A SIMPLE METHOD FOR EVALUATION OF AQUEOUS HUMOR DYNAMICS "A WEIGHT ON-OFF TEST" IN PATIENTS WITH GLAUCOMA

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ABSTRACT

Purpose: To evaluate aqueous humor (AH) dynamics in patients with glaucoma through a newly developed method termed the "A weight on-off test"

Methods: Subjects: patients with primary open angle glaucoma (POAG) (n=124, 227 eyes), primary angle closure glaucoma (PACG) (n=16, 29 eyes) or pseudoexfoliation syndrome (PEX) (n=17, 29 eyes), and 10 healthy volunteers. For evaluation of AH dynamics, a 50 g weight was placed onto the eye of a subject in a supine position for 5 min and then removed. Intraocular pressure (IOP) was measured before and immediately after removal, and thereafter every minute until IOP returned to baseline. Based upon IOP changes (decreases during the weight on and recovery after removal), we defined **AH outflow resistance**: IOP drop rate (IOP_{drop}) (%) = (P_0-P_e) – (P_5-P_e) /(P_0-P_e) x 100 (P_0: IOP at baseline, P_e: assumed episcleral venous pressure, P_5: IOP at 5 min) and AH outflow resistance index ($R_{aq\ out}$) = 100 - IOP_{drop}, and **AH production**:IOP recovery time (IOP_{rec}) (min) reached to baseline IOP, and AH production index (P_{aq}) was an IOP increase rate during the IOP_{rec} by least squares method.

Results: AH outflow resistance was significantly higher in glaucoma subjects than the control. AH production in glaucoma subjects was slightly increased compared to that in control. In POAG, prostaglandin-analogues (PG) caused a significant delay of AHproduction (IOP_{rec}).

Conclusions: The current data suggests that "A weight on-off test" may be simple and useful for estimating AH dynamics in patients with glaucoma and provides a better understanding of glaucoma etiology as well as its pharmacology.

Key words *- aqueous humor; glaucoma; intraocular pressure; tonography*

INTRODUCTION

Glaucoma is a group of optic neuropathies that cause irreversible but potentially preventable blindness[1,2]. Regarding treatment, several randomized control trials[3-5] have disclosed that intraocular pressure (IOP) brought to adequate low levels through medication or surgical intervention is effective. IOP is therefore the most critical risk factor for the development and progression of glaucoma. IOP is necessary to inflate the eye and maintain the proper shape and optical properties of the globe[6]. The basic concept that impairment in aqueous humor (AH) outflow results in elevation of the IOP is a central principle of glaucoma pathology and treatment[7]. Therefore, understanding the complex mechanisms that regulate AH dynamics is essential for improved understanding and management of glaucoma.

The AH provides a transparent and colorless medium between the cornea and the lens and constitutes an essential component of the eye's optical system[8]. The AH is secreted by the ciliary non-pigmented epithelium lining the ciliary processes and enters the posterior chamber. The circulating AH flows around the lens and through the pupil into the anterior chamber[9,10]. Within the anterior chamber, a temperature gradient creates a convective flow pattern, which is flowing downward close to the cornea where the temperature is cooler, and upward near the lens where the temperature is warmer.

The AH leaves the eye by passive flow via two pathways—the conventional pathway and uveoscleral pathway—at the anterior chamber angle, anatomically located at the limbus[11]. The conventional pathway consists of the AH passing through the trabecular meshwork, across the inner wall of Schlemm's canal, into its lumen, and into draining collector channels, aqueous veins and episcleral veins. The uveoscleral pathway is composed of the uveal meshwork and anterior face of the ciliary muscle[12]. The AH enters the connective tissue between the muscle bundles, passes through the suprachoroidal space, and then departs through the sclera. An equilibrium exists between the production and drainage of the AH. Disruption of AH outflow, usually through the conventional pathway, results in elevation of IOP, which is a major risk factor in the pathogenesis of glaucoma[13]. Therefore, in addition to IOP levels, evaluation of AH dynamics of the equilibrium between the AH's production and drainage should provide important information for understanding glaucoma etiology as well as allow for observation of the disease course in patients with glaucoma.

To determine the relationship between IOP and AH dynamics, Goldmann's equation is utilized as follows, with an assumed episcleral venous pressure of 8, 9, 10, or 11 mm Hg[14]:

$Ft = C(IOP-Pv)$, $Fu = Ft-C(IOP-Pv)$:

F_t is the rate of AH formation, C is the tonographic facility of outflow, P_v is the episcleral venous pressure, and F_u is the uveoscleral outflow.

To determine Pv and C values, fluorophotometry and tonography, respectively, are usually required. However, although these analytical methods are suitable for research using a limited numbers of subjects, the process of these methods is complicated and it is difficult to use them in our routine glaucoma clinic[15-17]. A more simple method for evaluating AH dynamics would be preferable for monitoring the disease course of patients with glaucoma.

