THE BLUE ARC ENTOPTIC PHENOMENON IN GLAUCOMA (AN AMERICAN OPHTHALMOLOGICAL THESIS)

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ABSTRACT

Purpose: To determine whether the blue arc entoptic phenomenon, a positive visual response originating from the retina with a shape that conforms to the topology of the nerve fiber layer, is depressed in glaucoma.

Methods: We recruited a cross-sectional, nonconsecutive sample of 202 patients from a single institution in a prospective manner. Subjects underwent full ophthalmic examination, including standard automated perimetry (Humphrey Visual Field 24-2) or frequency doubling technology (Screening C 20-5) perimetry. Eligible patients viewed computer-generated stimuli under conditions chosen to optimize perception of the blue arcs. Unmasked testers instructed patients to report whether they were able to perceive blue arcs but did not reveal what response was expected. We created multivariable logistic regression models to ascertain the demographic and clinical parameters associated with perceiving the blue arcs.

Results: In multivariable analyses, each 0.1 unit increase in cup-disc ratio was associated with 36% reduced likelihood of perceiving the blue arcs (odds ratio [OR] = 0.66 [95% confidence interval (CI): 0.53-0.83], P<.001). A smaller mean defect was associated with an increased likelihood of perceiving the blue arcs (OR=1.79 [95% CI: 1.40-2.28]); P<.001), while larger pattern standard deviation (OR=0.72 [95% CI: 0.57-0.91]; P=.005) and abnormal glaucoma hemifield test (OR=0.25 [0.10-0.65]; P=.006) were associated with a reduced likelihood of perceiving them. Older age and media opacity were also associated with an inability to perceive the blue arcs.

Conclusion: In this study, the inability to perceive the blue arcs correlated with structural and functional features associated with glaucoma, although older age and media opacity were also predictors of this entoptic response.

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INTRODUCTION

Standard automated perimetry is an accepted reference standard to assist in glaucoma detection.[1] Accurate assessment of retinal sensitivity requires an attentive patient to provide reliable subjective responses while maintaining steady central fixation as visual stimuli are projected to various retinal eccentricities. The inability to maintain steady fixation or to reliably indicate that visual stimuli are present could profoundly impact study outcome.[2] Furthermore, the prevalence of fixation loss >20% is relatively high, prompting a recommendation to relax the acceptable fixation loss rate to 33%.[3] It is now evident that structural and electrophysiologic changes in the macula do occur in glaucoma patients,[4-6] although the psychophysical correlates of these changes are not known.

We postulate that the macular changes that occur in glaucoma can be leveraged into a fixation-independent psychophysical test. Under appropriate psychophysical conditions in normal subjects, when a vertical stripe of light is presented in the macular region such that it stimulates the arcuate retinal ganglion axon bundles immediately above and below the fovea, an entoptic response with the shape of the nerve fiber layer (NFL) topology is generated.[7] Since glaucoma is a disease that affects the NFL, we postulate that this entoptic phenomenon is diminished in patients with this condition.

Entoptic images refer to positive visual phenomena generated from physiologic or pathologic processes within the eye.[8] The most well-known entoptic phenomenon is Moore's lightning streaks, which are seen when vitreous liquefaction produces retinal traction, resulting in photopsias often referred to as flashes of light.[9] Purkinje is credited with the first description of the blue arc entoptic phenomenon in the early 19th century. As Moreland describes it, Purkinje noticed the blue arcs while viewing the embers of a fire in the dark but did not completely understand their signifcance.[7] Subsequent investigation[10] indicated that the shape of the perceived blue arc images is strongly influenced by the anatomic topology of the NFL.

Various investigators reported on the optimum conditions for demonstrating the blue arc entoptic phenomenon. While stimuli of various shapes and sizes are capable of producing the blue arc entoptic phenomenon, vertical rectangular stimuli are best for eliciting the response.[7] The arcs are best seen in the dark after a 2- to 3-minute period of exposure to room light. The response is transient, lasting only approximately 0.5 seconds, and occurs immediately upon stimulus presentation.[7]

The mechanism for how the blue arc entoptic phenomenon is generated remains unknown. The arcs are always varying shades of blue, depending on the degree of dark adaptation. The optimum amount of dark adaptation (2 to 3 minutes) produces brilliant powder blue arcs, but these can fade to grey and ultimately white with longer periods of dark adaptation.[11] Regardless of the color of the stimulating light, the entoptic arcs are always varying shades of blue, but red light seems to be the best for generating the blue arcs.[12] Ingling and Drum[11] proposed that the blue color of the arcs is related to activation of the blue-yellow opponency system when presenting stimuli to partially dark-adapted retina. The short, medium, and long wavelength cones combine in antagonistic ways to produce two parallel color systems with connections to specified retinal ganglion cells: the blue-yellow system (where yellow results from a combination of long and medium wavelength cones that are opposed by short wavelength cones), which transmit via bistratified retinal ganglion cells,[13] and the red-green system (where long wavelength cones are opposed by medium wavelength cones), which transmits via midget retinal ganglion cells.[14]

