

Effects of Dilation on Electronic-ETDRS Visual Acuity in Diabetic Patients

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PURPOSE. To evaluate the effect of pupillary dilation on electronic-ETDRS visual acuity (EVA) in diabetic subjects and to assess postdilation EVA as a surrogate for predilation VA.

METHODS. DRCR.net-protocol refraction and EVA were measured before and after dilation in diabetic subjects by independent, masked examiners.

RESULTS. In 129 eyes of 66 subjects, the median (25th, 75th percentiles) predilation EVA score was 69 (54, 86) (Snellen-equivalent 20/40⁻¹ [20/80⁻¹, 20/20⁺¹]). Predilation VA was \geq 20/20, <20/20 to 20/40, <20/40 to 20/80, and <20/80 in 29%, 19%, 26%, and 26% of eyes, respectively. Median EVA change postdilation was -3 letters (-7, 0). The absolute change in EVA score was \geq 15 letters (\geq 3 ETDRS lines) in 9% of eyes and \geq 10 letters (\geq 2 ETDRS lines) in 19% of eyes. Extent of change (range +12 to -25 letters) was associated with baseline VA. No relationship was identified between EVA change and gender, race, lens status, refractive error, DR severity, or primary cause of vision loss.

CONCLUSIONS. In an optimized clinical trial setting, there is a decline in best corrected EVA after dilation in diabetic subjects. The large range and magnitude of VA change preclude using postdilation EVA as a surrogate for undilated VA. (*Invest Ophthalmol Vis Sci.* 2009;50:1580-1584) DOI:10.1167/iov.08-2426

Accurate determination of visual acuity (VA) and the ability to precisely follow changes in VA over time are key outcome measures in most clinical trials and in daily eye care practice. In ophthalmic clinical trials, these measures are frequently used as primary endpoints, underscoring the importance of establishing reliable VA measurement while permitting efficient patient evaluation and throughput.

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⁴A current list of the Diabetic Retinopathy Clinical Research Network is available at <http://www.drcr.net>.

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The methods of measuring VA in clinical trials have been extensively evaluated. Currently, the most common approach is based on the detailed and rigorous refraction and VA protocols of the Early Treatment Diabetic Retinopathy Study (ETDRS),^{1,2} widely considered the gold standard for assessing VA in the ophthalmic clinical research setting. These protocols include specific requirements for refraction and VA lanes, acuity chart type, lighting, and chart height and careful, protocol-defined algorithms for performing refraction and VA measurement.

Recently, an electronic version of the VA measurement protocol called Electronic-ETDRS VA (EVA) has been evaluated and validated.^{3,4} The reliability of VA measurements made with EVA compares favorably with the standard ETDRS VA protocol and has the benefits of being easier, requiring less space and reducing examiner bias. EVA testing has been accepted for use as a primary clinical trial endpoint by the United States Food and Drug Agency and has become the standard VA assessment tool for large clinical trial groups such as the Diabetic Retinopathy Clinical Research Network (DRCR.net) and other multicenter clinical trial groups.

Both ETDRS and EVA VA testing are typically performed before pupillary dilation. In many instances, however, the ability to obtain a postdilation VA that accurately reflects predilation VA would result in significant savings in time, efficiency, and convenience for both patients and clinicians. These benefits arise from the increased flexibility of VA testing permitting optimal use of ophthalmic resources and patient flow. In addition, identification of patients for many clinical research studies requires evaluation of the retina after pupil dilation and before any informed consent or formal clinical study refraction and VA measurement are performed. Accurate postdilation assessments of VA would allow immediate postdilation recruitment of patients for many clinical research studies that otherwise demand re-evaluation of potentially eligible subjects in the undilated state. As such, postdilation VA measurement would represent a valuable alternative to predilation VA testing. We therefore evaluated the effect of dilation on EVA measurements and whether postdilation EVA scores are a reliable reflection of predilation EVA scores in patients with diabetes and a wide range of predilation vision.

