Published in final edited form as:

Optom Vis Sci. 2014 February ; 91(2): 194–199. doi:10.1097/OPX.0000000000000128.

Neural Constraints on Visual Acuity in Proliferative Diabetic Retinopathy

J. Jason McAnany, PhD, Justin Wanek, MS, Ruth Zelkha, MS, Jennifer I. Lim, MD, Felix Chau, MD, and Mahnaz Shahidi, PhD

Department of Ophthalmology and Visual Sciences, University of Illinois at Chicago, Chicago, Illinois

Abstract

Purpose—Visual acuity (VA) in normally-sighted individuals is highly correlated with equivalent intrinsic blur, a measure of the amount of blur within the visual system that is generated by optical and neural sources. This study assessed the extent to which VA, equivalent intrinsic blur, optical blur, and neural blur are abnormal in subjects with proliferative diabetic retinopathy (PDR) and characterized the relationships among these parameters.

Methods—Best-corrected VA of 10 subjects with PDR (ages 25 to 68) and 10 normally-sighted individuals (ages 46 to 63) was measured for tumbling E optotypes. The Es were either unblurred or blurred through convolution with Gaussian functions of different widths. Values of equivalent intrinsic blur (σ_{int}) and unblurred VA (MAR_0) were derived using a standard model. Optical blur (σ_{opt}), a measure of blur generated by higher-order aberrations, was quantified using Shack-Hartmann aberrometry. An index of neural blur (η) was defined as $1 - \sigma_{\text{opt}}/\sigma_{\text{int}}$, which represents the remaining blur once the contributions of σ_{opt} to σ_{int} have been accounted for.

Results—Log MAR_0 and log σ_{int} were correlated significantly ($r = 0.98$, $p < 0.05$) for the PDR subjects and the values of these parameters ranged from normal to more than a factor of 2 above the upper limit of normal. In comparison, log MAR measured for the most blurred E was elevated by a relatively small amount for all PDR subjects and was not correlated significantly with log σ_{int} ($r = 0.40$, $p = 0.25$). MAR_0 , σ_{int} , and η differed significantly between the PDR subjects and the controls (all $p < 0.05$) but σ_{opt} did not ($p = 0.50$).

Conclusions—Subjects with PDR and VA loss had higher than normal equivalent intrinsic blur that was due primarily to neural blur elevations, suggesting that neural blur is an important factor that limits VA in these patients.

Keywords

visual acuity; Gaussian blur; intrinsic blur; optical blur; diabetic retinopathy

Diabetic retinopathy (DR) is the most frequent cause of vision loss among working-age adults in the Western world.¹ DR has classically been considered a microcirculatory disease of the retina and the clinical signs of DR primarily involve structural changes of the retinal vasculature, including microaneurysms, hemorrhages, and vascular occlusions. These vascular abnormalities can result in functional losses, particularly in cases of edema, capillary non-perfusion, and retinal detachment. Visual acuity (VA), which is the most

common measure of visual function in patients with DR, can be reduced when the vascular abnormalities affect the central macula.

In addition to the well-documented vascular changes, neural and optical abnormalities have also been described in patients with DR. Apoptosis has been reported in the retinal ganglion cell layer in these patients^{2,3} and the loss of cells results in a reduction of the retinal nerve fiber layer thickness.^{4,5} Furthermore, neural function may be indirectly affected by abnormalities in retinal glia that have been reported in animal models of DR including reactive gliosis,⁶ impaired neurotransmitter uptake,⁷ and altered metabolism.⁸ In addition to neural dysfunction, diabetic patients can have optical defects that include structural changes of the cornea and lens⁹ and elevated higher-order optical aberrations (HOA).¹⁰