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Electrophysiological studies indicate that rods and short-wavelength cones (also known as blue cones) provide inhibitory input to the peripheral portion of the receptive field of blue/yellow color opponency ganglion cells, whereas red (long wavelength) and green cones (medium wavelength) contribute positive, central yellow-on neuronal activity.[15,16] Immediately after shutting the lights off for a light-adapted subject, there is residual stimulation of the center of the field by red and green cones and peripheral inhibition by the rods. The simultaneous center-surround stimulation shuts off the red and green cones and activates the blue (short wavelength) cones. For stimulus presentation in the early dark adaptation period, rod inhibitory input accompanied by activation of short-wavelength cones and their specified ganglion cell axon elicits the blue arc entoptic phenomenon. Exactly how the blue cone–retinal ganglion cell axon complex is stimulated is unknown, but a bioluminescence phenomenon has been ruled out.[17,18] As the eye continues to dark adapt under scoptic conditions, yellow-on activity subsides and the arcs seen on stimulus presentation turn gray and eventually diminish altogether. Extinction of the blue arc imagery occurs because the center-on portion of the receptive field no longer requires peripheral inhibitory input by short wavelength cones, as the latter become inactive.

Duke-Elder's text mentions that the blue arcs are obliterated in patients with visual scotomas, but no investigator has explored the clinical utility of the blue arc entoptic phenomenon.[19] We hypothesize that the blue arc entoptic phenomenon is depressed in glaucoma for two reasons. First, NFL dropout occurs in glaucoma, and the blue arc entoptic phenomenon is strongly influenced by the NFL. Second, the blue arc entoptic phenomenon may depend on intact circuitry of the blue-yellow opponent system, and these circuits are defective in early glaucoma, as demonstrated by short-wavelength automated perimetry.[20]

Self-administered tests for glaucoma may be useful tools in disease detection, particularly for people highly motivated to have an early diagnosis, such as those with a family history of disease. The Proview phosphene tonometer is a handheld device that also leverages entoptic responses in the measurement of intraocular pressure (IOP), but some researchers regard these self-measures as unreliable relative to Goldmann applanation tonometry.[21,22] The rebound tonometer could be a viable alternative for self-assessment of IOP, as it does not require topical anesthesia and readings correspond well with Goldmann applanation tonometry, but the technology is expensive and does require a second party to administer.[23] Furthermore, it is well known that screening for glaucoma with tonometric point estimates of IOP is neither sensitive nor specific for disease detection.[24,25] Nonetheless, newer devices such as contact lenses that provide telemetric monitoring of IOP over extended time periods may have diagnostic utility in glaucoma.[26] Currently, the only available self-administered test of visual function in glaucoma is the Peristat test, which is a computer-based test fashioned after conventional perimetry.[27] We developed, and then administered, a computer-based, fixation-independent test designed to assess the blue arc entoptic phenomenon in glaucoma. As this was a novel test of unknown utility in disease detection, the purpose of this work is to ascertain the determinants of this entoptic phenomenon in a mixed population of normal subjects, glaucoma suspects, and patients with varying degrees of glaucoma severity.

METHODS

The Massachusetts Eye and Ear Infirmary Human Studies Committee approved all aspects of this prospective, noninterventional study, and written informed consent was obtained for all participants. The study was in compliance with all HIPAA regulations.

PATIENT POPULATION

We chose 202 nonconsecutive patients from the Massachusetts Eye and Ear Infirmary: 168 from the Glaucoma Service and 34 from the Comprehensive Ophthalmology Service over a 2-year period. Patients between the ages of 35 and 90 years were chosen, depending on availability of testers and clinic volume. Only patients with no prior ocular surgery (including laser surgery) in the previous 6 months were invited to participate. These subjects were required to have a best-corrected visual acuity of at least 20/50 in both eyes. To ascertain the potential utility of the blue arc entoptic phenomenon in detecting glaucoma, we purposefully did not exclude subjects with congenital dyschromatopsia, diabetes, diabetic retinopathy, and age-related macular disease, because these conditions are common in subjects at risk of having undiagnosed glaucoma.

Subjects from the Glaucoma Service all had standard automated perimetry (Humphrey visual field 24-2 SITA standard) within 1 year of participation in the study. We required that both eyes demonstrate acceptable reliability parameters on their most recent Humphrey visual field test (fixation loss ≤33%, false-positive rate ≤20%, and false-negative rate ≤20%). Glaucoma Service patients were recruited at the time of routine follow-up or at the time of initial presentation. For subjects from the Comprehensive Ophthalmology Service, we also required that they have no known family history of glaucoma. We recruited normal subjects with IOP <21 mm Hg, cup-disc ratio (CDR) <0.6, and CDR asymmetry <0.2. Eligible subjects from the Comprehensive Eye Service underwent frequency doubling technology (FDT) perimetry (screening C 20-5). We required FDT fields to have fixation loss and false-positive rates of ≤33%. On the day of testing for the blue arc entoptic phenomenon, all subjects underwent a complete eye examination. We specifically recorded color vision using 24 Ishihara color plates (Kanehara Shuppan Co, Tokyo, 1976), measured pupil size, and assigned a subjective media opacity grade ranging from 0 to 4+. Patients who were status post cataract extraction with open capsules were assigned a grade of 0. We also noted the vertical CDR and evaluated whether diabetic retinopathy or macular degeneration was present. We reviewed the latest visual fields for evidence of nasal steps, nasal depression in Bjerrum's area, arcuate defects, or temporal wedges. If patients had 3 or more contiguous points on the pattern deviation plot that were one-half log unit reduced in the nasal step zone, Bjerrum's area, or temporal wedge region, they were regarded as having a visual field defect.

