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Selective transscleral cyclophotocoagulation: mathematical modeling for evaluating the efficacy-safety balance in neovascular glaucoma

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Селективна транссклеральна циклофотокоагуляція: математичне моделювання балансу ефективності та безпеки при неоваскулярній глаукомі

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Abstract

Purpose. *To quantitatively evaluate the efficacy-safety balance of transscleral cyclophotocoagulation (TSCPC) through a mathematical modeling-based analysis of thermal tissue response in the ciliary body, and to determine the laser exposure parameters for achieving a selective coagulation effect in neovascular glaucoma (NVG).*

Material and Methods. *A model of heat transfer in the ciliary body was developed using the Pennes bioheat transfer equation. Continuous Wave (CW) TSCPC and MicroPulse TSCPC at 1 W and 2W for a single 2-s application and a series of 2-s applications were subjected to analysis. The following parameters were determined: maximum temperature (Tmax), time to reach 50 °C (t_{50}), time in the temperature range 50–60 °C (t50-60), and time in the temperature range above 60 °C (t(>60)). Integral thermal indices including the Therapeutic Exposure Index (TEI), Destructive Exposure Index (DEI), and Thermal Selectivity Index (TSI), and Safety Margin were calculated.*

Results. *A single 2-s CW-TSCPC application at 1 W enabled achieving the coagulation temperature threshold (Tmax = 50.8 °C; t_{50} = 1.44 s) without a transition to the destructive temperature range (> 60 °C), whereas that at 2 W was accompanied by tissue overheating (T_{max} = 61.8 °C; t_{50} = 0.4 s). A series of 2-s CW laser applications at 1 W enabled accumulation of the heat dose within the therapeutic window (t50–60 = 17.1 s; DEI = 0), whereas that at 2 W resulted in large $t_{(>60)}$ values ($t_{(>60)}$ = 39.7 s; DEI = 0.67). MicroPulse TSCPC did not result in reaching the coagulation threshold ($T_{max} \leq 49$ °C). The integral indices confirmed the optimal efficacy–safety balance for a CW-TSCPC application at 1 W.*

Conclusion. *The 60 °C temperature threshold determines the transition from coagulative to destructive tissue injury.*

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Therefore, CW-TSCPC at 1 W provides an optimal efficacy-safety balance due to a selective coagulative effect, and can be considered a pathophysiologically justified strategy for optimizing TSCPC parameters in NVG.

Keywords: *neovascular glaucoma, transscleral cyclophotocoagulation, mathematical modeling, temperature, intraocular pressure, Thermal Selectivity Index.*

Резюме

Мета. *На основі математичного моделювання кількісно оцінити баланс ефективності та безпеки транссклеральної циклофотокоагуляції шляхом аналізу температурної відповіді тканини циліарного тіла та визначити параметри лазерного впливу, що забезпечують селективний коагуляційний ефект при неоваскулярній глаукомі.*

Матеріал та методи. *Проведено математичне моделювання теплопереносу в тканині циліарного тіла з використанням рівняння біотеплопереносу Пеннеса. Аналізували безперервний (Continuous Wave, CW) та MicroPulse режими при потужності 1 Вт і 2 Вт для одиничних (2 с) і серійних (20×2 с) аплікацій. Визначали Tmax, час досягнення 50 °C (t_{50}), тривалість перебування в діапазонах 50–60 °C та >60 °C. Розраховували інтегральні індекси: TEI, DEI, TSI та Safety Margin.*

Результати. *Режим CW 1 Вт × 2 с забезпечував досягнення коагуляційного температурного порога (Tmax = 50,8 °C; t50 = 1,44 с) без переходу у деструктивний діапазон (>60 °C), тоді як CW 2 Вт супроводжувався перегрівом (Tmax = 61,8 °C; t50 = 0,4 с). При серійному впливі CW 1 Вт забезпечував накопичення теплової дози в межах терапевтичного вікна ($t_{50–60}$ = 17,1 с; DEI = 0), тоді як CW 2 Вт призводив до тривалого перебування у зоні >60 °C (39,7 с; DEI = 0,67). Режими MicroPulse не досягали коагуляційного порога ($T_{max} \leq$ 49 °C). Інтегральні індекси підтвердили оптимальне співвідношення ефективності та безпеки для режиму CW 1 Вт.*

Висновки. *Температурний поріг 60 °C є критичним для переходу від коагуляційного до деструктивного ушкодження тканин. Режим CW 1 Вт × 2 с забезпечує оптимальний баланс між гіпотензивною ефективністю та безпекою і може розглядатися як патофізіологічно обґрунтована стратегія оптимізації параметрів ТСК ЦФК при неоваскулярній глаукомі.*

