Clinical Application of Infrared-Light Microperimetry in the Assessment of Scotopic-Eye Sensitivity

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Purpose: The eye can see pulsed near-infrared (IR) radiation with the color corresponding to half of the wavelength used. Until recently, the technology required for measuring IR vision was confined to optical laboratories and was not studied clinically. The current investigation sought to determine the values for IR thresholds in a healthy population.

Methods: IR-light threshold was measured in 45 healthy participants, aged from 21 to 70 years. Ten patients with retinal pathology were included for comparison. Ocular media clarity was assessed with a straylight parameter. The sensitivity of dark-adapted eyes (expressed on a 0–26 dB scale) were tested using an IR microperimeter. The device consists of a femtosecond laser that emits 1045 nm light to project a stimulus at the retina.

Results: All participants were able to see the IR stimulus, which they perceived as green, and all performed the test. Measurements at seven locations revealed lower sensitivity at the fovea (15.5 dB) than in paracentral regions (18.2 dB). We noted a significant straylight increase with age. Although, in our study population, it was only a slight, -0.18 dB decline per decade of the average IR-sensitivity. The retinal-pathology group demonstrated impaired sensitivity to IR light.

Conclusions: We showed that IR-light sensitivity does not significantly decrease with age despite a straylight increase. A reference level for the IR threshold was proposed. The application of IR-light microperimetry can be extended to the assessment of retinal pathology.

Translational Relevance: IR-light microperimetry could be applied clinically to measure visual function.

Introduction

The human eye can perceive near-infrared (IR) light. In 1947, the limit of eye sensitivity was thought to be 1150 or 1200 nm¹; well beyond the visible range that ends at about 700 nm.² The boundary was pushed even further to 1350 nm³ and 1500 nm⁴ with the invention of an Nd:YAG laser. Although the perception of light at approximately 1050 nm was first reported as colorless when the source was a tungsten lamp,¹ later when the lamp was replaced with a pulsed laser source, it appeared green to many observers.³–⁷ Two mechanisms have been proposed to explain the perception of color in IR light. One is the emission of a photon with half of the fundamental (IR) wavelength in the process
of second-harmonic generation by the cornea or retinal tissue. However, a recent study has shown that the color vision results from two-photon absorption and photoisomerization of visual pigment in the retina, and no direct evidence of second-harmonic generation was found in that study.

Given that a different nonlinear process guides the color perception of pulsed IR laser light, there is conjecture that this technology might provide a diagnostic tool that measures a new visual-function parameter. We aimed to test the feasibility of IR-light sensitivity measurements in a clinical setting and establish the range of IR threshold in a healthy population. We also tested the IR-microperimetry in eyes with retinal pathology.

**Methods**

**Study Population**

The study protocol adhered to the tenets of the Declaration of Helsinki and was approved by the ethics committee of the University of Heidelberg. Written informed consent was obtained from all participants. Only subjects without ocular pathology, history of eye surgery (e.g. crystalline lens removal), or systemic disease who were at least 20 years old were eligible to take part in the normal population study. There was no upper age limit. The inclusion criteria were that a subject had a Snellen visual acuity (VA) of 0.8 or better, a hyperopic and myopic refractive error ≤ 4D, astigmatism ≤ 1.5D, and no pathological ocular media opacity (e.g. cataract or corneal scars). Only one eye was studied, which was chosen based on the criterion of a better VA. If, however, VA was identical in both eyes, a randomized selection was applied. The study population was divided by age into five groups, four of which included patients in the third to the sixth decade of life, and one group comprised of older patients. We recruited 10 or more subjects to each group except for the older group, in which there was a difficulty in finding subjects who could meet the inclusion criteria.

In addition to the distribution of the IR threshold in the healthy population, we studied the effect of retinal pathology. To this end, we included patients with diabetic retinopathy and age-related macular degeneration (AMD), who were recruited from the outpatient department of the Heidelberg University Eye Clinic. Patients with only one ocular condition were included. Although the refractive-error criterion had to be satisfied by all participants, the age and VA were not restricted in the eye-pathology group. In total, 10 participants were enrolled, 5 for each pathological condition.

