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1 General model for Patient-Ventilator interactions

GENERAL MODEL FOR PATIENT – VENTILATOR INTERACTIONS

For contributed volumes

L. Heyer, and P. Baconnier. [1]

1. INTRODUCTION

Understanding and furthermore control Patient – Ventilator interactions is of great importance for partial assisted modes of ventilation. In the classical situation of entrainment of the respiratory rhythm the ventilator imposes a stable stimulation (the "Zeitgeber") on a passive patient, while in partial assisted mode the active patient acts on the ventilator and reciprocally [1-2]. It is the general problem of reciprocal interactions between a complex biological system and a complex physical system. This kind of interactions between two complex systems exhibits complex behaviors. The aims of Patient – Ventilator interactions modeling are to explain the observed interactions, to determine the physical parameters and to characterize the physiological properties affecting interactions. It implies to study both the dynamics and structural characteristics of the Patient and the Ventilator systems.

2. MODELING

For the purpose of this study, simulations of the dynamics of the Patient – Ventilator interactions are generated by a Boolean motor [2]. The Patient's respiratory rhythm is given by sequences of neural inspiratory and expiratory passive or active activity. An active inspiratory onset and inspiratory cut off activity, an active expiratory onset and an active expiratory cut off activity govern transitions between neural states (Figure 1a). The Ventilator's rhythm is given by sequences of inflation and exhalation. A Ventilator cut-off mechanism of inflation

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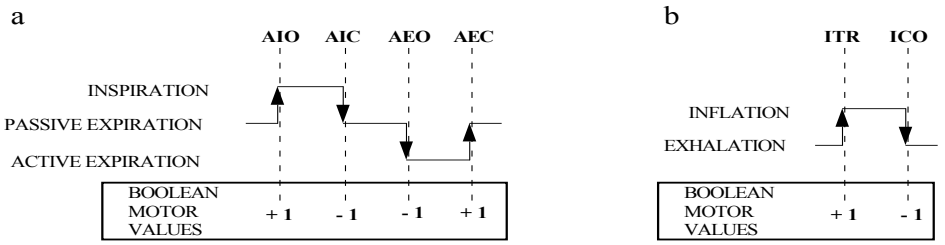

Figure 1a : Boolean motor of the respiratory neural activity. Boolean motor triggers transitions between neural states. AIO: Active inspiratory onset, AIC: Active Inspiratory cut off, AEO: Active expiratory onset, AEC: Active expiratory cut off.
Figure 1b : Boolean motor of the ventilator. Boolean motor triggers ventilator's transitions between inflation and exhalation states. ITR: Inflation trigger, ICO: Inflation cut off.

and exhalation governs transitions between the two Ventilator states (Figure 1b). Simple linear transformations of the neural activity in muscular output and mobilized volume, a constant flow inflation and the definition of the transition mechanisms according to volume allows to simulate realistic dynamics of Patient – Ventilator interactions (Matlab° program). Even though, this Boolean motor does not take into account the complex structure of the Ventilator flow generation system and the Patient volume generation system.

To investigate the impact of the model structure on the dynamics of Patient – Ventilator interactions, we develop a general mathematical model using concepts related to the Object-Oriented programming language. The Object-Oriented modeling describes Objects, each defined by its states (or attributes) and its competencies (or methods) in response to external stimulation (or messages). Thus, it allows modeling the static structure of a system by Objects and theirs relationships. The Patient – Ventilator interaction process is described as a patient's volume generator and a ventilator flow generator which both act on the passive respiratory system. For this purpose, in this model we define three objects, two active which both act on one passive object (Figure 2).

The passive object models the mechanical respiratory system with one state continuously described by the resultant volume, flow or pressure. This respiratory system's descriptor must fulfill two characteristics: One is to continuously summarize mechanical effects of the two other active objects. The other is to be continuously recognized by both generators. The passive respiratory system object's competencies are devoted to mechanical properties, which affects interactions.

The active objects are associated to their own Boolean motor, which determines transitions between object's discrete states accordingly to object's competencies. Two sets of competencies are individualized:

- One set governs transitions between object's states while no external stimulation act on the object. It corresponds to the minimum set of object's competencies required to assure

an autonomous function of his corresponding Boolean motor. For the patient's respiratory rhythm, it corresponds to an oscillator in free running configuration and for the ventilator's flow generator to a basic mode able to assure an autonomous flow or pressure generation.

- One second set of competencies is related to events able to affect the free running transitions. For the patient's respiratory rhythm those competencies formalize different type of control strategies and their actions on the transitions, which governs respiratory rhythm generation. For the ventilator's flow generator it corresponds to triggers and cut off mechanisms driven by the resultant effects of patient's activity on the respiratory system state.

3. ANALYSIS

The combination of a Boolean motor, which gives the dynamics, and an Object-Oriented modeling, which characterizes the complex static structure of the two systems, allows the study of the influences of system's structures on the Patient – Ventilator interaction dynamics.

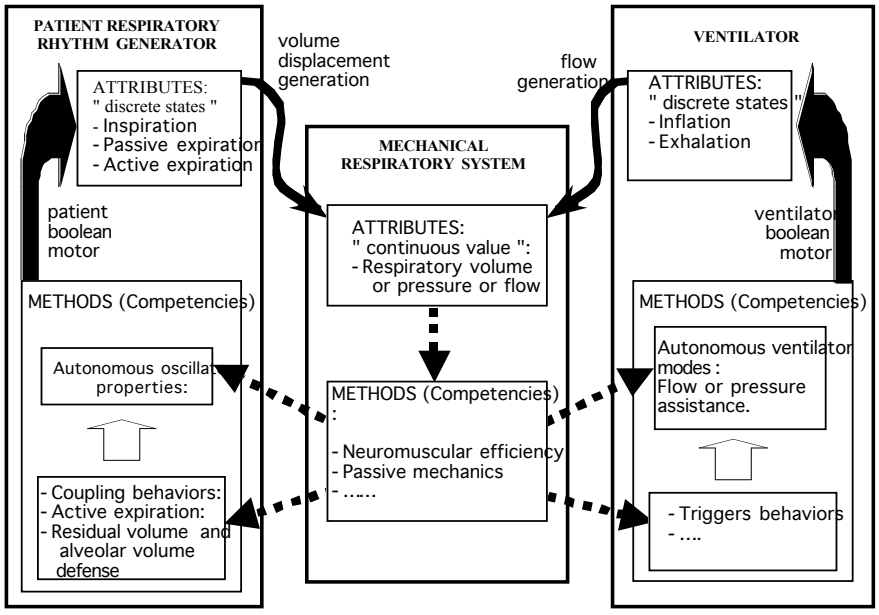

Figure 2: General diagram of the structure of the general model with schematic description of the objects, their attributes and competencies with their relationships. See text for legends and further explanations.

For this purpose we need taxonomy of the Patient – Ventilator interactions with the definition of two situations. 1) The ventilator dominates the patient or the patient dominates the ventilator. 2) The patient and the ventilator disclose interactions:

- The first situation describes two extreme clinical situations, one related to an absence of any patient's volume generation and the other to an absence of ventilator flow generation which is qualitatively equivalent to a spontaneous breathing situation. By extension, this situation also corresponds to cases where the patient's or the ventilator's activity don't affect the activity of the other one. In the model, those cases are well characterized by the work of one of the two Boolean motors in his autonomous mode. In those cases, one Boolean motor in his autonomous mode act on the other one but not the reciprocal, thus there is no interactions between the two Boolean motors. When the ventilator's activity is in an autonomous mode, the ventilator dominates the patient whatever his activity. When the patient's activity affect the ventilator's activity and when the patient's respiratory rhythm is in autonomous mode, the patient dominates the ventilator.
- In opposition, when the patient's activity affect the ventilator's activity but when the patient's respiratory rhythm is also affected by some patient's competencies, the patient and the ventilator disclose interactions.

Further clinically relevant classifications of interactions need to define a synchronous functioning situation and to characterize the fact that one generator drives the other. It allows to identify when the patient synchronously drives the ventilator or the reciprocal.

- A first Boolean motor drives the second one when all transitions from one state to another of the second Boolean motor arise in response to transitions of the first Boolean motor.
- Two Boolean motors interact synchronously when each transition of one Boolean motor is followed by a transition in the other. Nevertheless, two Boolean motors could be synchronous while we are unable to determine which Boolean motor drives the other. It is the case when one first Boolean motor drives one type of transition of the second motor and when simultaneously the second motor drives a transition of the first motor.

To have clinical applications, those definitions require the choice of minimal observation duration for the interaction's dynamics and of a hierarchy between different transition's states of the two Boolean motors. In the respiratory physiology field the inspiration or the inflation are highlighted and it's classical to use as a reference duration a respiratory cycle defined by the temporal duration between two successive inspiration onsets. Thus, patient drives the ventilator if an inflation always follows an inspiration whatever the modalities used for the expiratory or exhalation transitions. When each inspiration is followed by an inflation, the patient synchronously drives the ventilator. Consequently, a ventilator drives the patient if the patient never triggers inflation. When each inflation causes a patient's response that affects the ventilator's dynamics, the ventilator synchronously drives the patient. This case supposes that the patient's activity triggers the cut off mechanism of inflation. In case of ventilator's mode with a cut off mechanism insensitive to patient's activity like in volume control mode, the ventilator cannot drive the patient but could only dominate it.

4. RESULTS

In figures 3, a clinical example is shown with a qualitatively equivalent result generated with our model by an appropriate choice of its variables. For both clinical example and simulation, the corresponding states of the ventilator and patient's Boolean motor are shown.

5. DISCUSSION

This general model is developed as an investigator tools devoted to the Patient – Ventilator interactions description and analysis. The first objective of the model is to disclose realistic interactions qualitatively equivalent to the observed Patient – Ventilator interactions. As other models in that field, this model is based one a classical mechanical ventilation/respiratory system representation composed of a ventilator flow generator and a patient's volume displacement generator which both act on a passive respiratory system [3]. We restrict the structure of the model at only three major objects, two actives and one passive, all of them with limited states but with multiple competencies. In the active object one first set of competencies is introduced only to provide to a Boolean motor an autonomous mode of functioning in absence of any interactions. In opposition, a second set of competencies and their relationships are directly concerned with the problem of patient – ventilator interactions. This hierarchical structure facilitates a characterization of the interactions and provides basis for a classification approach.

With this model, interactions between the two generators result from the fact that each generator affects the other through a passive object. This passive object is only characterized by his mechanical properties while the generators are each characterized by two different functional parts. One part is a motor which gives the dynamics and one other part is concerned by regulatory functions which formalize control procedures that affects the motor's dynamics. This first allows for each generator to dispose of an autonomous mode in absence of any interactions when the generator is not influenced by the action of the other on the passive respiratory system. This particularity gives an easy way to distinguish interactions from domination. It also allows for the generator motor to dispose of different functional states with the introduction of some particular behaviors. This particularity distinguishes our model from others based on a patient generator output that can only be down regulated [4,5]. By this way, as in the model of Y. Yamada ET col., our model allows changes in the patient's generator behaviors with the introduction of an active expiratory state [6].

In our model we suppose that the nature of the interaction mainly depends on the ability of one generator to continuously detect actions of the other on the passive system. For this purpose, the passive system is characterized by continuous variables that may affect the autonomous mode of each generator. The existence of this continuous variable and its effects are crucial for the interaction dynamic. In the model of E. Giannouli ET col., this variable is not used when the PAV (Pressure Assist ventilation) mode is simulated [5]. As results, the simulations are restricted to only one type of interactions: the patient drives the ventilator.

