Editor’s Note: The product discussed in this article is not yet FDA-approved for use in the United States.

Various forms of energy-based technologies, such as radio waves and lasers, have been developed for use in aesthetic surgery and cosmetic medicine. A new device that emits high-intensity focused ultrasound (HIFU) is currently under clinical investigation in the United States (LipoSonix; Medicis Technologies Corporation, Bothell, Washington). Through an external transducer, HIFU energy can ablate targeted tissue through intact skin without affecting surrounding tissues or producing collateral damage above or below the focused energy zone. This is achieved through a controlled thermomechanical process. Focused ultrasound causes rapid heating within the predesignated focal area, where temperatures disruptive to living tissue can be achieved in one to two seconds. This nearly-instantaneous coagulative necrosis and cell death are confined to the targeted tissue, while surrounding areas remain unaffected. The mechanical effects of HIFU...
are the result of microscopic shear forces that generate additional frictional heating. HIFU can be used to ablate tissue with a high degree of precision, and the predictable and reproducible effects of HIFU have made it a promising tool that is being applied for the treatment of various diseases and medical conditions, such as tumors.

While nonfocused ultrasound systems were initially an adjunct to traditional liposuction methods, the properties of HIFU may make it well suited as a stand-alone technology for body sculpting without the need for invasive surgical procedures in select patients. The following preclinical research was performed to evaluate the feasibility of HIFU treatment for the removal of adipose tissue and aesthetic body contouring. Specifically, the studies were designed to assess the biochemical effects of HIFU on subcutaneous adipose tissue, evaluate the local cellular response, and observe any changes in lipid metabolism in a swine model.

**METHODS**

These studies were performed with a validated porcine model, in 26 pigs from a commercial Yorkshire breed. The subjects had a mean weight of 149.5 kg (range, 135.5-181.0 kg). Swine are often used in obesity research because their subcutaneous adipose tissue is very similar to that of humans, including the lobular organization of fat and collagenous fibrous septae. In addition, porcine skin and subcutaneous tissue closely resemble human skin with respect to histological, physiological, and immunological properties. In all studies, HIFU treatments were applied to the ventral (abdominal) surface of the animal.

Several different prototype devices were employed during these studies; however, extensive testing and monitoring of energy levels and acoustic output parameters demonstrated that the HIFU beam profile and output energy levels were consistent between prototypes. Each “dose” of focused ultrasound energy is expressed as Joules per square centimeters (J/cm²) and represents the amount of energy delivered when an ultrasound transducer is scanned once over a treatment area. Multiple doses of applied energy are additive such that two applications of 59 J/cm² results in a total energy dose of 118 J/cm².

This protocol was approved by the Institutional Animal Care and Use Committee of the testing facility and was conducted in general compliance with applicable requirements in the Good Laboratory Practices for Nonclinical Laboratory Studies 21 CFR Part 58. Animal housing and care conformed to the Guide for the Care and Use of Laboratory Animals, Institute of Laboratory Animal Resources, published by the National Academy of Sciences, 1996.

**Thermal Effects of HIFU on Subcutaneous Adipose Tissue and Laboratory Parameters**

Changes in temperature were recorded with hypodermic thermocouples and probe-type thermocouples, which were introduced into the tissue via small incisions. Thermocouples were positioned in the dermis and epidermis and at depths of 10 to 15 mm below the surface of the epidermis in the abdominal subcutaneous adipose tissue of seven animals. Thermocouples were specifically positioned to demonstrate that tissue-ablating temperatures in excess of 55°C occurred only at the focal point. Correct thermocouple placement was verified by ultrasound imaging. HIFU energy levels of 166 to 372 J/cm² were administered at a focal depth of 15 mm. Temperature data from the thermocouples were recorded every 500 milliseconds for the duration of the treatment and for several seconds afterward.

Histological examination of solid organs was performed with tissue samples from the brain, heart, kidney, liver, lungs, pancreas, and spleen. These samples were obtained from two animals at one and six weeks posttreatment, with HIFU energy levels ranging from 166 to 998 J/cm² (six treatments of 166 J/cm²). The organs of one animal were also examined following treatment with energy levels of 113 to 263 J/cm².

Blood samples were obtained from eight swine at baseline and at two, four, 12, 24, 48, and 72 hours following treatment with HIFU at energy levels of 68 (n = four) or 86 J/cm² (n = four).

**Assessment of Lesion Healing Following HIFU Treatment**

A group of eight swine were administered a series of three abdominal HIFU treatments over a period of eight weeks. The abdomen of each animal was marked for later identification. Each treatment site was treated only once. Energy levels ranging from 85.3 to 270 J/cm² were evaluated. The swine were sacrificed, and the tissue was harvested one week after the last treatment (four weeks after the second treatment and eight weeks after the initial treatment). Macrophage activity was assessed by injecting India ink into the treated adipose tissue.

**RESULTS**

**Thermal Effects of HIFU on Subcutaneous Adipose Tissue**

The use of thermocouples demonstrated that the temperature at the focal zone approached 70°C for one to two seconds—which is sufficient for producing tissue necrosis—and then quickly decreased. The temperature within the tissue surrounding the focal zone rose to nonlethal levels, while the temperature at the skin surface remained unchanged. Figure 1 shows temperature data recorded before, during, and after HIFU treatment at the skin surface, focal zone, and surrounding tissue.

