Corneal Hydration Control in Fuchs' Dystrophy

Robert B. Mandell,* Kenneth A. Poise,* Richard J. Brond,† David Vastine,‡
David DeMortini,‡ and Roanne Flom* 

Corneal hydration control was tested in 22 patients with Fuchs' dystrophy, and eight subjects of similar age without the disease, by measuring the corneal thickness recovery from swelling induced by hypoxia or following overnight sleep. Measurement precision was enhanced by using a modified optical pachometer and conducting two test procedures which were analyzed by a coupled exponential model. We have identified three parameters of the recovery from corneal swelling which may be used to describe hydration control: percent recovery per hour (PRPH) (mean 25.4% for Fuchs' and 34.2% for normals), time for 95% of corneal thickness recovery (mean 10.2 hr for Fuchs' and 7.1 hr for normals), and the open-eye steady-state thickness (mean 562 μm for Fuchs' and 537 μm for normals.).

A PRPH of 17.1%/hr was identified as the minimum below which the cornea could not regain its open-eye steady state during the entire day and approaches decompensation. Our test procedure quantifies the corneal hydration control mechanism and may provide a test of endothelial function which can be used to monitor the progression of Fuchs' disease and guide decisions related to corneal surgery. Invest Ophthalmol Vis Sci 30:845–852, 1989

Fuchs' dystrophy is a progressive disease of the corneal endothelium which is characterized initially by endothelial guttata, followed by stromal edema, epithelial edema and possible corneal decompensation.1–4 The biomicroscopic observation of these signs generally forms the basis for a clinical diagnosis but does not provide a quantitative index of endothelial function loss or a good basis for prognosis of corneal recovery following cataract surgery. For example, corneas judged subjectively to be nearly normal by biomicroscopic examination sometimes develop rapid decompensation after uncomplicated cataract extraction, in contrast to other corneas, which are observed preoperatively to have more advanced Fuchs' signs, but which may better tolerate equivalent surgical trauma.

A test which directly quantifies the functional status of the corneal endothelium would be useful for monitoring the progression of Fuchs' dystrophy and other corneal diseases. Unfortunately, direct assessment of endothelial function is difficult even in the research laboratory. However, by making an assessment of corneal hydration control, which presumably depends substantially on endothelial function, it is possible to obtain a surrogate measure which may be clinically useful. Potentially, a test of hydration control could assist the clinician in monitoring the progression of corneal disease, choosing the most effective therapy, and predicting the likelihood of corneal decompensation. It might provide the corneal surgeon with guidelines for deciding whether to perform a combined procedure (cataract extraction and corneal graft) or only a cataract extraction.

Several early investigators assumed that a more quantitative morphological analysis of the corneal endothelium might provide an evaluation of endothelial function, and efforts were made in this direction. These studies were aided by the introduction of specular microscopy, which provided a tool for more accurate morphometry of the endothelial mosaic and a means for calculating cell shape, area and density.5 Unfortunately, in most studies no association was found between characteristics of endothelial morphology and the various measures available for assessing corneal function. In addition, the results of attempts to relate endothelial morphological parameters to endothelial permeability as measured by fluorophotometry6 have been inconsistent.7

The primary evidence for an association between endothelial morphology and function was presented by Rao et al,8 who showed that after cataract extraction, individuals with considerable preoperative polymegathism tended towards longer periods of postoperative corneal edema, compared to those who did not show polymegathism. They postulated that polymegathism was associated with a reduced functional reserve, which led to the slower elimination of
the corneal edema that resulted from the effects of cataract surgery. However, other studies to substantiate this hypothesis have not been carried out.

We report the results obtained from testing corneal hydration control in a group of patients with Fuchs' dystrophy and a comparison group of similar age without the disease. The test is based primarily on monitoring the rate of recovery from induced corneal hydration. Corneal hydration is presumably controlled by the counterbalance between a passive system of fluid flow resistance by the limiting layers of the cornea and an active fluid pump, which resides mainly in the endothelium. We assume that observed differences in the dynamics of recovery from induced corneal swelling represent primarily the differences in the contribution by the endothelium to hydration control. However, the validity of this assumption will require further investigation and analysis.

