

# Objective optical assessment of tear-film quality dynamics in normal and mildly symptomatic dry eyes

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**PURPOSE:** To evaluate and compare the tear-film dynamics in normal eyes and in eyes with mild dry-eye symptoms using a new noninvasive optical method based on a double-pass instrument.

**SETTING:** Hospital Universitario Virgen de la Arrixaca, Murcia, Spain.

**DESIGN:** Evaluation of diagnostic test or technology.

**METHODS:** Dynamic recording of double-pass retinal images during unforced tear-film breakup was performed in eyes with mild dry-eye symptoms (study group) and in an asymptomatic control group. Series of consecutive retinal images were recorded every 0.5 seconds while the patient avoided blinking. Measurements were performed under low-light conditions to naturally increase pupil diameter and maximize the method's sensitivity. Additional clinical tests were performed for comparison and included tear breakup time (TBUT), Schirmer I tests, and a normalized questionnaire (McMonnies). From the retinal images, a quality metric, the intensity distribution index, was calculated. An objective TBUT value was estimated in each eye when the intensity distribution index surpassed a defined threshold value compared with the initial baseline.

**RESULTS:** The study group comprised 20 eyes and the control group, 18 eyes. Symptomatic dry eyes had a typical exponential increase in the intensity distribution index with time. The objective TBUT values in the study group were comparable to the clinical TBUT estimates.

**CONCLUSIONS:** The new objective optical method to evaluate the quality and stability of the tear film was sensitive in detecting mild symptoms of dry eye and differentiating from normal cases. The procedure may allow early detection and follow-up of patients' tear film-related complaints.

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The optical quality of the retinal image is the result of light passing through the ocular structures. The tear film is the first medium that modifies the optical path of the light that finally reaches the retina. The impact of the tear film on the quality of the retinal image depends greatly on the homogeneity of the tear pellicle. The loss of homogeneity in the tear film modifies its thickness locally,<sup>1</sup> and because of the refractive index variation across the air-tear interface, this may cause significant differences in the optical path of the eye's wavefront.<sup>2,3</sup> Moreover, small local changes in the tear film increase the light scattered in the anterior surface of the cornea, affecting overall ocular scatter.<sup>4,5</sup> In some eyes with dysfunctional tear syndrome, the epithelial opacities associated with dry eyes also affect

the scattered light.<sup>6</sup> The changes in ocular aberrations and scatter degrade the retinal image quality. The influence of the tear film on the retinal image might be especially important in eyes with pathology, such as dry eye. In these eyes, the homogeneity of the tear film and its temporal stability may be greatly compromised by the severity of the disease.<sup>7</sup>

The quality of the tear film may have a significant impact on the optical quality of the retinal image. Thus, an indirect approach can be used to quantify tear-film quality based on dynamic analysis of retinal images. Indirect approaches are, in fact, traditional. Rieger<sup>8</sup> first evaluated the severity of diagnosed dry eyes by quantifying visual acuity. This was followed by other studies that analyzed visual acuity<sup>9</sup> or

contrast sensitivity,<sup>10</sup> alone or in combination with other subjective measures such as glare disability.<sup>11</sup> These studies focused on the subjective evaluation of the changes in visual performance that correlated with the severity of different dry-eye conditions. Other studies analyzed objective parameters related to retinal image quality and affected by fluctuations in the tear film. Most studies evaluated the changes in corneal<sup>12</sup> or ocular<sup>13,14</sup> aberrations between blinks using corneal topographers or wavefront sensors. However, tear-film deterioration also affects intraocular scatter. The images of Hartmann-Shack wavefront sensors usually show a decrease in the contrast of the spots when measuring dry eyes.<sup>5</sup> This is produced by the increase in light scattering caused by the loss of homogeneity in the tear film.<sup>4</sup> Because the computation of the wavefront aberrations from Hartmann-Shack images does not take this effect into account, the isolated characterization of the ocular aberration does not take into account ocular scattering as a sign of loss of homogeneity of the tear film.

