Thermal accumulation in transscleral cyclophotocoagulation: mathematical modeling of controlled and destructive heat effects in secondary neovascular glaucoma

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Термоакумуляція при трансскліральній циклофотокоагуляції: математичне моделювання контрольованого та деструктивного теплового впливу при вторинній неоваскулярній глаукомі

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Abstract

Purpose. *To quantitatively assess temperature dynamics during serial transscleral cyclophotocoagulation (TSCPC) on the basis of mathematical modeling and to assess the possibility of using a thermal accumulation index (TAI) for describing changes in the initial temperature for the model zone of the ciliary body prior to sequential laser applications in secondary neovascular glaucoma (NVG).*

Material and Methods*. Temperature profiles of serial TSCPC were analyzed based on the results from the previously developed mathematical model for continuous-wave (CW) applications at 1 W and 2W. Additionally, we conducted a step-by-step scenario analysis for a series of 20 2-s CW laser applications separated by 1-s intervals. The initial temperature before each subsequent application was set with an increase of 0.3 °C. The initial temperature (T_{start}), maximum temperature (T_{max}), temperature increase during the ith application (ΔT) and heat loss from ith to (i+1)th applications (HeatLoss) were analyzed. The thermal accumulation index (TAI) was defined as the average excess of the initial temperature over the baseline level of 37 °C before applications.*

Results. *Maximal temperature in serial TSCPC for CW applications at 1 W was 50.21 °C, but for CW applications at 2 W was 63.83 °C (i.e., above the threshold of 60 °C), indicating a temperature profile with potentially destructive thermal effects. In the step-by-step scenario, the initial temperature prior to sequential laser applications increased from 37.0 to 42.7 °C in accordance with the temperature increase set. The TAI values for the entire series and its first and second halves were 2.85 °C, 1.35 °C, and 4.35 °C, respectively. Maximal temperature for the step-by-step scenario approached 50.6 °C and did not exceed 60 °C.*

Conclusion. *Mathematical modeling demonstrated that temperature profiles of serial TSCPC depended on the laser*

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power. Lower maximal temperatures in CW applications at 1 W are in agreement with the overheating prevention principles of low dose / slow coagulation. The TAI proposed enables quantitative characterization of the average excess of the initial temperature over the baseline level of 37 °C before applications within the given modeling scenario, but is not an independent measure of thermal dose or extent of tissue injury. Its application for predicting coagulation efficiency and the risk of thermal tissue damage requires further experimental and clinical validation.

Keywords: *secondary neovascular glaucoma, transscleral cyclophotocoagulation, thermal accumulation index, mathematical modeling, temperature dynamics, intraocular pressure, low-dose / slow coagulation, ciliary body.*

Резюме

Мета. *Кількісно охарактеризувати температурну динаміку при серійній трансскліральній циклофотокоагуляції (ТСК ЦФК) на основі математичного моделювання та оцінити можливість використання індексу термоакумуляції (TAI) для опису зміни початкової температури модельної зони циліарного тіла перед послідовними лазерними аплікаціями при вторинній неоваскулярній глаукомі.*

Матеріали та методи. *Проаналізовано температурні профілі серійної ТСК ЦФК за результатами раніше розробленої математичної моделі для режимів безперервного лазерного випромінювання (CW) потужністю 1 і 2 Вт. Додатково виконано покроковий сценарний аналіз серії з 20 аплікацій тривалістю 2 с із 19 міжаплікаційними інтервалами по 1 с. Початкову температуру перед кожною наступною аплікацією задавали з приростом 0,3 °C. Аналізували початкову (T_{start}) і максимальну (T_{max}) температури, приріст температури під час аплікації (ΔT) та її зниження між послідовними аплікаціями (HeatLoss). Індекс термоакумуляції (TAI) визначали як середнє перевищення початкової температури перед аплікаціями над базовим рівнем 37 °C.*

Результати. *За результатами раніше розробленої математичної моделі максимальна температура при серійній ТСК ЦФК у режимі CW 1 Вт становила 50,21 °C без перевищення 60 °C, тоді як при CW 2 Вт досягала 63,83 °C, що характеризувало температурний профіль із потенційним ризиком деструктивного теплового ушкодження. У додатковому покроковому сценарії початкова температура перед послідовними аплікаціями підвищувалася від 37,0 до 42,7 °C відповідно до заданого приросту. Значення TAI становило 2,85 °C, а для першої та другої половин серії – відповідно 1,35 і 4,35 °C. Максимальна температура в межах додаткового сценарію досягала 50,6 °C і не перевищувала 60 °C.*

