Retinal Temperature Increase during Transpupillary Thermotherapy: Effects of Pigmentation, Subretinal Blood, and Choroidal Blood Flow

Michael S. Ibarra,[1] *Jason Hsu,*[1] *Naureen Mirza,*[2] *I-Hui Wu,*[1] *Gui-shuang Ying,*[1] *Martin A. Mainster,*[3] *and Michael J. Tolentino*[1,2]

Purpose. To study the risk of adverse events in transpupillary thermotherapy (TTT) for age-related macular degeneration by measuring how laser-induced retinal temperature increase is affected experimentally by subretinal blood, choroidal blood flow, and chorioretinal pigmentation.

Methods. An ultrafine thermocouple technique was developed to measure retinal temperature increase during TTT in albino and pigmented rabbit eyes. TTT was performed with 60-second, 0.78-mm spot size, 810-nm infrared diode laser exposures with power settings ranging from 50 to 950 mW. Intraretinal and subretinal temperature increases were measured in pigmented and albino rabbits, with or without subretinal blood and choroidal blood flow.

Results. Threshold power settings for visible lesions in albino and pigmented rabbits were 950 and 90 mW, respectively, corresponding to retinal temperature increases of 11.8°C and 5.28°C, respectively. Power settings required to produce threshold lesions in albino rabbits caused retinal temperature increases in pigmented rabbits that were five times higher than in the albino rabbits. Temperature increases in albino rabbits were 1.5 times higher with subretinal blood than without it. Choroidal blood flow generally did not affect measured retinal temperature increases.

Conclusions. The results confirm prior theoretical recommendations that clinicians should consider decreasing TTT power settings in darkly pigmented eyes and proceed with caution in those with subretinal hemorrhage or pigment clumping. (*Invest Ophthalmol Vis Sci.* 2004;45:3678–3682) DOI:10.1167/iovs.04-0436

Transpupillary thermotherapy (TTT) was first used to treat intraocular tumors in 1995[1,2] and later to treat choroidal neovascularization (CNV) in age-related macular degeneration (AMD) in 1999.[3,4] Additional studies have suggested that TTT is useful for closing CNV lesions and improving or stabilizing visual acuity in AMD.[5–8] Prospective controlled clinical trials evaluating the efficacy of TTT for CNV in AMD are under way in the United States, Germany, and Japan.[9]

In TTT for CNV, infrared 810-nm diode laser radiation is used in a 60-second exposure, large spot size, low irradiance, and subvisible end point photocoagulation protocol.[3] Heat conduction during this lengthy chorioretinal laser exposure spreads the laser-induced temperature increase from light-absorbing pigmented tissues to nonpigmented tissues, producing reasonably uniform axial temperature distributions throughout the neural retina, retinal pigment epithelium (RPE), and choriocapillaris.[10–16] Although therapeutic mechanisms for retinal photocoagulation are not completely understood, it is believed that TTT causes less intraoperative neural retinal damage than conventional short-exposure, high-irradiance photocoagulation protocols.[16–18] To avoid over- or undertreatment of the retina, thermal dosimetry would be helpful.[19–22] However, noninvasive techniques for monitoring retinal temperature increases during clinical retinal photocoagulation are not currently available.[16,23]

Complications of TTT (Wren SM, et al. *IOVS* 2004;45:ARVO E-Abstract 5132),[6,23–27] photodynamic therapy,[29–35] and conventional short-pulse photocoagulation[35–42] (Do DV, et al. *IOVS* 2003;44:ARVO E-Abstract 1104) have included macular infarcts, RPE tears, and intraretinal hemorrhages. Modulating treatment intensity may help reduce these complications. Although thermocouple retinal temperature measurements have been performed previously, in these studies, small spot laser exposures were used in experimental animals with normal choroidal circulation and without subretinal hemorrhage.[43–46] We developed a thermocouple technique to measure retinal temperature increase during TTT in rabbits and studied how chorioretinal pigmentation, subretinal hemorrhage, and choroidal circulation affect thermal response and therefore the potential risk of adverse events in clinical applications of TTT.

