Agreement and repeatability of four different devices to measure non-invasive tear breakup time (NIBUT)

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Abstract

Purpose: Since tear film stability can be affected by fluorescein, the International Dry Eye Workshop (DEWSII) recommended non-invasive measurement of tear breakup time (NIBUT). The aim of this study was to investigate the agreement and repeatability of four different instruments in the measurement of NIBUT.

Methods: 72 participants (mean 24.2 ± 3.6 years) were recruited for this multi-centre, cross-sectional study. NIBUT was measured three times from one eye using each of the instruments in randomized order on two separate sessions during a day, separated by at least 2 hours. NIBUT was performed at three sites (Switzerland, Germany and UK) using the Tearscope Plus (Keeler, Windsor, UK) (TS), Polaris (bon Optic, Lübeck, Germany) (POL), EasyTear Viewplus (Easytear, Rovereto, Italy) (ET) and Keratograph 5M (Oculus Optikgeräte GmbH, Wetzlar, Germany) (KER). As the latter instrument only analyses for 24s, all data was capped at this value.

Results: NIBUT measurements between the four instruments were not statistically significant different: TS (median 10.4, range 2.0-24.0s), POL (10.1, 1.0-24.0s), ET (10.6, 1.0-24.0s) and KER (11.1, 2.6-24.0s)(p=0.949). The objective KER measures were on average (1.2s ± 9.6s, 95% confidence interval) greater than the subjective evaluations of NIBUT with the other instruments (mean difference 0.4s ± 7.7s, 95% confidence interval), resulting in a higher limits of agreement. The slope was -0.08 to 0.11 indicating no bias in the difference between instruments with the magnitude of the NIBUT. Repeated measurements from the two sessions were not significantly different for TS (p=0.584), POL (p=0.549), ET (p=0.701) or KER (p=0.261).

Conclusions: The four instruments evaluated for their measurement of tear stability were reasonably repeatable and give similar average results.

Key words: Non-invasive breakup time, tear film stability, dry eye, NIBUT, repeatability, tearscope, polaris, easy-tear, keratograph

Introduction

A stable pre-corneal tear film is essential to create a protective and lubricated environment for the tissues of the palpebral and bulbar surfaces and to provide the primary refracting surface for light entering the visual system [1]. Impaired tear film stability is one of the fundamental diagnostic criteria for diagnosing a loss of homeostasis of the tear film in dry eye disease and many ways of evaluating tear film stability have been described [2]. Tear film stability can be evaluated invasively by fluorescein breakup time (BUT) and non-invasively by projecting a grid or other pattern onto the tear film (NIBUT). The time interval following a complete blink to the first occurrence of breaks or a change in the reflected grid image is defined as the breakup time [3]. While the values of BUT are dependent on the amount, concentration, pH, drop size, presence of preservatives and the type of fluorescein used, the NIBUT method eliminates the physical disturbance of the tear film [4-6]. Furthermore, BUT can be affected by uneven tear mixing, illumination techniques and by inducing reflex tearing [5, 7-10]. Depending on the quantity of instilled fluorescein, the BUT cut-off values for dry eye have been reported to be ≤5 secs for micro-quantities and ≤10 secs for larger quantities of fluorescein [11-13].

NIBUT is recommended by the International Dry Eye Workshop (DEWS), with a cut off of ≥10secs for normal values, using subjective methods [2]. Recently two new handheld instruments, similar to the well established, but no longer commercially available Keeler Tearscope Plus (Keeler Ltd, Windsor, UK) and video topographers equipped with additional software for objective analysis of placido ring distortion, have been launched [14].

Consequently, the aim of this multicentre study was to investigate the agreement of four different instruments in the measurement of non-invasive tear film breakup time (NIBUT) and to propose guidelines for applying the measurements to the diagnosis of dry eye disease.

Material and methods

Participants

Seventy-two participants (twenty-four per site) with a mean age of 24.2 ± 3.6 (SD) years (54 females) were recruited at three test sites at Aston University, Birmingham, UK; School of Optometry (HFAK) Cologne, Germany and University of Applied Sciences (FHNW), Olten, Switzerland. A sample size of 63 allowed a 2.5s difference in NIBUT [SD of 6.8s] and 67 allowed a correlation of $r \geq 0.3$ to be detected with an α error probability of $p<0.05$ and power of 80% (G*Power) [13]. Participants were excluded if they had a current or previous condition known to affect the ocular surface or tear film; if were taking medication known to affect the ocular surface and/or tear film, and/or if they had worn any types of contact lenses on the day of measurement. All participants gave written informed consent before taking part in the study. All procedures obtained a favourable ethical opinion and governanceapproval of the Aston University Human Ethics Committee and were conducted in accordance with the requirements of the Declaration of Helsinki.

