New Technologies in Clinical Ultrasound

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Ultrasound (US) is the imaging modality of choice for a wide variety of clinical indications because of its excellent image quality combined with lack of ionizing radiation, relative portability, and low cost. Numerous advances in US technology over the past few decades, such as color and power Doppler, speckle reduction, compound imaging, harmonic imaging, and 3-D imaging have become the standard of care, adding critical information to the US examination. More recently, innovations in US technology, such as elastography, US contrast media, and high-intensity focused ultrasound (HIFU), have been introduced into clinical practice; other new technologies, such as capacitive micromachined ultrasonic transducers (CMUTs) and photoacoustic imaging, are in development and are nearly ready for clinical use. These new and emerging technologies are the subject of this review.

Elastography

Technology

Manual palpation has been a cornerstone of physical diagnosis for centuries, ever since the first physicians recognized that disease processes invisible to the naked eye could often be detected because they were firm to the touch. This differential hardness or stiffness between diseased and healthy tissue forms the basis for elasticity imaging. When combined with B-mode imaging (imaging of acoustic impedance differences) and Doppler imaging (imaging of flow and movement), elasticity imaging now adds a third tissue property—stiffness—to the US arsenal for lesion detection and characterization. Elastography relies on the premise that palpable abnormalities, such as malignancy or other pathology, tend to be “harder” (less elastic) than nonmalignant tissue.1,2 US has the ability to determine the relative stiffness of a lesion through several different techniques that take advantage of tissue characteristics and the interaction with sound and extrinsic compression.

In engineering terms, the stiffness of a material is described by its Young elastic modulus $E$, given by the relation

$$\frac{F}{A} = E \frac{\Delta L}{L_0}$$

where $F/A$ is the applied force per unit area (defined as the “stress”) measured in S.I. units of Pascals (Pa), and $\Delta L/L_0$ is the change in length of the object relative to its original length in response to the compressive force. This latter parameter $\Delta L/L_0$ is defined as the tissue strain; because it is dimensionless, the unit of $E$ is also Pascal. Hard materials are not readily deformed (small $\Delta L$) in response to an applied force, and therefore have low strain, and soft materials have high strain. Rearranging the above equation to

$$E = \frac{L_0}{\Delta L} \left( \frac{F}{A} \right)$$

one can see that the Young elastic modulus is inversely proportional to the amount of displacement $\Delta L$ that occurs in response to an applied pressure. In other words, low-strain (ie, hard) materials have large $E$, and vice versa.3,4

Types of Elastography

Sonographic elasticity imaging is currently implemented by 1 of 2 basic methods: strain imaging, which represents how readily tissue deforms in response to an applied compression; or shear-wave elastography, which represents the differences in speed of sound through tissues of varying stiffness. The fundamental principle of elasticity imaging is that stiffer tissues deform less (low strain) and propagate sound faster than softer tissues.

Strain Imaging

Most implementations of strain imaging involve application of external compression either manually or automatically using the same US transducer used for B-mode scanning. A region of interest is identified and its dimensions measured before and after compression. Alternatively, a compression-release cycle can be generated from an internal source, such as vessel pulsation or cardiac motion. Changes in the echo pattern before and after compression are analyzed using the manufacturer’s chosen software algorithm and used to generate an “elastogram”—a
qualitative map of relative tissue stiffness. The elastogram is typically displayed adjacent to the original B-mode image with an overlay in either gray scale or color depicting whether the lesion is hard or soft relative to the other tissues in the insonation field of view. Because this technique is qualitative and dependent on other tissues in the image, a given lesion can appear “hard” or “soft” depending on what other tissues are in the field of view. Compression techniques for strain imaging are also operator dependent, and the results are variable depending on how much “precompression”—external pressure applied when scanning to obtain the baseline B-mode image—has been used. In some systems very little external manual compression is needed to generate an elastogram, whereas in other systems the user must apply rhythmic compression-release cycles.