DEVELOPMENT AND IMPLEMENTATION OF A TEST TO ASSESS THE BLUE ARC ENTOPTIC PHENOMENON

In preliminary analyses we presented red vertical slits on a wall using a well-charged laser pointer under scotopic conditions in the previously light-adapted eye to 6 patients with unilateral severe glaucoma but preserved central fixation. We found that none of the

severely affected eyes could perceive the blue arc entoptic phenomenon, and 4 of 6 fellow eyes were able to perceive the entoptic response (12 of 12 controls could perceive the blue arc entoptic phenomenon in both eyes).

We subsequently developed a computer-based test to assess the blue arc entoptic phenomenon. The stimulus was presented on a standard cathode ray computer video display using Microsoft's PowerPoint program with the patient's eyes 40 cm from the display. The background computer monitor brightness was set to 0% and contrast was set to 100%. We found that it was essential to remove all stray light from the testing area, including background light coming from illuminated keyboards. A schematic of the stimulus design and presentation with expected entoptic response is provided in Figure 1. Trial and error indicated that a bright vertical red stripe presented just temporal to the fovea elicited the strongest entoptic response. We purposefully chose a single stimulus that straddled the superior and inferior portions of the horizontal meridian because prior published data using short-wavelength perimetry indicated that ocular hypertension patients with full automated perimetry tests could have diffuse loss in the central 10 degrees located above and below the horizontal meridian.[20] Furthermore, this approach helped to streamline testing and circumvented any concerns regarding the need to control fixation. It is interesting to note that the elicited normal entoptic response is limited to two arcs that originate from the superior and inferior poles of the stripe corresponding to the retinal ganglion cell arcuate bundles that emanate to the superior and inferior pole of the optic nerve.

During testing, we instructed patients to wear glasses if they felt it enhanced their ability to see the computer screen. The initial slides of the PowerPoint file were demonstration slides showing the stimulus alone and the stimulus plus computer-simulated blue arcs under photopic conditions. The testers, who were generally not masked to patient status, were scripted to instruct patients of the purpose of the test (whether or not the subject was able to perceive blue arcs when the red stimulus was presented) without revealing what response was expected. After the demonstration program, the patient was light-adapted for 2 minutes, then dark-adapted for 1 minute. Subsequently, with the left eye covered, the patient was asked to initially look at an X with the right eye while the stimulus was presented. Patients were not instructed to maintain fixation on the X during the testing period. We projected a vertical red slit with width of 0.86 degrees on a black background, 2.3 degrees temporal to fixation. The slit extended 5 degrees vertically above and below the horizontal (Figure 2). The stimulus intensity measured with a SSP-3 photometer (Optec Inc, Lowell, Michigan) was 5 cd/m^2. The stimulus was presented for 0.5 seconds 10 times, with 2 seconds between each presentation. Patients were then asked if they perceived the blue arcs, which would appear as illustrated in Figure 3 with the proviso that the demonstration is only a gross simulation of the phenomenon they may perceive. The patient was again light-adapted for 2 minutes, then dark-adapted for 1 minute, and the left eye tested in the same manner. We specifically designed the test to optimize the subject's perception of the blue arcs using the maximum allowable stimulus intensity available on the computer monitor and based on the recommendations of Moreland.[7]

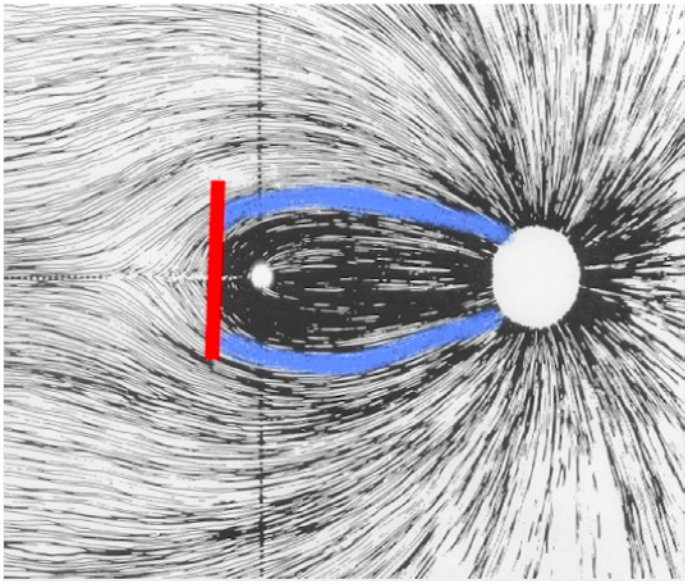

FIGURE 1

Juxtaposition of the test stimulus onto a topographic map of the nerve fiber layer for the right eye. The red rectangular stimulus is incident on the temporal parafoveal retina, and the entoptic blue arcs perceived are demonstrated.

