Clinical and Preclinical Applications of High-Frequency Ultrasound

Jeffrey A. Ketterling

Postal:
Lizzi Center for Biomedical Engineering
Riverside Research Institute
156 William Street
New York, New York 10038
USA

Email:
jketterling@riversideresearch.org

Ronald H. Silverman

Postal
Department of Ophthalmology
Harkness Eye Institute
Columbia University
Medical Center
635 W. 165th St.
New York, New York 10032
USA

Email:
rs3072@cumc.columbia.edu

High-frequency ultrasound technology is set to emerge as a common clinical tool after decades of niche applications.

Introduction

Ultrasound is widely used for medical imaging, and many of us saw our kids for the first time as gray-scale images or 3-dimensional (3-D) surface renderings at the doctor's office. Although clinical ultrasound made its debut a half century ago, enormous advances in technology and capability have taken place since then. Clinical ultrasound machines are now extremely powerful digital signal-processing engines, and tasks that may once have been done as postprocessing in a research lab are now performed in real time while a patient stares at a screen with a sense of awe (if not comprehension).

Early ultrasound imaging systems formed an image by mechanically scanning a focused, single-element transducer at limited frame rates. (In the optical world, a single-element ultrasound transducer would be analogous to a microscope objective that is raster scanned to generate an image.) These systems generally used frequencies of 1-5 MHz, which provided good penetration but not fine resolution. The trend over time has been replacement of mechanically scanned single-element transducers with arrays that operate at higher frequencies and that have an increasing number of independent transmit/receive channels. Analog technology has long been replaced by digital technology that now provides real-time 3-D and even 4-D (3-D over time) visualization. Digital signal-processing methods can extract information from the ultrasound echoes (e.g., blood flow and tissue stiffness) that goes well beyond the simple log-compressed, gray-scale images that were the hallmark of early ultrasound machines.

The field of high-frequency ultrasound (HFU) represents the evolution of clinical ultrasound technology to the present time and generally refers to frequencies above 20 MHz. The term HFU was initially intended to indicate a research field that emerged over time as advances in transducer technology permitted ultrasound imaging at frequencies beyond common, low-megahertz clinical frequencies. Twenty megahertz is really an arbitrary cutoff because there is nothing fundamentally different about HFU imaging or instrumentation versus conventional lower frequencies. HFU instrumentation must be specialized, and clinical (or research) applications must similarly be specialized to take advantage of the superb resolution of HFU but the limited penetration into tissue.

HFU is interesting because increased frequency results in a shorter acoustic wavelength that, in turn, results in improved spatial resolution. (The acoustic wavelength in the body at 1 MHz is 1.5 mm and at 20 MHz, it is 0.075 mm.) Acoustic attenuation, however, also increases with frequency, which means that increasing the frequency decreases the penetration depth. Because clinical ultrasound systems are generally intended for fairly deep imaging in the body (e.g., cardiac or fetal imaging), there is a limit to how high the frequency can go while still imag-

ing the organ of interest from outside the body. Or, to put it another way, HFU imaging is not the solution for all clinical imaging applications.

Although the methods required to instrument an ultrasound system and to fabricate an ultrasound transducer are well established for commercial clinical ultrasound systems, translating these methods to HFU is no simple task. The technology to build such systems pushed the limits in terms of piezoelectric transducer technology and digital components. HFU system complexity scales with frequency; increasing frequency means decreased dimensions for piezoelectric elements, increased bandwidth for the digital sampling components, increased quantity of digital data to process, and increased computational demands. These technological challenges are one reason HFU is not widely available in the clinic today. Another reason is the limited market forces driving development because clinical applications of HFU are still quite specialized.

For these reasons, HFU technology generally lagged behind what would be considered standard clinical ultrasound technology. By lagged, we mean that clinical applications of HFU were primarily based on mechanically scanned, single-element transducers rather than array transducers. The main clinical applications of HFU have been in ophthalmology and intravascular ultrasound (IVUS). HFU has also been extensively employed for preclinical, small-animal imaging. In fact, mouse mothers have been able to see their babies as ultrasound images for many years just as we humans have.

Equipment

Transducers

Ultrasound imaging probes come in many forms, with the simplest breakdown being between mechanically scanned, focused single-element probes and multielement transducer arrays. Single-element transducers offer simplicity and a well-defined sound field, whereas arrays have more complex sound fields and more complicated instrumentation.

Single-element transducers are still the most common transducers found in HFU instrumentation. There are several reasons that single-element transducers have persisted. First, HFU applications do not require very large lateral-imaging dimensions, so mechanical scanning is a practical way to form an image. Second, the methods and materials to make HFU transducers over 20 MHz were initially geared toward single-element transducers because this was the easiest way to evaluate material performance. Third, single-element transducers, although not very good for general imaging given their fixed focal length, are well suited to imaging specific regions of organs such as the front or back of the eye (**Figure 1**). Finally, HFU systems have to be reasonably priced, and mechanically scanned single-element approaches were the only means to accomplish this.

