PROSPECTS IN CLINICAL ULTRASOUND OVER THE NEXT DECADE

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Abstract

In the past three decades medical ultrasound has proved its usefulness in many applications. Diagnostic ultrasound is now used in almost all medical fields and has evolved into one of the preferred clinical imaging modalities. This paper briefly reviews the past 30 years of progress in diagnostic ultrasound imaging and technology and explores the influence that basic research focused on interaction between acoustic energy and biological tissue had on development of advanced real-time ultrasound machines. It is demonstrated that the understanding of nonlinear wave propagation in tissue resulted in the implementation of harmonic imaging modality providing real-time 3D high quality images of unparalleled resolution. The pivotal role that nonlinear propagation effects will have on the clinical ultrasound progress in the next decade is also examined and the development of a new generation of contrast agents leading to image enhancement, mediated drug delivery and localized drug release is pointed out. The paper concludes with a short review of competition that clinical ultrasound encounters.

Introduction

In the following the last three decades of development in diagnostic ultrasound imaging and technology are briefly reviewed and the most likely advances over the next decade and their clinical impact are discussed.

Diagnostic ultrasound is used in almost all medical fields and is quickly becoming the preferred imaging modality in a variety of clinical situations. For instance, in many cardiovascular diseases diagnostic ultrasound has replaced invasive methods as the primary means of evaluation. Also, as the equipment for ultrasound imaging is generally less expensive than the one used in radiographic, ionizing radiation techniques it is becoming more widely available.

Clinical ultrasound

Ultrasound image quality upon which the final diagnosis critically depends has improved significantly in the past decade and this would not have been possible without several engineering and technological innovations and breakthroughs. These major innovations include the introduction of a new generation of enhanced bandwidths transducers or scanheads, almost total elimination of analogue electronics and the advent of contrast agents. The super wideband, sensitive, multielement imaging transducers provided highly improved image quality which was further enhanced by the introduction of the digital technology platform including digital beamformers which assured high dynamic range (on the order of 120 dB) and electronically controlled multi-focal zones. The concurrent introduction of contrast agents led to discovery of harmonic imaging, which truly revolutionized the quality of images.

Harmonic imaging

There are two harmonic imaging modes: in contrast agent harmonic imaging, the higher frequencies are generated upon reflection and scattering from the microbubbles; in tissue or grey-scale harmonics the harmonic frequency energy is generated gradually as the ultrasonic wave propagates through the tissue. In contrast agent harmonic imaging the substantially higher material nonlinear acoustic qualities of a two-phase medium, comprising bubbles, is exploited for generation of harmonics to a fundamental frequency. In grey-scale harmonics formation the nonlinear distortion of a finite-amplitude mono-chromatic wave during its propagation through the tissue is exploited in the harmonic imaging process. Harmonic images have already proved to be capable of providing a degree of detail, which clearly surpasses that available with conventional, fundamental frequency grey scale imaging. Consequently, within the next half decade it may be expected that harmonic imaging capability will become a standard available in a new generation of ultrasound imaging equipment and will be widely used in all clinical ultrasound applications. For instance, one of the most challenging tasks in cardiology applications is myocardial perfusion imaging in which contrast agents are of great help. However, as a totally non-invasive procedure to assess the presence or absence of coronary disease and quantify its seriousness is preferable, grey scale harmonic imaging may provide a better solution. Harmonic imaging will also become routinely used in the diagnosis in the pancreas, billiary system and retopritoneum. In general, wherever the low megahertz frequency ultrasound exam is needed, harmonic imaging may prove advantageous. In abdominal applications, among the benefits of the harmonic imaging technology are reduced image artifacts, absence of body wall distortion, controlled spectrum, higher contrast images, and enhanced diagnostic confidence. The harmonic technology is also applicable in totally new diagnostic application. For example, common duct stones that are virtually invisible when using conventional (fundamental frequency) imaging can be better identified with harmonic imaging. This is of interest, as improved diagnosis of common duct stones might probably decrease the need for diagnostic endoscopic retrograde cholangiopancreatography (ERCP).