Procedures

NIBUT was measured using the Tearscope Plus (Keeler, Windsor, UK) (TS), Polaris (bon Optic, Lübeck, Germany) (POL), EasyTear Viewplus (Easytear, Rovereto, Italy) (ET) and Keratograph 5M (Oculus Optikgeräte GmbH, Wetzlar, Germany) (KER)

(Figure 1). Measurements were performed by one examiner per site with each of the instruments in a randomized order. Each measurement was filmed with aid of a digital slit lamp video camera and the masked recordings were analysed by an independent examiner. The ring pattern of the Keratograph 5M was illuminated by infrared light. Since, the upper cut-off set by the Keratograph 5M for NIKBUT measurements is < 24 seconds, for instrument comparison the same cut-off was applied to the other subjective instruments. NIBUT measurements were carried out three times with each instrument, with a minimum interval of two minutes between each individual measurement, in order to avoid the effect of tear film destabilisation induced by the measurement itself. To explore repeatability of these individual instruments, all measurements were repeated (by the same examiner) on each participating subject at least two hours later on the same day within the hours of 9am to 5pm.

Statistical analyses

The distribution of the data was generally significantly different from a normal (Kolmogorov-Smirnov test: Tearscope p=0.052, Polaris p=0.002; EasyTearView+ p=0.001; Keratograph p=0.009) and therefore the data is presented as medians (range) and analysed with non-parametric statistics. Means and standard deviations are included in table 1 to allow comparison with previous studies.

Data between instruments (1st session) and with repeated measurements (1st to 2nd session) were analysed with Bland-Altman plots, mean differences, their 95% confidence intervals and bias (heteroscedacity). In addition, differences between the instruments means were analysed using Friedman-test (as the data was significantly different from a normal distribution - Shapiro-Wilk test and QQ plots) and repeatability of measurement means using the Wilcoxon signed-rank test (Programme 'R', Version 3.5.0 and SigmaPlot 12, Systat Software Inc., Chicago, USA).

Results

The descriptive data are summarised in Table 1 (median and range for NIBUT and OSDI), as well as in Figure 2 (Boxplots for NIBUT median values). The Bland-Altman plots of the difference compared to the mean for each individual with each instrument combination are shown in Figure 3. The objective Keratograph measures were on average (1.2s ± 9.6s 95% confidence interval) greater than the subjective evaluations of NIBUT with the other instruments (mean difference 0.4s ± 7.7s 95% confidence interval), resulting in a higher limits of agreement. The slope was -0.08 to 0.11 indicating no bias in the difference between instruments with the magnitude of the NIBUT. Repeated measurements from the two sessions were not significantly different for Tearscope Plus (p=0.584), Polaris (p=0.549), Easytear (p=0.701) or Keratograph 5M (p=0.261; Figure 4). No bias was evident with the magnitude of the NIBUT (slopes -0.06 to 0.10). Intrasession repeatability (1st two measurements of session 1) were not significantly different for Tearscope Plus (p=0.484), Polaris (p=0.519), Easytear (p=0.912) or Keratograph 5M (p=0.0.75; Figure 4). No bias was evident with the magnitude of the NIBUT (slopes -0.08 to 0.14).

Discussion

This study prospective multicentre study reports on the use of four different devices to measure non-invasive tear breakup time (NIBUT). All of these instruments use the projection of a ring grid pattern to visualise the break-up of the tear film. The comparison of the handheld or slit-lamp mounted instruments (Tearscope Plus, Easytear, and Polaris) for subjective evaluation of NIBUT showed no significant difference between the NIBUT measurements. The NIBUT measurements for the subjective instruments (Tearscope Plus 15.2 ± 16.2s, Polaris 14.5 ± 14.0s, Easytear 15.0 ± 15.5s) are in good agreement with previously reported NIBUT values measured with the Tearscope in asymptomatic participants (Guillon et al.[15] (17.9 ± 14.1 seconds), Markoulli et al. [16] (15.9 ± 10.7 seconds).

