IDENTIFICATION OF A NON-LINEAR MODEL AS A NEW METHOD TO DETECT EXPIRATORY AIRFLOW LIMITATION IN MECHANICALLY VENTILATED PATIENTS

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ABSTRACT

Expiratory flow limitation (EFL) can occur in mechanically ventilated patients with chronic obstructive pulmonary disease and other disorders. It leads to dynamic hyperinflation with ensuing deleterious consequences. Detecting EFL is thus clinically relevant. Easily applicable methods however lack this detection being routinely made in intensive care. Using a simple mathematical model, we propose a new method to detect EFL that does not require any intervention or modification of the ongoing therapeutic. The model consists in a monoalveolar representation of the respiratory system, including a collapsible airway that is submitted to periodic changes in pressure at the airway opening: EFL provokes a sharp expiratory increase in the resistance Rc of the collapsible airway. The model parameters were identified via the Levenberg-Marquardt method by fitting simulated data on the airway pressure and the flow signals recorded in 10 mechanically ventilated patients. A sensitivity study demonstrated that only 8/11 parameters needed to be identified, the remaining three being given reasonable physiological values. Flow-volume curves built at different levels of positive expiratory pressure, PEEP, during "PEEP trials" (stepwise increases in positive end-expiratory pressure to optimize ventilator settings) have shown evidence of EFL in three cases. This was concordant with parameter identification (high Rc during expiration for EFL patients). We conclude from these preliminary results that our model is a potential tool for the non-invasive detection of EFL in mechanically ventilated patients.

Keywords: expiratory flow limitation, mathematical model, ventilatory assistance, PEEP, human beings.

1. INTRODUCTION

The term "expiratory flow limitation" (EFL) depicts a situation where the flow of gas leaving the lungs through the airway during a passive, tidal expiration corresponds to the maximal attainable expiratory flow. In other words, EFL is characterized by the uncoupling of expiratory driving pressure (the difference between airway opening pressure and alveolar pressure) and expiratory flow: increasing the former does not increase the latter. This condition promotes the progressive inflation of the lung and chest wall (dynamic hyperinflation) which in turn has various deleterious effects on both the passive and the active respiratory systems. Indeed, dynamic hyperinflation, defined by an end-expiratory volume above the relaxation volume of the respiratory system, creates a positive end-expiratory pressure (PEEP) within the lungs, that is generally referred to as being "intrinsic" (PEEPi). This impairs cardiac output through various mechanisms. This also imposes a mechanical load on inspiratory muscles, contributing to dyspnea or ventilatory failure in patients who rely on their intrinsic respiratory neuromuscular activity to breathe. In addition, dynamic hyperinflation can bring the respiratory system to a volume where its pressure-volume relationship is flat or nearly so. High alveolar pressures ensue. In mechanically ventilated patients, this has potentially severe deleterious effects such as pneumothoraces or ventilator-induced lung injury. Detecting EFL is thus clinically relevant, and all the more so in patients undergoing mechanical ventilation. In this setting, the identification of EFL should prompt clinicians to adopt ventilatory strategies aimed at minimizing dynamic hyperinflation, such as low tidal volume ventilation (with the corollary so-called "permissive hypercapnia"). This approach has been shown to be protective against lung damage in various animal models, and beneficial in terms of morbidity and mortality in several categories of patients. These include patients suffering from chronic obstructive pulmonary disease (COPD), of which EFL is among the hallmarks, but there has been evidence of EFL in other clinical settings, such as the acute respiratory distress syndrome (ARDS). To note, the application of an external positive expiratory pressure (PEEPe) can counterbalance EFL to some extent. This approach has been shown clinically to improve the expiratory dynamics of patients with EFL.

Various methods have been proposed to detect EFL in mechanically ventilated patients (Vassiliou *et al.*, 1996; Lourens *et al.*, 2001). However, they all are somewhat cumbersome and have thus not become popular to clinicians.

We have previously shown (Khirani *et al.*, 2001) that it is possible to predict the beneficial effects of moderate levels of positive end-expiratory pressures on EFL by use of a simple mathematical model. The present study was designed to evaluate the performances of a similar model to detect EFL, in the perspective of a fully non-invasive and eventually automated clinical application. To this aim, we recorded airway flow and pressure in 10 mechanically ventilated patients with various diseases, some of them suspected of EFL from clinical data. Routine "PEEP trials" (stepwise increases in positive end-expiratory pressure to optimize ventilator settings) were used to detect EFL or its absence through the construction of flow-volume curves (reference method, see Valta *et al.*, 1994). Then, in each patient, we identified the best set of model parameters by curve fitting, and asserted whether EFL was present or not from the resulting simulated behaviour. The curve fitting was carried out on the whole set of

recordings (i.e. at all PEEP levels). It was also carried out using only the recording made at the lowest PEEP level, to gain insights on the possibility of detecting EFL in mechanically ventilated patients without any modification of the ventilator settings.