METHODS

Patients with diabetes mellitus who were 18 years of age and older were recruited from the clinic population of the Beetham Eye Institute of the Joslin Diabetes Center, a tertiary eye care center specializing in diabetic eye disease. Written informed consent and authorization for medical information disclosure in accordance with HIPAA was obtained from all patients before study participation. The study design was approved by the DRCR.net Executive Committee and the Joslin Institutional Review Board and was in accordance with the Declaration of Helsinki.

Demographic data including date of birth, gender, ethnicity, education level, and ocular medications were obtained at the time of a

single study visit by experienced study-certified examiners. Eyes were stratified by predilation EVA score into four groups as follows: EVA \geq 85 (\geq 20/20), EVA from 70 to 84 ($<$ 20/20–20/40), EVA from 55 to 69 ($<$ 20/40–20/80) and EVA \leq 54 ($<$ 20/80).

Pupil size for each subject was manually measured with a standard millimeter pupil gauge before refraction in a room illuminated to match protocol lighting conditions for EVA testing. DRCR.net protocol refraction was performed on each eye; details are available at www.drcr.net. EVA was then recorded first for the right eye and then for the left eye according to the DRCR.net EVA protocol.

The EVA testing method has been described³ and differs from the use of a standard ETDRS chart in that it utilizes a high-resolution monitor linked to a personal computer to present letters of standardized luminance (85–105 cd/m²) and contrast (98%). EVA letter size is within approximately 2% of the letter size at each logMAR level on the ETDRS chart. EVA testing is performed at 3 m rather than the standard 4 m used with standard ETDRS charts. Letters are presented individually with crowding lines, and a letter score rather than a Snellen line acuity is generated. As with the ETDRS acuity score, the EVA letter score can be used to calculate a corresponding Snellen acuity, in that an EVA letter score of 85 is equivalent to 20/20 VA and each 5-letter decrease in EVA score corresponds to a 1-line decrease in VA.

Subjects then underwent a specified predilation slit lamp biomicroscope anterior segment eye examination that included assessment of corneal clarity (clear, peripheral opacity/stain, and central opacity/stain) and lens status (phakic/pseudophakic). All study results were recorded on standardized forms.

The pupils were then dilated by instillation of 2.5% phenylephrine and 1% tropicamide eye drops attempting to attain a dilated pupil size of at least 5 mm. After at least 20 minutes, pupil size was remeasured in a room illuminated to match protocol lighting conditions for EVA testing. Postdilation refraction and EVA measurements were then performed by an independent examiner who was masked to the findings of the predilation examiner. Postdilation refraction was obtained according to DRCR.net protocol, using the predilation refraction as the starting refraction. Visual acuity was measured first for the right eye and then for the left eye according to the DRCR.net EVA protocol.⁴ Subjects then underwent a postdilation anterior segment assessment of corneal clarity (clear, peripheral opacity/stain, central opacity/stain) and extent of cataract based on the AREDS (Age-Related Eye Disease Study) lens opacity grading scale (cataract absent, pseudophakic, or cataract less than or greater than or equal to AREDS Standard 2). Type of cataract was also recorded (nuclear sclerosis, cortical spoking, or posterior subcapsular). Collection of postdiluted fundus examination information included diabetic retinopathy (DR) severity level and primary cause of visual loss.

Commercial software (SAS ver. 9.1; SAS, Cary, NC) was used for all statistical analyses. Statistical comparisons of pre- versus postdilation VA and change in EVA score after dilation among subgroups were performed with nonparametric analysis based on ranks (Van der Waerden scores). Repeated-measures regression models were used to account for two eyes from the same subject. Because of multiple comparisons, $P > 0.01$ was not considered statistically significant.

RESULTS

This study evaluated 131 eyes of 66 study participants with diabetes (mean age 59 years). One subject had a phthisical eye that was not examined. Two eyes did not have complete examinations and were excluded from the analysis. Baseline characteristics of the 66 subjects and 129 analyzed eyes are presented in Table 1.

