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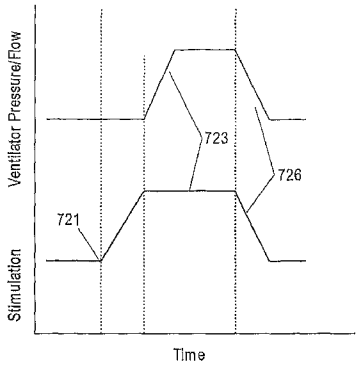

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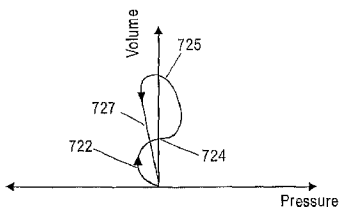

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(57) Abstract: Systems and methods are provided to improve respiratory function. Systems include an external electrical stimulator coupled to electrodes that stimulates diaphragm contraction and may optionally include a positive pressure mechanical ventilator. The system further includes an electrode suitable for temporary implantation. Electrical stimulation is provided to specific portions of the diaphragm, such as one hemidiaphragm preferentially over another. By preferentially contracting one hemidiaphragm, a specific portion of a lung may be expanded, such as a posterior portion. By the provision of the negative intrathoracic pressure from diaphragm contraction, greater expansion of specific portion of lung is achieved in relationship to air pressure within the lung, thereby improving compliance. Supplementation of stimulated diaphragm contraction with positive pressure driven air flow from a PPMV directs the air flow to specific portions of the lung. Such portion may include a posterior portion of a lung, and may cause a clearing of atelectasis in that portion.

WO 2007/103585 A2

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VENTILATORY ASSIST SYSTEM AND METHODS TO IMPROVE RESPIRATORY FUNCTION

REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to U.S. Provisional Patent Applications No. 60/767,201 which was filed on March 9, 2006, No. 60/861,568 which was filed on November 28, 2006, and No. 60/872,265 which was filed on December 1, 2006, all applications by inventors Ignagni and Onders. This application is also related to U.S. application no. 10/897,685, filed on July 23, 2004, and which was published as U.S. Pub. No. US 2005/0021102 on January 27, 2005. All of the aforementioned applications are hereby incorporated by reference.

FIELD OF THE INVENTION

[0002] The invention relates to apparatus and methods for supporting pulmonary function of patients in critical care settings.

BACKGROUND OF THE INVENTION

[0003] A patient may need respiratory assistance as a result of disease and/or injuries of various kinds. This need for respiratory assistance can be direct, especially when the injury or illness afflicts the patient's respiratory system. In one example, patients in acute respiratory failure may need respiratory assistance. The need for respiratory assistance can also be indirect, for example as during anesthesia. Typically, the extent of respiratory assistance may encompass a range from facilitating spontaneous breathing to total control of breathing.

[0004] A mechanical ventilator that moves gas into the lungs of a patient using positive pressure to move air into the lungs may be used to provide respiratory assistance. Although this respiratory assistance may be life saving, long-term use of a mechanical ventilator may not be ideal. For example, long-term mechanical ventilation use may result in weakening of the diaphragm of the patient because of disuse, and use of positive intrathoracic pressures may cause barotrauma, as well as provide inadequate ventilation of the posterior lobes of the lung, thereby possibly contributing to atelectasis, and generally compromising hemodynamics of the patient, which can have further deleterious consequences.

SUMMARY OF THE INVENTION

[0005] Embodiments of the invention include a method for supporting the respiration of patients that are typically in a critical care setting. Embodiments of the invention make use of a system that includes an external stimulator and one or more electrodes adapted for implanting at one or more sites in the diaphragm. The external stimulator is configured to stimulate the one or more electrodes

independently, the one or more electrodes connected to the external simulator. The method includes implanting the one or more electrodes in the diaphragm of the patient, initiating a breath, and stimulating the diaphragm with the one or more electrodes during a breath to increase tidal volume and/or to decrease maximal lung pressure during the breath, thereby improving respiratory compliance.

[0006] Embodiments of the invention include implanting the electrodes, or stimulating the implanted electrodes in such a way as to stimulate a specific portion of the diaphragm. Such a specific portion of the diaphragm may, for example, include the left hemidiphragm or the right hemidiaphragm, or any particular portion of the left or right hemidiaphragm. Such stimulation of a particular portion of a diaphragm may preferentially direct negative pressure to a particular portion of a patient's lungs, such as the right lung or the left lung. A particular portion of a lung may include the lower or posterior portion of the lung. In some embodiments, a particular portion of a lung may suffer from atelectasis, or collapse. In such embodiments, directing negative pressure to the collapsed portion may cause a decrease in – or clearing of atelectasis.

[0007] In some embodiments of the method, the patient initiates, or attempts to initiate a breath, which is then sensed by the system, such that the patient-initiated breath is subsequently supported to completion by the respiratory support system. Embodiments of the method include sensing the electrical activity in the diaphragmatic muscle through the electrodes of the system, which deliver electromyographic data to the system that are informative as to the diaphragmatic activity. Other embodiments of the method include sensing the initiation of a breath with a sensor placed at the airway of the patient; in some embodiments this is a pressure sensor, in other embodiments it is a flow sensor.

[0008] In other embodiments, the patient's breath is initiated by the external stimulator by way of stimulating the diaphragm. In such embodiments, the stimulator may provide a baseline breathing rate, in addition to supporting the breath through completion.

[0009] In other embodiments, the ventilator initiates the breath and the external stimulator is used to reduce pressures, increase gas delivered, and/or direct gas flow to dependent portions of the lungs. In such embodiments, the stimulator may be synchronized in timing with the ventilator breathing cycle or electronically triggered by the ventilator or gas flow to assist the ventilator at a specific point in the breathing cycle.

[00010] Embodiments of the method include the stimulator being able to vary stimulation parameters with regard to any one or more signal parameters including pulse rate, pulse frequency, pulse amplitude, pulse duration, and pulse ramping. The system may vary these parameters individually to each electrode, each electrode independently of others.

[00011] Application of the method, beyond broadly improving respiratory complains, may improve specific aspects of lung performance and patient health. The method may, for example, improve any of hemodynamics venous return, cardiac output, alveolar ventilation, type 1 muscle fiber condition. The method may decrease any of atlectasis, third spacing, time required for weaning from the PPMV, length of hospital stay, occurrence of pneumonia. The method may condition Type I muscle fibers, and may stimulate the conversion of Type IIb muscle fibers into Type I muscle fibers.

[00012] Some patients are at risk for the development of central hypoventilation syndrome (CHS), in such patients, the method may support a regular breathing rate during sleep. Disturbed sleep can decrease or prevent occurrence of REM sleep, accordingly, uninterrupted sleep as supported by a regular breathing rate may increase the occurrence or duration of REM sleep. Loss of REM sleep is considered a causative factor in intensive care unit (ICU) psychosis. Accordingly, the method may alleviate the severity or development of ICU psychosis.

[00013] In some embodiments, the method is applied to acute patients, who are expected to be weaned from the respiratory support system. In other embodiments, the patient has been previously supported by a positive pressure mechanical ventilator (PPMV), or by a combination of electrical diaphragm stimulation, per the presently described invention, and a PPMV. The method includes the support of these patients by the above described system, after the PPMV support has been discontinued.

[00014] As provided by embodiments of the invention, the electrodes may be implanted in the diaphragm any of several anatomical approaches and surgical methods. In some embodiments, the electrodes are implanted by insertion through the abdominal cavity, using either laparoscopic techniques or open surgical techniques. In some embodiments, the electrodes are implanted by insertion through the thoracic cavity, using either thoracoscopic techniques or open surgical techniques. In still other embodiments the electrodes are implanted in the diaphragm by way of insertion through natural orifices, using translumenal endoscopic techniques.

[00015] In some embodiments of the invention, the system for the method may further include a positive pressure mechanical ventilator (PPMV), the method further comprising ventilating the patient with the PPMV. In some embodiments, the external stimulator and the PPMV are configured such that the external stimulator controls the PPMV, the method further comprising controlling the PPMV. In such embodiments, controlling the PPMV includes controlling operational parameters of PPMV, the parameters including any of breath rate, gas volume delivered per breath, or airway pressure behind delivered gas. In other embodiments, the external stimulator and the PPMV are configured such that the PPMV controls the external stimulator, the method further comprising controlling the external stimulator. In such embodiments, controlling the external stimulator includes triggering stimulator output at a time in relationship to the PPMV reaching peak pressure. Generally in

embodiments that include a PPMV, the method may include controlling the PPMV with a constraint of a maximal tidal volume, or it may include controlling the PPMV with a constraint of a maximal airway pressure

[00016] In comparing the maximal airway pressure required to deliver a given tidal volume to a patient with a PPMV with and without diaphragmatic stimulation per embodiments of this invention, the airway pressure required by the PPMV is decreased by the concurrent diaphragmatic stimulation. High airway pressure from a PPMV is associated with barotrauma to the lungs of such treated patients, accordingly, inclusion of diaphragm stimulation may reduce the risk of PPMV-associated barotrauma.

[00017] Embodiments of the invention also include a method for treating a patient with an atelectatic lung region with a system including an external stimulator and one or more electrodes implanted at one or more sites in the diaphragm, the external stimulator configured to stimulate the one or more electrodes independently, and a positive pressure mechanical ventilator (PPMV). The method includes initiating a breath, ventilating the patient with the PPMV during the breath, stimulating the diaphragm with the one or more electrodes during the breath to increase tidal volume and/or to decrease maximal lung pressure during the breath. The electrodes have been implanted or a stimulated such that they preferentially stimulate a specific portion of the diaphragm such that the volume of atelectatic region is expanded, thereby clearing the atelectatic region.

[00018] Embodiments of the invention also include an electrode suitable for temporary placement in tissue that includes a needle at a first end, a central portion including a straight insulated lead, a helically wound insulated lead portion, and a deinsulated coiled portion, and a second end including a deinsulated barb and a stop. In some embodiments, the the stop comprises soft silicone. In other embodiments, the stop includes an absorbable suture material thermally bonded to the deinsulated coiled portion. In some embodiments, the needle is a break-away needle. In some embodiments the straight insulated lead and the helically wound insulated lead are joined at a junction, and the electrode further includes a bonding material disposed at the junction to form a bond configured to prevent the helically wound lead from unwinding.

[00019] Embodiments of the invention further include a method of inserting an electrode suitable for temporary placement in a tissue site, the electrode including a needle at a first end, a central portion comprising a straight insulated lead, a helically wound insulated lead portion, and a deinsulated coiled portion, and a deinsulated barb and a stop at a second end. The method includes inserting the electrode into a tissue site surface by the first end comprising the needle, and pulling the electrode through the tissue until the second end comprising the stop is at the tissue site surface.

BRIEF DESCRIPTION OF THE DRAWINGS

[00020] **Figure 1** is a block diagram of the external stimulator.

[00021] **Figure 2** shows an example of an implantable electrode.

[00022] **Figure 3** is a diagram illustrating a respiratory support system (system 1) including an external stimulator.

[00023] **Figure 4** is a diagram illustrating a respiratory support system (system 2) including an external stimulator and a PPMV, with an optional air flow sensor (breathing monitor) from the PPMV operably connected to both the PPMV and the external stimulator, but without a direct operable connection between the PPMV and the external stimulator.

[00024] **Figure 5** is a diagram illustrating a respiratory support system (system 3) including an external stimulator and a PPMV, with an optional air flow sensor (breathing monitor) from the PPMV operably connected to both the PPMV and the external stimulator, and with an operable connection between the PPMV and the external stimulator.

[00025] **Figure 6** is a block diagram showing three variations of respiratory support methods: (A) support with combination of PPMV and stimulator, with the stimulator initiating air flow into the lungs, (B) support with combination of PPMV and stimulator, with air flow being initiated by the PPMV, and (C) support by the stimulator alone, breath initiation either by the stimulator or by the patient, in which case the stimulator assists in completion of the breath.

[00026] **Figure 7** is a diagram illustrating an example of coordinated timing of respiratory support as provided by a combination of an external stimulator and a positive pressure mechanical stimulator.

[00027] **Figure 8** is a schematic graph that compares the relationship between internal lung pressure and lung volume over the course a breathing cycle, including an inhalation and an exhalation, in a patient supported by (A) positive pressure delivered by a positive pressure mechanical ventilator (PPMV) alone, and (B) the combination of negative pressure delivered by electrically stimulated diaphragm contraction and positive pressure delivered by a PPMV.

[00028] **Figure 9** shows a compliance pattern when respiration is supported by ventilation with a PPMV alone, without diaphragm stimulation.

[00029] **Figure 10** shows a compliance pattern when respiration is supported by diaphragm stimulation alone (without PPMV ventilation).