Висновки. *Результати математичного моделювання продемонстрували залежність температурних профілів серійної ТСК ЦФК від потужності лазерного випромінювання. Нижчі максимальні температури при CW 1 Вт узгоджуються з принципами обмеження надмірного нагрівання, покладеними в основу концепції low-dose / slow coagulation. Запропонований індекс TAI дозволяє кількісно характеризувати середнє перевищення початкової температури перед послідовними аплікаціями над базовим рівнем у межах заданого модельного сценарію, проте не є самостійним показником теплової дози або ступеня ушкодження тканини. Його застосування для прогнозування ефективності коагуляції та ризику термічного ушкодження потребує подальшої експериментальної та клінічної валідації.*

Ключові слова: *вторинна неоваскулярна глаукома; трансскліральна циклофотокоагуляція; індекс термоакумуляції; математичне моделювання; температурна динаміка; low-dose / slow coagulation; циліарне тіло.*

Introduction

Transscleral cyclophotocoagulation (TSCPC) remains an important method of treatment for refractory neovascular glaucoma (NVG), with a reduction in intraocular pressure (IOP) achieved mostly through the decrease in aqueous humor production secondary to the thermal effect on the ciliary body [1, 2]. Despite proven clinical efficacy, treatment outcomes are variable, which may be related both to laser emission parameters and to individual characteristics of tissue response.

The evaluation of laser-induced thermal effects is based on the analysis of maximum temperature, heating duration and cumulative temperature-time characteristics. In a serial TSCPC, the sequence of heating and cooling cycles becomes important, as the temperature status of the tissue before the next laser shot may potentially depend on the prior thermal effect. At the same time, the nature of such dependence is determined by the thermophysical properties of the tissue, heat dissipation conditions, time intervals and the spatial arrangement of laser shots.

In studies on laser-tissue interaction, the temperature range 50–60 °C is regarded as an approximate range in which coagulative tissue changes may develop, whereas the chances of apparent thermal damage to the tissue increase when the temperature is above 60 °C, especially for a long tissue exposure [3]. Additionally, studies on laser effects on retinal pigment epithelial cells demonstrated that the nature of tissue response to laser irradiation depends on laser settings and heating conditions [4]. The aforementioned temperature parameters are, however, not universal thresholds between controlled tissue coagulation

and irreversible tissue destruction, because the nature of biological response is determined not only by temperature but also by the duration of exposure and tissue properties. Therefore, the analysis of temperature dynamics in serial laser exposure should take into account not only peak temperatures, but also the temporal characteristics of heating and cooling.

Our previous mathematical modeling based study have proposed Therapeutic Exposure Index (TEI), Destructive Exposure Index (DEI) and, Thermal Selectivity Index (TSI) for characterizing temperature-time parameters for coagulative and potentially destructive effects of thermal exposure in TSCPC [5]. To obtain a more detailed description for a serial TSCPC, it is reasonable to separately analyze the start temperature of the modeling region before the application of consecutive laser shots. Such an approach makes it possible to consider the temperature status of the tissue (including not only the evaluation of the maximum temperature) at different stages of the series.

Retinal ischemia, neovascularization and impaired microcirculation are typical for secondary NVG, and studies on temperature response to laser irradiation may be important for improving laser treatment options for the disease. These processes may potentially affect local heat exchange conditions in ocular tissues, particularly the ciliary body. However, the magnitude and direction of temperature response depend on the blood supply patterns and thermophysical characteristics of the tissue and require a separate study. Mathematical modeling provides a way to analyze the temperature response for specified laser exposure parameters and gradually clarify the role of individual physical and physiological factors.

Thermal dose in clinical hyperthermia reported as cumulative equivalent minutes (CEM) at 43 °C (CEM43) takes into account temperature and heating duration and is used for the quantitative evaluation of tissue exposure to a temperature-time profile [6-8]. A relevant temperature-time profile is required to calculate the CEM43 thermal dose map. The start temperature of the modeling region before each subsequent laser shot is of interest for additional characterization of serial laser exposure. The thermal accumulation index (TAI) defined as the average elevation of the start temperature above baseline before consecutive laser shots is proposed for this purpose. Contrary to CEM43, this index does not characterize the cumulative thermal dose but is designed for describing a separate component of step-by-step temperature dynamics.

Therefore, the investigation of the applicability of TAI as an additional calculated parameter may broaden the description of the thermal response during serial TSCPC. Its physiological and clinical significance, however, requires further justification. This determines the feasibility of a step-by-step scenario analysis of temperature dynamics with a clear distinction between the specified modeling conditions, calculated characteristics and the results of the previously developed mathematical model.

