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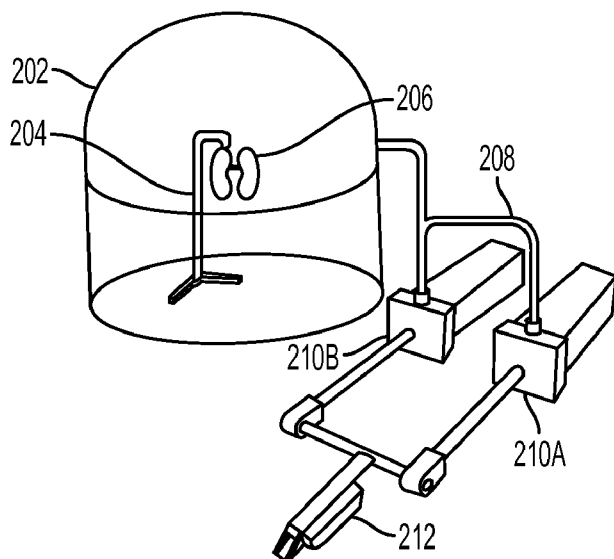


FIG. 2

(57) Abstract: Organs, such as a lung, may be rehabilitated ex vivo through the application of negative pressure to the organs in a pressure chamber. For example, the lung may be ventilated through application of negative pressure in a controlled environment around the lungs to cause the lung to expand and contract, similar to the expansion and contraction provided by a diaphragm while the organ is in vivo. The negative pressure may be controlled to simulate other human behaviors. For example, when the organ is a lung, the negative pressure may be controlled to simulate a cough or a sigh.

NEGATIVE PRESSURE EX VIVO LUNG VENTILATION AND PERFUSION SYSTEM

FIELD OF THE DISCLOSURE

[0001] This application claims the benefit of priority of U.S. Provisional Patent Application No. 61/941,363 to Mallidi et al. filed on February 18, 2014 and entitled “Negative Pressure Ex Vivo Lung Ventilation and Perfusion System,” which is hereby incorporated by reference.

FIELD OF THE DISCLOSURE

[0002] The instant disclosure relates to organ care. More specifically, this disclosure relates to preserving and rehabilitating organs *ex vivo*.

BACKGROUND

[0003] Lung transplantation is an important treatment for a number of end-stage pulmonary diseases, including chronic obstructive pulmonary disease (COPD), idiopathic pulmonary fibrosis, cystic fibrosis, sarcoidosis, bronchiectasis, and other debilitating ailments. Unfortunately, the number of available organs remains extremely limited. Of all patients who actually go on to donate organs after death, roughly one out of five will have lungs deemed suitable for transplantation, with the remaining organs discarded. Lungs have the lowest acceptance rate of all organs. The stringent criteria for acceptance contribute to the major organ shortage. In one study, the examination of lung tissue from rejected organs revealed that 41% had minimal to no histologic, microbiologic, or physiologic deficiencies. This implies that many organs, which appear to be untransplantable, may in fact have excellent potential. Recently, the concept of rehabilitation of rejected donor lungs *ex vivo* has proven that many organs are capable of improvement and can safely be transplanted.

[0004] In one conventional solution, *ex vivo* lung perfusion (EVLP) is used to evaluate and recondition lungs that were deemed unsuitable for transplant. FIGURE 1 is an illustration of a conventional *ex vivo* lung ventilation and perfusion system with a ventilator.

A conventional system 100 may include lung 102 with a trachea coupled to a ventilator 104. The ventilator 104 applies positive pressure to the lung 102 to ventilate the lung. Additionally, a hypertonic perfusion solution may be passed from a reservoir 108 through tubing 106 and the lung 102 by a centrifugal pump.

[0005] After the lung is removed from the donor, the hypertonic perfusion solution is passed through the lung's vasculature, drawing out the excess fluid from the interstitial space and therefore resolving pulmonary edema. Washing out all cells in the vasculature removes clots and circulating inflammatory cells, potentially reducing ischemia-reperfusion injury. Airway and pulmonary vascular pressures as well as oxygenation capacity can be monitored and reevaluated prior to accepting or rejecting lungs for transplant. Since EVLP was initially described, a number of lung transplant programs have adopted the technology and demonstrated significant increases in their donor pool as well as excellent post-transplantation outcomes. However, it is well known that positive-pressure ventilation can cause serious injury to the lungs. Likewise, positive pressure may damage other organs.

SUMMARY

[0006] Organs, such as a lung, may be rehabilitated *ex vivo* through the application of negative pressure to the organs in a pressure chamber. For example, the lung may be ventilated through application of negative pressure in a controlled environment around the lungs to cause the lung to expand and contract, similar to the expansion and contraction provided by the chest wall and diaphragm while the organ is *in vivo*. The negative pressure may be controlled to simulate other human behaviors. For example, when the organ is a lung, the negative pressure may be controlled to simulate a cough or a sigh. Other organs that may benefit from cyclical negative-to-negative or negative-to-positive pressure may include the heart, allowing expansion and contraction of its chambers in the absence of intrinsic cardiac electrical activity, or other organs that may be subjected to cyclical pressure to allow physical expansion and contraction of the organ parenchyma or of its blood vessels and other hollow structures.

[0007] In addition to rehabilitation of organs, such as lungs, a negative pressure system may also be used in therapeutic and experimental applications. In one

application, the organ may be removed from a patient and placed into a negative pressure chamber to allow maintenance of physiologic function, while high concentrations of chemotherapeutic agents, cytokines, or other drugs or therapies, which may be toxic if delivered systemically with the lungs *in vivo*, may be delivered in an isolated environment before transferring the organ back into the patient. For lungs, the therapies may be delivered directly into the airways, into the parenchyma, through the vasculature or into the chamber of air or fluid that surrounds the organ. In other applications, organs may be treated while undergoing rehabilitation prior to transplant, and therapeutic agents delivered into the airways, vasculature, parenchyma, or surrounding air or fluid may be used to improve rehabilitation and post-transplant function. These agents may include pharmacologic agents, cellular agents such as stem cells, cytokines, gene therapies, and other treatments.

[0008] According to one embodiment, a method may include controlling a pump to alter a pressure in a chamber. The step of controlling the pump may include generating a cyclical negative pressure in the chamber with the pump to ventilate a lung by simulating inspiration and expiration.

[0009] According to another embodiment, an apparatus may include a pressure chamber, a pump configured to alter a pressure within the pressure chamber, a pressure sensor configured to measure a pressure within the pressure chamber, and a controller coupled to the pump and configured to control the pump to generate a cyclical negative pressure in the pressure chamber to ventilate a lung by simulating expiration and inspiration.

[0010] The foregoing has outlined rather broadly the features and technical advantages of the present invention in order that the detailed description of the invention that follows may be better understood. Additional features and advantages of the invention will be described hereinafter that form the subject of the claims of the invention. It should be appreciated by those skilled in the art that the conception and specific embodiment disclosed may be readily utilized as a basis for modifying or designing other structures for carrying out the same purposes of the present invention. It should also be realized by those skilled in the art that such equivalent constructions do not depart from the spirit and scope of the invention as set forth in the appended claims. The novel features that are believed to be characteristic

of the invention, both as to its organization and method of operation, together with further objects and advantages will be better understood from the following description when considered in connection with the accompanying figures. It is to be expressly understood, however, that each of the figures is provided for the purpose of illustration and description only and is not intended as a definition of the limits of the present invention.