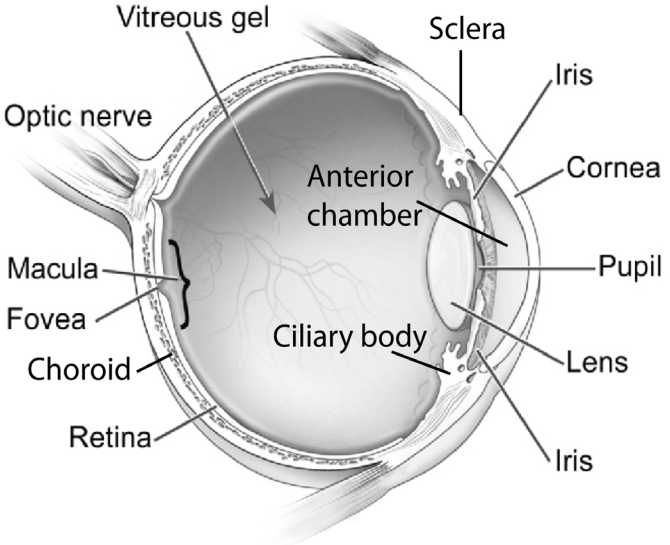

Figure 1. *Schematic of the front (anterior) and back (posterior) of the eye. Reprinted with permission from the National Eye Institute, National Institutes of Health.*

Single-element transducers are either focused or unfocused. Ophthalmic and small-animal systems use focused transducers. The −6 dB lateral beamwidth of a focused single-element transducer is $F^*\lambda$, where F represents the transducer focal ratio (focal length divided by transducer diameter [$F\#$]) and λ is the wavelength of sound in water. The depth of field, or range over which the image is in focus, is described by $9.68\lambda F^2$. A compromise must be made between resolution and the depth of field. A small $F\#$ provides the best lateral resolution but only over a limited depth range. This works out fine in the eye, for instance, where HFU is used for imaging the anterior segment and a 3-mm depth of field, which would be provided by a typical 50-MHz $F\# = 3$ probe, is sufficient to capture the structures of interest (**Figure 2a**). However, a transducer designed to image the anterior segment is useless for imaging the retina and optic nerve at the back of the eye (**Figure 2b**).

Unfocused single-element transducers are not ideal for imaging but are used in catheter-based IVUS probes. These probes need to be very small in order to be inserted into the vasculature. Placing electronics at the tip of a probe with a diameter of a few millimeters, let alone a multielement array transducer, is technically challenging. A simple solution is to use a small rectangular piece of piezoelectric material with

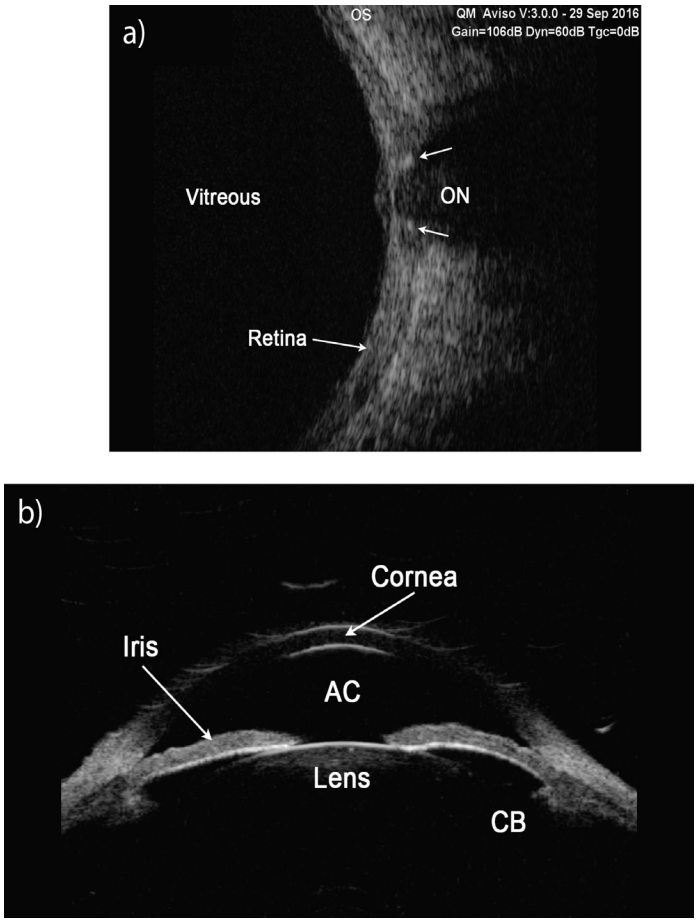

Figure 2. *Representative human eye images using a Quantel Aviso clinical ultrasound system with a 20-MHz and a 50-MHz imaging probe.* ***a:*** *The 20-MHz single-element probe (positioned to left of the image) is designed to image the back of the eye in the region of the retina. The optic nerve (ON) is also visible, but the deep focus of the transducer means that the front of the eye cannot be resolved.* ***b:*** *The 50-MHz single-element probe (positioned at top of the image) is designed to image the anterior chamber (AC). The region with the iris is within the transducer focus (as can be seen by the slightly brighter intensity of the image at this depth) and the resolution quickly degrades when moving away from this region. The top surface of the lens and the ciliary body (CB) are also visible. The cornea is partially resolved but only when the surface is close to perpendicular with the acoustic field.*

