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(71) Applicant: **BETH ISRAEL DEACONESS MEDICAL CENTER, INC.** [US/US]; 330 Brookline Avenue, Boston, MA 02215 (US).

(72) Inventors: **MASSEY, Michael, J.**; 514 Eliot Street, Milton, MA 02186 (US). **SHAPIRO, Nathan, I.**; 330 Brookline Avenue, Boston, MA 02215 (US).

(74) Agents: **HOOEVER, Thomas, O.** et al.; McCarter & English, LLP, 265 Franklin Street, Boston, MA 02110 (US).

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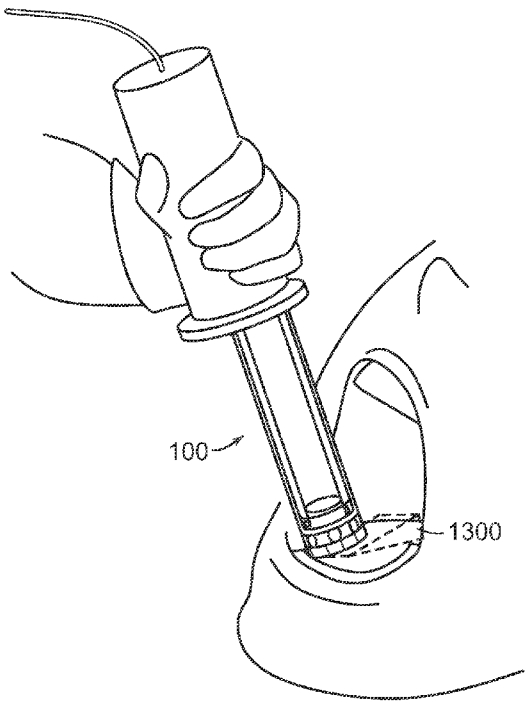


FIG. 13

(57) Abstract: Systems and methods of the present invention provide for the measurement of microcirculatory obstruction in the vascular system of a patient. A handheld device can include a pressure sensor to measure the pressure applied to a tissue surface while imaging microcirculatory flow.

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SYSTEMS AND METHODS FOR NON-INVASIVE MEASUREMENT OF HEMODYNAMICS IN CIRCULATORY SYSTEMS

RELATED APPLICATION

This application claims priority to United States Provisional Patent Application No. 62/253,504, filed November 10, 2015, the entire contents of which is incorporated herein by reference.

BACKGROUND OF THE INVENTION

Sepsis is a severe inflammatory condition that affects numerous patients each year in the United States and around the world. Because septic patients are weak and often suffer from a variety of conditions, it can be difficult to assess disease severity and whether a patient is properly responding to treatment or is continuing to worsen. In particular, severe forms of sepsis typically manifest in the form of insufficient oxygen supply to organs of the body. Although macrocirculatory flow may be adequate, microvascular failure can occur in the form of physiological shunting, maldistributed flow, and disrupted perfusion in small vessels. The microcirculation is defined as the collection of pre-capillary arterioles, capillaries, and post-capillary venules measuring less than approximately 100 micrometers in diameter. As endothelial dysfunction progresses, inflammation, coagulation, and leukocyte adhesion increase and fibrinolysis decreases leading to increased microvascular dysfunction. The lack of blood flow proceeds to hypoperfusion and hypoxia, which causes organ dysfunction. Thus, severe sepsis is associated with endothelial dysfunction and microcirculatory flow disturbances that are, in turn, predictive of subsequent organ failure and death. Early resuscitation attenuates endothelial dysfunction and improves patient survival. It is believed that improvements in microcirculatory flow at 24 hours after treatment may predict survival.

Present devices to measure microcirculatory blood flow have poor repeatability as the process is highly susceptible to iatrogenic factors such as the pressure applied by the user on the tissue. It is well-known that applying sufficient manual pressure to the tip of a clinical microscope can occlude microcirculatory blood flow. The lack of consistency in measurement of microcirculatory blood flow properties has impeded penetration of the technique into the clinic. In addition, standard semi-manual methods of quantifying blood flow have been unreliable and are too time-consuming for practical bedside use. Thus, further

improvements in the measurement of microcirculatory flow are needed to aid in treatment of a variety of conditions.

Measurement of the central venous pressure (CVP), among other indicators, is predictive of patient health in patients with a compromised cardiovascular system due to cardiovascular disease or infectious disease. The current standard of care involves threading a catheter along a major vein of the patient until the catheter is in the vicinity of the right atrium of the heart. A transducer at the tip of the catheter measures the pressure directly. This method, also known as running a central line, poses an elevated risk of infection and other complications in a clinical or emergency medicine setting. Improvements in measurement of the central venous pressure are required that can reduced these risks to an already compromised patient.

SUMMARY OF THE INVENTION

Systems and methods of the present invention provide measurements of the flow of bodily fluids or cellular biological material in combination with pressure measurements. Preferred embodiments can include imaging of microcirculatory blood flow that is correlated to pressure applied to the tissue overlying the imaged region. In preferred embodiments, the systems and methods described herein provide an optical probe and associated pressure sensor that work in combination with a computing device to provide diagnostic indicators for a clinician including values of critical pressure and density of perfused microvessels in a tissue of a patient. The inventors have observed that the amount of force (pressure) required to occlude microcirculatory blood flow varies by patient and believe that the critical pressure to occlude blood flow can be inversely proportional to severity of certain illnesses such as sepsis. For example, microcirculatory dysfunction coupled with hemodynamic dysfunction is significantly correlated with in-hospital mortality. Additional sensors including temperature and oxygenation sensors can be integrated into the device. The systems and methods described herein can be used, for example, in the monitoring of septic patients by evaluating the impact of therapeutic delivery of medication such as vasopressors or L-carnitine. The dosage can be adjusted based on the measured microcirculatory response.

In preferred embodiments, systems and devices of the present invention can include a detector to collect image data. The detector can be connected to a processing unit including internal and/or external memory. The processing unit can include one or more data processors programmed to perform computational analysis, image processing (such as vessel

segmentation and/or frame averaging), and image stabilization operations. The systems and devices can include a capacitive or resistive readout circuit to measure a change in capacitance or resistance within a pressure sensor.

In some embodiments, systems and methods presented herein are adapted to acquire measurements of microcirculatory blood flow in the submucosa along the sublingual cavity in a patient's mouth. The mucosa of the underside of the tongue or floor of the mouth is an advantageous place to perform measurements because the epithelial layer is thin and optically transparent in the visible portion of the electromagnetic spectrum and the tissue is embryonically similar to splanchnic tissue. Other tissue sites include tissue exposed during surgical procedures or using probes inserted into body cavities or by percutaneous insertion of such probes. Probe devices in accordance herewith can be handheld and connected by cable or wireless connection to a processing system, display, and data storage housing. Blood flow analysis can be performed to provide quantitative measures including microvascular flow index (MFI), portion of perfused vessels (PPV), perfused vessel density (PVD), heterogeneity index, and total vessel density.

Systems and methods of the present invention can be used to determine a first critical pressure and a second critical pressure in a microcirculation system. The first critical pressure is the point at which a first amount or proportion of microvessels are occluded or perfused as increasing pressure is applied. The second critical pressure is the point at which a second amount or proportion of microvessels are occluded or perfused as decreasing pressure is applied. The first and second critical pressures and first and second amounts or proportions are correlated with the severity of a patient's condition and can be used to determine diagnostic thresholds. In some embodiments, the first and second critical pressures and first and second amounts or proportions can be monitored over time to observe changes in their values. In the current standard of care, it is assumed that no occluding pressure is applied if the flow is unimpeded in post-capillary venules measuring greater than 50 micrometers in diameter.

In preferred embodiments of the present disclosure, ultrasound probes are provided that can acquire ultrasound data of tissue of a patient while simultaneously measuring applied pressure. Systems, methods, and devices described herein can be used to measure the applied pressure that causes reduction in flow within the internal jugular vein, for example, the initiation of vein collapse, or other conditions in which the pressure applied by the user to the transducer contact area can impact the image quality. The pressure data can be correlated to

central venous pressure of a patient to give a clinician a non-invasive method to monitor CVP.

Thus, preferred embodiments include an energy source such as a light source or ultrasound transducer that are used to illuminate the tissue of a patient. The response of the tissue to the illuminating energy can be correlated with the application of applied pressure to the tissue to provide quantitative information regarding applied pressure and circulatory condition of the tissue. The system can also include an imaging detector that generates still or video images of the tissue to record the circulatory state of the tissue.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1A depicts a system for measuring hemodynamics in a microcirculatory system according to various embodiments of the present invention.

Fig. 1B depicts a circuit board that may be included in the system described in connection with preferred embodiments.

Figs. 2A and 2B depict perspective and end views, respectively, of a cover for a probe according to various embodiments of the present invention.

Figs. 2C and 2D depict perspective and end views, respectively, of an imaging device according to various embodiments of the present invention.

Fig. 3 depicts an expanded view of a distal end of an assembled probe according to various embodiments of the present invention.

Fig. 4 depicts a schematic of a measurement of microcirculation properties in a tissue according to various embodiments of the present invention.

Figs. 5A-C depict dark field images of a standard and a pressure sensor bubble under low, medium, and high pressure, respectively, using a system according to various embodiments of the present invention.

Fig. 6A depicts a method of measuring a parameter of a circulatory system according to various embodiments of the present invention.

Fig. 6B depicts a method of image stabilization and modification according to various embodiments of the present invention.

Figs. 7A-C depict a dark field image and two filtered versions thereof obtained from a tissue under low pressure using a system according to various embodiments of the present invention.

Figs. 8A-C depict a dark field image and two filtered versions thereof obtained from a tissue under higher pressure than in Figs. 7A-C using a system according to various embodiments of the present invention.

Figs. 9A-C depict a dark field image and two filtered versions thereof obtained from a tissue under higher pressure than in Figs. 8A-C using a system according to various embodiments of the present invention.

Figs. 10A-C depict a dark field image and two filtered versions thereof obtained from a tissue under higher pressure than in Figs. 9A-C using a system according to various embodiments of the present invention.

Figs. 11A-C depict a dark field image and two filtered versions thereof obtained from a tissue under higher pressure than in Figs. 10A-C using a system according to various embodiments of the present invention.

Fig. 12 depicts an exemplary embodiment of a distal end of an imaging device according to various embodiments of the present invention.

Fig. 13 depicts a probe in a clinical setting according to various embodiments of the present invention.

Figs. 14A and 14B depicts an ultrasound probe including a pressure sensor in accordance with various embodiments of the present invention.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to improvements in measuring aspects of microcirculatory blood flow in a tissue and correlation of those measurements to a pressure applied to the tissue. As an external pressure is applied to a tissue, perfusion in the microcirculatory vessels (i.e., capillaries, arterioles, and venules) begins to cut off and the vessels become occluded. As external pressure is released from a tissue, the reverse occurs. The critical pressure values at which occlusion or perfusion pass a threshold amount or proportion can be indicative of the severity of a patient's condition.

Systems and methods described herein can include an optical probe and associated pressure sensor that work in combination with a computing device to provide images or video frames of microcirculation in a tissue that are correlated to values of applied pressure. In some embodiments, information about the applied pressure is embedded directly into the images of the microvasculature. In some embodiments, the pressure sensor is a transparent microbubble or capacitive sensor mounted on a disposable cover or enclosed tube that can be discarded after use to provide improved sterility for clinical applications.

Fig. 1A depicts a system for measuring hemodynamics in a microcirculatory system according to various embodiments. The system includes a probe 100 having an imaging device 120 and a disposable cover 110 that may be removed from the probe 100, discarded, and replaced. The disposable cover 100 includes a pressure sensor 150 and, optionally, temperature sensors 157 and oxygenation sensors to enable correlation between pressure measurements and hemodynamic measurements. A computing device 130 can be connected to the probe 100 and a display 132. The computing device 130 can receive data from the probe 100 including images and physical measurements such as voltage, resistance, or capacitance. In some embodiments, the computing device 130 can perform data operations to compute a hemodynamic metric that correlates to patient health.

Figs. 2A-2D illustrate isolated perspective and end views of a disposable cover 110 and an imaging device 120 according to various embodiments of the present invention. The imaging device 120 can include a proximally located handle from which a tubular body extends distally. The imaging device 120 can include a lumen 122 to allow light to pass in. In accordance with various embodiments, the lumen 122 can include one or more beam-steering elements such as lenses 126 or mirrors. In some embodiments, the lumen 122 includes optical fibers to transmit light from the distal end to the proximal end of the imaging device 120. In some embodiments, the imaging device can include a detector 128 such as a CCD or CMOS two-dimensional imaging sensor. The detector 128 can be mounted at any point within the lumen 122 including at the proximal or distal ends of the lumen 122. Optical fibers or one or more lenses can be used to couple the image to the detector.

The imaging device 120 also can include one or more illumination sources 126. In some embodiments, the illumination sources 126 can include light emitting diodes placed at or near the distal tip of the imaging device 120. In one embodiment, the light emitting diodes are mounted on the distal end of tubular body 125 and can include one or more LEDs that provide illumination at one or more wavelengths including, but not limited to, wavelengths in

the green and blue ranges. In alternative embodiments, the illumination sources 126 can include a light pipe or optical fibers that carry light from a source within the handle or even external to the imaging device 120 to the distal tip of the imaging device 120. The wavelengths and intensities of the one or more illumination sources 126 can be chosen to complement several factors in relation to the probe 100. For example, the wavelengths of the one or more illumination sources 126 can be chosen to minimize the appearance or interference from flexible or conductive membranes or bubbles 152 depending on their size, thickness, and distribution within the imaging field. In some embodiments, longer wavelengths may reduce the appearance of bubbles 152 and thereby reduce artifacts in the resulting images. In some embodiments, shorter wavelengths can improve image quality by increasing absorbance of the light by certain elements in the field of view such as water or hemoglobin. In some embodiments, a mixture of different illumination sources 126 having different peak wavelengths can be used.

The imaging device 120 can be connected to a power source 134 to provide power to one or more illumination sources 126 and/or to electronics embedded within the handle. The handheld device can be battery powered for wireless connectivity to the processor housing. As shown in greater detail in Fig. 1B, electronics that may reside on-board the probe 100 can include one or more printed circuit boards including one or more of the following: central processing unit 172, memory 174, capacitive or resistive readout circuits 175, temperature readout circuits 177, and interfaces 176 to allow the probe 100 to interface with an external computing device 130. Capacitive readout circuits that are compatible with embodiments of the present invention may be found, for example, in Nie, Baoqing, et al. "Iontronic microdroplet array for flexible ultrasensitive tactile sensing." *Lab on a Chip* 14.6 (2014): 1107-1116 and its associated Electronic Supplementary Information and in Li, Xiujun, and Gerard Meijer. "An accurate interface for capacitive sensors." *IEEE Transactions on Instrumentation and Measurement,* 51.5 (2002): 935-939, both of which are hereby incorporated by reference in their entirety.