The median predilation EVA letter score was 69 (20/40⁻¹), ranging from 95 to 0 (20/12.5 to $<$ 20/800). Predilation EVA had a Snellen VA equivalent of 20/20 or better in 38 (29%) eyes, $<$ 20/20 to 20/40 in 24 eyes (19%), $<$ 20/40 to 20/80 in 34 eyes (26%), and worse than 20/80 in 33 eyes (26%; Table 1). Thirty-

TABLE 1. Demographics

<i>Study Participant Characteristics, Mean \pm SD [Range] or n (%)</i>	
<i>n</i>	66
Age (y)	59 \pm 17 [23, 90]
DM duration (y)	23 \pm 12 [2, 59]
HbA1c (%)	8.1 \pm 1.2 [5.3, 10.5]
Gender	
Women/men	34 (52)/32 (48)
Race	
Caucasian	58 (88)
African-American	8 (12)
Education*	
High School	30 (46)
College	25 (38)
Postgraduate	10 (15)
DM type	
Type 1/type 2	29 (44)/37 (56)
<i>Ocular Characteristics, Median (Range) or n (%)</i>	
<i>n</i>	129†
Predilation EVA letter score (score/Snellen equivalent)	
Median	69 (20/40 ⁻¹)
Range	0 to 95 ($<$ 20/800 to 20/12.5)
EVA \geq 20/20	38 (29)
20/20 > EVA \geq 20/40	24 (19)
20/40 > EVA \geq 20/80	34 (26)
EVA < 20/80	33 (26)
Retinopathy severity	
No DR	24 (19)
Mild NPDR	18 (14)
Moderate NPDR	20 (16)
Severe NPDR	11 (9)
PDR	56 (43)

HbA1c, glycosylated hemoglobin A1C; NPDR, nonproliferative DR; PDR, proliferative DR.

* One observation missing.

† Excludes 1 phthisical eye and two eyes with missing pre- and postdilation visual acuity scores.

six eyes (28%) had no significant ocular disease other than refractive error. The primary cause of vision loss in the other eyes was diabetic macular edema in 35 (27%), cataract in 34 (26%), nondiabetic disease in 16 (12%), vitreous hemorrhage in 4 (3%), and current or previous retinal detachment in 4 (3%).

Overall, the median change in EVA score from predilation to postdilation was a loss of 3 letters (lower and upper quartiles of -7 and 0 letters lost, range $+12$ to -25 ; Table 2, $P < 0.001$). EVA postdilation tended to be reduced, reflecting a general drop in VA regardless of predilation EVA (Fig. 1, $r = -0.18$, 95% CI: -0.35 to -0.05). The median (lower, upper quartiles) absolute change in EVA after dilation was 4 (2, 8) letters. EVA declined significantly in all VA subgroups (Table 2, $P < 0.001$, $P = 0.007$, $P < 0.001$, and $P = 0.01$, respectively). A large range in postdilation EVA change was observed in all four VA groups, being $+3$ to -15 , $+3$ to -25 , $+12$ to -22 , and $+8$ to -25 letters in the 20/20 or better, $<$ 20/20 to 20/40, $<$ 20/40 to 20/80, and the worse than 20/80 groups, respectively.

The distribution of postdilation EVA score changes was associated with the baseline EVA score. As shown in Figure 2, worse baseline EVA was associated more frequently with a postdilation EVA change of 5 or more letters (change of 1 or more ETDRS lines), and less frequently with an EVA change of less than 5 letters (change of less than 1 ETDRS line). After dilation, a five or more letter change was observed in 18%, 50%, 53%, and 67% of eyes with baseline EVA of 20/20 or better, $<$ 20/20 to 20/40, $<$ 20/40 to 20/80, and worse than 20/80, respectively. In eyes with 20/20 or better baseline