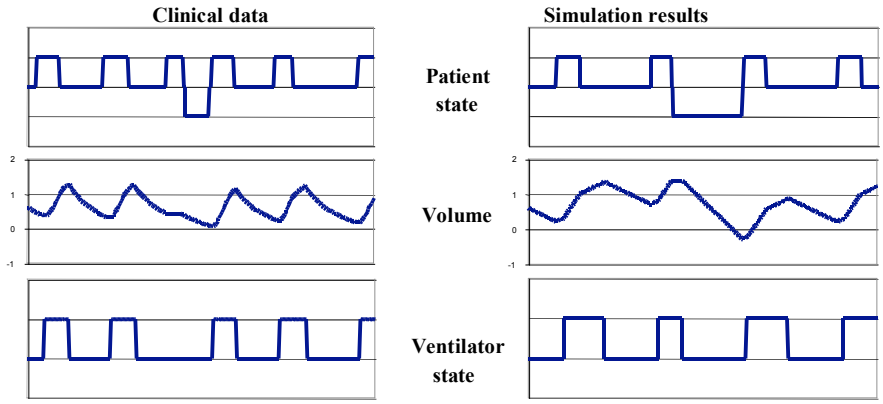

Figure 3: Left : volume signal recorded on a patient undergoing assisted ventilation together with its associated central respiratory (Patient) and ventilator states. Right:: simulated data obtained with an appropriate choice of model parameters

A definition of the patient's generator output as a volume displacement generator and the description of the passive respiratory system described by a unique variable, the lung volume, allows a detailed analysis of the patient – ventilator interactions. In the model, this volume displacement output is generated by the integration of Boolean neural value. The description of the passive respiratory system by a volume variable is a simple way to formalize regulatory functions of the patient's generator since some of the major chemical or non chemical control's systems loops could be defined with volume variables. Similarly, the trigger or cut off mechanisms of the ventilator may be defined through threshold values obtained as a flow – times duration product.

With this model we are able to describe all type of Patient – Ventilator interactions given by our taxonomy and thus analysis the determinant factors that can affects each type of interactions. In addition, those Patient – Ventilator interactions interaction still corresponds to relevant clinical situations.

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2 Ventilatory support: a dynamical systems approach.

VENTILATORY SUPPORT: A DYNAMICAL SYSTEMS APPROACH

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ABSTRACT

Misunderstanding of the dynamical behavior of the ventilatory system, especially under assisted ventilation, may explain the problems encountered in ventilatory support monitoring. Proportional assist ventilation (PAV) that theoretically gives a breath by breath assistance presents instability with high levels of assistance. We have constructed a mathematical model of interactions between three objects: the central respiratory pattern generator modelled by a modified Van der Pol oscillator, the mechanical respiratory system which is the passive part of the system and a controlled ventilator that follows its own law. The dynamical study of our model shows the existence of two crucial behaviors, i.e. oscillations and damping, depending on only two parameters, namely the time constant of the mechanical respiratory system and a cumulative interaction index. The same result is observed in simulations of spontaneous breathing as well as of PAV. In this last case, increasing assistance leads first to an increase of the tidal volume (V_T), a further increase in assistance inducing a decrease in V_T, ending in damping of the whole system to an attractive fixed point. We conclude that instabilities observed in PAV may be explained by the different possible dynamical behaviors of the system rather than changes in mechanical characteristics of the respiratory system.

1. INTRODUCTION

Breathing in humans relies on a neural network located in the brainstem and on the mechanical respiratory system, both constituting the ventilatory system (Figure 1). The oscillatory activity of the central respiratory pattern generator (CRPG) induces the rhythmic contractions of the respiratory muscles (mainly diaphragm) which, in turn, periodically inflate the lungs. Sensory inputs can modulate respiratory rhythm and pattern (Bianchi *et al*., 1995; Jammes, 2000). For example, chemical regulations allow the ventilatory system to adapt breathing to changes in metabolic state. Together with the ventilatory system, these regulatory mechanisms constitute what is usually called the respiratory system.

Although the description of the mechanical respiratory system and of the links between different elements of the whole system are well known, controls involved in the dynamical behavior of the whole system are still misunderstood and even unknown. Such knowledge becomes moreover crucial in the context of assisted ventilation wherein the aims of which are not only homeostasis but also barotraumatism minimizing and respect of patient's respiratory drive (Chopin and Chambrin, 1994). Important advances in the understanding of respiratory pathologies

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and ventilator management especially in the assisted mode have been made using models of the respiratory system. Pham Dinh *et al*. (1983) and Dang-Vu *et al*. (2000) have used an empirical approach. They have developed mathematical models of non-linear oscillators to build a system of differential equations the properties of which have to fit experimental data. The resulting models allow a good description of the system dynamics but involve the use of hidden variables (variables that have no counterpart in the real world). An object-oriented approach has been recently proposed by Heyer and Baconnier (2001). The proposed model, involving Boolean motors, mimics the patient-ventilator interactions using three objects representing respectively the central respiratory rhythm generator, the respiratory mechanical system and the ventilator. Due to its simplicity and intuitiveness, this approach allows a precise description of various patient-ventilator interaction patterns but does not contain a method to predict their occurrence.

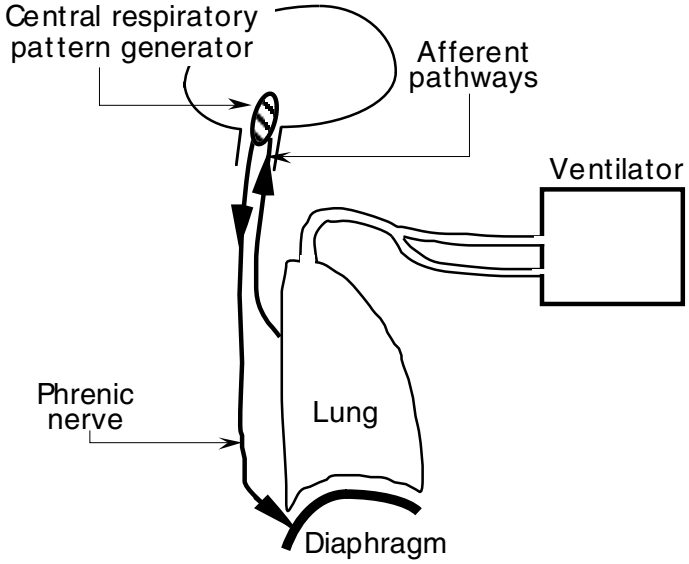

Figure 1. Schematic view of the interaction between the human ventilatory system and a ventilator. The central respiratory drive originating from the central pattern generator is supplied to the diaphragm through the phrenic nerve (efferent pathways). Afferent pathways coming from the lung parenchyma, the respiratory airways and the thoracic muscles bring information on the mechanical state of the system to the centers. The ventilator modifies the state of the mechanical system by providing changing positive pressure at the opening of respiratory airways.

Alternatively, more explicit approaches have been developed. For example, Younes and Riddle (1981) suggest a mathematical formalization of the numerous elements of the ventilatory system. Similarly, Ilya *et al*. (1997) propose a detailed model of CRPG using neural interactions. The main limitation of these approaches is the large number of parameters, which complicates analysis and makes the identification of the key parameters impossible.

We present a continuous mathematical model which contains the advantages of the above approaches: 1) the physiological meaning of variables and parameters using the object-oriented representation described by Heyer and Baconnier (2001); and 2) the ability to study the system dynamics using a set of differential equations similar to Pham Dinh *et al*. (1983). The stability of the mathematical system was investigated first. The behavior of this model was subsequently compared to different experimental situations such as vagotomy and PAV. A vagotomy experiment has been simulated by suppressing CRPG sensitivity to mechanical state. In PAV the ventilator generates pressure in proportion to the patient's effort (Younes, 1992). In our model we have implemented such a situation by adding, to the pressure generated by respiratory muscles, a positive pressure proportional to the resistive and elastic pressures the respiratory muscles have to overcome.

2. METHODS

The object oriented approach

In this approach, the Patient–Ventilator interaction process is described as a patient's respiratory pattern generator and a ventilator (active elements) which both act on a passive system (Figure 2). The passive object models the mechanical respiratory system characterized by its volume, flow and pressure.

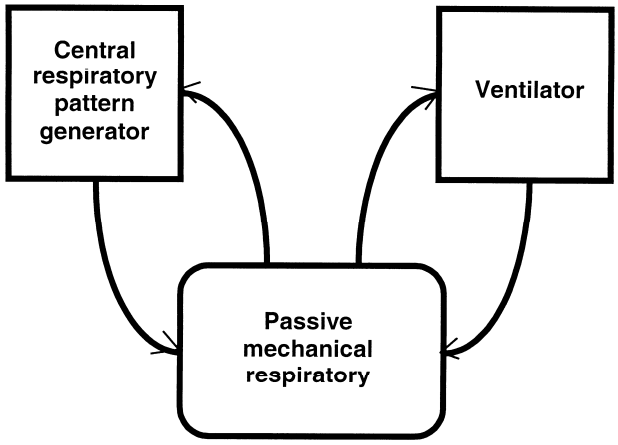

Figure 2. Diagram of interactions between CRPG, the mechanical ventilatory system and a ventilator.

The central respiratory pattern generator (CRPG)

The Van der Pol oscillator has been proposed as basis for modeling the respiratory rhythm generator (Linkens, 1973; Pham Dinh *et al*., 1983). We have used the modified Van der Pol oscillator developed by Pham Dinh *et al*. (1983) as a model of the CRPG when submitted to periodic perturbations:

$$\begin{cases} \dfrac{dx}{dt} = \dot{x} = h(y) \cdot x - g(y) + P(t) \\ \dfrac{dy}{dt} = \dot{y} = x \end{cases} \tag{1}$$

with
$$h(y) = \frac{1}{2} \cdot \frac{1 - y^2}{1 + 3y^2} \tag{2}$$

and
$$g(y) = \begin{cases} y \cdot \dfrac{1 + 0.08\,y}{1 + 1.8\,y} & y > 0 \\ y \cdot \dfrac{1 - 0.2\,y}{1 + 0.4\,y^2} & y < 0 \end{cases} \tag{3}$$

where t is time. When $y < 0$ (respectively $y > 0$) the oscillator is considered in inspiratory (respectively expiratory) phase. The periodic perturbations appear with the forcing term $P(t)$ in equation (1). In our model x is still a hidden variable but y is considered to be the CRPG output.

The passive mechanical respiratory system

In its simplest form, the human mechanical respiratory system is depicted as a single homogeneously ventilated alveolar compartment of a fixed elastance connected to a rigid airway of a fixed resistance (Otis *et al*., 1956). The differential equation of such a system satisfies can be written as:

$$P_{dr} = \mathrm{E} \cdot z + \mathrm{R} \cdot \frac{dz}{dt} \tag{4}$$

where z is the lung volume (l), E the elastance ($cmH_20.l^{-1}$) of the alveola, R the resistance of the tube ($cmH_20.l^{-1}.s$) and P_{dr} the driving pressure (cmH_20) that needs to be generated to impose lung volume and flow.