a length of several millimeters and a width of approximately 0.5 mm that rotates at the end of the catheter. This transducer rotates to create a 360° image in the plane normal to the catheter. Phased-array designs with elements wrapped in a cylindrical shape are also available (O'Donnell et al., 1997). Like ophthalmic ultrasound, the basic technology for IVUS has not changed much over time, and sophisticated array technology has not yet translated into clinical use.

One type of array transducer that sits between a single-element and a linear-array transducer is known as an annular array. Annular arrays are composed of a series of circular, concentric elements and they can have either a planar or spherical geometry. Annular arrays have long been known to provide superior image quality because of their radial beam symmetry, but they were not practical for general clinical use at low frequencies because they require mechanical scanning and real-time frame rates were not feasible over long scan lengths. However, HFU imaging, with the small scale of what is imaged, is well suited to annular-array imaging.

Linear arrays, though, still represent the ultimate trend for HFU because they do not need to be mechanically scanned and can be electronically focused throughout the field of view. The development of HFU linear arrays has been a slow, gradual process requiring new advances in piezoelectric materials and fabrication processes. The National Institutes of Health (NIH)-sponsored Transducer Resource Center at the University of Southern California (USC) (http://www.usc.edu/dept/biomed/UTRC/) and Pennsylvania State University has played an important role in exploring new transducer materials, developing probes, and building systems to test new imaging applications. On the commercial side, FUJIFILM VisualSonics (Toronto, ON, Canada) has refined an industrial process to make HFU linear arrays, has been selling a small-animal research system for nearly 10 years and, just recently, has released a system that is approved by the US Food and Drug Administration (FDA) for human use. In addition, companies such as Vermon (Tours, France) and Kolo Medical (San Jose, CA) now offer linear arrays at center frequencies up to 30 MHz.

Piezoelectric Materials

The key to any ultrasound transducer is the piezoelectric material from which it is made. The difficulty with HFU transducers is that the material thickness and element dimensions are inversely proportional to frequency. A typical linear array operating at 40 MHz would have a thickness of 50 μm and a center-to-center element spacing of 40 μm, whereas a 5-MHz transducer would have a 400 μm thickness and a pitch of 240 μm. The high-frequency transducer clearly requires more sophisticated fabrication to achieve the necessary small-length scale.

Materials such as lead zirconate titanate (PZT) have been used for many years for ultrasound sources in the low-megahertz frequency range and work very well. However,

it was quickly apparent that standard low-megahertz PZT composites did not scale well to high frequency because the grain size of the crystals is relatively large (5-10 μm). This made the material more difficult to machine and also led to material properties changing in ways that decreased performance at high frequency. Therefore, a great effort was placed on developing new piezoelectric materials for high-frequency applications (Zhou et al., 2011).

Initial efforts to make HFU transducers focused on single-element, large-surface-area transducers because the technical requirements were not as difficult as those for array-based transducers. Piezopolymer films such as polyvinylidene fluoride (PVDF) and polyvinylidene-trifluoroethylene (PVDF-TrFE) of 9-50 μm thickness proved particularly useful because they could be pressed into spherical shapes for focused transducers and their acoustic impedance was close to that of water, which reduced transmission and reception losses (Sherar and Foster, 1989). However, these piezoelectric films do not have particularly good electromechanical coupling (about 0.15%, where 100% would be perfect coupling with no losses), require high voltage to excite (>200 V peak-to-peak), and are not well suited to linear arrays where a small element size is required because their electrical impedance becomes quite high.

Composite materials were also pursued and good success was found with lithium niobate and lead magnesium niobate-lead titanate (PMN-PT). These materials require acoustic matching layers to better match the material impedance to water, but their much better electromechanical coupling (50%) helps improve overall performance. Piezocomposite materials at high frequency are usually ground down to create the necessary thickness and, thus, are planar. To create a single-element transducer with a focused geometry requires fracturing a thin disc of the piezocomposite by pressing the material against a rigid ball and then setting the material in a backing epoxy (Cannata et al., 2003). Reliable techniques were developed to do this, but the process is really only effective for single-element transducers.