The imaging device 120 can be covered with a disposable cover 110 in some embodiments. By allowing a new disposable cover 110 to be installed for each new measurement, the sterility of the probe 100 is improved and the potential for disease transmission between patients is eliminated. In some embodiments, the imaging device 120 includes a registration tab 127 to enable proper installation and alignment of the disposable cover 110.

The disposable cover 110 can be made of any material that meets requirements for sterility and medical use such as, but not limited to, various plastics or glasses. The proximal end of the disposable cover 110 can be shaped to beneficially attach to the imaging device 120. For example, the disposable cover 110 and imaging device may come together in a snap fit. The disposable cover 110 can include a registration notch 117 that mates with a complementary registration tab 127 on the imaging device 120 to enable proper alignment and installation. The distal end of the disposable cover is optically clear and can be flat or convex.

In various embodiments, the distal end of the disposable cover 110 can include a pressure sensor 150. The pressure sensor 150 can operate to measure pressure values using a variety of physical principles including, but not limited to, piezoelectric, piezoresistive, electromagnetic, capacitive, optical, and potentiometric principals. In exemplary embodiments, at least a portion of the pressure sensor 150 is transparent to allow light to pass through and into the lumen 123 of the imaging device 120. The pressure sensor 150 can include capacitive or resistive elements. These elements may be connected by wire 114 to contacts 124 on the imaging device 120. The signal from the capacitive or resistive elements can flow to readout circuitry 175 on the circuit board 170 of the imaging device 120. The wires 114 may be embedded within the material of the disposable cover 110 to prevent damage or interference during a clinical measurement operation and to ensure patient safety. In some embodiments, the pressure sensor 150 can include a temperature sensor 157 such as a thermistor, a liquid-crystal element, or another temperature-sensing element. The signal from the temperature sensor 157 can be connected by wire 114 to contacts 124 on the imaging device 120. The signal from the temperature sensor 157 can flow to readout circuitry 177 on the circuit board 170 of the imaging device 120.

Fig. 3 depicts the distal end of a probe 100 with particular focus on a pressure sensor 150 according to various embodiments of the present invention. In the depicted embodiment, the pressure sensor 150 includes one or more transparent polymer bubbles 152 enclosed in a compressible, transparent gel 151 and/or conductive membranes 153. As the pressure applied at the distal tip changes, the cross-sectional area of each of the bubbles 152 or a capacitance or resistance value as measured between conductive membranes 153 can change accordingly. As will be described in greater detail below, the imaging device 120 can be used to visualize a bubble 152 within the field of view of the detector 128, and image processing algorithms 133 stored within a memory 131 of the computing device 130 can be used to compute the

cross-sectional area of the bubble. In certain embodiments, the bubbles 152 may be an iontronic microdroplet array wherein the bubbles 152 correspond to droplets of an ionic liquid. In these embodiments, the volume of the microdroplets can be in a range of 3 nL to 3 μL, and the gel 151 may be a liquid or may include air or a gaseous dielectric in the gaps between neighboring microdroplets/bubbles. In addition, other devices can be used to measure the space or gap between electrodes. Other suitable pressure sensors are described in U.S. Patent Application No. 14/106,760 by Tingrui Pan *et al.* and International Patent Application PCT/US2014/070187 by Tingrui Pan *et al.*, the entire contents of both being incorporated herein by reference.

Although exemplary patterns of bubbles 152 are shown in Figs. 2A, 2B and 3, it will be understood by one skilled in the art that many different patterns of bubbles may be produced to suit application-specific requirements. In some embodiments of the pressure sensor 150, the pattern of bubbles 152 can include square or rectangular arrays, circular arrays, rings, ovals, or other suitable shapes. It will be understood that the spacing between bubbles 152 can be constant or varying throughout the pressure sensor 150 and that the size of each bubble 152 can be the same or different from other bubbles 152 throughout the pressure sensor 150. In certain embodiments, the interbubble spacing can be between 0.2 mm and 3 mm. In some embodiments, the size of the bubbles 152 may be chosen to minimize obstruction of the field of view. In addition, the size of the bubbles 152 may be chosen to complement the output wavelength of the illumination source 126 to reduce or increase interference effects. In some embodiments, the bubble can be tinted to improve visibility. For example, the bubble can be tinted a color (e.g., red, blue, green, or other colors) such that it will appear darker than the surrounding tissue and will be easier to segment using image processing algorithms.

The bubbles 152 and gel 151 may be sandwiched between conductive polymeric membranes 153. As the pressure applied at the distal tip changes, the conductive polymeric membranes 153 can accordingly produce an electronic capacitance or resistance. In some embodiments, the sensitivity of the pressure sensor 150 can be in a range of 0.1 to 1 nF/kPa. Changes in resistance or capacitance can be transmitted from the conductive polymeric membranes 153 to the imaging device 120 through the wires 114 and electrical contacts 124. In an exemplary embodiment, the conductive polymeric membranes 153 are substantially transparent to allow light to pass through the pressure sensor 150.

The pressure sensor 150 can also include one or more flexible membranes 154. In some embodiments, the flexible membranes 154 can enclose and secure the electrical and chemical elements of the pressure sensor 150 to keep them isolated from the surrounding environment. In addition, the flexible membranes 154 can provide a smooth and sterile surface to contact to a tissue.

Fig. 4 illustrates a schematic showing measurement of microcirculation hemodynamics in a tissue using a probe according to various embodiments of the present invention. The distal end of the probe 100 is placed in contact with a tissue 140. In an exemplary embodiment, the tissue 140 is the floor of a sublingual cavity. The illumination source or sources 126 emit light to illuminate the tissue 140. Light scatters from the tissue surface and from elements of the microcirculation 141 including capillaries, arterioles, and venules. The scattered light can be collected by a lens 123 or by optical collection fibers in the lumen 122 and transmitted to a detector 128.

To measure hemodynamics in the microcirculation 141 of the tissue 140, the probe 100 is positioned over a tissue 140 to be imaged. For example, the probe 140 can be placed in contact with the floor of a patient's mouth under the tongue (i.e., the sublingual cavity). Images of microcirculation elements such as capillaries, arterioles, and venules can be obtained as the user gradually applies pressure to the tissue 140. The pressure can be applied by a user by pressing the probe 100 directly against the tissue 140. In alternative embodiments, pressure can be applied by inflating a small balloon at or near the pressure sensor or by an appliance placed under the chin in the submaxillary triangle area.

The image obtained by a detector 128 in the schematic shown in Fig. 4 may contain a bubble from a pressure sensor within the field of view in certain embodiments. The shape or area of this bubble can be used to determine the value of applied pressure. A standard grid imaged through a probe of certain embodiments of the present invention is shown in Figs. 5A-C. Low, medium, and high pressure are being applied in Figs. 5A, 5B, and 5C, respectively. In the images, the glint from an edge of the bubble can be seen. Using image processing algorithms, each image is analyzed to determine best-fit ellipses for the inner and outer diameters of the bubble edge. The major and minor axes of the best-fit ellipses can be recorded for each image, and an average of the change in the major and minor axes between pressure values can be calculated. The change in area or shape of the bubble in the image will depend on parameters of the imaging system such as magnification and numerical aperture. In some embodiments, the average change in length of the major axis can be about 20 pixels

and the average change in length of the minor axis can be about 15 pixels. In some embodiments, the thickness of the edge of the bubble can be measured and correlated directly with the applied pressure.

As described above, the applied pressure at which microcirculatory blood flow is occluded can be an important indicator of patient health. A procedure to obtain information related to microcirculatory occlusion is detailed as follows. The probe can be applied to a tissue. Under no or very light pressure, an image or video frame of the microvasculature may be acquired. Subsequently, further images or video frames can be acquired as the level of pressure is increased. As the pressure and consequent force on the microvasculature increases, the density of microcirculatory vessels that can continue to allow flow, decreases. The images or video frames are transmitted to a computing device equipped with image processing algorithms. The algorithms can process the images or video frames to determine a density of occluded vessels or perfused vessels within the field of view. The pressure may be increased until a first critical pressure is reached. In some embodiments, the first critical pressure is the pressure at which a first threshold value of perfused or occluded vessel density is reached. Alternatively, the first critical pressure can be defined as the pressure at which a first threshold percentage of perfused or occluded vessel density is reached as referenced to an initial value. In another embodiment, the first critical pressure can be determined by a user during visual assessment of the field of view.

After obtaining images at the first critical pressure, the pressure can be slowly released while images and video frames of the microvasculature continue to be acquired. As the pressure is released, perfusion will be restored within the elements of the microvasculature. The pressure may be decreased until a second critical pressure is reached. In some embodiments, the second critical pressure can be defined as the pressure at which a second threshold value of perfused or occluded vessel density is reached. Alternatively, the second critical pressure can be defined as the pressure at which a second threshold percentage of perfused or occluded vessel density is reached as referenced to an initial value or as referenced to the first threshold percentage of perfused or occluded vessel density. In another embodiment, the second critical pressure can be determined by a user during visual assessment of the field of view. The values of the first critical pressure, second critical pressure, and (in certain embodiments) first threshold value, first threshold percentage, second threshold value, or second threshold percentage can be used to determine diagnostic thresholds.

Fig. 6A depicts a method 600 of measuring a parameter of a circulatory system according to various embodiments. The method 600 includes acquiring simultaneously image data indicative of the presence of circulation within tissue and data indicative of an applied pressure (step 602). The method also includes processing the image data using image processing algorithms to determine one or more features of interest (step 604) and processing the data indicative of an applied pressure to provide a pressure measurement (step 606). The method further includes comparing the one or more features of interest and the pressure measurement to determine a pressure at which circulation is reduced (step 608). The method can include subsequently repeating the measurements to monitor a condition of a patient (step 610). The method also optionally includes altering therapeutic treatment based on the measured data (step 612).

Step 602 of acquiring simultaneously image data indicative of the presence of circulation within tissue and data indicative of an applied pressure can include, but is not limited to, using a probe 100 to acquire image data of tissue 140 while also acquiring capacitive or resistive information from a pressure sensor 150 or images of bubbles 152 within a pressure sensor 150 as described above with reference to Figs. 1A-4. Step 604 of processing the image data using image processing algorithms to determine one or more features of interest may include, but is not limited to, performing the steps described in greater detail below with reference to Fig. 6B to identify parameters in image data such as density of perfused vessels in a tissue. Step 606 of processing the data indicative of an applied pressure to provide a pressure measurement may include, but is not limited to, performing the steps described in greater detail below with reference to Fig. 6B including extracting an image of a bubble 152 in a pressure sensor 150 to determine applied pressure. In alternative embodiments, step 606 can include using capacitive or resistive readout circuitry 175 to read capacitive data indicative of the pressure applied to a pressure sensor 150 as described above with reference to Figs. 1A and 1B.

Step 608 of comparing the one or more features of interest and the pressure measurement to determine a pressure at which circulation is reduced can include, but is not limited to, comparing the density of perfused vessels at a certain pressure measurement to find one or more critical pressure points as described in detail above with reference to Figs. 1A and 1B. Step 610 of subsequently repeating the measurements to monitor a condition of a patient can include, but is not limited to, making repeated measurements of the microcirculation of a septic patient to monitor patient health and determine whether the

condition is improving or worsening especially when the patient is subject to treatment as described above with reference to Figs. 1A-4. Optional step 612 of altering therapeutic treatment based on the measured data can include, but is not limited to, changing a drug or a dosage of a drug to treat a patient based on a response as measured through microvascular changes in accordance with the previous discussion with reference to Figs. 1A-4.

Images acquired by the probe 100 can be transmitted to a computing device 130 that optionally includes a memory 131 and image processing algorithms 133. At the time of image capture, several steps in a workflow can be executed. In some embodiments, a unique ID and metadata can be encoded into the filename of the captured images or video data as the data is stored to a storage medium. In some embodiments, the data can be uploaded to a cloud computer for storage. Additional preprocessing steps can be performed including, but not limited to, a Gaussian or Median noise filter, contrast enhancement such as contrast-limited histogram equalization, video stabilization, or automatic clipping for motion.

The computing device 130 can apply image processing algorithms 133 to the images or video frames to extract features of interest. Various algorithms and methods may be applied to an image or video frames to detect the features of interest. Methods for feature detection include, but are not limited to, edge detectors, ridge detectors, corner detectors, feature descriptors, and keypoint descriptors such as Frangi filters, Features from Accelerated Segment Test (FAST), or Fast Retina Keypoints (FREAK). In addition, image stabilization algorithms can be used to remove motion artifacts. The optical detection system can also be used to measure the spacing between membranes by interferometric or other techniques.

An exemplary workflow 620 for stabilizing and filtering frames of video or images is presented herein and depicted in Fig. 6B. In the first step (step 622), the images or video frames can be filtered to eliminate unwanted features or to highlight features of interest. For example, a Frangi filter can be applied to the video frames or images to emphasize strongly scattering elements such as vessel or bubble edges. Alternatively, a Frangi filter can also be applied to emphasize the dark centers of the blood vessels and filter out the strongly scattering elements. In some embodiments, an interpolation routine can be performed to fill areas where a filtered item or feature such as a bubble edge has been removed from the image or video frame. In step 624, a feature descriptor (such as the FAST algorithm) can be implemented to find corners or edges of features. The FAST algorithm can utilize a saliency function and thresholding in identifying local maxima.

In step 626, features can be identified using a feature descriptor. In one embodiment, an implementation of a FREAK keypoint descriptor can be utilized. The FREAK algorithm can compute a cascade of binary strings and compare pairs of image intensities over a multiscale retinal sampling pattern. By selecting pairs of sampling regions, the dimensionality of the descriptor may be reduced and the search can mimic the saccadic search of human sight. The FREAK descriptor may use a Hamming distance for the binary feature vector by calculating a bitwise XOR followed by bitcount. By sampling foveated "receptive fields", the density of points drops exponentially. In an exemplary embodiment, the FREAK feature descriptor can use 43 receptive fields including 17 octaves and the center. The FREAK descriptor can further use four clusters of 128 pairs. In an exemplary embodiment, the first 16 bytes of the FREAK descriptor represent coarse information (i.e., perifoveated). When the distance is below the threshold, the FREAK descriptor can be instructed to continue onto finer detail bytes.

