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# Respiratory mechanics studied by multiple linear regression in unsedated ventilated patients

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**ABSTRACT: Respiratory mechanics during artificial ventilation are commonly studied with methods which require a specific respiratory pattern. An alternative is to analyse the relationship between tracheal pressure (P) and flow ($V'$) by multiple linear regression (MLR) using a suitable model.**

**The value of this approach was evaluated in 12 unsedated patients, mechanically-ventilated for acute respiratory failure, and most with a history of chronic obstructive or restrictive respiratory disease. After correction for the non-linear resistance of the endotracheal tube, the data were analysed with the linear first order model: $P = P_0 + E \cdot V + R \cdot V'$ where E and R are total respiratory elastance and resistance, and $P_0$ is the static recoil pressure at end-expiration.**

**After exclusion of the cycles which clearly exhibited muscular activity, a good fit was observed in 25 out of 36 records (relative root-mean-square error <10%); the values of E and R were reproducible within cycles, and consistent with the patient's condition and the ventilatory mode. The intrinsic positive end-expiratory pressure (PEEPi), as derived from $P_0$ and the applied PEEP, averaged 1.1±1.0 hPa. Using more sophisticated models, allowing for mechanical non-homogeneity or non-linearity of R or E, rarely improved the fit and often provided unrealistic data. In several subjects the discrepancy between the data and the first order model was consistent with expiratory flow limitation, which may severely impair the analysis.**

**We conclude that, except in the case of expiratory flow limitation, the method is useful for routine clinical use and better implemented with the simple linear model.**

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Monitoring respiratory mechanics during artificial ventilation in patients with acute respiratory failure (ARF) is important for the optimal adjustment of the ventilator settings and to detect changes in the patient's condition. Although they are non-invasive, the methods recently used to this end invariably require a specific respiratory pattern during the measurements, including a constant flow inflation and/or an end-inspiratory airway occlusion [1–5]. Such patterns may easily be obtained with some, but not all, ventilators; they are not necessarily optimal for gas exchange and may influence the very properties that one is trying to monitor by changing gas distribution or end-inspiratory lung volume. An interesting alternative method is the analysis of the tracheal pressure and flow signals with a suitable model by multiple linear regression (MLR). The method does not require any specific shape of the signals and has been successfully applied in anaesthetized humans [6, 7], and in animal studies [7, 8]. To our knowledge, however, its value for monitoring respiratory mechanics in unsedated and non-paralysed mechanically-ventilated patients with ARF has not yet been investigated. The aim of this study was, therefore, to evaluate the usefulness of the MLR method in such patients, and to assess which model could be used to interpret the data.

## Methods

The study was conducted in 12 patients admitted to an Intensive Care Unit (Dept of Respiratory Diseases and Intensive Care, University Hospital, Nancy, France) for acute respiratory failure necessitating ventilatory support. Most patients had a history of obstructive or restrictive respiratory disease, and their episode of ARF was triggered by a recent infection (table 1). They were intubated transnasally with Portex cuffed endotracheal tubes (ET), 7–8.5 mm in internal diameter (ID). The study took place 2–11 days after intubation, at which time the patients were in a stable clinical condition. They were conscious and their informed consent was obtained by the primary physician.

Table 1. – Patients' characteristics

| Pt No. | Sex | Age yrs | ET ID mm | Vent. | $F_{IO_2}$ % | Diagnosis |
|---|---|---|---|---|---|---|
| 1 | M | 76 | 8.0 | DRA | 35 | COPD, acute bronchitis |
| 2 | F | 79 | 7.5 | OHM | 45 | Bronchopneumonia |
| 3 | M | 71 | 8.5 | OHM | 40 | COPD |
| 4 | M | 79 | 7.5 | SIE | 40 | COPD, acute bronchitis |
| 5 | M | 60 | 8.0 | OHM | 45 | COPD, acute bronchitis |
| 6 | M | 61 | 8.5 | OHM | 40 | COPD, legionellosis |
| 7 | M | 65 | 8.0 | OHM | 35 | TP seq., COPD, viral infection |
| 8 | M | 54 | 8.5 | DRA | 30 | COPD, bronchopneumonia |
| 9 | F | 66 | 7.5 | OHM | 40 | Obesity, acute bronchitis |
| 10 | F | 59 | 8.5 | OHM | 25 | TP seq., COPD, acute bronchitis |
| 11 | M | 42 | 8.0 | OHM | 50 | COPD, kyphoscoliosis, acute bronchitis |
| 12 | F | 67 | 7.0 | OHM | 30 | Kyphoscoliosis |

ET: endotracheal tube; Vent.: ventilator; $F_{IO_2}$: fractional inspiratory oxygen; DRA: ventilator Draeger EV-A; OHM: ventilator Ohmeda CPU1: SIE: Servo-ventilator Siemens 900C; COPD: chronic obstructive pulmonary disease; TP seq: sequela of pulmonary tuberculosis.

Respiratory flow (V') was measured with a slightly heated Fleisch No. 1 pneumotachograph, inserted between the endotracheal tube and the ventilator Y-piece, and connected to a differential pressure transducer (Honeywell Type 176PC). Tracheal pressure (P) was measured with an identical pressure transducer, matched to the first within 1% of amplitude and 2° of phase up to 20 Hz. The two signals were digitized at a sampling rate of 40 Hz by an Apple 2e microcomputer system and stored on diskettes for off-line processing.

