AQUEOUS FLOW MEASUREMENTS IN MAN BY THE PERILIMBAL SUCTION CUP TECHNIQUE*

II. COMPARISONS IN CHRONIC SIMPLE GLAUCOMA BEFORE AND AFTER PILOCARPINE

BY

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WITH the observation by Laqueur (1876) that tension of glaucomatous eyes could be reduced with physostigmine, and the corroboration of Weber (1877) that the same effect attended the use of pilocarpine, both substances have found a permanent place in therapy. Their precise action, however, remains obscure (Sugar, 1957; Becker and Shaffer, 1961).

Unlike carbonic anhydrase inhibitors, such as acetazolamide, which lower the intra-ocular pressure in glaucoma by reducing the rate of aqueous formation without alteration of the outflow facility, pilocarpine relieves the obstructed outflow of aqueous in glaucoma. This effect might be explained either by a direct action upon the aqueous outflow episcleral veins or by a direct reduction in the rate of aqueous formation. The suction cup technique, introduced by Ericson (1958) provides measurements of:

- (a) Rate of aqueous formation (mF in $\mu\text{l.}/\text{min.}$)
- (b) Coefficient of facility of aqueous outflow (C in $\mu\text{l.}/\text{min.}/\text{mm. Hg}$)
- (c) Rate of aqueous outflow (oFD in $\mu\text{l.}/\text{min.}$)
- (d) Outflow venous pressure (Vp in mm. Hg)

This technique appears therefore, suitable for the delineation of the site of action of pilocarpine in glaucoma. The details of the suction cup technique and a comparison of the results obtained in a series of normal subjects and glaucomatous patients have been provided in a previous study (Chandler, 1964). The present communication provides similar measurements in a separate series of eleven patients with chronic simple wide-angle glaucoma before and after the use of pilocarpine.

Material

Eleven unselected patients (mean age 55 years) with chronic simple glaucoma, who attended the Glaucoma Clinic of the Victoria General Hospital, Halifax, Nova Scotia, for diagnostic purposes before treatment, were studied by the suction cup technique. The relevant clinical details are summarized in Table I (opposite).

* Received for publication 20 December, 1963.

† In receipt of Public Health Research Grant #602.7.36. The National Health Grant Programme, Canada.

TABLE I
CLINICAL DATA OF ELEVEN CASES OF GLAUCOMA

Case No.	Age (yrs)	Corrected Visual Acuity	Angle of Anterior Chamber	Optic Disc	Resting Intra-ocular Pressure (mm. Hg)	Facility of Outflow (C) (μ l./min./mm./Hg)	Central Visual Field	Provocative Test and Result
1	37	20/20	Wide 3-4	Early cupping	22	0.14	Small enlargement of blind spot	Water-drinking 8 mm. Hg Rise
2	55	20/50	Wide 4	Not cupped	20	0.37	Normal	
3	55	20/20	Wide 3-4	Not cupped	22	0.27	Normal	
4	62	20/20	Wide 3-4	Early cupping	24	0.10	Seidel Scotoma	
5	67	20/25	Wide 3-4	Not cupped	17.7	0.16	Nasal depression	Water-drinking 10 mm. Hg Rise
6	53	20/20	Wide 3-4	Early cupping	24	0.14	Seidel Scotoma	
7	44	20/25	Wide 3-4	Moderate cupping	29.5	0.19	Bjerrum Scotoma	
8	65	20/20	Wide 4	Not cupped	20	0.08	Normal	
9	56	20/20	Wide 3-4	Early cupping	20	0.17	Small enlargement of blind spot	Water-drinking 9 mm. Hg Rise
10	45	20/20	Wide 4	Not cupped	22	0.21	Normal	
11	70	20/25	Wide 3-4	Not cupped	29.4	0.09	Nasal depression	

Methods

In this study the standard suction cup of Ericson (1958) was used. All patients were studied during recumbency and at similar times of the day, usually between 11 and 12 a.m. Both eyes were anaesthetized with 0.4 per cent. Dorsacaine applied topically and the steady-state resting pressure was determined with a Mueller* electronic tonometer. The mean of three readings, taken at 1-min. intervals was used as resting intra-ocular pressure (P_0).