Ключові слова: *неоваскулярна глаукома, транссклеральна циклофотокоагуляція, математичне моделювання, температура, внутрішньоочний тиск, Thermal Selectivity Index.*

Introduction

Transscleral cyclophotocoagulation (TSCPC) is a major treatment option for refractory glaucoma (particularly, neovascular glaucoma (NVG)), with a reduction in intraocular pressure (IOP) achieved through the inhibition of ciliary secretion [1, 2]. Treatment efficacy is especially important in patients with secondary NVG because fast progression of the disease is associated with severe and sometimes irreversible loss of visual function.

Although studies have demonstrated the clinical efficacy of TSCPC for NVG, treatment outcomes vary widely and depend on laser application parameters which determine the depth of, and type of thermal injury to, the ciliary body. Insufficient thermal exposure can result in poor IOP control, whereas excessive energy delivery is associated with increased risk of complications, including hypotonia, inflammation and phthisis bulbi [3].

The biological effect of tissue exposure to laser is determined by the temperature-time profiles. At a tissue temperature of 50 to 60 °C, protein denaturation occurs with coagulative tissue changes and relative preservation of tissue architecture, which corresponds to the therapeutic effect of photocoagulation, whereas coagulation necrosis with irreversible structural damage occurs at a tissue temperature exceeding 60 °C [4, 5]. Biological tissue response, however, is determined not only by peak temperature, but also by the duration of tissue exposure to laser, which is most fully described by the concept of cumulative equivalent dose at 43 °C (CEM43) [6].

The clinical evolution of TSCPC methods – from conventional continuous-wave (CW) high-energy laser delivery to more controlled approaches such as slow-coagulation and micropulse TSCPC – reflects the transition from a predominantly destructive to a more selective and functionally-oriented treatment strategy [3]. However, despite wide introduction of TSCPC into clinical practice, the selection of laser parameters still remains largely empirical, which limits the repeatability of treatment outcomes and makes it difficult to achieve the balance between the therapeutic benefits and potential complications.

In this context, mathematical modeling of ciliary response to temperature seems to be a promising instrument for the quantitative assessment of temperature distribution, determination of critical temperature thresholds and predicting the risk of transition from controlled coagulative to destructive tissue injury. The integration of these approaches creates the basis for the pathophysiologically justified personalization of TSCPC parameters and improvement in treatment efficiency and safety.

The purpose of this study was to quantitatively evaluate the efficacy-safety balance of TSCPC through a mathematical modeling-based analysis of thermal tissue response in the ciliary body, and to determine the laser

exposure parameters for achieving a selective coagulation effect in NVG.

Material and Methods

Study design

Mathematical modeling of the ciliary response to temperature during TSCPC. The biological effect of laser was assessed based on the concept of cumulative equivalent thermal dose of heating, with the tissue damage determined by the combination of temperature and exposure duration [7].

Given a limited clinical interpretability of classical characteristics (particularly, CEM43), in this study, we used an approach based on the analysis of the tissue residence time at the clinically significant temperature range, which enables to correlate the modeling results with the morphological and clinical effects of TSCPC directly.

A mathematical model of heat transfer

The temperature dynamics in ciliary body tissue was described based on the Pennes bioheat transfer equation:

$$\rho c \cdot \partial T/\partial t = k\nabla^2 T + Q,$$

where T is the tissue temperature (°C); t, time (s); k, thermal conductivity of the tissue [W/(m•K)]; ρ, tissue density (kg/m³); c, specific heat capacity of the tissue [J/(kg• K)]; and Q, volumetric density of the heat source (W/m³) which corresponds to absorption of laser radiation [8].

The model is 2D axisymmetric, which reflects the local geometry of the zone of laser irradiation effect on the sclera and ciliary body. The tissues were modeled as a two-layer structure (the sclera and ciliary body) with homogeneous thermophysical and optical properties within either layer.

A boundary condition of convective heat exchange with the environment (h = 10 W/m²•K) was set for the external scleral surface, and a fixed temperature corresponding to the temperature of the intraocular fluid (37 °C) was set for the internal scleral surface.

The heat source Q was determined by the Bouguer-Beer-Lambert law:

$Q(z) = \mu_a \cdot I0 \cdot \exp(-\mu_a \cdot z)$,

where μ_a is the optical absorption coefficient, I0 is the initial light intensity, and z is the depth of light penetration into the tissue. This approach has been widely used for modeling the interaction of laser radiation with tissue [9, 10].