In addition to measuring the recovery from induced corneal swelling, we wished to determine if Fuchs' corneas swelled the same magnitude as normals in response to hypoxia or overnight sleep. These results are considered in relation to the problem of morning blur experienced by many Fuchs' patients and whether it can be adequately explained by the occurrence of overnight corneal edema.

Materials and Methods

In this section, the study subjects used in this investigation and the hydration control test procedures, along with associated modeling and analysis techniques, are described.

Subjects

Twenty-two subjects (four male and 18 female) with clinically diagnosed Fuchs' corneal dystrophy were recruited from an ophthalmological practice that specializes in corneal and external disease. These patients (mean age 69.6, range 54 to 82 years) were diagnosed initially by the primary physician as having Fuchs' dystrophy and are likely representative of the general Fuchs' population, with the possible exception that they tended towards a higher than average socioeconomic status. The criteria for clinical diagnosis included the presence of corneal guttata and usually epithelial microcysts, Descemets' membrane folds, or stromal haze. (The sample included two non-guttate Fuchs' eyes.) Twelve of the 22 subjects had bilateral disease and hydration control testing was performed before surgical intervention. The remaining 10 subjects provided data for only one eye. Their contralateral eye could not be used because seven eyes had already received a corneal transplant, another two eyes had undergone cataract surgery and the remaining eye was afflicted with herpes zoster. A total of 34 eyes were available for analysis.

Sixteen eyes from eight subjects who did not have Fuchs' dystrophy were measured as a comparison group. Their mean age was 71.9 years and there was one male and seven females. These patients were referred from a university eye clinic and local senior citizen centers.

The procedures of the study were explained fully to all subjects and then an informed consent was obtained. (The U.C. Berkeley Committee for the Protection of Human Subjects approval was received for the research project and Consent Form.)

Apparatus

For the stress test procedure described below, transient corneal swelling was induced by covering the cornea with a low water content (38%) hydrogel contact lens (stress lens) having a thickness of 0.45 mm, to give a low oxygen transmissibility of $Dk/L = 4.5 \times 10^{-9}$ (cm/sec) (ml O$_2$/ml X mm Hg). The lenses had concentric surfaces, uniform thickness and were available in either of three posterior curve radii (8.8, 9.0 or 9.2 mm). A lens was selected for each patient that provided the best centration with minimum movement and least subjective sensation.

Conical thickness measurements were made with a modified Haag-Streit optical pachometer that was equipped with fixation and alignment lights and an electronic recording system for increasing instrument sensitivity and reproducibility. The pachometer was linked to a Commodore microcomputer (Model #64, Commodore Business Machines, West Chester, PA), which allowed on-line time monitoring and data collection. The details of this instrument and the modifications are described elsewhere.

Procedures

Corneal hydration dynamics were tested by measuring the amount of induced corneal swelling and the rate of recovery to the open-eye steady-state (OESS) corneal thickness. Before the data for this report were collected, preliminary studies were conducted to establish a test protocol that could be used in a clinical setting and would be able to provide sufficiently precise information about an individual cornea's deswelling response. We found that a good assessment of hydration control could not be obtained from simply monitoring a single deswelling response for the length of time that is feasible during one test day because the standard errors for the test parameters were too large for clinical relevance. In order to obtain a reliable assessment of the functioning of the corneal hydration control system, it was
found necessary to use one of two kinds of composite test procedures. Each composite test consisted of two component tests: (1) a stress test and a patch test; or (2) a stress test and a natural test, as described below.

Stress Test

For this test, pachometry readings (usually three sets of ten) were first obtained to establish the pre-test corneal thickness. Each eye was then fitted with a stress lens and the subject was given approximately 5 min to adapt to the lens with the eyes open. This brief adjustment period was found necessary in the pilot development of the stress test protocol, in order to eliminate some problems with subsequent decentering of lenses during the closed-eye phase of the test. Following the 5 min adjustment period, the eyes were patched to ensure lid closure and kept in the closed-eye state for 2 hr except for brief monitoring at approximately 30, 60 and 90 min into the swelling phase of the test to make sure the lens was still centered on the cornea.