The interactions

As is shown in Figure 2, the two active elements can affect the state of the passive one. The driving pressure P_{dr} is then given by the sum of the pressure generated by respiratory muscles (P_{mus}) and that generated by the ventilator (P_{vent}):

$$P_{dr} = P_{mus} + P_{vent} \tag{5}$$

Putting equation (5) in (4) we have:

$$\frac{dz}{dt} = \dot{z} = -\frac{\mathrm{E}}{\mathrm{R}} \cdot z + \frac{P_{mus} + P_{vent}}{\mathrm{R}} \tag{6}$$

When the afferent pathways are functional, the respiratory pattern generator activity can be modulated by the lung volume variations. As proposed by Pham Dinh *et al*. (1983), this sensitivity of CRPG to the mechanical state is taken into account by the addition of a forcing term in equation (1). However, instead of using a time-dependent term P(t) (see equation (1)) as in Pham Dinh *et al*. (1983), the effect of the mechanical system state on the CRPG (P) now depends on flow:

$$P(\dot{z}) = \mathrm{A} \cdot \dot{z} \tag{7}$$

A is a constant ($cmH_20.l^{-1}.s$). This is still in agreement with the original model (Pham Dinh *et al*., 1983) where the periodic perturbation was proportional to the flow imposed on the lungs.

The respiratory muscles

The pressure generated by the respiratory muscles is the result of the conversion by the muscles of the respiratory pattern generator output into a pressure; P_{mus} is then a function of y. This function has been taken to be as simple as possible to be:

$$P_{mus}(y) = -\mathrm{B} \cdot y \tag{8}$$

where B is a positive constant (cmH_20) and the minus in the equation (8) is a convention allowing us to have a positive pressure in the inspiration phase (y negative).

The ventilator

During spontaneous ventilation, no ventilator is connected to the patient and then $P_{ven} = 0$. When connected, the ventilator acts on the mechanical ventilatory system with a pressure P_{vent} which is a function of time and, in assisted ventilation, of the passive mechanical system state (characterized by z and $\dot{z}$). In PAV mode the ventilator generates a P_{vent} proportional to the flow $(\dot{z})$ and instant volume (z) that the patient breathes in.

$$P_{vent} = k_1 \cdot \mathrm{E} \cdot z + k_2 \cdot \mathrm{R} \cdot \dot{z} \tag{9}$$

where k_1 and k_2 are adjustable gain parameters. Using $k_1 = k_2 = \gamma$ (a classical clinical setting), we have:

$$P_{vent} = \gamma \cdot (\mathrm{E} \cdot z + \mathrm{R} \cdot \dot{z}) \tag{10}$$

where γ gives the percentage level of assistance.

The resulting dynamical system

Putting together equations (1) to (10) gives the following dynamical systems:

- under PAV:

$$\begin{cases} \dot{x} = h(y) \cdot x - g(y) + \mathrm{A} \cdot \dot{z} \\ \dot{y} = x \\ \dot{z} = -\dfrac{\mathrm{E}}{\mathrm{R}} \cdot z - \dfrac{\mathrm{B} \cdot y}{\mathrm{R} \cdot (1 - \gamma)} \end{cases} \tag{11}$$

- during spontaneous ventilation:
  the system is a limiting case of equation 11 by setting $\gamma = 0$.

A and B (and γ with PAV) quantify the level of the interactions between respiratory pattern generator and the mechanical respiratory system.

Computing method

All simulations have been made with Matlab® 5.2.11. Differential equations have been solved using the fourth order Runge Kutta method. The integration step used is 0.1s and the initial values used are $x_0 = 1$ (no unit), $y_0 = 3$ (no unit) and $z_0 = 0.5$ l. The A and B parameter values have been taken to be as simple as possible, A = 1 $cmH_20.l^{-1}$.s and B = 1 cmH_20. Values of other parameters are specified in figures depending on the case.

3. RESULTS

Qualitative analysis: dynamical study of the breathing system under PAV

Our system has only one fixed point for $\begin{pmatrix} x \\ y \\ z \end{pmatrix} = \mathbf{X}^* = \{0;0;0\}$. The stability property of a fixed point is given by the eigenvalue(s) (λ_i) of the jacobian matrix (J) of the system. A stable fixed point must satisfy the condition: $\forall\, i\ \Re e(\lambda_i) < 0$.

The expression of the jacobian matrix of the system (11) using equations (2) and (3) is:

$$\mathbf{J} = \begin{vmatrix} h(y) & \dfrac{\partial h(y)}{\partial y}\cdot x - \dfrac{\partial g(y)}{\partial y} - \dfrac{\mathrm{B}\cdot\mathrm{A}}{\mathrm{R}(1-\gamma)} & -\dfrac{\mathrm{E}}{\mathrm{R}}\cdot\mathrm{A} \\ 1 & 0 & 0 \\ 0 & -\dfrac{\mathrm{B}}{\mathrm{R}(1-\gamma)} & -\dfrac{\mathrm{E}}{\mathrm{R}} \end{vmatrix}. \qquad (12)$$

The characteristic polynomial of the jacobian in the neighborhood of the fixed point is:

$$\lambda^3 + \lambda\left(\beta - \frac{1}{2}\right) + \lambda\left(1 - \frac{1}{2}\cdot\beta - \alpha\right) + \beta = 0 \qquad (13)$$

where $\alpha = -\dfrac{\mathrm{A}\cdot\mathrm{B}}{\mathrm{R}(1-\gamma)}$ (cmH_2O) and $\beta = \dfrac{\mathrm{E}}{\mathrm{R}}$ (s^{-1}). This polynomial depends on only two parameters, α may be considered as a cumulative interaction index while β is simply the time constant of the mechanical respiratory system.

Thus, according to the Routh-Hurwitz criterion, the fixed point $\mathbf{X}^* = \{0;0;0\}$ is stable if and only if

$$\begin{cases} \beta > \frac{1}{2} \\ \alpha < 1 - \beta \left(\frac{1}{\beta - \frac{1}{2}} + \frac{1}{2} \right) \end{cases}. \quad (14)$$

These conditions underline the existence of two areas in the (α,β) plane (Figure 3) for values of parameters with physiological meaning ($\alpha < 0$ and $\beta > 0$ and no high magnitude).

- For $\alpha > 1 - \beta \left(\frac{1}{\beta - \frac{1}{2}} + \frac{1}{2} \right)$, the fixed point is unstable and simulations show the existence of a limit cycle.

- For parameter values in the stable fixed point area, $\alpha < 1 - \beta \left(\frac{1}{\beta - \frac{1}{2}} + \frac{1}{2} \right)$, all trajectories tend to the fixed point.

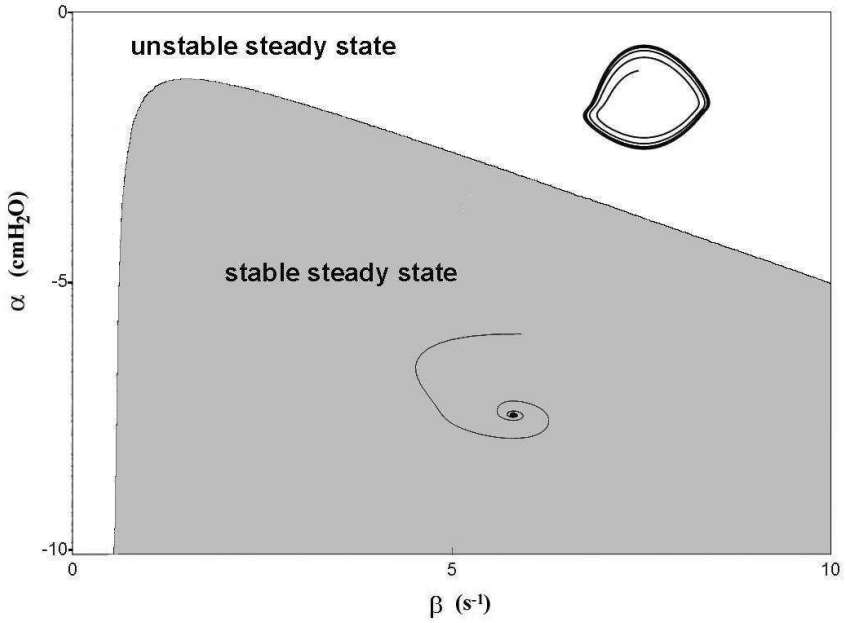

Figure 3. Diagram of stability as a function of parameters α and β. Stability is given around the fixed point **X*** = {0 ;0 ;0} for $\alpha \in$ [-10 ;0] and $\beta \in$ [0 ;10]. In the white area the fixed point is unstable and the system showed a limit cycle. In the grey area the fixed point is stable, all trajectories tend to it.

Simulation of a vagotomy

The vagus nerves are the anatomical support of afferent pathways (Figure 1) bringing information on the state of the mechanical respiratory system back to CRPG. Vagotomy interrupts this loop and usually results in a specific change in ventilation: the respiratory rhythm decreases while tidal volume (volume inspired and expired with each normal breath) increases (Coleridge and Coleridge, 1986). We simulated vagotomy by setting the value of A in equation (11) to zero during a simulation of spontaneous ventilation (no PAV, $\gamma = 0$). The simulation results (Figure 4) clearly exhibit a behavior that reproduces the experimental observations: before vagotomy (A = 1 $cmH_20.l^{-1}.s$), the period of the system is 10 s and the tidal volume (V_T) is 0.5 l, after (A = 0 $cmH_20.l^{-1}.s$) the period is around 13 s and the tidal volume is 0.8 l.

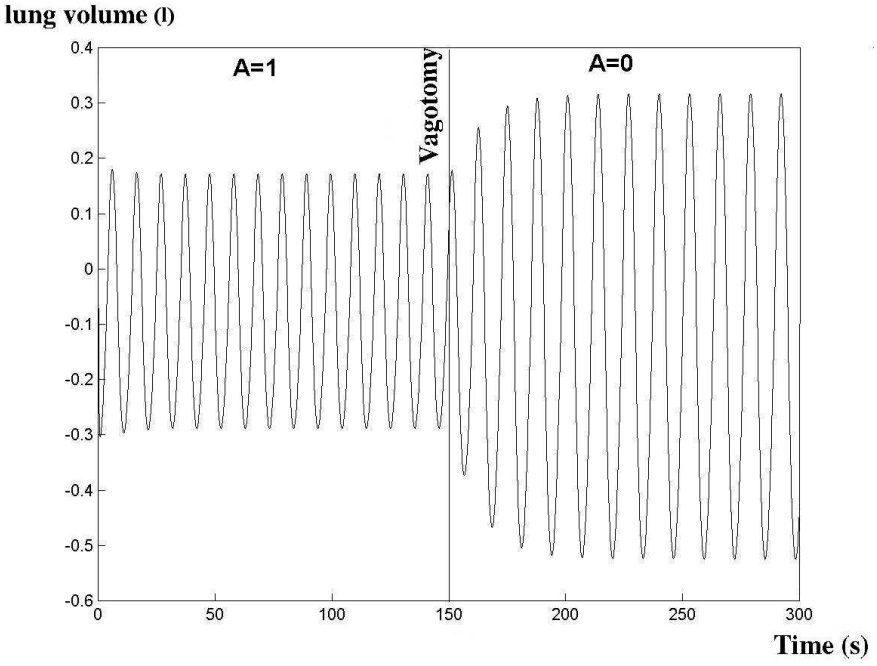

Figure 4. Lung volume variation under vagotomy simulating. Parameters values used are B = 1 cmH_20, E = 10 $cmH_20.l^{-1}$, R = 2 $cmH_20.l^{-1}.s$. Vagotomy is simulated at t = 150s by changing A value from A = 1 $cmH_20.l^{-1}.s$ to A = 0 $cmH_20.l^{-1}.s$.

