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(54) Title: METHOD OF IMPROVING SLEEP DISORDERED BREATHING

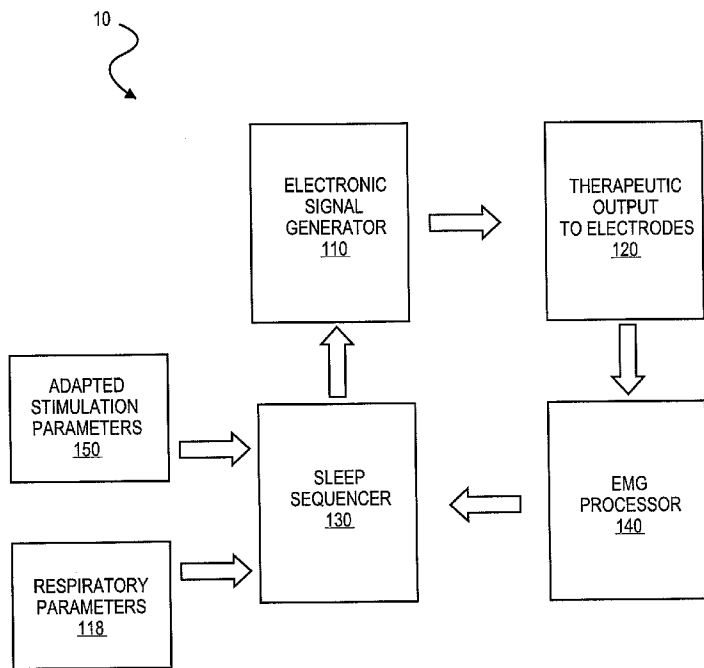


FIG. 2A

(57) Abstract: A diaphragm pacing stimulatory method and a system to implement the method are provided to improve respiratory function and the quality of sleep in patients whose sleep is compromised by poor respiration. The diaphragm pacing method includes adaptations that make it particularly compatible with the onset of sleep and sustaining sleep. Embodiments of the method are operated independently of breathing effort the patient may make during sleep. Patients for whom the invention is appropriate include those with a neuromuscular disease, such as amyotrophic lateral sclerosis (ALS). System elements include an external electrical stimulator coupled to one or more implanted electrodes that stimulate diaphragm contraction. The system and method provide for a pacing of the diaphragm, improved breathing, and improved sleep. Features of improved sleep include longer sleep time, an increased amount of REM sleep, and fewer episodes of wakefulness and restlessness.

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METHOD OF IMPROVING SLEEP DISORDERED BREATHING**CROSS REFERENCE TO RELATED APPLICATIONS**

[0001] This patent application claims priority to this U.S. Provisional Patent Application No. 60/983,915 of Ignagni and Onders, titled "Method of improving sleep disordered breathing", as filed on October 30, 2007.

INCORPORATION BY REFERENCE

[0002] All publications and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication or patent application were specifically, individually, and explicitly incorporated by reference in their entirety.

FIELD OF THE INVENTION

[0003] The invention relates to apparatus and methods for improving the quality of sleep in patients who have or are at risk of having sleep-disordered breathing. In particular, the apparatus and methods described herein relate to treatment of patients with disorders impacting upper motor neurons, including those with amyotrophic lateral sclerosis (ALS) and central sleep apnea.

BACKGROUND OF THE INVENTION

[0004] Patients with neuromuscular diseases such as amyotrophic lateral sclerosis often suffer from central nervous system-mediated sleep disorders that can cause orthopnea, nocturnal hypoventilation, and a reduction in REM sleep. Noninvasive positive pressure ventilation (NIPPV) therapy in the form of with bi-level positive airway pressure (BiPAP) or continuous positive airway pressure CPAP) is commonly provided to these patients, with some success, in an effort to restore sleep toward normal. Further, NIPPV therapy has been shown to increase survival times of ALS patients. However, a significant percentage of patients do not tolerate the positive pressure intervention well, at least in part because of bulbar symptoms, such as difficulty with management of swallowing, saliva, aspiration, and communication, or other coping issues. Other therapeutic approaches to improving the quality of sleep in patients with neuromuscular diseases and associated central nervous system mediated disorders of sleep are desirable.

SUMMARY OF THE INVENTION

[0005] The invention provided herein includes methods of improving sleep in patients with sleep disordered breathing and a system by which to implement such methods. A system for improving sleep in a patient with centrally-mediated sleep disordered breathing includes an electronic signal generator, one or more electrodes operably connected to the signal generator, the one or more electrodes configured to stimulate a diaphragm, an electromyographic (EMG) processor arranged to capture EMG activity data of the diaphragm while being paced by the one or more electrodes, and a

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sleep sequencer configured to integrate any combination of stimulation parameter input, respiratory parameter input, and EMG data, and to convey processed data from these inputs to the electronic signal generator. Embodiments of the electronic signal generator typically include a power supply, an impedance detector, a microcontroller, a waveform generator, and one or more signal drivers. In some embodiments, the EMG processor is configured to convey data to a display; in embodiments the EMG processor is configured to convey data to the sleep sequencer; in some embodiments, the EMG processor is configured to convey data both to a display and the sleep sequencer.

[0006] In some embodiments, the sleep sequencer is further configured to ramp up stimulus intensity to a threshold level. The sleep sequencer may be variously configured such that, for example, the stimulus intensity ramp up provides an increase in pulse duration followed by an increase in pulse amplitude, the stimulus intensity ramp up provides an increase in pulse amplitude followed by an increase in pulse duration, or the intensity ramp up may provide an interleaved increase in pulse amplitude and pulse duration. The sleep sequences may also be configured to provide a stimulus ramp up with various envelope forms; for example, the stimulus ramp may have a linear envelope, an exponential envelope, or it may have an arbitrarily-shaped envelope.

[0007] A method of improving sleep in a patient by using a system as summarized above, with one or more electrodes implanted in the diaphragm for stimulation of the diaphragm, may include adapting stimulation parameters to support respiration during sleep, and stimulating the diaphragm in a therapeutic regimen with the one or more electrodes to support respiration after the onset of sleep, the regimen including the adapted stimulation parameters. The stimulation typically operates independently of any voluntary respiratory effort of the patient or detection of such effort in terms of feedback from the diaphragm.

[0008] The method is therapeutically appropriate for various types of patients, thus prior to the adapting and stimulating steps, the method may include diagnosing a patient as having a neuromuscular disease, particularly those with a disorder impacting upper motor neurons, such as, for example, amyotrophic lateral sclerosis (ALS) and central sleep apnea. More generally, the method may include (prior to the adapting and stimulating steps) identifying the patient as being at risk for sleep disordered breathing. Such patients may be, for example, an ICU patient or a post-surgical patient. More particularly, a post-surgical patient at risk may be one who has undergone a bariatric procedure, as bariatric patients are already commonly at risk for sleep disordered breathing. Another general class of patients at risk for sleep disordered breathing includes any patient having an upper motor neuron dysfunction that results in temporary or permanent diaphragm paralysis.

[0009] The method as summarized above, prior to the adapting and stimulating steps, includes a procedure whereby one or more electrodes are implanted in the diaphragm of the patient. These

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electrodes are used during the adapting phase of the method, as summarized below, and in a therapeutic regimen that follows the adapting phase.

[00010] Continuing more specifically with the aspect of the method that involves patient selection, the method may include diagnosing the patient as having sleep-disordered breathing by any one or more criteria including morning headaches, daytime sleepiness, PSG recordings consistent with disordered sleep, diaphragm EMG recordings during sleep consistent with disordered sleep, or pulmonary function testing data consistent with disordered sleep. Further, in the event that sleep-disordered breathing is found, the method includes diagnosing the patient's sleep sleep-disordered breathing as being centrally-mediated.

[00011] With regard to the parameter-adapting aspect of the method, wherein particular values for stimulation parameters to support respiration during sleep are determined, the method may include determining any one or more of an appropriate time interval after the onset of sleep to lapse prior to initiating stimulation, a threshold level of stimulation sufficiently low so as to allow onset of sleep, a threshold level of stimulation sufficient to stimulate diaphragm contraction, or a threshold level sufficient to support breathing during sleep. By this aspect of the method, the therapeutic regimen can be tailored to the physiological status of the patient.

[00012] Embodiments of the method may further include monitoring the EMG of the patient during the therapeutic regimen. And in some embodiments of the method, stimulating the diaphragm to support respiration includes initiating a breath and supporting a breath to completion.

[00013] After implementing the therapeutic regimen, the method may further include evaluating the patient again for presence of sleep disordered breathing by any one or more same diagnostic criteria as above (*i.e.*, morning headaches, daytime sleepiness, PSG recordings consistent with disordered sleep, diaphragm EMG recordings during sleep consistent with disordered sleep, or pulmonary function test data consistent with disordered sleep) in order to know whether the therapy has been effective or if a revision of the patient-specific parameters is indicated. Accordingly, in the event of a finding of continued presence of sleep-disordered breathing, the method may further include revising the adapted stimulation parameters, and implementing a revised therapeutic regimen for the patient based on the revised parameters, the regimen comprising stimulating the diaphragm with the one or more electrodes to support respiration.

[00014] With further regard to the stimulating step of the method, stimulating the diaphragm in a therapeutic regimen after the onset of sleep typically includes waiting for a period of time after the onset of sleep before initiating stimulation. Determining the appropriate wait time after onset of sleep to initiate diaphragm stimulation may include determining the onset of sleep by monitoring the level of one or more physiological parameters and determining when they fall below a threshold value, the parameters including any of the diaphragm EMG, an EEG, or body movement. Still further with

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regard to the stimulating step, stimulating the diaphragm in a therapeutic regimen includes gradually ramping the stimulation over time to reach a steady state level of stimulation, as will be summarized in further detail below.

