

# Ultrasound therapy applicators for controlled thermal modification of tissue

E. Clif Burdette<sup>1\*</sup>, Carol Lichtenstiger<sup>2</sup>, Laurie Rund<sup>3</sup>, Mallika Keralapura<sup>5</sup>,  
Chad Gossett<sup>1</sup>, Randy Stahlhut<sup>1</sup>, Paul Neubauer<sup>1</sup>, Bruce Komadina<sup>1</sup>, Emery Williams<sup>1</sup>, Chris Alix<sup>1</sup>,  
Tor Jensen<sup>4</sup>, Lawrence Schook<sup>3</sup>, and Chris J. Diederich<sup>5</sup>

<sup>1</sup>Acoustic Medsystems, Inc., Champaign, IL USA

<sup>2</sup>Department of Pathobiology, College of Veterinary Medicine, University of Illinois, Urbana, IL, USA

<sup>3</sup>Department of Animal Sciences, University of Illinois, Urbana, IL, USA

<sup>4</sup>Institute for Genomic Biology, University of Illinois, Urbana, IL, USA

<sup>5</sup>Department of Radiation Oncology, University of California, San Francisco, CA USA

## ABSTRACT

Heat therapy has long been used for treatments in dermatology and sports medicine. The use of laser, RF, microwave, and more recently, ultrasound treatment, for psoriasis, collagen reformation, and skin tightening has gained considerable interest over the past several years. Numerous studies and commercial devices have demonstrated the efficacy of these methods for treatment of skin disorders. Despite these promising results, current systems remain highly dependent on operator skill, and cannot effectively treat effectively because there is little or no control of the size, shape, and depth of the target zone. These limitations make it extremely difficult to obtain consistent treatment results. The purpose of this study was to determine the feasibility for using acoustic energy for controlled dose delivery sufficient to produce collagen modification for the treatment of skin tissue in the dermal and sub-dermal layers. We designed and evaluated a curvilinear focused ultrasound device for treating skin disorders such as psoriasis, stimulation of wound healing, tightening of skin through shrinkage of existing collagen and stimulation of new collagen formation, and skin cancer. Design parameters were examined using acoustic pattern simulations and thermal modeling. Acute studies were performed in 201 freshly-excised samples of young porcine underbelly skin tissue and 56 in-vivo treatment areas in 60-80 kg pigs. These were treated with ultrasound (9-11MHz) focused in the deep dermis. Dose distribution was analyzed and gross pathology assessed. Tissue shrinkage was measured based on fiducial markers and video image registration and analyzed using NIH Image-J software. Comparisons were made between RF and focused ultrasound for five energy ranges. In each experimental series, therapeutic dose levels (60degC) were attained at 2-5mm depth. Localized collagen changes ranged from 1-3% for RF versus 8-15% for focused ultrasound. Therapeutic ultrasound applied at high frequencies can achieve temperatures and dose distributions which concentrate in a depth profile that coincides with the location of maximum structural collagen content in skin tissues. Using an appropriate transducer configuration produces coverage of significant lateral area, thus making this a practical approach for treatment of skin disorders.

**Keywords:** Ultrasound, Focused Transducer, Collagen, Skin Disorders, Blurred Focus, Conformal Ultrasound Therapy

## 1. DESCRIPTION OF PURPOSE

Consistent, reproducible treatment and clinical results continues to be a challenge to all current methods used to produce changes in collagen in the skin. The clinical opportunity skin tightening/wrinkle removal is significant, and established. However, the technologies being used for treatment of skin disorders today leave the physician users less than satisfied. These encompass aggressive skin cooling in conjunction with laser/light therapies (e.g. Cutera-Titan, Reliant-Fraxell) to provide treatment from just below the epidermis to approximately 0.5-1.0mm below the skin surface, as well as various RF induction methods, most notable being Thermage, with low reproducibility of clinical results/outcomes due to inherent limitations due to multiple and varied current paths and lack of spatial power density control. Although Laser

[\\*clifb@acousticmed.com](mailto:*clifb@acousticmed.com) phone 1 217 239-0900; fax 1217 239-0905; <http://www.acousticmed.com>

and RF are used successfully for applications where energy must be delivered to a region immediately adjacent to an applicator, they are less sophisticated means for delivering power to a deeper tissue, or in focusing the energy in a broader area of a particular region. The controlled volume focused ultrasound (VFU) approach described in this paper and its clinical success will depend on development and demonstrated effectiveness of new methods which provide significantly improved treatment volume and depth control and which are consistent, repeatable, and reproducible. Current technologies (radiofrequency and light) cannot apply energy deeply enough (light) or consistently enough (RF) to achieve clinically significant therapeutic results. The VFU design presented herein can both focus its energy at predetermined depths, provide significant lateral coverage, and provide consistency/reproducibility. In addition, ultrasound therapy using a VFU approach offers the only possibility of consistent and reproducible delivery of therapy at the target depth beneath the skin surface which results in clinical result consistency. Medtech Insight forecasts that 2.2 million laser procedures will be performed by 2010<sup>[1]</sup>. Of those combined surface ablative and non-surface-ablative procedures, almost 600,000 will be for thermal skin rejuvenation. It is forecasted that energy-based collagen tightening will grow from 100,000 in 2007 to 500,000 by 2012. There is an even greater potential if a product is provided to the market which provides consistent, reproducible outcomes based upon an appropriate optimized technological design for that purpose.

The purpose of the study described in this paper was to demonstrate the feasibility of using geometrically focused ultrasound transducers capable of producing a very shallow focus of significant lateral extent. This is counter-intuitive to the vast majority of acoustic wave focusing approaches. The challenge was to provide 5-20 mm lateral coverage while focusing at a tissue depth of 2-6 mm. A novel ultrasound thermal therapy design was created to enable achievement of these goals. In this study, we create localized heating of tissue with high frequency ultrasound (US) delivered by a hand-held water-coupled volume focused applicator. This approach permits both 3D mechanical and electronic targeting of thermal treatment and can ablate large, small, and/or geometrically complex volumes of tissue. An additional challenge is to determine a priori the placement positions and electronic patterns most likely to achieve the prescribed volume coverage. We envision this system approach working in conjunction with ultrasound-based thermal monitoring<sup>[2][3]</sup> to enable accurate treatment and control in the treatment of skin disorders and other sites requiring conformal therapy.