The patients were not premedicated. Measurements were performed with the ventilation and fractional inspiratory oxygen ($F_{IO_2}$) previously chosen by the primary physician, according to clinical criteria and to the patient's blood gases. The ventilators were used in the controlled mode. Data were collected for periods of 48 s with three different settings of the ventilator: 1) without end-inspiratory pause (IPA) and with zero end-expiratory pressure (EEP); EEP was, however, slightly positive in some instances due to the resistance of the expiratory circuit; 2) with a 0.4–1 s IPA and zero EEP, tidal volume was then readjusted to keep ventilation approximately constant; 3) with the same IPA as mode 2 and with an EEP of 5–10 hPa. The mean values of respiratory frequency, tidal volume, ventilation and EEP in the three conditions, computed from the records, are shown in table 2. The measurements were started a few minutes after resetting the ventilator, when the pressure and flow tracings suggested that the subject was adequately relaxed (or as relaxed as possible).

*Data analysis*

Pressure and flow data were analysed on a cycle-per-cycle basis. After identification of a cycle, the flow signal was corrected for any offset, using the assumption that inspired and expired volumes were identical. The pressure signal was then corrected for the pressure drop along the ET. The latter was separately measured at inspiratory and expiratory flows ranging 0–0.7 $l \cdot s^{-1}$, taking into account the observations of CHANG and MORTOLA [9] and of BEHRAKIS *et al.* [10]: the cuffed extremity of the ET was placed in a larger tube mimicking the trachea [10] and the pressure was measured from the opening of the ET to a point a few cm beyond its extremity, in order to avoid the zone where the streamlines separate from the "tracheal" walls [9]. The non-linear pressure-flow relationship was characterized by Rohrer's equation ($P=K_1 \cdot V' + K_2 \cdot V'^2$) [11] and the values of the constants were obtained by linear regression of P/V' *versus* V'. As $K_1$ and $K_2$ were similar during inspiration and expiration, a mean value was taken to correct the pressure data.

Table 2. – Ventilatory modes and variables

| Ventilatory mode | 1 | 2 | 3 |
|---|---|---|---|
| IPA | 0 | + | + |
| PEEP | 0 | 0 | + |
| $f$ cycles·min$^{-1}$ | 17.9±4.6 | 14.0±2.6 | 14.3±3.3 |
| $V_T$ $l$ | 0.63±0.16 | 0.71±0.17 | 0.71±0.18 |
| $V_E$ $l \cdot min^{-1}$ | 11.1±3.6 | 9.9±2.6 | 10.0±3.0 |
| EEP hPa | 2.0±1.5 | 2.4±2.0 | 10.2±1.5 |

Data presented are mean values±SD in 12 patients. IPA: end-inspiratory pause; PEEP: positive end-expiratory pressure; $f$: frequency; $V_T$: tidal volume; $V_E$: ventilation; EEP: end-expiratory pressure.

After correction the pressure and flow data were analysed with the following models:

Model 1 is the classical linear monoalveolar model, including total respiratory elastance (E) and resistance (R):

$$P = P_0 + E \cdot V + R \cdot V' \qquad (1)$$

The third constant $P_0$ represents the elastic recoil pressure of the respiratory system when volume (V) equals zero, that is at end-expiration; it includes both the end-expiratory pressure applied by the respirator (external

PEEP (PEEPe)) and any additional recoil pressure due to dynamic hyperinflation (intrinsic PEEP (PEEPi)) [12].

Model 2 is similar to Model 1 except that it allows for different resistances during inspiration and expiration, E and $P_0$ being common to the two phases:

$$\begin{aligned} \text{Inspiration } P &= P_0 + E\cdot V + Ri\cdot V' \\ \text{Expiration } P &= P_0 + E\cdot V + Re\cdot V' \end{aligned} \quad (2)$$

Model 3 includes a non-linear resistance, as described by Rohrer's equation [11]:

$$P = P_0 + E\cdot V + (K_1 + K_2\cdot |V'|)\cdot V' \quad (3)$$

With Model 4, resistance may vary linearly with lung volume:

$$P = P_0 + E\cdot V + (R_0 + K_3\cdot V)\cdot V' \quad (4)$$

where $R_0$ is the resistance at the end-expiratory level, and $K_3$ expresses the change in resistance per unit of lung volume.

With Model 5, it is elastance which may vary with lung volume:

$$P = P_0 + (E_0 + K_4\cdot V)\cdot V + R\cdot V' \quad (5)$$

where $E_0$ is the elastance at end-expiration and $K_4$ its change with volume.

Finally, Model 6 incorporates mechanical non-homogeneity of the respiratory system in the form of Otis' model [13]. It corresponds to a linear system with two compartments in parallel, each characterized by its resistance ($R_1$, $R_2$) and elastance ($E_1$, $E_2$):

$$P + T\cdot P' = P_0 + E\cdot V + A\cdot V' + B\cdot V'' \quad (6)$$

where P' and V'' are the time derivatives of P and V', respectively, and where:

$$\begin{aligned} T &= (R_1 + R_2)/(E_1 + E_2) \\ E &= E_1\cdot E_2/(E_1 + E_2) \\ A &= (R_1\cdot E_2 + R_2\cdot E_1)/(E_1 + E_2) \\ B &= R_1\cdot R_2/(E_1 + E_2) \end{aligned}$$

Equation (6) may also account for the viscoelastic properties of respiratory tissues [14].