**Study Protocol**

The subjects had received a comprehensive ocular examination by an ophthalmologist prior to being admitted to the study. The refractive error was corrected with trial glasses, and VA obtained using Snellen charts. To verify the subject’s eligibility, we performed a complete non-mydriatic slit-lamp evaluation of the anterior and posterior segments of the eye as well as optical coherence tomography (Spectralis; Heidelberg Engineering, Heidelberg, Germany). Retinal disease was classified in its severity by clinical grading; thus, diabetic retinopathy was graded from 0 (pathology absent) to 4 (proliferative diabetic retinopathy), and AMD was graded from 0 (no abnormalities) to 3 (advanced AMD). As a consequence of diabetic and senile miosis, and in contrast to the healthy subjects, the patients with retinal-disease performed the IR-vision test under pupil dilation using a mydriatic agent (Tropicamide, Mydriaticum Stulln; Pharma Stulln GmbH, Stulln, Germany). Optical-media clarity was quantified by light scattering measurement with a natural pupil using a C-Quant (Oculus Optikgeräte, GmbH, Wetzlar, Germany), which provides a straylight parameter expressed on a log scale as log(s). A young, healthy eye has a log(s) of 0.9, which naturally increases with age due to age-related changes to the crystalline lens. A normal 65-year-old eye has, on average, 1.2 log(s), but cataract causes a straylight elevation with values ranging from 1.37 to 1.67 log(s) depending on the type of cataract.

The experimental setup (Fig. 1) consisted of a femtosecond laser (HighQ-2; Spectra-Physics, CA) with a central wavelength of 1045 nm and 8.0 nm of full width at half maximum (63 MHz repetition rate and 250 fs pulse width). The laser power was converted to a Decibel Scale where 0 dB denoted the maximum (400 μW), and 26 dB denoted the minimum (1 μW) optical power. A Goldmann size-II stimulus with a diameter of 0.22° and a presentation time of 200 ms (ON) and 600 ms (OFF) was created by a high-speed scanning XY galvanometer mirror system, which was conjugated with the entrance pupil of the eye. The laser beam diameter (1/e²) at the cornea was 1.5 mm. The stimulus was projected at seven retinal loci, which included the fovea, 4 quadrants at 2° around the fovea (nasal, superior, temporal, and inferior), and 6° and 8° located temporally on the horizontal meridian (see Fig. 1). The position of the stimulus could be seen in fundus images recorded in real-time using integrated scanning laser ophthalmoscopy (SLO). Fixation was controlled manually by monitoring the SLO view and a pupil-preview camera (see Fig. 1). A 630-nm LED...
served as a fixation point, which was turned off while testing the central (foveal) sensitivity due to overlap. The fixation spot was overlaid on captured SLO images to enable the control of the patient’s steadiness of gaze. In addition, the eye’s position was monitored through the IR camera conjugated with the pupil plane. Images from the pupil camera were used to assess pupil size during measurements.

Following the ocular examination, each subject had been dark-adapted for 30 minutes before the IR vision test was performed. The visual threshold for IR light was determined using the method of adjustment, a psychophysical procedure, in which the participant gradually decreased the intensity of the stimulus until it was not detectable. The choice of this procedure may be considered unusual - rather than using forced-choice or staircase for example - but it was most appropriate because, at the outset of our study, the level of the IR light threshold in the population was unknown. In addition, given the lengthy nature of the experiment, the implementation of this method proved time-effective. Indeed, a recent study has shown that the use of the method of adjustment yields excellent repeatability of IR-light sensitivity measurements. In the current procedure, the light power was adjusted by rotation of a neutral-density filter (see Fig. 1), with the transmission gradually decreasing with the rotation angle. This was controlled by a subject’s mouse with a precision of 1 μW for each scroll-step (see Fig. 1). The test began with the strongest stimulus, and the subject continuously lowered the intensity until IR light was just not detectable. Once a patient confirmed the visibility threshold by a left-click, the stimulus intensity automatically increased threefold from the recorded (threshold) value. Then, the procedure was repeated until five measurements were performed at one eccentricity. As soon as testing was completed at that locus, the strongest stimulus reappeared, and sensitivity was assessed at another retinal location following the same method. The procedure terminated automatically once 35 IR threshold measurements per eye were made.

The IR-threshold measurements and SLO imaging were performed in compliance with international laser safety standards (ANSI Z136.1 and EN 60825-1). An internal power meter was implemented that measured the light power continuously during the measurement protocol to ensure the safety of all participants.

**Statistical Analysis**

Normality was assessed using the Kolmogorov-Smirnov test and a visual inspection of Q-Q plots. For the reason that not all data were normally distributed, nonparametric statistical methods were used. The
average IR threshold was compared among the four decades of life, and between different retinal loci using the Kruskal-Wallis test. A post hoc multiple comparison test was done with the Bonferroni method. Quantile regression was used to perform regression analysis. Because of unequal gender distribution, the study outcomes of female and male participants were compared with the Mann-Whitney U test. All visual-quality parameters were presented as the median (interquartile range). The data analysis was carried out in MATLAB (Mathworks, Inc., New York, NY) and R software (R Foundation for Statistical Computing, Austria, Vienna).