## 2. BACKGROUND AND APPROACH

The fundamental concept is the use of soft-focused ultrasound to provide controlled, shaped power deposition in targeted tissue structures and to measure its effect during the treatment. This permits the noninvasive treatment of tissues beneath the surface and the ability to monitor that treatment noninvasively, enhancing the effect and reducing the complications associated with overheating the tissue. In this study, energy was focused at the connective tissue in the sub-epidermal layers, causing the collagen in that tissue to remodel and constrict.

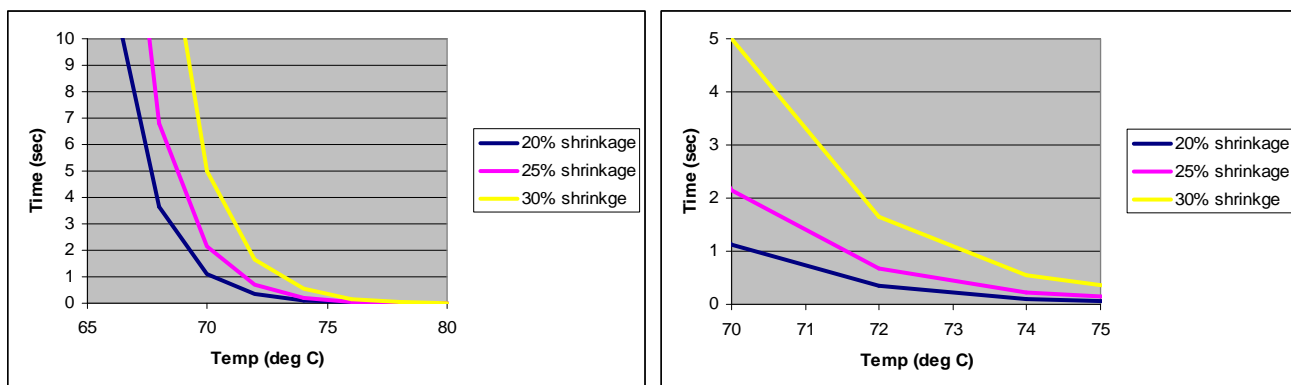
**2.1. Volume-Focused Ultrasound (VFU):** VFU can affect tissue by focusing energy from several transducers, or several regions of a single transducer within tissues at pre-determined depths and lateral extents. Ultrasound can transmit through tissue with reduced absorption proximal to the energy applicator (unlike most light and RF conductive). Acoustic energy can be directive along a line focus or spread focal region by employing more than one curvilinear transducer<sup>[4, 5]</sup>.

**2.2 Thermal remodeling of Collagen:** Collagen is a molecule that configures itself as a helix<sup>[6]</sup>. Cross-bonding of one collagen helix to another, or one portion of the helix within a collagen molecule to another portion of the helix in that same molecule, produces a system of molecules that can be likened to individual fibers in cloth, yarn, or puff (such as a cotton ball). The combination of helical strands and cross-linking provides both strength and flexibility to the tissue. Applying thermal energy to that collagen causes some of the cross-linking bonds to break<sup>[7,8]</sup>. This allows the helical coil to tighten and, if the other components of the tissue structure are compressible, decreases the volume and increases the density of the structure. When collagen cools, cross-linking bonds reform and the tighter, denser, structure is locked into place. As long as there are no excess sources of pressure (incompressible tissue, exercise exertion) the cross-linking continues with time, making the more compact structure more permanent.

Studies have shown that thermal remodeling of collagenous tissue can cause an increase in density of 20% to 50%<sup>[9]</sup>. Additionally, the damage inflicted on the tissue stimulates the generation of more collagen, or neocollagenesis. As this neocollagenesis occurs, it causes the tissue to fill in with more connective tissue – strengthening it, restoring many characteristics damaged in injury or which degrade with aging.

While the concept of using thermal energy to remodel the collagen in the skin is not novel, the concept of using VFU is new. Contrary to the use of heat for outright tissue destruction, high temperatures for thermal shrinkage of structural collagen alone (e.g. skin, ligaments) require short duration exposures of 55–75°C for effect [9-13]. Treatments to reduce sagging of the skin are variations on a common theme of heating collagen to cause it to contract. Collagen makes up 75% of the dry weight of skin. Most of that collagen is concentrated in the dermis, the layer of tissue underlying the epidermis (the outer layer of tissue, visible intact skin). The therapy mechanism is to heat the collagen in the dermis to a level where it will remodel, shrink, and stimulate neocollagenesis.

The means of collagen remodeling currently employed are chemical agents, light energy (including laser), radiofrequency (RF), or other forms of energy applied with the purpose of raising the temperature of the collagen in the dermis. Wall<sup>[9]</sup> demonstrated the time-temperature relationships to produce different shrinkage. Although shrinkage may occur at lower temperatures, an optimal range of time/temperature application are 60-70°C for 1-2 seconds.



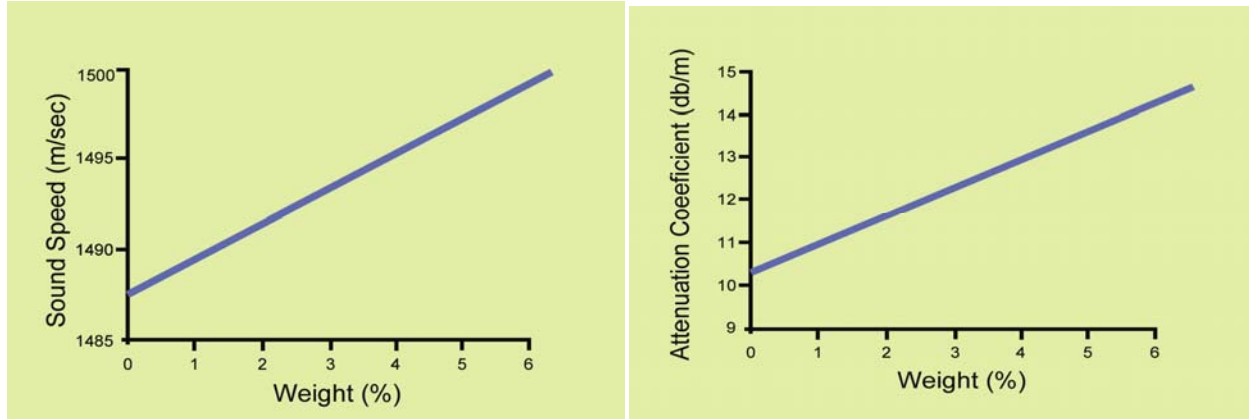
**Figure 1.** Collagen shrinkage as a function of temperature and time. [9] Small variations in temperature can lead to dramatic changes in shrinkage, resulting in over treatment or under treatment of tissue.