As single-element transducers began to enter clinical use, a great deal of effort was being applied to building HFU linear arrays. In addition, new fabrication techniques needed to be developed, particularly for cutting a piezoelectric material into individual elements (dicing) and for connecting elements to cabling (interconnects). Numerous prototypes were developed, particularly at the Transducer Resource Center of USC. The transducers were validated with prototype ultrasound imaging systems, but the main focus was research. The big commercial breakthrough came in 2007 when VisualSonics introduced a preclinical HFU system with arrays covering a range of center frequencies from 15 to 50 MHz (Foster et al., 2009). The release of the VisualSonics system represented the transition of high-frequency material development and array fabrication from a research topic to a commercially viable product.

Instrumentation

The basic instrumentation approach for HFU systems differs little from the low-megahertz clinical counterparts. The significant differences arise from the technical requirements related to the higher bandwidth of HFU systems. Although HFU instrumentation may simply be an extension of current clinical imaging systems, the mass-produced electronic components specifically designed for ultrasound array imaging only went up to sampling rates of about 40-50 MHz, which limited the maximum center frequency for transducer operation to about 15 MHz. Early HFU systems, therefore, were custom-made using components not necessarily designed for ultrasound imaging, and these systems were quite labor intensive to build as one-off prototypes (Hu et al., 2006). Once a system was ready to test, it was often already obsolete. As analog-to-digital sampling components have dropped in cost, increased in bit depth, and increased in maximum sampling rate, the "front end" of HFU systems has become easier to design and manufacture and the technical challenges of building an ultrasound system are now mostly related to transducer design, beamforming, and signal processing.

Applications

Ophthalmic Imaging

Human ophthalmic imaging was one of the earliest HFU applications (Pavlin et al., 1990, 1991). Ophthalmic ultrasound has unique requirements in that it needs to operate at or above 10 MHz and needs to be inexpensive so that it is affordable for an ophthalmologist. Low-megahertz array-based systems were not suitable for the eye because their image quality was poor and they were too expensive to use in ophthalmic practice. Thus, ophthalmic machines have been based on single-element transducers with an assortment of probes designed to image specific regions of the eye (**Figure 2**).

Ophthalmic ultrasound is split between anterior-segment (35- to 50-MHz) and posterior-segment (10- to 20-MHz) imaging. (The 35- to 50-MHz frequency range is often referred to as "ultrasound biomicroscopy" [UBM].) The rea-

son for this split is that the posterior pole of the eye, where the optic nerve, macula, and retina are located, is approximately 25 mm from the surface of the eye (**Figures 1** and **2**). Although the eye is largely filled with the vitreous gel, which at lower frequencies produces minimal attenuation, at frequencies above about 20 MHz, the long path length through the vitreous gel produces too much attenuation to provide a gray-scale image that reveals the posterior pole with an adequate signal-to-noise ratio (SNR). Although ultrasound can provide fairly deep penetration >1 cm, the relatively poor resolution provided by 10-MHz probes (about 150 μm axially by 450 μm laterally) has made optical coherence tomography, which provides an order of magnitude of superior resolution to a depth of about 1 mm, the preferred imaging modality for evaluation of the retina and optic nerve head. HFU, however, still has advantages because of its ability to visualize optically occult structures such as the ciliary body and the space behind the sclera (the white of the eye) and iris where optical methods cannot penetrate.

Commercial ophthalmic ultrasound systems typically support multiple transducers. For instance, Quantel Medical's Aviso system (Clermont Ferrand, France) supports a 10-MHz probe for axial length determination (crucial for cataract surgery); 10- and 20-MHz probes for imaging the vitreous gel, posterior pole, and orbit; and 25- and 50-MHz probes for imaging the anterior segment (**Figure 2**). In contrast, the ArcScan Insight[1] system (Golden, CO) is highly specialized, using a focused 35-MHz transducer that is scanned in an arc matching the curvature of the cornea so that the corneal surface is maintained at the focus at normal incidence during scanning.

As seen in **Figure 2**, current ophthalmic imaging equipment limits the depth of field that can be viewed in a single image because of the fixed focal length of single-element transducers. An annular array with only five elements overcomes the limits of a single-element transducer by offering the image quality of a linear-array system but with the simplicity of a single-element system (Ketterling et al., 2005). Annular arrays allow axial focusing and, in essence, approximate a single-element transducer with a variable focal length. **Figure 3** shows image examples of the human eye using a 20-MHz and a 40-MHz annular array (Silverman et al., 2011). Compared with the images in **Figure 2**, the annular-array images show a clear improvement in the depth of field and resolution over the depth of field.