An alternative and complementary objective technique is the analysis of double-pass retinal images. The double-pass technique has been widely used to measure the eye's optical quality in the laboratory<sup>15-17</sup> and in clinical applications.<sup>18,19</sup> The interest in this approach stems from the fact that double-pass images are affected by both ocular aberrations and scattering.<sup>20</sup>

In this study, we propose the use of dynamic analysis of double-pass retinal images as an indirect

indicator of the relative quality of the tear film in 2 groups of patients, one with dry eye and the other with no symptoms of dry eye.

## PATIENTS AND METHODS

### Patients

Patients with dry-eye symptoms were recruited at Hospital Universitario Virgen de la Arrixaca, Murcia, Spain. According to the tenets of the Declaration of Helsinki, all patients signed an informed consent form after receiving an explanation of the nature and possible consequences of the study. The Hospital Virgen de la Arrixaca ethics committee approved the study protocol.

Patient selection was made according to the score on the McMonnies dry-eye questionnaire.<sup>21</sup> Tear-film quality was evaluated by measuring the tear breakup time (TBUT) with a slitlamp and by performing a Schirmer I test. The study group comprised patients with mildly symptomatic dry eye and a McMonnies test score between 10 and 20. The control group comprised patients with known good tear-film quality and a McMonnies test score well below 10.

The exclusion criteria in both groups were a history of ocular surgery known to affect the tear film (eg, refractive surgery), diagnosed conjunctival allergy, or under treatment for dry eye while enrolled in the study.

### Dynamic Retinal Imaging

The double-pass retinal images were recorded using the Optical Quality Analysis System II (Visiometrics S.L.) with purpose-developed analysis software. The double-pass instrument is based on unequal pupil configuration,<sup>22</sup> with an entrance pupil diameter of 2.0 mm and an exit pupil of variable diameter. In this study, the exit pupil diameter was set to 7.0 mm. Figure 1 shows a schematic representation of the double-pass instrument. An infrared diode laser is collimated and, after passing the entrance aperture, enters the eye. After reflection in the retina and a double pass through the ocular media, the light is reflected in a beam splitter, passes the exit aperture, and is recorded by a charge-coupled device camera. In all cases, the double-pass images were acquired at best focus, corrected internally in the instrument by an optometer that ranged from  $-8.00$  diopters (D) to  $+6.00$  D. The patient's astigmatism was also corrected using

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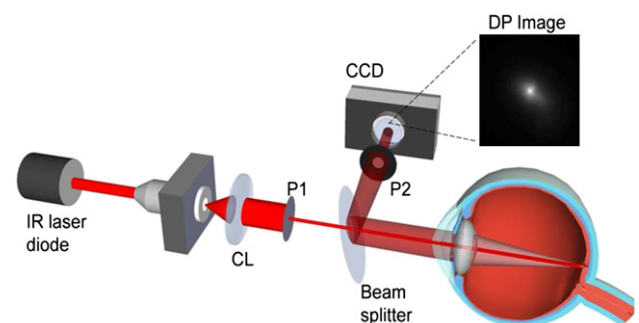
From Laboratorio de Óptica (Benito, Pérez, Artal), Universidad de Murcia, Murcia, Hospital Universitario Virgen de la Arrixaca (Marín, Mirabet), Murcia, and CD6, Universidad Politécnica de Cataluña (Vilaseca, Pujol), Tarrasa, Barcelona, Spain.

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**Figure 1.** Schematic of the double-pass method. An additional lens, hidden behind P2 in the illustration, forms the double-pass images on the camera (CCD = charge-couple device camera; CL = collimating lens; DP = double pass; IR = infrared; P1 = entrance aperture; P2 = exit aperture).

the appropriate cylindrical lens on a holder placed in front of the eye. The software of the instrument was modified to allow recording of temporal sequences of double-pass images while the patient fixated on a distant target. In each eye and during each experimental session, sequences of double-pass images were recorded every 0.5 seconds. The continuous recording group lasted 20 seconds (corresponding to 40 double-pass images) in the study group and 40 seconds (80 double-pass images) in the control group.

