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Human Lacrimal Production Rates from Modified Schirmer-Tear Test

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Abstract

SIGNIFICANCE: A simple methodology is presented to guantify basal tear production with a modified Schirmer-tear test. PURPOSE: We introduce a simple clinical procedure to measure guantitative basal tear-production flowrates, Q_{L} , from a modified Schirmer-tear test (STT). METHODS: Eight healthy subjects aged at least 18 years underwent modified STTs on both eyes for two visits each. Schirmer strips were sheathed with transparent tape before insertion. Topical anesthetic minimized reflex tearing. Wetting lengths were measured every 30 s for 5 min; Q_{L} was calculated from the linear slope of wetting length versus time. Determination of Q_1 requires mass-balance equations on the tear prism and Schirmer strip with strip imbibition kinetics obeying Darcy and Young-Laplace laws. RESULTS: Basal tear production rates varied from essentially 0 to about 2 μ l/min. With some exceptions, right and left eyes showed similar tear production rates. CONCLUSIONS: By following the modified STT, Q_L is established with minimal additional effort over a standard Schirmer test. We predict and observe four different subtypes of imbibition kinetics depending on how short or long the time is for first appearance of the wetting front and on how fast or slow is tear production. For slow lacrimal production rates, the standard 5-min wetting length does not correlate with basal tear production.



INTRODUCTION

Tear production rate is critical to eye health. When tear production is low and/or tear evaporation is high, dry-eye symptoms are likely. Indeed, dry eye is categorized as arising from aqueous deficiency or excessive evaporation or both.¹⁻⁴ The most prevalent clinical assessment of tear production is the

Schirmer-tear test.⁵ In a Schirmer-tear test, a standardized paper strip is inserted into the inferior tear lake and draped over the lower lid. After 5 min, wetting length is measured. Final measured wetted length qualitatively gauges the adequacy of lacrimal production.

As currently practiced, Schirmer-tear tests do not provide quantitative tear production rates (e.g., in μ l/min). Although Schirmer tests are routine,⁶ precise description of the wetting process is lacking.⁷⁻¹⁵ After the initial work of Holly and coworkers,^{7,11-13} we recently analyzed the dynamics of Schirmerstrip imbibition⁸ to obtain volumetric tear production rates, Q_L , from Schirmer-tear tests. The suggested procedure is to measure the 3- to 5-min slope of wetting length versus time. Given the cross-sectional area and porosity of the Schirmer strip, volumetric tear production rate follows directly. However, Telles et al.⁸ did not assess their proposed procedure against clinical data for individual subjects.

The purpose of this work is to evaluate clinically the suggested procedure of Telles et al.⁸ for obtaining quantitative tear production rates. To do so, modified Schirmer-tear tests are conducted on eight subjects after Telles et al.⁸ Anesthetic is applied to minimize reflex tearing, Schirmer strips are sheathed to avoid evaporation, and wetting lengths are measured at 3, 4, and 5 min, at least, to obtain the linear-time slope of the imbibition lengths. By following the outlined methodology, we successfully garner quantitative tear production rates of each eye for eight subjects on two visits. Basal lacrimal production rates vary from near 0.1 to about 2.0 μ /min among the studied subjects.

METHODS

Clinical

Standard Schirmer strips were supplied by Intervet, Inc. (Schirmer Tear Test; Merck Animal Health, Summit, NJ). Supplied strips are 0.2-mm thick (Whatman standard filter paper # 41), 5-mm wide, and 40-mm long (Table 1 lists pertinent properties of standard Schirmer strips).^{1,16-28} Strips are labeled sequentially with markings of 5-mm spacing and are impregnated with a narrow, transverse dye strip (FD&C Blue-1 dye; Spectrum Chemical MFG Corp, Gardena, CA) located just below the 5-mm marker.