[1] *Riverside Research Institute and R. Silverman have an equity interest in ArcScan, Inc.*

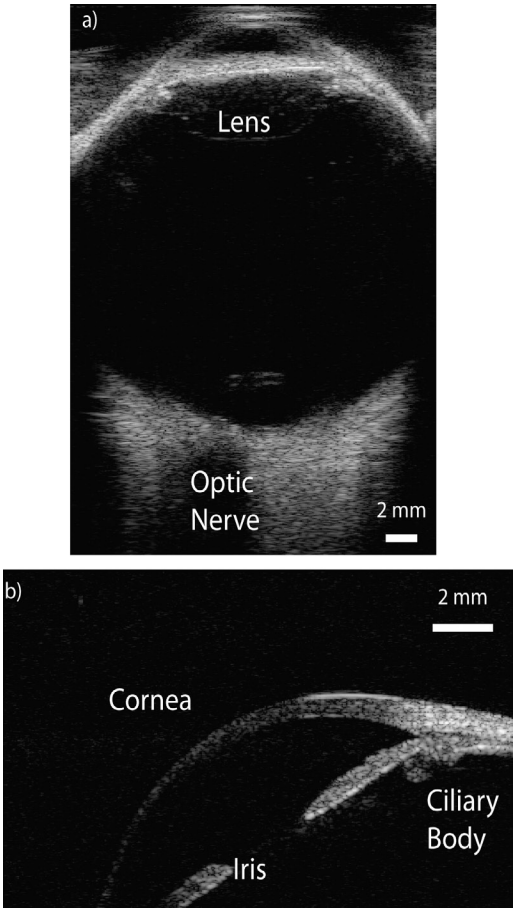

Figure 3. *Human-subject ophthalmic images using custom, five-element annular arrays.* ***a:*** *A 20-MHz image of the full eye. The retina and anterior chamber were resolved in a single image, something not possible with a single-element transducer. The outline of the lens was also faintly visible.* ***b:*** *A 40-MHz image of the anterior chamber showing the cornea, iris, ciliary body, and sclera while the patient was looking off the axis. Because the annular array has an extended depth of field, the image quality is less sensitive to movement of the eye.*

Small-Animal Imaging

HFU is used extensively for the imaging of mice in preclinical research including cancer, cardiovascular and development studies. Mouse embryo imaging plays an important role in developmental studies where embryos are studied for genetic developmental defects or for the effects of compounds on embryonic development (Foster et al., 2011). Ultrasound is the only imaging modality capable of noninvasive, real-time imaging of the mouse embryo in utero. **Figure 4** shows an *in vivo, in utero* image of a mouse embryo on embryonic day (E)12.5, where E0.5 is defined as noon of the day after successful overnight mating, obtained with a VisualSonics 3100 imaging system using a 40-MHz linear array. By acquiring a stack of adjacent image planes that span the whole embryo (see http://acousticstoday.org/ketterling), an embryo can be visualized in 3-D. **Figure 5** shows a volumetric representation of whole embryos over a 5-day development period and

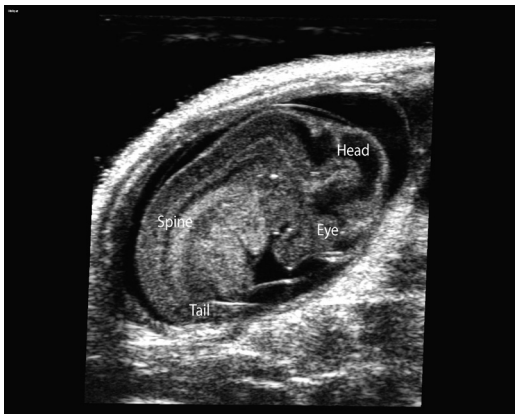

Figure 4. *Midsection sagittal view of an in utero mouse embryo on embryonic day (E) 12.5. The image was obtained with a Visual Sonics 3100 using a 40-MHz linear array transducer. It was acquired at the Skirball Institute of Biomolecular Medicine at New York University Langone Medical Center and is courtesy of O. Aristizábal.*

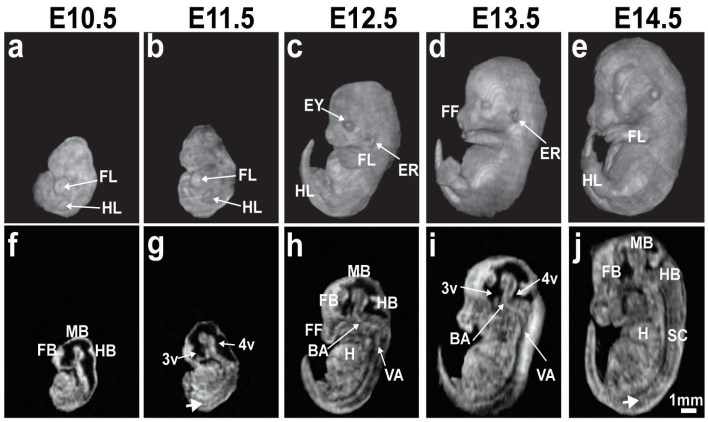

Figure 5*. Volume reconstructions (**a-e**) and the corresponding midsagittal sections (**f-j**) for embryonic stages E10.5 (**a** and **f**), E11.5 (**b** and **g**), E12.5 (**c** and **h**), E13.5 (**d** and **i**), and E14.5 (**e** and **j**) using data obtained with a 40-MHz annular array. The brain ventricles are easily identified in the embryo because they are filled with anechoic fluid and therefore have a high contrast relative to surrounding tissue. BA, basilar artery; EY, eye; ER, ear; FB, forebrain; FF, facial features; FL, forelimb; H, heart; HB, hindbrain; HL, hindlimb; MB, midbrain; SC, spinal cord; VA, vertebral artery; 3v, third ventricle; 4v, fourth ventricle. Large white arrows (**g** and **j**) indicate intersomitic blood vessels. Reprinted from Aristizábal et al. (2013), with permission from Elsevier.*

sagittal slices through the midsection of each embryo. The growth and development of the embryo are clearly visualized as the embryo ages.