[00015] In another aspect of the invention, a method of improving sleep in a patient with sleep-disordered breathing or at risk thereof includes electrically stimulating the patient's diaphragm with a sleep-specific stimulation protocol: That stimulation protocol includes initiating a sleep onset process, ramping the stimulation to a first level that does not exceed a level at which sleep onset is interrupted, (the patient) initiating sleep, synchronizing a natural sleep respiratory rate with a rate supported by the stimulation while ramping stimulation to a second level which is sufficient to provide detectable diaphragm contraction, and ramping the stimulation to a third level which is sufficient to support breathing during sleep.

[00016] Ramping the electrical stimulation of the diaphragm, as it occurs in these various phases of the therapeutic method, to varying levels at various steps, may include increasing pulse duration and then increasing pulse amplitude, increasing pulse amplitude and then increasing pulse duration, or increasing pulse amplitude and pulse duration in an interleaved manner. With regard to the general form of the ramping, ramping may occur with a linear envelope, with an exponential envelope, or with an envelope of an arbitrary or irregular shape.

[00017] Prior to the electrically-stimulating step, the method may include determining any one or more of an appropriate time interval after the onset of sleep to lapse prior to initiating stimulation, a threshold level of stimulation sufficiently low so as to allow onset of sleep, a threshold level of stimulation sufficient to stimulate diaphragm contraction, or a threshold level sufficient to support breathing during sleep.

BRIEF DESCRIPTION OF THE FIGURES

[00018] **Figure 1A** provides a simplified block diagram of a method for implementing the method.

[00019] **Figure 1B** provides an overview and further detail of the method of improving sleep-disordered breathing.

[00020] **Figure 2A** provides a simplified block diagram of a system for implementing the method.

[00021] **Figure 2B** provides an overview and further detail of a system for implementing the method.

[00022] **Figure 3A and 3B** provide two EMG charts of the breathing of a conscious (awake) ALS patient who had been implanted with DPS electrodes 18 months prior to these EMG readings. The upper chart shows normal awake breathing; the lower chart shows maximal breathing.

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[00023] **Figures 4A and 4B** provide two EMG charts showing sleep breathing of an ALS patient with sleep disordered breathing. **Figure 4A** shows a Cheyne-Stokes type breathing pattern. **Figure 4B** shows an EMG chart of the ALS patient breathing with and without diaphragm pacing ((DPS) support.

[00024] **Figures 5A and 5B** show EMG charts of an ALS patient showing an improvement in burst activity over the course of 11 weeks of DPS therapy. **Figure 5A** shows an EMG chart recorded at the outset of the therapy. **Figure 5B** shows an EMG chart recorded after 11 weeks of DPS therapy.

DETAILED DESCRIPTION OF THE INVENTION

[00025] Described herein are systems and methods of diaphragm pacing stimulation for the treatment of disordered sleep, including the treatment of disordered sleep (*e.g.*, apnea) in patients with neuromuscular diseases such as amyotrophic lateral sclerosis (ALS). Embodiments of the invention may also be usefully applied to patients with neuromuscular diseases other than ALS who experience central nervous system-mediated sleep disordered breathing. Embodiments of the invention may also be applied as therapy for patients with sleep disordered breathing due to other forms of sleep pathology, including those not-mediated by the central nervous system, such as obstructive or mixed (complex) apnea. Further, embodiments of the invention may be applied to patients who are considered to be temporarily at risk of respiratory compromise or failure, as for example, would be associated with surgery, anesthesia, or during the period of post-operative recovery with diaphragm activity monitored by clinical personnel. Some embodiments of the invention may be applied to the support of sleep in patients in a chronic manner, such as patients with a neuromuscular disease, in which embodiments electrodes adapted for long-term or permanent residence may be used. Other embodiments of the invention may be applied to patients that are in temporary need of respiratory surveillance or support, such as surgical patients, in which embodiments electrodes adapted for temporary placement may be used.

[00026] Improving the sleep by implementation of the inventive method can be appreciated by the patient in subjective terms, as well as measurable in objective terms. For example, improving sleep may include increasing total sleep time per night and/or increasing total REM sleep time per night. In some of the embodiments whereby REM sleep time is increased, the method further includes alleviating severity of or preventing development of intensive care unit psychosis. In other embodiments, improving sleep includes decreasing the level of sleep disturbance, such disturbances including, for example, periods of restlessness or wakefulness. In still other embodiments, improving sleep includes supporting a regular breathing rate during sleep. In some embodiments in which a regular breathing rate is instilled in the patient, the regular breathing rate prevents the development of central hypoventilation syndrome (CHS), or alleviates the severity thereof. In addition to these various relatively immediate undesirable consequences of disturbed sleep, sleep disturbance can contribute to

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many other adverse outcomes, such as cardiovascular disease and hypertension, can accrue over the longer term.

[00027] Aspects of the system and method as applied to diaphragm conditioning and acute support for respiratory-compromised patients have been described in U.S. Patent Application No. 10/897,685, filed on July 23, 2004, which was published as U.S. Pub. No. 2005/0021102 on January 27, 2005, and in U.S. Patent Application Serial No. 11/716,459, filed on March 9, 2007.

[00028] An overview of the open loop method is provided in **Figures 1A and 1B**. **Figure 1A** is a simplified flow diagram which outlines the method in terms of five phases (**201 – 205**), which are outlined in greater detail in **Figure 1B**, including 12 steps. A preparatory aspect of the method **201** includes implanting diaphragm pacing electrodes in a patient. This is **Step 1**, as shown in **Figure 1B**, and is detailed in further description below. In a preliminary aspect of the method **202**, patient-specific stimulatory parameter values are determined in a series of **Steps 5 – 7**, as shown in **Figure 1B**. A sleep-based therapeutic regimen that improves sleep-disordered breathing starts with an initial part **203** of a therapeutic regimen that occurs after a patient has made a decision to go to sleep, or after the patient has been observed to be in the early stages of falling asleep. This phase occurs in **Steps 5 – 7**, as shown in **Figure 1B**. During this phase **203**, stimulation is ramped up to a stimulatory threshold that was determined during the adapting phase **202** of the method. In a second part of the therapeutic regimen **204**, which occurs after the onset of sleep, stimulation is ramped up to a movement threshold, as determined during the adapting phase **202** of the method. This phase **204** occurs over the course of **Steps 8 – 11**, as shown in **Figure 1B**. In a third part of the therapeutic regimen **205**, sleep is ongoing and steady and stimulation is being delivered at a steady state, as represented by **Step 12** as shown in **Figure 1B**.

[00029] **Figure 1B** provides a more detailed view of the method, with individual steps included. Implantation of diaphragm pacing electrodes (**Step 1**) may be by way any of various conventional approaches, such as through laparoscopic approaches, a thoracic surgical approach, or by way of natural orifice transluminal endoscopic surgery (NOTES). **Step 1** is a preparatory procedure, which may take place at a time identified by a physician, after consulting with the patient, at any reasonable time prior to initiating a therapeutic regimen. **Steps 2 – 4** relate to aspects of the method that relate to adapting stimulation parameters to support respiration during sleep, such adapted parameters varying from patient-to-patient, and further, possibly varying with the patient over time. **Steps 5 – 12** relate to aspects of the implemented regimen, adapted to the patient particulars as determined in **Steps 2 – 4**.

[00030] **Steps 2 – 4** of the method (**Figure 1B**) relate to aspects of the initial clinical characterization which are performed in a clinic to characterize particular physiological aspects of the specific patient prior to formal implementation of a therapeutic regimen. Sensory threshold (S-thresh) identification (**Step 2**) is determined by identifying when patient first senses that stimulus is being

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applied. This characterization may be done through psychophysical testing or simply just turning intensity (pulse width / amplitude) until the patient reports that it is being felt. Movement threshold (M-thresh) is identified (**Step 3**) as the intensity when the diaphragm movement is visualized or palpated. Functional threshold identification (**Step 4**) relates to identifying the stimulation intensity threshold (F-thresh) that elicits inspiration at a level that is sufficient to functionally ventilate the patient during sleep. These steps may all be considered aspects of the method, as provided by the invention, where patient-specific data are collected and then used as input that determines aspects of a therapeutic regimen that are related both to the ramp up profile of stimulation and the steady state level of stimulation.

[00031] **Steps 5 – 7** of the method (**Figure 1B**) relate to a sequence of events that follow after the patient turns on the therapeutic device prior to going to sleep until a time when sleep actually begins. As such, these various steps relate to aspects of an initial phase of stimulating the diaphragm in a therapeutic regimen. **Step 5** refers to the initiation of events that occur immediately after a decision to go to sleep has been made, or as a healthcare provider observes that patient is preparing to go to sleep, or sleep is inevitable, whether intentionally or not. In **Step 6**, the stimulus intensity is cyclically ramped up over the duration of a predetermined amount of time to accommodate the sensory perception up to a threshold (determined in **Step 2**) that is likely to prevent the onset of sleep. The sleep onset time may be predetermined from polysomnographic (PSG) studies or set by the patient upon initiation (*i.e.* an adjustable sleep time). Alternatively, sleep may be detected through a sleep-detection algorithm with the cycle time completing with detection of sleep. Still further, sleep onset may be noted by observation of an attending health care professional.

[00032] **Steps 8 – 11 (Figure 1B)** of the method relate to steps that occur after sleep has begun. Once sleep is achieved a sequence of events (**Step 8**) is initiated such that the patient synchronizes his or her natural breathing to the rate being paced by the electronic signal generator. The stimulus intensity is cyclically ramped up from the sensory threshold to the movement threshold (**Step 9**). This signal ramping allows the patient's innate breathing to synchronize with the stimulated breathing, as such, synchronization is an aspect of the method performed by the patient. Synchronization occurs naturally and has been consistently observed to occur in patients with ALS who exhibit volitional breathing who have been implanted with a DPS. The time of synchronization can be predicted or estimated from studies that monitor the diaphragm EMG and determine when innate activity is consistently synchronized with DPS. Alternatively, the stimulation can be presented following the detection of innate breathing activity. **Step 10** refers to a decision point which requires an affirmative response before moving on to **Step 11**. In the absence of synchronization, **Step 9** continues.