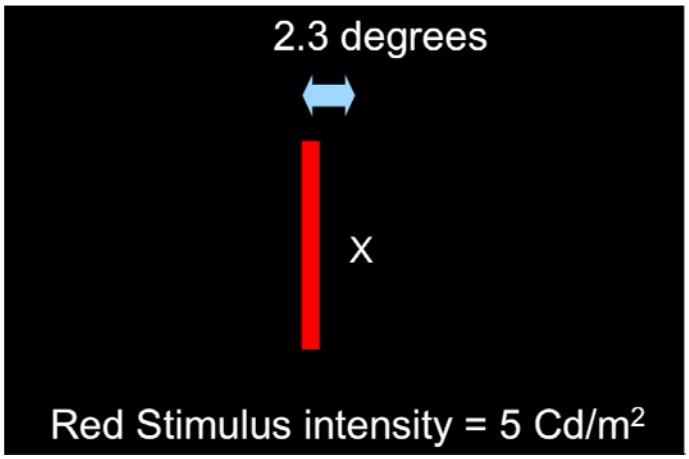

FIGURE 2

Schematic illustrating the stimulus position relative to the fixation target during assessment of whether the blue arc entoptic phenomenon is perceived. The subject fixates on X with the right eye while a red rectangular stimulus is flashed on and off on the computer screen using a PowerPoint application file. The stimulus is projected 2.3 degrees temporal to fixation and has a luminance of 5 cd/m^2.

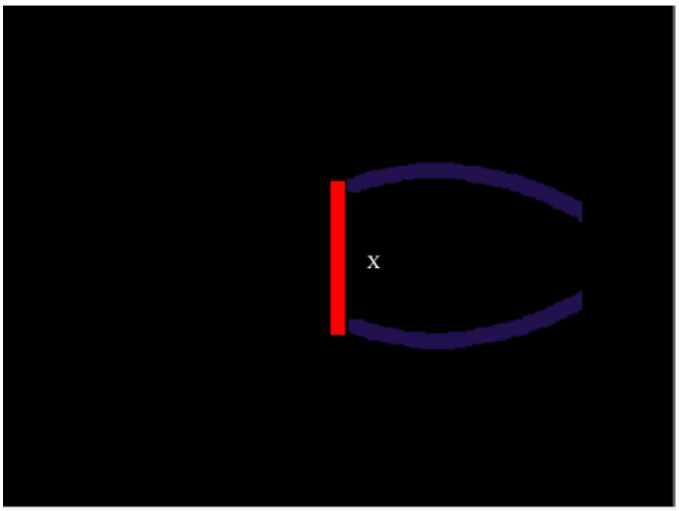

FIGURE 3

Schematic of a patient's perception if the blue arcs are perceived during stimulus presentation. A patient who is able to perceive the blue arc phenomenon with the right eye will notice blue arcing lights while the stimulus flashes. Note that if the arcs are perceived, they may not appear this shade of blue.

STATISTICAL ANALYSIS

First, descriptive statistics were used to study the relation between the probability of perceiving the blue arc entoptic phenomenon as a function of CDR, mean defect (MD), pattern standard deviation (PSD), and glaucoma hemifield test (GHT) for the right eye, left eye, and both eyes. Then logistic regression models of perceiving the blue arc entoptic phenomenon were created, accounting for demographic parameters (age, gender, and race) and ocular features (Snellen acuity, color vision, IOP, pupil size, lens clarity, presence or absence of any diabetic retinopathy, and presence or absence of age-related macular degeneration). In addition, the use of any medical therapy for glaucoma was also entered into the models as a binary covariate. Using the SAS software (Release 8.2; SAS Institute Inc, Cary, North Carolina), and adjusting for the above-mentioned covariates, the point estimate of the odds ratio (OR) and the accompanying 95% confidence interval (CI) were calculated for the relation between glaucoma-related attributes of interest (CDR, MD, PSD, and GHT) and the likelihood of perceiving the blue arc entoptic phenomenon. In multivariable analysis of the relation between CDR and likelihood of perceiving the blue arc entoptic phenomenon, CDR was coded as a continuous variable, where the effect size reflects the relative odds associated with a 0.1 unit increase in CDR. The variables PSD, MD, and GHT were not included in this model as they are correlated with CDR. Similarly, in models assessing the independent effects of PSD and of MD on perceiving the blue arc entoptic phenomenon, these global indices were also coded as continuous variables. For models assessing the relation between PSD and the ability to perceive the blue arc entoptic phenomenon, CDR and MD were excluded. Similarly, for models of the relation between MD and the ability to perceive the blue arc entoptic phenomenon, CDR and PSD were excluded. Finally, for models assessing the relation between GHT and the likelihood of perceiving the blue arc entoptic phenomenon, GHT was coded as a binary variable (either as abnormal or as normal/borderline) with CDR, MD, and PSD excluded as covariates.

RESULTS

Since the results were not materially different for right and left eyes, except where indicated, data are presented for the right eye only. Table 1 presents demographic factors distributed according to the ability to perceive the blue arc entoptic phenomenon in the right eye. The ability to perceive the blue arc entoptic phenomenon declined sharply with increasing age. African Americans were less likely to perceive the blue arc entoptic phenomenon compared to other ethnic groups. Table 2 displays the ocular characteristics that may affect psychophysical testing independent of glaucoma status distributed according to the ability to perceive the blue arc entoptic phenomenon in the right eye. The ability to perceive the blue arc entoptic phenomenon declined in subjects with miotic pupils and increasing lens opacity. All of these factors were accounted for in multivariable logistic regression analysis.