In step 628 of the exemplary workflow 620, features are matched in a first image or video frame to features in a second image or video frame. For example, features from the FREAK descriptor can be matched in different video frames or images. In step 630, a sample analysis tool such as, for example, a random sample consensus (RANSAC) method can be used to develop a motion model based on the matched features. In step 632, an interframe motion matrix can be output that is used to stabilize each image or video frame throughout a series of video frames or images.

In accordance with various embodiments, an image quality score may be assigned to an image or video frame to determine whether it is included or excluded through further image analysis. The video frame or image can be rated in one or more categories including, but not limited to, illumination, duration, focus, content, stability, and applied pressure. A score can be assigned to each category. In some embodiments, a score of zero can indicate that the image scores "good" in that category, a score of 1 can indicate that the image is "acceptable" in that category, and a score of 10 can indicate that the image is "unacceptable" in that category. The scores from each category can be added to determine an overall image quality score. In some embodiments, images with an overall image quality score over a certain threshold can be rejected from further analysis. In an embodiment, the threshold may be an overall image quality score of 9. In some embodiments, the overall image quality score can be used to sort video frames or images to guide selection of a limited sample size.

When stabilized images are obtained, a further image analysis step can automatedly detect areas or features of interest. The image analysis can include image enhancement, frame averaging, vessel segmentation, and blood flow analysis. Elements of blood flow analysis can include, but are not limited to, microvascular flow index (MFI), portion of perfused vessels (PPV), perfused vessel density (PVD), heterogeneity index, or total vessel density.

A sequence of images of microvasculature obtained under conditions of increasing pressure is shown in Figs. 7-11. The dark-field images of the vasculature in 7A-11A were obtained from a probe in accordance with the embodiments of the present invention. In this series of images, the capillaries, arterioles, and venules are clearly depicted with a bubble from a pressure sensor overlaid. The vasculature is least occluded (i.e., greatest amount perfused) in the first image and gradually becomes more occluded through the series of images.

The images in 7B-11B began as the respective images in 7A-11A before being subjected to image processing algorithms. Upon application of a Frangi filter, the images in 7B-11B contain only content from the black vessels and suppress the contribution of the specular reflections from the pressure sensing bubble. Similarly, the images in 7C-11C are obtained from the respective images in 7A-11A by applying a Frangi filter that emphasizes the specular reflection of the bubble edge and vessel edges while suppressing the dark vessels. The application of image filtering and processing methods to the images can allow the computing device to automatically fit and extract parameters from the images including, but not limited to, bubble shape, bubble area, density of perfused vasculature, and density of occluded vasculature. In some embodiments, the automated analysis of collected images can trigger an audible or visual alarm to warn the user that too much pressure is being applied or to adjust the probe position.

Fig. 12 illustrates a distal end view of an alternative embodiment of an imaging device 1200 according to various embodiments of the present invention. In this embodiment, the imaging device 1120 has at least two illumination sources: a first illumination source 1225 and a second illumination source 1226. The first illumination source 1225 and the second illumination source 1226 can have different output wavelengths. For example, the first illumination source 1225 can be a green LED and the second illumination source 1226 can be a blue LED. In some embodiments, there are eight equally spaced first illumination sources 1225 and 8 equally spaced second illumination sources 1226 wherein the first and second illumination sources alternate in sequence. In this embodiment, all of the illumination

sources can be individually controlled and indexed by a microcontroller, and the microcontroller can be synced to or triggered by a signal from the detector. Strategic manipulation of the illumination sources 1225, 1226 in this embodiment can enable various structured light techniques. For example, the illumination sources to one side of a dividing line 1227 can be activated while the sources on the opposite side of dividing line 1227 are de-activated. By alternating the activated half, features of the tissue can be differentially illuminated in subsequent images. Alternatively, the illumination sources may be programmed to illuminate in a sequential pattern optimized for the particular imaging technique that is desired. These techniques are the root of imaging methods known as phase-contrast imaging, differential phase-contrast microscopy, or differential interference contrast imaging. Analysis of these differentially illuminated images can provide structural or relief information including depth information of microvasculature within a tissue. Similarly, information such as position-resolved oxygenation measurements can be calculated by acquiring images under alternating illumination with different wavelengths.

Fig. 13 illustrates a probe 100 in use in a clinical setting according to embodiments of the present invention. The probe may be held by the hand of a user and positioned with the distal end near a tissue to be measured. The tissue may be the submucosal cavity within a patient's mouth. The user can brace the instrument against a patient's teeth to provide greater stability for the measurement. In some embodiments, the probe 100 may be placed in a mount 1300 to provide improved stability and allow for continuous monitoring. In an exemplary embodiment, the mount 1300 can pre-position the probe 100 at a tissue of interest and lock the probe 100 into place thereby reducing or eliminating motion artifacts. The mount 1300 can be a mouthpiece that is of a general shape or that is shaped specifically to fit within a user's mouth cavity. In some embodiments, the shape of the mount 1300 can be chosen according to volumetric data of a user's mouth or other tissue obtained from, for instance, photographs, video, CAT scan, 3-D laser object scanning, or any other suitable method. The mount 1300 can be manufactured using epoxies, quick-curing polymers, or 3-D printing methods, for example.

Although the probes described herein have been presented with reference to measurements of the submucosa in the sublingual cavity, it will be understood by those skilled in the art that the systems and methods presented in this disclosure can be used in other areas of a patient. For example, a probe as described above with reference to Fig. 1 can be used in an open surgical environment to measure circulation within a part of a body cavity

or to make circulation measurements percutaneously. In an exemplary application, the systems and methods described herein can be used to measure blood flow in a brain of a patient in particular during a surgical operation.

During clinical care for critically ill patients with compromised cardiovascular (CV) systems due to CV disease or infectious disease, measurements of central venous pressure (CVP) can be a key indicator of patient health. A physician can use transverse ultrasound (i.e., B-mode) to observe blood flow in the internal jugular vein. Applying external pressure by manually forcing the imaging head of the ultrasound (US) probe against the side of the neck can cause the internal jugular vein to collapse. The relationship between applied pressure and internal jugular vein collapse can relate directly to central venous pressure.

Figs. 14A and 14B depict pressure-sensitive ultrasound probes according to several embodiments of the present invention. As shown in Fig. 14A, the ultrasound probe 1400 can include a probe handle 1402 adapted to be gripped by a user. At the distal end of the probe handle 1402, the ultrasound probe 1400 can include a linear transducer array 1404. The linear transducer array 1404 can be covered by a cover 1406. The cover 1406 can include a pressure sensor 1450 to enable simultaneous acquisition of ultrasound data from a tissue and measurements of the applied pressure.

The cover 1406 can have a variety of conformations and can attach to the probe handle 1402 or linear transducer array 1404 in a variety of ways. In some embodiments, the cover 1406 is removable and disposable to improve sterility of the probe 1400. Alternatively, a portion of the cover 1406 such as the sheet 1408 may be disposable or none of the cover may be disposable. In an exemplary embodiment, the cover 1406 includes a rigid, plastic locking ring 1407 that locks to the probe handle 1402 to hold the cover 1406 in place. A sheet 1408 can be encapsulated within the locking ring 1407 to cover the linear transducer array 1404. The sheet 1408 can provide a sterile barrier between the tissue being examined and other elements of the probe 1400. In an exemplary embodiment, the sheet 1408 includes a polyvinyl alcohol film or film of another polymer that is flexible and transparent.

The pressure sensor 1450 can be placed in contact with the sheet 1408. In some embodiments, the pressure sensor 1450 lies embedded within the sheet 1408. The pressure sensor 1450 can be similar to the pressure sensor 150 as described above in greater detail with reference to Fig. 3. The pressure sensor 1450 can include capacitive or resistive sensing elements including conductive polymer membranes. In addition, the pressure sensor 1450 can

include one or more bubbles contained with a gel or other substance. Alternatively, the pressure sensor 1450 can contain one or more microdroplets of a fluid (for example, an ionic fluid) surrounded by air or a gaseous dielectric as described previously. The conformation of the one or more bubbles or microdroplets can be measured via optical or ultrasound means and correlated to an applied pressure.

Fig. 14B depicts an alternative embodiment of an ultrasound probe 1410 that includes an extended cover 1416 to provide sterility and enable measurements of applied pressure. The ultrasound probe can include a handle 1402 and a linear transducer array 1404. Although probes 1400, 1410 are described herein as having linear transducer arrays, it will be understood by one skilled in the art that any current or future ultrasound transducer technology can be compatible with the concepts presented herein including 2-D arrays and arrays of any number of elements or bit depths.

The extended cover 1416 can be affixed or attached to the probe handle 1402 or linear transducer array 1404 through a variety of means. In some embodiments, the extended cover 1416 includes buttressed supports or rigid L-brackets that connect to the handle 1402 to strengthen the extended cover 1416. In accordance with various embodiments, the extended cover 1416 is removable and disposable to improve sterility of the probe 1410. Alternatively, a portion of the extended cover 1416 such as the sheet 1418 may be disposable or none of the cover may be disposable. In an exemplary embodiment, the extended cover 1416 includes a ring 1417 and a sheet 1418 that covers at least the linear transducer array 1404 of the probe 1410. The sheet 1418 can be encapsulated within the ring 1417 and can provide a sterile barrier between the tissue being examined and other elements of the probe 1410. In an exemplary embodiment, the sheet 1418 includes a polyvinyl alcohol film or film of another polymer that is flexible and transparent.

The extended cover 1416 can include one or more pressure sensors 1452 disposed at various locations about the ring 1417. The pressure sensors 1452 can be substantially as described previously with reference to Fig. 3 and Fig. 14A. For example, the pressure sensors 1452 can include capacitive or resistive elements such as conductive polymer layers. In addition, the pressure sensor 1450 can include one or more bubbles contained with a gel or other substance. The conformation of the one or more bubbles can be measured via optical means and correlated to an applied pressure. Alternatively, the pressure sensors 1452 need not be transparent because their location on the ring 1417 does not interfere with the operation of the linear transducer array 1404. The pressure sensors 1452 can be opaque or can

reflect ultrasound radiation such that metallic resistive sensors may be used as well as capacitive or non-metallic resistive sensors. The larger area of the ring 1417 as compared to the embodiment of Fig. 14A allows a larger area of pressure to be applied to the neck of a patient. In addition, the use of a plurality of pressure sensors 1452 can allow measurement of a pressure distribution across the probe 1410.

The ultrasound probes 1400, 1410 can be used to measure central venous pressure (CVP) as follows. Cross-sectional (transverse) imagery of the internal jugular vein of a patient may be acquired. The clinician can apply a steady pressure to the patient through the probe 1400, 1410 until the internal jugular vein begins to collapse. The pressure sensor 1450, 1452 can measure the pressure or force at which the collapse begins to occur. In some embodiments, the pressure sensor 1450, 1452 and any associated electronics can be calibrated in standard units and an optional timestamp or other signal can be used to synchronize the pressure measurements with the ultrasound image. The clinician can go on to measure other values of applied pressure such as the pressure that will cause, for example, up to 50% or 90% of vessel collapse. In some embodiments, the probe 1400, 1410 can be connected to a computing device containing lookup tables or programmed functions that can translate the observed onset pressure of internal jugular vein collapse and other critical or target pressure values in relation to percent compression of vessel walls. In this way, the clinician can estimate clinically relevant data such as CVP. Each probe has a linear or two-dimensional array of transducer elements having 64, 128, or 256 elements or more, for example. Each probe can be connected by a cable to a data processor and display unit that displays ultrasound images. The ultrasound system can be integrated with the pressure, temperature, EKG, and other sensors and sensor circuits as described herein.

In another embodiment, an ultrasound probe can be attached at one end of a piston within a quasi-hydrostatic vessel that includes a fluid-filled balloon or bladder. The piston can form a pressure seal with the sides of the vessel wall, and the vessel wall can have any shape including cylindrical, elliptical, or rectangular that meets application-specific requirements. The end of the vessel opposite the piston can be shaped in a semi-circular fashion to fit comfortably against a patient's neck. The pressure inside the fluid-filled balloon or bladder can be monitored via a pressure sensor introduced into the sealed fluid chamber via feed-through. In this embodiment, the operator can maneuver the transducer and piston assembly together to produce an image of the jugular vein. Then, the operator can apply

pressure necessary to collapse the jugular vein as described above with respect to the embodiments of Figs. 14A and 14B.

While the present inventive concepts have been described with reference to particular embodiments, those of ordinary skill in the art will appreciate that various substitutions and/or other alterations may be made to the embodiments without departing from the spirit of the present inventive concepts. Accordingly, the foregoing description is meant to be exemplary and does not limit the scope of the present inventive concepts.

A number of examples have been described herein. Nevertheless, it should be understood that various modifications may be made. For example, suitable results may be achieved if the described techniques are performed in a different order and/or if components in a described system, architecture, device, or circuit are combined in a different manner and/or replaced or supplemented by other components or their equivalents. Accordingly, other implementations are within the scope of the present inventive concepts.

CLAIMS

1. A system to measure parameters of a circulatory system, comprising:

a probe including at least one energy source and a detector to provide image data indicative of the presence of circulation within tissue;

a pressure sensor to provide a measurement of pressure applied to the tissue; and

a computing device including a memory and a processor, the memory including processor-executable instructions that when executed by the processor perform the step of using the image data indicative of the presence of circulation and the measurement of pressure to determine a pressure at which circulation is reduced in the tissue.

2. The system of claim 1, wherein the probe is an optical probe, the at least one energy source is an illumination source, and the detector is an x-y detector for two-dimensional imaging.

3. The system of claim 2, further comprising one or more beam-steering elements to steer illumination from the illumination source.

4. The system of claim 2, further comprising optical fibers to transmit illumination from the illumination source.

5. The system of claim 2, wherein the illumination source is a first illumination source and the system further comprises a second illumination source having a different output wavelength than the first illumination source.

6. The system of claim 5, wherein the first illumination source and second illumination source are individually controllable.

7. The system of claim 1, wherein the tissue is submucosal tissue in a sublingual cavity.

8. The system of claim 1, wherein the tissue is an internal jugular vein.

9. The system of claim 1, wherein the pressure sensor includes resistive or capacitive elements.

10. The system of claim 9, further comprising a circuit board including readout circuitry, the resistive or capacitive elements being connected to the readout circuitry.

11. The system of claim 1, wherein the pressure sensor includes droplets of an ionic liquid, flexible membranes, or bubbles surrounded by a gel.

12. The system of claim 11, wherein the pressure sensor is optically transparent for at least one wavelength in the visible spectrum.