The degree to which the collagen is reduced in size by heating also affects the strength of the resulting tissue structure, and that may have a significant impact on the effectiveness and consistency of the treatment procedure. The tensile strength of shrunken collagen is also a function of the amount of shrinkage [9]. After the application of therapy that produces severe shrinkage, the resulting collagen structure is weakened to the point that, when opposing forces are applied, it will actually stretch to a greater overall length than if the tissue had not been shrunk in the first place. A stress of approximately 0.25MPa applied to a 10cm bovine ligament which has been thermally shortened to 6cm, the ligament will extend to 11cm. The same stress applied to an untreated (i.e. not shrunk) 10cm bovine ligament tissue demonstrates negligible deformation. If the collagen is shrunk less than 20% to 25% it remains stronger than untreated collagen, and for much higher stresses. Most thermal remodeling procedures do not control the heat applied to the tissue and have a goal of inducing maximum collagen shrinkage. The implications of this research are that collagen remodeling procedures are more likely to produce weakened tissue which will revert to the original condition – or worse – with stresses.

**2.3 Monitoring of the Collagen Treatment Process:** An interesting byproduct of the shrinkage of collagen is that it results in an increase in the density of the tissue. That increased density associated with thermal remodeling of the collagen means that the ultrasound image also changes. Youn [14] demonstrated a 1.5% increase in the acoustic velocity with a 5% increase in collagen density. A similar correlation was demonstrated in the attenuation coefficient. As shown in Figure 2, these two properties allow for a direct ultrasound measurement of the change in tissue density as a function of collagen content.

A 30% shrinkage in collagen would result in a 40% increase in the density of the collagen molecules in the skin tissue. That change in tissue density would result in a change in acoustic velocity of 10%.

In the skin treatment application, collagen changes could result in 30% attenuation and 10% acoustic velocity changes. This information has been used in cross-correlation algorithms to monitor the treatment in real time using the same transducers as are used for therapy. Additionally, the tissue may be imaged and structural changes correlated with the resulting cross-correlated acoustic property changes.



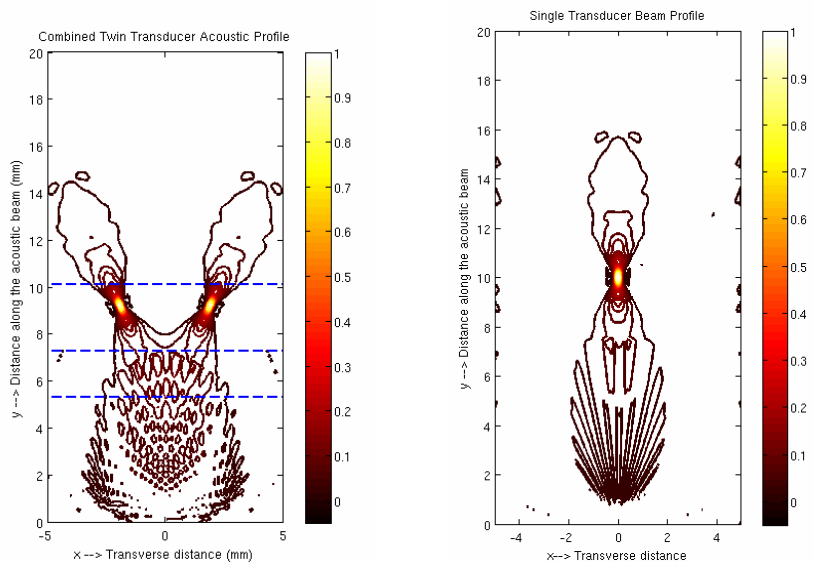
**Figure 2.** Variation in acoustic velocity and attenuation as a function of density associated with thermal remodeling of collagen.

#### 2.4. Ultrasound Skin Treatment Applicator Design Analysis and Thermal Simulation

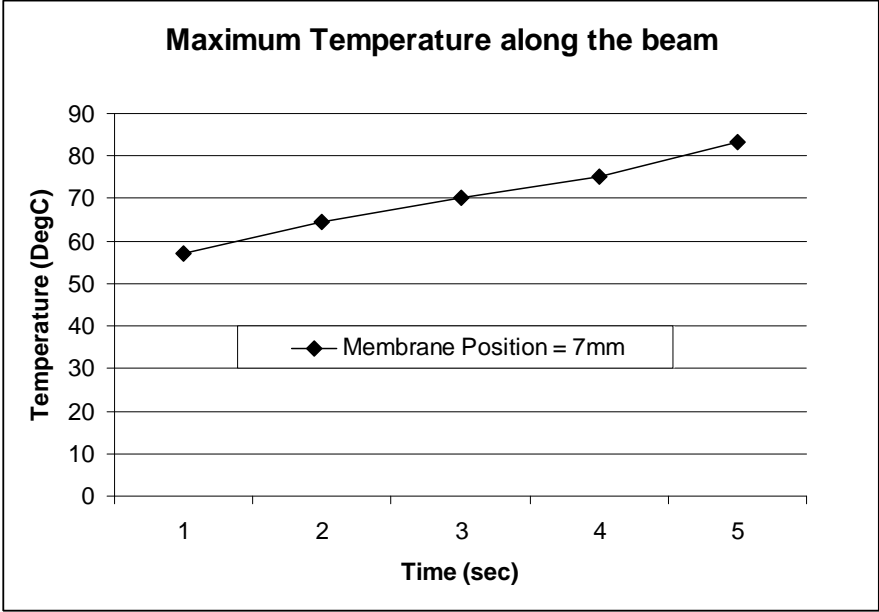
Several transducer designs and curvatures were examined and various mounting configurations were tested using a CAD system to evaluate mounting clearances, stresses, and feasibility of running drive power and cooling lines to both single and multiple transducers.

Acoustic field simulations were developed and run for single, dual and cross-beam transducer assemblies. The transducers are mounted at angles with respect to one another that produce a focus which can be located at a position in the dermis which produces a maximal therapeutic result with respect to skin tissue collagen structural changes. The simulation results for the single and dual transducer configurations are shown below in Figure 3.

