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The Relationship between Retinal Circulation and Aqueous Humor Outflow, Disc Cupping or Intraocular Pressure in Primary Open-Angle Glaucoma

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Abstract In order to investigate the relationship between retinal circulation and aqueous humor outflow, disc cupping or intraocular pressure (IOP) in patients with primary open-angle glaucoma (POAG), we measured the coefficient of the facility of outflow (C value), cupping/disc ratio (C/D ratio) and IOP. And then, we calculated build-up time (BT), time constant of washout rate (TC) and mean circulation time (MCT) in both retinal artery and vein by video-densitometric image analysis of fluorescein angiography. We studied two groups: Normal group was 12 eyes of 11 normal subjects, and POAG group was 10 eyes of 7 POAG patients. Moreover, we examined the effect of β -blocking instillation by 2% carteolol in POAG. The results were as follows:

1) In arteries, BT and TC in POAG group were slightly, and significantly more prolonged than those in normal group, respectively (TC: POAG 40.24 ± 23.99 vs Normal 24.79 ± 14.61 sec; $p < 0.01$).

2) In veins, BT and TC in POAG group were slightly, and significantly and markedly more prolonged than those in normal group, respectively (TC: POAG 54.93 ± 38.18 vs Normal 30.33 ± 22.00 sec; $P < 0.01$).

3) MCT in POAG group was significantly more prolonged than that in normal group (POAG 3.93 ± 1.84 vs Normal 2.96 ± 1.26 sec; $P < 0.05$).

4) There was a significant negative correlation between MCT and C value ($r = 0.389, p < 0.01$). There was a significant positive correlation between MCT and C/D ratio ($r = 0.350, P < 0.01$). However, there was no correlation between MCT and IOP ($r = -0.171, NS$).

5) In POAG group, MCT after therapy of carteolol was slightly shortened, but IOP after therapy was significantly decreased comparing to those before therapy. After therapy, there was a significant positive correlation between MCT and IOP ($r = 0.386$; $p < 0.01$).

These results suggested that in POAG patients, the prolonged retinal circulation was mainly caused by the markedly prolonged venous return, probably related to reduction of aqueous humor outflow and vein occlusion at lamina cribrosa. The effect of carteolol which affected the improvement of retinal circulation might be attributed to the reduction of intraocular pressure.

Key Word: Retinal circulation, Primary open-angle glaucoma, Video-densitometric image analysis, Fluorescein angiography, Carteolol instillation

Introduction

Primary open-angle glaucoma (POAG) is a chronic type glaucoma associated with an elevated intraocular pressure caused by an increase in outflow resistance of aqueous humor. Elevation in intraocular pressure may have important effects on both retinal and choroidal circulation, and may contribute to the disturbances of retinal receptors and/or nerve fiber bundles, and to the chronic damage of the optic disc. These effects caused the ischemic change of optic nerve¹⁾. The previous investigators have measured the retinal circulation in glaucoma by means of first-appearance time or fluorescein filling time using several techniques such as fluorescein photo-angiograms, photo-densitometer, transmission photometry, etc²⁾³⁾⁴⁾.

The update equipment for measurement of the retinal circulation is now developed using a video fundus-camera with a super-high sensitivity. The video fundus-camera shoots a relative stable and clear contrast free of artifacts, and has a high resolution of low illumination image during fluorescein angiography. In addition, compared to the photo-angiogram, the video-camera has a good time-shearing of 0.033 sec or less. In addition, the update computer system for image analysis is now a simple available equipment and has many memory areas and a high speed potency for calculation. Therefore, it is necessary to evaluate the retinal circulation in glaucoma using the update methods of both video-camera and computer image analysis.

In order to evaluate the kinetics of retinal circulation in glaucoma patients, we examined the fluorescein angiography by video-densitometric image analysis, and compared the differences of retinal circulation between POAG and normal patients. Further more, we evaluated the relationship between retinal circulation and intraocular pressure, aqueous humor outflow or disc cupping. In addition, we studied the clinical significance of decrease in intraocular pressure in POAG patients by the instillation of topical carteolol hydrochloride, which is a β -blocking agent and has a hypotensive effect of intraocular pressure through a decrease in aqueous humor secretion⁵⁾.