**Results**

We enrolled 45 healthy participants (45 eyes) with the median age of 44.1 years (31.6–53.1 years), with the range 21.4 to 70.3 years. The group was predominantly female (76%) and Caucasian (93%) and Asian (7%). Snellen VA was 1.0 (1.0–1.25) with the spherical equivalent of 0.50 (0–1.28) diopter (D), and scotopic pupil size of 6.8 (6.0–7.4) mm. The straylight parameter significantly increased with age \((P > 0.001)\) in the healthy population with a rate of 0.06 log unit per decade and had the median value of 0.92 log(s) (0.85–1.01 log[s]).

The retinal-disease group consisted of Caucasian patients with the median age of 74.8 years (66.9–79.3 years). Of the 10 patients, 2 were women. The pathology group had Snellen VA of 0.67 (0.5–0.8) with a spherical equivalent of zero Ds (-1.0 to 0.0 Ds). The straylight value was 1.21 log(s) (0.80–1.27 log[s]), and the pupil size was 6.2 mm (5.8–6.9 mm). Grade 3 was identified in all patients with AMD except one who had grade 2. Two eyes in the diabetic-retinopathy group were classified as grade 2; in the remaining cases, grades 1, 3, and 4 were noted.

All subjects perceived the stimulus as green. The IR-sensitivity of the healthy and retinal-disease group was 17.9 dB (17.0–19.1 dB) and 11.5 dB (9.6–12.0 dB), respectively (Fig. 2). The sensitivity level as a function of age in the healthy population was derived for the 50th percentile (see Fig. 2). The reference formula reads:

\[
\text{Average sensitivity} = -0.018 \cdot \text{Age} + 18.8 \; [\text{dB}]
\]

The age slope shows a decrease of -0.18 dB per decade; however, it was not statistically significant \((P = 0.48)\). Likewise, the difference between the age groups was not statistically significant \((P = 0.80, \text{Kruskal-Wallis})\). The Table details the results obtained for the four decades of life.

Figure 3 presents the IR thresholds measured at the seven locations of healthy eyes. The Kruskal-Wallis test revealed the statistically significant difference among the seven positions. However, the post hoc analysis showed that only the foveal sensitivity (15.5 [14.3–16.8] dB) differed from those measured at the other retinal locations (18.2 [16.9–19.9] dB) with \(P < 0.001\) in all but
one comparison (fovea vs. 8° temporal), which showed the $P$ value of 0.003. The relationship among the IR threshold and the other visual-quality metrics, namely, VA and straylight, was not statistically significant with $P = 0.31$ and $P = 0.46$, respectively. The comparison between the female and male subjects within the healthy population did not reveal significant differences in age ($P = 0.51$), spherical equivalent ($P = 0.27$), VA ($P = 0.14$), straylight ($P = 0.10$), and IR sensitivity ($P = 0.87$).

Discussion

We demonstrated that IR radiation is perceived as visible light, and the visibility threshold of the dark-adapted eye to the IR light can be assessed in a clinical setting. The IR sensitivity threshold for healthy eyes was determined, which can be used in future clinical studies to assess the effect of various eye conditions on IR-light perception.

Griffin et al. studied IR-light perception up to 1000 nm at the fovea and 1050 nm at 8° in the superior quadrant of the retina with a tungsten lamp and IR filters. They found that the peripheral retina is more sensitive to IR light than the fovea in a dark-adapted eye, which is in agreement with the results of the current study. The spectral sensitivity curve provided by Griffin et al. was later revised by Walraven and Leebeeke, who proposed a correction factor for the light transmittance of water in the IR range. Van den Berg and Spekreijse have shown that pure water absorption is a good approximation of the light transmittance of the ocular media in the IR region. Based on the absorption coefficients tabulated in that study, we estimated that the light transmittance of an average 23.44 mm-long eye at 1045 nm is about 71%. Although, in this study, we did not measure the axial length, a ±2.5 mm, difference found between longer (myopic) and shorter (hyperopic) eyes would account for a mere ±2.6% change in IR-light transmission. Griffin et al. concluded that the IR stimuli were perceived as colorless, but with the invention of laser technology, the appearance of color in response to IR radiation was reported. Sliney et al. studied the visual perception of a 1060 nm and 1064 nm laser source. They found that the perception of color changed with time exposure, as for a 0.1 second pulse, the laser light appeared red, but for shorter IR pulses it was seen as white, green, or blue. However, a 8° circular stimulus was always green, which was confirmed by our results but for a smaller (approximately 0.22°) stimulus and a fixed 250 fs pulse. This color perception was later studied in detail by Dmitriev et al. in a range between 800 nm and 1355 nm and most recently by Palczewska et al. from 950 nm to 1200 nm. In those studies, the perceived color generated by pulsed IR laser light was matched with the perception of the visible light. Those papers demonstrated that the perceived color does not precisely follow the frequency-doubled wavelength and that the IR radiation at about 1045 nm could be seen as green. The latter is in line with our findings.

