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High Intensity Focused Ultrasound*

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This document is approved for distribution to healthcare professionals only in the European Union and Canada.

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SUMMARY

Ultrasound is being used with increasing frequency for a variety of applications in human medicine. For years, diagnosticians have relied on ultrasound for medical imaging. Ultrasound technology is used to generate ultrasonic waves that penetrate the body, capture the reflected echoes and create an image of internal structures. These diagnostic ultrasound scanners operate at very low energy levels and have little or no effect on living tissues. In contrast, high energy ultrasound can be tightly focused into a small point which can rapidly heat and destroy targeted tissues. High Intensity Focused Ultrasound (HIFU) technology can be used for performing a variety of highly precise, non-invasive surgical procedures. Often called therapeutic or thermal ultrasound, the clinical uses of HIFU have grown to include the nonsurgical treatment of tumors, uterine fibroids, atrial fibrillation, and internal bleeding. Recently, the medical use of HIFU has been extended to include the ablation of unwanted subcutaneous adipose tissue as a non-invasive method of body sculpting.

High Intensity Focused Ultrasound (HIFU) technology can be used for performing a variety of highly precise, non-invasive surgical procedures. Recently, the medical use of HIFU has been extended to include the ablation of unwanted subcutaneous adipose tissue as a non-invasive method of body sculpting.

INTRODUCTION

Sound vs. Ultrasound

Sound is a mechanical compression wave that travels through some medium and is perceptible to human hearing. The key parameters of sound are the wave intensity (volume) and the frequency of the waves (pitch) which is measured in cycles per second, or Hertz (Hz).

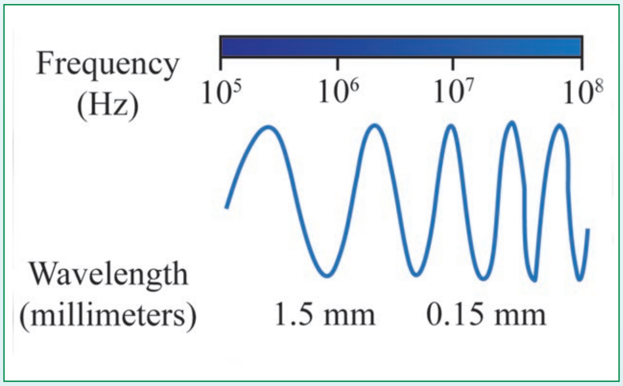

Figure 1. Similar to sound, the key parameters of ultrasound are wave amplitude and wave frequency measured in cycles per second or Hertz (Hz).

The speed of sound is different in dissimilar materials and increases with increasing medium stiffness. For example, sound travels at a speed of approximately 340 m/sec through air but approximately 1,540 m/sec through human tissue. The speed of sound is mathematically related to frequency and wavelength in the following way:

$$\text{Wavelength} = \frac{\text{Speed}}{\text{Frequency}}$$

For example,

$$\text{Wavelength} = \frac{\frac{1{,}540}{\text{m/sec}}}{2\ \text{MHz}} = 7.7\text{x}10^{-4}\ \text{m}\ (0.77\ \text{mm})$$

Similar to sound, ultrasound is also a mechanical compression wave that travels through some medium. Although the frequency of ultrasound is above the range of human hearing (> 20,000 Hz), it can be characterized by the same physical properties used to describe sound such as frequency, wavelength, and amplitude or intensity **(Figure 1)**. In medical ultrasonics, the operating frequency is typically in the low millions of Hertz or megaHertz (MHz). Other clinically important characteristics of ultrasound are reflection or echoes, and absorption or energy transfer.

Echoes: These occur when ultrasound encounters the interface between materials with different acoustic impedance. The acoustic impedance of a material is related to its density and stiffness. The greater the difference in impedance, the greater the amount of energy that is reflected as echoes. The difference in impedance between tissues and gases is very large and essentially all of the transmitted energy will be reflected. As a result, the presence of gas or air pockets in the path of diagnostic or therapeutic ultrasound will cause almost complete reflection of the ultrasound energy, blocking further penetration of ultrasound waves into the tissue.

Absorption: The propagation of ultrasound eventually loses energy, or becomes attenuated as it interacts with materials in its path. Reasons for the attenuation of ultrasound include scattering, reflection, and absorption. Absorbed ultrasound energy is converted into thermal or heat energy. As the frequency increases, absorption increases and greater amounts of energy are converted to heat more quickly while the depth of penetration decreases. As is passes through human tissue, ultrasound energy becomes attenuated at a rate of approximately 0.5 dB/cm/MHz (one-way). Based on this relationship, ultrasound is attenuated more quickly with increasing frequency. For example, a beam of ultrasound with a frequency of 2 MHz beam loses about half of its power after traveling 3.0 cm through human tissue while a 200 kHz beam must travel more than 30 cm before half of its power is lost.