Subjects and Methods

Subjects : The patient profiles were summarized in Table.1. The 18 patients were divided into two groups. The normal group was composed of 12 eyes of 11 patients (6 males and 5 females, age ranged from 41 to 67 years old, mean age was 52.9 ± 9.6). Each eye in normal group had a better refracted visual acuity of 20/20, a normal intraocular pressure of 19 mmHg or less, and a normal anterior segment and fundus. None in normal group was taking topical or systemic medication at the time of study. The POAG group was composed 10 eyes of 7 patients (5 males and 2 females, age ranged from 42 to 69 years old, mean age was 60.5 ± 9.8). Each eye in POAG group had a various refracted visual acuity from a hand movement to 20/15. The visual field loss varied from no-defect to severe glaucomatous loss, and cupping/disc ratio (C/D ratio) ratio also varied from 1.0 to 0.4. POAG patients had no medical treatment and no instillation for 3 or more days before study. Between two groups, there was no significant difference in age. In both normal and POAG group, males were larger in number than females. And also in both body length and weight, there was no difference between two groups.

The systolic (SBP, mmHg) and diastolic brachial blood pressure (DBP, mmHg) were measured by sphygmomanometry. The pulse rate (PR, beats/min) was measured on radial artery of forearm. The visual acuity was measured using a Landolt C at 5 meters. The measurement of intraocular pressure (IOP, mmHg) was performed using a Goldmann applanation tonometry. The coefficient of the facility of outflow (C value, $\mu\text{l}/\text{min}/\text{mmHg}$) in aqueous humor was studied using a tonography. The measurement of visual field defect or loss was examined using a computerized perimeter (Interzeag AG, Octopus^R 500). For measurement of vertical C/D ratio, the cup margins in optic disc defined by the pale areas on the color fundus photographs. We calculated the vertical C/D ratio by visual inspection. These measurements of IOP, C value and C/D ratio were examined by the same examiner. The patients associated with diabetes mellitus, valvular or ischemic heart disease, hypertension and drug allergy were excluded. From all patients, fluorescein allergy test was checked by subcutaneous skin test, and informed consent was obtained after the procedures had been explained.

Measurement of retinal circulation : The fluor-

Table 1 Subjects

Disease	No.	Age (yrs)	Sex	BL (cm)	BW (kg)	Examined Eye	Visual Acuity	C value	C/D Ratio	Visual Field Loss
Normal	1	41	F	160	51	R	1.2			
						L	1.2			
	2	42	M	163	58	L	1.2			
	3	44	M	159	55	L	1.5			
	4	45	M	171	75	L	1.0			
	5	46	M	170	69	R	1.2			
	6	53	F	162	54	L	1.2			
	7	58	F	145	60	L	1.0			
	8	60	F	153	53	R	1.2			
	9	62	M	165	62	L	1.0			
	10	64	F	145	50	R	1.0			
11	67	M	172	65	R	1.0				
(Mean±SD) 53±10				160±9	59±8					
POAG	1	42	F	164	59	R	1.2	0.15	0.8	Superior Defect
						L	1.2	0.13	0.8	Bjerrum Scotoma
	2	56	M	164	60	L	1.2	0.08	0.4	Full
	3	57	M	156	48	R	0.6	0.18	0.7	Arcuate Scotoma
	4	63	M	168	59	R	H M	0.05	1.0	Impossible Exam
						L	0.5	0.13	0.9	Central Island
	5	68	F	145	53	L	0.6	0.15	0.6	Nasal Step
6	69	M	166	60	R	1.0	0.18	0.6	Bjerrum Scotoma	
					L	0.9	0.12	0.6	Superior Defect	
7	69	M	160	60	L	0.3	0.18	0.8	Inferior Defect	
(Mean±SD) 60±10				160±8	57±5					

Abbreviations : No. = patient number ; BL=body length ; BW=body weight ; yrs=years old ; C/D Ratio=cupping/disc ratio (vertical diameter) ; C value=the coefficient of the facility of outflow ; M=male ; F=female ; R=right eye ; L=left eye ; HM=hand movement ; Exam=examination ; POAG=primary open-angle glaucoma

escein angiography was taken after pupillary dilatation with 1% tropicamide. The injection of fluorescein was performed according to the method by Shimizu⁶⁾ and Koyama et al.⁷⁾. A 21G needle was placed in antecubital vein, and the extension tube was filled with 1 ml of 10% Fluorescein-Na. Immediately after an injection of fluorescein, the saline solution of 20 ml was flashed into a vein. Photographic angle of camera was focused on the 20° or 35° of the fundus surrounding the optic disc. The eyes were positioned to permit a selection of any large vessels for measurement. An excitation interference filter ranged from 450 to 525 nm, and an emission filter ranged from 525 to 620 nm.

