Laser mediated cartilage reshaping

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Laser Mediated Cartilage Reshaping: An Overview and an Update on the State of the Art

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ABSTRACT

Context: The laser irradiation of cartilage results in a plastic deformation of the tissue allowing for the creation of new stable shapes. This technology is now being used in to correct septal deviations in an office-based setting 

Objective: The objective of this manuscript is to provide an overview of laser mediated cartilage reshaping including history, biophysics, animal experiments, and human trials. During laser irradiation, mechanically deformed cartilage undergoes a temperature dependent phase transformation which results in accelerated stress relaxation. This reshaped cartilage tissue can then in principal be used to recreate the underlying framework of structures in the head and neck. Optimization of this process requires an understanding of the biophysical processes accompanying reshaping and also determination of the laser dosimetry parameters which maintain graft viability. The laser reshaping of deviated septal cartilage in human subjects was begun in 1998, following extensive in vitro, ex-vivo, and in vivo animal investigations. The surgical technique is reviewed. Future directions for research and device design are discussed.

Introduction

Thermal mediated non-ablative tissue modification is an emerging field of interest, particularly with the advent of low-cost laser and radiofrequency (RF) devices. Recent examples of non-ablative applications of thermal energy in clinical medicine include spatially selective laser heating of the dermis to ameliorate of wrinkles (1), the tightening of ligaments and tendons to treat articular instabilities (2), and RF heating of the palate to treat snoring (3). Since heat alters protein conformation, it alters both the fine structure and bulk properties of the matrix that may also lead result in tissue remodeling. While industrial non-ablative laser applications are commonplace in semiconductor, alloy, ceramic, and polymer processing, lasers use in medicine predominantly has been to ablate and destroy tissue. Laser mediated cartilage reshaping is a new non-ablative laser application that changes tissue shape by creating subtle alterations in the matrix structures(4).

Cartilage specimens mechanically deformed under a constant load, undergo accelerated stress relaxation during laser heating resulting in plasticity and sustained shape change (5). Since cartilage is a composite amorphous polymeric material, its heating results in a phase transformation within the tissue matrix governed by heat and mass transfer processes (6). Cartilage undergoes the same temperature dependent phase transformations (melts, crystallization, glass transition etc.) as those that occur in synthetic polymers (7-9). Since laser reshaping can be performed using fiberoptic delivery systems and minimally invasive techniques (10), laser mediated cartilage reshaping has the potential to alter radically the practice of facial plastic surgery. While other heat sources can reshape cartilage, the principal advantages of using laser radiation for the generation of thermal energy are 1) minimization of cellular injury through the precise control of both the space-time temperature distribution and time-dependent thermal denaturation kinetics, 2) exact spatial localization, and 3) simplicity of delivery systems (11).

Figure 1 Laser Reshaping of Cartilage (after Wong et al) (34)

The reshaping process is schematically illustrated in Figure 1 a-e. A flat cartilage specimen (a) is mechanically deformed in a reshaping jig (b) and irradiated with light emitted from a laser source. Following cessation of laser irradiation, the specimen and jig are immersed in saline solution at ambient temperatures and allowed to rehydrate for 15 minutes. Following immersion and removal from the jig, a stable shape change results (c). During the reshaping process several non-contact techniques can be used to monitor alterations in tissue bulk material characteristic which correlate with changes in such biophysical properties as optical scattering, thermal conductivity/ temperature, and elastic modulus (12-14).

Mechanism of Cartilage Reshaping

Cartilage grafts are observed to warp and curve following cutting or carving (15-19), and surgical techniques used to minimize this distortion are
well established (20, 21). When a flat cartilage specimen is scored or carved only on one side, warping occurs with the convex surface oriented toward the surgically altered side. To describe the process whereby this new equilibrium state is established, Fry introduced the concept of "interlocked stresses" (22, 23). Stable shape change results when forces produced by expansile and tensile elements within the tissue matrix are balanced. Warping occurs when surfaces are freshly cut or perichondrium is removed. Fry also studied warping and shape change after heating, and determined that this phenomenon was dependent on both the proteoglycans and collagen in the tissue matrix and not cellular activity (24). In laser reshaping, fast heating of a mechanically deformed specimen results in a new equilibrium state with release of "interlocked stresses" (without cutting tissue) and establishment of stable tissue morphology (4, 6, 25).