Key Concepts:

Higher Frequency → Higher Absorption → More Heating → Less Penetration

What is High Intensity Focused Ultrasound?

When used diagnostically, low energy beams of convergent ultrasound are rapidly scanned over relatively broad areas of the body. The ultrasound energy is not directed at any one area long enough to permit significant tissue heating to occur. In contrast, HIFU energy is relatively high energy and highly convergent. It is tightly focused in a manner analogous to focusing sunlight with a magnifying glass ***(Figure 2)***. This enables HIFU to be focused to very high intensity at a specific location and in a very small volume. At the intensity levels used with HIFU, the temperature at the focal point quickly rises to levels that cause rapid cell death.

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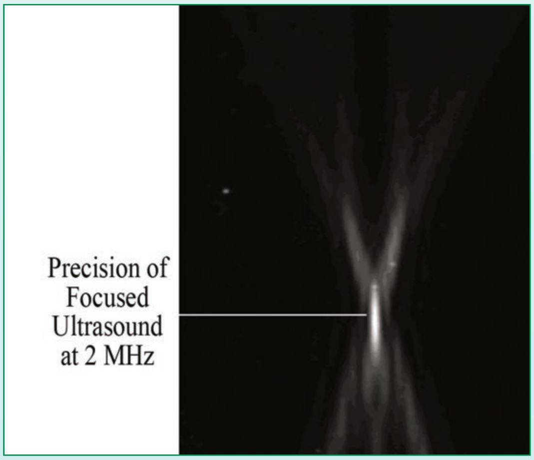

Figure 2. In contrast to diagnostic ultrasound, HIFU is high energy ultrasound which can be focused with very high intensity at a specific point.

Importantly, the intensity levels above and below the focal zone remains relatively low. When applied to the human body, the HIFU beam above the focal point passes through intact skin and superficial tissues without causing injury although thermal tissue damage occurs at the focal point (Dubinsky *et al.*, 2008). For example, the intensity of HIFU may reach over 1,000 Watts/cm^2 at a subcutaneous focal point while remaining a harmless 1-3 Watts/cm^2 at the skin surface ***(Figure 3)***. As the lesions produced by HIFU are spatially isolated within the treated tissue with no surrounding cellular damage, they are often referred to as "trackless" lesions (ter Haar and Coussios, 2007).

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What are the Physical Properties of HIFU?

High intensity focused ultrasound can be characterized by the same physical properties used to describe sound or radio waves, such as frequency, wavelength, and amplitude or intensity.

Fundamental Wave Physics

Impedance: The square root of the product of the material density and its stiffness.

Speed: The speed at which ultrasound propagates through materials is directly proportional to the impedance and inversely proportional to the density of the medium. Similar to sound waves, ultrasound travels at 340 m/sec through air but 1,480 m/sec through water (Ferraro *et al.*, 2008). In human tissue, ultrasound travels at a speed of approximately 1,540 m/sec.

Transmission: When an ultrasound transducer is electrically excited, ultrasound waves are generated which propagate outwardly from the source. These waves are said to be transmitted into the propagation medium. When these waves encounter a second medium with different impedance, only a certain proportion of the wave energy will be transmitted into the new medium while the remainder is reflected or scattered as described below.

Reflection: When propagating ultrasound waves encounter a medium with different acoustic impedance, some energy will be reflected. In the human body,

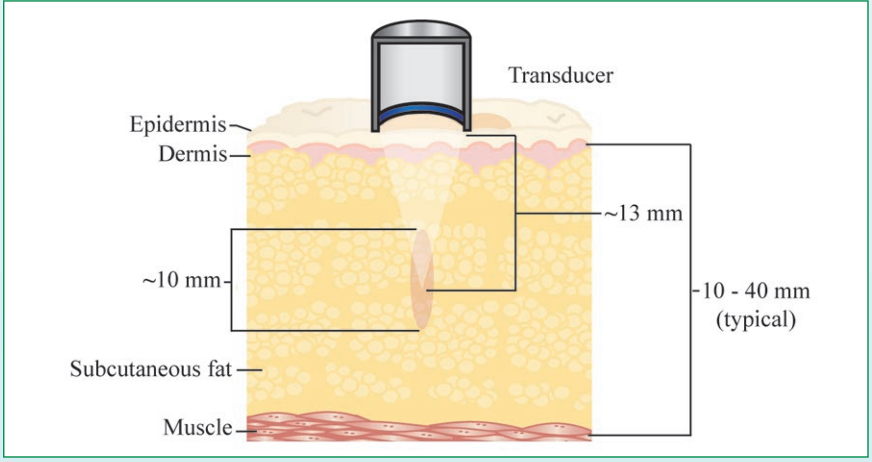

Figure 3. The HIFU energy beam passes through intact skin and superficial tissues without causing injury. Although the temperature at the focal point causes rapid cell death, the tissue immediately above and below the focal point remains unaffected.