TABLE 2. Pre- versus Postdilation VA

	Eyes (n)	Predilation EVA Score	+/- Change* (Letters)	Absolute Change† (Letters)	Range +/- Change* (Letters)	Absolute Change ≥5 Letters (%)	Absolute Change ≥10 Letters (%)	Absolute Change ≥15 Letters (%)
Overall	129	69 (54, 86)	-3 (-7, 0)	4 (2, 8)	+12 to -25	46	19	9
Predilation EVA Letter Score								
95-85 (≥20/20)	38	89 (86, 89)	-2 (-4, -1)	3 (1, 4)	+3 to -15	18	8	3
84-70 (<20/20 to ≥20/40)	24	78 (73, 82)	-5 (-9, 0)	5 (1, 9)	+3 to -25	50	25	8
69-55 (<20/40 to 20/80)	34	62 (59, 66)	-5 (-9, 0)	5 (2, 10)	+12 to -22	53	26	15
54-0 (<20/80)	33	45 (34, 52)	-4 (-9, +1)	6 (2, 9)	+8 to -25	67	21	9
84-0 (<20/20)	91	60 (50, 71)	-4 (-9, 0)	5 (2, 9)	+12 to -25	57	24	11

Data are median (25th, 75th percentiles) or %. n = 129 eyes from 66 subjects. Excludes one phthisical eye and two eyes with missing pre- and postdilation VA scores

* Post- minus predilation EVA. Positive value therefore denotes an improvement in vision after dilation.

† Absolute value of the change.

acuity, 3% experienced a change in acuity of 15 or more letters (≥3 ETDRS lines) after dilation.

After adjustment for baseline visual acuity, there was a tendency for older subjects to experience more EVA decline with dilation, although the associated P = 0.05 did not achieve the threshold of statistical significance given the multiple comparisons performed (Table 3). Median losses were 2, 3, and 5 letters for persons <50, 50 to <70, and ≥70 years of age, respectively (Table 3). With increasing age, the median absolute change in EVA increased from 2 to 7 letters. In subjects less than 50 years of age, 23% had a postdilation EVA change of 5 or more letters; however, at age 70 or older, 61% were changed by 5 or more letters.

As shown in Table 3, there was a tendency for postdilation corneal opacity/staining (e.g., staining induced by applanation tonometry or corneal desiccation) and smaller predilation pupil size to be associated with greater EVA decline after dilation. The study participant's gender, race, predilation corneal clarity, lens status, and DR severity level did not substantially affect EVA change (Table 3). We also could not detect a relationship between EVA change and the subject's education level, phakic refractive error, extent of cataract (either nuclear sclerotic, cortical spoking, or posterior subcapsular), primary cause of vision loss, or examiner (data not shown).

Refractive error did not change substantially from pre- to postdilation in subjects overall or in the subset of study participants who were phakic. The median predilation manifest refraction spherical equivalent was -0.125 D (-1.250, +0.875 D, n = 129) in all subjects and -0.125 D (-1.188, +1.063, n = 96) in phakic subjects. The median postdilation manifest spherical equivalent was -0.250 D (-1.125, +0.625) and -0.125 D (-1.063, +1.063) in these two groups, respectively. The median absolute change in manifest spherical equivalent from before to after dilation was 0.250 D (0.125, 0.500) in all subjects and 0.250 D (0.125, 0.500) in phakic subjects. In general, there was also minimal astigmatic change induced by dilation. The median postdilation change in cylinder in both phakic and pseudophakic eyes was 0 D (quartiles 1, 3: 0 D, 0.25 D for both phakic and pseudophakic eyes). Change in spherical equivalent refractive error from before to after dilation appeared unrelated to change in EVA from before to after dilation or to baseline VA, age, predilation pupil size, or DR severity level.

