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(54) **Title**: PORTABLE DEVICE TO INITIATE AND MONITOR TREATMENT OF STROKE VICTIMS IN THE FIELD

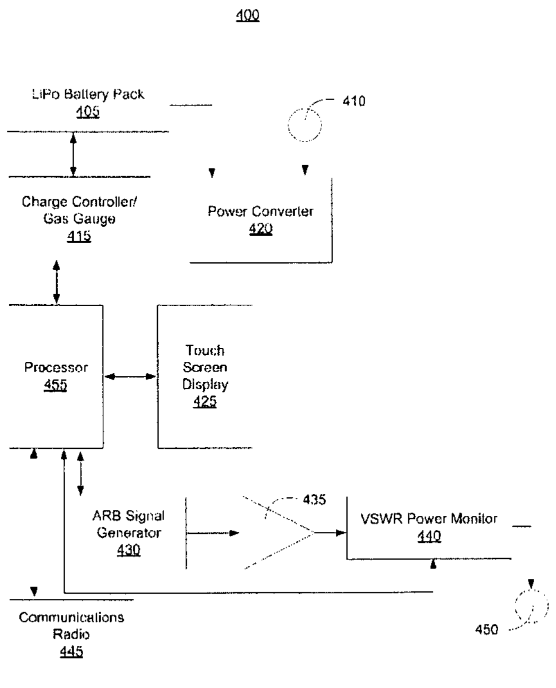

Figure 4

(57) **Abstract**: Methods and apparatuses are provided for initiating stroke treatment in the field and/or during the transport of the patient to a care facility. The capability is provided to adjust automatically to the individual therapeutic window for each single patient, which is crucial because of the significant differences in skull morphology between humans of different age, gender and race. Further, the methods and apparatuses are based on the use of non-invasive application of ultrasound, as well as the non-invasive application of ultrasound in combination with an acoustically active agent, such as microbubbles, where stable cavitation of the microbubbles caused by the ultrasound may be relied upon as an underlying mechanism for both the therapeutic application as well as its control.

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PORTABLE DEVICE TO INITIATE AND MONITOR TREATMENT OF STROKE VICTIMS IN THE FIELD

[0001] This invention was made with government support under HL091043 awarded by National Institute of Health. The government has certain rights in the invention.

TECHNICAL FIELD

[0002] The present invention relates to treating victims of stroke or stroke-like events, and in particular, to providing a portable device to initiate treatment and monitor victims "in the field" and/or during transport to a care facility by applying ultrasound non-invasively, as well as in combination with intravenously administered microbubbles, through an intact skull.

BACKGROUND

[0003] A stroke or cerebrovascular accident (CVA) refers to a rapid loss of brain function due to a disturbance in the brain's blood supply, for example, due to a lack of blood flow (referred to as ischemia) caused by blockage, e.g., thrombosis or arterial embolism, or a hemorrhage. Stroke is the second leading cause of death worldwide and the third leading cause of death in the United States, between cardiac diseases (the number one worldwide common cause of death) and tumor diseases (the number three worldwide common cause of death). The majority of acute ischemic strokes (80%) are caused by thrombo-embolism, and in comparison to, e.g., cardiac and tumor-related diseases, the amount of acute cell death in ischemic stroke during the initial phase of a stroke event is significantly greater. That is, neuronal brain cells (neurons) are very sensitive to oxygen supply, which may be interrupted, for example, due to a sudden arterial vessel occlusion. Thus, neurons turn into apoptosis within the first 60 seconds of oxygen deprivation. Apoptosis is defined as a programmed cell death, which means that neurons start to die irreversibly even at this very early point in time if recanalization, and therefore providing an oxygen supply, does not occur.

[0004] Figure 1 illustrates one example of a normal vessel, indicated by arrow 10, an example of an occluded vessel, indicated by arrow 20, and an example of a recanalized vessel at, e.g., 25 minutes after occlusion, indicated by arrow 30. Figure 1 further illustrates an example of a blood clot 40, as observed prior to the application of ultrasound treatment, as well as an example the blood clot 40, as observed post-ultrasound application.

[0005] In the case of acute ischemic stroke, it has been shown that an average of 1,900,000 neurons die every minute due to intracranial arterial vessel occlusion. Hence, it is a worldwide, common understanding that therapeutic options to recanalize the affected brain artery should be applied as early as possible. Recent advances in stroke care, such as the installation of specialized Stroke Centers/Units or TeleMedicine concepts, have improved stroke care in selected areas. However, all of these activities are either initiated or coordinated mainly by well-known academic centers in developed countries, and the overall impact of these improvements on stroke care are negligible.

[0006] It should be noted that the cause of the worldwide growing incidence of stroke may be attributed to three main causes. First, there is a lack of public awareness of the disease and its symptoms. Second, all conventional therapeutic interventions require hospitalization of the patient. Third, and among people of all ages, more than 85% of global deaths from stroke occur in either low or middle-income countries, where approximately 85% of the world's total population resides. Figure 2 illustrates that deaths attributable to stroke in middle income individuals was approximately 3 million in the early 2000s, and is increasing, as indicated by line 210, almost 2 million for low income individuals and also increasing, as indicated by line 220. In contrast, and as indicated by line 230, deaths attributable to stroke amongst high income individuals in the early 2000s and projected through 2030 remains under 1 million.

[0007] Currently, there is no known therapeutic option which allows the treatment of acute stroke patients to begin "in the field," e.g., at the site of the emergency and/or during transport to a care facility, such as a hospital. In the field treatment can be considered to be of critical importance since the majority of strokes occur in suburban or rural areas, often a great distance from specialized stroke centers. In these cases, the time delay between an emergency call, e.g., 911 call, arrival at the site of the emergency, and transport to the specialized stroke center may often be a limiting factor as to whether a patient survives, suffers from lifelong invalidity, or fully recovers without any deficits.

[0008] One recently developed device, which aims to treat stroke victims using ultrasound, is a device, referred to as the CLOTBUST™-ER by Cerevast Therapeutics, Inc. However, the

CLOTBUST™-ER ultrasound stroke treatment device has been developed for stroke treatment in an emergency room, after a patient's admission to a hospital, and in combination with Tissue Plasminogen Activator (tPA), currently the only FDA approved lytic drug for stroke treatment. Accordingly, and again, even with such a device, treatment in the field remains lacking for stroke victims.

SUMMARY

[0009] Various embodiments of the present invention are directed to methods and devices for initiating stroke treatment "in the field" and/or during the transport of the patient to a care facility. The capability is provided to adjust automatically to the individual "therapeutic window" for each single patient, which is crucial due of the significant differences in skull morphology between humans of different age, gender and race. Further, the methods and devices are based on the combinational use of microbubbles and stable cavitation as an underlying mechanism for both the therapeutic application as well as its control.

BRIEF DESCRIPTION OF THE DRAWINGS

[0010] For a more complete understanding of example embodiments of the present invention, reference is now made to the following descriptions taken in connection with the accompanying drawings in which:

[0011] Figure 1 are illustrations of a normal vessel, an occluded vessel, and a recanalized vessel, and the effects of ultrasound on a blood clot;

[0012] Figure 2 is a graph illustrating the prevalence of stroke-related deaths among different socio-economic groups;

[0013] Figure 3 illustrates an example implementation of a power and control module configured and utilized in accordance with various embodiments for in-field treatment of a stroke victim;

[0014] Figures 4 is a schematic representation of the power and control module of Figure 3;

[0015] Figure 5 is an illustration of time delay effects and possible tissue damage reduction upon use of various embodiments; and

[0016] Figure 6 illustrates example processes performed for treating stroke victims in the field in accordance with various embodiments.

DETAILED DESCRIPTION

[0017] Various embodiments disclosed herein are directed to methods and apparatuses for treating patients who may suffer from an acute ischemic stroke in the field and/or during transport to a care facility. In accordance with one embodiment, such treatment can be effectuated by applying ultrasound noninvasively, through an intact skull/cranium, to trigger various biophysical effects. In accordance with another embodiment, such noninvasive application of ultrasound can be performed in combination with intravenously administered microbubbles through an intact skull/cranium, to trigger various biophysical effects. Among other effects, the aforementioned biophysical effects triggered in accordance with the utilization of various embodiments may include, but are not limited to the following: a) the improvement of collateral and interstitial flow; b) restoration of arterial flow in an affected vascular supply area; c) reduction of concomitant edema; d) activation of chaperone proteins; e) potential progenitor cell stimulation; and f) the actual lysis of a vessel occluding blood clot.

[0018] Ultrasound can be applied in a pulsed manner using a transmit frequency of, e.g., 200 kHz, at which the distortion of an applied ultrasound beam by the skull is negligible. The ultrasound can be applied from, e.g., both sides of a patient's head in an alternating fashion. Applying ultrasound in such a manner can increase the treatment area, as well as avoid in parallel potential side effects, due to the overlay of individual sound fields. In particular, two ultrasound probes/electrodes can be placed in the anatomical area of the temporal bone and close to the ear. The two ultrasound probes can be disposable, and have the capability to transmit an ultrasound beam, as well as receive acoustic signals, caused by ultrasound microbubble induced cavitation events, in accordance with certain embodiments.

[0019] In accordance with one embodiment, the pulse width of an applied ultrasound bean may be short (e.g., 100μs) to allow a high pulse repetition rate (e.g., 5 kHz) to provide sufficient energy deposition. The acoustic output power may be rather low (e.g., 4 W) to accomplish a focal maximum intensity below the Food and Drug Administration (FDA)-suggested limit of

$720mW/cm^2$. With regard to beam forming, a chirp mode may be utilized, although other embodiments can utilize fundamental or phase inversion modality.

[0020] In accordance with another embodiment, and as alluded to previously, ultrasound may also be applied in combination with an acoustically active agent (e.g., microbubbles). Furthermore, it should be noted that the ultrasound may be applied continuously over an extended period of time (e.g., several hours). Similar to the previously described embodiment, the pulse width of an ultrasound beam transmitted by the ultrasound probes described above can be short (e.g., 10μs -1000μs) in combination with a duty cycle between, e.g., 1-50%. The acoustic output power may be chosen to accomplish a focal maximum intensity below the FDA-suggested limit of $720mW/cm^2$.

[0021] The application of noninvasive ultrasound either alone, or in combination with intravenously administered acoustically active agent such as microbubbles, can be performed with ultrasound transducers and a power and control device/module that can be relatively small, preferably pocket-sized. The power and control device may be battery charged to allow for portable and/or wireless functionality. Additionally still, the power and control device can have a substantially easy-to-use user interface, as well as being durable and waterproof. Other features and/or functionalities may be incorporated into one or more designs of the control device as, e.g., dictated by the environment(s) in which the device may be utilized. In accordance with one embodiment, the power and control device may be provided with an on/off switch, not more than two control buttons, and a main control display. Such control buttons may include, but are not limited to the following: an automated adjustment of acoustic output power ("Automated PCD Control") button, where PCD can refer to Passive Cavitation Detection; and a manual adjustment of acoustic power ("Manual PCD Control") button. It should be noted that in accordance with certain embodiments, manual adjustment of acoustic power may involve selection of one of a plurality of output power ranges that can depend on one or more, but not necessarily limited to the following: patient age group, e.g., a) <20, b) 20-40, b) 41-60, c) 61-75, d) >76 years of age; gender, e.g., a) Female, b) Male; and race, e.g., a) Caucasian, b) Hispanic, c) Asian, d) African/African-American. Additionally, the power and control device may include one or more lights, such as light emitting diode (LED) lights, for example, to present cavitation control and upper power limit indications (e.g., yellow, green, and red) to a user.

[0022] Similar to electrocardiography (ECG) pads, the power and control device may utilize disposable ultrasound transducers which can be connected to the power and control device via some type of wired connection, and which can be discarded after use. The ultrasound transducers, as described above, can be placed onto the temporal bone area on both sides of a patient's head. The ultrasound transducer can be held in place using a gel-like temporary glue, such as that used for ECG pads, for example, as will be described in greater detail below. To provide sufficient conductivity between the ultrasound transducers and the patient's skin, hair may be removed at the location where the ultrasound transducers are applied. After the ultrasound transducers have been positioned, the power and control device can be powered on using the on/off switch. As described above, lights can be used in the control device to present certain indications to a user. For example, a yellow control light can be used to provide visual confirmation to the user that the control device is operative, e.g., transmitting sound waves (i.e., ultrasound beams). It should be noted that a default acoustic output power value can be set after turning the control device on, which can be in the milliWatts range (e.g., 20 mW).

[0023] Subsequent to powering on the power and control device, options may be provided to the user via, e.g., the main control display. A first option may be effectuated if the user chooses to press the Automated PCD Control button, where the power and control device can automatically increase the acoustic output power until the green control light illuminates. This green control light can be used as confirmation of the occurrence of stable cavitation of microbubbles. Stable cavitation is suggested as the underlying mechanism to trigger the biophysical effects mentioned above. Therefore, illumination of the green control light may represent the intended therapeutic activity or, in other words, the "therapeutic window." A red control light can indicate that this therapeutic window has been exceeded, for example. In this case, the acoustic output power will be decreased automatically until the red control light turns off and the green control light turns on.

[0024] A second option can be effectuated if the user chooses to press the Manual PCD Control button, where the power and control device can allow the user to increase the acoustic output power manually. As described above, manual acoustic output power can be chosen/adjusted up or down depending on one or more factors, e.g., the patient's age, sex, and/or race. During manual control, the user may, e.g., increase the acoustic output power and utilize the green control light as a gauge, where the green control light (as previously discussed) can indicate operation of the power and control device in a "proper" therapeutic window. If the acoustic output power is exceeded using the Manual PCD Control function, the power and control device can either shut down or switch back to a default setting (i.e., that indicated by a yellow control light as described previously).

[0025] The power and control device can further drive the ultrasound transducers, where power can be supplied by, e.g., a lithium polymer (LiPo) or similar battery (which can also power the aforementioned features and/or functionality of the power and control device). A power conversion control circuit can produce a desired ultrasound frequency. Another circuit of the power and control device can be used to control the output power level, which can consider input provided by a user pertaining to the patient, e.g., gender, race, and age. Still another circuit can be used to modulate the output frequency in such a way that intracranial ultrasound standing waves are prevented from occurring. Yet another circuit can be used to sense whether the ultrasound transducers are connected, functional, and/or energized.

[0026] As alluded to previously, the power and control device can be relatively small, for example, pocket/hand-held sized, and made of one or more materials that can withstand, e.g., hard use in environments like that experienced in an emergency response vehicle/scenarios in which an emergency response vehicle is needed. For example, the power and control device may be approximately the size of a hand-held digital multimeter, e.g., approximately 2 x 4 x 8 inches. Although, as described above, the battery can be rechargeable (e.g., a lithium polymer batter), it should be noted that the power and control device may alternatively, or additionally, have the ability to be operated directly from a stationary power source, such as a wall outlet. Additionally, the power and control device can be configured such that the battery is easily replaceable.

[0027] Also as previously alluded to, the power and control device may have one or more buttons, user interfaces, etc. that can allow a user to interact with the power and control device. Accordingly, the power and control device can have a control panel through which those various buttons and user interfaces can be implemented and/or presented for interaction, e.g., turning the device on/off; verifying that the ultrasound transducers are energized when appropriate; ascertaining how much battery life is left, automated adjustment of acoustic output power, and manual adjustment of acoustic power. Further, the power and control device may include, as part of the control panel or separate therefrom, the aforementioned control lights indicative of, e.g., cavitation control and upper power limit. The power and control device can further include one or more connector receptacles. A first connector receptacle may be configured for recharging the battery and/or operation from a wall outlet, while a second connector receptacle may be configured to receive a cable for connecting the ultrasound transducers to the power and control device.

[0028] A transmit signal can be generated by the power and control device using an oscillator circuit tuned to, e.g., a nominal 200 kHz continuous sine wave. The sine wave can be amplified to an appropriate power level, and this transmit signal can be applied to a switching circuit that alternates transmission between two sets of leads (one per ultrasound transducer), for example, every 100μs, in a case where the ultrasound transducers are positioned at the temporal bone on both sides of a patient's head. This transmit signal can be applied to the ultrasound transducers that have been positioned and secured to the head of the stroke patient via aforementioned cable. The switching circuit can create, for example, a 100μs on-time followed by a 100μs off-time for each ultrasound transducer, such that when one ultrasound transducer is in the on state, the other ultrasound transducer is in the off state. During the ultrasound transducer on state, the ultrasound transducer can transmit ultrasound energy through the patient's skull. During the ultrasound transducer off state, the ultrasound transducer can receive acoustic signals allowing it to be utilized as a passive cavitation detector, when ultrasound is applied in conjunction with an acoustically active agent.

[0029] Additionally still, the power and control device can include, e.g., two switches or actuators, although more or less switches may be included depending on need/desired level of control of operation. A first switch may be used to turn the power and control device on, and a second switch may be used to send the aforementioned transmit signal/voltage to the ultrasound transducers. Moreover, an input device such as a touchpad may be used to input patient information or further interact with the power and control device. When the ultrasound transducers are connected, but before they are energized, an indication that the ultrasound e transducer is connected and functional can be presented to a user. This may be a light or a message on the touchpad, for example. When the required preliminary conditions have been met (e.g., patient information, transducer functionality, etc.) then the user may energize the ultrasound transducers, and when this is done, an indicator can also show this condition.

[0030] Figure 4 illustrates an example schematic diagram of a power and control device 400 designed in accordance with various embodiments. The power and control device 400 may be powered by a battery power source, such as LiPo battery pack 405. Charging of the LiPo battery pack 405 can be performed by a direct current (DC) charging port 410. Additionally, the power and control device can be powered from, e.g., a wall outlet, via the DC charging port 410. The power and control device 400 can include a charger controller and gas gauge 415 (e.g., a BQ series charge controller/gas gauge) for monitoring cavitation as described in greater detail below, as well as a power converter 420. Further still, the power and control device 400 may have a touch screen display 425, such as an organic light emitting diode (OLED) touch screen display through which a user may be presented with various information/interact with the power and control device 400. As well, the power and control device 400 may include a signal generator 430, such as an arbitrary waveform generator (ARB) signal generator, a power amplifier 435, and a voltage standing wave ratio (VSWR) power monitor 440 for the generation/control/transmission of ultrasound as described herein. The power and control device 400 may also include one or more communications radio modules 445, which may be, e.g., a Bluetooth® radio, through which the aforementioned wireless communications can be effectuated. To allow connection of the ultrasound transducers to the power and control device 400, a probe connector(s) 450 may also be provided on the power and control device 400. Moreover, operation of the various functionality of the power and control device 400 described herein can be performed by a processor 455, which may be, e.g., an ARM3 core processor, or a combination of processors/controllers. It should be noted that more or less elements/modules/components can be included in the power and control device 400 in accordance with desired features and/or functionality. Moreover, the various elements/modules described herein can implemented as separate elements/modules, or combinations thereof.