At 2 MHz, the tightly focused transducer of the *LipoSonix* system creates cigar-shaped lesions about 1 mm in diameter and 10 mm long.

this occurs at the boundaries between organs and surrounding fluid and between regions of tissue with differing acoustic impedance. In ultrasonography, the sound wave energy reflected at the interface between different tissues is captured by a transducer which converts ultrasound waves into electrical pulses which are used to create an image.

Scattering: When a wave encounters small discrete structures (approximately the size of the wavelength of the propagating wave) with different impedance than the propagating medium, the wave will be broken up and scattered into many directions. These scattered waves are eventually absorbed by the medium and the energy of the forward propagating wave is reduced.

Absorption: Propagating ultrasound eventually becomes absorbed as is interacts with materials in its path. Reasons for the absorption of ultrasound in human tissue are complex but are mostly the result of conversion of ultrasound wave energy into molecular vibrations in tissue resulting in heat.

Attenuation: As it passes through tissue, much of the ultrasound energy is absorbed or scattered into the tissue itself where it is converted into thermal or heat energy. In the human body, ultrasound energy with a frequency of 2 MHz is attenuated at a rate of approximately 1 dB/cm of tissue. As the frequency increases, a greater amount of heat can be deposited in tissue, but the depth of penetration decreases. Frequencies as low as 0.5 MHz can be used for procedures requiring high penetration while frequencies as high as 8 MHz are used for more superficial procedures.

Key Parameters

Frequency: Frequencies near 1 MHz are useful for heat deposition with frequencies as low as 0.5 MHz being used for deep treatments and as high as 8 MHz for shallower treatments (ter Haar and Coussios, 2007). The optimal choice of HIFU frequency is therefore application-specific and represents a balance between the desired treatment depth and the rate of heating. For example, extensive studies performed by Medicis Technologies Corporation (Phase 2 Studies P-0003, P-OUS, and CDN-01. 2008. Sponsored by LipoSonix, Inc. Data on file, Medicis Technologies Corporation) and others (Ferraro *et al.*, 2008) has established that 2 MHz is the optimal frequency for focusing HIFU within subcutaneous tissue layers at selected depths.

Higher frequencies are attenuated more quickly than lower frequencies and therefore cannot penetrate as deeply into tissues. This provides an added margin of safety when using HIFU clinically. As one increases the frequency, the ability to focus a beam of HIFU increases while the depth of penetration decreases due to attenuation (Ferraro *et al.*, 2008; ter Haar and Coussios, 2007).

Energy Intensity: Doses of HIFU energy are expressed as Joules/cm^2 (1 Joule = 1 Watt-second). The dose of HIFU energy and time required to deliver that energy can be adjusted by changing peak power. Increasing the power increases the amount of energy delivered which increases the axial length of the lesions it produces. The ability to change the dose of administered HIFU energy provides the flexibility needed to make HIFU suit different clinical requirements.

Focusing: Ultrasound energy can be focused in two ways: Electronic focus relies on coordinated waves of energy from the elements of an array transducer. Mechanical focus relies on the shape of the transducer to form an acoustic lens which focuses the ultrasound energy.

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HIFU EQUIPMENT CONSTRUCTION

The LipoSonix™ System

Ultrasound is generated using a piezoelectric transducer which converts electrical energy into mechanical energy in the form of ultrasound waves. This is essentially the same energy source used in diagnostic ultrasound; however, the power used to generate HIFU is higher by several orders of magnitude. For example, the *LipoSonix* system generates an electrical waveform of varying amplitudes at 2 MHz. When this is sent to the transducer, it oscillates at the same frequency and thus transmits acoustic energy at a frequency of 2 MHz. The *LipoSonix* system uses a spherically-shaped transducer to mechanically focus the generated ultrasound energy (Figure 3).

The *LipoSonix* system was developed for performing body contouring by using HIFU energy to non-invasively destroy adipose tissue. HIFU energy, by its definition, can only ablate tissue at one focal point at one time. Therefore, the transducer must be moved repeatedly to treat large areas of tissue. The *LipoSonix* system is equipped with a programmable pattern generator which consistently and automatically directs HIFU energy over the entire treatment area. In this way, the *LipoSonix* system can treat an 8 cm^2 treatment area in approximately 30 seconds. To treat an entire abdomen requires about 15-20 minutes per pass. Two or three passes may be needed to achieve the desired aesthetic effect.

The LipoSonix system was developed for performing body contouring by using HIFU energy to non-invasively destroy adipose tissue in the anterior abdomen.

The amount of HIFU energy delivered by the *LipoSonix* system may be adjusted by changing the peak power and by changing the duration of energy delivery. In addition, the system has a user-adjustable focal depth 1.1-1.8 cm. Together, these features provide the operator with the ability to adjust the amount and location of HIFU energy delivered to meet different clinical situations.