Toward that end, for the present study we developed a new simpler method that allowed us to evaluate AH dynamics, AH production, and outflow resistance. We have termed this the "A weight on-off test" and through this methodology, we were able to evaluate AH dynamics, production, and outflow resistance in patients with several types of glaucoma and control subjects.

1. SUBJECTS AND METHODS

This study was conducted at Sapporo Medical University Hospital, Japan, after approval by the local Ethics Committee and according to the tenets of the Declaration of Helsinki and national laws for the protection of personal data. Informed consent was obtained from all participants in the study.

1-1. Subjects

Patients with primary open angle glaucoma (POAG) (n=124, 227 eyes), primary angle closure glaucoma (PACG) (n=16, 29 eyes) or pseudoexfoliation syndrome (PEX) (n=17, 29 eyes) were included in the present study (Table 1). All glaucoma subjects underwent a complete ophthalmological examination before inclusion, including medical history, best-corrected visual acuity, slit-lamp biomicroscopy, central corneal thickness (CCT) measurements, Goldmann applanation tonometry, gonioscopy, standard automated perimetry using the Humphrey Field Analyzer II and the SITA standard 30-2 algorithm, and a dilated fundus examination. A clinical diagnosis of the patients with POAG was assessed based upon the following diagnostic criteria: 1) gonioscopically normal open angles; 2) glaucomatous visual field defects corresponding with the glaucomatous optic disc changes; 3) no history or findings of PEX or secondary glaucoma; 4) no other ocular, neurological, otolaryngological or systemic diseases affecting optic disc damage. The diagnosis of angle closure was determined by gonioscopy, which aids in identifying regions of apposition of the iris to the trabecular meshwork. Clinical criteria for PACG included observation of angle closure, defined as the presence of appositional or synnechial closure of the anterior chamber angle involving at least 270 degrees observed by gonioscopy in either eye. PEX diagnosis was based on observation of PEX material on the anterior lens capsule and/or pupillary margin after mydriasis by slit lamp biomicroscopy. IOP, cup-disc ratio, and visual field defects criteria for PACG and PEX were similar to POAG as above. As a control, senile cataract patients without other eye diseases were used (n=93, 125 eyes). 10 healthy volunteers (Mongolian 9 and Caucasian 1, male 5 and female 5, 34.5±7.92 year-old) were also included to determine suitable experimental conditions. Subjects were enrolled between April 1, 2011 and March 31, 2013. Participants were 20 years or older. All subjects were free from corneal pathology that could limit the accuracy of tonometry readings.

Table 1. Characterization on control subjects and patients with several types of glaucoma

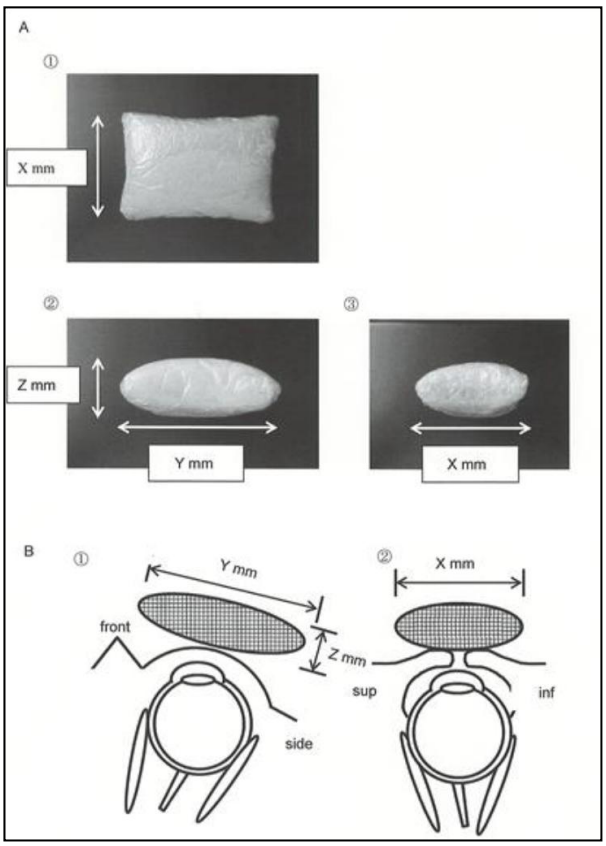
	Control n=93 (125 eyes)	**POAG n=124 (227 eyes)**	**PACG n=16 (29 eyes)**	**PEX n=17 (29 eyes)**
Gender (male/female)	37 / 56	55 / 69	2 / 14	8 / 9
Age (years)	70.6±10.2[a] (68.5～72.7[b])	65.5 ± 11.6* (63.43～67.57)	72.1±7.10 (68.3～75.89)	72.2±12.4 (65.8～78.58)
Intraocular pressure (mmHg)	16.0±4.02 (15.3～16.71)	16.9±4.66 (16.2～17.51)	15.6±3.07 (14.4～16.8)	17.63±5.29 (15.6～19.64)
Refractive errors (D)	-1.88±3.20 (-2.6～-1.12)	-3.26±3.47 (-3.7～-2.81)	0.07±1.22 (-0.39～0.53)	-3.28±4.09 (-4.84～-1.72)
CCT (μm)	531.6±39.6 (522.2～541.0)	542.4±44.2 (536.1～548.7)	553.9±38.5 (539.2～568.5)	540.7±44.72 (523.0～585.4)
No. of glaucoma medications	0	1.70±3.48 (1.53～1.87)	1.31±1.00 (0.93～1.69)	1.93±1.44 (1.38～2.48)
One drop (eyes)	0	55	10	5
PG	0	49	4	2
Other	0	6	6	3
Two drops (eyes)	0	31	8	3
PG + β	0	17	4	1
PG + CAI	0	8	0	0
Others	0	6	4	2
Three drops (eyes)	0	91	4	10
PG + β + CAI	0	73	2	6
others	0	18	0	4
Four drops (eyes)	0	20	0	4

