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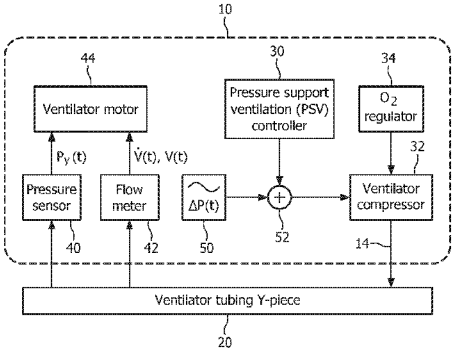
(54) **Title**: ENHANCEMENT OF SIMULTANEOUS ESTIMATION OF RESPIRATORY PARAMETERS VIA SUPERIMPOSED PRESSURE SIGNAL



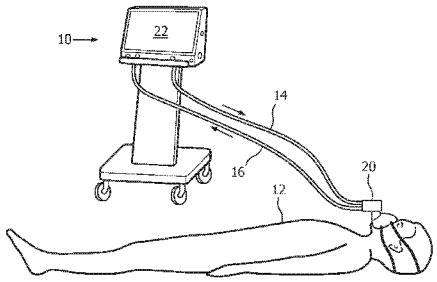


FIG. 1

(57) **Abstract**: A ventilator system includes a ventilator (10) configured to deliver an air flow at positive pressure to a ventilated patient (12). A signal generator (50) is configured to generate a non-therapeutic pressure signal having amplitude less than the maximum positive pressure of the air flow delivered to the ventilated patient and having the highest frequency component of at least 0.5 Hz. A signal combiner (52) is configured to superimpose the non-therapeutic pressure signal on the air flow delivered to the ventilated patient. A ventilator monitor (44) is programmed to estimate respiratory system's resistance *R* and compliance *C* and respiratory muscle pressure generated by the ventilated patient based on pressure and air flow measurements. The non-therapeutic pressure signal is effective to impart a signal component with frequencies beyond normal respiratory signal frequency range to the measured pressure and air flow, which improves the robustness of the estimation task.

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Enhancement Of Simultaneous Estimation Of Respiratory Parameters Via Superimposed Pressure Signal

The following relates to the respiratory therapy arts, respiratory monitoring arts, and related arts.

Various types of respiratory therapy employ a mechanical ventilator. In passive patient therapy, the patient is unable to breathe, and the ventilator operates in a pressure control mode in which the ventilator performs the entire work of breathing (WoB). In active patient therapy, the patient can perform some of the necessary work but cannot meet the respiratory demands independently. Thus, ventilator operates in a pressure support mode to provide sufficient pressure to overcome any deficiency in the patient's ability to breathe. Volume control modes of ventilator operation are also known, in which flow rate or volume is the controlled parameter, rather than controlling pressure (although pressure limit settings may also be applied to guard against pulmonary barotrauma), and are mainly used for passive patient therapy.

In determining ventilator settings and subsequent monitoring of a mechanically ventilated patient, it may be advantageous to measure various respiratory parameters. In the case of pressure support mode ventilation (PSV), assessment of the patient's work of breathing, which is the clinical parameter commonly used to infer the patient's effort per breath, is facilitated by evaluating the respiratory muscle pressure, $P_{mus}(t)$, over the breathing cycle. More specifically, the WoB is computed by integrating $P_{mus}(t)$ over the inhaled volume. For passive patient ventilation, it may be advantageous to verify that $P_{mus}{\sim}0$ throughout the breathing cycle (indicating no appreciable WoB is being provided by the patient). Respiratory parameters such as respiratory resistance (R) and compliance (C) may also be of interest, or may need to be determined in order to assess other parameters.

Estimating $P_{mus}(t)$ in support modalities of mechanical ventilation enables the ventilator to be set such that the patient and ventilator share the mechanical work performed on the respiratory system. Quantitative assessment of $P_{mus}(t)$ can be used to select the appropriate level of ventilation support in order to prevent both atrophy and fatigue of patient's respiratory muscles. The respiratory muscle pressure $P_{mus}(t)$ is typically assessed by measuring the esophageal pressure (P_{es}) via insertion of a balloon-tipped catheter in the patient's esophagus. The measured $P_{es}(t)$ is assumed to be a good proxy for the pleural pressure (P_{pl}) and can be used, in conjunction with an estimate of chest wall compliance C_{cw},

to compute the WoB via the so-called Campbell diagram or, equivalently, via explicit computation of $P_{mus}(t)$ and then of WoB.

Estimates of respiratory R and C are important *per se*, as they provide quantitative information to the physician about the mechanical properties of the patient's respiratory system and can be used to diagnose respiratory diseases and to select the appropriate ventilation modalities and therapeutic paths. Moreover, R and C can also be used to estimate $P_{mus}(t)$ as a non-invasive alternative to the use of the esophageal catheter. Assuming R and C are known, $P_{mus}(t)$ is suitably calculated by the following equation (known as the Equation of Motion of the Lungs):

$$P_y(t) = R\dot{V}(t) + \frac{V(t)}{C} + P_{mus}(t) + P_0 \qquad (1)$$

where $P_y(t)$ is the pressure measured at the Y-piece of the ventilator (also known as pressure at the mouth of the patient), $\dot{V}(t)$ is the flow of air into and out of the patient respiratory system (measured again at the Y-piece), $V(t)$ is the net volume of air delivered to the patient (measured by integrating the flow signal $\dot{V}(t)$ over time), and P_0 is a constant term to account for the pressure at the end of expiration.

In the case of a passive patient expending no breathing effort, it follows that $P_{mus}(t) = 0$ throughout the breathing cycle and Equation (1) reduces to $P_y(t) = R\dot{V}(t) + \frac{V(t)}{C} + P_0$. For the passive patient, $P_y(t)$, $\dot{V}(t)$, and $V(t)$ waveforms are fully determined by the selected ventilator settings and directly measureable, so that it is straightforward to generate a sufficient data set to determine R and C. By contrast, in the case of an active patient who is providing some WoB, the value of $P_{mus}(t)$ varies with time over the breath cycle, and Equation (1) is not easily solved.

For active patients, Equation (1) has generally been applied to non-invasively estimate $P_{mus}(t)$ using a two-step approach, where R and C are estimated first and then Equation (1) is applied to compute $P_{mus}(t)$ using the estimated values of R and C. Estimation of R and C may be performed by applying the flow-interrupter technique (also called End Inspiratory Pause, EIP). However, the flow-interrupter technique has the disadvantage of interfering with the ventilation pattern supplied to the patient. Moreover, the patient's respiratory muscles ought to be fully relaxed during the EIP maneuver in order for the computation of R and C to be valid, which may not always be the case. Another difficulty is

that the values for R and C assessed via the EIP maneuver may be different from the R and C values attained during the ventilation pattern for which $P_{mus}(t)$ is to be determined. The EIP maneuver is performed in a specific ventilation mode (Volume Assisted Control, VAC) and the resulting R and C values might not be representative of the corresponding values that determine the dynamics of the lung mechanics under other ventilation modes, such as PSV, potentially leading to error in the subsequently computed $P_{mus}(t)$.

Another approach for estimating R and C in the case of an active patient is to apply least-squares fitting of Equation (1) to flow and pressure measurements under specific conditions for which the term $P_{mus}(t)$ is assumed to be zero. Some conditions for which $P_{mus}(t)$ could be assumed to be close to zero include: (1) periods of patient paralysis while Continuous Mandatory Ventilation (CMV) is applied; (2) periods of high Pressure Support Ventilation (PSV) levels; (3) specific portions of every pressure-supported breath that extend both during the inhalation and the exhalation phases; and (4) exhalation portions of pressure-supported breaths, where the flow signal satisfies specific conditions that are indicative of the absence of patient inspiratory efforts. However, Conditions (1) and (2) are undesirable clinical states that cannot be properly induced as an expedient for measuring R and C. The assumption of $P_{mus}(t)\sim 0$ for Condition (3) is questionable, especially during the inhalation phase. Condition (4) provides only a limited amount of data for the least squares fitting procedure. In sum, it has been difficult to attain a clinically useful period of sufficient time duration for which $P_{mus}(t)\sim 0$ is reliably achieved in an active patient in order to estimate R and C.

The following provides a new and improved system and method which overcome these problems and others.