Parameter	Symbol	Value (common)	(SI units)	Source(s)/references
Tear surface tension	Y	45 mN/m	0.045 N/m	[17]
Tear viscosity	μ	1.5 cP	0.0015Pa s	[18]
Lid-margin perimeter	λ	30 mm	0.03 m	[19]
Blink-filled tear-prism volume	V _{BF}	2.5 µl	$2.5 \times 10^{-9} \text{ m}^3$	[1,20,21]
Tear-prism inscribed radius	Rins	0.233 mm	$2.33\times10^{-4}~\text{m}$	Calculated
Tear-prism height	hTP	0.70 mm	7.0×10^{-4} m	[22]
Tear-prism side length	LTP	0.81 mm	8.1×10^{-4} m	Calculated
Tear-prism volume	VIP	8.5 µl	$8.5 \times 10^{-9} \text{ m}^3$	Calculated
Lid-bend height	LB	1.3 mm	1.3×10^{-3}	Estimated
Schirmer-strip porosity	φ	0.7	0.7	[23-25]
Schirmer-strip thickness	δ	0.2 mm	2.2×10^{-4} m	[16,26]
Schirmer-strip width	W	5 mm	5×10^{-3} m	[16,26]
Schirmer-strip angle	θ	20°	20°	Measured
Schirmer-strip pore size	Rp	11 µm	1.1×10^{-5} m	[16, 26]
Schirmer-strip permeability†	ĸ	0.45 µm ²	$4.5\times10^{-13}\text{m}^2$	[23, 26, 27
Schirmer-strip notch length	Ly	5 mm	5.0×10^{-3} m	[16]

*After Telles et al.⁸ with permission. †From measured Herzberg filtration time of 54 s.^{23,26,27} Also, pore-size-squared scaling of the Carman–Kozeny expression²⁸ from the measured permeability ($\kappa = 0.062 \,\mu m^2$)²³ and pore radius ($R_p = 4 \,\mu m$)^{23,26,27} of Whatman 40 filter paper gives a value of 0.45 μm^2 .

Eight subjects were enrolled, aged at least 18 years, and free from ocular disease or ocular abnormality. Subjects using tranquilizers, hypertension medication, or any systemic allergy medication were excluded from the study along with subjects with any history of ocular surgery. Informed consent was obtained from all participants after a full description of the goals, potential risks and benefits, and procedures of the studies. This research adhered to the tenets of the Declaration of Helsinki and was approved by the institutional review board (Committee for Protection of Human Subjects, University of California, Berkeley, Berkeley, CA).

The study consisted of two 30-min visits for each subject; the second visit was separated by a minimum of 1 day and scheduled within the same period $(\pm 2 h)$. Subjects waked within $\pm 1 h$ for each of the two visits and were awake for at least 4 h before the Schirmer test. At the beginning of each visit, room temperature, humidity, and subject visual acuity were measured along with a health assessment of the ocular surface. Shortly before insertion, strips were sheathed after the notch on both sides with water-impermeable transparent tape (Wexford Packing Duct Tape; Walgreens, Berkeley, CA), and folded at the notch located 5 mm from the rounded end of the strip. Application of cling wrap (i.e., Saran wrap) did not provide an adequate seal against evaporation.

To minimize reflex tearing, two drops of proparacaine (Akorn Pharmaceuticals, Lake Forest, IL) were administered to each eye with a 1min interval. Strips were inserted 1 min after the second anesthetic application. Some stinging was reported with anesthetic instillation that lasted no more than a few seconds. Order of strip insertion to the eyes was randomized for all subjects. Once strips were gently inserted into each eye, subjects closed their eyes for measurement duration. Wetted lengths from the notch were measured visually every 30 s for 5 min. After 5 min, the angle of each strip from vertical was documented. Final ocular-surface health and visual acuity were assessed after strip removal.