HFU has been used to study many other features of the mouse embryo including the eyes, liver, and heart (Zhou et al., 2002). The heart is particularly interesting because imaging the mechanics of the heart requires fine temporal resolution and this was hard to achieve with single-element transducers. Therefore, early studies utilized retrospective methods that acquired data in one location, synchronized to the heartbeat, and then moved to a new location to acquire another batch of data (Chérin et al., 2006). Retrospective methods are prone to errors from out-of-plane motion or unsteady heart rates but are still able to generate quite good high-speed movies of the beating heart, considering it takes several minutes to acquire a full set of data. With the introduction of HFU linear-array systems, true high-speed movies could be acquired of the beating heart, with frame rates of up to 1,000 frames per second over a limited field of view (Foster et al., 2009).

Recent Developments

As noted in **Applications**, HFU has had a foothold in the clinic for many years but has not emerged as a common tool for general imaging. This was a classic chicken-and-egg situation in that there was no FDA-approved HFU machine so new clinical applications were not aggressively pursued. This situation has finally changed because VisualSonics released a HFU imaging platform that operates within the FDA 510(k) safety limits for acoustic exposure. It is too early to tell what specific clinical applications will prove to be ideal for HFU diagnosis, but they will likely be in areas of the body near the skin where commonly available ultrasound systems provided poor resolution.

Multimodality Imaging

Medical imaging in general has been moving to multimodality imaging approaches where two imaging methods are combined to provide complementary information that improves disease diagnosis. In HFU, this trend is seen with the photoacoustic, small-animal imaging system sold by VisualSonics (Vevo LAZR). Photoacoustics refers to a method of imaging where a short pulse of light is absorbed by tissue in such a way that an acoustic wave is generated and detected by an ultrasound transducer (Emelianov et al., 2009). The photoacoustic mode provides information related to the molecular absorption of light at a specific wavelength and the ultrasound mode provides mechanical information about tissue structure. The image information from each modality is coregistered and can be used to detect targeted contrast agents, areas of vasculature, or blood oxygenation in the regions of specific organs.

IVUS imaging is also an area with numerous examples of the ultrasound probe being combined with other modalities. Because IVUS probes are catheter based, the engineering challenges are quite significant when adding a second modality. Examples of modalities being combined with IVUS are photoacoustic, optical coherence tomography and near infrared (Ma et al., 2016).

High-Speed Imaging

Although traditional Doppler is used extensively for blood flow measurements in general, low-megahertz ultrasound imaging, it is not commonly used to image the eye. The primary reason for this is that traditional Doppler modes generally exceed the stringent FDA 510(k) ophthalmic ultrasound exposure limits. Thus, very little is known about real-time blood flow in the eye as it relates to healthy and diseased eyes. HFU linear arrays and an emerging technique known as plane-wave imaging may offer a means to overcome the above obstacles and provide new blood flow-related information for studying and diagnosing ophthalmic diseases such as glaucoma, macular degeneration, retinopathy of prematurity, and tumors. The technique can also be used to image cardiovascular function in mice or other small animals.

High-speed plane-wave or diverging-wave imaging has been enabled by advances in ultrasound equipment (Tanter and Fink, 2014). In a conventionally operated linear array, groups of adjacent elements emit a focused, converging wave front, and the elements must wait until echoes are received before the next group can be excited. This process is then iterated across the length of the array to acquire one image. In plane-wave imaging, all elements of the array fire to emit a single unfocused wave front. Plane-wave imaging thus permits full-frame transmission rates up to the round-trip propagation time of a transmit-and-receive event. For instance, a 2-cm depth from the face of a transducer could be imaged at 36,000 frames per second. High-speed plane-wave imaging is well suited to cases with transient high-speed motion or blood flow such as cardiovascular imaging or shear-wave imaging (Tanter and Fink, 2014).

The trade-off with plane-wave imaging is that because the transmit beam is unfocused, the resolution is degraded and the acoustic intensity is reduced. This can be partially overcome by transmitting a batch of electronically steered plane waves and then summing (i.e., compounding) the resulting beamformed data. As the number of transmission angles per image increases, the SNR and resolution improve, although the overall effective frame rate necessarily decreases. For instance, an experiment may entail emitting batches of 10 plane waves at a rate of 20 kHz over a ±15° angle range. Because 10 angles are compounded to form one image, the final effective frame rate is 2 kHz.