After the 2 hr test period, the lenses were removed and the central corneal thickness was measured at about 30 min intervals for at least 3 hr. Each episode of monitoring corneal thickness typically produced two thickness values, each based on the mean of a set of ten or more replicate measurements separated by realigning and refocusing the pachometer. Between sets of ten replicate measurements the subject’s head was retracted and then repositioned in the instrument. Replicate corneal thickness values were treated as independent measurements in the least-squares analysis used to estimate deswelling parameters for each individual. Ignoring some statistical dependence between replicate measurements made in close time proximity should have little effect on the estimates of deswelling parameters that were used as the raw material for the group comparisons in this report. However, ignoring some statistical dependence in the replicate measurements could exaggerate the estimated precision of an individual’s estimated deswelling parameter. Consequently, this issue must be considered before the analysis procedures are finalized for finding individual results for clinical applications where valid measures of precision will be required.

Patch Test and Natural Test

For the patch test the patient was instructed in the proper technique of patching one eye, which was done before retiring on the night preceding the test visit. The patient was brought to the test facility by a companion, as early in the morning as possible. The patch was removed and both the patched and unpatched eyes were measured by pachometry at 30 min intervals over a period of 4 to 5 hr. The unpatched eye which was tested under these conditions at the same visit was referred to as the natural test.

Analysis of Composite Hydration Control Test Data

Analysis of the combined data from both components of a composite hydration control test can be based on coupled models that are briefly described below. In the stress test, the deswelling response after the stress lens is removed can be described reasonably well by the exponential model:

\[ TH(t) = B + S1 \times e^{-Dt} + E, \quad t \geq 0, D \geq 0 \]  

In this model \( TH(t) \) is the corneal thickness at time \( t \) measured in minutes from the start of the deswelling phase of the test, which begins with the removal of the stress lens. The error in pachometric measurement is represented by \( E \), which is not directly observable. The model has three parameters: \( B \) (open-eye steady-state corneal thickness), \( S1 \) (the initial swelling present when the deswelling phase of the test begins), and \( D \) (the deswelling rate). The first two parameters, \( B \) and \( S1 \), are directly interpretable, but \( D \) is easier to interpret after it has been converted to alternative forms described below.

The deswelling response in the Patch or Natural test can be represented analogously by the model:

\[ TH(t) = B + S2 \times e^{-Dt} + E, \quad t \geq 0, D \geq 0 \]  

which is structurally the same as the stress test deswelling response model, but it has a different initial swelling parameter, \( S2 \).

The pair of models for a composite test are coupled because the \( B \) and \( D \) parameters are the same in both models since they represent corneal properties that are presumed to be stable from one component test to another. An analysis of composite test results, which use all of the test data available for a given eye to estimate \( B \), \( D \), \( S1 \) and \( S2 \) (if needed), can be implemented by using standard nonlinear regression techniques, as described more fully elsewhere. Sample programs which illustrate the analysis of composite test data with SAS procedure NLIN are available on request.

The deswelling rate, \( D \), can be more readily interpreted if it is converted to give the percent recovery per hour. The PRPH, which ranges from 0 to 100%, is the deswelling that occurs in any 1 hr interval expressed as a percentage of the swelling that exists at the start of the interval. It is defined by:

\[ \text{PRPH} = \frac{[TH(t) - B] - [TH(t + 60) - B]}{TH(t) - B} \times 100 \]
It can be shown that, for the exponential deswelling model,

\[ \text{PRPH} = (1 - e^{-60D}) \times 100 \]

when \( D \) is expressed in units of \((1/\text{min})\). For example, when \( D = 0.015 \, (1/\text{min}) \), which is a typical value for an older normal subject, then \( \text{PRPH} = (1 - e^{-60 \times 0.015}) \times 100 = 34.3\% \).

The deswelling rate \( D \) can also be converted to give the time required to reach 95% recovery back to OESS thickness. The time to 95% recovery, \( T_{95\%} \), can be computed from \( D \) by the conversion formula,

\[ T_{95\%} = \frac{-\ln (0.05)}{D} = \frac{2.996}{D} \]

For example, when \( D = 0.007 \, (1/\text{min}) \) then \( T_{95\%} = 2.996/0.007 = 428 \, \text{min} = 7.1 \, \text{hr} \).

Alternatively, a measure of deswelling time could be provided by the half-life, \( T_{50\%} = 0.693/D \), which gives the time for a reduction of swelling by 50%. However, the \( T_{95\%} \) which gives the time for nearly complete return to OESS seems to be more directly interpretable for clinical purposes.