The mean CDR in the right eye of this cohort was 0.5 ± 0.2. Table 3 shows that a lower proportion of subjects with large CDR perceived the blue arc entoptic phenomenon when compared to subjects with smaller CDR. Using logistic regression modeling to control for demographics (age, race, and gender) and ocular characteristics (presence of glaucoma therapy, Snellen acuity, color vision, pupil size, IOP, media opacity, diabetic retinopathy, and macular degeneration), we found that CDR was an independent predictor of perceiving the blue arc entoptic phenomenon. Subjects with larger CDR in the right eye were less likely to perceive the blue arc entoptic phenomenon (OR=0.66 [95% CI: 0.53-0.83], $P<.001$). Specifically, each 0.1 unit increase in CDR was associated with a 36% reduced chance of perceiving the blue arc entoptic phenomenon. Older age ($P=.0016$) and increased nuclear or capsular opacity ($P=.03$) were also associated with reduced odds of perceiving the blue arc entoptic phenomenon (OR=0.94 [95% CI: 0.90-0.98] and OR=0.47 [95% CI: 0.23-0.94], respectively) in this model.

The average MD in the right eye was -2.6 ± 4.4 dB among subjects who completed Humphrey visual field testing. The majority of participants (78%, or 133 of 170 participants) had MD better than or equal to -4dB. Table 3 demonstrates that a much lower percentage of patients with large MD perceived the blue arc entoptic phenomenon when compared to patients whose MD was closer to

zero. No patient with a MD worse than -12 dB was able to perceive the blue arc entoptic phenomenon. Logistic regression modeling, controlling for other potential demographic and ocular determinants, indicates that MD is a strong independent predictor of perceiving the blue arc entoptic phenomenon ($P<.001$). For subjects with MD closer to zero, there was an increased likelihood of perceiving the blue arc entoptic phenomenon (OR=1.79 [95% CI: 1.40-2.28]). This model also revealed that older age ($P<.001$), reduced color vision on the Ishihara color plates ($P=.03$), and increased lens opacity ($P=.03$) were also associated with reduced ability to perceive the blue arc entoptic phenomenon. Reduced color vision remained associated with a reduced ability to perceive the blue arc entoptic phenomenon even after excluding subjects who were felt to have congenital dyschromatopsia (data not shown).

TABLE 1. DEMOGRAPHIC CHARACTERISTICS ACCORDING TO THE ABILITY TO PERCEIVE THE BLUE ARC ENTOPTIC PHENOMENON (BAEP) IN THE RIGHT EYE OF PATIENTS WITH AND WITHOUT GLAUCOMA

CHARACTERISTIC	N	% OF COHORT	% PERCEIVED BAEP
Age (years)*			
<40	15	7	87
40-49	41	20	80
50-59	45	22	73
60-69	49	24	59
70-79	36	18	36
80-89	16	8	6
Gender			
Male	107	53	64
Female	95	47	60
Race/ethnicity			
Caucasian	141	70	64
African American	34	17	53
Hispanic	15	7	66
Other	12	6	58

*Mean ± SD: 60 ± 14.

TABLE 2. OCULAR FEATURES ACCORDING TO THE ABILITY TO PERCEIVE THE BLUE ARC ENTOPTIC PHENOMENON (BAEP) IN THE RIGHT EYE OF PATIENTS WITH AND WITHOUT GLAUCOMA

FEATURE	N	% OF COHORT	% PERCEIVED BAEP
Pupil size (mm)			
1-2	30	15	40
3-4	89	44	61
5-6	40	20	78
7-8	43	21	68
Media opacity			
Clear	121	60	73
1+	52	26	52
2+	24	12	38
3+	5	2	20
Age-related macular degeneration			
Yes	11	5	37
No	191	95	63
Diabetic retinopathy			
Yes	5	2	40
No	197	98	63

The mean PSD for the right eye was 2.8 ± 2.5 dB among subjects who completed Humphrey visual field testing. The majority of these study participants (80%, or 142 of 170 participants) had a PSD ≤2 dB. Table 3 illustrates that a smaller percent of subjects with high PSD were able to perceive the blue arc entoptic phenomenon when compared to their counterparts with PSD closer to zero. After controlling for all ocular (except CDR, MD, and GHT, which are highly correlated with PSD) and demographic characteristics, PSD was also a strong independent determinant of perceiving the blue arc entoptic phenomenon ($P=.005$). For patients with higher PSD, there is a reduced likelihood of perceiving the blue arc entoptic phenomenon (OR=0.72 [95% CI: 0.57-0.91]). Again, more advanced age ($P=.003$) and increased media opacity ($P=.03$) were the only other factors associated with a reduced likelihood of perceiving the

blue arc entoptic phenomenon (OR=0.94 [95% CI: 0.90-0.98] and OR=0.46 [95% CI: 0.22-0.95]), respectively.

Finally, 44 of 170 subjects who had HVF testing had an abnormal GHT in the right eye. An abnormal GHT (vs a normal or borderline GHT) was associated with markedly reduced odds of perceiving the blue arc entoptic phenomenon (OR=0.25 [95% CI: 0.10-0.65]; *P*=.006) in multivariable analysis. As seen in other models, age (*P*=.0002) and media opacity (*P*=.02) were also associated with a reduced odds of perceiving the blue arc entoptic phenomenon.