The purpose of this study was to quantitatively assess temperature dynamics during serial TSCPC on the basis of mathematical modeling and to assess the possibility of using the TAI for describing changes in the start temperature for the modeling region of the ciliary body before consecutive laser shots in secondary NVG.

Material and Methods

Mathematical model and input temperature data

A 2D axisymmetric model of heat transfer in the sclera and ciliary body has been developed previously using the Pennes bioheat transfer equation [9], and was used as a theoretical basis for this study. Thermophysical, optical and geometric parameters in the model, boundary conditions and laser irradiation characteristics have been presented previously [5].

The specified sequence of start and maximum temperatures for a series of 20 laser shots was used in the additional step-by-step analysis. The start temperature before each subsequent shot was increased by 0.3 °C, starting from 37 °C. Maximum temperature values were also used as input parameters in the scenario analysis but not as the results of new independent solutions to the bioheat transfer equation. Based on these values we calculated ΔT, HeatLoss and TAI.

Start temperature (T_{start}) and maximum temperature (T_{max}) of the tissue were determined for each laser shot. The temperature increase during the ith shot was calculated as the difference between the maximum and start temperature.

$$\Delta T(i) = T_{max}(i) - T_{start}(i)$$

The inter-shot temperature loss HeatLoss was defined as the difference between the maximum temperature of the current shot and the start temperature of the next shot.

$$HeatLoss(i) = T_{max}(i) - T_{start}(i+1),$$

where i = 1, …, 19.

HeatLoss was not determined for the 20th shot, because the next shot was absent. HeatLoss characterizes a calculated temperature loss between consecutive shots expressed in °C, and is not a directly evaluated loss of thermal energy.

Step-by-step modeling of serial TSCPC

Serial TSCPC was modeled as a series of 20 2-s laser shots separated by 1-s intervals (with a total time of 59 s). The process was divided into discrete cycles, with each cycle consisting of the following:

- 2-s heating (ON) phase
- 1-s cooling (OFF) phase between subsequent shots

Additionally, times to reach 50 °C and 60 °C temperature thresholds (t_{50} and t_{60}, respectively) were assessed.

In the clinical scheme, adjacent laser exposure zones overlap with each other, but the shot-to-shot shift in shot center location along the projection of the ciliary body and spatial heat propagation between adjacent exposure zones were not modeled separately within the step-by-step analysis. A serial scenario was used to estimate the time

component of residual heat accumulation in the modeling zone under conditions of repeated cycles of heating and incomplete cooling.

In the clinical practice, TSCPC is performed by applying consecutive laser shots along the projection of the ciliary body while taking into account the selected treatment protocol [10].

Fig. 1 shows a schematic arrangement of laser shots applied in the upper hemisphere of the eye with overlap between adjacent exposure zones.

Therefore, the step-by-step approach characterizes the time component of residual heat accumulation in the modeling zone and does not fully simulates the spatial temperature distribution across individual laser shots applied.

Integrated assessment of thermal effects

For the quantitative evaluation of a temperature-time profile, we determined:

- total time spend by the tissue in the coagulative temperature range (50–60 °C): $t_{50–60}$, and
- total time spend by the tissue in the potentially destructive temperature range (>60 ºC): t>60

Thermal accumulation index (TAI)

The proposed TAI was used to quantitatively characterize the increase in start temperature above baseline before consecutive laser shots. The index was calculated using the formula

$$TAI = \frac{1}{n}\sum_{i=1}^{n}(T_{start,i} - T_0)$$

where n is laser shot count (n = 20); Tstart(i) is the start temperature of the modeling zone before ith shot; T is the baseline tissue temperature (37 °C).

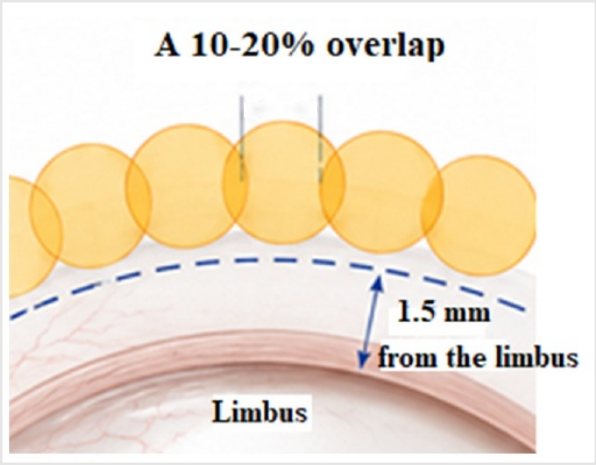


Fig. 1. Schematic arrangement of shots in transscleral cyclophotocoagulation in the clinical setting. Laser shots are applied on the upper hemisphere of the eye at 1.5 mm from the limbus, avoiding the 3 o'clock and 9 o'clock positions, with an overlap (~10–20%) between adjacent exposure zones. The scheme illustrates the arrangement of shots in the clinical setting and does not reflect spatial geometry of the calculated model.