The neural abnormalities can alter retinal signal processing and optical abnormalities can degrade the retinal image by reducing contrast and introducing phase shifts. These neural and optical abnormalities may lead to an elevated level of blur within the visual system, which is expected to adversely impact visual function. However, the relative contribution of optical and neural blur to VA loss in patients with DR is not well understood at present. One approach to evaluate the relative contributions of these sources of blur is to measure the total amount of blur within the visual system (i.e. “equivalent intrinsic blur”)^{11, 12} and then partition the equivalent intrinsic blur measurement into optical and neural components.¹³ An estimate of optical blur can be derived from the optical point spread function (PSF), whereas neural blur can be defined as the blur that remains once the contributions of optical blur to equivalent intrinsic blur are accounted for. Thus, this definition of neural blur includes neural factors such as apoptosis, as well as factors that indirectly affect neural function such as glial abnormalities, ischemia, microaneurysms, and edema.

The purpose of the present study was to characterize the relationships among VA, equivalent intrinsic blur, optical blur, and neural blur in patients with proliferative diabetic retinopathy (PDR). Measurements obtained from patients with PDR were compared to a group of normally-sighted individuals to determine the extent to which equivalent intrinsic blur, optical blur, and neural blur differ from normal.

METHODS

The study was approved by an institutional review board at the University of Illinois at Chicago and conformed to the tenets of the Declaration of Helsinki. Written informed consent was obtained from each subject. Ten subjects diagnosed with PDR (7 males and 3 females, ages 25 to 68 years) and 10 normally-sighted control subjects (5 males and 5 females, ages 46 to 63 years) participated in the study. The mean age ($\pm$ standard deviation; SD) of the subjects with PDR (48.5 ± 12.6 years) was not significantly different from that of the controls (54.4 ± 4.9 years) ($t = 1.38$, $p = 0.18$). Subjects with PDR were recruited from the Retina Service at the University of Illinois at Chicago. The subjects had a diagnosis of clinically significant diabetic macular edema (CSDME), vitreous hemorrhage (VH), and/or central retinal vein occlusion (CRVO). Table 1 provides the characteristics of the subjects, including sex, age, diagnosis, and chart acuity as assessed with the Lighthouse Distance Acuity Chart.

The pupil of the tested eye was dilated with 2.5% phenylephrine hydrochloride drops prior to testing. All measurements were made after determining the best optical correction of low-order aberrations (2nd order) and the subjects viewed the stimuli through a 3-mm artificial pupil to control the retinal illuminance. Control subjects had chart VA that ranged from -0.16 to 0.06 log MAR (approximately 20/14 to 20/23 Snellen equivalent) and the subjects

with PDR had chart VA that ranged from 0.00 to 0.66 log MAR (approximately 20/20 to 20/90 Snellen equivalent).

The methodology for the psychophysical measurement of equivalent intrinsic blur (σ_{int}) is described in detail elsewhere.^{13,14} In brief, test stimuli consisted of unblurred or blurred tumbling E optotypes. The blurred Es were generated by convolution with 2D low-pass Gaussian functions of 4 different standard deviations (σ_{stim}): 0.0 (unblurred), 0.4, 1.6, and 6.5 arcmin. Threshold log MAR for each value of σ_{stim} was determined using a two-alternative forced-choice staircase procedure. Threshold log MAR values were plotted as a function of log σ_{stim} and were fit with the log form of the following equation:¹²

$$MAR = MAR_0 \left(1 + (\sigma_{stim} / \sigma_{int})^2 \right)^{1/2}, \quad (1)$$

where MAR_0 represents VA for the unblurred target ($\sigma_{stim} = 0$) estimated by the fit and σ_{int} represents equivalent intrinsic blur. MAR_0 and σ_{int} were free parameters that were adjusted to minimize the mean squared error between the data and the fit. Equivalent intrinsic blur was defined as the value of log σ_{stim} that increased log MAR_0 by 0.15 log units (i.e., log 2, which is the knee-point of the fit), consistent with a previous definition.^{12, 13}

Optical blur was derived from Shack-Hartmann (SH) wavefront measurements as described previously.¹³ Briefly, the wavefront aberration function for high order (third- to sixth-order) aberrations was measured over a 3-mm pupil diameter. From these measurements, the two-dimensional optical PSF was derived according to standard transformations,¹⁵ radially averaged to provide a one-dimensional line profile, normalized to unity, and fit with a Gaussian function. The standard deviation of the best-fit Gaussian function defined optical blur (σ_{opt}). The Gaussian function provided an excellent description of the PSF over the central region from the peak to 1.5 arcmin (mean $\pm$ SD R^2 value of 0.99 ± 0.002 ; $N = 20$).

