Thermal Effects of CO_2, KTP, and Blue Lasers with a Flexible Fiber Delivery System on Vocal Folds

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Summary: Objective. To determine the differences in thermal effects on vocal folds between four fiber-routed lasers.

Methods. In this experimental laboratory study the thermal effects of an AcuPulse Duo CO_2 (CO_2 AP), UltraPulse Duo CO_2 (CO_2 UP), KTP, and Blue laser were analyzed using a Schlieren technique on a human tissue mimicking gel model. Power, laser duration, laser fiber distance to tissue and mode (continuous wave [CW] vs pulsed [P] modes) were evaluated in varying combinations in order to compare the effects of the tested lasers and to explore the individual effect on thermal expansion and incision depth of each setting. The model was validated by comparing the results from the Schlieren model with histology of *ex vivo* fresh human vocal folds after laser irradiation using a selection of the same laser settings, and calculating the intraclass correlation coefficient (ICC).

Results. One thousand ninety-eight Schlieren experiments and 56 vocal cord experiments were conducted. In comparison with CW mode, less thermal expansion occurred in P mode in all lasers, while incisions were deeper in the CO_2 and more superficial in the KTP and Blue lasers. The mean thermal expansion was found to be minimally smaller, whereas incision depth was pronouncedly smaller in the KTP and Blue compared to the CO_2 lasers. Duration of laser irradiation was the most important factor of influence on thermal expansion and incision depth for all lasers in both CW and P modes. The ICC for consistency between the results of the Schlieren model and the vocal cord histology was classified from fair to excellent, except for the thermal expansion of the Blue laser, which was classified as poor.

Conclusion. This study demonstrates important differences in thermal effects between CO_2, KTP, and Blue lasers which can be explained by the different physical characteristics of the P modes and divergence of the fiber delivery system. The Schlieren imaging model is a good predictor of the relative thermal effects in vocal fold tissue. Our results can be used as a guidance for ENT surgeons using fiber-routed lasers, in order to achieve effective treatment of vocal fold lesions and prevention of functional impairment of vocal folds.

Key Words: Flexible endoscopic laser—Thermal effects—Vocal folds.

INTRODUCTION

For years, various types of lasers have been used to treat vocal fold lesions. The most common laser treatment is performed under general anesthesia during suspension microlaryngoscopy using a laser system with an articulated arm attached to a microscope. However, technological advancements, such as the incorporation of a working channel in chip-on-tip flexible laryngoscopes and the development of fiber-based laser systems, facilitated the use of laser surgery in an office-based setting.[1] This technique offers an alternative for patients who cannot be treated under general anesthesia due to anatomical limitations or severe comorbidity. When used for benign and premalignant laryngeal lesions, office-based laser surgery is effective, has a shorter procedure duration, and lower hospital costs compared to conventional laser surgery under general anesthesia.[2-5]

Lasers can deliver high energy to tissue at a distance, causing photoangiolysis, coagulation, and ablation, by which laryngeal lesions can be effectively treated. However, the same properties can cause collateral thermal damage to healthy tissue surrounding the lesion. With vocal folds being delicate anatomical structures consisting of different functional layers, collateral damage from any kind of surgery should be avoided to minimize scarring and subsequent dysphonia. Therefore, it is important to understand which lasers and which settings result in the least amount of collateral thermal damage.

Nowadays, several lasers have incorporated flexible fiber laser delivery systems. The use of a (hollow wave guide) fiber-routed CO_2 laser was first described by de Snaijer et al in 1998.[6] With a wavelength of 10.6 μm, the energy of the CO_2 laser is absorbed by water. As human tissue largely consists of water, all types of human tissue are targeted by this laser which makes it a powerful hemostatic scalpel. The first in-office use of a Potassium Titanyl Phosphate (KTP) laser for vocal fold lesions was reported in 2002 by Hirano

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et al.[7] This silica-based fiber-routed laser has a wavelength of 532 nm which is absorbed by hemoglobin which leads to different thermal properties than the CO_2 laser. The effect is angiolytic, while preserving the integrity of the epithelium. Therefore, this laser is mostly used to treat vascular lesions, although it is also used for the treatment of non-vascular lesions, such as papilloma, granuloma, and selected T1 and T2 glottic carcinoma.[8-10] More recently, a silica-based fiber-routed Blue laser (microchip diode) became available with a wavelength of 445 nm, which is better absorbed by hemoglobin compared to the KTP laser. This laser combines photoangiolytic and cutting properties, so it claims to be used for broader indications than the KTP laser.[11] Recommendations made by manufacturers for setting selection in all these lasers are commonly based on empirical research, but the actual histological effects remain unknown.[11-13]

Few articles have been published studying the histological effects of different laser settings,[14-20] and no systematic analysis of the effects of individual laser settings has been performed, apart from our previous study with a CO_2 laser.[21] Therefore, this study aims to investigate the effect of power, laser duration, fiber tip distance to tissue, and mode (continuous vs pulsed wave) on the thermal expansion and incision depth after laser irradiation by two types of CO_2 lasers, a KTP, and a Blue laser, all using a flexible fiber delivery system. A wide range of settings was applied on a human tissue mimicking model in which the thermal effects could be visualized using the dynamic Schlieren imaging technique.[22] To validate this model, the outcomes of the experiments with the Schlieren model were compared with conventional histologic evaluation of *ex vivo* fresh human vocal folds after laser irradiation with these lasers. A broad overview of the differences in thermal effects between the tested lasers and tested settings is demonstrated in this study.

