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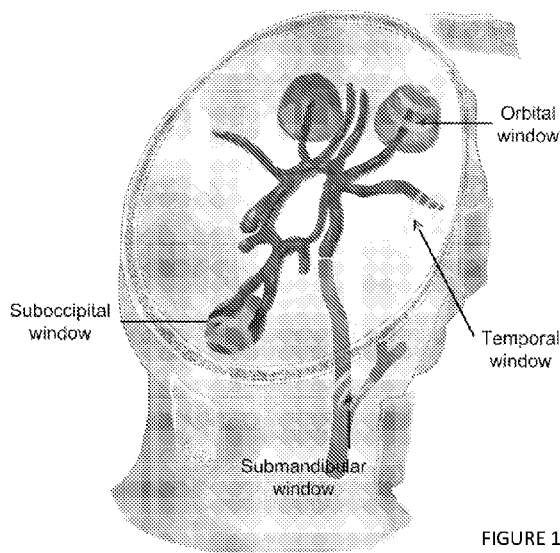


FIGURE 1

(57) Abstract: A method for performing ultrasound imaging of a region of interest in a subject includes attaching to the subject a wearable conformal ultrasound transducer array having a plurality of phased array transducer elements. A plurality of diverging ultrasonic acoustic waves is transmitted from the plurality of phased array transducer elements at a plurality of insonation angles using different time-delay profiles. Reflected ultrasonic signals are received from the region of interest using the phased array transducer elements. The reflected ultrasonic signals are processed using volumetric beamforming and coherent compounding to recombine the reflected ultrasonic signals from all of the insonation angles. The recombined reflected ultrasonic signals are filtered to provide filtered data in which tissue motion signals are separated from blood flow signals. A volumetric power Doppler image is reconstructed from the filtered data using a power Doppler calculation. The reconstructed volumetric power Doppler image is caused to be displayed.



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**TRANSCRANIAL VOLUMETRIC IMAGING USING A CONFORMAL
ULTRASOUND PATCH**

GOVERNMENT FUNDING

[0001] This invention was made with government support under 1R21EB027303-01A1 awarded by the National Institutes of Health (NIH). The government has certain rights in the invention.

CROSS-REFERENCE TO RELATED APPLICATION

[0002] This application claims the benefit of U.S. Provisional Application Serial No. 63/443,504, filed February 6, 2023, the contents of which are incorporated herein by reference.

BACKGROUND

[0003] Cerebral blood flow supplies oxygen and energy substrates and removes metabolic wastes to maintain proper brain function. Continuous monitoring of cerebral hemodynamics enables screening and diagnosing brain disorders (e.g., vasospasm, stenoses, aneurysms, and embolism) as well as understanding neurovascular functions (e.g., sensory, motor, and cognitive controls). However, assessment of cerebral blood flow is challenging because relevant cerebral vasculature is embedded deep inside the brain and protected by the skull that causes strong signal attenuation and phase aberration. Various modalities to measure cerebral blood flow have been explored, including positron emission tomography, computed tomography and magnetic resonance imaging, which all provide adequate spatial resolution, but require bulky and costly equipment that prohibits continuous use. Emerging thermal, electrical, and optical probes can be miniaturized for continuous monitoring, but cannot provide sufficient spatiotemporal resolutions.

[0004] TCD is widely used for cerebral hemodynamic monitoring because of its safety, low cost, portability, versatility, and relatively high spatiotemporal resolutions. Prolonged cerebral blood flow monitoring is beneficial for providing timely feedback for therapeutic interventions and studying chronic neural activity. However, existing TCD probes have several limitations that prevent them from achieving accurate and continuous monitoring of cerebral blood flow. First, conventional TCD probes are

rigid and need to be manually held by a well-trained clinician or affixed via a tight headset for continuous monitoring. Slight misalignment between the ultrasound beam and the target vessel, often caused by hand movement, poor headset fastening, or patient motion, can cause fluctuation, degradation, or complete loss of signals. Therefore, the headset is usually very tight, causing patient discomfort, thus limiting the typical recording time to <30 min. Second, conventional TCD probes usually use a single transducer or a linear array of transducers, which can only image part of the intricate 3D network of cerebral arteries. Different operators may acquire signals from different segments of the 3D network, affecting repeatability and reproducibility. To address this problem, volumetric imaging may better depict the 3D network to guide target segment selection. Two-dimensional matrix arrays can provide volumetric imaging, but currently such probes have limited spatiotemporal resolutions because of technical barriers in probe fabrication and data acquisition.

SUMMARY

[0005] In one aspect, the present disclosure addresses the aforementioned problems arising with existing TCM probes by providing a conformal ultrasound patch for hands-free volumetric imaging and continuous monitoring of cerebral blood flow. The use of low frequency ultrasound waves reduces the attenuation and phase aberration caused by the skull. Ultrafast ultrasound imaging based on diverging waves increases the target region size and spatiotemporal resolutions, which accurately renders complex three-dimensional (3D) vascular networks and minimizes human errors during examinations. Focused ultrasound waves allow recording blood flow spectra at selected locations continuously. These combined strategies represent provide a platform for studying cerebral hemodynamics and related neurological pathologies.

[0006] In another aspect, a method for performing ultrasound imaging of a region of interest in a subject is provided. In accordance with the method, a wearable conformal ultrasound transducer array having a plurality of phased array transducer elements is attached to the subject. A plurality of diverging ultrasonic acoustic waves is transmitted from the plurality of phased array transducer elements at a plurality of insonation angles using different time-delay profiles. Reflected ultrasonic signals are received from the region of interest using the plurality of phased array transducer elements. The reflected ultrasonic signals are processed using volumetric

beamforming and coherent compounding to recombine the reflected ultrasonic signals from all of the insonation angles. The recombined reflected ultrasonic signals are filtered to provide filtered data in which tissue motion signals are separated from blood flow signals. A volumetric power Doppler image is reconstructed from the filtered data using a power Doppler calculation. The reconstructed volumetric power Doppler image is caused to be displayed.

[0007] This Summary is provided to introduce a selection of concepts in a simplified form that are further described below in the Detailed Description. This Summary is not intended to identify key features or essential features of the claimed subject matter, nor is it intended to be used as an aid in determining the scope of the claimed subject matter. Furthermore, the claimed subject matter is not limited to implementations that solve any or all disadvantages noted in any part of this disclosure.

BRIEF DESCRIPTION OF THE DRAWINGS

[0008] Fig. 1 shows the common transcranial windows with relatively lower acoustic attenuation and phase aberration for TCD sonography.

[0009] Fig. 2 shows a schematic diagram of ultrasound fields of different beamforming strategies.

[0010] Figs. 3a-3c show an overview of one example of a conformal ultrasound patch for TCD.

[0011] Figs. 4a-4n are simulations illustrating the ultrasound beam steering process.

[0012] Fig. 5a show an optical image of the copper mesh electromagnetic shielding layer; Figs. 5b-5f show optical images of the five-layers of the stretchable electrode; and Fig. 5g shows an optical image of the common ground electrode.

[0013] Figs. 6a-6f depict the autonomous envelope tracking and parameter calculation.

[0014] Fig. 7a shows a schematic illustration of the imaging process; Fig. 7b shows different views of the volumetric power Doppler image of major cerebral arteries in a

60×60×60 mm³ region, acquired through the temporal window; Fig. 7c compares the volumetric power Doppler images before and during compression of the left common carotid artery; and Fig. 7d is a bar graph showing the power Doppler amplitudes of representative landmarks of bilateral arterial segments before and during compression of the left common carotid artery.

[0015] Fig. 8 shows a comparison of blood flow spectra from different sample volumes.

[0016] Fig. 9a shows a schematic diagram of an arrangement for performing emboli detection on a phantom by a conformal ultrasound patch; and FIG. 9b shows the flow spectra of baseline, with gas emboli, with 0.5 mm solid emboli, and with 2 mm solid emboli, respectively.

DETAILED DESCRIPTION

[0017] Wearable ultrasound devices allow intimate and reliable contact with the skin surface for sensing physiological signals in deep tissues. However, probing inside the brain is a major challenge due to the strong signal attenuation and phase aberration caused by the skull. Described herein, in one aspect, is a conformal ultrasound patch for accurate and continuous monitoring of cerebral blood flow that overcomes this challenge.

[0018] We use low frequency ultrasound waves to reduce the skull-induced signal attenuation and phase aberration. We adopt an ultrafast imaging technique to insonate the entire target region with thousands of compounded waves per second, which improves the signal-to-noise ratio. The signal-to-noise ratio is further enhanced by adding a copper mesh shielding layer to the transducer array. The reconstructed 3D vascular network shows ample spatiotemporal resolutions, which reveal blood flow distribution in all major cerebral arteries and avoids aspects of operator dependency. This enables reliable volumetric mapping and continuous long-term monitoring of intracranial vessels, representing a powerful platform for both clinical and fundamental hemodynamic studies.

[0019] To minimize acoustic attenuation and phase aberration, four transcranial windows (e.g., temporal, orbital, submandibular, and suboccipital) are commonly used for TCD. These windows are relatively small ($\sim 5 \text{ cm}^2$ in adults), requiring a compact device design. On the other hand, the cerebral arterial network has multiple major components, including the anterior cerebral arteries (ACA), middle cerebral arteries (MCA), posterior cerebral arteries (PCA), ophthalmic arteries (OA), internal carotid arteries (ICA), basal artery (BA), and vertebral arteries (VA). Most of these arteries are deep (~ 40 to 100 mm) and widely distributed inside the brain, requiring devices with a wide ultrasound field. Therefore, we used diverging waves to image the entire arterial network and focused waves to monitor local blood flow spectra at target arterial sections. Diverging waves extend the ultrasound field from a limited acoustic window (i.e., 12 mm by 12 mm) to a much larger region (i.e., $\sim 60 \text{ mm}$ by 60 mm at 50 mm depth in this work), which allows for simultaneous insonation of multiple cerebral arteries. Focused waves minimize unnecessary ultrasound exposure to surrounding tissues for long-term monitoring of blood flow spectra.