As the wetting front penetrates the strip, tear evaporates from the portion of the strip exposed to the environment. Previous works^{8,9} demonstrate that depending on the relative humidity of the environment, evaporation can significantly retard wetting kinetics. Appendix A (available at http://links.lww.com/OPX/A337) reports in vitro measurements Schirmer strips under unimpeded, vertical imbibition that confirm this observation. Appendix B (available at http://links.lww.com/OPX/A338) provides further in *vivo* confirmation. Therefore, to obtain quantitative *in vivo* tear production rates, evaporation should be minimal. The Intervet Inc. Schirmer strips were, therefore, sheathed with transparent tape, as described above. However, we found that sheathing the strips ahead of time noticeably slowed wetting kinetics. Accordingly, sheathing was performed just prior to strip insertion. Sheathing for short times demonstrated no alteration in wetting kinetics. We further observed that the Blue-1 dye front spread out behind the tearwetting front. Appendix B (available at http://links.lww.com/OPX/A338) details this finding. Consequently, we measured only the tear-wetting front, and not the dye front.

Schirmer-Strip Wetting Behavior

Fig. 1 shows typical measured wetting lengths relative to the strip notch, L (open symbols), as a function of time for four trials among three subjects (subjects 4, 6, and 8). Results for these four particular trials are graphed simply to illustrate the range of behaviors observed. Error bars on each datum correspond to ±0.5 mm precision in visual-length assessment. The horizontal dashed line corresponds to the 5-mm marker on the Schirmer strip. Data below the dashed line, denoted by L_5 , are obscured by the lid and eyelashes, and cannot be recorded. These points are labeled by filled circles with an accompanying short-dashed vertical line. A striking feature of the wetting kinetics, correctly predicted by Telles et al.,⁸ is the consistent linear increase in wetting lengths beyond L_5 for all eight subjects studied. The constant slope indicates a constant imbibition-front velocity. Each subject in the linear-length period, however, exhibits a different constant slope.



FIGURE 1. Clinical Schirmer-strip wetting lengths of rour typical subjects (open symbols) versus time. L_5 is the distance from the notch to the dyed 5-mm marker. Wetted lengths below L_5 are obscured by the inferior eyelid and lashes and cannot be recorded (filled circles). Curve labels are defined in the text: slow-small (SS); slow-large (SL); fastsmall (FS); fast-large (FL). Error bars correspond to visual measurement of wetted length of ±0.5 mm.

A second important feature of Fig. 1 is the time delay before the wetting front of each subject reaches L_5 . Four general types of wetting kinetics are predicted by the physical model presented below and are confirmed in modified Schirmer-tear tests on all studied subjects. Fig. 1 highlights these four types: (1) slow arrival to L_5 (long delay) and small slope (SS); (2) slow arrival to L_5 (long delay) and large slope (SL); (3) fast arrival to L_5 (short delay) and large slope (FL). To our knowledge, these behaviors have not been enunciated previously. To obtain lacrimal production rates from the data in Fig. 1, the physical basis for the four types of behavior must be explained and quantified.

Physical Explanation

To understand the clinical Schirmer-strip wetting kinetics in Fig. 1, we extend the theory of Telles et al.⁸Fig. 2 pictures the pertinent geometry. A closedeye tear prism is illustrated with gravity acting in the horizontal direction. A Schirmer strip is inserted into the tear prism and into the tear lake under the lower lid adjacent to the tear prism (shown to the right in Fig. 2). The portion of the strip immersed in the tear lake is filled with tear and is assumed not to participate in strip-wetting dynamics. The Schirmer strip is folded at the notch and bends around the lid for a length, L_B , and then tilts at an angle θ from the gravity direction. We approximate the tear prism as an equilateral triangle²² of inscribed radius R_{ins} and edge length L_{TP} (chosen physical dimensions are listed in Table 1). The prism extends out of the plane of the drawing a distance λ corresponding to the lid-margin length (not shown). For convenience, lacrimal production enters the tear prism from the left. Lacrimal volumetric flow rate (i.e., Q_L) empties into the tear menisci of the prism that, in turn, supply tear to the Schirmer strip. Total wetting length, L_F , is gauged from the bottom of the tear prism (right side in Fig. 2), whereas wetting length is measured from the strip notch located at L_{TP} and reported in Figs. 1 and 2 as $L (= L_F - L_{TP})$. Radius of the tear meniscus (or tear menisci at low volumes) in the tear prism is R_m . Table 1 lists anatomical dimensions.