Contrast agents

The rapidly advancing field of ultrasound contrast agents will continue to challenge the performance of the imaging devices. So far the new applications of contrast agents have been achieved by modifying the existing equipment to match the characteristics of the contrast medium. However, it can be expected that in the future these agents will be optimized for desirable harmonic characteristics. For instance, it is conceivable that contrast agents that are specifically developed for a given application such as tissue perfusion will become available. Also, further developments in contrast agents can lead to improved imaging of tumor neovascularity. Coating biodegradable and biocompatible agents with adhesive peptides specific to cell integrin receptors could provide non-invasive markers of angiogenesis. In addition, such coated microspheres could prove themselves as tools for monitoring angiogenic therapies in vivo. Overall, further advancements in contrast agents will promote synergy between therapeutic and diagnostic applications of ultrasound by allowing the agents to act initially as image enhancement bodies and subsequently as targeted drug delivery devices. The drug delivery itself will take place by increasing the diagnostic pulse amplitude to the level sufficient to cause the implosion of the microbubble or microsphere and thus releasing the drug in or in the immediate vicinity of the tissue volume to be treated. Ultrasound assisted thrombolysis where blood clot will be identified using imaging modality and subsequently dissolved via targeted drug delivery will also become available.

3D imaging

In addition to contrast agent applications, the advancements in harmonic imaging will most likely make this technique indispensable for ultrasound grey scale imaging, especially during the examination of technically challenging patients. This is because, as indicated above, harmonic imaging offers better resolution both in cardiologic and deep tissue imaging applications and hence, it will contribute to make the images less operator dependent. A variety of new contrast agents will also promote three-dimensional (3D) ultrasound imaging. Preliminary results indicate that the 3D reconstruction of harmonic data obtained with a contrast agent can provide vascular anatomy details not available using conventional grey scale, colour and power Doppler. In addition, as 3D data are digitally encoded they allow manipulation of images by removing anatomy that may inhibit diagnosis and provide the view of the underlying tissue structure. This feature of 3D imaging is already proving to be of invaluable assistance to the clinicians in advance planning of difficult surgeries. Echocardiography and vascular imaging, particularly of the carotids and veins in the legs, also appear to be some of major future applications for 3D. At present, most of the 3D imaging is implemented with arrays that generate 2D slices and the third dimension is obtained by mechanical movement, which, in general, is too slow for moving structures like the heart. Real-time heart imaging needs a frame rate of (ideally) 30 or more per second to be of diagnostic interest, which, in turn, calls for 2D transducer array.

Currently used arrays typically contain between 48 and 192 elements and an equivalent 2D array would need tens of thousands of channels making it economically unaffordable. Therefore, using conventional multi-element, piezo-composite based scan-heads, a viable solution for the future development of 3D imaging would require the design of substantially less expensive "sparse" arrays, which would employ number of elements of the same order of magnitude as in the existing arrays. In this context, it is interesting to note, that very recently, real-time, both B-mode and Doppler 3D imaging was introduced in top-of-the-line diagnostic machines using piezo-composite 2D arrays. In addition to application in echocardiography, the availability of real time 3D imaging will prompt applications in obstetrics, as in general, three-dimensional data can improve the operator's comprehension. In particular, 3D ultrasound shows great promise in improving the ability to detect and differentiate between many types of functional abnormalities such as those present within the fetus (including improved congenital abnormality detection) as well as in tumours to study vascular distribution. However, a wider implementation of the 3D modality would require another technological breakthrough in transducer array design.

Advanced non-resonant transducers

Such a breakthrough appears now to be within a reach, and the new generation of imaging transducers is briefly described below. In contrast to the current transducer design, where the operating frequency is primarily controlled by the thickness mode of vibration, the new transducers are intentionally designed as non-resonant. They can be manufactured using silicon technology and do not require any dicing, needed in conventional array design to minimize acoustic coupling and cross-talk between the individual elements. The principle of operation of those silicon transducers that are often referred to as CMUTs or capacitive mechanical ultrasound transducers resembles that of a condenser micro-phone. The additional advantage of a single CMUT cell is that it has extremely small (on the order of hundred microns) physical dimensions. A cluster of cells can be readily formed into true two-dimensional array. As the cells can be manufactured using proven integrated circuit technology the price of these transducers is expected to be significantly lower than that of presently used 1.25 or 1.5 D piezo-composite arrays. Yet another advantage offered by the CMUTs is that they can be conveniently fabricated as annular arrays that can be scanned electronically. Annular arrays that offer superior image resolution lost their appeal in the early eighties due to the then need for mechanical scanning and were totally replaced by multi-element arrays with dynamic focusing and beam deflection controlled in fully electronic manner. The use of non-resonant design is likely to double the fractional bandwidth of the current state-of-the-art piezo-composite transducers. That would make it possible to use one single CMUT scanhead for multiple applications, including a possible 3rd harmonic or multi-harmonic imaging. In general, the development in transducer materials and new transducer technologies are expected to contribute essentially to the advances in clinical ultrasound.