The *LipoSonix* system manufacturer recommends the use of purified water as a coupling agent to prevent the occurrence of significant acoustical reflections from air pockets at the HIFU treatment head/skin interface. In addition to being highly effective, water is readily available, non-allergenic, and easy to clean. The *LipoSonix* system alerts the operator if coupling of the ultrasound energy from the transducer into the body is inadequate.

The *LipoSonix* system has been approved for sale and use in Canada and the European Union for treatment of subcutaneous adipose tissue in the anterior abdomen. It has not been approved for sale in the United States.

The Effect of HIFU on Tissue

Heating

The injury that occurs when HIFU is applied to living tissue is the result of a thermo-mechanical process. As the name implies, this involves two distinct but inseparable mechanisms. The ultrasound energy which is absorbed by tissue causes molecular vibrations resulting in heat energy and a rapid rise in temperature in the focal zone. Additionally, the repeated compressions and rarefactions (decreased pressure) that occur as waves of ultrasound propagate through living tissue result in powerful shear forces. On a cellular level, this microscopic shearing motion results in frictional heating (Duck, 1990).

In biological tissues, raising tissue temperature above 56 °C for 1 second causes rapid cell death *via* coagulative necrosis (Kennedy *et al.*, 2003; Kim, 2008). As described above, this rapid increase in temperature is sufficient to destroy living tissue at the focal point while the surrounding tissue remains unaffected. The guiding principle of HIFU is that an ultrasonic beam should be able to destroy a sharply defined region of tissue rapidly with minimal effects to surrounding tissues (ter Haar and Coussios, 2007). At HIFU energy levels capable of destroying adipose tissue, collagen fiber contraction also occurs (Ferraro *et al.*, 2008).

As the frequency increases, the ability to focus the waves of ultrasound also increases. Additionally, increasing the frequency increases the attenuation of the ultrasound energy and the transfer of ultrasound to heat energy (ter Haar and Coussios, 2007). These relationships make HIFU extremely well-suited for performing non-invasive ablative therapy.

At 2 MHz with a tightly focused transducer, HIFU will create an oblong lesion about 1 mm in diameter and 10 mm long (Figure 3) although the exact size and shape is strongly affected and precisely controlled by the dose of energy used (Duck *et al.*, 1998). Due to the steep temperature gradient between the heated focal zone and surrounding tissue, the area of tissue necrosis is confined to the focal zone (Duck *et al.*, 1998). Adipose tissue and collagen are affected by HIFU and some small capillaries may be occluded by clotting blood; however, larger blood vessels may remain relatively unaffected, possibly due to the cooling effect of blood perfusion.

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Table 1 Important HIFU Properties*

Low Frequency (<1 MHz)	Slower delivery and lower tissue absorption may cause cavitation. Difficult to tightly focus due to longer wavelengths. Typically has little effect on collagen.
High Frequency (1-10 MHz)	More rapidly and highly absorbed into tissue, achieves thermo-mechanical effects. Can achieve very precise focus at these frequencies. Can contract collagen.
Low Intensity (0.1-20 Watts/cm^2)	Limited thermal effects; cavitation may occur. Typically used in diagnostic devices or simple physical therapy devices.
High Intensity (>1,000 Watts/cm^2)	Produces thermo-mechanical effects. Can be used therapeutically to modify tissue.

*Note: These categories are necessarily arbitrary and are only intended to illustrate typical behaviors.

Cavitation

If the HIFU frequency is too low (0.1-1 MHz), a large transducer source is required to achieve a focused beam, the absorption of ultrasonic energy becomes lower and a phenomenon known as cavitation is more likely to occur. As ultrasound propagates, the material becomes compressed as the waves of pressure enter the medium and expands again as they leave. In living tissue, these repeated compressions and rarefactions may cause microscopic bubbles to form in biological fluids which grow in size, and oscillate until they eventually implode. High

The principles of cavitation are being applied in lithotripsy which uses HIFU to break apart kidney stones while other potential medical applications include thrombolysis, drug and gene delivery, and as a contrast agent in echocardiography. Aesthetic applications include body contouring.

temperatures can occur inside the bubbles and the forces generated by collapsing bubbles can cause cell death through mechanical processes (Dubinsky *et al.*, 2008).

Noninertial or stable cavitation is the process by which small bubbles in a liquid are forced to oscillate in the presence of an acoustic field when the intensity of the acoustic field is insufficient to cause total bubble collapse; however, when a volume of liquid is subjected to a sufficiently low pressure, it may form a cavity and then rupture. This form of cavitation is called inertial cavitation and occurs, for example, in the water behind the blade of a rapidly-rotating propeller. Very large pressure gradients created by inertial cavitation can cause mechanical erosion of very hard materials, such as metallic propeller blades.