[0020] Fig. 1 shows the common transcranial windows with relatively lower acoustic attenuation and phase aberration for TCD sonography. Through the orbital window, the ultrasound beam is directed toward the optic canal and does not pass through the skull. When using the temporal window, the ultrasound beam only needs to transmit through the thin temporal bone. The submandibular window is located at the neck. Through this window, the ultrasound beam can target at the internal carotid artery without transmitting through the skull. The subject can bow the head forward to open up a gap between the cranium and the atlas. The ultrasound beam is directed toward this gap when the patch is attached to the suboccipital window.

[0021] Fig. 2 shows a schematic diagram of ultrasound fields of different beamforming strategies. By using different time-delay profiles, the transducer array can transmit focused, plane, and diverging waves. The focused waves have an ultrasound beam at a local region of the cerebral vascular network. The plane waves have a wider ultrasound field than the focused waves, but its ultrasound field is still rather limited. The diverging waves have ultrasound fields tunable with the view angle. In this work, a view angle of 40° can appropriately insonate the entire cerebral

vessels. A view angle of 20° is too narrow whereas a view angle of 60° is redundant, spreading the ultrasound energy to unneeded areas.

Conformable Ultrasound Patch

[0022] Figs. 3a-3c show an overview of one example of a conformal ultrasound patch for TCD. FIG. 3a (left) shows the patch attached to the scalp for volumetric mapping of major arteries in the brain so that blood flow spectra of different target arteries can be recorded. Fig. 3a (right) shows schematic exploded view of the patch structure. In the illustrative embodiment the patch includes a 16 by 16 array of piezoelectric transducers connected by a five-layer stretchable electrode and a common ground electrode. A copper mesh is used as an electromagnetic shielding layer to enhance the signal-to-noise ratio. The entire device is encapsulated by a water-proof and biocompatible silicone elastomer. Additional detailed concerning one example of suitable conformal ultrasound patch is shown in U.S. Appl. Serial No. 17/431,572, which is hereby incorporated by reference in its entirety. Fig. 3b shows simulation results of diverging and focused ultrasound fields based on 2D matrix array beamforming. The derated spatial peak temporal average intensity of the focused ultrasound field is $\sim 100 \text{ mW/cm}^2$ for spectra monitoring, far below the Food and Drug Administration recommended 720 mW/cm^2 threshold³⁵. The simulation results share the same scale bar. Fig. 3c are optical images of the patch on a spherical surface and a cylindrical surface. The inset images show the zoomed-in transducer array and the electromagnetic shielding layer. In Fig. 3c FFC denotes the flat flexible circuit.

[0023] The 16 by 16 matrix array of piezoelectric transducers illustrated in Fig. 3a has a $750 \text{ }\mu\text{m}$ pitch and a 2 MHz center frequency. The choice of a low frequency (i.e., 2 MHz in one example) reduces signal attenuation and phase aberration, and thus enhances transcranial penetration depth. The pitch is comparable to the ultrasound wavelength (i.e., $770 \text{ }\mu\text{m}$ in soft tissues at 2 MHz), enabling a large tilting angle of the ultrasound beam in three dimensions.

[0024] Figs. 4a-4n are simulations illustrating the ultrasound beam steering process. Figs. 4a-4g show ultrasound waves focused at a 50 mm depth with a beam tilting angle of 0° , 5° , 10° , 15° , 20° , 25° , and 30° , respectively. The grating lobe is growing and becomes more obvious when the beam tilting angle is larger. Figs. 4h-4n show

diverging ultrasound waves with a beam tilting angle of 0° , 2.5° , 5° , 7.5° , 10° , 12.5° , and 15° , respectively. All simulation results share the same scale bars.

[0025] The matrix array has an aperture of 12 mm by 12 mm, similar to that of established TCD probes, which enables insonation through the skull and focusing on deep targets. Five layers of serpentine interconnections are used to address the 256 elements individually. The matrix array has excellent properties such as high electromechanical coupling coefficient, small bandwidth, and negligible crosstalk, resulting in high sensitivity to Doppler shift. We designed a serpentine copper mesh as an electromagnetic shielding layer, which increases the signal-to-noise ratio on average by 5 dB. Encapsulation of the entire device by silicone elastomer allows for electrical insulation and conformal contact on various surfaces. The final illustrative patch is 1.3 mm thick, 20 mm wide, and 28 mm long, with a total weight of 0.945 g.

[0026] Fig. 5a show an optical image of the copper mesh electromagnetic shielding layer, Figs. 5b-5f show optical images of the five-layers of the stretchable electrode, and Fig. 5g shows an optical image of the common ground electrode. This design permits individual activation of each element in the 2D matrix array while keeping the overall device a small footprint (20 mm $\times$ 28 mm). The optical images share the same scale bar.

[0027] To perform automatic tracking of the blood flow envelope, histogram equalization was first applied to enhance the contrast between the blood flow spectra and background noise, which improved the accuracy of envelope tracking. After that, we defined a step function to fit the spectra at each moment, which had a value of 1 in the frequency band lower than f_{step} (the envelope to be extracted), and 0 in the frequency band higher than f_{step} . The sum of the absolute differences at all frequencies between the spectra and the step function was defined as the error to quantify the fitting. We swept the frequency f_{step} from the lower (0 Hz) to the higher frequency (2850 Hz) boundaries of the spectra and obtained the corresponding error values. The f_{step} value corresponding to the smallest error was the extracted envelope at this moment.

[0028] Figs. 6a-6f depict the autonomous envelope tracking and parameter calculation. In particular, Fig. 6a shows the spectrum Doppler of blood flow in one cardiac cycle.

As shown in Fig. 6b, The spectrum Doppler is first normalized. Then, the spectrum with an amplitude higher than 0.2 is set 1, while the spectrum with an amplitude lower than 0.1 is set 0. This enhances the contrast between spectrum Doppler and noise. The curve in Fig. 6c is the amplitude snapshot of the enhanced spectrum in Fig. 6b. The enhanced spectrum has a similar shape like a step function. Therefore, we fit the spectrum using a step function to extract the envelope. The dashed black curve is one example of a step function. Changing f_{step} will form different step functions. To find the step function that fits the spectrum the best, as shown in FIG. 6d, the sum of absolute errors is defined to quantify the difference between the spectrum curve and the step function. f_{step} sweeps from 0 to 2850 Hz. The f_{step} corresponding to the minimum sum of absolute errors is the desired $f_{envelope}$. Fig. 6e shows the $f_{envelope}$, which is the envelope corresponding to the spectrum at one moment. As shown in Fig. 6f, the entire envelope is extracted using the above method. The peak systolic velocity, mean flow velocity, end diastolic velocity, pulsatility index, and resistance index are calculated based on the tracked envelope. The spectra share the same scale bar.

[0029] The conformal ultrasound patch described herein may be fabricated using any suitable techniques. In one particular technique, fabrication of the conformal ultrasound patch can be divided into two steps: (1) electrode design and patterning and (2) electronic packaging.

[0030] Regarding electrode design and patterning, the electrode includes a common ground electrode, a five-layer stretchable electrode, and a copper mesh electromagnetic shielding layer. First, polyimide ([poly(pyromellitic dianhydride-co-4,4'-oxydianiline) amic acid solution, PI2545 precursor, HD Microsystems] was spin-coated on copper sheets (Oak-Mitsui Inc.) at 4000 rpm for 60 s, followed by soft baking on a hotplate at 100 °C for 3 min and subsequently at 150 °C for 1 min, and then hard baking in a nitrogen oven at 300 °C for 1 hour, yielding a 2 μm thick polyimide layer coated on 20 μm thick copper sheets.

[0031] Polydimethylsiloxane (Sylgard 184 silicone elastomer) was then spin-coated at 3000 rpm for 60 s on a glass slide and cured in an 80 °C oven as a temporary substrate for electrode transfer. To improve bonding, the polyimide-coated copper sheets and

the polydimethylsiloxane-coated glass slides were activated by ultraviolet light (PSD series Digital UV Ozone System, Novascan) for 3 min.

[0032] The polyimide-coated side of the copper sheet was then attached to the polydimethylsiloxane-coated glass slide. The bilayer copper/polyimide film was laser ablated (Laser Mark's, central wavelength, 1059 to 1065 nm; power, 0.228 mJ; frequency, 35 kHz; speed, 300 mm/s; and pulse width, 500 ns) following electrode patterns designed with AutoCAD (Autodesk).

[0033] To perform electronic packaging, on two separate glass slides, polymethyl methacrylate (495PMMA, Kayaku Advanced Materials), serving as a sacrificial layer, was spin-coated at 2000 rpm for 60 s and cured at 80 °C for 30 min. Then, a 12 µm thick silicone (Ecoflex-0030, Smooth-On) was spin-coated at 4000 rpm for 60 s and cured at room temperature for 2 hours.

[0034] To assemble the patch, a water-soluble tape (5414 Transparent, 3M) was first used to transfer-print the ground electrode to an Ecoflex-coated glass slide and the copper mesh electromagnetic shielding layer to another Ecoflex-coated glass slide. The water-soluble tape was then removed by immersing it in 80 °C water for 30 min. Conductive epoxy (Von Roll 3022 E-Solder, EIS) was placed on the 256 bonding pads of the island-bridge layout of the common ground electrode. After that, the 2D matrix array of 1-3 composites (Del Piezo Specialties) was bonded to the bonding pads by curing a conductive epoxy for 8 hours at room temperature and then 2 hours at 40 °C to avoid high-temperature induced depolarization of the 1-3 composites.