BRIEF DESCRIPTION OF THE DRAWINGS

[0011] For a more complete understanding of the disclosed system and methods, reference is now made to the following descriptions taken in conjunction with the accompanying drawings.

[0012] FIGURE 1 is an illustration of a conventional *ex vivo* lung ventilation and perfusion system with a ventilator.

[0013] FIGURE 2 is an illustration of an *ex vivo* lung ventilation and perfusion system with a negative pressure chamber according to one embodiment of the disclosure.

[0014] FIGURE 3 is a block diagram illustrating components of an *ex vivo* ventilation and perfusion system for obtaining negative pressure in a chamber according to one embodiment of the disclosure.

[0015] FIGURE 4 is a flow chart illustrating operation of a controller for maintaining negative pressure in a chamber according to one embodiment of the disclosure.

[0016] FIGURE 5 is a graph illustrating oscillating pressure within a negative pressure chamber of an *ex vivo* lung ventilation and perfusion system according to one embodiment of the disclosure.

[0017] FIGURE 6 is a flow chart illustrating operation of a controller for simulating a cough *ex vivo* in lungs according to one embodiment of the disclosure.

[0018] FIGURE 7 is a flow chart illustrating operation of a controller for simulating a sigh *ex vivo* in lungs according to one embodiment of the disclosure.

[0019] FIGURE 8 is a circuit for operating pumps for generating negative pressure in a chamber according to one embodiment of the disclosure.

[0020] FIGURE 9 is a screen shot illustrating an interface for controlling an *ex vivo* lung ventilation and perfusion system with a negative pressure chamber according to one embodiment of the disclosure.

[0021] FIGURE 10A is a is an illustration of an *ex vivo* lung ventilation and perfusion system with a negative pressure chamber controlled by a piston and actuator according to one embodiment of the disclosure.

[0022] FIGURE 10B is a is an illustration of an *ex vivo* lung ventilation and perfusion system with a negative pressure chamber controlled by an air compressor according to one embodiment of the disclosure.

[0023] FIGURE 10C is a is an illustration of an *ex vivo* lung ventilation and perfusion system with a negative pressure chamber controlled by a vacuum input according to one embodiment of the disclosure.

DETAILED DESCRIPTION

[0024] FIGURE 2 is an illustration of an *ex vivo* lung ventilation and perfusion system with a negative pressure chamber according to one embodiment of the disclosure. A pressure chamber 202 may be sealed airtight. Pressure within the chamber 202 may oscillate between varying degrees of positive-to-negative or negative-to-negative pressure changes. Altering the pressure within the chamber 202 may be accomplished through either an internal or external pump mechanism. For example, in the embodiment shown in FIGURE 2, external pumps 210A-B may be coupled to the chamber 202 through tubing 208. In one embodiment, the pumps 210A-B may be a linear piston pump or any other form of pump, to move air or water in and out of a sealed chamber. Pressure changes created within the chamber 202 may be transmitted to a lung 206 mounted on a stand 204, although the lung may also be laid out unsuspended within the chamber. The pressure changes in the chamber 202 may cause passive expansion or recoil of the airways in the lung 206, which allow a physiologic method for lung ventilation.

[0025] Although not shown in FIGURE 2, additional connections to the chamber 202 may be present. For example, one or more sealed fluid lines may couple the chamber 202 to a fluid reservoir and a fluid pump. The fluid lines may provide perfusion fluid to the lungs, such as blood or another medium for oxygenating or providing other forms of gas exchange, chemotherapy drugs for cancer treatment, cytokine rich fluid, gene therapies, hypertonic perfusion fluid, or other fluids. In another example, one or more sealed gas lines may couple to the chamber 202 to a gas reservoir and a gas valve. The gas lines may provide air to the lung 206 in the chamber 202. Alternatively, the lungs may be open to the chamber 202 and receive air from the chamber 202. In one embodiment, the gas lines may also be coupled to a humidifier (not shown) to humidify the gas before contact with the lung 206.

[0026] The lung 206 airways may be open and in direct continuity with the chamber 202, or they may be isolated from the chamber, allowing a separate pathway for air that passively or actively moves in and out of the lung as the organ expands and recoils in response to changing pressures within the chamber. This may be accomplished by placement of an endotracheal tube, which also allows monitoring of lung airway parameters, including inspiratory pressure, expiratory pressure, lung compliance, tidal volume, and/or other variables. The air that enters the chamber 202 or the airways through a separate pathway may be humidified or altered to maintain a desired organ or experimental environment, including experimental drugs, gene therapies, cytokines, and other agents.

[0027] While the lung or other organ is maintained in the negative pressure chamber, treatments and procedures may be performed on the organ. For example, genetic material may be introduced via gene therapy to prevent rejection, promote organ tolerance in the host, promote resistance to infection, cancer, and other detrimental organ maladies, through conventional techniques for gene therapy. These may include, but are not limited to, viral and/or non-viral vector systems, including both *in vivo* treatment or *in vitro/ex vivo* treatment followed by transfer of treated cells back to the organ in the negative pressure chamber. Vectors include DNAs, RNAs, plasmids, cosmids, viruses (bacteriophage, animal viruses, and plant viruses), and artificial chromosomes (e.g., YACs). Other techniques for genetic material transfer may include microinjection of DNA directly into cells, delivery via

lipoplexes (lipid DNA complexes), application via a biolistic particle delivery system (delivery of gold or tungsten particles coated with DNA through high-pressure transfer), delivery via calcium phosphate method, electroporation, lipofection, and/or other methods of genetic transfer.

[0028] FIGURE 3 is a block diagram illustrating components of an *ex vivo* ventilation and perfusion system for obtaining negative pressure in a chamber according to one embodiment of the disclosure. A system 300 may include a controller 302, such as a microcontroller, an application-specific integrated circuit (ASIC), or a general purpose central processing unit (CPU) executing code to perform specific functions. For example, the controller 302 may be coupled to sensors 312, such as a pressure sensor in the chamber 202 or sensors on the endotracheal tube, and configured to receive measurements from the sensors 312, store the received measurements, and/or control other devices based on the received measurements. Pressure may be monitored by the sensors 312 located within the chamber or its tubing to ensure pressure changes remain within a physiologic range that allow lung ventilation without organ injury. In some embodiments, pressure sensors may be located within the lung airway circuit as well as within the chamber to relay information to the controller 312. The controller 302 may also be coupled to a pressure pump 304 for altering a pressure within the chamber 202. For example, the controller 302 may implement algorithms for ventilating the lung 206 by oscillating a pressure in the chamber 202, or simulating other behavior in the lung 206 including a cough and a sigh, as described in further detail below with reference to FIGURES 2, 3, and 4.