TAI characterizes the average elevation of the start temperature above baseline before consecutive laser shots and is expressed in °C. The characteristic reflects the temperature status of the modeling zone at the start of each shot, but is not a direct equivalent of absorbed thermal energy or cumulative temperature-time dose.

TAI is a modeling index proposed by the authors and has not been clinically validated at this point. It experimental and clinical validation requires further research.

The purpose of modeling was not to directly simulate the individual tissue temperature response in vivo, but to analyze temporal temperature patterns under fixed parameters of influence with minimization of the effect of inter-individual variability of thermophysical and hemodynamic characteristics of the tissue.

Modeling assumptions

Modeling was performed at fixed thermophysical and optical characteristics of the tissue and specified laser settings. The baseline temperature was assumed to be 37 °C. Inter-individual variability in ischemia, microcirculation, pigmentation and morphology of the ciliary body was not simulated. This is in agreement with the limitations specified previously [5].

Spatial shot-to-shot movement of the probe was not simulated in the step-by-step analysis. Direct experimental or intraoperative validation of temperature characteristics was not performed.

The results obtained should be interpreted as modeling assessment of tissue exposure to a temperature-time profile but not as directly in-vivo measured temperatures of the ciliary body.

Modeling data processing and analysis

We determined start temperature (Tstart) and maximum temperature (T_{max}) for each shot, the temperature increase during the shot, temperature increase (ΔT) and inter-shot temperature loss (HeatLoss) to characterize the step-by-step temperature dynamics. TAI was determined as the average elevation of the start temperature above baseline (37 °C) before consecutive laser shots. Additionally, the TAI for the first and second halves of a series was determined to compare different stages of laser exposure with regard to temperature dynamics.

The results of the previously published model [5] for a single 2-s CW-TSCPC application at 1 W and 2 W (particularly, Tmax and the time spend by the tissue in the temperature ranges 50–60 °C and above 60 °C) were also used. The analysis was descriptive; no statistical hypothesis testing was performed.

Results

We have previously found [5] that the temperature response of the modeling zone of the ciliary body in serial TSCFC (a series of 20-s shots with 19 1-s inter-shot intervals) depended on the laser power.

In a 1-W continuous-wave (CW) mode, Tmax and the temperature at the end of series were 50.21 °C and 50.18

°C, respectively. Additionally, time to reach a temperature of 50 °C was 35.3 s, time at a temperature between 50 and 60 °C, 17.1 s, and the temperature did not reach a threshold of 60 °C.

In a 2-W CW mode, Tmax and the temperature at the end of series were 63.83 °C and 63.77 °C, respectively. Additionally, time to reach a temperature of 50 °C was 8.2 s, time at a temperature between 50 and 60 °C, 11.2 s, and time at temperature above 60 °C, 39.7 s.

Therefore, previous results have demonstrated that a 1-W CW mode enabled achieving a coagulative temperature range without exceeding the 60 °C threshold, whereas a temperature-time profile with a long time in the potentially destructive temperature range formed in a 2-W CW mode.

In the additional step-by-step-analysis, a change in the start temperature of the modeling region before each subsequent laser exposure cycle was assessed. Its value increased from 37.0 °C before the first shot to 42.7 °C before the 20th shot with an increase in the start temperature per cycle set to 0.3 °C. The average elevation of the start temperature above baseline as assessed by TAI was 2.85 °C.

TAI values in the separate analyses for the first and second halves of a series were 1.35 and 4.35 °C, respectively. Therefore, the elevation of the start temperature above baseline was 3.0 °C larger for the second half than for the first half of a series. The step-by-step analysis showed that the temperature increase for the shot (ΔT) increased from 2.2 °C for the first shot to a maximum value of 8.4 °C for the 17th shot and gradually decreased thereafter to 7.9 °C for the 20th shot. The calculated inter-shot temperature loss (HeatLoss) followed a similar pattern of dynamics, with an increase from 1.9 °C after the first shot to 8.1 °C after the 17th shot, with a decrease thereafter to 7.8 °C after the 19th shot.

For the examined step-by-step scenario, the maximum temperature was 50.6 °C and did not exceed 60 °C. Additionally, the sequential increase in shot-start temperature characterized the scenario-defined residual heating pattern within the modeling region (Table 1).

