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Development of compression-controlled low-level laser probe system: towards clinical application

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Abstract

Various physico-chemical tissue optical clearing (TOC) methods have been suggested to maximize photon density in tissue. In order to enhance photon density, a compression-controlled low-level laser probe (CCLLP) system was developed by utilizing the principle of mechanical tissue compression. Negative compression (NC) was applied to the laser probes built in various diameters and simultaneously the laser was irradiated into ex-vivo porcine skin samples. Laser photon density (LPD) was evaluated as a function of NC and probe diameter by analyzing 2D diffusion images of the laser exposures. The CCLLP system resulted in a concentrated laser beam profile, which means enhancement of the LPD. As indicators of LPD, the laser peak intensity increased and the full width at half maximum (FWHM) decreased as a function of NC. The peak intensity at −–30 kPa increased 2.74, 3.22, and 3.64 fold at laser probe diameters of 20, 30, and 40 mm, respectively. In addition, sample temperature was measured with a thermal camera and increased 0.4 K at −30 kPa after 60 s of laser irradiation as a result of enhanced LPD. The CCLLP

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system effectively demonstrated enhancement of the LPD in tissue and potentially its clinical feasibility.

Keywords

Photon density; Low-level laser; Compression; Tissue optical clearing

Introduction

Tissue optical clearing (TOC) methods have attracted public attention in a short period of time due to the maturity of light therapy and diagnostics, which are based on light–tissue interactions [1], such as absorption, reflection, transmission, and scattering [2]. Among all of the complex light–tissue interactions, optical scattering limits the light penetration depth in tissue and, consequently, photon density. Various chemical (hyperosmotic chemical agent [HCA]), thermal (temperature), and mechanical (compression and stretching) methods have been suggested as effective TOC methods for reducing optical scattering. Even though such methods have shown some promise, further studies are needed for clinical application.

Chemical methods are based on the mechanism of skin dehydration [3–5], replacement of interstitial or intracellular water by HCA, structural modification or dissociation of collagen fibers [6, 7], and refractive index matching [3, 8]. However, further studies are required to understand the complex biological interaction mechanisms [9] and to develop better physical methods to maximize the HCA diffusion rate through the skin barrier. Laufer et al. demonstrated that the changes in the optical properties of human dermis and sub-dermis can occur in response to temperature changes [10]. Mechanical compression demonstrated TOC effect for clinical application [11] and has advantages in low-level laser therapy as a non-invasive modality. Previous studies have evaluated the changes in tissue optical properties due to compression [12, 13]. Shangguan et al. [14] demonstrated that both the absorption and scattering coefficients increased as a function of compression (0–1.5 kg/cm^2) and the irreversibility of tissue optical properties due to the compression. In that study, overall transmittance increased, and tissue thickness and weight decreased about 72% and 40%, respectively.

Based on the compression effect in tissue, a compression-controlled low-level laser probe (CCLLP) system was developed to enhance the laser photon density (LPD) in soft tissue by quantitatively controlling tissue compression. The laser probes of three different diameters were built and their potential clinical usefulness was investigated with ex-vivo porcine skin samples.

Materials and methods

Sample preparation

Ex-vivo abdominal porcine skin samples were obtained from a local abattoir and used because their structural and immunohistochemical characteristics were similar to those of human skin [15–17]. The samples were prepared to a size of 70×160 mm^2 with an average thickness of 2.8 mm.

Compression-controlled low-level laser probe system

A CCLLP system was developed to enhance the LPD in tissue. Figure 1a shows a schematic diagram of the probe, which consisted of a vacuum hole to supply negative compression (NC), a supporter for guiding the optical fiber, and an acrylic probe body to observe skin

deformation. The CCLLP system was designed to control both NC and laser parameters simultaneously. In order to evaluate the LPD as a function of probe diameter, three different probes were built with diameters of 20, 30, and 40 mm as shown in Fig. 1b.