POAG; primary open-angle glaucoma, PACG; primary angle-closure glaucoma, PEX; pseudoexfoliation syndrome, PG; prostaglandin-derivatives, β; β-blocker, CAI; carbonic anhydrase inhibitor, [a] Mean ± SD（all such values）, [b] 95% CI in parentheses (all such values),* t test, $P < 0.001$

1-2．"A weight on-off test"

For the "A weight on-off test", a weight consisted of 10, 30, 50, or 70 g of salt wrapped in plastic food wrap (Fig. 1A). As shown in Fig. 1B, these weights were suitably configured to compress an eyeball when this was placed on orbit.

Figure 1. Schema of weight



(A) ①: up view; ②: side view; ③: front view

(B)weight placed on an orbit (①: horizontal view; ②: sagittal view)

Size: 10 g; X=25 mm, Y=30 mm, Z=20 mm, 30 g; X=35 mm, Y=40 mm, Z=25 mm, 50 g; X=40 mm, Y=50 mm, Z=25 mm, 70 g; X=40 mm, Y=55 mm, Z=35 mm.

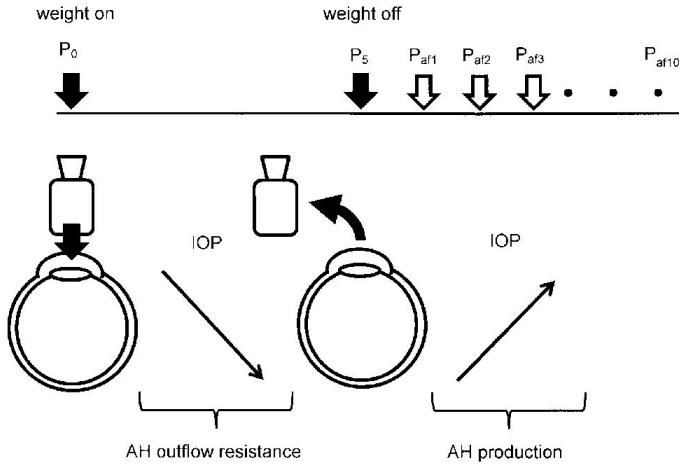
To study how a plastic wrapped weight compressed an eyeball, topographic measurement of its pressure to the eyeball was estimated using a tactile pressure sensor system (DigiTacts Single Point Sensor; Pressure Profile System, Inc, Los Angeles, CA). The flexible pressure sensor panel covered with silicone rubber (size 25 mm x 65 mm, thickness approximately 0.4 mm, model #3579) containing 3 x 8 active element arrays (each element size 8 mm x 8 mm) was placed on a desk or orbit. A 10, 30, 50 or 70 g plastic wrapped weight was then placed onto the pressure sensor panel. The pressure sensor panel was connected to a personal computer, and the measurements were made automatically every 0.03 sec at a sensitivity of 0.7 kilopascals (1 kPa is approximately 5 mmHg) with a range of 0 to 140 kPa. Topography of pressure distribution of the weights was visualized in a three-dimensional shape and the compression pressures were calculated by the peak heights.

Experimental protocol and basic principles of the "A weight on-off test" are shown in Figs. 2 and 3. Subjects assumed a supine position 10 min before the test and maintained this throughout its duration. A salt wrapped weight (10, 30, 50 or 70 g) was put on one eye for 5 min (Fig. 3A). During the 5 min, subjects gazed at a target with their other eye to keep their primary eye position (Fig. 3B). IOP was measured with the rebound tonometer (ICare®, Finland) prior to placement of the weight and immediately after its removal, and thereafter every one minute until IOP returned to the pre-weight placement levels. At the time of measurements, subjects turned their necks to a lateral position so that IOP could be suitably measured by the rebound tonometer (Fig. 3C). All measurements were

conducted between 1 pm through 4 pm by trained ophthalmologists.