Although images were recorded with a 7.0 mm exit aperture, not all eyes reached a natural pupil size of 7.0 mm or larger; thus, double-pass images were recorded for different pupil sizes, which affected the energy distribution in the recorded double-pass images. Before the measurements started, patients were trained to blink freely until the registration of the double-pass images began. They were then asked to blink twice and to not blink again to the extent possible, even if they felt uncomfortable. When 1 series of double-pass images was completed, at least 2 minutes passed before a new series of images was recorded. This was to prevent an abnormally increased amount of tear film caused by the itchy sensation commonly reported during the double-pass registration; the sensation is secondary to tear-film breakage. For each patient, between 2 to 4 series of double-pass images were recorded. Only well-recorded double-pass images taken between blinks were analyzed.

From each double-pass image, an image quality metric, the intensity distribution index, was calculated. First, R1 was calculated; this is the ratio between the light recorded inside an annular area between 12 minutes and 20 minutes of arc and the light recorded at the closer surroundings of the central peak (a circular area with a radius of 1 minute of arc). As this value increases, more light is scattered in the outer part than in the center. Next, R2 was calculated; this is the ratio between the intensity recorded in the central region (1 minute of arc) in the actual image and the mean value computed for the 3 initial images of the corresponding series. This value provides an indication of the overall degradation of image quality.

The intensity distribution index was obtained by direct multiplication of the 2 ratio parameters (intensity distribution index = R1 × R2). This represents an index of the degradation in the retinal image considering small angles (1 minute) and small eccentric areas (up to 20 minutes). The intensity distribution index can be expressed by

$$\text{IDI} = R1 \times R2 = \left[ \frac{I(12', 20') \text{ image}}{I(0', 1') \text{ image}} \right] \times \left[ \frac{I(0', 1') \text{ image}}{I(0', 1') \text{ 1st images}} \right] = \left[ \frac{I(12', 20') \text{ image}}{I(0', 1') \text{ 1st images}} \right]$$

where IDI is the intensity distribution index and  $I$  is the intensity in the appropriate area of the double-pass image.

Finally, the intensity distribution index was normalized again to the first value of the series by subtracting the initial intensity distribution index value from the first image in the series. In every case, the initial intensity distribution index value would be zero. This would allow comparison between patients by eliminating the effect of different uncontrolled, although mainly static, factors (eg, different pupil size, retinal scatter, ocular aberrations).

When the tear film is in good condition, the normalized intensity distribution index would remain nearly stable around the initial value, showing only small changes with time. The symptomatic dry eyes commonly would present

a similar initial behavior, followed by an increase in the intensity distribution index value; the increase would be related to tear-film breakage.

From the temporal series of double-pass retinal images, an objective TBUT was estimated as the elapsed time from the beginning of the series to the moment the normalized intensity distribution index, fitted to an exponential ( $y = y_0 + a \times b^x$ ), reached a predefined threshold. The threshold value of 1 was obtained from the average normalized intensity distribution index found in eyes with normal tear film (see below). From the fitting data ( $y_0, a, b$ ), the objective TBUT was directly estimated for each series of double-pass images. For each double-pass image series recorded in every eye, the objective TBUT was obtained when the fitting was possible; this value was compared with the standard clinical TBUT.

To interfere as little as possible with the natural dynamics of the patients' tear film, measurements were performed in the following order: McMonnies test, double-pass retinal image measurements, Schirmer I test, and, after approximately 10 minutes, TBUT. The double-pass measurements were taken after the patient was adapted to a dimly illuminated room with the purpose of obtaining the largest possible natural pupil.

## RESULTS

The study group (mildly symptomatic dry eyes) comprised 20 eyes of 20 women with a mean age of 47.9 years ± 8.3 (SD). The control group (asymptomatic eyes) comprised 18 eyes of 4 men and 14 women with a mean age of 29.9 ± 7.5 years. Table 1 shows the results for the tear-film tests by group.

Figure 2 shows an example of the temporal evolution of the double-pass images in 1 symptomatic dry-eye patient and the corresponding intensity distribution index values. In this case, the double-pass images degraded significantly after approximately 10 seconds.