13. The system of claim 11, wherein the pressure sensor is provided at a distal end of the probe.

14. The system of claim 12, wherein the energy source provides illumination that scatters from the tissue and passes through the pressure sensor before reaching the detector.

15. The system of claim 11, wherein the bubbles are tinted to appear darker than surrounding tissue.

16. The system of claim 11, wherein the measurement of pressure corresponds to a shape or a cross-sectional area of at least one bubble included in the image data.

17. The system of claim 11, wherein the droplets of an ionic liquid form an iontronic microdroplet array.

18. The system of claim 11, wherein the volume of each of the droplets is in a range from 3 nL to 3μL.

19. The system of claim 11, wherein the spacing between bubbles is in a range between 0.2 mm and 3 mm.

20. The system of claim 11, wherein the flexible membranes isolate electrical and chemical elements of the pressure sensor from the surrounding environment.

21. The system of claim 1, wherein the processor-executable instructions further include the step of processing the image data indicative of the presence of circulation to stabilize the image or to identify one or more features of interest within the image data.

22. The system of claim 21, wherein identifying one or more features of interest within the image data includes determining a density of occluded or perfused blood vessels in the image.

23. The system of claim 21, wherein the one or more features of interest within the image data include the edges of a bubble.

24. The system of claim 21, wherein stabilizing the image data includes:

applying a Frangi filter to eliminate unwanted features or highlight features of interest;

finding corners or edges of features using a feature descriptor such as Features from Accelerated Segment Test (FAST);

identifying features using a feature descriptor such as Fast Retinal Keypoints (FREAK);

matching features in the image data to features in second image data;

using a sample analysis tool to develop a motion model based on the matched features; and

outputting an interframe motion matrix that operates to stabilize the image data.

25. The system of claim 21, wherein processing the image data includes performing an interpolation routine to fill in removed or missing areas.

26. The system of claim 1, wherein a step of comparing the image data indicative of the presence of circulation and the measurement of pressure to determine a pressure at which circulation is reduced includes identifying a first critical pressure at which a first threshold value related to circulation is reached and identifying a second critical pressure at which a second threshold value related to circulation is reached.

27. The system of claim 26, wherein the first threshold value and second threshold value are one of perfused or occluded blood vessel density.

28. The system of claim 1, further comprising at least one of a temperature sensor or oxygenation sensor to enable hemodynamic measurements.

29. The system of claim 1, further comprising a disposable cover that includes the pressure sensor, and wherein the detector comprises an imaging device.

30. The system of claim 29, wherein the disposable cover includes a registration notch that mates with a complementary registration tab on the imaging device.

31. The system of claim 1, further comprising a mount to lock the probe in place adjacent to the tissue.

32. The system of claim 1, wherein the probe is an ultrasound probe.

33. The system of claim 32, wherein the probe includes a linear transducer array and a cover attached to the pressure sensor.

34. The system of claim 33, further comprising a sheet to act as a sterile barrier to isolate the linear transducer array and/or the pressure sensor from tissue.

35. The system of claim 32, wherein the pressure sensor is positioned between the linear transducer array and tissue.

36. The system of claim 32, wherein the pressure sensor is located on a ring surrounding the linear transducer array.

37. A method of measuring a parameter of a circulatory system, comprising:

acquiring image data indicative of the presence of flow within tissue and data indicative of an applied pressure;

processing the image data using image processing algorithms to determine one or more features of interest;

processing the data indicative of an applied pressure to provide a pressure measurement; and

using the one or more features of interest and the pressure measurement to determine a pressure at which circulation is reduced in the tissue.

38. The method of claim 37, wherein the tissue is submucosal tissue in a sublingual cavity.

39. The method of claim 37, wherein the tissue is an internal jugular vein.

40. The method of claim 37, wherein the data indicative of an applied pressure includes measurements acquired from resistive or capacitive elements.

41. The method of claim 37, wherein the data indicative of an applied pressure includes image data.

42. The method of claim 41, wherein processing the data indicative of an applied measurement includes segmenting the image data to identify a bubble or droplet of liquid, and determining one of a cross-sectional area, a shape, a length of a major axis, or a length of a minor axis of the bubble or droplet.

43. The method of claim 38, wherein the image data is a two-dimensional image obtained from an x-y detector.

44. The method of claim 43, wherein the one or more features of interest include a density of occluded or perfused blood vessels in the image.

45. The method of claim 43, wherein processing the image data includes stabilizing the image data.

46. The method of claim 45, wherein stabilizing the image includes:

applying a Frangi filter to eliminate unwanted features or highlight features of interest;

finding corners or edges of features using a feature descriptor such as Features from Accelerated Segment Test (FAST);

identifying features using a feature descriptor such as Fast Retinal Keypoints (FREAK);

matching features in the image data to features in second image data;

using a sample analysis tool to develop a motion model based on the matched features; and

outputting an interframe motion matrix that operates to stabilize the image data.

47. The method of claim 38, wherein processing the image data includes performing an interpolation routine to fill in removed or missing areas.

48. The method of claim 38, wherein the image data is acquired from an ultrasound probe.

49. The method of claim 50, wherein the one or more features of interest include volume of blood flow through a vein.

50. The method of claim 38, wherein the pressure at which circulation is reduced is a first critical pressure.

51. The method of claim 50, further comprising:

acquiring second image data indicative of the presence of flow within tissue and second data indicative of an applied pressure;

processing the second image data using image processing algorithms to determine one or more second features of interest;

processing the second data indicative of an applied pressure to provide a second pressure measurement; and

using the one or more second features of interest and the second pressure measurement to determine a second critical pressure.

52. The method of claim 51, further comprising altering therapeutic treatment based on a comparison of the first critical pressure and the second critical pressure.

53. A probe for measuring parameters of a circulatory system, comprising:

at least one energy source;

a detector to provide image data indicative of the presence of circulation within tissue; and

a pressure sensor to provide a measurement of pressure applied to the tissue, and

wherein the image data indicate a level of circulation within tissue that is correlated with the measurement of pressure to determine a pressure at which circulation is reduced in the tissue.

54. The probe of claim 53, wherein the at least one energy source is an illumination source and the detector is an x-y detector for two-dimensional imaging.

55. The probe of claim 54, further comprising one or more beam-steering elements to steer illumination from the illumination source.

56. The probe of claim 54, further comprising optical fibers to transmit illumination from the illumination source.

57. The probe of claim 54, wherein the illumination source is a first illumination source and the system further comprises a second illumination source having a different output wavelength than the first illumination source.

58. The probe of claim 57, wherein the first illumination source and second illumination source are individually controllable.

59. The probe of claim 53, wherein the tissue is submucosal tissue in a sublingual cavity.

60. The probe of claim 53, wherein the tissue is an internal jugular vein.

61. The probe of claim 53, wherein the pressure sensor includes resistive or capacitive elements.

62. The probe of claim 61, further comprising a circuit board including readout circuitry, the resistive or capacitive elements being connected to the readout circuitry.

63. The probe of claim 53, wherein the pressure sensor includes droplets of an ionic liquid, flexible membranes, or bubbles surrounded by a gel.

64. The probe of claim 63, wherein the pressure sensor is optically transparent for at least one wavelength in the visible spectrum.

65. The probe of claim 63, wherein the pressure sensor is provided at a distal end of the probe.

66. The probe of claim 64, wherein the energy source provides illumination that scatters from the tissue and passes through the pressure sensor before reaching the detector.

67. The probe of claim 63, wherein the bubbles are tinted to appear darker than surrounding tissue.

68. The probe of claim 63, wherein the droplets of an ionic liquid form an iontronic microdroplet array.

69. The probe of claim 63, wherein the volume of each of the droplets is in a range from 3 nL to 3 μL.

70. The probe of claim 63, wherein the spacing between bubbles is in a range between 0.2 mm and 3 mm.

71. The probe of claim 63, wherein the flexible membranes isolate electrical and chemical elements of the pressure sensor from the surrounding environment.

72. The probe of claim 53, further comprising at least one of a temperature sensor or oxygenation sensor to enable hemodynamic measurements.

73. The probe of claim 53, further comprising a disposable cover that includes the pressure sensor, and wherein the probe is an imaging device.

74. The probe of claim 73, wherein the disposable cover includes a registration notch that mates with a complementary registration tab on the imaging device.

75. The probe of claim 53, wherein the probe is engageable with a mount to lock the probe in place adjacent to the tissue.

76. The probe of claim 53, wherein the probe is an ultrasound probe.

77. The probe of claim 76, wherein the probe includes a linear transducer array and a cover attached to the pressure sensor.

78. The probe of claim 77, further comprising a sheet to act as a sterile barrier to isolate the linear transducer array and/or the pressure sensor from tissue.

79. The probe of claim 76, wherein the pressure sensor is positioned between the linear transducer array and tissue.

80. The probe of claim 76, wherein the pressure sensor is located on a ring surrounding the linear transducer array.

81. The probe of claim 53 further comprising a light emitting diode light source.

82. The probe of claim 53 further comprising an annular array of light sources at a distal end of the probe.

83. The probe of claim 53 wherein the probe comprises a handle and a tubular body attached to the handle.

84. The probe of claim 53 comprising a handle including a circuit that is connected to an external processing device with a cable.

85. The probe of claim 84 wherein the detector is mounted to the handle and is optically coupled to a distal end of the probe with a lens.

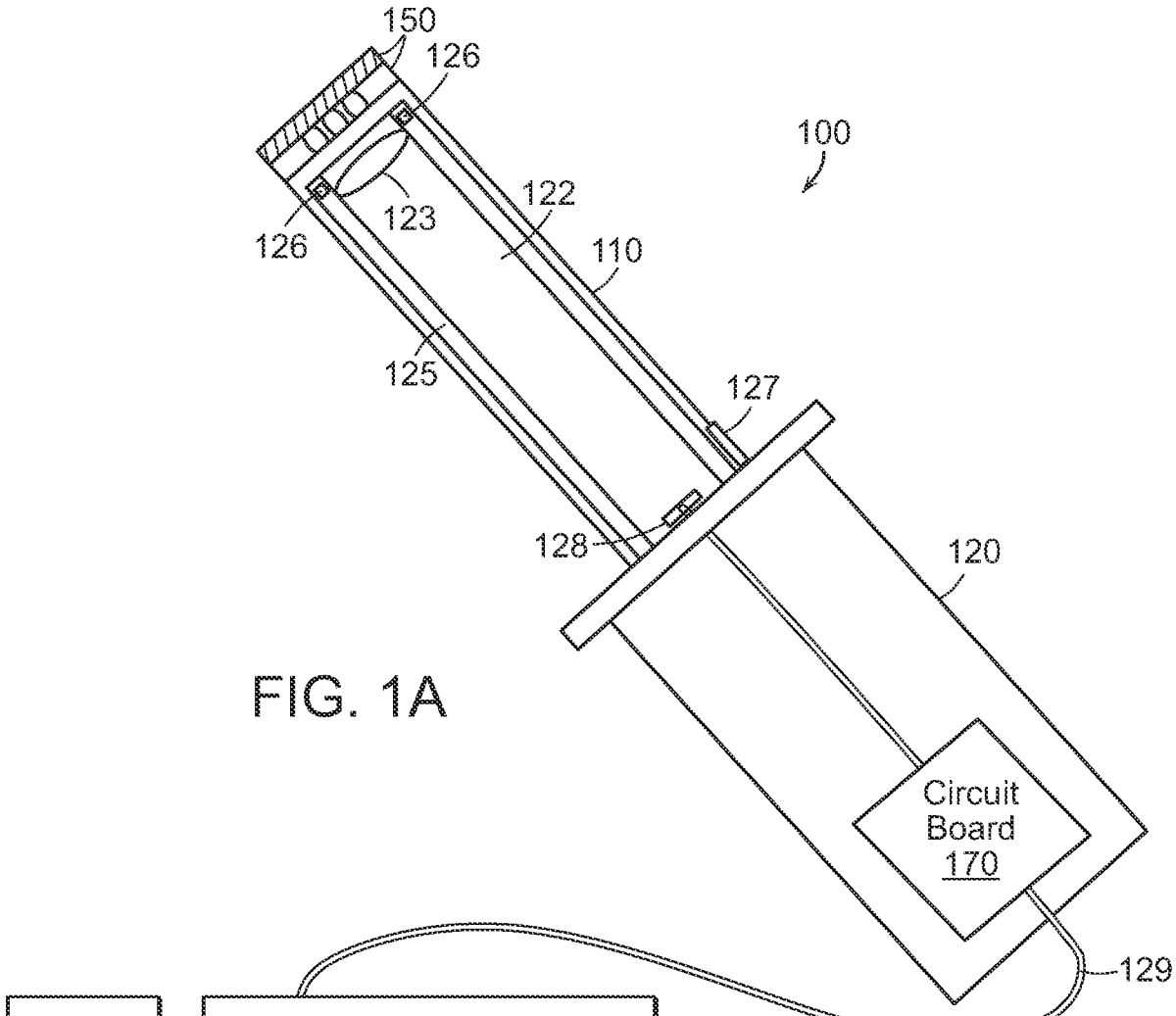

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100
122
123
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120
Circuit Board 170
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Display 132
Computing Device 130
Memory 131
Image Processing Algorithms 133
Power Source 134

FIG. 1A

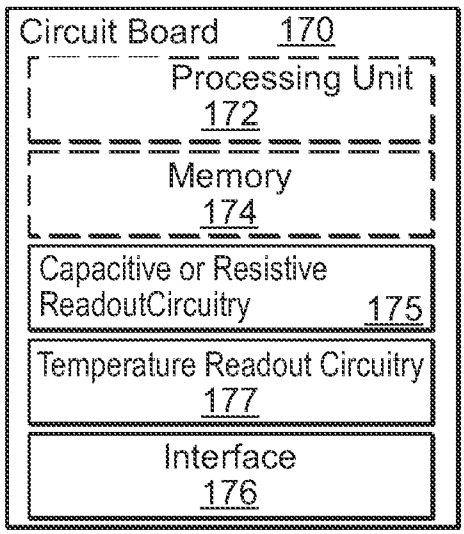

Circuit Board 170
Processing Unit 172
Memory 174
Capacitive or Resistive ReadoutCircuitry 175
Temperature Readout Circuitry 177
Interface 176