MATERIALS AND METHODS

Laboratory laser set-up

Four different lasers were used to perform the experiments: two CO_2 lasers with a wavelength of 10.6 μm (AcuPulse Duo (*CO_2 AP*) and UltraPulse Duo (*CO_2 UP*), both using a 500 μm diameter FiberLase hollow wave guide, 3° divergence; Lumenis, Yokneam, Israel), a KTP laser (IDAS (*KTP*), Quantel Derma GmbH, Erlangen, Germany, with a single-use 220 μm core and 2000 μm outer diameter Endoprobe fiber, 20° divergence, CeramOptec GmbH, Bonn, Germany) and a Blue laser (WOLF TruBlue laser (*Blue*), with a 400 μm diameter fiber, 25° divergence, A.R.C. Laser, Nuremberg, Germany). Information about the technical specifications of the lasers was obtained from the manufacturers.

Each laser had its own compatible fibers with different characteristics, diameters and divergence, which, depending on the distance to the tissue, affected the spot size and consequently the total energy delivered to the gel or tissue. The divergence of the fibers used for the KTP and Blue lasers is much wider than the hollow wave guide of the CO_2 lasers which results in a wider expansion of the heat in the tissue and less ablative effect (>100°C), because the total energy is divided over a larger volume of tissue. This difference was *not* corrected for, as we aimed to assess the laser properties for their clinical applicability. Similarly, the underlying mechanisms of pulse modes differ between the CO_2, KTP, and Blue lasers. The CO_2 lasers can deliver a very high peak power in (microsecond) pulse mode, whereas the KTP and Blue lasers use ‘chopped’ (millisecond) modes, delivering much lower peak power per pulse. No correction was made for these differences, in order to test the lasers in the way they are used in daily clinical practice.

The lasers were tested with a wide range of settings ([average] power, laser duration, laser distance, mode) in triplicate in the Schlieren model and a selection of these settings was chosen to test on the vocal folds (Table 1).

Dynamic color schlieren imaging technique

We used a model for measurements of the thermal effects based on the color Schlieren imaging technique, which visualizes a temperature gradient in a transparent human tissue mimicking gel. This technique uses a parallel LED beam that is passed through and two lenses, a transparent gel which is irradiated with the laser and a rainbow Schlieren filter made of multicolored concentric rings.[21,22] It is based on the premise that rise in temperature (after irradiation with the laser) changes the refractive index of the gel. By using a multicolored filter, the temperature gradient becomes “visible” during irradiation and is captured on

TABLE 1.
Laser Parameter Settings Schlieren Experiments and Vocal Fold Experiments

	Schlieren Experiments (gel)				*Vocal Folds*		
Laser	*CO_2 AP*	*CO_2 UP*	*KTP*	*Blue*	*CO_2 AP*	*KTP*	*Blue*
Power (W)	4, 6, 8, 10	4, 6, 8, 10	4, 6, 8	4, 6, 8, 10	6, 10	4, 8	6, 10
Laser duration (s)	1, 2, 3	1, 2, 3	1, 2, 3	1, 2, 3	1, 3	1, 3	1, 3
Laser distance (mm)	2, 5, 10, 15	2, 5, 10, 15	2, 5, 10	2, 5, 10	2, 10	2, 5	2, 5
Mode	CW, P, SP	CW, UP	CW, P	CW, P	CW, P, SP	CW, P	CW, P

Notes: P: pulsed mode (CO_2 AP [AcuPulse]: pulses of 40 W, pulse width 0.5-20 ms depending on power setting, 50 Hz; CO_2 UP (UltraPulse): pulses of 200 W, pulse width <1-2 ms, variable Hz depending on power setting; KTP and Blue laser: pulse width 50 ms, 10 Hz); SP: SuperPulse (pulses of 160-180 W, pulse width <0.3 ms, variable Hz depending on power setting) Laser distance: distance between tip of laser fiber and gel or vocal fold.
Abbreviation: CW, continuous wave.

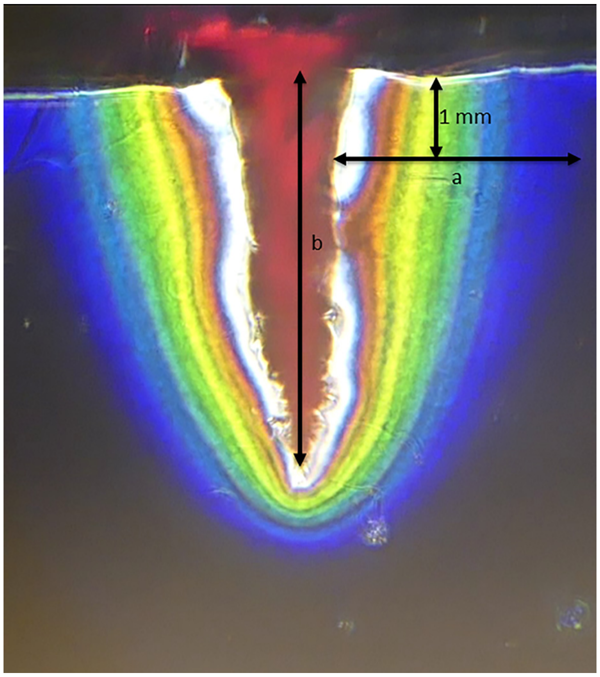

FIGURE 1. Schlieren image during laser irradiation of the human tissue mimicking gel using the CO_2 AP laser. The black arrows indicate the thermal expansion (a) and incision depth (b) measurements.

camera: white indicates the largest temperature (and refractive index) gradient whereas black indicates a constant temperature (Figure 1). This model is described in detail in our previous article. For the experiments with the KTP and Blue laser, the gel was stained with human blood, as these lasers target a specific color (red, ie, hemoglobin) in the light spectrum. This blood was obtained from the Dutch blood bank Sanquin, with patients' permissions for scientific use of the material.