Within the model, the volumetric density of the heat source Q was corrected using the coefficients reflecting the biophysical and anatomical factors relevant to heat transfer to the ciliary body (Table 2).

The model was developed taking into account the clinical application of TSCPC in NVG; however, the current version of the model simulates average heat transfer without individualization of the parameters associated with ischemia, microcirculation, pigmentation and morphological remodeling of the ciliary body.

Factors of heat effect modification (gain parameters)

Within the model, the volume density of the heat source power was corrected taking into account the coefficients reflecting the biophysical and anatomical factors relevant to heat transfer to the ciliary body (Table 2).

The use of gain parameters allows taking into consideration the individual anatomical and clinical features that can modify the temperature profile in TSCPC.

The effective volumetric density of the heat source power was determined as follows:

$Qeff = Q \cdot G\lambda \cdot Gsclera \cdot Gcompression \cdot Gpigment \cdot Gthermal$,

where Gλ, Gsclera, Gcompression, Gpigment, and Gthermal are corresponding corrective coefficients.

The use of gain parameters allows taking into account the variability of energy penetration associated with scleral thickness, probe compression, pigmentation level and optical characteristics of tissues.

Table 1. Physical and optical parameters used in a heat transfer model

Parameter	Designation	Value	Units
Tissue density [11]	ρ	1050	kg/m³
Specific heat capacity [12]	c	3600	J/(kg· K)
Thermal conductivity [11]	k	0.5	W/(m· K)
Optical absorption coefficient (at 810 nm) [9]	μ_a	100–300	cm^{-1}
Scattering coefficient [9]	μ_s	50–100	cm^{-1}
Temperature of the intraocular fluid [8]	T_0	37	°C
Convective heat exchange coefficient [12]	h	10	W/(m²·K)
Laser wavelength	λ	810	nm

Note: ρ, tissue density (kg/m³); c, specific heat capacity of the tissue [J/(kg· K)]; k, thermal conductivity of the tissue [W/(m·K)]; μ_a, optical absorption coefficient; μ_s, scattering coefficient; T_0, initial temperature (°C); h, heat exchange coefficient [W/(m²·K)]

Table 2. Correcting coefficients (gain parameters) of a hear exposure model

Factor	Designation	Typical value	Range
Wavelength	G_{λ}	0.9	0.5–0.9
Scleral thickness	G_{sclera}	0.7	0.6–0.9
Probe compression	$G_{compression}$	1.2	1.0–1.3
Pigmentation	$G_{pigment}$	1,0	0.8–1.2
Thermal scaling	$G_{thermal}$	k/(ρc)	—

Note: G_{λ}, wavelength coefficient; G_{sclera}, sclera thickness coefficient; $G_{compression}$, compression coefficient; $G_{pigment}$, pigmentation coefficient; $G_{thermal}$, heat transformation coefficient, enables transformation of the consumed power into the change in temperature (W → °C/s) taking into account the thermophysical properties of the tissue

Optical parameters were assigned for the 820-nm wave length and generalized based on the experimental studies on the optical properties of ocular tissues and laser-tissue interaction models. The thermophysical parameters corresponded to the typical values for the soft biological tissues used in biothermal modeling.

To provide a correct comparison among different transscleral laser treatment scenarios, thermophysical, optical and geometric parameters in the model were assigned fixed values, and only laser radiation parameters were variable [11, 13, 14, 15].

Such an approach allows isolating the effect of laser energy parameters on the temperature profile and provides a correct comparison among different TSCPC modes.

Temperature thresholds and clinical interpretation

Three temperature ranges were considered separately:

- < 50°C, a subcoagulative temperature range (no significant structural damage)
- 50–60°C, a coagulative temperature range (selective protein denaturation with a therapeutic effect), and
- > 50°C, a destructive temperature range (coagulative necrosis with stromal and vascular lesions).

This distribution reflects current understanding of laser-tissue interactions and mechanisms of thermal injury in tissues [4, 5].

Modeling scenarios

Two types of tissue exposure to TSCPC were considered:

- A single 2-s laser application
- A series of 20 2-s laser applications separated by one-second intervals (with a total time of 59 s).

Two TSCPC modes were modeled (a continuous-wave (CW) mode and a micropulse mode), with two values of laser power, 1 W and 2W, for either mode. Micropulse mode modeling was performed for average laser wattage and a 31.3% duty cycle without direct simulation of the microsecond pulse structure, which should be taken in account while interpreting the results.