More recently, less operator-dependent strain imaging techniques, such as acoustic radiation force imaging (ARFI), have been developed. In this method, a short high-intensity “push pulse” is applied to a region of interest along the axis of the US beam to generate tissue compression, and the strain-based displacement of the tissue is measured. The resulting strain in the region of interest is displayed in either gray scale or color; with low-strain (hard) materials typically represented as black and high-strain materials as white. A variety of strain-based quantitative metrics, such as strain index, have also been studied for clinical applications.

**Shear-wave elastography.** ARFI technology and other “push-pulse” techniques can also be used for quantitative assessment of tissue elasticity by measuring the speed of a shear wave generated in the tissue perpendicular to the axis of the push pulse by the tissue displacement (Fig. 1). The shear-wave propagation velocity is then used to calculate the Young modulus in kPa of the region of interest using a well-defined mathematical relationship. Shear waves propagate faster through stiffer tissues, so the numerical value of the speed of shear-wave propagation within a region of interest is a reasonable representation of tissue stiffness in that region.

Techniques relying on measuring the speed of sound in tissue have the advantage of being quantitative, reproducible, and less operator dependent. However, regions of interest must be selected by the user for interrogation to obtain the quantitative values, which can produce varying results depending on the area imaged. Newer commercially available machines help the user select appropriate areas for interrogation by providing color-coded shear-wave velocities overlaid upon a gray-scale view.

**Clinical Applications**

Focal masses within superficial tissues that are readily accessible to compression with the US transducer are the most readily assessed with sonoelastography. These include lesions of the breast, thyroid, and prostate gland, as well as lymph nodes and peripheral veins. Diffuse disease processes in deep organs, such as the liver and kidney, can also be evaluated with elastography, but because normal tissue cannot serve as a reference, some means of calibration must be devised for the stiffness measurement. A detailed review of the clinical applications and results to date of sonoelastography is beyond the scope of this article, but experience to date in 2 common applications is discussed below.

**Breast**

Breast masses were among the first to be investigated using sonoelastography. As might be expected from their properties on palpation, malignant masses indeed have lower strain than normal breast tissue, fibrocystic areas, or benign masses such as fibroadenomas. In addition, breast cancers appear larger on elastography than gray-scale imaging, which is thought to be due to the presence of an adjacent desmoplastic reaction, although this has not been confirmed with pathology (Fig. 2). A variety of elastographic criteria to distinguish benign from malignant breast masses has shown sensitivities and specificities of 70.1%-86.5% and 52%-95.7%, respectively. Nevertheless, because the performance of B-mode sonography is already strong, the incremental value of strain elastography imaging techniques for making this determination is not yet clear. Even apart from its ability to characterize masses as benign vs malignant, strain elastography appears to increase the conspicuity of breast malignancies compared with B-mode imaging, and may offer advantages in providing guidance for breast biopsy by identifying the hardest areas in the tumor.

**Liver**

Liver biopsy is considered the gold standard in determining degree of liver fibrosis, which helps predict patient prognosis and guide treatment decisions in patients with chronic liver disease. Unfortunately, liver biopsies are invasive and carry inherent risks of bleeding, infection, and potential sampling...
Elastography appears to be a promising and non-invasive alternative. The most extensively used and tested method for evaluation of liver fibrosis and staging is transient elastography (TE; or FibroScan, Echosens, Paris, France). In this method, which does not produce images, a piston-mounted US transducer is applied to the skin overlying the liver and used to generate a shear wave that propagates through it. FibroScan then measures the shear-wave velocity and computes the estimated elastic modulus of the liver. This nonimaging method has been shown to have excellent performance for detecting cirrhosis and staging fibrosis, but the accuracy is slightly decreased in extremes, such as early-stage fibrosis and severe fibrosis or cirrhosis.

Alternative elastography methods have also been studied in liver fibrosis evaluation. A recent meta-analysis by Friedrich-Rust et al (2012) of the diagnostic accuracy of ARFI in evaluating liver fibrosis and cirrhosis showed accuracies of 0.87 and 0.93 for liver fibrosis and cirrhosis, respectively. Another study of ARFI in 90 subjects showed a sensitivity of 88% and specificity of 90% for the differentiation of cirrhosis from normal liver. A head-to-head comparison of TE, real-time tissue elastography, and ARFI by Colombo et al showed that TE and ARFI performed better than real-time elastography alone in the evaluation of cirrhosis.