Experiments in polyacrylamide gel

Using the Schlieren imaging technique, a real-time thermal image of the gel was captured with a digital single-lens reflex camera. FIJI imaging software (ImageJ; National Institutes of Health, Bethesda, MD) was used for the measurements of thermal expansion and incision depth.[23] Thermal expansion was defined as the distance from the lateral edge of the incision to the end of the gradient in the horizontal axis measured at 1 mm depth (Figure 1). In experiments in which an incision depth of 1 mm was not reached, the distance from the center of the color gradient to the end of the gradient was taken. Incision depth was defined as the distance between the surface of the gel and the deepest point of the incision. Incision depth was recorded as 5.1 mm in case the incision depth exceeded the limits (5 mm) of image by the camera (CO_2 AP, CW: n =19, P: n =79, SP: n = 49; CO_2 UP, CW: n = 53, UP: n = 85).

Experiments in vocal fold tissue

To validate the Schlieren model, we carried out experiments on *ex vivo* fresh human vocal folds with the CO_2 AP, KTP, and Blue laser. The CO_2 UP laser was not validated, as the underlying mechanism is similar to the CO_2 AP laser. A total of 21 larynges (42 vocal folds) were available for this study, obtained from fresh-frozen human cadavers and the experiments were performed at room temperature. The vocal folds were irradiated with three lasers, using the aforementioned settings (Table 1). The histological evaluation of thermal expansion and incision depth, as previously described,[21] was performed by a pathologist blinded to the laser settings.

Statistical analysis

For the calculations of the mean thermal expansion and incision depth for all four lasers, measurements using a power of 10 W and using 15 mm of laser tip distance were excluded, because the KTP was not tested with a power of 10W and both KTP and Blue lasers were not tested with laser tip distance of 15 mm. For the calculations of mean incision depth for the CO_2 lasers, measurements that exceeded the Schlieren image (>5 mm) were included as 5.1 mm. Therefore, the values of mean incision depth of both CO_2 lasers should be interpreted as *larger than* the stated value.

The effects of power, laser duration, laser distance, and mode were investigated using multivariable linear regression analysis. Because an interaction existed between laser mode (CW vs P) and the other parameters, the effects of these parameters were analyzed for CW and (S)P modes separately. CO_2 laser measurements of incision depths that were >5 mm were excluded from these analyses. The unstandardized β coefficient (B) was calculated for all three parameters (power, laser duration, laser tip distance) to determine the effect on thermal expansion and incision depth, representing the increase or decrease of the thermal expansion or incision depth in mm when increasing one of the parameters with one unit. To validate the Schlieren model, the intraclass correlation coefficient (ICC) for absolute agreement and consistency was calculated. The data analysis was performed using IBM SPSS Statistics version 25 (IBM, Armonk, NY) for Windows (Microsoft, Redmond, WA). P-values <0.05 were considered to be statistically significant. The results of CO_2 AP laser were published previously, still we incorporated these results in this article in order to give a more complete overview of the different laser properties in comparison to the other lasers.[21]

RESULTS

In this study, we conducted 1098 experiments using the polyacrylamide gel: 432 with the CO_2 AP, 288 with the CO_2 UP, 162 with KTP, and 216 with the Blue laser (Table 1). Details of the multivariable linear regression analyses (B, F, R^2, P-values) are presented in the Appendix.

TABLE 2.
Intraclass Correlation Coefficients

		CO_2 AP	KTP	Blue
Thermal expansion	Consistency	0.462	0.619	0.174
	Absolute agreement	0.058	0.607	0.079
	p	0.010	0.005	0.253
Incision depth	Consistency	0.534	0.768	0.736
	Absolute agreement	0.221	0.413	0.608
	p	0.037	0.000	0.000

Comparison of tissue effects

Figure 2 demonstrates the mean thermal expansion and incision depth of all measurements in the tested lasers. Thermal expansion was smaller in P mode compared to CW in all lasers. Specifically for the CO_2 AP laser, thermal expansion was comparable for all modes, while P mode led to the deepest incisions. Also in the CO_2 UP laser the incision was deeper when using P mode. On the contrary, the KTP and Blue lasers show more superficial incisions in P mode compared to CW mode. A large difference in mean incision depth existed between the CO_2 lasers and the KTP and Blue laser.

For the calculations of mean incision depth for the CO_2 lasers, measurements that exceeded the Schlieren image (>5 mm) were included as 5.1 mm. Therefore, the values of mean incision depth of both CO_2 lasers should be interpreted as larger than the stated value.

Laser parameter evaluation

The multivariable linear regression analyses demonstrated that duration of laser irradiation was the most important contributor to both thermal expansion and incision depth in all lasers (Figures 3 and 4). For example, in the CO_2 UP laser in CW mode, every second of laser duration led to an increase of thermal expansion of more than 0.3 mm (Figure 3) and an increase of incision depth of 0.8 mm

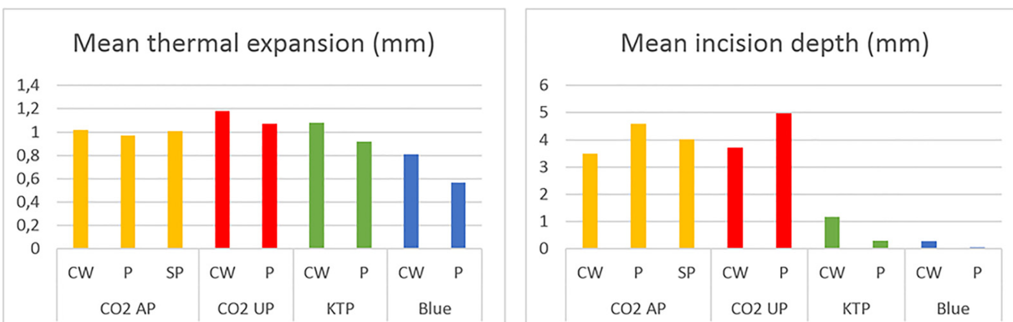

FIGURE 2. Mean of all measurements of thermal expansion and incision depth of the CO_2 AP, CO_2 UP, KTP, and Blue laser.