DISCUSSION

The results of this study demonstrate that in a well-controlled clinical trial setting using experienced examiners, there is a

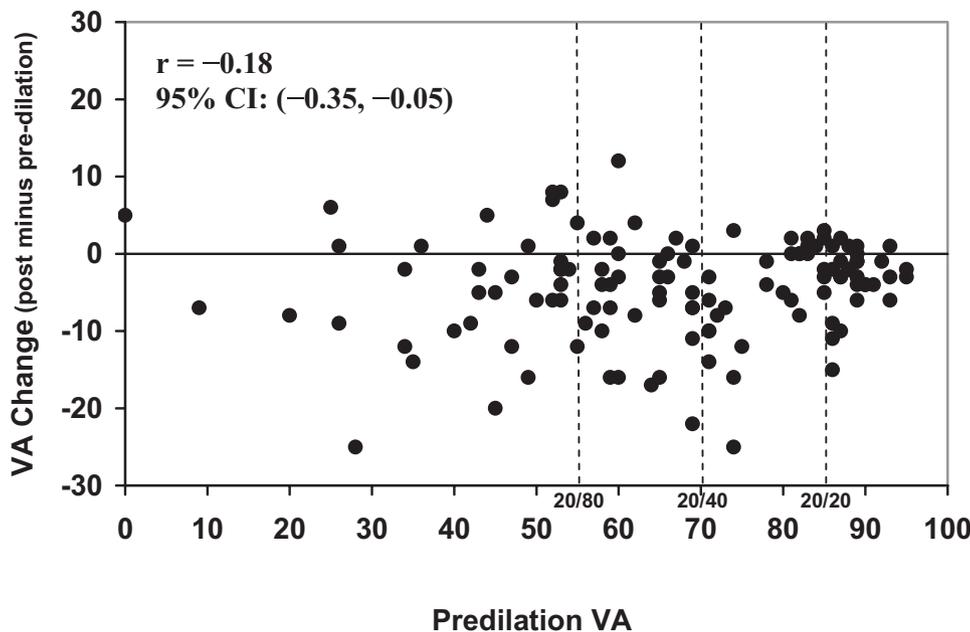


FIGURE 1. Change (±) in VA versus predilation VA.

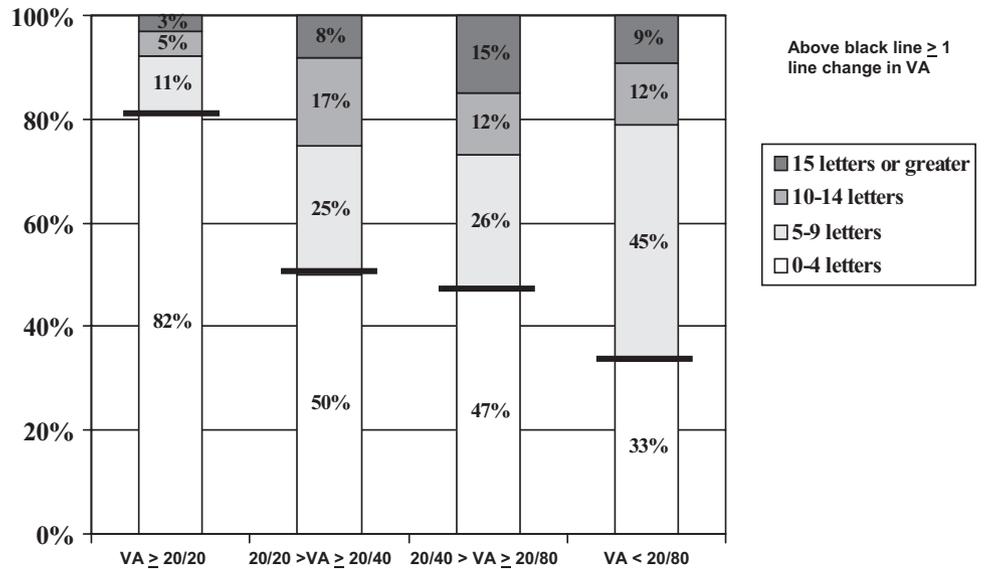


FIGURE 2. Absolute change in number of letters between pre- and post-dilation (percentages within each visual group).