The neural blur index (η) was defined as:

$$1 - \sigma_{opt} / \sigma_{int}. \quad (2)$$

The value of η provides an index of blur that is introduced by neural (i.e., non-optical) sources. When η is equal to 0.50, the optical and neural contributions to σ_{int} are equal, whereas higher values of η are associated with increased neural contributions to σ_{int} .

RESULTS

log MAR vs. log σ_{stim}

Figure 1 presents log MAR VA as a function of log σ_{stim} for the 10 subjects with PDR (the symbols representing the individual patients correspond to those given in Table 1) compared to the range of normal (gray region). The corresponding Snellen equivalents of the log MAR values are shown on the right y-axis for reference. The range of normal was derived by first determining the maximum and minimum threshold log MAR for each σ_{stim} for the 10 control subjects and these data were then fit with Eq. 1. The curves fit to the patients' data are the least-squares best fits of Eq. 1. This function transitions from a slope of 0 at low values of log σ_{stim} to a slope of 1 at high values. Eq. 1 provided an excellent fit to the data for the subjects with PDR and for the control subjects, yielding a mean $\pm$ SD R^2 value of 0.96 ± 0.05 ($N = 20$).

For subjects with PDR, threshold log MAR for the unblurred E (MAR_0 ; $\sigma_{stim} = 0$) spanned a broad range (0.82 log units). Despite the variation in log MAR_0 for the subjects with PDR, the mean log $MAR_0 \pm SD$ for the PDR subjects (0.42 ± 0.26) was significantly greater ($t = 5.38$, $p < 0.05$) than that of the control subjects (-0.05 ± 0.09). As σ_{stim} was increased, the log MAR differences among the PDR subjects decreased, such that the data points for individual patients tended to converge for the most blurred E ($MAR_{6.5}$; $\sigma_{stim} = 6.5$ arcmin). Thus, log $MAR_{6.5}$ spanned a relatively narrow range (0.17 log units) and the mean log $MAR_{6.5}$ for the subjects with PDR was significantly greater than that of the control subjects ($t = 9.71$, $p < 0.05$). Of note, there were 3 subjects with PDR (numbers 1 – 3) who had normal or nearly normal log MAR_0 (log MAR_0 of 0.14 or less), but log $MAR_{6.5}$ that was outside of the normal range.

Equivalent Intrinsic Blur

Figure 2 shows the relationship between log MAR_0 and log σ_{int} for the subjects with PDR and the controls. Data for the control subjects are represented by the open circles and data for the subjects with PDR are represented by the symbols corresponding to those given in Table 1. As in Figure 1, the corresponding Snellen equivalents of the log MAR values are shown on the right y-axis for reference. Log MAR_0 increased linearly with log σ_{int} (slope = 1.32) and there was a significant correlation between the two parameters ($r = 0.93$, $p < 0.05$; $N = 20$). The 3 PDR subjects (numbers 1 – 3) with relatively good log MAR_0 all had normal σ_{int} . The remaining 7 PDR subjects had substantial log MAR_0 elevations (log MAR_0 of 0.38 or greater) and all had elevated levels of σ_{int} . The mean $\pm SD$ σ_{int} for the 10 subjects with PDR (2.03 ± 0.98 arcmin) was significantly higher ($t = 2.88$, $p < 0.05$) than that of the control subjects (1.12 ± 0.22 arcmin).