In accordance with one aspect, a medical ventilator system comprises: a ventilator configured to deliver a therapeutic air flow at positive pressure to a ventilated patient; a signal generator configured to generate a non-therapeutic pressure signal having amplitude less than the maximum positive pressure of the ventilatory pattern delivered to the patient and having a frequency component of at least 0.5 Hz (and more preferably at least 1 Hz, and still more preferably at least 5 Hz); and a signal combiner configured to superimpose the non-therapeutic pressure signal on the therapeutic one, thus altering the air flow delivered to the ventilated patient. The non-therapeutic pressure signal may, for example, be is a sinusoidal signal, a square wave signal, a triangle or saw-tooth wave signal, or a non-cyclical chirp or frequency sweeping signal. In some embodiments the ventilator

includes a ventilator compressor configured to deliver the air flow to the ventilated patient; and a ventilator controller comprising a microprocessor programmed to generate and send a control signal to the ventilator compressor in order to deliver pressure support ventilation to the ventilated patient. In such embodiments the signal combiner may be configured to superimpose the non-therapeutic pressure signal on the PSV control signal that is sent to the ventilator compressor, and the signal generator and signal combiner may in narrower embodiments comprise said ventilator controller programmed to generate and superimpose the non-therapeutic pressure signal on the PSV control signal generated by the ventilator controller.

In accordance with another aspect, a non-transitory storage medium is provided, which stores instructions readable and executable by one or more microprocessors of a medical ventilator to command the medical ventilator to perform a method comprising: generating a non-therapeutic pressure signal; and superimposing the non-therapeutic pressure signal on air flow delivered by the medical ventilator to a ventilated patient. The method may further include operating the medical ventilator to deliver the air flow to the ventilated patient under pressure support ventilation (PSV), and the non-therapeutic pressure signal may be superimposed on a PSV control signal that is sent to a ventilator compressor of the medical ventilator. The superimposed non-therapeutic pressure signal is effective to impart signal components to patient pressure and airflow waveforms provided by the medical ventilator. The method may further comprise computing respiratory muscle pressure generated by the ventilated patient during respiration based on at least the patient pressure and airflow measurements acquired by the medical ventilator.

In accordance with another aspect, a medical ventilation method consists of delivering ventilation to a ventilated patient using a medical ventilator, and superimposing a cyclical or non-cyclical non-therapeutic pressure signal with a frequency component higher than the patient respiration rate on the ventilation delivered to the ventilated patient. In some embodiments, the method comprises: delivering pressure support ventilation (PSV) to the ventilated patient; measuring pressure at a Y-piece or T-piece coupled to the ventilated patient using a pressure sensor; measuring air flow at the Y-piece or T-piece coupled to the ventilated patient using a flowmeter; and computing respiratory muscle pressure generated by the ventilated patient during respiration based at least on the measured pressure and air flow. Computing the respiratory muscle pressure may comprise solving a system of equations formed by applying an equation of motion of the lungs to the pressure and air flow measured at a plurality of successive times while the superimposed cyclical non-therapeutic pressure

signal has a cycle frequency that is effective to make the data matrix of the system of equations well-conditioned.

One advantage resides in providing reduced noise in respiratory data analysis of a ventilated patient without impacting the ventilation therapy.

Another advantage resides in more accurate estimation of respiratory parameters such as respiratory system's resistance R and compliance C, respiratory muscle pressure $P_{mus}(t)$, and Work of Breathing (WoB), especially for (but not limited to) the case of a patient providing some WoB such that $P_{mus}(t)$ varies over the breath cycle.

Further advantages of the present invention will be appreciated to those of ordinary skill in the art upon reading and understand the following detailed description.

The invention may take form in various components and arrangements of components, and in various steps and arrangements of steps. The drawings are only for purposes of illustrating the preferred embodiments and are not to be construed as limiting the invention.

FIGURE 1 diagrammatically shows a ventilation system.

FIGURE 2 diagrammatically shows a data analysis algorithm disclosed herein which simultaneously estimates multiple respiration parameters by approximating the respiratory muscle pressure $P_{mus}(t)$ by a low-order polynomial function.

FIGURE 3 plots simulated respiration waveforms over about three breaths, with sensitivity of the parameter matrix plotted in the lowermost plot of FIGURE 3.

FIGURE 4 plots simulated respiration waveforms over about three breaths with a small amplitude, high frequency pressure signal $\Delta P(t)$ superimposed on the ventilator-applied pressure, with sensitivity of the parameter matrix plotted in the lowermost plot of FIGURE 4.

FIGURE 5 plots simulated values for respiratory system's resistance R and compliance C, and respiratory muscle pressure $P_{mus}(t)$ for the same simulation shown in FIGURE 3, along with values for these parameters estimated from the data of FIGURE 3 using the approach described with reference to FIGURE 2.

FIGURE 6 plots simulated values for respiratory system's resistance R and compliance C, and respiratory muscle pressure $P_{mus}(t)$ for the same simulation shown in FIGURE 4, along with values for these parameters estimated from the data of FIGURE 4 using the approach described with reference to FIGURE 2.

With reference to FIGURE 1, a medical ventilator system includes a medical ventilator **10** that delivers air flow at positive pressure to a patient **12** via an inlet air hose **14**. Exhaled air returns to the ventilator **10** via an exhalation air hose **16**. A Y-piece **20** of the ventilator system serves to couple air from the discharge end of the inlet air hose **14** to the patient during inhalation and serves to couple exhaled air from the patient into the exhalation air hose **16** during exhalation. Note that the Y-piece is sometimes referred to by other nomenclatures, such as a T-piece **20**. Not shown in FIGURE 1 are numerous other ancillary components that may be provided depending upon the respiratory therapy being received by the patient **12**. Such ancillary components may include, by way of illustration: an oxygen bottle or other medical-grade oxygen source for delivering a controlled level of oxygen to the air flow (usually controlled by the Fraction of Inspired Oxygen (FiO_2) ventilator parameter set by the physician or other medical personnel); a humidifier plumbed into the inlet line **14**; a nasogastric tube to provide the patient **12** with nourishment; and so forth. The ventilator **10** includes a user interface including, in the illustrative example, a touch-sensitive display component **22** via which the physician, respiratory therapist, or other medical personnel can configure ventilator operation and monitor measured physiological signals and operating parameters of the ventilator **10**. Additionally or alternatively, the user interface may include physical user input controls (buttons, dials, switches, et cetera), a keyboard, a mouse, audible alarm device(s), indicator light(s), or so forth.

With continuing reference to FIGURE 1, in an upper portion some additional salient aspects of the ventilator system are diagrammatically illustrated in a block diagram format, including the ventilator **10** represented as a simplified block diagram, and the Y-piece **20** as a diagrammatic box with operative connections indicated by connecting arrows. In the illustrative example, the ventilator **10** is operating in a pressure support ventilation (PSV) mode as implemented by a controller **30**. PSV is an appropriate ventilation mode for an active patient who is capable for expending at least some Work of Breathing (WoB) – that is, whose diaphragm and other chest muscles are acting to at least assist in operating the lungs to perform breathing. In the PSV mode, the pressure provided by the ventilator **10** via the inlet air hose **14** operates together with the patient's WoB to perform the breathing. More generally, the controller **30** may implement various ventilation modes depending on the patient's condition and the therapy to be delivered. For example, in the case of a passive patient who is providing no WoB, the controller **30** may operate the ventilator **10** in a Pressure Control Ventilation (PCV) mode. (Note that in some classification schemes PSV is considered a type of PCV mode, since in both PCV and PSV the pressure applied by the

ventilator **10** is a controlled parameter). Volume control ventilation modes are also sometimes used, although pressure limit settings may also be applied in volume control ventilation to guard against pulmonary barotrauma. In general, the ventilation controller **30** is implemented as a microprocessor with ancillary electronics such as read-only memory (ROM), electronically erasable read only memory (EEPROM), flash memory, or another non-volatile memory component storing software or firmware executed by the microprocessor, random access memory (RAM) chip(s) to provide working memory, and so forth. If EEPROM, flash memory, or other updatable memory is used to store the software or firmware, then capabilities of the ventilator **10** can advantageously be updated (within the limits of its hardware components) by updating the software or firmware.

The PSV controller **30** outputs a desired pressure control signal as a function of time, which is used to control a ventilator compressor **32** (e.g. a pneumatic pump, turbopump, or so forth) that generates air flow at the controlled positive pressure that is applied to the Y-piece **20** via the inlet air hose **14**. Depending upon the respiratory therapy to be provided, an oxygen regulator **34** may add a controlled fraction of oxygen to the air flow to achieve a Fraction of Inspired Oxygen (FiO_2) set by the physician, respiratory specialist, or other medical personnel who sets the configuration of the ventilator **10** for the patient **12**. The pressure of the air flow may vary during the breathing cycle to provide pressure-driven or pressure-assisted inhalation and to reduce pressure to facilitate exhalation.