[0031] As indicated previously, the therapeutic approach described herein can be based on the application of ultrasound either alone or in conjunction with an acoustically active agent, such as microbubbles, which relies on a stable cavitation mechanism. Furthermore, the utilization of the acoustically active agent, e.g., microbubbles, allows for the monitoring function described herein to be achieved. It should be noted that the term "microbubbles" can refer to an agent designed for diagnostic purposes to enhance image quality. It should be noted that as utilized herein, the term microbubbles is not meant to be restricted to merely their diagnostic application. Rather, and in accordance with various embodiments, the microbubble concept may additionally be applicable to agents not primarily designed for diagnostic purposes.

[0032] That is, diagnostic microbubbles can refer to spheres with an average diameter of, e.g., 2-3μm. The shell structure of such spheres or microbubbles can be either a phospholipid or human albumin, whereas the inside of such spheres may be filled with a perfluorocarbon gas. The agents can be administered, in accordance with various embodiments intravenously, e.g., via a peripheral vein, and are stabilized to pass through the lungs to enter arterial circulation. The half-life of such agents may be within the range of minutes.

[0033] When ultrasound waves are transmitted through a physical medium, the ultrasound waves can compress and stretch the molecular spacing of the physical medium, such as human tissue. Accordingly, and when a microbubble passes an ultrasound field it undergoes frequent pressure changes, leading to either bubble oscillation (i.e., stable cavitation) or bubble destruction (i.e., inertial cavitation). Whereas inertial cavitation might cause harm to human tissue, specifically the endothelial layer, stable cavitation has been shown to be effective with respect to clot lysis and improvement of tissue perfusion, stable cavitation occurs at lower ultrasound energies.

[0034] Referring back to the control lights implemented in the power and control device, a green control light can be illuminated when the therapeutic window has been reached, i.e., when stable cavitation can be detected. As inertial cavitation can require higher energies to occur, inertial cavitation may occur predominantly when energies might be increased beyond the therapeutic window. In this case, a red control light can be illuminated.

[0035] Referring back to the ultrasound transducers utilized for transmitting ultrasound, and to provide control over cavitation, the ultrasound transducers may be designed such that they are capable of detecting cavitation signals whenever they are not transmitting (e.g., in an off phase). The ultrasound transducers can further be designed to cover a bandwidth of, e.g., 100 – 300 kHz to capture a subharmonic frequency (0.5 x transmit frequency: 0.5x200kHz=100kHz), as well as a first ultraharmonic frequency (1.5 x transmit frequency: 1.5x200kHz=300kHz). Given this capability, cavitation can be detected and characterized by the device as being one of stable or inertial cavitation.

[0036] It should be noted that after the ultrasound transducers are in place on a patient's head, the intravenous infusion with microbubbles has been initiated, and the preferred or optimal acoustic output power has been chosen, it is contemplated that continuous insonation (application of ultrasound) be started at the earliest point possible, i.e., after first aid has been administered and the patient's vital functions have been stabilized. This could be either at the site of the emergency or during patient transport to a care facility. Furthermore, continuous insonation may last until further in-hospital diagnostic or therapeutic procedures are provided, the patient's symptoms are fully resolved, the patient's symptoms have worsened, and/or at any given point in time, a care-taking physician recognizes a significant medical indication to discontinue such treatment.

[0037] As described above, the ultrasound transducers can be positioned onto a patient's head via gel-pads using, e.g., a conductive gel, similar to that utilized for affixing ECG electrodes to a patient's chest wall. The ultrasound transducers may be positioned on either side of the patient's head, over the temporal bone region forward of the ears, or alternatively, on the very top of the head (vertex). The latter, alternative positioning may be preferable in certain scenarios as this transskull pathway may have advantages due to its specific acoustic properties.

[0038] Again, it is preferred that the ultrasound transducers are designed for a single-use application, and packaged so as to maintain sterility until use, although the ultrasound transducers can be designed for multiple-use applications as well. The transducer/gel-pad combination, being pliant, can conform to the shape of a patient's head/skull, and can aid in the transmission of the ultrasound energy/waves into a target region of the patient's brain. The conductive gel can have acoustic properties similar to, e.g., coupling gels used in ultrasonography. The portion of the gel-pad that contacts the patient's scalp may have a peel-away strip that will expose a layer of adhesive that can help keep the ultrasound transducer in place, and also aid in the transmission of ultrasound energy/waves by helping to eliminate potential air pockets, for instance, due to a patient's hair. Optionally, as previously indicated, shaving of the ultrasound transducer application area may be considered.

[0039] An ultrasound transducer itself can be contained in the gel-pad portion. The transducer can include a piezo-electric element (e.g., disc-shaped), approximately 3cm in diameter and 2mm thick. The piezo-electric material can be a material used for medical ultrasound, such as lead zirconate titanate (PZT), or any other suitable material. The piezo-electric material, also referred to as the crystal, can have both faces, but not necessarily the edge, coated with an electricity-conducting material, which can be referred to as the electrodes of the ultrasound transducer. The crystal may further have an insulating coating, over which a shield layer is applied. Wire leads, such as lightweight and flexible cable (twisted, shielded pair) can be attached (e.g., soldered) to the electrodes for the purpose of conducting electricity to the crystal, and the subsequent generation of ultrasound energy. It should be noted that other materials may be used for additional coatings as required, such as a quarter-wave matching layer on a side of the crystal nearest the patient to aid in energy transmission, a backing layer on the side of the crystal away from the patient, a shielding layer to prevent electro-magnetic interference (EMI), and/or another insulating coating to prevent inadvertent shocking of the patient.

[0040] Designed for single use, as described above, the ultrasound transducers need not require any housing material or special connectors. Rather, the ultrasound transducers can be integrated into, e.g., a low-profile and lightweight plastic bag that has dimensions slightly larger than the ultrasound transducers themselves. One side of the plastic bag may contain a dispenser for the adhesive coupling gel, and another side may have an air pocket to provide air-backing for the ultrasound transducers. Such a package can be sealed within a disposable envelope or similar enclosure to maintain sterility. Upon use, the disposable envelope can be opened and an ultrasound transducer removed. An additional membrane/peel-away strip can be removed from one side of the ultrasound transducer to expose the adhesive and coupling gel, and the ultrasound transducer may be applied to a selected area on a patient's head.

[0041] The ultrasound transducers can fit inside the gel-pads in such a way that some thickness of gel can be maintained between the energy-emitting face of the ultrasound transducer and the patient's scalp. This may be accomplished for instance, by incorporating a sleeve in the gel pad into which the ultrasound transducer can be inserted during the manufacturing process. The electrode leads of the ultrasound transducer can exit the gel-pad in such a way that they are secured against inadvertent snagging and breakage during emergency deployment. A cable can be used to connect the electrode leads to the aforementioned power and control device.

[0042] It should be noted that in accordance with another embodiment, the ultrasound transducers can be implemented in a headband, where the electrode leads can exit the gel-pad portions of the headband, and may be incorporated into the headband material to secure against inadvertent snagging and breakage during emergency deployment. The leads from each of the ultrasound transducers may terminate at a convenient portion of the headband, such as the portion positioned over the back of the head. This termination may be a connector built into the headband, or may be a length of cable that terminates in a connector. Another cable, separate from the headband, can be used to connect the headband to the power and control device.

[0043] Figure 3 illustrates an example configuration of the ultrasound transducers and power and control device, as well as the use thereof. Figure 3 illustrates a power and control device 300. As previously described, the power and control device can be relatively small, battery powered, and have wireless communication functionality, and can power and control ultrasound transducers. Connected to the power and control device are ultrasound transducers 310 shown as being attached to the head of a patient 320. Again, the ultrasound transducers 310 can be connected to either side of the head of the patient 320 via a gel-pad. The ultrasound transducers, including ultrasound transducer 310 may be connected to the power and control unit via cables 330.

[0044] The ultrasound transducers themselves may be designed to operate at a frequency of 200 kHz, or in a band of frequencies centered about 200 kHz. Again, the acoustic field at such frequencies is not necessarily subject to distortion when passing through the skull, as is the case with higher frequencies in the MHz range. As a result, the acoustic field that is applied to the brain may be designed according to known physical principles with a high degree of predictability. Additionally, the ultrasound transducers can be configured as, e.g., flat unfocussed disks with a diameter between, e.g., 2 cm and 3 cm, resulting in a radius of, e.g., 1 cm and 1.5cm, respectively.

[0045] In acoustic terms, the radius of an ultrasound transducer is typically represented as $\boldsymbol{a}$. The acoustic field emanating from such an ultrasound transducer is essentially columnar until it travels a distance ***d***, when it begins to spread in a conical fashion. The distance ***d*** is also known as the far-field transition, and can be represented by the following equation:

$$d = \frac{a^2}{\lambda}$$

where $\boldsymbol{\lambda}$ is the wavelength of the ultrasound wave. In water and body tissue at 200 kHz, $\boldsymbol{\lambda}$ can be approximately 0.75 cm. Hence, and for an ultrasound transducer with a radius of, e.g., 1 cm, the distance ***d*** is approximately 1.3cm, and for a radius of 1.5 cm, the distance ***d*** is 3cm.

[0046] Past distance ***d***, the acoustic energy of an ultrasound wave can spread in a conical shape that is subtended by an angle $\boldsymbol{\theta}$, the angle between the acoustic axis and one side of the conical shape. This angle $\boldsymbol{\theta}$ may be calculated by the following equation:

$$\theta = \tan^{-1}\left(\frac{a}{d}\right)$$

[0047] It can be seen from these equations that for a given ultrasound frequency, the acoustic beam shape is primarily controlled by the radius of the ultrasound transducer. Beam shape in turn, can determine the peak intensity of the acoustic field. As the radius of the beam expands according to the angle $\boldsymbol{\theta}$, the beam intensity decreases as the square of the radius. The beam intensity can also decrease with distance due to attenuation by the brain tissue. Such effects can be a factor regarding the safety and possibility of creating standing waves (discussed in greater detail below) in the cranial region of a patient.

[0048] The following example illustrates the design, operation and inherent safety of various embodiments. An ultrasound transducer of radius 1.5cm has a transition distance of 3cm, which can be the point of peak acoustic intensity, inasmuch as beyond this distance, the beam transmitted by the ultrasound transducer becomes wider. If the acoustic output power of the ultrasound transducer has been adjusted to produce, e.g., 600 mW/cm^2 acoustic intensity at this point of peak acoustic intensity, at a 5cm depth, the acoustic intensity can drop off to less than 300 mW/cm^2, and at 6cm, the acoustic intensity can drop off to approximately 125 mW/cm^2. Given an average skull diameter of 16cm, the acoustic intensity of the beam can be on the order of 20 mW/cm^2 by the time it reaches the opposite skull surface. Any standing waves generated by reflection at the contralateral interior skull surface should be of negligible amplitude. And yet, the intensity of the ultrasound energy that is most likely to have a therapeutic effect is contained in the clinically relevant depth of 30-60 cm on the ipsilateral side of the brain midline.

[0049] Further to the above, a pulse duration of between 10-10000μs may be contemplated, with a 1-50% duty cycle, at a frequency of 200 kHz (a convenient paradigm in another sense because the wavelength for this frequency is approximately 7.5mm in soft tissue). A 20-cycle burst, given, for example, a pulse duration of 100μs, and a duty cycle of 50%, would be 15cm in total length, or nearly the diameter of the average cranium from one temporal bone to the other. If the two ultrasound transducers alternate active times, previously referred to as on-time, the acoustic field of a first ultrasound transducer would be much diminished by the time the energy of the second ultrasound transducer passes through, thus minimizing any likelihood of creating standing waves. As described above, to provide this alternating activity, the power and control device may utilize a switching circuit to switch, e.g., a 200 kHz CW signal from one set of conductors to another set every 100μs to create alternating 20 cycle bursts between the ultrasound transducers. It should be noted that the same or similar considerations are applicable in an embodiment where a single ultrasound transducer is utilized and positioned at the vertex of a patient's head.

[0050] Regarding the application of an acoustically active agent in accordance with one embodiment, and as described above, the ultrasound transducers have the capability to receive acoustic signals during an off-time. Relying on stable cavitation as the underlying mechanism to achieve the aforementioned biophysical effects, and relying on inertial cavitation used as a control and safety measure, the ultrasound transducers may have a minimum bandwidth between 100 – 300 kHz. This range has been chosen, as also described above, to capture the subharmonic frequency (100 kHz) as well as the ultraharmonic frequency (300kHz). The occurrence of both frequencies indicates the presence of stable cavitation, and therefore, describes the individual therapeutic window. The occurrence of primary inertial cavitation may be characterized by a combination of an increased area under the curve of the fundamental frequency (at 200 kHz) and a raise of the noise floor. Sub and ultra-harmonic frequencies may still be present, but are not dominant. Should inertial cavitation be detected by the ultrasound transducers, the power and control device can be configured to automatically lower acoustic output until only stable cavitation can be detected (i.e., the Automated PCD Control button). Alternatively, the power and control device can be configured to shut down instantaneously or automatically reset to its preset mode (i.e., the Manual PCD Control button).

[0051] Figure 6 illustrates example processes performed to treat victims of stroke or stroke-like events in the field in accordance with various embodiments. At 600, ultrasound energy is non-invasively applied to a cranium of a patient via first and second ultrasound transducers attached as disparate locations about the cranium of the patient. At 610, application of the ultrasound energy is controlled such that the first and second ultrasound transducers alternately apply the ultrasound energy in pulses to the cranium of the patient, wherein the non-invasive application of the ultrasound energy occurs in the field. Optionally, at 620, the application of the ultrasound energy can be performed in conjunction with intravenously administering an acoustically active agent to the patient. For example, and as described herein, the administration of, e.g., microbubbles, and stable cavitation caused by the application of ultrasound energy at particular levels can promote lysis, restoration of arterial flow, etc.

[0052] Additionally, the design of the ultrasound transducers in accordance with various embodiments can provide a guaranteed minimum half-life of 24 hours. For subacute/chronic applications, the requirements for the ultrasound transducers half-life might be different in the sense of longer term durability, assuming proper care and maintenance in a controlled environment (e.g., hospital, rehabilitation center, or retirement home).

[0053] Regarding macrocirculation, there is evidence that ultrasound-induced clot lysis to recanalize a vessel can be improved in combinational use with ultrasound microbubbles. Thus, and in accordance with still another embodiment, ultrasound sequences can be built into the power and control device for the use of microbubbles during ultrasound exposure. The microbubble compounds used for this purpose can be standard, commercially available agents which are primarily used for diagnostic purposes or agents which are specifically developed for the purpose of ultrasound enhanced clot lysis.

[0054] As to microcirculation, there is growing evidence that ultrasound in combination with microbubbles may induce the release of nitric oxide from endothelial cells, resulting in a vasodilatative effect, which in turn can result in improved tissue perfusion. In accordance with another embodiment, microcirculation techniques can be incorporated into the various embodiments previously described to improve the tissue perfusion through mechanical and biochemical vasodilatation.

[0055] It should be noted that the various embodiments disclosed herein for treating stroke victims are also applicable to other ischemic diseases caused by embolic or thrombo-embolic events, such as myocardial infarction (MI) or deep vein thrombosis (DVT). That is, the underlying cause for all these diseases is the sudden occlusion of a vessel by a blood clot with the consequence of consecutive cell death in the supplied area due to lack of oxygen supply. All of these diseases have in common, the acuity of onset and the need for a therapeutic option at the earliest time point possible. Hence, a treatment which could be provided at the site of emergency and/or during transport to a care facility would be advantageous. Accordingly, various embodiments can include alternative ultrasound transducer designs, as well as ultrasound sequences, that may be dedicated for application to other ischemic diseases, such as MI or DVT. Moreover, various embodiments may be utilized to address ischemic diseases in almost any organ system.

[0056] Further still, and beyond application in acute ischemic diseases, various embodiments disclosed herein may also be used as a long-term, recurrent treatment option, for example, in patients suffering from subacute/chronic ischemic diseases. Such patients may include those with chronic ischemic white matter disease, patients suffering from vascular dementia or post stroke patients. In these patient populations, various embodiments could be utilized, for example, during hospitalization, during rehabilitation, or as a regular treatment at private homes or in retirement facilities. The use of various embodiments may further be utilized in the context of neurodegenerative diseases, such as Alzheimer's or Parkinson's disease, following a similar approach. That is, various embodiments disclosed herein are contemplated for use in the treatment of any subacute or chronic brain-diseased patients for whom improved tissue perfusion, the potential stimulation of stem cell proliferation, neuromodulation or the induction of chaperone protein release could be beneficial. Various embodiments may also be utilized in various neurological applications, e.g., the treatment of seizures or neuropsychiatric diseases (e.g. schizophrenia, depression).

[0057] Other embodiments may include monitoring or feedback functionality at the power and control device, for example, to establish, e.g., the time of vessel recanalization or improvement of tissue perfusion. Still other embodiments may include one or more sensing elements into the transducer/gel-pad combination, such as infrared lasers or cavitation receivers, to monitor, e.g., the improvement of tissue perfusion during the procedure, or to prevent exceeding safety limits by cavitation detection.

[0058] As alluded to above, the power and control device may have wireless functionality. Such wireless functionality may encompass wireless communication between, e.g., paramedic teams in the field and medical personal in a receiving care facility, where such communications have conventionally been sparse. Still other embodiments may utilize the wireless communication capabilities for the transmission of real-time data from the power and control device (e.g., data regarding/associated with the aforementioned monitoring/feedback functionality) directly to an allocated server at the receiving care facility, or to a portable computing device using a variety of wireless communication technologies, including for example, but not limited to 2G (e.g., Global System for Mobile Communications (GSM), etc.), 2.5G (e.g., General Packet Radio Service (GPRS), etc.), 3G (e.g., Enhanced Data for GSM Evolution (EDGE), Wideband Code Division Multiple Access (WDMA), CDMA2000, etc.), and 4G (e.g., LTE, WiMAX, etc.) technologies, and Bluetooth®.