Elastography has also been explored as a means to distinguish active inflammation from fibrosis in inflammatory bowel disease; this application is discussed further by Wilson et al elsewhere in this publication. Other organs studied by elastography include the thyroid and prostate gland, although results to date have been variable, these remain active areas of investigation.

### US Contrast Media Technology

US imaging uses the echoes generated by sound waves interacting with tissues to create 2- or 3-D anatomical images that allow for the discrimination of macrovasculature from organs without the use of contrast agents, due to the inherent contrast differences between solid tissues and blood. Although US methods, such as Doppler imaging, are very effective at visualizing and measuring blood flow in large vessels with rapidly moving blood, they are unable to accurately detect flow in smaller vessels and capillaries. The development of microbubbles (MBs) as contrast agents for US has subsequently allowed for the imaging of small vessels with slowly moving blood owing to MBs’ ability to scatter acoustic waves as well as the unique harmonics that they create when exposed to US. This allows for safe, high-spatial resolution imaging of the vasculature in real time, without the use of ionizing radiation.

### Clinical Applications

MBs are small (1-4 μm) gas-liquid emulsions consisting of a gas core surrounded by a stabilizer shell made from biocompatible materials. Owing to their size, MBs injected into a peripheral vein remain confined to the vasculature, including microcapillaries, and can be detected in circulation, from several minutes up to 60 minutes depending on their composition, injection method, and dose, before their gas core diffuses out of the shell and the components are cleared by the reticuloendothelial system. This time frame is well within the window to obtain useful information about vascularity, perfusion rates, and potential tumor detection in many different tissues including the heart, liver, spleen, bowel, pancreas, kidneys, ovaries, and prostate. Contrast-enhanced US (CEUS) has been used in the heart for identifying atherosclerotic carotid plaques at risk for rupture as well as improving visualization of vessel wall irregularities. It has also been successful at identifying masses in organs including the kidney, pancreas, ovaries, and prostate, though the most common clinical use in lesion detection has been in the liver.

Owing to the vascular structure of focal liver lesions, differences in filling time, and washout of the MB contrast agent can facilitate not only the identification of focal lesions from within the surrounding tissue (Fig. 3), but also their characterization. Enhancement patterns of focal liver masses...
on CEUS are analogous to those on computed tomography or magnetic resonance imaging (MRI); for example, peripheral nodular enhancement with centripetal fill-in is observed in hemangiomas. Unlike computed tomography or MRI, however, characterization of lesions on US must be done essentially 1 lesion at a time as the transducer must remain stationary during the transit of contrast medium through the lesion. CEUS is already being used in over 50 countries primarily in Europe, Asia, and Canada. US contrast agent approval in the USA was delayed by a Food and Drug Administration’s black-box warning in 2007 on 2 contrast agents used for echocardiography (DEFINITY, Lantheus Medical Imaging; Optison, GE Healthcare) after 11 deaths were temporally related to but not clearly caused by contrast injection. Since then, this warning has been partially removed by the Food and Drug Administration after several new studies clearly confirmed safety of US contrast agents. Currently, a Phase III clinical trial is under way of a second-generation contrast agent (SonoVue, Bracco) for characterization of focal liver lesions. In addition, technical improvements in 3D US are under way that may