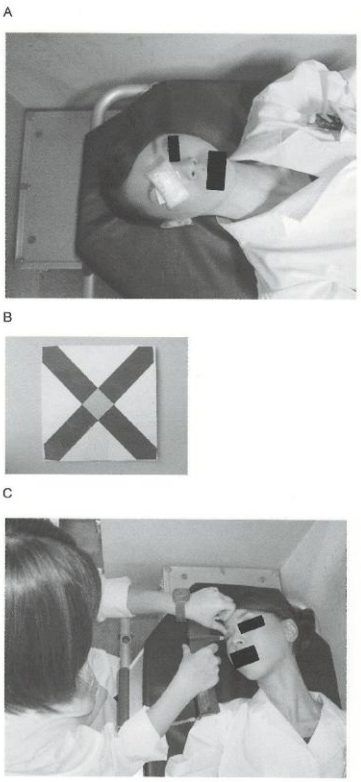
Values were the mean results of three to six consecutive measurements until the inter-measurement variability was less than 5 %.

Figure 2. Schema of protocol and basis of "A weight on-off test"



A weight consisting of 50 g of salt wrapped in plastic food wrap was put on one eye for 5 min and then removed. IOP was measured with the rebound tonometer at before placement (P_0) and immediately upon removal (P_5), and thereafter every one minute until IOP returned to pre-placement levels or until 10 min elapsed after the weight was removed (P_{af1}, $P_{af2,}$ P_{af3},,,P_{af10}). AH outflow resistance and AH production were estimated based upon the IOP changes (decreases with the weight on the eye and recovery after removal).

Figure 3. Representative photographs of "A weight on-off test"



Subject assumed a supine position from 10 min before and through the duration of the test. A 50 g salt-wrapped weight was put on one eye for 5 min (A). During the 5 min the weight was on the eye, the subject gazed at a target (B) with the other eye to maintain a primary eye position. Subjects turned their necks to a lateral position so that IOP could be suitably measured by the rebound tonometer (C) IOP was measured before weight placement and immediately after its removal, and thereafter every one minutes until IOP returned to pre-weight placement levels.

AH outflow resistance factors; IOP drop rate (IOPdrop) (%) and AH outflow resistance index (Raq out), and AH production factors; IOP recovery time (IOP_{rec}) min and AH production index (P_{aq})

As shown in Fig. 4, AH dynamics, AH outflow resistance, and AH production were estimated by decreases in IOP during the 5 min weights were placed on eyes and recovery of IOP after their removal. We defined AH outflow resistance factors; (1) IOP drop rate (IOP_{drop}) (%) and (2) AH outflow resistance index ($R_{aq\ out}$), and AH production factors; (3) IOP recovery time (IOP_{rec}) (min) and (3) AH production index (P_{aq}) as follows;

(1) IOP drop rate (IOP_{drop}) (%)

IOP_{drop} (%) = $(P_0\text{-}P_e) - (P_5\text{-}P_e) / (P_0\text{-}P_e)$ x 100

P_0: IOP at baseline, P_e: an assumed episcleral venous pressure of 8 mm Hg, P_5: IOP at 5 min after weight on an eye.

(2) AH outflow resistance index ($R_{aq\ out}$)

$100 - IOP_{drop}$

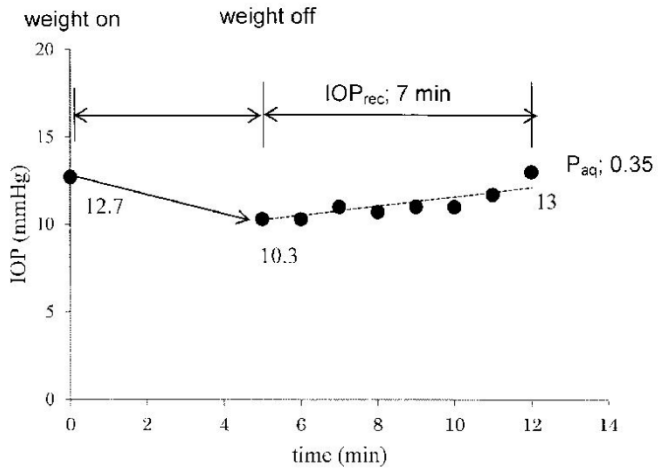
(3) IOP recovery time (IOP_{rec}) (min)