Effect of PAV mode

Any increase in percentage level of assistance (γ) brings the representative point (β,α) down. If this point is above the limit between unstable and stable regions before PAV is applied, PAV may bring this point to the stable region. We have simulated the effect of increasing levels of PAV assistance on two conditions: in a healthy subject and in a patient suffering from pulmonary edema, renal failure and chronic obstructive

pulmonary disease (COPD) (patient number 2 in Marantz *et al*., 1996). Table 1 gathers the corresponding parameters and the resulting β and α threshold values.

Table 1. Characteristic parameters for a healthy subject and a patient. E is given in $cmH_20.l^{-1}$, R in $cmH_20.l^{-1}.s$, β in s^{-1}, α threshold in cmH_20. Only looping parameters involved in α change in healthy subject and patient. α threshold corresponds, for a given β value, to the threshold value of α for which the fixed point is stable or unstable $\left(\alpha = 1 - \beta\left((1/(\beta - \frac{1}{2})) + \frac{1}{2}\right)\right)$.

Parameters	E	R	β	α Threshold
Healthy Subject	10	2	5.00	-2.61
Patient	20	9	2.22	-1.40

Simulation of PAV ventilation with different levels of assistance (Table 2) on a healthy subject demonstrates a decrease in the magnitude of y from its value (100%) in spontaneous breathing (SB) ($\gamma = 0$) to 0 for a 90% level of assistance ($\gamma = 0.9$). At the same time V_T increases up to 134% V_T in SB for a 60% level of-assistance and decreases to 0 for a 90% level of assistance. Thus, for 90% level of assistance, α is under its threshold (Table 1), which leads to the damping of the system (Figure 3).

In the pathological case, increasing PAV simulation (Table 2) shows a decrease in the magnitude of y as in a healthy subject. Similarly V_T increases up to a 80% level of assistance and decreases for 90% level of assistance. The essential difference is that α never goes below its threshold value whatever the percentage level of PAV assistance. Hence the damping of the system, due to the presence of a stable fixed point, has not been reached.

Table 2. Quantified effect of PAV. PAV is given in percentage of assistance (γ parameter), α in cmH_20, the CRPG output (y) in percentage of y in spontaneous breathing (SB), tidal volume (V_T) in percentage of V_T in SB. Parameters used to characterize a healthy subject and patient are given in Table 1.

PAV (% of assist)	Healthy Subject			Patient		
	α	y (% of y in SB)	V_T (% of V_T in SB)	α	y (% of y in SB)	V_T (% of V_T in SB)
0	-0.50	100	100	-0.11	100	100
50	-1.00	61	130	-0.22	77	154
60	-1.25	48	134	-0.28	68	171
70	-1.67	32	128	-0.37	57	192
80	-2.50	9	65	-0.56	40	211
90	-5.00	0	0	-1.11	13	164

4. DISCUSSION

In this work we have established a mathematical model for the study of the interaction between the CRPG and the mechanical respiratory system. Moreover, the model may be used when the system is under assisted ventilation. In a first step the simulation of vagotomy on the ventilatory system exhibits a good qualitative resemblance to experimental data as described by Coleridge and Coleridge (1986). Sectioning of the pneumogastric nerve leads to decreased respiratory frequencies and to increased respiratory magnitudes.

Simultaneously, the dynamical study of the ventilatory system shows two different states, a physiological one and a pathological one according to the value of two parameters: α, the feedback parameter and β, the time constant parameter.

Moreover, increase in feedback (the modulus of the value of α) implies an increase in the frequency and a decrease in the magnitude until a threshold for which oscillations damp down (Figure 3), as is found in the case of fall of respiration and period of apnea of Cheyne-Stokes breathing (Cherniack and Longobardo, 1986).

In a second step we have investigated the effect of a new ventilatory assistance mode, PAV. In this case, the stability is obtained under the same conditions than those found for the ventilatory system alone, except the α parameter which includes γ (level of assistance). Thus, increase of assistance unavoidably leads, for high levels, to the damping of respiration. For simplicity of the dynamical study we have considered both the inspiratory and the expiratory phase as active, as well as PAV efficient during inflow and outflow. However with only active inspiration and efficient PAV during inflow, the model leads to runaway phenomena as described by Marantz *et al*. (1996) in some cases of high levels of assistance.

As long as the stability parameter values remain in the limit cycle area, an increase in level of PAV reduces CRPG work and, accordingly, inspiratory muscle effort as described by Navalesi *et al*. (1996). On the contrary, increase in level of PAV assistance induces lung volume increase until a certain value for which a paradoxical decrease in V_T appears close to the stable fixed point area. This phenomenon has been noted by Marantz *et al*. (1996).

Our model suggests that instabilities occurring during PAV apparently involve intrinsic properties of the patient ventilator interaction process (Figure 2) rather than variation of mechanical respiratory system properties. Thus, changes in elastance and resistance, such as changes in respiratory neural output, muscle pressure, lung state interactions, may be considered as perturbations that lead to different oscillatory or damping behavior of the system.

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3 Choix des paramètres de la fonction ApEn(N,r,M) de Pincus.

Le calcul d'ApEn demande un choix approprié des paramètres de la fonction. Il s'agit d'abord du paramètre « r » qui fixe le filtre des artéfacts extraordinaires. Pour les séquences biologiques de type activité cardiaque ou respiratoire, « r » est une valeur fixée à une fraction de l'écartype (SD) du signal analysé. La valeur de cette fraction est habituellement choisie entre 0.1 et 0.2. Ensuite, il s'agit de la longueur « N » de la séquence analysée. La longueur minimale requise est de N = 100 et pour pouvoir être les comparer, les ApEn doivent être calculés sur des séquences de longueur égale dans tous les groupes :

Pour guider le choix des paramètres, les données de la littérature sont limitées. Une seule étude rapporte des valeurs d'ApEn sous ventilation partielle :

- Engoren et al. 1995 [151]. r = 0.15*SD, N=100 ; 300 ; 1000 et série temporelle de la durée cycle à cycle du temps total du cycle mécanique. Sujets contrôle en CPAP (n = 12) : 0,464+- 0.011 ; 0,627 +- 0.019 ; 0,773 +- 0,039 respectivement (moyenne +- SEM). Patients explorés sous pression partielle (n = 21 et niveau d'assistance de 12 +- 5 cm H2O) soit en situation de succès du test de sevrage (n =59) : 0,459 +- 0,013, 0,654 +- 0,015, 0,851 +- 0.021 ou d'échec de test de sevrage (n=14) : 0,454 +- 0.022, 0,633 +- 0.013, 0,797 +- 0,018 respectivement pour les 3 valeurs de N. Dans cette étude, il n'existe pas de différence entre les valeurs des sujets contrôles et des patients que le test de sevrage soit positif ou non.

Plusieurs études rapportent des valeurs d'ApEn en ventilation spontanée :

- Caldirola et al. 2004 [150]: r = 0,1*SD, N=200 et série temporelle cycle à cycle sur la durée du temps total du cycle mécanique. Sujets : 1,13 +- 0,20. Patients avec attaque de panique : 1,27 +- 0,18 et 1,44 +- 0,26 selon la présence ou non de soupirs. Les valeurs d'ApEn chez les patients avec des soupirs sont plus élevées que chez les patients sans soupirs.
- Burioka et al. 2003 [171] : r = 0,2*SD, N= 1800 et série temporelle d'une mesure des mouvements thoraciques par impédance échantillonné à 10 Hz;. Sujet calme : 1,39 +- 0,14; sommeil lent : 1,37 +- 0,18; sommeil profond : 1,13 +- 0,14, REM : 1,48 +- 0,12 (moyenne +- SD). Les valeurs sont différentes selon les stades du sommeil avec des valeurs significativement plus basses en sommeil lent profond.

Il est à noter que les valeurs d'ApEn calculées en ventilation spontanée sont plus élevées que les valeurs calculées en pression partielle. Pour les deux études qui utilisent des séries temporelles similaires [150, 151], les différences de valeurs des paramètres n'expliquent pas ce résultat. Au contraire, le choix de valeurs plus élevés des paramètres (N et r) dans l'étude sous ventilation mécanique auraient plutôt comme effet d'augmenter les valeurs d'ApEn. Cette différence sous-tend l'hypothèse que la ventilation mécanique affecte la génération de l'activité inspiratoire des patients et la rend plus déterministe avec des valeurs d'ApEn plus faible qu'en ventilation spontanée. Néanmoins, dans cette étude, les valeurs calculées dans le groupe contrôle en CPAP ne sont pas différentes des valeurs mesurées sous assistance partielle et il n'est pas exclu que la valeur de r fixée à 0,15*SD puisse avoir filtré les événements permettant de distinguer les dynamiques observées en CPAP de celles en ventilation partielle. Dans ce cas, le choix inapproprié des paramètres, qui causerait un filtrage excessif, expliquerait alors les faibles valeurs d'ApEn observées sous ventilation partielle.

Afin de tester l'impact de ces paramètres sur l'analyse, les valeurs d'ApEn sont calculées pour nos patients sur des séquences d'enregistrement de longueur de 100 ou 200 cycles et avec une valeur de r à 0.1*SD ou 0.2*SD (SD est l'écartype de la séquence analysée). Les valeurs de N sont choisies comme la valeur minimale admise de 100 et la valeur maximale donnée par le

nombre le plus faible de cycles observés chez un patient pendant la durée d'enregistrement de 30 minutes qui est de 200 cycles (Tableau 5-1). De plus, cette population étudiée est partitionnée en deux groupes selon leur valeur d'iPEEP mesurée et sa réponse à l'application de la PEEP. Un premier groupe « CONFORT » regroupe les patients sans iPEEP (< 8 cmH20 en ZEEP) et dont la valeur est inchangée par l'application d'une PEEP ne modifie pas l'intensité de la demande inspiratoire (3,5 +- 1,2 en ZEEP et 2,6 +- 1,3 en PEEP, p = 0.08). Le deuxième groupe « INCONFORT » regroupe les autres patients qui ont une iPEEP mesurée supérieure à 8 cmH20 en l'absence de PEEP et qui est abaissée par l'application d'une PEEP (11,9- +- 3,8 en ZEEP et 6,7 +- 3,0 en PEEP, p = 0,0005). Un seul des cinq patients « CONFORT » a une histoire de BPCO et quatre d'entre eux seront totalement sevrés à la sortie du service, le cinquième bénéficiant d'une ventilation non invasive temporaire. Huit des dix patients « INCONFORT » ont une histoire clinique certaine de BPCO et six d'entre eux seront trachéotomisés à la sortie du service. La valeur de l'iPEEP est différente entre les groupes « CONFORT » et « INCONFORT » en ZEEP ou en PEEP (p = 0,0004 et p = 0,01 respectivement) alors que la PEEP appliquée est similaire dans les deux groupes (4,6 +- 2,2 et 5,5 +- 3,0 cmH2O dans le groupe « CONFORT » et « INCONFORT » respectivement).