The resulting TAI value is determined by a specified sequence of start temperatures and is not an independent solution of the initial two-dimensional bioheat transfer model. Consequently, this index should be considered as an additional calculated parameter of temperature dynamics within the studied scenario, but not as an independent criterion of thermal safety or destructive tissue damage.

Graphical analysis of step-by-step temperature dynamics showed a gradual increase in the start temperature in the modeling region before consecutive shots. ΔT(i) and HeatLoss(i) increased until the 17th shot, and somewhat decreased thereafter. Additionally, T_{start} (i+1) was always by 0.3 °C higher than T_{start} (i), which corresponded to the specified conditions of the step-by-step scenario.

The maximum temperature in the examined scenario was not higher than 60 °C. Therefore, the simulated temperature sequence was characterized by a gradual increase in shot start temperature without reaching a potentially destructive threshold temperature (Fig. 2).

Discussion

The results indicate that the temperature response of the modeling zone of the ciliary body in serial TSCFC is determined not only by the peak temperature, but also by the characteristics of thermal exposure, particularly, heating and cooling durations. The results of the previous mathematical modeling study [5] demonstrated the difference between temperature profiles depending on the laser power. The additional step-by-step scenario analysis enabled quantitative characterization of changes in the start temperature of modeling region before consecutive laser

Table 1. Step-by-step parameters of temperature dynamics and calculation of the thermal accumulation index (TAI) in serial transscleral cyclophotocoagulation (TSCPC)

Number of the shot	T_{start}(i), °C	T_{max}(i), °C	ΔT(i), °C	HeatLoss(i), °C
1	37.0	39.2	2.2	1.9
2	37.3	39.6	2.3	2.0
3	37.6	40.0	2.4	2.1
4	37.9	40.5	2.6	2.3
5	38.2	41.0	2.8	2.5
6	38.5	41.6	3.1	2.8
7	38.8	42.2	3.4	3.1
8	39.1	42.9	3.8	3.5
9	39.4	43.6	4.2	3.9
10	39.7	44.4	4.7	4.4
11	40.0	45.2	5.2	4.9
12	40.3	46.1	5.8	5.5
13	40.6	47.0	6.4	6.1
14	40.9	48.0	7.1	6.8
15	41.2	49.0	7.8	7.5
16	41.5	49.8	8.3	8.0
17	41.8	50.2	8.4	8.1
18	42.1	50.4	8.3	8.0
19	42.4	50.5	8.1	7.8
20	42.7	50.6	7.9	—

Note: T_{start}(i), start temperature of the modeling zone before the ith shot; T_{max}, maximum temperature during the shot; $\Delta T = T_{max}(i) - T_{start}(i)$, temperature increase during the ith shot; $HeatLoss\ (i) = T_{max}(i) - T_{start}(i + 1)$, calculated shot-to-shot temperature loss expressed in °C. HeatLoss (20) was not assessed. The thermal accumulation index (TAI) was calculated as average elevation of T_{start} (i) above a baseline temperature of 37 °C for 20 shots; TAI = 2.85 °C. TAI value is not a cumulative thermal dose.