After angiography, the patients in POAG group received two consecutive drops with instillation of 2% carteolol. One hour later, POAG patients were once more measured by SBP, DBP, PR and IOP. And then, video-fluorescein angiography

was again examined. The POAG patients with bronchial asthma who had a contraindication for β -blocker were excluded.

Fig.1 shows the measurement system which we used. As our previous reports⁸⁾⁻¹¹⁾, the system consisted of an available fundus camera (TOPCON, TRC-50VT) for a fluorescein angiography, a video fundus-camera with a super-high sensitivity (Hamamatsu Photonics, C2400), a videotape recorder (MITSUBISHI, S-VHS, HV-V36) and a video timer (FORA, VTG-33) with time indication by 1/100 sec. The timer immediately started after injection, and video-fluorescein angiography was recorded in a videotape recorder for about one minute. Every one video-frame per 0.33 sec was digitalized and input to the computer system for image analysis using a time-base corrector (FORA, FA-300). Image analysis of angiography was performed by a computer system (Nippon-Avionics, TVIP

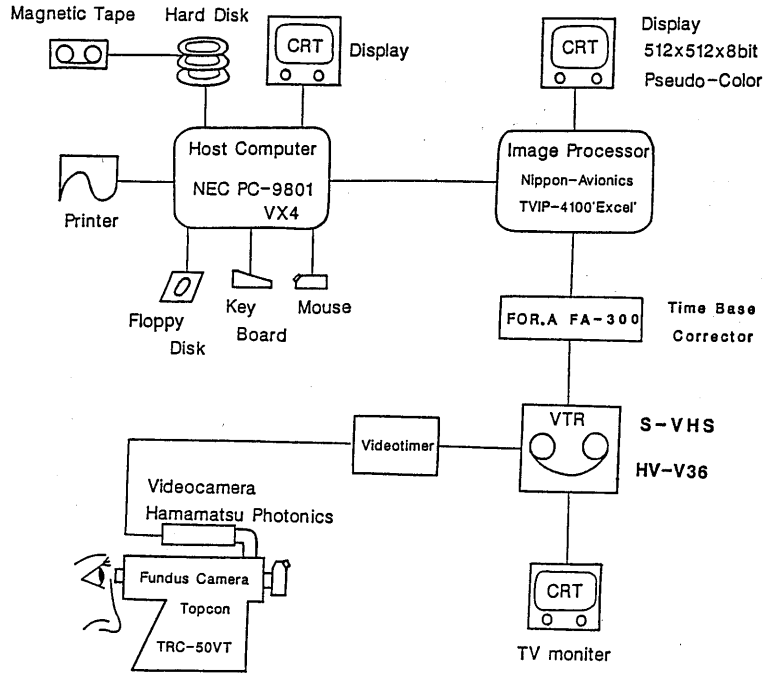


Fig. 1 A fundus camera for fluorescein angiography, a super-high sensitivity video-camera and sequential computer-systems for image analysis.

-4100). The resolution characteristics of our system are 512×512 pixels and 256 (8bits) gray scale for one frame. The system of image analysis was controlled by a host personal-computer (NEC, PC-9801VX4). Digitalized image was stocked in a hand disk and backed up into a magnetic tape (TEAC, SB-2000).

As shown in Fig.2, the retinal circulation was measured by setting the region of interest (ROI) on arteries and veins at a distance less than twice disc-diameter distance from the center of optic nerve head. For setting the ROI, sites close to venous junctions or arteriovenous crossing were avoided, as well as sites where two vessels lay close to each other. Each ROI was a regular square with a small size of 4×4 or 3×3 pixels to avoid an expansion over the vessel. And then, the center of ROI was aligned to the center of vessel as closely as possible. The positions of ROI consisted of 2 points in upper and lower arteries, and 2 points in upper and lower veins, in the temporal side. If the vessels could be measured in the nasal side, the positions of ROI consisted of 4 points in