In addition to the hydration control characteristics that appear as parameters in the coupled exponential deswelling model, a derived quantity, the swelling stimulated by the stress test, has also been obtained by a two-step calculation. First, the "residual swelling" was determined by subtracting the estimated OESS thickness from the mean of the initial status pachometry measurements made just before fitting the stress lens. Then, the swelling stimulated by the stress test was estimated by subtracting the estimated residual swelling from the estimated initial swelling provided by the estimate of the \( S_1 \), a parameter in the exponential deswelling model for the stress test.

The differences between Fuchs' and normal groups, with respect to various characteristics of corneal hydration control, were studied by use of general mixed model analysis of variance using program P3V, which is part of the BMDP statistical software.\textsuperscript{15} By this method the statistical dependence between measurements from a subject's pair of eyes and the presence of both paired- and single-eye data in the Fuchs' group are taken into consideration. For the study of percent recovery per hour, program P3V was first applied separately to the Fuchs' and normal group to allow for different amounts of variability in these two groups, then the results from the two separate analyses were used to construct a test statistic for comparing the two groups.

**Results**

Figure 1 illustrates the typical pattern of recovery from induced corneal swelling that was observed during the stress-patch composite test procedure. The solid lines in Figure 1 show the coupled exponential model that best fits the data that were obtained from testing the left eye of one subject, a 67-year-old woman with Fuchs' dystrophy. The initial swelling at the start of the stress test was estimated to be 89 \( \mu \text{m} \). The OESS thickness, which both recovery curves are approaching, was estimated to be 545 \( \mu \text{m} \). The deswelling rate, \( D \), in the exponential model was estimated to be 0.01075 \((1/\text{min})\) and the percent recovery per hour (PRPH) and time to 95% recovery \( T_{95\%} \) corresponding to this deswelling rate are 40.1% and 343 min, respectively.

The pattern of recovery observed with stress-natural composite tests was usually similar to that observed in Figure 1 except that the initial swelling with the natural test was typically less than that observed with the patch test.

There were several variations from the characteristic recovery pattern illustrated by Figure 1. For subjects with poor hydration control the recovery was so slow that the data looked more linear than exponential, presumably because there was not enough time for the exponential pattern to be revealed. An example of this kind of pattern is illustrated in Figure 2, which presents data from the right eye of a 65-year-old woman with Fuchs' dystrophy.
Another anomaly occurred in some of the natural test data, in which the corneal thickness seemed to drift upward 10 or 15 μm and then decline during the course of monitoring. This may have been the result of unnoticed eye closure by elderly subjects between measurements during the course of the test. Finally, in a few stress-patch tests, the initial swelling found when the patch was removed exceeded the swelling that was reached by application of hypoxic stress. This occurred in subjects with poor corneal recovery who may have been experiencing transient decompensation, which introduced day-to-day variation in the baseline corneal thickness upon which any stress-induced or overnight swelling was superimposed.

**Percent Recovery per Hour**

The percent recovery per hour, which provides a measure of an individual eye's hydration recovery capacity, is used to compare the Fuchs' group with a group of similarly aged normal subjects in Figure 3. The PRPH estimates for the 12 subjects for whom data are available for pairs of eyes are represented by the connected points on the right side of Figure 3, and were found to have a mean value of 23.9%/hr. The mean PRPH for the ten unilateral subject eyes was 28.8%/hr. The approximately 5%/hr difference between single-eye and paired Fuchs' eye data could simply be a chance difference (two-sided $P = 0.42$).

Alternatively, the difference may reflect a selection bias in the single-eye Fuchs' data that results from systematically having to exclude from the study those eyes which had prior corneal transplants and may have had lower PRPH values on the average.

For purposes of comparing the Fuchs' data with the similar-aged normals, we have combined the two Fuchs' data sets to give one overall group of 34 eyes. Taking into consideration the mixture of single eye data and statistically dependent paired eye data in the Fuchs' group, the resulting estimate for the mean PRPH for the combined group of Fuchs' subjects is 25.4%/hr in contrast to 34.2%/hr observed in the normal group. Despite the fact that the mean PRPH in the pooled Fuchs' data may be biased upward by the systematic exclusion of eyes that already received corneal transplants, the difference between the Fuchs' and normal groups is statistically significant (two-sided $P < 0.05$).

