Aqueous humor dynamics in glaucomato-cyclitic crisis

Shigetoshi Nagataki and Saiichi Mishima

The transfer coefficients of fluorescein in the anterior chamber by flow, \( k_f \), and by diffusion, \( k_d \), can be calculated for an individual human eye, through an analysis of fluorescein concentrations in the anterior chamber, pupillary aqueous, and serum ultrafiltrates following intravenous injection. Using this technique, aqueous humor dynamics was studied in eight patients with glaucomato-cyclitic crisis. In seven patients, the coefficients determined during the attacks averaged \( 1.23 \pm 0.08 \) (S.E.M.) \( \times 10^{-2} \) min\(^{-1} \) for \( k_f \), in the involved eye, and \( 0.91 \pm 0.12 \times 10^{-2} \) min\(^{-1} \) for \( k_d \), in the fellow eye. The differences in the coefficients between the two eyes were statistically significant (\( P < 0.05 \)). In six patients, the coefficients were measured during the remission, giving average values of \( 0.81 \pm 0.08 \times 10^{-2} \) min\(^{-1} \) for \( k_f \), and \( 1.36 \pm 0.16 \times 10^{-2} \) min\(^{-1} \) for \( k_d \), in the involved eye, and \( 0.78 \pm 0.07 \times 10^{-2} \) min\(^{-1} \) for \( k_f \), and \( 1.30 \pm 0.10 \times 10^{-2} \) min\(^{-1} \) for \( k_d \), in the fellow eye. The differences in the coefficients between both phases were statistically significant (\( P < 0.05 \)). In five patients, the determinations were repeated during the attack and remission, and the differences in the coefficients between both phases were statistically significant (\( P < 0.05 \)) in the involved eye.

Key words: aqueous humor dynamics, glaucomato-cyclitic crisis, transfer coefficients by flow and diffusion, intraocular pressure, prostaglandins, aqueous humor formation, outflow facility, uveitis.

The glaucomato-cyclitic crisis comprises a clinical entity characterized by recurrent attacks of unilateral ocular hypertension associated with mild cyclitic symptoms.\(^1\) Tonographic studies revealed a significant reduction in the outflow facility during the attacks and it was thought to be the main cause of ocular hypertension.\(^2,3\) Controversial results were, however, obtained concerning alteration in aqueous humor formation rate. Recently, prostaglandins, particularly prostaglandin E, were found at a high concentration in aqueous humor during the attack of this syndrome, suggesting involvement of this substance in the chain of events leading to the hypertensive attacks.\(^4\) In animal experiments, prostaglandin E was shown to induce a breakdown of the blood-aqueous barrier resulting in augmentation of aqueous humor formation rate.\(^5\)
It is, therefore, of interest to re-examine aqueous humor dynamics in this syndrome, with particular emphasis on aqueous humor formation rate and blood-aqueous barrier permeability.

Use of fluorescein permits investigation of human aqueous humor dynamics on the basis of a theory on substance transfer dynamics. Substance transfer dynamics in the anterior chamber is described by a differential equation involving two transfer coefficients relating substance concentrations in the posterior chamber, the anterior chamber and in blood serum; the transfer coefficient by flow ($k_{f}$) is defined as volume of aqueous humor flowing into and out of the anterior chamber per unit time in fraction of the anterior chamber volume and the transfer coefficient by diffusion ($k_{dp}$) is related to diffusional substance exchange between the anterior chamber and blood. The fluorophotometer designed by Maurice enables fluorescein concentration determinations in a small part of the anterior chamber. Thus, the concentration could be measured in the pupillary aqueous, i.e., aqueous humor bulging out through the pupil from the posterior into the anterior chamber. On the basis of this finding, a new method was developed allowing independent calculations of both transfer coefficients in an individual human eye. This report deals with application of this technique to patients with glaucomatocyclitic crisis.

Materials and methods
The subjects of the present study were eight cases of glaucomatocyclitic crisis; six males and two females, their age ranging between 21 and 65 years. The both coefficients of aqueous humor dynamics were determined during the early period of the attacks before commencement of medical treatment, and also during the remission when the intraocular pressure of the involved eye was...
Fig. 3. Analyses of the results shown in Fig. 1 (solid circles) and in Fig. 2 (open circles). Lines were fitted by a least-square method. For detail, see the method.

lower than that in the fellow eye. In the latter period, the determinations were carried out at least two months after cessation of medication.