[0059] Further still, the functionality disclosed herein and described as being implemented utilizing ultrasound transducers connectable to and powered by a power and control device can be implemented in existing devices, such as existing diagnostic ultrasound devices. Moreover, recent research in the field of local drug delivery involves the delivery of therapeutic agents at a target site. In particular, certain research suggests using microbubbles as transport vehicles, and ultrasound as a source to release these therapeutic agents at the target site. For example, certain research has been focused on the beneficial effect of oxygen carriers for tissue preservation and neuroprotection. Accordingly, various embodiments may implement dedicated ultrasound sequences allowing the methods and apparatuses disclosed herein for the delivery of drugs locally, or to enhance the effect of oxygen carriers.

[0060] As described herein, various embodiments provide methods and apparatuses to initiate stroke treatment in the field and/or during the transport of a patient to a care facility, as well as for other diseases, and for more prolonged use, such as in rehabilitation scenarios. Various embodiments may be adjusted, e.g., automatically, to an individual "therapeutic window" for each patient, often a crucial factor due to significant differences in skull morphology between humans of different age, gender, and/or race. Further, various embodiments can be utilized for ultrasound transmission in combination with the use of acoustically active agents, such as microbubbles, where stable cavitation is an underlying mechanism for both the therapeutic application as well as its control.

[0061] Accordingly, the millions of patients who suffer from acute stroke-like syndromes can be treated, worldwide, for whom therapeutic options to-date do not exist. Additionally still, use of this approach can be incorporated into a future Standard of Care for the treatment of acute stroke in the field, much like the defibrillator has become the Standard of Care for cardioconversion. The potential for reduction in delays experienced in the treatment of acute stroke in both rural and metropolitan areas is significant, as illustrated in Figure 5. In a metropolitan area, for example, an emergency 911 call may be received, and 10 minutes may pass until emergency medical services (EMS) personnel arrive at the site where a patient has experienced a stroke/stroke-like event. Application of ultrasound/ultrasound in conjunction with microbubbles, for example, in accordance with various embodiments can be accomplished in the field within, e.g., 5 minutes thereafter. Admission to a care facility may occur 10 minutes after that. Hence, in this example, at least 10 minutes can be saved during which a dramatic reduction in tissue damage can be effectuated. In a rural environment, arrival of EMS personnel may not occur until 45 minutes after an initial emergency 911 call. Again, within 5 minutes, the application of ultrasound alone or in conjunction with microbubbles can occur in accordance with various embodiments. In such a rural scenario, admission to a care facility may not occur for another 115 minutes thereafter. In this instance, it can be appreciated that 115 minutes during which tissue damage due to stroke can be avoided through the utilization of various embodiments.

[0062] The various diagrams illustrating various embodiments may depict an example architectural or other configuration for the various embodiments, which is done to aid in understanding the features and functionality that can be included in those embodiments. The present disclosure is not restricted to the illustrated example architectures or configurations, but the desired features can be implemented using a variety of alternative architectures and configurations. Indeed, it will be apparent to one of skill in the art how alternative functional, logical or physical partitioning and configurations can be implemented to implement various embodiments. Also, a multitude of different constituent module names other than those depicted herein can be applied to the various partitions. Additionally, with regard to flow diagrams, operational descriptions and method claims, the order in which the steps are presented herein shall not mandate that various embodiments be implemented to perform the recited functionality in the same order unless the context dictates otherwise.

[0063] It should be understood that the various features, aspects and/or functionality described in one or more of the individual embodiments are not limited in their applicability to the particular embodiment with which they are described, but instead can be applied, alone or in various combinations, to one or more of the other embodiments, whether or not such embodiments are described and whether or not such features, aspects and/or functionality is presented as being a part of a described embodiment. Thus, the breadth and scope of the present disclosure should not be limited by any of the above-described exemplary embodiments.

[0064] Terms and phrases used in this document, and variations thereof, unless otherwise expressly stated, should be construed as open ended as opposed to limiting. As examples of the foregoing: the term "including" should be read as meaning "including, without limitation" or the like; the term "example" is used to provide exemplary instances of the item in discussion, not an exhaustive or limiting list thereof; the terms "a" or "an" should be read as meaning "at least one," "one or more" or the like; and adjectives such as "conventional," "traditional," "normal," "standard," "known" and terms of similar meaning should not be construed as limiting the item described to a given time period or to an item available as of a given time, but instead should be read to encompass conventional, traditional, normal, or standard technologies that may be available or known now or at any time in the future. Likewise, where this document refers to technologies that would be apparent or known to one of ordinary skill in the art, such technologies encompass those apparent or known to the skilled artisan now or at any time in the future.

[0065] Additionally, the various embodiments set forth herein are described in terms of exemplary block diagrams, flow charts and other illustrations. As will become apparent to one of ordinary skill in the art after reading this document, the illustrated embodiments and their various alternatives can be implemented without confinement to the illustrated examples. For example, block diagrams and their accompanying description should not be construed as mandating a particular architecture or configuration.

[0066] Moreover, various embodiments described herein may be described in the general context of method steps or processes, which may be implemented in one embodiment by a computer program product, embodied in, e.g., a non-transitory computer-readable memory, including computer-executable instructions, such as program code, executed by computers in networked environments. A computer-readable memory may include removable and non-removable storage devices including, but not limited to, Read Only Memory (ROM), Random Access Memory (RAM), compact discs (CDs), digital versatile discs (DVD), etc. Generally, program modules may include routines, programs, objects, components, data structures, etc. that perform particular tasks or implement particular abstract data types. Computer-executable instructions, associated data structures, and program modules represent examples of program code for executing steps of the methods disclosed herein. The particular sequence of such executable instructions or associated data structures represents examples of corresponding acts for implementing the functions described in such steps or processes.

[0067] As used herein, the term module can describe a given unit of functionality that can be performed in accordance with one or more embodiments. As used herein, a module might be implemented utilizing any form of hardware, software, or a combination thereof. For example, one or more processors, controllers, ASICs, PLAs, PALs, CPLDs, FPGAs, logical components, software routines or other mechanisms might be implemented to make up a module. In implementation, the various modules described herein might be implemented as discrete modules or the functions and features described can be shared in part or in total among one or more modules. In other words, as would be apparent to one of ordinary skill in the art after reading this description, the various features and functionality described herein may be implemented in any given application and can be implemented in one or more separate or shared modules in various combinations and permutations. Even though various features or elements of functionality may be individually described or claimed as separate modules, one of ordinary skill in the art will understand that these features and functionality can be shared among one or more common software and hardware elements, and such description shall not require or imply that separate hardware or software components are used to implement such features or functionality.

Where components or modules of the invention are implemented in whole or in part using software, in one embodiment, these software elements can be implemented to operate with a computing or processing module capable of carrying out the functionality described with respect thereto. The presence of broadening words and phrases such as "one or more," "at least," "but not limited to" or other like phrases in some instances shall not be read to mean that the narrower case is intended or required in instances where such broadening phrases may be absent.

WHAT IS CLAIMED IS

1. A method, comprising:

non-invasively applying ultrasound energy to a cranium of a patient via first and second ultrasound transducers attached at disparate locations about the cranium of the patient; and

controlling application of the ultrasound energy such that the first and second ultrasound transducers alternately apply the ultrasound energy in pulses to the cranium of the patient, wherein the non-invasive application of the ultrasound energy occurs in the field.

2. The method of claim 1, wherein the non-invasive application of the ultrasound energy occurs in the field and prior to arrival of the patient at a care facility.

3. The method of claim 1, wherein the disparate locations about the cranium of the patient comprise temporal bone regions forward of the ears of the patient.

4. The method of claim 1 further comprising, intravenously administering an acoustically active agent to the patient.

5. The method of claim 4, wherein the acoustically active agent comprises microbubbles.

6. The method of claim 4 further comprising, exciting the acoustically active agent by the ultrasound energy to cause stable cavitation, and detecting a state of inertial cavitation of the acoustically active agent as an indication that the application of the ultrasound energy has exceeded a level commensurate with a therapeutic window.

7. The method of claim 6, wherein the controlling of the application of the ultrasound energy comprises controlling an output power of the ultrasound energy such that stable cavitation is maintained, the stable cavitation triggering a plurality of biophysical effects in the patient.

8. The method of claim 7, wherein the controlling of the output power of the ultrasound energy is performed either automatically or manually.

9. The method of claim 8 further comprising, performing the automatic control of the output power of the ultrasound energy in accordance with at least one of patient-specific characteristics

10. The method of claim 9, wherein the at least one of the patient-specific characteristics comprises age, gender, race, skull bone characteristics, and morphology.

11. The method of claim 6 further comprising, reducing an output power of the ultrasound energy upon the acoustically active agent reaching the state of inertial cavitation.

12. The method of claim 1 further comprising, performing the non-invasive application of the ultrasound energy and the controlling of the application of the ultrasound energy to counteract effects of at least one of, myocardial infarction, deep vein thrombosis, and a cerebrovascular accident due to ischemia.

13. The method of claim 1, wherein each of the first and second ultrasound transducers are connected via cables to a portable, battery-operated power and control device, and wherein the first and second ultrasound transducers comprise one of single-use ultrasound transducers and multiple-use ultrasound transducers.

14 The method of claim 13, wherein the single-use ultrasound transducers comprise disk-shaped piezo-electric elements.

15. The method of claim 13, wherein the single-use ultrasound transducers operate at either a frequency of 200 kHz or in a band of frequencies centered about 200 kHz, and wherein the single-use ultrasound transducers receive acoustic signals in a minimum bandwidth between 100 to 300 kHz.

16. An apparatus, comprising:

a first ultrasound transducer element;

a second ultrasound transducer element; and

a power and control module, the power and control module being portable and battery-operated, and generating ultrasound energy to be transmitted in an alternating and pulsed fashion by the first and second ultrasound transducer elements, noninvasively, to the skull of a patient.

17. The apparatus of claim 16, wherein the power and control module further comprises circuitry for the generation of the ultrasound energy at an acoustic output power level and frequency to cause at least one of stable cavitation and inertial cavitation of an acoustically active agent.

18. The apparatus of claim 16, wherein the first and second ultrasound transducer elements comprise disk-shaped piezo-electric elements operative at either a frequency of 200 kHz or in a band of frequencies centered about 200kHz.

19. The apparatus of claim 18, wherein each of the disk-shaped piezo-electric elements have a diameter ranging from 2 to 3 cm, a radius ranging from 1 to 1.5cm, and a thickness of 2mm.

20. The apparatus of claim 18, wherein two faces of each of the disk-shaped piezo-electric elements are coated with an electricity-conducting material comprising electrodes of each of the first and second ultrasound transducer elements.

21. The apparatus of claim 20, wherein the two faces of each of the disk-shaped piezo-electric elements are coated with at least one of a quarter-wave matching layer on a side facing the patient to aid in energy transmission, a backing layer on a side facing away from the patient, a shielding layer preventing electro-magnetic interference, and an insulating coating preventing inadvertent shock to the patient.

22. The apparatus of claim 16, wherein each of the first and second ultrasound transducer elements comprise flat, unfocused disks.

23. The apparatus of claim 16, wherein each of the first and second ultrasound transducer elements are driven by the power and control module with a pulse duration between 10 to 1000 μs and a duty cycle between 1 to 50%.

24. The apparatus of claim 16, wherein each of the first and second ultrasound transducer elements receive acoustic signals from within the skull of the patient to detect whether a response of the acoustically active agent administered to the patient is stable cavitation or inertial cavitation.

25. The apparatus of claim 16, wherein each of the first and second ultrasound transducer elements is operative within a minimum bandwidth in the range of 100 to 300 kHz.

26. The apparatus of claim 16, wherein each of the first and second ultrasound transducer elements are configured to capture a subharmonic frequency and a first ultraharmonic frequency.

27. The apparatus of claim 26, wherein the subharmonic frequency is 100 kHz and the ultraharmonic frequency is 300 kHz.

28. The apparatus of claim 16, wherein each of the first and second ultrasound transducer elements are designed for single-use application and packaged so as to maintain sterility until used.

29. The apparatus of claim 16, wherein each of the first and second ultrasound transducer elements are contained in a gel-pad portion, the gel-pad portion being pliant to conform to the shape of the skull of the patient, and aiding in transmission of the ultrasound energy into a target region of the brain of the patient.

30. The apparatus of claim 29, wherein a section of the gel-pad portion contacting the scalp of the patient comprises a peel-away strip configured to expose a layer of adhesive to maintain each of the first and second ultrasound transducer elements in place.

31. The apparatus of claim 16, where each of the first and second ultrasound transducer elements have a minimum half-life of twenty-four hours.

32. The apparatus of claim 1, wherein the power and control module comprises a switching circuit in which a 200 kHz continuous wave signal is switched from one set of conductors to another set of conductors at predefined timepoints to create alternating bursts from the first and second ultrasound transducer elements.

33. The apparatus of claim 32, wherein the predefined timepoints occur at every 100μs.

34. The apparatus of claim 32, wherein a transmit signal is generated using an oscillation circuit tuned to a nominal 200 kHz continuous sine wave.

35. The apparatus of claim 34, wherein the 200 kHz continuous sine wave is amplified to an appropriate power level, and applied to the switching circuit.

36. The apparatus of claim 32, wherein the switching circuit creates an on time followed by an off time for each of the first and second ultrasound transducer elements, such that when one of the first and second ultrasound transducer elements is in an on state, the other of the first and second ultrasound transducer elements is in an off state.

37. The apparatus of claim 36, wherein the on and off times comprise 100μs periods.

38. The apparatus of claim 36, wherein the one of the first and second ultrasound transducer elements in the on state transmits the ultrasound energy through the skull of the patient, and the

other of the first and second ultrasound transducer elements in the off state receives acoustic signals and is utilized as a passive cavitation detector.

39. The apparatus of claim 16 further comprising, two cables, each of which operatively connect each of the first and second ultrasound transducer elements to the power and control module.

40. The apparatus of claim 16, wherein the power and control module further comprises a control display for displaying visual information to a user of the apparatus.

41. The apparatus of claim 16, wherein the power and control module is configured to verify that each of the first and second ultrasound transducers are energized.

42. The apparatus of claim 16, wherein the power and control module is configured to allow for automated adjustment of acoustic output power of the ultrasound energy.

43. The apparatus of claim 16, wherein the power and control module is configured to allow for manual adjustment of acoustic output power of the ultrasound energy.

44. The apparatus of claim 16, wherein the power and control module comprises three lights for indicating cavitation control and an upper power limit of the ultrasound energy.

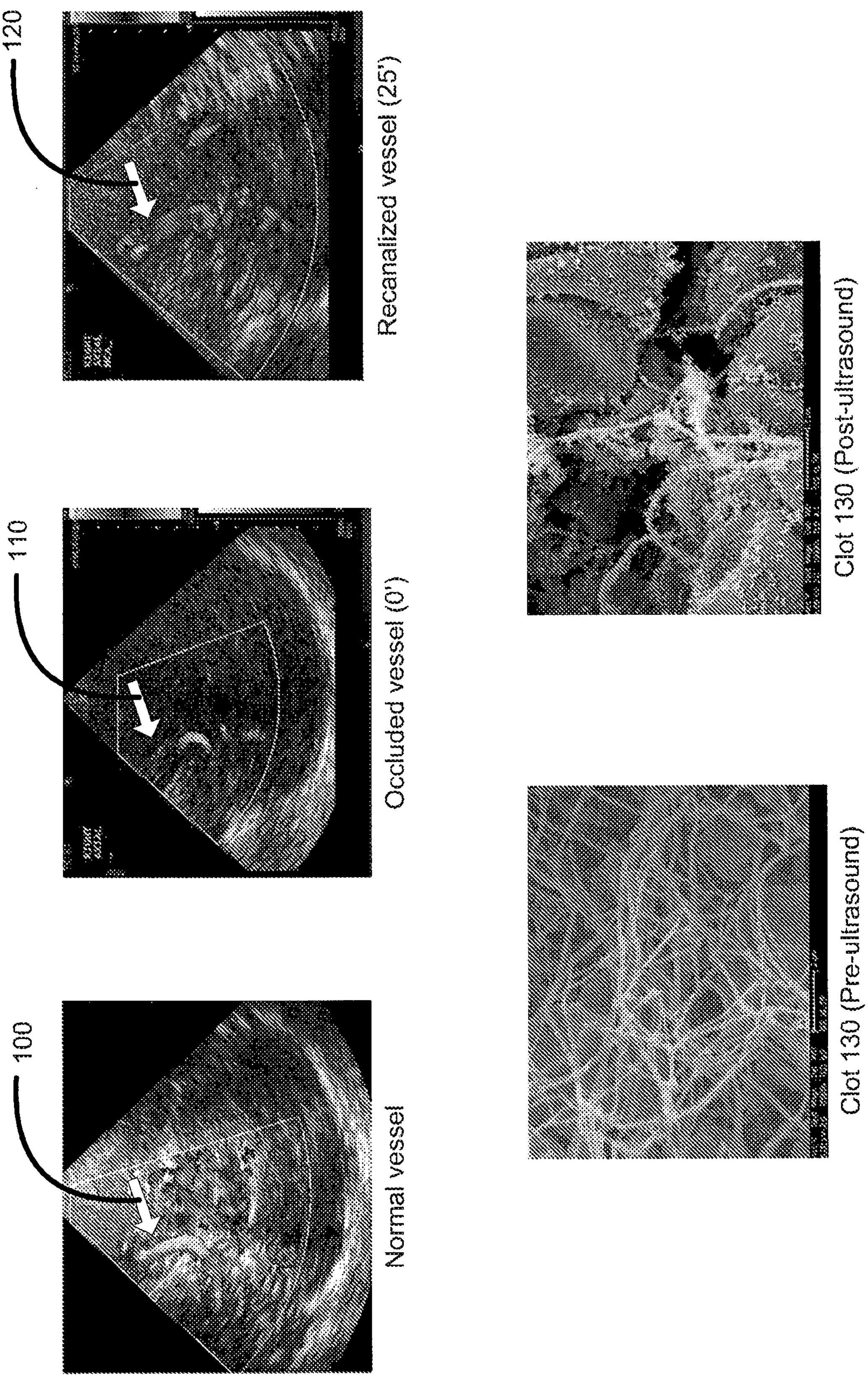
100
Normal vessel
110
Occluded vessel (0')
120
Recanalized vessel (25')
Clot 130 (Pre-ultrasound)
Clot 130 (Post-ultrasound)