In all instances the values of the coefficients which minimized the root-mean-square difference (RMSD) between the right (Mr) and the left (Ml) members of the equation were obtained by multiple linear regression:

$$RMSD = (\Sigma\ (Ml\text{-}Mr)^2/n)^{1/2} \quad (7)$$

where n is the number of experimental points in the cycle. The RMSD also expresses the quality of the fit between the model and the data.

A condition for analysing tracheal pressure in terms of the passive properties of the respiratory system is that the subject be relaxed. Even if this appeared to be the case when the measurements were started, examination of the records occasionally revealed signs of muscular activity in the form of transient variations in the pressure and flow signals. One possibility was to exclude the corresponding cycles on the basis of their aspect, but it is somewhat subjective and is difficult to automize. Reasoning that occasional muscular activity should in general decrease the quality of the fit to the model, we chose rather to discard cycles whose RMSD did not meet the following criteria with Model 1:

RMSD <1.5 RMSDmin **or** RMSD-RMSDmin <0.5 hPa

where RMSDmin was the lowest RMSD observed in the considered piece of record. The combination of an absolute and a relative criterion was used to avoid the possibility that the severity of the selection depended too much upon the adequacy of the model. The thresholds were chosen in such a way that obviously good and obviously bad cycles were properly categorized. In 22 out of 36 records no cycle was discarded. The percentages of rejected cycles in the three ventilatory modes were 5.7, 10.6 and 17.6, respectively. The number of selected cycles ranged 4–16. The same cycles were analysed with all the models.

Models 2–6 include Model 1 and, therefore, may only improve the fit. The statistical significance of the difference in RMSD between two models may be assessed using the F test suggested by EYLES *et al.* [15]:

$$F = (n - p_2)\ (RMSD_1^2 - RMSD_2^2)/(p_2 - p_1)\cdot RMSD_2^2 \quad (8)$$

where indices 1 and 2 designate the two models, and $p_1$ and $p_2$ are their respective number of parameters. In this study, however, we observed that, due to the large number of points per cycle, F could already be significant when the RMSD decreased by as little as 0.01 hPa, whilst a visually discernible improvement required a decrease of at least 0.2 hPa. We, therefore, decided to use more severe criteria of improvement, and to consider that a model was more satisfactory than Model 1 when the following conditions were met: 1) reduction of the RMSD by at least 20% and at least 0.3 hPa; 2) physiologically acceptable values, *i.e.* positive values for Ri, Re, $K_1$, $K_2$, $R_0$, $E_0$, A, B, T, E, and negative value for $K_3$.

Statistical analysis included Student's t-test on paired data and linear regression.

## Results

The results obtained with Model 1 are summarized in table 3. The RMSD was <1 hPa in 14 out of 36 records, and <1.5 hPa in 25 instances, whilst the root-mean-square of the pressure signal (corrected for the tracheal tube) averaged 15.5±4.3 hPa. The RMSD was significantly lower with than without an external PEEP ($p<0.05$). Examples corresponding to one of the best cases and to the worst case are shown in figure 1.

Table 3. – Coefficients obtained with Model 1 in the three ventilatory modes

| Pt No. | Ventilatory mode 1 | | | | Ventilatory mode 2 | | | | Ventilatory mode 3 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | RMSD hPa | $P_0$ hPa | E hPa·$l^{-1}$ | R hPa·$l^{-1}$·s | RMSD hPa | $P_0$ hPa | E hPa·$l^{-1}$ | R hPa·$l^{-1}$·s | RMSD hPa | $P_0$ hPa | E hPa·$l^{-1}$ | R hPa·$l^{-1}$·s |
| 1 | 2.5 | 3.7 | 11.3 | 18.8 | 3.1 | 2.0 | 15.0 | 15.6 | 1.3 | 9.6 | 11.7 | 7.7 |
| 2 | 2.4 | 5.7 | 36.5 | 10.7 | 2.0 | 5.7 | 28.2 | 13.9 | 1.1 | 11.1 | 19.7 | 13.4 |
| 3 | 1.7 | 0.8 | 24.8 | 5.6 | 1.2 | 2.5 | 16.1 | 8.9 | 0.6 | 9.0 | 13.7 | 8.1 |
| 4 | 1.4 | 2.8 | 18.7 | 12.4 | 0.9 | 6.8 | 18.7 | 14.2 | 0.9 | 11.2 | 18.5 | 10.6 |
| 5 | 1.1 | 2.6 | 20.8 | 29.3 | 1.0 | 2.8 | 20.4 | 30.1 | 0.5 | 12.7 | 17.5 | 20.7 |
| 6 | 1.0 | 8.5 | 24.5 | 13.4 | 0.8 | 10.3 | 19.7 | 13.7 | 0.8 | 14.1 | 25.3 | 12.9 |
| 7 | 1.9 | 2.1 | 29.9 | 19.4 | 1.7 | 1.9 | 31.4 | 19.0 | 0.6 | 10.4 | 26.5 | 12.3 |
| 8 | 0.7 | 1.4 | 13.2 | 9.0 | 0.9 | 2.6 | 16.9 | 12.1 | 0.5 | 10.9 | 16.3 | 8.2 |
| 9 | 1.4 | 3.2 | 19.7 | 14.9 | 1.1 | 2.6 | 19.5 | 12.0 | 1.9 | 12.1 | 16.7 | 4.3 |
| 10 | 2.5 | 2.0 | 25.8 | 22.3 | 2.7 | 2.0 | 30.1 | 25.9 | 1.9 | 11.4 | 29.9 | 24.1 |
| 11 | 0.6 | 1.9 | 35.7 | 5.9 | 0.6 | 2.0 | 34.4 | 6.2 | 0.8 | 9.2 | 38.0 | 4.7 |
| 12 | 1.1 | 1.4 | 44.2 | 10.3 | 1.1 | 2.2 | 40.8 | 10.9 | 1.4 | 9.4 | 36.8 | 2.6 |
| Mean | 1.54 | 2.99 | 24.4 | 14.3 | 1.43 | 3.61 | 24.2 | 15.2 | 1.03* | 10.9** | 22.5 | 10.8* |
| SD | 0.69 | 2.15 | 9.8 | 7.0 | 0.78 | 2.61 | 8.4 | 6.8 | 0.50 | 1.5 | 8.7 | 6.5 |