**Figure 3.** Acoustic field patterns for the dual transducer configuration (left) and a single transducer (right); Membrane location=6mm from face of transducer; Power=25W; Skin ultrasonic attn=15Np/m/MHz.

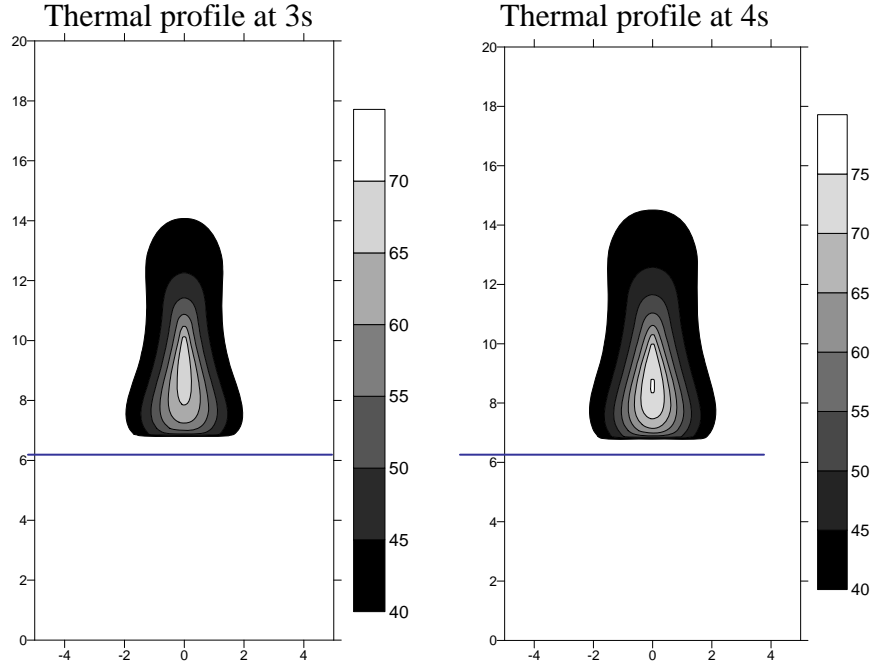


Thermal modeling of the profile of maximum temperature along the beam as a function of time is shown in Figure 4; 60 degrees C is achieved in an exposure of 1.5 seconds. Coupling membrane is 7 mm from transducer.



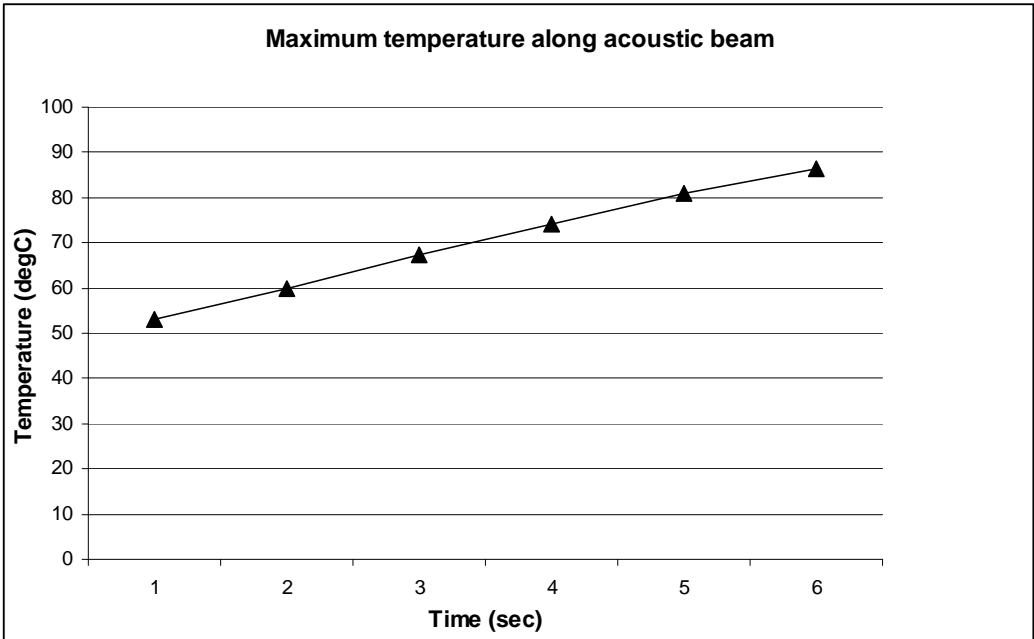
**Figure 4.** Temperature along the beam shown as a function of time. Coupling membrane distance from transducer is 7mm; Power=25W; Skin ultrasonic atn=15Np/m/MHz.

The thermal profiles at 3 and 4 second exposures are shown in Figure 5. Note that the maximum temperature is approximately 2 mm from the coupling membrane interface.

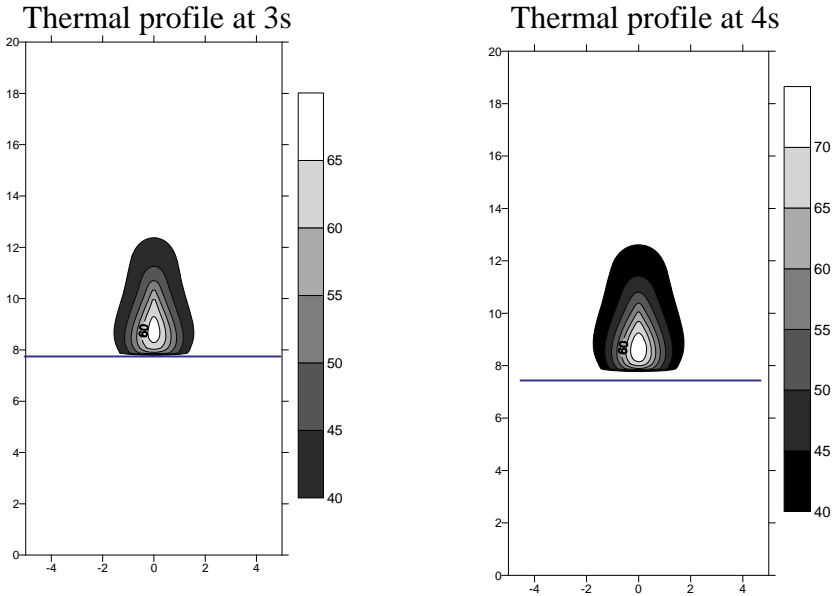


**Figure 5.** Thermal profile of a single focused curvilinear transducer following 3 and 4 seconds exposure. Membrane location=7mm; Power=25W; Skin ultrasonic atn=15Np/m/MHz.