[0029] The controller 302 may also control other optional devices that generate a simulated environment for the lung 206. For example, a fluid pump 306 may be coupled to and controlled by the controller 302 to perfuse fluid through the lung 206. In another example, a gas valve 308 may be coupled to and controlled by the controller 302 to flow air through the lung 206. In yet another example, a humidifier 310 may be coupled to and controlled by the controller 302 to humidify air released through the gas valve 308. The controller 302 may control each of these optional devices based on input parameters received through a user interface and/or based on input received from sensors 312. For example, one

of the sensors 312 may be an air flow sensor coupled to the gas valve. In another example, one of the sensors 312 may be a fluid pressure sensor coupled to an output of the fluid pump.

[0030] The controller 302 may carry out operations to alter pressure within the chamber and simulate human behavior, such as ventilating the lungs with negative pressure. FIGURE 4 is a flow chart illustrating operation of a controller for maintaining negative pressure in a chamber according to one embodiment of the disclosure. A method 400 begins at block 402 with controlling a pump to obtain a negative pressure within a chamber containing a lung or other organ. In one embodiment, the pump is a piston pump and the controller 302 may operate the pump by actuating a linear actuator coupled to the piston pump. Then, at block 404, the pressure in the chamber may be oscillated to ventilate the lung or to perform another function on an organ.

[0031] One example of an oscillating pressure is illustrated in FIGURE 5. FIGURE 5 is a graph illustrating oscillating pressure within a negative pressure chamber of an *ex vivo* lung ventilation and perfusion system according to one embodiment of the disclosure. A line 500 illustrates the pressure within the chamber oscillating over time between approximately -30 and -5 mm Hg and at a frequency of about 10 Hertz. The range of oscillation and frequency of oscillation may be varied and controlled by the controller 302.

[0032] Other human behavior may be simulated within the chamber, such as a cough. FIGURE 6 is a flow chart illustrating operation of a controller for simulating a cough *ex vivo* in lungs according to one embodiment of the disclosure. A method 600 for simulating a cough may include the generation of sufficient negative pressure within the chamber to allow inspiration of about 1 to 3 liters of air at block 602. Then, at block 604, approximately complete tracheal occlusion may be achieved by a mechanism to occlude the trachea such that air cannot pass through the trachea while the obstructing mechanism is in place. At block 606, the pressure may be altered through positive pressure generation within the chamber to allow intrapulmonary pressure rise to approximately 100 mm Hg or higher, followed by sudden reopening of the occluded trachea to allow rapid expulsion of the previously inspired air. At block 608, control of the pressure may return to oscillating the pressure to ventilate the lung. For a cough, deep inspiration may be achieved by maintaining or increasing negative pressure to a value that allows approximately 1-3 liters of air to enter

the lung, which may use pressures ranging from approximately -5 to -100 mmHg. In some aspects, the pressure may range from -5, -10, -20, -30, -40, -50, -60, -70, -80, -90 or -100 mmHg to 5, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110 or 120 mmHg, or any value derivable therein. After sufficient air has entered the lung, the trachea may be occluded using a balloon device or other methods for physical, airtight obstruction of the trachea. Airway pressures may then be increased to an intrapulmonary pressure of approximately 100 mmHg, which may use negative or positive pressure within the chamber and may vary based on lung compliance. Once a desired intrapulmonary pressure is achieved, usually within several seconds, the tracheal obstruction may be relieved and air allowed to rapidly leave the lung, thus simulating a cough that may help to clear the airway.

[0033] Another human behavior simulated within the chamber may include a sigh. FIGURE 7 is a flow chart illustrating operation of a controller for simulating a sigh *ex vivo* in lungs according to one embodiment of the disclosure. A method 700 begins at block 702 with maintaining a high negative pressure within the chamber for a period of time to allow alveolar recruitment. Then, at block 704, the chamber may return to an oscillating pressure to ventilate the lung. For a sigh, deep inspiration may be achieved by maintaining or increasing negative pressure to a value that allows approximately 1-3 liters of air to enter the lung, which may use pressures ranging from approximately -5 to -100 mmHg, held for approximately 2-10 seconds, and release back to a pressure that allows maintenance of a desired end expiratory pulmonary pressure such that alveolar recruitment is maintained.

[0034] Alveolar recruitment techniques and airway clearance mechanisms, such as a deep sigh or cough described above with reference to FIGURES 6 and 7, may be built into the controller 302 or computer code executing on the controller 302 and may be set to occur periodically to maintain lung function.

[0035] FIGURE 8 is a circuit for operating pumps for generating negative pressure in a chamber according to one embodiment of the disclosure. A circuit 800 includes a linear actuator 802, represented by approximately a one kiloOhm resistor. A power supply 804 may be used to control the linear actuator 802 and may be selectively coupled to the linear actuator 802 by relays 812A-B. The power supply 804 may be, for example, 13.3 Volts, but may be any voltage sufficient to operate the linear actuator 802. The relays 812A-

B may be controlled by transistors 814A-B. The transistors 814A-B may be controlled by analog outputs switching current through optical isolators 806A-B. Changing the state of the relay 812A switches power on and off to the linear actuator 802. Changing the state of the relay 812B changes the direction of operation of the linear actuator 802. Light emitting diodes (LEDs) 808A-B may be coupled between the transistors 814A-B and the relays 812A-B, respectively, to indicate when the relays 812A-B are activated.

[0036] Referring back to FIGURE 3, a computer 320 may be coupled to the controller 302 to provide a user interface for providing input parameters to the controller 302 and provide a graphical interface for retrieving data from the controller 302. FIGURE 9 is a screen shot illustrating an interface for controlling an *ex vivo* lung ventilation and perfusion system with a negative pressure chamber according to one embodiment of the disclosure.

[0037] The computer 320 may perform data acquisition functions through a user interface 900. For example, the user interface 900 may sample, process, and display the signals from the distance sensor for the piston pumps and/or the pressure sensor for the chamber. The sampling rate and number of samples used by each cycle of the control system may be varied by the user in text boxes 916 and 914, respectively. Values being recorded from the controller 302 may be displayed in text boxes 902 and 904 corresponding to "Pressure" and "Position." The data being collected may be recorded and saved as, for example, a spreadsheet file by pressing a "Write to File" button 906 to begin and clicking again to end. Lung volume and compliance values may be calculated based on a distance and/or pressure measurements and displayed in text boxes 908 and 910, respectively. Lung volume may be calculated based on Boyle's Law ($P_1V_1 = P_2V_2$, where P_1 and P_2 are a pressure in the lung and a pressure in the chamber or pump, and V_1 and V_2 are a volume of the lung and a volume in the chamber or pump). Lung compliance may be measured by change in lung volume divided by change in lung pressure. The chamber pressure measurement may be calibrated by clicking the "Calibrate Pressure" button 912 to zero out the value when the chamber is open.

[0038] The computer 320 may also perform ventilator control functions through the user interface 900. For example, boundaries for the linear actuator may be established in the controller 302. The linear actuator 212 may draw a variable amount of

current based on an amount of resistance encountered. Allowing the linear actuator 212 to compress or extend near limits causes the piston shafts to place a strain on the motor, the electronics, and other components of the ventilator assembly. Therefore, the controller 302 may be programmed to automatically cut power to the linear actuator 212 when the position exceeds upper or lower boundaries set by a user through the user interface 900 through text boxes (not shown). A “Within Bounds” LED indicator 922 may turn red when boundaries are exceeded. These boundary limits may be set by constants within the Block Diagram as constants. The boundary protection may be disabled by pressing the “Boundaries” button 924.