[00033] **Step 11 (Figure 1B)** relates to activity that occurs after synchronization has been achieved, when the stimulus intensity can be ramped up to a functional level to ventilate the patient. Alternatively, if the diaphragm EMG is detected for synchronization, the absence of activity can cause

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the stimulus intensity to elicit a functional contraction. Absence of activity can be predetermined as a time equivalent to the definition of an apneic event (*i.e.* 10 seconds) or a time based on the periodicity of prior breathing.

[00034] As described above, parameters that are individually adapted to the patient during an early phase of the method **202** (**Figure 1A**) generally allow a comfortable merging of electrically-paced breathing into a natural course of sleep onset and continuing through the sleep cycle of a patient who is not on full time pacing. One feature of the method that allows this comfortable merger is the delay in onset of the pacing until an appropriate time after the patient has begun to sleep. Thus, in some embodiments of the method, the stimulation protocol includes an onset delay period before the onset of stimulation (*e.g.*, approximately 5 minutes, 10 minutes, 20 minutes, 30 minutes, *etc.*).

[00035] Another feature of the method that supports merging of the patient's normal breathing with paced breathing during sleep includes ramping of stimulation of the patient's diaphragm to support breathing, as it occurs at various phases of the method. The role of ramping is at least two-fold. In one aspect, ramping serves the purpose of not interrupting or disturbing the onset of sleep. In another aspect, stimulation level ramping serves to allow a synchronization of the patient's own breathing rate to the rate being driven by pacing stimulation. Ramping the electrical stimulation of the diaphragm may occur in various forms, such as increasing pulse duration and then increasing pulse amplitude, increasing pulse amplitude and then increasing pulse duration, or increasing pulse amplitude and pulse duration in an interleaved manner. With regard to the general form of the ramping, ramping may occur with a linear envelope, with an exponential envelope, or with an envelope of an arbitrary or irregular shape.

[00036] Embodiments of the method for improving sleep disordered breathing may be implemented by a system **10** which will be described first in general terms, as shown in **Figure 2A**, and then depicted (**Figure 2B**) and described in more detail below. Embodiments of the system **10** typically include various primary subsystems. One subsystem is represented by an apparatus or assembly of components that act as an electronic signal stimulator or diaphragm pacing system (DPS) **110** (including components surrounded by a dotted line) that provides electrode-delivered stimulation to the diaphragm of a patient to regulate the patient's breathing. An example or typical embodiment of apparatus **110** is provided by the NeuRx DPS™ System (Synapse Biomedical, Inc. of Oberlin, Ohio), which includes electrodes to deliver the stimulation to the target, a stimulation device to generate charge balanced waveforms, a microprocessor to format and coordinate stimulus delivery, and various peripheral components that embody the device. The output **120** of the electric signal generator **110** is directed to electrodes implanted in the diaphragm of the patient, which control the breathing rate.

[00037] A sleep sequencer processor **130** represents another subsystem, which may be a separate device or a component incorporated into the main apparatus of the DPS System that includes the

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electronic signal generator, provides the appropriate cyclic timing to ramp between the thresholds identified in the method as shown in **Figure 1B**. The sleep sequencer **130** may use observation- or experience-based settings or a user adjustable input to determine the timing of the onset of sleep. Sequencing from the sensory threshold to the movement threshold may be accomplished by providing the appropriate cyclic timing to ramp stimulation based on a experience-based setting, or it may use the detection of electromyographic diaphragm activity in the contralateral diaphragm upon delivery of stimulation and an absence of electromyographic activity without stimulation to sense if the innate breathing has synchronized with the stimulation. Finally, the sleep sequencer may ramp stimulation up to the functional threshold to elicit functional contractions to ventilate the patient. The functional contraction may be set to the same stimulation level as the movement threshold. Alternatively, once the sensory threshold is achieved, the sleep sequencer may be set to deliver functional stimulation in the absence of electromyographic activity when inspiration should be occurring, *i.e.* during a central apneic event.

[00038] Representing still another component subsystem, the system may also include electromyographic activity sensing component **140** which receives diaphragm EMG activity data from the electrodes implanted in the patient diaphragm. This electromyographic activity may be processed and displayed for manual use in manual operation of the system in a monitored clinical setting or EMG data may be fed into the DPS System or sleep sequencer to automate the apparatus. In a monitored clinical setting the absence of diaphragm activity, when inspiration should be occurring (*e.g.* within 10 second of the last recorded activity), could be used as a diagnostic tool and be coupled with the further intervention of application of the diaphragm stimulation.

[00039] Features of the system described above in general terms will now be described in greater detail with reference to **Figure 2B**, and in a manner that tracks the flow of electrical signals. In one embodiment, the electrical signal generator **110** shown may 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** may include one or more channels that can independently control the amplitude, frequency, timing and pulse width of the corresponding electrodes connected thereto. 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. Example of a suitable electrical signal generator include a NeuRx RA/4 stimulator of the NeuRx DPS™ System (Synapse Biomedical, Inc. of Oberlin, Ohio), which are four-channel devices with independent parameter programmability, that can, accordingly 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

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partially implanted radio-frequency signal generator system is the "XTREL" system available from Medtronic, Inc.

[00040] The electrical signal generator 110 depicted in **Figure 2A and 2B** is comprised of several blocks to produce a coordinated stimulus output. The core of the electrical signal generator 110 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 specifically for the respiratory support needs and desired electrode features for the particular patient. A waveform generator 112 assembles the control signals from the microcontroller in the necessary waveform patterns to be conveyed 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, timing parameters 118 and stimulation parameters 150 and EMG data 142, all by way of a sleep sequencer 130. 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.

[00041] With further reference and in greater detail regarding the sleep sequencer 130, electromyographic signals from electrodes 120 implanted in the diaphragm are collected and conveyed to an electromyographic processor 140. The processor 140, in turn, can both display resulting EMG data (available for clinical review by a health care professional) and transmit data to a sleep sequencer 130. The sleep sequencer 130 has already received stimulation parameter values input 150 that were collected during an early aspect of the method, when parameter adaptation studies were run on the patient (**Steps 2, 3, and 4 of Figure 1B**). The sleep sequencer further receives input 188 regarding respiratory timing parameters, which may include a manually adjustable timing input 132. The sleep sequencer thus integrates information regarding the parameter adaptations, stimulus level ramping, respiratory timing, and EMG feedback from the diaphragm while it is being paced by the electrical signal generator assembly. (It may be appreciated that these feedback data do not include EMG data from the diaphragm that are associated with independent breathing effort.) Further, it can be appreciated that input regarding the stimulation parameters 150 and the respiratory timing parameters 118 can be adjusted or revised during the therapeutic regime, based on changes in the status of the patient and observation. These data are integrated by the sleep sequence 130 and conveyed to the microcontroller 111.

[00042] In some embodiments, the output of drivers 113 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

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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.

[00043] 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 – 200 μ s
Voltage	0 - 65 V
Pulse Frequency	10-20 Hz

[00044] 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, as the patient is falling off to sleep and during sleep. For example, the electrical stimulation can be delivered to the diaphragm of the patient at specified intervals, for a certain period of time per interval. In typical embodiments of the method, the stimulation is delivered constantly, albeit at rates and intensity that vary between the initial phase of sleep and the stable portion of sleep.

[00045] 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. Examples of appropriate electrodes and their features are described in detail in U.S. Patent Application 11/716459 of Ignagni, entitled " Ventilatory assist system and methods to improve respiratory function", as filed on August 1, 2007, which is incorporated herein in its entirety by this reference.

[00046] The inventive system and method have been developed and tested on patients under appropriate protocols and safety guidelines. **Figures 3 – 5** provide examples of the human subject data that have been collected. Exemplary electromyographic recordings are shown in **Figure 3A and 3B** that were obtained from an ALS patient that had been implanted with pacing electrodes 18 months prior to the time these recordings were made. The two sets of traces show the electromyographic

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recording from right and left hemi-diaphragms. (There is a difference between the right and the left traces that is a result of differences in placement; that difference does not distract from the significance of the data as they relate to reflecting EMG activity.) In **Figure 3A** a depressed, low level, electromyographic recording is shown during a period of normal awake breathing. In **Figure 3B** a significant increase in the magnitude of the electromyographic recording is shown during a period of maximally volitional breathing. This demonstrates the ability of the system to detect electrode myographic activity and to differentiate the amount diaphragm movement based on magnitude of electromyographic recordings. An absence of activity or a minimal of activity may be used to as diagnostic criteria or feedback indicating an insufficient diaphragm contraction.

[00047] An exemplary episodic view of sleep disordered breathing in an ALS patient, exhibiting deficits in upper motor neuron function is shown in **Figures 4A and 4B**. The upper panel (**Figure 4A**) shows a Cheyne-Stokes type breathing pattern with the right and left hemidiaphragms exhibiting apneic events followed by two quick bursts of diaphragm activity followed by another apneic event and two quick bursts of diaphragm activity. The bottom trace of the upper panel (**Figure 4A**) shows the pulse oximetry (SPO₂) fluctuating, as expected, following the apneic events. The upper trace of the lower panel (**Figure 4B**) shows the patient without the support of DPS demonstrating respiratory instability as evidenced by the ongoing oscillation of the pulse oximetry. The patient shows resolution of the respiratory instability with the addition of DPS, in the bottom trace.