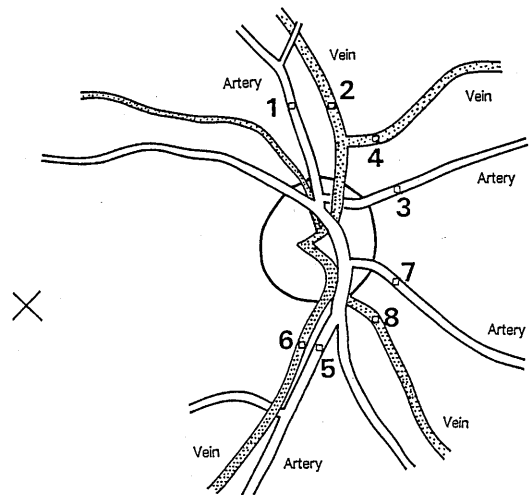


Fig. 2 A schematic disc area and the setting region of interest (ROI) on retinal arteries and veins.

upper and lower arteries, and 4 points in upper and lower veins, in both temporal and nasal sides.

Consequently, we calculated the mean value of intensity in each ROI and plotted the results every 0.33 sec to make the time-intensity curve. According to the method of Koyama et al.⁷⁾, data points from the early phase of time-intensity curve in arteries and veins were applied to a gamma function by the non-linear least squares method using the SALS program (designed by computer center of Tokyo University). Subsequently, fitting results to a gamma function were reconstructed by the interpolation using a spline function.

We displayed the fitting reconstructed time-intensity curve as shown in Fig.3 (Top figure).

We evaluated the following parameters from the fitting results using a gamma function in early phase of time-intensity curve : 1) Build-up time (BT, sec) was an interval from the appear-

ance time of fluorescein in retinal artery and vein to the peak time. 2) Time constant of washout rate (TC, sec) was calculated by fitting the down slope of early phase the first exponential function using a least squares method to obtain the reciprocal of the slope (Fig.3, Bottom figure). 3) Mean circulation time (MCT, sec) was a time difference in mean transit times between the artery and vein, according to the method of Riva et al.¹²⁾.

Thus, we summed up the BT, TC and MCT by adding the values of 4 or 8 points in artery and vein, according to the method of Shimizu et al.⁶⁾. Consequently, we compared the BT, TC and MCT between POAG and normal group, and evaluated the relationship between MCT and C value, C/D ratio or IOP. And then, we compared the BT, TC and MCT between before and after carteolol instillation in POAG group.

Statistics analysis : Statistical analysis was used by methods of F-test for BT, TC and of Student's paired T-test for age, body length, body weight, SBP, DBP, PR and IOP. The P value lower than 0.05 was considered to be significant. The mean value was represented as Mean±Standard deviation (SD).

Result

BT of arteries and veins : As shown in Fig.4 (Left), BT of arteries in POAG group (5.6 ± 1.6 sec) was slightly more prolonged than that in normal group (4.6 ± 1.4 sec), but not statistically significant. As shown in Fig.

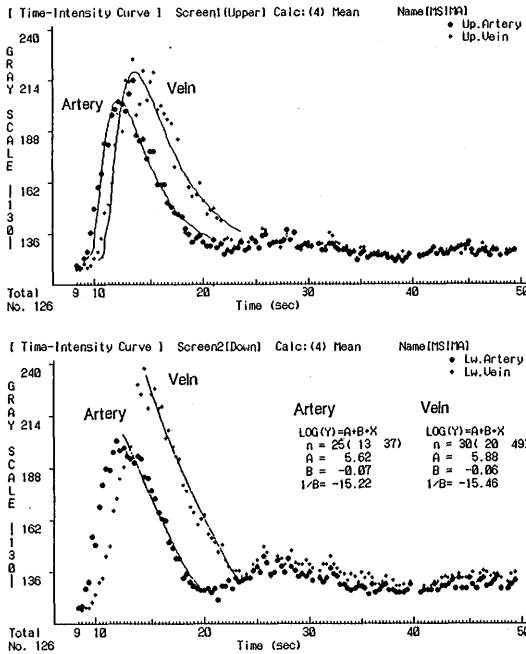


Fig. 3 Time-intensity curves of retinal artery and vein.

Upper : fitting curves to a gamma function by the non-linear least square during initial early phase of time-intensity curve. Fitting curves were interpolated by a spline function.