2. MATERIALS AND METHODS

Patients

Ten patients admitted to two separate intensive care units were studied (Table 1). The patients were mechanically ventilated (Siemens Servo 900C or 300 ventilator, Siemens-Elema, Solna, Sweden for all patients but #1: Evita 4, Dräger, Germany) in pressure or volume controlled modes via an endotracheal tube or via a tracheotomy. They were sedated and some of them were paralysed. They were in supine position. The study conformed to local legislation that waives the need for ethical approval and patient consent for observational studies. The degree of dynamic hyperinflation was appreciated from routine measurements of PEEPi during end-expiratory occlusions, repeated twice before or after each PEEP trial.

Table 1. Characteristics of the patients. Abbreviations: COPD = Chronic Obstructive Pulmonary Disease; ARF = Acute Respiratory Failure; ALI = Acute Lung Injury; CRF = Chronic Respiratory Failure; CVA = Cerebral Vascular Accident; RF = respiratory frequency; VT = tidal volume; PEEPe= external PEEP imposed by the ventilator, and set by the clinician; PEEPi = intrinsic PEEP measured during end-expiratory pauses; PC = Pressure Controlled mode; VC = Volume Controlled mode; ACV = Assisted-Controlled Ventilation.

Patient #	Weight (kg)	Age (years)	History	I/E ratio	RF (min^{-1})	VT (ml)	PEEPe (hPa)	PEEPi (hPa)	Ventilatory mode
1	56	53	COPD – ARF	1:1.8	16	600	2	5	ACV
2	90	43	Polytraumatism–Pneumothorax	1:1.3	16	650	5	1	VC
3	70	50	ALI – Polytraumatism	1:1.5	16	650	6	1	VC
4	102	78	COPD – Hyperuricemy	1:2.9	15	700	0	12	PC
5	74	84	Chronic Asthma – CRF	1:3.0	16	500	0	8	VC
6	114	42	CVA – Hypertension	1:1.5	18	580	12	3.5	ACV
7	120	72	COPD – CVA	1:1.8	15	600	5	8	ACV
8	56	92	Cardiopathy – CVA	1:2.0	15	450	5	5	ACV
9	49	55	CVA – Shock – Pneumopathy	1:2.0	18	450	10	1.5	ACV
10	92	63	Shock – Hyperuricemy	1:2.2	20	700	4	3.5	ACV

Respiratory measurements

A pneumotachometer (Flow sensor, Hamilton Medical, Inc., Reno, USA) was placed in series on the endotracheal tube and connected to a differential pressure transducer (for patients #1 to 5: PPT 0002D, Honeywell, NJ; for patients #6 to 10: Spirometer ML140, AD Instruments, Castle Hill, NSW, Australia) to measure flow. Airway opening pressure was measured proximal to the pneumotachometer using a pressure transducer (for patients #1 to 5: PPT 0100A, Honeywell, NJ; for patients #6 to 10: Validyne MP45, Northridge, CA). All connections between the measurement site and the transducers were as short as possible to ensure a flat frequency response up to 10 Hz for each measurement set. Before each experiment, zero pressure and flow and calibrations were done. Flow was calibrated using a flowmeter (Fisher Controls) and sometimes, for practical reasons, using the ventilator settings. The pressure was calibrated using a water filled U-shaped manometer. Data were gathered via an acquisition unit (for patients #1 to 5: MP100 Systems, BIOPAC Systems, Inc., CA; for patients #6 to 10: PowerLab 8SP, AD Instruments, Castle Hill, NSW, Australia) at a sampling rate of 100 or 200 Hz, stored and visualized using a computer. Digitised signals were stored into separate ASCII files. Volume signal was obtained by numerical integration of the flow signal.

PEEP trials were carried out in the standard manner, by applying different PEEPe levels in ascending and descending orders. At least four PEEPe levels were used, interspaced by one (patients #1, 2 and 10), two (patients #3, 4, 7, 8 and 9), three (patient #5) or even four (patient #6) hPa, between 0 and the imposed PEEPe or the observed PEEPi. The mean duration of a PEEP trial was 5 min. Each PEEPe level was maintained during 10 cycles, until a steady state evidenced by a stable end-expiratory airway opening pressure. Beginning and finishing the PEEP trial by imposing the same PEEPe level minimizes the drift of volume obtained after integration of the flow signal.