Cartilage graft shape is determined by a balance of electrostatic forces, ion and fluid flow, and the tensile properties of collagen fibers within the matrix (26-30). The matrix is a fiber-reinforced gel in which a three-dimensional lattice of Type II collagen fibers enmesh complex protein- polysaccharide (proteoglycan) macromolecules that possess negatively charged carboxyl and sulfate groups (31, 32). The electrostatic repulsion between these negatively charge ions results in an expansion of the proteoglycan molecules that is limited by the surrounding tensile collagen framework. Free counter ions (Ca$^+$ and Na$^+$) in solution only partially balance the negative charge density. As a consequence, compressive or flexural strains are resisted either by the Coulomb potential between the negatively charged moieties residing on adjacent proteoglycan units or by the collagen framework.

Although the precise molecular basis for cartilage reshaping is not fully understood, the mechanism is dependent on the bound to free water phase transition in the matrix which is observed at approximately 70°C (4, 6, 33). Under physiologic conditions and temperatures, water molecules are "bound" to matrix proteoglycan subunits via hydrogen bonds and Van der Waals attractions. Heat increases molecular vibrations that overcome these weak forces and results in the liberation of this bound water. In turn, this bound to free water transition reduces steric hindrance and charge shielding of proteoglycan subunits. The mechanical stress relaxation (reshaping) observed following heating may be attributed to several mechanism including: 1) local mineralisation of carboxyl and sulfate moieties with free Na$^+$ or Ca$^{2+}$ ions; 2) possible depolymerisation and reassembly of proteoglycan sub-units; 3) transient breaking of bonds between the collagen and proteoglycan sub-systems; and 4) denaturation of the collagen framework. (4, 13, 34, 35)

Figure 2 Laser Dosimetry Parameter Space (after Sviridov et al) (12)

Optimal laser-mediated cartilage reshaping maximizes stress relaxation while minimizing thermal injury and subsequent chondrocyte death. Determining the laser dosimetry parameter space which satisfies these two objectives requires evaluation of irradiance and exposure time pairs for each laser wavelength. (Figure 2) Presently, only a limited number of laser wavelengths, devices, and parameters have been systematically evaluated (13, 36). Determination of safe and effective laser parameters demands rigorous evaluation of tissue material properties and biologic behavior following laser irradiation. Indirect methods to measure changes in the molecular properties of the tissue during heating are necessary since real-time monitoring of mechanical properties during laser heating is technologically challenging (14). Fortunately, changes in matrix molecular structure also alter bulk tissue physical characteristics (optical and thermal properties, elastic modulus etc.) which can be readily measured using non-contact techniques in real-time. The measurements may therefore be incorporated into clinical instruments to monitor reshaping (37). Temperature dependent dynamic changes in the optical (38-40), thermal (34, 41), and mechanical properties of cartilage (12, 13, 42) during reshaping have already been characterized. Several theoretical models of light distribution (43, 44), heat and mass transfer during the laser ablation process have also been developed (34, 41).

Tissue Viability and Laser Wavelengths

Protein denaturation, coagulative necrosis, and subsequent cell death are a function of the time dependent heating profile generated during laser
irradiation (45). Although cartilage can be reshaped using other thermal methods such as microwave, ultrasound, and contact heating, tissue viability may be compromised due to the slow temporal pattern of heat generation associated with these modalities. Cartilage viability after heating has not been closely studied, because until recently there was little clinical motivation or utility to heat cartilage particularly using non-ablative laser fluences. Some studies have attempted to measure the biostimulatory effects of low power laser radiation on cartilage metabolism and histology (46-52), (53, 54) but these investigations did not correlate biologic behavior with alterations in tissue physical properties (such as temperature or elasticity) during heating.