[0035] On the glass slide with the copper mesh electromagnetic shielding layer, the five-layer stretchable electrode was sequentially transfer-printed and stacked one on top of another by water-soluble tape. Each layer was bonded to a flat flexible circuit cable (Premo-Flex FPC Jumper, Molex) via solder paste ($\text{Sn}_{42}\text{Bi}_{57.6}\text{Ag}_{0.4}$ (melting point, 138 °C)) and spin-coated with a 25 µm thick Ecoflex layer at 2200 rpm for 60 s and cured at room temperature for 2 hours. Laser ablation was used to create vertical interconnect accesses through the Ecoflex layers to expose the 256 bonding pads in the five-layer stretchable electrode⁷². Then, this glass slide was bonded to the 1-3 composite on the other glass slide using conductive epoxy followed by curing.

[0036] Finally, the gaps between the two glass slides were filled with Ecoflex followed by curing at room temperature. The glass slides were removed by dissolving the polymethyl methacrylate in acetone to release the conformal ultrasound patch.

[0037] It should be noted that while the methods and techniques presented herein for performing ultrasound imaging will be illustrated using the particular conformal ultrasound patch described above, more generally other conformal ultrasound patches may be employed as well.

[0038] The ultrasound intensity of the ultrasound patch was measured in a water tank. We limited the maximum derated spatial peak temporal average intensity of all ultrasound transmissions in this work to $\sim 370 \text{ mW/cm}^2$. We limited the maximum derated mechanical index to 0.70. These values are well below the Food and Drug Administration Track 1 maximum recommended levels (i.e., 720 mW/cm^2 and 1.9 respectively) for transcranial Doppler application. After penetrating through a temporal bone specimen, the measured maximum derated spatial peak temporal average intensity was reduced by $\sim 83\%$ to $\sim 63 \text{ mW/cm}^2$. For orbital window scans, the maximum derated spatial peak temporal average intensity and mechanical index were reduced to conform to Food and Drug Administration Track 1 recommended maximum levels for ophthalmic scans (17 mW/cm^2 and 0.23 respectively).

[0039] To characterize its thermal effect, we attached the ultrasound path to the scalp of a normal human volunteer and activated the device for four hours. The maximum temperature rise on the skin surface was $<1^\circ\text{C}$. Furthermore, for estimated temperature changes of internal tissues during prolonged ultrasound exposure, we calculated the thermal index, the ratio between the incident acoustic power and the power required to raise the tissue temperature by 1°C , which were 0.62 for soft tissue thermal index and 0.38 for cranium thermal index. According to an official statement of the American Institute of Ultrasound in Medicine, for a thermal index ≤ 1.5 , there is no time limit for adult transcranial ultrasound because any thermal exposure would be below thresholds for bioeffects.

Volumetric ultrafast power Doppler imaging

[0040] The temporal window is the most widely used imaging window for TCD and has become the standard for cerebral artery assessment. Through the temporal

window, we can achieve ultrasound insonation of the terminal ICA (TICA), which delivers blood from the neck to the major arteries in the brain, as well as the ACA, MCA, and PCA, which deliver blood to most of the four brain lobes (i.e., frontal, parietal, temporal, and occipital).

[0041] The cerebral arteries can be mapped by ultrafast ultrasound data acquisition followed by subsequent volumetric image reconstruction. Compared to conventional volumetric Doppler imaging, this method substantially enhances the signal-to-noise ratio. Fig. 7a shows a schematic illustration of the imaging process. The 256 elements are activated to emit five diverging waves at different insonation angles at a 3000 Hz pulse repetition frequency. For all insonation angles, the backscattered raw radiofrequency signals are saved. During subsequent image reconstruction, beamforming and coherent compounding are performed on the raw signals, which allows the backscattered signals from all insonation angles to be recombined. Because signals from different insonation angles produce images of the same target object but different artifacts, signal recombination causes constructive summation of the target object but destructive summation of artifacts, boosting the object to background contrast. A spatiotemporal clutter filter (e.g., singular value decomposition in this work) separates tissue motion signals from blood flow signals in the compounded data based on the difference in their spatiotemporal coherences (discussed in more detail below). Spatio temporal clutter filtering is discussed in Demene, C. *et al.* Spatiotemporal Clutter Filtering of Ultrafast Ultrasound Data Highly Increases Doppler and fUltrasound Sensitivity. *IEEE Trans. Med. Imaging* 34, 2271-2285 (2015), which is hereby incorporated by reference in its entirety. Finally, the filtered data are used to reconstruct a volumetric power Doppler image. The diverging waves and the multi-angle compounding method provide a wide ultrasound field, which simultaneously insonates the bilateral ACA, MCA, PCA, and TICA, mapping a large vascular network. Fig. 7b shows different views of the volumetric power Doppler image of major cerebral arteries in a $60 \times 60 \times 60 \text{ mm}^3$ region, acquired through the temporal window.

[0042] Conventionally, an ultrasound image is obtained by a focused wave scanning line by line at different lateral positions. This method tremendously sacrifices the

temporal resolution to generate an optimal image because numerous transmission and receiving events are required).

[0043] Coherent compounding is a method that combines backscattered echoes from several different angles of insonation to produce a single image with higher object conspicuity (i.e., object to background contrast). Coherent compounding is discussed in Montaldo, G., Tanter, M., Bercoff, J., Benech, N. & Fink, M. Coherent plane-wave compounding for very high frame rate ultrasonography and transient elastography. *IEEE Trans. Ultrason. Ferroelectr. Freq. Control* 56, 489-506 (2009), which is hereby incorporated by reference in its entirety. The speckle, clutter, and other acoustic artifacts may have different patterns (i.e., different phases) from different insonation angles. Combining the received echoes from a few different angles of insonation will enhance the target signals and reduce the artifacts, therefore increasing the image quality. For a given image quality, because less transmission and receiving events are required for coherent compounding based on diverging waves, it substantially increases the frame rate compared to conventional imaging using focused waves.

[0044] Ultrafast ultrasound imaging as employed herein introduces a new paradigm for Doppler imaging. Ultrafast ultrasound imaging is discussed in Bercoff, J. *et al.* Ultrafast compound Doppler imaging: Providing full blood flow characterization. *IEEE Trans. Ultrason. Ferroelectr. Freq. Control* 58, 134-147 (2011), which is incorporated herein by reference in its entirety. By using diverging wave transmissions, a large number of backscattered echoes can be acquired at a very high frame rate in all fields of view, which significantly increases the sensitivity of Doppler shift⁵⁸. In a Doppler image, clutter refers to stationary and slowly moving tissues whose signals need to be removed to highlight blood flow signals and visualize vessels precisely. Conventional clutter filtering assumes that tissue motion signals and blood flow signals have completely different spectral characteristics. The tissue motion is very slow whereas red blood cells are moving fast, meaning that demodulated tissue motion signals and blood flow signals would not overlap. Therefore, theoretically, tissue motion signals could be simply removed by a high-pass filter. In reality, however, tissue motion and blood flow signals overlap, which makes it impossible to separate them based on temporal information only.

[0045] To address this problem, the present disclosure considers the spatiotemporal characteristics of tissue motion signals, which are different from those of blood scatterers. Tissue motion is spatially coherent, which means that tissue movement tends to drive the surrounding tissues to move in the same way/direction because of the cohesive nature of tissues. These movements can be seen as a spatial shift of a group of speckles. On the other hand, the motion of red blood cells represents a reorganization of the scatterers and does not exhibit this spatial coherence. Therefore, adopting such spatiotemporal information for clutter filtering can potentially improve the separation of tissue motion and blood flow.

[0046] Singular value decomposition is a mathematical operation on a matrix that can be used as a clutter filter. This method decomposes a multi-dimensional matrix (e.g., three dimensions for space and one dimension for time in this work) into a series of singular values and corresponding vectors. Because tissue motion signals are highly correlated, the signals from different spatial pixels exhibit a high degree of correlation and can be represented by larger singular values and corresponding vectors. In contrast, blood flow signals have much less spatial coherence and lower amplitudes, which can be represented by smaller singular values and corresponding vectors⁵⁹. Therefore, the singular value decomposition can locate the higher covariance values, which represent the tissue motion signals that can be removed.

[0047] We recorded volumetric power Doppler images during a carotid compression test and captured the flow variations in different arterial segments, which helps identify different cerebral arteries. Fig. 7c compares the volumetric power Doppler images before and during compression of the left common carotid artery. The thickness-coded arrows indicate the directions and magnitudes of blood flow in different arterial segments. Compressing the left common carotid artery caused a decrease in flow in the left TICA and left MCA, a change in flow direction in the left ACA, an increase in flow in the left PCA, and an increase in flow in the majority of contralateral vessels. To semiquantitatively evaluate the vascular network capacity, we evaluated the changes in the amplitude of the power Doppler signal of selected representative landmarks within each arterial segment. The results indicate that the collateral circulation could be recorded reliably. Fig. 7d is a bar graph showing the power Doppler amplitudes of representative landmarks of bilateral arterial segments

before and during compression of the left common carotid artery. The measurements were repeated three times. Error bars indicate standard deviations of the three measurements. To better evaluate the relative change before and after compression, we normalized the results before compression and only considered the relative change of the blood flow during compression. In Fig. 7, SVD denotes singular value decomposition. L denotes left, R denotes right and CCA denotes compressing carotid artery.

[0048] An illustrative method of performing volumetric ultrafast power Doppler imaging can be divided into two steps: ultrafast signal acquisition and post-processing. For signal acquisition, we used different time-delay profiles to transmit the diverging waves from five virtual sources distributed in a plane that was 22.30 mm behind the device to obtain a view angle of 40° (see Fig. 2a). We used three cycles of tone burst centered at 2 MHz at a pulse repetition frequency of 3000 Hz to activate the transducers. A group of five diverging waves was transmitted and received repeatedly 600 times within 1 s (see Fig. 2a). The digitization rate of the received analog signals was 7.8125 MHz.