Although the effects of cavitation on tissue are unpredictable and difficult to control (Kennedy *et al.*, 2003; Kim *et al.*, 2008), it does have therapeutic applications. The principles of cavitation are being applied in lithotripsy which uses HIFU to break apart kidney stones (Yoshizawa *et al.*, 2009) while other potential medical applications include thrombolysis, drug and gene delivery, and as a contrast agent in echocardiography (Djikman *et al.*, 2004). Aesthetic applications include body contouring (Brown *et al.*, 2009).

In contrast to the well-defined tissue lesions generated by thermal HIFU, cavitation results in irregular holes of varying size, ranging up to several millimeters in diameter. The size of the lesion generally increases with decreasing frequency. The cavitation threshold is highly dependent on local and variable tissue conditions such as the level of hydration and the presence of cavitation nuclei. While the lesions caused by cavitation are generally contained within the focal zone of the transducer, the presence of cavitation nuclei in areas outside the focal zone can also generate lesions at relatively low intensities. As lesions caused by cavitation are the result of mechanical forces created by an imploding cavity, resistance to tissue injury is a function of the structural integrity of the treated tissue (Brown *et al.*, 2009).

The mechanism of action for lesion resolution of thermal induced lesions in the subcutaneous adipose tissue has been documented up to 14 weeks post treatment in both animal models and human subjects. The healing response for cavitation induced lesions in the subcutaneous adipose tissue has been documented in animal models for up to three days (Brown *et al.*, 2009).

THERAPEUTIC APPLICATIONS OF HIFU

When the temperature of living tissue exposed to HIFU is elevated to more than 56 °C for 1 second, rapid cell death via coagulative necrosis occurs (Kennedy *et al.*, 2003). A report by Wu *et al.* describes the pathologic changes observed when HIFU was used to treat 164 patients with several types of cancers including liver and breast cancer, malignant bone tumor, soft tissue sarcoma and other malignant tumors. This group ablated tumors using HIFU at frequencies of 0.8-3.2 MHz and focal peak intensities from 5,000-20,000 Watts/cm^2. To observe the tissue changes associated with the use of HIFU, surgical removal of the malignancy was performed in a subgroup of 30 patients following HIFU treatment. Their observations are briefly summarized here (Wu *et al.*, 2001):

Macroscopic changes

Thermal lesions in intervening tissue were not observed in any treated patient, demonstrating the ability of HIFU to produce "trackless lesions." Macroscopic examination of tissues revealed a sharp boundary between the HIFU necrosis and viable tissue around the focal zone. The treated area consisted of severe tissue destruction with coagulation necrosis in the center of the lesion surrounded by a ring of congestion. Outside the area of necrosis, the tissue was normal with an extremely well-defined boundary between the necrotic and healthy tissue.

Microscopic changes

Histologic examination showed the HIFU lesions consisted of homogeneous areas of coagulative necrosis with no viable tumor cells. Distorted tumor cells with pyknotic or shrinking nuclei, cell debris and destroyed healthy tissue were often observed surrounding the necrotic area. In breast and liver tumors, the border between the treated and untreated areas was extremely sharp and only a few cell layers in thickness. Vascular injury was confined to blood vessels less than 2 mm in diameter.

Tissue healing

A small amount of granulation tissue formed 7 days following HIFU treatment with the presence of immature fibroblasts, numerous inflammatory cells and new capillaries in the boundary region. After 10-14 days, destroyed tumor cells were no longer aggregated and had no distinct cytoplasm and nucleus. The boundary area was generally replaced by mature fibrous tissue, and the HIFU-damaged area was partially absorbed and replaced with new proliferative repair tissue. Lesion repair followed the processes of necrotic tissue absorption and granulation tissue replacement.

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Medical Applications

Oncology

HIFU can be applied transrectally at a frequency of 3 MHz for the treatment of prostate cancer in patients who are poor candidates for traditional surgery (Maestroni *et al.*, 2008; Blana *et al.*, 2008). The value of HIFU for the treatment of other forms of cancer is currently under evaluation in preclinical or pilot studies including breast cancer (Wu *et al.*, 2003; Wu *et al.*, 2005), liver cancer (Li *et al.*, 2009; Noterdaeme *et al.*, 2009), renal tumors (Klatte and Marberger, 2009; Klingler *et al.*, 2008), and pancreatic cancer (Wang and Sun, 2002; Hwang *et al.*, 2009).

Wu *et al.* used HIFU at frequencies of 0.8 to 3.2 MHz and peak intensities of 5,000 to 20,000 Watts/cm^2 to treat a broad range of different malignancies (Wu *et al.*, 2001). A laparoscopic HIFU probe has been used to ablate renal tumors at a frequency of 4.0 MHz (Klingler *et al.*, 2008). Similar to prostate cancer, HIFU can also be applied transrectally for the treatment of benign prostatic hypertrophy (Hegarty and Fitzpatrick, 1999).