Despite the considerable number of papers published on the Tearscope and Tearscope Plus, these instruments are no longer in production [17]. However, the new Polaris and Easytear are two instruments that are very similarly constructed. This is the first study reporting the agreement and repeatability of these two instruments. Both instruments can be used hand-held or mounted on a slit lamp. As with the Tearscope, the instruments are suitable not only as an interferometer for observation of the tear film lipid layer, but also allow the observation of NIBUT after inserting a grid. In contrast to the Tearscope, these two instruments use a LED light source. The Polaris receives power through a USB connection. It has a smaller device head, two illumination levels but no stopping watch included. The device head of the Easytear is similar to the that of the Tearscope, with an integrated stop watch. The instrument has a rechargeable battery and therefore can be used without a power connection. It has five illumination levels and in addition a blue LED for fluorescein illumination.

NIBUT values obtained with the Easytear and the Polaris did not differ to a statistically significant degree from those obtained with the Tearscope. Both instruments showed good repeatability, comparable to the Tearscope Plus and to previously reported data of Tearscope Plus [16, 18, 19].

The Keratograph 5M projects a ring pattern from a placido disc onto the tear film surface and automatically detects a disruption. The ring pattern can be illuminated by white or infrared light. This instrument measurement results in two outcomes, the first disruption in the projected placido rings ($NIKBUT_{first}$) and an average tear film break-up of the sections across the cornea ($NIKBUT_{average}$). Furthermore, a tear film map shows the location and size of the tear film break regions. In this study the objectively measured Keratograph 5M NIBUT values were moderate positively correlated with the subjectively obtained NIBUT values. The objective Keratograph 5M NIBUT mean values were shorter than subjective instruments, but only if its cut-off at 24s was not applied to the other instruments.

First reports using the Keratograph 4 and another objective automated system (RT-7000 Auto Refractor-Keratometer; Tomey Corporation), found statistically significantly shorter NIBUT values in comparison to the subjective measurements or BUT using fluorescein [20-23]. As a consequence, Hong et al. suggested a shorter cut-off value (<2.65 seconds) for the Keratograph 4 for best sensitivity (84.1%) and specificity (75.6%) [22].

Comparing the Tearscope Plus to Keratograph 5M, Markoulli et al.[16] reported that NIBUT was significantly greater (5.2 s) than $NIKBUT_{first}$ ($p = 0.006$), but the difference to $NIKBUT_{average}$ (2.5 s) was not significantly greater ($p=0.08$). Using the Keratograph 5M Koh et al. [24] report $NIKBUT_{first}$ (9.7 ± 6.7 s) for the healthy eyes and (4.6 ± 1.3 s) for the dry eyes. In contrast, Hong et al. [22] reported $NIKBUT_{first}$ values of 4.3 ± 0.3 s for the healthy eyes and 2.0 ± 0.2 s for the dry eyes using Keratograph 4. This difference may be explained by the different Keratograph versions, Keratograph 4 versus Keratograph 5M.

For the healthy eyes assessed in this study, the $NIKBUT_{average}$ was in concordance with $NIKBUT_{average}$ of 12.7 ± 6.5s reported by García-Montero et al. [25], using Keratograph 5M in a healthy group of similar age range (26.3 ± 2.5 years). Tian et al. reported a slightly shorter $NIKBUT_{average}$ of 10.4 ± 4.2s [26], using Keratograph 5M in a slightly older group (37.7 ± 9.8 years).

Previous studies have reported poor repeatability using Keratograph 4 [27], and better repeatability for dry eye patient in comparison to healthy participants using Keratograph 5M [26]. Repeatability, for the automated measurements with the Keratograph 5M in healthy participants in this study was good and similar to the repeatability of the subjective measurements with Tearscope Plus, Polaris and Easytear.

Conclusions

NIBUT data of this study suggests that the four instruments for tear stability measurement give reasonably repeatable values that can be used interchangeably as long as objective instrument cut-offs are applied.

Conflict of interest

None

References

[1] Willcox MDP, Argueso P, Georgiev GA, Holopainen JM, Laurie GW, Millar TJ, et al. TFOS DEWS II Tear Film Report. Ocul Surf. 2017;15:366-403.

[2] Wolffsohn JS, Arita R, Chalmers R, Djalilian A, Dogru M, Dumbleton K, et al. TFOS DEWS II Diagnostic Methodology report. Ocul Surf. 2017;15:539-74.

[3] Norn MS. Desiccation of the precorneal film. I. Corneal wetting-time. Acta Ophthalmol (Copenh). 1969;47:865-80.

[4] Wang MT, Murphy PJ, Blades KJ, Craig JP. Comparison of non-invasive tear film stability measurement techniques. Clin Exp Optom. 2018;101:13-7.