Figure 3 Principles of contrast-enhanced ultrasound (US) imaging using both nontargeted and molecularly targeted microbubbles (MB). (A) MB are vascular-restricted contrast agents that are comprised of a protective shell (lipid or protein) surrounding a gas core (often perfluorocarbon), making them highly echogenic. When exposed to US pulse, they are driven into nonlinear oscillations (expansion and contraction), creating unique harmonics that are distinguishable from surrounding tissue. (Right) Transverse US scan in a 70-year-old female with liver metastasis (arrows) from colon cancer acquired at 16 seconds and 98 seconds following intravenous administration of US contrast agent. Although metastasis is only vaguely seen on B-mode image, metastasis is well depicted on contrast-enhanced US imaging and appears highly vascularized on arterial-phase imaging with substantial washout on delayed phase image compared with surrounding normal liver parenchyma. (B) Example of US molecular imaging using MBs targeted to inflammatory marker P-selectin. P-selectin-targeted MBs (MBP-selectin) bind to and accumulate on vascular endothelial cells expressing P-selectin on their surface. (Right) US signal from colon wall of normal control mouse and mouse with chemically induced acute colitis that were injected with both MBP-selectin and MBcontrol. Note high US signal in colon of colitis mouse when injected with MBP-selectin (top left) compared with control mouse; injection of MBcontrol did not result in significant increase of imaging signal in colon wall of colitis and control mouse. (Adapted and reprinted with permission from Deshpande et al.58) (Color version of figure is available online.)
Further improve the reproducibility and standardization of CEUS in the clinical arena.  

Other promising potential applications of CEUS come from the molecular targeting of the MB contrast agents, enabling not only identification of anatomical and vascular structures, but imaging of biological processes including angiogenesis and inflammation (Fig. 3B). Molecular targeting of MBs occurs when a targeting peptide, receptor ligand, or antibody are coupled to the protective shell, allowing them to bind and accumulate in areas expressing the complementary protein. Among the targets being explored are proangiogenic factors, including VEGFR2, endoglin, and integrin αvβ3,56,57 that are used to target, visualize, and monitor angiogenesis, and P-selectin or mucosal addressin cellular adhesion molecule (MadCAM) to target and monitor inflammation.58,59

In summary, CEUS is a safe, inexpensive clinical imaging modality for visualizing tissue vascularity and perfusion in patients, and is realizing its potential for tumor detection and characterization. Advances in 3D US will not only improve its reliability, but will likely make it more translatable to the clinic. With the recent preclinical developments in molecular targeting of MBs, CEUS could be paired with other imaging modalities for unparalleled identification and monitoring of disease.

HIFU Technology

High-intensity focused ultrasound (HIFU) is a promising tool for the selective ablation of targeted tissues in the human body, and one that has been employed for a range of applications in medicine, including the ablation of benign and malignant tumors.50,61 The HIFU process involves the generation of long bursts or continuous waves of US energy of sufficient intensity to raise targeted tissue temperatures that range between 50°C and 80°C, causing rapid thermal coagulation of cellular proteins and irreversible tissue destruction. These temperatures are much higher than those used in hyperthermia treatment of cancer (typically about 42°C-43°C), and indeed the goal of HIFU is the complete and rapid ablation of targeted tissues, rather than the provision of longer-term antineoplastic effects.60,62

A number of physical approaches to the generation of the high ultrasonic intensities required for tissue ablation have been realized, with most involving a high degree of focusing of a sonic beam. This approach is generally implemented using a large-area piezoelectric transducer, the surface of which is curved so as to achieve a tight focus of the US emitted from its surface when excited (Fig. 4). In this approach, a treatment volume for targeted tissue ablation is created by bringing all US emitted by a large, curved piezoelectric transducer to a focus, and the summation of all emitted energy within the small volume leads to rapid tissue heating by US absorption.

This basic design has been employed to create systems that insonate targeted tissues with HIFU from outside the body, termed extracorporeal HIFU. Typically the treatment volumes generated are described as being about the size of a grain of rice, approximately 1 mm in diameter and several millimeters long. Systems for extracorporeal HIFU typically involve incorporation of the transducer arrangement shown in Figure 4 into a treatment couch designed for acoustic coupling of the body with the transducer system. Using such an arrangement, it is possible to translate the treatment volume entirely throughout a targeted region, such as a tumor, permitting ablation of an entire tumor during a single treatment session. Limitations of the clinical application of the extracorporeal approach include the necessity of avoiding damage to tissues overlaying or adjacent to a targeted region, and interference with transmission of sonic energy resulting from air or bowel gas, or from bone.