TABLE 3. Change in Visual Acuities by Subgroup

	Eyes (n)	Predilation EVA Score	+/- Change* (Letters)	P†
Overall	129	69 (54, 86)	-3 (-7, 0)	
Gender				0.71
Women	66	71 (53, 87)	-2 (-7, 0)	
Men	63	68 (56, 85)	-4 (-8, 0)	
Age (years)				0.05
<50	35	88 (82, 89)	-2 (-4, 0)	
50-<70	61	69 (53, 83)	-3 (-10, 0)	
≥70	33	58 (49, 68)	-5 (-8, -1)	
Race				0.65
Caucasian	113	69 (55, 86)	-3 (-7, 0)	
African American	16	65 (50, 84)	-3 (-9, 0)	
Predilation pupil size (mm)				0.04
1.5-3.0	36	61 (51, 70)	-6 (-12, -2)	
3.5-5.0	83	72 (53, 86)	-3 (-7, 0)	
5.5-7.0	10	90 (87, 93)	-1 (-3, 0)	
Predilation Corneal Clarity‡				0.93
Clear	76	79 (65, 88)	-3 (-6, 0)	
Peripheral opacity/stain	37	58 (47, 81)	-5 (-9, -1)	
Central opacity/stain	14	53 (35, 59)	-3 (-9, +2)	
Post-dilation corneal clarity§				0.07
Clear	53	69 (58, 87)	-2 (-4, +1)	
Peripheral opacity/stain	40	70 (54, 86)	-5 (-10, -2)	
Central opacity/stain	28	65 (52, 82)	-5 (-12, +1)	
Lens status				0.76
Phakic	96	78 (60, 87)	-3 (-7, 0)	
Pseudophakic	33	52 (43, 62)	-4 (-8, +1)	
Retinopathy severity				0.18
No DR	24	88 (73, 89)	-3 (-5, -1)	
Mild NPDR	18	80 (60, 84)	0 (-4, +2)	
Moderate NPDR	20	69 (54, 86)	-5 (-13, -2)	
Severe NPDR	11	85 (53, 87)	-2 (-10, 0)	
PDR	56	60 (47, 72)	-5 (-9, 0)	

n = 129 eyes of 66 subjects and excludes one phthisical eye and two eyes with missing pre- and postdilation VA scores. Data are expressed as the median (25th, 75th percentiles). NPDR, nonproliferative DR; PDR, proliferative DR

* Postdilation minus predilation EVA. Positive value therefore denotes an improvement in vision after dilation.

† Adjusted for predilation EVA score. Based on ranks using van der Waerden scores.

‡ Missing for two eyes.

§ Missing for eight eyes.

general decline in best corrected VA in patients with diabetes, as measured by EVA after pupil dilation. The magnitude of change varied greatly between patients and could be surprisingly large. In this study, the results were not significantly influenced by which examiner performed EVA testing first or second. Regardless, it is unlikely that different pre- and postdilation EVA examiners would have contributed substantially to EVA variability, since the EVA testing protocol is standardized and automated, and thus the examiner does not determine the stopping point or how many letters to administer at each level. In addition, the EVA testing protocol is specifically structured to minimize examiner influence by requiring subject response to letters that are near or below threshold acuity and by presenting single letters to preclude the risk of patient errors due to reading speed.

Although the median change in dilated EVA score was a loss of 3 letters, the effect of dilation ranged from a gain of 12 letters to a loss of 25 letters. Overall, after dilation 9% and 19% of eyes experienced a ≥ 15 letter or ≥ 10 letter absolute change in EVA score, respectively. These percentages are substantially higher than those seen in test-retest reliability studies of EVA in subjects with undilated pupils: only 0.4% and 2% of subjects experience an absolute change of ≥ 15 letters and ≥ 10 letters, respectively when EVA is repeated with pupils left undilated in a nondiabetic population comparable in age, gender mix, and ethnic makeup.³ This suggests that the wide range of postdilation EVA change demonstrated in this study is due to dilation rather than test-retest error.