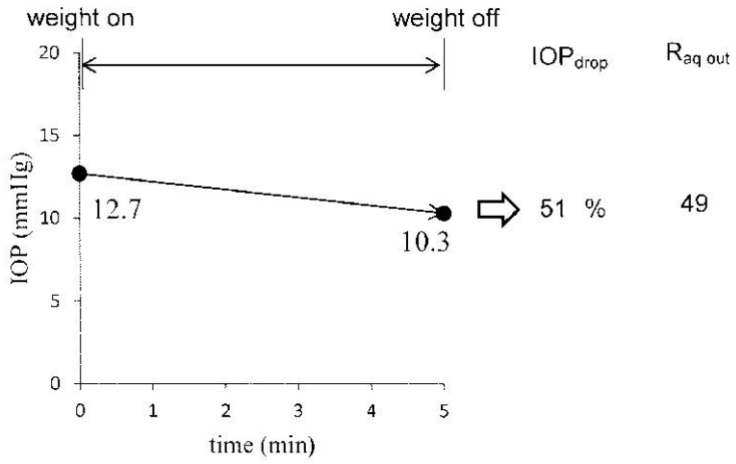
IOP_{rec} was defined as time (min) that IOP reached to the base line level after removal of the weight.

(4) AH production index (P_{aq})

P_{aq} defined as a rate of IOP increase during the IOP_{rec} was calculated by least squares method using Microsoft Excel®.

Figure 4. Schematic examples of AH outflow resistance factors, IOP drop rate (IOP_{drop}) (%) and AH outflow resistance index ($R_{aq\ out}$) (upper panel) , and AH production factors, IOP recovery time (IOP_{rec}) (min) and AH production index (P_{aq}) (lower panel)





In the case #1 (Table 2), in which IOP decreased to 10.3 mmHg from baseline IOP (12.7 mmHg) during weight placement, IOP drop rate (IOP_{drop}) (%) and AH outflow resistance index (Raq out) were calculated as follows:

IOP_{drop} (%) = (P0; 12.7-Pe; 8) – (P5; 10.3-Pe; 8) / (P0; 12.7-Pe; 8) x 100 = 51
AH outflow resistance index ($R_{aq\ out}$) = 100 - IOP_{drop} = 49

In this case upon removal of the weights IOP increased to 10.3 mmHg after 1 min, 11.0 mmHg after 2 min, 10.7 mmHg after 3 min, 11.0 mmHg after 4 min and 5 min, 11.7 mmHg after 6 min, and 13.0 mmHg after 7 min after weight removal, IOP_{rec} was 7 min, and P_{aq} was 0.35 calculated by least squares method.

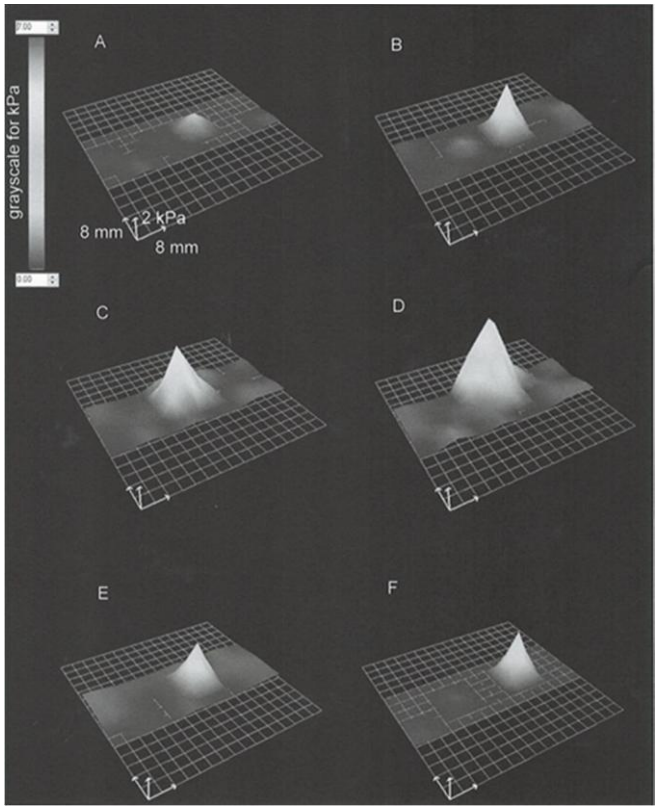
1-3. Other analytical methods

Tonography was performed with the patient supine, according to previously described methods[18], using a Pneumotonometer (model 30TM, Reichet Technologies Inc.,) Measures of outflow facility were calculated as described previously[18]. All statistical analyses were calculated with commercial software (SPSS, ver. 15.0; SPSS Inc., Chicago, IL).