Figure 1

200

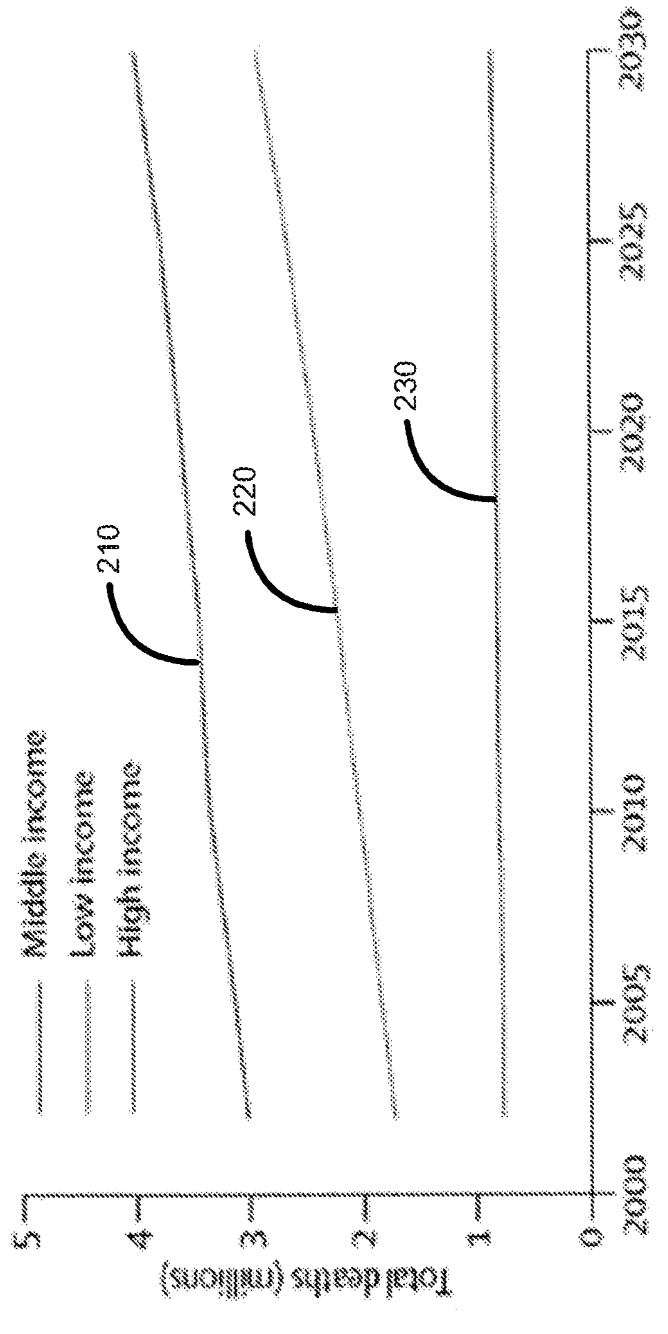
Middle income
Low income
High income
Total deaths (millions)
0
1
2
3
4
5
2000
2005
2010
2015
2020
2025
2030
210
220
230

Figure 2

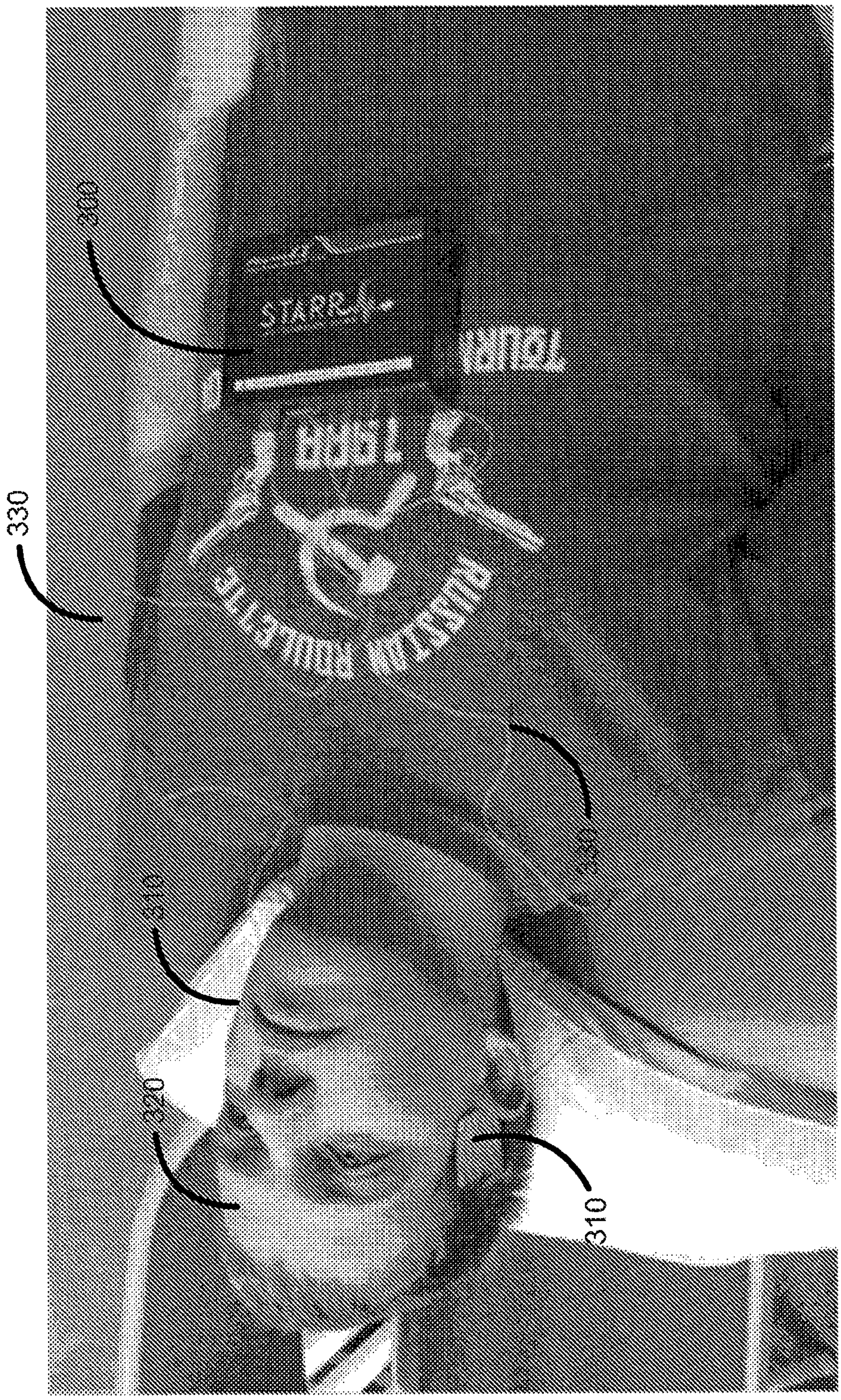

Figure 3

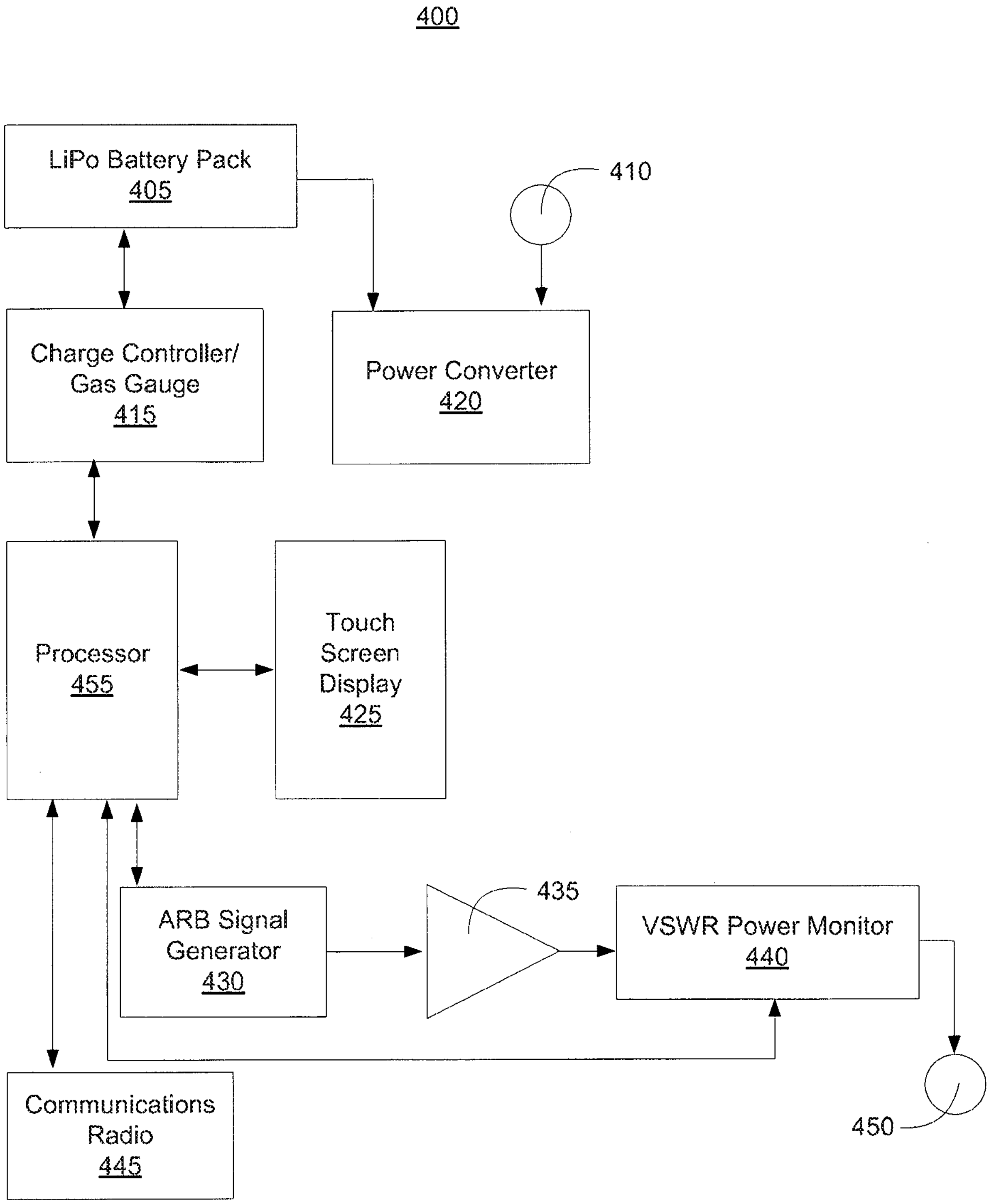
400
LiPo Battery Pack
405
410
Charge Controller/
Gas Gauge
415
Power Converter
420
Processor
455
Touch
Screen
Display
425
ARB Signal
Generator
430
435
VSWR Power Monitor
440
Communications
Radio
445
450

Figure 4

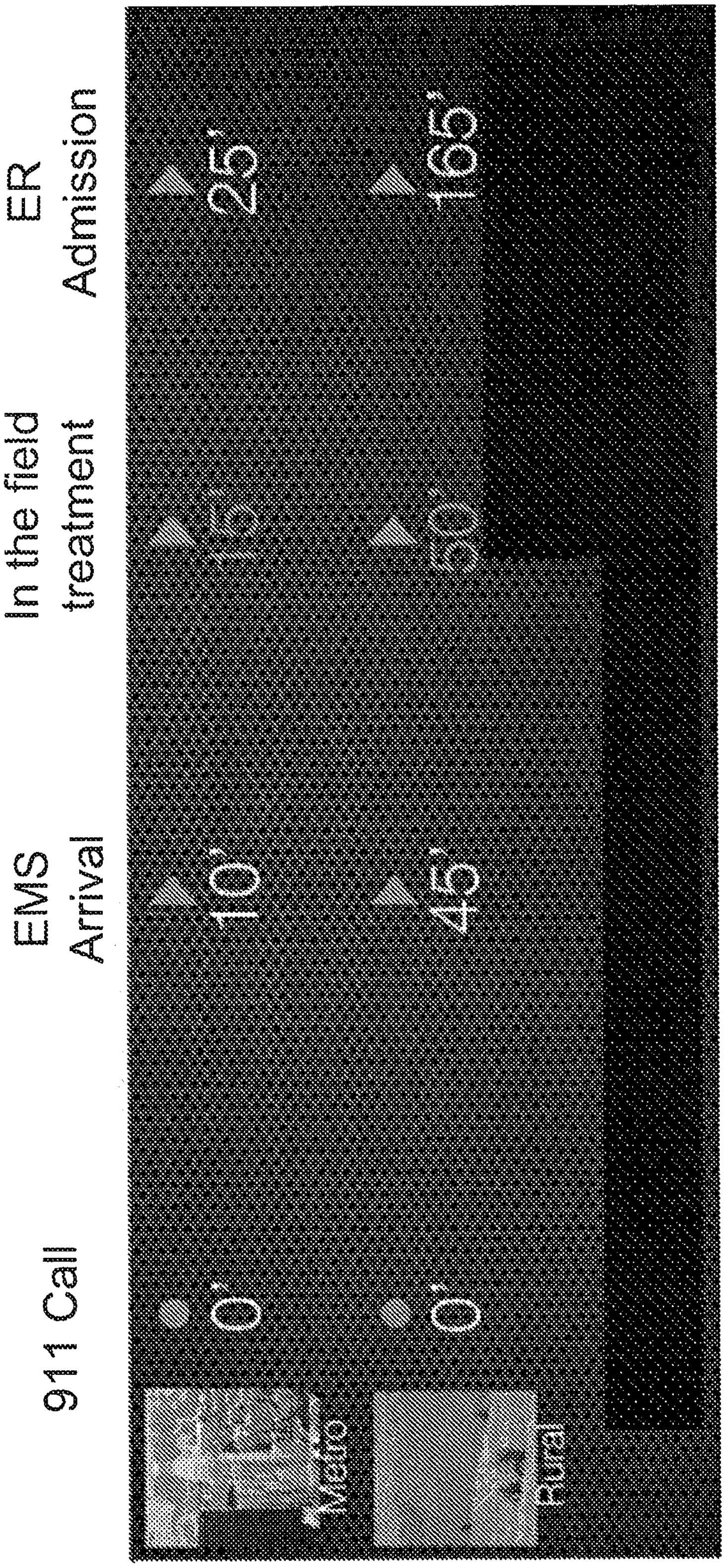
911 Call
EMS Arrival
In the field treatment
ER Admission
Metro
0'
10'
15'
25'
Rural
0'
45'
50'
165'

Figure 5

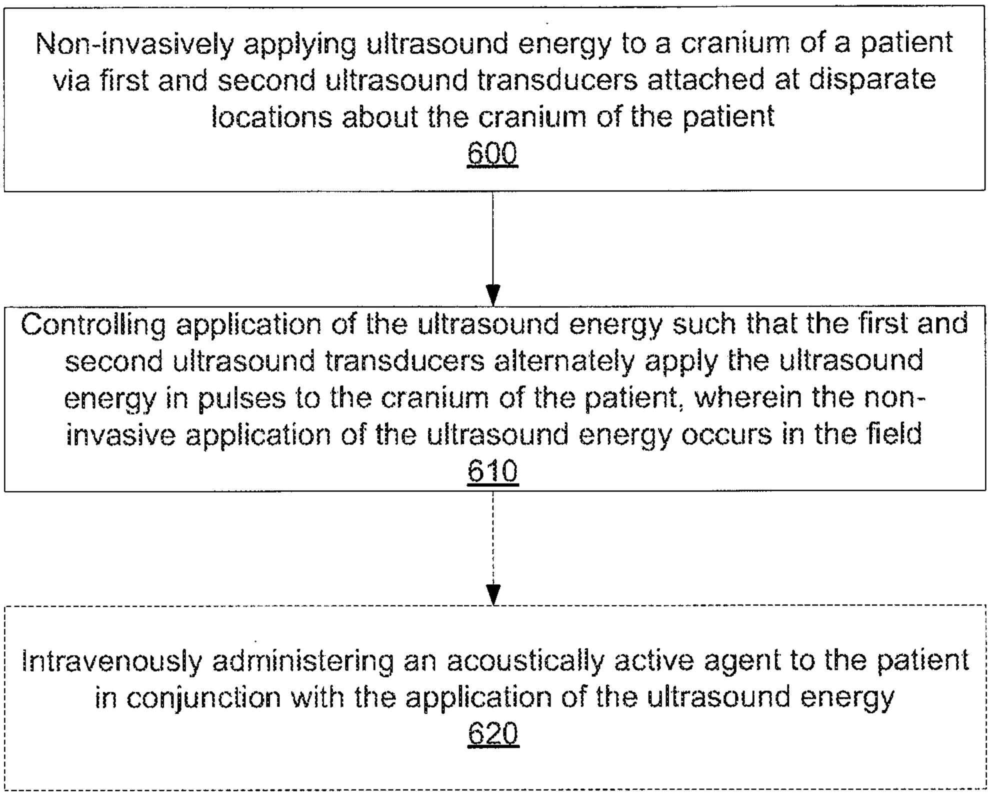
Non-invasively applying ultrasound energy to a cranium of a patient via first and second ultrasound transducers attached at disparate locations about the cranium of the patient
600
Controlling application of the ultrasound energy such that the first and second ultrasound transducers alternately apply the ultrasound energy in pulses to the cranium of the patient, wherein the non-invasive application of the ultrasound energy occurs in the field
610
Intravenously administering an acoustically active agent to the patient in conjunction with the application of the ultrasound energy
620

Figure 6

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2013/040664

A. CLASSIFICATION OF SUBJECT MATTER

A61N 7/00(2006.01)i, A61H 23/02(2006.01)i

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)
A61N 7/00; A61B 18/00; A61B 5/055; A61H 23/02

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
Korean utility models and applications for utility models
Japanese utility models and applications for utility models

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
eKOMPASS(KIPO internal) & Keywords: ultrasound transducer, portable battery, piezo-electric

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X A	US 2012-0083718 A1 (ALLEMAN, A. J. et al.) 5 April 2012 See abstract; paragraphs 119, 129, 142, and 217; claims 1, 7, and 15.	16,17,22-44 18-21
A	US 2011-0112394 A1 (MISHELEVICH, D. J.) 12 May 2011 See abstract; paragraph 25; claims 1, 2, and 5.	16-44
A	US 2012-0083717 A1 (ALLEMAN, A. J. et al.) 5 April 2012 See abstract; claims 1-3.	16-44
A	US 2008-0033297 A1 (SLIWA, J. W.) 7 February 2008 See abstract; claims 1 and 10.	16-44
A	US 5601526 A (CHAPELON, J. Y. et al.) 11 February 1997 See abstract; claim 1.	16-44

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"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	Date of mailing of the international search report
05 September 2013 (05.09.2013)	**06 September 2013 (06.09.2013)**

Name and mailing address of the ISA/KR
Korean Intellectual Property Office
189 Cheongsa-ro, Seo-gu, Daejeon Metropolitan City, 302-701, Republic of Korea
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Authorized officer
HAN In Ho
Telephone No. +82-42-481-3362

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2013/040664

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 1-15
   because they relate to subject matter not required to be searched by this Authority, namely:
   Claims 1-15 pertain to methods for treatment of the human and thus relate to a subject-matter which this International Searching Authority is not required, under Article 17(2)(a)(i) of the PCT and Rule 39.1(iv) of the Regulations under the PCT, to search.