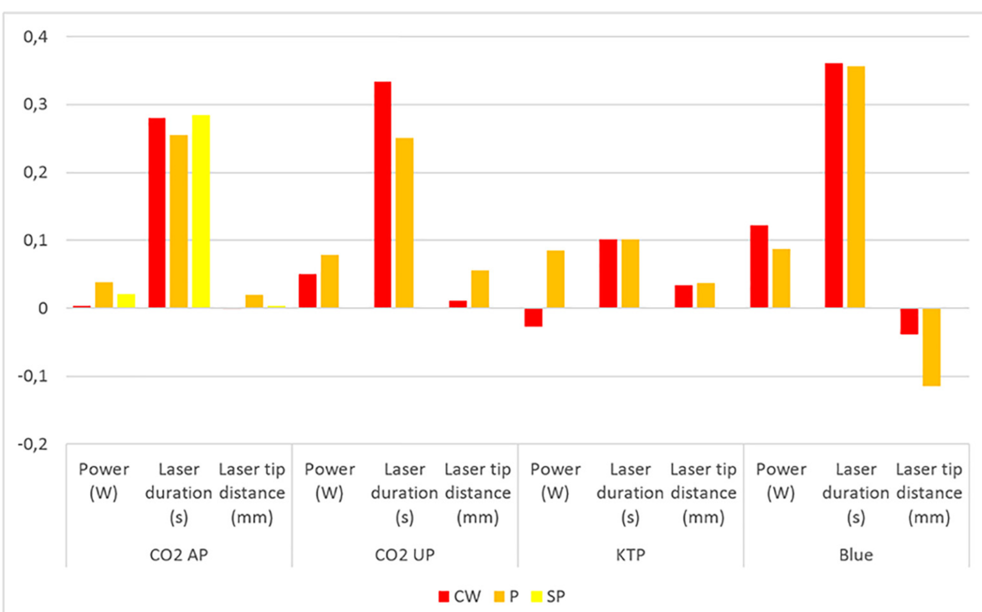

FIGURE 3. Plotted results of multivariable linear regression analyses of thermal expansion in mm (unstandardized B-coefficient).

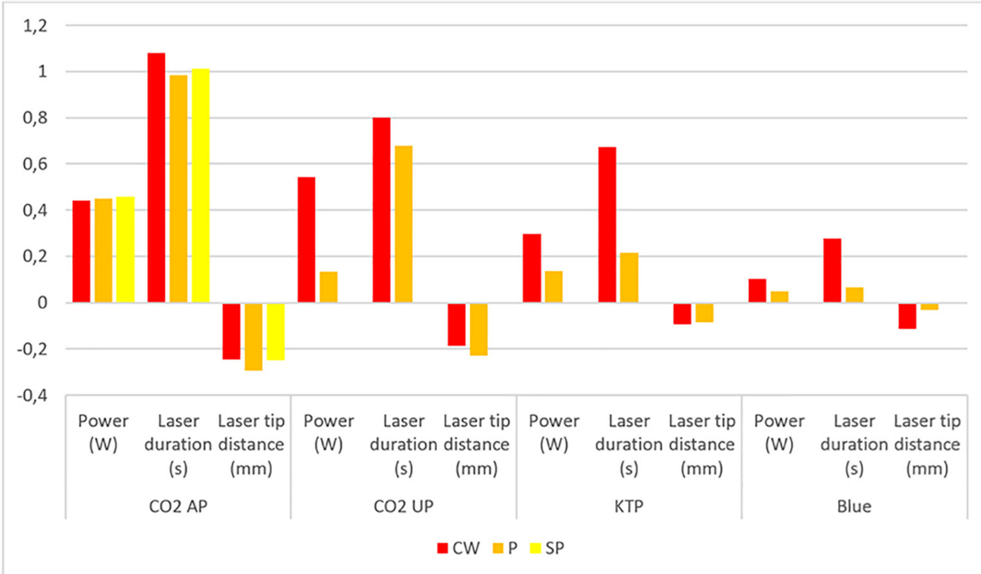

FIGURE 4. Plotted results of multivariable linear regression analyses of incision depth in mm (unstandardized B-coefficient).

(Figure 4), when keeping all other parameters constant. Increasing power usually led to more thermal expansion and deeper incisions, except for the KTP laser in CW mode, which is not what is expected and might indicate a measurement error. Furthermore, increasing the distance between laser tip and the tissue-mimicking gel resulted in more superficial incisions in all lasers, whereas thermal expansion increased, except in the Blue laser.

Additionally, the effect of power on incision depth in the CO_2 UP laser was much smaller using P mode compared to CW mode, ie, increasing power with 1W, when keeping other parameters constant, led to an increase in incision depth of 0.133 mm in P mode compared to 0.544 mm CW mode. Also in the KTP and Blue laser, the effects power, as well as duration and tip distance, were much smaller in P mode compared to CW mode.

Validation with vocal fold experiments

The results of the Schlieren model were compared with results from histological analyses of *ex vivo* fresh human vocal folds irradiated with a selection of laser settings (Table 1, n = 56) by calculating the ICC (Table 2). Using the Cicchetti interpretation guidelines,[24] the ICC for consistency in thermal expansion results of the Schlieren and vocal fold experiments for the CO_2 AP, KTP and Blue laser were classified as fair, good and poor, respectively. The ICC for consistency in incision depth was fair, excellent and good for the CO_2 AP, KTP, and Blue laser, respectively.