Procedures for transfer coefficients determinations. Since the details of the method and data analysis were reported previously, it will be briefly outlined below. Ten per cent fluorescein solution, 0.1 ml. per kilogram of body weight, was injected into the cubital vein and subsequent changes in fluorescein concentrations in the anterior chamber (F_a) and the pupillary aqueous humor (F_p) were measured for both eyes, using a slit-lamp microphotometer constructed according to Maurice's design (Hamamatsu T. V. Co., Hamamatsu, Japan). Ten milliliters of blood was withdrawn from the cubital vein at intervals and the serum samples were subjected, after centrifugation, to ultrafiltration. Fluorescein concentrations of the serum ultrafiltrates (F_p) were determined. At the end of in vivo fluorescein concentration measurements, which lasted usually five to six hours, the intraocular pressure of both eyes was measured with Goldmann's applanation tonometer.

The time courses of changing fluorescein concentrations in the anterior chamber, in the pupillary aqueous and serum ultrafiltrate, such as shown in Fig. 1, were analyzed on the basis of the following equation:

\[
\int_{t_1}^{t_2} (F_a - F_p) \, dt / \int_{t_1}^{t_2} (F_p - F_a) \, dt \times 10^{-2}
\]

\[
(F_a)_{t_2} - (F_a)_{t_1} = k_{dp} \left( F_a \right)_{t_1} + k_{fa} \left( F_p \right)_{t_1} \\
\int_{t_1}^{t_2} (F_p - F_a) \, dt
\]

where \( k_{dp} \) and \( k_{fa} \) are the transfer coefficients by diffusion and flow, respectively. Graphical integrations were carried out every half hour on \( F_a, F_p, \) and \( F_p \) curves, starting from one hour after injection; the results were plotted as shown in Fig. 3. A straight line was fitted by a least-square method and \( k_{fa} \) was calculated from the slope of the line and \( k_{dp} \) from the intersect with the vertical axis. Both coefficients were expressed as min^{-1}.

Results

The transfer coefficients during the attack. The determinations of the transfer coefficients were carried out in seven patients during the early period of ocular hypertension; the patients did not receive any medication before the determinations. Fig. 1 shows an example of fluorescein concentration changes in the serum ultrafiltrate, in the anterior chamber and in the pupillary aqueous humor, measured in the involved eye. Concentration changes in the
Table I. Transfer coefficients by flow ($k_{fn}$) and diffusion ($k_{dpa}$) during attack

<table>
<thead>
<tr>
<th>Subject</th>
<th>Sex</th>
<th>Age</th>
<th>IOP (mm Hg)</th>
<th>$k_{fn}$ min$^{-1}$ $\times 10^{-2}$</th>
<th>$k_{dpa}$ min$^{-1}$ $\times 10^{-3}$</th>
<th>IOP (mm Hg)</th>
<th>$k_{fn}$ min$^{-1}$ $\times 10^{-2}$</th>
<th>$k_{dpa}$ min$^{-1}$ $\times 10^{-3}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>21</td>
<td>50</td>
<td>1.26 $\times 10^{-2}$</td>
<td>3.30 $\times 10^{-3}$</td>
<td>12</td>
<td>0.85 $\times 10^{-2}$</td>
<td>0.89 $\times 10^{-3}$</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>23</td>
<td>27</td>
<td>1.10</td>
<td>1.79 $\times 10^{-3}$</td>
<td>14</td>
<td>0.74 $\times 10^{-2}$</td>
<td>0.57 $\times 10^{-3}$</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>41</td>
<td>42</td>
<td>1.40</td>
<td>5.10</td>
<td>18</td>
<td>1.12 $\times 10^{-2}$</td>
<td>2.04 $\times 10^{-3}$</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>29</td>
<td>22</td>
<td>0.98</td>
<td>1.62</td>
<td>14</td>
<td>0.47 $\times 10^{-2}$</td>
<td>0.42 $\times 10^{-3}$</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>28</td>
<td>28</td>
<td>1.33</td>
<td>3.68</td>
<td>16</td>
<td>1.51 $\times 10^{-2}$</td>
<td>3.20 $\times 10^{-3}$</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>65</td>
<td>44</td>
<td>1.00</td>
<td>1.68</td>
<td>14</td>
<td>0.89 $\times 10^{-2}$</td>
<td>0.57 $\times 10^{-3}$</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>33</td>
<td>45</td>
<td>1.51</td>
<td>7.40</td>
<td>14</td>
<td>0.80 $\times 10^{-2}$</td>
<td>1.82 $\times 10^{-3}$</td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td></td>
<td></td>
<td>1.23 $*$$\times 10^{-2}$</td>
<td>3.51 $\dagger$$\times 10^{-3}$</td>
<td></td>
<td>0.91 $\times 10^{-2}$</td>
<td>1.36 $\times 10^{-3}$</td>
</tr>
<tr>
<td>S.E.M.</td>
<td></td>
<td></td>
<td></td>
<td>0.077</td>
<td>0.81</td>
<td></td>
<td>0.12 $\times 10^{-2}$</td>
<td>0.39 $\times 10^{-3}$</td>
</tr>
</tbody>
</table>

Average for 24 normal eyes (Reference No. 15) $k_{fn}$: $0.922 \pm 0.073$ (S.E.M.) $\times 10^{-5}$ min$^{-1}$, $k_{dpa}$: $0.974 \pm 0.094$ (S.E.M.) $\times 10^{-6}$ min$^{-1}$.  