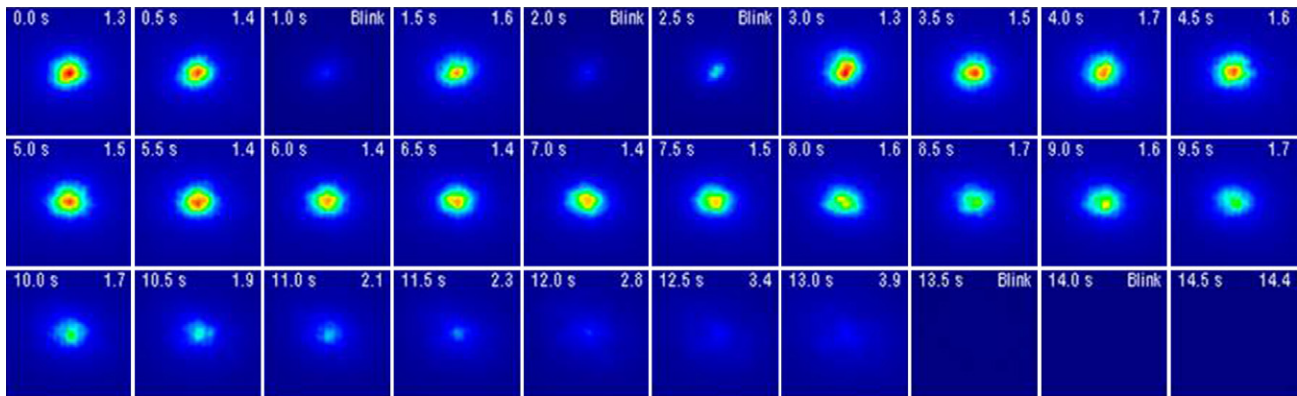
Figure 3 shows the results of the intensity distribution index as a function of time for all eyes in the control group. The threshold of normal tear film quality was 1. This value was used to estimate the objective TBUT, as described in the Methods section. The threshold intensity distribution index of 1 was determined as the average (0.45) plus twice the standard deviation (SD) of the dispersion (± 0.25) in the control group. Every eye in the control group had intensity distribution index values below this threshold (1), even in cases in

**Table 1.** Mean test results.

Test	Mean ± SD	
	Study Group	Control Group
McMonnies	15.8 ± 3.6	4.1 ± 2.8
Schirmer I (mm)	13.1 ± 5.7	19.3 ± 5.2
TBUT (s)	6.2 ± 2.8	14.1 ± 2.4

TBUT = tear breakup time

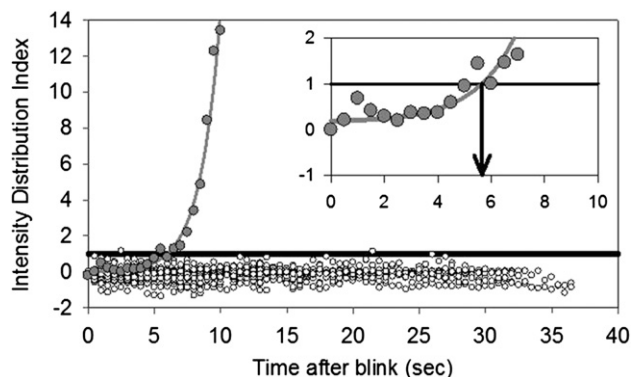




**Figure 2.** A series of double-pass images from the right eye of a symptomatic dry-eye patient. A series of 40 consecutive images was recorded every 0.5 seconds. When the system started image acquisition, the patient was told to blink twice and then keep the eyes open. The blank images correspond to those blinks. The numbers on each image indicate the time (right) and intensity distribution index value.

which the recording lasted for more than 30 seconds. However, in the study group, there was a systematic increase in intensity distribution index over time that could be modeled with an exponential function. (See case with solid symbols in Figure 3). In the patient with significantly degraded double-pass images after approximately 10 seconds, the objective TBUT was 5.7 seconds, obtained as the time when the fitted exponential (gray line) to the intensity distribution index values reached the threshold value of 1 (black line). The main purpose of Figure 3 is to show how the threshold value of 1 was defined. The TBUT in the control group was approximately 14 seconds (Table 1).