[00048] An example of processing electromyographic activity of an ALS patient is shown in **Figures 5A and 5B**. In this case, the sampled electromyographic activity was processed by filtering to remove the undesired EKG signal, rectified, and then an average magnitude of the signal amplitude was calculated. Data were collected at two time points 11 weeks apart (**Figure 5A** at the outset of the study, **Figure 5B** after 11 weeks of therapy). In the example shown, the electromyographic activity is seen to increase over time with conditioning of the diaphragm in a patient experiencing respiratory insufficiency. These EMG data correlated well with fluoroscopy data showing diaphragm movement. Similarly the amplitude of the activity can be used to discriminate a functional contraction from a non-functional contraction.

[00049] In another example, a clinical study was run to evaluate the effect of diaphragm pacing treatment, in accordance with the inventive method, on patients with neuromuscular disease who had disordered sleep patterns and disordered breathing during sleep. The results of the study suggest that benefits may derive from the treatment; accordingly, some general observations and considerations will be described, and some relevant data will be provided below.

[00050] Patients that cannot readily tolerate non-invasive positive pressure ventilation (NIPPV) may be particularly benefited by the methods and systems described herein. Considerations that particularly recommend the use of this inventive therapeutic method for these patients are indications

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that NIPPV may actually accelerate the deconditioning of the diaphragm and the dependence of ALS patient on increasing amounts of NIPPV (Aboussouan, *et al.*, "Effect of noninvasive positive pressure ventilation on survival in amyotrophic lateral sclerosis". *Ann Intern Med* 1997; 127: 450 - 453). The trade off between the benefit of immediate assistance in breathing against the acceleration the disease progression is, of course, very undesirable. Combining diaphragm pacing stimulation (DPS) therapy with NIPPV may slow or eliminate this nocturnal deconditioning of the diaphragm, and further slow the patient's progression toward complete dependence on NIPPV support. Before implementation of diaphragm pacing stimulation, particularly during sleep, various operational parameter settings for diaphragm pacing stimulation that provide a level of respiratory assistance without arousing the patient from sleep may be determined.

[00051] Embodiments of the DPS method, as provided herein, typically involve the implanting of a DPS device and an extended period of DPS therapy. The diaphragm pacing stimulation includes sufficient stimulation to initiate a breath and further stimulation sufficient to support a breath to completion. As described herein, the method may be adapted for the therapeutic application of improving the quality of sleep, and may be further adapted to the physiological and temperamental particulars of each patient (**Steps 2 – 4 of Figure 1**). These adaptations for diaphragm pacing during sleep may include, for example, any one or more of a delay of stimulation onset to allow patient to fall asleep, a gradual ramping of diaphragm stimulation level over time after onset of stimulation, setting a steady state level of stimulation so as to minimize arousal from sleep, and the monitoring of diaphragm EMG during system use.

[00052] A programmable delay in the onset of stimulation, merely by way of example, may be set for an interim of 15 seconds to 30 seconds after initiation of sleep. A ramping period after initiation of electrode stimulation may be, merely by way of example, of about 30 minutes, wherein a minimal stimulation is provided at the outset, and a plateau level of stimulation is reached at 30 minutes, and such plateau level is continued through the sleep period. Further, a sleep-appropriate plateau level of respiration may be set that permits sleep without awakening, such level, as driven by diaphragm pacing may be set, merely by way of example, within a range of about 8 to 20 respirations per minute.

[00053] Additionally, the stimulus frequency may be set such that the delivered stimulation is at a level to produce fused contractions of the diaphragm muscle. The fusing of contractions in a diaphragm, which is composed primarily of slow twitch type IIB muscle fiber, will exhibit unfused contraction at a low frequency. A threshold level of stimulation is required to elicit a desirable and sustainable fused contraction. Accordingly, the frequency may be ramped up over the initiation period to produce a more forceful contraction while remaining below a level that would cause the patient to awake. Increases in delivered stimulus may be performed based on the charge (the product of pulse duration and amplitude) delivered on a pulse-by-pulse basis. By initiating each inspiration with a very gradual ramping, the stimulus may be delivered slowly, and then increased with a steeper ramp to

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create a greater inspiratory pressure and thus greater volume for each breath. Following a determination and setting of stimulation parameters that have been adapted or optimized for sleep, a therapeutic regimen of diaphragm stimulation may be implemented.

[00054] The implanted DPS electrodes may be used to record diaphragm EMG during the polysomnographic recording, or they may be used in a stand alone manner to determine the amount of diaphragm activation during a diagnostic sleep session. In either context, the EMG data may provide a physician with information that allows an evaluation of the disease state and the efficacy of the diaphragm pacing in improving sleep. In some embodiments of the method, the parameters that have been adapted to make the diaphragm pacing stimulation appropriate for sleep may be evaluated by a physician and revised in accordance with accumulated EMG data, or any other relevant clinical data. Following such revision of parameters adapted for stimulation of the diaphragm during sleep, a revised therapeutic regimen may be implemented.

[00055] It can be noted that although it may be technically feasible to include a feedback loop in the method, whereby patient initiated breathing effort during sleep would be incorporated into the control of breathing by DPS. In the view of the inventors, however, this approach appears disadvantageous for several reasons, including the complexity and likely temperamental or unstable nature of such a method that included such feedback, the associated burden of training physicians in the method, and the cost of the system. On the whole, inventors believe that a system that operates under the discretionary control of health professionals exercising clinical judgment with an open loop implementation (instead of the automatic control of a voluntary respiratory effort feedback loop) offers an approach that makes the method safe, robust, and effective. Accordingly, a feedback loop that incorporates patient-initiated breathing effort data as feedback into the system control is not included in the inventive method.

[00056] In the clinical study referred to above, twelve of the 16 ALS patients had bulbar symptoms, such symptoms being consistent with poor tolerance of noninvasive positive pressure ventilation therapy. At the time of implant of the DPS device, the patients had a median forced vital capacity (FVC) of 57% of the predicted value, and a median score of 26 on the ALS Functional Rating Scale – revised (ALSFRS-R). The study patients have a mean survival from diagnosis of 3.0 ± 0.7 years. From reports in the literature (Louwse, *et al.*, "Amyotrophic lateral sclerosis: morality risk during the course of the disease and prognostic factors". Publications of the Universiteit van Amsterdam, Netherlands. 1997), the median survival time from diagnosis was 1.4 years (95% confidence interval, 1.3 – 1.6 years).

[00057] This clinical study also yielded observations that indicate that ALS patients may be more tolerant of DPS than NIPPV, and that they can make use of the DPS stimulation for extended periods to improve their breathing, which may improve the quality of their sleep. A few of patients in the pilot

study voluntarily switched from BiPAP therapy to DPS because of their perception of greater ease in breathing. For example, some patients have fallen asleep while using the DPS system and reported that they then slept better than they had in some time.

[00058] Another measure of outcomes in ALS is provided by the revised Functional Rating Scale (ALSFRS-r). This is a disease-specific scale that measures global function as grouped around several elements such as limb function, bulbar function, and respiratory function. The slope of ALSFRS over time has a greater correlation with survival than does the slope of forced vital capacity. In a large retrospective clinical study the effects of Neurontin, it was found that three groups of patients could be classified by the rate of progression of their ALSFRS-r score. Slowly progressing patients (patients with a rate of decline less than -0.44 ALSFRS units per month) had median survival of more than 3 years, moderately progressing patients (patients with a rate of decline between -1.04 and -0.44) had a median survival of 2.3 years, and rapidly progressing patients (patients with a rate of decline greater than -1.04) had a median survival of 1.3 years. Performing a paired comparison of the rate of decline of patients in the DPS clinical study performed by the inventors yields an average survival improvement of 9 months ($p=0.03$).

[00059] As the diaphragm is the principal (or sole) respiratory muscle active during REM sleep, reduced or lost function of this muscle leads to sleep irregularities with fragmentation by multiple arousals and awakenings. Polysomnographic recordings of sleep with and without rhythmic diaphragm pacing stimulation demonstrate this effect. Overnight EMG recordings of the diaphragm with nocturnal pulse oximetry in ALS patients implanted with the NeuRx DPS™ System demonstrate that low levels of blood oxygen are associated with depressed diaphragm contraction.

[00060] It should also be understood that this therapeutic method may be applied in patients who are being treated more generally for ALS and hypoventilation, and with goals directed toward improving ventilation and the quality of life. Accordingly, for example, a primary efficacy endpoint of improvement in breathlessness may be measured using the Modified BORG Scale. This unidimensional, health related, quality of life instrument provides a recognized, reproducible measure of physical effort, and more specifically in this context, the intensity of the sensation of breathing effort or breathlessness. Measurements can be made, as the patient is able, without support (*i.e.*, without NIPPV or DPS) and in combinations of support. These measurements can be recorded prior to implantation of the DPS electrodes for baseline data, and then at regular intervals following the initiation of DPS treatment. Other endpoints include the daily use of DPS and NIPPV, as patients will record categorized hours used of each therapy and the weekly preference for ventilation therapy on the log form. Finally, a measure of nocturnal hypoventilation can be performed at regular week intervals by recording the nighttime SpO₂ with a software-driven recording system such as Crystal PSG™ device. The nocturnal oxygen desaturation index (ODI) and the % of monitoring time spent in hypoxia (SpO₂ < 90%) pre-implant and post-implant can be calculated. The ODI represents the

number of times per hour of monitoring that the SpO₂ desaturates by more than 4%. Measurements of breathlessness and ODI can be made under consistent conditions with respect to the patients' use of supplemental oxygen and will be made with and without DPS.

[00061] In addition to ALS patients, other types of patients could benefit from DPS supported breathing during sleep. Any patient, for example, with upper motor neuron dysfunction, even in conjunction with lower motor neuron dysfunction that results in temporary or permanent diaphragm paralysis is an appropriate candidate for DPS therapy. Periodic respiratory instability, as demonstrated in patients with central sleep apnea and congestive heart failure are prime candidates for DPS intervention. Other examples of diaphragm paralysis have been reported in patients with Charcot-Marie-Tooth disease, associated with diabetes mellitus, spinal cord injury, poliomyelitis, Guillain-Barre' syndrome, diabetes, diphtheric neuropathy, beriberi, alcoholic neuropathy, brachial plexus neuropathy, lead neuropathy, trauma, myotonic dystrophy, Duchenne's muscular dystrophy, paraneoplastic syndrome, and idiopathic conditions.