[0049] For post-processing, volumetric beamforming was performed on the collected raw radiofrequency data from each transducer 3000 times. The beamformed data with different diverging waves were coherently compounded to form 600 frames of images. We implemented spatiotemporal clutter filtering (e.g., singular value decomposition in this work) to separate blood flow (incoherent motion within the volume) from tissue motion (coherent motion within the volume). After filtering, the energy of the temporal signal was integrated over the whole imaging block to calculate power Doppler intensity in 3D (see Fig. 2a). The computational load is inversely proportional to the size of each reconstructing voxel in the target region. Reducing the voxel size can increase the spatial resolution of the reconstructed image when the voxel size is larger than the theoretical maximum spatial resolution. When the voxel size is similar to or smaller than the theoretical maximum spatial resolution, further reducing the voxel size cannot help increase the spatial resolution. We used a $0.77 \times 0.77 \times 0.77 \text{ mm}^3$ voxel, which corresponds to one wavelength of the ultrasound at 2 MHz in soft tissues, to maintain a reasonable computational load.

Processing and validation of cerebral blood flow measurements

[0050] Measurements by the conformal ultrasound patch were validated with a conventional TCD probe. We chose the circle of Willis as the model, which is composed of multiple major arteries that provide blood supply to the entire brain. It has widespread branches, so the circle of Willis is usually measured through all four transcranial windows. Each window targets different arterial segments: the temporal is best for the ACA, MCA M2, MCA M1, PCA, and TICA, the orbital for the OA and ICA siphon, the submandibular for the ICA (Fig. 3c), and the suboccipital for the BA and VA.

[0051] Doppler processing to acquire high resolution blood flow spectra was performed with functions such as automatic spectral envelope tracking, sample volume customization, and audio. The recorded spectra have a temporal resolution >200 Hz, a velocity resolution <0.01 cm/s, and a 128-colormap of Doppler signal intensities, which are similar to the performance of the latest conventional TCD system. This allows us to correlate variations in blood flow velocities to the corresponding cardiac phases. Spectral envelope tracking provides peak systolic velocity and end diastolic velocity, which enables the computation of mean flow velocity, pulsatility index, and resistive index. Sample volume customization can provide blood flow distribution across the entire target arterial segment, which is valuable for identifying pathologic turbulent flow in the low velocity zone.

[0052] Fig. 8 shows a comparison of blood flow spectra from different sample volumes. The 0D sample volume (single pixel, $\sim 0.77 \times 0.77 \times 0.77$ mm³) only contains partial blood flow distributions, while the 3D sample volume (216 pixels, $\sim 4.62 \times 4.62 \times 4.62$ mm³) contains the entire blood flow distributions of the target blood vessel segment. For patients with cerebral arterial diseases such as stenosis, the turbulence flow pattern may happen in the zone of low frequency shift (i.e., low blood flow velocity), which can be seen only if an appropriate 3D sample volume is selected. The spectra share the same scale bars.

[0053] Compared to other blood flow spectra that contain limited information, we optimized the algorithms for improving the blood flow spectra resolution and integrated necessary functions for TCD sonography. The conventional processing of blood flow signals simultaneously provides B-mode images, color Doppler images, and spectrum Doppler waveforms. Each modality requires the Verasonics system to

transmit and receive ultrasound waves and process the data separately. In this work, to enhance the quality of blood flow spectra, we paused the B-mode and color Doppler imaging processes and concentrated the computation power for spectra recording. The temporal resolution of the spectra was increased from ~15 Hz to >200 Hz. The velocity resolution was improved from ~4 cm/s to <0.01 cm/s. The intensity resolution reached the threshold of conventional TCD probes (128-colormap).

[0054] For comparison, blood flow velocities of 10 arterial segments were collected from four adult volunteers at three separate time-points from a conformal ultrasound patch and a conventional TCD probe. Bland-Altman plots show that the mean differences and standard deviations of the differences between these two devices are -0.75 ± 1.97 cm/s, -0.12 ± 0.98 cm/s, 0.19 ± 1.16 cm/s, -0.0137 ± 0.0510 , and -0.0061 ± 0.0193 for peak systolic velocity, mean flow velocity, end diastolic velocity, pulsatility index, and resistive index, respectively. These biases are much smaller than these metrics per se, indicating good agreement between these two devices.

[0055] Because it allows hands-free, wearable measurements, the conformal ultrasound patch is particularly useful for prolonged surveillance. For example, intracranial B waves during sleep are closely related to the glymphatic system activities, which is critical for toxic waste byproduct removal in the brain and disease recovery. Those events are accompanied by slow, spontaneous oscillations in the cerebral blood flow velocity (i.e., B waves) at 0.3 to 4 cycles per minute. With the conformal ultrasound patch at the temporal window, we monitored the cerebral blood flow spectra in the MCA in a participant for four hours continuously. The recording has a high signal-to-noise ratio, except for transient signal fluctuations during extensive head motions. A cascade of B waves was identified when the participant felt drowsy. Prolonged surveillance is also valuable for cerebral emboli monitoring and therefore embolic stroke prevention. Evidence suggests that extending the recording time can capture more embolic signal positive patients. The conformal ultrasound patch could detect flowing emboli in a phantom, demonstrating the promise for prolonged recording using the conformal patch in a clinical setting.

[0056] Fig. 9a shows a schematic diagram of an arrangement for performing emboli detection on a phantom by a conformal ultrasound patch. Three different types of emboli are used, including gas emboli, 0.5 mm solid emboli, and 2 mm solid emboli.

FIG. 9b shows the flow spectra of baseline, with gas emboli, with 0.5 mm solid emboli, and with 2 mm solid emboli, respectively. The spectra share the same scale bars.

Discussion

[0057] TCD is an ultrasound modality with a wide range of potential clinical and research applications. However, conventional TCD probes require a well-trained operator to identify the correct target arterial segments for measurement, and although serial imaging of the vasculature provides a measure of disease progression, the lack of continuous imaging limits the potential of this modality. The conformal ultrasound patch offers a platform for volumetric vascular network imaging, which reduces potential operator errors in this identification process. More importantly, the conformal ultrasound patch enables long-term transcranial monitoring of cerebral hemodynamics, with implications for both medical research and clinical practice.

[0058] In addition to cerebral monitoring, the devices and methods described herein can also be used to study complex hemodynamics in other clinically important vessels. For example, the aorta is the largest artery in the body and supplies oxygenated blood to all vital organs. Its cane-shaped morphology gives rise to turbulent blood flow, which subjects the arterial walls to shear stress and makes the aorta more vulnerable to atherosclerosis. Another example is the carotid bifurcation, which also induces turbulent blood flow and therefore atherosclerosis. Continuous, long-term monitoring of these targets may prove valuable in understanding the interaction between blood flow and pathological changes of the vessels.

[0059] Additionally, the devices and methods described herein will help understand the mechanisms of emboli generation and propagation, and enable timely clinical intervention. Although important, there are presently no devices available to continuously monitor emboli in the heart or lungs (other than the precordial stethoscope for air embolism). The conformal ultrasound patch technology not only shows potential for prolonged monitoring for the detection of cerebral emboli, but also opens up new possibilities for embolic event monitoring in the heart, lungs, peripheral vasculature, and many other critical visceral organs.

[0060] In some embodiments, device performance and functionality may be enhanced by using contrast agents such as microbubbles, as microbubbles generate much higher-amplitude backscattered echoes compared to the surrounding tissues. In addition, time reversal can be used in some cases to calculate precise time delays on each element of the transducer array and thus partially compensate for the phase aberration of the skull. In addition, the imaging contrast and spatial resolution can be further enhanced by harmonic imaging. The incident ultrasound waves can drive the microbubbles to vibrate nonlinearly, generating strong harmonic components in backscattered echoes. Moreover, ultrafast ultrasound localization microscopy can be adopted to overcome the diffraction limit, enabling super-resolution transcranial imaging and full reconstruction of deep vascular systems down to the level of capillaries.

[0061] In some embodiments the volumetric reconstruction speed can be increased using a multi-threaded process with much higher computational power for image reconstruction. The calculation and image rendering processes could be highly parallelized and optimized for real-time imaging, which would be valuable for understanding the real-time functional connectivity of the brain. Finally, the data can be integrated with platforms typically used in the clinical workflow (e.g., RapidAI, Viz.ai). Synchronization of real-time cerebral blood flow spectra and volumetric vessel images collected by the conformal ultrasound patch can add to the clinical value of the device for real-time surveillance, offering opportunities for timely interventions to improve patient outcomes.

[0062] Although the subject matter of the present disclosure has been described with reference to particular embodiments of a conformable ultrasound patch for use in performing TCD ultrasonography, more generally the techniques described herein may be employed a wide range of different conformable ultrasound patches that are used in other applications as well.

[0063] More generally, a method for performing ultrasound imaging of a region of interest in a subject is provided. In accordance with the method, a wearable conformal ultrasound transducer array having a plurality of phased array transducer elements is attached to the subject. A plurality of diverging ultrasonic acoustic waves is transmitted from the plurality of phased array transducer elements at a plurality of

insonation angles using different time-delay profiles. Reflected ultrasonic signals are received from the region of interest using the plurality of phased array transducer elements. The reflected ultrasonic signals are processed using beamforming to recombine the reflected ultrasonic signals from all of the insonation angles. The recombined reflected ultrasonic signals are filtered to provide filtered data in which tissue motion signals are separated from blood flow signals. A volumetric power Doppler image is reconstructed from the filtered data using a power Doppler calculation. The reconstructed volumetric power Doppler image is caused to be displayed.

[0064] In some embodiments the beamforming is volumetric beamforming.

[0065] In some embodiments processing the reflected ultrasonic signals using volumetric beamforming includes using volumetric beamforming and coherent compounding to recombine the reflected ultrasonic signals from one or all of the insonation angles.

[0066] In some embodiments the conformable ultrasound patch is attached to the scalp and the region of interest is a cerebral vascular network. The cerebral vascular network may be continuously monitored, in some cases for at least 1 hour and in other cases at least 3 hours.

[0067] In some embodiments the recombined reflected ultrasonic signals are filtered using a singular value decomposition filter.

[0068] In some embodiments, based at least in part on the reconstructed volumetric power Doppler image, focused acoustic waves are transmitted from the plurality of phased array transducer elements to a targeted location within the region of interest.