For definitions see equations (1) and (7). Significance of differences between ventilatory modes 3 and 1 (paired t-test): *: $p<0.05$, **: $p<0.001$. RMSD: root-mean-square difference.

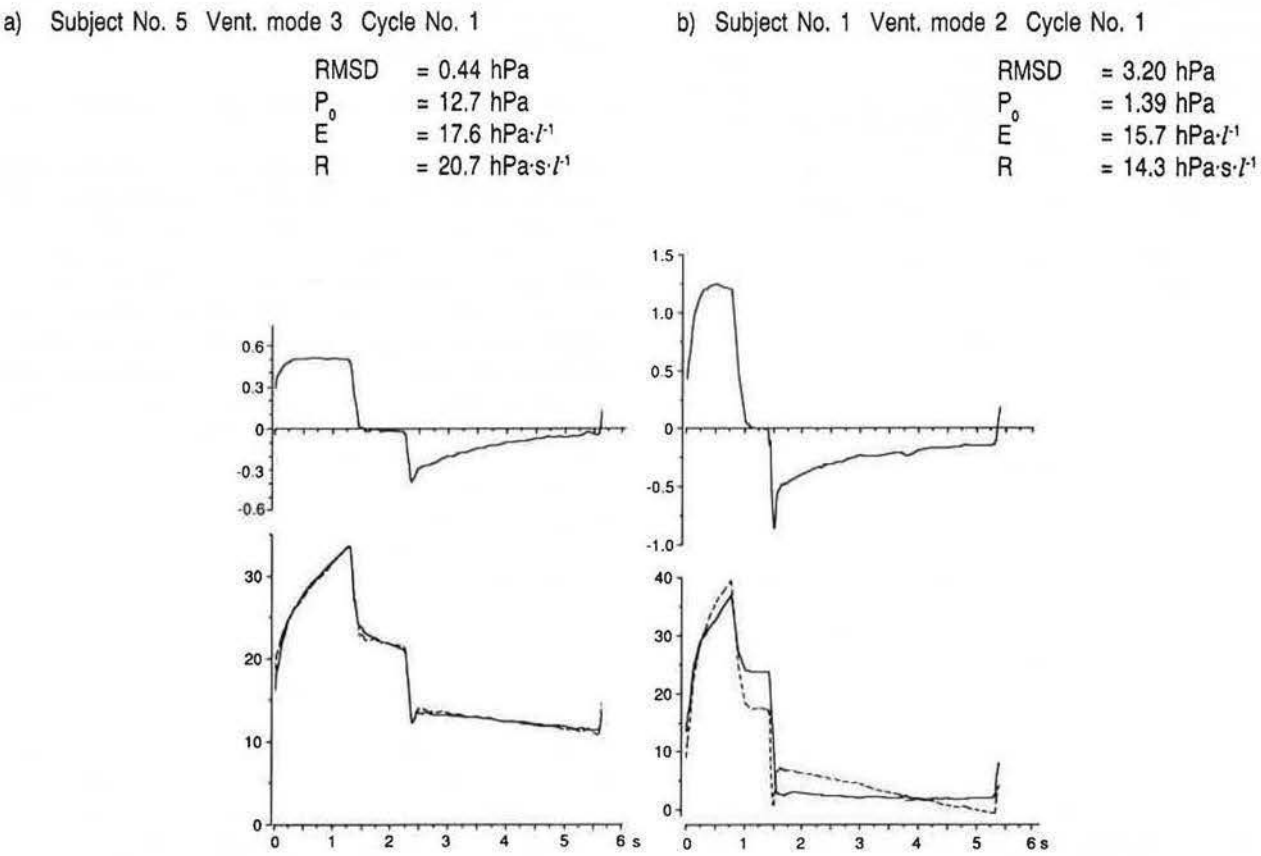


Fig. 1. – Examples of flow (top) and tracheal pressure (bottom) recordings in two subjects. The discontinuous line is the pressure recomputed from equation (1) using the observed flow and the coefficients obtained by linear regression. One of the best cases and the worst case are shown. RMSD: root mean square difference; $P_0$: elastic recoil pressure of the respiratory system when volume equals zero; E: total respiratory elastance; R: total respiratory resistance.