*Difference between both eyes $p < 0.05$.  
†Difference between both eyes $p < 0.02$.  

fellow eye of the same patient are illustrated in Fig. 2. The anterior chamber concentration in the involved eye was significantly higher than that in the fellow eye, while the concentration in the pupillary aqueous humor was similar in both eyes, indicating increased fluorescein permeation from blood into the anterior chamber in the involved eye. The maximum anterior chamber fluorescein concentration ranged between $1.65 \times 10^{-7}$ and $5.30 \times 10^{-7}$ Gm. ml.$^{-1}$ and $F_h$ values ranged from $0.2 \times 10^{-7}$ to $1.0 \times 10^{-7}$ Gm. ml.$^{-1}$ in the involved eye.

An analysis of the time course of changing fluorescein concentrations in the three body fluids was carried out on the basis of the above equation, and a linear relationship was obtained as shown in Fig. 3. The two coefficients were calculated therefrom and in this particular case, a value of $1.40 \times 10^{-2}$ min$^{-1}$ was obtained for $k_{fn}$ and $5.10 \times 10^{-3}$ min$^{-1}$ for $k_{dpa}$ in the involved eye. In the fellow eye a value of $1.12 \times 10^{-2}$ min$^{-1}$ was obtained for $k_{fn}$ and $2.04 \times 10^{-3}$ min$^{-1}$ for $k_{dpa}$.

Similar analysis was carried out for the results obtained in six other patients and the values for the both transfer coefficients are given in Table I. Average values in the involved eye were $1.23 \pm 0.08$ (S.E.M.) $\times 10^{-2}$ min$^{-1}$ for $k_{fn}$ and $3.51 \pm 0.81$ (S.E.M.) $\times 10^{-3}$ min$^{-1}$ for $k_{dpa}$, respectively; these values were significantly greater ($p < 0.05$) than those in the fellow eye, i.e., $0.91 \pm 0.12 \times 10^{-2}$ min$^{-1}$ for $k_{fn}$ and $1.36 \pm 0.39 \times 10^{-3}$ min$^{-1}$ for $k_{dpa}$. For reference, the average values for both coefficients in 24 normal eyes are given in Table I. The differences in the both coefficients between the involved eyes and the normal eyes are statistically significant ($p < 0.05$), but the differences between the fellow eyes and the normal eyes are not significant.

The transfer coefficients during the remission. The determinations of both coefficients were carried out in five out of the above seven patients and one other patient during the remission when the intraocular pressure in the involved eye was lower than that in the fellow eye. The results obtained from these six patients are given in Table II. The values during the remission averaged $0.81 \pm 0.08$ (S.E.M.) $\times 10^{-2}$ min$^{-1}$ for $k_{fn}$ and $1.36 \pm 0.16 \times 10^{-3}$ min$^{-1}$ for $k_{dpa}$ in the involved eyes, and $0.78 \pm 0.07 \times 10^{-2}$ min$^{-1}$ for $k_{fn}$ and $1.20 \pm 0.10 \times 10^{-3}$ min$^{-1}$ for $k_{dpa}$ in the fellow eyes. The differences in the two coefficients between both eyes were not significant. These values were not in significant variance from the values in the normal eyes.

In five patients, where the determinations could be repeated during the attacks and remission, differences in $k_{fn}$ and $k_{dpa}$ values of the involved eyes were statisti-
Table II. Transfer coefficients by flow (k_f) and diffusion (k_d) during remission

