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BIOMEDICAL OPTOACOUSTICS

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Optoacoustics is a promising modality for biomedical imaging, sensing, and monitoring with high resolution and contrast. In this paper, we present an overview of our studies for the last two decades on optoacoustic effects in tissues and imaging capabilities of the optoacoustic technique. In our earlier optoacoustic works we studied laser ablation of tissues and tissue-like media and proposed to use optoacoustics for imaging in tissues. In mid-90s we demonstrated detection of optoacoustic signals from tissues at depths of up to several centimeters, well deeper than the optical diffusion limit. We then obtained optoacoustic images of tissues both *in vitro* and *in vivo*. In late 90s we studied optoacoustic monitoring of thermotherapy: hyperthermia, coagulation, and freezing. Then we proposed and studied optoacoustic monitoring of blood oxygenation, hemoglobin concentration, and other physiologic parameters.

Keywords: Optoacoustics; imaging; monitoring; laser ablation; nanoparticles.

Biomedical optics has found a number of important diagnostic and therapeutic applications, in part due to high optical contrast which is based on spectral properties of tissue chromophores.[1] The high contrast is a major advantage of optical diagnostic techniques compared to other imaging modalities such as ultrasonography. However, pure optical technologies have limited resolution due to strong light scattering in tissues, in particular, at depths greater than the light penetration depth.

Optoacoustic imaging is based on generation of ultrasound in tissues by short optical pulses. This yields high (optical) contrast and high (ultrasound) resolution that can be used for imaging, sensing, and monitoring in tissue. For the last two decades we have been working in the field of biomedical optoacoustics. We proposed using optoacoustics for a number of diagnostic applications and studied optoacoustic effects and capabilities of the optoacoustic technique in tissues *in vitro* and *in vivo* and tissue phantoms. In early 90s we studied pulsed laser ablation of tissues and tissue-like media using optoacoustics.[2] Pulsed laser ablation can remove biological tissue with minimal thermal and mechanical damage to adjacent tissues if optimal irradiation conditions are applied. We quantitatively studied optoacoustic effects during pulsed laser irradiation of tissues and tissue phantoms. Absolute pressure values of the thermoelastic optoacoustic waves generated by nanosecond laser pulses were measured below and above the ablation threshold using specially designed ultrasound wide-band transducers with high temporal resolution. The amplitudes and profiles of the acoustic pulses generated in atherosclerotic human aorta tissues and aqueous solutions of absorbing dyes were studied as a

function of the laser pulse fluence. Moreover, in this work we described informational capabilities of the optoacoustic waves, in particular, for absorption-based imaging in tissues and for measurement of optical properties of tissues.[2]

Since then we measured laser-induced thermoelastic and recoil pressure and estimated their effects on tissue phantoms, cells, and tissues.[3−10] We used time-resolved measurement of the optoacoustic waves with simultaneous characterization of the sub-ablation and ablation process in the irradiated volume by scattering-based techniques, laser-flash photography, and electrical conductivity.[3−10]

Cavitation induced outside of irradiated volume (inside tissue phantoms) by optoacoustic waves with relatively high amplitude was studied in Ref. 11. Gel slabs with various collagen concentrations (10−20%) were irradiated in air by nanosecond laser pulses from both sides. Under these conditions bipolar pressure pulses with compression and tensile phases were generated on each side of the gel slabs. Interaction of these pressure pulses resulted in transient compression and tension with the amplitude two times higher in the middle of the gel slabs. The tensile phase induced cavitation was detected by using scattering of a He−Ne probe beam from the cavitation bubbles or by optical microscopy. Two types of cavitation were found: transient (with bubble collapse) and permanent leading to formation of stable bubbles. Transient cavitation was observed only in gels with low collagen concentration. Transient cavitation in the gel with 10% concentration had a threshold of 28 bar and duration of approximately 3 μs (formation and growth of cavitation bubbles for 1 μs and bubble collapse for 2 μs). Permanent cavitation threshold and total volume of permanent bubbles were studied by optical microscopy. Three types of permanent cavitation were found: (1) cavitation with the following collapse accompanied by rupture and formation of small residual cavitation bubbles for gels with low (approximately 10%) collagen concentration; (2) cavitation without collapse and with coalescence resulting in large bubble formation for gels with approximately 14% collagen concentration; and (3) cavitation without coalescence for gels with high, approximately 20% collagen concentration.

