarbital sodium anesthesia, all PCAs were exposed in the retrobulbar region up to their sites of entry into the eyeball, without cutting any of the extraocular muscles or interfering with any other arterial supply to the globe. All PCAs were cut by a cautery near their site of entry into the eyeball in 7 eyes of normal, healthy rhesus monkeys and in 8 eyes of old, atherosclerotic, hypertensive rhesus monkeys. The orbitotomy wound was closed in layers. All the eyes were evaluated by repeated ophthalmoscopy, color fundus photography and fluorescein fundus angiography before the occlusion, about one hour, and one day after the occlusion, and serially thereafter during the follow-up period, until the animals were sacrificed. The fundus was evaluated in the peripapillary, macular, middle and peripheral regions, and the optic disc. Intraocular pressure was measured in all the eyes serially during the initial and later stages of the study.

The study design complied with the National Institute of Health's Guidelines, the Association for Research in Vision and Ophthalmology Statement for the Use of Animals in Ophthalmic and Vision Research, as well as the University of Iowa's Institutional Guidelines for the Care and Use of Laboratory Animals.

In the atherosclerotic, hypertensive monkeys, atherosclerosis had been produced experimentally by feeding the animals a special atherogenic diet continuously, for many years. The atherogenic diet contained (according to the manufacturer) 17.45% protein, 20.92% fat, 44.52% carbohydrates and 1.26% cholesterol, with a caloric value of 4.36 kcal/gram of diet (16% from protein, 43.2% from fat and 40.8 % from carbohydrates). Serial fasting plasma lipid estimations in these animals showed a sustained rise in fasting plasma cholesterol level of up to 665%, without any significant change in the mean high density lipoprotein values, and triglyceride levels were elevated in some of the animals. Autopsy studies performed in all animals in the atherosclerotic group showed extensive atherosclerotic lesions in the aorta and coronary, renal and other major arteries. In these animals, also, chronic arterial hypertension was produced by modified Goldblatt's

procedure⁴ and maintained for a period of years, as confirmed by serial blood pressure measurements.

Results

Fundus changes during the acute phase

Table 1 summarizes the severity of acute fundus changes after the occlusion of the PCAs in the young healthy monkeys, and table 2 in the old, atherosclerotic, hypertensive monkeys. The normal fundus in rhesus monkeys has a dark brown appearance; ischemic infarction of the retinal pigment epithelium and the outer retinal layers (Fig. 2), supplied by the PCA circulation, initially manifested as whitish retinal opacity (Figs. 3, 4A). Acute ischemia of the optic nerve head resulted initially in development of optic disc edema (Figs. 3, 4A), which represented anterior ischemic optic neuropathy. There were no changes in the inner retina (Fig. 2) and retinal vessels (Figs. 4B, E).

To find out if there was any difference in the severity of the various acute ischemic lesions during the acute phase in the fundus and the optic disc between the two groups of animals, a statistical analysis was performed, comparing the young, healthy monkeys without atherosclerosis and arterial hypertension to the old monkeys with atherosclerosis and chronic arterial hypertension. Table 3 summarizes the findings. It showed no statistically significant difference between the two groups in the severity of various acute fundus lesions during the acute phase.

Fluorescein fundus angiographic findings during the acute phase

Soon after the occlusion of the PCAs, there was no filling of the entire choroid and the optic disc in both groups of animals (Fig-5), except for some late filling of the peripapillary choroid in most of them (Figs 4B, 6), and late staining of the edematous optic disc and patchy filling of the choroid via collaterals (described elsewhere⁵) (Fig. 4C). In eyes with no optic disc edema, the disc filled on fluorescein angiography. The retinal circulation filled normally in eyes in both the groups.

Late fundus changes

All eyes with optic disc edema later on progressively developed optic atrophy because of anterior ischemic optic neuropathy (Figs. 4D, 7). In both groups, the white opacity of the fundus seen during the acute phase gradually resolved in about 2–3 weeks, and the involved part of the fundus assumed a greyish, granular, depigmented appearance, with unmasking of the large choroidal vessels, except for the peripapillary choroid in some of the eyes (Figs. 4D, 7).