The ventilator system typically further includes physiological monitoring sensors, such as an illustrative pressure sensor **40** and an illustrative flowmeter **42**. The pressure sensor **40** measures the pressure at the Y-piece **20** (also known as pressure at the mouth of the patient), which is denoted here as $P_y(t)$. The flowmeter **42** measures the air flow rate into and out of the Y-piece **20**, denoted herein as $\dot{V}(t)$. The flowmeter **42** also directly or indirectly provides the net volume of air delivered to the patient, denoted herein as $V(t)$, which may be directly measured or may be derived by integrating the flow rate $\dot{V}(t)$ over time. These measured values $P_y(t)$, $\dot{V}(t)$, $V(t)$, optionally along with other information such as the ventilator settings (e.g. FiO_2, the pressure profile delivered by the PSV control, et cetera) may be variously used by a ventilator monitor **44** to efficacy of the mechanical ventilation, to detect any deterioration of the state of the patient **12**, to detect any malfunction of the ventilator **10**, or so forth. As with the ventilator controller **30**, the ventilator monitor **44** is implemented as a microprocessor with ancillary electronics, and may be updateable by updating the software or firmware. In some embodiments, the ventilator controller **30** and the ventilator monitor **44** may be implemented by a common microprocessor, and the controller

and monitor functions may be integrated at various levels – for example, it is contemplated to provide feedback-based ventilation control based on the measured values $P_y(t)$, $\dot{V}(t)$, $V(t)$ or parameters derived therefrom.

Of salient interest here is assessment of the Work of Breathing (WoB), or of its derivative, the respiratory muscle pressure $P_{mus}(t)$. In general, WoB can be computed by integrating $P_{mus}(t)$ over the inhaled volume. In approaches disclosed herein, the assessment leverages the Equation of Motion of the Lungs given in Equation (1) herein, and hence the respiratory system's resistance R and compliance C are also salient parameters of interest. Equation (1) is evaluated with respect to a dataset of N data points measured over one or more breath cycles. Formally, the problem can be stated as follows:

$$Y = X\theta \tag{2}$$

where:

$Y = \left[P_y(1)\ P_y(2)\ \ldots\ P_y(N) \right]^T$	Pressure at Y-piece at times 1,…,N
$\dot{V} = \left[\dot{V}(1)\ \dot{V}(2)\ \ldots\ \dot{V}(N) \right]^T$	Flow rate at times 1,…,N
$V = [\, V(1)\ V(2)\ \ldots\ V(N)\,]^T$	Net air volume at times 1,…,N
$\theta = [\, R\ \ 1/C\ \ P_{mus}(1)\ P_{mus}(2)\ \ldots\ P_{mus}(N)\,]^T$	Parameters to be determined

and matrix X is an $(N+2) \times N$ matrix given by $X = \left[\dot{V}\ V\ I_N \right]$, where I_N is an $N \times N$ identity matrix. By solving the system of equations $Y = X\theta$ for the parameter vector θ, the resistance R, compliance C, and respiratory muscle pressure $P_{mus}(t)$ can be obtained. However, the system of equations represented by Equation (2) has more unknowns (N+2 unknowns) than equations (N equations), and hence is an underdetermined problem that cannot be solved because it has an infinite number of solutions, only one of which is the true "physical" solution.

In addition to being underdetermined, the inventors have found that the set of equations represented by matrix Equation (2) is very sensitive to measurement noise, unknown disturbances and unmodeled dynamics. Problematically, the noise is on the same time scale as the variations in the measured signals $P_y(t)$, $\dot{V}(t)$, $V(t)$ and in the estimated respiratory muscle pressure $P_{mus}(t)$. Thus, even if the underdetermined nature of the

simultaneous estimation problem is somehow overcome, the resulting parameter values tend to be noisy and hence of limited clinical value.

With continuing reference to FIGURE 1, it is disclosed herein to counteract the effect of noise by superposing a relatively high-frequency and small-amplitude pressure signal, denoted as $\Delta P(t)$ herein, generated by a signal generator **50**, onto the normal pressure profile supplied by the ventilator **10**. As illustrated in FIGURE 1, this can be done by adding a small-amplitude sinusoidal $\Delta P(t)$ to the controlled pressure signal output by the controller **30** using a signal combiner **52** prior to its input to the ventilator compressor **32**. The amplitude of $\Delta P(t)$ is preferably chosen to be low enough to not appreciably impact the therapeutic value of the PSV signal output by the controller **30**. That is, the superimposed cyclical pressure signal should be a non-therapeutic pressure signal that does not contribute to the ventilation therapy delivered to the ventilated patient **12**, and also does not adversely affect the ventilation therapy delivered to the ventilated patient **12**. The frequency of $\Delta P(t)$ is preferably high enough to be significantly higher than the breath frequency (e.g. typically a few breaths per minute corresponding to a frequency of, e.g., about 0.2 Hz for 5-sec breaths).

To illustrate, matrix Equation (2) is solved in an illustrate approach disclosed herein as follows. The simultaneous estimation of the R, C and $P_{mus}(t)$ characterizing one breath (made of, without loss of generality, N recorded time samples) by Equation (2) is an underdetermined problem, since it requires the computation of $N + 2$ unknowns (N values for the N time samples of $P_{mus}(t)$, plus an additional unknown for R, and an additional unknown for C) from N equations corresponding to the N time samples. However, it is recognized herein that the N equations are not independent. Rather, it can be expected that the value of $P_{mus}(t)$ for neighboring samples should be continuous, because $P_{mus}(t)$ should vary relatively slowly over time. As disclosed herein, $P_{mus}(t)$ is approximated locally (that is, over a small number of samples $s < N$) by a nth-order polynomial function suitably written as $P_{mus}(t) = a_0 + a_1 t + \cdots + a_n t^n$. This approximation is used to construct a least squares (LS) problem over a time window of s samples (where $s < N$) in which the unknowns are R, C, and a_0, ..., a_n. By keeping $n + 3 < s$ (and in some embodiments $n \ll s$), the underdeterminacy is overcome. The local approximation of $P_{mus}(t)$ by a polynomial is supported by the physiological intuition that $P_{mus}(t)$ is a smooth signal, with no abrupt discontinuities, and should vary relatively slowly over time.

The resulting LS problem to be solved is fully determined (and preferably overdetermined), but the inventors have found that it still tends to be sensitive to noise and/or disturbances in the measurements. The reason lies with the fact that the flow and volume

signals (in particular the latter) can be approximated by a polynomial as well, being smooth functions of time. More generally, noise in the measured signals $P_y(t)$, $\dot{V}(t)$, $V(t)$ typically has comparable time-domain characteristics to the time-domain characteristics of $P_y(t)$, $\dot{V}(t)$, $V(t)$, and $P_{mus}(t)$, so that the fitted polynomial representation of $P_{mus}(t)$ can erroneously fit to a noise component. The noise problem is fundamental to any analysis of the breathing cycle due to the many sources of noises such as air flow-induced vibration or other motion of the Y-piece **20**, vibrations from the compressor **32**, cycling (opening and closing or other actuation) of the oxygen regulator **34**, and so forth. As disclosed herein, such noise is suitably addressed by superposition of a small-amplitude and relatively-high frequency pressure signal $\Delta P(t)$ onto the PSV or other ventilation pressure profile normally supplied by the ventilator **10**. The small-amplitude, high frequency superimposed pressure variation $\Delta P(t)$ imparts a corresponding small-amplitude, high frequency variation in the pressure $P_y(t)$ at the Y-piece **20** and in the air flow $\dot{V}(t)$ (and, to a lesser extent, to the net volume $V(t)$, although here the integration may partly remove the impact of $\Delta P(t)$). This makes the measured signals of interest different in kind from the noise, leading to more robust extraction of the respiratory muscle pressure $P_{mus}(t)$ from these signals. Thus, the LS solution (or other analysis of the breath cycle measurements) is made robust against noise and disturbances.