Experimental setup

Figure 2 shows the experimental setup designed to acquire the 2D diffusion images of laser beam profile (LBP) transmitted by the skin samples. The setup consisted of a compression controller, image acquisition, and diode laser compartments. The compression controller compartment is composed of a 12-V DC motor pump (KPV36E-12A, KOGE Electronics, Xiamen, China), NC manometer, and DC power supply. The diode laser compartment was composed of an 808-nm diode laser (L808P200, Thorlabs, Kansas, USA), which has a maximum output power of 200 mW and is operated in continuous-wave mode, an optical fiber port (PAF-SMA-11-B, Thorlabs, Kansas, USA), a diode laser mount (LDM21, Thorlabs, Kansas, USA) equipped with aspheric lenses (C570TM-B, A230TM-B, Thorlabs, Kansas, USA), and a multi-mode optical fiber patch cord (FT1.5EMT, Thorlabs, Kansas, USA). For LPD study by NC, the maximum power of the laser was adjusted to 43 mW at the distal end of optical fiber in order to avoid light saturation. The 2D diffusion images were acquired with a CCD camera (cs8620i, Toshiba Teli Corp, Tokyo, Japan) placed on the opposite side of the skin samples. The CCD camera has a field of view of 29.9°(H)×22.6° (V) with a C-mount lens and detector size of 768(H)×494(V) pixels with an 8.4×9.8 μm pixel size. The 251×251 pixel window, including the LBP, was extracted and analyzed with a laboratory-built MATLAB program. The CCD camera in Fig. 2 was replaced with a thermal imaging camera (Thermovision A40, FLIR Systems, Boston, MA, USA) in order to evaluate the temperature profile by the LPD. The thermal imaging camera has a spatial resolution of 1.3 mrad and a field of view of 24×18°/0.3 m with a 35-mm lens. Sensing temperature ranges from −40°C to +500°C with thermal sensitivity of 0.08°C in spectral range from 7.5 through 13 μm. The output power of the laser was adjusted to 134 mW for thermal effect investigation by LPD.

Procedures

LPD was quantitatively evaluated by analyzing the full width at half maximum (FWHM) and peak intensity of LBP as a function of NC and probe diameter. The NC was applied from 0 through −30 kPa with −5 kPa increment because tissue optical properties can be irreversibly affected by over compression [14]. To verify the fidelity of the experiment results, five experiments were performed with five different samples.

The sample temperature variation by the LPD was evaluated by analyzing thermal images taken every 5 s using the 40-mm probe at −30 kPa. The sample, which has an initial temperature of 16.42°C, was irradiated by the laser for 60 s in order to minimize artifacts by sample dehydration. Three experiments were performed with three different samples. An aluminum sample holder (Fig. 1) was used to fix the samples during NC. Room temperature was maintained at 16.19°C during the experiments.

Mathematical modeling of temperature variation by LPD

In a mathematical model, the temperature in biological tissue is described by the following bio-heat transfer equation, which is based on the energy exchange between blood vessels and the surrounding tissue [22, 23]:

$$\rho c\frac{\partial T}{\partial t}=\nabla\cdot(k\nabla T)+Q_s+Q_p \quad (1)$$

where T is the tissue temperature depending on time t; ρ is the tissue density; c is the tissue specific heat; k is the tissue thermal conductivity; Q_s is the external heat source; Q_p is the heat removal due to perfusion. In this study, ρ, c, and k are constant, Q_p is zero, and Q_s is

$$Q_s = \mathrm{A}\int_0^t \delta(C,\tau)d\tau \tag{2}$$

where C is a point in the tissue right under the probe in our experiment and A is a constant laser intensity for the time, t. Assuming the following: (1) tissue geometry is a two-dimensional plane; (2) temperature depends only on distance from point C; (3) temperature goes to zero as time goes to zero; and (4) the temperature goes to zero at large distances from point C, then the solution of Eq. (1) is given as follows:

$$T(r,t) = T_0 + \frac{\mathrm{A}}{4\pi \mathrm{k}|r|}\mathrm{erfc}\left(\frac{|r|\sqrt{\rho \mathrm{c}}}{2\sqrt{\mathrm{k}t}}\right) \tag{3}$$

where T_0 is the initial temperature and A=134 mW, ρ = 1,000 (kg/m^3), c=4,200 (J/kgK), and k=1.8 (W/mK) [24] in mathematical modeling. In a previous study, Cain et al. [24] used a thermal conductivity k for water immerged porcine skin in a numerical simulation. However, the k was assumed to be three times larger value in this study because fresh skin sample was considered to be more dehydrated than the previous study.

Results

Figure 3 shows 3D images of LBPs at 0, −15, and −30 kPa (from left to right in each figure) for (a) 20, (b) 30, and (c) 40 mm probes. Although the images show an anisotropic pattern because of the complex morphological structure and non-homogeneity of biological tissue, the results illustrates the enhancement of LPD by NC. For all probe diameters, LBPs were enhanced as a function of NC.