N	200				100			
r/SD	0,2		0,1		0,2		0,1	
Moyenne (SD)	ZEEP	PEEP	ZEEP	PEEP	ZEEP	PEEP	ZEEP	PEEP
Total	0,98 (0,16)	0,98 (0,07)	0,72 (0,15)	0,63 (0,15)	0,78 (0,10)	0,74 (0,10)	0,49 (0,12)	0,42 (0,16)
CONFORT (5)	1,01 (0,07)	0,99 (0,04)	0,63 (0,12)	0,60 (0,11)	0,74 (0,12)	0,69 (0,08)	0,38 (0,12)	0,32 (0,13)
INCONFORT (10)	0,96 (0,19)	0,97 (0,09)	0,77 (0,14)	0,65 (0,17)	0,80 (0,10)	0,76 (0,11)	0,54 (0,08)	0,48 (0,15)

Tableau 5-1 Valeur d'ApEn dans la population de l'étude en fonction des paramètres du calcul de la fonction ApEn de Pincus. Pour les mêmes séries temporelles, les valeurs d'ApEn dépendent des valeurs des paramètres et elles augmentent avec les valeurs de N et de r/SD. Les deux groupes « CONFORT » et « INCONFORT » correspondent à une partition de la population étudiée selon leur valeur d'iPEEP et sa réponse à l'application de la PEEP.

Les valeurs d'ApEn sont proches des valeurs rapportées dans la littérature pour caractériser l'imprévisibilité de l'activité respiratoire sous ventilation partielle (Engoren et al). Pour les valeurs des paramètres les plus basses (N=100 ; r = 0.1*SD), les valeurs d'ApEn sont superposables à celles rapportées dans cette étude. Un choix d'une valeur élevée pour r à 0,2*SD augmente les valeurs d'ApEn mais masque les réponses induites par l'application d'une PEEP (Figure 5-1). Aussi, pour l'analyse et la comparaison des scores, la valeur de r sera fixée à 0,1*SD. De même, la longueur N de la séquence analysée sera fixée à 200 cycles, soit la longueur maximale disponible.

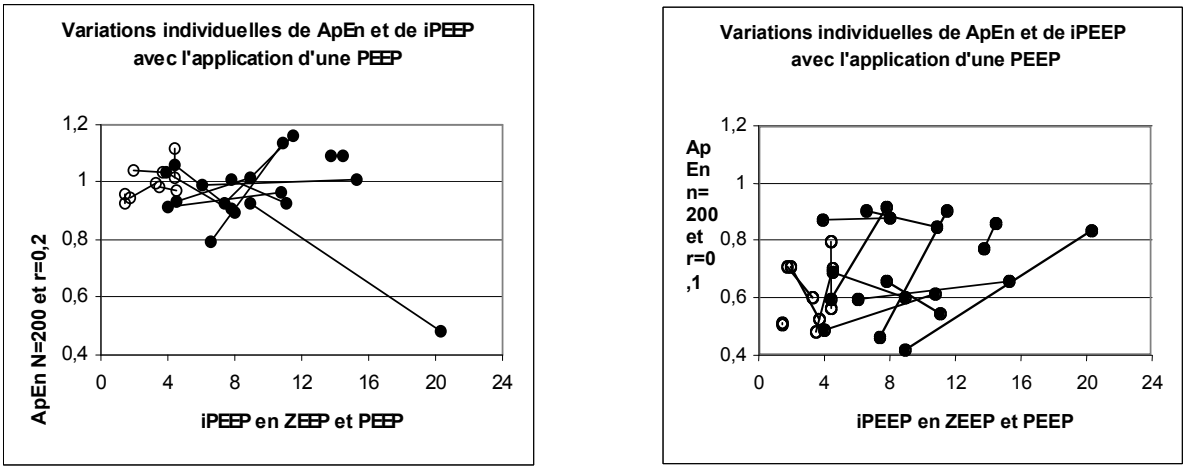
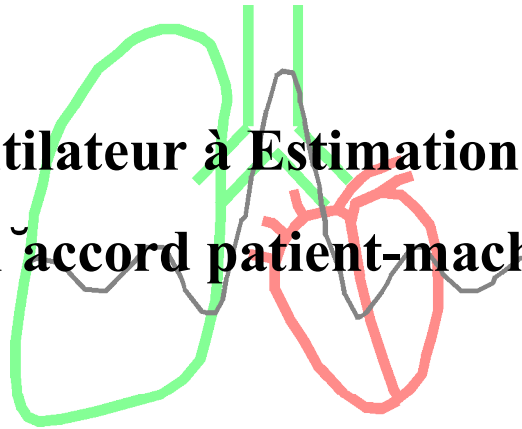


Figure 5-1 Impact du choix des paramètres de la fonction ApEn de Pincus sur le résultat du calcul. Le graphe de gauche présente les résultats individuels en ZEEP et en PEEP avec une valeur de r = 0,2*SD et le graphe droite présente les résultats des mêmes patients avec r = 0.1*SD. Les deux mesures avec et sans PEEP de chaque patient sont reliées par une ligne. Les valeurs d˘ApEn calculées avec r = 0.2*SD apparaissent inchangées lors de la manipulation de la PEEP alors que les valeurs calculées avec r = 0.1*SD changent. Les patients du groupe « CONFORT » sont représentés par les ronds vides alors que les patients du groupe « INCONFORT » sont représentés par des ronds pleins.

4 CIT/VEQU – Ventilateur à Estimation de la Qualité de l'accord patient-machine.

Guméry Pierre-Yves



VEQU ¯ Ventilateur à Estimation de la Qualité de l ˘accord patient-machine

Compte rendu de fin de recherche d ˘opération d ˘une recherche financée par le ministère de la jeunesse, de l ˘éducation et de la recherche.

Juin 2007 **N° de Décision n° 03 B 272**

Organisme bénéficiaire : Laboratoire des ¨Techniques de l ¨Ingénierie Médicale et de la Complexité ˘(TIMC-IMAG)

Responsable scientifique : Pierre-Yves Guméry

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La Tronche

Résumé signalétique

Ce projet s'inscrit dans le cadre de recherches sur l'optimisation des stratégies et des méthodes de surveillance et d'assistance de la fonction respiratoire en anesthésie et réanimation. Les progrès en anesthésie et en réanimation ont pour objectifs la réduction de la durée de la surveillance et l'amélioration de la qualité de la récupération.
Une assistance respiratoire doit assurer une ventilation efficace et non délétère avec un confort acceptable pour le patient. Dans ce contexte, l'accord entre un patient et sa machine d'assistance respiratoire est déterminant. En situation clinique, la détection d'un éventuel désaccord est essentielle pour l'optimisation de la stratégie thérapeutique.
Le projet se base sur une méthode de détection de l'effort inspiratoire, alternative des méthodes invasives classiques. Cette méthode permet d'estimer en continu la pression exercée par les muscles respiratoires (Pmus) à partir des signaux débit et pression mesurés à l'entrée des voies aériennes. Le principe repose sur l'utilisation d'un modèle de la mécanique respiratoire du patient, réactualisé cycle à cycle. Les objectifs du projet sont l'implémentation sur un ventilateur de type eXtend (société TAEMA - partenaire industriel) de la méthode de détection et d'un score permettant de qualifier, sous forme symbolique et interprétable par le clinicien, la qualité de l'accord patient-machine. La validation s'est située à deux niveaux. Un premier niveau correspond à l'analyse métrologique et sur banc de mesure de la détection. Un deuxième niveau correspond à la validation clinique du score obtenu. Nous avons proposé ici une comparaison avec un score de référence construit sur l'analyse de signaux électromyographiques (EMG) mis en jeu lors de la respiration (juge de paix, indicateur de la demande centrale inspiratoire).
Au total, le score proposé est un outil adapté à la détection des épisodes de désynchronisation sévère ce qui paraît un atout essentiel dans le cadre clinique.

Mots clefs : Ventilation, Surveillance, Modèle, Electromyographie, Accord, Pression

Musculaire, Score.

5 Clinical validation of a non-invasive evaluation of passive respiratory mechanics in ventilated patients

CLINICAL VALIDATION OF A NON-INVASIVE EVALUATION OF PASSIVE RESPIRATORY MECHANICS IN VENTILATED PATIENTS. L. Heyer, S. de Susanne, A. Eberhard, P. Baconnier. T.I.M.C. Grenoble. France.

To validate the accuracy of a computer based evaluation of the passive respiratory mechanics in ventilated patients, the computer-based detection of the first respiratory muscle activity at the recovery of an anesthesia is compared to the clinical detection performed by the anesthesiologist.

The study was performed in 8 consecutive patients free of any respiratory disease anesthetized and ventilated for a peripheral orthopedic intervention. The computer based detection: As the anesthetic procedure is alleviated, a non-invasive evaluation of the passive respiratory system is obtained by the analysis of the tracheal pressure and flow signals with a suitable model (modified Otis˘Model) by multiple linear regressions (R. Peslin 1992). Further, the measured tracheal pressure is continuously adjusted by a pressure calculated with the values of the model˘s parameters and the measured flow. The respiratory system was considered to be passive as long as the absolute instantaneous difference between the measured and the calculated pressure remains low (< 2 cmH2O),. A first respiratory muscle activity is thus defined by a brutal and suitable increase of the difference above 2 cmH2O. The clinical based detection: As the anesthetic procedure is alleviated, a first respiratory muscle activity is detected by the same anesthesiologist for the 8 patients and not awarded of the computer-based detection results. This detection is based on respiratory pattern observation and on current anesthetic monitoring analysis.

The computer-based detection always detects the first respiratory muscle activity before the anesthesiologist (5 to 90 seconds or 1 to 14 respiratory cycles before the clinician).

This computer based non-invasive evaluation of the passive respiratory mechanics in ventilated patients is valuable for the detection of changes in the patient˘s conditions.

TAEMA

6 Non-invasive detection of respiratory muscles activity during assisted ventilation

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Model-driven acquisition / Acquisition conduite par le modèle

Non-invasive detection of respiratory muscles activity during assisted ventilation

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Abstract – The instantaneous pressure applied by the respiratory muscles [$P_{mus}(t)$] of a patient under ventilatory support may be continuously assessed with the help of a model of the passive respiratory system updated cycle by cycle. Inspiratory activity (*IA*) is considered present when P_{mus} goes below a given threshold. In six patients, we compared *IA* with (*i*) inspiratory activity (IA_{ref}) obtained from esophageal pressure and diaphragmatic EMG and (*ii*) that (IA_{vent}) detected by the ventilator. In any case, a ventilator support onset coincides with an IA onset but the opposite is not true. IA onset is always later than IAref beginning ((0.21 ± 0.10 s) and IA end always precedes IAref end (0.46 ± 0.16 s). These results clearly deteriorate when the model is not updated. ***To cite this article: L. Heyer et al., C. R. Biologies 325 (2002) 1–9.*** © 2002 Académie des sciences / Éditions scientifiques et médicales Elsevier SAS

breathing / mechanical ventilation / model

Résumé – Détection non invasive de l'activité des muscles respiratoires en ventilation assistée. La pression exercée par les muscles respiratoires (P_{mus}) d'un patient sous assistance ventilatoire est estimée en continu à partir d'un modèle du système respiratoire passif réactualisé cycle à cycle. Une activité inspiratoire (*AI*) est détectée lorsque P_{mus} passe sous un certain seuil. Chez six patients, nous avons comparé *AI* avec (*i*) l'activité inspiratoire (AI_{ref}), obtenue à partir de la pression œsophagienne et de l'EMG diaphragmatique, et (*ii*) celle (AI_{vent}) détectée par le ventilateur. Dans tous les cas, un déclenchement du ventilateur coïncide avec le début d'une *AI*, mais certaines *AI* ne déclenchent pas le ventilateur. Le début de *AI* est toujours situé après le démarrage de $AI_{réf}$ (–0,14 ± 0,09 s) et la fin de *AI* précède celle de $AI_{réf}$ (0,46 ± 0,16 s). Ces résultats sont nettement dégradés avec un modèle non réactualisé. ***Pour citer cet article : L. Heyer et al., C. R. Biologies 325 (2002) 1–9.*** © 2002 Académie des sciences / Éditions scientifiques et médicales Elsevier SAS

respiration / ventilation mécanique / modèle

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. Version abrégée

Des études récentes sur l'interaction entre un patient et son ventilateur d'assistance montrent le besoin d'une détection fine de l'activité respiratoire du patient. Nous proposons une méthode alternative des méthodes invasives classiques (électromyographie diaphragmatique EMGdi, pression œsophagienne), permettant d'estimer en continu la pression exercée par les muscles respiratoires (P_{mus}) à partir des signaux débit et pression à l'entrée des voies aériennes. Cette méthode repose sur l'utilisation d'un modèle de la mécanique respiratoire du patient, réactualisé à chaque cycle ventilatoire.