DISCUSSION

This is the first study that systematically compared thermal effects of four different lasers using a flexible delivery system. We aimed to give a broad overview of the differences in thermal effects between the tested lasers and laser settings in order to improve flexible endoscopic laser surgery on vocal folds. The first major finding was that thermal effects in P modes in the CO_2 lasers are seemingly contradictory to the effects in this mode in the KTP and Blue lasers, i.e. incision depth slightly increased in the CO_2 and strongly decreased in the KTP and Blue lasers using P mode compared to CW mode, whereas thermal expansion decreased in all lasers. However, this observation can be explained by the different underlying mechanisms of the P modes of these lasers. Additionally, laser duration was the most important factor of influence on thermal expansion and incision depth for all tested lasers in both CW and P modes. In the CO_2 UP laser, a remarkable finding was that the effect of power was smaller when using P mode compared to CW mode. To understand these differences, it is important to elaborate on laser-tissue interaction.

Understanding laser-tissue interaction

Essentially, the reported differences can be explained by the total amount of energy that is delivered by the lasers in a particular timeframe, which can be calculated using the formula *Energy (J) = Power (W) x Time (s)*. As the CW mode gives a continuous beam of energy with a preset power, it is easy to predict the thermal effect depending on the exposure time (Figure 5). The premise of pulse modes is that the energy is delivered in a pulsed beam, varying in frequency, pulse width and peak power, which enables the tissue to heat up rapidly and cool down between the pulses, which reduces thermal damage.[25] But there are several ways in which the pulse modes can be set up, and this differs significantly between the CO_2 and the KTP and Blue lasers, which makes the total amount of delivered energy different between these lasers.

The P modes of the KTP and Blue lasers are most simple to explain: in our study, pulse width was set at 50 milli seconds with a frequency of 10 Hz, so in 1 second 500 milli seconds of

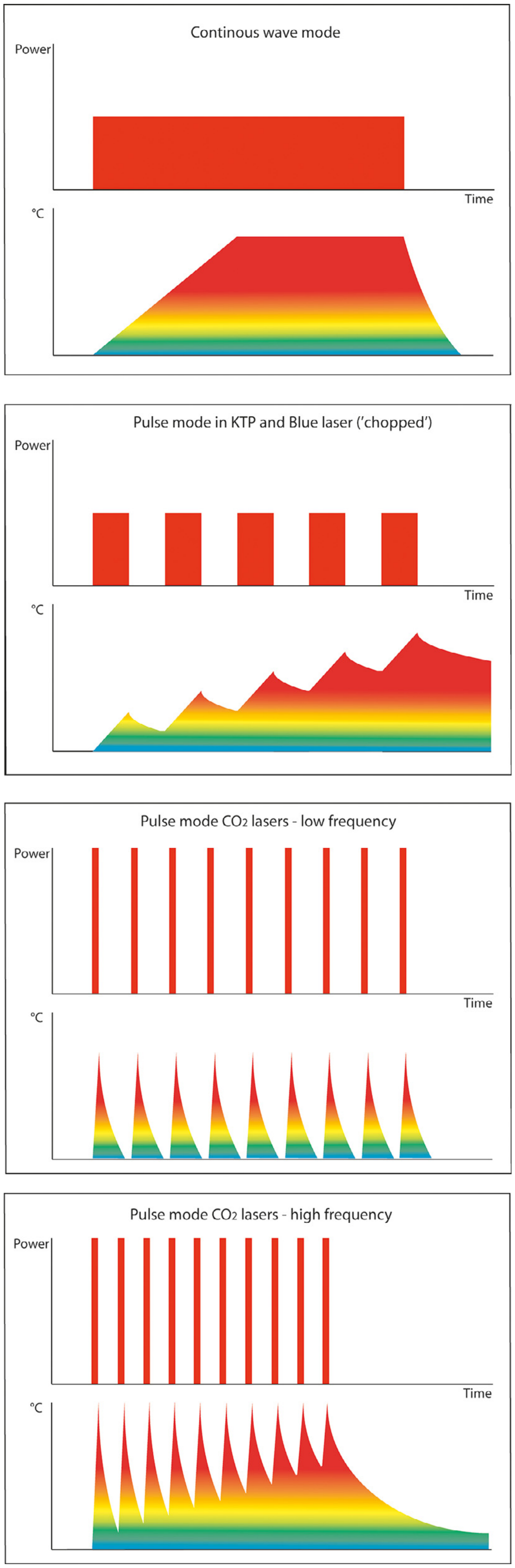

FIGURE 5. Differences in thermal effects in CW and P modes.

laser irradiation was generated. For example, using a power of 6 W in P mode results in 3 W of energy delivered in 1 second (6 W x 0.5 second). So, the total energy delivered by the KTP and Blue laser in P mode is half of the energy delivered in CW mode. The term pulsed mode is misleading and should be called 'chopped' or "intermittent" mode (Figure 5). This explains our finding that P modes in these lasers led to less thermal expansion and more superficial incisions.

The CO_2 lasers have a 'real' pulsed mode. In these lasers, the (S)P modes give very short pulses (0.1-0.5 milli second) with high peak power (40-200 W). In the P mode of the CO_2 AP laser, pulse width is adjusted to the selected power, whereas in the SP mode of this laser and P mode in the CO_2 UP laser, the frequency of pulses is adjusted depending on the selected power. The total energy delivered is similar to CW mode, so still a double amount of energy compared to the KTP and Blue lasers. Additionally, the high peak power leads to a stronger ablative effect, because the tissue instantly heats over 100°C, evaporating the tissue into explosive water vapor creating the incision crater. The heat will be partly transported into the air as hot vapor instead of heating the surrounding tissue.[26] This explains the decreased thermal expansion and increased incision depth in P mode of the CO_2 laser.