Methods

Animals

We studied 17 eyes of nine New Zealand albino rabbits and 14 eyes of seven Dutch belted pigmented rabbits. All animal procedures were performed in accordance with the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research. Rabbits were anesthetized by intramuscular injection of preanesthetic acepromazine (1 mg/kg) followed by ketamine (20 mg/kg) and xylazine (2 mg/kg). Rabbit eyes were locally anesthetized with 1 drop of 0.5% proparacaine hydrochloride ophthalmic solution. Dilation of pupils was achieved with 1 drop each of 2.5% phenylephrine hydrochloride ophthalmic solution and 1% tropicamide ophthalmic solution. A quartz vitrectomy contact lens (OLV-3; Ocular Instruments, Bellevue, WA) was sutured to the conjunctiva to view the posterior pole of the fundus and counterbalance the minimizing effect of the rabbit's eye. Animals were euthanatized with ketamine and xylazine before the effects of TTT were evaluated in the absence of choroidal blood flow.

From the [1]Department of Ophthalmology, Scheie Eye Institute, and the [2]F. M. Kirby Center for Molecular Ophthalmology, University of Pennsylvania, Philadelphia, Pennsylvania; and the [3]Department of Ophthalmology, University of Kansas Medical School, Kansas City, Kansas.

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Corresponding author: Michael J. Tolentino, Scheie Eye Institute, Department of Ophthalmology, University of Pennsylvania, 51 North 39th Street, Philadelphia, PA 19104; mtolent95@aol.com.

TABLE 1. Comparison of Retinal and Subretinal Temperature Increases from Baseline in Albino and Pigmented Rabbits during TTT

Power Setting (mW)	Mean (SE) of Temperature Change		Difference (SE)	95% CI	*P*
	Retinal	Subretinal			
Albino group					
90	0.84 (0.19)	0.69 (0.17)	0.15 (0.33)	−0.50–0.79	0.66
200	1.88 (0.29)	1.29 (0.15)	0.59 (0.38)	−0.16–1.34	0.13
400	4.58 (0.70)	3.44 (0.44)	1.14 (0.50)	0.17–2.11	0.02
600	7.44 (1.19)	6.64 (0.76)	0.80 (0.82)	−0.81–2.41	0.33
800	9.42 (1.49)	8.75 (0.19)	0.67 (1.42)	−2.12–3.47	0.64
850	9.92 (1.23)	10.4 (0.32)	−0.50 (1.15)	−2.76–1.76	0.67
900	10.7 (1.02)	10.8 (0.24)	−0.11 (0.92)	−1.91–1.69	0.91
950	11.8 (1.00)	12.3 (0.37)	−0.51 (0.86)	−2.19–1.17	0.55
Combined	7.10 (0.81)	6.80 (0.22)	0.29 (0.65)	−0.97–1.56	0.65
Pigmented group					
50	2.18 (0.13)	1.94 (0.27)	0.24 (0.30)	−0.35–0.82	0.43
60	2.82 (0.26)	2.27 (0.14)	0.55 (0.35)	−0.13–1.23	0.12
70	3.35 (0.26)	3.23 (0.20)	0.13 (0.26)	−0.38–0.64	0.63
80	3.88 (0.21)	4.08 (0.47)	−0.20 (0.42)	−1.02–0.62	0.63
90	5.28 (0.28)	4.80 (0.80)	0.48 (0.76)	−1.00–1.96	0.53
Combined	3.42 (0.18)	3.19 (0.31)	0.24 (0.38)	−0.51–0.98	0.53

From GEE, with the intereye correlation of measurements in same rabbits adjusted. Temperature changes and differences are in degrees Celsius.

Photocoagulator

We used a modified 810-nm slit lamp diode laser photocoagulator (IRIS Medical OcuLight SLx photocoagulator; Iridex Corp., Mountain View, CA) and 60-second exposures throughout our study. The photocoagulator spot size setting was 0.8 mm for all lesions, producing a 0.78-mm retinal spot size in a rabbit eye with the quartz vitrectomy contact lens. Power settings ranged from 50 to 950 mW. Each of the 17 eyes from the albino rabbits had eight laser treatments performed with power settings at 90, 200, 400, 600, 800, 850, 900, and 950 mW. Similarly, each of the 14 eyes from the pigmented rabbits had nine laser treatments performed with power settings at 50, 60, 70, 80, 90, 200, 400, 600, and 800 mW. Within each eye, a different location was used for each power setting, with the lowest power treatment occurring first and working up to the highest power treatment.