$P_{mus}(t)$ est obtenue en soustrayant à la pression des voies aériennes mesurée une pression calculée à partir des variations de débit (F) et de volume (V), selon la formule :

$$P_{RS} = P_0 + E\,V + (\alpha|F| + R_0)\,F$$

où P_{RS} représente la pression nécessaire pour imposer au système respiratoire passif les mouvements observés, P_0 est une estimation de la pression régnant dans les poumons à la fin de l'expiration, E est l'élastance du système respiratoire et α et R_0 les coefficients de la relation linéaire entre résistance et débit du système respiratoire.

Les paramètres (P_0, E, α et R_0) de ce modèle sont estimés cycle par cycle à partir des signaux de pression et de débit à l'entrée des voies aériennes par une méthode des moindres carrés appliquée sur une partie du cycle. Cette partie retenue correspond aux zones du cycle où la probabilité d'occurrence d'une activité inspiratoire est la plus faible et où le modèle peut être identifié. Sont donc exclus le tout début de l'insufflation, le passage de l'insufflation au dégonflement et la fin du cycle, lorsque celle-ci est caractérisée par une phase à débit nul. Le calcul ne nécessite aucune modification du régime ventilatoire du patient. On considère qu'il existe une activité inspiratoire du patient (IA) lorsque $P_{mus}(t)$ (négative en inspiration) passe en dessous d'un seuil, qui est fonction de la qualité d'ajustement du modèle sur la partie retenue.

Nous avons étudié six patients de réanimation sous assistance ventilatoire équipés de capteurs de pression œsophagienne et gastrique ainsi que d'un cathéter d'EMGdi. Ces derniers permettent d'établir l'activité inspiratoire de référence (IA_{ref}) basée sur la présence d'une activité électromyographique confirmée par l'évolution de la pression œsophagienne. Au cours d'une phase initiale de ventilation contrôlée, les paramètres de mécanique passive des patients ont été mesurés par la méthode de l'insufflation à débit constant, ainsi que la pression positive de fin d'expiration intrinsèque à partir de la pression œsophagienne. Ensuite, dix enregistrements ont été effectués (entre un et trois par patient) dans les conditions de ventilation assistée en pression déterminées par le médecin en charge du patient. Entre sept et 40 cycles ont été obtenus par enregistrement, en fonction de la durée entre deux ajustements des paramètres de la ventilation assistée.

Nous avons alors comparé les résultats des mesures de IA_{ref} avec les activités détectées par notre méthode (IA) et avec la détection réalisée par le ventilateur, lorsqu'il est déclenché par le patient. Pour cela, nous avons mesuré le temps écoulé entre le début de IA et le déclenchement du ventilateur (Δ_{ven}), la différence de temps entre le début de IA et le début de IA_{ref} (Δ_{beg}) et la différence de temps entre la fin de IA et la fin de IA_{ref} (Δ_{end}). Par ailleurs, nous avons réalisé les même calculs à partir d'une pression musculaire estimée par un modèle simple non réactualisé de la mécanique ventilatoire, utilisant les paramètres de mécanique passive mesurés en ventilation contrôlée.

Dans tous les cas (209 cycles au total), un déclenchement du ventilateur coïncide avec le début d'une activité détectée par notre méthode (IA) et le début de IA précède le déclenchement du ventilateur : $\Delta_{ven} = 0{,}15 \pm 0{,}10$ s (moyenne ± écart type). Il arrive qu'une activité détectée par notre méthode ne parvienne pas à déclencher le ventilateur.

Le début de IA est toujours situé après le démarrage de IA_{ref} : $\Delta_{beg} = -0{,}14 \pm 0{,}09$ s. La fin de $_{IA}$ précède celle de IA_{ref} : $\Delta_{end} = 0{,}43 \pm 0{,}19$ s. La faible variabilité observée globalement se retrouve au niveau de chaque enregistrement et démontre une bonne reproductibilité de la méthode.

Les résultats obtenus avec la méthode, qui s'appuient sur un modèle simple non réactualisé, sont nettement moins bons : les différences alors obtenues, $\Delta_{beg,o}$ et $\Delta_{end,o}$ ont des valeurs aberrantes ($\Delta_{beg,o} > 0$ et $\Delta_{end,o} < 0$) et une variabilité importante ($\Delta_{beg,o} = 0{,}16 \pm 0{,}67$ s; $\Delta_{end,o} = -0{,}14 \pm 0{,}49$ s).

La comparaison entre les valeurs des paramètres de mécanique passive obtenues au préalable et celles obtenues en cours de ventilation assistée en pression montre la nécessité de la réactualisation de ces paramètres : les valeurs obtenues au préalable diffèrent notablement de celles observées en cours de ventilation assistée ; ces dernières évoluent d'un enregistrement à l'autre chez un même patient.

L'utilisation d'un modèle de la mécanique ventilatoire permet donc d'obtenir une détection non invasive de l'activité inspiratoire d'un patient sous assistance ventilatoire. Ceci passe cependant par une réactualisation des paramètres de ce modèle, réactualisation que nous avons obtenue par une estimation par moindres

carrés à chaque cycle, sur une partie seulement du cycle. L'estimation indirecte de l'activité inspiratoire d'un patient par l'observation de grandeurs mécaniques reste soumise aux limitations de la transmission de la commande ventilatoire au système respiratoire passif. En particulier, la perte de performance de notre méthode en fin d'inspiration peut s'expliquer par la baisse d'efficacité de l'action du diaphragme à haut volume pulmonaire.

1. Introduction

Management of acute respiratory failure implies usually the use of mechanical ventilation. Assisted modes of mechanical ventilation were developed to address the need for maintaining patient's intrinsic respiration, a necessary condition for eventual weaning from the ventilator. Assisted ventilation aims at reducing excessive respiratory efforts while improving gas exchange by applying positive pressure to the airway thereby unloading the respiratory muscles. Recent approaches even tend to let the patient totally control the ventilator either mechanically [1] or through the neural drive issued from the patient's respiratory centers [2], but these techniques are still under development. In assisted ventilation, although the patient's inspiratory effort triggers the mechanical breath, coordination between spontaneous breathing and mechanical assistance is not guaranteed, owing to poor interaction between the patient and the ventilator. A solution would be to monitor the patient's inspiratory activity over some breaths and to subsequently and interactively adjust the ventilator settings so as to improve this interaction. This points to the need for non invasively detecting respiratory muscle activity during ventilatory support. The present study aims to demonstrate the feasibility of a proposed non invasive method.

Usually, respiratory muscles activity is detected or quantified via esophageal and gastric pressure measurement or diaphragmatic EMG obtained from an esophageal probe. These techniques are invasive and moreover not reliable when applied during long periods in intensive care conditions [3]. Recently, a theoretical method has been proposed that can determine the pressure developed by the respiratory muscles (P_{mus}) in partially supported ventilation [4]. $P_{mus}(t)$ is obtained as the difference between the observed airway pressure and a pressure calculated from observed flow and volumes variations via a model of the passive respiratory system.

We have adapted this method to the long-term continuous detection of inspiratory activity in pressure support ventilated patients. Two modifications of the method are needed and a detection rule has to be defined. First, the initial model of the passive respiratory system is adapted to current patients by taking into account a possible intrinsic P_{EEP} (P_{EEPi}, positive end expiratory pressure due to air trapping in the alveoli, the expiration duration being too short for the lung to empty) and a non linearity of the resistance parameter. The modified model includes then four parameters instead of two. Second, these four parameters are estimated cycle-by-cycle from airway pressure and flow signals with a selective least squares method [5]. The detection rule is as simple as possible: an inspiratory activity is 'detected' when P_{mus} goes below a given threshold. We present a comparison of our results with reference data obtained with invasive measurements as well as results obtained with the original method in six patients.

2. Materials and methods

2.1. Patients

After institutional approval and informed consent were obtained, six tracheally intubated patients were enrolled in the study (Table 1). All of them were

Table 1. Demographic and passive mechanical data.

Patient	Age (yr)	Weight (kg)	Height (cm)	ETT (mm)	E_p (cm H_2O l^{-1})	R_p (cm H_2O l^{-1} s)	P_{EEPi} (cm H_2O)
C	71	53	155	8	36	28	5.3
D	63	45	175	9	41	26	8.5
F	72	65	170	9	36	18	6.5
G	60	79	170	9	22	30	6.1
P	77	88	160	8	21	27	5.5
Q	70	50	160	8	14	8	5.2

ETT: endo-tracheal tube caliber. E_p, R_p: respectively, elastance and resistance of the respiratory system measured during a period of passive controlled ventilation.

Table 2. Assisted ventilation data.

Recording	P_{EEP} (cm H_2O)	Pressure support (cm H_2O)	n
C1	2	28	12
D1	7	26	25
D2	12	26	36
D3	10	27	28
F1	6	15	6
G1	3	13	28
G2	3	13	19
P1	5	16	18
P2	5	15	17
Q1	3	15	20

P_{EEP}: pressure imposed by the ventilator during deflation; pressure support: inspiratory pressure given by the ventilator; n: number of recorded cycles.

admitted to the intensive care unit for acute respiratory failure of chronic obstructive pulmonary disease (COPD). At the time of the study, all patients were receiving partial ventilatory support (PSV, Dräger Evita II) and were able to sustain spontaneous breathing for at least 5 min.

During PSV, each breath is assisted by an inspiratory pressure generated by the ventilator at a preset value. This is synchronized with the patient's effort to breathe. The assisted breath is initiated when the spontaneous inspiratory flow reaches a preset threshold value of $3\ l\ min^{-1}$ (flow triggering level). The insufflation is stopped when the instantaneous flow is lower than 25% of the maximal value of the inspiratory flow.

Throughout the study, the applied positive end-expiratory pressure and the inspiratory pressure were set by the attending physician and were not modified for the study (Table 2). All patients were in a semi-recumbent position during measurements. Some patients were recorded several times because of a change in the assisted ventilation parameters (Table 2).