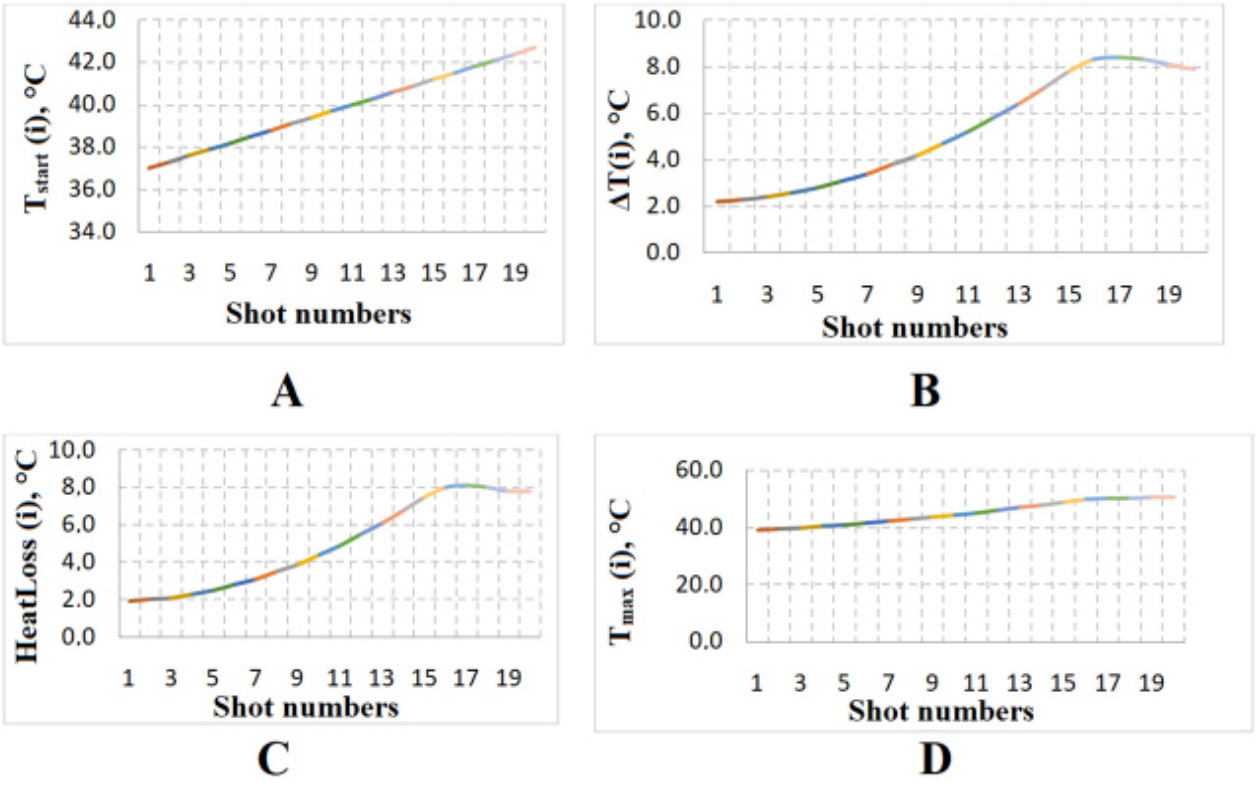


Fig. 2. Step-by-step temperature dynamics in serial transscleral cyclophotocoagulation (TSCPC) under the specified modeling scenario (a series of 20 2-s shots with 1-s shot-to-shot intervals). (A) Dynamics of the pre-shot temperature (Tstart(i)) reflects a specified step-by-step increase in temperature. (B) Dynamics of the temperature increase during the ith shot (ΔT(i) = Tmax(i) - Tstart(i)). (C) Dynamics of the shot-to-shot temperature loss (HeatLoss (i) = Tmax(i) − Tstart(i + 1)). HeatLoss (20) was not calculated. (D) Dynamics of the maximum temperature during the ith shot (Tmax(i)) reflects changes in peak temperature over a series of laser shots.

shots and evaluation of the potential for using the proposed TAI for the description of this component of temperature dynamics.

The temperature range 50–60 °C is an important landmark for the interpretation of temperature profiles, and coagulative tissue changes may occur at a temperature within this range in the presence of exposure of a particular duration. Temperatures exceeding 60 °C may be associated with an increased likelihood of apparent thermal injury including coagulative necrosis [3]. These temperature values are, however, not universal thresholds between reversible and irreversible changes, as the nature of damage is determined by a combination of temperature, duration of exposure and tissue properties. Recent studies on laser-tissue interactions have confirmed the complex, non-linear nature of the thermal response of the tissue which depends on energy absorption and heat conductivity and removal [11].

In the previous model [5], in a 1-W CW mode, Tmax was 50.21 °C (i.e., the 60 °C threshold was not exceeded), whereas in a 2-W CW mode, Tmax was 63.83 °C, and the modeling region was exposed to temperatures exceeding 60 °C for a rather long time. Such a discrepancy indicates a significant impact of laser power on the calculated temperature profile and a potential risk of excessive tissue heating. It is, however, impossible to directly determine the nature of histological changes (i.e., severity, type, location and extent of morphological damage) solely from these temperature characteristics.

The additional step-by-step analysis demonstrated that, under conditions of the examined scenario, the start temperature in the modeling zone for each subsequent shot was always higher than that for the previous shot. The temperature increase for the shot (ΔT) increased until the 17th shot and somewhat decreased thereafter. The calculated inter-shot temperature loss (HeatLoss) followed a similar pattern of changes. Additionally, a consecutive increase in the start temperature was determined by the start temperature increase per cycle which had been set at 0.3 °C. Therefore, the resulting dynamics characterizes a particular modeling scenario and cannot be considered an independent confirmation of the mechanism of residual heat accumulation in the ciliary body.