Gynecology

HIFU devices are under development for the treatment of gynecological disorders such as uterine fibroids as a non-invasive alternative to hysterectomies (Chan *et al.*, 2002). In one pilot study, a 1.07 MHz ultrasound source was used which permitted treatment at tissue depths ranging from 0 to 10 cm. In 12 patients scheduled to undergo abdominal hysterectomy, the application of 5-60 pulses of HIFU energy intensities of 3,200-6,300 Watts/cm^2 were applied to the uterus through the intact skin, safely and effectively destroying uterine fibroids (Fruehauf *et al.*, 2008).

Neurology

The ability of HIFU to disrupt nerve conduction has been known since the 1950s when Fry reported results in experimental animal models (Fry *et al.*, 1958). More recently, a quantifiable reduction in compound muscle action potentials lasting from hours to days post-treatment has been described (Foley *et al.*, 2008). These results were achieved by intentionally exposing nerve bundles to HIFU. Thus, another potential clinical application of HIFU might be the treatment of chronic spasticity or pain (Foley *et al.*, 2004). Current treatments for controlling spasticity include injections of neurotoxin, such as botulinum toxin (Lukban *et al.*, 2009).

Cardiology

Atrial fibrillation is routinely being treated using a device consisting of an array of multiple ultrasound transducers that are positioned around the pulmonary veins of the left atrium. A programmed algorithm sequentially activates the transducers using a combination of frequency (3.8-6.4 MHz), power (15-130 Watts), and duration to perform circumferential ablation of the epicardium. In this manner, unwanted electrical impulses are blocked, providing an effective treatment of atrial fibrillation (Ninet *et al.*, 2005; Mitnovetski *et al.*, 2009).

Other cardiovascular uses for HIFU include causing hemostasis in actively bleeding organs and blood vessels. In animals, HIFU has been shown to quickly stop bleeding in experimentally injured livers (Vaezy *et al.*, 2004) and blood vessels (Greaby *et al.*, 2007).

Aesthetic Applications

Subcutaneous adipose tissue, or white body fat, is loose connective tissue located beneath the skin where it provides a storage site for lipids and offers a layer of thermal insulation. Adipose tissue is primarily composed of adipocytes which contain triglyceride droplets. Other types of cells found in adipose tissue include fibroblasts, macrophages and endothelial cells ***(Figure 4)***. These cells are held together by a network of collagen fibers. Adipose tissue also contains many small blood vessels and each adipocyte is in contact with at least one capillary.

As fats accumulate within adipocytes, the stored lipid droplets increase in size until the nucleus and cytoplasm of the cell become squeezed against the cell membrane. When existing adipocytes reach a critical size, precursor adipocyte cells are stimulated to divide and differentiate into additional mature adipocytes, increasing the overall mass of adipose tissue. The increase in adipocytes plays an important role in the development of obesity as newly formed adipocytes remain a permanent part of adipose tissue. Approximately 60 to 85% of the weight of white adipose tissue is lipid, with 90-99% existing as triglyceride. Lesser components include free fatty acids, diglyceride, cholesterol, phospholipid, cholesterol ester and monoglyceride.

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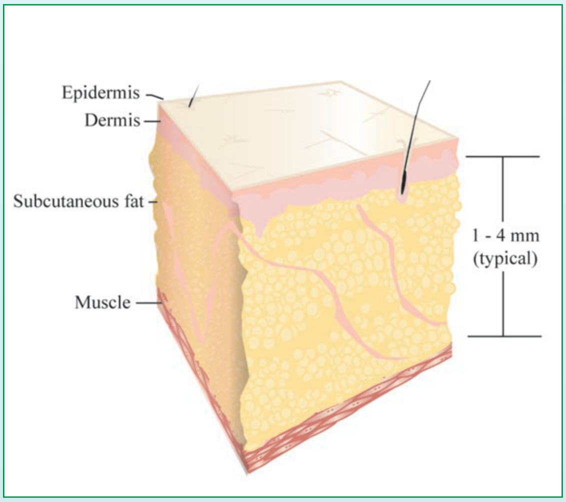

Figure 4. Subcutaneous adipose tissue, or white body fat, is primarily composed of adipocytes which contain triglyceride droplets. Other cell types include fibroblasts, macrophages and endothelial cells. Adipose tissue is held together by a network of collagen fibers.

Effects of HIFU on Adipose Tissue: Preclinical Studies

Due to the similarities with human skin and subcutaneous tissue structure, the use of transcutaneous HIFU for the ablation of adipose tissue was first evaluated using a swine model. The volume of treated adipose tissue ranged from 75-950 cc. Gross pathology and histology revealed discrete, well-defined areas of ablated tissue within the targeted treatment zones with the release of triglyceride molecules and fatty acids into the interstitium.