FIG. 1B

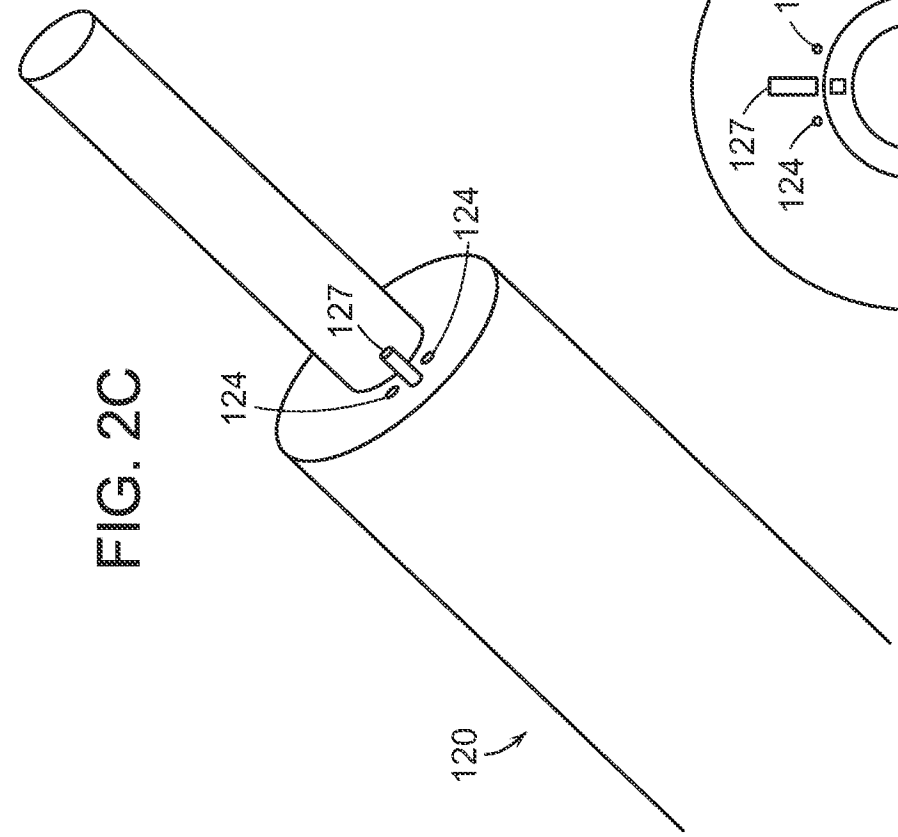


FIG. 2C

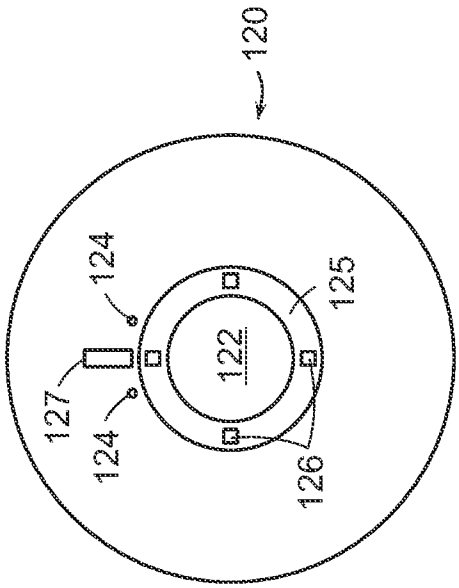


FIG. 2D

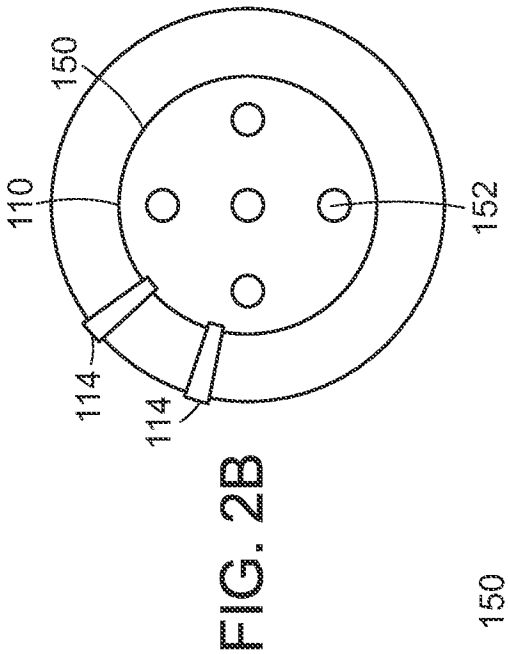


FIG. 2B

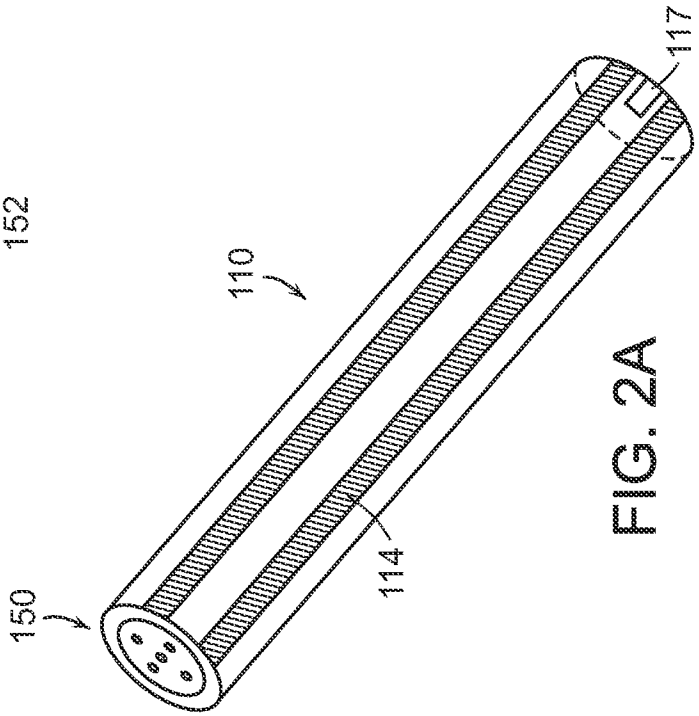


FIG. 2A

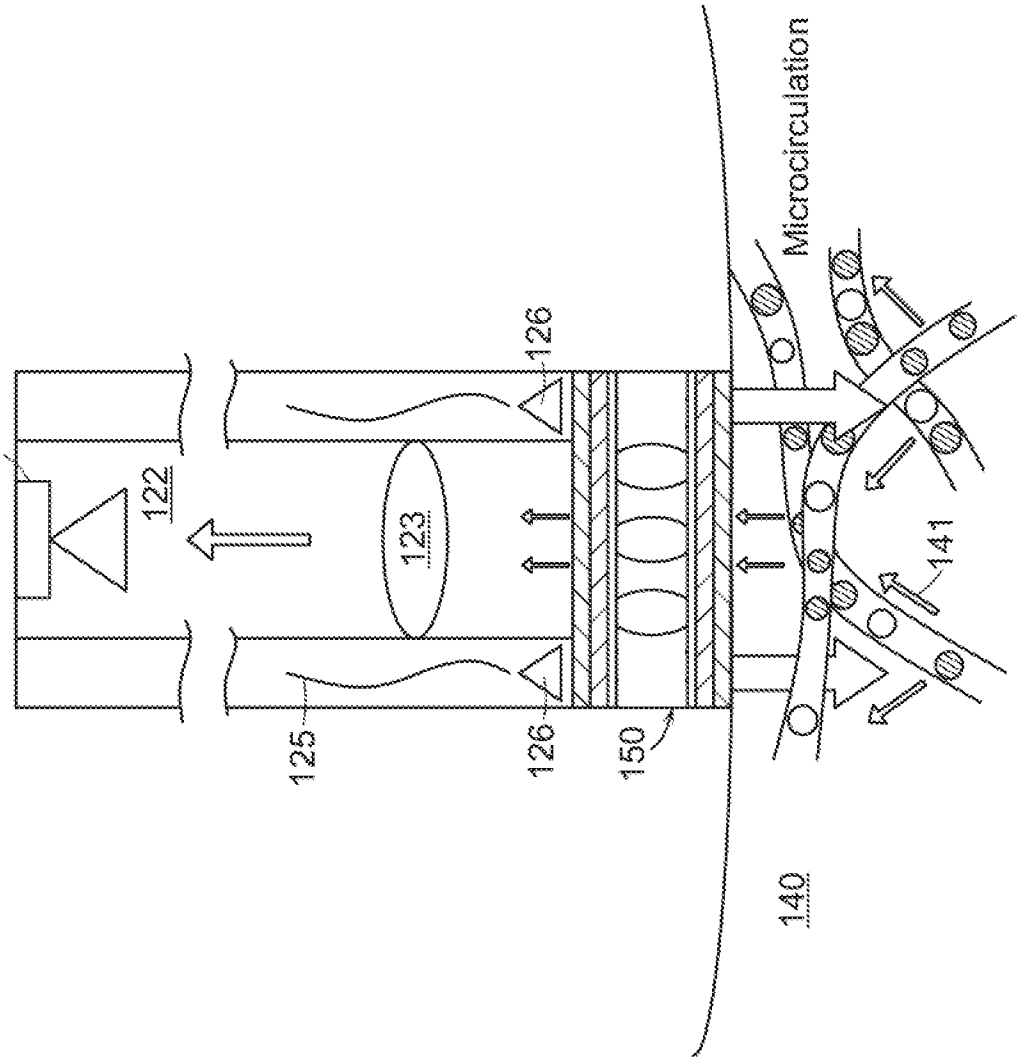

Microcirculation
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126
125
126
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FIG. 4