[00030] **Figure 11** shows a compliance pattern where diaphragm stimulation initiates a breath that is later supported by PPMV ventilation.

[00031] **Figure 12** shows a compliance pattern where a breath is initiated by the PPMV, and is later supported by diaphragm stimulation.

[00032] **Figures 13A – 13D** provides views of airway pressure waveforms on positive pressure mechanical ventilator monitor under various conditions: **Figure 9A** shows normal airway pressure waveform with ventilator only. Figure 9B shows airway pressure with diaphragm stimulation starting approx. 1 sec into inspiration demonstrating ability to increase tidal volume and modulate airway pressure. **Figure 9C** shows airway pressure with diaphragm stimulation started near beginning of inspiration and lasting for approx. 1 sec – demonstrating an ability to reduce airway pressure and maintain tidal volume. **Figure 78** shows airway pressure with stimulation in first inspiration and no stimulation in second inspiration.

[00033] **Figure 10** shows airway compliance shift measured on positive pressure mechanical ventilator.

DETAILED DESCRIPTION OF THE INVENTION

System components

[00034] Components of the system for providing respiratory support by the methods described herein include an external stimulator for electrically stimulating a portion of the diaphragm of a patient, electrodes suitable for implanting in the diaphragm, and a positive pressure mechanical ventilator (PPMV). In some embodiments, the system includes only the stimulator and electrodes for respiratory support; other embodiments include the PPMV as well.

External electrical stimulator and implanted electrodes

[00035] In one embodiment, the electrical signal generator 110 shown in **Figure 1** can be configured to generate pulses and/or signals that may take the form of sinusoidal, stepped, trapezoidal waveforms or other relatively continuous signals. The electric signal generator 110 can include one or more channels that can independently control the amplitude, frequency, timing and pulse width of the corresponding electrodes connected thereto.

[00036] In one embodiment, the electrical signal generator 110 can be an external signal generator that is electrically connected to or in electrical communication with the electrodes. One example of a suitable electrical signal generator is the NeuRx RA/4 stimulator that is manufactured by Synapse Biomedical, Inc. of Oberlin, Ohio. The NeuRx RA/4 stimulator is a four-channel device with independent parameter programmability. It will be appreciated that since the NeuRx RA/4 stimulator has four channels, it has the capability to independently control up to four electrodes. In an alternative embodiment, the electrical signal generator 110 can be an implantable signal generator. One suitable example of a fully implanted signal generator is the "Precision" electrical signal generator available from Boston Scientific / Advanced Bionics. One example of a partially implanted radio-frequency signal generator system is the "XTREL" system available from Medtronic, Inc.

[00037] The external stimulator 110 depicted in **Figure 1** is comprised of several blocks to produce coordinated stimulus output. The core of the device is a supervisory microcontroller 111 that coordinates parameter and sensed inputs, display, and stimulus / trigger outputs. The stimulus and timing parameters are stored in non-volatile memory and are programmed, via a serial interface (not shown), specific to the respiratory support needs and electrode muscle recruitment characteristics of the particular patient. The waveform generator 112 assembles the control signals from the microcontroller in the necessary waveform patterns to be output through the output stage signal drivers 113. The microcontroller 111 receives power from a power supply 114. It receives input of sensing information 115, impedance detection 116, stimulation parameters 117 and timing parameters 118. The microcontroller 111 provides output to a trigger output 119 and an LCD 121, in addition to the waveform generator 112. The output stage comprising drivers 113 also provide output to the impedance detector 116. The drivers 113 provide output in the form of stimulation of the electrodes 120.

[00038] In the preferred embodiment the resultant output is a capacitively coupled, current regulated biphasic waveform. With each stimulus output the circuit impedance is detected and fed back to the microcontroller to display electrode circuit integrity. The microcontroller may be driven to send the control signals to the waveform generator from an external sensed source (either a digital level or analog signal, such as diaphragm EMG) or from internal timing that is based on the stored timing parameters. The microcontroller may also be programmed to send out an analog or digital trigger signal to an external device based on a programmed sequence or event.

[00039] In one example, the electrical signal generator can supply the implantable electrodes with an electrical signal that serves as electrical stimulation to the respiratory system of the patient. For example, the electrical signal can be a capacitively-coupled, charge balanced, biphasic, constant current waveform with adjustable parameters as shown below in **Table 1**. It will be appreciated that the electrical signal can take the form of other waveforms for electrical stimulation such as monophasic or rectangular biphasic.

Table 1

Parameter	Range
Stimulation Interleave Rate	1 – 100
Trigger Delay (from inspiration)	1.0 – 4.0s
Stimulation Time	0.8 – 1.5s
Output Pulse Period	20 – 250 ms
Pulse Width Modulation Count	0 – 10
Cathodic Current Amplitude	5 – 25 mA
Cathodic Current Pulse Width	20 – 200μs
Voltage	0 - 65 V
Pulse Frequency	10-20 Hz

[00040] Although the stimulatory signal can be delivered to a variety of locations in the body of a patient to stimulate the respiratory system, in one example, the electrical stimulatory can be delivered to the diaphragm of the patient, through the electrodes, continuously or periodically. For example, the electrical stimulation can be delivered to the diaphragm of the patient at specified intervals per day (*e.g.* 5-6 sessions per day) for a certain period of time per interval (*e.g.* 5 minutes per session totaling about 25-30 minutes per day). It will be appreciated that the electrical stimulation can be delivered at different intervals depending on the needs of a particular patient.

[00041] The external electrical stimulator makes use of one or more intramuscular electrodes that are suitable for implanting into muscle tissue. In some embodiments, the intramuscular electrode can serve as a cathode. In some embodiments, the electrode is particularly adapted for temporary implantation. Features of implantation that provide long term stability, as in a more permanent placement, tend to work against suitability for short-term placement. It is desirable for an electrode to be able to stably remain in the muscle tissue without migrating from the target implant site, and thus supplemental anchoring is generally helpful. However, for an electrode to be appropriate for temporary placement, it needs to be able to be withdrawn intact without significant trauma to the muscle when no longer needed, and supplemental anchoring tends to complicate withdrawal. Similarly, tissue ingrowth, as encouraged by the anchoring or by features of the electrode is desirable for stabilization and protecting the entry site, but such ingrowth can complicate removal. In some instances the electrode may be treated as temporary by just abandoning its use, however that is unsatisfactory as presents risks to the patient of potential migration of unsecured portions, imaging artifact, or thermal/electrochemical effects if exposed to inappropriate MRI or diathermy.

[00042] One example of a suitable long-term intramuscular electrode is the Peterson intramuscular electrode (P/N 21-0002) manufactured by Synapse Biomedical, Inc. of Oberlin, Ohio. In one configuration, the Peterson intramuscular electrode is a double helix wound from multistrand stainless steel wire insulated in fluoropolymer with a polypropylene core and barb. The electrode can have a barb that is flattened and bent back along the line of the electrode, a polypropylene skirt, and a deinsulated coil under the skirt. The electrode lead can terminate with a stainless steel pin crimped to the de-insulated end and back-filled with silicone adhesive for strain relief. It will be appreciated that the intramuscular electrode can take the form of other shapes, sizes, and configurations, and can be made of other materials suitable for implantation into a patient.

[00043] Another example of an electrode suitable for short-term implantation is shown in **Figure 2.** This electrode 900 includes five primary elements: a deinsulated stimulating segment 902, a stop 904, a length of helically coiled insulated lead 906, a length of straight insulated lead 908, and a needle 910. The stop may comprise a soft silicone plug. The electrode is inserted, needle end first, into a target site, such as diaphramatic muscle, and pulled through until the stop at the opposite end is reached. Insertion in this manner results in the deinsulated stimulating segment ending up at the

surface of the target muscle at the needle entry point. The insulated lead is guided or tunneled to an appropriate exit site and the needle brought through the skin until the insulated coiled lead protrudes from the skin. The junction of the coiled to straight segment of insulated wire is secured with silicone adhesive or other suitable material to maintain the coiled configuration as it is drawn through the muscle tissue and skin interface. The coiled lead allows for tissue ingrowth at the skin exit site, thereby reducing the potential for infection entering and tracking along the lead. The needle may be a breakaway type of needle that can be used to terminate the electrode into the appropriate connector or the straight length of lead may be cut, deinsulated, and terminated into an appropriate connector. The stop may be a small amount of silicon adhesive or a piece of absorbable suture thermally locked on to the deinsulated lead.

[00044] Another example of a suitable short term intramuscular electrode was disclosed in a U.S. Provisional Patent Application filed on Feb 5, 2007 by Ignagni, Enders, Gelbke, and Crish, entitled "Intramuscular Electrode". In one embodiment of this intramuscular electrode it comprises a single helix multistrand wire stainless steel wire insulated in fluoropolymer with a polypropylene core and barb. Embodiments of this electrode either do not have the additional skirt of the Peterson electrode, or have a skirt of a lighter gauge polypropylene skirt than that of the Peterson intramuscular electrode, so that the electrode may be withdrawn without the complication of significant ingrowth of tissue around the skirt. The lead can be implanted under video guidance or direct visualization, using the attached needle to thread it into the diaphragm. The needle and lead-in polypropylene core would be cut off after implantation. To withdraw the electrode after the intervention is completed, the electrode would be withdrawn from the opposite end by straightening the helically wound wire and pulling on the polypropylene core and wire simultaneously. This would allow for the electrode to slide out from the tissue with minimal trauma and the polypropylene core would provide the mechanical support to prevent breakage of the wire in the body.

[00045] In one embodiment, the electrodes can be implanted into target sites in the diaphragm of the patient. For example, the electrodes can be implanted into or adjacent the phrenic nerve motor points of the diaphragm (*i.e.*, where the phrenic nerve enters the diaphragm) of the patient. The phrenic nerve motor points of the diaphragm are locations in the diaphragm that provide the greatest muscle fiber recruitment in response to an applied stimulation.

Respiratory support system variations and operating modes

[00046] **Figure 3** is a diagram illustrating a respiratory support system (System 1) including an external stimulator but without a PPMV. **Figure 3** is a diagram illustrating an example system 300 for assisting breathing in a patient, the patient's lungs represented as 330. Generally, the system 300 may include a stimulator 305 and one or more implantable electrodes 310 operably connected to the stimulator 305. The stimulator 305 may be configured to emit a stimulatory signal that is

communicated to the implantable electrodes 310 through an operable connection 335. The stimulatory signal may be of a variety of types. Example stimulatory signals may include electrical, magnetic, and other signals.

[00047] **Figure 4** is a diagram illustrating a respiratory support system (System 2) including an external stimulator and a PPMV, with an optional air flow sensor (breathing monitor) from the PPMV operably connected to both the PPMV and the external stimulator, but without a direct operable connection between the PPMV and the external stimulator. **Figure 4** is a diagram illustrating an example system 500 for assisting breathing in a patient. Generally, the system 500 may include a stimulator 505 and one or more implantable electrodes 510 operably connected to the stimulator 505. The system 500 may also include a mechanical ventilator 515. The system 500 may also include an airflow measuring instrument or flow sensor 520.

[00048] Generally, the mechanical ventilator 515 may be configured to cycle a gas into the lungs 525 of a patient. The mechanical ventilator 515 may also be configured to cycle the gas out of the lungs 525 of the patient. In one example, the gas is delivered from the mechanical ventilator 515 to the lungs 525 of the patient through a patient circuit 530. One type of patient circuit 530 may include a set of flexible tubes. Generally, one end of the patient circuit 530 may connect to the mechanical ventilator 515 and one end of the patient circuit 530 may connect to the patient through, for example, an endotracheal tube, a tracheostomy tube, a mask covering the patient's face, and the like.

[00049] The stimulator 505 may be configured to emit a stimulatory signal that is communicated to the implantable electrodes 510 through an operable connection 535. The stimulatory signal may be of a variety of types. Example stimulatory signals may include electrical, magnetic, and other signals.

[00050] An example airflow measuring instrument 520 of flow sensor may interact with the system 500 along the ventilation breathing circuit (*e.g.*, between the mechanical ventilator 515 and the lungs 525 of the patient). The airflow measuring instrument 520 generally is capable of sensing and/or measuring inspiratory and/or expiratory air flow in the ventilatory breathing circuit or cycle (*e.g.*, measuring air flow in the ventilatory breathing circuit). One type of airflow measuring instrument 520 may be a pneumotachometer.