The effect of the amplitude and duration of the optoacoustic tensile waves on the threshold of cavitation-induced ablation was studied in Ref. 12. Absorbing aqueous solutions of potassium chromate with various concentrations were irradiated by third harmonic of Q-switched Nd:YAG laser. The ablation threshold was dependent on both amplitude and temporal characteristics of the tensile pressure waves. Resonance and cooperative phenomena during cavitation, coalescence of cavitation bubbles in the irradiated volume, and influence of initial distribution of cavitation bubbles on cavitation were investigated as well.

We proposed to use optoacoustic imaging for medical diagnostics.[13] To provide high resolution and contrast in optoacoustic images, one should use stress-confined irradiation of tissues. Short optical pulses are used for stress-confined irradiation and can generate optoacoustic pressure with sufficient amplitude in absorbing media.[14] Typically, nanosecond laser pulses are used for optoacoustic imaging in tissues with high resolution, contrast, and signal-to-noise ratio.[15−24] Using the stress-confined irradiation and time-resolved detection of optoacoustic waves with specially designed wide-band acoustic transducers, we demonstrated optoacoustic imaging in layered tissues, measured optical properties of tissues, and studied fluence distribution in tissues.[15−24] In some studies,[20] we compared the experimental results with Monte Carlo modeling technique, which was developed in Ref. 25.

Capabilities of deep laser optoacoustic imaging in tissues were experimentally investigated in Ref. 22. We quantitatively studied three important parameters of optoacoustic imaging: (1) maximal depth of optoacoustic signal detection; (2) acoustic attenuation of laser-induced optoacoustic pressure waves; and (3) limit of resolution. Bovine liver, a tissue with higher absorption coefficient, was placed inside chicken breast muscle, a tissue with low absorption coefficient. Optoacoustic pressure waves were generated by Q-switched Nd:YAG-laser pulses in small, mm-sized liver samples (tumor model). Pressure wave amplitude, duration, and propagation time were measured using a wide-band acoustic transducer. Our results demonstrated that the optoacoustic signals from the tissues with higher absorption coefficient were measurable at depth five times greater than the penetration depth of radiation. We demonstrated the feasibility of the proposed optoacoustic imaging to detect 3 mm^3 liver samples placed inside 80 mm muscle tissue.[22]

The capability of the optoacoustic technique to detect absorbing volumes deeply in tissue is important for a variety of imaging applications including breast

cancer detection.[18] We experimentally and theoretically demonstrated high sensitivity of laser optoacoustic imaging in detection of small deeply embedded model tumors at depths of up to several centimeters.[26] Moreover, optoacoustic images had higher contrast compared to the existing tumor imaging modalities such as ultrasonography and X-ray imaging.[27] High-resolution optoacoustic images were obtained in tissue phantoms with small model tumors of different sizes, shapes, and at different depths.[28] Optoacoustic pressure waves were detected from the phantoms at different angles and 2D images were reconstructed. Comparison of optoacoustic images with ultrasound and X-ray images proved that optoacoustic method has substantially higher contrast and resolution. The study confirmed that laser optoacoustic imaging technique can be an important tool for breast cancer diagnostics, in particular, for detection of breast tumors less than 5 mm in diameter.[28]