Szabó and colleagues [12] examined the impact of cumulative energy in repeated applications of subliminal

TSCPC for glaucoma. They assessed cumulative energy in eyes undergoing repeated treatment sessions, but not a direct shot-to-shot residual heat accumulation. The results of their study confirm the relevance of taking into account the cumulative energy load, but do not directly confirm the relevance of the proposed TAI.

Bioheat transfer models (particularly, the Pennes bioheat transfer equation) [9] have provided a theoretical basis for the analysis of heating and cooling processes in biological tissues. The use of these models enables taking into account temporal characteristics of the temperature response. However, to accurately simulate thermal accumulation, temperature calculations should be performed while taking into account the conditions of previous tissue heating and cooling as well as spatial temperature distribution.

Interpretation of TAI

In this study, the TAI is proposed for use as an additional calculated parameter to quantify the increase in the start temperature for the modeling region of the ciliary body before consecutive laser shots. Unlike the maximum temperature (Tmax) which characterizes peak heating during a shot, the TAI determines the average pre-shot elevation of the start temperature above baseline (37 °C). Therefore, the TAI complements the description of the step-by-step temperature dynamics, but is not an independent characteristic of the thermal dose or the severity of thermal damage to the tissue.

The TAI value within the examined scenario and for the first and second halves of the series was 2.85 °C, 1.35 and 4.35 °C, respectively. A larger TAI value for the second half of the series reflected the increase in the average elevation of the start temperature above baseline. This distinction is, however, a mathematical consequence of the specified sequence of start temperatures, but not an independently established pattern of heat accumulation in the tissue.

The cumulative equivalent minutes at 43 °C (CEM43) is used for the quantitative evaluation of tissue exposure to a temperature-time profile in studies on thermal tissue damage [6, 7, 8, 14]. CEM43 calculation is based on the temperature and exposure duration and can be performed either for continuous or intermittent heating if a corresponding temperature-time profile is available. Unlike CEM43, TAI is determined only on the basis of start temperatures before individual shots without integrating the entire temperature curve. Therefore, these two indices have different physical meanings and are not interchangeable. TAI can be considered an additional descriptive characteristic of temperature dynamics along with the previously proposed TEI, DEI and TSI, but cannot replace the evaluation of a temperature-time dose.

A TAI value of 2.85 °C characterizes the examined scenario only and by itself does not confirm a controlled coagulation effect or the absence of a risk of thermal injury. It is premature to establish universal threshold values of TAI for classifying thermal accumulation as mild, moderate or critical, given that the index has not been experimentally and clinically validated. Further research on the index should compare its values not only with the temperature profiles obtained by direct solution of bioheat transfer equations, but also with experimental characteristics of thermal tissue response.

The arrangement of shots delivered in TSCFC in the clinical setting (particularly, an overlap between adjacent laser exposure zones arranged in a fish-scale pattern) may potentially have effects on spatial temperature distribution. Laser handpiece zone-to-zone movements and spatial heat propagation between these zones were, however, not simulated in the additional step-by-step scenario. Therefore, the TAI values obtained cannot be directly associated with a particular clinical pattern for applying laser shots. Further spatio-temporal modeling taking into account laser exposure geometry is required to study this issue.

From the clinical point of view, the results of the previous model enable a theoretical evaluation of temperature profile differences between CW TSCPC modes with different laser power settings. Under modeled conditions, a 2-s 1-W CW TSCPC mode was characterized by lower Tmax and temperatures below 60 °C, which is in agreement with the principles of prevention of the excessive heat exposure which underlie the concept of low dose/ slow coagulation [15, 16]. Such modes have been considered for reducing the rate of complications while maintaining hypotensive efficacy [17-19]. An increase in laser power or exposure duration in TSCPC, however, has been associated with more intensive heating and a potential increase in the risk for thermal tissue damage [1, 2, 20]. Directly translating calculated temperature values into clinical outcomes without clinical validation is inadvisable.

Optical properties of biological tissues (particularly, laser radiation absorption and scattering coefficients) determine the spatial distribution of absorbed energy and, correspondingly, affect the formation of the temperature field in the laser exposure zone [21].

Temperature response studies may have special significance in patients with secondary NVG. Since the ciliary body is the target tissue of TSCPC, impairment of its vascularization and microcirculation may potentially alter local heat dissipation conditions. Ischemic and neovascular processes can affect heat exchange, but the direction and magnitude of these effects depend on local tissue and blood flow characteristics [22, 23]. As individual changes in tissue perfusion were not evaluated in this study, it is impossible to determine their contribution into temperature profile formation. Therefore, the model requires further refining while taking into account hemodynamic characteristics of the ciliary body.