The effect of dilation on EVA scores was partially dependent on baseline EVA. In eyes with EVA of 20/20 or better predilation, 3% experienced a 15 or more letter change after dilation. In contrast, a 15 or more letter change was observed in nearly 15% of eyes with EVA of <20/40 to 20/80 at baseline. Dilation-induced changes of 10 or more letters were observed in 8% and 26% of eyes in these groups, respectively.

This study was not designed to directly address the causes of acuity differences between pre- and postdilation VA. There are several potential reasons for these differences including postdilation changes in retinal illuminance, greater exposure to optical irregularities in the cornea or lens, and/or changes in the ocular surface due to corneal drying or tonometry. It is also possible that VA in different individuals is affected by more than one of these considerations at the same time. The results from this study suggest that changes in refractive error after dilation did not contribute significantly to VA change.

The ability to use postdilation VA as a surrogate for best corrected VA in diabetic patients would be advantageous for both patients and clinicians for several reasons, including efficiencies in time, convenience, and clinical trial recruitment. The results of the present study, however, do not support postdilation EVA as an accurate surrogate for an individual's undilated VA. Given the wide range of EVA change after dilation (up to 25 letters in this study), postdilation EVA testing cannot reliably substitute as a surrogate for an individual's undilated VA. It is unknown at this time whether baseline-to-endpoint visual acuity change in clinical trials would be similar if postdilation VA were used at both baseline and follow-up throughout a trial compared with only undilated vision evaluation throughout the trial.

Under selected circumstances, evaluation of postdilation EVA should be considered, due to its general correlation with predilation EVA. Postdilation EVA may be of some use in estimating overall predilation EVA in large cohorts, especially those with good baseline VA. Patients with EVA equal to or better than 20/20 and equal to or better than 20/40, had EVA changes postdilation ranging from +3 to -15 and +3 to -25

letters, respectively. Thus, one might conclude that in these groups, a postdilation EVA was unlikely to have been worse by a line or more before dilation, but could have been substantially better. Given this conclusion, postdilation EVA testing might be useful in a situation such as initial screening for patients to meet a study enrollment criterion of EVA not worse than 20/20 or 20/40. If postdilation EVA assessment is used in such a case, it may be appropriate for clinicians to avoid corneal staining related to tonometry measurements or corneal drying from infrequent blinking after anesthetic drops, since the extent of EVA change after dilation appears related to postdilation corneal clarity.

Given the previously reported high correlation between VA measured by EVA and ETDRS chart protocols and the high test-retest correlation with EVA,³⁻⁵ we would expect a similar degree of VA spread and worsening postdilation if this study had been performed in our patient population using standard ETDRS charts. It is also possible that similar results would arise in other, nondiabetic populations since previous studies with nondiabetic patient cohorts have also found visual worsening after dilation.⁶⁻⁸ Previous studies of postdilation VA have generally focused on the effects of dilation on functional performance of specific tasks such as driving. These studies suggest that dilation not only impairs accommodation due to cycloplegia, but may also alter aspects of functional vision including acuity, and both contrast and glare sensitivity.⁶⁻⁸ A study of 105 consecutive patients assessed using ETDRS and Snellen charts found a similar mean reduction of 4.8 letters read from the ETDRS chart after dilation and an association with baseline VA.⁸ We are not aware of any prior studies evaluating the effects of pupil dilation on vision measured by EVA nor studies specifically in the diabetic population.

In summary, this study demonstrates that in a well-controlled clinical trial setting using experienced examiners, it is common for best corrected VA to change substantially after pupillary dilation in patients with diabetes. Dilation generally reduced VA and changes of up to 25 letters (5 lines) were observed. Given the wide range and large magnitude of VA change after dilation, postdilation EVA testing cannot reliably substitute as a surrogate for undilated VA.

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