[0039] In one embodiment, the user interface 900 may be used to manually control the ventilator system. Using “Power” button 926 and “Direction” button 928, a user may adjust the position of the pistons. The “Power” button 926 may allow the user to control if the linear actuator is provided power or not. The “Direction” button 928 may determine the direction of travel of the linear actuator. LED indicators 930 and 932 may inform the user of the current action in progress. In one embodiment, manual control may be exerted through pressure and volume measurements or calculations (not shown). Additionally, the user interface 900 may allow control over other aspects of the system that are not shown. For example, the user interface 900 may control inflating a balloon or using another obstructive mechanism within the chamber.

[0040] In another embodiment, the user interface 900 may be used to instruct the linear actuator to go to a particular distance. The user may indicate a desired position through a “High” text box 918. When the piston is within a certain range of the distance, the power will stop and a yellow “Desired Position” indicator 934 may turn on.

[0041] In yet another embodiment, the user interface 900 may be used to instruct the linear actuator to oscillate between two distances, while pausing for a set span of time after each stroke. The upper and lower bounds of oscillation are indicated by the user through “High” text box 918 and “Low” text box 920. A delay (such as in seconds) after each stroke may be input with a “Delay” text box 936.

[0042] The negative pressure system described above may be implemented using various means for obtaining pressure variation within the chamber. In one embodiment, illustrated in FIGURE 10A, an *ex vivo* lung ventilation and perfusion system with a negative pressure chamber may be controlled by a piston and actuator. A chamber 1002 may contain an organ, such as human lungs. The chamber 1002 may be connected to a piston 1012 through a regulator 1004, such as a solenoid, through tubing. The piston 1012 may be further connected to an actuator 1014 for controlling the piston 1012 to generate pressure differences in the chamber 1002. A pressure sensor 1008 may be located inside the chamber 1002 and connected to a controller 1006 through a sealed opening in the chamber 1008. The controller 1006 may monitor the output by the pressure sensor 1008 and control operation of the actuator 1014 and/or the regulator 1004 to regulate the pressure within the chamber. The controller 1006 may implement features described above with respect to controller 302 of FIGURE 3 and execute methods described above in the flow charts of FIGURE 4, FIGURE 6, and FIGURE 7. The controller 1006 may be operated by a user through a user interface, such as the interface illustrated in FIGURE 9.

[0043] In another embodiment, as illustrated in FIGURE 10B, an *ex vivo* lung ventilation and perfusion system with a negative pressure chamber may be controlled by an air compressor. The chamber 1002 of FIGURE 10B may be coupled through the regulator 1004 to an air compressor 1022. The controller 1006 may be configured to control the air compressor 1022 and/or the regulator 1004 to obtain certain pressures within the chamber 1002. The controller 1006 may use output from the pressure sensor 1008 as feedback in regulating the pressure of the chamber 1002. Additionally, a valve 1024 may be included with the chamber 1002 to normalize pressure within the chamber 1002. The valve 1024 may be manually operated or automatically controlled by the controller 1006.

[0044] In a further embodiment, as illustrated in FIGURE 10C, an *ex vivo* lung ventilation and perfusion system with a negative pressure chamber may be controlled by a vacuum input. The chamber 1002 may be used in health care provider environments, such as a hospital, or a laboratory, either of which may offer a vacuum connection provided by a central facility. In these environments, the chamber 1002 may be configured to connect to a central vacuum connection 1032 through the regulator 1004. The controller may control the

regulator 1004 and/or the valve 1024 based, at least in part, on input from the pressure sensor 1008 to obtain a desired pressure within the chamber 1002. Although the embodiments of FIGURE 10A, 10B, and 10C are described separately, features from each of the embodiments may be combined, along with other features described above. For example, a chamber 1002 may be configured with both an air compressor push air back and a vacuum connection to suck air out.

[0045] If implemented in firmware and/or software, the functions described above may be stored as one or more instructions or code on a computer-readable medium. Examples include non-transitory computer-readable media encoded with a data structure and computer-readable media encoded with a computer program. Computer-readable media includes physical computer storage media. A storage medium may be any available medium that can be accessed by a computer. By way of example, and not limitation, such computer-readable media can comprise RAM, ROM, EEPROM, CD-ROM or other optical disk storage, magnetic disk storage or other magnetic storage devices, or any other medium that can be used to store desired program code in the form of instructions or data structures and that can be accessed by a computer; disk and disc, as used herein, includes compact disc (CD), laser disc, optical disc, digital versatile disc (DVD), floppy disk and blu-ray disc where disks usually reproduce data magnetically, while discs reproduce data optically with lasers. Combinations of the above should also be included within the scope of computer-readable media.

[0046] In addition to storage on computer readable medium, instructions and/or data may be provided as signals on transmission media included in a communication apparatus. For example, a communication apparatus may include a transceiver having signals indicative of instructions and data. The instructions and data are configured to cause one or more processors to implement the functions outlined in the claims.

[0047] Although the present disclosure and its advantages have been described in detail, it should be understood that various changes, substitutions and alterations can be made herein without departing from the spirit and scope of the disclosure as defined by the appended claims. Moreover, the scope of the present application is not intended to be limited to the particular embodiments of the process, machine, manufacture, composition of

matter, means, methods and steps described in the specification. As one of ordinary skill in the art will readily appreciate from the present invention, disclosure, machines, manufacture, compositions of matter, means, methods, or steps, presently existing or later to be developed that perform substantially the same function or achieve substantially the same result as the corresponding embodiments described herein may be utilized according to the present disclosure. Accordingly, the appended claims are intended to include within their scope such processes, machines, manufacture, compositions of matter, means, methods, or steps.

CLAIMS

What is claimed is:

1. A method, comprising:
 - controlling a pump to alter a pressure in a chamber, wherein controlling the pump comprises:
 - generating a cyclical negative pressure in the chamber with the pump to ventilate a lung by simulating inspiration and expiration.
2. The method of claim 1, further comprising perfusing the lung with a liquid.
3. The method of claim 2, wherein perfusing the lungs comprises perfusing the lung with hypertonic perfusion fluid.
4. The method of claim 2, wherein perfusing the lung comprises applying chemotherapy to the lung.
5. The method of claim 1, wherein controlling the pump further comprising simulating a cough in the lung.
6. The method of claim 5, wherein simulating the cough comprises:
 - altering the pressure in the chamber to cause inspiration of between approximately one and three liters of air in the lung;
 - inflating a balloon or using another obstructive mechanism to obtain complete tracheal occlusion in the lung; and
 - altering the pressure in the chamber to cause intrapulmonary pressure in the lung to rise to approximately 100 mm Hg, followed by release of tracheal occlusion and rapid expulsion of air from the lung.