The peak intensity (Fig. 4) was computed as a function of NC and probe diameter. For all probe diameters, the peak intensity greatly increased at the initial −5 kPa and then, linearly increased as a function of the NC with a similar slope. At the maximum −30 kPa, the peak intensities (Fig. 4) increased by a factor of 2.74, 3.22, and 3.64 and the FWHM (Fig. 5) decreased by a factor of 1.35, 1.57, and 3.55 for probe diameters of 20, 30, and 40 mm, respectively. The largest probe diameter resulted in the highest peak intensity for all NCs. Figure 6 shows the sample temperature variation by NC as a function of time. The sample temperature decreased 0.19 K at 0 kPa but increased 0.4 K at-30 kPa after 60 s of laser irradiation. In addition, Fig. 6 shows the mathematical modeling result based on the analytic solution in Eq. (3) and experimental results with and without NC.

Discussion

Previous studies [13, 14] demonstrated that mechanical compression of an elastin biomaterial resulted in changes in the tissue optical properties due to both tissue thickness reduction and water content loss. The tissue thickness reduction contributes to a decrease in optical pathlength, and the water content loss contributes to the spatial decrease between elastin layers and therefore, refractive index matching. Most previous mechanical compression studies were mainly focused on water and blood movement in tissue, thermal change in adipose regions, or changes in tissue morphological or mechanical properties [6,

18–20]. In this study, the mechanical compression method was employed to achieve a TOC effect and therefore, non-invasively enhance the LPD in soft tissue.

At present, low-level laser probes are simply attached on the skin surface using medical tape or passively and manually handled by operators. Such manipulations cannot precisely control tissue compression and therefore the penetration depth and LPD. In order to partially address this limitation, the CCLLP system was developed to control both the NC and laser parameters simultaneously. The self-sustaining capability of the probe was confirmed during the application of NC by visually monitoring the airtight of the probe.

The LBP was more concentrated as a function of NC as shown in Fig. 3, demonstrating the efficacy of the probe for enhancement of the LPD in soft tissue. Figure 4 shows the quantitative analysis as a function of NC and probe diameter. The peak intensity was linearly increased, implying the enhancement of LPD at the region of interest (ROI). A greater increase in the peak intensity at the initial –5 kPa might be due to abrupt tissue deformation (e.g., tissue stretching) and therefore, abrupt reduction in epidermal thickness. Hendriks et al. reported a 7% reduction of tissue thickness at 20 kPa and 17% at 35 kPa [21]. The initial changing ratio was greater in larger probe diameters. It might be because the larger probe results in more tissue deformation (stretching) and therefore, reduction of optical pathlength in tissue. The peak intensity linearly increased as a function of NC (−5 through −30 kPa) across all probe diameters. As a result, the LPD might be effectively controlled by controlling both the NC and probe diameter, which affect skin deformation. As another indicator of LPD, the FWHM decreased as a function of the NC and probe diameter (Fig. 5). The probes with diameters of 20 and 30 mm resulted in a similar decreasing rate of FWHM without correlation with NC. However, the FWHM of the 40 mm laser probe was greatly affected by NC, resulting in a maximum decrease at −30 kPa.

The NC resulted in a temperature rise in the porcine skin samples due to the enhanced LPD. However, sample temperature without NC decreased to room temperature, implying that the temperature in soft tissue might not be affected only by laser irradiation without compression because the photon energy of the laser might not be efficiently delivered to the ROI. Tissue optical properties can be changed by temperature variation [6, 10]. Therefore, a temperature rise due to NC might result in changes in tissue optical properties, which causes additional enhancement in the LPD by minimizing the refractive index mismatch. Both Figs. 4 and 6 imply that the probe might be useful for therapeutic applications. In the mathematical modeling, we could confirm a similar pattern between the modeling and experimental results (Fig. 6) although there is a small difference between them, since many mathematical assumptions were given in the modeling.

The probe can be built in various diameters depending on the intended therapeutic purpose and ROI. In addition, the shape of the optical fiber can be varied by using an optical fiber bundle to manipulate the LBP pattern in tissue and therefore, potentially obtain further enhancement of LPD. Other methods such as temperature and hyperosmotic chemical agents, which also contribute TOC, can be combined into the probe system to further enhance LPD.

Conclusions

This study demonstrated that the CCLLP system can effectively enhance the LPD in soft tissues by controlling NC and probe diameter. Its clinical usefulness was potentially validated with various probe diameters and self-sustaining capability of the probe. In future studies, the positive compression applied to tissue by an optical fiber and the variation in

tissue thickness by NC must be experimentally and numerically studied for better understanding of the CCLLP system.