With reference now to FIGURE 2, the illustrative approach for overcoming the underdeterminancy of matrix Equation (2) is described in additional detail. The estimation of R, C, and $P_{mus}(t)$ at each time 1,…,N is obtained by solving a LS problem over a window of length s. For the usual case in which $s < N$, the window slides forward in time (that is, the window of width s is applied to successive increments of width s in the time series of samples 1,..,N). In real-time patient monitoring, this can be done as a sliding window – as each successive group of s samples are acquired, the fitting is performed so as to provide a real-time simultaneous estimate for R, C, $P_{mus}(t)$. The windows of width s can be non-overlapping; alternatively, it is contemplated for the neighboring windows of width s to overlap, which can provide a smoothing effect. FIGURE 2 illustrates the case in which the polynomial approximation of $P_{mus}(t)$ over the time window of width s is of order $n = 2$, that is, a polynomial: $P_{mus}(t) = a_0 + a_1 t + a_2 t^2$. The matrix Equation (2) solved for the window of width s has the same form as Equation (2), but the parameters vector is different. To distinguish, the parameter vector is written as ϕ (rather than the parameter vector θ of Equation (2)), the matrix X is replaced by a matrix χ, and the set of equations becomes:

$$Y = \chi\phi \tag{2a}$$

where:

$Y = [\, P_y(1)\ P_y(2)\ \ldots\ P_y(s)\,]^T$ For window of s samples

$\dot{V} = [\, \dot{V}(1)\ \dot{V}(2)\ \ldots\ \dot{V}(s)\,]^T$ For window of s samples

$V = [\, V(1)\ V(2)\ \ldots\ V(s)\,]^T$ For window of s samples

$\phi = [\, R\ \ 1/C\ \ a_0\ \ a_1\ \ \ldots\ \ a_n\,]^T$ Reduced to $n + 3$ unknowns

and matrix χ is an $s \times (n + 3)$ matrix given by:

$$\chi = \begin{pmatrix} \dot{V}(1) & V(1) & 1 & 1 & \ldots & 1^n \\ \dot{V}(2) & V(2) & 1 & 2 & \ldots & 2^n \\ \ldots & \ldots & \ldots & \ldots & \ldots & \ldots \\ \dot{V}(s) & V(s) & 1 & s & \ldots & s^n \end{pmatrix}$$

In the above notation, the first sample in the window of width s is designated without loss of generality as sample t=1, so that the last sample in the window is designated as sample $t = s$. Matrix Equation (2a) thus represents a set of s equations with $n + 3$ unknowns, and is overdetermined so long as $s > (n + 3)$. More typically, $s \gg n$. For example, in one illustrative example $n = 2$ (quadratic approximation for $P_{mus}(t)$), the sampling rate is 100 Hz, and the window is 0.6 sec long corresponding to $s = 60$.

Assuming an overdetermined set of equations, the matrix Equation (2a) can be solved in the least squares sense according to:

$$\phi = (\chi^T\chi)^{-1}\chi^T Y \tag{3}$$

Alternatively, an iterative least squares approximation approach such as gradient descent or Levenberg-Marquardt can be used to solve Equation (3) for the parameters ϕ.

The illustrative approach employs a polynomial approximation of order n of $P_{mus}(t)$ over the time window of width s. The order n is chosen to be $n \geq 2$. Choosing a higher order provides the polynomial approximation with greater flexibility to represent changes in $P_{mus}(t)$ over the time window of width s; however, it also adds additional

parameters (the total number of parameters is $n + 3$) which makes the least squares fitting less robust. It is expected that $n = 2$, $n = 3$, or $n = 4$ will be sufficient in most instances, although $n > 4$ is also contemplated. Moreover, it will be appreciated that the approach can be generalized to approximating $P_{mus}(t)$ over the time window of width s by any continuous function that is smooth over the window of width s (i.e. that is fully differentiable over the window of width s). Other contemplated continuous and smooth approximation functions include spline functions, e.g. cubic spline functions.

The sensitivity of the solution to noise and/or disturbances present in the measured data can be quantified by the condition number of the data matrix (X or χ, depending on whether Equation (2) or Equation (2a) is considered). The condition number of a matrix can be interpreted as a (worst-case) amplification gain of errors in the data matrix entries. Although replacing X by χ as just described reduces the number of unknowns in order to make the problem tractable, noise can still be an issue.

To illustrate, with reference to FIGURE 3 the normal interaction between the ventilator and a patient is emulated using a computer-simulated Lung Emulator. This normal interaction gives rise to waveforms of flow and volume, plotted in FIGURE 3, that make the data matrix ill-conditioned. Hence, the parameters estimated via Equation (3), are sensitive to noise or error in the measured data. In FIGURE 3, the sensitivity of the data matrix is plotted in the lowermost plot of FIGURE 3. Note in this plot that the sensitivity ordinate ranges [0 , 200,000].

As previously described, this noise can be counteracted by superimposition of the low amplitude, high frequency component $\Delta P(t)$.

To illustrate, FIGURE 4 shows how the superposition of a sinusoidal signal $\Delta P(t)$ of small-amplitude (1 cmH_2O in this example) and relatively high-frequency (5 Hz in this example) significantly reduces the sensitivity (condition number) of the data matrix, thus improving the robustness against noise. Note that in FIGURE 4 the lowermost sensitivity plot has a sensitivity ordinate range of only [0 , 5000].

Without being limited to any particular theory of operation, it is believed that the superposed signal $\Delta P(t)$ introduces variations in the flow and volume signals which cannot be described by the polynomial structure chosen for $P_{mus}(t)$. This enhances the algorithm robustness, making it less sensitive to measurement noise, unknown disturbances and unmodeled dynamics. More generally, the superposed signal $\Delta P(t)$ is believed to introduce variations in the measured signals, e.g. $P_y(t)$, $\dot{V}(t)$, $P_{mus}(t)$, which are different in

kind from the variations due to typical sources of noise or disturbance, which enhances the robustness of any data analysis performed on these signals.

With reference to FIGURES 5 and 6, as further illustration the robustness of the estimates obtained from the data of FIGURE 3 with noise added is shown in FIGURE 5, while the robustness of the estimates obtained from the data of FIGURE 4 with noise added is shown in FIGURE 6. In other words, FIGURE 5 shows the estimation robustness when no small amplitude, high frequency pressure signal $\Delta P(t)$ is superimposed, while FIGURE 6 shows the estimation robustness when the pressure signal $\Delta P(t)$ is superimposed. The reduction in estimation error observed in FIGURE 6 compared with FIGURE 5 is readily apparent.

The superposition of the pressure signal $\Delta P(t)$ is designed to improve the estimation process while not interfering with the patient respiration. The magnitude of $\Delta P(t)$ (e.g. 1 cmH_2O in illustrative FIGURES 4 and 6) is small enough that the ventilation therapy is not affected. Yet the superimposed pressure signal $\Delta P(t)$ provides a significant benefit in terms of noise robustness (or equivalently, a decrease in sensitivity) in the simultaneous assessment of R, C, and $P_{mus}(t)$.

In some embodiments the signal generator **50** and signal combiner **52** are implemented in software or firmware as part of the software or firmware of the ventilator controller **30**. In such embodiments, the components **50**, **52** can be implemented in the factory state, or as a retrofit to an existing ventilator by an appropriate control software or firmware update. Such software or firmware, either in the factory state or as a software or firmware update, is suitably provided in the form of a non-transitory storage medium storing instructions readable and executable by the microprocessor of the controller **30** to cause the ventilator **10** to perform ventilation of the ventilated patient **12** including the superimposing the cyclical signal $\Delta P(t)$ onto the positive pressure of the air flow delivered to the patient. The non-transitory storage medium may, for example, comprise a flash memory, optical disk, or other storage medium directly loaded into or physically connected with the ventilator **10**, or may comprise a RAID or other storage medium accessed via a network server in which case the ventilator **10** connects with the network (e.g. the Internet or a hospital network) in order to download the software or firmware from the network server.

In other embodiments, it is contemplated for the signal generator **50** and signal combiner **52** to be components separate from the ventilator controller **30**. For example, the signal generator **50** could be a voltage-controlled oscillator (VCO) or other oscillator circuit outputting the cyclical signal $\Delta P(t)$, and the signal combiner **52** could be an operational

amplifier (op-amp)-based signal combiner circuit or other signal combiner circuit implemented in hardware.

The superimposed signal $\Delta P(t)$ should contain sufficiently high frequencies to make the data matrix X or χ well-conditioned. At the same time, such frequencies should be within the bandwidth of the ventilator hardware and the patient's respiratory system. While $\Delta P(t)$ has been described herein as sinusoidal in illustrative examples, more generally the superimposed signal $\Delta P(t)$ can have a shape other than sinusoidal (e.g. a square wave). In general the superimposed high frequency signal $\Delta P(t)$ has a frequency component, e.g. the frequency of a sinusoid in the case of a sinusoidal signal, or the inverse of the square wave period in the case of a square wave signal, or the inverse of the triangle wave period in the case of a saw-tooth or other triangular signal, or so forth. The cycle frequency (or another frequency component of the superimposed high frequency signal $\Delta P(t)$) should be higher than the respiration rate (i.e. the frequency of the breathing cycle) so that $\Delta P(t)$ (and its impact on other signals such as flow rate $\dot{V}(t)$) can be distinguished from respiration-related signal variations. Normal adult respiration rate is on the order of 12-20 breaths/minute (0.20-0.34 Hz); thus, in some embodiments the cycle frequency is at least 0.5 Hz, and more preferably at least 1 Hz. In the illustrative embodiment of FIGURES 4 and 6 the cycle frequency is 5 Hz. On the other hand, infants can have respiration rate of as high as 60 breaths/minute (1 Hz), so for an infant ventilator the superimposed signal $\Delta P(t)$ preferably has a cycle frequency of at least 3 Hz, and more preferably at least 5 Hz. Since ventilators are sometimes not infant- or adult-specific, in some embodiments a cycle frequency sufficient for infants is preferable. However, the superimposed signal $\Delta P(t)$ can also be a non-cyclical signal with significant high frequency components, such chirp signal or frequency sweep signal.