TABLE 3. OPTIC NERVE AND VISUAL FIELD FEATURES OF THE COHORT DISTRIBUTED ACCORDING TO THE ABILITY TO PERCEIVE THE BLUE ARC ENTOPTIC PHENOMENON (BAEP) IN THE RIGHT EYE OF PATIENTS WITH AND WITHOUT GLAUCOMA

FEATURE	N	% OF COHORT	% PERCEIVED BAEP
Cup-disc ratio			
0.1-0.2	25	12	92
0.3-0.4	53	26	72
0.5-0.6	74	37	69
0.7-0.8	36	18	31
≥0.9	14	7	7
Mean defect (dB)*			
≥0	41	24	85
-0.1 to -4	93	55	54
-4.1 to -8	21	12	25
-8.1 to -12	10	6	10
<-12	5	3	0
Pattern standard deviation (dB)*			
0-2	105	62	68
2.1-4	37	22	46
4.1-8	17	10	18
>8	11	6	18

*Based on 170 subjects who had Humphrey visual field testing.

Using the patient as the unit of analysis and defining glaucoma as having an abnormal GHT in one or both eyes (N=170), the sensitivity and specificity of perceiving the blue arc entoptic phenomenon were 0.72 and 0.63, respectively. For all subjects (N=202), when glaucoma was defined as having a glaucomatous visual field defect (nasal step, nasal depression, arcuate defect, paracentral scotoma, temporal wedge, or abnormal GHT) on HVF or FDT in either eye, the sensitivity and specificity were 0.70 and 0.74, respectively. Interestingly, 32 of 34 subjects (94%) from the Comprehensive Ophthalmology Service, chosen because they had no risk factors for, or signs of, glaucoma were able to perceive the blue arc entoptic phenomenon in both eyes. Also, 21 of 24 subjects with ocular hypertension (88%) vs only 30 of 74 patients with a diagnosis of POAG (41%) were able to perceive the blue arc entoptic phenomenon in both eyes. Table 4 provides the distribution of perceiving the blue arc entoptic phenomenon according to glaucoma diagnosis.

TABLE 4. GLAUCOMA DIAGNOSIS OF THE COHORT DISTRIBUTED ACCORDING TO THE ABILITY TO PERCEIVE THE BLUE ARC ENTOPTIC PHENOMENON (BAEP)

GLAUCOMA DIAGNOSIS	N	% BAEP POSITIVE	
		OD	OS
Normal	34	94	94
Ocular hypertension	24	88	88
Normal-tension glaucoma suspect	14	100	93
Normal-tension glaucoma	16	63	50
Primary open-angle glaucoma	74	41	41
Secondary open-angle glaucoma	26	58	57
Narrow-angle and chronic angle-closure glaucoma	14	29	36

We found 10 patients (2 from the Comprehensive Ophthalmology Service and 8 from the Glaucoma Service) with congenital red-green color deficiency (9 of whom were male). We arbitrarily defined this congenital dyschromatopsia as an inability to identify at

least 50% of the Ishihara color plates in both eyes. When these subjects are excluded from analysis, increasing age, lens opacity, CDR, MD, PSD, and GHT remained as independent predictors of the ability to perceive the blue arc entoptic phenomenon ($P \leq .03$; data not shown). Furthermore, the sensitivity (0.69) and specificity (0.72) of our test to detect glaucoma were not significantly altered. Finally, while a reduced ability to read the Ishihara color plates was independently associated with a reduced likelihood of perceiving the blue arc entoptic phenomenon in one model, patients with red-green color blindness were able to perceive the blue arcs. Nine of 9 eyes with congenital dyschromatopsia who had CDR <0.6, MD <-2 dB, PSD <2 dB and normal GHT were able to perceive the blue arc entoptic phenomenon (Table 5).

TABLE 5. THE BLUE ARC ENTOPTIC PHENOMENON (BAEP) RESPONSE IN PATIENTS WITH CONGENITAL DYSCHROMATOPSIA ALONG WITH THEIR DEMOGRAPHIC AND OCULAR FEATURES

SUBJECT NO.	AGE (YEARS)	LENS GRADE	CDR	MD (DB)	PSD (DB)	GHT	BAEP
				OD/OS			
8	74	2+/0	0.6/0.9	0.67/-22.6	1.67/11.7	NL/Abnl	-/-
80	52	1+/1+	0.3/0.2	0/-1.84	1.17/1.48	NL/NL	+/+
102	79	0/0	0.7/0.6	-2.72/-1.34	3.47/1.76	NL/NL	-/-
104	50	0/0	0.3/0.3	1.33/1.6	0.98/1.2	NL/NL	+/+
105	36	0/0	0.6/0.6	-2.1/-2.06	2.22/2.0	Abnl/NL	-/+
125	80	3+/0	0.6/0.7	0.71/-2.03	1.23/2.0	NL/Abnl	-/-
137	65	1+/0	0.7/0.5	-3.3/-1.0	6.8/1.3	Abnl/NL	-/+
151	73	1+/1+	0.6/0.6	0.01/-0.63	1.6/1.69	NL/NL	+/+
172*	64	0.0	0.2/0.2	NA/NA	NA/NA	NA/NA	+/+
176*	44	0.0	0.4/0.3	NA/NA	NA/NA	NA/NA	+/+

Abnl, abnormal; CDR, cup-disc ratio; dB, decibels; GHT, glaucoma hemifield test; MD, mean defect; NA, not available; NL, normal; PSD, pattern standard deviation.
*Humphrey visual testing was not performed on subjects 172 and 176, as they were normal controls recruited from the comprehensive eye service.