2. ☐ Claims Nos.:
   because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
   because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required addtional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/US2013/040664

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2012-0083718 A1	05/04/2012	None	
US 2011-0112394 A1	12/05/2011	None	
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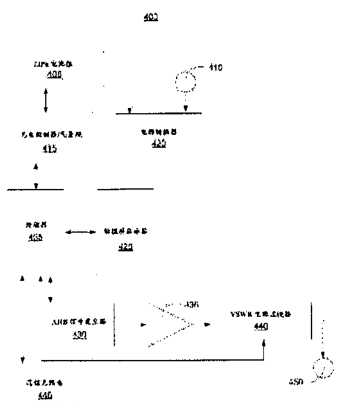
(54) 发明名称

在现场启动并监视中风患者治疗的便携式设备

(57) 摘要

提供了用于在现场和/或在把病人运输到护理设施期间启动中风治疗的方法和装置。为每个单个病人提供了对个人的治疗窗口自动调节的能力，由于不同年龄、性别和种族的人之间颅骨形态的显著区别，这是至关重要的。另外，所述方法和装置基于使用超声波的非侵入式施加，以及结合诸如微泡的声活化剂的超声波的非侵入式施加，其中可以依赖由超声波造成的微泡的稳定空化作为用于治疗应用及其控制的底层机制。



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1. 一种方法，包括：

经由附连在围绕病人头颅的不同位置处的第一超声波换能器和第二超声波换能器非侵入式地向所述病人的头颅施加超声波能量；及

控制所述超声波能量的施加，使得所述第一超声波换能器和第二超声波换能器交替地以脉冲向所述病人的头颅施加超声波能量，其中所述超声波能量的非侵入式施加是在现场发生的。

2. 如权利要求1所述的方法，其中所述超声波能量的非侵入式施加是在现场并且在病人到达护理设施之前发生的。

3. 如权利要求1所述的方法，其中所述围绕病人头颅的不同位置包括在病人耳朵前面的颞骨区域。

4. 如权利要求1所述的方法，还包括向病人静脉注射声活化剂。

5. 如权利要求4所述的方法，其中所述声活化剂包括微泡。

6. 如权利要求4所述的方法，还包括：通过所述超声波能量刺激所述声活化剂以产生稳定空化，以及检测所述声活化剂的惯性空化状态，作为所述超声波能量的施加已经超过与治疗窗口相当的水平的指示。

7. 如权利要求6所述的方法，其中对所述超声波能量的施加的控制包括控制所述超声波能量的输出功率，使得维持稳定空化，该稳定空化触发病人内的多种生物物理效应。

8. 如权利要求7所述的方法，其中对所述超声波能量的输出功率的控制是自动或手动执行的。

9. 如权利要求8所述的方法，还包括根据至少一个特定于病人的特征执行对所述超声波能量的输出功率的自动控制。

10. 如权利要求9所述的方法，其中所述至少一个特定于病人的特征包括年龄、性别、种族、颅骨特征以及形态。

11. 如权利要求6所述的方法，还包括在所述声活化剂达到惯性空化状态时减小所述超声波能量的输出功率。

12. 如权利要求1所述的方法，还包括执行所述超声波能量的非侵入式施加以及对所述超声波能量的施加的控制，以抵消由于局部缺血造成的脑血管意外、心肌梗塞和深静脉血栓形成中的至少一个的影响。

13. 如权利要求1所述的方法，其中所述第一超声波换能器和第二超声波换能器中的每一个都经电缆连接到便携式、靠电池操作的电源和控制设备，以及其中所述第一超声波换能器和第二超声波换能器包括单次使用超声波换能器和多次使用超声波换能器之一。

14. 如权利要求13所述的方法，其中单次使用超声波换能器包括盘形状的压电元件。

15. 如权利要求13所述的方法，其中单次使用的超声波换能器操作在200kHz的频率或者中心在大约200kHz的频带中，以及其中单次使用超声波换能器接收在100至300kHz之间的最小带宽内的声信号。

16. 一种装置，包括：

第一超声波换能器元件；

第二超声波换能器元件；及

电源和控制模块，所述电源和控制模块是便携式并且靠电池操作的，并且生成超声波

能量，所述超声波能量要由所述第一超声波换能器元件和第二超声波换能器元件以交替和脉冲的方式非侵入式地向病人颅骨发送。

17. 如权利要求 16 所述的装置，其中所述电源和控制模块还包括用于以导致声活化剂的稳定空化和惯性空化当中的至少一个的声输出功率电平和频率来生成超声波能量的电路。

18. 如权利要求 16 所述的装置，其中所述第一超声波换能器元件和第二超声波换能器元件包括能够在 200kHz 的频率或者中心在大约 200kHz 的频带中操作的盘形状的压电元件。

19. 如权利要求 18 所述的装置，其中每个盘形状的压电元件都具有范围从 2 至 3cm 的直径、范围从 1 至 1.5cm 的半径，以及 2mm 的厚度。

20. 如权利要求 18 所述的装置，其中每个所述盘形状的压电元件的两个面涂覆有导电材料，所述导电材料包括所述第一超声波换能器元件和第二超声波换能器元件中的每一个的电极。

21. 如权利要求 20 所述的装置，其中每个所述盘形状的压电元件的两个面涂覆有以下中的至少一个：在面向病人的一侧上的用以帮助能量输送的四分之一波匹配层、在背离病人的一侧上的背衬层、防止电磁干扰的屏蔽层和防止对病人的无意电击的绝缘涂层。

22. 如权利要求 16 所述的装置，其中所述第一超声波换能器元件和第二超声波换能器元件中的每一个都包括平的非聚焦盘。

23. 如权利要求 16 所述的装置，其中所述第一超声波换能器元件和第二超声波换能器元件中的每一个都被所述电源和控制模块以 10 至 1000μs 之间的脉冲持续时间和 1 至 50％之间的占空比驱动。

24. 如权利要求 16 所述的装置，其中所述第一超声波换能器元件和第二超声波换能器元件中的每一个都从病人的颅骨内接收声信号，以检测注射到所述病人的声活化剂的响应是稳定空化还是惯性空化。

25. 如权利要求 16 所述的装置，其中所述第一超声波换能器元件和第二超声波换能器元件中的每一个是能够在 100 至 300kHz 范围内的最小带宽内操作的。

26. 如权利要求 16 所述的装置，其中所述第一超声波换能器元件和第二超声波换能器元件中的每一个被配置为捕捉子谐波频率和第一超谐波频率。

27. 如权利要求 26 所述的装置，其中所述子谐波频率是 100kHz，所述超谐波频率是 300kHz。

28. 如权利要求 16 所述的装置，其中所述第一超声波换能器元件和第二超声波换能器元件中的每一个都设计成用于单次使用应用并且被封装以便在使用之前保持无菌。

29. 如权利要求 16 所述的装置，其中所述第一超声波换能器元件和第二超声波换能器元件中的每一个都包含在凝胶垫部分中，该凝胶垫部分是柔韧的，以顺应病人颅骨的形状，并且帮助将所述超声波能量发送到病人大脑的目标区域中。

30. 如权利要求 29 所述的装置，其中所述凝胶垫部分的接触病人头皮的部分包括剥离带，该剥离带配置为暴露粘合剂层，以便把所述第一超声波换能器元件和第二超声波换能器元件中的每一个维持在适当的位置。

31. 如权利要求 16 所述的装置，其中所述第一超声波换能器元件和第二超声波换能器

元件中的每一个都具有二十四小时的最小半衰期。

32. 如权利要求 1 所述的装置，其中所述电源和控制模块包括切换电路，在所述切换电路中，200kHz 的连续波信号在预定义的时间点被从一组导体切换到另一组导体，以从所述第一超声波换能器元件和第二超声波换能器元件产生交替猝发。

33. 如权利要求 32 所述的装置，其中每 100μs 出现所述预定义的时间点。

34. 如权利要求 32 所述的装置，其中发送信号是利用调谐到额定 200kHz 的连续正弦波的振荡电路生成的。

35. 如权利要求 34 所述的装置，其中所述 200kHz 的连续正弦波被放大到适当的功率电平，并被施加到所述切换电路。

36. 如权利要求 32 所述的装置，其中所述切换电路为所述第一超声波换能器元件和第二超声波换能器元件中的每一个都产生接通时间，后面跟着关闭时间，使得当所述第一超声波换能器元件和第二超声波换能器元件中一个处于接通状态时，所述第一超声波换能器元件和第二超声波换能器元件中另一个处于关闭状态。

37. 如权利要求 36 所述的装置，其中所述接通和关闭时间包括 100μs 的周期。

38. 如权利要求 36 所述的装置，其中所述第一超声波换能器元件和第二超声波换能器元件中处于接通状态的一个发送超声波能量通过病人的颅骨，而所述第一超声波换能器元件和第二超声波换能器元件中处于关闭状态的另一个接收声信号并且用作被动空化检测器。

39. 如权利要求 16 所述的装置，还包括两根电缆，每根电缆可操作地将所述第一超声波换能器元件和第二超声波换能器元件中的每一个连接到所述电源和控制模块。

40. 如权利要求 16 所述的装置，其中所述电源和控制模块还包括用于向装置的用户显示视觉信息的控制显示器。

41. 如权利要求 16 所述的装置，其中所述电源和控制模块配置来验证所述第一超声波换能器元件和第二超声波换能器元件中的每一个都通电。

42. 如权利要求 16 所述的装置，其中所述电源和控制模块配置为允许对所述超声波能量的声输出功率进行自动调节。

43. 如权利要求 16 所述的装置，其中所述电源和控制模块配置为允许对所述超声波能量的声输出功率进行手动调节。

44. 如权利要求 16 所述的装置，其中所述电源和控制模块包括用于指示空化控制和所述超声波能量的功率上限的三个灯。

在现场启动并监视中风患者治疗的便携式设备

[0001] 本发明在 National Institute of Health 资助的 HL091043 政府支持下进行的。该政府拥有本发明中的某些权利。

技术领域

[0002] 本发明涉及治疗中风或类中风情况的患者，并且更具体而言，涉及这样的便携式设备，其通过经颅骨原样非侵入地施加超声波，以及与静脉注射的微泡 (intravenously administered microbubble) 相结合，来提供"现场"和／或在运输到护理设施期间启动治疗并监视患者。

背景技术

[0003] 中风或脑血管意外 (cerebrovascular accident)(CVA) 指由于大脑血液供应的障碍，例如由于由阻塞或大出血造成的血流缺乏（称为局部缺血），而造成大脑功能的快速丧失，其中阻塞例如血栓或动脉栓塞。中风是全世界造成死亡的第二主导原因和美国造成死亡的第三主导原因，在心脏疾病（全世界第一位的常见死因）和肿瘤疾病（全世界第三位的常见死因）之间。大部分急性缺血性中风 (80％) 是由血栓栓塞造成的，并且与例如心脏和肿瘤相关的疾病相比，在缺血性中风中，中风事件初始阶段期间急性细胞死亡的数量显著更大。即，神经元脑细胞（神经元）对氧气供应非常敏感，其中氧气供应会由于例如突然的动脉血管闭塞而中断。因而，神经元在缺氧的前 60 秒内转入细胞凋亡 (apoptosis)。细胞凋亡定义为程序性的细胞死亡，这意味着，如果重通 (recanalization) 以及因此提供氧气供应没有发生，则甚至在这个非常早的时间点，神经元也开始不可逆地死亡。

[0004] 图 1 示出了由箭头 10 指示的正常血管的一个例子，由箭头 20 指示的闭塞血管的例子，以及由箭头 30 指示的在闭塞例如 25 分钟之后重通的血管的例子。图 1 还示出如在施加超声波治疗之前观察到的血栓 40 的例子，以及如在施加超声波之后观察到的血栓 40 的例子。

[0005] 在急性缺血性中风的情况下，已经显示每分钟平均有 1,900,000 个神经元由于颅内动脉血管闭塞而死亡。由此，全世界公认的理解就是应当尽可能早地施加治疗措施来重通受影响的大脑动脉。中风护理的最近发展，诸如远程医疗概念或者专业中风中心／单位的建立，已经改善了选定地区的中风护理。但是，所有这些行为都是主要由发达国家众所周知的学术中心启动或协调的，并且这些改进对中风护理的整体影响可以忽略不计。

[0006] 应当指出，全世界日益增长的中风发病率的原因可以归结到三个主要原因。首先，缺乏对该疾病及其症状的公众意识。第二，所有常规的治疗干预都需要病人住院治疗。第三，在所有年龄的人当中，全球死于中风的超过 85％是发生在全世界总人口中大约 85％的人口居住的低或中等收入国家。图 2 示出中等收入个人由于中风造成的死亡在 21 世纪初是大约 3 百万，并且在增加，如由线 210 指示的，对于低收入个人是将近 2 百万并且也在增加，如由线 220 指示的。作为对比，如由线 230 指示的，高收入个人由于中风造成的死亡在 21 世纪初并且预计至 2030 年都保持在 1 百万以下。

[0007] 目前，还没有允许对急性中风病人的治疗"在现场"（例如在急救地点和／或在运输到诸如医院的护理设施期间）开始的已知治疗选项。现场治疗可以被认为是至关重要的，因为大部分中风发生在郊区或农村地区，常常离专业中风中心有很大的距离。在这些情况下，急救呼叫（例如 911 呼叫）、到达急救地点和运输到专业中风中心之间的时间延迟对于病人是否幸存、是否遭受终身残疾或者是否完全恢复而没有任何缺陷常常是限制因素。

[0008] 一种最近开发出的设备是由 Cerevast Therapeutics 公司开发的被称为 CLOTBUST™-ER 的设备，该设备旨在利用超声波治疗中风患者。但是，CLOTBUST™-ER 超声波中风治疗设备是为在病人被允许入院之后急救室内的中风治疗开发的，并且结合组织纤溶酶原激活剂（tPA），这是目前用于中风治疗的唯一 FDA 批准的溶解药物。因而，并且再一次，即使利用这种设备，也仍然缺乏对中风患者的现场治疗。

发明内容

[0009] 本发明的各种实施例涉及用于"现场"和／或在把病人运输到护理设施期间发起中风治疗的方法和设备。为每个单个病人提供了对个人的"治疗窗口"自动调节的能力，由于不同年龄、性别和种族的人之间颅骨形态的显著区别，这是至关重要的。另外，所述方法和设备基于微泡和稳定空化的组合使用，作为用于治疗应用及其控制两者的底层机制。

附图说明

[0010] 为了更完整理解本发明示例实施例，现在参考以下结合附图的描述，在附图中：

[0011] 图 1 是正常血管、闭塞血管和重通血管以及超声波对血栓的影响的图示；

[0012] 图 2 是示出在不同社会－经济群体中与中风相关的死亡的流行程度的图；

[0013] 图 3 示出了根据用于中风患者的现场治疗的多种实施例来配置和使用的电源和控制模块的示例实现方式；

[0014] 图 4 是图 3 电源和控制模块的示意性表示；

[0015] 图 5 是在使用多种实施例时可能的组织损害减少以及时间延迟影响的图示；及

[0016] 图 6 示出了根据多种实施例为在现场治疗中风患者而执行的示例过程。

具体实施方式

[0017] 本文所公开的各种实施例针对用于在现场和／或在运输到护理设施期间治疗可能遭受急性缺血性中风的病人的方法和装置。根据一个实施例，这种治疗可以通过经原样的颅骨／头颅地非侵入地施加超声波以触发各种生物物理效应来实现。根据另一个实施例，超声波的这种非侵入的施加可以经过原样的颅骨／头颅与静脉注射微泡结合来执行，以触发各种生物物理效应。除了其它的效应，以上提到的根据各种实施例的利用而被触发的生物物理效应可以包括，但不限于，以下：a）侧支和间质流的改善；b）受影响的血管供应区域中动脉流的恢复；c）伴生水肿的减少；d）伴侣蛋白的激活；e）潜在祖细胞的刺激；及 f）血管闭塞血栓的实际溶解。

[0018] 超声波可以利用例如 200kHz 的发送频率以脉冲的方式施加，在这个频率，颅骨导致的所施加超声波束的变形是可忽略的。超声波可以例如以交替的方式从病人头部的两侧施加。由于各个声场的重叠，以这种方式施加超声波可以增加治疗面积，并避免并行的潜在

的副作用。具体地，两个超声波探针／电极可以放在颞骨的解剖区域并且靠近耳朵。根据某些实施例，两个超声波探针可以是一次性的，并且具有发送超声波束以及接收由超声波微泡引起的空化(cavitation)事件产生的声信号的能力。