The results of mathematical modeling should also be considered in conjunction with experimental studies on post-TSCPC histopathological changes. The relationship between the laser exposure parameters and the nature of

ciliary body damage (particularly, the possibility of the formation of coagulation changes or more apparent tissue destruction) has been reported [24, 25]. However, to establish a correspondence between specific temperature profiles and morphological tissue changes, experimental studies require simultaneous temperature monitoring and histological evaluation.

Therefore, the results of the previous model [5] demonstrate that the temperature profile depends on the laser power, whereas the step-by-step analysis enables describing the change in the start temperature prior to consecutive laser shots with the help of TAI. The proposed index broadens the descriptive analysis of the modeled temperature dynamics, but cannot provide a standalone assessment of the efficacy of tissue coagulation or the risk for destructive tissue damage. Further refining the modeling while taking into account spatial heat distribution, local perfusion and experimentally confirmed temperature-time characteristics may lay the groundwork for quantitatively justifying the parameters of TSCPC in secondary NVG.

Advantages of the study

The study proposed to use the TAI developed by authors as an additional calculated parameter enabling quantitative characterization of the increase in start temperature above baseline before consecutive laser shots in TSCPC. The previously obtained temperature profiles for 1-W and 2-W CW modes, when used in combination with step-by-step scenario analysis, enable consideration of various aspects of temperature response, including peak heating, the time spend by the tissue in the specified temperature ranges, and cycle-to-cycle changes in the start temperature. Advantages of the proposed approach include easy calculation of TAI and clear definition of its physical meaning and limits of its interpretation. Findings of the study may provide a basis for further refining mathematical models and an investigation of options for optimizing the parameters of TSCPC in secondary TSCPC.

Limitations of the study

The study is based on mathematical modeling without in vivo or ex vivo experimental verification of temperature parameters. The underlying model is deterministic and based on generalized thermophysical and optical characteristics of tissues and does not account for individual variability in local perfusion, pigmentation and the morphology of the ciliary body.

The additional step-by-step scenario provided for a 0.3 °C per cycle increase in the start temperature, but not for the independent calculation of the temperature based on the bioheat transfer equation. Therefore, the resulting TAI value depends directly on the adopted scenario assumption.

Moreover, laser handpiece zone-to-zone movements and spatial heat propagation between these zones were not simulated in the additional step-by-step scenario, which limits the translation of study findings into the clinical setting. As the proposed index (TAI) has not been experimentally and clinically validated, it cannot be used as independent criterion of the efficacy or safety of TSCPC. Further research should involve checking the calculated temperature profiles for conformance to the results of independent numerical modeling and experimental measurements and evaluating TAI sensitivity to changes in model parameters.

Conclusion

Mathematical modeling of serial TSCPC demonstrated that the temperature response of the modeling region of the ciliary body depends on the laser power. Our previous study showed that Tmax was 50.21 °C (i.e., did not exceed 60 °C) for a 1-W CW TSCPC but did exceed 60 °C for a 2-W CW TSCPC, which characterized the temperature profile with a potential risk for destructive thermal tissue damage.

The additional step-by-step scenario for a series of 20 2-s laser shots separated by 1-s intervals allowed quantitatively characterizing the specified increase in the start temperature in the modeling zone from 37.0 to 42.7 °C. The TAI proposed by authors is defined as the average elevation of the start temperature above baseline (37 °C) before consecutive laser shots; it was 2.85 °C and reflected the temperature conditions of the examined scenario.

The TAI may be used an additional descriptive characteristic of the change in the shot-to-shot start temperature, thus complementing the analysis of maximum temperature and time spent by the tissue in the specified temperature ranges. TAI values, however, depend on the adopted modeling assumptions, and cannot be used as an independent criterion of the efficacy or safety of TSCPC. Establishing the prognostic value of TAI assessments with regard to thermal tissue damage requires further experimental and clinical validation.

Author Contributions

OG, PO, VV, AKh and VK contributed to Conceptualization, Study Design, Data Collection, Analysis and Interpretation of Results, Mathematical Modeling and Manuscript Preparation. All authors read and approved the final manuscript.

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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.

Disclaimers

The views expressed in this article are solely those of the authors and do not necessarily represent the official position of their affiliated institution or any funding source.

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.

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Abbreviations

ΔT(i), temperature increase during the ith application; CEM43, cumulative equivalent dose of heating at 43 °C; CW, continuous wave; IOP, intraocular pressure; NVG, neovascular glaucoma; HeatLoss(i), heat loss from ith to (i+1)th applications; TAI, thermal accumulation index; Tmax(i), maximum temperature during the ith application; TSCPC, transscleral cyclophotocoagulation; Tstart(i), initial temperature before the ith application.

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