7. The method of claim 1, wherein controlling the pump further comprising simulating a sigh in the lung.
8. The method of claim 7, wherein simulating the sigh comprises maintaining a high negative pressure within the chamber for a period of time to allow alveolar recruitment in the lung.
9. The method of claim 1, wherein controlling the pump comprises:
 - measuring, by a controller, a pressure within the chamber; and
 - actuating, by the controller, a linear actuator coupled to the pump to control an output of pump and generate the cyclical negative pressure in the chamber based, at least in part, on the measured pressure.
10. The method of claim 1, further comprising performing gene therapy on the lung while maintaining a desired pressure in the chamber by controlling the pump.
11. An apparatus, comprising:
 - a pressure chamber;
 - a pump configured to alter a pressure within the pressure chamber;
 - a pressure sensor configured to measure a pressure within the pressure chamber; and
 - a controller coupled to the pump and the pressure sensor, wherein the controller is configured to control the pump to generate a cyclical negative pressure in the pressure chamber to ventilate a lung by simulating expiration and inspiration.

12. The apparatus of claim 11, wherein the pump comprises a piston pump, and further comprising a linear actuator coupled to the piston pump and to the controller, wherein the controller is configured to actuate the linear actuator to control an output of the piston pump and generate the cyclical negative pressure in the pressure chamber.
13. The apparatus of claim 12, further comprising infrared (IR) sensors or other sensors such as pressure sensors coupled to the controller and configured to detect a position of the linear actuator.
14. The apparatus of claim 13, wherein the controller is configured to maintain the linear actuator within a predetermined boundary.
15. The apparatus of claim 11, further comprising:
 - sealed fluid lines coupling a fluid reservoir to the pressure chamber; and
 - a fluid pump coupled to the sealed fluid lines and configured to circulate fluid from the fluid reservoir to the lungs.
16. The apparatus of claim 15, wherein the fluid reservoir comprises hypertonic (or other tonicities) perfusion fluid.
17. The apparatus of claim 15, wherein the fluid reservoir comprises chemotherapy drugs, cytokines, gene transfer vectors, or other agents.
18. The apparatus of claim 11, further comprising a computer coupled to the controller, wherein the computer is configured to present a user interface for altering the pressure in the pressure chamber and configured to communicate with the controller to control the pump based on input to the user interface.

19. The apparatus of claim 11, further comprising:
 - an endotracheal tube coupled to the lung;
 - sealed air lines coupling a gas reservoir to the lung through the endotracheal tube; and
 - a valve coupled between the sealed air lines and the gas reservoir and configured to provide gas to the lung through the endotracheal tube.
20. The apparatus of claim 19, wherein the endotracheal tube comprises at least one of an inspiratory pressure sensor, an expiratory pressure sensor, a lung compliance sensor, and a tidal volume sensor.
21. The apparatus of claim 19, further comprising a humidifier coupled between the gas reservoir and the endotracheal tube and configured to humidify the gas.