The amplitude of the superimposed signal $\Delta P(t)$ should be lower than the maximum positive pressure of the air flow delivered to the ventilated patient by the ventilator **10**. More preferably, the superimposed signal $\Delta P(t)$ should be substantially lower than this maximum positive pressure, i.e. sufficiently lower that the superimposed signal $\Delta P(t)$ does not interfere with the therapeutic ventilation of the patient. The superimposed signal $\Delta P(t)$ is a non-therapeutic pressure signal that does not contribute, positively or negatively, to the ventilation therapy delivered to the patient.

The invention has been described with reference to the preferred embodiments. Modifications and alterations may occur to others upon reading and understanding the preceding detailed description. It is intended that the invention be construed as including all such modifications and alterations insofar as they come within the scope of the appended claims or the equivalents thereof.

CLAIMS:

1. A medical ventilator system comprising:

a ventilator (10) configured to deliver an air flow at positive pressure to a ventilated patient (12);

a signal generator (50) configured to generate a non-therapeutic pressure signal having amplitude less than the maximum positive pressure of the air flow delivered to the ventilated patient and having a frequency component of at least 0.5 Hz; and

a signal combiner (52) configured to superimpose the non-therapeutic pressure signal on pressure waveform delivered to the ventilated patient.

2. The medical ventilator system of claim 1 wherein the non-therapeutic pressure signal has a frequency component of at least 1 Hz.

3. The medical ventilator system of claim 1 wherein the non-therapeutic pressure signal is cyclical with a cycle frequency of at least 1 Hz.

4. The medical ventilator system of any one of claims 1-4 wherein the non-therapeutic pressure signal is a sinusoidal signal, a square wave signal, a triangle or sawtooth wave signal or a non-cyclical chirp or frequency sweeping signal.

5. The medical ventilator system of any one of claims 1-4 wherein the ventilator (10) includes:

a ventilator compressor (32) configured to deliver the air flow to the ventilated patient; and

a ventilator controller (30) comprising a microprocessor programmed to generate and send a control signal to the ventilator compressor in order to deliver pressure support ventilation (PSV) to the ventilated patient.

6. The medical ventilator system of claim 5 wherein the signal combiner (52) is configured to superimpose the non-therapeutic pressure signal on the PSV control signal that is sent to the ventilator compressor (32).

7. The medical ventilator system of claim 6 wherein the signal generator (50) and the signal combiner (52) comprise said ventilator controller (30) programmed to generate and superimpose the non-therapeutic pressure signal on the PSV control signal generated by the ventilator controller.

8. The medical ventilator system of claim 6 wherein:

the signal generator (50) comprises an oscillator circuit; and

the signal combiner (52) comprises a signal combiner circuit.

9. The medical ventilator system of any one of claims 1-8 further comprising:

an inlet air hose (14) conveying the air flow from the ventilator (10) to the ventilated patient (12); and

a Y-piece or T-piece (20) connected with the discharge end of the inlet air hose to convey the air flow from the inlet air hose into the ventilated patient.

10. The medical ventilator system of any one of claims 1-9 further comprising:

a pressure sensor (40) configured to measure pressure of air inspired by or expired from ventilated patient (12);

a flowmeter (42) configured to measure air flow into or out of the ventilated patient; and

a ventilator monitor (44) comprising a microprocessor programmed to process information including at least the pressure measured by the pressure sensor and the air flow measured by the flowmeter to generate information about ventilation of the ventilated patient;

wherein the non-therapeutic pressure signal superimposed on the therapeutic respiratory pattern delivered to the ventilated patient is detectable in the pressure measured by the pressure sensor and is detectable in the air flow measured by the flowmeter.

11. The medical ventilator system of claim 10 wherein the ventilator monitor (44) is programmed to estimate respiratory system's resistance R and compliance C and respiratory muscle pressure generated by the ventilated patient based on at least the pressure measured by the pressure sensor (40) and the air flow measured by the flowmeter (42).

12. A non-transitory storage medium storing instructions readable and executable by one or more microprocessors of a medical ventilator (10) to cause the medical ventilator to perform a method comprising:

generating a non-therapeutic pressure signal; and

superimposing the non-therapeutic pressure signal on air flow delivered by the medical ventilator to a ventilated patient (12).

13. The non-transitory storage medium of claim 12 wherein the non-therapeutic pressure signal has a frequency component of at least 1 Hz.

14. The non-transitory storage medium of claim 12 wherein the non-therapeutic pressure signal is cyclical with has a cycle frequency of at least 5 Hz.

15. The non-transitory storage medium of any one of claims 12-14 wherein method further comprises:

operating the medical ventilator (10) to deliver the air flow to the ventilated patient under pressure support ventilation (PSV).

16. The non-transitory storage medium of claim 15 wherein the superimposing comprises:

superimposing the non-therapeutic pressure signal on a PSV control signal that is sent to a ventilator compressor (32) of the medical ventilator (10).

17. The non-transitory storage medium of any one of claims 12-16 wherein the superimposed non-therapeutic pressure signal is effective to impart a signal component to patient pressure and airflow measurements acquired by the medical ventilator (10), and the method further comprises:

estimating respiratory system's resistance R and compliance C and respiratory muscle pressure produced by the ventilated patient during respiration based on at least the patient pressure and airflow measurements acquired by the medical ventilator.

18. A medical ventilation method comprising:

delivering ventilation to a ventilated patient (12) using a medical ventilator (10); and

superimposing a cyclical or non-cyclical non-therapeutic pressure signal with a frequency component higher than the patient respiration rate on the ventilation delivered to the ventilated patient.

19. The medical ventilation method of claim 18 wherein the delivering comprises delivering pressure support ventilation (PSV) to the ventilated patient (12), and the method further comprises:

measuring pressure at a Y-piece or T-piece (20) coupled to the ventilated patient (12) using a pressure sensor (40);

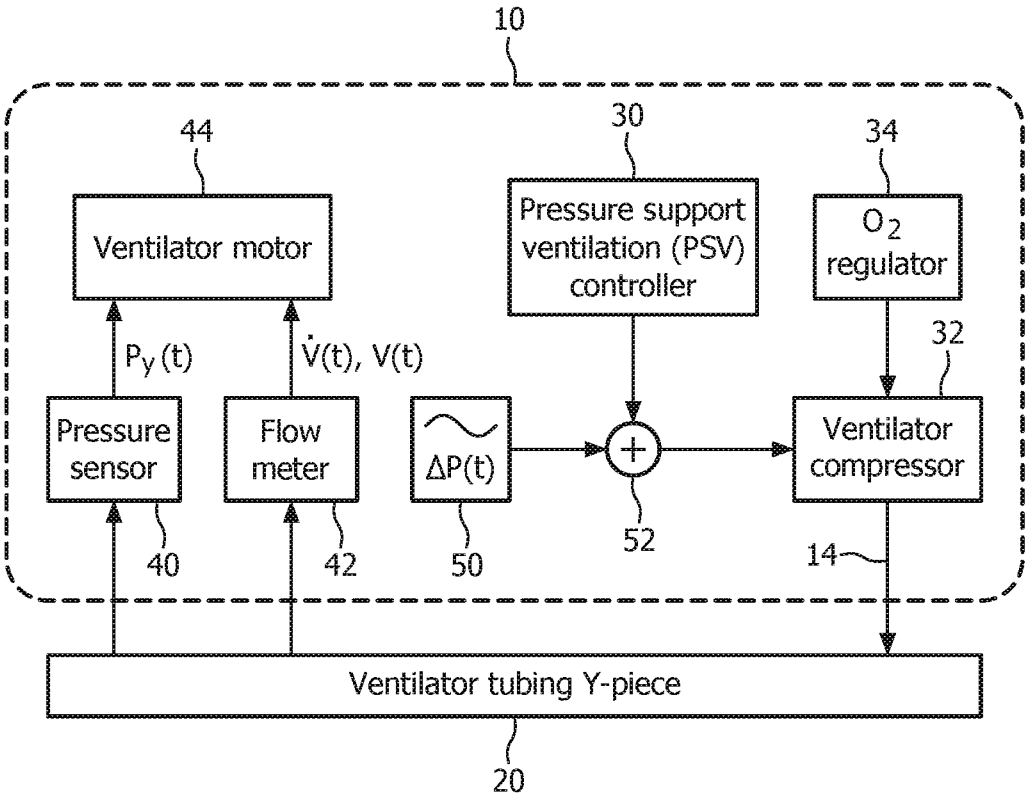
measuring air flow at the Y-piece or T-piece (20) coupled to the ventilated patient (12) using a flowmeter (42); and

computing respiratory muscle pressure produced by the ventilated patient during respiration based at least on the measured pressure and air flow.