2. RESULTS

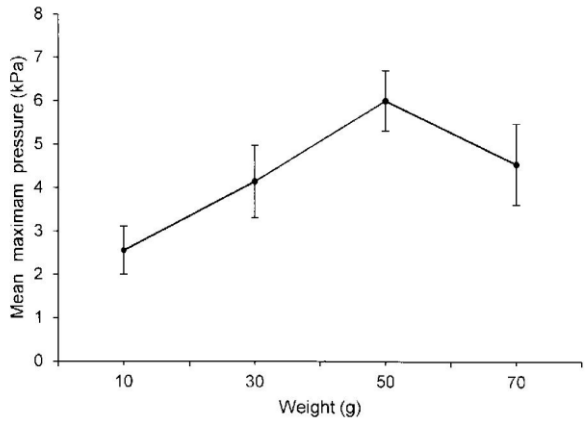
Prior to evaluating the effects of the "A weight on-off test", we wanted to know how much weight was minimally required to cause IOP to decrease effectively through compression of the eyeball. As such, we prepared 10, 30, 50 and 70 g salt weights wrapped in plastic wrap (Fig. 1A). To determine whether these weights compressed not just the eyeball but also the orbital bone (Fig. 1B), we studied the weight's topography of compression using a tactile pressure sensor. As shown in Figs 5 and 6, the weight could effectively compress eyeball beyond the eyelid in a weight-dependent manner until 50 g. Using these weights, 5 min tests similar to those described above were performed using 10 adult healthy volunteers (Mongolian 9 and Caucasian 1, male 5 and female 5, 34.5±7.92 year-old.) . A 50 or 70 g weight for 5 min caused a significant decrease in IOP in all subjects' eyes while such decreases were seen in only 10 % or 50 % of subjects eyes using a 10 or 30 g weight. Based on these results, we decided to use a 50 g weight for following study.

Figure 5. Topographic view of pressure distribution by several weights on table or eyes



Topographic pressure distribution by a 10, 30, 50 or 70 g weight to eyeball was measured using a flexible pressure sensor panel covered with silicone rubber This sensor panel was placed on a table (A through D) or a healthy volunteer's eye (E; 32 year-old female Mongolian or F; 30 year-old male Caucasian). Next, a 10 (A), 30 (B), 50 (C, E, F) or 70 g (D) plastic wrapped weight was placed onto the pressure sensor panel. The pressure sensor panel was connected to a personal computer, and the measurements were made automatically every 0.03 sec at a sensitivity of 0.7 kilopascals (1 kPa is approximately 5 mmHg) with a range of 0 to 140 kPa. Topography of pressure distribution of the weights was visualized in a three-dimensional shape. The compression pressures were calculated by the peak heights.

Figure 6. Changes of compression pressures by weights



Upon place of a 10, 30, 50 or 70g weights on eyeballs of healthy volunteers (Mongolian 9 and Caucasian 1, male 5 and female 5, 34.5±7.92 year-old), its compression pressures measured by a flexible pressure sensor panel as above were plotted. Data represents mean ± SD.

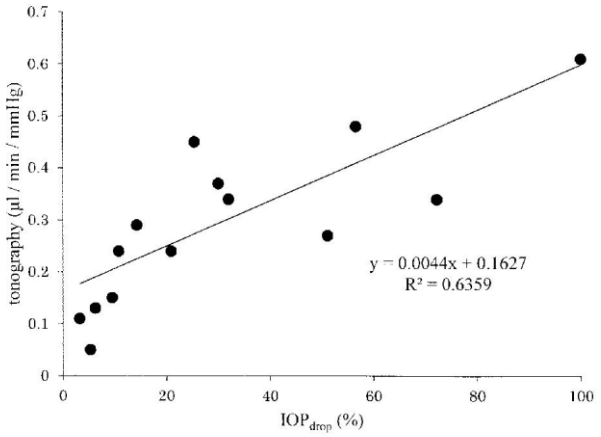
To measure the AH dynamics, AH outflow resistance, and AH production, in patients with several types of glaucoma (POAG, n=124, 227 eyes; PACG, n=16, 29 eyes; PEX, n=17, 29 eyes) and control subjects (n=93, 125 eyes) (Table 1), "A weight on-off test" was performed. As for initial consecutive 12 patients, tonography measurements were also performed between 1 pm through 4 pm on the next day of their "A weight on-off test" to compare these analyses. As shown in table 2 and Fig. 7, AH resistance index of both weight on-off test (IOP_{drop}, %) and tonography (μl/min/mmHg) were well correlated (R^2=0.6359) suggesting that "A weight on-off test" maybe useful for evaluating AH dynamics.