Flow-Volume curves and expiratory flow limitation

We constructed expiratory flow-volume (FV) curves using the measured flow vs. the corresponding exhaled volume obtained by integration of the flow. In each patient, FV were drawn at least at three different PEEPe levels. EFL was deemed present in the event of a flow overlap between at least two FV curves obtained under two different PEEPe values. Such an overlap indicates that increasing the driving pressure fails to increase flow.

Model

The proposed model consists of a nonlinear two-compartment system (see Figure 1) and has been previously described (Khirani *et al.*, 2001). Briefly, one of the compartments represents the collapsible airways and mimics its dynamic compression, the other represents the alveolar compartment.
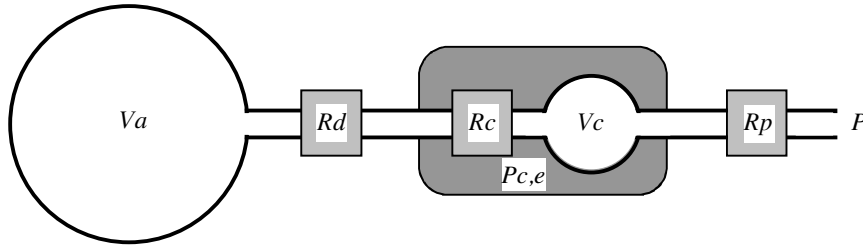
Figure 1. A simple model of expiratory airflow limitation. Alveolar compartment (volume Va) is connected to the outside through a series of resistances representing respectively distal (Rd), compressible (Rc) and proximal (Rp) airways. The resistance Rc is function of the collapsible compartment volume Vc which is in turn a function of internal (Pc,i) and external (Pc,e) pressures of this compartment. Pressure (P) is the forcing input of the model.

The elastic behaviour of the collapsible airways is defined according to a two–segment linear pressure-volume relationship where the slope (elastance of the collapsible compartment, Ec) differs according to the state (distended or collapsed) of this compartment, depending on whether its volume (Vc) is lower or higher than a given threshold volume (Vs). The external pressure exerted on the collapsible compartment (Pc,e) corresponds to the pleural pressure in the real respiratory system. This pressure is a linear function of the system distension, the slope being the thoracic elastance estimated to be half the total elastance (E) of the system.

The elastic behaviour of the two compartments is described by the following equations:

$$Pa = E \cdot Va, \tag{1}$$

where Pa and Va are respectively the alveolar pressure and volume over the relaxation volume, and

$$Pc,i - Pc,e = Ec \cdot (Vc - Vs), \tag{2}$$

where Pc,i is the pressure inside the collapsible compartment and Pc,e is the external (pleural) pressure given by

$$Pc,e = \frac{E}{2} \cdot Vtot + C, \tag{3}$$

where $Vtot = Va + Vc$ and C is the pleural pressure at relaxation volume.

The flow from the alveolar to the collapsible compartment is given by:

$$\frac{dVa}{dt} = \frac{(Pc,i - Pa)}{(Rc + Rd)}, \tag{4}$$

where Rc and Rd are respectively collapsible and distal resistances.

The flow at the airways opening is expressed by

$$\frac{dVtot}{dt} = \frac{(P - Pc,i)}{Rp} \tag{5}$$

where Rp is the proximal resistance.

The behaviour of the collapsible compartment depends on its volume:

$$\begin{cases} Vc < Vs \Rightarrow Rc = k \cdot (Vs - Vc) + R_0; \quad Ec = Ec_0 \\ Vc \geq Vs \Rightarrow R = R_0; \quad Ec = n \cdot Ec_0, \end{cases}$$

where k and R_0 are the slope and the constant parameters of the linear relationship between collapsible resistance and volume, and Ec_0 is the elastance of the collapsible compartment when compressed. The model thus obeys the differential system:

$$\begin{pmatrix} \dfrac{dv}{dt} \\ \dfrac{dVa}{dt} \end{pmatrix} = \begin{pmatrix} a & b \\ c & d \end{pmatrix} \begin{pmatrix} v \\ Va \end{pmatrix} + \begin{pmatrix} e \\ f \end{pmatrix}, \tag{6}$$

where $v = Vc - Vs$ and

$$a = -\left(Ec + \frac{E}{2} \right) \cdot \left(\frac{1}{Rp} + \frac{1}{Rc + Rd} \right); \qquad b = \frac{E}{2} \cdot \left(\frac{1}{Rc + Rd} - \frac{1}{Rp} \right);$$

$$c = \left(Ec + \frac{E}{2} \right) \cdot \frac{1}{Rc + Rd}; \qquad d = -\frac{E}{2} \cdot \frac{1}{Rc + Rd};$$

$$e = \frac{P}{Rp} - \left(C + \frac{E.Vs}{2} \right) \cdot \left(\frac{1}{Rp} + \frac{1}{Rc + Rd} \right); \quad f = \left(C + \frac{E.Vs}{2} \right) \cdot \frac{1}{Rc + Rd},$$

and with the conditions

$$\begin{cases} v < 0 \Rightarrow Rc = -k \cdot v + R_0; \quad Ec = Ec_0 \\ v \geq 0 \Rightarrow Rc = R_0; \qquad Ec = n.Ec_0. \end{cases}$$