Temperature Monitoring

We made a pars plana sclerotomy with a microvitreoretinal blade in each rabbit eye. A 36-gauge ultrathermocouple (Omega Engineering, Inc., Stamford, CT) was inserted through the sclerotomy and advanced until the tip reached the retinal inner limiting membrane at the posterior pole. Thermocouple readings at that location will be referred to as retinal temperature measurements. For subretinal measurements, the thermocouple tip was inserted through the sclerotomy and then through a peripheral retinotomy. From this peripheral location, the thermocouple was advanced in the subretinal space to the posterior pole. No pigment accumulation was visibly apparent on the tip of the probe. In addition, no complications, such as hemorrhages or secondary retinal elevation, occurred during subretinal thermocouple placement. Real-time temperature measurements were obtained by placing the tip adjacent to the laser spot as TTT was delivered. The thermocouple was connected to a microcomputer that recorded temperature changes. During each 60-second laser exposure, a temperature measurement was taken each second for a total of 60 temperature readings. The mean of these readings was used for the data analysis. For eyes into which subretinal blood was injected, the tip was placed on the retinal surface only.

The effects of choroidal blood flow were determined by measuring retinal temperature increase during TTT in the right eye of seven living rabbits (three albino and four pigmented). Temperature measurements were then compared to those taken during TTT in the left eye of the same rabbit immediately after euthanasia.

Subretinal Blood Placement

We used a transscleral approach to insert a 27-gauge needle under the retina of six albino rabbit eyes under corneal contact lens visualization. Autologous blood (0.25 mL) obtained from an ear vein was injected into the subretinal space. Retinal temperature increase was then recorded as TTT was applied to the area of subretinal blood.

Statistics

Because multiple temperature readings were recorded at each power setting, we performed descriptive analyses by calculating means and standard errors of temperature change from baseline. To examine differences in laser-induced temperature increases between either living and euthanatized rabbits or retinal and subretinal space, linear mixed models were fitted with the intereye correlation of temperature changes from the same rabbits accounted for by the generalized equation estimates (GEE) approach. Comparisons of temperature change in albino versus pigmented rabbits and in the presence versus the absence of subretinal blood were also performed with GEE. All data analyses were performed on computer (SAS 8.0; SAS Institute, Inc., Cary, NC).

RESULTS

We used the same 60-second exposure and 0.78-mm retinal spot size on all lesions. TTT power required for threshold faint retinal graying was 950 mW in albino and 90 mW in pigmented rabbit eyes, corresponding to mean temperature increases of 11.8°C in albino and 5.28°C in pigmented eyes.

At each power setting and overall, we found no significant difference between the retinal and subretinal temperature increases in either albino ($P = 0.65$) or pigmented ($P = 0.53$) eyes. In albino eyes, mean temperature change with power settings ranging from 90 to 950 mW was 7.1°C for retinal and 6.8°C for subretinal measurements (Table 1). In pigmented eyes, mean temperature change with power settings from 50 to 90 mW was 3.42°C for retinal and 3.19°C for subretinal measurements (Table 1).

When the higher power settings needed for albino eyes (90–800 mW) were applied to pigmented eyes, the retinal temperature increase in pigmented eyes was at least five times

TABLE 2. Comparison of Retinal Temperature Increase in Albino and Pigmented Rabbits under Identical Power Settings during TTT

Power Setting (mW)	Mean (SE) of Temperature Change		Difference (SE)	95% CI	*P*
	Albino (n = 8 eyes)	Pigmented (n = 6 eyes)*			
90	0.97 (0.32)	4.81 (0.41)	−3.83 (0.52)	−4.84 to −2.82	<0.0001
200	2.13 (0.47)	15.2 (0.51)	−13.1 (0.70)	−14.4 to −11.7	<0.0001
400	4.22 (0.72)	30.1 (2.79)	−25.9 (2.88)	−31.5 to −20.2	<0.0001
600	5.91 (0.81)	37.1 (3.30)	−31.2 (3.40)	−37.9 to −24.5	<0.0001
800	7.77 (0.75)	46.1 (4.47)	−38.4 (4.53)	−47.2 to −29.5	<0.0001

Data are as in Table 1.
*n = 10 eyes for the power setting = 90 mW.

greater than in albino eyes (Table 2). This difference was statistically significant at all power settings ($P < 0.0001$).

Albino eyes with and without injected subretinal blood were then treated with TTT powers ranging from 90 to 950 mW. The temperature increase was at least 1.5 times greater in the presence of subretinal blood (Table 3). This difference was statistically significant ($P < 0.0001$) at TTT powers ranging from 200 to 950 mW.