[0069] In some embodiments, automatic spectral envelope tracking is performed to provide peak systolic velocity and end diastolic velocity within an arterial segment. Mean flow velocity, pulsatility index, and/or resistive index may be determined from the peak systolic velocity and end diastolic velocity within the arterial segment.

[0070] In some embodiments the reconstructed volumetric power Doppler image is an image of a cerebral vascular network.

[0071] In some embodiments, embolic density may be monitored within an arterial segment based on an intensity difference between embolic signals and blood flow signals.

[0072] It should be understood that the various techniques described herein may be implemented in connection with hardware components or software components or, where appropriate, with a combination of both. Illustrative types of hardware components that can be used include Field-programmable Gate Arrays (FPGAs), Application-specific Integrated Circuits (ASICs), Application-specific Standard Products (ASSPs), System-on-a-chip systems (SOCs), Complex Programmable Logic Devices (CPLDs), etc. The methods and apparatus of the presently disclosed subject matter, or certain aspects or portions thereof, may take the form of program code (i.e., instructions) embodied in tangible media, such as floppy diskettes, CD-ROMs, hard drives, or any other tangible machine-readable storage medium where, when the program code is loaded into and executed by a machine, such as a computer or processor, the machine becomes an apparatus for practicing the presently disclosed subject matter.

[0073] Although exemplary implementations may refer to utilizing aspects of the presently disclosed subject matter in the context of one or more stand-alone computer systems, the subject matter is not so limited, but rather may be implemented in connection with any computing environment, such as a network or distributed computing environment. Still further, aspects of the presently disclosed subject matter may be implemented in or across a plurality of processing chips or devices, and storage may similarly be affected across a plurality of devices. Such devices might include personal computers, network servers, and handheld devices, for example.

[0074] The foregoing description, for the purpose of explanation, has been described with reference to specific embodiments. However, the illustrative discussions above are not intended to be exhaustive or to limit the invention to the precise forms disclosed. Many modifications and variations are possible in view of the above teachings. The embodiments were chosen and described in order to best explain the principles of the embodiments and its practical applications, to thereby enable others skilled in the art to best utilize the embodiments and various modifications as may be

suited to the particular use contemplated. Accordingly, the present embodiments are to be considered as illustrative and not restrictive, and the invention is not to be limited to the details given herein, but may be modified within the scope and equivalent of the appended claims.

CLAIMS

1. A method for performing ultrasound imaging of a region of interest in a subject, comprising:
 - attaching to the subject a wearable conformal ultrasound transducer array having a plurality of phased array transducer elements;
 - transmitting a plurality of diverging ultrasonic acoustic waves from the plurality of phased array transducer elements at one or a plurality of insonation angles using different time-delay profiles;
 - receiving reflected ultrasonic signals from the region of interest using the plurality of phased array transducer elements;
 - processing the reflected ultrasonic signals using beamforming to recombine the reflected ultrasonic signals from one or all of the insonation angles;
 - filtering the recombined reflected ultrasonic signals to provide filtered data in which tissue motion signals are separated from blood flow signals; and
 - reconstructing a volumetric power or color Doppler image from the filtered data using a power or color Doppler calculation.
2. The method of claim 1, wherein the beamforming is volumetric beamforming.
3. The method of claim 2, wherein processing the reflected ultrasonic signals using volumetric beamforming includes using volumetric beamforming and coherent compounding to recombine the reflected ultrasonic signals from one or all of the insonation angles.
4. The method of claim 1, further comprising causing the reconstructed volumetric power or color Doppler image to be displayed.

5. The method of claim 1, wherein the region of interest is a cerebral vascular network.
6. The method of claim 1, further comprising continuously monitoring cerebral blood flow within the cerebral vascular network.
7. The method of claim 6, wherein the cerebral blood flow is continuously monitored for at least 1 hour.
8. The method of claim 1, wherein filtering the recombined reflected ultrasonic signals includes filtering the recombined reflected ultrasonic signals using a singular value decomposition filter.
9. The method of claim 1, further comprising, based at least in part on the reconstructed volumetric power or color Doppler image, transmitting focused acoustic waves from the plurality of phased array transducer elements to a targeted location within the region of interest.
10. The method of claim 1, further comprising: performing automatic spectral envelope tracking to provide peak systolic velocity and end diastolic velocity within an arterial segment and determining mean flow velocity, pulsatility index, and/or resistive index from the peak systolic velocity and end diastolic velocity within the arterial segment.
11. The method of claim 1, wherein the reconstructed volumetric power and color Doppler image is an image of a cerebral vascular network.
12. The method of claim 1, further comprising monitoring embolic density within a vascular segment based on an intensity difference between embolic signals and blood flow signals.
13. A non-transitory computer readable medium comprising instructions that, when executed by at least one processor, cause a system to:

receive reflected ultrasonic signals from a region of interest within a subject using a plurality of phased array transducer elements in a wearable conformal ultrasound transducer array that is attached to the subject, the reflected ultrasonic

signals arising from transmission of a plurality of diverging ultrasonic acoustic waves from the plurality of phased array transducer elements at a plurality of insonation angles using different time-delay profiles;

process the reflected ultrasonic signals using to recombine the reflected ultrasonic signals from one or all of the insonation angles;

filter the recombined reflected ultrasonic signals to provide filtered data in which tissue motion signals are separated from blood flow signals;

reconstruct a volumetric power or color Doppler image from the filtered data using a power or color Doppler calculation; and

cause the reconstructed volumetric power or color Doppler image to be displayed.

14. The non-transitory computer readable medium of claim 13, wherein the beamforming is volumetric beamforming.

15. The non-transitory computer readable medium of claim 14, wherein the instructions, when executed by at least one processor, cause the system to process the reflected ultrasonic signals using volumetric beamforming and coherent compounding to recombine the reflected ultrasonic signals from one or all of the insonation angles.

16. The non-transitory computer readable medium of claim 14, wherein the instructions, when executed by at least one processor, cause the system to continuously monitor cerebral blood flow within the cerebral vascular network.

17. The non-transitory computer readable medium of claim 13, wherein the instructions, when executed by at least one processor, cause the system to filter the recombined reflected ultrasonic signals using a singular value decomposition filter.

18. The non-transitory computer readable medium of claim 13, wherein the instructions, when executed by at least one processor, cause the system to transmit focused acoustic waves from the plurality of phased array transducer elements to a

targeted location within the region of interest based at least in part on the reconstructed volumetric power or color Doppler image.

19. The non-transitory computer readable medium of claim 13, wherein the instructions, when executed by at least one processor, cause the system to: perform automatic spectral envelope tracking to provide peak systolic velocity and end diastolic velocity within an arterial segment; and determine mean flow velocity, pulsatility index, and/or resistive index from the peak systolic velocity and end diastolic velocity within the arterial segment.

20. The non-transitory computer readable medium of claim 13, wherein the instructions, when executed by at least one processor, cause the system to monitor embolic density within a vascular segment based on an intensity difference between embolic signals and blood flow signals.