20. The medical ventilation method of claim 19 wherein:

the computing comprises solving a system of equations formed by applying an equation of motion of the lungs to the pressure and air flow measured at a plurality of successive times, and

the superimposing comprises superimposing said cyclical or non-cyclical non-therapeutic pressure signal having a frequency component that is effective to make a data matrix of the system of equations well-conditioned.


10
44
30
34
Ventilator motor
Pressure support ventilation (PSV) controller
O_2 regulator
32
$P_y(t)$
$\dot{V}(t)$, V(t)
Pressure sensor
Flow meter
ΔP(t)
Ventilator compressor
40
42
50
52
14
Ventilator tubing Y-piece
20

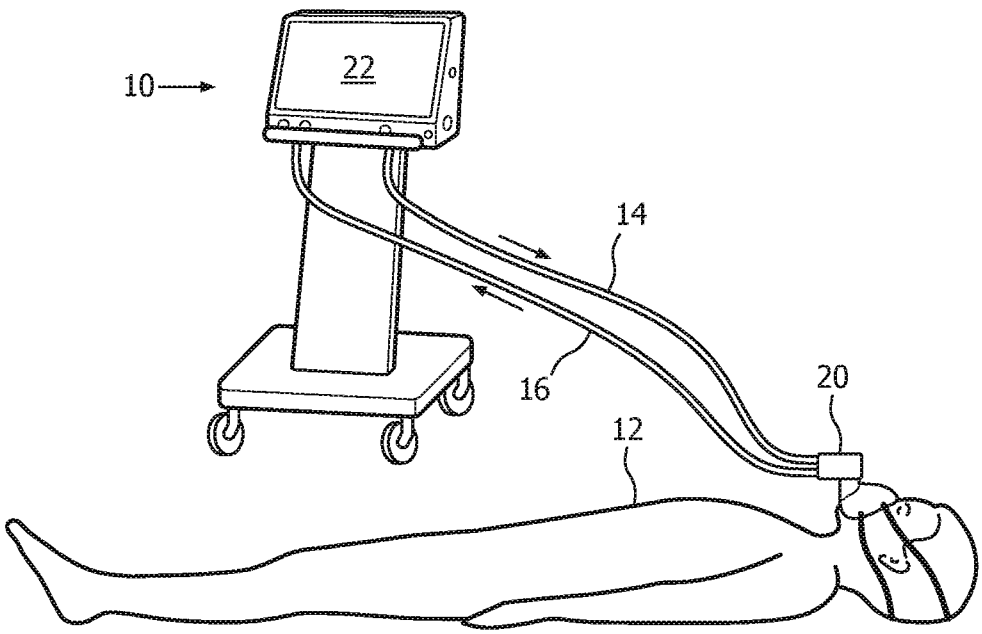

10
22
14
16
20
12

FIG. 1

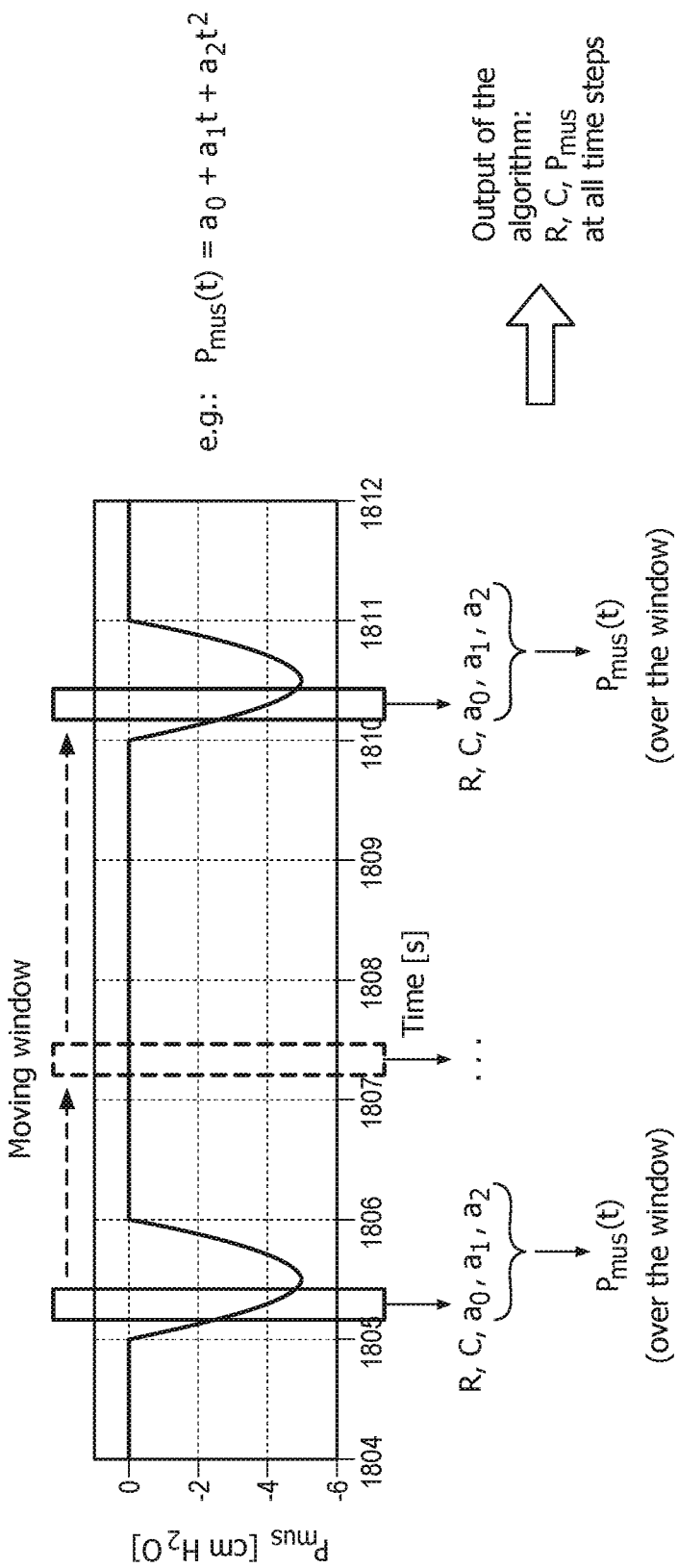

e.g.: $P_{mus}(t) = a_0 + a_1 t + a_2 t^2$
Output of the algorithm: R, C, P_{mus} at all time steps
Moving window
P_{mus} [cm H_2O]
0
-2
-4
-6
1804
1805
1806
1807
1808
1809
1810
1811
1812
Time [s]
R, C, a_0, a_1, a_2
$P_{mus}(t)$
(over the window)
R, C, a_0, a_1, a_2
$P_{mus}(t)$
(over the window)