[00051] The airflow measuring instrument 520 may be capable of emitting a signal or facilitating an associated or separate logic and/or software, for example, of emitting a signal related to the sensed or measured airflow. This signal may be communicated or transmitted, directly or indirectly, to the mechanical ventilator 515. This signal may be communicated, for example, via an operable connection 540 between the airflow measuring instrument 520 and the mechanical ventilator 515. The signal from the airflow measuring instrument 520 may also or alternatively be communicated or transmitted, directly or indirectly, to the stimulator 505. This signal may be communicated, for example, via an operable connection 545 between the airflow measuring instrument 520 and the

stimulator 505. The signals may facilitate timing or synchronization of a ventilatory cycle with delivery of a stimulatory signal or of delivery of a stimulatory signal with a ventilatory cycle. The signals may also or alternatively facilitate adjustment or variability in one or both of the ventilatory cycle and stimulatory signal.

[00052] **Figure 5** is a diagram illustrating a respiratory support system (System 3) including an external stimulator and a PPMV, with an optional air flow sensor (breathing monitor) from the PPMV operably connected to both the PPMV and the external stimulator, and with an operable connection between the PPMV and the external stimulator. **Figure 5** is a diagram illustrating an example system 700 for assisting breathing in a patient. Generally, the system 700 may include a stimulator 705 and one or more implantable electrodes 710 operably connected to the stimulator 705. The stimulator 705 may be configured to emit a stimulatory signal that is communicated to the implantable electrodes 710 through an operable connection 740. The system 700 may also include a mechanical ventilator 715. The mechanical ventilator 715 may be configured to cycle a gas into and/or out of the lungs 730 of a patient via a patient circuit 735. The system 700 may also include an airflow measuring instrument 720. The airflow measuring instrument 720 may be capable of sensing and/or measuring inspiratory and/or expiratory air flow in the ventilatory breathing circuit. The airflow measuring instrument 720, or an example logic associated with or separate from the airflow measuring instrument 720, may be capable of emitting a signal related to the sensed or measured airflow. This signal may be communicated or transmitted, directly or indirectly, to the mechanical ventilator 715. This signal may be communicated, for example, via an operable connection 745 between the airflow measuring instrument 720 and the mechanical ventilator 715.

[00053] The system 700 may also include a breathing sensor and control circuit 725. The breathing sensor and control circuit 725 can be configured to detect and/or determine certain breathing attributes of the patient (*e.g.*, the inspiration phase of a breath, the duration of the inspiration phase, the exhalation phase of a breath, the duration of the exhalation phase, tidal volume, airway pressures, and/or flow rate). These breathing attributes may be communicated to the breathing sensor and control circuit 725 via, for example, an operable connection 750 between the airflow measuring instrument 720 and the breathing sensor and control circuit 725. The breathing sensor and control circuit 725 may process these signals and transmit them to the stimulator 705, for example, via an operable connection 755 between the breathing sensor and control circuit 725 and the stimulator 705. The system 700 may also include an operable connection 760 between the mechanical ventilator 715 and the breathing sensor and control circuit 725. The operable connection 760 may facilitate, for example, timing of a ventilatory cycle with delivery of a stimulatory signal.

[00054] In another example, the system 700 can include a pressure gauge (not shown) and gas meter (not shown), provided along the ventilator breathing circuit, to measure the pressure and/or gas-related parameters of the patient's breathing. Also, a physiological measurement unit can be connected

to the patient to measure certain physiological parameters such as blood pressure, blood values, body temperature, etc. These measurements may be used by the system 700 to adjust or modify parameters of ventilation controlled by the mechanical ventilator 715 and or parameters of the stimulatory signal delivered by the stimulator 705.

[00055] Examplary methods may be better appreciated with reference to the **flow diagram** of **Figure 6** which shows three variations of respiratory support methods: (**6A**) support with combination of PPMV and stimulator, with the stimulator initiating air flow into the lungs, (**6B**) support with combination of PPMV and stimulator, with air flow being initiated by the PPMV, and (**6C**) support by the stimulator alone, breath initiation either by the stimulator or by the patient, in which case the stimulator assists in completion of the breath. Methods shown in **6A** and **6B** thus depict respiration support with the combination of electrical stimulation of diaphragm contraction that is further supported by positive airway pressure from the PPMV. By method **6A**, the stimulator initiates the breath, and the PPMV provides supplemental gas under pressure to the patient as needed. In method **6B**, the breath is initiated by the PPMV initiating a breath by flowing air into the lungs of the patient. In a variation of this method, the patient may initiate a breath that is detected by a gas flow detector on the PPMV, as which point the PPMV provides gas flow to support continuation of the breath. By either variation of method **6B**, however, the breath is not initiated by the external stimulator, but the stimulator does activate after the breath is initiated independently of it, from which point forward the stimulator supports the breath by the diaphragm creating negative pressure within the chest. And further, by virtue of the electrode stimulation being to a specific portion of the diaphragm, the gas flow, also being supported by the PPMV is directed to a specific portion of the lung. In method **6C**, the respiration is supported by the electrical stimulation of the electrodes, without participation of the PPMV. In embodiment **6C**, the breath is typically initiated by the patient volitionally, and the diaphragm stimulation directs the breath by stimulating a specific portion of the diaphragm, which directs airflow toward a specific portion of the lung. In a variation of method **6C**, the stimulator may initiate the breath, and then further support it as described.

Respiratory support by electrical stimulation of the diaphragm

[00056] This invention generally relates to manipulating respiratory compliance in patients in need of respiratory support, manipulating compliance in specific portions of the lung, and manipulating compliance toward specific therapeutic benefits. Compliance is manipulated or modulated through the coordinated activity of two therapeutic approaches. A first approach is by electrical stimulation of the diaphragm (diaphragm pacing), which supports respiration by way of generating negative intrathoracic pressure that expands lung volume by an external pull. Embodiments of the invention actually include therapy by this approach alone; other embodiments simultaneously include the second approach as well. The second approach is by way of a positive

pressure mechanical ventilator, which supports respiration by generating a positive pressure within the lungs that expands lung volume with an outward push.

[00057] The positive pressure approach to respiratory support is quite powerful, as the mechanical ventilator can easily provide sufficient pressure to expand lung volume. This approach by itself, however has some limitation. The first limitation is that pressure, while effective in expanding lungs, can also damage lung tissue if it is too high, and used for too long a period of time. The second limitation is that positive pressure delivered by a PPMV, by itself, cannot be specifically directed to a portion of a lung. Diaphragm stimulation as a base therapeutic approach provides respiratory support that does not stress lung tissue with high internal pressure, and further, provides a capability to steer volume expansion to particular regions of lung that are in particular need of expansion, such a an atelectatic region. The combining of the two therapeutic approaches not only decreases the need for high airway pressure from the ventilator, but also adds a steering to the moderated internal pressure that the ventilator does provide. In addition to the specific therapeutic benefit of clearing an atelectatic region of a lung, for example, a number of aspects of broader hemodynamic health are provided to the patient by the generally improved respiratory compliance.

[00058] Embodiments of the described invention provide a system and methods to support the respiration of patients in a critical care setting. Such patients are typically in acute need of respiratory support, but they are anticipated to be able to recover from the need for respiratory support. These patients are thus not considered to be in need of chronic support, and accordingly, the electrodes used in this therapeutic method are implanted in the diaphragm in a manner that may be considered temporary. The invention, however, is not limited to acute patients, and may in some instances be appropriate for longer term or chronic management of respiratory disease.

[00059] The system includes an external electrical stimulator and one or more electrodes adapted to be temporarily placed in the diaphragm of a patient, the electrodes being connected to and under the control of an external stimulator. The external stimulator is configured to be able to stimulate each of the electrodes independently of each other. The method by which respiration is supported by electrical stimulation of the diaphragm includes implanting the one or more electrodes in the diaphragm of the patient, initiating a breath, and stimulating the diaphragm with the one or more electrodes during a breath to increase tidal volume and/or to decrease maximal lung pressure during the breath, thereby improving respiratory compliance. As described further below, the breath may be initiated either by the patient or by the respiratory support system. Also, as described further below, the system may further include a positive pressure mechanical ventilator. Basics of the system and method of respiratory support by diaphragmatic stimulation is provided as a stand alone therapy (*i.e*, in the absence of positive pressure support) is not substantially changed by the inclusion of ancillary positive pressure support, and thus will be described first as a stand alone therapy, to be followed by particulars that come with the inclusion of positive pressure support.

[00060] A breath may be understood as a breathing cycle that includes a single inspiration phase followed by a single exhalation. As provided by embodiments of the method, a breath or an attempted breath may be initiated the patient, and the patient-initiated breath is then supported at least in some portion through the cycle by diaphragm stimulation. In other embodiments of the method, the breath is initiated by the diaphragm stimulation, and then further supported at least through a portion of the cycle by further or continued diaphragm stimulation. Such an embodiment is appropriate for patients unable to initiate a breath. In this embodiment, the electrical stimulation of the diaphragm not only supports the breath, but it also determines the breathing rate. Regardless of the source of the breath initiation (patient or system), the system then supports the breath through independent stimulation of electrodes, through variation in various signal parameters as described further below, and through variable timing throughout the breath cycle, whether such stimulation is at the beginning, middle, or end of the cycle, or throughout the cycle.

[00061] Returning to the embodiment in which the breath is initiated by the patient, the initiation is sensed by the system through the electrodes themselves. In this embodiment, breath initiation, whether it would ultimately be successful without respiratory support or not, manifests as electrical activity in the diaphragmatic muscle. Such electrical activity is be captured by electrodes in the form of electromyographic data, which are processed by the microcontroller of the system (**Figure 1**), and interpreted as a breath initiation attempt.

[00062] The electrodes may be implanted in the diaphragm by any of several anatomical approaches and by various surgical methods and tools. In some embodiments, the electrodes are implanted by insertion through the abdominal cavity, using either laparoscopic techniques or open surgical techniques. In other embodiments, the electrodes are implanted by insertion through the thoracic cavity, using either thoracoscopic techniques or open surgical techniques. In still other embodiments the electrodes are implanted in the diaphragm by way of insertion through natural orifices, using translumenal endoscopic techniques.

[00063] The placement of electrodes may be done under direct visualization (*e.g.*, open surgical technique) or with video observation through a surgical camera. Location of electrode placement may be assisted with electrical stimulation mapping of the diaphragm to identify the phrenic nerve motor point or specific branches. It may be desirable to identify specific branches so as to recruit the largest anatomical surface area (*e.g.* anterior or posterior) portions of the diaphragm. Mapping may be done in an open procedure, thoracoscopically, or laparoscopically, or endoscopically (using a transgastric approach). Prior laparoscopic and endoscopic techniques have been described in associated patents filings (U.S. Application No. 60/597440, U.S. Pat. No. 5,472,438, and U.S. Patent Published Application No. 2005/0107860) and are incorporated and enhanced with this invention. While direct visualization of the phrenic nerve may be accomplished with an open thoracic or thoracoscopic

approach, it may be desirable, as provided by embodiments of this invention, to verify the placement location with electrical stimulation mapping of the diaphragm.

[00064] Electrodes may be implanted in the diaphragm muscle with an electrode delivery instrument; one exemplary instrument is described in U.S. Patent No. 5,797,923. Another method, as provided by embodiments of this invention, include the use of an apparatus to puncture through the skin and provide a channel for introduction of a needle loaded with a barbed intramuscular electrode that may be inserted into the diaphragm under thoracoscopic, laparoscopic, or endoscopic visualization. If implanted during an open procedure the intramuscular electrode may be sewn into the diaphragm using a special electrode that is incorporated into this invention.

[00065] Embodiments of the method include the targeting to specific portions of the diaphragm to stimulate. Such targeting may be brought about by the selection of the diaphragm sites in which the electrodes are implanted, and it may also include the stimulation of a subset of implanted electrodes that are located in a diaphragm site of interest. A specific portion of the diaphragm may, for example, include the left hemidiphragm or the right hemidiaphragm, or any particular portion of the left or right hemidiaphragm. Stimulation of a particular portion of a diaphragm, the right or left hemidiphragm, for example, has the effect of directing or steering negative pressure to a particular portion of a patient's lungs, such as the right lung or the left lung, respectively. A particular portion of a lung may include the lower or posterior portion of the lung. In some embodiments, a particular portion of a lung may suffer from atelectasis, or collapse. In such embodiments, directing negative pressure to the collapsed portion may cause a decrease in or clearing of atelectasis.