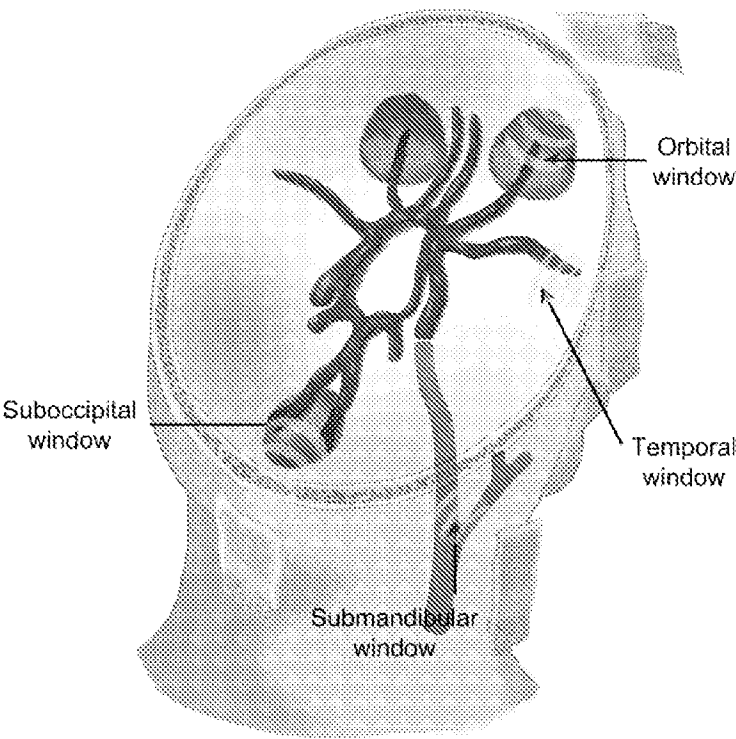


FIGURE 1

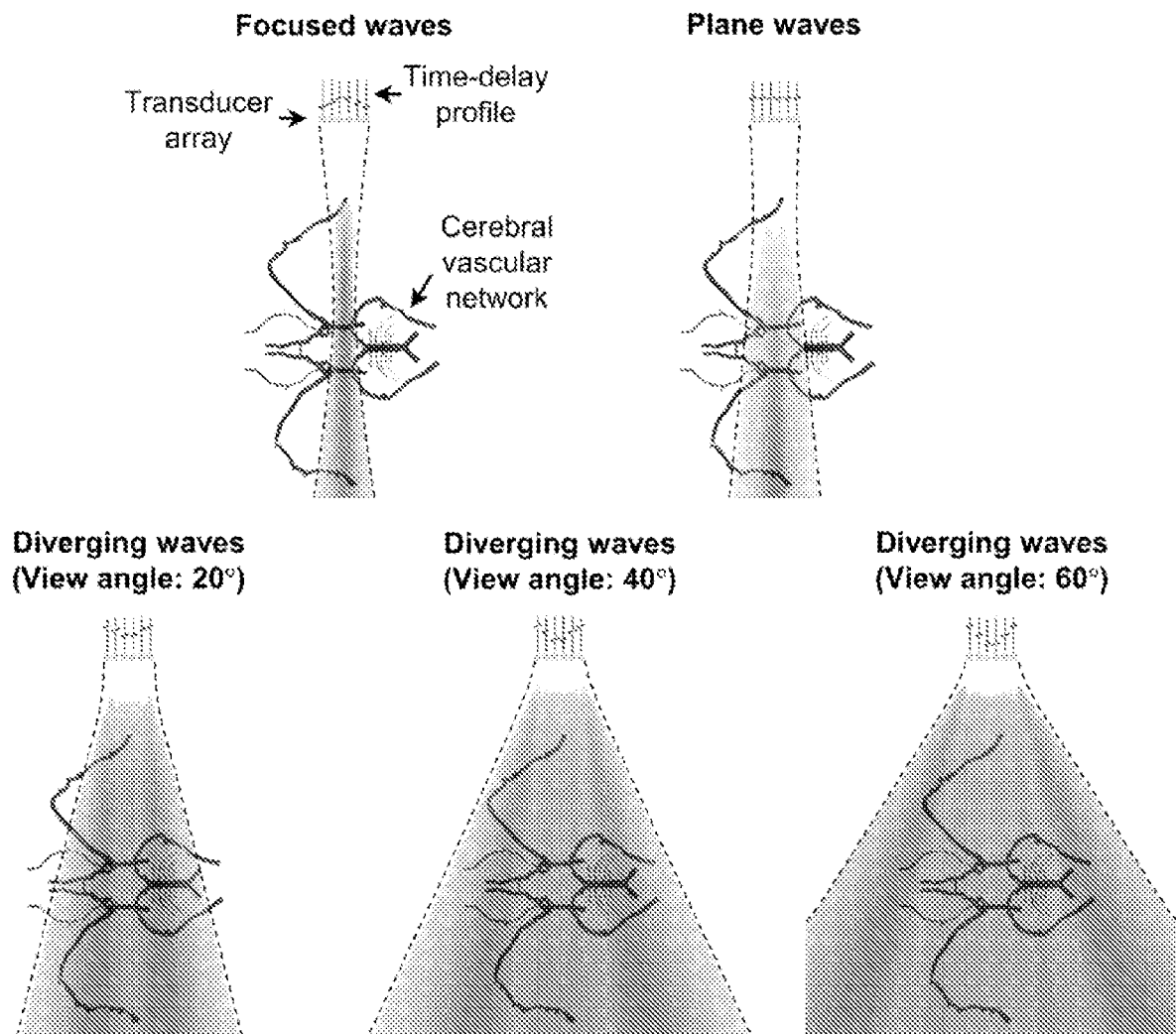


FIGURE 2

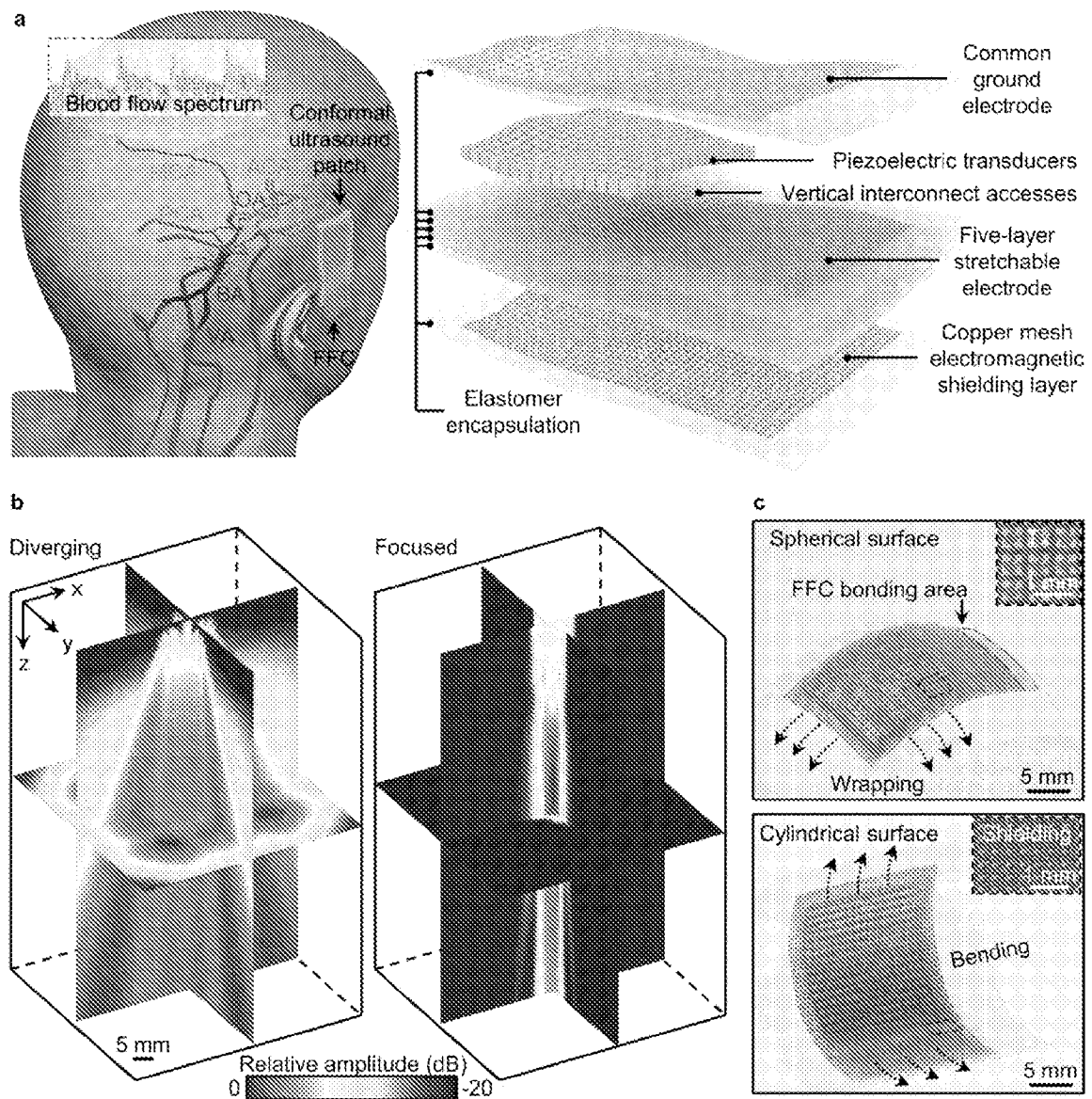


FIGURE 3

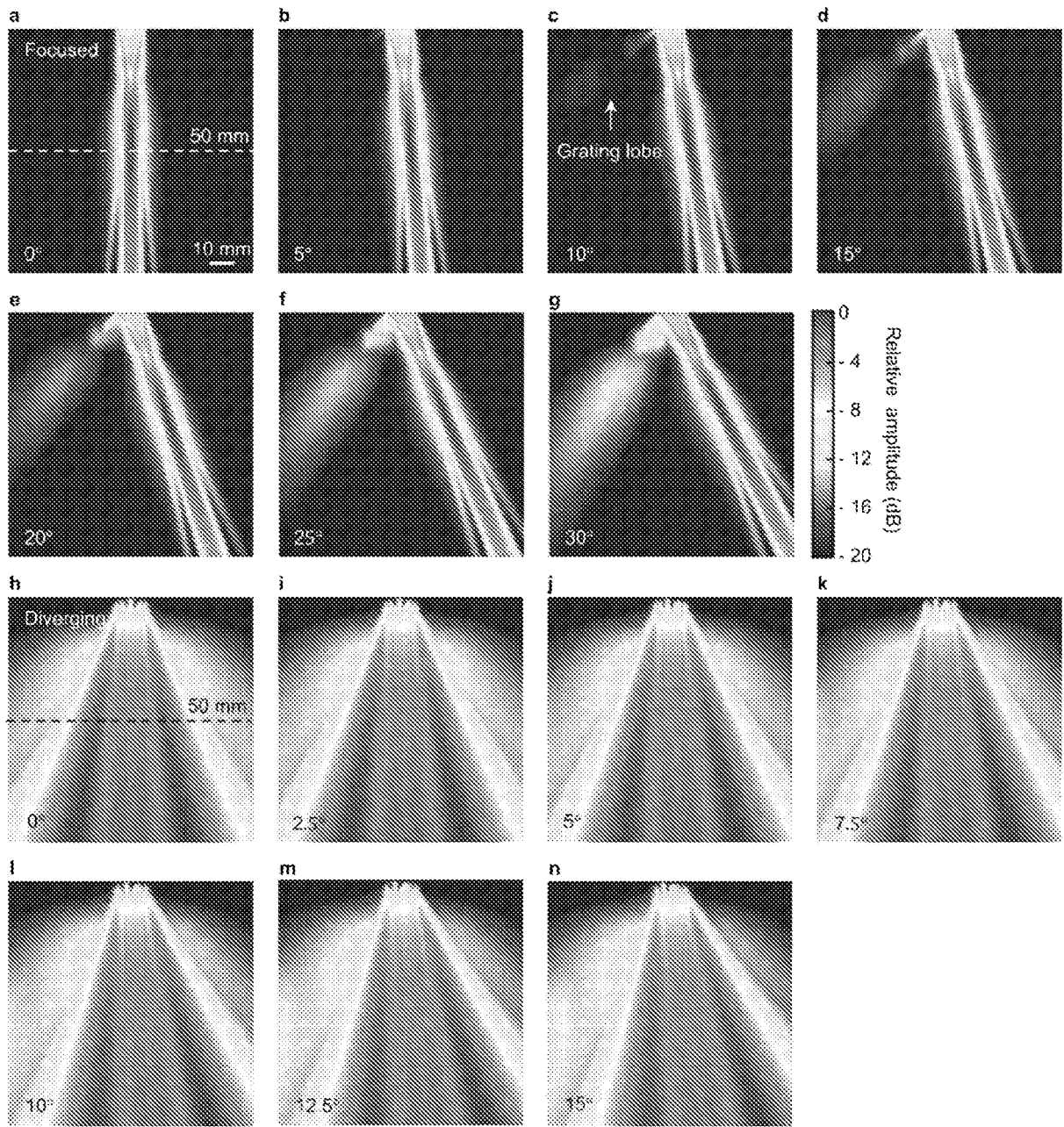


FIGURE 4

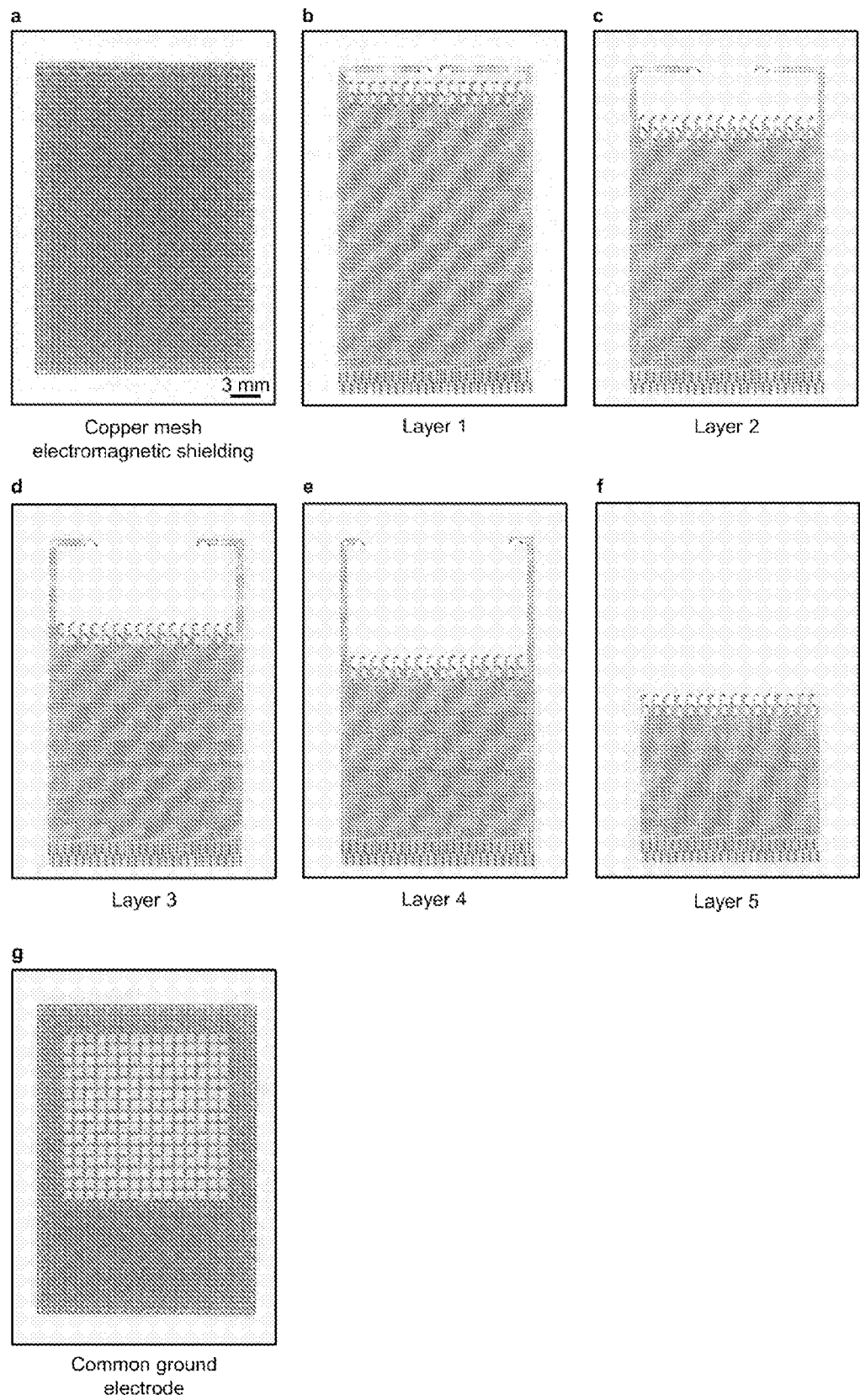


Figure 5

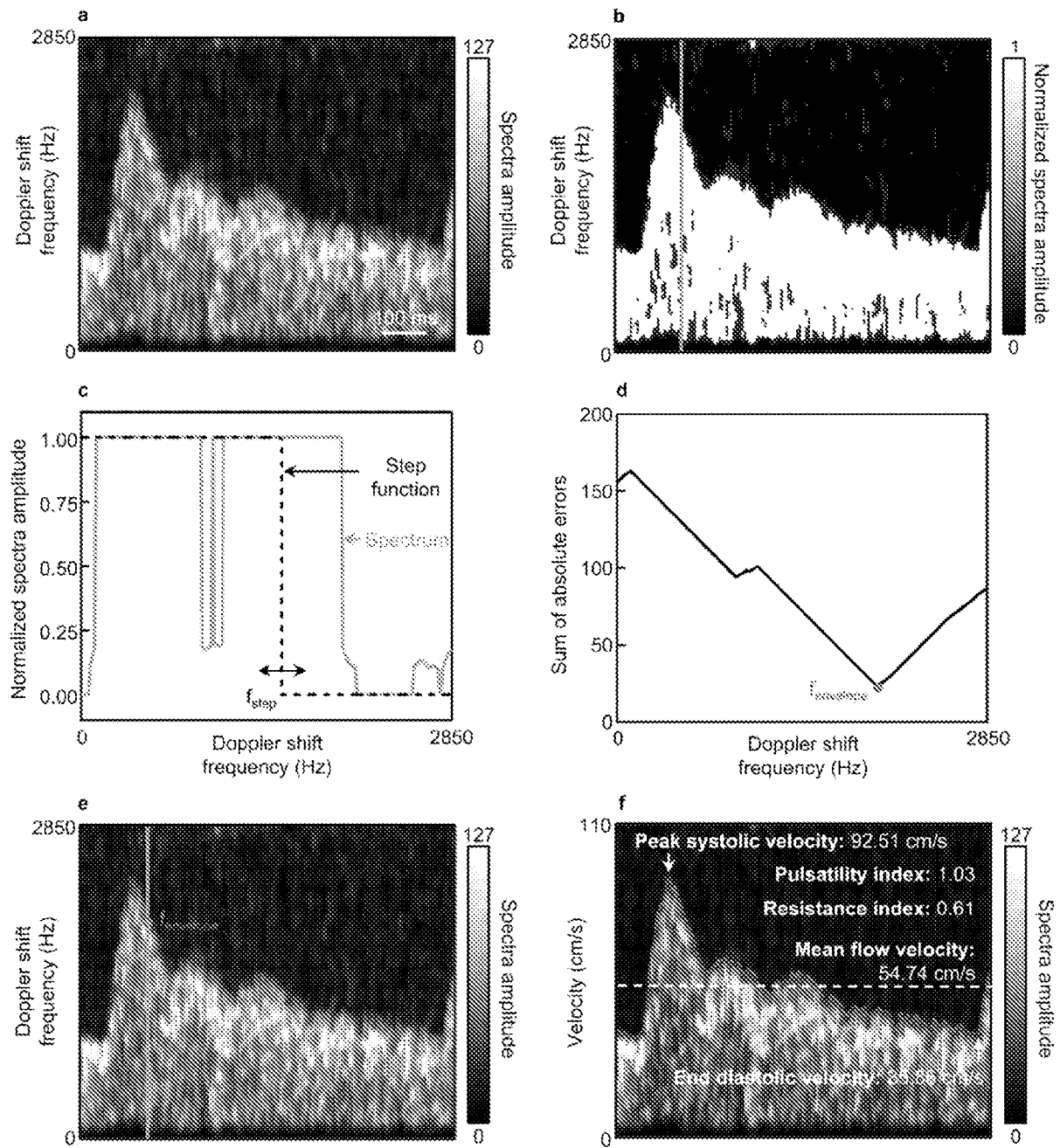


FIGURE 6

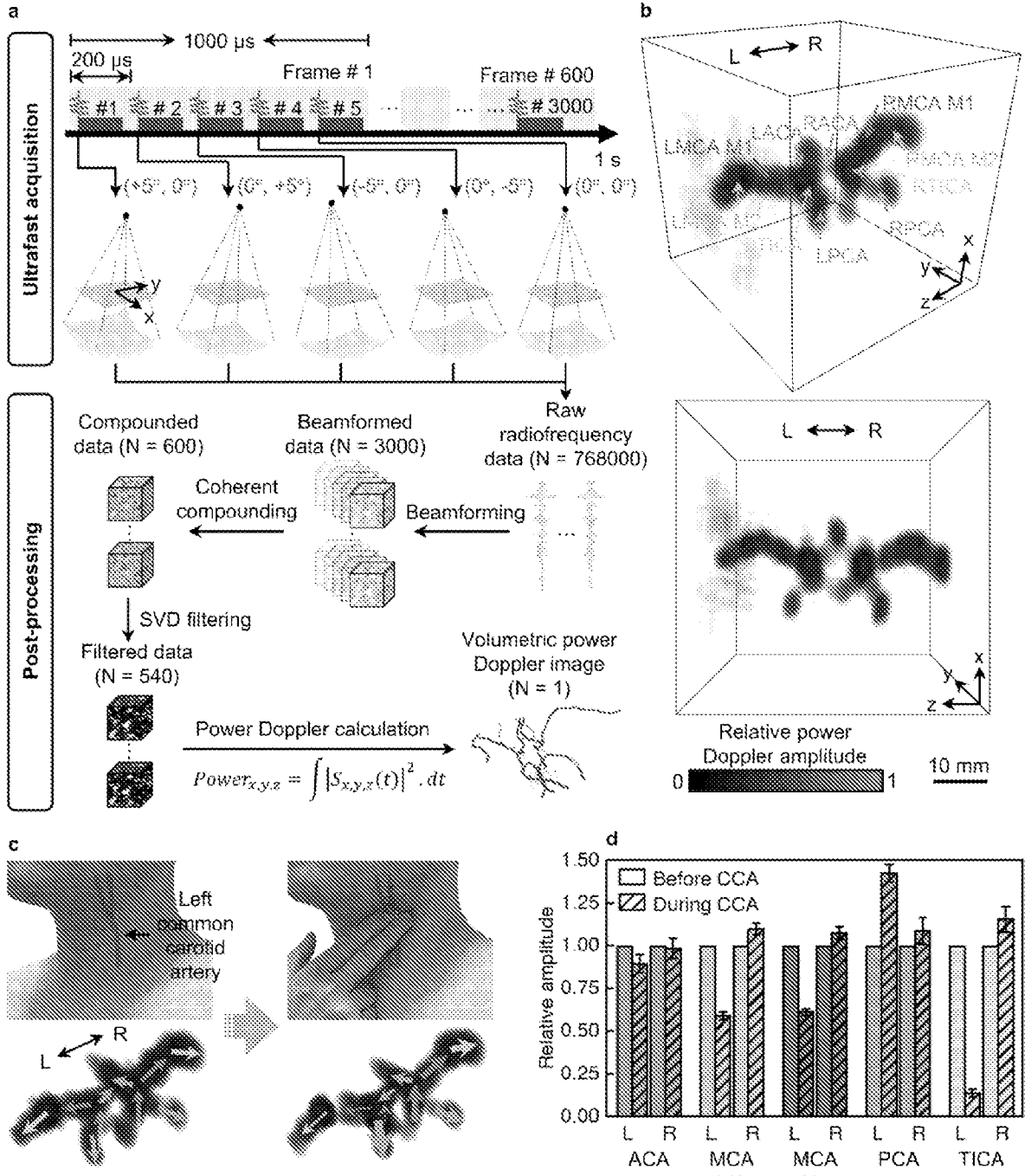


FIGURE 7

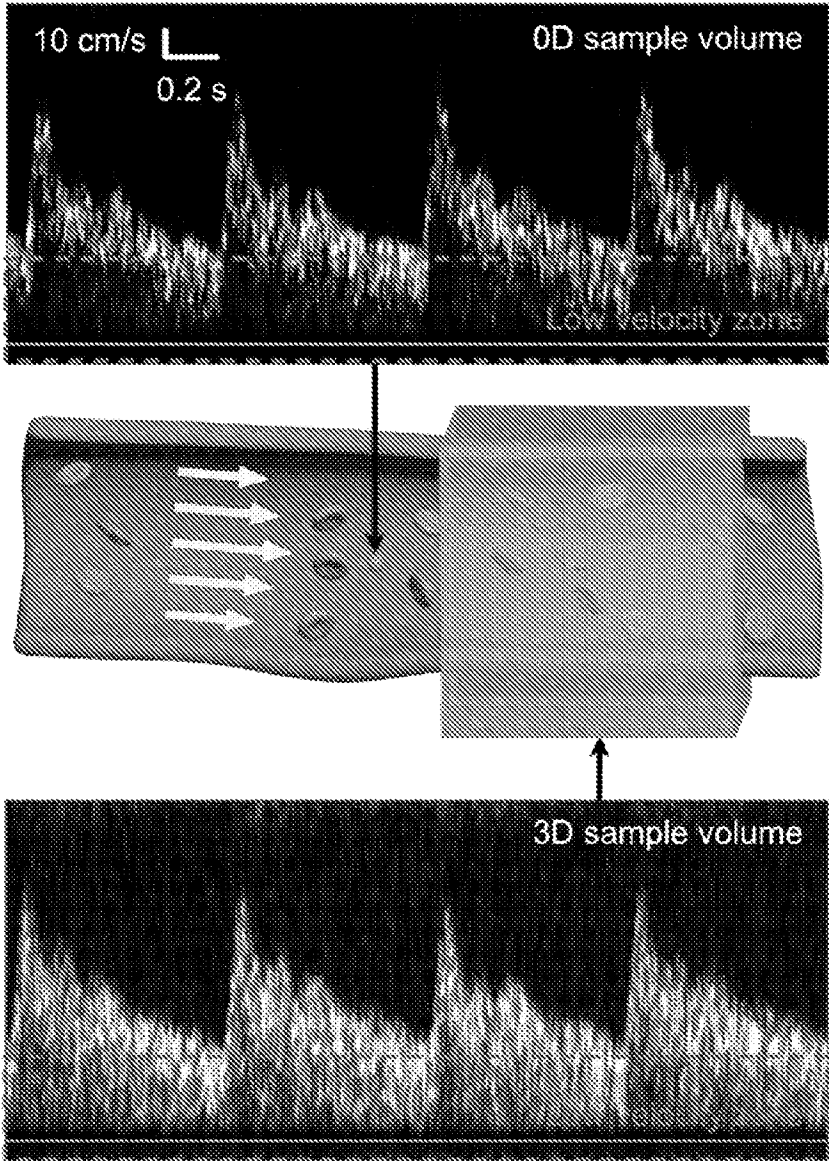
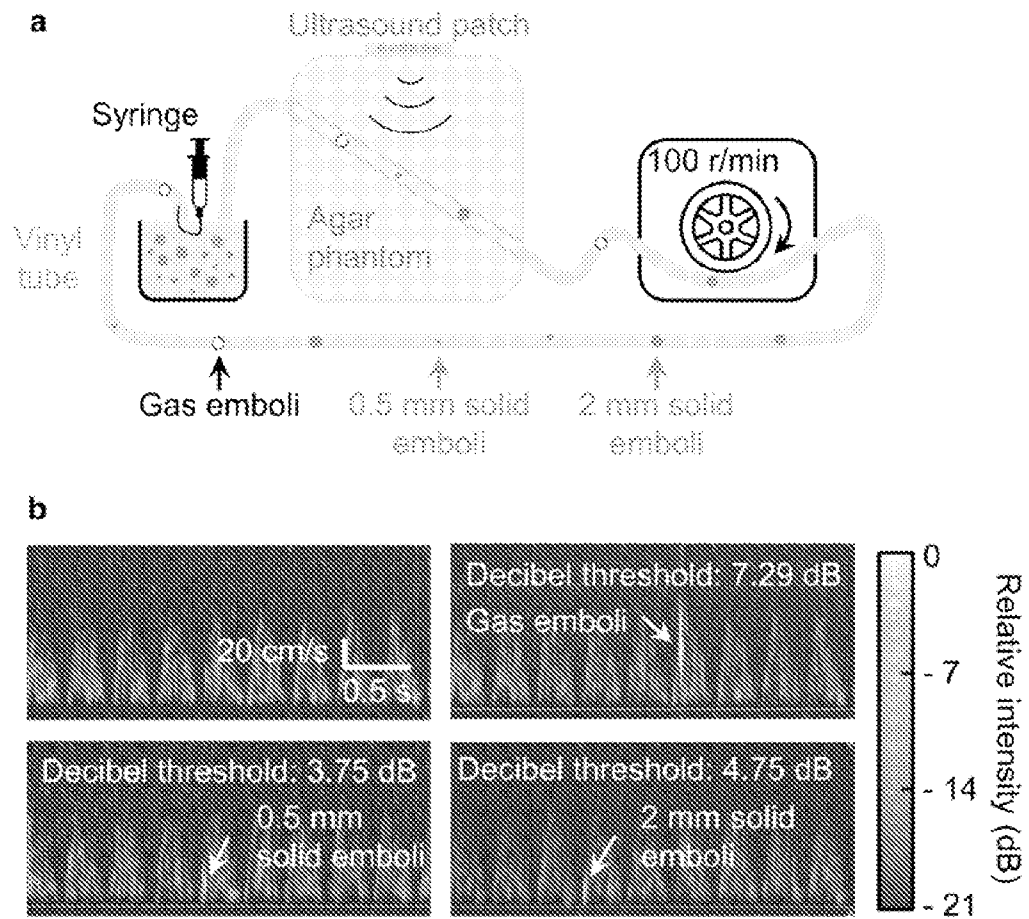


FIGURE 8



INTERNATIONAL SEARCH REPORT

International application No.

PCT/US24/14590

A. CLASSIFICATION OF SUBJECT MATTER

IPC - INV. A61B 8/00 (2023.01)

ADD. A61B 5/03 (2023.01)

CPC - INV. A61B 8/4236; A61B 8/4488; A61B 8/4494; A61B 8/483; A61B 8/488; A61B 8/5207