Integral temperature indices and their clinical value

In order to evaluate quantitatively the effect of temperature-time combinations on the ciliary body tissue, we developed a set of integral indices that reflect the balance between the therapeutic and destructive components of thermal exposure.

Therapeutic exposure index (TEI) characterizes the percentage of time the tissue was exposed to a temperature within a coagulative temperature range (50–60°C) and reflects the magnitude of the therapeutic effect: TEI = t50−60 / ttotal; destructive exposure index (DEI) characterizes the percentage of time the tissue was exposed to a temperature within a destructive range (> 60°C) and reflects the risk of irreversible tissue damage: DEI = t(>60) / ttotal; thermal selectivity index (TSI) determines the relationship between the therapeutic exposure and the destructive exposure: TSI = t50−60 / (t(>60) + 0.01); and Safety Margin is the difference between the critical temperature threshold (60 °C) for a transition to destructive temperature exposure, and the maximum tissue temperature (Tmax) achieved in the model: Safety Margin = 60 – Tmax.

The indices proposed represent a clinically oriented adaptation of the thermal dose concept, enabling a transition from the descriptive analysis of temperature curves to the quantitative evaluation of the efficacy and safety of TSCPC.

The parameters examined for each scenario included maximum temperature (Tmax), temperature at the end of exposure (Tend), time to reach a temperature of 50 °C (t50), time in the range 50–60 °C (t50−60) and time in the range above 60 °C (t(>60)).

Table 3 presents the main modeling parameters and their clinical interpretation.

The parameters presented in Table 3 were used for the quantitative assessment of the temperature-time profile for exposure to laser and the balance between the therapeutic and effects of TSCPC. Parameters Tmax, t50, t50-60 and t(>60) reflect the dynamics of tissue heating, whereas the integral indices (TEI, DEI, and TSI) and the Safety Margin can be used for generalized evaluation of the efficacy and safety of laser tissue exposure.

Statistical analysis

Statistical analysis of modeling results was performed using descriptive statistics and comparison for tempera-

Table 3. Main modeling parameters and their clinical values

Parameter	Designation	Clinical value
Maximum temperature	T_{max}	Risk of destructive injury
Temperature at the end of exposure	T_{end}	Cumulative effect
Time to reach a temperature of 50 °C	t_{50}	Rapidity of therapeutic effect
Time in the range 50–60 °C	$t_{50\text{-}60}$	Effective coagulation
Time in the range above 60 °C	$\mathbf{t_{(>60)}}$	Risk of necrosis
TEI	$t_{50\text{-}60}/ t_{total}$	Proportion of therapeutic effect
DEI	$t_{>60} / t_{total}$	Proportion of destructive effect
TSI	$t_{50\text{-}60}/ (\mathbf{t_{(>60)}} + 0.01)$	Effect-risk balance
Safety margin	$60 – T_{max}$	Safety margin

Note: T_{max}, maximum temperature; T_{end}, temperature at the end of exposure; t_{50}, time to reach a temperature of 50 °C; $t_{50\text{-}60}$, time in the range 50–60 °C; $\mathbf{t_{(>60)}}$, time in the range above 60 °C; TEI, Therapeutic Exposure Index; DEI, Destructive Exposure Index; TSI, Thermal Selectivity Index; t_{total}, total exposure time

ture parameters and integral indices between exposure scenarios. Analysis of relative differences and ratio analysis were used for the quantitative characteristic of the effect of laser power and energy delivery mode. Classical parametric statistical tests were not used because of the deterministic nature of the model. Temperature parameters (Tmax, Tend, t50, t50-60, and t(>60)) and integral indices (TEI, DEI, and TSI) were examined for each exposure scenario. The effect of changes in optical absorption coefficient (±10–20%) on the time for achieving critical temperatures was also evaluated.

Results

Thermal tissue response to a single laser application

Comparative modeling revealed substantial differences in ciliary body response to laser exposure depending on laser energy delivery mode and power level. In a single CW-TSCPC application for 2 seconds, a power of 1 W enabled achieving a coagulation threshold temperature without a transition to the destructive temperature range, which conformed to the minimum controlled coagulation effect. An increase in power to 2 W resulted in fast thermal tissue response above the threshold of 60 °C, which indicated the development of potentially destructive thermal effects even in a single CW-TSCPC application over 2 seconds.

In the MicroPulse mode for the both laser power settings examined, the magnitude of thermal tissue response was substantially lower and below the coagulation threshold (Table 4).