Because not all series of double-pass images showed the same temporal behavior, several were recorded to obtain an average objective TBUT value in each eye.



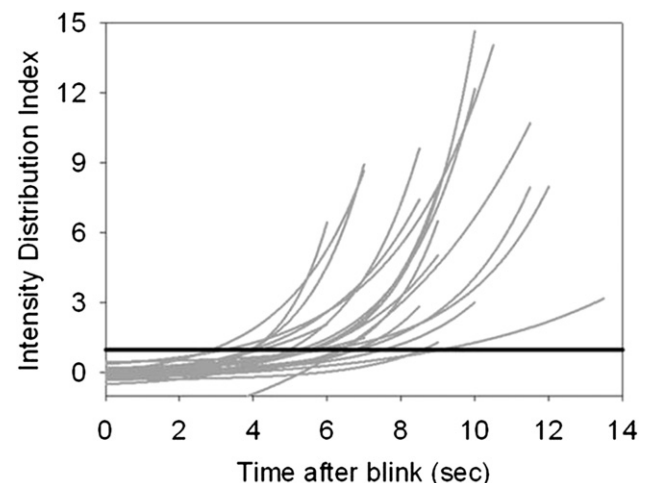
**Figure 3.** Normalized intensity distribution index values obtained from double-pass image series in 18 eyes with good tear film (open circles) and 1 symptomatic dry eye (solid circles). In the control eyes, the intensity distribution index was nearly constant, without surpassing the threshold (black line). In study eyes, the intensity distribution index values tended to increase with time exponentially. The objective TBUT parameter is defined as the time that the intensity distribution index value is higher than the threshold (1). See inset for details of a shorter time interval.

Figure 4 shows the exponential fitting to intensity distribution index values versus time for each eye in the study group. The regression factor ( $r^2$ ) was 0.8 or higher in most eyes in the study group.

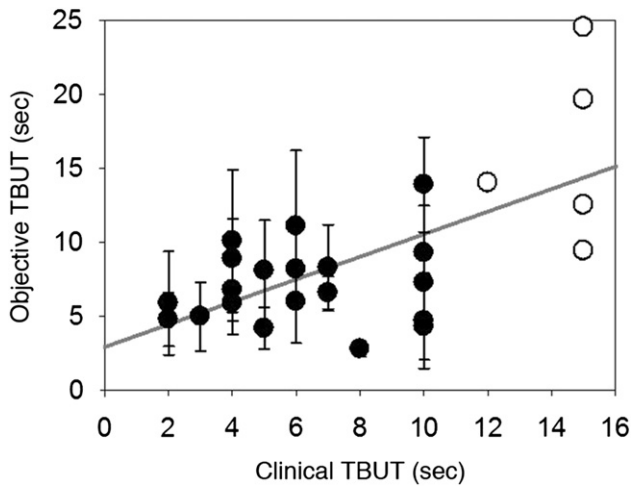
In the study group, the mean clinical TBUT value was  $6.2 \pm 2.8$  seconds, which was in good agreement with the mean objective TBUT value of  $7.1 \pm 2.7$  seconds. Figure 5 compares the clinical TBUT value and the objective TBUT value. Because of the defined threshold value, the objective TBUT was obtained in few eyes in the control group. The correlation between the clinical TBUT and the objective TBUT was modest ( $r^2 = 0.41$ ).

## DISCUSSION

Because of the dynamic nature of the tear film, the results were variable when comparing different patients



**Figure 4.** Example of the exponential fitting of the intensity distribution index results for all symptomatic dry eyes. The individual objective TBUT were estimated for each eye from the crossing of the exponential fitting and the threshold horizontal line (black line).