Glossary	
E, Ec, Ec_0	Elastance of, respectively, the alveolar compartment, the collapsible compartment and the collapsible compartment when compressed $(hPa \cdot l^{-1})$
Va, Vc	Volume of respectively alveolar and collapsible compartment (l)
$Vtot$	$Va + Vc$ (l)
Vs	Threshold volume of the collapsible compartment (l)
v	$Vc - Vs$ (l)
Pc,e, Pc,i	Pressure outside and inside (respectively) the collapsible compartment (hPa)
Pa, Paet	Pressure inside alveolar compartment and end tidal Pa (respectively) (hPa)
P	Pressure at the entry of the airways, (hPa)
Rd, Rc, Rp	Distal, collapsible and proximal resistances $(hPa \cdot l^{-1} \cdot s)$
C	Pleural pressure at relaxation volume
k, R_0	Slope $(hPa \cdot l^{-2} \cdot s)$ and constant $(hPa \cdot l^{-1} \cdot s)$ parameters of the linear relationship between Rc and v
n	Ratio between compressed and distended collapsible compartment elastances

Computational procedure

All calculations were carried out on a PowerMac G4 computer (Apple™, Cupertino, CA) with Berkeley Madonna™ V 8.1 software (Berkeley, CA). Simulations were solved by the fourth order Runge-Kutta numerical integration technique, with an integration time step of $0.5 \cdot 10^{-3}$ s. The input variable is the pressure measured at the airways opening (P). The simulated output signal is the total flow ($dVtot/dt$). The procedure for parameter identification is made of two phases:

i) a simulation with a chosen input signal and an arbitrary initial set of parameters, including initial values of Va and Vc ($Va(0)$, $Vc(0)$); and

ii) an identification based on a gradient descent procedure i.e. a minimization of the error function (distance between the simulated and the measured output signals) in the parameter space.

A preliminary sensitivity analysis is used to ascertain how the model output depends upon the input parameters. Parameters which do not influence the model output much may be discarded in order to lighten the identification computation. The sensitivity analysis procedure was carried out in two steps. A preliminary identification was performed for each patient, taking the whole measured pressure signal as input and different arbitrary initial parameter sets. This step gave evidence of the convergence of the identification procedure to the same parameter set whatever the initial set. In the second step, the resulting parameter set of each patient was used for the sensitivity analysis.

A curve fit on the corresponding recorded flow signal was then performed with the parameters retained after sensitivity analysis. The whole procedure (simulation, curve fit) has been carried out for each patient first on the entire recording and then on the restricted part of the recording with the lowest imposed PEEPe. The goodness of fit was evaluated by the Root Mean Square Deviation (RMSD).

In order to assess if the identification process indicates existence of EFL, one may check from simulation results i) the maximal value of Rc during expiration (Rcmax); and ii) the simulated driving pressure-flow relationship during expiration ($Pa - P$ vs flow). Plotting the simulated driving pressure against flow at different levels of PEEPe allows detection of whether different driving pressures produce similar flow, giving evidence of simulated flow limitation.