DISCUSSION

Currently there are no electrophysiological or psychophysical tests that assess NFL function directly. Such tests would be useful particularly as researchers explore IOP-independent mechanisms to treat glaucoma. Furthermore, novel glaucoma detection tools may lead to alternative phenotypic definitions of the disease, which may hasten discovery of its pathophysiology. Since the blue arcs of the blue arc entoptic phenomenon have a shape that conforms exactly to NFL anatomy and may involve the blue-yellow opponency system, we were interested in studying the relation between perceiving this entoptic response and glaucoma damage. We purposefully designed a supratheshold test of the parafoveal area because it was simple, fast (<4 minutes per eye), inexpensive, and fixation-independent and we wanted to ascertain if testing for the blue arc entoptic phenomenon had any potential clinical utility in detecting glaucoma, a disease categorized by thinning of the NFL. We defined a clinic-based population of subjects with a spectrum of glaucomatous changes ranging from none to severe, but the majority of our subjects had mild or moderate damage. Increasing CDR, worsening MD, worsening PSD, and an abnormal GHT were associated with an inability to perceive the blue arc entoptic phenomenon in this cross-sectional analysis. Older age and media opacity were also found to be independent predictors of perceiving the blue arc entoptic phenomenon. These latter findings clearly limit the ability of the currently configured test to elicit the blue arc entoptic phenomenon as a glaucoma-screening tool. Increased media opacity and age also influence conventional psychophysical tests used to detect glaucoma. Specifically, increased age and cataract are associated with worsening of MD on HVF testing, but strategies to minimize the effect of these factors on detecting glaucomatous changes have been developed.[28-30]

Our data suggest that the current version of the test has potential clinical utility in selected patients with glaucoma, particularly in patients under age 60 with clear media. One feature of using the blue arc entoptic phenomenon that may make it uniquely suited to detect glaucoma is that it can be designed to test macular function. The stimulus used in our study assesses retinal function within the central 3 degrees of the visual field. Although central standard automated perimetry defects from glaucoma typically occur in the later stages, it is known that ganglion cell loss occurs centrally even early in the disease. Furthermore, standard automated perimetry does not assay central retinal sensitivity in a high throughput manner. Finally, the unique nature of the test described here (we are assessing whether an entoptic phenomenon related to the NFL is present and not whether a stimulus can be detected) may afford advantages for early disease detection. Desatnick and colleagues[31] found that in experimental nonhuman primate glaucoma, loss of central ganglion cells was present even in eyes with mild glaucomatous damage. Structural thinning of the perifoveal retinal thickness can be detected

in early glaucoma.[32] Functional defects lag behind structural loss in this region, likely because of the higher density of ganglion cells centrally.

In this study, there did not appear to be a strong correlation between location of visual field defects among glaucoma patients and the ability to perceive the blue arc entoptic phenomenon. In this study, 17 of 21 patients (81%) with paracentral visual field loss OD and 19 of 24 eyes (79%) with similar loss OS were unable to see the blue arc entoptic phenomenon. On the other hand, 17 of 23 right eyes (74%) and 25 of 41 left eyes (61%) with visual field defects not involving the central 5 degrees were unable to see blue arc images. These data suggest that our current test is assessing some unique aspect of macula function in glaucoma that is different than that assessed by standard automated perimetry.

The best theory for the psychophysical basis of the blue arc entoptic phenomenon is that it involves the blue-yellow opponency system. The efferent retinal ganglion cell axons for the blue-yellow receptive fields are certainly larger than those for the red-green system.[13,14] Quigley and colleagues[33] also found that blue signals travel in larger-diameter axons, which are more susceptible to damage from elevated IOP than smaller axons. In fact, short-wavelength automated perimetry (SWAP) was developed to take advantage of this fact.[20] In SWAP, blue light is projected onto a yellow background in various portions of the visual field. Interestingly, blue-yellow color vision was a good predictor of visual field loss in glaucoma suspects, whereas red-green color vision was not, perhaps because the smaller-diameter efferent retinal ganglion cells of the red-green system are more resistant to the glaucomatous process.[34,35] If the blue arc entoptic phenomenon is related to an intact and active blue-yellow system, it is interesting to note that this system is not restricted to the fovea.[36] In fact, it shows similar sensitivity and distribution to the achromatic vision as a function of retinal eccentricity. Interestingly, the author has been able to detect a blue arc entoptic phenomenon for a stimulus directed at the retina nasal to the disc and was able to visualize diffuse whitish arcs emanating toward the optic nerve. This suggests it may be possible to threshold the blue arc entoptic phenomenon as a function of retinal eccentricity to develop an entoptic visual field map, just as it is possible to measure retinal sensitivity with standard achromatic automated perimetry. More research is needed to determine whether perception of the blue arc entoptic phenomenon requires an intact blue-yellow opponent system.