[5] Johnson ME, Murphy PJ. The Effect of instilled fluorescein solution volume on the values and repeatability of TBUT measurements. Cornea. 2005;24:811-7.

[6] Mengher LS, Bron AJ, Tonge SR, Gilbert DJ. A non-invasive instrument for clinical assessment of the pre-corneal tear film stability. Curr Eye Res. 1985;4:1-7.

[7] Mengher LS, Bron AJ, Tonge SR, Gilbert DJ. Effect of fluorescein instillation on the pre-corneal tear film stability. Curr Eye Res. 1985;4:9-12.

[8] Korb DR, Craig, J.; Doughty, M.; Guillon J.P.;Smith, G.;Tomlinson, A.;. The tear film: structure, function and clinical examination. Oxford: Elsevier Science Ltd; 2002.

[9] Vanley GT, Leopold IH, Gregg TH. Interpretation of tear film breakup. Arch Ophthalmol. 1977;95:445-8.

[10] Cho P, Brown B, Chan I, Conway R, Yap M. Reliability of the tear break-up time technique of assessing tear stability and the locations of the tear break-up in Hong Kong Chinese. Optom Vis Sci. 1992;69:879-85.

[11] Abelson MB, Ousler GW, 3rd, Nally LA, Welch D, Krenzer K. Alternative reference values for tear film break up time in normal and dry eye populations. Adv Exp Med Biol. 2002;506:1121-5.
[12] Patel S, Murray D, McKenzie A, Shearer DS, McGrath BD. Effects of fluorescein on tear breakup time and on tear thinning time. Am J Optom Physiol Opt. 1985;62:188-90.
[13] Nichols JJ, Nichols KK, Puent B, Saracino M, Mitchell GL. Evaluation of tear film interference patterns and measures of tear break-up time. Optom Vis Sci. 2002;79:363-9.
[14] Bandlitz S, Pult H. Advances in tear film assessment. Optometry in Practice. 2016;17:81-90.
[15] Guillon M, Styles E, Guillon JP, Maissa C. Preocular tear film characteristics of nonwearers and soft contact lens wearers. Optom Vis Sci. 1997;74:273-9.
[16] Markoulli M, Duong TB, Lin M, Papas E. Imaging the Tear Film: A Comparison Between the Subjective Keeler Tearscope-Plus and the Objective Oculus(R) Keratograph 5M and LipiView(R) Interferometer. Curr Eye Res. 2018;43:155-62.
[17] Tong L, Teng LS. Review of Literature on Measurements of Non-invasive Break Up Times, Lipid Morphology and Tear Meniscal Height Using Commercially Available Hand-held Instruments. Curr Eye Res. 2018;43:567-75.
[18] Nichols KK, Mitchell GL, Zadnik K. The repeatability of clinical measurements of dry eye. Cornea. 2004;23:272-85.
[19] Fernandez J, Rodriguez-Vallejo M, Martinez J, Tauste A, Garcia-Montesinos J, Pinero DP. Agreement and repeatability of objective systems for assessment of the tear film. Graefes Arch Clin Exp Ophthalmol. 2018;256:1535-41.
[20] Best N, Drury L, Wolffsohn JS. Clinical evaluation of the Oculus Keratograph. Cont Lens Anterior Eye. 2012;35:171-4.

[21] Gumus K, Crockett CH, Rao K, Yeu E, Weikert MP, Shirayama M, et al. Noninvasive assessment of tear stability with the tear stability analysis system in tear dysfunction patients. Invest Ophthalmol Vis Sci. 2011;52:456-61.
[22] Hong J, Sun X, Wei A, Cui X, Li Y, Qian T, et al. Assessment of tear film stability in dry eye with a newly developed keratograph. Cornea. 2013;32:716-21.
[23] Jandl A, Jaeger K, Bandlitz S. Vergleich verschiedener Messinstrumente zur nicht invasiven Beurteilung der Tränenfilmstabilität (NIBUT). Die Kontaktlinse. 2017;51:6-9.
[24] Koh S, Ikeda C, Fujimoto H, Oie Y, Soma T, Maeda N, et al. Regional Differences in Tear Film Stability and Meibomian Glands in Patients With Aqueous-Deficient Dry Eye. Eye Contact Lens. 2016;42:250-5.
[25] Garcia-Montero M, Rico-Del-Viejo L, Lorente-Velazquez A, Martinez-Alberquilla I, Hernandez-Verdejo JL, Madrid-Costa D. Repeatability of Noninvasive Keratograph 5M Measurements Associated With Contact Lens Wear. Eye Contact Lens. 2019.
[26] Tian L, Qu JH, Zhang XY, Sun XG. Repeatability and Reproducibility of Noninvasive Keratograph 5M Measurements in Patients with Dry Eye Disease. Journal of ophthalmology. 2016;2016:8013621.
[27] Cox SM, Nichols KK, Nichols JJ. Agreement between Automated and Traditional Measures of Tear Film Breakup. Optom Vis Sci. 2015;92:e257-63.