Furthermore, the mean incision depth of the KTP and Blue lasers was much smaller than in the CO_2 lasers. In the P modes, this can be easily explained by the reduced amount of energy that is delivered However, also in CW mode the effects of the CO_2 laser are much stronger due to the higher absorption of the laser light in tissue (depending on wavelength) and due to the differences in fiber divergence. The CO_2 fibers deliver a very narrow beam (3°), whereas the beam of the KTP and Blue fibers have much wider divergence (20-25°). Tissue effect does not only depend on the total amount of energy, but also on the volume of the tissue to which the energy is delivered (Figure 6). By increasing the divergence (which can also be done by increasing laser tip distance to tissue), the volume of targeted tissue is also increased, so the delivered energy has to be distributed over a greater volume of tissue. In this way, the ablative effect reduces, while the thermal expansion increases. In contrast to the other lasers, the Blue laser showed decreasing thermal expansion when increasing laser tip distance. The explanation for this finding probably lies in the fact that the sensitivity of the Schlieren model was not sufficient to detect the small temperature changes caused by the Blue laser.

The most important finding from the multivariable linear regression analyses was that laser duration had the largest effect on thermal expansion and incision depth. This finding is also explained by the aforementioned formula on the total amount of delivered energy. This means that when less thermal effect is desired, it is most effective to reduce laser irradiation time and have sufficient time between laser irradiation for thermal relaxation of the tissue (up to tens of seconds). The effect of power is less relevant. Remarkable is that the effect of power on incision depth strongly decreases in P mode compared to CW mode in the CO_2 UP laser. This is an important finding, eg, when using P mode and less thermal effect is desired, reducing power would not be as effective as expected.

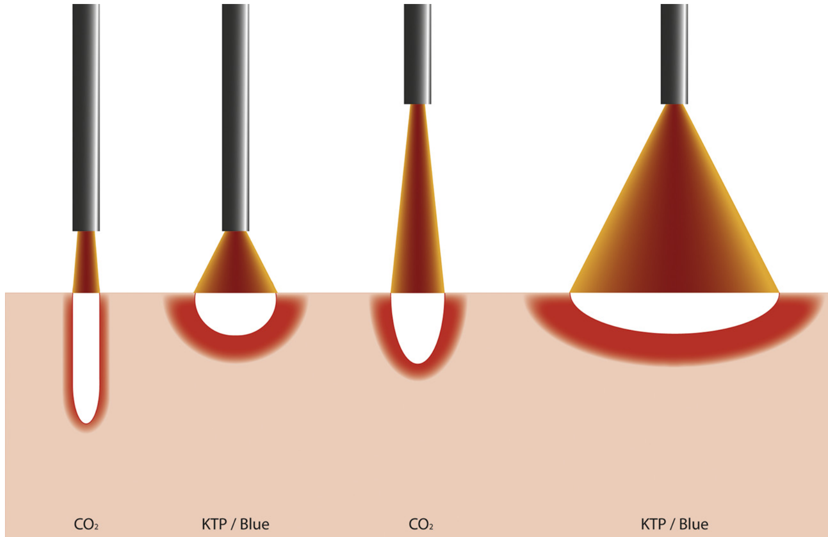

FIGURE 6. Tissue effects depending on fiber diameter and divergence. When distance between laser tip and tissue increases, more thermal expansion and less ablation occurs.

It is interesting to explore the differences of P modes of the CO_2 lasers and what the additional value is of SP mode in CO_2 AP and P mode in CO_2 UP. As the UP CO_2 laser uses the highest peak power (200 W), it has the best cutting properties. Since the effect on thermal expansion is similar for all P modes, our results suggest that the P mode of the CO_2 UP laser is most appropriate to use when the desired surgical effect is cutting, and that there is no additional value of SP mode of the CO_2 AP laser.

Our results demonstrated that the KTP laser was more capable of cutting than the Blue laser. This is in contrast with the premise of the Blue laser to have stronger cutting properties because of higher absorption of its wavelength by hemoglobin. However, there could be an artifact in our measurements. Although, we used human blood to mimic the absorption of tissue, there was no scattering of the light like in normal tissue, which has an effect on the energy distribution. The actual absorption of the laser light in the stained gel was not measured and was assumed to provide a relative comparison. Still, the Schlieren model was validated by the *ex vivo* vocal fold experiments with good to excellent ICC values for incision depth. Another artifact could lie in the use of fresh frozen vocal fold tissue (thawed at room temperature), which contains damaged hemoglobin caused by freezing or lower content of blood cells and thereby could lead to less absorption of the laser light of both lasers. It is important to notice that absorption and heat production from each laser differs within the vocal fold, as it consists of multiple layers with different tissue properties. For example, the squamous epithelium, basal membrane, superficial lamina propria and vocal ligament contain more water and less blood compared to the deeper situated vocalis muscle. Hence, the CO_2 lasers affect the upper layers of the vocal folds more than the KTP and Blue lasers. As our histologic analysis of the irradiated vocal folds was limited to incision depth and thermal expansion, this distinction in tissue properties was not evaluated. Another limitation of our study is the limited amount of experiments that was performed on vocal folds. Fortunately, this was enough to reach good ICC values, except for thermal expansion of the Blue laser. This can be explained by two mechanisms: first, the Schlieren measurements of the thermal expansion of the Blue laser contains many outliers, since there are over 60 outcomes of 0 (due to the limited sensitivity of this Schlieren model to detect smaller temperature changes), which complicates the comparison with the vocal folds measurements. Second, there is a limited variation in thermal expansion measured in the vocal folds which necessarily leads to a small ICC as the relation between the outcomes of the two methods is more difficult to determine. Lastly, the range of measurements of incision depth in the Schlieren model was limited to 5 mm, which was exceeded frequently by the CO_2 lasers and led to a substantial amount of missing values in the multivariable analyses. Despite these limitations, this study remains the first to analyze the thermal effects of four different lasers in such systematic extent. Therefore, we believe that this study is an important step in bridging the gap between laser physics and clinical application.