3. RESULTS

Flow-volume curves

Figure 2 shows examples of expiratory FV curves obtained in patient #1 (Figure 2A) and in patient #4 (Figure 2B), in both cases at three levels of PEEPe. In patient #1, the three FV curves do not overlap, indicating the absence of expiratory flow limitation. A 1 hPa change in PEEPe resulted in an immediate increase in end-expiratory volume of about 100 ml. In patient #4, the FV curve obtained with a PEEPe of 0 and a PEEPe of 2 hPa are almost one and the same. The FV curve obtained with a PEEPe of 6 hPa is only slightly different from the former ones (slightly shifted towards higher volumes, at least 50% of the curve being similar to the two others). This denotes the presence of expiratory flow limitation (Valta *et al.*, 1994).
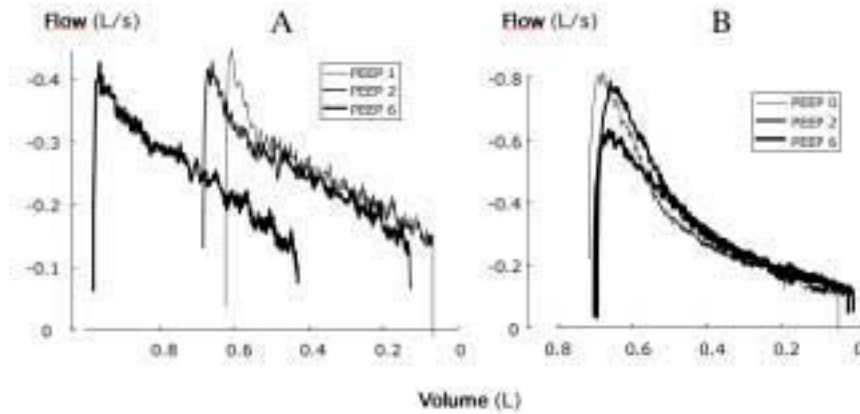
Figure 2. Expiratory Flow-Volume curves of two patients (A) patient #1, (B) patient #4. In patient #1, the different FV curves, obtained at different levels of PEEPe (1, 2 and 6 hPa), are completely distinct, reflecting the absence of expiratory flow limitation. In patient #4, the FV curves obtained at three PEEPe levels (0, 2 and 6 hPa) do overlap, denoting expiratory flow limitation.

According to this approach, patients #4, 5 and 7 exhibited strong evidence for flow limitation, whereas in patients #2, 3, 8, 9 and 10 there was no EFL at all. The case of patient #6 was intermediate, with an overlap over less than 20% of the explored volume and at lower PEEPe levels only.

Sensitivity analysis

Whatever the input pressure P (i.e. for the 10 simulations), the sensitivity analysis gave the same result: the model is less sensitive to n, k and Ec, the most sensitive parameters being Vs and C. The relative sensitivity to n, k and Ec is 1/10 to 1/100 the sensitivity to other parameters. Parameters n, k and Ec were then fixed respectively at 10, 500 hPa·l^{-2}·s and 100 hPa·l^{-1}, which are approximate mean values obtained from first identifications on all patients.

Parameter identification

There is evidence of the quality of the curve fit on Figure 3 where the recorded and simulated flow signals are plotted for patient #1 at PEEP 1 and patient # at PEEP 0 during 10 seconds.

The simulated alveolar pressure at end expiration (end tidal Pa, noted Paet) at a PEEPe of 0 can be considered as a simulated value of the measured PEEPi. We have compared the mean value of Paet of each patient to the corresponding measured PEEPi (for patient #1, the simulated value of Paet is obtained at PEEPe 2). Figure 4 illustrates the good concordance found between these variables. The values for PEEPi ranged from 1 to 12 hPa (4.85 ± 3.58 hPa) whereas the values for Paet ranged from 1.4 to 11.5 hPa (4.35 ± 3.75 hPa) (R = 0.936, 95% confidence interval 0.745-0.985,