Acknowledgments

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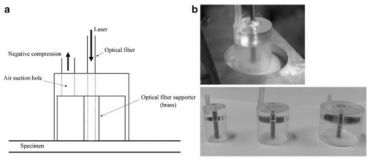

Fig. 1.

a Schematic diagram of compression-controlled low-level laser probe, which consists of an air suction hole, optical fiber supporter, and optical fiber. **b** The upper image shows the probe applied on an ex-vivo porcine skin sample, and the bottom images from left to right show the probes with the diameters of 20, 30, and 40 mm

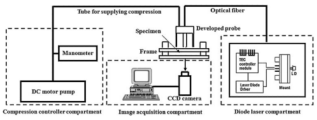

Fig. 2.
Experimental setup to measure the laser photon density in soft tissue consisting of a compression controller, image acquisition, and diode laser compartment

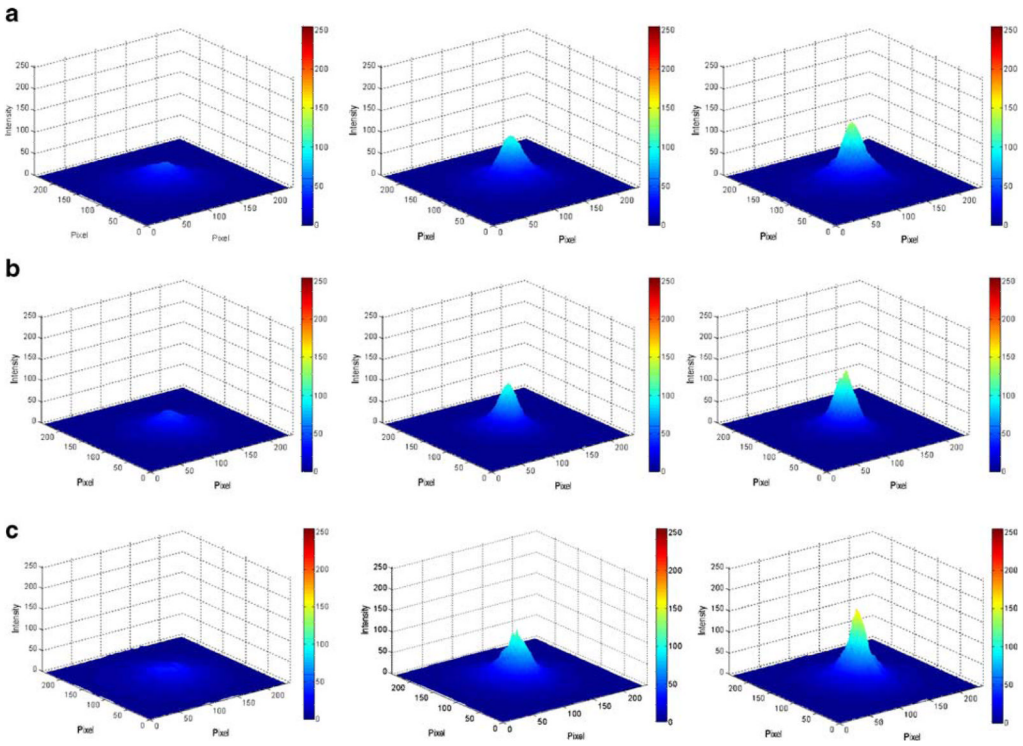

Fig. 3.

3D image analysis of laser beam profile as a function of probe diameters of (**a**) 20, (**b**) 30, and (**c**) 40 mm. The images from left to right at each row were obtained at 0, −15, and −30 kPa

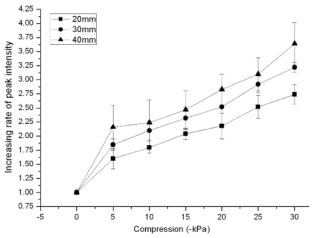

Fig. 4.