Plane-wave imaging permits near-instantaneous Doppler flow information to be obtained throughout a full-image frame. For a similar number of transmissions used in plane-wave imaging, traditional Doppler methods are only able to obtain flow information in a small region because the transmit beam is focused using a subset of array elements. Therefore, plane-wave imaging is able to provide detailed flow information but at a lower acoustic intensity than with traditional Doppler approaches.

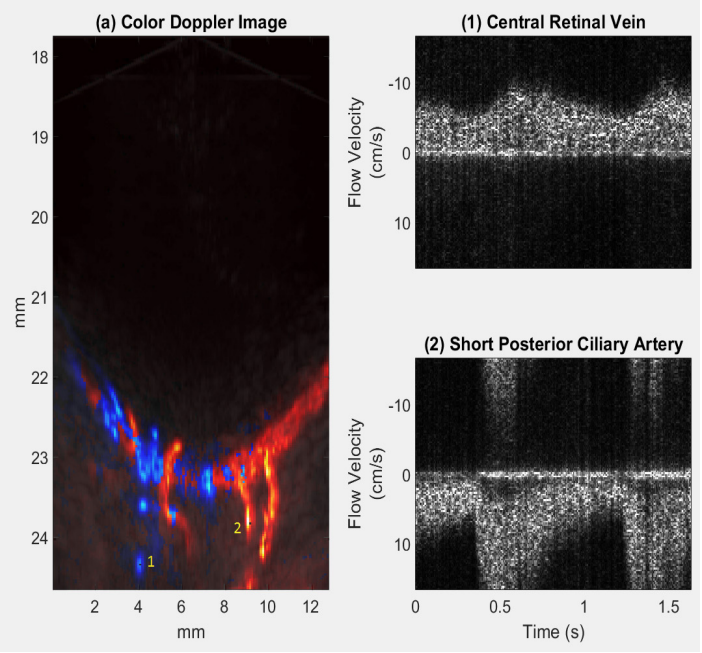

Figure 6*. Image of blood flow in the region of the optic nerve in a normal human eye. The image was obtained using a technique called coherent compound plane-wave imaging (Urs et al., 2016). In this case, 20,000 images per second were acquired at 5 angles using an 18-MHz linear array.* ***Red****, arterial flow;* ***blue****, venous flow. The Doppler spectrograms on the right display flow velocities in the central retinal vein (1) and posterior ciliary artery (2) over a 1.6-second period.*

An example of the plane-wave technique applied to the eye using an 18-MHz linear array is shown in **Figure 6**. It shows blood flow in the major retrobulbar vessels (central retinal artery and vein, ophthalmic artery, short and long ciliary arteries, and vortex vein) as well as flow in the choroid. Most importantly, the instantaneous and temporally averaged acoustic intensities are well within FDA 510(k) ophthalmic safety limits (Urs et al., 2016).

Conclusions

HFU represents the gradual progression of ultrasound technology to higher and higher frequencies. The technology in use for HFU has tended to lag behind what is used on a daily basis for low-megahertz clinical ultrasound. The early HFU systems were focused on ophthalmic, small-animal, and intravascular applications, and the devices filled a specialized niche. Today, we are finally seeing HFU enter the mainstream of clinical ultrasound with FDA approval of a HFU linear-array system for clinical use. At the same time, im-

provements in computer-processing power and data-transfer bandwidth are allowing the emergence of high-speed imaging methods based on unfocused plane and diverging waves. Overall, these are exciting times for medical ultrasound imaging that continues to offer surprises, considering that the basic methods of ultrasound imaging were perfected many decades ago.

Acknowledgments

Portions of this work were supported by Grant EY025215 from the National Eye Institute, National Institutes of Health, to Ronald H. Silverman and Grant EY024434 from the National Eye Institute and Grant EB022950 from the National Institute of Biomedical Imaging and Bioengineering, National Institutes of Health, to Jeffrey A. Ketterling. We thank Raksha Urs and Orlando Aristizábal for helpful input and discussions.

Biosketches

Jeffrey A. Ketterling is the associate research director of the Frederic Lizzi Center for Biomedical Engineering at the Riverside Research Institute in New York, NY. His past work has focused on high-frequency ultrasound and, in particular, high-frequency annular arrays for small-animal and ophthalmic imaging applications. He was the technical chair of the Biomedical Acoustics Committee of the Acoustical Society of America (ASA) from 2008 to 2011 and is a Fellow of the ASA. He received his PhD degree in mechanical engineering from Yale University, New Haven, CT, in 1999.