Optical Blur

Figure 3 shows the relationship between log MAR_0 and log σ_{int} for the subjects with PDR and the controls. There was no statistically significant correlation between log MAR_0 and log σ_{opt} for the combined patient and control data ($r = 0.32$, $p = 0.17$; $N = 20$) or for correlations performed separately on the control data ($r = 0.04$, $p = 0.92$; $N = 10$) and patients' data ($r = 0.48$, $p = 0.16$; $N = 10$). Furthermore, the mean σ_{opt} for the PDR subjects did not differ significantly from that of the control subjects (0.40 ± 0.02 arcmin and 0.40 ± 0.01 arcmin for the patients and controls, respectively; $t = 0.69$, $p = 0.50$).

Neural Blur

Figure 4 shows the relationship between η and σ_{int} . Data for the control subjects are represented by the open circles and data for the subjects with PDR are represented by the symbols corresponding to those given in Table 1. The dashed horizontal line at $\eta = 0.50$ represents equal contributions of optical and neural blur to σ_{int} . The solid curve is a prediction derived from Eq. 2 by varying σ_{int} between 0.60 and 4.2 arcmin and setting σ_{opt} equal to 0.40 arcmin (the mean σ_{opt} for the PDR and control subjects). Because the value of σ_{opt} was constant in the fit, increasing σ_{int} results in an increase in the relative contribution of neural blur to σ_{int} . As expected, this curve provided an excellent description of the data ($R^2 = 0.99$; $N = 20$), substantiating that as σ_{int} increased, the relative contribution of neural blur to σ_{int} increased for the PDR and control groups. The data points of nearly all subjects fell above 0.50, indicating that σ_{int} had a greater contribution from neural blur than optical blur. The values of η for the control subjects were typically between 0.50 and 0.75. In comparison, 7 of 10 subjects with PDR (the same 7 subjects with elevated log MAR_0 ; Figs. 1 and 2) had values above 0.75, indicating a large contribution of neural blur to σ_{int} . In contrast, the 3 subjects with PDR who had normal or near-normal log MAR_0 also had η within the range of normal. Mean η of the PDR subjects was significantly greater than that

of the controls (0.63 ± 0.08 and 0.75 ± 0.14 for the patients and controls, respectively; $t = 2.23$, $p = 0.04$).

DISCUSSION

Evidence from human subjects with DR and from animal models of DR suggests that elevations in both neural and optical blur could contribute to visual dysfunction. Therefore, it is of interest to evaluate equivalent intrinsic blur, optical blur, and neural blur in these patients to determine the relative contributions of these sources of blur to VA reductions. Subjects with PDR who had substantial VA reduction ($\log MAR_0$ of 0.38 or greater) had elevated equivalent intrinsic blur levels compared to visually-normal control subjects. Furthermore, our index of neural blur (η) was also abnormally high in these patients, suggesting that elevated neural blur is an important factor in their VA loss. In contrast, these patients all had values of optical blur that were within the range of normal.

The similar levels of optical blur due to higher-order aberrations in the PDR and control subjects suggests that optical blur had a negligible contribution to the VA loss of the PDR subjects in the current study. A previous report¹⁰ showed small but significant elevations in optical blur in diabetic patients compared to visually-normal control subjects, but that study did not evaluate VA. The apparent discrepancy between the two studies may be attributed to the PSF calculation over a larger pupil size (6 mm), as compared to the current study (3 mm), or to differences in patient samples.

Although all of the patients had PDR, their clinical manifestations varied, with patients having CRVO, VH, and/or CSDME. Despite these differences, $\log MAR_0$ was highly correlated with $\log \sigma_{int}$ in our sample of patients. The four patients with ETDRS chart VA better than approximately 20/25 had CSDME that did not affect the fovea, which likely accounts for why these four patients had relatively well-preserved VA. Three of these four patients (numbers 1 – 3) also had normal or near-normal $\log MAR_0$, σ_{int} , σ_{opt} , and η . Four other patients (numbers 5 – 8) with VH had moderate losses of ETDRS chart VA (20/33 to 20/48) and elevated σ_{int} and η . The two patients with the worst ETDRS chart VA of our sample had CSDME that affected the fovea (number 9) and CRVO (number 10), respectively, and these two patients had elevated σ_{int} and η . The source of the elevated η in patients with VA loss is presently uncertain, as several factors could elevate η , including apoptosis, gila abnormalities, edema, and/or ischemia. Future work is needed to define the relative contributions of these factors to the VA loss in patients with PDR.