[0019] 根据一个实施例，施加的超声波束的脉宽可以短（例如，100μs），以允许高脉冲重复率（例如，5kHz）来提供足够的能量沉积。声输出功率可以相当低（例如，4W），以实现低于食品和药物管理局(FDA)推荐限值 720mW/cm² 的病灶最大强度。关于射束形成，可以利用线性调频(chirp)模式，但是其它实施例可以利用基本模式或相位反转模式。

[0020] 根据另一实施例，并且如前面提到的，超声波也可以结合声活化剂（例如，微泡）来施加。此外，应当指出，超声波可以在延长的时间段上（例如，几个小时）持续地施加。类似于前面所述的实施例，由上述超声波探针发送的超声波束的脉宽可以是短的（例如，10μs-1000μs）并且结合例如在 1-50％之间的占空比。声输出功率可以选择成实现低于 FDA 推荐限值 720mW/cm² 的病灶最大强度。

[0021] 可以利用超声波换能器以及电源和控制设备／模块（其可以是相对小的，优选地是口袋尺寸的）来执行非侵入超声波单独施加或者与静脉注射声活化剂（诸如，微泡）相结合的施加。电源和控制设备可以是电池充电的，以允许便携式和／或无线功能。此外还有，电源和控制设备可以具有基本上容易使用的用户界面，并且耐用且防水。其它特征和／或功能可以结合到控制设备的一个或多个设计中，如由例如设备在其中使用的一个或多个环境所规定的。根据一个实施例，电源和控制设备可以具有接通／关闭(on/off)开关、不多于两个控制按钮，以及主控制显示器。这种控制按钮可以包括，但不限于，以下：声输出功率的自动调节（“自动 PCD 控制”）按钮，其中 PCD 可以指被动空化检测；以及声功率的手动调节（“手动 PCD 控制”）按钮。应当指出，根据某些实施例，声功率的手动调节可以涉及对多个输出功率范围之一的选择，这种选择可以取决于下列中一个或多个（但不必局限于）：病人年龄组，例如 a)<20，b)20-40，c)41-60，d)61-75，e)>76 岁；性别，例如 a) 女性，b) 男性；及种族，例如 a) 高加索人，b) 西班牙人，c) 亚裔，d) 非洲裔／非洲裔美国人。此外，电源和控制设备可以包括一个或多个灯，诸如发光二极管(LED)灯，例如以向用户呈现空化控制和功率上限指示（例如，黄、绿和红）。

[0022] 类似于心电图(ECG)垫片，电源和控制设备可以利用一次性超声波换能器，所述一次性超声波换能器可以经某种类型的有线连接连接到电源和控制设备并且在使用后丢弃。如上所述，超声波换能器可以放到病人头部两侧上的颞骨区域上。超声波换能器可以利用像凝胶那样的暂时性粘胶（诸如像用于 ECG 垫的粘胶）保持在适当的位置，如以下将更具体描述的。为了提供超声波换能器和病人皮肤之间的充分传导性，可以除去施加超声波换能器的位置处的头发。在超声波换能器定位之后，可以利用接通／关闭开关将电源和控制设备通电。如上所述，灯可以在控制设备中用来向用户呈现某些指示。例如，黄色控制灯可以用来向用户提供控制设备在操作（例如在发送声波（即，超声波束））的视觉确认。应当指出，缺省的声输出功率值可以在接通控制设备之后设置，这个功率可以在毫瓦范围（例如，20mW）。

[0023] 在电源和控制设备通电之后，可以经例如主控制显示器向用户提供选项。如果用户选择按自动 PCD 控制按钮，则第一选项可以被实行，其中电源和控制设备可以自动增加声输出功率，直到绿色控制灯点亮。这个绿色控制灯可以用作微泡的稳定空化发生的确认。

稳定空化被建议作为触发以上提到的生物物理效应的底层机制。因此，绿色控制灯的点亮可以代表期望的治疗行为，或者，换句话说，“治疗窗口”。红色控制灯可以指示例如已经超过了该治疗窗口。在这种情况下，声输出功率将自动减小，直到红色控制灯关闭并且绿色控制灯接通。

[0024] 如果用户选择按手动 PCD 控制按钮，则可以实行第二选项，其中电源和控制设备可以允许用户手动地增加声输出功率。如上所述，手动的声输出功率可以依赖于一个或多个因素（例如病人的年龄、性别和／或种族）被向上或向下调节／选择。在手动控制期间，用户可以例如增加声输出功率并且利用绿色控制灯作为量规 (gauge)，其中绿色控制灯（如前面所讨论的）可以指示电源和控制设备在“适当的”治疗窗口内工作。如果利用手动 PCD 控制功能超过了声输出功率，则电源和控制设备可以或者关闭或者切换回缺省设置（即，如前面所述由黄色控制灯所指示的）。

[0025] 电源和控制设备还可以驱动超声波换能器，其中电力可以由例如锂聚合物 (LiPo) 或类似的电池（其还可以给以上提到的电源和控制设备的特征和／或功能供电）提供。电源转换控制电路可以产生期望的超声波频率。电源和控制设备的另一个电路可以用来控制输出功率电平，这可以考虑由用户提供的关于病人的输入，例如性别、种族和年龄。还有另一个电路可以用来以防止颅内超声波驻波发生的方式调制输出频率。还有另一个电路可以用来感测超声波换能器是否被连接、可使用 (functional) 和／或激励。

[0026] 如前面所提到的，电源和控制设备可以是相对小的，例如，口袋／手持式尺寸，并且由可以经受例如在像救护车／其中需要救护车的场景中所经历的环境中大量使用 (hard use) 的一种或多种材料制成。例如，电源和控制设备可以大致为手持式数字万用表的尺寸，例如，大约 2x4x8 英寸。虽然如上所述电池可以是可再充电的（例如，锂聚合物电池），但是应当指出，电源和控制设备可以替代地或者附加地具有直接从固定电源（诸如墙上的电源插座 (outlet)）操作的能力。此外，电源和控制设备可以配置为使得电池容易替换。

[0027] 而且如前面所提到的，电源和控制设备可以具有一个或多个按钮、用户界面等，其可以允许用户与电源和控制设备交互。因而，电源和控制设备可以具有控制面板，通过该控制面板，可以实现和／或呈现那些各种按钮和用户界面，以用于交互，例如，接通／关闭设备，在合适的时候验证超声波换能器被激励，确定还剩多少电池寿命，声输出功率的自动调节，以及声功率的手动调节。另外，电源和控制设备可以包括前面提到的控制灯，指示例如空化控制和功率上限，作为控制面板的一部分或者与其分离。电源和控制设备还可以包括一个或多个连接器插座。第一连接器插座可以配置用于从墙上的电源插座给电池再充电和／或操作，而第二连接器插座可以配置来接收用于把超声波换能器连接到电源和控制设备的电缆。

[0028] 发送信号可以由电源和控制设备利用被调谐到例如额定 200kHz 连续正弦波的振荡器电路生成。可以将该正弦波放大到适当的功率电平，并且该发送信号可以施加到在两组导线（每个超声波换能器一组）之间交替发送的切换电路，例如，在超声波换能器放置于病人头部两侧颞骨处的情况下，每 100μs 交替发送。这种发送信号可以施加到已通过前面提到的电缆放置并固定到中风病人头部的超声波换能器。对于每个超声波换能器，切换电路可以生成例如 100μs 的接通时间然后是 100μs 的关闭时间，使得当一个超声波换能器处于接通状态时，另一个超声波换能器处于关闭状态。在超声波换能器接通状态期间，超声

波换能器可以发送超声波能量通过病人的颅骨。在超声波换能器关闭状态期间，当结合声活化剂施加超声波时，超声波换能器可以接收声信号，允许超声波换能器用作被动空化检测器。

[0029] 此外，电源和控制设备可以包括例如两个开关或致动器，但是，根据对操作控制的需要／期望水平，可以包括更多或更少开关。第一开关可以用来接通电源和控制设备，而第二开关可以用来把前面提到的发送信号／电压发送到超声波换能器。另外，诸如触摸板的输入设备可以用来输入病人信息或者进一步与电源和控制设备交互。当连接超声波换能器时，但在它们被激励之前，可以向用户呈现超声波换能器已连接并且可使用的指示。例如，这可以是灯或者触摸板上的消息。当所需要的预备条件已经满足（例如，病人信息、换能器功能等），那么用户就可以激励超声波换能器，并且当这个完成时，指示器也可以显示该状况。

[0030] 图 4 示出了根据多种实施例设计的电源和控制设备 400 的示例示意图。电源和控制设备 400 可以由电池电源（诸如，LiPo 电池组 405）供电。可以通过直流 (DC) 充电端口 410 执行对 LiPo 电池组 405 的充电。此外，电源和控制设备可以经 DC 充电端口 410 从例如墙上的插座供电。电源和控制设备 400 可以包括用于如以下更具体描述的用于监视空化的充电控制器和气量规 415（例如，BQ 系列充电控制器／气量规），以及电源转换器 420。此外，电源和控制设备 400 可以具有触摸屏显示器 425，诸如有机发光二极管 (OLED) 触摸屏显示器，通过该显示器，可以向用户呈现各种信息／与电源和控制设备 400 交互。另外，电源和控制设备 400 可以包括信号发生器 430，诸如任意波形发生器 (ARB) 信号发生器、功率放大器 435 及电压驻波比 (VSWR) 电源监视器 440，用于如本文所述的超声波的生成／控制／发送。电源和控制设备 400 还可以包括一个或多个通信无线电模块 445，这可以是例如 **Bluetooth®**无线电，通过它可以实现以上提到的无线通信。为了允许超声波换能器连接到电源和控制设备 400，也可以在电源和控制设备 400 上提供一个或多个探针连接器 450。此外，本文所述的电源和控制设备 400 的各种功能的操作可以由处理器 455 执行，其可以是例如 ARM3 核心处理器，或者处理器／控制器的组合。应当指出，可以根据期望的特征和／或功能，在电源和控制设备 400 中包括更多或更少的元件／模块／组件。此外，本文所述的各种元件／模块可以实现为单独的元件／模块，或者其组合。

[0031] 如前面所指出的，本文所述的治疗方法可以基于单独施加超声波或者结合声活化剂（诸如，微泡）施加超声波，这取决于稳定空化机制。此外，声活化剂（例如微泡）的使用允许实现本文所述的监视功能。应当指出，术语“微泡”可以指设计用于诊断目的以增强图像质量的试剂。应当指出，如在本文所使用的，术语“微泡”不意味着局限于仅其诊断应用。而是，根据不同实施例，微泡概念可以另外应用于主要不是设计用于诊断目的的试剂。

[0032] 也就是说，诊断微泡可以指平均直径为例如 2-3μm 的球体。这种球体或微泡的壳结构可以是磷脂或者是人血清蛋白，而这种球体的内部可以填充全氟碳 (perfluorocarbon) 气体。根据不同实施例，可以静脉注射这些试剂，例如经外围血管，并且试剂被稳定化以通过肺部进入动脉循环。这种试剂的半衰期可以在几分钟的范围内。

[0033] 当超声波被发送经过物理介质时，超声波可以压缩和拉伸物理介质（诸如，人体组织）的分子间距。因而，当微泡通过超声波场时，它经历频繁的压力变化，从而导致泡震荡（即，稳定空化）或者泡解构（即，惯性空化 (inertial cavitation)）。而惯性空化可能

对人体组织造成伤害，尤其是内皮层（endothelial layer），稳定空化已经显示对于血栓溶解和组织灌注的改进是有效的，稳定空化在较低的超声波能量发生。

[0034] 回过头来参考在电源和控制设备中实现的控制灯，当已经到达治疗窗口时，即，当可以检测到稳定空化时，可以点亮绿色控制灯。由于惯性空化会需要更高的能量才发生，因此，当能量可能增加到超过治疗窗口时，会主要地发生惯性空化。在这种情况下，可以点亮红色控制灯。

[0035] 回过头来参考用于发送超声波的超声波换能器，并且为了提供对空化的控制，可以设计超声波换能器使得它们能够在它们不发送的任何时候（例如，在处于关闭阶段时）检测空化信号。超声波换能器还可以设计成覆盖例如 100-300kHz 的带宽，以捕捉子谐波频率（0.5x 发送频率：0.5x200kHz = 100kHz），以及第一超谐波频率（1.5x 发送频率：1.5x200kHz = 300kHz）。利用这种能力，可以通过该设备检测空化并将空化表征为稳定空化或惯性空化之一。

[0036] 应当指出，在超声波换能器放到病人头部合适的位置，已经启动了具有微泡的静脉滴注，并且选择了优选的或优化的声输出功率之后，构思在最早可能的点，即，在已经给予急救并且病人的维持生命所必需的机能已经稳定之后，开始连续声波作用（超声波的施加）。这可以是在急救地点时或者在病人运输到护理设施期间。此外，连续声波作用可以持续到提供进一步的医院内诊断或治疗程序，病人的症状完全消退，病人的症状已经恶化，和/或直到在任何给定的时间点，看护的医生认识到停止这种治疗的显著医疗指示。

[0037] 如上所述，超声波换能器可以经利用例如传导性凝胶的凝胶垫定位到患者的头部上，其中该凝胶类似于用于把 ECG 电极固定到病人胸壁的凝胶。超声波换能器可以定位在病人头部的任一侧，在耳朵前方颞骨区域之上，或者替代地，在头部的最顶端（头顶）上。在某些场景下，后一种替代的定位可能是优选的，因为这种经颅骨（transskull）路径可能由于其特定的声学属性而具有优点。

[0038] 此外，优选将超声波换能器设计成用于单次使用的应用，并且被包装以便在使用之前保持无菌，但是超声波换能器也可以设计成用于多次使用的应用。由于是柔韧的，因此换能器/凝胶垫组合可以顺应病人头部/颅骨的形状，并且可以帮助把超声波能量/波发送到病人大脑的目标区域中。传导性凝胶可以具有类似于例如在超声波扫描术中所使用的接合凝胶的声学属性。凝胶垫接触病人头皮的部分可以具有将要暴露粘合剂层的剥离条，这层粘合剂可以帮助把超声波换能器保持在合适的位置，并且通过帮助消除潜在的气囊（例如由于病人头发造成的气囊）还将帮助超声波能量/波的传输。可选地，如前面所指出的，可以考虑对超声波换能器应用区域的须发剃掉。

[0039] 超声波换能器本身可以包含在凝胶垫部分当中。换能器可以包括压电元件（例如，盘形状的），大约 3cm 直径和 2mm 厚。压电材料可以是用于医学超声波的材料，诸如锆钛酸铅（PZT），或者任何其它合适的材料。压电材料，也称为晶体，其两个面（但并不必然是边缘）可以涂覆有导电材料，该导电材料可以被称为超声波换能器的电极。晶体还可以具有绝缘涂层，在该绝缘涂层之上涂屏蔽层。引线（诸如，轻型且柔性的电缆（屏蔽的双绞线）可以附连（例如，焊接）到电极，用于向晶体导电并用于随后超声波能量的生成。应当指出，

[0040] 可以根据需要使用其它材料以用于附加的涂层，诸如在晶体最靠近病人的一侧上

帮助能量传输的四分之一波匹配层、晶体背离病人的一侧上的背衬层、防止电磁干扰（EMI）的屏蔽层、和／或防止病人的无意电击的另一绝缘涂层。

[0041] 如上所述，通过设计成单次使用，超声波换能器不需要任何外罩材料或特殊的连接器。而是，超声波换能器可以集成到例如尺寸稍大于超声波换能器本身的低外廓且轻型的塑料袋中。塑料袋的一侧可以包含用于粘性接合凝胶的分配器，并且另一侧可以具有提供用于超声波换能器的气垫衬的气囊。这种包装可以密封在一次性封套或类似的封装中以保持无菌。在使用时，一次性封套可以被打开并且移出超声波换能器。附加的膜／剥离条可以从超声波换能器的一侧除去，以暴露粘合剂和接合凝胶，并可以将超声波换能器应用到病人头部的选定区域。

[0042] 超声波换能器可以以这样的方式适配到凝胶垫中：使得一定厚度的凝胶可以维持在超声波换能器的能量发射面和病人的头皮之间。这可以例如通过在凝胶垫中结合套筒(sleeve)来实现，在制造过程中，可以将超声波换能器插入该套筒中。超声波换能器的电极引线可以以这样的方式离开凝胶垫：使得它们免受急救部署期间无意的缠结(snagging)和破损。电缆可以用来把电极引线连接到前面提到的电源和控制设备。

[0043] 应当指出，根据另一个实施例，超声波换能器可以实现在头带中，其中电极引线可以离开头带的凝胶垫部分，并且可以结合到头带材料中，以免受急救部署期间无意的缠结和破损。来自每个超声波换能器的引线可以在头带的方便的部分处（诸如，位于头后部上方的部分）终止。这种终止可以是内置到头带中的连接器，或者可以是在连接器中终止的一定长度的电缆。与头带分开的另一根电缆可以用来把头带连接到电源和控制设备。

[0044] 图 3 示出了超声波换能器及电源和控制设备的示例配置及其使用。图 3 示出了电源和控制设备 300。如前所述，电源和控制设备可以是相对小的、由电池供电，并且具有无线通信功能，并且可以给超声波换能器供电并控制超声波换能器。超声波换能器 310 连接到电源和控制设备，其被示为附连到病人 320 头部。再次地，超声波换能器 310 可以经凝胶垫连接到病人 320 头部任一侧。超声波换能器，包括超声波换能器 310，可以经电缆 330 连接到电源和控制单元。

[0045] 超声波换能器本身可以设计成以 200kHz 的频率操作或者在中心在大约 200kHz 的频带内操作。再次地，处于这种频率的声场经过颅骨时，不必经受变形，如利用 MHz 范围的更高频率的情况那样。因此，可以根据已知的物理原理高度可预测性地设计施加到大脑的声场。此外，超声波换能器可以配置为例如具有在例如 2cm 和 3cm 之间直径（从而分别为例如 1cm 和 1.5cm 的半径）的平的非聚焦盘。

[0046] 在声学术语中，超声波换能器的半径通常表示为 a。从该超声波换能器发射的声场基本上是柱形的，直到它行进距离 d，此时它开始以锥形方式展开。距离 d 也称为远场转变，并且可以由下式表示：