Thermal tissue response to a series of laser applications

Modeling thermal tissue response to series of 20 2-s CW laser applications separated by 1-s intervals demonstrated a cumulative thermal effect. At 1 W, there was a gradual accumulation of heat, and the coagulation temperature range, but not the overheating temperature range was reached by the end of the series; this conformed to a controlled coagulation effect.

In contrast, at 2 W, there was a significantly more intensive cumulative heat accumulation, with fast reaching the threshold temperatures followed by a relatively durable tissue exposure to a destructive temperature above 60 °C, which indicated a high risk for tissue overheating and severe thermal injury.

Therefore, a series of CW laser applications at 1 W enables gradual falling into the temperature window for coagulation without an excessive thermal load on the tissue, whereas a series at 2 W results in early and durable tissue exposure to temperatures within a destructive range (Table 5).

Thermal exposure thresholds

Analysis of the time for reaching temperature thresholds demonstrated that an increase in laser power led to a sharp reduction in time to reach the coagulation and destruction temperature ranges, with the t50 at 1 W and 2 W being 1.44 s and 0.40 s, respectively, for a single CW-TSCPC application, and 35.3 s and 8.2 s, respectively, for a series of CW laser applications. These findings confirm the existence of a critical temperature threshold of around 60 °C, with an exceedance of the threshold followed by a sharp increase in the thermal load on the tissue (Fig. 1).

The graph shows the relationship between the duration of exposure and the ciliary body temperature, with the grey zone corresponding to the coagulation range (50–60 °C). It was demonstrated that the CW mode enabled a faster and more significant increase in temperature than the MicroPulse mode. In the CW mode at 2 W, the temperature exceeded 60 °C, but in the CW mode at 1 W or in the MicroPulse mode, it was below this threshold.

Integral interpretation of the results

The results obtained confirm the existence of a critical temperature threshold of around 60 °C, with an exceed-

Table 4. Temperature parameters for a single 2-s application at different TSCPC modes

Mode	Wattage	T_{end}, °C	T_{max}, °C	t_{50}, s	t_{50-60}, s	$t_{(>60)}$, s
CW	1 W	50.8	50.8	1.44	0.58	0
CW	2 W	61.8	61.8	0.40	0.86	0.76
MicroPulse	1 W	43.2	43.2	—	0	0
MicroPulse	2 W	49.0	49.0	—	0	0

Note: T_{max}, maximum temperature; T_{end}, temperature at the end of exposure; t_{50}, time to reach a temperature of 50 °C; t_{50-60}, time in the range 50–60 °C; $\mathbf{t_{(>60)}}$, time in the range above 60 °C; CW, continuous wave mode

Table 5. Temperature parameters for a series of 20 2-s applications

Mode	Power	T_{end}, °C	T_{max}, °C	t_{50}, s	t_{50-60}, s	$t_{(>60)}$, s
CW	1 W	50.18	50.21	35.3	17.1	0
CW	2 W	63.77	63.83	8.2	11.2	39.7

Note: T_{max}, maximum temperature; T_{end}, temperature at the end of exposure; t_{50}, time to reach a temperature of 50 °C; t_{50-60}, time in the range 50–60 °C; $\mathbf{t_{(>60)}}$, time in the range above 60 °C; CW, continuous wave mode

ance of the threshold followed by the transition from the controlled coagulation effect to destructive tissue injury. Even with a series of laser applications, the CW mode at 1 W enabled falling into the temperature window for coagulation (50–60 °C) without an excessive thermal load on the tissue, which conformed to the selective damage of the secretory epithelium. In contrast, the CW mode at 2 W was characterized by fast reaching temperatures above 60 °C with a relatively durable tissue exposure to these temperatures, which indicated a high risk for severe thermal injury. MicroPulse TSCPC resulted not in reaching the coagulation threshold, but in subcoagulative heating (Table 6).

Our quantitative analysis of temperature profiles with the use of integral indices demonstrated principal differences among the modes of TSCPC examined. A single CW-TSCPC application at 1 W enabled achieving the coagulation temperature range without a transition to the destructive temperature range, which conformed to the maximum temperature selectivity (TSI → ∞ at t(>60) = 0).

In contrast, a single CW-TSCPC application at 2 W resulted in faster tissue heating, with a significant overheating (> 60°C) component, an increase in the DEI and an abrupt reduction in the TSI, which conformed to selectivity loss and an increase in the risk for destructive injury.