Recommendations for clinical practice

Our results suggest that, when the fiber-routed CO_2 laser is used for cutting, this is best performed by selecting P mode and high power, keeping the laser fiber at short distance from the targeted tissue. In contrast, when aiming for superficial evaporation of a vocal fold lesion, we suggest to use CW mode at low power, keeping the fiber tip at further distance from the tissue. The KTP and Blue laser were found to have much smaller cutting effects, therefore we advocate to use these types of laser only for superficial evaporation of vocal fold lesions. To reduce collateral thermal expansion and prevent deep thermal damage, our results suggest to use

P mode at low power with sufficient time (up to tens of seconds) between laser irradiation to promote thermal relaxation. Because the thermal effects are relatively small in these lasers, it is advisable to keep the laser tip at short distance of the tissue. In all lasers, exposure time should be limited as much as possible, in order to prevent thermal damage to the surrounding healthy tissue. To reduce exposure time, the "*scanning*" technique can be used, which means that the laser beam is moving back and forth over the targeted tissue. Future research on this topic should consist of a randomized controlled trial in order to define which laser and which settings are appropriate to treat specific vocal folds lesions, exploring the balance between effective treatment and preserving vocal folds function.

CONCLUSION

This study demonstrates important differences in thermal effects among CO_2, KTP, and Blue lasers which can be explained by the different physical characteristics of the P mode and divergence of the fiber delivery system. It is important to realize that the P modes in the CO_2 lasers consist of short high peak power pulses ablating/cutting the tissue efficiently. In contrast, the P mode in the KTP and Blue lasers simply "chops" the CW energy into intermittent 'pulses', delivering a lower total energy. Further, the divergence of hollow waveguides used with CO_2 lasers is far smaller compared to the silica-based fibers used for the KTP and Blue laser resulting in higher ablative effects, even at larger distance from the tissue. We found that the Schlieren imaging model is a good predictor of the relative thermal effects in vocal fold tissue. Our results can be used as a guidance for ENT surgeons using lasers with a flexible delivery system, in order to achieve both effective treatment and prevention of functional impairments of vocal folds.

CONFLICTS OF INTEREST

The authors have no conflicts of interests to declare.

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APPENDIX

See Appendix Table A.

TABLE A.
Multivariable Linear Regression Analysis (Unstandardized B Coefficients) of Thermal Expansion and Incision Depth (in mm)

	Thermal Expansion				*Incision Depth*			
	CO_2 AP	*CO_2 UP*	*KTP*	*Blue*	*CO_2 AP*	*CO_2 UP*	*KTP*	*Blue*
Continuous wave								
Power (W)	0.003*	0.050	−0.027	0.122	0.441	0.544	0.296	0.101
Laser duration (s)	0.280	0.334	0.101	0.361	1.080	0.799	0.674	0.278
Laser tip distance (mm)	− 0.001*	0.011	0.034	−0.038	−0.245	−0.187	−0.094	−0.112
	$F(3,140) = 231.6$	$F(3,127) = 98.8$	$F(3,79) = 22.3$	$F(3,100) = 16.2$	$F(3,121) = 329.8$	$F(3, 83) = 98.2$	$F(3,80) = 57.5$	$F(3,101) = 42.2$
	$P < 0.05$	$P < 0.05$	$P < 0.05$	$P < 0.05$	$P < 0.05$	$P < 0.05$	$P < 0.05$	$P < 0.05$
	$R^2 = 0.832$	$R^2 = 0.700$	$R^2 = 0.458$	$R^2 = 0.327$	$R^2 = 0.891$	$R^2 = 0 .780$	$R^2 = 0.683$	$R^2 = 0.556$
Pulse mode								
Power (W)	0.038	0.078	0.085	0.087	0.449	0.133	0.137	0.049
Laser duration (s)	0.255	0.251	0.101	0.356	0.983	0.680	0.215	0.066*
Laser distance (mm)	0.020	0.055	0.037	−0.115	−0.293	−0.229	−0.084	−0.031
	$F(3,140) = 192.8$	$F(3,140) = 152.5$	$F(3,78) = 19.8$	$F(3,100) = 71.9$	$F(3,62) = 42.1$	$F(3,48) = 31.8$	$F(3,80) = 30.8$	$F(3,101) = 9.5$
	$P < 0.05$	$P < 0.05$	$P < 0.05$	$P < 0.05$	$P < 0.05$	$P < 0.05$	$P < 0.05$	$P < 0.05$
	$R^2 = 0.805$	$R^2 = 0.766$	$R^2 = 0.432$	$R^2 = 0.683$	$R^2 = 0.671$	$R^2 = 0.666$	$R^2 = 0.536$	$R^2 = 0.220$
Superpulse mode								
Power (W)	0.021				0.457			
Laser duration (s)	0.285				1.012			
Laser distance (mm)	0.003*				−0.248			
	$F(3,140) = 194.4$				$F(3,90) = 64.8$			
	$P < 0.05$				$P < 0.05$			
	$R^2 = 0.806$				$R^2 = 0.684$			

* All unstandardized B coefficients were statistically significant (P < 0.05) except for the values marked with an asterisk.