**Figure 5.** Comparison between the clinical TBUT and the corresponding objective TBUT. For every symptomatic dry eye (*black solid symbols*), the SDs of the objective TBUTs estimated from several double-pass series are shown as error bars. White symbols correspond to control eyes (TBUT = tear breakup time).

and different series of double-pass images from the same patient. This can be partially explained by the fact that dry eye is a multifactorial disease.<sup>23,24</sup> The impact of the disease on the homogeneity of the tear film is variable, and the correlation between symptoms and signs in dry-eye patients is still under investigation.<sup>25,26</sup> In particular, dry eyes might affect the optical quality of the retinal image as a result of several different factors. For example, an uneven optical surface would cause local differences in the wavefront, or epithelial opacities in more severe cases could produce even more scattered light.<sup>6</sup>

The area of the tear film that we evaluated was limited to that projected to the pupil area (in most cases, around a 7.0 mm diameter central portion of the cornea). As a consequence, the method would not detect quality degradation if the tear inhomogeneities were located in peripheral areas. However, this could help discriminate between different types of dry-eye syndromes by determining whether they affect the area of the cornea with a direct effect on the retinal image. Our procedure captured information on the portion of the tear film with a direct impact on foveal vision. The asymmetric configuration of pupils in the system (ie, a small entrance and a larger exit pupil) would cause random noise in the measured parameters. Depending on the area covered by the entrance pupil, the retinal image could be degraded differently. This effect was reduced somewhat by the normalization to the first recorded images. In addition, the protocol for double-pass image collection forces the entrance beam to be nearly centered over the eye's pupil. Near-infrared light is used in the double-pass

instrument, which increases patient comfort. However, the retinal image in infrared is affected by retinal scatter, and this could produce artificially elevated intensity distribution index values compared with measurements with visible light.<sup>27</sup> However, this is not relevant to this study because we considered only dynamic variations that were normalized to first images and the effect of retinal scatter impact would be nearly constant over time. There are some differences between the use of wavefront sensors and the double-pass method to evaluate tear-film quality. This results from the different type of measurements, aberration only in wavefront-sensors versus aberrations and scatter in double-pass.<sup>20</sup>

Dry eye is a common, yet frequently under-recognized clinical condition whose etiology and management challenge clinicians and researchers alike. Although there are many methods to evaluate dry-eye symptoms, there is a lack of successful, truly noninvasive approaches in clinical practice. Different optical-based methods have been proposed for testing the quality of the tear film. Some studies characterize the tear-film meniscus to estimate tear-film quality by applying optical coherence tomography techniques.<sup>28</sup> Dubra et al.<sup>29</sup> propose a different approach based on the interferometric analysis of tear-film homogeneity that could be translated into a wavefront aberration map. Other studies explore the use of the Hartmann-Shack wavefront sensor<sup>30</sup> to diagnose dry-eye syndrome by analyzing the changes in the aberrations produced by a distorted tear film<sup>5</sup> or by measuring the differences between the modal and zonal maps obtained from Hartmann-Shack measurements.<sup>31</sup>

The optical procedure we propose was designed to provide a straightforward and clinically simple estimation of the tear-film quality based on the dynamic recording and analysis of double-pass images. An image-quality parameter, the intensity distribution index, was defined as an indicator of tear-film quality and stability. When the double-pass image is degraded as a result of tear-film breakage and subsequent increases in ocular scattering and aberrations, the intensity distribution index parameter also increases. The relative nature of the procedure ensures that other factors affecting the retinal image in a more stable manner would not affect this indirect estimation of tear-film quality. This renders the approach more robust and relatively independent of common sources of errors, such as uncorrected refractive errors, cataract opacities, or elevated aberrations.

We have proposed and evaluated a new objective optical method for the indirect evaluation of the quality of the tear film. It is based on temporal analysis of double-pass retinal images of a point source. From these measurements, we introduced an objective

parameter conceptually similar to the clinical TBUT. This objective TBUT value is set when an image quality index, calculated for each image, surpasses a defined threshold value compared with the initial baseline value. To obtain a good correlation between the objective TBUT and the clinical TBUT in these patients, a lower threshold value would be required. However, our main intention was to set a value to better discriminate between symptomatic eyes and asymptomatic eyes. Therefore, a larger value is more appropriate toward that end.