[00062] By way of further examples, post surgical patients that are at risk of mechanical ventilation in the intensive care unit (ICU) may benefit from monitoring and intervention. An example of an at-risk surgical population would include bariatric patients. These patients, because of their obesity are already prone to sleep dysfunction and often have difficulty with the recovery and regulation of CO₂ as a result of a laparoscopic surgical procedure for their obesity. An evaluation period according to **Steps 2 – 4** of the method (**Figure 1**) may appropriately be performed prior to surgery in order to obtain patient specific parameter values. A typical bariatric procedure involves work at or around the diaphragm, and thus could easily include placement of intramuscular electrodes in the diaphragm for subsequent monitoring of diaphragm EMG activity during recovery. If sporadic diaphragm contraction is observed by ICU staff, then rhythmic diaphragm contraction would be commenced to avoid apneas and potential intubation for the patient. Stimulation would then proceed throughout the night, until the patient awakens and diaphragm respiration can be supplemented with intercostal and accessory muscle respiration under volitional control centers of the patient.

[00063] Unless defined otherwise, all technical terms used herein have the same meanings as commonly understood by one of ordinary skill in the art to which this invention belongs. Specific methods, devices, and materials are described in this application, but any methods and materials similar or equivalent to those described herein can be used in the practice of the present invention. While embodiments of the inventive device and method have been described in some detail and by way of exemplary illustrations, such illustration is for purposes of clarity of understanding only, and is not intended to be limiting. Various terms have been used in the description to convey an understanding of the invention; it will be understood that the meaning of these various terms extends to common linguistic or grammatical variations or forms thereof. It will also be understood that when terminology referring to devices or equipment has used trade names, brand names, or common names,

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that these names are provided as contemporary examples, and the invention is not limited by such literal scope. Terminology that is introduced at a later date that may be reasonably understood as a derivative of a contemporary term or designating of a subset of objects embraced by a contemporary term will be understood as having been described by the now contemporary terminology. Further, while some theoretical considerations have been advanced in furtherance of providing an understanding, for example, of ways that embodiments of the invention beneficially intervene in the physiology of muscles and neural pathways responsible for breathing, and the role of this physiology in sleep, the claims to the invention are not bound by such theory. Moreover, any one or more features of any embodiment of the invention can be combined with any one or more other features of any other embodiment of the invention, without departing from the scope of the invention. Still further, it should be understood that the invention is not limited to the embodiments that have been set forth for purposes of exemplification, but is to be defined only by a fair reading of claims that are appended to the patent application, including the full range of equivalency to which each element thereof is entitled.

CLAIMS

We claim:

1. A method of improving sleep in a patient by using a system comprising an external stimulator and one or more electrodes implanted in the diaphragm for stimulation of the diaphragm, the method comprising:
adapting stimulation parameters to support respiration during sleep, and
stimulating the diaphragm in a therapeutic regimen with the one or more electrodes to support respiration after the onset of sleep, the regimen including the adapted stimulation parameters, the stimulation operating independently of any voluntary respiratory effort of the patient.
2. The method of claim 1 comprising, prior to the adapting and stimulating steps, diagnosing the patient as having a neuromuscular disease.
3. The method of claim 2 further comprising diagnosing the patient as having amyotrophic lateral sclerosis (ALS).
4. The method of claim 1 comprising, prior to the adapting and stimulating steps, identifying the patient as being at risk for sleep disordered breathing.
5. The method of claim 4 wherein the patient at risk is any of an ICU patient or a post-surgical patient.
6. The method of claim 5 wherein the post-surgical patient at risk has undergone a bariatric procedure.
7. The method of claim 1 comprising, prior to the adapting and stimulating steps, identifying the patient as having an upper motor neuron dysfunction that results in temporary or permanent diaphragm paralysis.
8. The method of claim 1 comprising, prior to the adapting and stimulating steps, implanting one or more electrodes in the diaphragm of the patient.
9. The method of claim 1 comprising, prior to the adapting and stimulating steps, diagnosing the patient as having sleep-disordered breathing by any one or more criteria including morning headaches, daytime sleepiness, PSG recordings consistent with disordered sleep, diaphragm EMG recordings during sleep consistent with disordered sleep, or pulmonary function testing data consistent with disordered sleep.
10. The method of claim 9, in the event that sleep-disordered breathing is found, further comprising diagnosing the patient's sleep sleep-disordered breathing as being centrally-mediated.

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11. The method of claim 1 wherein adapting stimulation parameters includes determining any one or more of an appropriate time interval after the onset of sleep to lapse prior to initiating stimulation, a threshold level of stimulation sufficiently low so as to allow onset of sleep, a threshold level of stimulation sufficient to stimulate diaphragm contraction, or a threshold level sufficient to support breathing during sleep.
12. The method of claim 1 further comprising monitoring the EMG of the patient during the therapeutic regimen.
13. The method of claim 1 wherein supporting respiration comprises initiating a breath and supporting a breath to completion.
14. The method of claim 1, after implementing the therapeutic regimen, further comprising evaluating the patient again for presence of sleep disordered breathing by any one or more diagnostic criteria including morning headaches, daytime sleepiness, PSG recordings consistent with disordered sleep, diaphragm EMG recordings during sleep consistent with disordered sleep, or pulmonary function test data consistent with disordered sleep.
15. The method of claim 13, in the event of a finding of continued presence of sleep-disordered breathing, further comprising revising the adapted stimulation parameters, and implementing a revised therapeutic regimen for the patient based on the revised parameters, the regimen comprising stimulating the diaphragm with the one or more electrodes to support respiration.
16. The method of claim 1, wherein stimulating the diaphragm in a therapeutic regimen after the onset of sleep comprises waiting for a period of time after the onset of sleep before initiating stimulation.
17. The method of claim 1, wherein the stimulating the diaphragm after onset of sleep comprises determining the onset of sleep by monitoring the level of one or more physiological parameters and determining when they fall below a threshold value, the parameters including any of the diaphragm EMG, an EEG, or body movement.
18. The method of claim 1, wherein stimulating the diaphragm in a therapeutic regimen comprises gradually ramping the stimulation over time to reach a steady state level of stimulation.
19. A method of improving sleep in a patient with sleep-disordered breathing or at risk thereof, the method comprising:
 - electrically stimulating the patient's diaphragm with a stimulation protocol comprising:
 - initiating a sleep onset process;
 - ramping the stimulation to a first level that does not exceed a level at which sleep onset is interrupted;

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- initiating sleep;
 - synchronizing a natural sleep respiratory rate with a rate supported by the stimulation while ramping stimulation to a second level which is sufficient to provide detectable diaphragm contraction; and
 - ramping the stimulation to a third level which is sufficient to support breathing during sleep.
20. The method of claim 19 wherein ramping includes increasing pulse duration and then increasing pulse amplitude.
21. The method of claim 19 wherein ramping includes increasing pulse amplitude and then increasing pulse duration.
22. The method of claim 19 wherein ramping includes increasing pulse amplitude and pulse duration in an interleaved manner.
23. The method of claim 19 wherein ramping includes ramping with a linear envelope.
24. The method of claim 19 wherein ramping includes ramping with an exponential envelope.
25. The method of claim 19 wherein ramping includes ramping with an arbitrary envelope shape.
26. The method of claim 19, prior to the electrically-stimulating step, comprising determining any one or more of an appropriate time interval after the onset of sleep to lapse prior to initiating stimulation, a threshold level of stimulation sufficiently low so as to allow onset of sleep, a threshold level of stimulation sufficient to stimulate diaphragm contraction, or a threshold level sufficient to support breathing during sleep.
27. A system for improving sleep in a patient with centrally-mediated sleep disordered breathing comprising:
 - an electronic signal generator;
 - one or more electrodes operably connected to the signal generator, the one or more electrodes configured to stimulate a diaphragm;
 - an EMG processor arranged to capture EMG activity data of the diaphragm while being paced by the one or more electrodes; and
 - a sleep sequencer configured to integrate any combination of stimulation parameter input, respiratory parameter input, and EMG data, and to convey processed data from these inputs to the electronic signal generator.
28. The system of claim 27 wherein the electronic signal generator comprises a power supply, an impedance detector, a microcontroller, a waveform generator, and one or more signal drivers.
29. The system of claim 27 wherein the EMG processor is configured to convey data to a display.

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30. The system of claim 27 wherein the EMG processor is configured to convey data to the sleep sequencer.
31. The system of claim 27 wherein the sleep sequencer is further configured to ramp up stimulus intensity to a threshold level.
32. The system of claim 31 wherein the stimulus intensity ramp up includes an increase in pulse duration followed by an increase in pulse amplitude.
33. The system of claim 31 wherein the stimulus intensity ramp up includes an increase in pulse amplitude followed by an increase in pulse duration.
34. The system of claim 31 wherein the stimulus intensity ramp up includes an interleaved increase in pulse amplitude and pulse duration.
35. The system of claim 31 wherein the stimulus ramp up has a linear envelope.
36. The system of claim 31 wherein the stimulus ramp up has an exponential envelope.
37. The system of claim 31 wherein the stimulus ramp up follows an arbitrary envelope shape.