REFERENCES

1. Rosen CA, Amin MR, Sulica L, et al. Advances in office-based diagnosis and treatment in laryngology. *Laryngoscope*. 2009;119(suppl 2): S185–S212. https://doi.org/10.1002/lary.20712.
2. Wellenstein DJ, Honings J, Schimberg AS, et al. Office-based CO(2) laser surgery for benign and premalignant laryngeal lesions. *Laryngoscope*. 2020;130:1503–1507. https://doi.org/10.1002/lary.28278.
3. Schimberg AS, Wellenstein DJ, van den Broek EM, et al. Office-based vs. operating room-performed laryngopharyngeal surgery: a review of cost differences. *Eur Arch Otorhinolaryngol*. 2019;276:2963–2973. https://doi.org/10.1007/s00405-019-05617-z.
4. Wellenstein DJ, Schutte HW, Takes RP, et al. Office-based procedures for the diagnosis and treatment of laryngeal pathology. *J Voice*. 2017. https://doi.org/10.1016/j.jvoice.2017.07.018.
5. Koufman JA, Rees CJ, Frazier WD, et al. Office-based laryngeal laser surgery: a review of 443 cases using three wavelengths. *Otolaryngol Head Neck Surg*. 2007;137:146–151. https://doi.org/10.1016/j.otohns.2007.02.041.
6. de Snaijer A, Verdaasdonck R, Grimbergen M, et al. Design and realization of a fiber delivery system for the continuous-wave and pulsed CO2 laser. *SPIE*. 1998.
7. Hirano S, Kojima H, Tateya I, et al. Fiberoptic laryngeal surgery for vocal process granuloma. *Ann Otol Rhinol Laryngol*. 2002;111:789–793. https://doi.org/10.1177/000348940211100905.
8. Zeitels SM, Akst LM, Bums JA, et al. Pulsed angiolytic laser treatment of ectasias and varices in singers. *Ann Otol Rhinol Laryngol*. 2006;115:571–580. https://doi.org/10.1177/000348940611500802.
9. Zeitels SM, Burns JA. Oncologic efficacy of angiolytic KTP laser treatment of early glottic cancer. *Ann Otol Rhinol Laryngol*. 2014;123:840–846. https://doi.org/10.1177/0003489414538936.
10. Lin DS, Cheng SC, Su WF. Potassium titanyl phosphate laser treatment of intubation vocal granuloma. *Eur Arch Otorhinolaryngol*. 2008;265:1233–1238. https://doi.org/10.1007/s00405-008-0628-6.
11. Hess MM, Fleischer S, Ernstberger M. New 445 nm blue laser for laryngeal surgery combines photoangiolytic and cutting properties. *Eur Arch Otorhinolaryngol*. 2018;275:1557–1567. https://doi.org/10.1007/s00405-018-4974-8.
12. Remacle M, Ricci-Maccarini A, Matar N, et al. Reliability and efficacy of a new CO2 laser hollow fiber: a prospective study of 39 patients. *Eur Arch Otorhinolaryngol*. 2012;269:917–921. https://doi.org/10.1007/s00405-011-1822-5.
13. Mallur PS, Johns 3rd MM, Amin MR, et al. Proposed classification system for reporting 532-nm pulsed potassium titanyl phosphate laser treatment effects on vocal fold lesions. *Laryngoscope*. 2014;124:1170–1175. https://doi.org/10.1002/lary.22451.
14. Broadhurst MS, Akst LM, Burns JA, et al. Effects of 532 nm pulsed-KTP laser parameters on vessel ablation in the avian chorioallantoic membrane: implications for vocal fold mucosa. *Laryngoscope*. 2007;117:220–225. https://doi.org/10.1097/mlg.0b013e31802b5c1c.
15. Torkian BA, Guo S, Jahng AW, et al. Noninvasive measurement of ablation crater size and thermal injury after CO2 laser in the vocal cord with optical coherence tomography. *Otolaryngol Head Neck Surg*. 2006;134:86–91. https://doi.org/10.1016/j.otohns.2005.09.016.
16. Buchanan MA, Coleman HG, Daley J, et al. Relationship between CO2 laser-induced artifact and glottic cancer surgical margins at variable power doses. *Head Neck*. 2016;38(suppl1):E712–E716. https://doi.org/10.1002/hed.24076.
17. Goharkhay K, Moritz A, Wilder-Smith P, et al. Effects on oral soft tissue produced by a diode laser in vitro. *Lasers Surg Med*. 1999;25:401–406.
18. Devaiah AK, Shapshay SM, Desai U, et al. Surgical utility of a new carbon dioxide laser fiber: functional and histological study. *Laryngoscope*. 2005;115:1463–1468. https://doi.org/10.1097/01.mlg.0000171021.73635.3b.
19. Azevedo AS, Monteiro LS, Ferreira F, et al. In vitro histological evaluation of the surgical margins made by different laser wavelengths in tongue tissues. *J Clin Exp Dent*. 2016;8:e388–e396. https://doi.org/10.4317/jced.52830.
20. Wilder-Smith P, Arrastia AM, Liaw LH, et al. Incision properties and thermal effects of three CO2 lasers in soft tissue. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 1995;79:685–691.
21. Schimberg AS, Klabbers TM, Wellenstein DJ, et al. Optimizing settings for office-based endoscopic CO(2) laser surgery using an experimental vocal cord model. *Laryngoscope*. 2020;130:E680–e685. https://doi.org/10.1002/lary.28518.
22. Verdaasdonk RMSC, Grimbergen MCM. Rem AI Imaging techniques for research and education of thermal and mechanical interactions of lasers with biological and model tissues. *J Biomed Optics*. 2006;11:1–15.
23. Schindelin J, Arganda-Carreras I, Frise E, et al. Fiji: an open-source platform for biological-image analysis. *Nature Methods*. 2012;9:676. https://doi.org/10.1038/nmeth.2019.
24. Cicchetti DV. Guidelines, criteria, and rules of thumb for evaluating normed and standardized assessment instruments in psychology. *Psychol Assessment*. 1994;6:284–290. https://doi.org/10.1037/1040-3590.6.4.284.
25. Yan Y, Olszewski AE, Hoffman MR, et al. Use of lasers in laryngeal surgery. *J Voice*. 2010;24:102–109. https://doi.org/10.1016/j.jvoice.2008.09.006.
26. Ansari MA, Erfanzadeh M, Mohajerani E. Mechanisms of laser-tissue interaction: II. Tissue thermal properties. *J Lasers Med Sci*. 2013;4:99–106.