The modest correlation between the clinical TBUT and the objective TBUT was expected because of the significant differences between the procedures. The TBUT is an invasive method in which some fluorescein is put into the eye. Then, the observer counts the seconds until the tear film, in green under the blue light of the slitlamp, shows the typical black spaces, corresponding to the corneal areas uncovered by the tear film. In contrast, the objective TBUT is a fully noninvasive optical parameter.

Our procedure was sensitive in detecting mild symptoms of dry eye and differentiating dry-eye cases and normal cases. This promising approach may allow early detection and follow-up of tear film-related patient complaints.

## REFERENCES

- Prydal JI, Artal P, Woon H, Campbell FW. Study of human precorneal tear film thickness and structure using laser interferometry. *Invest Ophthalmol Vis Sci* 1992; 33:2006–2011. Available at: <http://www.iovs.org/cgi/reprint/33/6/2006.pdf>. Accessed April 29, 2011
- Benedetto DA, Clinch TE, Laibson PR. In vivo observation of tear film dynamics using fluorophotometry. *Arch Ophthalmol* 1984; 102:410–412. Available at: <http://archophth.ama-assn.org/cgi/reprint/102/3/410>. Accessed April 29, 2011
- Licznanski TJ, Kasprzak HT, Kowalik W. Application of Twyman–Green interferometer for evaluation of in vivo breakup characteristic of the human tear film. *J Biomed Opt* 1999; 4:176–182
- Tutt R, Bradley A, Begley C, Thibos LN. Optical and visual impact of tear break-up in human eyes. *Invest Ophthalmol Vis Sci* 2000; 41:4117–4123. Available at: <http://www.iovs.org/cgi/reprint/41/13/4117>. Accessed April 29, 2011
- Thibos LN, Hong X. Clinical applications of the Shack–Hartmann aberrometer. *Optom Vis Sci* 1999; 76:817–825. Available at: [http://research.opt.indiana.edu/Library/SHclinical/ClinicalAppsSHA\\_ENL1793.pdf](http://research.opt.indiana.edu/Library/SHclinical/ClinicalAppsSHA_ENL1793.pdf). Accessed April 29, 2011
- Chen JJ, Rao K, Pflugfelder SC. Corneal epithelial opacity in dysfunctional tear syndrome. *Am J Ophthalmol* 2009; 148:376–382
- Johnson ME, Murphy PJ. Changes in the tear film and ocular surface from dry eye syndrome. *Prog Retin Eye Res* 2004; 23:449–474
- Rieger G. The importance of the precorneal tear film for the quality of optical imaging. *Br J Ophthalmol* 1992; 76:157–158. Available at: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC504194/pdf/brjophth00051-0029.pdf>. Accessed April 29, 2011
- Goto E, Yagi Y, Matsumoto Y, Tsubota K. Impaired functional visual acuity of dry eye patients. *Am J Ophthalmol* 2002; 133:181–186
- Rolando M, Lester M, Macrí A, Calabria G. Low spatial-contrast sensitivity in dry eyes. *Cornea* 1998; 17:376–379
- Huang F-C, Tseng S-H, Shih M-H, Chen FK. Effect of artificial tears on corneal surface regularity, contrast sensitivity, and glare disability in dry eyes. *Ophthalmology* 2002; 109:1934–1940
- Montés-Micó R, Alió JL, Charman WN. Dynamic changes in the tear film in dry eyes. *Invest Ophthalmol Vis Sci* 2005; 46:1615–1619. Available at: <http://www.iovs.org/cgi/reprint/46/5/1615>. Accessed April 29, 2011
- Li KY, Yoon G. Changes in aberrations and retinal image quality due to tear film dynamics. *Opt Express* 2006; 14:12552–12559
- Koh S, Maeda N, Hirohara Y, Mihashi T, Bessho K, Hori Y, Inoue T, Watanabe H, Fujikado T, Tano Y. Serial measurements of higher-order aberrations after blinking in patients with dry eye. *Invest Ophthalmol Vis Sci* 2008; 49:133–138. Available at: <http://www.iovs.org/cgi/reprint/49/1/133>. Accessed April 20, 2011-04-29