It may be seen that a RMSD of 0.4 hPa corresponds to an almost perfect fit between the observed pressure and the pressure recomputed from equation (1) using the observed flow and the coefficients provided by the analysis. It is also clear that the model is quite inadequate in the other example: compared to the observed pressure, that computed from the model was a little larger at end-inspiration and substantially lower during the pause; for the expiratory phase, after a brief transient corresponding to the peak expiratory flow, it was first larger, and then lower than the observed pressure. Several of these features were present, but much less marked, in five other subjects, especially with ventilatory modes 1 and 2.

Total respiratory elastance was fairly reproducible within a piece of record with a coefficient of variation averaging 5.5%. E varied significantly with the ventilatory mode in two subjects (Nos 2 and 3), but not in the group. A highly significant correlation was observed between the values obtained in the three modes (r=0.89 between modes 1 and 2, and r=0.90 between modes 1 and 3). Resistance was more variable between cycles, with a coefficient of variation averaging 8.5%. Although it was not the case in all of the subjects, R was significantly lower in the group with ventilatory mode 3 than with mode 1 ($p<0.05$) and mode 2 ($p<0.001$). Significant correlations were also present between the values obtained with the different modes (r=0.95 between modes 1 and 2, r=0.87 between modes 2 and 3).

$P_0$, the elastic recoil pressure at end-expiration, was fairly reproducible between cycles, with a standard deviation (SD) averaging 0.35 hPa. It was similar and highly correlated (r=0.83) with ventilatory modes 1 and 2, and, of course, much larger ($p<0.001$) when a positive end-expiratory pressure was used. The intrinsic PEEP, as obtained from the difference between $P_0$ and the observed EEP averaged 1.04, 1.17 and 0.72 hPa in ventilatory modes 1, 2 and 3, respectively, (total range -0.80–3.17 hPa). It was not significantly different between modes.

The average data with the four-parameter models are summarized in table 4. Allowing for different inspiratory and expiratory resistances decreased the RMSD by only 0.11 hPa. The improvement met the 20% and 0.3 hPa criteria in two out of 36 records, but the data were physiologically meaningful (positive Ri and Re) in only one of them. In that instance Re was 83% larger than Ri. In the group, Model 2 provided slightly lower values of $P_0$ and E than Model 1 ($p<0.01$) with ventilatory mode 1 and slightly larger values of $P_0$ with the other modes. The coefficients obtained with the two models, however, were highly correlated (r=0.99 and 0.98 for $P_0$ and E, respectively). Re was significantly lower than Ri with ventilatory mode 1 ($p<0.01$), and significantly higher with the two other modes ($p<0.05$ and $p<0.01$). The variability of Re and Ri was larger than that of R, both between cycles and between individuals.

Allowing for flow-dependence of resistance decreased the RMSD by 0.2 hPa on average. The RMSD improvement criteria were met in eight records. The values of $P_0$ and E were highly correlated to those obtained with Model 1, and were not significantly different, except for $P_0$ with ventilatory mode 2, which was slightly larger ($p<0.05$). Both $K_1$ and $K_2$ had very large intra-individual and interindividual variabilities; they were negative in 2 and 26 out of 36 records, respectively; in particular, either $K_1$ or $K_2$ was negative in seven of the eight cases where the model improved the fit.