Respiratory support by combination of diaphragm stimulation and positive pressure

[00066] As mentioned above, some embodiments of the method include the use of a system that includes a positive pressure mechanical ventilator (PPMV) supplying positive airway pressure to the lungs in addition to the external stimulator stimulating the diaphragm to supply negative pressure external to the lungs. In these embodiments, the external stimulator generally controls the operation of the mechanical ventilator, as the two components are configured in a master – slave relationship. The positive pressure mechanical ventilator may either be invasive (*e.g.*, endotracheal intubation or tracheostomy) or non-invasive (*e.g.*, mask ventilation). The external stimulator may control the operation of PPMV with regard to any of the breath rate, the gas volume delivered per breath, or the airway pressure behind delivered gas. The PPMV can be set at a back-up rate so that the breathing rate is controlled by the stimulator such that either delivered gas volume or delivered airway pressure is controlled during a breath cycle. The PPMV may be controlled in such a way that maximal tidal volume is a constraint. The PPMV may also be controlled such that maximal airway pressure is a constraint.

[00067] The PPMV may be set in assist mode, where it assists within a breath cycle initiated either by the patient or by a diaphragm contraction that is stimulated by electrodes, or, alternatively the PPMV may be directly controlled by the external stimulator so that an inspiration initiated by the external stimulator triggers the PPMV to deliver supplemental gases. Further, with regard to the external stimulator, as described above, the stimulator may be configured to provide stimulation at the beginning, middle, or end of an inspiration cycle or coincidental with the entire cycle. The level of stimulation provided may be modulated during the cycle or remain constant (whether the cycle is initiated by the external stimulator or the PPMV). The stimulation may be delivered to all implanted electrodes simultaneously, to electrodes grouped by hemi-diaphragm, or to individual electrodes to preferentially contract portions of a diaphragm. The timing between stimuli delivered to specific electrodes may be sequenced so that the stimuli are delivered simultaneously, spaced throughout the stimulus cycle, or anywhere in between.

[00068] Various sequences of respiratory support with regard to the interplay of the PPMV and diaphragm stimulation are provided. For some patients in acute respiratory distress, an initial period of respiratory support that includes contributions of both a PPMV and diaphragm stimulation may be appropriate upon admission to an intensive care unit. With recovery of function, or clearing of atelectasis, for example, it may be clinically appropriate to wean the patient from the PPMV, discontinue it, and continue respiratory support with the diaphragm stimulation alone. In other cases, diaphragm stimulation may be a sufficient and appropriate mode of therapy alone, without the PPMV support. In still other cases, the condition of a patient on diaphragm stimulatory support may experience a worsening of condition, and benefit from the inclusion of positive pressure support.

[00069] **Figure 7** is a diagram illustrating one example of timing between mechanical ventilation and a stimulatory signal 400. The diagram illustrates initiation of a stimulatory signal 405 with the beginning of inspiration 410 that is provided or assisted by a mechanical ventilator. The diagram also illustrates an increase in the level of the stimulatory signal 415 later in the inspiratory cycle 420. This increased stimulatory signal 415 may facilitate moving gases into the lower lobes of the lungs of the patient, for example.

[00070] The profile of generation or delivery of the stimulatory signal in relation to a ventilatory cycle, one example of which is shown in **Figure 7**, may be modified for individual patients. These modifications may include, but are not limited to, the magnitude of the stimulation, the timing of the stimulation relative to the ventilatory cycle, and the rate (*e.g.*, ramping) at which the stimulatory signal is changed during the cycle. These modifications may be implemented or facilitated by, for example, software or logic.

[00071] It will also be appreciated that stimulation of the diaphragm of the patient may not be synchronized with breathing or attempts at breathing made by the patient and, thus, can be applied during any portion of a breath or ventilatory cycle.

Respiratory compliance

[00072] Respiratory compliance refers to the relationship between lung volume and air pressure within the lung. Optimal lung function is favored good compliance, *i.e.*, by a high degree of responsiveness of a change in lung volume in response to change in pressure, as an increase in volume opens alveolae and creates greater lung surface area for gas exchange. Poor compliance impedes the amount of gas exchanged during a breath, which has a number of deleterious and well known consequences. Compliance involves a quality of lung tissue and resistance of airways that is associated with the state of health and integrity in a general sense, but is also a functional quality that can be manipulated or modulated by diaphragm stimulation.

[00073] Mechanical ventilation clearly provides significant benefits that follow from overcoming resistance of airways, expanding constricted alveolae that are associated with a poorly compliant lung, and generally increasing tidal volume. However, mechanical ventilation also has the potential to create high pressures that can traumatize and damage lung tissue. Patients with collapsed portions of lung, or atelectasis, have poor compliance as a consequence of the collapsed portion not expanding in response to pressure. The coordinated action of mechanical ventilation and electrical stimulation of specific diaphragm sites, as provided by the system and methods of this invention, improves compliance.

[00074] The dynamics of pressure and volume in a lung that is being supported by positive pressure mechanical ventilation (PPMV) alone and by a combination of diaphragm stimulation and PPMV is shown in an idealized schematic version in **Figure 8A and 8B**. A more detailed set off examples is described below, as depicted in **Figures 9 – 12. Figure 8A** (support by PPMV only) and **8B** (support by diaphragm stimulation plus PPMV) both depict lung volume as a function of air pressure within the lung through a breath cycle of a single inspiration and a single exhalation. Pressure is shown on the X-axis, and is relative to atmospheric pressure, atmospheric pressure representing zero on the X-axis. The volume is shown on the Y-axis, and is shown in terms of the increase in volume over the functional reserve capacity of the lung, i.e., the volume at the low point of a normal exhalation. The maximal volume achieved during a normal inhalation is termed the tidal volume.

[00075] The time course through the breath cycle is indicated by arrows. The graphs show the maximal volume achieved in both breaths to reach the same value. It can be seen that the breath supported by positive pressure alone (**figure 8A**) shows the intralung air pressure to increase steadily from the point of initiation of the inspiration to its conclusion, at the upper right point where the

inhalation concludes. Following a different trajectory, shifted to the left, the ratio of volume to pressure falls as a smooth function back to the origin. In contrast, the time course of the volume/pressure ratio of a lung during a breath that is supported by both PPMV and diaphragm-stimulated intrathoracic negative pressure may begin with an immediate drop in pressure if the driving force from the diaphragm stimulation either precedes or is greater than the positive pressure from the PPMV. This pressure drop is due to the stimulated contraction of the diaphragm. At the same time, however, air may be flowing into the lung from the PPMV, and at a certain point that PPMV driving force from the PPMV becomes greater than that of the diaphragm stimulation the pressure reverses while the inflow of air continues. As the pressure begins to rise, the pressure crosses the baseline level, and climbs to the same peak level depicted in **figure 8B**. The pressure may drop from the peak pressure and be held at a plateau to sustain the given volume. As the pressure falls below the elastic force of the lungs and chest the volume falls steadily back to the origin during exhalation. The specific form of the curve depicted in **figure 8B** varies with timing of the stimulation, and according to other stimulatory parameters, but the point of this depiction is that under conditions of **figure 8B**, the lung is more compliant, and for a given maximal volume, the lung tissue is exposed to a significantly lower pressure.

[00076] Lung compliance may be improved, for example, by modifying diaphragm stimulation parameters to elicit a higher change in tidal volume with each inspiration or by maintaining tidal volume while reducing the delivered pressures. Compliance may be modified, preferentially, on the right or left lobes of the lungs, by separately controlling stimulation levels to the right or left hemi-diaphragm to pull gas to an otherwise unventilated region. This preferential directing of internal gas movement by way of controlling negative intrathoracic pressure can be used to reduce or clear an atelectic region. Contraction of the diaphragm also preferentially pulls the gas to the posterior or dependent lobes of the lungs and helps to prevent pneumonias.

[00077] The addition of negative pressure during the inspiration cycle may also be used to reduce the intra-thoracic pressure and thereby improve the venous return. This has the effect of increasing the cardiac stroke volume and cardiac output, thus improving the patient's hemodynamics. This should also improve any third-spacing that may be a result of PPMV. To optimize hemodynamic improvement outcome the external stimulator may be triggered by the cardiac cycle to provide optimal timing between the left ventricular filling and the contraction of the diaphragm.

[00078] Application of the method, beyond broadly improving respiratory compliance, may consequently improve a number of specific aspects of lung performance and patient health. The method may, for example, improve any of hemodynamics venous return, cardiac output, alveolar ventilation, type 1 muscle fiber condition. The method may decrease any of atlectasis, third spacing, time required for weaning from the PPMV, length of hospital stay, occurrence of pneumonia. The

method may condition Type I muscle fibers, and may stimulate the conversion of Type IIb muscle fibers into Type I muscle fibers.

[00079] Some patients are at risk for the development of central hypoventilation syndrome (CHS), in such patients, the method may support a regular breathing rate during instances of hypopnea or apneas, particularly during sleep. Disturbed sleep can decrease or prevent occurrence of REM sleep, accordingly, uninterrupted sleep as supported by a regular breathing rate may increase the occurrence or duration of REM sleep. Loss of REM sleep is considered to be a causative or risk factor for intensive care unit (ICU) psychosis. Accordingly, the method may alleviate the severity or development of ICU psychosis.

[00080] What follows now (**Figures 9 – 12**) is a series of specific comparisons of compliance patterns that manifest under various respiratory support regimens as provided by diaphragm stimulation or PPMV support, alone and in combination. In each example an **upper graph A** shows a time sequence of activity of both the ventilator (above, if present) and the external electrical stimulation (below, if present), and a **lower graph B** shows the same data displayed as an graph of volume as a function of pressure. These examples include a pattern (**Figure 9**) conventional ventilator compliance pattern without diaphragm stimulation, a compliance pattern (**Figure 10**) with diaphragm stimulation only, a compliance pattern (**Figure 11**) the breath is initiated by stimulation and is further supported by the PPMV, and a compliance pattern (**Figure 12**) where the PPMV initiates the breath and diaphragm stimulation further supports the breath.

[00081] **Figure 9** shows a compliance pattern when respiration is supported by ventilation with a PPMV alone, without diaphragm stimulation. As the ventilator pressure/flow starts to increase during inspiration (701) the volume build slowly increases (702). At a given point (703) the airflow resistance decreases and the rate of volume to pressure increase becomes greater until the peak pressure (704) is reached. Once the desired volume is attained the plateau pressure is maintained (705) and the volume is held (706). Upon expiration (707), the volume is maintained (706) until the pressure falls below the elastic force of the respiratory system and an exhalation occurs (708).

[00082] **Figure 10** shows a compliance pattern when respiration is supported by diaphragm stimulation alone (without PPMV ventilation). The stimulation is initiated (711) causing a negative pressure increase with volume drawn into the lungs (712). Once the peak stimulation level (714) is reached the peak pressure (713) is obtained and the volume held (715). Once the stimulation is turned off or ramped down (716) the inspired volume will be exhaled (717).

[00083] **Figure 11** shows a compliance pattern where diaphragm stimulation initiates a breath that is later supported by PPMV ventilation. The stimulation initiates the breath (721) causing a negative pressure with increasing volume (722). If the ventilator pressure exceeds the negative pressure force from the stimulation (723) the pressure curve will become positive with increasing volume (724). If

the ventilator pressure is less than the negative pressure force from the stimulation (723) the pressure curve will remain negative with increasing volume (not shown). After the plateau pressure and maximum volume (725) is reached the exhalation phase may commence. The pressure is decreased until the elastic recoil of the lungs and chest causes exhalation (727). The pressure may become negative again depending on the relative force from the stimulation to the PPMV (726).

[00084] **Figure 12** shows a compliance pattern where a breath is initiated by the PPMV, and is later supported by diaphragm stimulation. The PPMV initiates the breath (731) causing a positive pressure with increasing volume (732). If the ventilator pressure is less than the negative pressure force from the stimulation (733) the pressure curve will become negative with increasing volume (734). If the ventilator pressure exceeds the negative pressure force from the stimulation (733) the pressure curve will remain positive with increasing volume (not shown). After the plateau pressure and maximum volume (735) is reached the exhalation phase may commence. The pressure is decreased until the elastic recoil of the lungs and chest causes exhalation (737). The pressure may become positive again depending on the relative force from the stimulation to the PPMV (736).

Examples of Applying the Invention

Example 1. Interaction of respiratory support by positive pressure ventilation and negative intrathoracic pressure by diaphragm stimulation

[00085] **Figures 13A – 9D** show screenshots of patient data collected from a study in which positive pressure ventilation and diaphragm stimulation were variously applied. **Fig 13A** (bottom left) shows a normal airway pressure waveform with ventilator support only, without diaphragm stimulation. These data show the typical increase in airway pressure until the desired tidal volume (V_T = 0.52 liters) is achieved. A peak airway pressure (P_{PEAK}) of 17 cm H_2O and mean airway pressure (P_M) of 5 cm H_2O is reached under the ventilator only conditions. The minute ventilation of 4.2 liters/minute is displayed for the given V_T and the measured respiratory rate (RR = 8 breaths per minute) with is calculated as MV = V_T * RR.