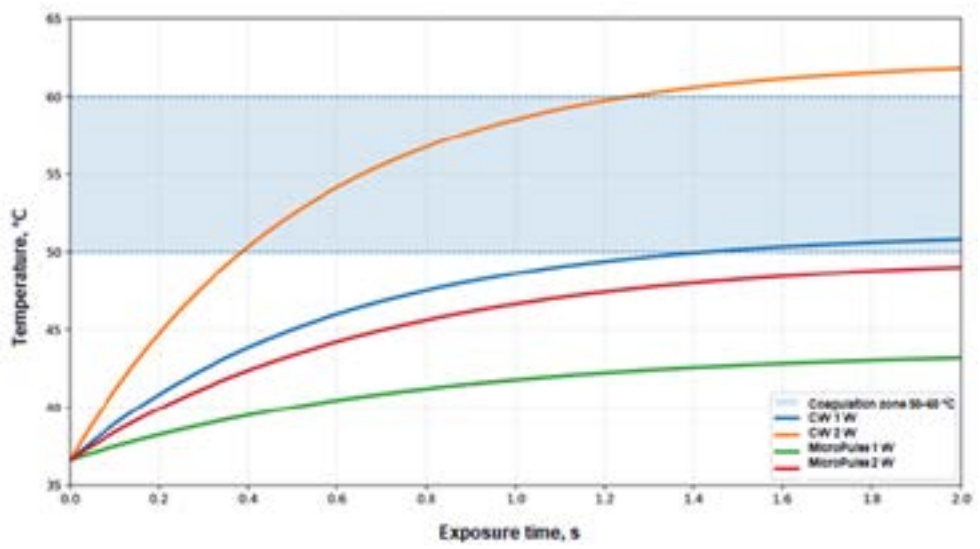

Fig. 1. Temperature dynamics for different laser exposure modes (a single 2-s CW-TSCPC application at 1 W, a single 2-s CW-TSCPC application at 2 W, a single MicroPulse TSCPC application at 1 W, and a single MicroPulse TSCPC application at 2 W). The average temperature profile calculated on the basis of the equivalent average power without direct simulation of the microsecond pulse structure is presented for a MicroPulse TSCPC application

Table 6. Average temperature profiles and integral indices for different TSCPC modes

Scenario	T_{max}, °C	t_{50}, s	$t_{50–60}$, s	$t_{(>60)}$, s	TEI	DEI	Safety Margin, °C	TSI
CW 1 W, 2 s	50.8	1.44	0.58	0	0.29	0.00	+9.2	58.0
CW 2 W, 2 s	61.8	0.40	0.86	0.76	0.43	0.38	−1.8	1.12
MicroPulse 1 W, 2 s	43.2	–	0	0	0.00	0.00	+16.8	0
MicroPulse 2 W, 2 s	49.0	–	0	0	0.00	0.00	+11.0	0
CW 1 W, 20×2 s	50.21	35.3	17.1	0	0.29	0.00	+9.79	∞
CW 2 W, 20×2 s	63.83	8.2	11.2	39.7	0.19	0.67	−3.83	0.28

Note: TEI, proportion of time in the range 50–60 °C; DEI, proportion of time in the range above 60 °C; Safety Margin = $60-T_{max}$; TSI = $t_{50–60}/(t_{(>60)} + 0.01)$, ratio of therapeutic exposure to destructive exposure

These patterns intensified with a series of CW laser applications, and a series of CW-TSCPC applications at 1 W enabled consistent coagulation without excessive tissue heating, whereas those at 2 W led to apparent thermal dose accumulation in the destructive range.

MicroPulse TSCPC resulted not in reaching the coagulation threshold, but in subcoagulative heating.

Therefore, CW-TSCPC at 1 W provided an optimal efficacy-safety balance due to a selective coagulative effect, whereas CW-TSCPC at 2 W was associated with an excessive thermal load on the tissue and temperature selectivity loss. TSCPC efficacy is determined not only by reaching the threshold temperature, but also by the time the tissue spends in the coagulation temperature range.

Discussion

The results of this study confirm that the temperature-time profile is a key determinant of the type of thermal injury to the ciliary body and determines the balance between hypotensive efficacy and the risk of complications in TSCPC. The existence of a clear temperature threshold of around 60 °C was established, with an exceedance of the threshold followed by a transition from a controlled coagulation effect to a destructive thermal injury. At 50–60 °C, protein denaturation occurs with relative preservation of tissue architecture, which corresponds to the selective thermal injury to the ciliary process pigment epithelium, whereas coagulation necrosis with stromal and vascular destruction and irreversible morphological alterations occurs at a temperature exceeding 60 °C [4, 5].