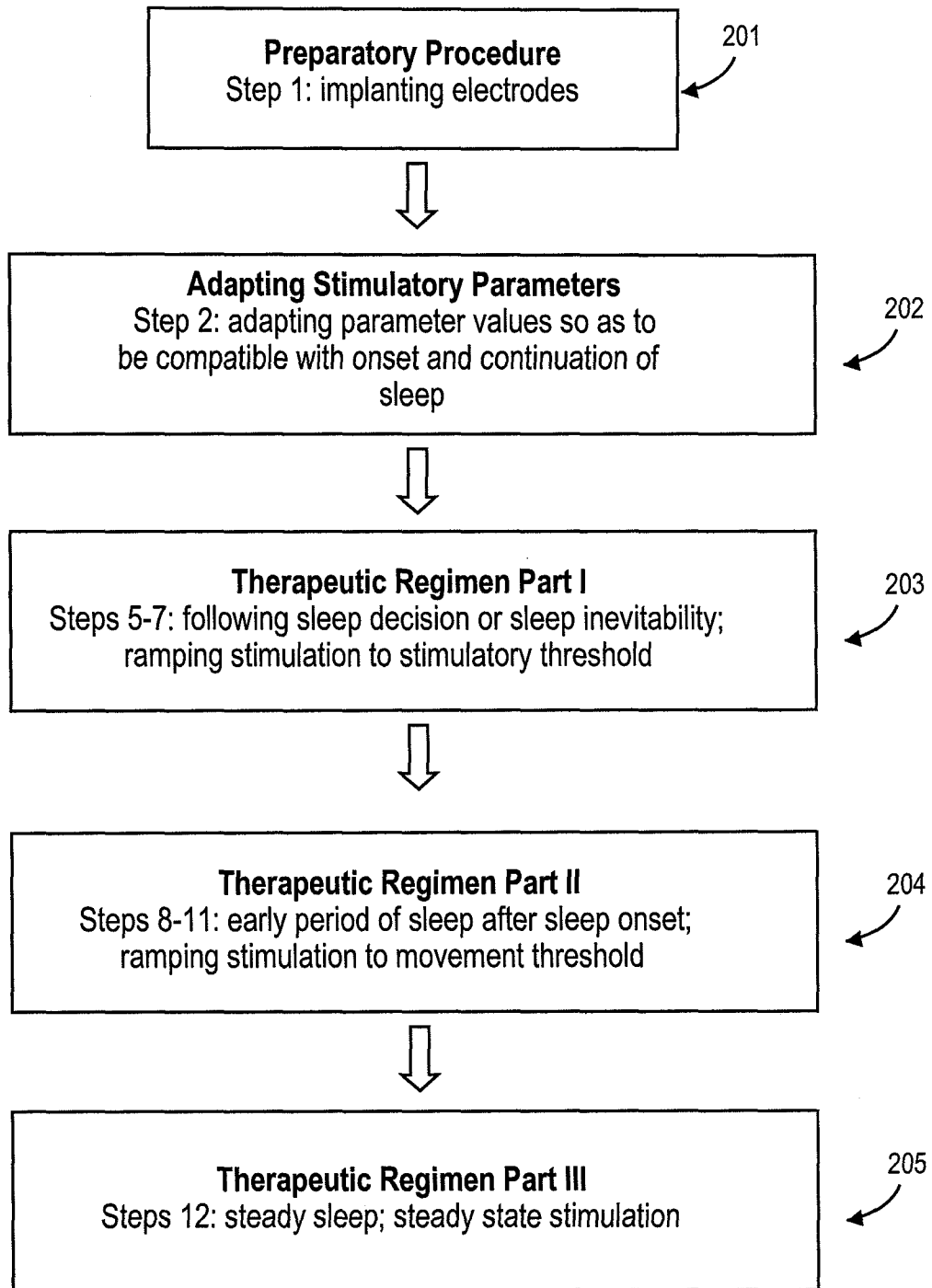


FIG. 1A

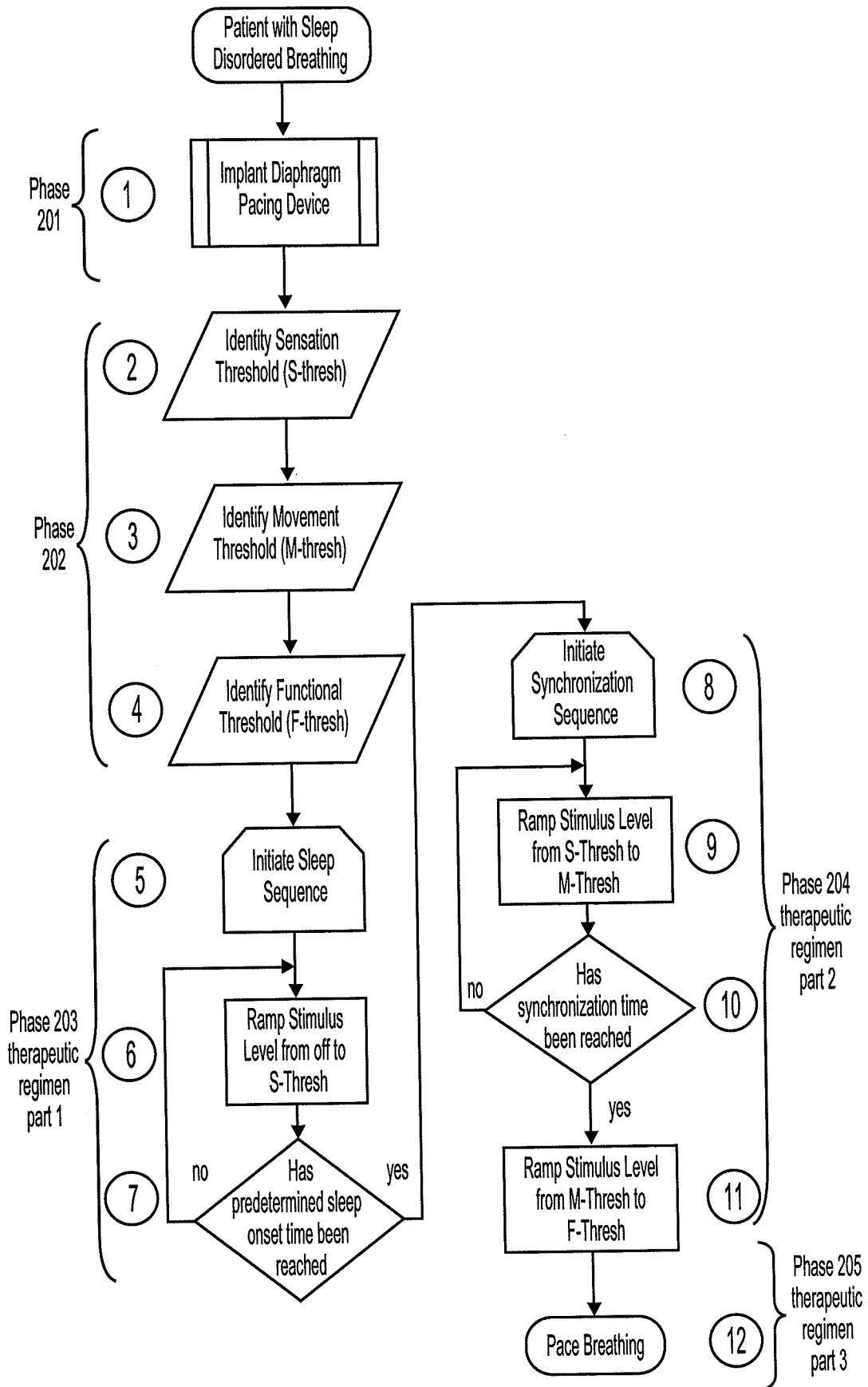


FIG. 1B

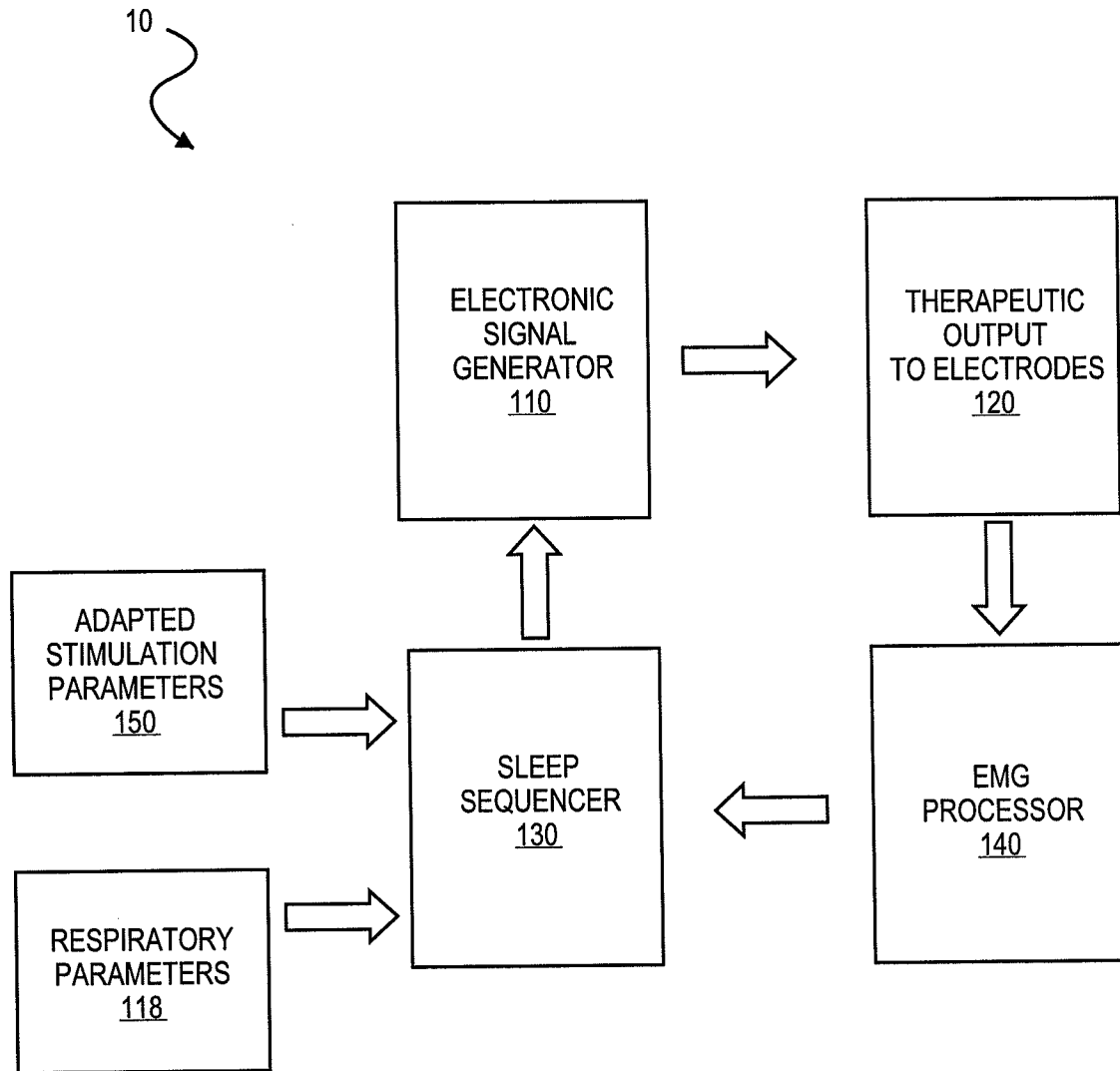


FIG. 2A

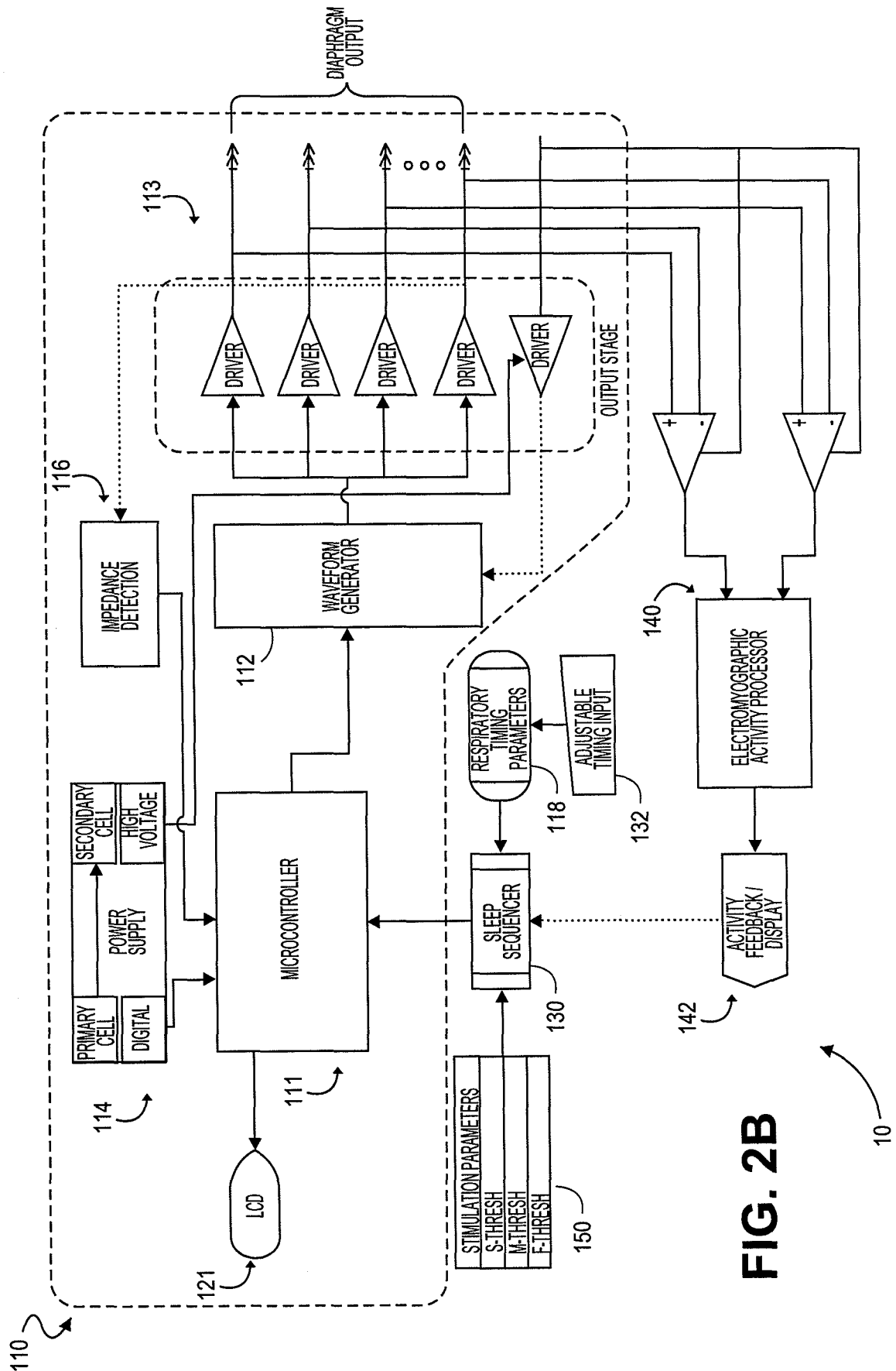


FIG. 2B

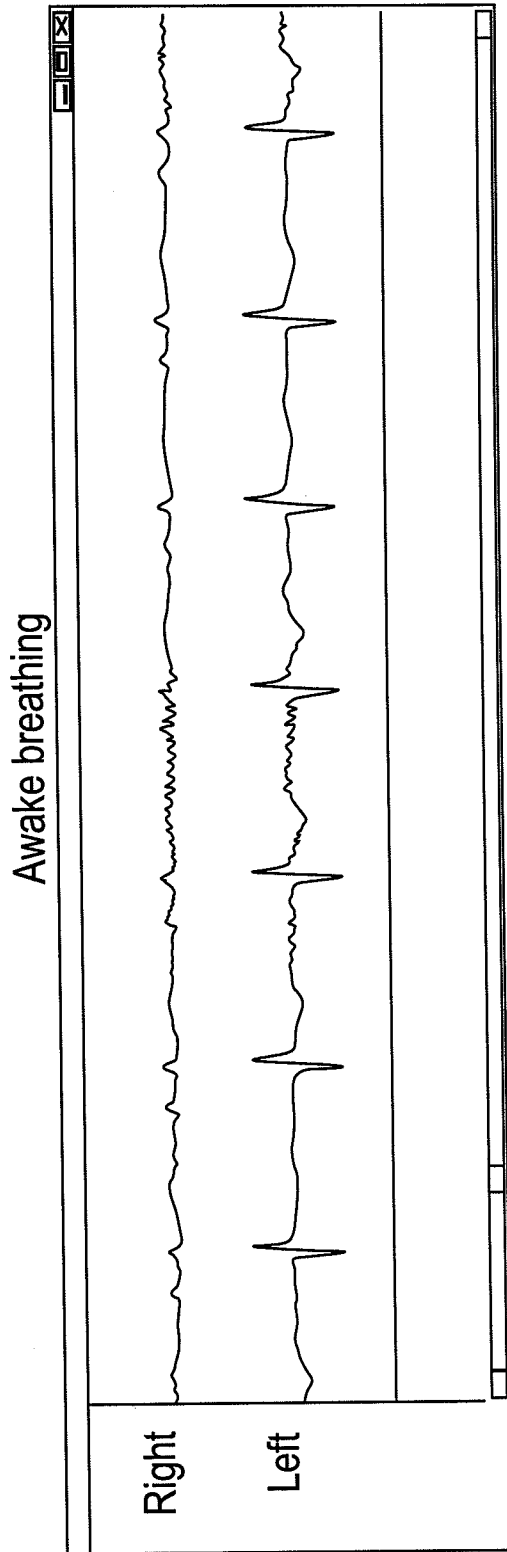


FIG. 3A

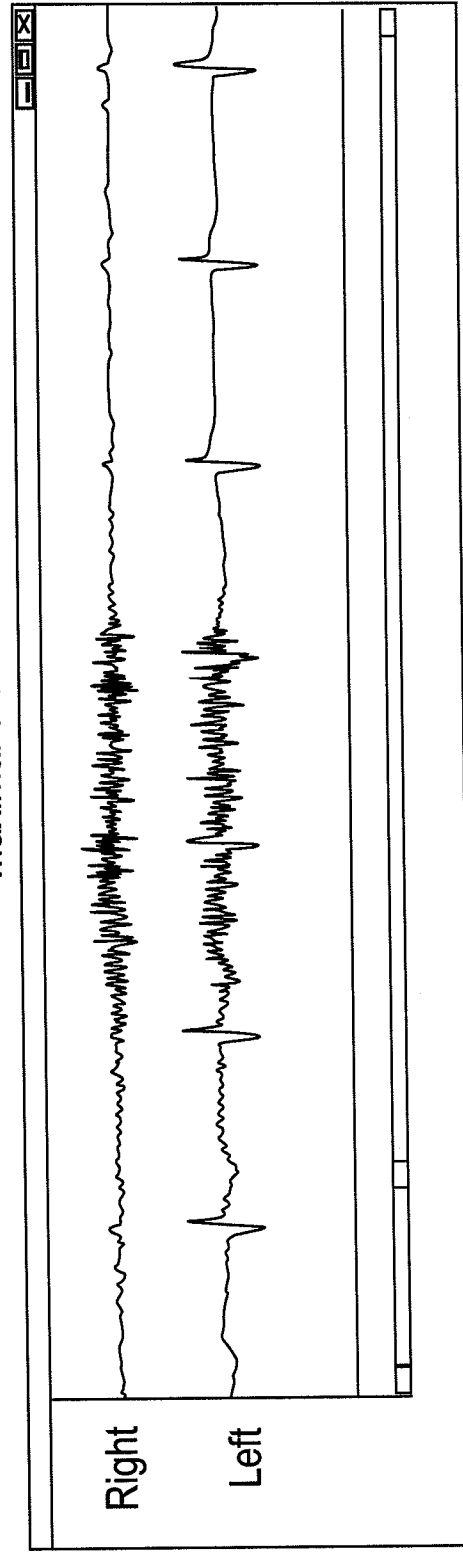


FIG. 3B

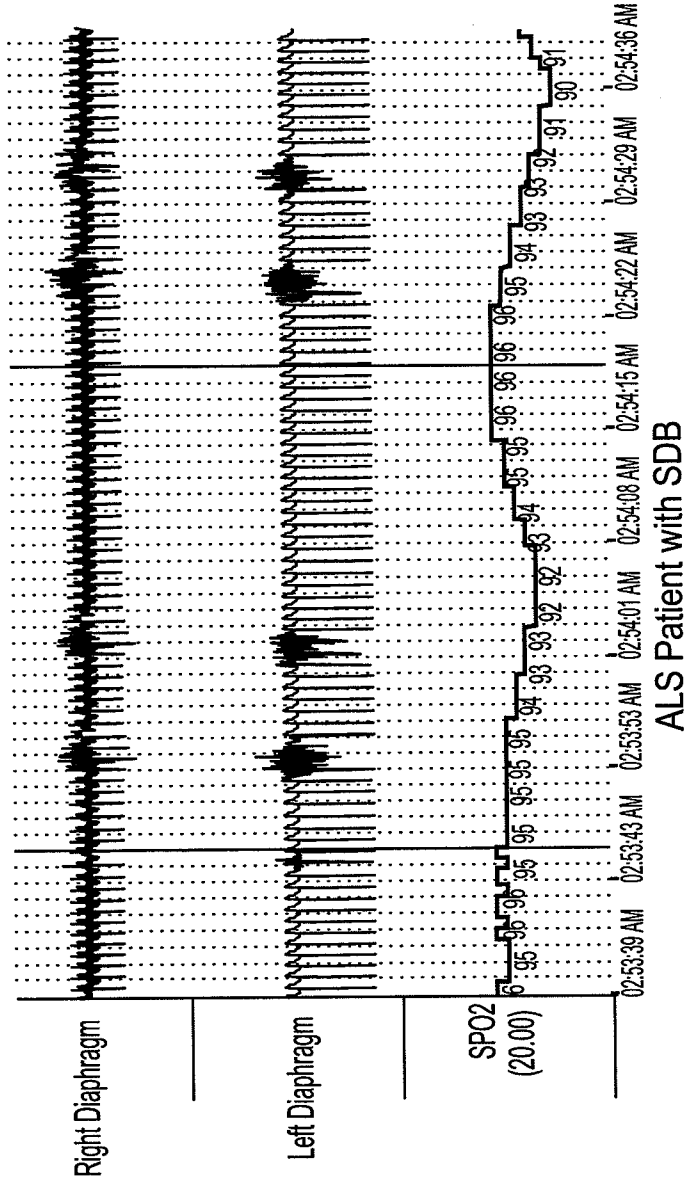


FIG. 4A

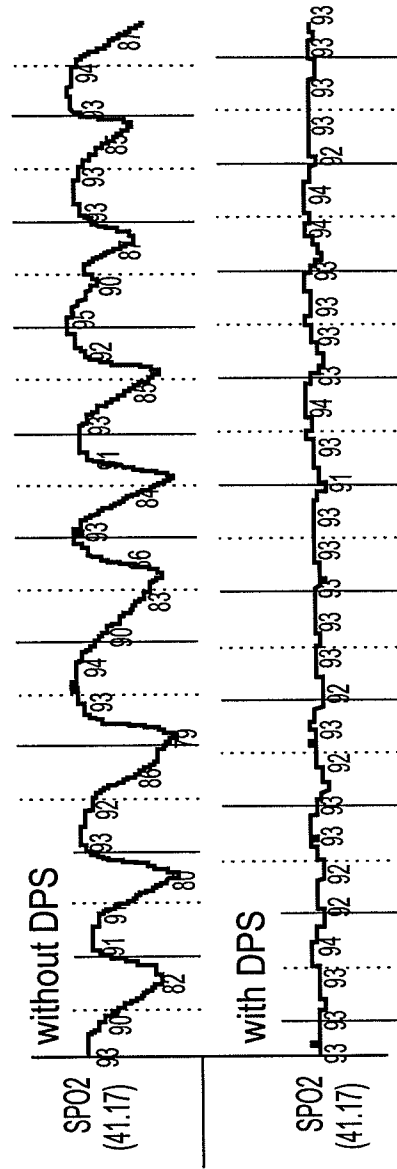


FIG. 4B

Oxygen Desaturation in split sleep study of ALS patient on BiPAP

DPS use increases Burst Activity
Correlates to improved Movement on Flouroscopy
Rectified EMG amplitude increased from 49uv to 62uv

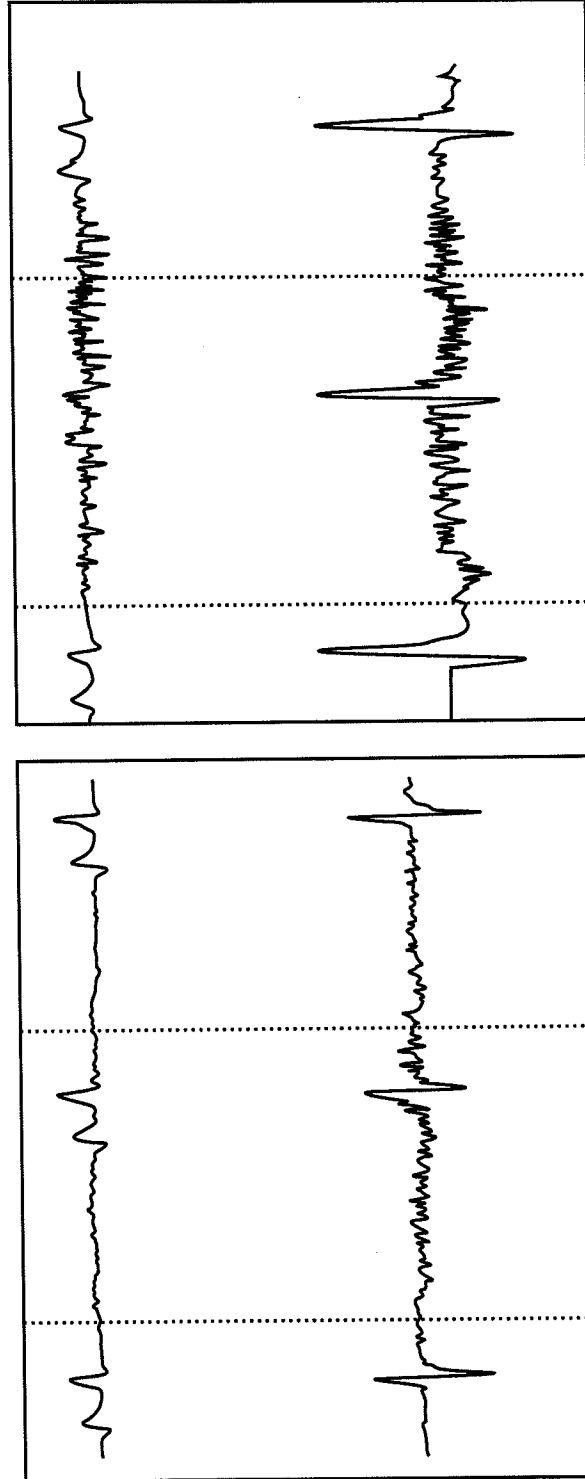


FIG. 5B

FIG. 5A

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2008/081833

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61N1/36

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61N

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 1 634 617 A (PACESETTER INC [US]) 15 March 2006 (2006-03-15) paragraphs [0001], [0008]; figure 1 paragraph [0016] - paragraph [0085]; figures 2,6,8 -----	27-37
X	WO 2007/058938 A (INSPIRATION MEDICAL INC [US]) 24 May 2007 (2007-05-24) paragraph [0057] - paragraph [0128]; figures 1-3 -----	27-37