Lower : Fitting curves to the first exponential function by the least squares method during the down slope of initial early phase.

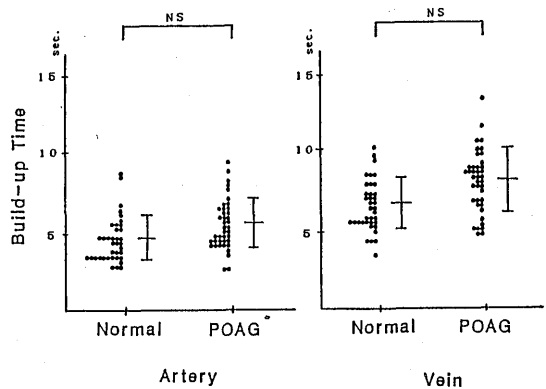


Fig. 4 Differences of build-up time in retinal artery and vein between normal (Normal) and primary open-angle glaucoma (POAG) group.

4 (Right), BT of veins in POAG group (8.2 ± 2.0 sec) was slightly more prolonged than that in normal group (6.7 ± 1.6 sec), but not statistically significant.

TC of arteries and veins : As shown in Fig.5 (Left), TC of arteries in POAG group (40.2 ± 24.0 sec) were significantly more prolonged than that in normal group (24.8 ± 14.6 sec) ($P < 0.01$). Also as shown in Fig.5 (right), TC of veins in POAG group (54.9 ± 38.2 sec) was significantly and markedly more prolonged than that in normal group (30.3 ± 22.0 sec) ($P < 0.01$).

MCT : As shown in Fig.6, MCT in POAG group (3.93 ± 1.8 sec) was significantly more prolonged than that in normal group (2.96 ± 1.26 sec) ($P < 0.05$).

Relationship between MCT and C value, C/D ratio or IOP : As shown in Fig.7, there was a significant negative correlation between MCT and C value ($r = -0.389$, $p < 0.01$). Moreover, as shown in Fig.8, there was a significant positive correlation between MCT and C/D ratio ($r = 0.350$, $p < 0.01$). However, as shown in Fig.9 (Top figure), there was no correlation between MCT and IOP ($r = -0.171$, NS).

Retinal circulation after carteolol instillation : In POAG group, the r results of PR,

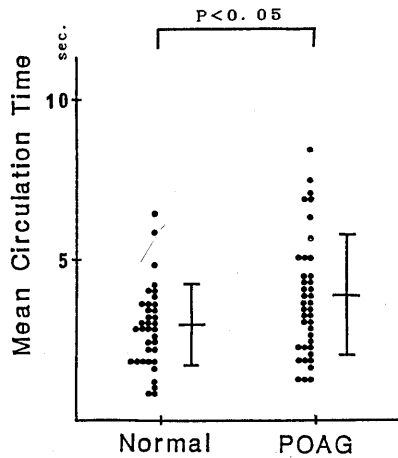


Fig. 6 Differences of mean circulation time between normal and POAG group.

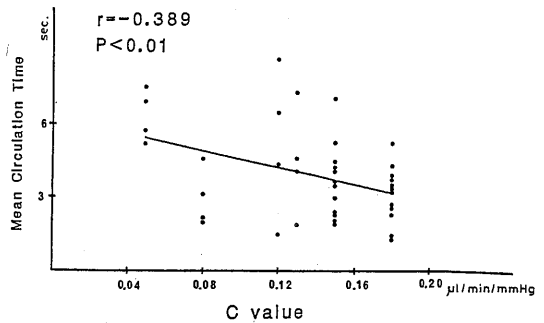


Fig. 7 Relationship between mean circulation time and C value in POAG group.

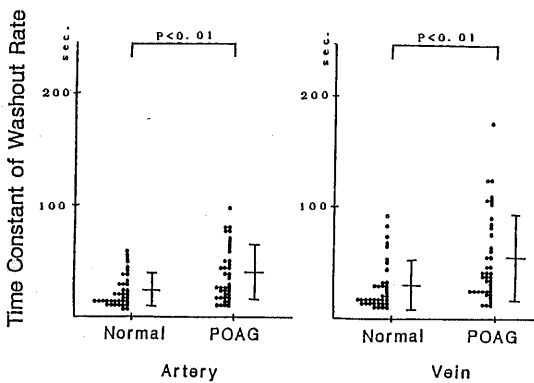


Fig. 5 Differences of time constant of washout rate in retinal artery and vein between normal and POAG group.