The suction cup was placed perilimbally and a negative pressure of 50 mm. Hg was applied to the cup by a mercury manometer, providing a contact pressure of 28.7 mm. Hg. After 15 min. the vacuum was reduced and the cup removed from the eye. The intra-ocular pressures were then recorded at 1-min. intervals for the first 5 min. and thereafter at 2-min. intervals until the resting steady-state intra-ocular pressure was once again approached. The pressure calculated by extrapolation to zero time on the pressure decay curve is designated as P_1 .

The calculations of aqueous flow, facility of outflow, and aqueous outflow venous pressure were conducted in accordance with the methods outlined elsewhere (Chandler, 1964).

After the administration of topical pilocarpine 2 per cent. three times daily for one week, all observations were repeated in the manner outlined above.

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Results

(a) Before Pilocarpine

Table II (upper section) shows the actual measurements in the eleven glaucoma patients before treatment with pilocarpine. The mean resting intra-ocular pressure (P_0) was 22.78 ± 3.8 mm. Hg and rose to a mean of 34.5 ± 4.8 mm. Hg (P_1) after 15 min. of the suction cup application, providing a mean rise of 0.78 ± 0.32 mm. Hg./min. The mean rate of aqueous formation during the 15 min. of the procedure (mF) was 1.1 ± 0.42 μ l./min. The mean coefficient of outflow facility (C) was 0.14 ± 0.052 μ l./min./mm./Hg.

TABLE II
FINDINGS BEFORE AND AFTER PILOCARPINE

	Case No.	P_0 (mm. Hg)	P_1 (mm. Hg)	Mean Rise (mm. Hg./min.)	mF Inflow (μ l./min.)	Return Time to P_0 (min.)	C (μ l./min./mm./Hg)	k (μ l./min.)	V_p (mm. Hg)	$oFD-A$ Outflow (μ l./min.)	oFD_B Outflow (μ l./min.)	$\Delta f = oFD-A - mF$
Before Pilocarpine	1	22.0	42.4	1.36	1.70	30	0.10	-0.08	5.0	0.85	1.20	-0.85
	2	20.0	29.2	0.61	0.90	25	0.25	-0.20	16.4	0.56	0.70	-0.34
	3	22.0	32.8	0.72	0.90	25	0.08	+0.15	10.7	0.59	0.67	-0.31
	4	24.0	30.0	0.40	0.50	28	0.10	+0.04	19.0	0.27	0.40	-0.23
	5	17.7	28.4	0.71	1.10	22	0.12	+0.30	8.6	0.76	0.90	-0.34
	6	24.0	33.2	0.61	0.80	30	0.20	-0.08	20.0	0.38	0.67	-0.42
	7	29.5	35.8	0.42	0.40	12	0.18	+0.50	27.3	0.51	0.53	-0.11
	8	20.0	31.0	0.73	1.00	35	0.10	0.00	10.0	0.44	0.80	-0.56
	9	20.0	36.2	1.08	1.44	40	0.13	+0.03	8.9	0.55	1.13	-0.89
	10	22.0	41.0	1.26	1.60	55	0.15	-0.63	11.3	0.43	0.97	-1.17
	11	29.4	39.2	0.65	0.77	40	0.15	-0.20	24.3	0.29	0.52	-0.48
	Mean	22.78	34.5	0.78	1.10	31.09	0.14	-0.07	14.68	0.51	0.77	-0.52
After Pilocarpine	1	24.0	40.60	1.11	1.30	11	0.20	+0.40	18.5	1.72	1.30	+0.42
	2	18.0	29.90	0.79	1.10	14	0.10	+0.50	7.0	1.19	1.10	+0.09
	3	14.3	22.00	0.51	0.97	16	0.20	+0.53	11.4	0.91	0.91	-0.06
	4	17.0	27.20	0.67	1.10	25	0.10	+0.30	6.0	0.66	0.43	-0.44
	5	18.5	25.00	0.43	0.70	9	0.13	+1.03	13.1	1.12	0.70	+0.42
	6	17.0	26.40	0.63	1.20	22	0.18	+0.20	10.40	0.70	0.80	-0.50
	7	22.8	31.00	0.55	0.67	6	0.33	+0.70	20.8	1.65	0.70	+0.98
	8	18.2	32.40	0.95	1.40	20	0.28	-0.30	13.2	1.04	1.20	-0.36
	9	17.0	30.60	0.91	1.35	21	0.15	+0.20	8.0	0.97	1.10	-0.38
	10	18.5	33.40	0.99	1.40	30	0.15	0.00	9.2	0.70	1.00	-0.70
	11	23.8	29.00	0.35	0.45	16	0.22	0.00	21.8	0.43	0.42	-0.02
	Mean	19.00	29.77	0.72	1.06	17.3	0.185	+0.39	12.67	1.01	0.88	-0.11

The mean return time to resting steady-state pressure (P_0) was 31.09 ± 11.3 min.