Light blue color indicates tear in the strip while light-blue, dotted regions denote tear outside the strip. Dashed circles inside the tear prism represent tear-prism menisci as the tear prism drains over time. $L_F(t)$ is the length between the wetted front and right bottom corner of the tear prism. L(t) represents the length between the wetted front and the strip notch. Drawing is not to scale.

To explain the *in vivo* data in Fig. 1, we follow Telles et al.⁸ The tear prism partially fills during strip insertion and lid closure. Tear then imbibes into the Schirmer strip, partially draining the tear prism, as seen by the dashed circles in Fig. 2. Initially, uptake into the strip is fast and does not reflect basal tear production. Once wetted lengths emerge somewhat beyond the strip notch at L_{TP} , the tear prism is nearly empty. At this time, curvature of the tear-prism menisci, $1/R_m$, nearly equal the suction curvature of the strip pores at the wetting front, $2/R_p$, where R_p is the average pore radius of the Schirmer strip. Subsequently, the tear-prism arc-menisci radii remain essentially constant. Tear supply to the Schirmer strip is restricted. Only

lacrimal flow feeds the strip through nearly constant volume tear-prism menisci.⁸ If tear production is constant, the result is a linear-time increase in wetted lengths beyond L_5 , as observed in Fig. 1.

Physical Model

Calculation of tear production rate from measured wetted lengths requires a quantitative physical model. We adopt the approach of Telles et al.⁸ by satisfying mass-balance equations on tear in the tear prism and tear in the Schirmer strip (diagrammed in Fig. 2). Appendix C (available at http://links.lww.com/OPX/A339) gives the details.

Fig. 3 presents model-equation solutions of Schirmer-strip wetting dynamics in terms of the wetted length beyond the notch, L, as a function of time. Two lacrimal production rates $Q_L = 0.75$ and 2.0 μ /min and two initial tear-prism volumes $V_0 = 1.80$ and 3.60 µl are shown. The four combinations of this production rate and initial tear-prism volume predict the range of behaviors observed in the clinical Schirmer-tear tests of Fig. 1. All curves in Fig. 3 show an initial fast rise in wetting length followed by a slower linear rise in time that continues out to the 5-min experimental time period. These results are in agreement with those predicted by Telles et al.⁸ The fast rise is caused by rapid initial capillary wicking by the strip reducing tear-prism liquid volume and decreasing the corner arc-menisci radii close to those in the strip pores. Thereafter, the corner menisci exhibit nearly constant radii, and the wicking rate into the strip is limited to that furnished by lacrimal flow. Once the wetted front emerges beyond L_5 , only lacrimal production feeds the strip. A linear rise in time means that lacrimal production is constant and, consequently, reflects basal values. A non-straight line in the long-time period signals a varying tear production rate.¹³



(FS); fast-large (FL). A dashed horizontal line locates L₅.

Small initial tear volumes in the prism attain the linear-length period more quickly because little fluid need drain before the menisci curvatures attain those in the strip pores and vice versa. With a quick arrival to the linear-length period, the front lags in reaching L_5 (see solid and short-dashed curves in Fig. 3). Conversely, large initial tear volumes take somewhat longer to reach the linear-length region, but the wetting front appears more quickly at L_5 . We use double designations to accentuate this behavior. The first designation is "slow" (S) or "fast" (F) arrival to L_5 . The second designation is "large" (L) or "small" (S) slopes. Large linear slopes yield large tear production rates and vice versa. Thus, Q_L and V_0 values control the range of wetting behaviors predicted from the model analysis.