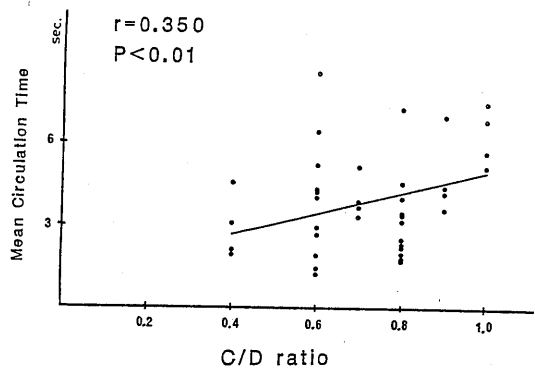


Fig. 8 Relationship between mean circulation time and C/D ratio in POAG group.

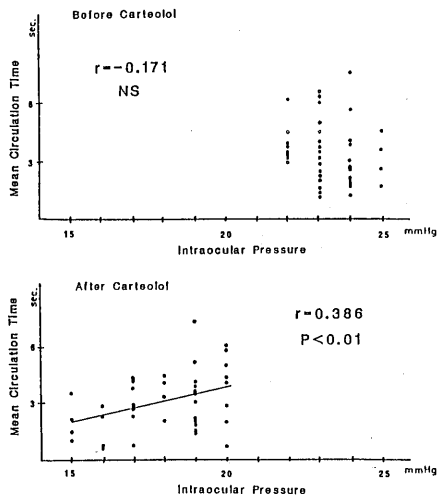


Fig. 9 Relationship between mean circulation time and intraocular pressure in POAG group.

Upper : Before carteolol instillation.
Lower : After carteolol instillation.

SBP, DBP and IOP before and after carteolol instillation were summarized in Table 2. When these measurements between before and after therapy were compared, there was no significant difference in PR (Before 66.7 ± 6.5 vs After 64.8 ± 11.7 beats/min), SBP (Before 136.7 ± 17.4 vs After 136.0 ± 18.5 mmHg) and DBP (Before 75.0 ± 8.4 vs After 80.2 ± 10.2 mmHg). On the other hand, IOP after therapy (18.0 ± 1.7 mmHg) was significantly more decreased than that before therapy (23.3 ± 0.9 mmHg) ($P < 0.001$) (Table 2).

BT after carteolol : In arteries, BT after therapy (6.5 ± 2.0 sec) was slightly more prolonged than before therapy, but not statistically significant (Fig.10, Left). In veins, BT after therapy (8.3 ± 1.8 sec) was slightly more prolonged than that before therapy, but not statistically significant (Fig.10, Right).

TC after carteolol : In arteries, TC after therapy (36.5 ± 22.6 sec) was slightly more

Table 2 Measurement of pulse rate, brachial artery blood pressure (BP) and intraocular pressure (IOP) before and after the instillation of carteolol in POAG patients

No.	Age Sex (yrs)	Examined Eye		PR (beats /min)	SBP (mmHg)	DBP (mmHg)	IOP (mmHg)
1	42 F	R	Before	68	112	60	23
			After	84	130	70	19
		L	Before	67	115	61	24
			After	83	131	72	19
2	56 M	L	Before	54	120	80	24
			After	54	120	84	17
3	57 M	R	Before	72	148	80	22
			After	72	148	80	20
4	63 M	R	Before	66	140	85	23
			After	64	122	80	20
		L	Before	64	130	80	22
			After	64	102	64	15
5	68 F	L	Before	78	140	74	25
			After	52	150	80	19
6	69 M	R	Before	62	140	78	23
			After	60	158	90	16
		L	Before	64	162	80	24
			After	51	160	82	18
7	69 M	L	Before	72	160	72	23
			After	64	140	100	17
(Mean \pm SD)			Before	67 ± 6	137 ± 17	75 ± 8	$23.3 \pm 0.9^*$
			After	65 ± 11	136 ± 18	80 ± 10	$18.0 \pm 1.7^*$

Abbreviations : PR=pulse rate ; SBP=systolic brachial artery blood prssure ; DBP=diastolic brachial artery blood prssure ; IOP=intraocular prssure*= $P < 0.001$; Student's-T test