p < 0.0001). The mean difference between PEEPi and *Pa*et (bias) was -0.5 hPa (standard deviation of bias 1.270) with 95% limits of agreement from -2.289 hPa (underestimation of PEEPi by *Pa*et) to -1.989 hPa (overestimation of PEEPi by *Pa*et) (Figure 4 left). The results of the Passing and Bablok (1983) regression of *Pa*et against PEEPi are shown in Figure 4 right**.** The 95% confidence interval of the intercept of this regression included 0 (-0.781 to 0.928) and the 95% confidence interval of the slope included one (0.714 to 1.125), indicating the absence of systematic differences between the two measures.
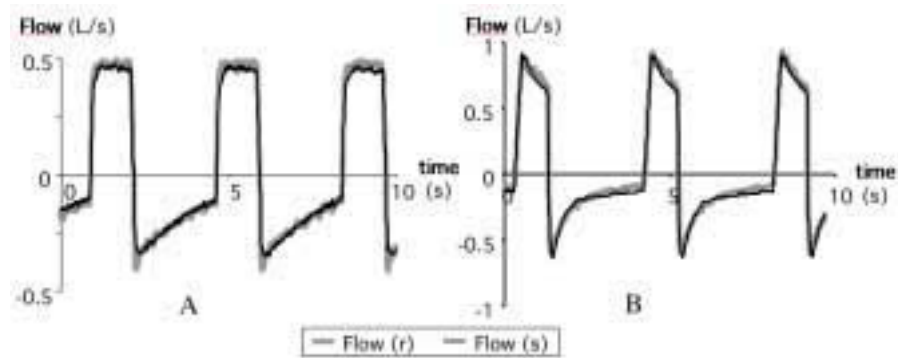
Figure 3. (A) Recorded (Flow (*r*)) and simulated (Flow (*s*)) flow signals for patient #1 at PEEP = 1 hPa; (B) Recorded (Flow (*r*)) and simulated (Flow (*s*)) flow signals for patient #4 at PEEP = 0 hPa.
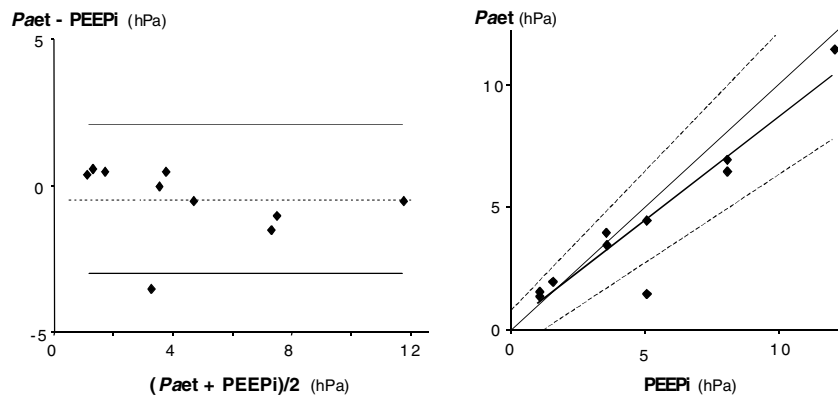
Figure 4. Bland and Altman (1986) (left) and Passing and Bablok (1983) (right) graphic representations of concordance between *Pa*et and PEEPi. Dotted lines (right) represent the limits of confidence interval of the regression line, the thick line is the regression line and the thin line is the identity line.

Among the estimated parameters only those related to mechanics (E, Vs, C, Rd, Rp, R_0) are presented in Table 2, those related to initial conditions ($Vs(0)$, $Va(0)$) are not meaningful as they depend on the time of record start. Results are presented both from

identification on entire recordings and on limited parts (40 s) at the lowest PEEP level. Initial volume values ($v(0)$ and $Va(0)$) were also identified but are meaningless as they depend on the time of the start of the recording. Table 2 clearly indicates that the identification results are very similar whether the curve fit is carried out on the entire recording (namely, at different levels of PEEPe) or on the lowest PEEPe segment only (a paired *t*-test gives no significant difference, p > 0.05, whatever the parameter). Root mean square deviation (RMSD), an estimation of the quality of fit, is reported only for identification on the entire recording, as RMSD for identification on lowest PEEP level is not different.

Table 2. Results of model parameter estimation by curve fitting for all patients. Resistances are expressed in hPa.l^{-1}·s, elastances in hPa·l^{-1}; Vs in ml; C in hPa; RMSD: root mean square deviation. For each parameter, left: identification on the entire recording, right: identification at lower PEEP. RMSD is not different between identifications for each patient.

Patient #	E		Vs		C		Rd		R$_O$		Rp		RMSD
1	10.8	*10.9*	18	*9*	0.7	*0.2*	10.9	*13.9*	1.4	*0.0*	6.5	*6.0*	0.03
2	27.8	*27.7*	15	*8*	1.3	*1.6*	5.5	*3.8*	0.4	*0.9*	8.7	*9.8*	0.05
3	24.3	*20.2*	11	*16*	0.4	*1.5*	1.8	*4.5*	0.5	*0.5*	15.7	*11.6*	0.06
4	20.5	*13.0*	101	*70*	9.4	*10.0*	1.4	*0.0*	0.4	*1.9*	19.7	*19.2*	0.04
5	34.4	*34.0*	107	*122*	7.4	*7.6*	3.3	*1.6*	0.3	*0.7*	18.2	*19.5*	0.04
6	9.4	*9.2*	30	*93*	3.0	*1.4*	1.3	*5.1*	1.0	*0.0*	11.4	*7.4*	0.13
7	16.3	*18.9*	60	*26*	4.9	*5*	2.0	*1.1*	0.1	*1.1*	15.6	*17.8*	0.06
8	22.2	*21.2*	14	*0*	0.0	*-0.7*	1.7	*1.7*	0.4	*0.5*	15.7	*16.7*	0.05
9	17.5	*14.7*	17	*23*	1.5	*-0.8*	1.7	*1.5*	0.4	*0.6*	14.5	*14.4*	0.06
10	13.3	*12.6*	96	*74*	1.3	*1.4*	1.9	*1.1*	0.2	*1.0*	13.9	*13.2*	0.05