Late fluorescein fundus angiographic findings

One day after the occlusion, the vascular filling pattern was usually similar to that soon after the occlusion of the PCAs. After that, the choroid gradually started to show patchy filling at first, and more marked later on (Fig-4E). The optic disc filling also started to improve slowly – much faster and better in the old, atherosclerotic, hypertensive group than the young animals. The unmasked choroidal vessels could be seen distinctly (Fig. 4E). Where the

fundus was normal or the retinal pigment epithelium was only partly destroyed by ischemia, choroidal fluorescence was seen, but where there was complete loss of the choriocapillaris, no choroidal fluorescence was seen (Fig. 4E).

Other late findings

In the old, atherosclerotic, hypertensive group, 5 eyes developed iris neovascularization 2–3 weeks after the PCA occlusion and one developed corneal neovascularization; none of the young monkeys developed any of that.

Discussion

Our study showed that the severity of acute ischemic lesions produced by occlusion of the PCAs did not differ significantly between the young rhesus monkeys without atherosclerosis and arterial hypertension and the old monkeys with atherosclerosis and arterial hypertension. During follow-up of these animals for about 3 months, there were only the following minor differences:

1. On follow-up, in the old, atherosclerotic, hypertensive group, on fluorescein fundus angiography, the optic disc filling started to improve faster and better than in the young animals, without any difference in the choroidal filling pattern. I have no definite explanation for this difference. The peripapillary choroid is the major source of supply to the optic nerve head (Fig. 1). Soon after the occlusion of the PCAs, many eyes showed slow filling of the peripapillary choroid (Figs. 4B, 6) via its pial collaterals (discussed elsewhere⁵) (Fig. 1), but there was no apparent difference in the two groups in the frequency of their filling. That does not seem to explain this disparity in the improved, faster and better filling of the optic disc in the older group than the younger one.
2. In the old, atherosclerotic, hypertensive group, 5 of the 8 eyes developed iris neovascularization 2–3 weeks after the PCA occlusion and one developed corneal neovascularization; but none of the young monkeys developed any of that. The cause seems to be that in the older group the two small, long posterior ciliary arteries, which supply blood to the anterior segment of the eye, developed atherosclerotic, hypertensive changes; the additional effect by the PCA occlusion could have further impaired the blood supply and resulted in anterior segment ischemia.

As mentioned above, our previous experimental study in rhesus monkeys^{1,2} showed that acute retinal ischemic damage was much less severe following central retinal artery occlusion in old, atherosclerotic, hypertensive monkeys compared with young, healthy monkeys. We discussed the reason for that disparity elsewhere.^{2,3} However, following PCA occlusion, there was no such difference between the two groups. The study protocols for the occlusions of central retinal artery and PCAs were similar for the fundus and angiographic evaluations, but retinal function evaluation facility was available in the central retinal artery occlusion study and, unfortunately, not during my PCA occlusion studies – that is a limitation in the later studies. In spite of that, the difference in the severity of acute ischemic lesions between the central retinal artery occlusion and PCA occlusion is relevant in old,

atherosclerotic, hypertensive monkeys, because the central retinal artery supplies the inner part of the retina and the PCAs supply the outer part of the retina as well as the optic nerve head. Naturally, the question arises: why the difference?

It is well-established that the choroidal vascular bed supplied by the PCAs has some unique properties, and these include the following:^{6,7}

1. About 85% of the total ocular blood flow is in the choroid.
2. The choroidal blood flow is about 20 times the retinal blood flow.
3. The blood flow through the choroid is the highest in the body. It is about 10 times the cerebral blood flow.⁸
4. The choroid supplies about two-thirds of the oxygen to the retina, while the central retinal artery supplies the rest.
5. The oxygen content of the choroidal venous blood is about 95% of that in the arterial blood.
6. There is no autoregulation in the choroidal vascular bed.
7. The vessels of the choriocapillaris have a lumen 10–50 μ compared to 3.5 to 6 μ of the retinal capillaries.
8. The choriocapillaris have numerous circular fenestrations in the wall which make them markedly leaky, compared to the retinal capillaries, which possess a blood–retinal barrier.