The negative compression effect in laser photon density was quantitatively evaluated by analyzing the increasing rate of laser peak intensity as a function of the negative compression at probe diameters of 20, 30, and 40 mm

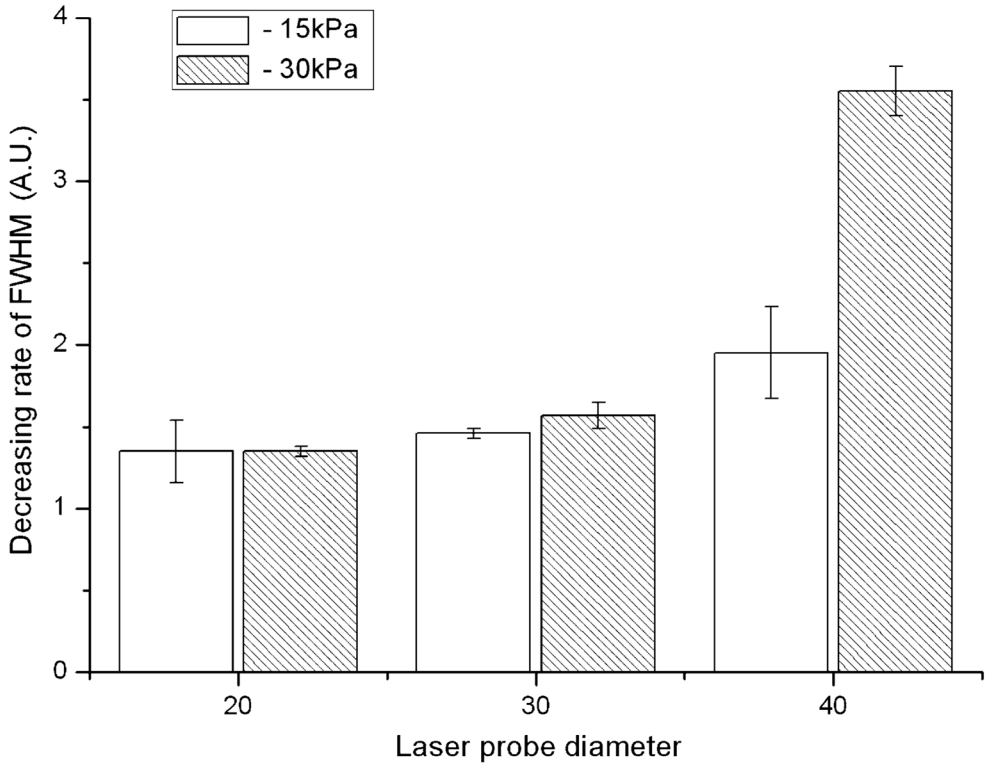

Fig. 5.
Full width at half maximum (FWHM) decreasing rate of laser beam profile as a function of probe diameters at −15 and −30 kPa

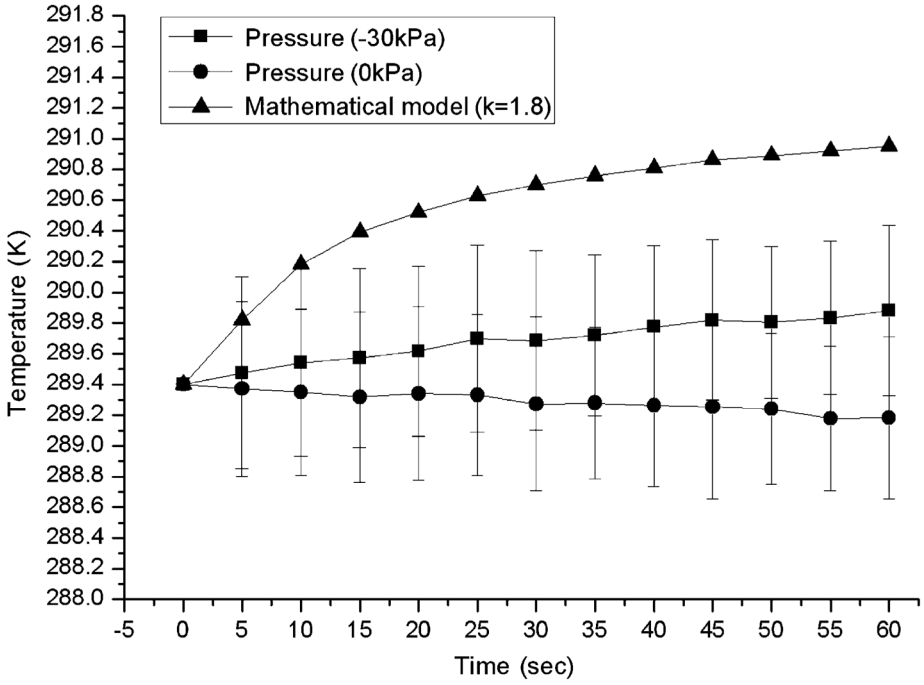

Fig. 6.

The effect of the temperature variation by negative compression and comparison with mathematical modeling. The−30 kPa was applied to the 40 mm laser probe in order to induce maximum laser photon density in sample