Sonoelasticity

The future research in diagnostic ultrasound will also entail sonoelastic images constructed from the recorded differences in viscoelastic properties of the tissue. Sonoelasticity may become a major pathology correlation tool in such applications as sonomammography, where sonographic pathology correlation and evaluation of cystic and solid lesions of the breast are of importance. It can also be expected that sonoelasticity will come to play a major role in assessment and evaluation of prostate malignancies. Further development of imaging procedures based on determination of elastic properties of tissues methods will provide tools allowing remote virtual palpation and generation of elasticity images using Shear Wave Elasticity Imaging (SWEI). SWEI will be helpful in assessing muscle conditions in a dynamic way and will also aid in determining muscle dystrophy and atrophy. Acoustic radiation force induced shear waves can be generated by using two overlapping beams having carefully selected, yet different frequencies. By measuring Lamé constants of the longitudinal and shear waves, viscoelastic properties of the interrogated tissue volume can be determined. Quantitative tissue characterization using shear waves should produce data on dynamic shear stiffness, dynamic shear viscosity, shear velocity and shear attenuation. Another option is to use Ultrasound Stimulated Acoustic Emission (USAE) that uses ultrasound waves to probe mechanical tissue properties.

Second-order effects

The continuing studies of nonlinear acoustic wave propagation in tissue will lead to development of new processing algorithms, which would further improve image quality and also open a possibility to use associated second-order phenomena, such as radiation force or acoustic streaming to estimate mechanical or viscoelastic properties of interrogated tissue volume. Earlier attempts to characterize biological tissues by means of their second-order acoustical nonlinearity coefficients, being closely related to the molecular structure of the tissues, have shown a substantial inaccuracy of the data obtained. However, new second-order measurement techniques may improve the precision of the data and lead to a revival of the real time nonlinear parameter tomography, and thus to success in quantitative tissue characterization. This will facilitate clinical diagnosis and aid in distinguishing between malignant and benign tumours. The confidence of the diagnosis will be augmented by a new generation of high frequency Doppler machines capable of making reliable differentiation between solid and liquid cysts (of great importance in breast cancer screening) as they will be able to induce a low velocity acoustic streaming pattern within the cyst and will exhibit sensitivity adequate to detect extremely low liquid velocity (less than a few mm/s). Measurement of streaming parameters will also provide information on the viscosity of the liquid within the cyst and thus will allow evaluation of the solidity of lesions. The advances in Doppler technology will also make this technique directly applicable in intra- and post microsurgery to evaluate the flow in the narrow vessels or capillaries affected by the procedure. The results of preliminary experiments also indicate that monitoring of acoustic streaming could be useful as a tool in distinguishing between the stagnant blood versus tissue, and clotted and normal blood. In therapy, improvements in transducers for hyper-thermic cancer treatment and for calculus disintegration shall be expected, and these transducers may also be used to monitor the effectiveness of the therapy. The question of safety will remain continuously under review, but the emphasis will shift from bioeffects towards prudent use.

Very high-frequency imaging

Further advancement in diagnostic ultrasound will also include very high frequency imaging and it can be expected that the current imaging frequency range (1 - 15 MHz) will be enhanced by the micro-sonography devices which will offer sub-millimetre resolution imaging at the frequencies ranging from 20 - 100 MHz. Those frequencies will be widely employed in the design of catheter-based ultrasound transducers. These miniature (less than 2 mm in diameter) devices can be placed within the blood vessels, urethras, etc., to study abnormalities from within. For instance, the catheters offer the ability to observe the function of the esophagus with detection of abnormalities and functional disorders, as they are capable of producing images showing more details than the images made from the information obtained from the external body scanning. A limiting factor for the use of these small, catheter borne transducers will be the ultrasonic power radiated. However, the development in new charge forming materials may improve the power transfer for high-quality imaging.

Also, further advances in digital technology will allow instantaneous optimization of spatial and contrast resolution and penetration. This, in turn, will facilitate diagnosis of technically difficult patients. Automatic optimization of the images will additionally improve image quality, minimize the possible operator dependent inconsistency in the images and, therefore, also contribute to the increase of diagnostic confidence.

Portable scanners

The availability of portable, battery operated ultrasound scanners delivering high resolution image data in digital form will facilitate archiving and retrieving of images and will also enhance the possibility of providing clinical expertise globally, via remote, wireless consultation or via internet. Overall, the increased diagnostic power combined with its non-invasive character will make diagnostic ultrasound imaging one of the most preferred screening tools (e.g. in early breast cancer screening) in the hands of skilled physicians. The availability of high quality portable scanners would open up numerous new applications. It is conceivable, that standard emergency kits, such as those available onboard of commercial aircrafts will soon include dual-use diagnostic/therapeutic ultrasound units capable of monitoring cardiac output during resuscitation and generating acoustic radiation pressure to assist circulation.