[00086] **Figure 9B** (bottom right) shows airway pressure with diaphragm stimulation starting approximately 1 sec into inspiration, thus demonstrating ability to increase tidal volume and modulate airway pressure. In a "failure to oxygenate" patient the airway pressures and tidal volumes would be specifically controlled to recruit collapsed lung units (*e.g.* decrease atelectasis). These data demonstrate the ability to increase V_T (= 0.62 liters) while decreasing the airway pressures (P_{PEAK} = 13, P_M = 2) as compared to the ventilatory only readings. Normally, a clinician would increase the airway pressures and tidal volume to recruit collapsed lung units. By adding in the diaphragm stimulation at appropriate time during the ventilatory cycle, the peak airway pressure needed to overcome any large airway resistances may be applied and the plateau pressure (P_{PLAT}) reduced or

eliminated thus avoiding overdistension of the lungs. In the displayed data, a stimulation pulse of 25mA / 100μs was used to recruit diaphragm muscle contraction at a maximal level.

[00087] **Figure 13C** (top left) shows airway pressure with diaphragm stimulation started near the beginning of inspiration and lasting for approximately. 1 sec, thus demonstrating ability to reduce airway pressure and maintain tidal volume. For these data, a lower level of stimulation was used, 10mA / 100μs pulse, to reduce airway pressures (P_{PEAK} = 12 cm H_2O, P_M = 3 cm H_2O) while maintaining a constant tidal volume (V_T = 0.52 liters).

[00088] **Figure 13D** (top right) shows airway pressure with stimulation in first inspiration and no stimulation in second inspiration. These data demonstrate the ability to modulate the airway pressure on a breath by breath basis.

[00089] **Figure 14** demonstrates the addition of synchronous breaths to a volume ventilator and the effect upon respiratory system compliance (C_{RS}). The nominal settings, without diaphragm stimulation, provided P_{PEAK} = 14 cm H_2O, P_{PLAT} = 12 cm H_2O, C_{RS} = 67 ml / cm H_2O, and V_T = 720ml. The addition of diaphragm stimulation early in the inspiratory cycle caused the pressure to initiate negative with increasing volume and then proceed with the continued delivery of the ventilator volume positive prior to returning to zero with completion of expiration, as shown in the pressure-volume curve in the upper left portion of the figure. The resultant tidal volume was the "stacked" volumes from the diaphragm and the ventilator, V_T = 1,580ml. Because of the high volume delivered the pressures increased (P_{PEAK}=25cm H_2O, P_{PLAT}=23cm H_2O). The respiratory system compliance also increased with the corresponding increase in volume and pressure (C_{RS} = 73 ml / cm H_2O).

Example 2. Application of diaphragm pacing to treatment of ALS patients

[00090] Amyotrophic lateral sclerosis (ALS, Lou Gehrig's Disease) is a condition leading to fatal motor neuron degeneration. Muscular weakness typically progresses at the rate of 1.8% to 3.5% per month. When the muscle deterioration reaches the diaphragm, the patient develops hypercarbic respiratory failure, leading to death. ALS patients may experience different rates of decline in their left and right hemidiaphragms.

[00091] A mechanical ventilator (also known as positive pressure mechanical ventilator or PPMV) can be used to maintain breathing in ALS patients in an invasive (with tracheostomy) or non-invasive (with mask or nasal cannula) manner, but there are certain negative aspects to mechanical ventilation. In addition to the significant costs of ventilators, ventilated patients suffer from speech difficulty, further reduced mobility, and create a heightened burden on caregivers. More significant are the deleterious physiologic effects of positive pressure ventilation, such as a decrease in remaining diaphragm strength due to atrophy of the muscle and to conversion of Type I fibers to Type IIb. The increased thoracic pressure caused by PPMV can lead to decreased cardiac output and barotrauma, with possible posterior lobe collapse, atelectasis and/or pneumonia. Further, many ALS patients do

not tolerate non-invasive PPMV, due to the bulbar symptoms of the disease, and most of them do not accept invasive PPMV.

[00092] Functional electrical stimulation of the diaphragm, with or without PPMV, can pace the diaphragm to maintain diaphragm function. In addition to assisting breathing by causing diaphragm contraction through direct stimulation at phrenic nerve motor points, diaphragm pacing can induce new nerve branching in the diaphragm, counteract muscle atrophy and slow the decline of forced vital capacity (FVC) in ALS patients. Diaphragm pacing can reduce patient airway pressure, increase overall ventilation, increase diaphragm strength, maintain Type 1 diaphragm muscle fibers, improve cardiac output and provide increased posterior lobe ventilation.

[00093] Twelve patients with FVC between 50 - 80% and >45% at the time of surgery (average 58% FVC) were enrolled in the study. Electrodes were implanted laparoscopically in the patients' two hemidiaphragms at motor points determined during an earlier mapping procedure, and stimulation was provided in 30 minute sessions three to five times per day. Stimulation was provided at 12 Hz, with the pulse width and amplitude as much as the patient could tolerate (typically around 10 ma, pulse width 150 ms) to provide the patient with 8 – 15 breaths per minute. Patients were permitted to increase stimulation utilization over time if desired. In addition to measuring FVC and other lung capacity parameters, diaphragm thickness was measured ultrasonically, blood gases were sampled, and patient quality of life information was surveyed.

[00094] The diaphragm pacing system used for stimulation can provide different stimulation signals to each electrode in each hemidiaphragm. Stimulation parameters can be varied by amplitude, frequency, rate, pulse width and pulse modulation. Diaphragm muscle mass increased over the course of the diaphragm pacing as shown in the **Table 2** below:

Table 2

Test Location	Pre-Implant (mm)	Post-implant (mm)	P-value
L @ expiration	3.9 +/- 0.7	4.8 +/-1.2	0.02
R @ expiration	3.8 +/- 0.9	4.7 +/- 1.1	0.01

[00095] In addition, improved diaphragm movement was observed under fluoroscopy. Diaphragm contraction increased with stimulation compared to volitional movement an average of 1.5 cm per hemidiaphragm. Furthermore, the decline of FVC decreased from 2.8% to 1.0%, thereby delaying the time when the ALS patient would need to begin using mechanical ventilation.

[00096] The diaphragm stimulation in ALS patients was also shown to sustain the respiratory function of the patients as measured by standard means using the revised ALS Functional Rating Scale (ALSFRSr). In the set of patients studied the overall functional rating score decreased at a rate

of 0.7 points per month while the respiratory subscore remained constant. These same patients showed a decline in physical and emotional domains of a standard quality of life instrument, the SF-36 prior to treatment and demonstrated an improving trend in scores post treatment.

[00097] Diaphragm pacing can also be used together with non-invasive mechanical ventilation in the ALS patients to decrease peak airway pressure and increase tidal volume, making the intervention of non-invasive PPMV tolerated by a greater portion of ALS patients. This intervention would also increase respiratory compliance, reduce atelectatic lung regions and thereby reduce the risks of acute respiratory failures.

Example 3. Respiratory support for a heavily sedated ICU patient

[00098] For a heavily sedated ICU patient with no respiratory drive a volume ventilator mode may be used to provide ventilatory needs. The diaphragm pacing may be used to assist in this case to (1) preferentially ventilate the dependent portions of the lungs to avoid atelectasis, (2) reduce the applied pressures, and (3) reduce the work of breathing by increasing the respiratory system compliance, as outlined below.

1. To preferentially ventilate the dependent portions of the lungs the stimulation may be applied after the volume delivery commences (after the peak pressure but prior to completion of the positive gas flow) to draw the delivered air to the posterior lobes. With a heavily sedated patient higher stimulus parameters may be used, if needed, as any discomfort from the stimulus would not be felt by the patient.
2. To reduce the applied pressures the stimulation may initiate coincidental to the ventilated breath to reduce peak airway pressure or subsequent to the peak to reduce the plateau pressure. The stimulation could be ramped on at a rate (over the gas delivery) to avoid an in-rush of negative inspiratory force and stacked breaths.
3. The stimulation may be applied at a lower level (*e.g.* amplitude of 10mA as opposed to 25mA) at the beginning of the ventilatory cycle to reduce initial peak pressures or throughout the gas delivery to reduce peak and plateau pressure while maintaining the tidal volume (as in **figure 3C**) thus increasing the respiratory system compliance.

[00099] For a patient that is not heavily sedated and/or is appropriate for pressure support ventilation the stimulation can be used to provide the primary ventilatory support with the ventilator as a backup. The diaphragm stimulation would be set to obtain the desired volume at stimulation values that the patient could tolerate. For a typical patient the stimulus may be set in a range of 10 – 25mA at a pulse duration of 100μs and pulse frequency of 10 – 15Hz. If adequate ventilation is obtained the ventilator would be set to provide only backup to the stimulated support. If adequate volumes are not obtained the ventilator pressure would be increased until adequate volumes are obtained. This support could be done with endotracheal or mask ventilation.

[000100] All publications, patents, and patent applications cited herein are hereby incorporated by reference in their entirety for all purposes to the same extent as if each individual publication, patent, or patent application were specifically and individually indicated to be so incorporated by reference.

[000101] Other variations of method and aspects of the system can be employed to achieve the objectives of the invention without departing from the scope of the invention, as will be appreciated by those skilled in the art. While various embodiments of the present invention have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. The invention generally relates to manipulating respiratory compliance toward therapeutic ends, and in describing the invention, the application has offered some theoretical explanation as to how these ends may be achieved. It should be understood, however, that such theories and interpretation do not bind or limit the claims with regard to the therapeutic benefits brought about by the practice of the invention. Numerous variations, changes, and substitutions will occur to those skilled in the art without departing from the invention. It should be thusly and further understood that various alternatives to the embodiments of the invention described herein that may be employed in practicing the present invention are considered equivalents to the invention, and that it is intended that the scope of the invention includes such equivalents.

CLAIMS

We claim:

1. An electrode suitable for temporary placement in tissue comprising:
a needle at a first end,
a central portion comprising a straight insulated lead, a helically wound insulated lead portion, and a deinsulated coiled portion, and
a deinsulated barb and a stop at a second end.

2. The electrode of claim 1 wherein the stop comprises soft silicone.

3. The electrode of claim 1 wherein the stop comprises an absorbable suture material thermally bonded to the deinsulated coiled portion.

4. The electrode of claim 1 wherein the needle is a break-away needle.

5. The electrode of claim 1 wherein the straight insulated lead and the helically wound insulated lead are joined at a junction, the electrode further comprising a bonding material disposed at the junction to form a bond configured to prevent the helically wound lead from unwinding.

6. A method of inserting an electrode suitable for temporary placement in a tissue site, the electrode comprising a needle at a first end, a central portion comprising a straight insulated lead, a helically wound insulated lead portion, and a deinsulated coiled portion, and a deinsulated barb and a stop at a second end,
the method comprising inserting the electrode into a tissue site surface by the first end comprising the needle, and pulling the electrode through the tissue until the second end comprising the stop is at the tissue site surface.

7. The method of claim 6 wherein the electrode stop comprises soft silicone.

8. The method of claim 6 wherein the electrode stop comprises an absorbable suture material thermally bonded to the deinsulated coiled portion.

9. The method of claim 6 wherein the electrode needle is a break-away needle.

10. The method of claim 6 wherein the electrode's straight insulated lead and the helically wound insulated lead are joined at a junction, the electrode further comprising a bonding material disposed at the junction to form a bond configured to prevent the helically wound lead from unwinding.