The primary cellular inflammatory response consisted primarily of macrophages with negligible neutrophils, plasma cells, and lymphocytes. After 8 weeks, gross pathology demonstrated excellent resorption of damaged adipose tissue ***(Figure 5)***. Necropsy studies performed after 1 and 6 weeks did not reveal any fatty liver changes or other organ abnormalities. There were no clinically significant changes from baseline plasma lipid panels and urinalyses did not show evidence of ketosis or fat globules (Garcia-Murray *et al.*, 2005; Fodor *et al.*, 2006).

Effects of HIFU on Adipose Tissue: Clinical Studies

Subsequent clinical studies involved the use of HIFU to ablate abdominal adipose tissue in human subjects prior to undergoing elective abdominoplasty. The volume of treated adipose tissue ranged from 25-225 cc. Following treatment, computed tomography and magnetic resonance imaging demonstrated that HIFU treatment zones were confined to the subcutaneous adipose tissue with no injury to the skin or intra-abdominal organs. Gross pathology revealed discrete areas of coagulative necrosis of the adipose tissue at the focal site with no damage to the skin or intervening tissues. The depth of each lesion was limited to the adipose tissue and did not extend into the dermis, rectus muscle or fascia. Histological examination of abdominal adipose tissue excised at different times up to 86 days following HIFU treatment revealed a well-demarcated zone of adipocyte disruption. Remaining cells demonstrated degenerating plasma membranes with pyknotic nuclei. Most of the treated tissue was resorbed within 8-12 weeks after the initial HIFU treatment and 95% was resorbed after 18 weeks. The minimal inflammatory response after 4 and 18 weeks consisted predominantly of macrophages (Garcia-Murray *et al.*, 2005; Garcia-Murray *et al.*, 2006; Fodor *et al.*, 2006; Smoller *et al.*, 2006). Following a single HIFU treatment, the average waist circumference reduction achieved by patients was > 2cm (Phase 2 Studies P-0003, P-OUS, and CDN-01. 2008. Sponsored by LipoSonix, Inc. Data on file, Medicis Technologies Corporation).

Histological examination of abdominal adipose tissue excised at different times up to 86 days following HIFU treatment revealed a well-demarcated zone of adipocyte disruption.

HIFU-induced injury of adipose tissue has been shown to be frequency-dependant. When applied to adipose tissue at a frequency of 1 MHz, only minor cell changes are observed while HIFU at frequencies of 2 to 3 MHz result in complete derangement of fat tissue (Ferraro *et al.*, 2008). Extensive testing has established that 2 MHz is the optimal frequency for focusing HIFU within subcutaneous tissue layers at selected depths.

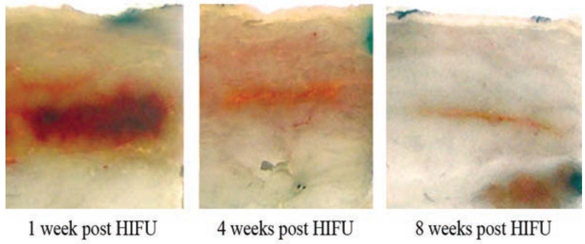

Figure 5. Swine tissue excised at various times after treatment shows the well-defined area of ablation followed by normal healing over an 8-week period.

Effects of HIFU on Collagen

In addition to local cellular necrosis, the application of heat using HIFU causes collagen fibers to denature and contract in the subcutaneous fat layer. Heat contracts collagen by breaking intramolecular hydrogen bonds causing the chains of collagen to fold and assume a more stable configuration. The result is a thickening and shortening of collagen fibers. The application of HIFU in adipose tissue has demonstrated partial denaturization of collagen fibers at a frequency of 1 MHz and diffuse contraction of collagen fibers at 2-3 MHz (Ferraro *et al.*, 2008).

Safety of HIFU

During treatment as recommended, patients may experience discomfort, pain, cold, prickling, tingling, or warmth. The most common post-treatment side effects include temporary erythema, mild ecchymosis, discomfort, and edema. Lipid panels including free fatty acids, total cholesterol, low-, very low- and high-density lipoproteins, and triglyceride obtained over a 4-week period did not reveal any clinically-significant changes. Other clinical laboratory measures including a comprehensive metabolic panel obtained for up to 3 months remained within normal limits. Histological examination of tissues revealed no evidence of dystrophic calcification, abscess, or fistulae (Garcia-Murray *et al.*, 2005; Garcia-Murray *et al.*, 2006; Fodor *et al.*, 2006; Smoller *et al.*, 2006).

Following the investigation of HIFU for abdominal tissue ablation, 46 subjects completed a patient satisfaction survey: 91.3% responded that the flatness of their abdomen had improved after treatment and 88.6% would likely repeat the procedure if it were necessary to achieve the best effects.