Other challenges include the accurate targeting of tissues to be ablated, and the monitoring of temperature within and adjacent to targeted tissues to ensure adequate ablation without significant harm to normal structures. These latter considerations have led to substantial contemporaneous efforts to incorporate the HIFU technology into MR scanners, which are capable of accurate targeting of tissues, such as tumors, and monitoring tissue temperature using MR techniques like phase-sensitive imaging.63,64

Clinical Applications

In addition to extracorporeal HIFU, intracavitary techniques for sonic ablation of targeted tissues have been developed, which offer great promise for ablation of specific organs. Both transrectal65,66 and transurethral HIFU devices have been designed and evaluated for indications such as ablation of prostate tissue for the treatment of benign prostate hyperplasia (BPH) and prostate cancer, an area in which HIFU has been tested clinically more than any other. Although there has been a great deal of experience with transrectal HIFU for the treatment of BPH and prostate cancer over the past 10-15 years, it is important to point out that the devices used in these studies did not allow for the effective targeting and thermal monitoring of ablation promised by MRI. Recent reviews of this early work have indicated that transrectal HIFU without...
MRI control has not led to durable relief of BPH. Although early studies of prostate cancer ablation have been interpreted as successful, it has been argued that more effective targeting and thermal monitoring will be necessary if more effective treatment is to be achieved. An in vivo example of the use of MRI guidance and thermal monitoring is shown in Figure 5.

These HIFU techniques have great appeal for the minimally invasive treatment of benign and malignant tumors, as they offer the prospect of an effective means of destroying targeted tissue without significant damage to normal tissues. Commercial development of integrated systems allowing MRI targeting and thermal monitoring is actively under way by several manufacturers. Although the field of MRI-guided HIFU is still in its early stages, recent reports have indicated substantial promise for uterine fibroid ablation, and the ablation of hepatic, renal, pancreatic, and brain tumors. An even wider range of applications seems inevitable if the promise of this exciting new technology is realized.

CMUTs

Technology

An US transducer converts mechanical energy into electrical energy, and vice versa. Since its inception, US imaging has been implemented with transducers made of piezoelectric materials. Piezoelectricity is an inherent property of certain materials, in which application of a mechanical stress induces a voltage and conversely, an applied voltage induces a mechanical stress. The word piezoelectricity is derived from the Greek piezein, which means to squeeze or press, and electric or electron from the classical Latin electrum, Greek elektron, which means amber, referring to amber's attractive properties.

Ceramics made with lead zirconate titanate (PZT) are the most common type of piezoelectric materials used in US applications (eg, PZT-5A and PZT-5H). Most US imaging probes today contain a piezoelectric transducer array, consisting of multiple transducer elements that are individually accessible and arranged in an orderly fashion in 1 or 2 dimensions for 2- or 3-D imaging, respectively. Piezoelectric transducers require several labor-intensive steps to manufacture and their fabrication is particularly demanding for small-scale applications such as intravascular and intracardiac imaging.

The capacitive micromachined ultrasonic transducer is an alternative US transducer invented in the early 1990s. Each CMUT array element is typically composed of several unit cells connected in parallel. In turn, each of the CMUT unit cells is essentially a capacitor composed of a fixed plate and a flexible plate separated by a vacuum cavity, which can be of any shape, such as a cylinder, cube, etc. The 2 electrodes of the capacitor reside in the fixed and flexible plates; the flexible plate is anchored around the edges and, for the most part, determines the operating frequency of the CMUT (Fig. 6A). To transmit an US wave, an alternating current electric field is applied across the 2 CMUT electrodes, causing the flexible plate to vibrate and transmit a wave of ultrasonic frequency into the surrounding medium. Conversely, an US wave impacting the CMUT induces vibration of the flexible plate, which can then be detected. Silicon micromachining techniques have enabled the creation of highly efficient CMUTs as an alternative to piezoelectric transducers.

CMUTs are manufactured using well-developed electronics microfabrication techniques, leading to great flexibility in transducer design in a wide range of frequencies and geometries, sometimes even within the same wafer. They have been shown to easily achieve a fractional bandwidth of over 100% in medical imaging applications, implying a high axial image resolution. By contrast, piezoelectric transducers typically require matching and backing layers to achieve wide bandwidth, which further complicates the manufacturing.
process (Fig. 6B). Additionally, being fabricated primarily on silicon wafers, CMUTs conveniently and naturally integrate into supporting electronic circuitry. Such integration is an essential component in many applications, such as intravascular and volumetric imaging, where signal integrity, probe size, amount of received data, and number of cable connections are of primary concern.