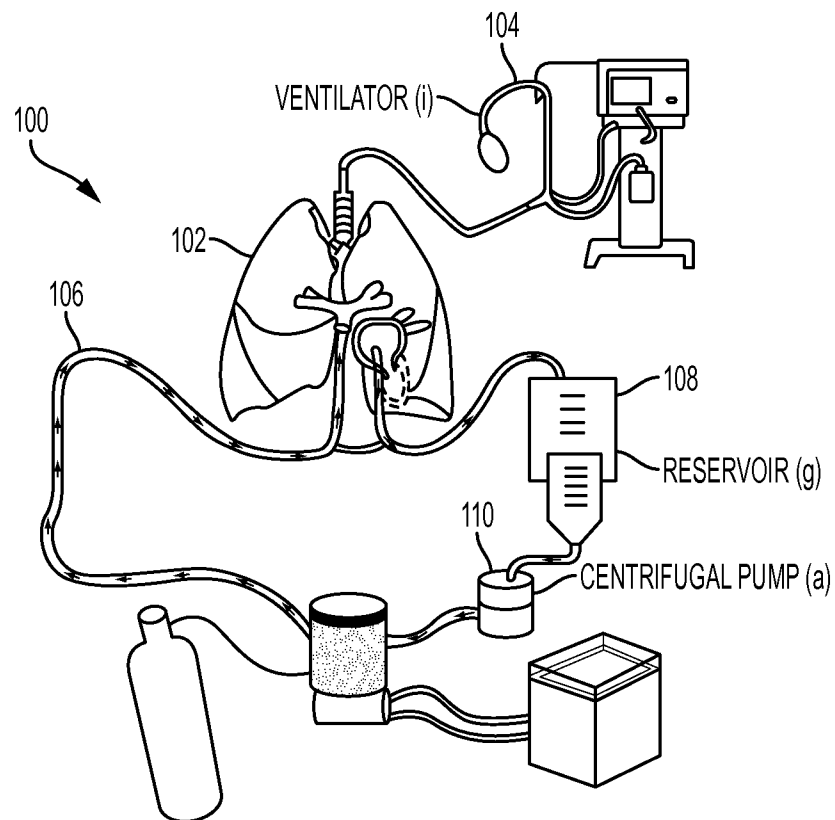


FIG. 1
PRIOR ART

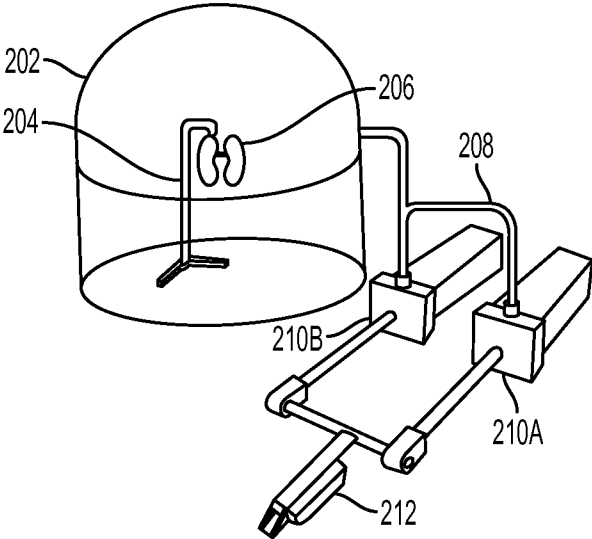


FIG. 2

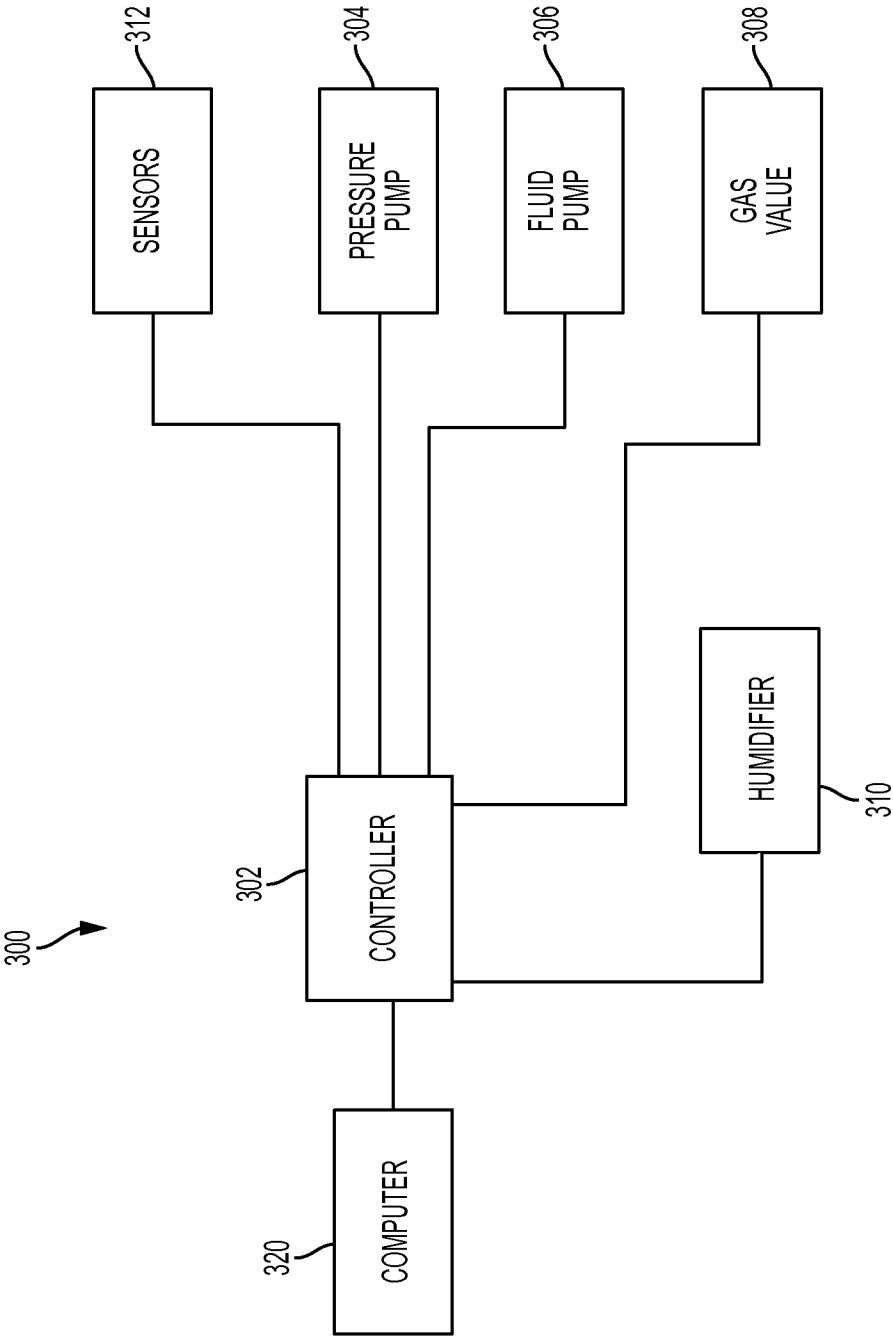


FIG. 3

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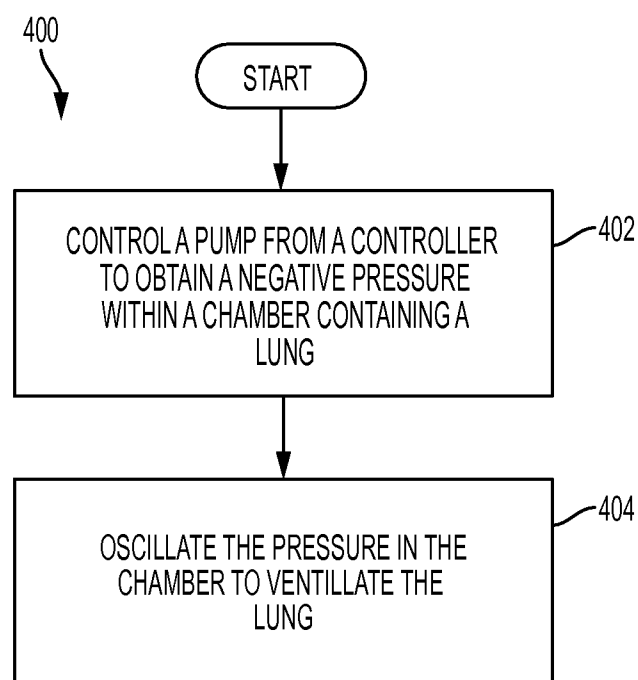