2.2. Measurements

Esophageal (P_{es}) pressure was measured with a micro pressure transducer-tipped catheter (MTC P3FC 3F; Dräger ME, Best, The Netherlands). The airway pressure (P_{ao}) was recorded 1 cm from the oral end of the endotracheal tube by using another external transducer (Sims, Kirchseeon, Germany). The validity of P_{es} measurement was assessed by performing 'occlusion tests', as proposed by Baydur et al. [6]. The gas flow (F) was measured by using a Fleish (No. 2) pneumotachograph connected to a differential pressure transducer (Validyne MP45; ±2 cm H_2O). The diaphragmatic electromyogram (EMGdi) was recorded by an esophageal probe positioned at the level of the gastro-esophageal junction (MCT-Cond.M 8F; Dräger ME). This probe consists of eight steel rings at a distance of 9 mm from each other, two adjacent electrodes forming a pair. With the esophageal probe in place, the optimal pair giving the best-quality signal was chosen. The raw EMG was amplified and the band pass-filtered between 20 and 500 Hz. All pressure, flow, and EMGdi signals were digitized by an analog-to-digital converter with a 16-bit resolution at a sampling frequency of 1 000 Hz (MP100 Biopac System Inc., Santa Barbara, CA). The removing of cardiac artifacts from the EMGdi tracing was done manually on the computer screen. Then, the "intEMGdi" signal was obtained by a moving average (30 ms) upon its absolute value.

Neural inspiratory activity (IA_{ref}) was obtained from intEMGdi and validated from P_{es} signal in the following way (Fig. 1): the onset of intEMGdi, which coincides with the point of rapid decline in P_{es}, was used to define the onset of IA_{ref}, and the end of IA_{ref} was defined as the onset of the rapid decline in intEMGdi, contemporary of the return of P_{es} to the base line [7].

All patients underwent a period of passive mechanically controlled ventilation. This was achieved by increasing the respiratory rate of the controlled ventilation. During this period, passive elastance E_p and resistance R_p of the respiratory system were measured according to Rossi and associates [8] during constant flow inflation. The intrinsic PEEP (P_{EEPi}) was measured as the difference in P_{es} between the beginning of the inspiratory effort and the start of inspiratory flow. These characteristics are gathered in Table 1. Measurements during PSV were performed after patients had a 2-min period of spontaneous breathing, and recordings

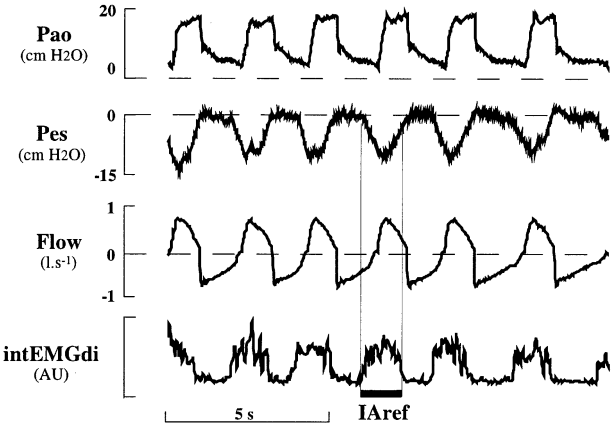

Fig. 1. Individual tracings of airway pressure (P_{ao}), esophageal pressure (P_{es}), flow (*Flow*) and integrated electromyodiaphragmatic activity (intEMGdi) in arbitrary units (AU) in a patient (patient P) during application of partial support ventilation. Neural inspiratory activity (IA_{ref}) is indicated by the large horizontal bar (see text for its determination).

started once the decrease in ventilatory drive associated with PSV onset was completed [9]. Recordings were continued until 30 cycles were acquired or any ventilator setting was changed.

2.3. Signal analysis and calculation

Digitized signals were transferred as text files and then processed using programs written in MATLAB™ (The MathWorks®) language. Flow signal was first corrected for a possible departure of zero flow from zero value. The digital integration of flow over time provided then the volume (V) data.

2.3.1. Model

The analysis is based on a mathematical model involving two main components in the pressure, P_{RS}, needed to communicate to the passive respiratory system the observed movement: (i) the elastic pressure ($P_{el} = P_0 + E\,V$) depending both on a constant elastance E and on a residual pressure P_0 at the end of expiration (depending on the imposed ventilation pattern), (ii) the resistive pressure ($P_{res} = (\alpha\,|F| + R_0)\,F$), which points out a flow-dependent resistance (R_0 and α are respectively the constant and slope parameters of the resistance–flow relationship). The motion equation of the passive system, is then:

$$P_{RS} = P_0 + E\,V + (\alpha|F| + R_0)\,F \qquad (1)$$

In this equation, the residual pressure at the end of expiration is labeled P_0, instead of P_{EEPi}, as it is a parameter of the model to be identified, while P_{EEPi} is measured. This mathematical model is likely to correspond to the system made up of one patient and his tracheal tube, because tubes exhibit such a flow-dependent resistance.

This system is submitted to two pressure sources, namely the respiratory muscles, supplying a pressure P_{mus}, and the ventilator, supplying a pressure P_{ao}. From the arrangement of these pressure sources, one can deduce that the relationship between P_{ao}, P_{mus} and P_{RS} is:

$$P_{ao} = P_{RS} + P_{mus} \qquad (2)$$

P_{mus} is then obtained as:

$$P_{mus} = P_{ao} - P_0 - EVv - (\alpha|F| + R_0)\,F \qquad (3)$$

2.3.2. Selection

The four parameters (P_0, E, α and R_0) are obtained for each cycle by a least squares algorithm that minimizes the mean squared difference between P_{ao} and P_{RS} signals on a part of the respiratory cycle (Fig. 2) most likely (i) to include little respiratory muscle activity (this excludes the transition between expiration and inspiration) and (ii) to fit closely the proposed model (which excludes the transition between inspiration and expiration, where fast transients cannot be taken into account by a model without inertia coefficient).

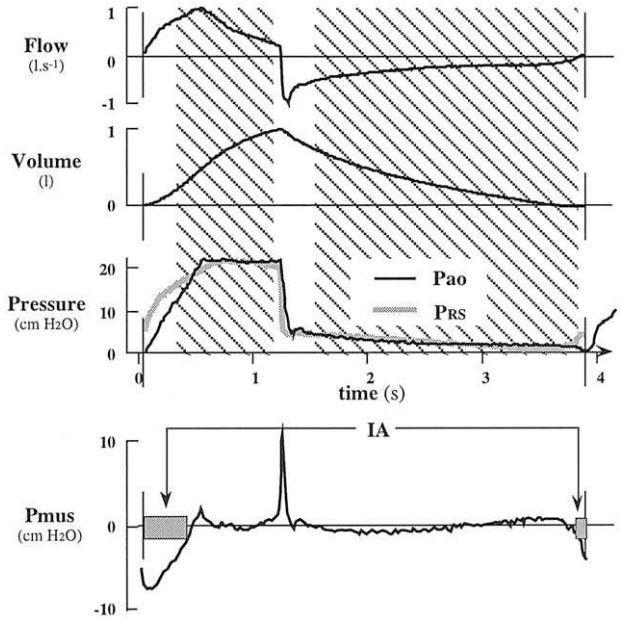

Fig. 2. Selective least squares and detection of inspiratory activity procedures illustrated on a respiratory cycle (patient C). Hatched areas correspond to the zone where parameters of the model are estimated by the least squares method. Vertical lines delimitate the cycle. P_{RS} obtained from parameter estimation is superimposed to P_{ao}. P_{mus} is the difference between P_{RS} and P_{ao}. Grey rectangles on the P_{mus} curve indicate periods where inspiratory activity (IA) has been detected ($P_{mus} < IA_{thr}$).

The first selected zone starts 0.3 s after beginning of insufflation and finishes 0.1 s before its end; the second selected zone starts 0.3 s after beginning of deflation and finishes at the end of the cycle or as soon as the absolute value of flow goes below 0.1 l s^{-1}.

2.3.3. Automatic detection of activity

Inspiratory muscle activity (IA) is considered present when $P_{mus}(t)$ goes down below a predetermined threshold (IA_{thr}). This threshold has been chosen as a function of the standard deviation observed between P_{RS} and P_{ao} on the zone selected for parameter estimation. Namely $IA_{thr} = 1.5$ SD. As is the case in Fig. 2, in most cycles IA is detected at the beginning and at the end of the cycle. Our automatic algorithm was designed to provide the end of the first detected IA and the beginning of the last detected IA of the cycle. Other detected IAs were not taken into account, as they cannot be faced to ventilator detection.

The same procedure has been carried out with the original estimation of P_{mus} based on the passive mechanical parameters obtained before PSV [4].

$$P_{mus,o} = P_{ao} - P_{EEPi} - E_p V - R_p F . \quad (4)$$

In this case, the threshold ($IA_{thr,o}$) has been set at 1.0 cm H_2O, which corresponds to the mean value of all IA_{thr}. The corresponding detected *IA* will be called IA_o.

2.4. Comparison criteria

The time differences between detected and reference estimate of *IA* onset (Δ_{beg} = IA_{ref} onset time – *IA* onset time) and end (Δ_{end} = IA_{ref} end time – *IA* end time) indicate the precision of our method and their standard deviations give an estimation of its reproducibility. The difference between detected *IA* onset and ventilator triggering (Δ_{ven} = inflation start time – *IA* onset time) evaluates the sensibility of our method compared to that of the ventilator trigger. All these differences are illustrated in Fig. 3, where *IA* (and the pressure signal from which it originates) and IA_{ref} (and the corresponding intEMGdi signal) are represented for the same neural inspiration in patient P.

Similar comparisons have been done with $P_{mus,o}$: for each detected *IA*, $\Delta_{beg,o}$ (= IA_{ref} onset time – IA_o onset time) and $\Delta_{end,o}$ (= IA_{ref} end time – IA_o end time) were obtained.

We calculated a mean value (and standard deviation) of each time difference for each recording (for graphical presentation) and over all recordings. Statistical comparison has been carried out by paired or univariate *t*-test over all recordings.

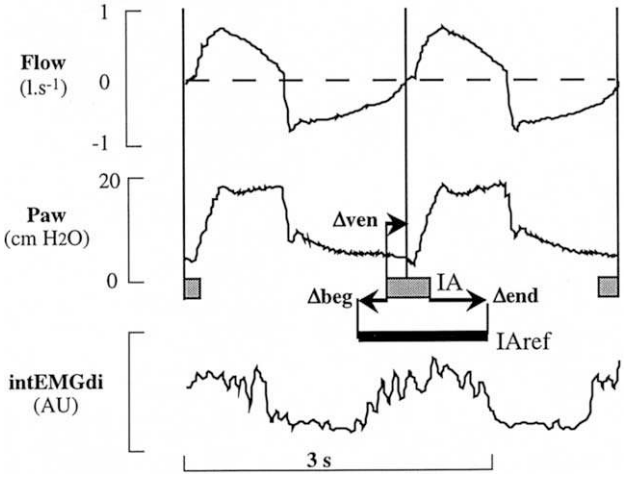

Fig. 3. Comparison between detected *IA* and IA_{ref}. In this enlarged part of Fig. 1 (P_{es} signal has been excluded for sake of simplicity), the corresponding *IA* is positioned relative to the IA_{ref} given in Fig. 1 (remaining *IA* of the two cycles are mentioned without corresponding IA_{ref}). Long vertical lines delimitate cycles from flow signal. *IA* representation: same as in Fig. 2.

3. Results

3.1. Sensitivity

In all cycles, ventilator triggering coincides with an *IA* detection (inversely, some detected *IA* do not trigger the ventilator, but we did not take them into account). Our method detects inspiratory activity in advance (Δ_{ven} significantly > 0, *t*-test, $p < 0{,}01$) on the ventilator (mean difference ± SD calculated on all recordings: $\Delta_{ven} = 0.15 \pm 0.10$ s).