FIG. 2

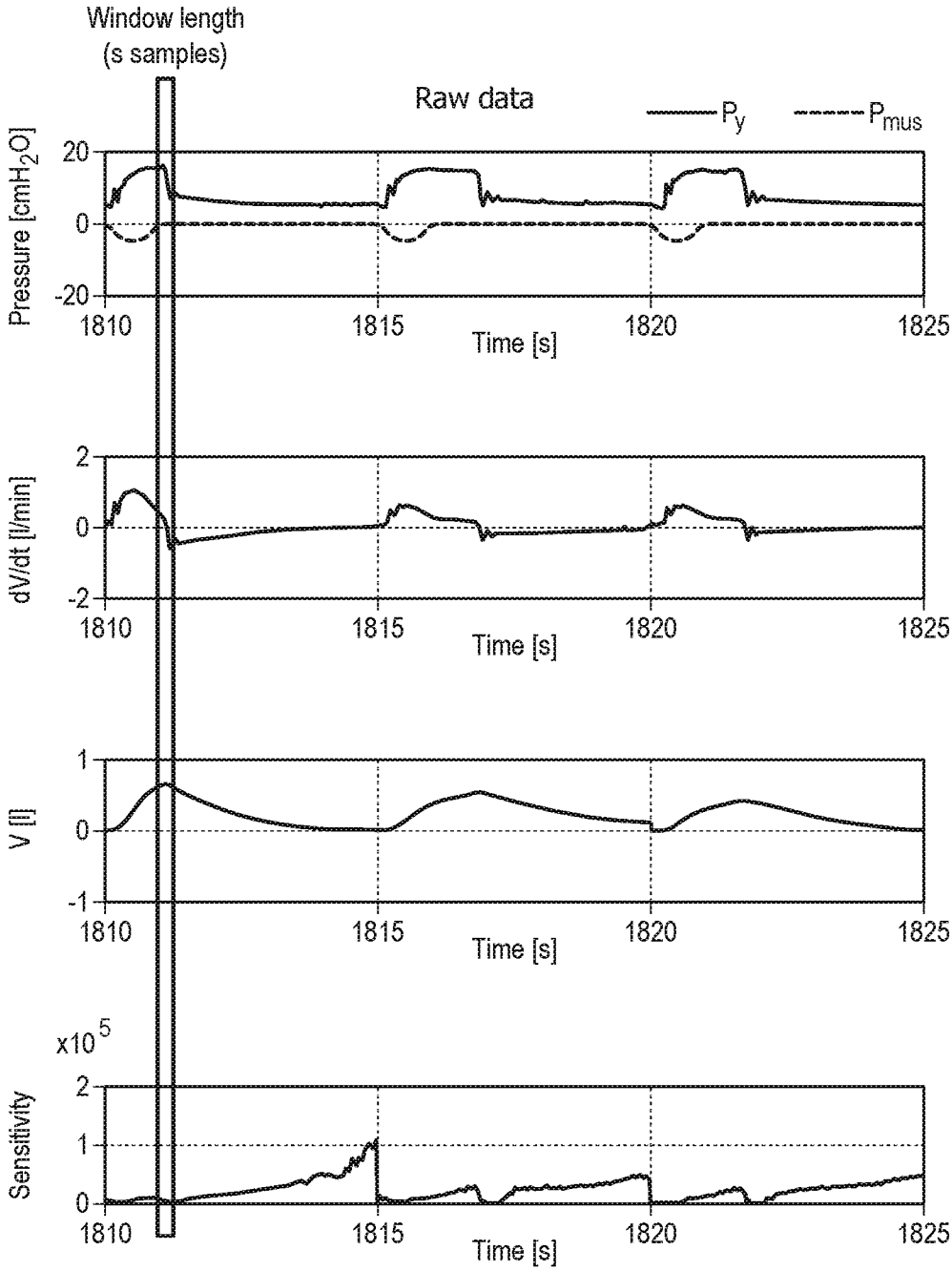

Window length
(s samples)
Raw data
P_y
P_{mus}
Pressure [cmH2O]
20
0
-20
1810
1815
1820
1825
Time [s]
dV/dt [l/min]
2
0
-2
V [l]
1
0
-1
x10^5
Sensitivity
2
1
0

FIG. 3

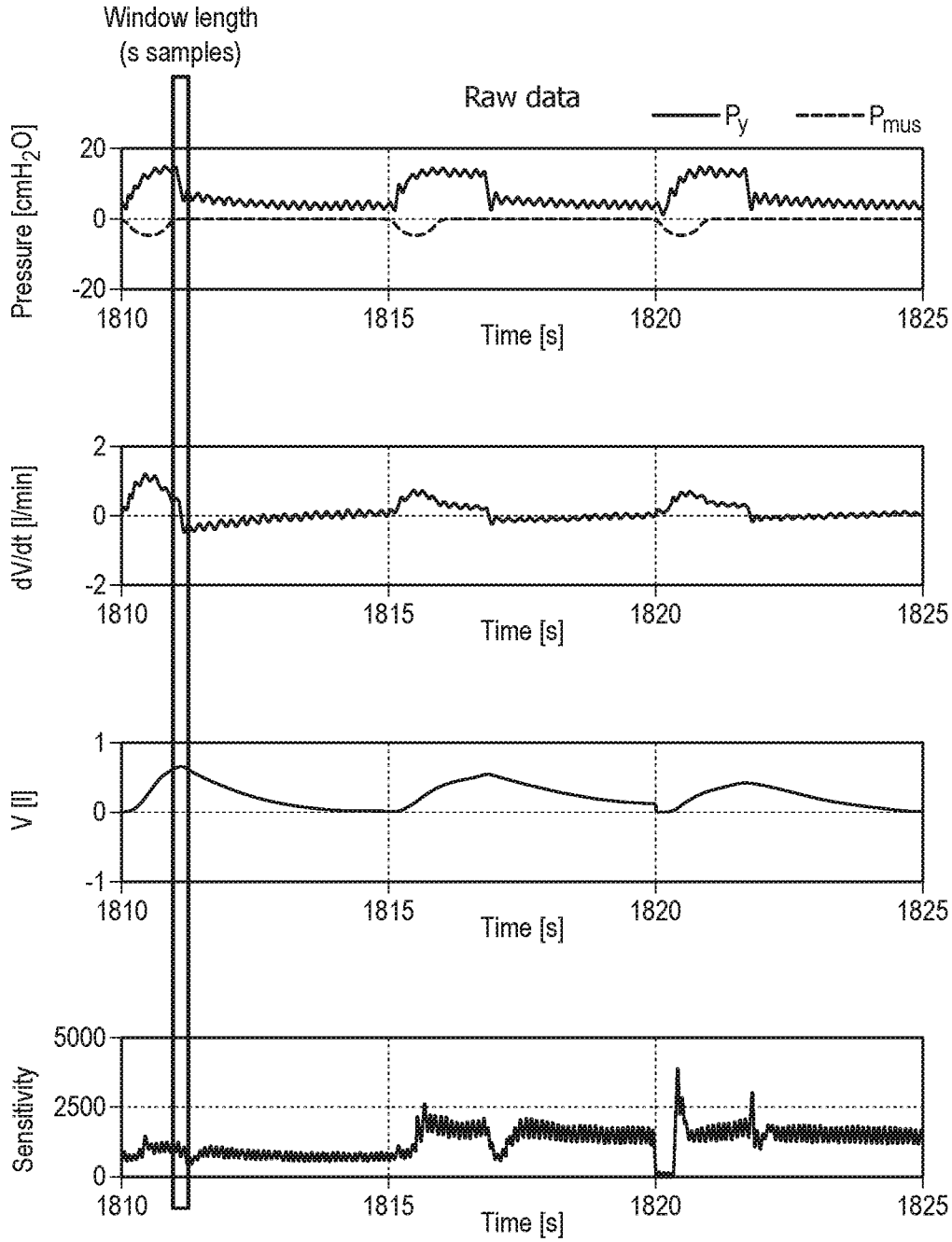

Window length
(s samples)
Raw data
P_y
P_{mus}
Pressure [cmH2O]
20
0
-20
1810
1815
1820
1825
Time [s]
dV/dt [l/min]
2
0
-2
V [l]
1
0
-1
Sensitivity
5000
2500
0