There were two notable findings for VA measurements made with the most blurred E ($\log MAR_{6.5}$) for the patients with PDR. First, there was relatively small variation in $\log MAR_{6.5}$ among these subjects, which is in contrast to their substantial variation in $\log MAR_0$. A likely explanation for this finding is that $\log MAR_{6.5}$ was not dependent on equivalent intrinsic blur because the amount of stimulus blur (6.5 arcmin) exceeded the amount of blur within the visual system. Once the effects of equivalent intrinsic blur were overcome by the high stimulus blur, the VA values for the subjects with PDR were similar. There was also less variation in $\log MAR_{6.5}$ (0.19 log units) than in $\log MAR_0$ (0.28 log units) for the control subjects.

The second finding of interest for VA made with the most blurred E is that $\log MAR_{6.5}$ was outside of the normal range for all subjects with PDR, including those who had normal or near-normal $\log MAR_0$ (subjects 1–3). Thus, from a practical view, measurement of VA for highly blurred letter optotypes may be useful for some patients with PDR because it can reveal VA deficits that are not apparent by conventional chart acuity testing. Future studies are needed to identify the source of the VA deficit for the highly blurred optotypes, but the

deficit is unlikely related to optical or neural blur because the amount of stimulus blur exceeded these levels. Additional work is also needed to investigate the clinical utility of measuring VA for highly blurred optotypes to determine if this measure of visual function could be applied as an outcome measure in clinical trials or for monitoring disease progression in patients with PDR.

Acknowledgments

This research was supported by National Institute of Health grants R00EY019510 (JJM), R01EY014275 (MS), P30EY001792 (departmental core grant), the Department of Veterans Affairs (MS), the Cless Family Foundation Fund for Retina Research (JL), and Research to Prevent Blindness unrestricted departmental and Senior Scientific Investigator (MS) awards.

References

1. Fong DS, Aiello L, Gardner TW, King GL, Blankenship G, Cavallerano JD, Ferris FL 3rd, Klein R. Diabetic retinopathy. *Diabetes Care*. 2003; 26:226–9. [PubMed: 12502685]
2. Abu El-Asrar AM, Dralands L, Missotten L, Geboes K. Expression of antiapoptotic and proapoptotic molecules in diabetic retinas. *Eye (Lond)*. 2007; 21:238–45. [PubMed: 16424911]
3. Barber AJ, Gardner TW, Abcouwer SF. The significance of vascular and neural apoptosis to the pathology of diabetic retinopathy. *Invest Ophthalmol Vis Sci*. 2011; 52:1156–63. [PubMed: 21357409]
4. Lopes de Faria JM, Russ H, Costa VP. Retinal nerve fibre layer loss in patients with type 1 diabetes mellitus without retinopathy. *Br J Ophthalmol*. 2002; 86:725–8. [PubMed: 12084737]
5. van Dijk HW, Verbraak FD, Kok PH, Garvin MK, Sonka M, Lee K, Devries JH, Michels RP, van Velthoven ME, Schlingemann RO, Abramoff MD. Decreased retinal ganglion cell layer thickness in patients with type 1 diabetes. *Invest Ophthalmol Vis Sci*. 2010; 51:3660–5. [PubMed: 20130282]
6. Rungger-Brandle E, Dosso AA, Leuenberger PM. Glial reactivity, an early feature of diabetic retinopathy. *Invest Ophthalmol Vis Sci*. 2000; 41:1971–80. [PubMed: 10845624]
7. Puro DG. Diabetes-induced dysfunction of retinal Muller cells. *Trans Am Ophthalmol Soc*. 2002; 100:339–52. [PubMed: 12545700]
8. Lieth E, Barber AJ, Xu B, Dice C, Ratz MJ, Tanase D, Strother JM. Penn State Retina Research Group. Glial reactivity and impaired glutamate metabolism in short-term experimental diabetic retinopathy. *Diabetes*. 1998; 47:815–20. [PubMed: 9588455]
9. Ishiko S, Yoshida A, Mori F, Abiko T, Kitaya N, Konno S, Kato Y. Corneal and lens autofluorescence in young insulin-dependent diabetic patients. *Ophthalmologica*. 1998; 212:301–5. [PubMed: 9693285]
10. Shahidi M, Blair NP, Mori M, Zelkha R. Optical section retinal imaging and wavefront sensing in diabetes. *Optom Vis Sci*. 2004; 81:778–84. [PubMed: 15557852]
11. Watt RJ, Morgan MJ. Spatial filters and the localization of luminance changes in human vision. *Vision Res*. 1984; 24:1387–97. [PubMed: 6523759]
12. Levi DM, Klein SA. Equivalent intrinsic blur in spatial vision. *Vision Res*. 1990; 30:1971–93. [PubMed: 2288101]
13. McAnany JJ, Shahidi M, Applegate RA, Zelkha R, Alexander KR. Contributions of optical and non-optical blur to variation in visual acuity. *Optom Vis Sci*. 2011; 88:716–23. [PubMed: 21460756]
14. McAnany JJ, Alexander KR, Lim JJ, Shahidi M. Object frequency characteristics of visual acuity. *Invest Ophthalmol Vis Sci*. 2011; 52:9534–8. [PubMed: 22110062]
15. Thibos LN, Hong X, Bradley A, Applegate RA. Accuracy and precision of objective refraction from wavefront aberrations. *J Vis*. 2004; 4:329–51. [PubMed: 15134480]