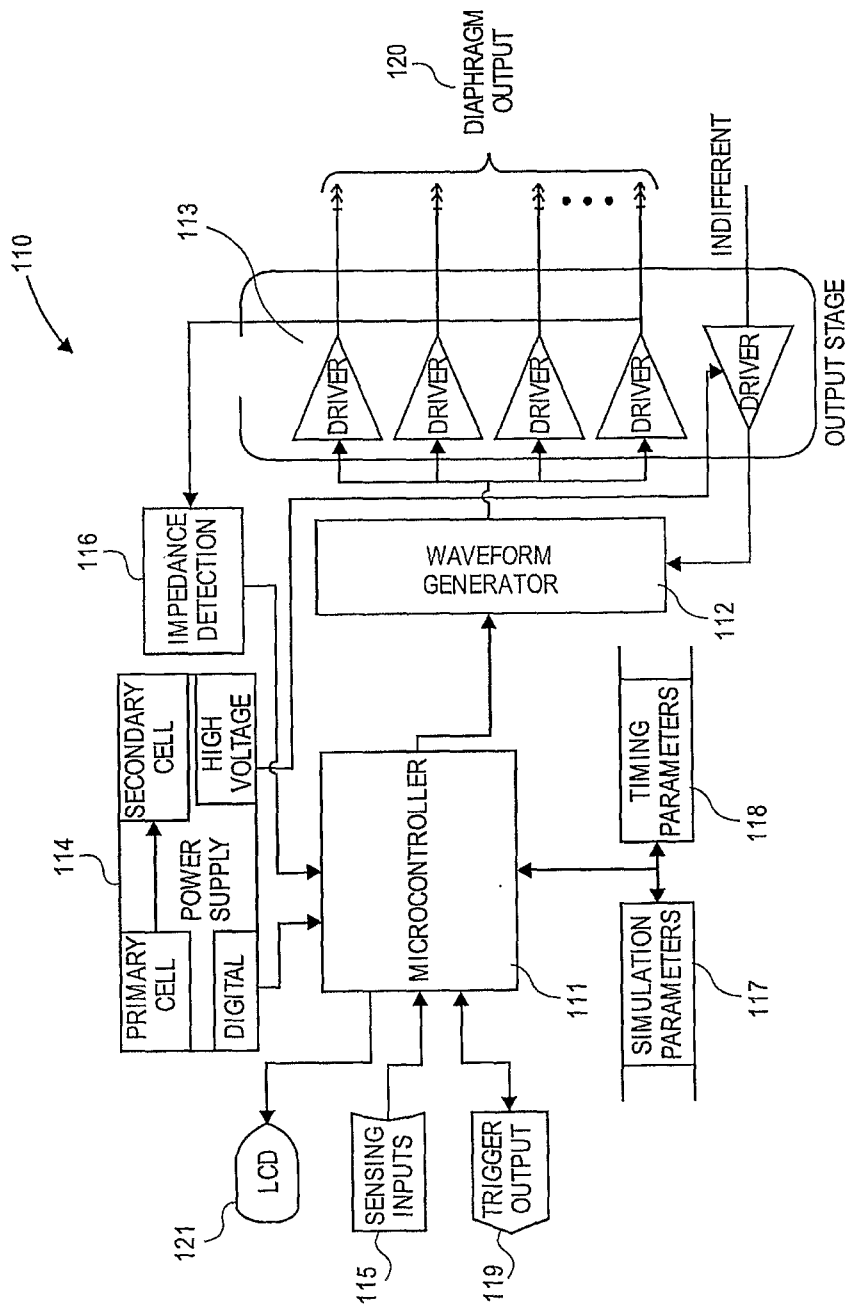

110
113
120
DIAPHRAGM OUTPUT
INDIFFERENT
DRIVER
DRIVER
DRIVER
DRIVER
DRIVER
OUTPUT STAGE
116
IMPEDANCE DETECTION
WAVEFORM GENERATOR
112
SECONDARY CELL
HIGH VOLTAGE
114
POWER SUPPLY
PRIMARY CELL
DIGITAL
MICROCONTROLLER
111
TIMING PARAMETERS
118
SIMULATION PARAMETERS
117
LCD
121
SENSING INPUTS
115
TRIGGER OUTPUT
119

FIG. 1

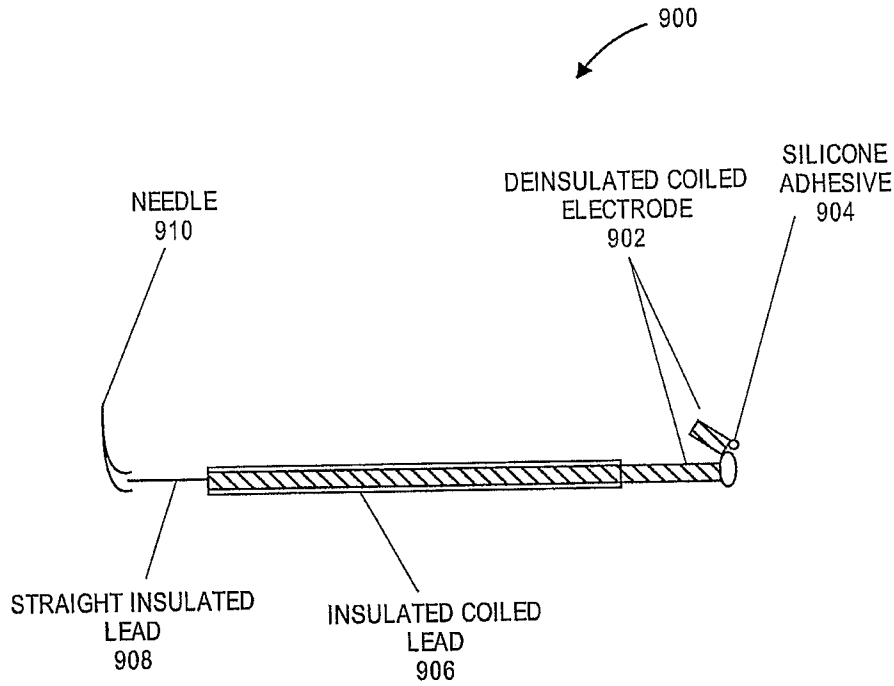

900
NEEDLE
910
DEINSULATED COILED
ELECTRODE
902
SILICONE
ADHESIVE
904
STRAIGHT INSULATED
LEAD
908
INSULATED COILED
LEAD
906