X	WO 2007/103585 A (SYNAPSE BIOMEDICAL INC [US]; IGNAGNI ANTHONY R [US]; ONDERS RAYMOND P) 13 September 2007 (2007-09-13) the whole document -----	27-37
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Further documents are listed in the continuation of Box C. See patent family annex.

- * Special categories of cited documents :
- *A* document defining the general state of the art which is not considered to be of particular relevance
 - *E* earlier document but published on or after the international filing date
 - *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
 - *O* document referring to an oral disclosure, use, exhibition or other means
 - *P* document published prior to the international filing date but later than the priority date claimed
 - *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
 - *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
 - *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
 - * & * document member of the same patent family

Date of the actual completion of the international search 5 February 2009	Date of mailing of the international search report 13/02/2009
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Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer Sopelana Martínez, J
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INTERNATIONAL SEARCH REPORT

International application No

PCT/US2008/081833

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2005/021102 A1 (IGNAGNI ANTHONY R [US] ET AL) 27 January 2005 (2005-01-27) cited in the application the whole document -----	27-37

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2008/081833

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

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

1. Claims Nos.: **1-26**
because they relate to subject matter not required to be searched by this Authority, namely:
Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy
2. Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

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

1. As all required additional search fees were timely paid by the applicant, this international search report covers allsearchable claims.
2. As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.
3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No PCT/US2008/081833

Patent document cited in search report	A	Publication date	Patent family member(s)	Publication date
EP 1634617	A	15-03-2006	US 2007156199 A1 US 2006058852 A1	05-07-2007 16-03-2006
WO 2007058938	A	24-05-2007	NONE	
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US 2005021102	A1	27-01-2005	NONE	