In Figure 5 simulated driving pressure and measured flow signals (left) are gathered for three respiratory cycles at three different PEEP for patients #1 and 4. In the same figure the corresponding *x/y* graphs (right) are presented. For patient #1, whatever the driving pressure and the PEEPe level, an increase in pressure induces an increase in flow and similar driving pressures give similar flows. The same is true for patients #3, 8, 9 and 10. For patient #4 there are obviously regions where different simulated driving pressures give a similar flow. This is also observed for patients #5 and 7. According to this approach, patients #4, 5 and 7 exhibit strong evidence of simulated flow limitation, whereas in patients #1, 3, 8, 9 and 10 there is no EFL at all. In patients #2 and 6 this phenomenon is restricted to low PEEPe levels.
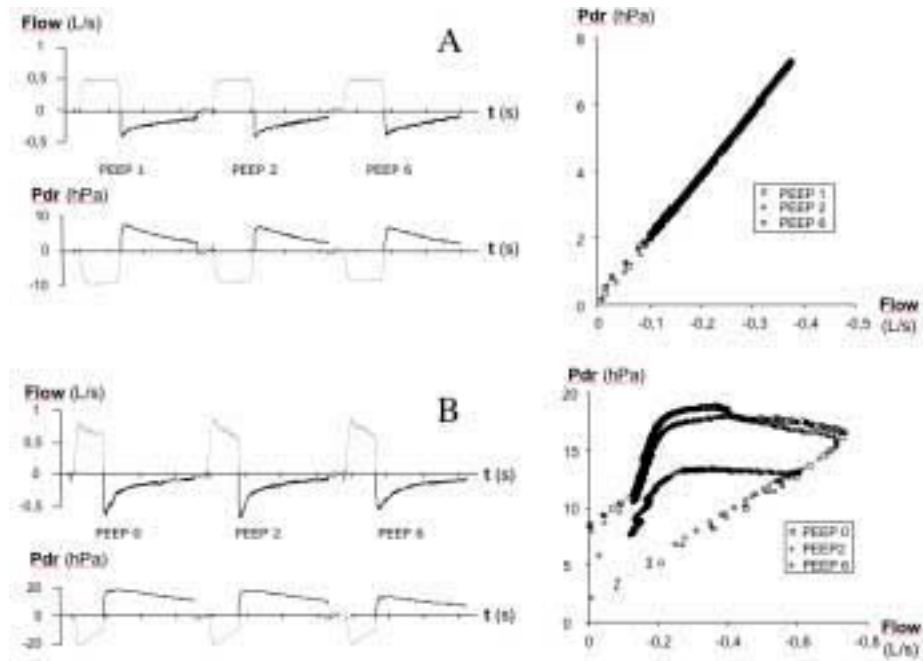
Figure 5. Simulated driving pressure (*Pdr*) and measured flow (Flow) for three respiratory cycles at three different PEEPe levels (in hPa) for patient #1 (A) and #4 (B). Left: signals; right: *x*/*y* graph presenting *Pdr* as a function of flow. In patient #4, a given expiratory flow (-0.3 *L/s*, for example), is obtained at different driving pressures.

Table 3. Comparison of EFL as evaluated by FV curves and model identification. PEEP for EFL: PEEP levels at which different driving pressures lead to similar flow. *Rc*max was obtained from identification on the entire recording (in brackets: values obtained from identification at lower PEEP).

Patient #	FV curves overlap	PEEP for EFL (Pdr/Flow curves)	C (hPa)	Rcmax (hPa·l⁻¹·s)	
1	none	none	0.2	7.3	(3)
2	none	0 ; 1	1.6	7.4	(9)
3	none	none	1.5	0.5	(7)
4	> 50%	all	10.0	66.0	(70)
5	> 50%	all	7.6	51.0	(50)
6	< 20%	0 ; 2	1.4	6.4	(15)
7	> 50%	all	5.0	30.0	(27)
8	none	none	-0.7	0.4	(1)
9	none	none	-0.8	2.0	(9)
10	none	none	1.4	0.1	(3)

In Table 3 we gathered the indexes of EFL for each patient obtained from FV curves (overlap proportion of FV curves) and from model identification (characteristic values of model parameter (C), Rcmax, PEEP levels at which different driving pressures lead to similar flow). Table 3 shows that EFL simulated by the model (PEEP for EFL) coincides with EFL detected by FV curves (FV curves overlap) for severe flow limitation (Patients #4, 5 and 7). One can notice that these severe EFL are characterized by high values of Rcmax and $C \geq 5$ hPa while for other patients, Rcmax is low and C is very small or even negative. The same holds true when considering parameters obtained from identification at lower PEEP.