FIG. 4

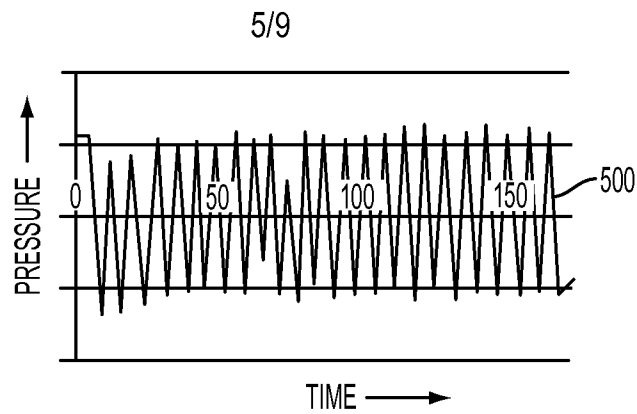


FIG. 5

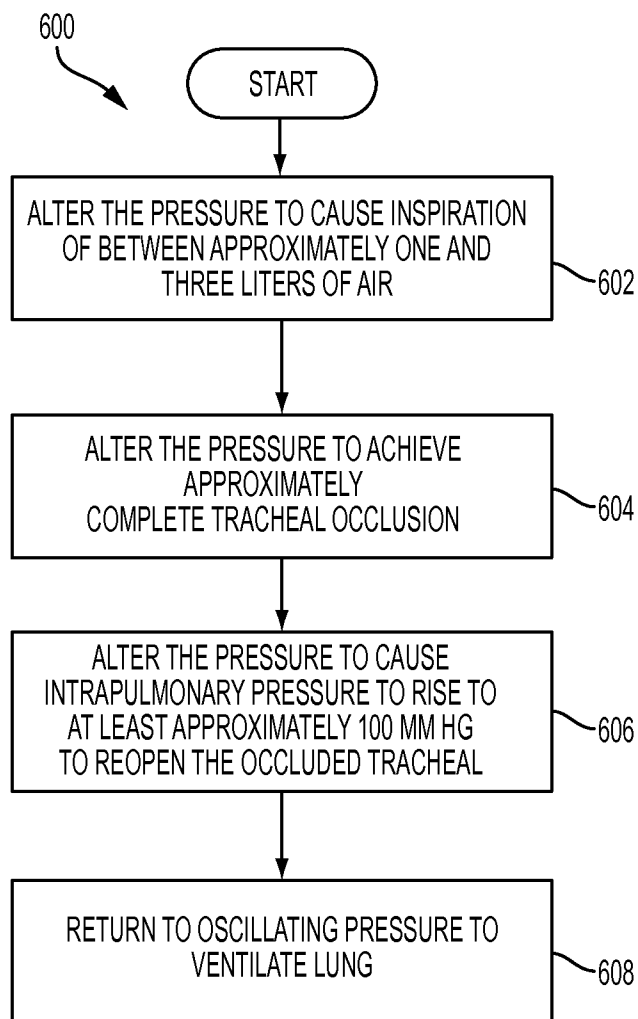


FIG. 6

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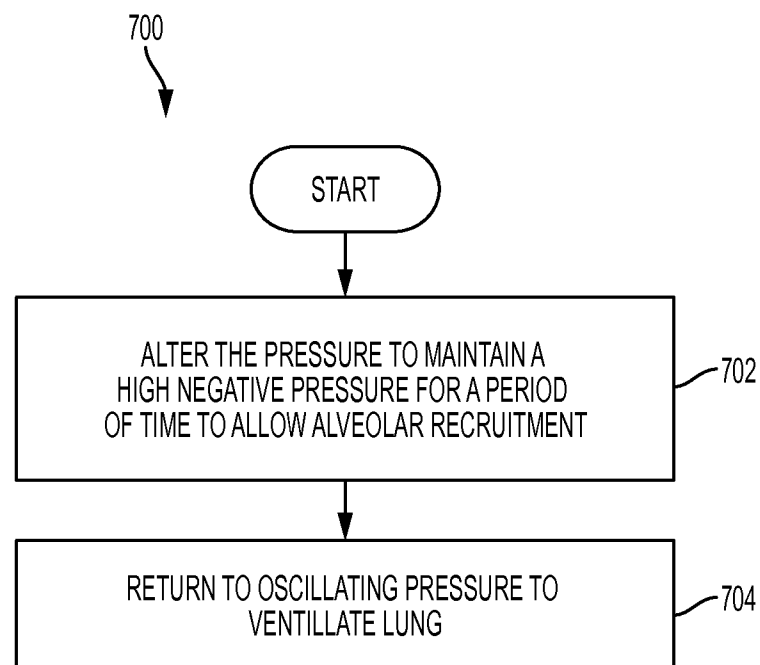