FIG. 4

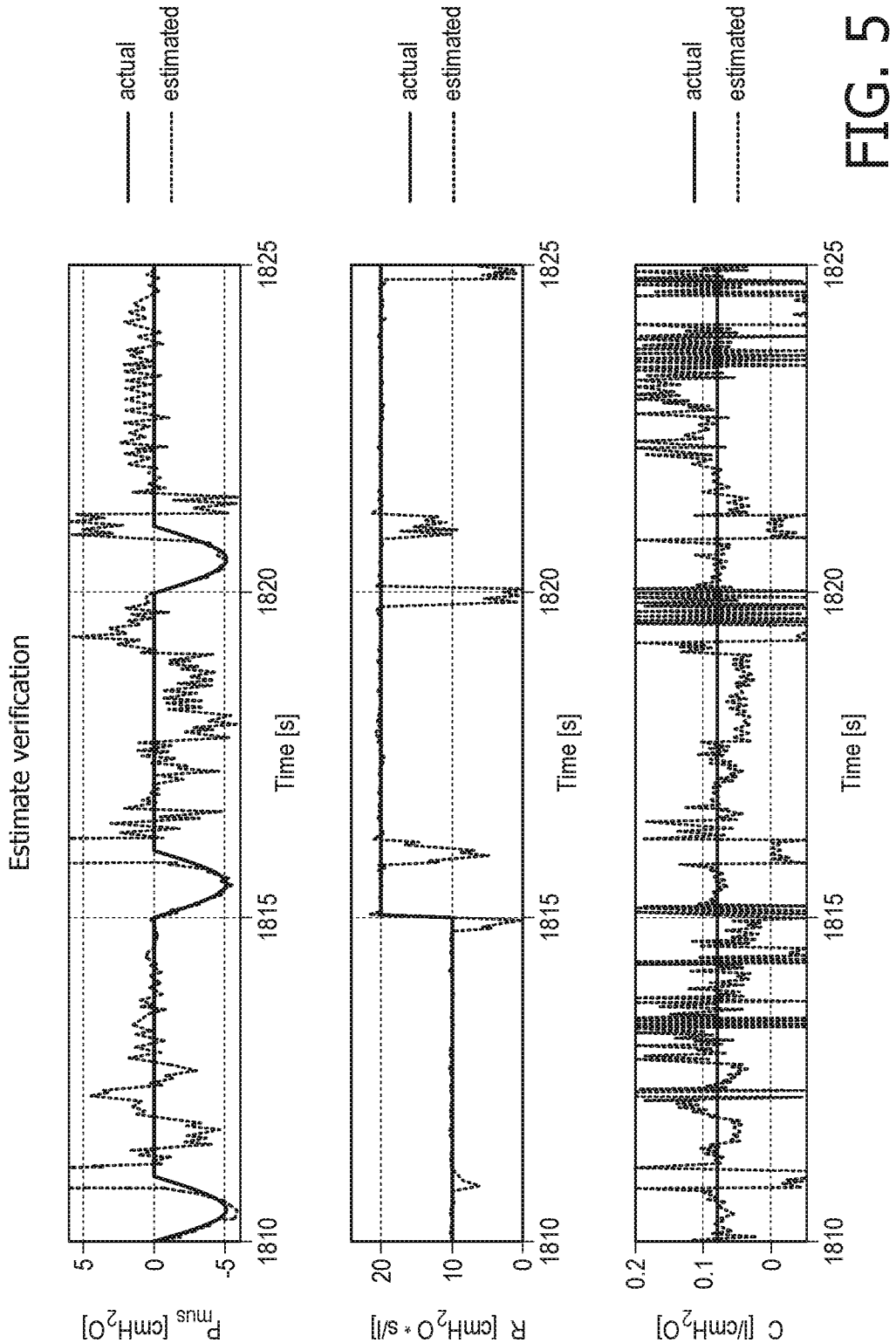

Estimate verification
actual
estimated
P_{mus} [cmH_2O]
5
0
-5
1810
1815
1820
1825
Time [s]
actual
estimated
R [$cmH_2O * s/l$]
20
10
0
1810
1815
1820
1825
Time [s]
actual
estimated
C [l/cmH_2O]
0.2
0.1
0
1810
1815
1820
1825
Time [s]

FIG. 5

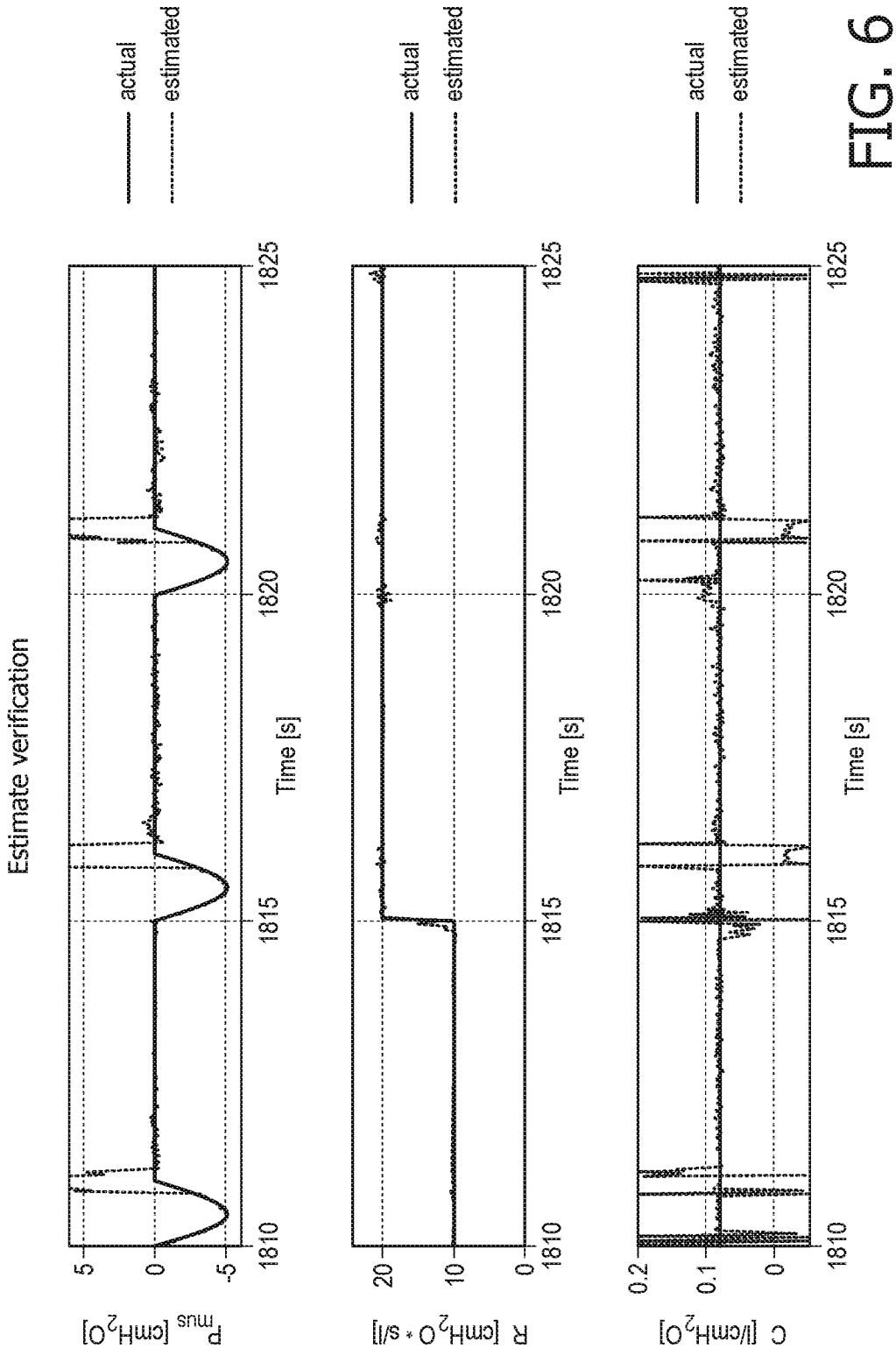

Estimate verification
actual
estimated
P_{mus} [cmH_2O]
5
0
-5
1810
1815
1820
1825
Time [s]
actual
estimated
R [$cmH_2O * s/l$]
20
10
0
1810
1815
1820
1825
Time [s]
actual
estimated
C [l/cmH_2O]
0.2
0.1
0
1810
1815
1820
1825
Time [s]

FIG. 6

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2016/050807

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61M16/00
ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61M

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6 257 234 B1 (SUN JIANGUO [US]) 10 July 2001 (2001-07-10) column 8, line 38 - column 9, line 10; figures 1-10 column 10, lines 12-35 column 11, lines 12-63 column 15, lines 13-31 column 16, lines 1-11 column 21, lines 7-33 -----	1-17
X	US 2015/027445 A1 (GARDE SMITA [US] ET AL) 29 January 2015 (2015-01-29) paragraph [0034] -----	1-17
X	US 2012/101400 A1 (KUROSAWA HAJIME [JP] ET AL) 26 April 2012 (2012-04-26) paragraphs [0051] - [0053], [0069] -----	1,2,4-17

-/--

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

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of 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	Date of mailing of the international search report
19 April 2016	11/05/2016

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

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2016/050807

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 4 821 709 A (JENSEN ROBERT L [US]) 18 April 1989 (1989-04-18) column 3, line 10 - column 4, line 8 column 14, lines 27-46 -----	1-17
A	EP 1 106 197 A2 (SIEMENS ELEMA AB [SE]) 13 June 2001 (2001-06-13) paragraphs [0003], [0004], [0005] -----	1-17

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2016/050807

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. [X] Claims Nos.: 18-20
because they relate to subject matter not required to be searched by this Authority, namely:

see FURTHER INFORMATION sheet PCT/ISA/210

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 all searchable 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.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.1

Claims Nos.: 18-20

The subject matter of claim 18 involves delivering ventilation to a patient which is considered a medical method for the treatment of the human body by therapy. Such methods are excluded from search (Rule 39(iv) PCT) and preliminary examination (Rule 67(iv) PCT). Therefore no opinion is given with regard to novelty, inventive step or industrial applicability for claim 18 and its dependent claims 19 and 20.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2016/050807

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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