ADD. A61B 5/031

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

See Search History document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

See Search History document

Electronic database consulted during the international search (name of database and, where practicable, search terms used)

See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2022/0133269 A1 (THE REGENTS OF THE UNIVERSITY OF CALIFORNIA) 05 May 2022; Paras. [0038], [0049], [0050]	1, 2, 4-14, 16-20
Y	US 2021/0085280 A1 (KONINKLIJKE PHILIPS N.V.) 25 March 2021; Paras. [0049], [0070]	1, 2, 4-14, 16-20
Y --- A	US 2020/0187910 A1 (THE UNIVERSITY OF NORTH CAROLINA AT CHAPEL HILL) 18 June 2020; Paras. [0093], [0100]	2, 5-8, 11, 14, 16-17 --- 3, 15
Y	US 5,287,753 A (ROUTH ET AL.) 22 February 1994; Col. 1, Lns. 5-9, 24-44	10, 19
Y	US 2002/0091319 A1 (MOEHRING ET AL.) 11 July 2002; Para [0036], Fig. 8	12, 20
P,X	WO 2023/049529 A1 (LIMINAL SCIENCES, INC.) 30 March 2023; entire document	1-20

☐ Further documents are listed in the continuation of Box C.☐ See patent family annex.

* Special categories of cited documents:

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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

24 May 2024 (24.05.2024)

Date of mailing of the international search report

JUN 21 2024

Name and mailing address of the ISA/

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