The profile of maximum temperature along the beam as a function of time for a membrane is shown in Figure 6. A temperature of 60 degrees C is achieved in an exposure of 2 seconds. Coupling membrane is 8 mm from transducer.

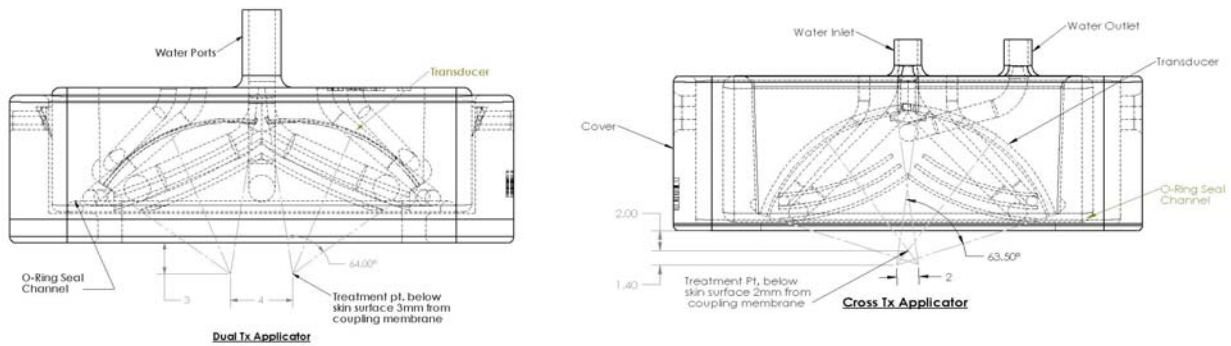


**Figure 6.** Temperature along the beam shown as a function of time. Coupling membrane distance from transducer is 7mm; Power=25W; Skin ultrasonic attn=15Np/m/MHz. The thermal profiles at 3 and 4 second exposures are shown in Figure 7. Note that the maximum temperature is approximately 1.5 mm from the coupling membrane interface.



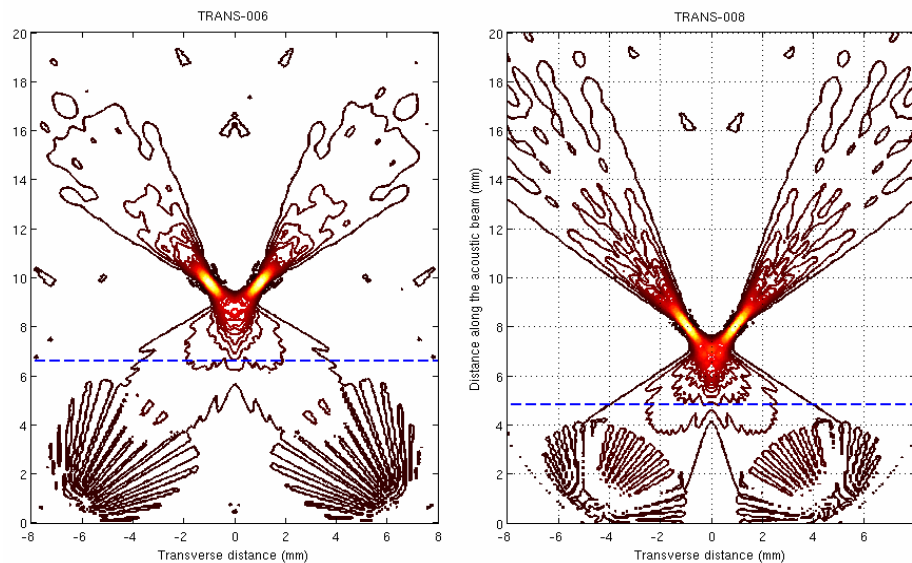
**Figure 7.** Thermal profile of a single focused curvilinear transducer following 3 and 4 seconds exposure. Membrane location=8mm; Power=25W; Skin ultrasonic attn=15Np/m/MHz.

Designs were developed for dual side-by-side focused transducers and crossed-beam transducers. The dual beam focused design mounted in an applicator housing which provides acoustic coupling for the active concave face of the array as shown in Figure 8 (left). The geometric focus is 3 mm below the coupling membrane interface and focal separation is 4 mm. The cross-beam design crosses the focal beams from two arcuate transducers to a predetermined distance between the foci of 2-4 mm as shown in Figure 8 (right), with a focal depth of 2.5 – 3 mm and beam crossing depth at 2.0 mm. The beam separation at the foci is 2 mm.



**Figure 8** (Left) Dual beam therapy applicator with adjacent focus separation of 4 mm and focal depth of 3 mm; (Right) Cross beam applicator with focal region 2.0 – 3.4 mm depth and 2 mm focus separation.

Figure 9 (left) displays the thermal pattern from a cross-beam applicator with 2.24 mm transducer spacing and 2.5 mm focal depth. Figure 9 (right) is the thermal pattern for a different cross beam applicator with 2.06 mm separation and 3 mm focal depth.