[0047] $$d=\frac{a^2}{\lambda}$$

[0048] 其中 λ 是超声波的波长。在水和身体组织中，在 200kHz，λ 可以是大约 0.75cm。由此，并且对于具有例如 1cm 半径的超声波换能器，距离 d 大约为 1.3cm，并且对于 1.5cm 的半径，距离 d 是 3cm。

[0049] 经过距离 d 之后，超声波的声能可以以锥形形状展开，其中该锥形以角度 θ 对向

(subtend)，该角度 θ 是声轴和锥形形状一边之间的角度。这个角度 θ 可以由下式计算：

[0050] $$\theta = \tan^{-1}\left(\frac{a}{d}\right)$$

[0051] 从这些式子可以看到，对于给定的超声波频率，声束形状主要由超声波换能器的半径控制。声束形状又可以确定声场的峰值强度。当声束的半径根据角度 θ 扩张时，声束强度以半径的平方减小。声束强度还可以由于大脑组织的衰减而随距离减小。该效应可以是关于在病人的头颅区域生成驻波（以下更具体地讨论）的可能性和安全性的因素。

[0052] 以下例子示出了各种实施例的设计、操作和固有安全性。半径为 1.5cm 的超声波换能器具有 3cm 的转变距离，这可以是峰值声学强度的点，因为当超过这个距离时，由超声波换能器发送的声束将变得更宽。如果已经调节超声波换能器的声输出功率在这个峰值声学强度点产生例如 600mW/cm^2 的声强度，则在 5cm 深度，声强度可以减小至小于 300mW/cm^2，并且在 6cm，声强度可以减少至约 125mW/cm^2。给定 16cm 的平均颅骨直径，当其到达相对的颅骨表面时，声束的声强度可以是大约 20mW/cm^2。通过在对侧内部颅骨表面反射所生成的任何驻波都应当具有可忽略的幅值。但是，最有可能具有治疗效果的超声波能量的强度包含在大脑中线身体同侧的 30-60cm 的临床相关深度中。

[0053] 对以上所述更近一步，可以构思 10-10000μs 之间的脉冲持续时间，以及 1-50％的占空比，在 200kHz 的频率（在另一个意义上，是方便的范例，因为在软组织中该频率的波长是大约 7.5mm）。给定例如 100μs 的脉冲持续时间和 50％的占空比，20 个周期的猝发（burst）的总长度将是 15cm，或者几乎是从一个颞骨到另一个颞骨的平均头颅直径。如果两个超声波换能器交替激活时间（激活时间在前面被称为接通时间），则第一超声波换能器的声场在第二超声波换能器的能量通过时之前，将减弱很多，因而使造成驻波的任何可能性最小化。如上所述，为了提供这种交替活动，电源和控制设备可以利用切换电路每 100μs 就把例如 200kHz 的 CW 信号从一组导体切换到另一组导体，以便在超声波换能器之间生成交替的 20 周期猝发。应当指出，相同或相似的考虑在使用单个超声波换能器并且该换能器位于病人头顶的实施例中也适用。

[0054] 关于声活化剂的应用，根据一个实施例，并且如上所述的，超声波换能器具有在关闭时间（off-time）期间接收声信号的能力。依赖于作为实现以上提到的生物物理效应的底层机制的稳定空化，并且依赖于用作控制和安全性测量的惯性空化，超声波换能器可以具有 100-300kHz 之间的最小带宽。也如上所述，选择这个范围以捕捉子谐波频率（100kHz）以及超谐波频率（300kHz）。这两个频率的出现都指示稳定空化的存在，并且因此描述单个的治疗窗口。主要的惯性空化的出现可以以基频（在 200kHz 处）的曲线下方增加的面积和本底噪声的上升的组合为特征。子谐波频率和超谐波频率可以仍然存在，但是不是主导的。如果惯性空化被超声波换能器检测到，则电源和控制设备可以配置为自动地减低声输出，直到只能检测到稳定空化（即，自动 PCD 控制按钮）。或者，电源和控制设备可以配置为立刻关掉或自动复位到其预设的模式（即，手动 PCD 控制按钮）。

[0055] 图 6 示出了根据多种实施例的为了在现场治疗中风或类中风情况的患者而执行的示例过程。在 600，经附连在围绕病人头颅的不同位置的第一超声波换能器和第二超声波换能器非侵入式地将超声波能量施加到病人的头颅。在 610，控制超声波能量的施加，使得第一超声波换能器和第二超声波换能器以脉冲交替地向病人的头颅施加超声波能量，其中

所述超声波能量的非侵入式施加是在现场进行的。可选地，在620，可以结合向病人静脉注射声活化剂来执行超声波能量的施加。例如，并且如本文所描述的，例如微泡的注射，以及由在特定水平的超声波能量的施加所造成的稳定空化可以促进溶解、动脉流的恢复等。

[0056] 此外，根据多种实施例的超声波换能器的设计可以提供24小时的确保的最小半衰期。对于亚急性／慢性应用，就长期持续性而言，假设在受控环境（例如，医院、康复中心或者老人院）下正确的护理和维护，对超声波换能器半衰期的需求可能不同。

[0057] 关于大循环(macrocirculation)，有证据证明，结合使用超声波微泡可以改善超声波引起的血栓溶解以重通血管。因而，并且根据又另一个实施例，超声波序列可以内置到电源和控制设备中，以供在超声波暴露期间微泡的使用。用于这个目的的微泡复合物可以是标准的、主要用于诊断目的的商业可用的试剂，或者是专门为超声波增强的血栓溶解而开发的试剂。

[0058] 关于微循环，越来越多证据证明超声波与微泡的结合可以引起一氧化氮从内皮细胞释放，从而导致血管扩张效果，这又会导致改进的组织灌注。根据另一个实施例中，微循环技术可以结合到之前描述的各种实施例中，以通过机械和生物化学血管扩张来改进组织灌注。

[0059] 应当指出，本文所公开的用于治疗中风患者的各种实施例还可以应用到由栓塞或血栓栓塞情况造成的其它缺血性疾病，诸如心肌梗塞(MI)或深静脉血栓形成(DVT)。即，所有这些疾病的潜在原因都是血管突然被血块闭塞，其结果就是由于缺乏氧气供应造成的供氧区域内持续的细胞死亡。所有这些疾病都共同具有发病剧烈以及对在可能的最早时间点的治疗选项的需要。由此，可以在紧急情况的场所和／或在运输到护理设施期间提供的治疗将是有利的。因而，各种实施例可以包括可以专用于应用于其它缺血性疾病（诸如MI或DVT）的替代的超声波换能器设计以及超声波序列。此外，多种不同实施例可以用来解决几乎任何器官系统中的缺血性疾病。

[0060] 还有，在急性缺血性疾病中的应用以外，本文所公开的各种实施例还可以用作长期、可重复发生的治疗选项，例如，用在遭受亚急性／慢性缺血性疾病的病人中。这种病人可以包括具有慢性缺血性白质疾病的病人、遭受血管性痴呆的病人或中风后的病人。在这些病人群体中，各种实施例可以在例如住院治疗期间、在康复中心或者作为常规治疗在私人家中或者在养老设施中被利用。遵循类似的方法，各种实施例的使用还可以在神经退行性疾病（诸如阿尔茨海默氏症(Alzheimer)或帕金森(Parkinson)疾病）的背景下使用。即，本文所公开的各种实施例预期在任何亚急性或慢性脑部疾病病人的治疗中使用，对于这些病人，改进的组织灌注、干细胞增殖的潜在刺激、神经调制或伴侣蛋白质释放的诱发会是有益的。各种实施例还可以在各种神经病学应用中使用，例如癫痫或神经精神病（例如，精神分裂症、抑郁症）的治疗。

[0061] 其它实施例可以包括在电源和控制设备的监视或反馈功能，例如，建立例如血管重通或组织灌注改善的时间。还有其它实施例可以将一个或多个感测元件（诸如红外线激光器或空化接收器）包括到换能器／凝胶垫组合中，以监视例如手术期间组织灌注的改善，或者通过空化检测防止超过安全限值。

[0062] 如以上提到的，电源和控制设备可以具有无线功能。这种无线功能可以涵盖例如现场救护队与接收护理设施中的医疗人员之间的无线通信，其中这种通信常规上是稀疏

的。还有其它实施例可以利用无线通信能力,来利用各种无线通信技术将来自电源和控制设备的实时数据(例如,与以上提到的监视/反馈功能相关/关联的数据)直接发送到位于接收护理设施的服务器,或者发送到便携式计算设备,所述无线通信技术包括例如,但不限于:2G(例如,全球移动通信系统(GSM),等等)、2.5G(例如,通用分组无线电服务(GPRS),等等)、3G(例如,GSM 增强数据演进(EDGE)、宽带码分多址(WDMA)、CDMA2000,等等),以及4G(例如,LTE、WiMAX,等等)技术,及蓝牙®。

[0063] 此外,本文所公开并且描述的功能,实现为利用可连接到电源和控制设备并由电源和控制设备供电的超声波换能器,可以在现有的设备(诸如现有的诊断超声波设备)中实现。此外,在局部药物输送领域中的最近研究涉及在目标点处输送治疗试剂。具体地,某些研究建议使用微泡作为运输手段,以及超声波作为源来把这些治疗试剂释放在目标点。例如,某些研究已经集中到氧载体对组织保护和神经保护的有益效果。因而,各种实施例可以实现专用的超声波序列,从而允许本文所公开的方法和装置用于药物的局部输送,或者增强氧载体的效果。

[0064] 如本文所描述的,各种实施例提供了在现场和/或在把病人运输到护理设施期间启动中风治疗的方法和装置,也用于其它疾病以及用于更延长的使用,诸如在康复场景下。可以例如自动地调节各种实施例为用于每个病人的单个"治疗窗口",由于不同年龄、性别和/或种族的人之间颅骨形态的显著区别,这常常是至关重要的因素。另外,可以结合声活化剂(诸如微泡)的使用来利用各种实施例用于超声波发送,其中稳定空化是用于治疗应用及其控制的底层机制。

[0065] 因而,全世界遭受像急性中风症状的数百万病人可以得到治疗,对于这些病人,到目前为止还不存在治疗选项。此外还有,这种方法的使用可以结合到用于现场急性中风的治疗的未来护理标准中,这很像除颤器已经变成用于心脏电复律(cardioconversion)的护理标准。对减少在农村和城市地区的急性中风治疗中所经历的延迟的潜力是显著的,如图 5 中所示出的。在城市地区,例如,可以接收急救 911 呼叫,并且在急救医疗服务(EMS)人员到达病人经历中风/类中风情况的地点之前可能经过 10 分钟。例如,根据各种实施例的超声波/超声波结合微泡的应用可以在现场在其后例如 5 分钟实现。进入护理设施可以在之后 10 分钟发生。由此,在这个例子中,可以节省至少 10 分钟,在这期间,可以实现组织损坏的大幅度减少。在农村环境下,在最初急救 911 呼叫之后 45 分钟之内 EMS 人员不会到达。同样,在 5 分钟内,可以根据各种实施例发生单独超声波或者结合微泡的应用。在这种农村场景下,进入护理设施不会在其后另一个 115 分钟之内发生。在这种情况下,可以认识到,可以通过各种实施例的使用避免在 115 分钟期间由于中风造成组织损坏。

[0066] 示出各种实施例的各个图可以绘出用于各种实施例的示例体系架构或其它配置,这是为了帮助理解可以包括在那些实施例中的特征和功能。本公开内容不限于所示出的示例体系架构或配置,而是可以利用各种备选体系架构和配置来实现期望的特征。实际上,可以如何实现备选功能、逻辑或物理分区和配置以实现各种实施例对本领域普通技术人员来说将是显然的。此外,除本文所绘出的那些之外的多个不同组成模块名称可以应用到各种分区。此外,关于流程图、操作描述和方法权利要求,在本文中给出步骤的次序将不要求各种实施例实现为以相同的次序执行所述功能,除非上下文另外指出。

[0067] 应当理解,在一个或多个单独实施例中描述的各种特征、方面和/或功能不限于

它们对关于其进行描述的特定实施例的应用，而是代替地可以单独地或者以各种组合应用到一个或多个其它实施例，不管这种实施例是否描述过或者这种特征、方面和／或功能是否作为所述实施例的一部分给出。因而，本公开内容的广度和范围不应当受任何上述示例性实施例所限制。

[0068] 除非另外明确声明，否则在本文档中所使用的术语和短语，及其变体，应当认为是开放式的，而不是限制性的。作为前面所述的例子：术语“包括”应当认为指“包括但不限于”等；术语“例子”用来提供讨论项的示例性实例，而不是其详尽或限制列表；术语“一”或“一个”应当认为指“至少一个”、“一个或多个”等；以及诸如“常规的”、“传统的”、“正常的”、“标准的”、“已知的”的形容词以及相似意义的术语不应当认为把所述的项限制到给定的周期或者限制到在给定时间可用的项，而是应当认为涵盖现在或将来任何时间可用或已知的常规的、传统的、正常的或标准的技术。同样，在本文档提到对本领域普通技术人员显然或已知的技术时，这种技术涵盖现在或将来任何时间对本领域技术人员显然或已知的那些技术。

[0069] 此外，本文所阐述的各种实施例是就示例性框图、流程图和其它说明来描述的。如在阅读本文档后将对本领域技术人员变得显然的，所示出的实施例及其各种备选方案可以不受所说明例子的限制来实现。例如，框图及其附带的描述不应当认为要求特定的体系架构或配置。

[0070] 此外，本文所述的各种实施例可以在方法步骤或过程的通用背景下描述，在一个实施例中，这可以由实现在例如非临时性计算机可读存储器中的计算机程序来实现，包括可以由联网环境中的计算机执行的计算机可执行指令，诸如程序代码。计算机可读存储器可以包括可移动和不可移动存储设备，包括但不限于只读存储器(ROM)、随机存取存储器(RAM)、光盘(CD)、数字多样化盘(DVD)等。一般而言，程序模块可以包括执行特定任务或实现特定抽象数据类型的例程、程序、对象、组件、数据结构等。计算机可执行指令、关联的数据结构和程序模块代表用于执行本文所公开的方法步骤的程序代码的例子。这种可执行指令的特定序列或关联数据结构代表用于实现在这种步骤或过程中所描述的功能的对应动作的例子。

[0071] 如本文中所使用的，术语“模块”可以描述可以根据一种或多种实施例执行的给定的功能单元。如本文中所使用的，模块可以利用任意形式的硬件、软件或者其组合来实现。例如，可以实现一个或多个处理器、控制器、ASIC、PLA、PAL、CPLD、FPGA、逻辑组件、软件例程或其它机制来构成模块。在实现中，本文所述的各种模块可以实现为离散的模块，或者所描述的功能或特征可以部分地或者整个地共享在一个或多个模块中。换句话说，如在阅读本描述之后对本领域普通技术人员将明显的，本文所描述的各种特征和功能可以在任何给定的应用中实现并且可以以各种组合和排列在一个或多个独立或共享的模块中实现。虽然功能的各种特征或元件可以作为独立的模块单独描述或要求保护，但是本领域普通技术人员将理解，这些特征和功能可以在一个或多个公共的软件和硬件元件中共享，并且这种描述将不要求或暗示独立的硬件或软件组件用来实现这种特征或功能。当本发明的组件或模块整体地或部分地利用软件实现时，在一个实施例中，这些软件元件可以实现为与这样的计算或处理模块一起操作，所述计算或处理模块能够执行关于所述软件描述的功能。在有些情况下诸如“一个或多个”、“至少”、“但不限于”或类似短语的扩展词或短语的存在将不被