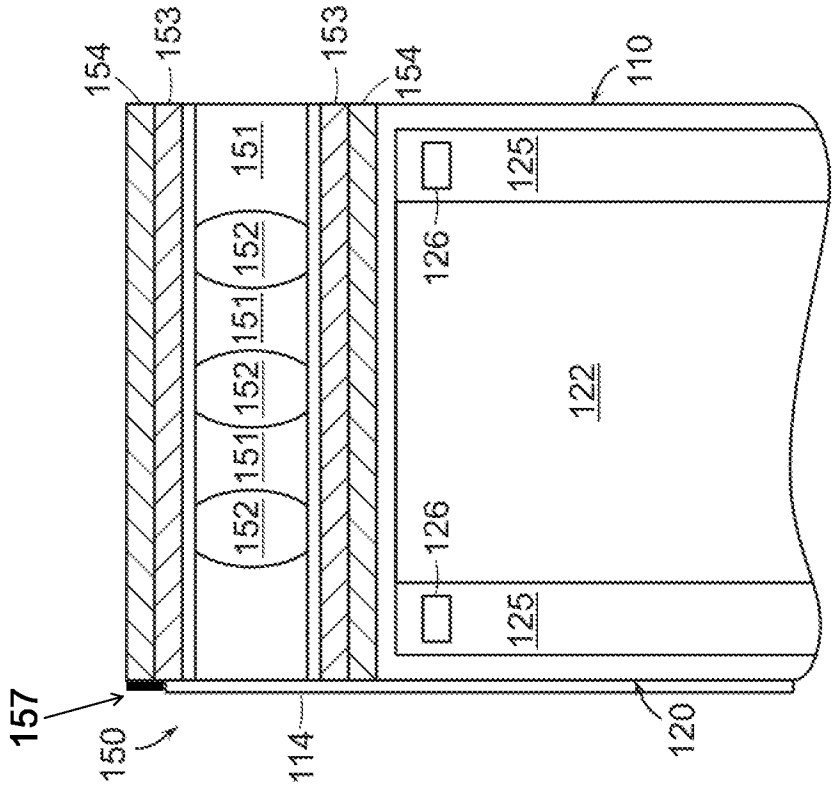

154
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FIG. 3

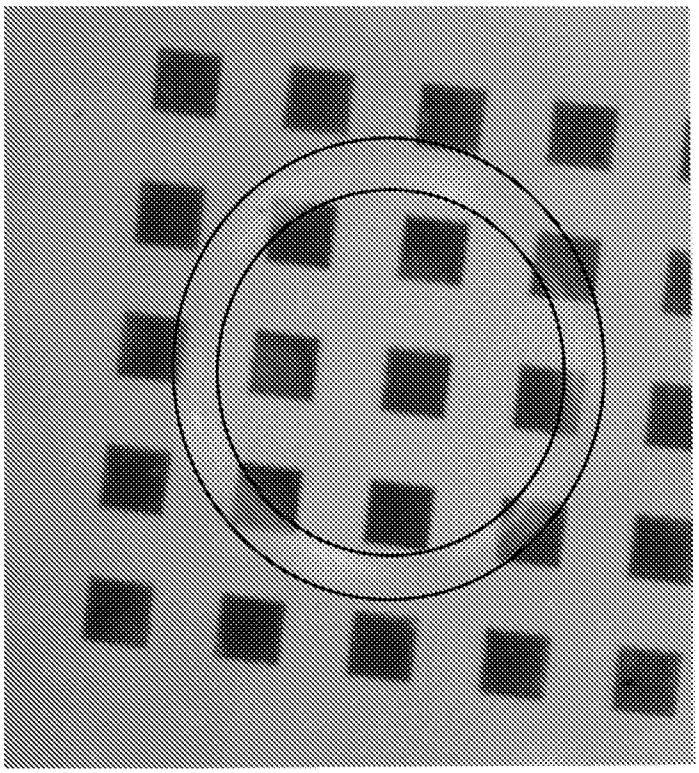


Fig. 5B

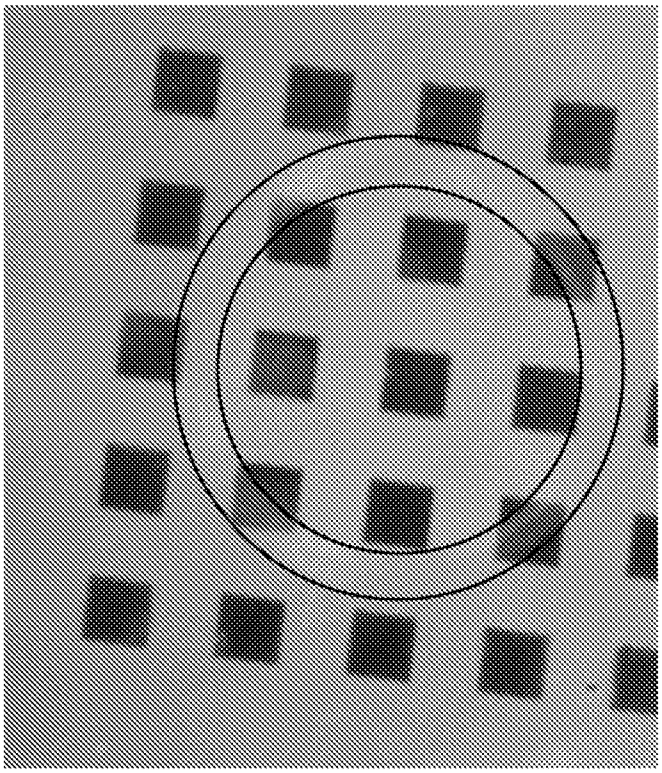


Fig. 5C

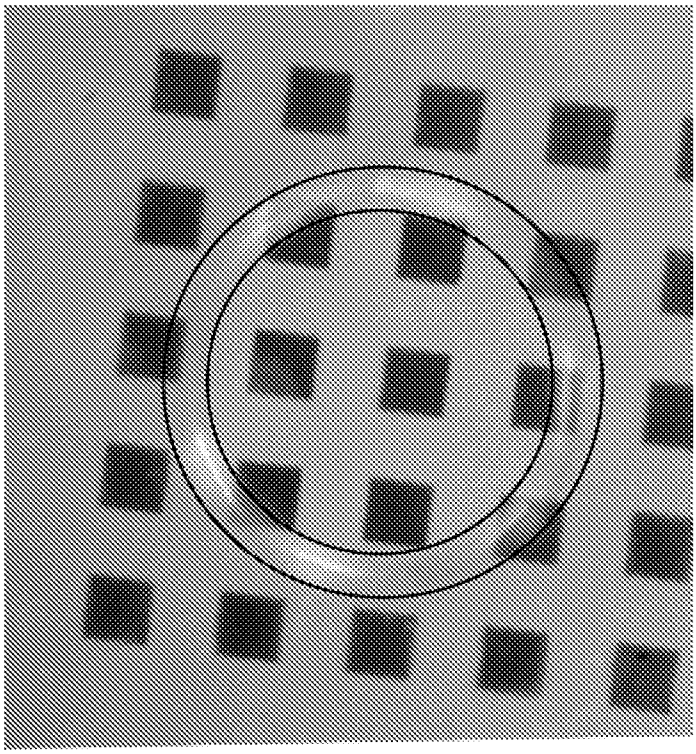


Fig. 5A

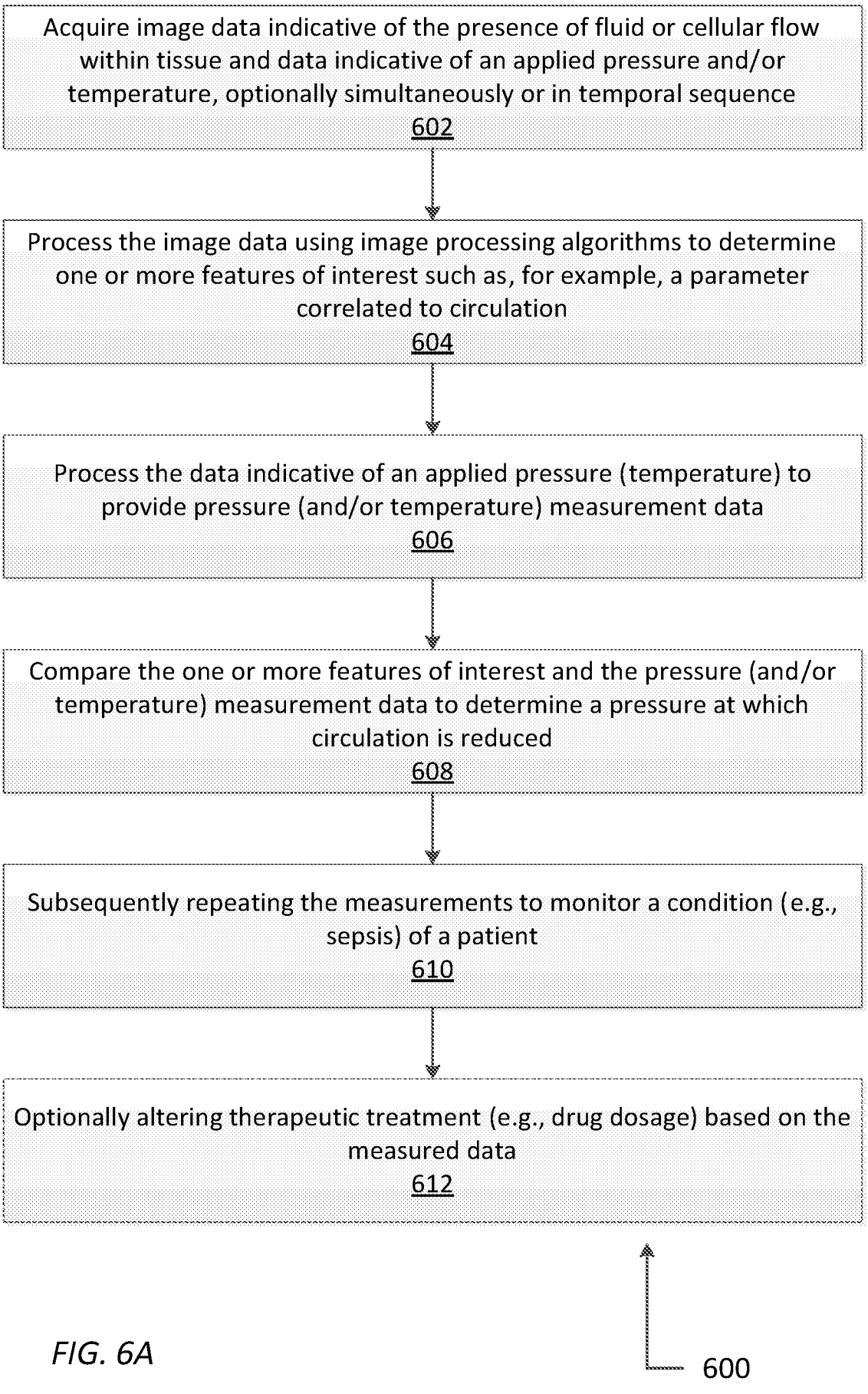

Acquire image data indicative of the presence of fluid or cellular flow within tissue and data indicative of an applied pressure and/or temperature, optionally simultaneously or in temporal sequence
602
Process the image data using image processing algorithms to determine one or more features of interest such as, for example, a parameter correlated to circulation
604
Process the data indicative of an applied pressure (temperature) to provide pressure (and/or temperature) measurement data
606
Compare the one or more features of interest and the pressure (and/or temperature) measurement data to determine a pressure at which circulation is reduced
608
Subsequently repeating the measurements to monitor a condition (e.g., sepsis) of a patient
610
Optionally altering therapeutic treatment (e.g., drug dosage) based on the measured data
612
600

FIG. 6A

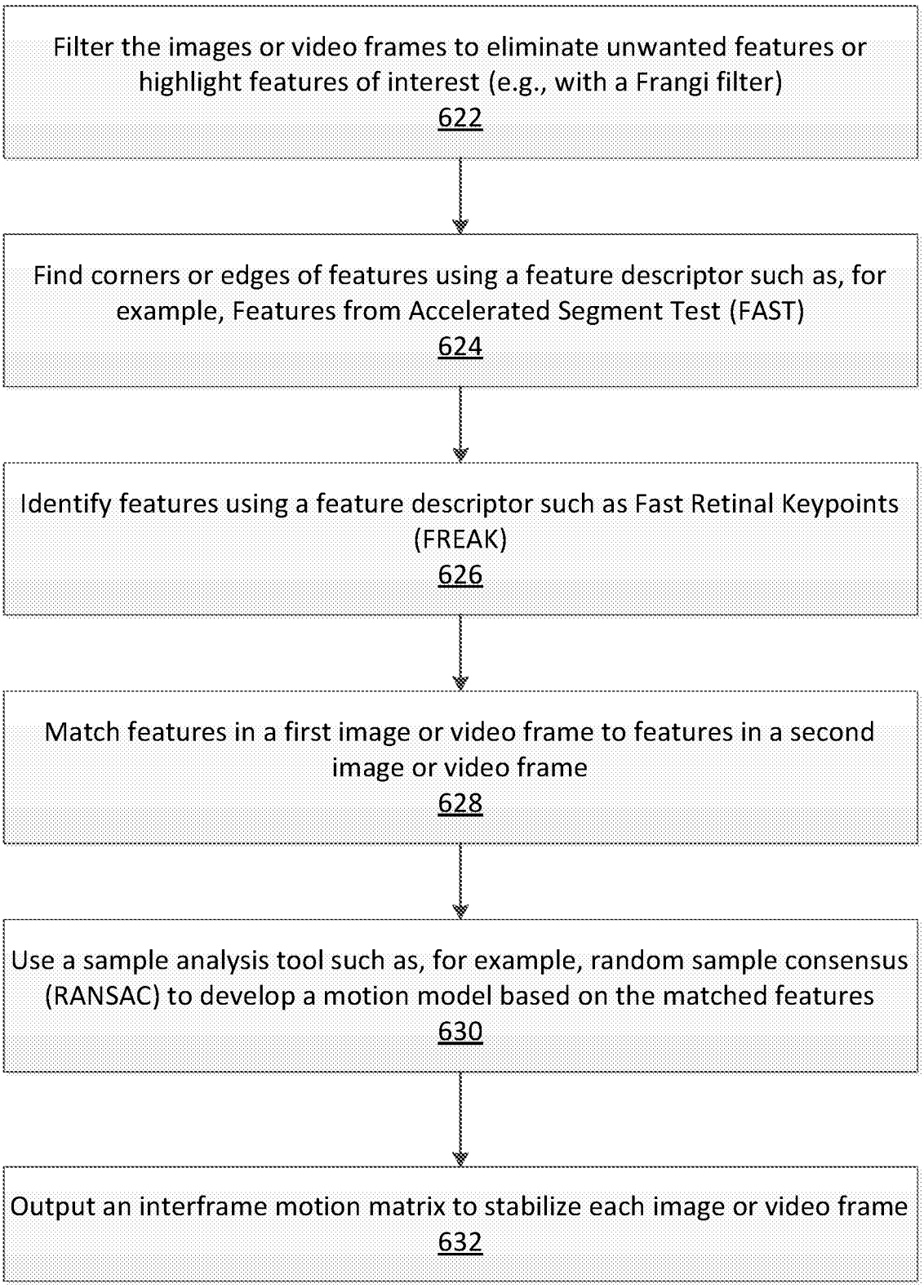

Filter the images or video frames to eliminate unwanted features or highlight features of interest (e.g., with a Frangi filter)
622
Find corners or edges of features using a feature descriptor such as, for example, Features from Accelerated Segment Test (FAST)
624
Identify features using a feature descriptor such as Fast Retinal Keypoints (FREAK)
626
Match features in a first image or video frame to features in a second image or video frame
628
Use a sample analysis tool such as, for example, random sample consensus (RANSAC) to develop a motion model based on the matched features
630
Output an interframe motion matrix to stabilize each image or video frame
632
620