- Santamaria J, Artal P, Bescós J. Determination of the point spread function of human eyes using a hybrid optical-digital method. *J Opt Soc Am A* 1987; 4:1109–1114
- Artal P. Calculations of two-dimensional foveal retinal images in real eyes. *J Opt Soc Am A* 1990; 7:1374–1381
- Artal P. Understanding aberrations by using double-pass techniques. *J Refract Surg* 2000; 16:S560–S562
- Vilaseca M, Arjona M, Pujol J, Issolio L, Güell JL. Optical quality of foldable monofocal intraocular lenses before and after injection; comparative evaluation using a double-pass system. *J Cataract Refract Surg* 2009; 35:1415–1423
- Nanavaty MA, Stanford MR, Sharma R, Dhital A, Spalton DJ, Marshall J. Use of the double-pass technique to quantify ocular scatter in patients with uveitis: a pilot study. *Ophthalmologica* 2011; 225:61–66
- Díaz-Doutón F, Benito A, Pujol J, Arjona M, Güell J, Artal P. Comparison of the retinal image quality with a Hartmann–Shack wavefront sensor and a double-pass instrument. *Invest Ophthalmol Vis Sci* 2006; 47:1710–1716. Available at: <http://www.iovs.org/content/47/4/1710.full.pdf>. Accessed April 20, 2011
- McMonnies CW. Key questions in a dry eye history. *J Am Optom Assoc* 1986; 57:512–517
- Artal P, Iglesias I, López-Gil N, Green DG. Double-pass measurements of the retinal-image quality with unequal entrance and exit pupil sizes and the reversibility of the eye's optical system. *J Opt Soc Am A* 1995; 12:2358–2366
- Albietz JM. Dry eye: an update on clinical diagnosis, management and promising new treatments. *Clin Exp Optom* 2001; 84:4–18. Available at: <http://onlinelibrary.wiley.com/doi/10.1111/j.1444-0938.2001.tb04930.x/pdf>. Accessed April 29, 2011
- Baudouin C. The pathology of dry eye. *Surv Ophthalmol* 2001; 45(suppl 2):S211–S220
- Begley CG, Chalmers RL, Abetz L, Venkataraman K, Mertzanis P, Caffery BA, Snyder C, Edrington T, Nelson D, Simpson T. The relationship between habitual patient-reported symptoms and clinical signs among patients with dry eye of varying severity. *Invest Ophthalmol Vis Sci* 2003; 44:4753–4761. Available at: <http://www.iovs.org/content/44/11/4753.full.pdf>. Accessed April 29, 2011
- Nichols KK, Nichols JJ, Mitchell G. The lack of association between signs and symptoms in patients with dry eye disease. *Cornea* 2004; 23:762–770
- López-Gil N, Artal P. Comparison of double-pass estimates of the retinal-image quality obtained with green and near infrared light. *J Opt Soc Am A* 1997; 14:961–971
- Shen M, Li J, Wang J, Ma H, Cai C, Tao A, Yuan Y, Lu F. Upper and lower tear menisci in the diagnosis of dry eye. *Invest Ophthalmol Vis Sci* 2009; 50:2722–2726. Available at:

- <http://www.iovs.org/content/50/6/2722.full.pdf>. Accessed April 29, 2011
29. Dubra A, Paterson C, Dainty C. Double lateral shearing interferometer for the quantitative measurement of tear film topography. *Appl Opt* 2005; 44:1191–1199
  30. Prieto PM, Vargas-Martín F, Goelz S, Artal P. Analysis of the performance of the Hartmann–Shack sensor in the human eye. *J Opt Soc Am A Opt Image Vis Sci* 2000; 17:1388–1398
  31. Liu H, Thibos L, Begley C, Bradley A. Measurement of the time course of optical quality and visual deterioration during tear break-up. *Invest Ophthalmol Vis Sci* 2010; 51:3318–3326. Available at: <http://www.iovs.org/content/51/6/3318.full.pdf>. Accessed April 29, 2011