The results of our modeling supported the findings of previous experimental histological studies on TSCPC which demonstrated that an increase in the thermal tissue load was accompanied by a transition from selective pigment epithelium lesions to severe destruction of the ciliary body [16, 17]. This confirms that the model proposed simulates correctly the pathophysiological mechanisms of laser-induced damage and enables interpreting quantitatively the morphological changes through temperature parameters.

The status of the microcirculation is a substantial factor modifying the thermal tissue response. The heat transfer in the eye is determined by the interaction of thermal conductivity, tissue perfusion and intraocular hydrodynamics [8, 9, 12]. In NVG, these mechanisms undergo substantial changes due to ischemia, neovascularization and blood flow abnormalities, which reduces the efficacy of heat removal and contributes to faster reaching critical temperatures even with standard exposure parameters [18]. It was demonstrated within the framework of the modeling analysis that a 10–20% increase in the optical absorption coefficient resulted in the shift of the temperature profile towards earlier threshold reaching, which emphasizes the sensitivity of thermal tissue response to individual characteristics of tissues.

Our findings are in agreement with recent studies that have combined computer modeling with clinical observations. Grippo and colleagues [15] evaluated thermal dynamics associated with CW-TSCPC and MicroPulse TSCPC such as temperature peak and exposure duration and thermal spread in a ciliary body simulation using computer modeling. They confirmed a key role of the temperature-time profile as an efficacy and safety determinant, which is in conceptual agreement with our findings.

Additionally, clinical studies have confirmed that the efficacy of TSCPC depended on laser exposure energy. In a large cohort of patients with different types of refractory glaucoma, Sari and colleagues [19] demonstrated that transscleral diode cyclophotocoagulation was least effective in eyes with NVG, likely due to altered microcirculation and heat transfer changes. This provides additional justification for the need to personalize treatment parameters for the patients of this category.

Recent studies on nonlinear heat transfer processes and phase transitions in tissues provide additional theoretical ground for the interpretation of the results of this study. Particularly, it has been demonstrated that, with high tissue temperatures achieved using laser treatment vaporization heat begins playing a role by changing the pattern of distribution of thermal energy and can result in either local

stabilization of temperature or a sharp increase in thermal damage, depending on the conditions of exposure [20]. This is in agreement with our finding of the threshold pattern of the transition through a temperature of about 60 °C and explains nonlinearity of the temperature response to increased laser power.

Moreover, recent extensions and modifications of the Pennes bioheat transfer equation have demonstrated that the classical Pennes model may underestimate the complexity of heat processes in biological tissues, especially especially under conditions of heterogeneous perfusion and anisotropic tissue properties [21]. It has a special value in the context of NVG, because ischemia, neovascularization and perfusion changes may substantially modify local hear transfer. Therefore, the model employed in this study reflects generalized temperature response, while further development of mathematical approaches taking into account fractional diffusion and phase effects may improve the accuracy of predicting thermal profiles in TSCPC.

From the clinical point of view, a 1-W CW treatment over 2 seconds formed the most balanced temperature profile, enabling the achievement of a coagulation effect without a transition to the destructive temperature range even with a series of laser applications. Such a heating pattern conforms to the concept of a well-controlled inhibition of ciliary body function and is associated with effective IOP lowering while minimizing the risk of complications [1, 22]. In contrast, a 2-W CW treatment over 2 seconds resulted in rapid achievement of temperatures above 60 °C, which is associated with increased risk of hypotonia, inflammation and phthisis bulbi [2, 3].

The current clinical approaches to optimize TSCPC safety include the use of slow coagulation for improved control of thermal dose accumulation and reduction of complication risks [23, 24]. This is in complete agreement with the findings of the current study and supports the concept of controlled, low-power laser exposure as a pathophysiologically justified treatment strategy.

The results of MicroPulse TSCPC modeling indicate that MicroPulse TSCPC had a subcoagulation effect and the tissue did not achieve a temperature range of 50 to 60 °C. This is in agreement with the clinical data that, compared to CW-TSCPC, MicroPulse TSCPC has an advantageous safety profile, although the IOP-lowering effect may be less marked [3, 25, 26]. One should, however, take into account that our MicroPulse mode modeling was performed for average laser wattage, which does not allow simulating microscopic peak temperatures. It is likely that the effect of MicroPulse TSCPC is implemented through subcellular mechanisms involving local overheating of pigment granules, cell stress and thermoelastic effects.