FIG. 6B

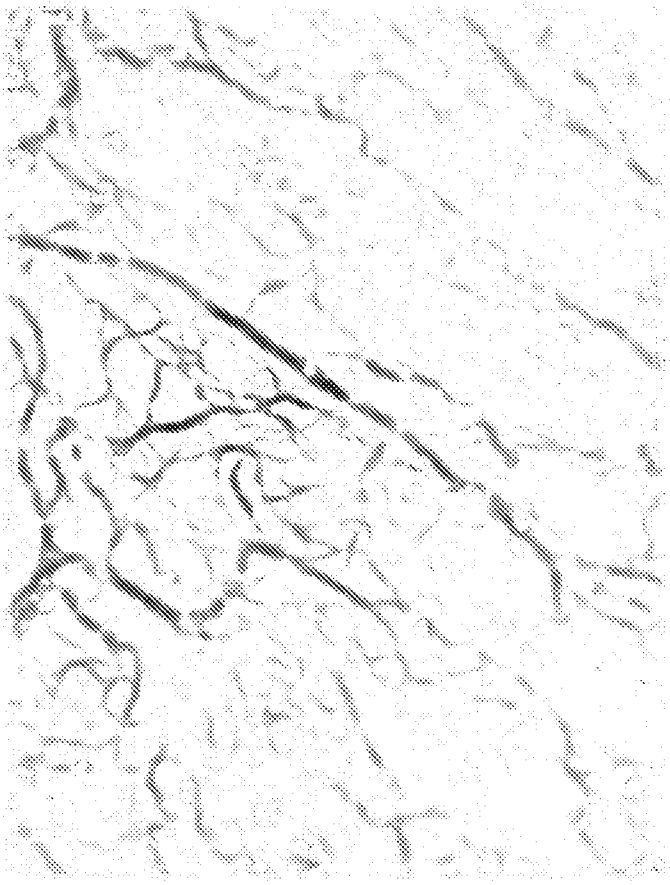


Fig. 7B

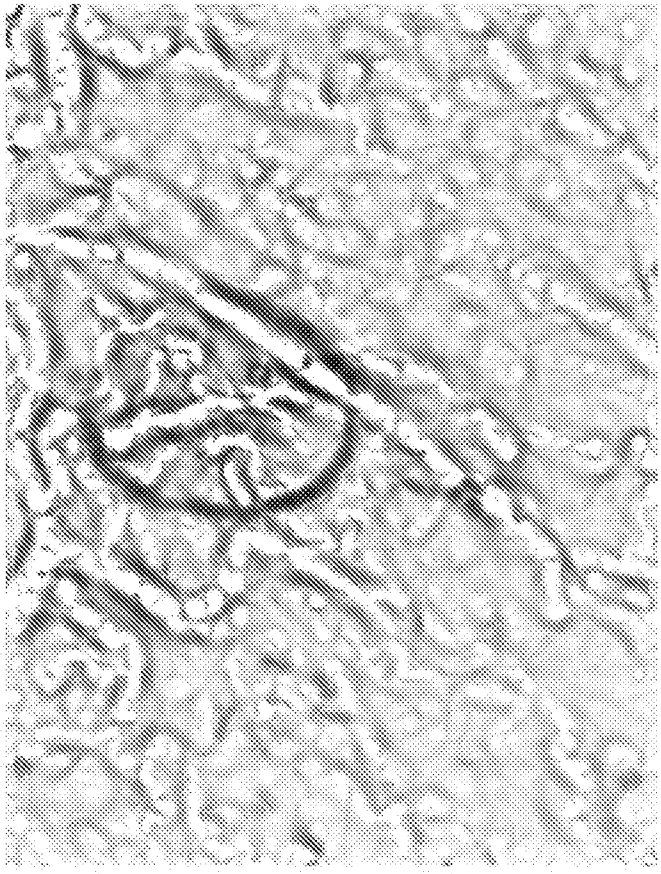


Fig. 7C

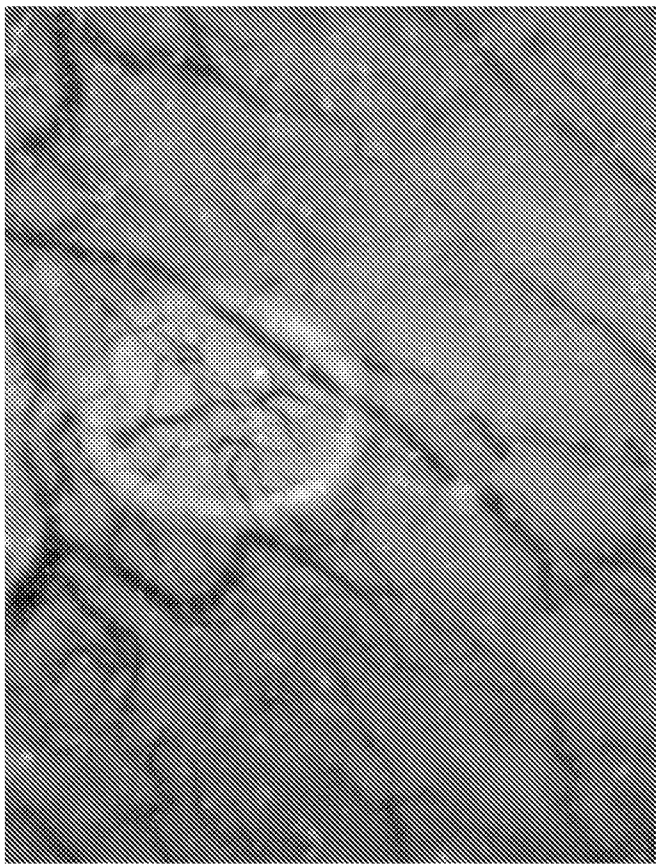


Fig. 7A

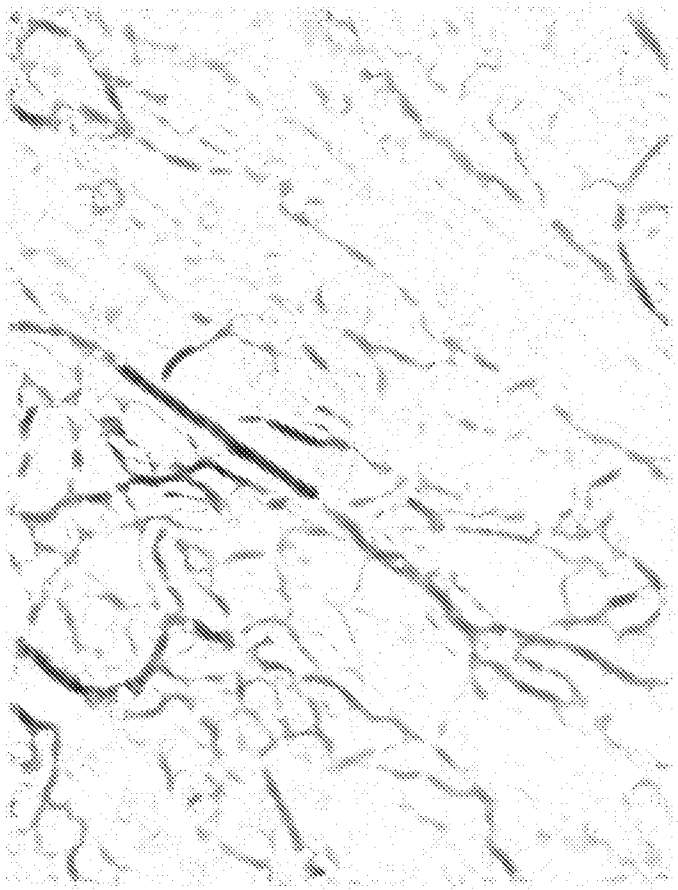


Fig. 8B

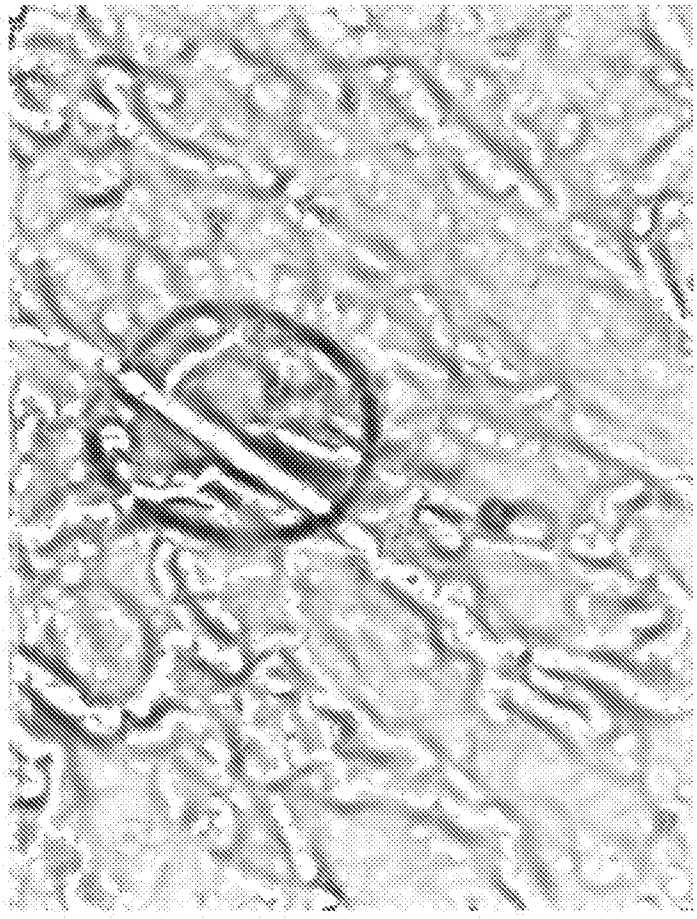


Fig. 8C



Fig. 8A



Fig. 9B

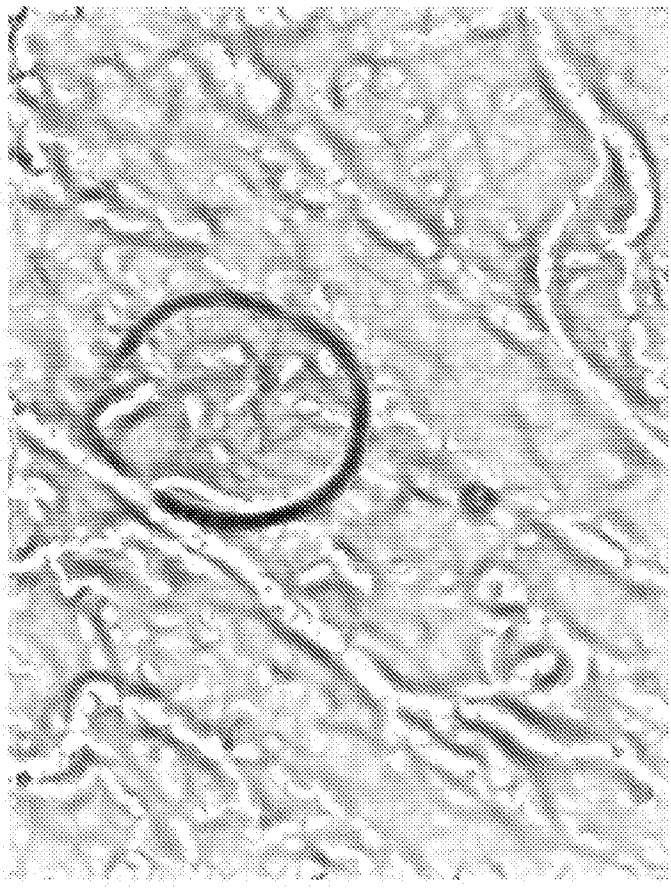


Fig. 9C

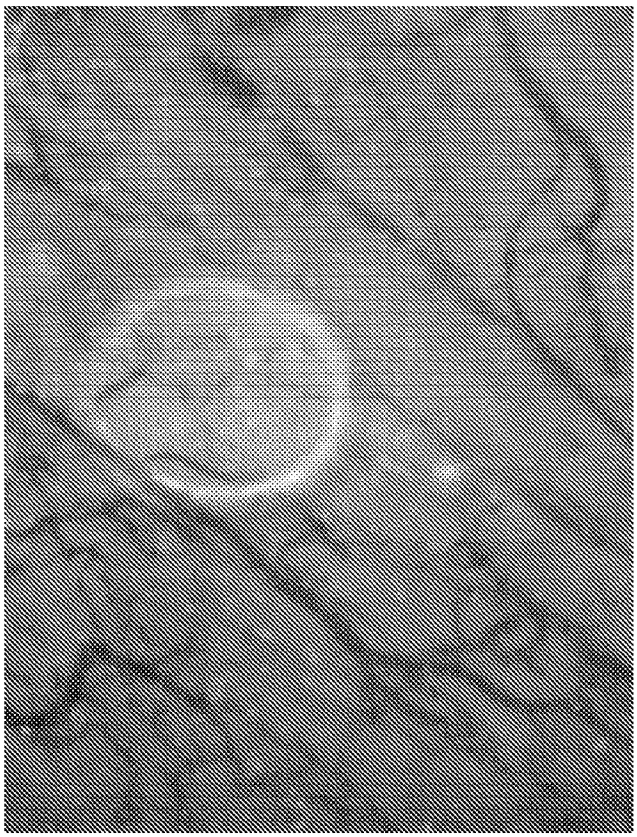


Fig. 9A



Fig. 10B

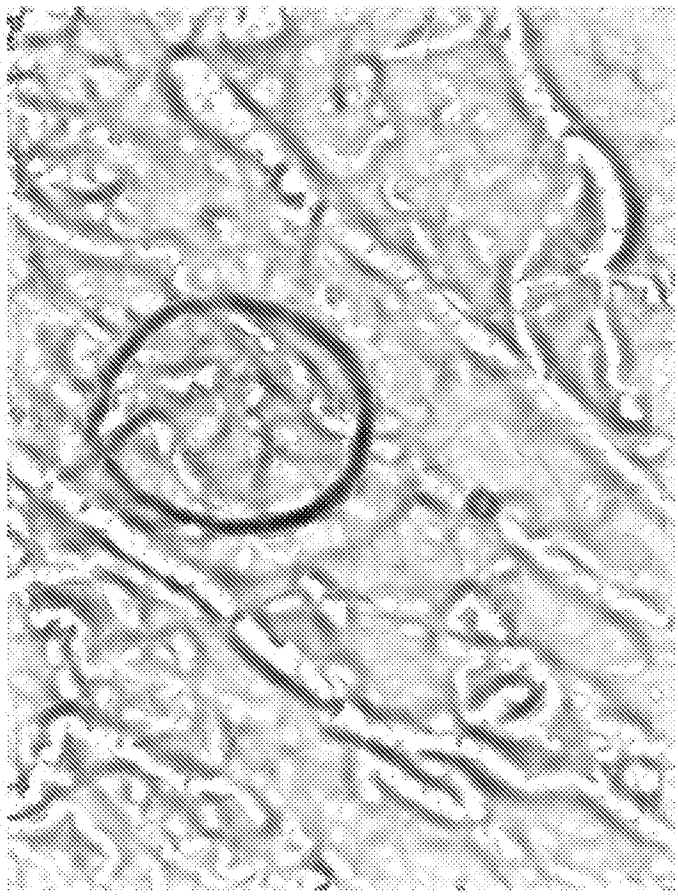


Fig. 10C

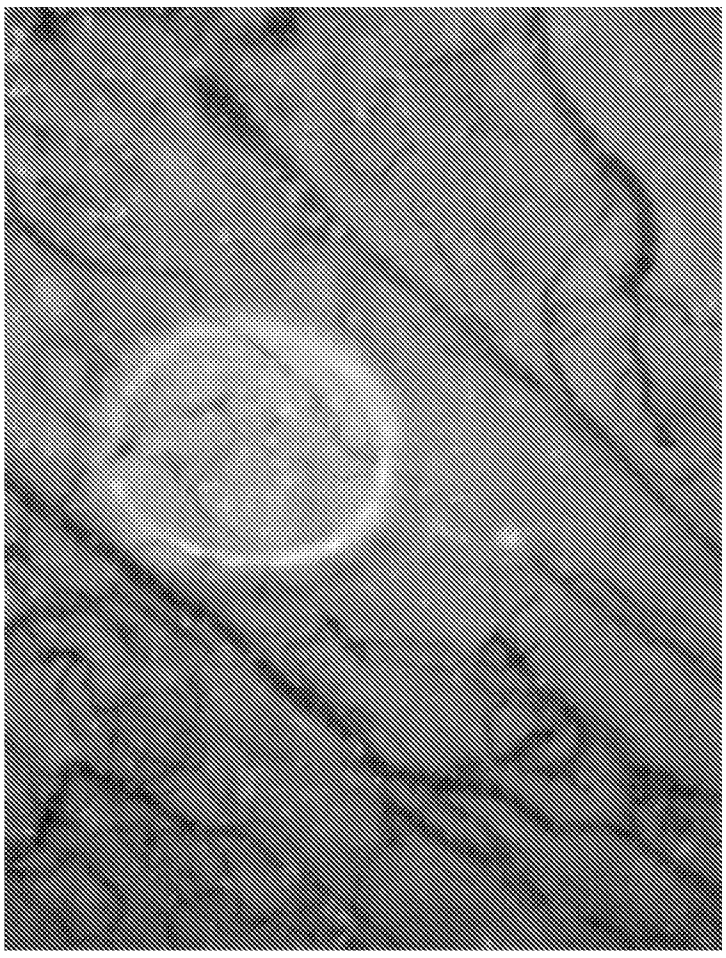


Fig. 10A

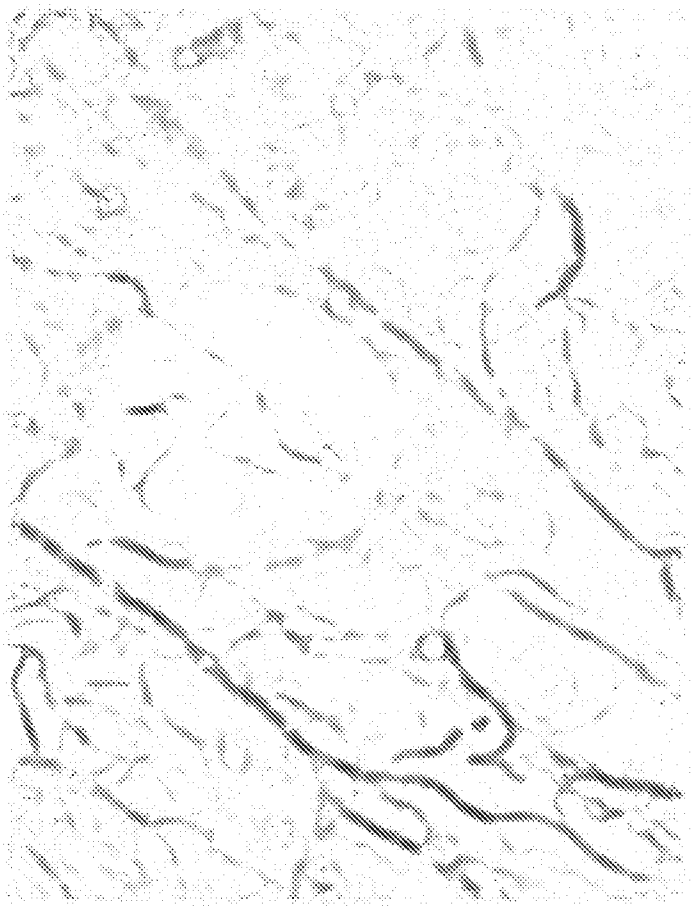


Fig. 11B

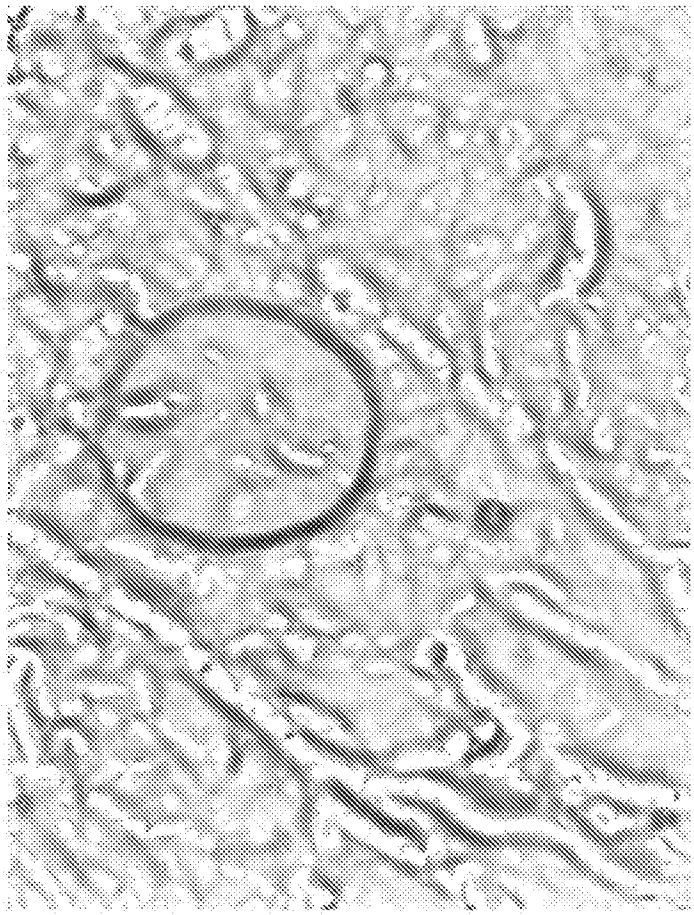


Fig. 11C



Fig. 11A

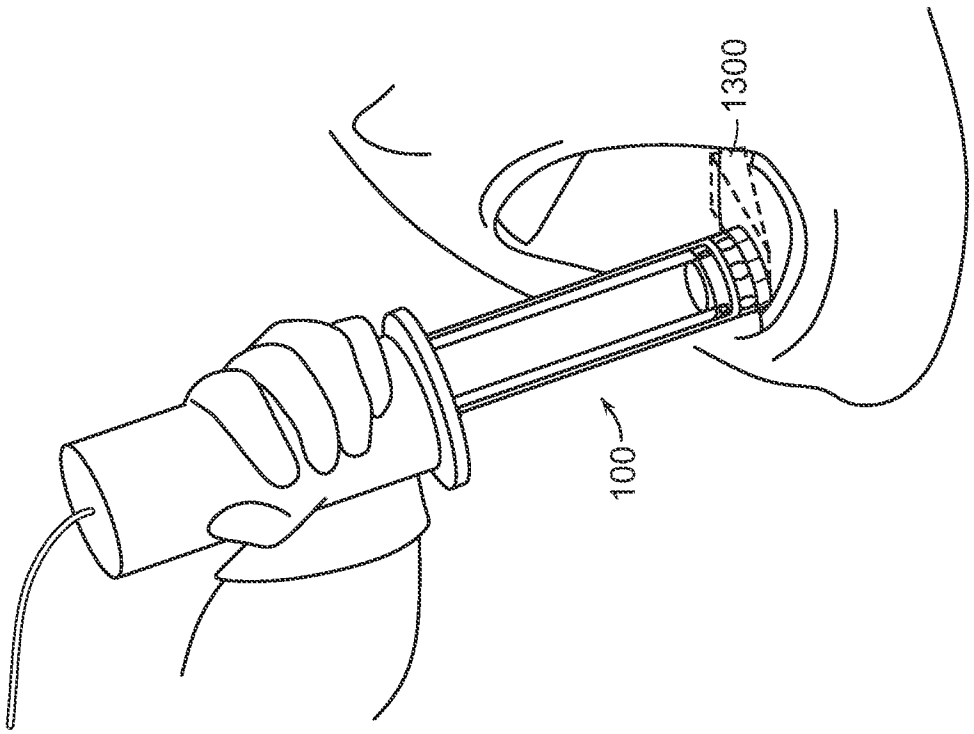


FIG. 13

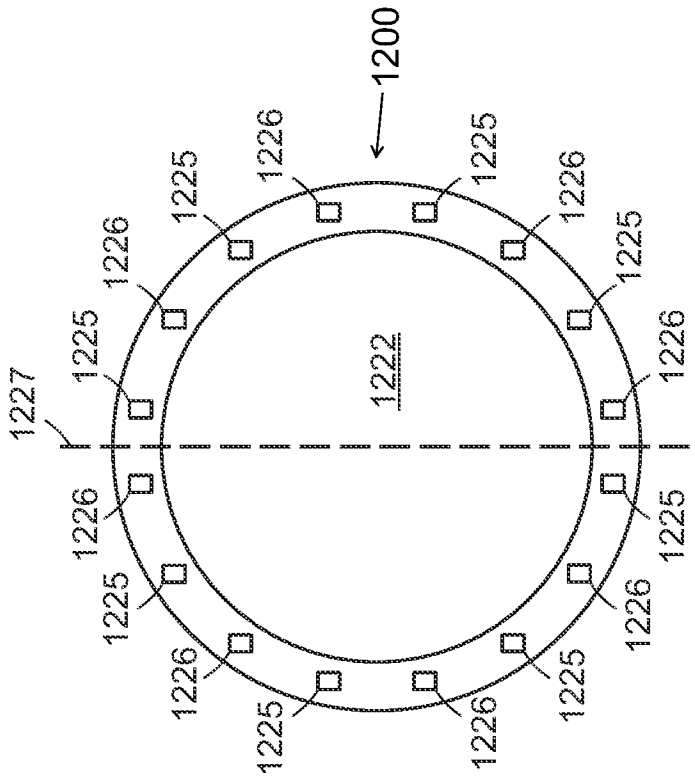


FIG. 12

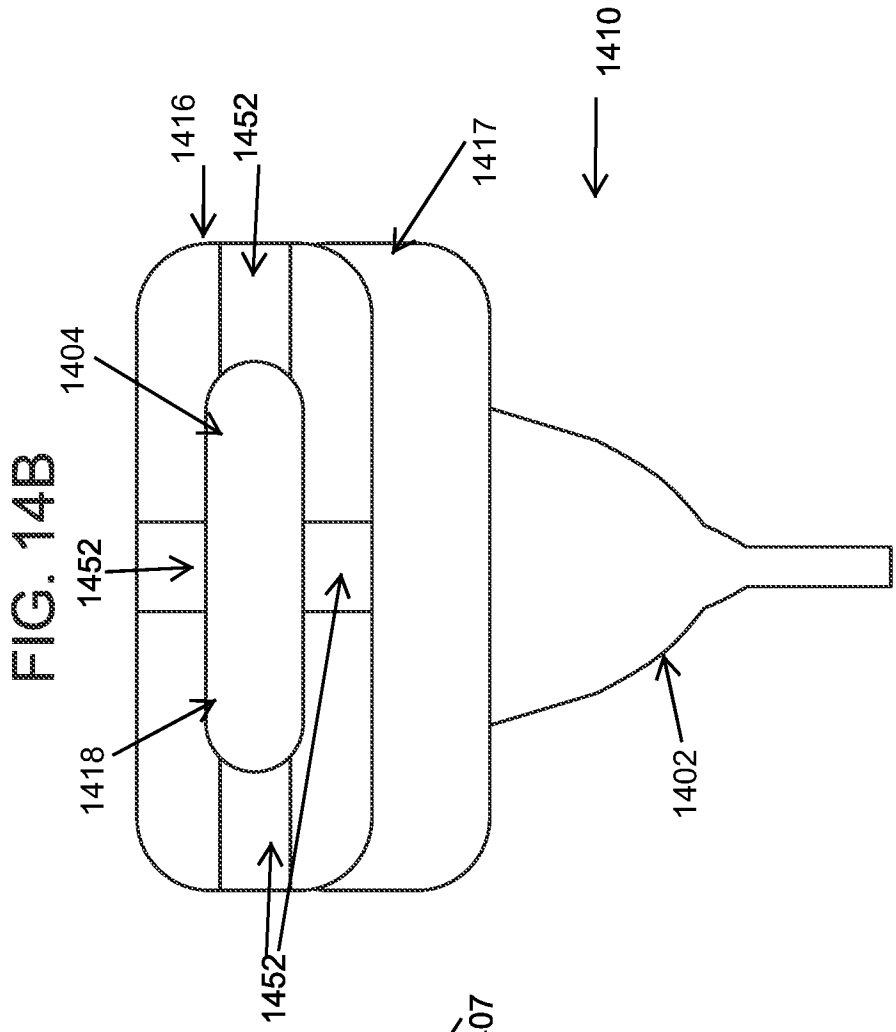


FIG. 14B

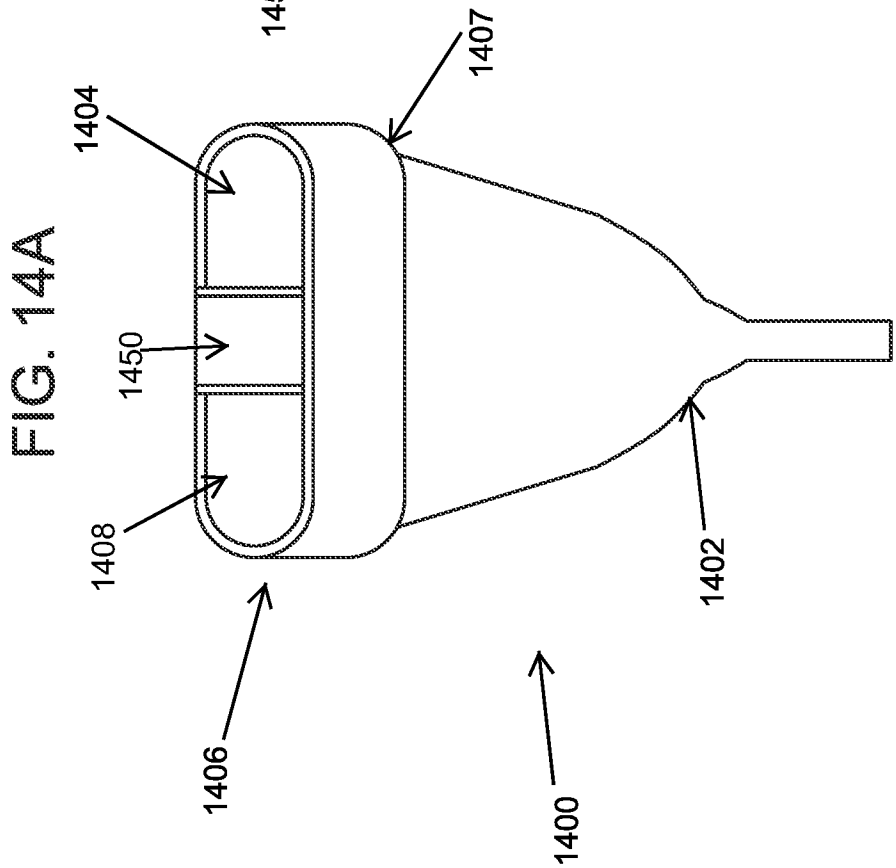


FIG. 14A

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2016/061434

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61B5/00 A61B5/026 A61B5/02 G06T7/00
ADD.

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)
A61B G06T

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2015/085240 A1 (VERISKIN LLC [US]) 11 June 2015 (2015-06-11) figures 1, 3, 5, 7-12 paragraphs [0002], [0009], [0050], [0107], [0132], [0140], [0146], [0152], [0159] paragraphs [0160], [0169], [0175], [0179], [0205], [0206] ----- -/--	1-85

[X] Further documents are listed in the continuation of Box C.