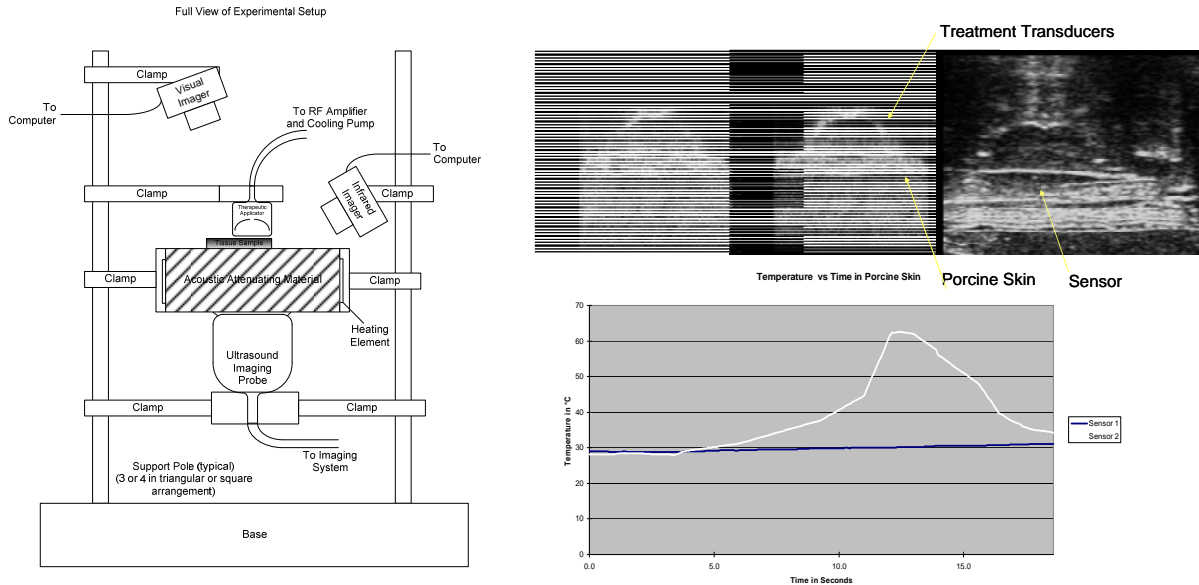
**Figure 9.** Cross beam thermal patterns for focal separation of 2 mm and focal depth of 2.5 mm and 2.24 mm transducer spacing(left) and 3 mm and 2.06 mm, respectively (right). Yellow is the highest intensity.

### 3. EX-VIVO TISSUE EXPERIMENTS

Ex-vivo experiments were performed using the underbelly skin of young pigs which were slaughtered the same day as the experiment. The test setup which was used for performing tissue studies is shown in Figure 10. The tissue specimen is located atop a tissue phantom maintained at 37 degrees C. An ultrasound imaging probe is located underneath to collect RF ultrasound data prior to, during, and immediately post treatment. An infrared camera views the edge of the test tissue sample, the video camera records the process. The video camera and fiducials in the image were used to spatially register the sample. Very fine thermocouple linear array sensors are inserted laterally at two depths, one within

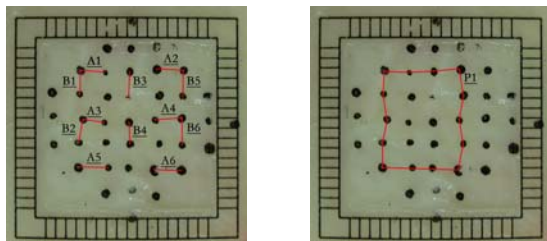


and one beneath, the test tissue sample. Online monitoring of temperature profile and thermal dose delivered is performed during the treatment. The sampling rate is 10 Hz; treatments varied from 2 sec to 30 sec.



**Figure 10.** (Left) Experimental setup used for ex-vivo tissue heating study; (Right-upper) Ultrasound image of array of arcuate treatment transducers above tissue sample atop tissue phantom; image taken from beneath phantom; (Right-lower) Temperature-time profile of sensors placed within treatment region of tissue sample and placed immediately adjacent to the treatment site.

An image analysis computer program available from National Institutes of Health (Image-J) was used to analyze tissue images both pre- and post-treatment to determine extent of tissue contraction (collagen shortening/shrinkage). The tissue surface for treatment was tattooed in a grid pattern and images taken prior to and post treatment. Lateral tissue tightening, both linearly in two directions and by area reduction, was measured and analyzed using Image-J, as illustrated in Figure 11.

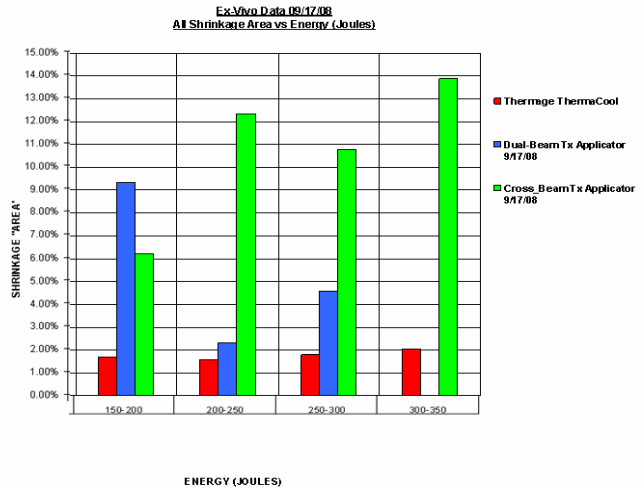
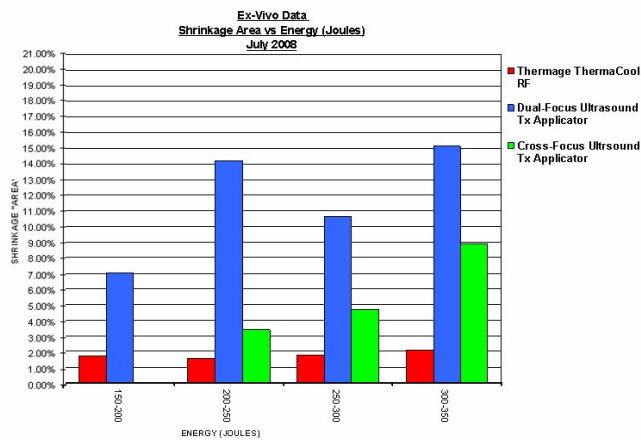


**Figure 11.** Fiducial grid on tissue samples was measured pre- and post-treatment to determine change in area; Left: 6 x and y linear samples averaged for each measurement set; Right: area of tissue region measured for each measurement set. Both methods were used to determine change for each sample.

Over eleven experimental sessions of treatment of excised skin tissue, a total of 138 samples were treated using different thermal dose and energy parameters. A near equal number of cases were treated with dual focused beams and cross focused beams. Further, approximately 35% of the total samples were treated with a commercially available RF treatment system. The RF system used cryogenic cooling on the surface to minimize surface tissue burning. Equivalent energy ranges (Joules) were used for both US and RF modalities. For US, the thermal dose was monitored and recorded. The RF device provided information only for total energy in Joules.