We desire measurement of basal tear production. As established in Appendix D (available at http://links.lww.com/OPX/A340), careful asymptotic analysis of Eqs. C3 and C4 at long times when the linear-length period emerges reveals that

$$Q_L = \varphi w \delta \frac{\Delta L}{\Delta t} \tag{1}$$

where $\Delta L/\Delta t$ is the linear wetting-length slope, φ is strip porosity, w is strip width, and δ is strip thickness. Values of strip porosity, width, and thickness are listed in Table 1. Equation 1 allows calculation of tear production from the measured linear slopes, $\Delta L/\Delta t$, in Figs. 1 or 3. We emphasize that details

of the initial fast period before the wetting front is visualized at L_5 do not abrogate Eq. 1.⁸

Following Eq. 1, we calculated the dynamic wetting-front slopes for the four trials in Fig. 1 from wetted-length measurements between 3 and 5 min. Results are illustrated in Fig. 4 and summarized in the last column of Table 2. Values of basal tear production fall between 0.77 ± 0.08 and $2.0 \pm 0.2 \mu$ /min, in good accord with literature.²⁹ Listed error limits of about 10% arise from error propagation based on the precision in visually measuring wetting lengths (i.e., ±0.5 mm).



FIGURE 4. Fitting of Schirmer-strip linear-length dynamics (straight lines) to clinical data in Fig. 1 (open symbols). Tear production rate is calculated from Eq. 1 and best-fit slopes (see Tables 2 and 3).

Subject/visit	Eye	Delay (s)	Slope (mm/s)	V ₀ (μl)	QL (µl/min)
8/1 (SS)	L	120	0.020	1.7±0.2	0.9±0.1
4/2 (FS)	R	30	0.017	3.7±70.4	0.8±0.1
8/2 (FL)	R	30	0.043	5.4±0.5	2.0±0.2
6/1 (SL)	R	60	0.043	1.7±0.2	2.0±0.2

Column 5 of Table 2 lists theory-predicted initial tear prism volumes obtained from fits to measured delay times for reaching L_5 given the best-fitted tear production rates in column 6. That is, predicted delay times depend on both V_0 and Q_L . For the same tear production rate, wetting-front appearance at L_5 takes longer the smaller is V_0 . Likewise, for the same initial tear-prism volume, delay time is longer the smaller is Q_L . Predicted V_0 values, although not precise, are reasonable. Blink-swept tear-prism liquid volume is about 2.5 μ l (see Table 1). Values of V_0 larger than 2.5 μ l likely occur because of initial reflex tearing upon strip insertion. With anesthetic, reflex tearing apparently diminishes within a minute or so after strip insertion. Otherwise, the wetting front must not display a straight line in time. Fortunately, tear production rates are not infected by the initial tear-prism drainage kinetics. Our modified Schirmer-strip clinical procedure successfully garners tear production rates from classical Schirmer-tear tests.

RESULTS

Fig. 4 and Table 2 confirm that quantitative basal tear production rates emerge from our modified Schirmer-tear test. Table 3 summarizes the results for each eye of the eight total subjects studied over two visits. All subjects mimic the behavior shown in Fig. 1 but with differing delay times and differing linear-length slopes. Analysis of the wetting-length kinetics by Eq. 1 gives values of Q_L ranging between essentially zero and 2 µl/min. With notable exceptions, both eyes in our limited study show similar tearproduction rates. There is also some, but not uniform, consistency between visits. Classical Schirmer-tear tests have a reputation for lack of repeatability.³⁰ Further studies are warranted to ascertain repeatability and reproducibility of our modified Schirmer-tear test.

Subject	Visit	R QL (µl/min)	L Q _L (µl/min)
1	1	_*	0.9 ± 0.1
	2	-	0.5 ± 0.1
2	1	0.8 ± 0.1	1.5 ± 0.2
	2	0.5 ± 0.1	1.2 ± 0.1
3	1	1.2 ± 0.1	1.2 ± 0.1
	2	1.5 ± 0.2	1.1 ± 0.1
4	1	0.6 ± 0.1	-
	2	0.8 ± 0.1	1.1 ± 0.1
5	1	$1.1 \pm 0.1^{\dagger}$	-
6	1	2.0 ± 0.2	2.2 ± 0.2
	2	1.5 ± 0.2	2.0 ± 0.2
7	1	1.2 ± 0.1	0.8 ± 0.1
	2	0.5 ± 0.1	1.9 ± 0.2
8	1	_†	0.9 ± 0.1
	2	2.0 ± 0.2	2.0 ± 0.2

*Hyphen indicates that Q_L is zero to within the precision of the measurement. †First appearance of wetting front at L_5 occurs after 3 min. Slope to determine Q_L uses points after first appearance.