Advances in micro-miniaturization of electronic circuits and advent of the next generation, non-resonant silicon technology based imaging transducers will provide fully wearable, PC based, lightweight ultrasound scanners with image quality similar to or even exceeding that achievable today with top-of-the-line systems. These wearable ultrasound scanners will be most useful in remote sites, doctors offices, underdeveloped countries and already mentioned aircrafts and other human transportation units that have no or very limited access to hospitals or clinics.

Competition to clinical ultrasound

As evidenced above it seems that as clinical modality ultrasound will continue to play a significant role in the near future. However, it is appropriate to note that ultrasound faces a strong competition from such modalities as Magnetic Resonance Imaging (MRI) and Computerized Tomography that not only produce high-resolution images, but also can deliver superb quality images of acoustically impenetrable organs. On the other hand, in comparison with MRI, ultrasound offers full portability and high frame rates for true real-time imaging at the fraction of the price. Ultrasound machines, in contrast to CT scanners, make use of non-ionizing energy, and provide unique performance in hemodynamics-based diagnosis.

To further improve its attractiveness the ultrasound scanners will need to make clinical examination less operator dependent. Also, to keep up further ahead, the upcoming generation of scanners needs to ensure the always-desirable improvements in image quality. Such improvements appear to be within a reach with the advent of the CMUT silicon transducers operating as versatile, beam deflectable 2D annular arrays. True 2D arrays will not only be able to display heart movements in real time and three dimensions, but also provide 3D images of the organs prior to surgery. This will allow the surgery procedure to be computer modelled with the aid of appropriate software algorithms. Such an approach would provide optimization of the surgery, lower mortality, minimize patient discomfort and may lead to cost reduction of the clinical procedure. Improvements in image quality could also be achieved by using, e.g., spatial compounding that provides enhancement of tissue contrast and boundary outlining. The issue of image distortion due to probing wave aberration caused by local changes in speed of sound will most likely be overcome by fast correction algorithms and implementation of imaging procedures that will make use of time reversal. Multi-frequency or multi-harmonic imaging that can be readily introduced once the capacitive micromachined ultrasound transducers as ultrasonic imaging sources are fully developed, will augment the contrast in imaging of solid masses. A variety of new contrast agents will aid ultrasound technology and provide tissue contrast enhancement and visualization of blood flow. To stay abreast, the ultrasound machine manufacturers will also focus on improvements in Doppler–mode operation. As noted earlier, Doppler technology is capable of delivering high-quality data and images from hemodynamic studies in peripheral vessels such as carotid arteries, and also from deep vessels. It is conceivable that Doppler ultrasound used as functional monitor will find wider application as a modality of choice after transplant surgeries. By providing early warning about tissue rejection, Doppler monitoring will reduce the number of biopsies and possibly other invasive catheter studies, such as coronary angiography, and intravascular and intra-coronary examinations.

The studies of interaction of ultrasound and biological tissue will continue to strengthen as the outcome of such studies is indispensable in further advances in sonophoresis or, in general, the studies of behaviour of cell membrane permeability when exposed to ultrasound. Moreover, determination of adequate ultrasound exposure matrices would intensify therapeutic applications of ultrasound. As already mentioned, a new generation of ultrasound machines can be soon capable of providing high resolution image for diagnosis and immediate or concurrent therapeutic treatment. Diagnostic capabilities of ultrasound scanners could also be enhanced. For instance, an amendment in Power Doppler signal processing could enable non-invasive hematocrit measurements. Similarly, a modification of B-mode operation could provide information needed to evaluate broadband ultrasound attenuation (BUA) in bones. BUA is an accepted indicator for assessment of osteoporosis and is currently evaluated in transmission mode, where ultrasound energy is interrogating a heel bone being positioned between an acoustic source and receiver.

Conclusions

In closing, it is appropriate to note that the above review hardly covers all possible future developments, however, it brings into focus the most likely avenues and prospects of clinical ultrasound in the near future.

A note on references:

A comprehensive list of references would need to include hundreds of entries and would be impractical here. Instead, the authors would like to acknowledge their extensive use of refereed publications. ***In particular, IEEE Transactions UFFC, Journal of Ultrasound in Medicine, Nature, Science, Ultrasonics and Ultrasound in Medicine and Biology were found to be an excellent source of information about potential advances of medical applications of ultrasound and its technology.***