4. DISCUSSION

FV Curves

A commonly used method to detect EFL consists of changing the driving pressure between the alveoli and the airways opening and looking at the resulting changes in flow-volume curves. Changing the driving pressure can be obtained by negative pressure applied at the airway opening during expiration (NEP), bypassing the expiratory line of the ventilator by exhaling into the atmosphere (ATM) (Valta *et al.*, 1994) or external resistances applied on the expiratory line (Lourens *et al.*, 2001). In the present study, we decided to take advantage of a common procedure in the Intensive Care Unit, the best PEEP trial, to modify the driving pressure and to obtain a reference way to detect EFL without modifying the therapeutic procedure. This procedure has not been validated as such but the obtained FV curves are totally similar to those obtained by other procedures.

Model

Our model uses a classical concept of flow limiting mechanism during expiration: the intermediate airway collapsibility (Mead *et al.*, 1967; Golden *et al.*, 1973). Similar models have recently been proposed (Liu *et al.*, 1998; Avanzolini *et al.*, 2001; Barbini *et al.*, 2001, 2003), these were often more detailed because the aim of the corresponding studies was mainly the elucidation of mechanisms. They confirm the need of a collapsible airway compartment to simulate flow limitation. However, identification of model parameters has not been applied with multiple patient data.

In order to simplify the identification process, we propose a model of collapsible airways consisting of a compartment the elasticity of which is described by a two segment law. The distinctive feature of our model resides in the linear relationship between total volume and pleural pressure: this relationship introduces a constant term C that proved to be important in the identification process. Indeed, the model is very sensitive to this parameter, as it is to the threshold volume Vs of the collapsible airways.

Most of similar studies mention that lung inhomogeneities should be included in models of ventilatory system (Liu *et al.*, 1998; Khirani *et al.*, 2001). As our identification results show a good agreement between simulated and recorded signals (Figure 3), we can state that the simple monoalveolar model together with a collapsible airway is sufficient to reflect the ventilatory system behaviour in case of

EFL. This applies to a patient where both expiration and inflation are passive, but it could be also true in assisted ventilation when the model of the passive respiratory system still applies during large parts of the cycle (Heyer *et al.*, 2002).

Parameter identification

A similar identification approach was undertaken by Liu *et al.* (1998) to simulate forced vital capacity manoeuvre. The input of the model was the oesophageal pressure, an estimate of pleural pressure measured in an invasive way. The model itself simulated both mechanical behaviour of the respiratory system and gas exchanges through this system. It needed at least 15 parameters for the mechanical part. Our model used only seven parameters and simulated satisfactorily the recorded situations (RMSD very low). A possible explanation for so many parameters in the Liu *et al.* (1998) study is that the mechanical characteristics of the respiratory system are more stable under resting breathing conditions, or even during mechanical ventilation with PEEP trials, than during forced vital capacity manoeuvre.

Results

FV curves at different PEEPe levels indicate the presence of EFL in some patients among the population investigated. Model identification gives identical indication except for one patient: patient #2 goes from "no EFL" (no overlap in FV curves) to "moderate EFL" (simulated flow limitation at low PEEPe levels). In this patient, presence of a pneumothorax (see Table 1) may induce a shortage of the model, the constant alveolar elastance hypothesis being questionable in such circumstances.

The quality of the fit obtained for each record supports the hypothesis that the model is sufficient to simulate EFL in the studied conditions. Moreover, the model seems capable of predicting the individual ventilatory characteristics of the patient, PEEPi for example can be estimated with a ± 2 hPa error, which is clinically acceptable.

A notable fact is that the same results were found when identification was done at the lowest PEEPe level. We thus submit that it is possible to detect EFL in ventilated patients by identifying the parameters of our model from pressure and flow signals recorded at a given PEEPe level, however low, without any intervention on the ventilator settings and without the need for a PEEP trial.

It appears that a high value of Rcmax (>30 hPa$\cdot$l$\cdot$s^{-1}) indicates severe expiratory flow limitation. This result deserves to be validated in a large population of patients but the coincidence between FV curves indications and model simulations for strong EFL is encouraging. If validated, Rcmax could be a quantitative index of EFL. The distinct higher values of estimated pleural pressure at relaxation volume (C) encountered in flow limited patients could be expected as EFL usually occurs in hyperinflated lungs, a situation inducing positive pleural pressure at end expiration.

In conclusion, our method based on model identification not only requires no modification of the therapeutic protocol but it also allows a quantitative estimation of EFL when present. This method needs to be validated in a large population of patients, and compared to other classical methods of detection. If validated, we could be able to propose a quantitative index of the degree of expiratory flow limitation according to the different values of Rcmax.

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