It is apparent from an examination of Figure 3 that the distribution of PRPH values in the Fuchs' group is substantially more variable than that which is observed in the comparison group of normal subjects. One of the single Fuchs' eyes showed noticeably better hydration control than was observed in the comparison group of normal subjects. However, the main reason for the increased variability in the Fuchs' group is the substantial number of Fuchs' eyes (12 out of 34) which were found to have PRPH values below the lowest value (21.1%/hr) found in the normal group.

Another way to contrast the recovery capacity of the normal and Fuchs' groups is provided by Figure 4. Each curve in Figure 4 illustrates the exponential pattern of recovery that would be expected had the initial swelling amounted to 10% corneal thickening. The slowest, average and fastest recovery patterns corresponding to the PRPH values observed in the normal comparison group are described by the dashed lines. The rather narrow range of recovery capacities found in the normal group is bracketed by the more heterogeneous Fuchs' group, whose slowest, average and fastest recovery patterns are illustrated by the heavy solid lines. These curves are graphed for 16 hr to illustrate the degree of recovery from 10% initial swelling that would be expected to occur during a typical 16 hr daytime period.

One of the features of an exponential recovery model is that the corneal thickness approaches the open-eye steady-state (OESS) thickness asymptotically, but theoretically it is never reached. Thus, to
Time (Hrs)

Fig. 4. The extreme and mean curves of exponential recovery from 10% corneal swelling for the Fuchs' and normal groups.

arrive at a definable endpoint, it is necessary to adopt some operational definition for “recovery to OESS thickness.” For this purpose we have used 95% recovery as the criterion and employed the time to 95% recovery (T95%) as an alternative way to express recovery capacity. As noted in the Methods section, the T95% is mathematically determined by the deswelling rate D or equivalently by the PRPH. The relationship between T95% and PRPH is shown graphically in Figure 5.

The time for 95% recovery in the Fuchs' subjects which corresponds to the mean PRPH was 10.2 hr, which is somewhat greater than was found for the corresponding mean of 7.1 hr in the similarly aged normals. Many Fuchs' patients took considerably longer than normals to reach the 95% recovery level. It may be seen from Figure 5 that once the PRPH falls below 17.1%/hr the time for the cornea to recover (95%) from swelling exceeds the number of waking hours in a typical 16 hr day.

Open-Eye Steady-State Thickness

The open-eye steady-state thickness of the cornea can be defined as the thickness level the cornea will approach and eventually reach if the eye is kept open sufficiently long after removing a stimulus (eg, hypoxia, sleep) that induces an increase in corneal hydration. Direct measurement of OESS thickness is, in principle, possible if one can be assured that the eye has been open sufficiently long to reach this level. However, for this report with older normal subjects and Fuchs' subjects, the OESS thickness has been estimated by fitting the coupled exponential model that has OESS thickness as one of its parameters: namely, the B parameter.

Even this method was not satisfactory for six of the Fuchs' eyes because the resulting estimates were unreliable. In these six instances it was possible to get usable estimates for the PRPH but the estimated standard errors for the OESS thickness were larger than 15 μm, so it was decided to omit them from analysis.

For the subjects for whom reliable estimates of OESS thickness could be obtained, the resulting data are presented in Figure 6. The average OESS corneal thickness for the Fuchs' group was 562 μm, compared to 537 μm for the normal group (two-sided P = 0.083).

The stimulated swelling that was produced by the stress test was calculated for the Fuchs' and normal eyes and is shown in Figure 7. The Fuchs' eyes showed considerably less stimulated swelling as a result of the stress test (47.3 μm) than was found in the normals (66.0 μm), and the difference was statistically significant (two-sided P = 0.029). One Fuchs' patient showed an unusually high stimulated swelling that was nearly double the normal average. Fifteen of 28 eyes, however, had stimulated swelling that was below the lower limit of the range for normals.
Discussion

We have evaluated four characteristics of corneal hydration control—the PRPH, the T95%, the OESS and the stimulated swelling—that might be useful for differentiating between corneal function in Fuchs' and normal subjects. At this time, we have not tried to identify the specific physiological mechanism that determines these characteristics, since the basis for corneal hydration control is not fully understood.