理解为指在没有这种扩展短语的情况下预期或要求更窄的情况。

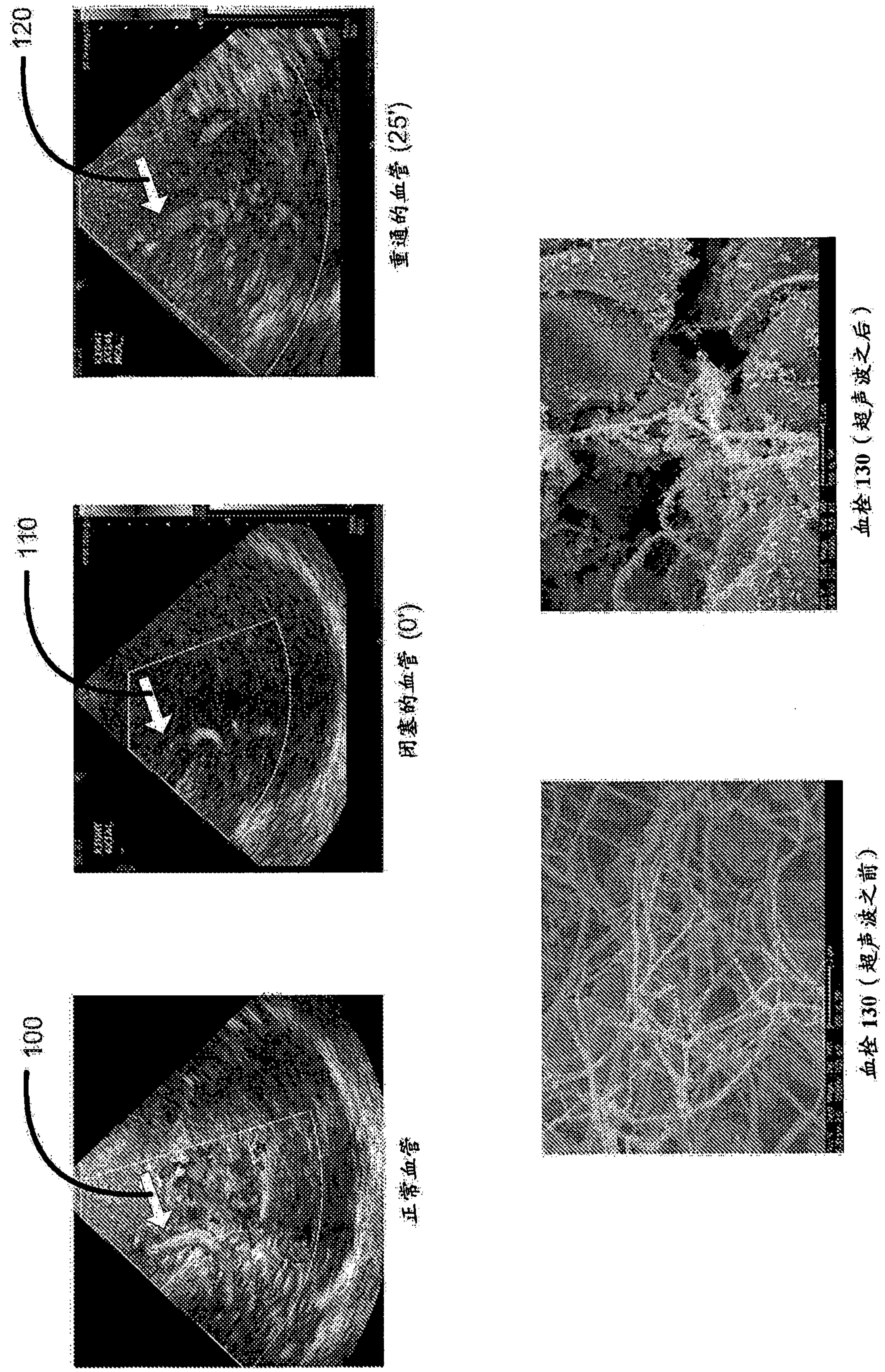

图 1

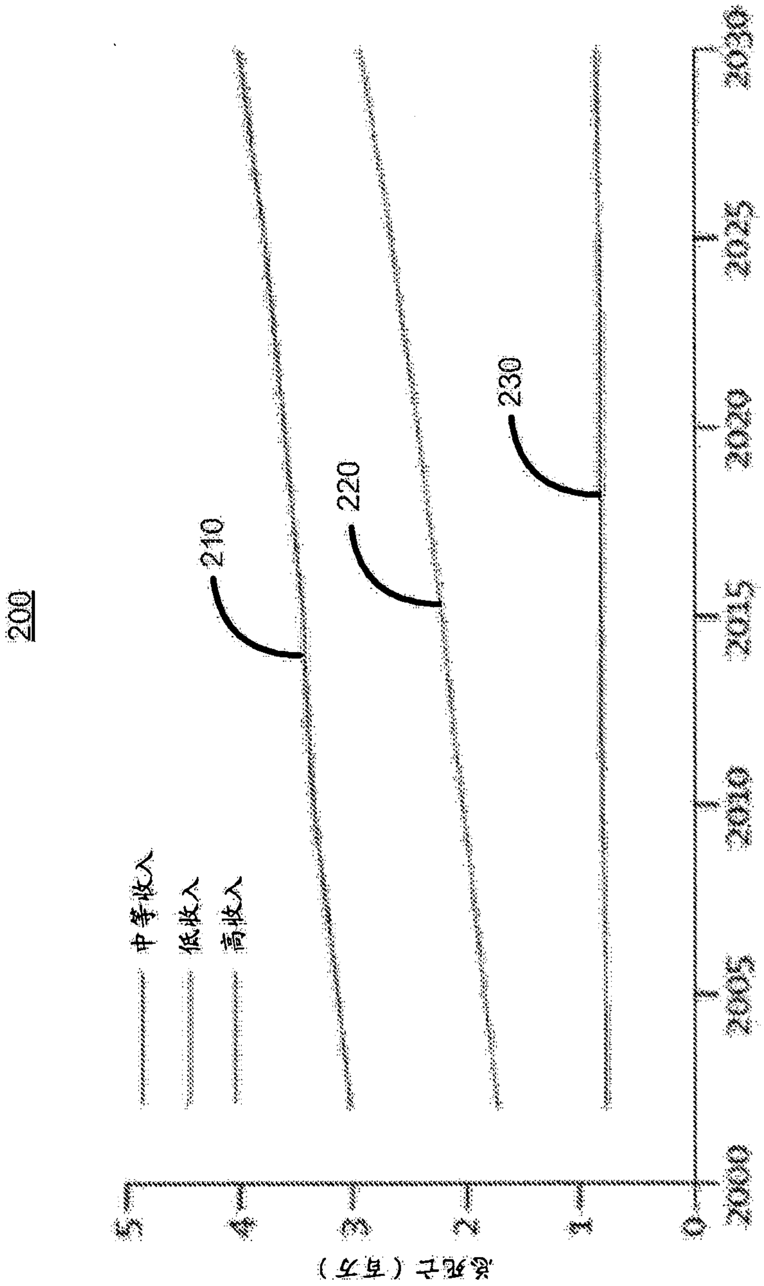
200
210
220
230
中等收入
低收入
高收入
0
1
2
3
4
5
2000
2005
2010
2015
2020
2025
2030

图 2

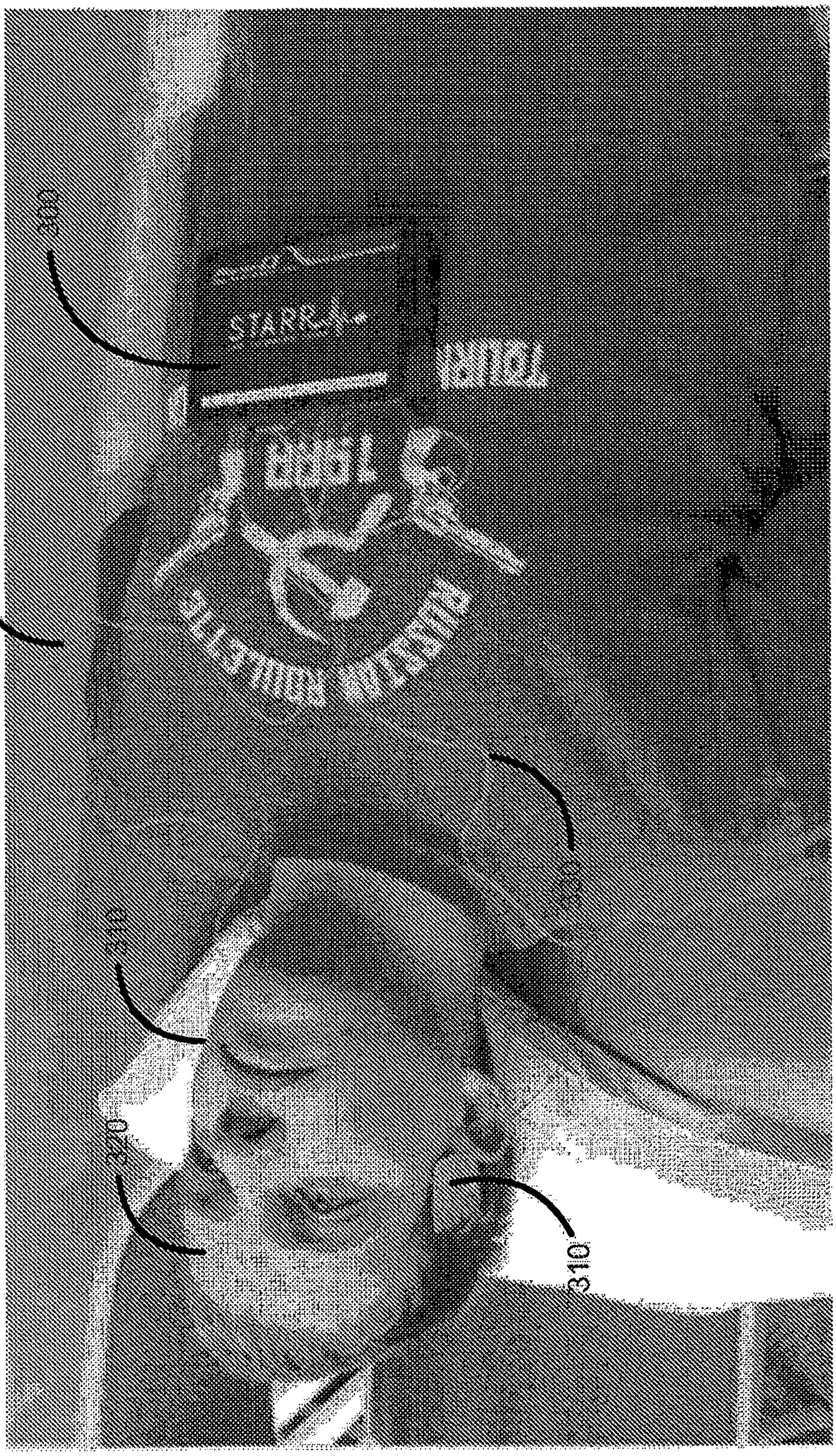

图 3

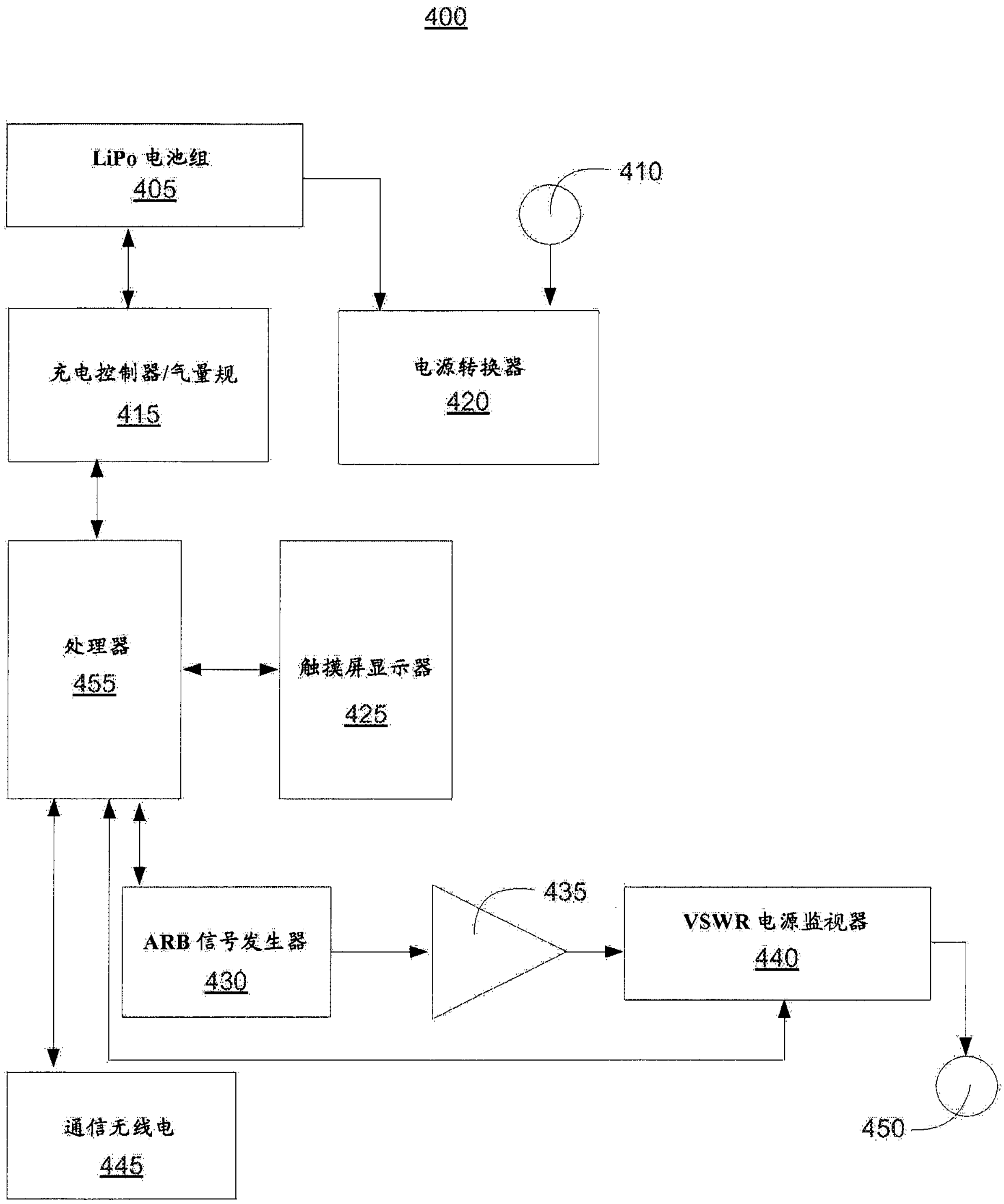
400
LiPo 电池组
405
410
充电控制器/气量规
415
电源转换器
420
处理器
455
触摸屏显示器
425
435
ARB 信号发生器
430
VSWR 电源监视器
440
通信无线电
445
450

图 4

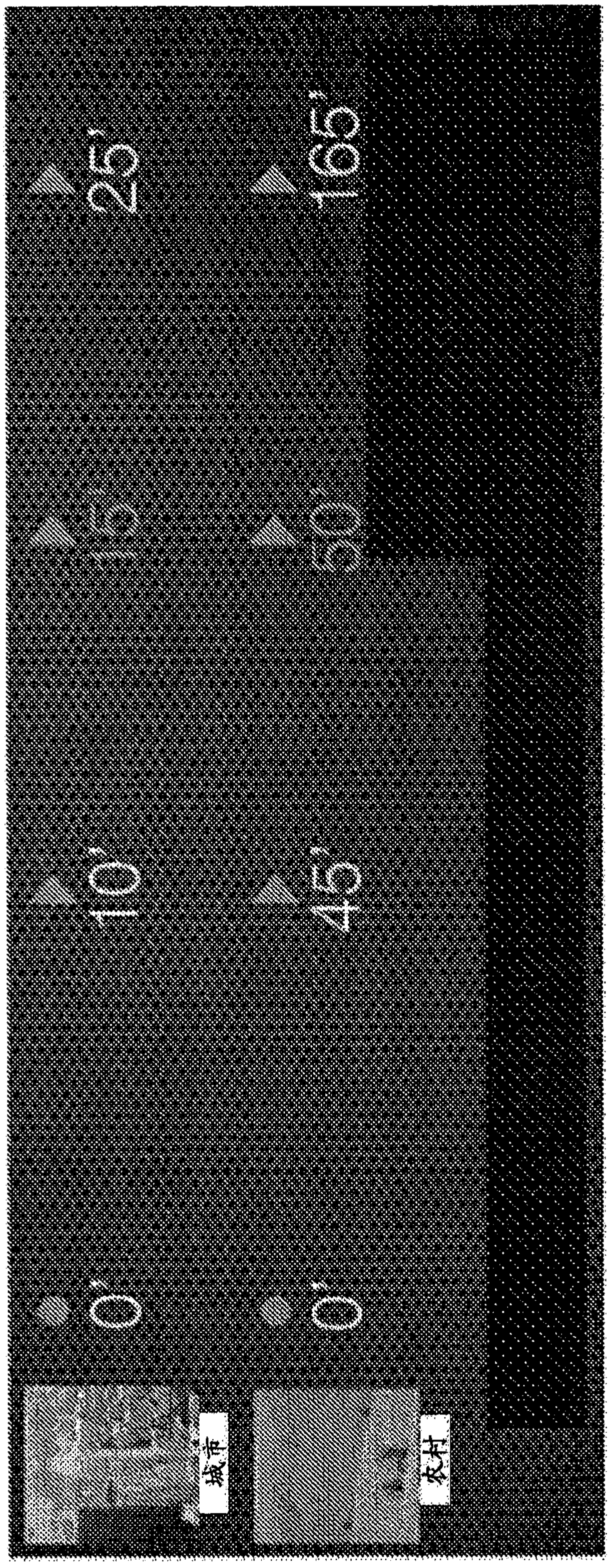

图 5

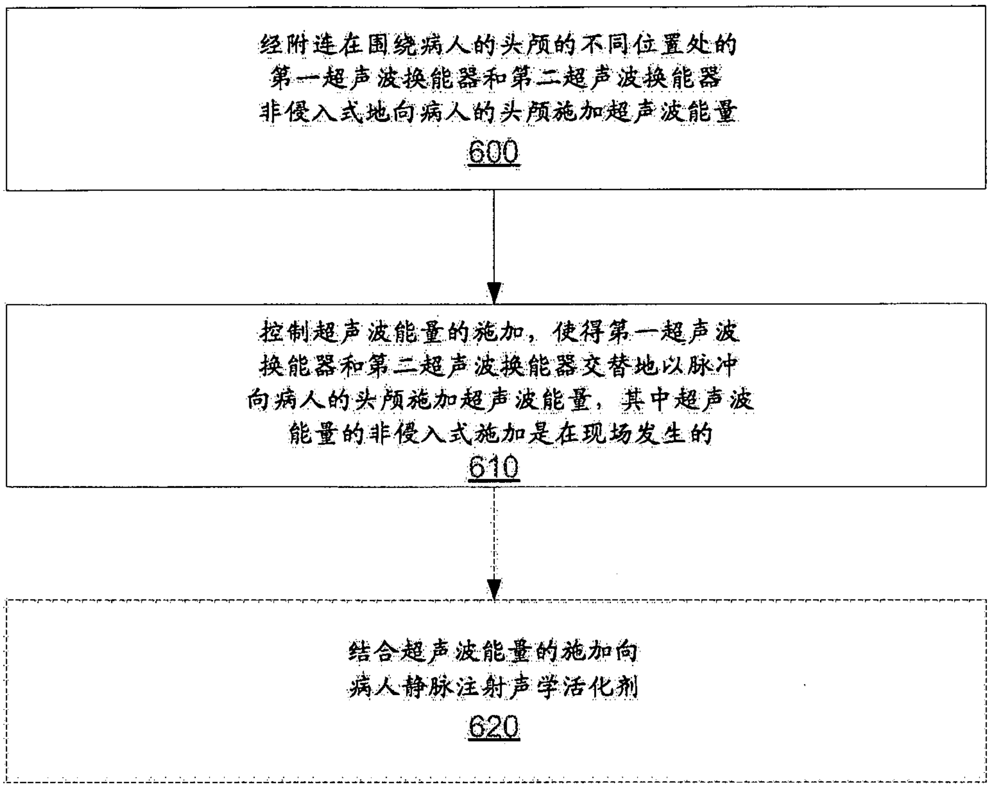
经附连在围绕病人的头颅的不同位置处的
第一超声波换能器和第二超声波换能器
非侵入式地向病人的头颅施加超声波能量
600
控制超声波能量的施加，使得第一超声波
换能器和第二超声波换能器交替地以脉冲
向病人的头颅施加超声波能量，其中超声波
能量的非侵入式施加是在现场发生的
610
结合超声波能量的施加向
病人静脉注射声学活化剂
620

图 6