A summary of all the results of the ex-vivo experimental studies are shown in Figure 12. The mean lateral area reduction results analyzed using Image-J are shown for treatments delivered with both RF and volume focused ultrasound over four different delivery energy ranges. Total thermal dose for ultrasound for all energy ranges was 150MEq to over 3200MEq [15]. The collagen tightening in the skin for ultrasound therapy was least for 200 Joules delivered using the cross beam focused applicator; however, this was a factor of 2X the results for RF (Thermage ThermoCool). The maximum difference in results was a factor of 8X between the dual beam focused ultrasound applicator and the RF device.





**Figure 12.** Reduction in tissue surface area achieved in ex-vivo experiments using RF as compared to both the focused cross beam and dual beam US applicators for four delivered energy levels.

#### 4. IN-VIVO ANIMAL EXPERIMENTS

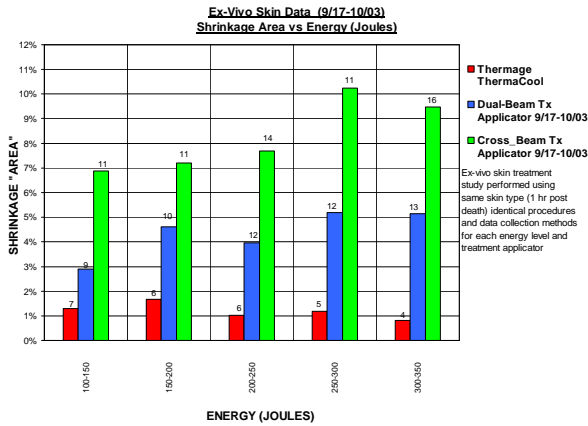
We performed a pilot study to evaluate devices for treating skin conditions. An IACUC protocol was approved for a study to compare the skin collagen tightening and histological analysis of thermal therapy delivered by a dual beam ultrasound therapy device, a cross beam ultrasound therapy device and RF device.

Acute studies were performed in an anesthetized farm pig, of approximately 60 kg. The anesthetized animal was placed in a supine position. Skin of the soft underbelly was shaven clean and prepped. Multiple areas on the skin surface were demarcated and tattooed (Figure 13). Test treatment parameters were applied, using a thermal therapy technology, to the region of porcine skin under test. Fine-wire thermocouple temperature sensors were placed at positions approximately 2mm below the skin surface and on the skin surface prior to the test. After 2-3 hours of procedure time the first animal was sacrificed and portions of skin sliced/removed and placed in TTC for 30 min followed by 10% formalin fixing solution and preserved for histological assessment. Photos of the experiment were taken, both of the overall setup and the treated tissues. The identical procedure was also performed for a second animal, except the animal was not sacrificed, but maintained for a period of two weeks. At two weeks, the second animal was sacrificed in accordance with the 2007 Report of the AVMA Panel on Euthanasia. The treated areas of the skin will be removed and the same procedure described above was followed.

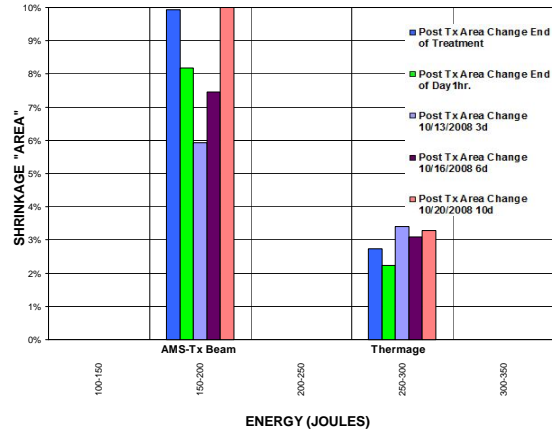


**Figure 13.** (Left) One of the animal subjects used in the study; (Right) Treatment areas marked on prepared skin surface.

The results of the in-vivo study are summarized in Figures 14 and 15. Dose distribution was analyzed and gross pathology assessed. Tissue shrinkage was measured based on fiducial markers and video image registration and analyzed using NIH Image-J software. Comparisons were made between RF and focused ultrasound for five energy ranges. In each experimental series, therapeutic dose levels (60degC) were attained at 2-5mm depth. Localized collagen changes ranged from 1-3% for RF versus 8-15% for focused ultrasound (Figure 14). In every case, shallow focused ultrasound outperformed RF therapy. Short-term durability is shown in Figure 15.



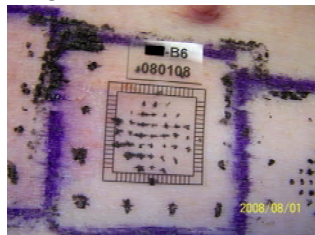
**Figure 14.** Reduction in area of marked skin treatment with dual beam US, cross beam US and RF.



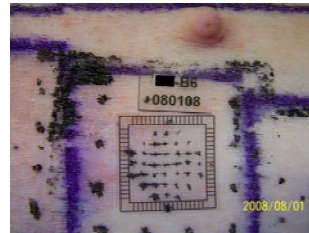
**Figure 15.** Reduction in treated area with US and RF at treatment end, 1 hr, 3 days, and 10 days post-Rx.

Histological evaluation of tissue samples was performed for each therapy device and for each energy level used. A specific case for treatment with the dual beam US applicator is shown in Figure 16. Treatment energy was 110 Joules. Figure 17 shows the histological results analysis for a specific case treated with the cross beam US applicator (148 Joules). Figure 18 shows the histological evaluation for a treatment with the Thermage RF device (233 Joules).

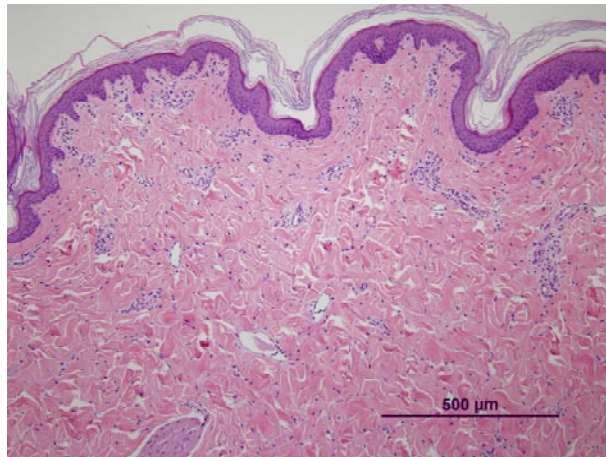
**Exp#16 Location B6 on Pig 1 – Applicator: Dual Beam**