The mean intercept constant on the ΔF ordinate obtained from the pressure-volume relationship plot (Fig. 1, opposite) was -0.07 ± 0.03 μ l./min. and cannot, therefore, be added to mF .

The mean aqueous outflow venous pressure, calculated from the relationship

$$V_p = P_0 - \frac{F}{C}$$

was 14.68 ± 7.18 mm. Hg.

FIG. 1.—Pressure-volume relationships derived from decay curves of Case 11, showing negative intercept of $0.2 \mu\text{l./min.}$ before pilocarpine which has increased to zero after treatment with pilocarpine.

The mean rate of aqueous outflow taken over the whole of the pressure decay curve (oFD_A) was $0.51 \pm 0.178 \mu\text{l./min.}$ The mean rate of outflow (oFD_B) calculated from the first 15 min. of the pressure decay curve was $0.77 \pm 0.26 \mu\text{l./min.}$

The mean difference between mF and oFD_A was significant at the 5 per cent. level ($P < 0.05$) and indicates a reduced mean rate of aqueous outflow in untreated glaucoma.

(b) After Pilocarpine

Table II provides precisely the same measurements in this group of patients after one week of 2 per cent. pilocarpine therapy.

The means of the two sets of observations and their statistical analysis are summarized in Table III (overleaf).

The mean resting intra-ocular pressure (P_0) is lower at $19.00 \pm 3.3 \text{ mm. Hg}$ ($P < 0.05$) as well as the intra-ocular pressure after the procedure (P_1), namely $29.77 \pm 4.9 \text{ mm. Hg}$ ($P < 0.05$). The mean rise in pressure of $0.72 \pm 0.25 \text{ mm. Hg}$ is not significantly different ($P > 0.1$). No significant difference attaches to the mean rate of aqueous inflow mF , which at $1.06 \pm 0.32 \mu\text{l./min.}$ is the same as before treatment ($P > 0.1$). The mean return time to resting intra-ocular pressure has been significantly reduced to $17.3 \pm 7.2 \text{ min.}$ (see Fig. 2).

FIG. 2.—Pressure decay curve of Case 11 before and after pilocarpine, showing fall in resting pressure (P_0) and reduced time of return to this level after administration of pilocarpine.

The coefficient of facility of outflow (C) has not significantly changed with treatment, but the mean of $0.185 \pm 0.072 \mu\text{l./min./mm. Hg.}$ ($P > 0.1$) is higher after therapy. The intercept constant (k) has become positive in eight and less negative in the remaining three, providing a mean of $+0.39 \pm 0.31 \mu\text{l./min.}$ (Fig. 1). This change is significant ($P < 0.01$) and permits the total mean rate of aqueous inflow to be expressed

as tF (i.e. $mF + k = tF$), which increases the mean rate of aqueous inflow after pilocarpine to $1.45 \mu\text{l./min.}$ The mean aqueous outflow venous pressure has not significantly altered ($P > 0.1$).

The mean rate of aqueous outflow (oFD_A) over the total pressure decay curve has significantly increased to $1.01 \pm 0.4 \mu\text{l./min.}$ ($P < 0.01$), and the differences between the means of the rate of aqueous inflow and outflow are no longer significant ($P > 0.1$).

The mean rate of aqueous outflow expressed over the first 15 min. of the pressure decay curve (oFD_B) was $0.88 \pm 0.297 \mu\text{l./min.}$ and showed no significant difference ($P = > 0.1$).

Discussion

The suction cup technique established significant differences which follow the use of pilocarpine in chronic simple wide-angle glaucoma in respect of the time function of the pressure decay curve, the conversion of the intercept constant (k) to a positive value, and the mean rate of aqueous outflow.