<table>
<thead>
<tr>
<th>Subject*</th>
<th>Sex</th>
<th>Age</th>
<th>IOP mm Hg</th>
<th>k_f min⁻¹ x 10⁻³</th>
<th>k_d min⁻¹ x 10⁻³</th>
<th>Involved eye</th>
<th>Fellow eye</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>21</td>
<td>12</td>
<td>0.95</td>
<td>2.03</td>
<td>IOP mm Hg</td>
<td>k_f min⁻¹ x 10⁻³</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>23</td>
<td>14</td>
<td>0.99</td>
<td>1.16</td>
<td>21</td>
<td>0.99</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>41</td>
<td>11</td>
<td>0.50</td>
<td>1.09</td>
<td>16</td>
<td>0.68</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>29</td>
<td>12</td>
<td>0.75</td>
<td>0.93</td>
<td>13</td>
<td>0.75</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>28</td>
<td>14</td>
<td>0.65</td>
<td>1.38</td>
<td>15</td>
<td>0.56</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>30</td>
<td>14</td>
<td>0.99</td>
<td>1.58</td>
<td>18</td>
<td>0.99</td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td></td>
<td></td>
<td>0.81</td>
<td>1.36</td>
<td>0.78</td>
<td>1.20</td>
</tr>
<tr>
<td>S.E.M.</td>
<td></td>
<td></td>
<td></td>
<td>0.084</td>
<td>0.16</td>
<td>0.071</td>
<td>0.096</td>
</tr>
</tbody>
</table>

*Subjects Nos. 1 through 5 are the same individuals in Tables I and II.

Discussion

The present study revealed increases in both transfer coefficients by flow and diffusion during the attacks of the glaucomato-cyclitic crisis; increase in the latter coefficient was more pronounced than in the former. During the remission, both coefficients did not differ significantly from the normal values.

Accuracy of the present determinations was evaluated concerning the two aspects, i.e., accuracy of F_f determinations and the effect of aqueous-cornea fluorescein exchange on the values of the coefficients. Due to high peak F_f values in the involved eye during the attack, F_f values were thought to suffer from some errors which were estimated by comparisons between the present combinations of F_n and F_f values and those of the previous experiments on the model of pupillary aqueous humor. It was found that errors in F_f did not exceed ten per cent, which had only negligible effects on the final values of the coefficients. In two patients, fluorescein concentrations in the cornea were determined concurrently with concentration measurements in aqueous humor. The results were analyzed on the basis of the following equation:

\[
k_{f} = k_{f} (F_{f} - F_{c}) + k_{d} (F_{f} - F_{c})
\]

where \( F_{c} \) is fluorescein concentration in the cornea, \( r_{nc} \) is the fluorescein distribution ratio between the anterior chamber and the cornea and \( k_{nc} \) is the transfer coefficient between the aqueous and the cornea as referred to the anterior chamber volume. Using \( k_{nc} \) and \( r_{nc} \) values reported by Ota, Mishima, and Maurice, the two transfer coefficients, \( k_{f} \) and \( k_{d} \), were calculated. Both coefficients were found to be underestimated when calculations were carried out without regard to the cornea; underestimation in \( k_{f} \) was 4 and 13 per cent in the involved eyes and 2.5 and 2 per cent in the fellow eyes. The values of \( k_{d} \) were underestimated by 21 and 30 per cent in the involved eye and by 18 and 8.5 per cent in the fellow eyes. Thus, underestimations were more pronounced in the involved than in the fellow eyes and also in \( k_{d} \) values than in \( k_{f} \). Despite some errors in the actual values of the coefficients, these considerations give further support to the present conclusion on increase in both of the coefficients during the attack of the glaucomato-cyclitic crisis.

During the hypertensive attack of this syndrome, a significant increase was found in aqueous humor content of prostaglandins, the concentration levels of prosta-
glandin E being correlated with the levels of intraocular pressure. It was, therefore, thought that prostaglandin E played a role in the manifestation of the hypertensive attacks. It seems that the present findings on increases in the both coefficients are in keeping with observations in animal eyes wherein prostaglandin E was found to increase blood-aqueous barrier permeability and ultrafiltration leading to sustained elevation of the intraocular pressure. Changes in the outflow facility may be estimated using the present data, on the assumption that the anterior chamber volume was 174 µl and the episcleral venous pressure was 9 mm Hg. The average facility values were 0.09 µl min⁻¹ mm Hg⁻¹ for the involved eyes during the attack and 0.39 µl min⁻¹ mm Hg⁻¹ for those during the remission. For the fellow eyes, the facility values averaged 0.26 µl min⁻¹ mm Hg⁻¹. The outflow facility was greater during remission than that of the fellow eye, and this has previously been reported and corroborated. In agreement with the results in previous tonographic studies, a pronounced reduction is found in the outflow facility during the attacks. Thus, it may be concluded that the ocular hypertension is due to decrease in the outflow facility and also to increase in aqueous humor formation. In rabbit eyes, however, the outflow facility was reported to undergo little change by prostaglandin E application. It remains to be investigated in the future in what way the outflow facility reduction in this syndrome can be related with increase in aqueous humor content of prostaglandin E.

REFERENCES


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