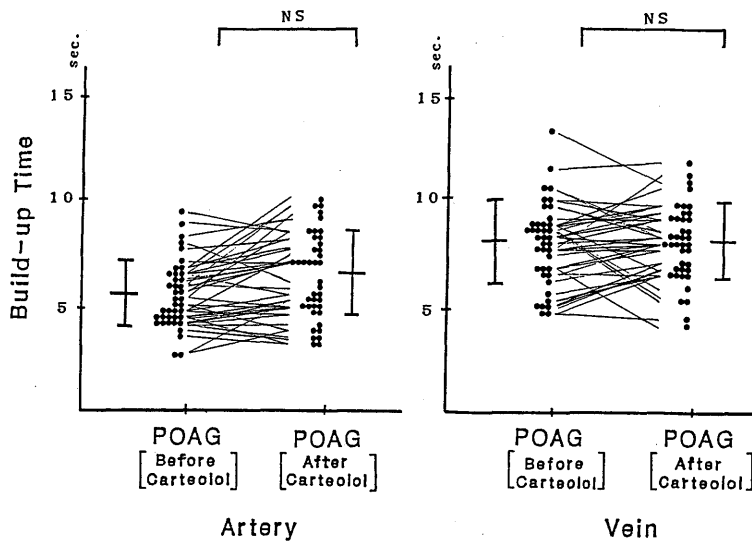


Fig. 10 Differences of build-up time in retinal artery and vein in POAG group between before and after carteolol instillation.

shortened than that before therapy, but not statistically significant (Fig. 11, Left). In veins, TC after therapy (43.2 ± 27.2 sec) was significantly more shortened than that before therapy ($P < 0.05$) (Fig. 11, Right).

MCT after carterolol: MCT after therapy (3.11 ± 1.53 sec) was slightly more shortened than that before therapy, but not statistically significant (Fig. 12).

Relationship between MCT and IOP after carteolol: Before carteolol, there was no significant correlation between MCT and IOP (Fig. 9, Top). On the other hand, after carteolol, there was a significant positive correlation between them ($r = 0.386$, $P < 0.01$) (Fig. 9, Bottom). Thus, in POAG group, the lower IOP reduced, the shorter MCT became.

Discussion

Retinal circulation in primary open-angle glaucoma: In the previous clinical reports, Ferrer²⁾ showed that the prolonged appearance time of fluorescein photo-angiography in glaucoma was caused by the change in intraocular pressure. Schwarz et al.³⁾ measured the kinetics of retinal circulation in

ocular hypertension and glaucoma using a photo-angiographic densitometry. They demonstrated that the build-up time of both arteries and veins was prolonged in the order of normal, ocular hypertension and glaucoma group. On the other hand, the close relationship between acute central retinal vein occlusion and chronic glaucoma has been recognized in clinical studies¹³⁾¹⁴⁾¹⁵⁾. Vannas et al.¹³⁾ studied that there was a high prevalence of glaucoma in the central retinal vein occlusion, but that there was no correlation between occlusion and outflow facility. In pathological study Dryden et al.¹⁴⁾ reported that the occlusions of central retinal vein in glaucoma are usually found in or just behind the lamina cribrosa, and that the close proximity of the artery and vein predisposed the vein to the degenerative state. In experimental reports, Armaly and Araki¹⁶⁾ demonstrated that the elevated ocular pressure produced a reduction in blood-flow rate of retinal artery using the heated thermo-couple technique. Emery et al.¹⁷⁾ revealed that the elevation of intraocular pressure might cause the backward movement of cribriform plate with disorganization of axons. They showed that the compressive changes in lamina cribrosa might also reduce or obliterate blood supply