FIG. 2

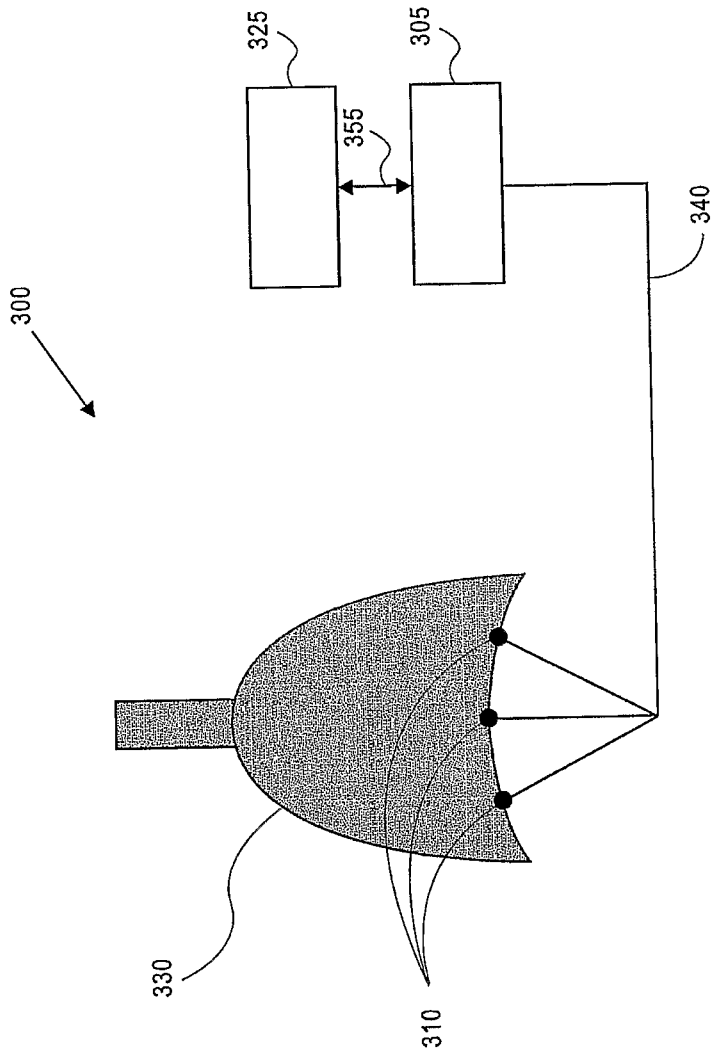


FIG. 3

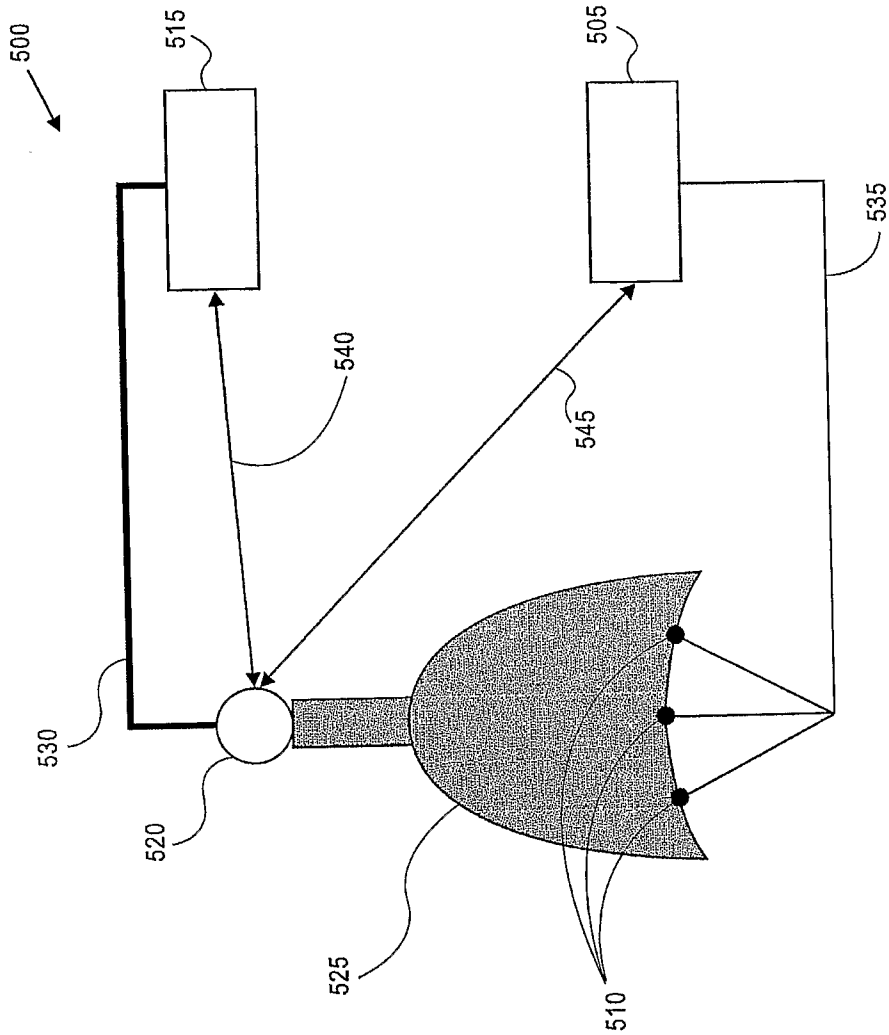


FIG. 4

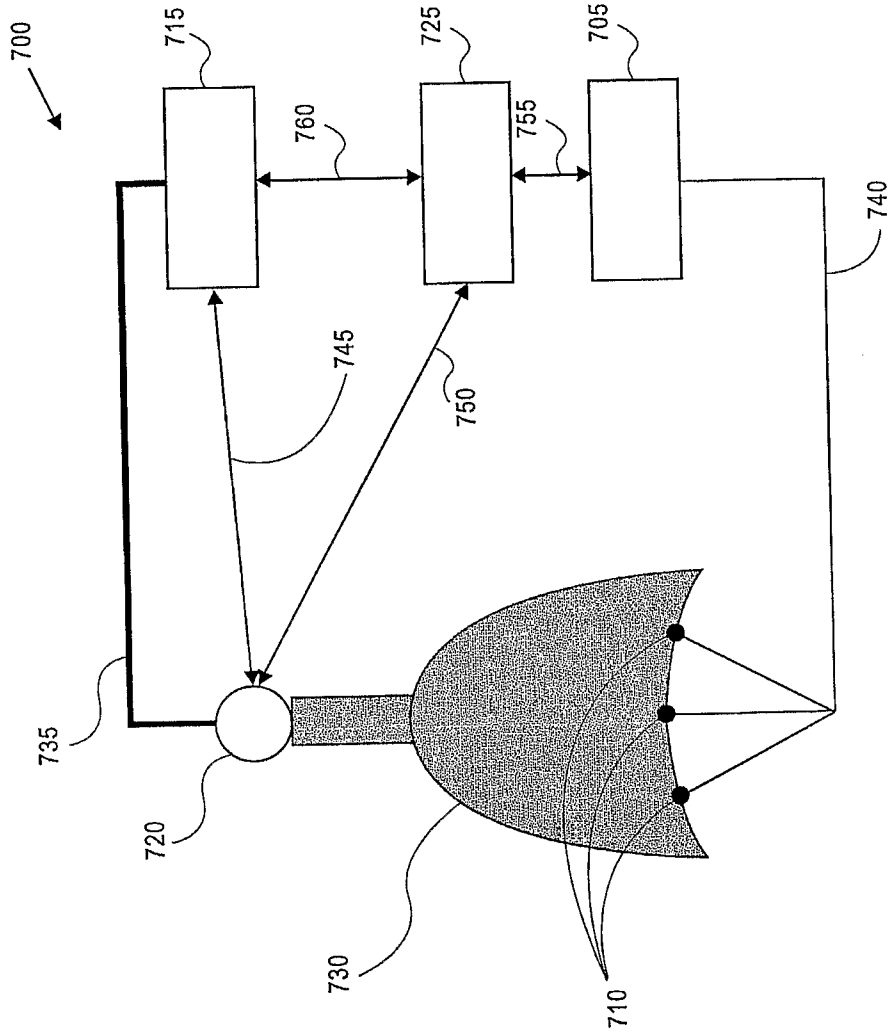


FIG. 5

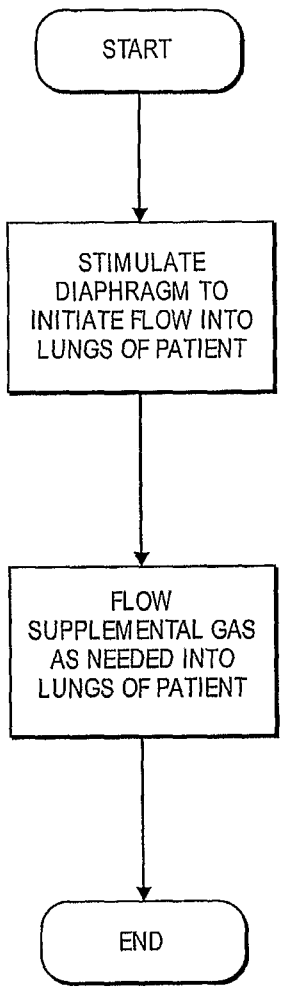


FIG. 6A

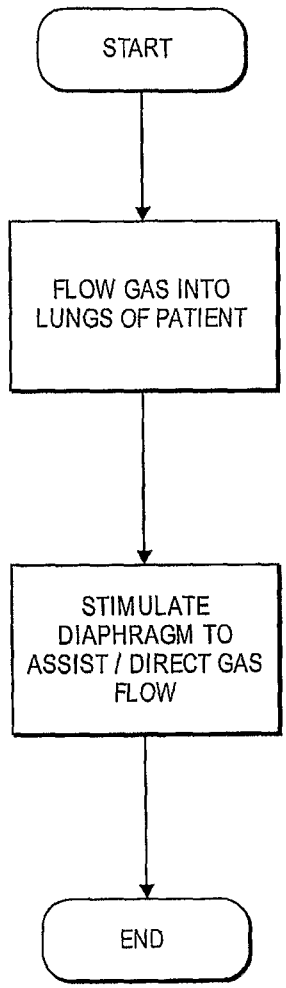


FIG. 6B

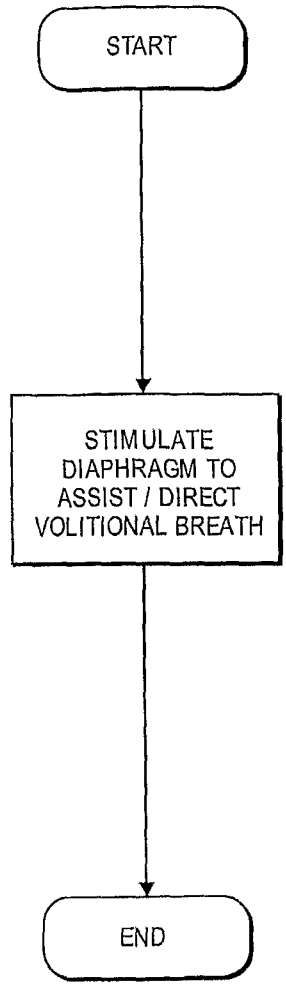


FIG. 6C

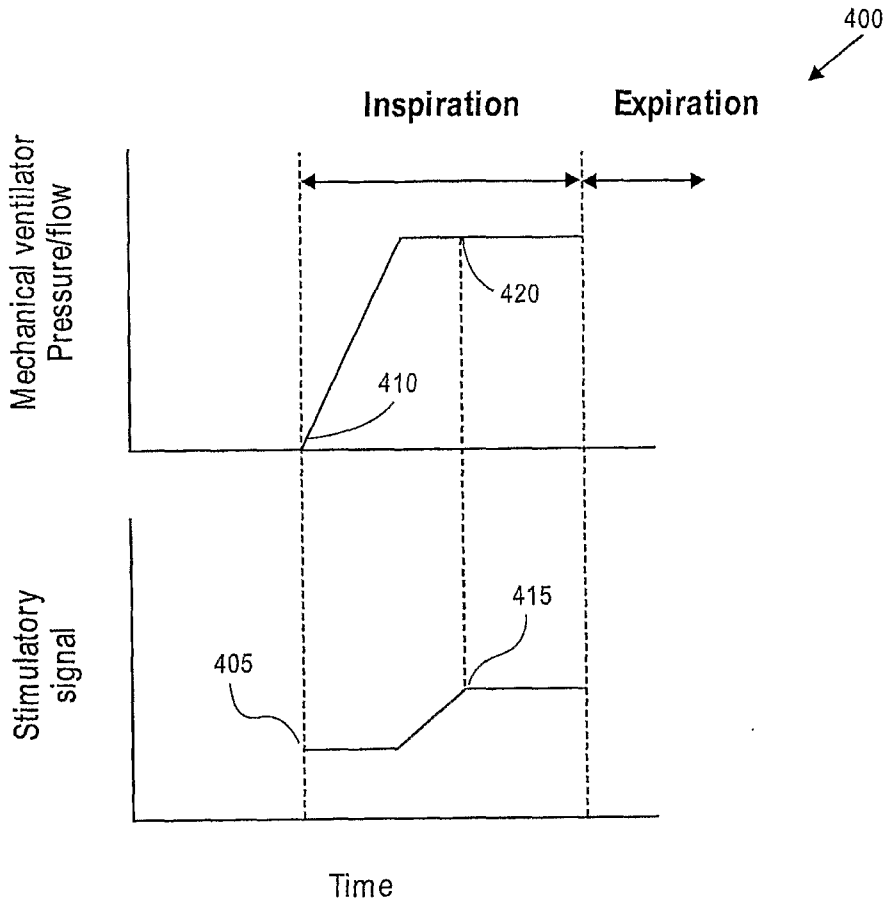

400
Inspiration
Expiration
Mechanical ventilator Pressure/flow
420
410
Stimulatory signal
415
405
Time

FIG. 7

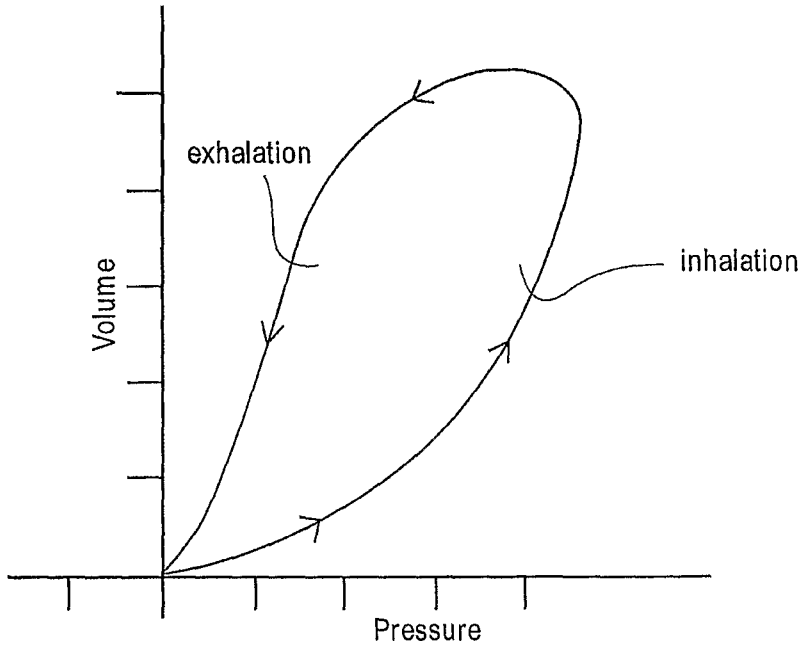

exhalation
inhalation
Volume
Pressure

FIG. 8A

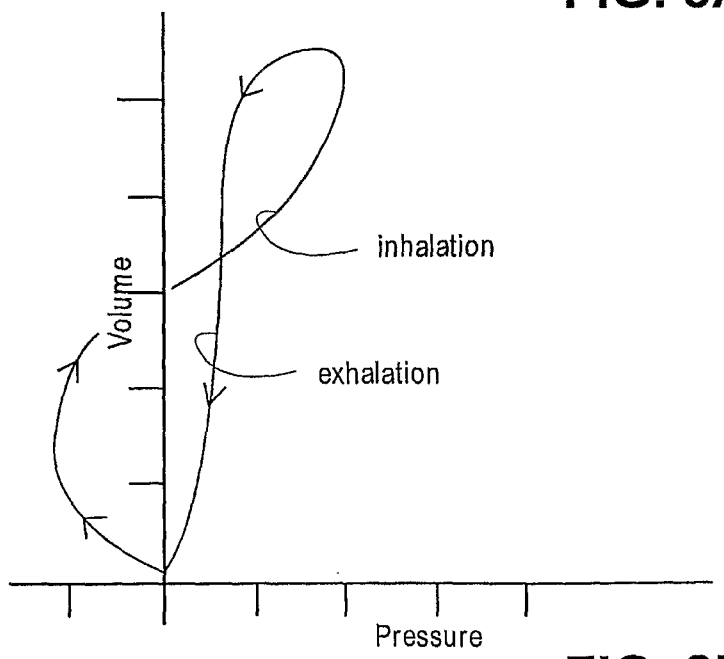

inhalation
exhalation
Volume
Pressure

FIG. 8B

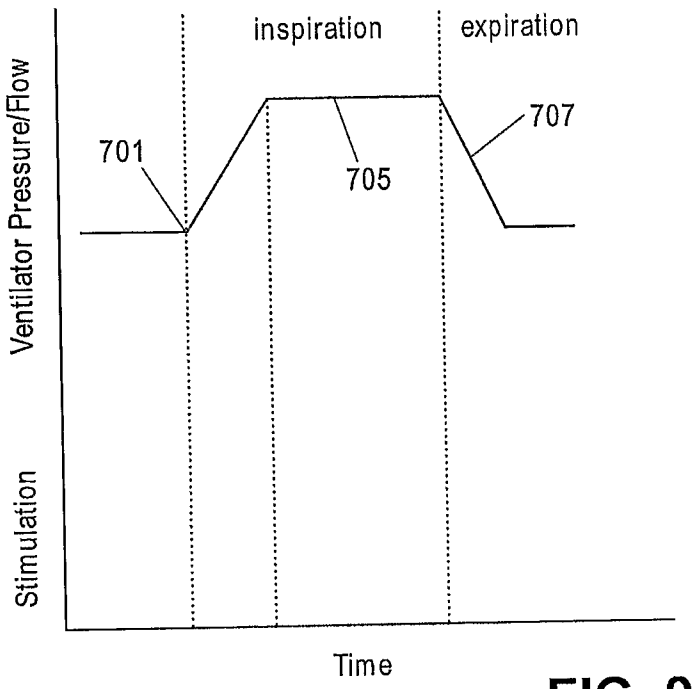

inspiration
expiration
Ventilator Pressure/Flow
701
705
707
Stimulation