We also compared TTT-induced temperature increases with and without choroidal blood flow. Choroidal blood flow did not affect retinal temperature increase in pigmented eyes at TTT powers between 50 and 90 mW or in albino eyes at TTT powers between 90 and 800 mW and at 950 mW. We found a statistically significant difference in retinal temperature increase in albino eyes, with and without choroidal blood flow, at TTT powers of 850 and 900 mW (Table 4).

DISCUSSION

The retinal temperature increase during laser photocoagulation is proportional to retinal power density (irradiance or laser power per unit area) with a particular spot diameter, exposure duration, wavelength, and fundus pigmentation.[10,14,47] The primary light-absorbing chorioretinal pigment is melanin.[14,15,48] Lightly pigmented tissues are less effective at converting laser energy into heat energy and temperature increase than densely pigmented tissues.[47,48] Longer laser wavelengths, such as krypton red (647 nm) or diode infrared (810 nm) are absorbed less effectively by melanin compared with shorter wavelengths such as argon green (514 nm). As a result, longer wavelengths penetrate deeper into the choroid.[48] Similarly, any given clinical photocoagulation wavelength penetrates the choroid more deeply in lightly pigmented than in densely pigmented tissues.[15,48]

A visible lesion occurs when laser light is absorbed by RPE and choroidal melanin, thereby increasing the temperature of these pigmented tissues. Heat conduction spreads this temperature increase to the overlying neural retina, which loses its transparency and scatters ophthalmoscopic light back toward observers.[48] This backscattered light may have a whitish or grayish color depending on the treatment site's spectral reflectance and absorption.

We found that the mean temperature increase needed to produce a visible TTT lesion was 11.8°C in albino and 5.28°C in pigmented rabbit eyes. Therefore, visible threshold is an unreliable temperature indicator. In addition, these results should be interpreted in light of the fact that tissue laser damage is determined by its temperature history.[49] Because we used the same spot size and exposure duration for all lesions, we expected similar threshold temperature increases if the same amount of damage was occurring in both albino and pigmented eyes. However, this did not happen for two reasons. First, the laser-induced lesions are deeper and more dependent on hemoglobin absorption in albino than pigmented eyes.[48] Second, laser lesions are harder to detect in lightly pigmented tissues because there is less contrast between backscattered light from the neural retina and light from underlying pigmented tissues. As a result, to produce visible threshold lesions, we needed 950 mW in albino eyes but only 90 mW in pigmented eyes.

Earlier retinal thermocouple studies confirmed the accuracy of computer models for calculating retinal temperature increases from laser radiation absorption.[10,43–47] However, they did not examine differences in retinal temperature increase

TABLE 3. Comparison of Retinal Temperature Change in the Presence and Absence of Subretinal Blood in Albino Rabbits under Identical Power Settings during TTT

Power Setting (mW)	Mean (SE) of Temperature Change		Difference (SE)	95% CI	*P*
	Absent (n = 8)	Present (n = 6)			
90	0.97 (0.32)	1.44 (0.09)	−0.47 (0.33)	−1.12 to 0.19	0.1600
200	2.13 (0.47)	3.36 (0.29)	−1.23 (0.55)	−2.31 to −0.16	0.0200
400	4.22 (0.72)	7.77 (0.27)	−3.55 (0.77)	−5.05 to −2.04	<0.0001
600	5.91 (0.81)	12.5 (1.33)	−6.59 (1.56)	−9.64 to −3.54	<0.0001
800	7.77 (0.75)	18.1 (1.42)	−10.3 (1.60)	−13.4 to −7.16	<0.0001
900	9.05 (0.57)	22.8 (0.33)	−13.7 (0.66)	−15.0 to −12.4	<0.0001
950	9.97 (0.61)	22.1 (1.18)	−12.1 (1.33)	−14.7 to −9.48	<0.0001

Data are as in Table 1.