Clinical Applications
To date, CMUTs have been demonstrated in many different medical imaging applications. An integrated 2-D CMUT array has been reported targeting 3-D intracavitary US imaging applications. Fully integrated 1-D and 2-D ring CMUT catheters have been developed for intracardiac US guidance of electrophysiological interventions and successfully demonstrated using in vivo porcine animal models. HIFU therapy using CMUTs under MR guidance has also been demonstrated in addition to a wide variety of other nonmedical applications. Indeed, CMUT technology promises to yield many other applications in the future.

Photoacoustic Imaging
Technology
Photoacoustic imaging is an emerging hybrid imaging modality that permits imaging of tissue optical characteristics with the superior depth penetration and spatial resolution of acoustic imaging. Photoacoustic imaging is performed by illuminating an area of interest with short-duration laser pulses, which induce photon scatter and light absorption by chromophores (light-absorbing molecules) within tissue. A tiny local temperature rise results, which in turn causes transient expansion in the surrounding material. This phenomenon, termed thermoelastic expansion, creates pressure waves that are transmitted at ultrasonic frequency and detectable by US transducers. A single-element US transducer or ultrasonic array (for parallel data acquisition) then scans the tissue of interest to form an image (Fig. 7).

Photoacoustic imaging affords greater depth penetration than conventional optical imaging because acoustic scattering is typically 2-3 orders of magnitude less than optical scattering in biological tissues. Therefore, when imaging beyond 1 mm in depth, photoacoustic imaging provides a higher spatial resolution than pure optical modalities.

Photoacoustic imaging systems are generally divided into 2 broad categories: photoacoustic tomography (PAT) and photoacoustic microscopy (PAM). In PAT, an unfocused array of ultrasonic transducers (or single scanned detector) and an inverse reconstruction algorithm are utilized. In PAM systems, a focused ultrasonic transducer scans across an illuminated area, coupled with confocal optical illumination, as a result, PAM does not require a reconstruction algorithm. Each implementation has specific advantages and applications; the PAT system, for example, may be used for larger volume imaging, such as in vivo brain imaging or breast imaging, whereas PAM is useful for small superficial structures, such as cutaneous or subcutaneous vasculature, acute skin burns, or skin cancer evaluation.

Clinical Applications
Although photoacoustic imaging has yet to be incorporated into human clinical imaging, many areas are currently being investigated in which optical contrast yields information on structural, functional, and molecular properties of tissue. Tumor angiogenesis and hypermetabolism in cancers result in neovascularity, altered blood flow, and changes in tissue oxygen tension, which in turn affect the degree of oxyhemoglobin and deoxyhemoglobin in tumors. These 2 molecules are the main optical targets (chromophores) in photoacoustic imaging. Currently photoacoustic imaging is being investigated in early-stage cancer detection and lesion characterization in breast, prostate, and skin cancer. Hemoglobin as a target chromophore has also been used in neurologic research to provide high-contrast images of brain structures, lesions, and functional imaging. Melanin, another endogenous optical target, has been studied in mouse models and in resected human sentinel lymph nodes in melanoma patients. Because signal-to-noise ratio has proven to be a limiting factor in photoacoustic imaging, exogenous optical-absorption contrast agents, such as indocyanine green, or labeled particles, such as gold nanoparticles, are currently being investigated to enhance this promising imaging technology.

Conclusion
In summary, many exciting new US technologies are currently being developed that are likely to dramatically enhance the
scope and power of sonography. Centuries-old staples of physical diagnosis, such as palpation of pathology, may now be extended to deeper tissues beyond the reach of the human hand with elastography or photoacoustic imaging techniques. Innovative electronics that permit precise and controlled tissue heating in HIFU or novel transducer fabrication, such as CMUT, are transforming US practice. Lastly, both nontargeted and targeted molecular US contrast agents may allow for visualization and characterization of lesions previously invisible with conventional US.

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