Aqueous humor dynamics in glaucomato-cyclitic crisis*

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The transfer coefficients of fluorescein in the anterior chamber by flow, $k_{fa}$, and by diffusion, $k_{diff}$, 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 $1.23 \pm 0.08 \times 10^{-2}$ min$^{-1}$ for $k_{fa}$ in the involved eye, and $3.51 \pm 0.81 \times 10^{-2}$ min$^{-1}$ for $k_{diff}$ in the involved eye, and $0.91 \pm 0.12 \times 10^{-2}$ min$^{-1}$ for $k_{fa}$ in the fellow eye, and $1.36 \pm 0.39 \times 10^{-3}$ min$^{-1}$ for $k_{diff}$ 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 $k_{fa}$ and $1.36 \pm 0.16 \times 10^{-2}$ min$^{-1}$ for $k_{diff}$ in the involved eye, and $0.78 \pm 0.07 \times 10^{-2}$ min$^{-1}$ for $k_{fa}$, and $1.30 \pm 0.10 \times 10^{-3}$ min$^{-1}$ for $k_{diff}$ in the fellow eye. The differences in the coefficients between the two eyes were not significant. 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. 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. 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. In animal experiments, prostaglandin E was shown to induce a breakdown of the blood-aqueous barrier resulting in augmentation of aqueous humor formation rate.
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 ($k_{f_a}$) 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 ($k_{dpa}$) is related to diffusional substance exchange between the anterior chamber and blood.$^{10, 11}$ The fluorophotometer designed by Maurice enables fluorescein concentration determinations in a small part of the anterior chamber.$^{12}$ Thus, the concentration could be measured in the pupillary aqueous,$^{13}$ i.e., aqueous humor bulging out through the pupil from the posterior into the anterior chamber.$^{14}$ On the basis of this finding, a new method was developed allowing independent calculations of both transfer coefficients in an individual human eye.$^{15}$ 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...
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 determina-
tions.** 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 an-
terior chamber (Fa) and the pupillary aqueous
humor (Fp) were measured for both eyes, using
a slit-lamp microphotometer constructed accord-
ing 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 centri-
fugation, to ultrafiltration. Fluorescein concentra-
tions of the serum ultrafiltrates (Fp) were de-
determined. At the end of in vivo fluorescein con-
centration measurements, which lasted usually
two to six hours, the intraocular pressure of both
eyes were measured with Goldmann's appplanation
tonometer.

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

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

\[
(F_a)_{t_2} - (F_a)_{t_1} = k_{dp} + k_{f} \int_{t_1}^{t_2} (F_a - F_s) dt
\frac{\int_{t_1}^{t_2} (F_p - F_a) dt}{\int_{t_1}^{t_2} (F_p - F_s) dt}
\]

where \( k_{dp} \) and \( k_{f} \) are the transfer coefficients by
diffusion and flow, respectively. Graphical inte-
gratings were carried out every half hour on \( F_a, \)
\( F_p \), and \( F_s \) 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 \( k_{f} \) was calculate 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 at-
tack.** The determinations of the transfer coefficients were carried out in seven pa-
tients during the early period of ocular hyperten-
sion; the patients did not receive any medication before the determinations.

Fig. 1 shows an example of fluorescein concentration changes in the serum ultra-
filtrate, 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 \((k_{fa})\) and diffusion \((k_{dpn})\) during attack

<table>
<thead>
<tr>
<th>Subject</th>
<th>Sex</th>
<th>Age</th>
<th>IOP (\text{mm. Hg})</th>
<th>(k_{fa}) (\text{min}^{-1} \times 10^{-2})</th>
<th>(k_{dpn}) (\text{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</td>
<td>3.30</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>23</td>
<td>27</td>
<td>1.10</td>
<td>1.79</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>41</td>
<td>42</td>
<td>1.40</td>
<td>5.10</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>29</td>
<td>22</td>
<td>0.98</td>
<td>1.62</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>28</td>
<td>28</td>
<td>1.33</td>
<td>3.68</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>65</td>
<td>44</td>
<td>1.00</td>
<td>1.68</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>33</td>
<td>45</td>
<td>1.51</td>
<td>7.40</td>
</tr>
</tbody>
</table>

Mean            | 1.23* 3.51† |

S.E.M.           | 0.077 0.81 0.12 0.39 |

Average for 24 normal eyes (Reference No. 15) \(k_{fa} = 0.922 \pm 0.073 \text{ (S.E.M.)} \times 10^{-2} \text{ min}^{-1}\), \(k_{dpn} = 0.974 \pm 0.094 \text{ (S.E.M.)} \times 10^{-3} \text{ min}^{-1}\).  