Resolution of optoacoustic images obtained in our works was substantially better than that of optical imaging. However, the resolution may degrade due to either attenuation or/and diffraction of optoacoustic waves in tissue. We measured the axial resolution of optoacoustic imaging as a function of acoustic attenuation and diffraction of optoacoustic waves in water with absorbing layers, in breast phantoms, and in tissues.[29] Absolute values of optoacoustic pressure were measured using calibrated piezoelectric transducers. An absorbing layer or a small absorbing sphere was placed in a medium with lower optical absorption. To study the acoustic attenuation and diffraction effects, the distance between the transducer and the absorbing object was varied. The location of layers or spheres was measured from recorded optoacoustic pressure profiles and compared with actual values measured with a micrometer. The experimental results were analyzed using theoretical models for spherical and planar acoustic waves. Our studies demonstrated that despite strong acoustic attenuation of high-frequency ultrasonic waves, the axial resolution of laser optoacoustic imaging may be as high as 20 μm for tissue layers located at a 5-mm depth. Axial resolution of 10−20 μm was demonstrated for an absorbing layer at a distance of 5 cm in water, when the resolution was affected only by diffraction. For the laser optoacoustic imaging in breast phantoms, the axial resolution was better than 0.5 mm.

Optoacoustic monitoring of tissue optical properties and speed of sound in real time may provide fast and accurate feedback information during thermotherapy with various heating or cooling agents.[30−40] Amplitude and temporal characteristics of optoacoustic pressure waves are dependent on tissue properties. Detection and measurement of the optoacoustic waves during thermotherapy in real time may be used to monitor the extent of tissue hyperthermia, coagulation, or freezing with high resolution and contrast.

To improve the safety and efficacy of hyperthermia, it is necessary to map tissue temperature in real time with sub-millimeter spatial resolution. Accurate temperature mapping may provide precise thermotherapy of abnormal tissues with minimal damage to surrounding normal tissues. Amplitude of optoacoustic pressure waves induced in water linearly increases with temperature due to temperature dependence of the thermal expansion coefficient. Our experimental studies demonstrated linear dependence of optoacoustic pressure amplitude in tissue phantoms and tissues (liver and myocardium).[31] In another set of experiments we induced temperature gradients in tissue and tissue-like samples and monitored the temperature distribution using the optoacoustic technique.[35,37] The tissue temperature was also measured with a multisensor temperature probe inserted in the samples. The accuracy of optoacoustic temperature monitoring was better than 1°C, while the spatial resolution was about 1 mm.

Real-time optoacoustic monitoring of thermal coagulation induced by conductive heating or laser radiation was studied in Refs. 30, 32, and 38. Thermal coagulation results in increase of tissue effective attenuation coefficient which was measured using optoacoustic signal slopes in Ref. 30. The dimensions of interstitial coagulation lesions were monitored in real time with the optoacoustic technique during CW laser-induced heating.[38] Tissue hypothermia and freezing were optoacoustically monitored during conductive cooling with liquid nitrogen in Refs. 33 and 36.

Poor delivery of anti-cancer drugs from blood into tumor cells is one of the major problems of cancer therapy. We proposed a novel technique to alter properties of these barriers and enhance drug delivery in tumor cells with minimal damage to normal tissues.[41] This technique is based on interaction of electromagnetic radiation (light, microwave, or radiofrequency) with strongly absorbing exogenous nano- and micro-particles (gold, silver,

carbon, etc.) that results in thermal and mechanical damage in the tumors. This approach can be used for thermotherapy of tumors and other abnormal lesions without drugs.[41–43] We used the optoacoustic technique to monitor accumulation of nanoparticles in tumors of nude mice and to monitor the nanoparticle-mediated laser thermotherapy of these tumors.[44]

We also developed a noninvasive, optoacoustic diagnostic platform that can accurately and continuously measure total hemoglobin concentration, venous oxygenation (both cerebral and central), and other important physiological parameters in large populations of patients.[45–54] We built optoacoustic systems for monitoring these parameters and performed *in vitro*, animal, and clinical tests of the systems including highly portable laser diode-based systems. The proposed platform can be used for single measurement, continuous measurement, and monitoring, as well as for 2D, 3D, and 4D imaging of these parameters in tissues or specific blood vessels.

Dr. R. O. Esenaliev is a co-owner of Noninvasix, Inc., a UTMB-based startup that has licensed the rights to optoacoustic monitoring technology.

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