The viability of laser reshaped cartilage ex vivo has been primarily evaluated using histologic and biochemical techniques. The first histologic studies of laser reshaped cartilage examined ex vivo human septal cartilage specimens irradiated with a CO₂ laser (120 W/cm², 0.5 sec exposure time) using light (toluidine blue stain) and transmission electron microscopy (55, 56). Regions of chondrocyte damage and marked collagen denaturation were identified which resulted from the intense heat generated by this laser. Further, the shallow optical penetration of depth of this laser in tissue precludes use in clinically relevant cartilage specimens. Hence, investigators focused more on the use of infrared wavelengths between one and two microns [i.e. Holmium:YAG (λ=2.09 and 2.12 μm), Nd:YAG (λ=1.32 and 1.44 μm), and diode pumped Erbium doped fiber (λ=1.56 μm)].

Using a Holmium:YAG laser (0.5-3.2 J/cm² with 4-20 sec exposure time), Sviridov et al observed cytoplasmic vacuolation and nuclear condensation (findings suggestive of thermal injury) in ex vivo human septum specimens and compared these observations with measurements of tissue temperature and stress relaxation (13). Based upon these histologic observations and physical measurements, safe laser parameters resulting in effective reshaping with the Holmium:YAG laser irradiation were determined.

Four parallel investigations by Wong and collaborators focused on tissue viability following Nd:YAG laser exposure (25 W/cm², 5-12 sec exposure time)(36, 57-59). Proteoglycan synthesis rates were measured using radiolabeled Na²³⁵SO₄ and were observed to decrease with repeated laser irradiation in a dose dependent manner and which correlated with characteristic alterations in tissue optical , thermal, and mechanical properties (36). High resolution multi-photon imaging over several days of individual chondrocytes in irradiated cartilage grafts maintained in tissue culture showed the presence of normal chondrocytes morphology but with some alteration in cellular redox state (57). Recently, quantitative measurement of chondrocyte viability using tissue culture and chondrocyte isolation techniques (60) combined with trypan blue dye exclusion demonstrated the dependence of viability on thermic load (58) supporting biochemical studies (36). Presently, FACS is being used in our laboratory to determine chondrocyte viability for the laser dosimetry parameter space at several wavelengths and irradiances.

Animal Studies

In the first reshaping experiment involving animals, a CO₂ laser was used to bend rabbit ears (62). While this preliminary investigation demonstrated the feasibility laser mediated cartilage reshaping, CO₂ was abandoned in favor of deeper penetrating laser wavelengths more suitable for use with thicker cartilage specimens. Shortly thereafter, Wang et al used a Nd:YAG laser irradiation (λ=1.44 μm) to restore shape to crushed tracheal rings in a canine airway model (10). Transmucosal irradiation of the deformed tracheal rings with non-ablative irradiances (280 W/cm²) combined with prolonged laser irradiation, translation of the laser spot, and intraluminal stenting resulted in restoration of normal tracheal anatomy. Six weeks following surgery, endoscopic evaluation demonstrated normal intraluminal appearance. Histologic examination of the laser irradiated tracheal rings showed the presence of regenerating chondrocytes within the matrix. Large animals studies were begun by Sviridov et al in Russia where porcine ears were reshaped in situ (63). An optical fiber delivering Ho:YAG (λ=2.12 μm) laser energy was inserted through a series of parallel stab incisions in the skin of the auricle to irradiate the cartilage and create sharp bends in the ear. Following reshaping external splits were applied for 20 minutes to stabilize the initial shape change. The bent ears of two pigs after laser reshaping are illustrated in Figure.
Clinical Trials

Although lasers are widely used in middle ear, laryngeal, and sinus surgery, laser applications to correct cartilage deformities in the head and neck are uncommon. Two notable laser procedures are the reduction of cartilaginous septal spurs (along with overlying mucosa) using CO2 laser energy (64) and the creation of the neo-antihelical crease in otoplasty operations using flash-scanned CO2 laser ablation (Z. Kadri, personal communication, 1996). Both of these procedures involve the ablation of cartilage tissue, albeit using devices which minimize thermal injury by satisfying the conditions for thermal confinement (11). True laser mediated cartilage reshaping in humans was first performed in 1992 by Helidonis and Sobol (4, 5) (56). Deformed septal cartilages were removed from three patients undergoing submucous resection, irradiated with a CO2 laser, and then reinserted into the mucosal pocket. While long term follow-up is not available, straight septi with normal mucosa were observed after one to two months (4).