Table 2 Analysis of AH dynamics by "A weight on-off test" and tonography

No.	eys	age	sex	type	weight on (AH resistance)		weight off (AH production)								IOP_{drop} (%)	IOP_{rec} (min)	tonography (μl/min/mmHg)
					P_0	P_5	P_{af1}	P_{af2}	P_{af3}	P_{af4}	P_{af5}	P_{af6}	P_{af7}	P_{af8}			
1	OS	48	M	POAG	12.7	10.3	10.3	11	10.7	11	11	11.7	13		51.1	7	0.27
	OD	48	M	POAG	10.3	9	10.7								56.5	1	0.48
2	OD	65	M	POAG	11.7	11.3	12.3								10.8	1	0.24
3	OS	79	F	POAG	14.3	13.7	14.7								9.5	1	0.15
4	OD	61	F	POAG	14.7	13.3	13	12.7	15						20.9	3	0.24
5	OD	48	M	POAG	14.7	13	12.3	12.7	13.7	14	14.3	14.7			25.4	6	0.45
6	OS	83	F	PACG	17.3	17	18.3								3.2	1	0.11
7	OS	77	F	POAG	10.3	8	7.7	8.7	8.3	9.7	9.7	10	10	10.3	100.0	8	0.61
8	OD	58	F	POAG	19	15.7	18	18.3	20	-					30.0	3	0.37
	OS	58	F	POAG	22.7	18	21.7	21	22	23					32.0	4	0.34
9	OD	69	M	POAG	24	23	26.3								6.3	1	0.13
10	OD	91	F	POAG	19.3	18.7	20.3								5.3	1	0.05
11	OD	69	F	POAG	15	14	14.3	14.7	15.3						14.3	3	0.29
	OS	69	F	POAG	17.7	10.7	14	15	15.3	16.3	16.3	17.3	17.7		72.2	7	0.34

AH; aqueous humor, POAG; primary open-angle glaucoma, PACG; primary angle-closure glaucoma, PEX; pseudoexfoliation syndrome, P_0; IOP at baseline, P_5; IOP at 5 min after weight on an eye, $P_{af1, af2, af3,,, af7}$; IOP at 1, 2, 3,,, 7 min after weight off an eye, IOP_{drop}; IOP drop rate, IOP_{rec}; IOP recovery time

Figure 7. Comparison of AH dynamics factors obtained by "A weight on-off test" (IOP_{drop},%) and tonography (μl/min/mmHg).



To compare AH dynamics factors obtained by "A weight on/off test" (IOP_{drop},%) and tonography, tonography measurements were performed between 1 pm through 4 pm on the next day of their "A weight on-off test" using initial consequtive 16 eyes from 12 patients. Both AH resistance index of weight on-off test (IOP_{drop},%) and tonography (μl/min/mmHg) were plotted (R^2=0.6359).

2-1. AH outflow resistance factors in several types of glaucoma

As shown in Table 3, AH outflow resistance factors, IOP_{drop} (%) and $R_{aq\ out}$, in POAG, PACG or PEX patients were significantly lower and higher, respectively, than in control subjects. Thus, AH outflow resistance was significantly higher in glaucoma patients than in the control. To study effects of anti-glaucoma drops on the AH outflow resistance, IOP_{drop} (%) and $R_{aq\ out}$ among several types and combinations of anti-glaucoma medication were compared. In comparison with the POAG patients not receiving medication, AH outflow resistance was slightly increased in POAG patients receiving double or triple anti-glaucoma medications (Table 4).

Table 3. AH outflow resistance factors in control and patients with several types of glaucoma

	Control n=125 eyes	POAG n=227 eyes	PACG n=29 eyes	PEX n=29 eyes
IOP_{drop} (%)	31.7	24.7*	21.5*	21.8*
$R_{aq\ out}$	68.3	75.3*	78.5*	78.2*

IOPdrop; IOP drop rate, Raq out; AH outflow resistance index, POAG; primary open-angle glaucoma, PACG; primary angle-closure glaucoma, PEX; pseudoexfoliation syndrome,
* $P < 0.05$ (t test)

Table 4. AH outflow resistance factors in POAG compared with medication

	none n=42 eyes	PG n=30 eyes	PG /β n=12 eyes	PG / CAI n=7 eyes	PG /β/ CAI n=38 eyes
IOP_{drop} (%)	28.5	30.0	25.3	23.3	17.5
$R_{aq\ out}$	71.5	70.0	74.7	76.7	82.5

POAG; primary open-angle glaucoma, IOP_{drop}; IOP drop rate, $R_{aq\ out}$; AH outflow resistance index, PG; prostaglandin-derivatives, β; β-blocker, CAI; carbonic anhydrase inhibitor

2-2. AH production factors in several types of glaucoma

For patients with POAG, PACG or PEX, the recovery time for decreased IOP to return to baseline IOP levels (IOP_{rec}) was slightly shorter than that for control subjects, and their P_{aq} levels were slightly greater (Table 5). Concerning the effects of anti-glaucoma medication toward AH production in POAG patients, prostaglandin-derivatives (PG) caused significant delays of IOP_{rec} and slightly decrease in P_{aq} (Table 6).