Time

FIG. 9A

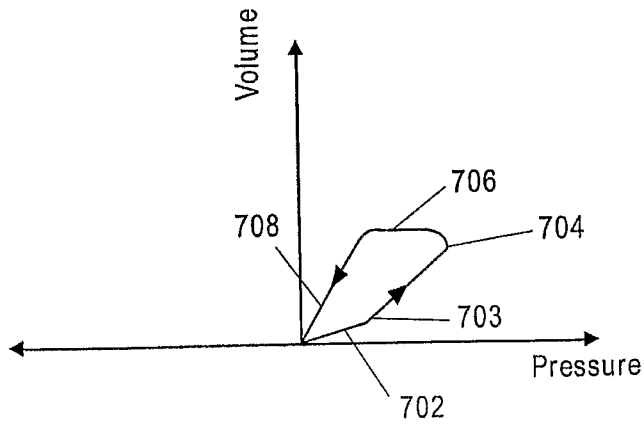

Volume
706
708
704
703
Pressure
702

FIG. 9B

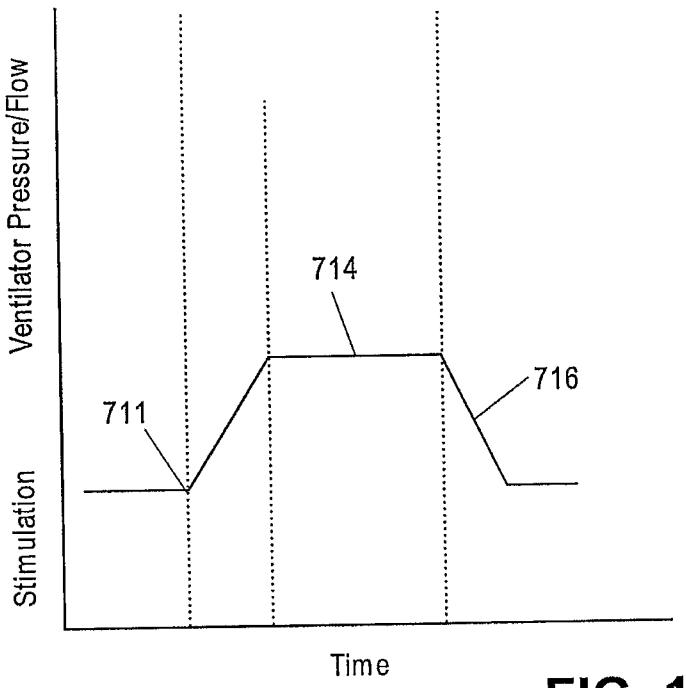


FIG. 10A

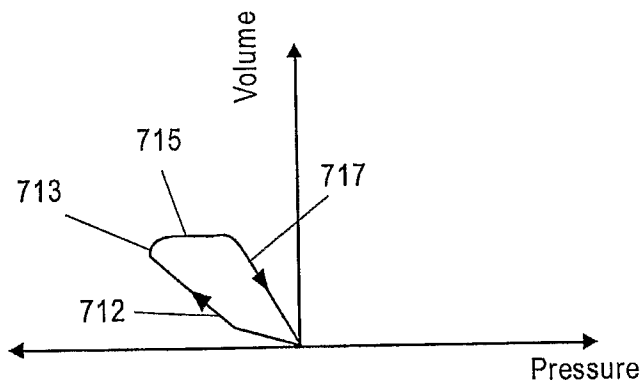


FIG. 10B

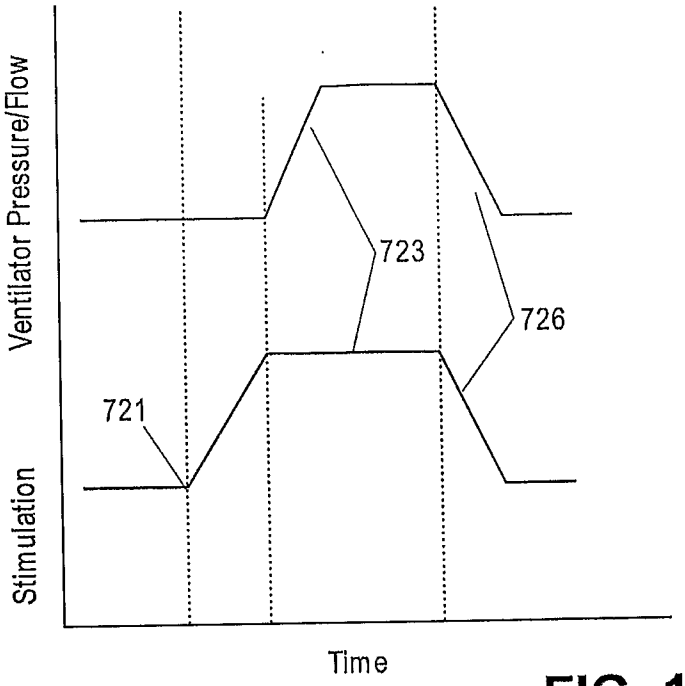


FIG. 11A

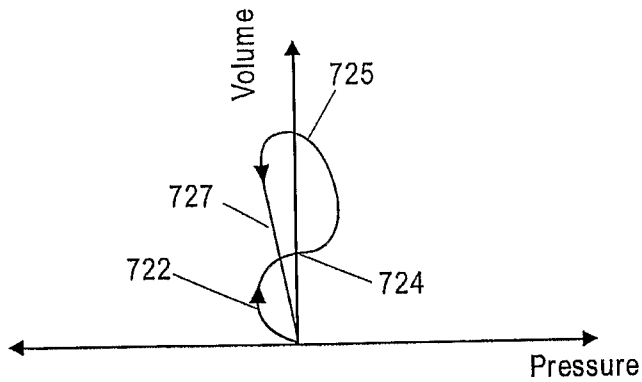


FIG. 11B

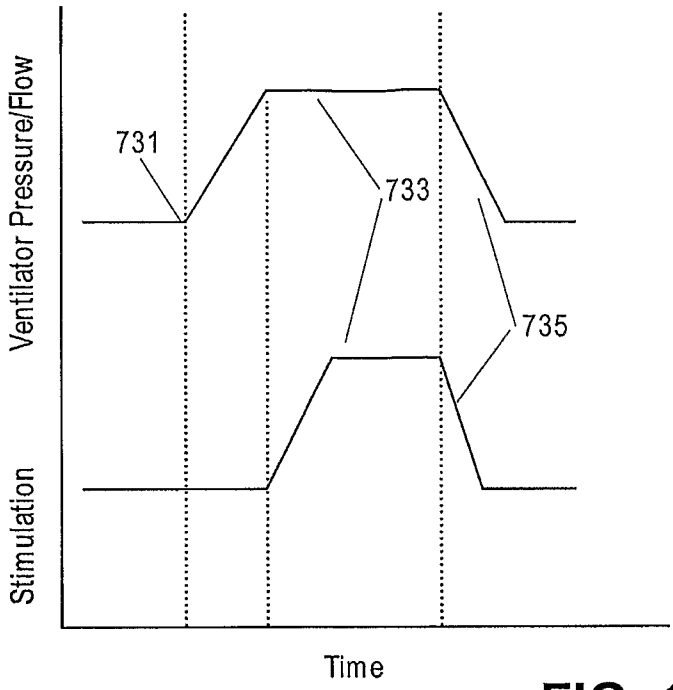


FIG. 12A

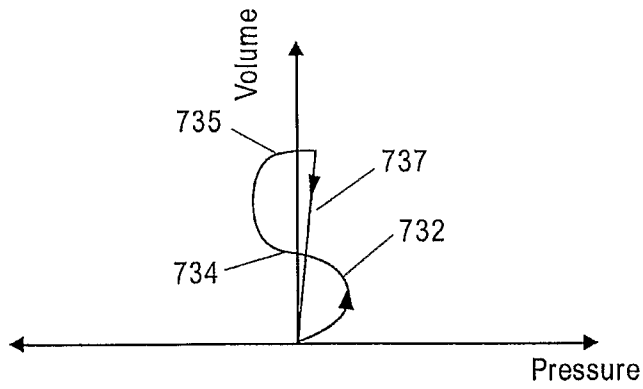


FIG. 12B

FIG. 13C

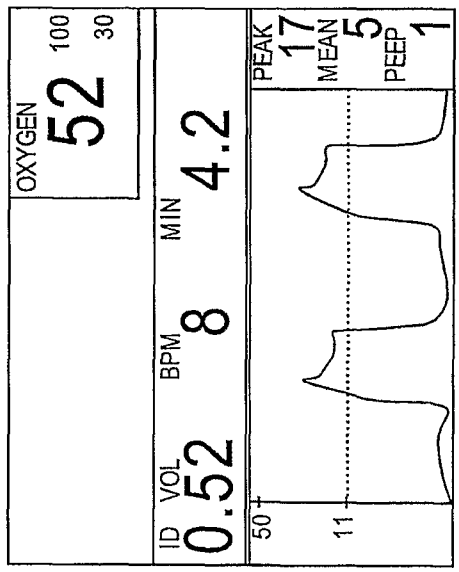


FIG. 13D

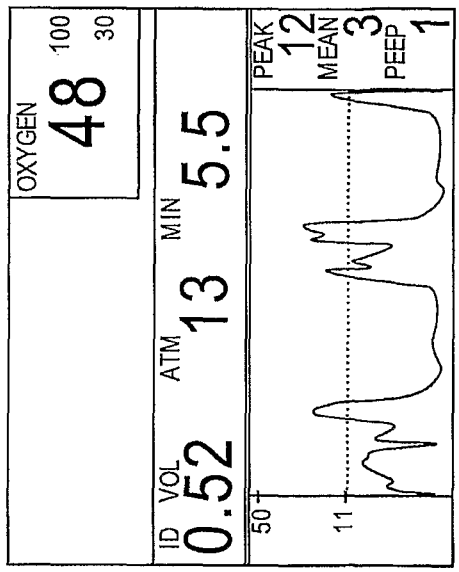


FIG. 13A

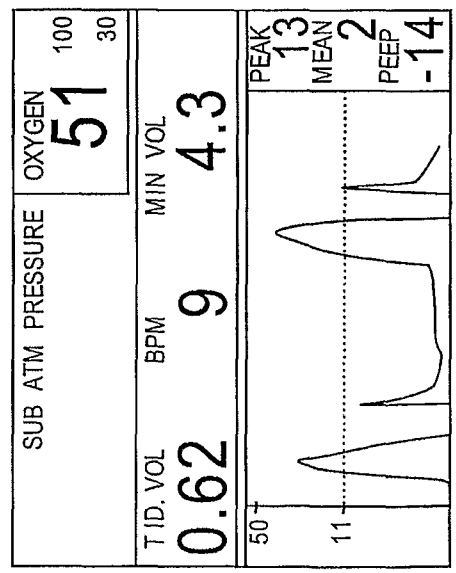
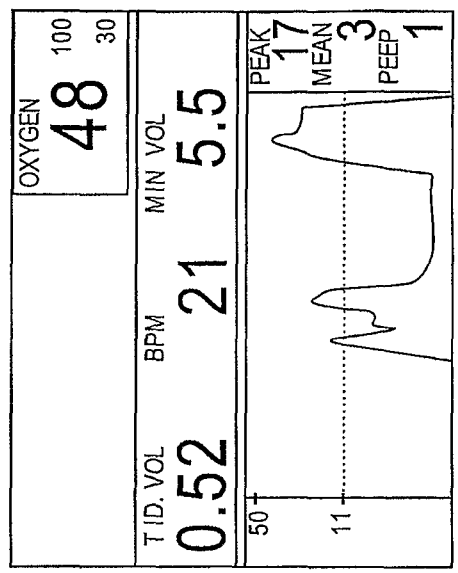


FIG. 13B



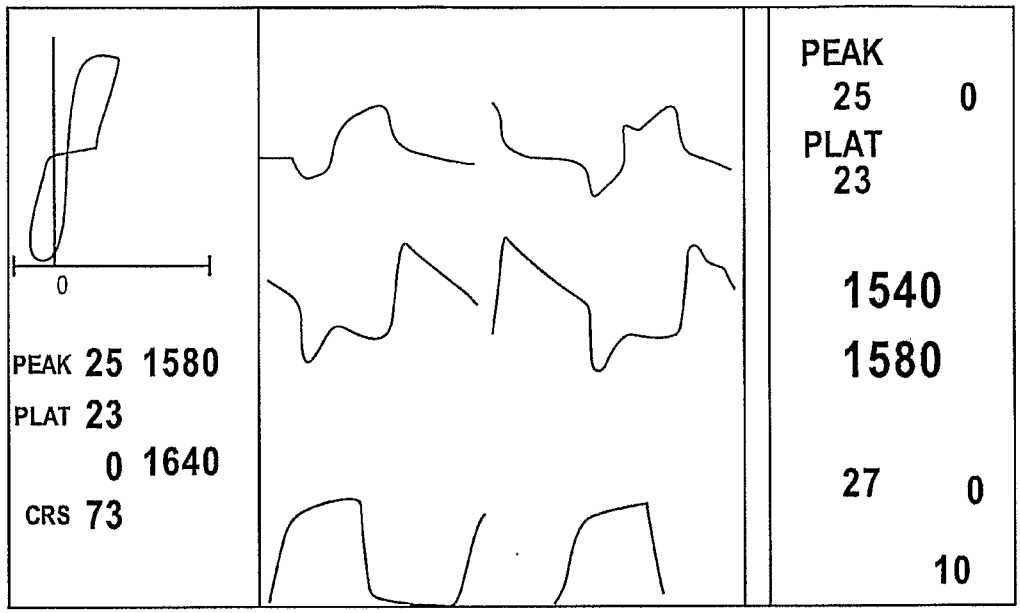

0
PEAK 25 1580
PLAT 23
0 1640
CRS 73
PEAK
25 0
PLAT
23
1540
1580
27 0
10

FIG. 14