DISCUSSION

We introduce a modified Schirmer-tear test that quantifies volumetric tear production rates. Following Telles et al.,⁸ modification includes sheathing the Schirmer strip to prevent evaporation, applying anesthetic to minimize reflex tearing, visually measuring the undyed tear-front position at several times between 3 and 5 min (with a minimum of three time points), evaluating the

linear slope of the wetting front versus time, and calculating tear production rate from Eq. 1. The recommended modifications are simple extensions of the classical Schirmer-tear test and require minimal additional effort.

For all subjects, we observe a time delay between strip insertion and first appearance of the wetting front at the 5-mm marker from the notch (i.e., at L_5). After first appearance, the wetting front obeys a linear increase of the wetting-front length in time. The linear-length behavior again applies to all eight subjects studied. Within this general behavior, we observe four different subtypes of imbibition kinetics, not previously noted. Arrival times to L_5 can be fast (F) or slow (S), and the linear-length slopes can be large (L) or small (S). Permutation leads to the four classes of FL, SL, FS, and SS, respectively.

A simple physical model of Schirmer-strip imbibition kinetics is proposed. The tear prism partially fills upon strip insertion and eye closure. Initial prism tear is wicked rapidly into the strip. Consequently, the tear prism quickly drains until the curvatures of the arc menisci in the tear prism essentially match those in the strip pores at the wetting front. At this time, wicking practically stops; all supply to the Schirmer strip originates from the lacrimal glands. Linear-length kinetics emerges when lacrimal production is constant and, therefore, basal. All four types of wetting behavior are mimicked by the proposed theory. They are classified by the values chosen for the initial tear volume in the prism, V_0 , and the tear production rate, Q_L . Careful analysis of the proposed physical model derives the simple result of Eq. 1 allowing direct calculation of basal tear production rates independent of the early time imbibition kinetics. Appendices C and D (available at http://links.lww.com/OPX/A339 and http://links.lww.com/OPX/A340) outline the details.

Clinical application of the modified Schirmer-tear test to eight subjects confirms that it is correct and practical. We successfully obtain meaningful tear production rates ranging from near zero up to about 2 μ l/min differing among subjects and between left and right eyes for the same subject. For the first time, basal tear production rates are available to evaluate subject tear production independent of tear evaporation.¹

A standard Schirmer-tear test measures only one wetted length at 5 min or L(5 min). Lacrimal production is traditionally classified as "normal" when the wetted length is more than 10 mm, as "deficient" or "dry eye" if less than 5 mm,^{16,31,32} and "equivocal" when lying between 5 and 10 mm. To provide insight into how this classification scheme relates to quantitative tear production rates, Fig. 5 graphs L(5 min) versus Q_L for the eight subjects in Table 3. The result is fascinating. There is an expected general trend of increasing 5-min wetting lengths with increasing in tear production rate. For subjects with normal tear production, both the standard Schirmer-tear test and the modified Schirmer-tear test give synonymous results. However, examination of the data at near-zero tear production reveals a major

discrepancy. For three subject trials with zero tear production, L(5 min) lies between 5 and 10 mm. Thus, for these subjects, the standard Schirmer-tear test reveals equivocal to adequate tear production, whereas the modified Schirmer-tear test proposed here reveals essentially zero tear production. Said in another way, a horizontal line drawn at L(5 min) = 10 mm in Fig. 5 demonstrates that tear production at L(5 min) = 10 mm in Fig. 5 demonstrates that tear production at L(5 min) = 10 mm corresponds to a range from zero to almost 1.5 µl/min. Use of the standard interpretation of Schirmer-strip data can be misleading.



The proposed modified Schirmer-tear test is simple, practical, and quantitative. It opens an avenue for studying, for example, the role of environmental factors and contact lenses on tear production and possibly for diagnosing aqueous deficient and evaporative dry eye.

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