FIG. 7

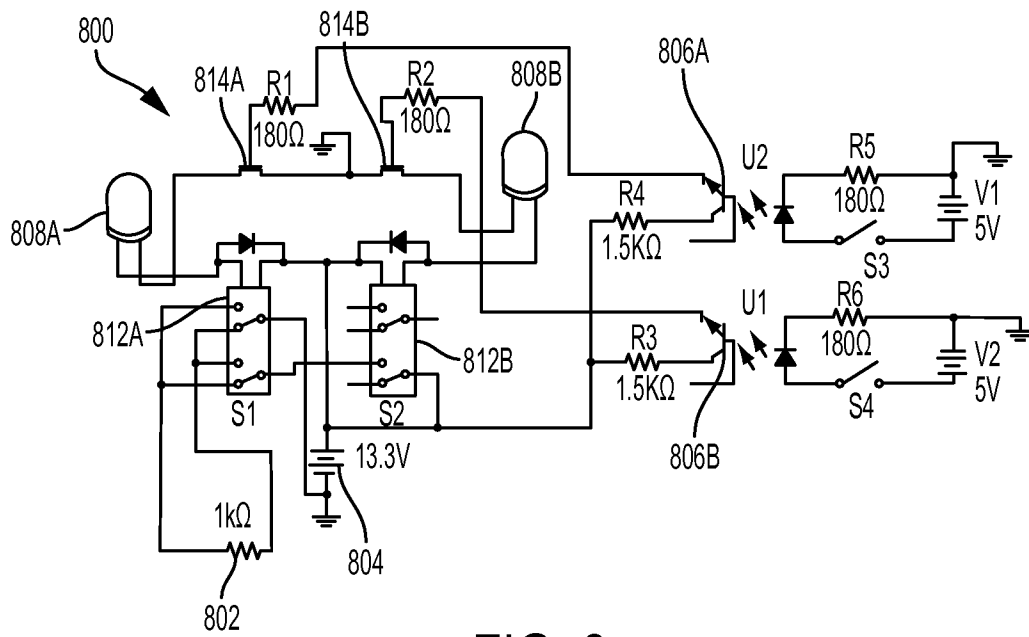


FIG. 8

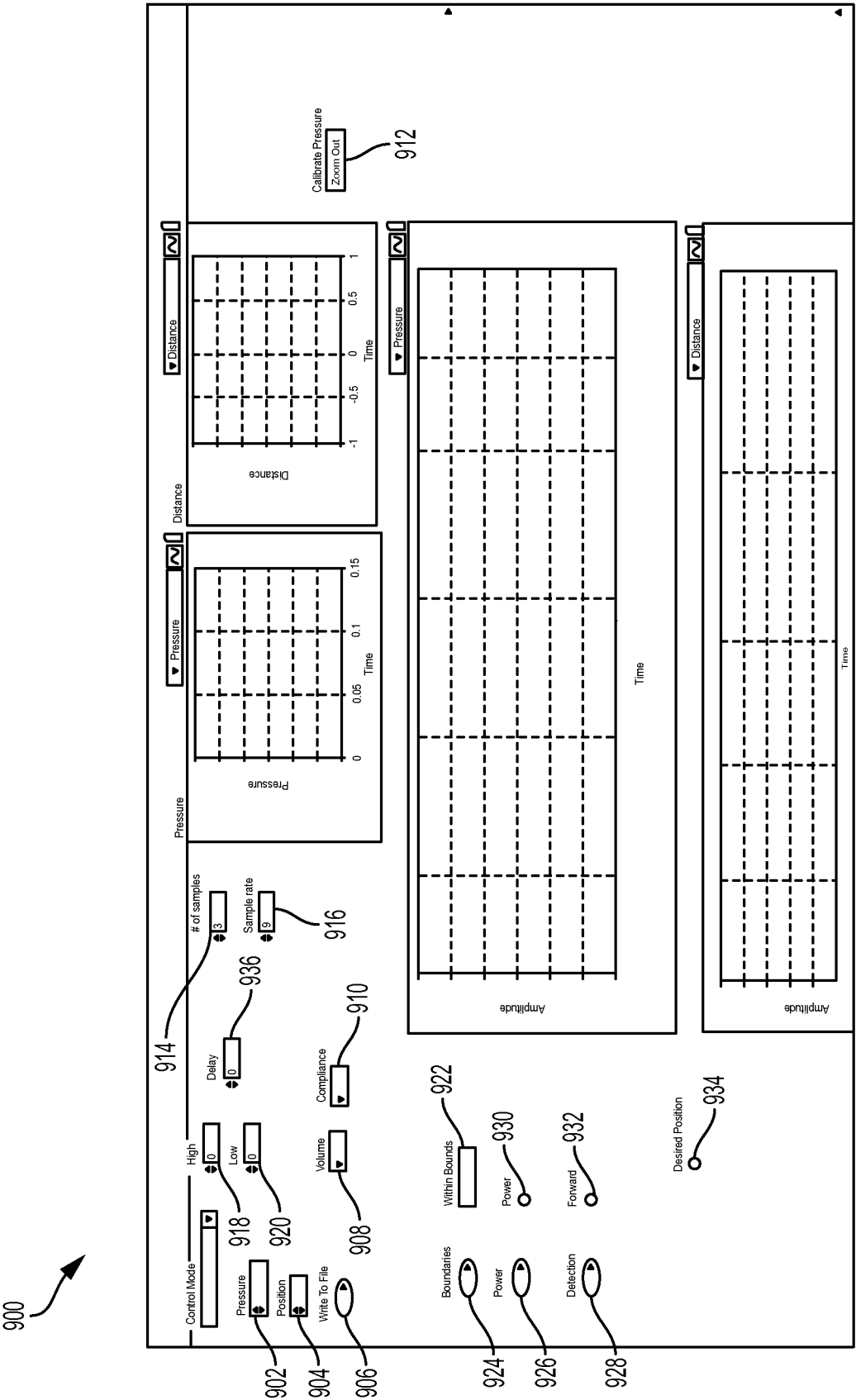


FIG. 9

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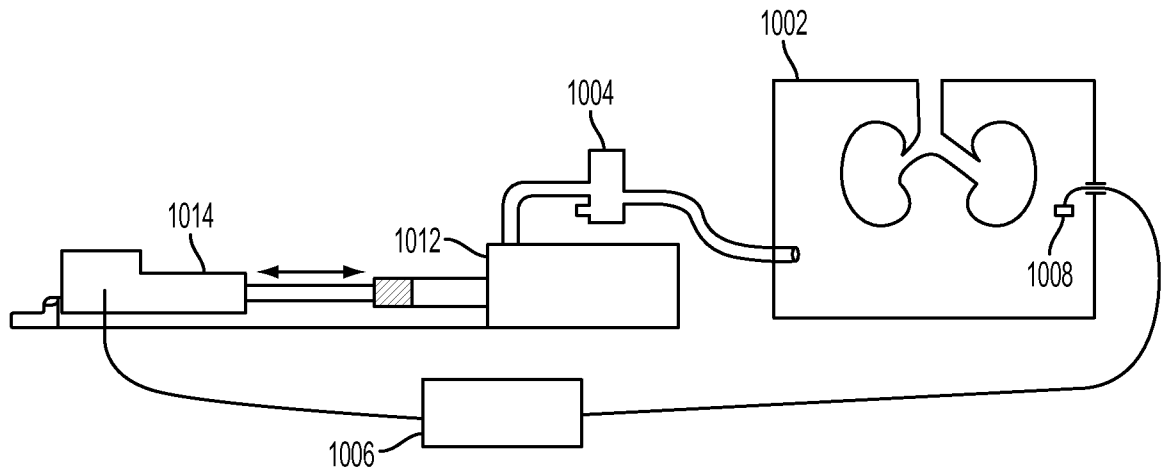


FIG. 10A

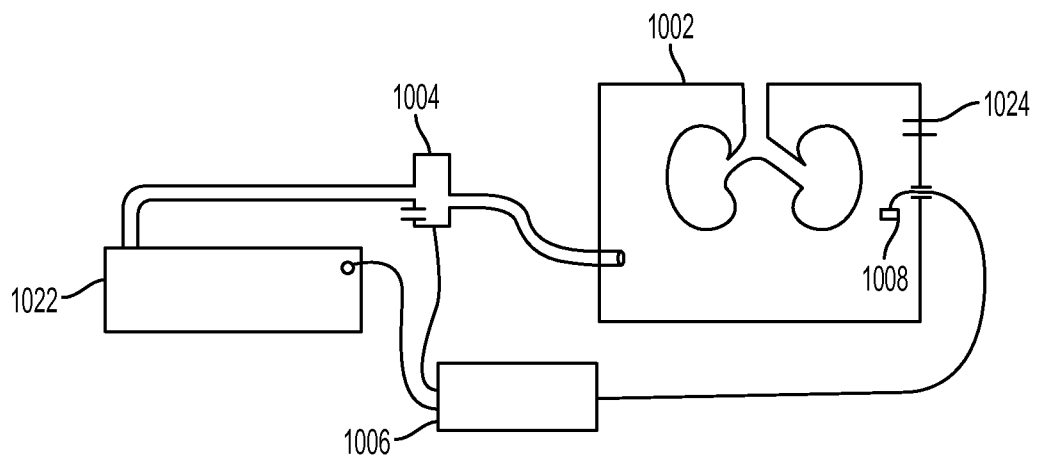


FIG. 10B

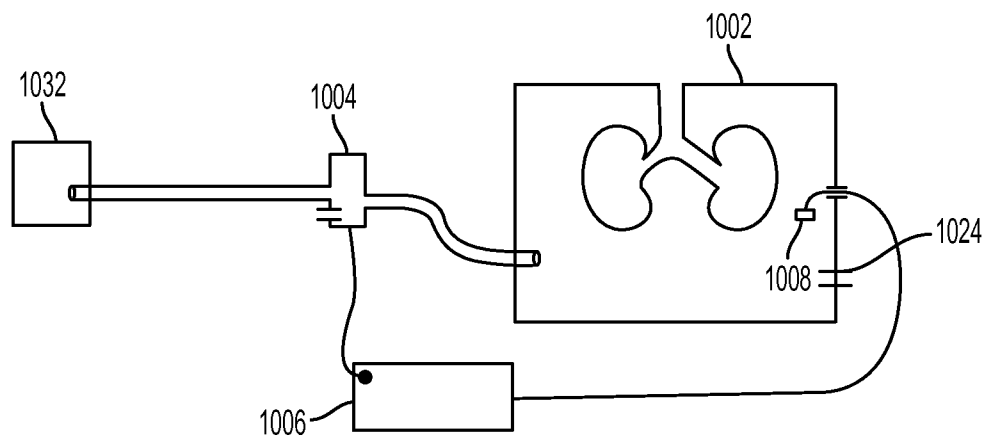


FIG. 10C

INTERNATIONAL SEARCH REPORT

International application N°
PCT/US2015/016223

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A01N 1/02 (2015.01)

CPC - A01N 1/021 (2015.04)

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)

IPC(8) - A01N 1/02 (2015.01)

CPC - A01N 1/021, 1/0247 (2015.04)

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

USPC - 435/1.2 (keyword delimited)

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

Orbit, Google Patents, Google Scholar

Search terms used: negative pressure, lung, transplant, recondition, ex vivo, pump, perfusion, chamber, air, gas, line, cough, sigh, humidifier

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2013/0157248 A1 (TRANSMEDICS, INC) 20 June 2013 (20.06.2013) entire document	1-2, 4, 7-15, 17-20
Y		3, 16, 21
Y	US 5,066,578 A1 (WIKMAN-COFFELT) 19 November 1991 (19.11.1991) entire document	3, 16, 21
A	US 2012/0064050 A1 (CALLE et al) 15 March 2012 (15.03.2012) entire document	1-21
A	US 2011/0294108 A1 (ARGOUEDELIS et al) 01 December 2011 (01.12.2011) entire document	1-21
A	US 2013/0011823 A1 (HASSANEIN et al) 10 January 2013 (10.01.2013) entire document	1-21

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

* Special categories of cited documents:

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"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

20 April 2015

Date of mailing of the international search report

28 MAY 2015

Name and mailing address of the ISA/US

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