3.2. Comparison with the reference method

IA onset is almost always (198/209) late with respect to IA_{ref} onset. When this is not the case, the difference is small (< 0.01 s). This evidences that we detect inspiratory activity **after** it appears on EMGdi, but the difference as well as the standard deviation are small: $\Delta_{beg} = -0.14 \pm 0.09$ s (mean ± SD, calculated on all recordings). The end of *IA* is detected prematurely in almost all cases (205/209) by our method. This demonstrates that our method does not indicate existence of inspiratory activity **after** it disappears on EMGdi. The difference and the standard deviation are greater: $\Delta_{end} = 0.43 \pm 0.19$ s (mean ± SD, calculated on all recordings).

Individual recording results are shown in Fig. 4. Differences vary from one recording to another and between patients, but they stay comparable for Δ_{beg} as well as for Δ_{end}.

3.3. Results obtained with the original P_{mus} estimation

In eight cycles, detection of IA with original P_{mus} fails to detect any *IA*. In the remaining cycles, the advance on the ventilator is erratic ($\Delta_{ven,o} = 0.51 \pm 0.78$ s).

The difference $\Delta_{beg,o}$ has an unrealistic statistically significant (*t*-test, $p < 0.01$) positive mean value ($\Delta_{beg,o} = 0.16 \pm 0.67$ s) corresponding to a detection of IA **before** the onset of IA_{ref} in seven out of ten recordings ($p < 0.01$). Similarly, the difference $\Delta_{end,o}$ has an unrealistic statistically significant (*t*-test, $p < 0.01$) negative mean value ($\Delta_{end,o} = -0.14 \pm 0.49$ s) corresponding to a detection of IA **after** the end of IA_{ref} in two recordings ($p < 0.05$). As illustrated in Fig. 5, which gathers the results of both methods for each recording, the detection of *IA* with P_{mus} calculated in

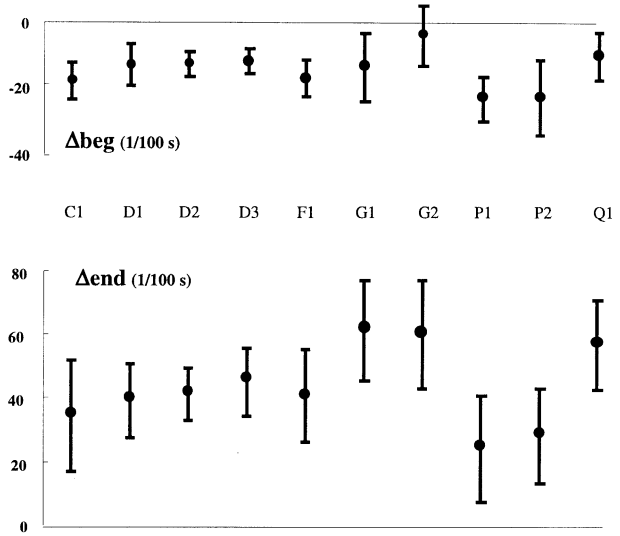

Fig. 4. Differences between detected *IA* and IA_{ref} for individual recordings. Δ_{beg} negative indicates a delay taken by our method to detect *IA* onset relative to the reference based on diaphragmatic EMG. Δ_{end} gives the same information for the end of *IA*, a positive value indicates an advance in detecting *IA* end. Vertical bars represent one SD.

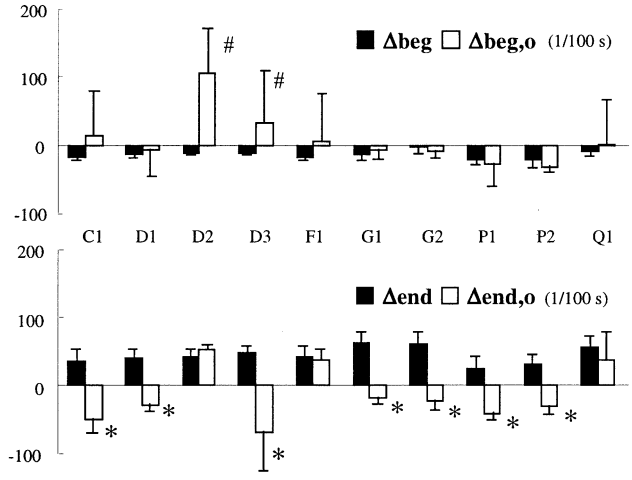

Fig. 5. Comparison of the results of our method (full rectangles) with that obtained with the original computation of P_{mus} (empty rectangles) for individual recordings. Vertical bars represent one SD.

the original way gives unrealistic results (mean $\Delta_{beg,o} > 0$, or mean $\Delta_{end,o} < 0$) in numerous recordings and exhibits a high variability as compared to our method.

3.4. Comparison of the mechanical parameters

Our method gives a cycle-by-cycle estimation of respiratory mechanics parameters. In order to compare these values to the ones calculated during passive controlled ventilation, we first calculated for each cycle a mean resistance value (R_m) and we calculated then mean values of elastance (E), resistance (R_m) and P_0 for each recording. Table 3 summarizes these data together with the passive mechanical data of Table 2. While P_0 is generally close to P_{EEPi}, other mechanical parameters exhibit great significant ($p < 0.05$) differences between passive controlled situation and PSV and even between recordings on the same patient (D for example).

4. Discussion

As an alternative to invasive methods, we used an estimation of the instantaneous pressure applied by the respiratory muscles [$P_{mus}(t)$] derived from [4] to detect inspiratory activity in pressure support ventilated patients. In [4], this estimation was used for the analysis of work of breathing under various levels of pressure support ventilation (PSV) and has been validated in patients who did not exhibit intrinsic PEEP. However, the work of breathing obtained by this method exhibited a poor correlation with the work of breathing obtained from P_{es} measurements. This original method has two main drawbacks: (*i*) the model of the respiratory mechanical system on which it relies is too simple and (*ii*) the parameters of this model, once determined in controlled ventilation mode, are never reevaluated.

Our COPD patients all exhibit intrinsic PEEP (Table 3) and this had to be included in the computation of P_{mus}. Moreover, to take into account the behavior of tracheal tube, we introduced a non-linearity on flow resistance. The resulting model of passive respiratory mechanics has four parameters instead of two, which is not problematic, as the least squares technique allows to evaluate any multi-linear model [10]. Moreover, Peslin et al. [10] conclude that this 4-parameter model is satisfactory in all their patients; then, this model, even if not the only plausible one, remains the most likely to provide satisfactory results on many patients. Our patients are not numerous enough to allow us to assert that the proposed method will always work for any patient; however, their respiratory mechanical characteristics as well as the used PEEP and Pressure Support cover a wide range of values (Tables 1 and 2).

This least squares technique is well adapted to the second modification we needed to bring to the original P_{mus} estimation method: a continuous reevaluation of the model parameters. For each successive cycle, we apply this technique selectively to parts of the cycle where inspiratory activity is not likely to occur during PSV (our results do not contradict this hypothesis). Another selection of favorable zones for least squares

Table 3. Mechanical parameters obtained during passive controlled ventilation (E_p, R_p, P_{EEPi}) and by least squares estimation (E, R_m, P_0) during PSV.

Patient	Recording	E_p	E	R_p	R_m	P_{EEPi}	P_0
C	C1	36	15 (1)	28	18 (2)	5.3	5 (2)
D	D1	41	11 (2)	26	16 (2)	8.5	11 (1)
	D2		27 (4)		36 (2)		15 (1)
	D3		8 (2)		11 (1)		13 (3)
F	F1	36	24 (2)	18	9 (1)	6.5	7 (1)
G	G1	22	15 (7)	30	11 (4)	6.1	4 (2)
	G2		7 (2)		13 (2)		6 (1)
P	P1	21	20 (7)	27	10 (1)	5.5	7 (2)
	P2		20 (5)		9 (2)		6 (2)
Q	Q1	14	7 (1)	8	3 (1)	5.2	7 (1)

Elastances are expressed in cm $H_2O\ l^{-1}$, resistances are in cm $H_2O\ l^{-1}$ s, and pressures in cm H_2O. Estimated values are mean (SD).

fitting has already been used in other circumstances [11, 12]. Such a continuous method has at least two advantages: (*i*) it is totally non-invasive, as the estimation of respiratory mechanics parameters is obtained without the need for any maneuver from the ventilator, and (*ii*) it allows a follow-up of the state of the patient's passive respiratory system.

In order to validate our results, we had to call for a reference method. Recently, Parthasarathy et al. [13] evaluated the concordance of neural inspiratory time measurements based on flow, esophageal pressure and transdiaphragmatic pressure with a more direct measurement of neural activity. This implied the use of esophageal electrode recordings of diaphragmatic EMG that we also used as references. These authors conclude that indirect estimates of onset and duration of neural inspiratory time displayed poor agreement with diaphragmatic EMG measurements. In fact, their results exhibit a huge variability that we do not observe in our results. This comes probably from the fact that their indirect evaluation of neural inspiratory time relies on robust but too simple criteria.

The interpretation of P_{mus} variations into an inspiratory activity needs the use of a threshold. We decided to adapt this threshold that we use to the local quality of the model and of the pressure and of the flow signal that we get (standard deviation between measured and modeled pressures). This can be discussed on the basis that this threshold always stays around 1 cm H_2O and is only significantly modified when the patient exerts an inspiratory effort not detected by the ventilator. In such a circumstance, the standard deviation increases and consequently increasing the threshold will not bring any robustness but will increase the risk of missing this effort already undetected by the ventilator. The 1.5 coefficient we used (IA_{thr} = 1.5 SD) was chosen to give a compromise between sensitivity and specificity. The method is relatively robust as regards this coefficient: results are almost identical (less than 10% variation in all estimates) when this coefficient takes values between 1.0 and 2.0.

On the whole, our method gives satisfactory results in the detection of inspiratory activity. The major defect resides in the detection of the end of this activity: our method does not 'see' this activity up to its end as defined by diaphragmatic EMG. This seems rather unavoidable, since presence of activity on diaphragmatic EMG does not imply that diaphragm contraction is efficient. Indeed, at high lung volume, which is the case in ventilated patients with high intrinsic PEEP at the end of insufflation, diaphragm contraction may have no efficiency at all. This may explain the discrepancy between our indirect method and the reference one based on diaphragmatic EMG. The fact that the lag of our method on EMGdi is stable on one patient nevertheless allows detecting a significant change in inspiratory effort duration.

The comparison of our results with those obtained with a simpler evaluation of P_{mus} underlines the need for a continuous reevaluation of respiratory mechanics; this is even more obvious when putting together parameter evaluations: Table 3 evidences the fact that for the same patient, respiratory mechanics evolve significantly from one situation to another. Incidentally, the fact that evaluation methods differ cannot afford the difference observed. Such observations should revive development of computer programs for automatic measurement of respiratory mechanics in ventilated patients [14].

5. Conclusion

We conclude that non-invasive detection of respiratory muscle activity is possible during pressure support ventilation. This implies the use of a model of passive respiratory mechanics; this model has to be reevaluated

continuously. Simple methods are available for this and have been satisfactorily applied on clinical data. A non-negligible spin-off of this study is the follow-up of respiratory mechanics in pressure support ventilation. The shorter detected inspiratory activity as compared to EMG diaphragmatic activity may be predicted by the lower mechanical output of diaphragm at high lung volume.

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