Tables

Table 1. Descriptive data for median (min) and means (± standard deviation) for comparison with other studies during sessions 1 and 2 (with cut-off of 24s).

Figures:

Figure 1. Instruments for the measurement of non-invasive tear film break up time (NIBUT)

Figure 2. Boxplots for NIBUT measurements performed with the different instruments.

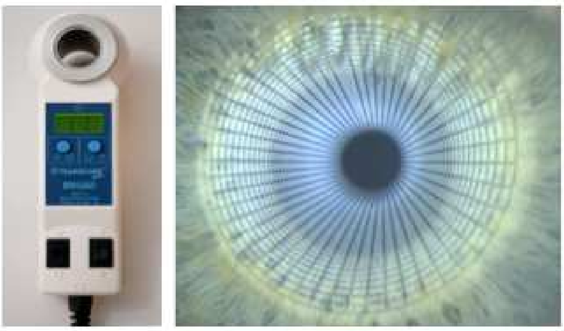
Figure 3. Bland-Altman plots showing differences in NIBUT measurements between the different instruments (n=72).

Figure 4. Bland-Altman plots showing differences in NIBUT measurements between two sessions (black symbols/text) and intrasession (grey symbols/text) for the different instruments (n=72).

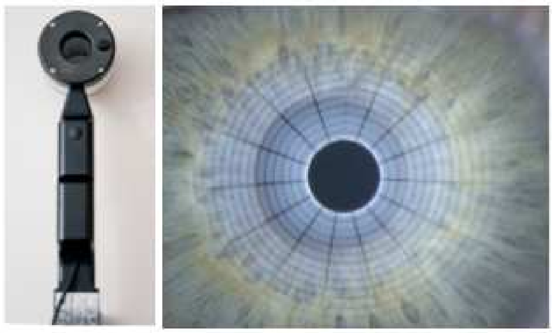
Table 1

	Median (min) mean (± SD) session 1 (s)	**Median (min) mean (± SD) session 2 (s)**	**Median (min) mean (± SD) Total (s)**
Tearscope Plus	10.6 (2.0) 12.4 ± 6.8	10.2 (2.0) 11.9 ± 6.5	10.4 (2.0) 12.1 ± 6.6
Polaris	10.6 (1.0) 12.0 ± 6.4	10.1 (2.6) 12.0 ± 6.5	10.1 (1.0) 12.0 ± 6.4
Easytear	10.0 (1.0) 11.8 ± 6.5	11.0 (2.0) 12.5 ± 6.7	10.6 (1.0) 12.2 ± 6.6
Keratograph	11.3 (2.6) 13.3 ± 7.0	10.6 (2.7) 12.5 ± 6.7	11.1 (2.6) 12.9 ± 6.8
OSDI			12.5 (0-41.7) 13.2 ± 10.7

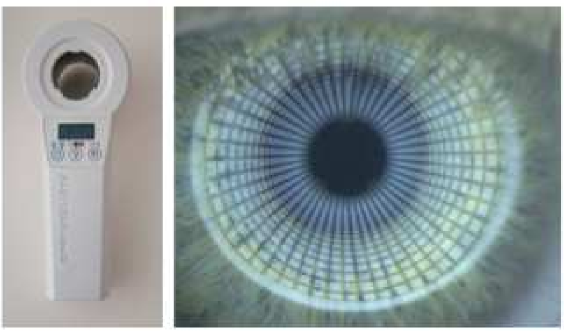
Figure 1



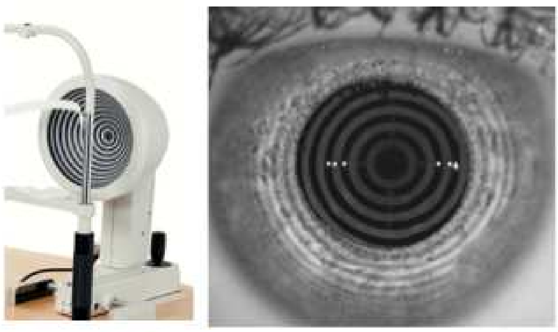
Tearscope Plus (Keeler Ltd, Windsor, UK)