*Difference between both eyes \(p < 0.05\).  
†Difference between both eyes \(p < 0.02\).

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 \(0.81 \pm 0.08 \text{ (S.E.M.)} \times 10^{-2} \text{ min}^{-1}\) for \(k_{fa}\) and \(1.36 \pm 0.16 \times 10^{-3} \text{ min}^{-1}\) for \(k_{dpn}\). 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.

In five patients, where the determinations could be repeated during the attacks and remission, differences in \(k_{fa}\) and \(k_{dpn}\) values of the involved eyes were statistically significant (\(p < 0.05\)) than those in the fellow eye, i.e., \(0.91 \pm 0.12 \times 10^{-2} \text{ min}^{-1}\) for \(k_{fa}\) and \(1.36 \pm 0.39 \times 10^{-3} \text{ min}^{-1}\) for \(k_{dpn}\). 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 values were significantly greater \((p < 0.05)\) than those in the fellow eye, i.e., \(0.91 \pm 0.12 \times 10^{-2} \text{ min}^{-1}\) for \(k_{fa}\) and \(1.36 \pm 0.39 \times 10^{-3} \text{ min}^{-1}\) for \(k_{dpn}\). 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.

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Table II. Transfer coefficients by flow (k_{fa}) and diffusion (k_{dpd}) during remission

<table>
<thead>
<tr>
<th>Subject*</th>
<th>Sex</th>
<th>Age</th>
<th>IOP mm. Hg</th>
<th>k_{fa} min^{-1} \times 10^{-2}</th>
<th>k_{dpd} min^{-1} \times 10^{-2}</th>
<th>IOP mm. Hg</th>
<th>k_{fa} min^{-1} \times 10^{-2}</th>
<th>k_{dpd} min^{-1} \times 10^{-2}</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
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<td>12</td>
<td>0.95</td>
<td>2.03</td>
<td>14</td>
<td>0.73</td>
<td>1.27</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>
<td>1.16</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>
<td>1.28</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
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<td>0.93</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>
<td>0.98</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>
<td>1.58</td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td></td>
<td></td>
<td>0.81</td>
<td>1.36</td>
<td></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></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_a determinations and the effect of aqueous-cornea fluorescein exchange on the values of the coefficients. Due to high peak F_i values in the involved eye during the attack, F_b values were thought to suffer from some errors which were estimated by comparisons between the present combinations of F_a and F_b values and those of the previous experiments on the model of pupillary aqueous humor.15 It was found that errors in F_b 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 equation15:

\[ \frac{dF_c}{dt} = k_{dpd} (F_b - F_a) + k_{fa} (F_b - F_c) \]

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_{dpd} is the transfer coefficient between the aqueous and the cornea as referred to the anterior chamber volume. Using k_{dpd} and r_{nc} values reported by Ota, Mishima, and Maurice,16 anterior chamber volume of 174 \mu l, and the corneal volume of 70 \mu l (the corneal area and thickness were assumed to be 140 mm.^2 and 0.5 mm., respectively), the two transfer coefficients, k_{fa} and k_{dpd}, were calculated. Both coefficients were found to be underestimated when calculations were carried out without regard to the cornea; underestimation in k_{dpd} 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_{dpd} 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 fellow eyes and in k_{dpd} values than in k_{fa}. 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 prostaglandins...
glandin E being correlated with the levels of intraocular pressure.\(^7\) 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.\(^8\) Changes in the outflow facility may be estimated using the present data, on the assumption that the anterior chamber volume was 174 \(\mu l\) and the episcleral venous pressure was 9 mm. Hg.\(^9\) The average facility values were 0.09 \(\mu l\) min.\(^{-1}\) mm. Hg\(^{-1}\) for the involved eyes during the attack and 0.39 \(\mu l\) min.\(^{-1}\) mm. Hg\(^{-1}\) for those during the remission. For the fellow eyes, the facility values averaged 0.26 \(\mu l\) min.\(^{-1}\) mm. Hg\(^{-1}\). The outflow facility was greater during remission than that of the fellow eye, and this has previously been reported\(^2\) and corroborated.\(^3\) In agreement with the results in previous tonographic studies,\(^2\text{-}\text{6}\) 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.\(^17\) 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