Ronald Silverman is a professor of ophthalmic science at Columbia University Medical Center (CUMC) in New York, NY. His postgraduate training was in bioengineering and computer science at Polytechnic University in Brooklyn, NY. After 28 years of research and the clinical application of ultrasound in the Department of Ophthalmology at Weill-Cornell Medical Center in New York, NY, he moved to the Harkness Eye Institute of CUMC, where he continues his research in ultrasound for imaging the eye. His primary interests now include high-frequency ultrasound for biometric and biomechanical mapping of the cornea and ultrafast imaging of ocular blood flow.

References

Aristizábal, O., Mamou, J., Ketterling, J. A., and Turnbull, D. H. (2013). High-throughput, high-frequency 3-D ultrasound for in utero analysis of embryonic mouse brain development. *Ultrasound in Medicine and Biology* 39, 2321-2332.

Cannata, J. M., Ritter, T. A., Chen, W. H., Silverman, R. H., and Shung, K. K. (2003). Design of efficient, broadband single-element (20-80 MHz) ultrasonic transducers for medical imaging applications. *IEEE Transactions on Ultrasonics, Ferroelectrics, and Frequency Control* 50, 1548-1557.

Chérin, E., Williams, R., Needles, A., Liu, G., White, C., Brown, A. S., Zhou, Y. Q., and Foster, F. S. (2006). Ultrahigh frame rate retrospective ultrasound microimaging and blood flow visualization in mice in vivo. *Ultrasound in Medicine and Biology* 32, 683-691.

Emelianov, S. Y., Li, P.-C., and O'Donnell, M. (2009). Photoacoustics for molecular imaging and therapy. *Physics Today* 62, 34-39.

Foster, F. S., Mehi, J., Lukacs, M., Hirson, D., White, C., Chaggares, C., and Needles, A. (2009). A new 15-50 MHz array-based micro-ultrasound scanner for preclinical imaging. *Ultrasound in Medicine and Biology* 35, 1700-1708.

Foster, F. S., Hossack, J., and Adamson, S. L. (2011). Micro-ultrasound for preclinical imaging. *Interface Focus* 1, 576-601.

Hu, C. H., Xu, X. C., Cannata, J. M., Yen, J. T., and Shung, K. K. (2006). Development of a real-time, high-frequency ultrasound digital beamformer for high-frequency linear array transducers. I*EEE Transactions on Ultrasonics, Ferroelectrics, and Frequency Control* 53, 317-323.

Ketterling, J. A., Aristizábal, O., Turnbull, D. H., and Lizzi, F. L. (2005). Design and fabrication of a 40-MHz annular array transducer. *IEEE Transactions on Ultrasonics, Ferroelectrics, and Frequency Control* 52, 672-681.

Ma, T., Zhou, B., Hsiai, T. K., and Shung, K. K. (2016). A review of intravascular ultrasound-based multimodal intravascular imaging: The synergistic approach to characterizing vulnerable plaques. *Ultrasonic Imaging* 38, 314-331.

O'Donnell, M., Eberle, M. J., Stephens, D. N., Litzza, J. L., San Vicente, K,, and Shapo, B. M. (1997). Synthetic phased arrays for intraluminal imaging of coronary arteries. *IEEE Transactions on Ultrasonics, Ferroelectrics, and Frequency Control* 53, 317-323.

Pavlin, C. J., Sherar, M., and Foster, F. S. (1990). Subsurface ultrasound biomicroscopic imaging of the intact eye. *Ophthalmology* 97, 244-250.

Pavlin, C. J., Harasiewicz, K., Sherar, M. D., and Foster, F. S. (1991) Clinical use of ultrasound biomicroscopy. *Ophthalmology* 98, 287-295.

Sherar, M. D., and Foster, F. S. (1989). The design and fabrication of high-frequency poly(vinylidene fluoride) transducers. *Ultrasonic Imaging* 11, 75-94.

Silverman, R. H., Ketterling, J. A., Mamou, J., Lloyd, H. O., Filoux, E., and Coleman, D. J. (2011). Pulse-encoded ultrasound imaging of the vitreous with an annular array. *Ophthalmic Surgery Lasers Imaging Retina* 43, 82-86.

Tanter, M., and Fink, M. (2014). Ultrafast imaging in biomedical ultrasound. *IEEE Transactions on Ultrasonics, Ferroelectrics, and Frequency Control* 61, 102-119.

Urs, R., Silverman, R. H., and Ketterling, J. A. (2016). Ultrafast ultrasound imaging of ocular anatomy and blood flow. *Investigative Ophthalmology & Visual Science* 57, 3810-3816.

Zhou, Q., Lau, S., Wu, D., and Shung, K. K. (2011). Piezoelectric films for high frequency ultrasonic transducers in biomedical applications. *Progress in Materials Science* 56, 139-174.

Zhou, Y. Q., Foster, F. S., Qu, D. W., Zhang, M., Harasiewicz, K. A., and Adamson, S. L. (2002). Applications for multifrequency ultrasound biomicroscopy in mice from implantation to adulthood. *Physiological Genomics* 10, 113-126.