Although this study was not specifically designed to ascertain the spectral sensitivity of the photoreceptor mechanisms mediating IR vision, the perception of a 1045-nm pulsed laser beam as green, suggests M- and L-cone activation. Furthermore, recent publications confirm that both cones and rods play a role in this process. Spectrally sensitive measurements in wild type and rod transducing-α-subunit knock-out, Gnat1-/-, mouse photoreceptors, and in primate L- and M-cones demonstrated that mammalian cones and rods can be activated by IR light by a two-photon excitation. The color-matching experiment by Palczewska et al. provided further evidence for the existence of cone-mediated IR vision and was confirmed by objective tests with rhodopsin and green cone pigment. That experiment showed that bleaching with a pulsed 1000-nm laser was reversible after adding 11-cis-retinal; thus, activation of rods and at least green cones was feasible. Moreover, a subject with documented autosomal cone-mediated recessive achromatopsia, perceived the pulsed IR beam. In another paper, Rumiński et al. showed that, despite green color perception, scotopic eye sensitivity differs between IR and visible light. Furthermore,
they demonstrated retinal topographic data obtained with both 522.5- and 1045-nm wavelengths showing decreased IR sensitivity as compared to visible light by 0.410^3 in the fovea center and 3.310^3 in the perifovea. In Figure 3, we also observed that sensitivity increases beyond the fovea, which is consistent with the results by Rumiński et al. who reported a steep increase in macular sensitivity as the stimulus moved from the center to 4º. In that study, however, measurements beyond 5º eccentricity were not performed. Although publications on one-photon rod-mediated vision revealed a gradual increase of sensitivity with eccentricity, we found that the differences between parafoveal responses were not statistically significant. The cone contribution to IR vision, which results in green color perception, may be a potential explanation for the flattening of the sensitivity as a function of retinal eccentricity. Thus, our results and those presented in the literature imply that both cones and rods are effective in mediating IR vision.

The latest explanation of the mechanism of the direct isomerization of the photopigment in photoreceptors by two-photon absorption of IR light provided by Palczewska et al. confirmed that this process differs from normal visual perception. Therefore, one can propose a new parameter to assess retinal function, which has the potential to be used in the assessment of eye pathology. To test the usefulness of IR microperimetry in the evaluation of retinal disorders, we recruited 10 patients with diabetic retinopathy and AMD and asked them to perform the test. We found that the absolute threshold of the eyes with retinal pathology was decreased compared to that of the healthy population by 6.4 dB. Nitalla et al. reported compromised retinal sensitivity in diabetic-retinopathy eyes measured in white light. They found that at 2º from the fovea, sensitivity was lower by 5.1 dB than that of normal controls. Wu et al. also demonstrated decreased visible-light sensitivity in patients with AMD by 2.4 dB in a matched comparison with healthy subjects. Those results from the literature agree with our preliminary findings. However, the current comparison was performed on a limited number of retinal disease participants whose age range did not correspond precisely with that of the healthy population. In addition, one may wonder about the impact of pupil dilation on the IR-threshold. Although, the pupil size of the diseased patients was still smaller by 0.6 mm than that of the healthy ones. Further research is required to confirm the potential of IR-light microperimetry to detect retinal disorders.

The age effect on scotopic sensitivity was measured with the 1045-nm laser light, which was seen as green. Although the visual sensation corresponds to the perception of light having approximately half of the fundamental wavelength (i.e. 522.5 nm), fovea sensitivity to IR light is ninefold lower than to green light, as discussed earlier. This must be realized in making comparisons with studies in the literature where solely visible light was used. Hammond et al. measured the visibility threshold in patients aged 20 to 65 years old by projecting a 550-nm stimulus at only one retinal locus (6º temporally), as an earlier study had shown that the sensitivity loss with age does not differ with eccentricity. This finding was confirmed by a later study on a larger population. Hammond et al. did not find a significant decrease in scotopic sensitivity in older patients, which was, on average, 0.02 log unit per decade. However, nicotine usage was found to be a confounding factor. Although, in that study, a larger (2.8º) stimulus and a 550-nm light source were used, our results showed a similar trend with a loss of 0.018 log unit (0.18 dB) for each decade. Pulos et al. assessed the threshold of the dark-adapted eye at 6 retinal positions with a 1º circular pattern at 460 nm, 490 nm, and 580 nm. Healthy subjects were at the age of 19 to 61 years. Following correction for the crystalline lens density, pupil size, and the macular pigment absorption, they found a nonsignificant sensitivity loss of 0.05 log unit within a 1º region independent of the wavelength used.