It would seem that these marked differences in their physiological properties between the vascular beds of the central retinal artery and the choroid may be responsible for the difference in the development of severity of acute ischemic damage following PCAs occlusion and the central retinal artery occlusion in the old, atherosclerotic, hypertensive monkeys.

It has been shown that retinal ischemic preconditioning may increase ischemic tolerance. I have discussed the subject of development of retinal ischemic preconditioning elsewhere.^{2,3} Ischemic preconditioning has been reported in the brain⁹ and heart also. The exact mechanism of ischemic preconditioning, however, is still debated. As mentioned above, our previous study showed that central retinal artery occlusion in old, atherosclerotic, hypertensive monkeys produced less severe retinal ischemic damage than the young, healthy monkeys.² Atherosclerotic and arterial hypertensive changes, as well as arteriosclerosis from old age, must reduce the lumen of the central retinal artery, causing chronic subclinical ischemia, which acts as a retinal ischemic preconditioning factor. By contrast, (a) the choroid is supplied by 1–5 PCAs, usually 2 in 48% and 3 in 39%,¹⁰ (b) about 85% of the total ocular blood flow is in the choroid, (c) the choroidal blood flow is about 20 times the retinal blood flow, and (d) the choroid supplies about two-third of the retina's oxygen supply. All these factors and other properties of the choroidal vascular bed discussed above, compared to the retinal vascular bed supplied by only one central retinal artery, would prevent development of ischemic preconditioning in the tissues supplied by the choroid in old, atherosclerotic, hypertensive monkeys. Consequently, unlike central retinal artery

occlusion, the old, atherosclerotic, hypertensive monkeys are as susceptible to develop severe ischemic damage as the young healthy ones in occlusion of all the PCAs.

From time to time, questions have been raised about how well the monkey findings correlate with those observed in humans. After more than half a century of extensive basic and experimental studies in rhesus monkeys, and basic and clinical studies in humans, I can state with confidence that the two correlate very closely.

In conclusion, the present experimental study, dealing with the occlusion of all the PCAs showed that the severity of ischemic damage was similar in both the young and healthy and the old, atherosclerotic, hypertensive monkeys. This is in contrast to the findings of our similar study dealing with central retinal artery occlusion, where the young suffered much severe ischemic damage than the old.

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Fig. 1.

Schematic representation of blood supply of the optic nerve head. (Reproduced from Hayreh SS. Structure and Blood Supply of the Optic Nerve. In: Heilmann K, Richardson KT, editors. Glaucoma: Conceptions of a Disease. Stuttgart: Georg Thieme Publishers; 1978. p. 78–96.)

Abbreviations: C = choroid; CRA = central retinal artery; LC = lamina cribrosa; NFL = surface nerve fiber layer of the disc; ON = optic nerve; P = pia; PCA = posterior ciliary artery; PLR = prelaminar region; R = retina; RA = retinal arteriole; S = sclera.

Fig. 2. Microphotograph, after PCA occlusion, shows microscopic acute infarct changes, including necrosis of the retinal pigment epithelium and outer retina. Hematoxylin and eosin staining. PCA = posterior ciliary artery.

Fig. 3.

A composite fundus photograph of the right eye, one day after occlusion of all the PCAs in a young monkey without atherosclerosis and hypertension. It shows extensive white outer retinal infarcts, extending up to the equator, optic disc edema, and few patches of normal-looking fundus (dark brown areas). PCAs = posterior ciliary arteries.

Fig. 4.

A to C: *One day after occlusion of all the PCAs of the right eye of an old atherosclerotic and hypertensive monkey:*

(A) Fundus photograph shows extensive white outer retinal infarct, optic disc edema, and few patches of normal-looking fundus (dark brown areas).