The reduction of the return time towards the steady-state resting level (P_0) from a mean of 31.09 to 17.3 min. profoundly influences the calculation of the mean rate of aqueous outflow and indicates that pilocarpine has its major effect on this parameter. The slope of decay curves approaches that of the normal and some of the instability seen in glaucoma is eliminated. No convincing change, however, can be depicted in the slope or calculation of the facility of outflow (C) after treatment with pilocarpine, and the main effect upon the pressure-volume relationship is indicated by a shift of the mean of this relationship to produce a positive intercept on the ΔF ordinate (Fig. 1). The calculated mean rate of aqueous formation and mean rate of outflow are thus rendered similar and this eliminates the discordant differences in means of rate of formation and outflow in the untreated state. The reduction in return time to P_0 of the pressure decay curve is so striking that this aspect, in particular, provides a useful additional facet in the assessment of drug effects in chronic simple glaucoma.

TABLE
MEANS AND SIGNIFICANCE OF

Measurements	P_0 (mm. Hg)		P_1 (mm. Hg)		Mean Rise (mm. Hg/ min.)		mF Inflow ($\mu\text{l./min.}$)		Return Time to P_0 (min.)	
	Before	After	Before	After	Before	After	Before	After	Before	After
Pilocarpine										
Mean	22.78	19.00	34.5	29.77	0.78	0.72	1.10	1.06	31.09	17.3
S.D. $\pm$	3.8	3.3	4.8	4.9	0.32	0.25	0.42	0.32	11.3	7.2
Significance of Difference	$P < 0.05$		$P < 0.05$		$P > 0.1$		$P > 0.1$		$P < 0.01$	

Difference between $\bar{x}mF$ and $\bar{x}oFD_A$

The mean rate of aqueous formation (mF) was 1.1 $\mu\text{l./min.}$ before and 1.06 $\mu\text{l./min.}$ after pilocarpine, and no statistical significance attaches to this slight difference of the means. This estimate, in conjunction with essentially identical mean rates of intra-ocular pressure increments before and after therapy, suggests that pilocarpine has no effect upon aqueous formation.

The aqueous outflow venous pressure (Vp) might be expected to be larger in the untreated group, principally because of the higher P_0 pressure introduced into the relationship

$$Vp = P_0 - \frac{F}{C}$$

The apparent rise in the calculated mean facility of outflow after pilocarpine, however, eliminates the effect upon this relationship of a lower resting P_0 pressure. The comparison of Vp before and after therapy shows no significant difference, and in this respect seems to corroborate the direct observations of Goldmann (1948), Linnér (1955), and Weekers, Delmarcelle, and Prijot (1953), and to conflict with those of Duke-Elder (1952), Löhlein (1950), and Thomassen (1947).

The precise mechanism whereby pilocarpine effects an obvious increase in the mean rate of aqueous outflow cannot be established by this technique and continues to evade anatomical localization. Theoretical explanations have been advanced concerning miosis and changes in the alignment of the trabecular meshwork (Grant, 1955), but these still require convincing demonstration.

Summary

The suction cup technique of Ericson (1958) was used in eleven patients with chronic simple wide-angle glaucoma before and after treatment with 2 per cent. pilocarpine.

Estimates of the mean rates of aqueous formation were not found to be different. Significant differences were established after pilocarpine in respect of an obvious reduction in the time function of the pressure decay curve after removal of the cup, the conversion of the intercept constant (k) to a positive value, and principally in regard to a rise in the mean rate of aqueous outflow.

III

DIFFERENCES AFTER PILOCARPINE

C ($\mu\text{l./min.}$ / mm. Hg)		k ($\mu\text{l./min.}$)		Vp (mm. Hg)		$oFDA$ Outflow ($\mu\text{l./min.}$)		$oFDB$ Outflow ($\mu\text{l./min.}$)		Δf ($oFDA - mF$)	
Before	After	Before	After	Before	After	Before	After	Before	After	Before	After
0.14	0.185	-0.07	+0.39	14.68	12.67	0.51	1.01	0.77	0.88	-0.52	+0.11
0.052	0.072	0.03	0.31	7.18	5.5	0.178	0.4	0.26	0.297	0.32	0.12
$P > 0.1$		$P < 0.01$		$P > 0.1$		$P < 0.01$		$P > 0.1$		$P < 0.03$	

{ $P < 0.05$ before treatment.
 { $P > 0.1$ after treatment.

No significant differences were demonstrable between the means of the facility of outflow (C) and aqueous outflow venous pressure (Vp).

No anatomical explanation can be provided concerning the site of action of Pilocarpine.

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