A refined understanding of the physical processes and mechanisms accompanying photothermal stress relaxation along with results from animal studies prompted a second clinical series in Russia starting in 1998 (65-67). The procedure is performed under local anesthesia with focal transmucosal irradiation of the septal cartilage. The deviated septal cartilage is mechanically deformed with a stainless steel jig into the new desired conformation. Light from a Holmium:YAG laser (λ=2.09, 5-10 Hz pulse repetition rate, 0.1-0.5 J per pulse) delivered via a side firing optical fiber is delivered to septum along the lines of maximum mechanical stress. A number of points along these lines are irradiated for 3-8 seconds, resulting in very small focal regions of mucosal injury. The total duration of the procedure is approximately 5 minutes, and soft nasal packs are placed post-operatively for 24 hours. To date over 110 patients have been treated using this transmucosal technique performed in office-based settings. Nasal endoscopy and rhinomanometry revealed sustained correction of the deviation, and improved airflow which is consistent with the improvement in symptoms noted by the patients (65,67). Representative pre (Figure 4 a) and postoperative (Figure 4 b) endoscopic images of the nasal fossa and septum demonstrate sustained shape change ten months after reshaping. The septum is on the left side of each image. No epistaxis and only minimal crusting over the irradiation sites were observed following the procedure. There was mild return of
curvature in some patients where laser irradiance was too low to cause optimal reshaping. The procedure is not performed in patients in whom the cause of nasal obstruction is due to a septal spur or a severe posterior deviation. Presently, a compact diode pumped Erbium doped fiber laser ($\lambda=1.56 \mu m$) is being used to perform this procedure.

Figure 4  Endoscopic image of nasal septum and fossa before (a) and ten months after laser reshaping. The septum is at the left side of both images.

Conclusions and Future Directions

*Ex vivo and in vivo* investigation of cartilage reshaping has demonstrated the clinical efficacy of this procedure, though significant basic investigation and device development must be completed before this technology can be implemented outside of specialized research centers. Reshaping is exquisitely sensitive to laser irradiance; overheating may cause a septal perforation while inadequate heating results in retention of shape. This underscores the importance of laser dosimetry and feedback control of the reshaping process. Feedback control is already used in several commercially available devices to modulate both laser (68) and RF heating (3) using contact or radiometric estimates of temperature. Since tissue structure changes during heating, real-time measurement of changes in other tissue biophysical properties may also be used to assess changes in tissue structure (69-71). Optical and acoustical measurements during cartilage reshaping have recently been used to control this process (37, 72). More sophisticated techniques are currently in design within our laboratories. The degree of thermal injury still remains the principle concern and feedback control mechanisms must be developed to minimize uncontrolled heat generation.

Further work on the biologic behavior (viability) of cartilage tissue in response to fast photothermal heating needs to be performed. While a simple matrix comparing viability with pulse duration and irradiance for all relevant wavelengths and devices would be of value, it is important to emphasize that tissue/ cellular viability alone is inadequate as effective shape change is an equally important outcome variable. Cell viability is critically dependent on time dependent temperature profile generated during laser heating. Given the recent availability of data on the optical and thermal properties of cartilage tissue, the temperature field in cartilage generated during laser heating can now be modeled using numerical techniques (44). Despite the development of phenomenological theories which allows prediction of the size and structure of thermally altered regions in laser irradiated cartilage tissue (34), a comprehensive model describing shape change remains elusive as the mechanism has not been precisely determined which is the principle research focus in our laboratories.

Though septoplasty is one of the most common elective operations performed in the US, it generally requires use of an operating room and some degree of conscious sedation or anesthesia. Following surgery, there may be a protracted recovery time generally resulting in limitation of most activities such as school, exercise, or work. The use of laser energy to reshape distorted nasal septal cartilages has been performed in a clinic setting in much the same manner as turbinate or palatal snoring operations. The cost savings and benefits to the patient would be...
substantial. While the clinical investigation has focused on septoplasty procedures, laser mediated cartilage reshaping may have application in surgery of trachea, laryngeal framework, external ear, and even nasal tip.

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