TABLE 4. Comparison of Retinal Temperature Change in the Presence and Absence of Choroidal Blood Flow in Albino and Pigmented Rabbits during TTT

Power Setting (mW)	Mean (SE) of Temperature Change		Difference (SE)	95% CI	*P*
	Alive	Dead			
Albino group					
90	0.85 (0.17)	0.68 (0.09)	0.17 (0.22)	−0.27 to 0.60	0.45
200	1.85 (0.27)	1.32 (0.07)	0.53 (0.30)	−0.06 to 1.12	0.08
400	3.72 (0.49)	4.29 (0.79)	−0.57 (0.79)	−2.11 to 0.98	0.47
600	6.05 (0.50)	8.02 (1.52)	−1.97 (1.34)	−4.60 to 0.66	0.14
800	8.05 (0.35)	10.1 (1.45)	−2.06 (1.41)	−4.82 to 0.70	0.14
850	9.07 (0.57)	11.3 (1.12)	−2.19 (1.12)	−4.38 to 0.00	0.05
900	9.67 (0.51)	11.8 (0.90)	−2.17 (0.90)	−3.93 to −0.40	0.02
950	11.0 (0.70)	13.0 (1.05)	−2.03 (1.28)	−4.54 to 0.48	0.11
Combined	6.28 (0.36)	7.62 (0.84)	−1.33 (0.83)	−2.96 to 0.29	0.11
Pigmented group					
50	2.08 (0.25)	2.04 (0.17)	0.03 (0.31)	−0.57 to 0.64	0.92
60	2.30 (0.30)	2.80 (0.21)	−0.50 (0.46)	−1.40 to 0.40	0.28
70	3.40 (0.34)	3.19 (0.33)	0.21 (0.56)	−0.88 to 1.30	0.70
80	4.07 (0.38)	3.90 (0.47)	0.17 (0.62)	−1.05 to 1.40	0.78
90	4.91 (0.40)	5.16 (0.67)	−0.25 (0.60)	−1.43 to 0.92	0.67
Combined	3.12 (0.34)	3.49 (0.26)	−0.38 (0.51)	−1.38 to 0.62	0.46

Data are as in Table 1.

due to fundus pigmentation, subretinal blood, and retinal versus subretinal location.

Thermal modeling predicts that retinal temperature increase is roughly 10°C during clinical TTT, which is well below the 40°C to 60°C temperature increases with conventional short-pulse photocoagulation.[14,16,48,50] We found that the mean temperature increase with a threshold lesion was 11.8°C in albino and 5.28°C in pigmented eyes, corresponding roughly to theoretical predictions.[16] We found no significant difference between retinal and subretinal temperature increases. This finding is again consistent with thermal modeling which predicts that heat conduction would cause TTT temperature increases to be roughly the same in the neural retina, RPE, and choriocapillaris after a second or two of laser exposure.[10–16] Thus, the exact axial placement of the probe within small subretinal distances would not appreciably alter temperature measurements. Uniformity in axial temperature distributions with lengthy exposures occurs because heat conduction spreads temperature increases from pigmented tissues that are heated directly by light absorption to overlying nonpigmented tissues or adjacent unexposed tissues.

Next, we found that identical power settings produced at least a five times greater temperature increase in pigmented than in nonpigmented tissues (Table 2). This result is consistent with (1) experiments demonstrating that much higher TTT radiant exposures are needed for threshold lesions in albino than pigmented rabbit eyes,[52] (2) human studies showing that the same TTT exposure parameters are more likely to cause retinal damage in highly pigmented than lightly pigmented eyes,[18] and (3) theoretical calculations showing that thermal source strength is proportional to optical absorption in pigmented tissues.[14,48] Our additional finding that TTT temperature increase had little dependence on chorioretinal blood flow is consistent with previous findings that ocular compression has little effect on the radiant exposure needed to produce a threshold lesion in albino and pigmented rabbit eyes.[51]

Although hemoglobin is a less-effective light absorber than melanin, a sufficiently thick hemorrhage can still block laser light penetration.[23,48,52,53] We showed that retinal temperature increase was higher in the presence of subretinal blood, demonstrating that light absorption in hemoglobin generates significant thermal energy, thereby limiting penetration of laser radiation to underlying tissues.

Our experimental study confirms the validity of previous theoretical recommendations that TTT power settings be decreased in patients with highly pigmented eyes and that TTT be performed only after due deliberation in patients with subretinal hemorrhage or with regional chorioretinal pigmentation, such as pigment clumping.[16,23] It also suggests that choroidal blood flow, and thus contact lens pressure,[16] may not have a significant effect on clinical outcomes. In the ongoing clinical trials of TTT for CNV, visible test burns have not been used. Our study substantiates the theory that test lesions are unlikely to be useful, because threshold retinal temperature increase depends on pigmentation, which may vary between test and treatment sites. The value of TTT for CNV in AMD can only be assessed accurately by ongoing prospective controlled clinical trials, but our study provides an experimental foundation for reducing the risk of some potential adverse outcomes.

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