[X] 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

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"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
20 January 2017	30/01/2017

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Almeida, Mariana

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Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2014/378779 A1 (FREEMAN GARY A [US] ET AL) 25 December 2014 (2014-12-25)	1-8, 12-14, 20-31, 33-39, 41-60, 64-66, 71-75, 77-85
A	figures 4, 9 paragraphs [0004], [0086], [0090], [0106], [0108], [0135]	9-11, 15-19, 32,40, 61-63, 67-70,76

X	US 2010/286515 A1 (GRAVENSTEIN DIETRICH [US] ET AL) 11 November 2010 (2010-11-11)	9,10,16, 18,19, 29,30, 33,34, 40,61, 62,69, 70,73, 74,77, 78,85
	figures 2, 5, 8, 10 paragraphs [0001], [0042], [0047], [0050], [0051], [0053], [0055], [0056]	

A	US 2015/196271 A1 (NAIR ANUJA [US]) 16 July 2015 (2015-07-16) paragraph [0011]	16,18, 19,69,70

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2016/061434

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		US 2016310023 A1	27-10-2016
		WO 2015085240 A1	11-06-2015
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		WO 2009045374 A2	09-04-2009
US 2015196271 A1	16-07-2015	CN 105899142 A	24-08-2016
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		US 2015196271 A1	16-07-2015
		WO 2015106188 A1	16-07-2015