The purpose of this study was to determine if eliciting the blue arc entoptic phenomenon has any clinical utility in detecting glaucoma. Since we studied a single suprathreshold stimulus in a 2-forced choice paradigm, we did not calculate receiver operator curves, but it is important to examine the discriminatory power of the blue arc entoptic phenomenon to detect glaucoma. While the sensitivity and specificity for our test was only approximately 70% in this study, several facts need to be kept in mind. First, 32 of 34 subjects from the Comprehensive Ophthalmology Service, chosen because they were normal with full and reliable FDT in both eyes, were able to perceive the blue arc entoptic phenomenon in both eyes. Other subjects labeled as not having glaucoma because their visual fields were normal (participants from the Glaucoma Service who were suspects for glaucoma on the basis of a positive family history for disease, suspicious cups, ocular hypertension, narrow angles, or occludable angles) may have preperimetric glaucoma, resulting in a reduction in specificity. With respect to sensitivity, only 1 of 14 patients with CDR of 0.9 OD was able to perceive the blue arc entoptic phenomenon in the right eye. That patient had normal-tension glaucoma with a normal GHT OD and abnormal GHT OS (OS also had a CDR = 0.9, but the patient could still see the blue arc entoptic phenomenon OS). Only 1 of 15 patients with MD >8 dB was able to perceive the blue arc entoptic phenomenon. This patient had significant glaucomatous optic neuropathy, and it is unclear why he was able to perceive the blue arc entoptic phenomenon. Finally, the sensitivity reported here for the use of the blue arc entoptic phenomenon to detect glaucoma compares favorably to values reported for matrix FDT perimetry (69%), standard automated perimetry (68%), and SITA SWAP (59%)[37]; however, the specificities for these tests were much higher than our test (>97%). Perhaps the lower specificity associated with our test relates to the fact that we did not know a priori that age and lens opacity might alter the abilities to detect the blue arcs.

Some discussion of how to build upon the current paradigm to study the blue arc entoptic phenomenon in the diagnosis of glaucoma is warranted, especially given the emerging evidence that the inferior macular arcuate fibers are particularly vulnerable to damage in early glaucoma.[38] First, a stand-alone platform that is custom-designed to detect the blue arc entoptic phenomenon as a function of retinal eccentricity allowing for a threshold response would be helpful so the inferior macular arcuate fibers could be targeted. Stimuli projected to this region would generate a blue streak and not a blue arc.[7] Only a limited number of retinal loci could be tested, as the blue arcs tend to fade with continued dark adaptation, but it would be appropriate to map out thresholds for the superior and inferior arcuate macula bundles separately. Furthermore, age-matched normative data could be generated for threshold stimuli that generate the blue arc entoptic phenomenon, and strategies could be developed to address the confounding effect of cataract.

There are several caveats about this study that merit discussion. First, assessment of the blue arc entoptic phenomenon is a subjective test like conventional perimetry, and it is possible that an inability to perceive the blue arc entoptic phenomenon may be simply because the blue arcs are not dramatic in nature. We purposefully limited this study to patients with reliable conventional perimetry results. More study is required to determine whether patients who are presumably normal but are poor testers on automated perimetry can perceive the blue arc entoptic phenomenon. Second, testers who were not masked to the ophthalmic characteristics of the subjects performed the assessments of the blue arc entoptic phenomenon. Every attempt was made by the testers to administer the test in an impartial fashion, but one cannot rule out tester bias as influencing the results. It should be pointed out, however, that multivariable analysis did reveal plausible determinants of the blue arc entoptic phenomenon, some of which were related to glaucoma and others that were not (lens opacity, for example). Future studies masking examiners to the ophthalmic characteristics of the patient would be useful. Third, the test of the blue arc entoptic phenomenon, as currently configured, has suboptimal sensitivity and specificity as a screening tool for glaucoma. The main goal of this work was to identify whether glaucoma features, such as CDR, were determinants of perceiving the blue arc entoptic phenomenon. Screening inclusion criteria (age cutoffs) or test modifications

would be needed before this version of the test was implemented in a general population. Fourth, we studied too few patients to determine the effect of congenital dyschromatopsia, diabetes, diabetic retinopathy, and age-related macular degeneration on the ability to perceive the blue arc entoptic phenomenon. More study on populations with these conditions who do not have glaucoma are needed. Finally, an inability to perceive the blue arc entoptic phenomenon may not be limited to patients with glaucomatous optic neuropathy. Patients with retinal disease, nonglaucomatous optic nerve disease, or higher visual pathway lesions may also demonstrate an inability to perceive the blue arc entoptic phenomenon.

CONCLUSION

The ability to perceive the blue arc entoptic phenomenon correlates with structural and functional changes associated with glaucomatous optic neuropathy. The ability to perceive the blue arc entoptic phenomenon is also dampened in older patients and in those with moderate cataract. In the future, a carefully designed computer-based test or smart phone application of central entoptic function may be a useful self-administered glaucoma-screening tool in selected populations. Such tools may be useful adjunctive instruments in telemedicine programs designed for the self-detection of glaucoma.

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