It is known that reduced tear tonicity or hypoxia at the anterior corneal surface will induce corneal swelling by increasing hydration and either these or other mechanisms may have been operating in our test procedure. However, regardless of the source of the corneal swelling, the differences between the thickness recovery characteristics of the Fuchs' and normal corneas are substantial and there is considerable variability within the Fuchs' group. This within-group variability is much greater than would be expected to occur from the measurement errors in the estimates of PRPH.

Our test sample included Fuchs' patients who were identified clinically to be at all stages of the disease process. Presumably, the patients have a range of impairment of endothelial function which varies from nearly normal to advanced, and is associated with the observed differences in the PRPH. The broad range of impairment included in the test samples presented some difficulty for differentiating the Fuchs' corneas from normals, due to the overlap that occurred in the distributions of the parameters that were measured.

A substantial proportion of the Fuchs' corneas were found to have a PRPH that was below the normal range, which indicates an impaired hydration control mechanism. This interpretation would be strengthened by a larger sample size for the normal group, which would establish more definite limits to the expected normal range for the age group in the study. Other Fuchs' corneas had a PRPH that fell within the range of the normals. Some of these subjects may have had minor amounts of corneal impairment, which could not be determined because a pre-Fuchs' reference value was not available. Such impairment might be detectable on a longitudinal basis if the testing were to be carried out repeatedly to show individual changes through time.

The mean PRPH for our control group of subjects was slower than that obtained previously by O'Neal and Poise11,16 for ten subjects of similar age. This difference may have occurred because they used pre-test corneal thickness measurements, which likely included residual overnight swelling, to represent steady-state baseline values. This reduced the time to recovery and appeared to increase the recovery rate.

The T95% parameter is a mathematical transform
of the PRPH, so it gives no additional information that may be used for differentiating the integrity of the Fuchs' hydration control mechanism from normals. However, the T95% parameter is useful in comparing the time requirements for swelling recovery in Fuchs' and normal corneas. Our results have shown that compared to normals the average Fuchs' cornea requires a significantly longer time after overnight sleep to return to the OESS thickness and indeed some Fuchs' corneas may not reach this level during the entire day. When the OESS is not reached it indicates that the recovery rate is below the potential level for compensation, and suggests that the Fuchs' cornea has a diurnal corneal thickness cycle that is shifted upward.

Earlier investigators found that the average corneal thickness of Fuchs' patients was somewhat greater than for normals. This may have occurred because the measurements were made at arbitrary times, when the corneas were at various stages of recovery from overnight swelling instead of being at OESS. However, from our OESS measurements, which were obtained by a method that circumvents the problems of measurement timing, the Fuchs' eyes also tended on average to be 25 \( \mu \)m thicker than normals, although the difference was not highly significant \( (P = 0.08) \) with the sample sizes available. Nevertheless, these results are compatible with the earlier findings.

There was considerable overlap in the OESS corneal thickness distributions for Fuchs' and normal patients. Presumably, prior to onset of Fuchs' dystrophy, some patients originally had corneal thicknesses in the lower region of the normal range. This would allow considerable thickening to occur before their corneas would exceed the normal range. Given these considerations, it is not possible to identify the stage of progression of Fuchs' dystrophy from corneal thickness alone. Since previous studies, in which corneal thickness measurements were made at arbitrary times, likely included subjects at various stages of recovery from overnight corneal swelling, attempts to associate these thickness data with other corneal parameters may have had misleading results.

For some Fuchs' patients, baseline corneal thickness may be constantly elevated above their pre-Fuchs' status so that the increase which occurs during overnight sleep is sufficient to produce the visual symptom of blur. This blur may persist for several hours due to the low rate at which the Fuchs' cornea recovers from the overnight swelling. Morning blur is an indicator of abnormally high corneal swelling but is too variable and subjective to provide a reliable quantitative indicator of Fuchs' corneal status.

A result which we cannot explain at present is that the stimulated swelling from the stress test is significantly less for Fuchs' patients than for normals. This may reflect the elevated status of the OESS thickness in Fuchs' subjects and represent a limit to the swelling imposed by the hydration control mechanism.

It would be useful to determine if an association exists between our test parameters and the usual clinical signs of Fuchs' disease that are identified by slit-lamp biomicroscopy. This will be investigated in the future when a sample size adequate for this purpose has been obtained.

Key words: cornea, corneal decompensation, corneal hydration, corneal swelling, Fuchs' dystrophy, endothelial function

References