Both studies were later criticized by Jackson et al. for lacking the comprehensive retinal-health assessment. Jackson’s group studied the change of photopic and scotopic eye sensitivity with age. They allocated subjects into age groups ranging from the 20s to 80s and tested the sensitivity threshold using a 1.7º (Goldmann V) stimulus with a wavelength of 600 nm and 500 nm for photopic and scotopic conditions, respectively. Jackson et al. demonstrated a 0.04 and 0.08 log unit loss of sensitivity, indicating a more rapid decline of rod-mediated vision with age. In this study, the decrease of the scotopic sensitivity was four-times lower than that found by Jackson et al. One explanation for this discrepancy may be the difference arising due to the property of light used in this study (1045 nm) and the study by Jackson et al. (500 nm). In addition, the difference in the population age range makes the direct comparison difficult, as in Jackson’s group, the age spanned from the 20s to 80s. In this study, however, it was 20 to 60 years (with only 3 older subjects), which may be considered a limitation of the current paper. More research is needed to determine an IR threshold in the elderly population.

In studies on scotopic sensitivity, lens density has typically been accounted for by the estimation of the individual parameter to correct for intersubject variability in lenticular absorption. In the current
study, despite a significant increase of lens density with age, which was quantified by measuring ocular stray-light, a correction was not required as the crystalline lens absorption for longer wavelengths is negligible. The limiting factor of macular pigment absorption has also often been taken into account in visible-light sensitivity measurements. However, a minimal photo-absorption of the macular pigment may be expected with the application of IR light, which may also prove advantageous. Another factor affecting eye sensitivity measurements is the natural pupil size, which may decrease during testing due to pupillary reflex. A recent study has shown that the magnitude of the pupillary contraction is 1.5-fold higher in 520 nm than short-pulsed 1040-nm light in a similar setup, as described here. Although we did not administer mydriatic agents in the healthy group, their pupil diameter, on average, was nearly 4.5-fold larger than the laser beam during testing. In this study, only 2 subjects had the pupil size below 5 mm (i.e. 4.7 and 4.8 mm), which was considered by Sloan the minimum size that does not influence the determination of the visual threshold. Later, Herse demonstrated the lack of significant differences in retinal sensitivity measured with 3- and 8-mm pupils at various eccentricities. Wood et al. reported that the pupil size within the standard range does not influence sensitivity outcomes. The conjugation of the laser scanners with the pupil plane and the assessment of centrally located retinal loci may also limit the impact of pupil size on the current results. Although the use of IR light may overcome some of the limitations of visible light, IR microperimetry is also affected by age-related nonpathological changes at the site of the retina. Retinal factors that may cause the impairment of scotopic sensitivity has been discussed in the review by Owsley. The presence of cataract has the potential to lower retinal sensitivity further by approximately 2.7 to 3.5 dB, which was independent of the cataract classification. An earlier study on standard automated perimetry appears to confirm those conclusions. The application of IR microperimetry in such cases might prove beneficial. Rumiński et al. studied the impact of lens opacification on the visibility threshold measured with 522.5 nm and 1045 nm. They inserted postmortem crystalline lenses in the optical path of their device and performed the sensitivity test. Rumiński et al. found that the increase of the 522.5-nm threshold was 2.3 to 2.7 times that of IR light. They also demonstrated a better penetration of IR light objectively through turbid media compared to visible light. This may suggest that IR microperimetry is less affected by lens opacity than one that uses visible light. Although their results are promising, further research is required to confirm these findings clinically.

In conclusion, we demonstrated that a pulsed IR laser light is seen as visible, which conforms to historical data. For the first time, however, this test was performed in a clinical setting on a well-defined population. The IR-light sensitivity threshold is a new parameter that provides information on retinal function. As IR light has higher transmission than visible light through (turbid) ocular media, IR microperimetry has the potential to improve sensitivity testing in eyes with straylight elevation due to, for example, early cataract. The sensitivity of the human eye to IR radiation is much lower than it is to visible light, hence, this novel approach may also prove advantageous in the detection of retinal disorders. However, more research is needed to confirm the applicability of IR-light microperimetry in the detection and functional assessment of retinal pathology and the impact of lens opacity on the IR threshold. The data we report for the healthy population can serve as a reference in those future studies.

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