Patient Satisfaction

Following the investigation of HIFU for abdominal tissue ablation, 46 subjects completed a patient satisfaction survey: 91.3% responded that the flatness of their abdomen had improved after treatment and 88.6% would likely repeat the procedure if it were necessary to achieve the best effects (repeated treatment using HIFU for abdominal tissue ablation has not been tested). (Phase 2 Studies P-0003, P-OUS, and CDN-01. 2008. Sponsored by LipoSonix, Inc. Data on file, Medicis Technologies Corporation).

Other Energy Sources

Other energy sources such as radio frequency (RF) and lasers are also widely used clinically; however, these electromagnetic waves do not share the physical properties of ultrasound. These systems are unable to penetrate subcutaneous tissue and achieve a focusing effect in subcutaneous tissue based on wavelength, scattering effects or high absorption of energy near the skin surface.

Photonic sources

These are light-based energy sources of electromagnetic energy and include lasers and intense pulsed light (IPL) devices. IPL devices generate a broad range of wavelengths in the visible light spectrum while lasers typically generate a single wavelength of light. As a class, lasers can generate a wide range of wavelengths ranging from infrared to ultraviolet (Carroll and Humphreys, 2006). Similar to HIFU, lasers can deliver heat energy to the target area resulting in rapid coagulative necrosis and essentially instant cell death; however, photonic energy typically has little effect in the subcutaneous adipose tissue. Laser surgery is being used to ablate malignancies such as hepatic carcinoma; however, similar to RF described below, the laser probe must be placed in close proximity with the tissue to be treated using imaging techniques such as magnetic resonance imaging (Gough-Palmer *et al.*, 2008). In aesthetic medicine, the topical application of laser energy can be used for facial skin tightening (Key, 2007).

Radiofrequency (RF) sources

Similar to light, radio waves are a form of electromagnetic energy which is used for performing thermal tissue ablation. For example, RF is advancing the nonsurgical treatment of some thoracic malignancies. While it is described as a minimally invasive procedure, it does require the insertion of a probe into the chest cavity while the patient is maintained under conscious sedation. Computerized tomography is used to guide the RF probe into close proximity of the tumor or cancer to be ablated. A single probe is used to ablate small tumors (< 4 cm) while a cluster of RF probes can be used to treat larger tumors (Dupuy *et al.*, 2002). Two types of RF devices are currently used in aesthetic medicine.

Monopolar devices deliver RF energy through an electrode at a single contact point. A grounding pad attached to a distal part of the body serves as a low resistance path for current flow to complete the electrical circuit. Monopolar electrodes concentrate most of their energy near the point of contact which rapidly diminishes as the current flows toward the grounding electrode (Atiyeh and Dibo, 2009). Bipolar devices use two electrodes positioned very close together and RF energy passes between them. They cannot send energy deep into the body (Atiyeh and Dibo, 2009). Within the field of aesthetic medicine, the application of RF is being used to increase the thickness of collagen fibers and skin (Kaplan and Gat, 2009) and is being used in aesthetic procedures (Kushikata *et al.*, 2005; Hodgkinson, 2009).

SUMMARY

Unlike diagnostic ultrasound, HIFU uses highly focused energy to ablate subcutaneous tissue. While not a replacement for surgical procedures which can remove large amounts of adipose tissue, HIFU is less invasive than procedures such as liposuction and addresses the growing demand for effective, non-invasive, nonsurgical reduction of abdominal fat. The non-invasive nature of HIFU provides several advantages over surgical procedures such as eliminating the need for sedation and reduced risk of infection. Based on the frequency and intensity of energy used, the mechanism of action of HIFU is unique. Unlike other devices whose mode of action relies on photonic energy, radio-frequency energy and low-energy ultrasound, the thermal effects of high-energy HIFU rapidly heat and destroy adipose tissue with a high degree of precision.

Unlike diagnostic ultrasound, HIFU uses highly focused energy to ablate subcutaneous tissue. While not a replacement for surgical procedures which can remove large amounts of adipose tissue, HIFU is less invasive than procedures such as liposuction and addresses the growing demand for effective, non-invasive, nonsurgical reduction of abdominal fat.

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Important Safety Information

During treatment as recommended, patients may experience discomfort, pain, cold, prickling, tingling, or warmth. The most common post-treatment side effects include temporary erythema, ecchymosis, discomfort, and edema. The *LipoSonix* system is not for use in patients with a coagulation disorder, using anticoagulants or platelet inhibitors, or who have an implanted electrical device. Not for use in patients with a BMI >30 or in areas with less than 1 cm of adipose tissue beyond the selected focal depth, or in areas previously treated with injection lipolysis, liposuction, abdominoplasty or other surgery including laparoscopic, or where hernia, implanted material, sensory loss or dysesthesia are present. Treatment is contraindicated for patients with cancer, systemic disease, or who are pregnant or suspected to be pregnant.

For additional product and safety information please visit www.LipoSonix.com or refer to the *LipoSonix* System User Manual.

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