Table 5. AH production factors in control and patients with several types of glaucoma

	control n=54 eyes	POAG n=59 eyes	PACG n=3 eyes	PEX n=10 eyes
IOP_{rec} (min)	5.20	4.36	3.67	3.60
P_{aq}	0.87	0.96	0.96	0.94

IOP_{rec}; IOP recovery time, P_{aq} ; AH production index, POAG; primary open-angle glaucoma, PACG; primary angle-closure glaucoma, PEX; pseudoexfoliation syndrome

Table 6. AH production factors in POAG compared with medication

	none n=22 eyes	PG n=12 eyes	PG /β n=5 eyes	PG / CAI n=3 eyes	PG /β/ CAI n=12 eyes
IOP_{rec} (min)	3.41	7.17*	5.40	3.00	3.00
P_{aq}	1.19	0.52	0.57	0.82	1.16

POAG; primary open-angle glaucoma, IOP_{rec}; IOP recovery time, P_{aq} ; AH production index, PG; prostaglandin-derivatives, β; β-blocker, CAI; carbonic anhydrase inhibitor,
* $P < 0.05$ (t test)

3. DISCUSSION

It is well known that AH outflow resistance increases in patients with glaucoma and in some cases AH production also increases, in addition to IOP level. Thus, evaluation of the AH production and AH outflow facility is quite important information to understand glaucoma etiology as well as diagnosis and treatment for patients with glaucoma. When measuring IOP levels, the Schiotz tonometer with a 5.5, 7.5 and 10 g plunger load is often utilized to determine external compression of the eye globe [19,20].

Schiotz tonography[21-23] or

pneumatonography[24,25] is often used to estimate the AH outflow. In turn, AH production was estimated by the recovery from decreased IOP by the ocular compression to the initial level of the IOP. External compression is therefore a powerful methodological basis for measuring IOP as well as AH dynamics. However, for the purpose of measuring the AH outflow facility by tonography, pneumatonography and Schiotz tonography showed similar results, but neither had good reproducibility[17]. In the present study, we developed a simple method to evaluate AH dynamics, AH production and AH outflow resistance, called "A weight on-off test" based upon the external ocular compression. When conducting this test, we observed that AH outflow resistance factors (IOP_{drop} and $R_{aq\ out}$) were significantly lower and higher, respectively, in POAG, PACG or PEX subjects than in control subjects, but these factors were not significantly affected by anti-glaucoma medications. Additionally, AH production (IOP_{rec} and P_{aq}) in POAG, PACG or PEX subjects was slightly decreased and increased, respectively, when compared to production in control subjects. In POAG patients, PG caused a significant delay of IOP_{rec} and slightly decrease in P_{aq}.

Regarding ocular rigidity and elasticity, there are numerous studies using porcine eyes[26,27] or enucleated or living human eyes[28-33] that demonstrate how the elasticity of the cornea and sclera is constant during the 15-50 mm Hg increase in IOP, thus confirming that rigidity increases with increasing IOP. Pallikaris et al. described that the mean ocular rigidity coefficient was found with statistically significant positive correlation with age of the patient (P = 0.02) but not with ocular parameters such as axial length, (P = 0.09) and corneal thickness (P = 0.12) or several pathologic states including diabetes mellitus (P = 0.39), age-related macular degeneration (P = 0.55), and hypertension (P = 0.45). These observations suggest that the ocular shell consisting of the cornea and sclera should be stable within the physiological IOP levels (10-30 mmHg). Based upon these facts, ocular compression methods have been utilized to measure IOP as well as AH dynamics[34,35]. In terms of glaucoma study, a bulbar suction test[35], ocular compression test[36-38] and tonography[40,41] have been conducted and these tests were effective in screening patients with glaucoma and their results have contributed to the pharmacological study of anti-glaucoma medication. Mansour and Adnan analyzed decrease of IOP by ocular compression as well as its recovery after removal of the ocular compression[42]. Their results were similar to those of the present study, although their data varied among subjects because their experimental methods for ocular compression and IOP measurement were different.

A limitation in the present study is its single-centered study, meaning there was a limited number of appropriate subjects available. However, despite the relatively small number of subjects, proper statistical analysis was used and ocular compression by weights was characterized as much as possible by a sensitive newly developed flexible sensor. Another limitation is that "A weight on-off test" measurements took place between 1 and 4 pm. Due to circadian and day-to-day IOP fluctuations, there was the possibility that results could fluctuate significantly depending on the hour or day the tests were administered. These limitations will need to be addressed as we embark on our next project.

In conclusion, our present data suggests that a newly developed "A weight on-off test" may be simple and useful for estimating AH dynamics in patients with glaucoma and could help provide a better understanding of glaucoma etiology as well as pharmacology of anti-glaucoma medications.

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