The area of each treatment site size was 25 × 25 mm, and the volume of adipose tissue treated during these animal studies ranged from 75 to 950 mL. At the dose levels applied in this study, HIFU was effective in causing thermal coagulative necrosis of subcutaneous adipose tissue within the predetermined focal zone only. This was confirmed by
the gross examination of treated tissue (Figure 2). Following treatment, there was gross evidence of mild tissue ecchymosis from capillary damage.

The results of these studies also demonstrated the ability of the HIFU to produce the desired effect at the focal point without causing damage to intervening anatomical structures. No injury was observed to intervening nerves (Figure 3) or arterioles (Figure 4) within the path of the HIFU beam. Histological examination of treated tissue demonstrated disruption of the adipose tissue with well-demarcated borders, consistent with the known thermomechanical effects of ultrasound energy. Additionally, collagen within the focal zone showed evidence of contraction and thickening (Figure 5).

Assessment of Solid Organs and Laboratory Parameters

Extensive blood testing did not provide any evidence of clinically-significant changes in baseline clinical chemistry or hematology parameters up to 72 hours following HIFU treatment.

Lipid panels—including free fatty acids, triglycerides, high- and low-density lipoprotein, and total cholesterol—remained within normal limits. Additionally, no significant changes were observed in liver function tests, including ALT (alanine transaminase), AST (aspartate transaminase), alkaline phosphatase, and total bilirubin. Mean values for AST, ALT, cholesterol, and free fatty acids are shown in Figure 6. Urinalysis did not show evidence of ketosis or fat globules. During necropsy, no evidence of fat emboli or fat accumulation in any organs was observed (including the brain, heart, kidney, liver, lungs, pancreas, and spleen).

Assessment of Lesion Healing Following HIFU Treatment

Gross pathology studies revealed normal healing with gradual resorption of damaged adipose tissue. Resolution of thermal lesions was nearly complete by eight weeks posttreatment, with energy levels ranging from 85.3 to 270 J/cm². Figure 7 shows lesion healing in a single animal after treatment. There was evidence of chemotactic signal activation in treated tissues, with the migration of...
macrophages into the damaged tissue engulfing the released cellular debris (including lipid particles).

To determine the mechanism of cell debris and lipid removal, treated areas were injected with carbon particles in the form of India ink. Macrophages ingested carbon particles with released lipids and other cellular debris; then they migrated through the lymphatic system. Macrophages containing ink particles were observed within excised lymph nodes (Figure 8).

**DISCUSSION**

Other forms of energy-based technology have been used in aesthetic surgery and cosmetic medicine—namely, radio frequency and laser energy; however, these energy sources do not share certain properties of focused ultrasound. Specifically, externally-applied light and radio frequency waves cannot be focused deep into tissue and cannot achieve the same subcutaneous energy-focusing effect of HIFU. Consequently, the use of lasers is limited to ablative and nonablative skin resurfacing procedures, skin tightening, and adjunctive (enhancing) treatment with liposuction. Other available HIFU devices use relatively...
low-energy ultrasound to generate thermal effects through cavitation.\textsuperscript{17-19} The HIFU device investigated in this study can raise the temperature of the target area with a high degree of precision.\textsuperscript{3} The placement of implanted thermocouples in swine has demonstrated that HIFU raised the temperature at the target zone to 70°C at the focal area, while surrounding temperatures did not deviate substantially from the normal body temperature of the animal (36.8°C).\textsuperscript{20}

The bulk heating of large amounts of tissue to near-lethal burn temperatures in most laser lipolysis protocols involves a different set of risks than the transient, localized heating observed with thermal HIFU.\textsuperscript{21} Following HIFU treatment, the tissue-based inflammatory response reported with surgical wounds\textsuperscript{22} or injection lipolysis\textsuperscript{23} was not encountered.

Laser energy can be delivered into tissues via fiber optic transmission to achieve bulk heating of subcutaneous tissue during surgical liposuction procedures. Current clinical evidence indicates that laser energy only minimally improves clinical outcomes when compared with other commonly-employed methods of liposuction.\textsuperscript{15} We believe that the effect of thermal HIFU within the midlamellar collagen matrix includes a reduction in adipocyte volume and also a tightening effect on the collagen. As part of the normal healing process, macrophages then transport the engulfed debris away from the treated area via lymphatic vessels. Interestingly, thermal HIFU did not invoke an inflammatory wound-healing response like those observed in surgical wounds,\textsuperscript{22} nor the deep, long-term tissue inflammation reported following injection lipolysis.\textsuperscript{23} HIFU-treated tissue did not exhibit any evidence of fat necrosis, inflammation, or collateral damage to vascular structures, which has been shown to occur when fat tissue is heated to 55°C.\textsuperscript{15}

Based on the promising results in the porcine model, subsequent studies will assess the safety of HIFU for the removal of adipose tissue in humans.\textsuperscript{24}

**CONCLUSIONS**

The application of HIFU to subcutaneous adipose tissue in swine resulted in thermal lesions without affecting the skin, fascia, or other tissue surrounding the focal area. Changes to adipose tissue and collagen were consistent with the known thermomechanical properties of focused ultrasound. Following treatment with HIFU, no systemic abnormalities were observed in solid organs or in blood parameters (including plasma lipids) in this porcine model. The contents of disrupted fat cells (including lipids) were removed by macrophages, and the lesions healed normally. In this swine model, the controlled thermal effect of HIFU appeared to provide a safe and effective means for ablating subcutaneous adipose tissue.

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