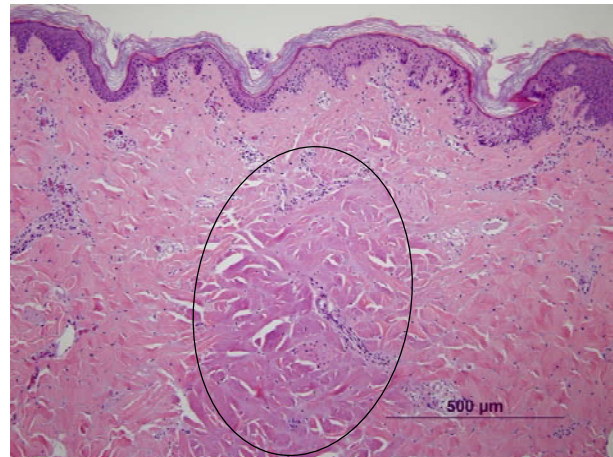
**Pre-Tx 20080801 1:39PM**



**Post-Tx 20080801 1:49PM**



Sample B6: **Area of normal skin.** Pig skin is sparsely haired and the epidermis forms short rete pegs. H&E, original magnification 100x.



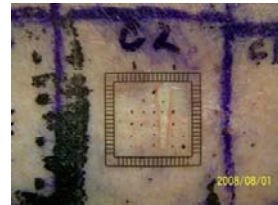
Sample B6: Focus of epidermal and **dermal necrosis** consistent with thermal injury. Under polarized light (not shown) the collagen in the necrotic dermis lost about 50% of its normal birefringency. H&E, original magnification 100x. Acoustic Treatment Energy: 110 Joules

**Figure 16.** Histological analysis of tissue sample treated with dual beam ultrasound device.

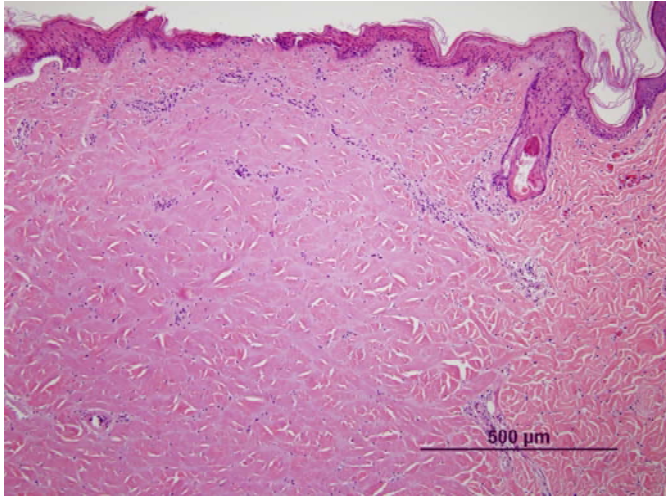
**Exp#3 Location C2 on Fig 1 – Applicator: Cross Beam**



**Pre-Tx 20080801 10:16AM**



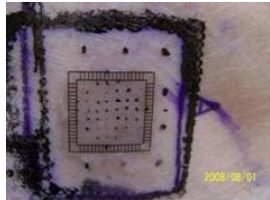
**Post-Tx 20080801 3:23PM**



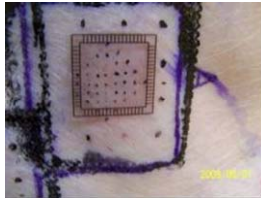
Sample C2: Focus of epidermal and dermal necrosis larger than field. The necrosis includes the hair follicle toward the right edge. To the right of the hair follicle is unaffected skin. Under polarized light, not shown, the collagen in the necrotic dermis lost about 70% of its normal birefringency. H&E, original magnification 100x. Acoustic Treatment Energy: 148 Joules

Figure 17. Histology for case treated with the cross beam ultrasound device.

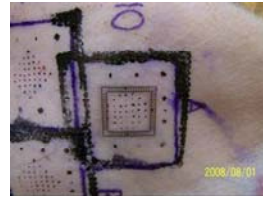
**Exp#20 Location A10 on Fig 1 – Applicator: Thermage**



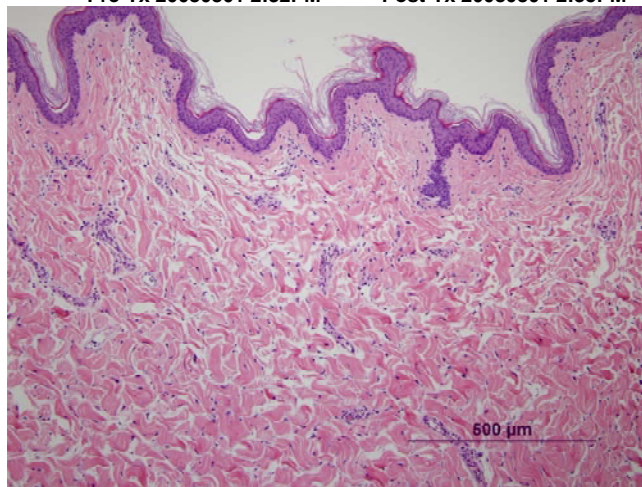
**Pre-Tx 20080801 2:32PM**



**Post-Tx 20080801 2:35PM**



**Post-Tx 20080801 3:30PM**



Sample A10: No lesions in sample. H&E, 100x. RF Treatment Energy: 233 Joules

Figure 18. Histology for case treated with the Thermage RF device.



## CONCLUSIONS

Initial experiments demonstrate feasibility of arcuate ultrasound applicator arrays to achieve significant change in the collagen in skin tissue as compared to existing methods. Shallow, volume focused ultrasound may have multiple applications by modifying the angle and intensity of the active ultrasound elements in a curvilinear array to “sculpt” treatment to match the desired treatment depth and lateral extent. This could be useful for multiple types of skin disorders or other superficial tissue disease having lateral extent.

## NEW OR BREAKTHROUGH WORK / RELATIONSHIP TO OTHER PUBLICATIONS

As mentioned in the sections above, we present two novel approaches: (1) This is the first electronically steerable ultrasound ablator, and (2) This is the first system able to treat skin with a shallow broad focal region ultrasound therapy.

**Requested Statement of Originality:** This work is neither published nor submitted to any other journal.

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