Our findings are in agreement with recent clinical reports on the comparative efficacy of different TSCPC modes in the treatment of glaucoma. Hwang and colleagues [24] demonstrated that, compared with micropulse transscleral laser treatment, slow-coagulation TSCPC showed a greater IOP-lowering effect and had a comparable favorable safety profile. These clinical observations are well explained by our modeling results: a 1-W CW treatment developed a temperature profile within the coagulation range without a transition to the destructive temperature range, which conformed to the selective inhibition of ciliary body function. In contrast, within the parameters examined, MicroPulse TSCPC did not result in the achievement of the coagulation temperature range on the macroscopic level, which can explain a less marked IOP lowering effect, despite a better safety profile than CW-TSCPC. Therefore, the results obtained create a pathophysiologically justified argument for clinical discrepancies between these modes and confirm the validity of a controlled low-power coagulation approach to the treatment of secondary NVG.

The assessment of cumulative thermal dose is qn important aspect of modeling the thermal tissue response to TSCPC. Szabó and colleagues [28] found that, in repeated procedures of subliminal TSCPC, cumulative energy scales determine the duration of the IOP-lowering effect, which is in agreement with the concept of integral thermal load and confirms the validity of using the TEI, DEI and TSI.

The indices proposed enable a transition from the descriptive analysis of temperature curves to the quantitative evaluation of the efficacy and safety of TSCPC, which opens up opportunities for standardizing the parameters of TSCPC and developing predictive models [6, 29]. Integration of such parameters into machine learning algorithms may provide a transition to personalized treatment planning [30]. Our results are in agreement with current approaches to the mathematical modeling of heat transfer in the eye which take into account the relationship between temperature fields and ocular hydrodynamics [31].

The model has, however, several limitations associated with the simplification of tissue structure and the absence of dynamic perfusion and individual variations of thermophysical and optical properties [9, 12]. Particularly, it does not take into account the factors critical for NVG, including the grade of ischemia, variability in pigmentation, scleral thickness and features of ocular hydrodynamics. Taking these parameters into account in further studies may substantially improve the accuracy of the prognosis of temperature profiles and clinical outcomes.

Therefore, the integration of mathematical modeling with experimental and clinical data forms a consistent concept according to which the optimization of TSCPC parameters should be based on the control of the cumulative thermal dose and the dynamics of thermal tissue response to TSCPC. This is especially important in patients with NVG, in whom individual anatomical and physiological features of heat transfer may determine the efficacy and safety of treatment.

Conclusion

Mathematical modeling demonstrated that the temperature-time profile is a key determinant of the type of thermal injury to the ciliary body and determines the balance between hypotensive efficacy and safety in TSCPC.

It was found that a selective coagulation effect with a controlled thermal injury to the pigment epithelium develops at the tissue temperature range of 50 to 60 °C, whereas the exceedance of the tissue temperature threshold (60 °C) is associated with a transition to the destructive injury with an increased risk of complications.

A 1-W CW treatment over 2 seconds formed an optimal temperature profile, with the achievement of a coagulation effect without an excessive thermal load, which provided the most favorable balance of efficacy and safety. In contrast, a 2-W CW treatment over 2 seconds resulted in a disproportionately increased thermal dose with an increased risk of a destructive injury.

MicroPulse TSCPC resulted in subcoagulative heating, which explains its better safety profile with a potentially less marked IOP-lowering effect.

The integral indices proposed (TEI, DEI, and TSI) enable evaluating quantitatively the relationship between the therapeutic and destructive components of thermal exposure and may be used for optimizing the parameters of TSCPC.

The results of this study justify the validity of a controlled low-power coagulation approach as a pathophysiologically justified strategy with an optimal balance of efficacy and safety for the treatment of NVG.

Author Contributions

OG, OZ, PO, VV, AKh and AK contributed to Conceptualization, Study Design, Data Collection, Analysis and Interpretation of Results, Mathematical Modeling and Manuscript Preparation.. All authors have read and approved the final manuscript and agree to be responsible for all aspects of the work.

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Conflict of Interest

The authors state that they have no conflict of interest that could influence their view on the subject matter or materials described and discussed in this manuscript.

Data Availability Statement

All the data relevant to this study has been included in this article. Further inquiries can be directed to the corresponding author.

Abbreviations

CEM43, cumulative equivalent dose of heating at 43 °C; CW, continuous wave; DEI, Destructive Exposure Index; IOP, intraocular pressure; MP, micropulse; t50, time to reach a temperature of 50 °C; t50-60, time in the temperature range 50–60 °C; t(>60), time in the temperature range above 60 °C; TEI, Therapeutic Exposure Index; Tend, temperature at the end of exposure; Tmax, maximum temperature; TSCPC, transscleral cyclophotocoagulation; TSI, Thermal Selectivity Index.

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