Figure 1.

Log MAR as a function of $\log \sigma_{stim}$ for the 10 subjects with PDR (symbols correspond to those in Table 1) and the range of normal (gray region). The right y-axis indicates the Snellen equivalents of the log MAR values. The solid lines represent the least-squares best fit of equation 1 to the data. A color version of this figure is available online at www.optvissci.com.

Figure 2.

Log MAR_0 as a function of log σ_{int} for the control subjects (open circles) and for the subjects with PDR (symbols correspond to those in Table 1). The right y-axis indicates the Snellen equivalents of the log MAR_0 values. The line is a linear regression fit to the data, as described in the text. A color version of this figure is available online at www.optvissci.com.

Figure 3.

Log MAR_0 as a function of log σ_{opt} for the control subjects (open circles) and for the subjects with PDR (symbols correspond to those in Table 1). The right y-axis indicates the Snellen equivalents of the log MAR_0 values. A color version of this figure is available online at www.optvissci.com.

Figure 4.

η for the control subjects (open circles) and for the subjects with PDR (symbols correspond to those in Table 1) as a function of σ_{int} . The solid line represents the predicted η , given a constant σ_{opt} , as described in the text. The horizontal dashed line represents equal contributions of optical and neural blur to σ_{int} . A color version of this figure is available online at www.optvissci.com.

Table 1

Subject characteristics.

Subject No.	Symbol	Sex	Age (years)	Diagnosis	Chart VA (logMAR)
1		M	66	DM2; CSDME	0.00
2		M	40	DM1; CSDME; VH	0.02
3		M	47	DM2; CSDME	0.10
4		F	47	DM2; CSDME	0.12
5		F	56	DM2; VH	0.22
6		M	43	DM2; VH	0.30
7		M	49	DM2; VH	0.32
8		M	25	DM1; CSDME; VH	0.38
9		F	68	DM2; CSDME	0.58
10		M	44	DM2; CRVO	0.66
Control range					46 to 63 -0.16 to 0.06

CRVO, central retinal vein occlusion; CSDME, clinically significant diabetic macular edema; DM1, diabetes mellitus type 1; DM2, diabetes mellitus type 2; VH, vitreous hemorrhage.