Polaris (bon Optic, Lübeck, Germany)



EasyTear View+ (Easytear, Rovereto, Italy)



Keratograph 5M (Oculus, Wetzlar, Germany)

Figure 2:

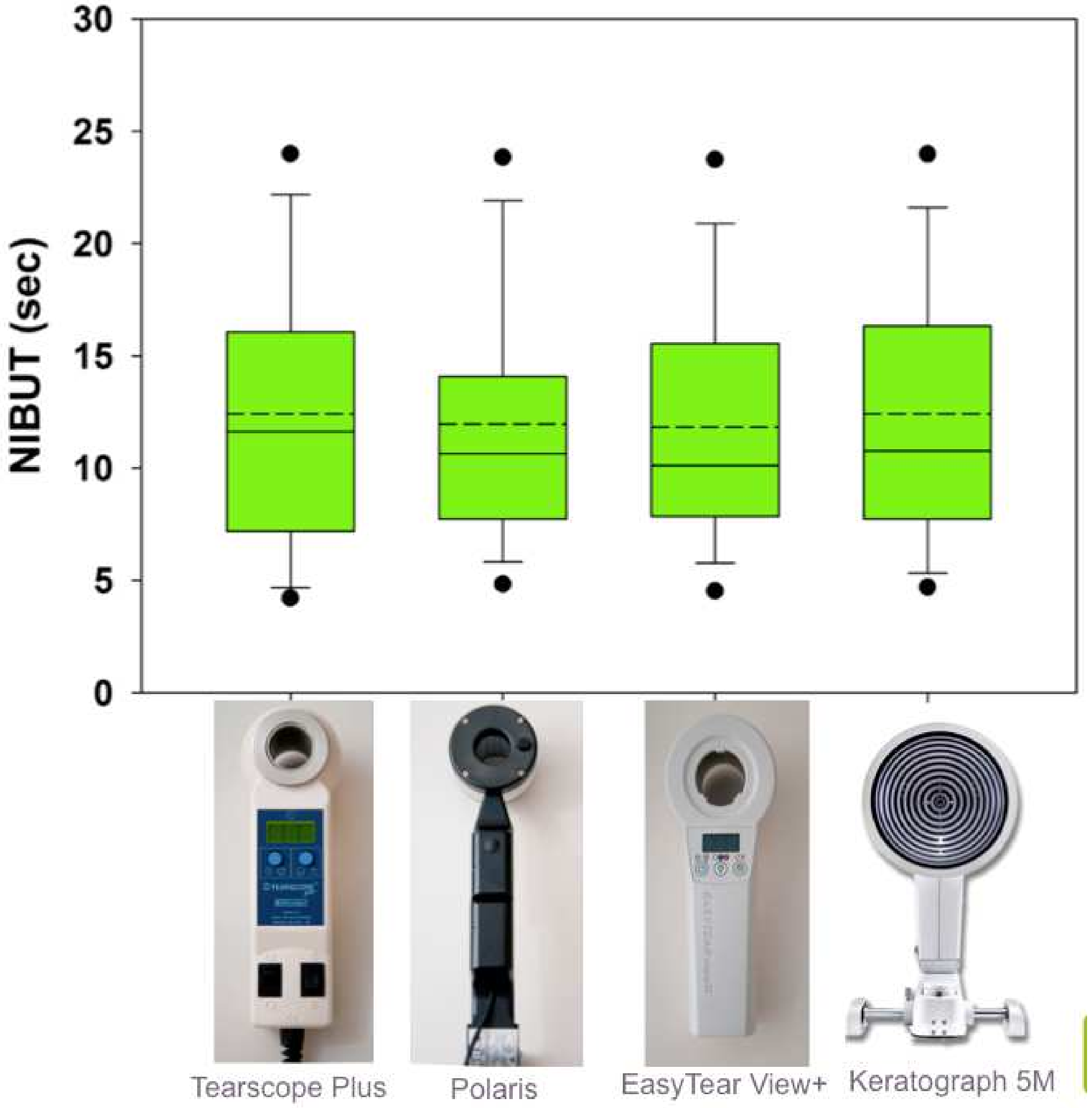

30
25
20
15
10
5
0
NIBUT (sec)
Tearscope Plus
Polaris
EasyTear View+
Keratograph 5M

Figure 3:

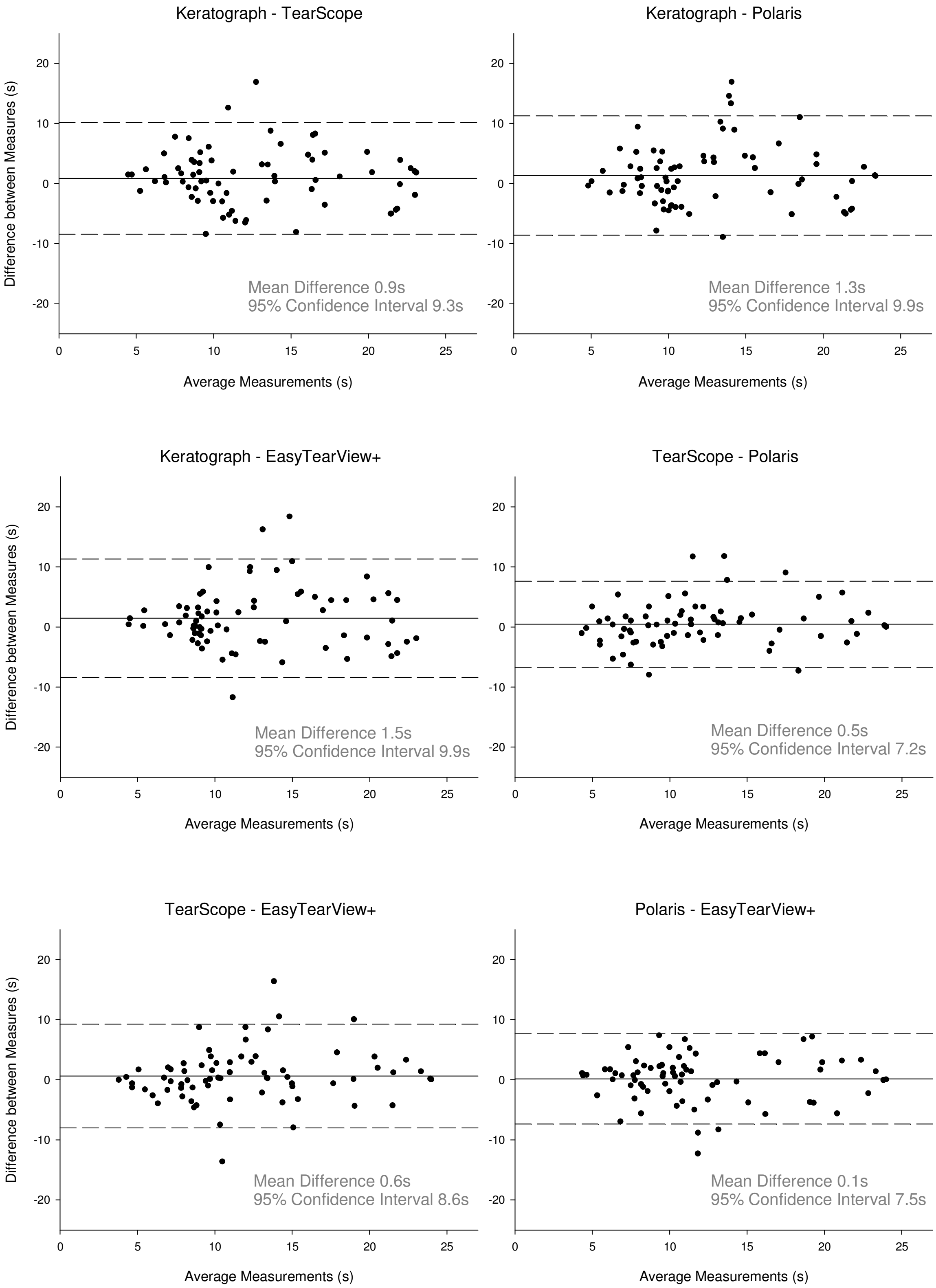
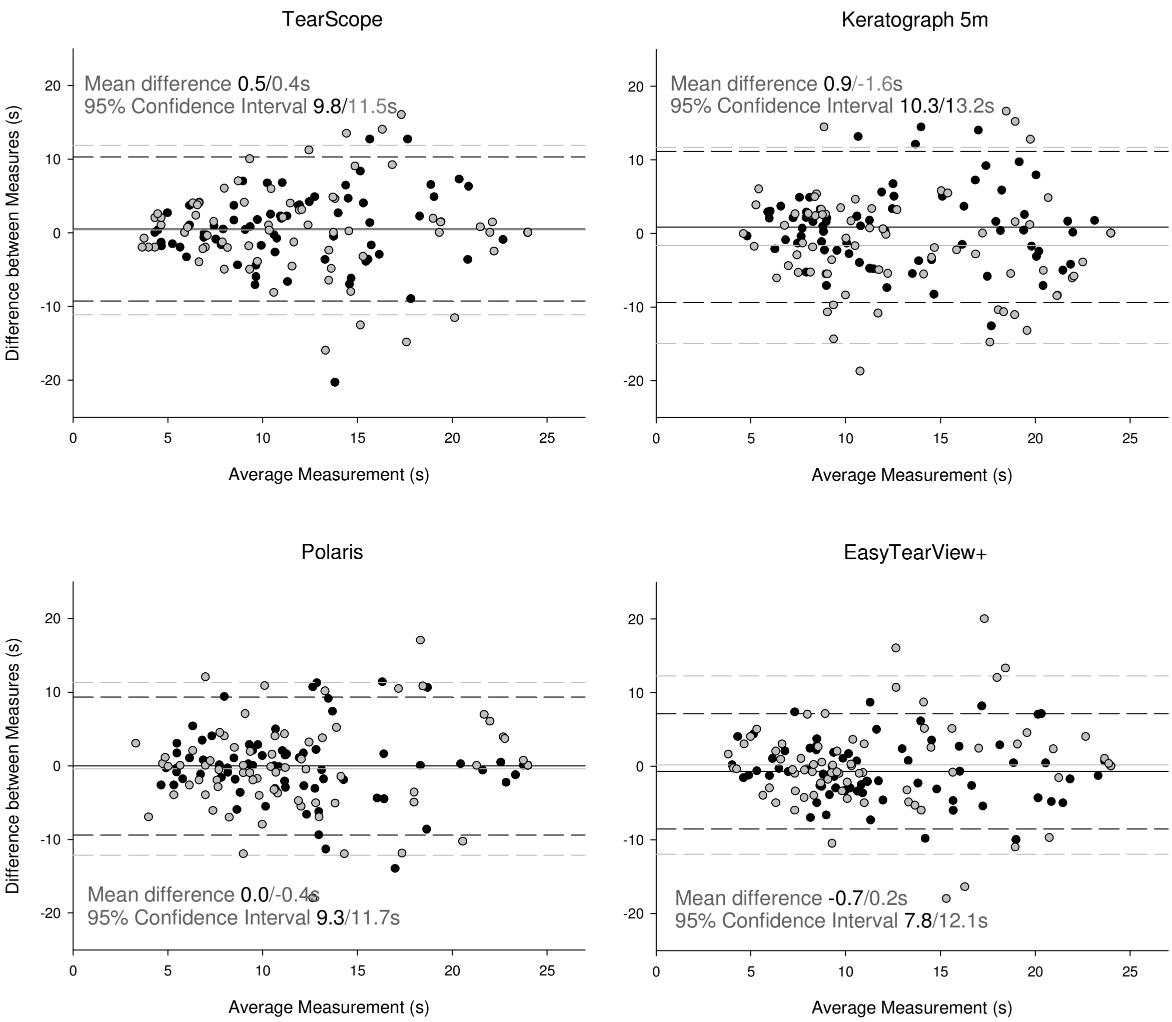

Keratograph - TearScope
Mean Difference 0.9s
95% Confidence Interval 9.3s
Keratograph - Polaris
Mean Difference 1.3s
95% Confidence Interval 9.9s
Keratograph - EasyTearView+
Mean Difference 1.5s
95% Confidence Interval 9.9s
TearScope - Polaris
Mean Difference 0.5s
95% Confidence Interval 7.2s
TearScope - EasyTearView+
Mean Difference 0.6s
95% Confidence Interval 8.6s
Polaris - EasyTearView+
Mean Difference 0.1s
95% Confidence Interval 7.5s
Difference between Measures (s)
Average Measurements (s)
20
10
0
-10
-20
0
5
10
15
20
25

Figure 4:


TearScope
Mean difference 0.5/0.4s
95% Confidence Interval 9.8/11.5s
Keratograph 5m
Mean difference 0.9/-1.6s
95% Confidence Interval 10.3/13.2s
Polaris
Mean difference 0.0/-0.4s
95% Confidence Interval 9.3/11.7s
EasyTearView+
Mean difference -0.7/0.2s
95% Confidence Interval 7.8/12.1s
Difference between Measures (s)
Average Measurement (s)