(B, C) Fluorescein fundus angiograms: (B) During the retinal arteriovenous, shows filling of a few choroidal patches; (C) During the late phase, shows late staining of the optic disc and faint patchy choroidal filling.

D and E: *3 months after occlusion of all the PCAs:*

(D) Fundus photograph shows optic atrophy, extensive retinal pigment epithelial and choroidal degeneration and unmasking of the large choroidal vessels.

(E) Fluorescein fundus angiogram during the retinal arterial phase shows patchy filling of the choroid in the peripapillary region and temporal to the macular region, and choroidal vessels.

Fig. 5. Fluorescein fundus angiogram of the right eye of a young monkey without atherosclerosis and hypertension during the retinal arterial phase, soon after occlusion of all the PCAs, shows no filling of the choroid and mild filling of the optic disc. PCAs = posterior ciliary arteries.

Fig. 6. Fluorescein fundus angiogram of the right eye of an old atherosclerotic and hypertensive monkey during the retinal arteriovenous phase, 6 days after occlusion of all the PCAs, shows filling of the optic disc and the peripapillary choroid except in the inferior temporal region and no filling of the rest of the choroid. PCAs = posterior ciliary arteries.

Fig. 7.
Fundus photograph of a young monkey without atherosclerosis and hypertension about 3 months after occlusion of the PCAs shows optic atrophy, extensive retinal pigment epithelial and choroidal degeneration and unmasking of the large choroidal vessels. PCAs = posterior ciliary arteries.

Severity of acute fundus lesions after the occlusion of the PCAs in the young, healthy monkeys

Table 1

Eye number	Time interval between PCAO and first post-occlusion examination (Days)	Fundus opacity (0=none, 1=minimal, 2= mild, 3= moderate, 4=severe)				Optic disc changes	
		Peripapillary	macular	middle	Peripheral	Optic disc edema	Optic disc changes
1	1	0	3	4	4		4
2	2	0	4	4	4		4
3	1	0	4	4	4		2
4	1	0	4	4	4		4
5	1	0	4	4	4		2
6	1	0	4	4	4		0
7	1	4	4	4	4		3

PCA = Posterior ciliary artery
PCAO = Posterior ciliary artery occlusion

Severity of acute fundus lesions after the occlusion of the PCAs in the old, atherosclerotic, hypertensive monkeys

Table 2

Eye number	Time interval between PCAO and post-occlusion first examination (Days)	Fundus opacity (0=none, 1=minimal, 2= mild, 3= moderate, 4=severe)				Optic disc changes	
		Peripapillary	macular	middle	Peripheral	Optic disc edema	Optic disc changes
1	2	4	4	4	4		4
2	6	0	4	4	4		0
3	1	0	3	3	1		3
4	6	0	4	4	1		3
5	1	4	4	4	4		3
6	1	0	4	4	4		3
7	1	0	4	4	4		3
8	1	0	4	3	0		0

PCA = Posterior ciliary artery
PCAO = Posterior ciliary artery occlusion

Table 3

Comparison of fundus lesions during the acute phase in Old AH vs. Young without AH monkeys

Variable	Old AH (n=8 eyes)	Young without AH (n=7 eyes)	Wilcoxon Rank-sum Exact p-value
Peripapillary fundus opacity			
None	6 (75%)	6 (86%)	1.0
Severe	2 (25%)	1 (14%)	
Macular fundus opacity			
Moderate	1 (12%)	1 (14%)	1.0
Severe	7 (88%)	6 (86%)	
Middle fundus opacity			
Moderate	2 (25%)	0 (0%)	0.467
Severe	6 (75%)	7 (100%)	
Peripheral fundus opacity			
None	1 (12%)	0 (0%)	0.200
Minimal	2 (25%)	0 (0%)	
Severe	5 (63%)	7 (100%)	
Optic disc edema			
None	2 (25%)	1 (14%)	0.601
Mild	0 (0%)	2 (29%)	
Moderate	5 (63%)	1 (14%)	
Severe	1 (12%)	3 (43%)	

AH = Atherosclerotic and hypertensive monkeys