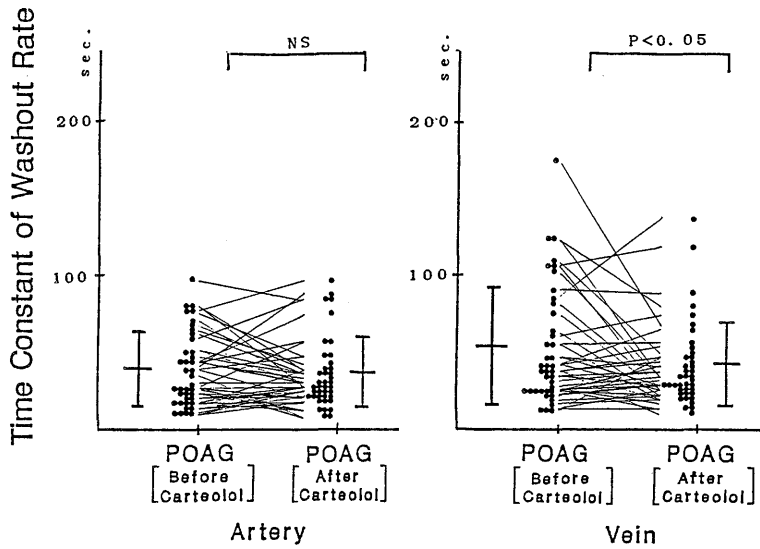


Fig. 11 Differences of time constant of washout rate in retinal artery and vein in POAG group between before and after carteolol instillation.

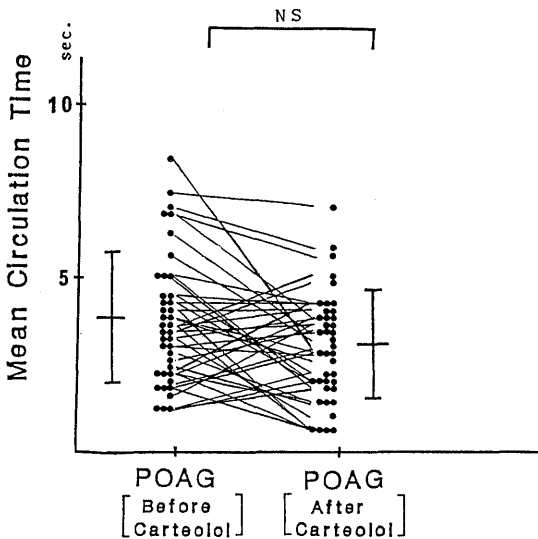


Fig. 12 Differences of mean circulation time in POAG group between before and after carteolol instillation.

and cause a hemodynamic change in retinal blood flow. Hitchings et al.¹⁵⁾ proposed that the increased intraocular pressure and the enlarged optic cup in glaucoma resulted in the retinal vein distortion and complicated venous occlusion.

In our present study, the build-up time of both arteries and veins in glaucoma was prolonged than that in normal, but not significant. This result was compatible with the result of Schwarz et al³⁾. In addition, both time constant of washout rate and mean circulation time in glaucoma were significantly more prolonged than those in normal, especially those of retinal veins. We considered that the prolongation of both time constant of washout rate and mean circulation time might be caused by the decrease in blood flow consequent on the elevated intraocular pressure, the compressive or disorganized change in lamina cribrosa, or both. These factors might contribute to the vein occlusion at lamina cribrosa. The markedly prolonged time constant of washout rate in vein affected to the prolonged mean circulation time, and might be caused by the occurrence of central vein occlusion in glaucoma.

In our study, there were significant correlations between mean circulation time and C value or C/D value. C value reflected on the blockage in the outflow of aqueous humor. C/D ratio reflected on both the enlargement of disc cupping and the progressive degree of glaucoma. On the other hand, intraocular pressure did not directly reflect on the patho-

logical disc change in glaucoma, since there was no disc change in patients of ocular hypertesion and there was various disc change in patients of low tension glaucoma¹⁸⁾. In our present study, mean circulation time as well as C value and C/D ratio might reflect on the progressive degree of glaucoma.

Retinal circulation after carteolol : Grunwald et al.¹⁹⁾ reported efficacy of β -blocker (timolol) in normal eyes for retinal circulation using a laser doppler velocimetry. They showed a significant decrease in an intraocular pressure, and a significant increase in both retinal blood flow speed and flow rate after timolol. In our study, the results showed a significant decrease in an intraocular pressure one hour after carteolol. Mean circulation time was clearly shortened. Especially, time constant of washout rate was shortened in vein.

Perhaps, carteolol might reduce the production of the aqueous humor and lead to the improvement of retinal circulation in vein system rather than in artery system.

Clinical implication : The disturbance of retinal circulation is frequently observed in POAG patients. The treatment by a decrease of intraocular pressure and improvement of retinal circulation would lead to repairment of optic nerve disorder and maintenance of optic function.

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