Table 4. – Results obtained with the four and five-coefficient models

| | Vent. Mode 1 | Vent. Mode 2 | Vent. Mode 3 |
|---|---|---|---|
| **Model 2** | | | |
| RMSD hPa | 1.47±0.67 | 1.33±0.67 | 0.87±0.34 |
| $P_0$ hPa | 2.63±2.09* | 4.17±2.27* | 11.56±1.67* |
| E hPa·$l^{-1}$ | 23.8±10.1* | 24.4±8.2 | 22.5±8.6 |
| Ri hPa·s·$l^{-1}$ | 15.7±8.4 | 14.0±6.2 | 9.1±6.9 |
| Re hPa·s·$l^{-1}$ | 13.4±4.3 | 17.8±9.5 | 13.6±8.0 |
| **Model 3** | | | |
| RMSD hPa | 1.31±0.62 | 1.15±0.58 | 0.92±0.46 |
| $P_0$ hPa | 3.48±2.02 | 4.46±2.10* | 11.17±1.54 |
| E hPa·$l^{-1}$ | 25.5±8.7 | 23.6±8.0 | 22.4±9.0 |
| $K_1$ hPa·s·$l^{-1}$ | 20.4±16.6 | 22.0±14.0 | 12.1±11.0 |
| $K_2$ hPa·$s^2$·$l^{-2}$ | -11.3±19.1 | -11.4±14.3 | -0.5±12.5 |
| **Model 4** | | | |
| RMSD hPa | 1.31±0.63 | 1.30±0.81 | 0.95±0.45 |
| $P_0$ hPa | 2.99±2.15 | 3.61±2.62 | 10.92±1.52 |
| E hPa·$l^{-1}$ | 25.4±9.8 | 24.3±8.4 | 22.6±8.7 |
| $R_0$ hPa·s·$l^{-1}$ | 15.8±9.9 | 17.0±7.5 | 9.8±6.2 |
| $K_3$ hPa·s·$l^{-2}$ | -4.2±15.2 | -5.3±6.8 | 3.7±5.0 |
| **Model 5** | | | |
| RMSD hPa | 1.30±0.59 | 1.08±0.47 | 0.82±0.39 |
| $P_0$ hPa | 3.78±2.10* | 4.93±2.29* | 11.71±1.56* |
| $E_0$ hPa·$l^{-1}$ | 14.0±15.9 | 10.9±13.7 | 12.9±8.0 |
| $K_4$ hPa·$l^{-2}$ | 24.9±30.0 | 20.7±22.5 | 15.8±19.2 |
| R hPa·s·$l^{-1}$ | 14.3±7.0 | 15.2±6.8 | 10.8±6.5 |
| **Model 6** | | | |
| RMSD hPa | 1.35±0.56 | 1.38±0.76 | 0.97±0.48 |
| $P_0$ hPa | 3.40±2.09* | 3.80±2.59* | 11.34±1.62* |
| E hPa·$l^{-1}$ | 23.7±9.9* | 23.9±8.3 | 22.1±8.6 |
| A hPa·s·$l^{-1}$ | 14.4±7.7 | 14.8±7.1 | 10.6±6.9 |
| B hPa·$s^2$·$l^{-1}$ | -0.15±0.11 | -0.18±0.08 | -0.13±0.09 |
| T ms | 5.1±21.4 | -5.8±10.7 | 0±17.2 |

Data are presented as mean±SD in 12 patients. For abbreviations see equations (2) to (7). *: significantly different from Model 1. Vent.: ventilatory; RMSD: root-mean-square difference.

The values of $P_0$ and E found with Model 4 were always identical to those obtained with Model 1. Introducing volume-dependence of resistance substantially improved the fit in four records, but $K_3$ had the expected sign, *i.e.* was negative, in only two of them.

Among the four-coefficient models, allowing for volume-dependence of elastance was most effective in decreasing the RMSD (-0.25 hPa on average). The values of R were identical to those found with Model 1, but the values of $P_0$ were significantly larger in the

three ventilatory modes. $K_4$ was always positive, *i.e.* elastance increased with lung volume, but $E_0$ was negative or unrealistically low (<5 hPa·$l^{-1}$) in a number of instances, including seven of the 10 records where the model improved the fit substantially.

Finally, the five-coefficient model allowing for mechanical non-homogeneity decreased the RMSD very little (-0.1 hPa on average): the 20% and 0.3 hPa criteria were met in a single record. $P_0$ and E were highly correlated to the values obtained with Model 1 ($r>0.97$ in all ventilatory modes) but were, respectively, slightly larger and slightly lower. The flow coefficient A was almost identical to R with r values >0.99. The acceleration coefficient B was small and negative in most instances, and the time constant T ranged -0.023–0.048 s. In the three instances where all the coefficients were positive, the first compartment of Otis' model was similar to that found with Model 1, and the second had a low resistance and a huge elastance (>300 hPa·$l^{-1}$). In none of these instances was the RMSD substantially decreased.

## Discussion

Previous studies have demonstrated the feasibility of measuring respiratory mechanics during artificial ventilation in unsedated and unparalysed patients [2–5]. The difficulty is to assess if the patient is sufficiently relaxed to obtain meaningful data. In this study the pressure and flow tracings showed occasional signs of muscular activity in a number of records. The most frequent occurrences were a change in the slope of the pressure signal during inspiration, with a transient decrease of inspiratory flow, and an attempt to trigger the ventilator at end-expiration. The corresponding cycles usually provided outlying values of the coefficients. Also, their RMSD were larger and clearly related to the level of muscular activity. We, therefore, used the RMSD to recognize such activity and discard the corresponding cycles. This selection is based on the reasonable assumption that the pressure developed by the muscles is unlikely to be related to volume and flow as postulated in the models, so that muscular activity may only increase the RMSD. That selection appeared very effective in improving the reproducibility of E and R between cycles: on average the coefficients of variation decreased from 18.8 to 7.1%, and from 23.4 to 14.7% for E and R, respectively, in the records where cycles were discarded. It is likely that more severe criteria than used in this study would further improve the data.

Taking into account that some of the RMSD (about 0.3 hPa) was due to experimental noise on the pressure and flow signals, Model 1 almost perfectly described the data in about one third of the records, including one of the examples shown in figure 1. The values of the coefficients were always physiologically meaningful and consistent with the patient's condition. So were the changes in $P_0$ and R seen when applying a PEEP. The only surprising result was that PEEPi, as obtained from the difference between the EEP and $P_0$, was substantially lower than previously observed in mechanically-ventilated chronic obstructive pulmonary disease (COPD) patients using different methods: Broseghini *et al.* [2] reported a value of 13.6±6.7 hPa during the first day of mechanical ventilation, whilst Bernasconi *et al.* [5] and Rossi *et al.* [3] found a value of 5.1±3.2 and 3.8±2.2 hPa, respectively, in clinically stable patients. In contrast, PEEPi was only 1.1±1.0 hPa in our eight COPD patients with Model 1, and 1.9±1.3 hPa with Model 5, which provided the largest values of $P_0$. This discrepancy may be due to the fact that these patients were always ventilated with an expiratory time (Te) which was much larger than their mechanical time constant ($\tau$), as given by the ratio of their resistance and elastance. Indeed, assuming linear behaviour, the expected PEEPi may be computed from:

$$PEEPi = E \cdot V_T \cdot \sum_{j=1}^{\infty} e^{-j \cdot Te/\tau} \quad (9)$$

Using this equation, the predicted value of PEEPi was of 0.55 hPa, which is even lower than the observed value. This prediction, however, is based on the assumption that the values of resistance and elastance obtained with Model 1 are correct, which may be questioned in a number of subjects (fig. 1b). The point is further discussed below.

Almost all of the patients included in this study had a medical history of severe obstructive or restrictive respiratory disease, likely to promote inhomogeneous and nonlinear behaviour of the respiratory system. The systematic discrepancies between the observed pressure and that computed with Model 1 in a number of patients, as well as the improved RMSD when using a PEEP, also suggested that the model could not fully account for the pressure-flow relationship present with the other ventilatory modes. We were, therefore, surprised to observe that Models 2–6 rarely appeared more satisfactory than Model 1. With the RMSD and sign criteria taken in this study this was only the case in one instance for Model 2 and Model 3, two instances for Model 4, and three instances for Model 5; it was never the case for Model 6. As far as flow dependence is concerned, the reason may be that the shape of the signals during artificial ventilation (almost constant inspiratory flow and zero flow during the end-inspiratory pause), is inadequate to reveal non-linear behaviour. Indeed, it has been shown by Lorino *et al.* [16], on ventilated mechanical analogues, that better estimates of Rohrer's $K_2$ could be obtained from the expiratory phase, where flow is more variable, than from the whole cycle. Both flow and volume dependences could also be obscured by some undetected muscular activity. For instance, a small degree of expiratory effort in late inspiration could mask the decrease in pressure associated with a negative volume dependence of resistance or elastance. This may also explain the unrealistic values of $K_2$, $K_3$ and $K_4$ observed in some instances.

In most of our subjects a slight decrease in tracheal pressure, probably related to mechanical non-homogeneity of the lung, could be seen during the

end-expiratory pauses. We were, therefore, surprised that Model 6 did not better fit the data than Model 1 and generally provided negative values of the coefficients T and B, which is inconsistent both with Otis' model [13] and with lung and chest viscoelasticity [14]. Our interpretation is that the frequency content of the signals during artificial ventilation is too narrow to make the influence of mechanical non-homogeneity discernible with the approach used in this study, particularly when confusing factors like non-linearity and some muscular activity are also present. Assessing mechanical non-homogeneity, therefore, seems better accomplished by analysing the changes in tracheal pressure during a prolonged end-inspiratory occlusion [2, 5, 14].

An interesting and comforting finding in this study was that the values of the corresponding coefficients were highly correlated and differed little in general between models. Elastance was identical with Models 1 and 4, and individual differences rarely reached 10% in the other instances. Resistance was the same with Models 1 and 5. This suggests that non-linearity of R cannot be responsible for a serious misestimation of E, and conversely. For $P_0$, individual differences between Model 1 and Models 2, 3 and 5 exceeded 1 hPa in 4, 9 and 12 out of 36 records, respectively; the values found with Models 1 and 4 were identical.

A common assumption to all the models used in this study is that flow is related to airway opening pressure. This is no more the case when expiration is flow-limited, in which case expiratory flow is independent of the downstream pressure. The occurrence of flow-limitation during passive expiration in ventilated patients has been noted in several studies [4, 17–19]. It may be suspected when "supra-maximal" flow transients [4] are present either at the beginning of expiration [19] or following flow interruption [4]. Such transients correspond to the emptying of a small compartment with a short time-constant and are likely to result from dynamic airway compression. In this study, recognizable flow transients at the beginning of the expiratory phase were seen in one subject (No. 1) with the three ventilatory modes, in two subjects (Nos 7 and 10) with ventilatory modes 1 and 2, and in one subject (No. 2) with ventilatory mode 1. In all instances, the RMSD obtained with Model 1 was large, ranging from 1.3–3.1 hPa, and the discrepancies between the observed pressure and that computed from the model were of the type seen in subject No. 1 (fig. 1b). Flow-limitation may, therefore, be invoked in these subjects. To assess this possibility we first attempted to limit the analysis to the inspiratory phase and compare the data to those obtained on the whole cycle. It appeared, however, that, with the almost constant inspiratory flow rate provided by the respirators used in this study, a good separation between the constant $P_0$ and the flow term $R \cdot V'$ of equation (1) could not be obtained from inspiratory data only. We then examined how flow-limitation could influence the fit of the data to Model 1 and the coefficients obtained with this model. For this, we numerically simulated a system which obeyed equation (1) during inspiration and could exhibit flow-limitation during expiration. Maximal expiratory flow varied linearly with lung volume according to:

$$Vmax' = Vo' + a \cdot V \qquad (10)$$

where Vo' is maximal flow at the static equilibrium volume of the system (SEV), and a is the slope of the maximal expiratory flow-volume curve. Vo' and a were given values which ensured flow-limitation during the whole passive expiratory phase. The simulation was performed with different values of Vo', a, R, E and a variety of respiratory patterns. Starting the simulation from the SEV, five to eight cycles were usually necessary before the system reached a steady end-expiratory volume. The pressure and flow data during the subsequent cycles were analysed with Model 1. An example of the results is shown in figure 2. By comparing figure 2 and figure 1b, it can be seen that the discrepancies between the observed and computed pressures were strikingly similar to those observed in the above-mentioned subjects: compared to the actual pressure, that computed from the model was in all instances lower during the end-inspiratory pause and at end-expiration, and was higher during the first part of expiration. During inspiration the slope of the computed pressure could either be larger or smaller than the actual one, depending on the respiratory pattern; this was also true of the computed elastance.

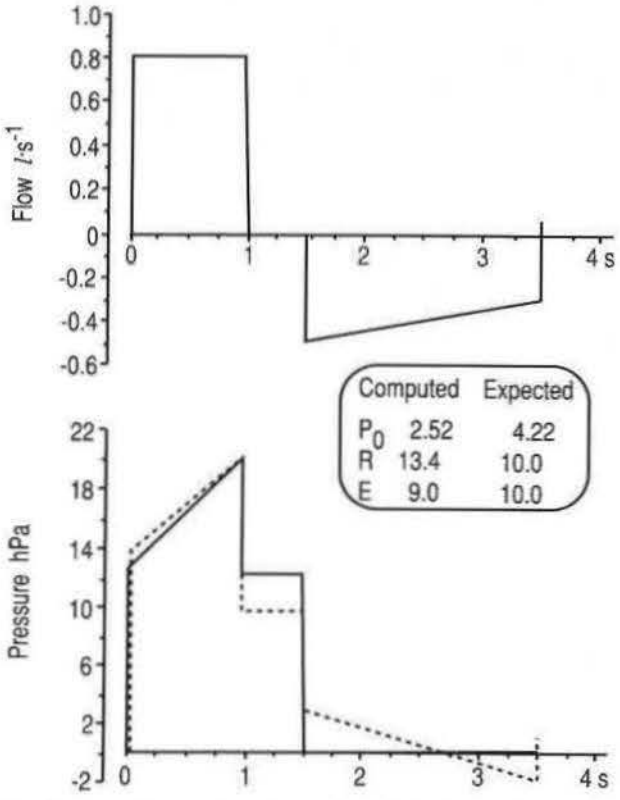


Fig. 2. – Influence of expiratory flow limitation on the analysis with the first order model. Continuous lines: simulated pressure and flow data with expiratory flow limitation (Vmax' ($l \cdot s^{-1}$)=0.2+0.4 V ($l$)). Discontinuous line: best fit of the pressure with the first order model. For further abbreviations see legend to figure 1.

In contrast, $P_0$ was always underestimated, sometimes by as much as 80%, and resistance was always overestimated, sometimes by as much as 100%. From this, we conclude that flow limitation could explain the poor performance of Model 1 in some of our subjects, and that the coefficients provided by the analysis in these subjects may be grossly inaccurate. In particular, the systematic underestimation of $P_0$ may, in part, be responsible for the low value of PEEPi found in the group.

To summarize our findings, this study demonstrates that, except in the case of expiratory flow-limitation, the MLR method is adequate for monitoring respiratory mechanics in unsedated ventilated patients with acute respiratory failure. Its main advantages over other methods are that it does not require a specific respiratory pattern and that it provides an index of the adequacy of the model. The latter index may also be used to detect muscular activity and discard the corresponding cycles. As far as the modelling is concerned, this study shows that, in the absence of flow-limitation, the simple first order model is, in general, sufficient: allowing for mechanical non-homogeneity or for non-linearity of resistance or elastance was rarely effective in improving the fit and often provided unrealistic values of the additional coefficients. This study also revealed in one third of the subjects systematic discrepancies between the data and the models, which are consistent with expiratory flow limitation. Whilst these discrepancies may be of diagnostic value, flow-limitation may be responsible for large errors on intrinsic PEEP and respiratory elastance and resistance. Other approaches, involving specific flow patterns [1–5], are, therefore, necessary in the presence of expiratory flow limitation.

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## References

1. Jonson B, Nordstrom L, Olsson SG, Akerback D. – Monitoring of ventilation and lung mechanics during automatic ventilation. A new device. *Bull Eur Physiopathol Respir*, 1975; 11: 729–743.
2. Broseghini C, Brandolese R, Poggi R, Polese G, Manzin E, Milic-Emili J, Rossi A. – Respiratory mechanics during the first day of mechanical ventilation in patients with pulmonary edema and chronic airway obstruction. *Am Rev Respir Dis*, 1982; 138: 355–361.
3. Rossi A, Gottfried SB, Zocchi L, Higgs BD, Lennox S, Calverley PMA, Begin P, Grassino A, Milic-Emili J. – Measurement of static compliance of total respiratory system in patients with acute respiratory failure during mechanical ventilation. *Am Rev Respir Dis*, 1985; 131: 672–678.
4. Gottfried SB, Rossi A, Higgs BD, Calverley PMA, Zocchi L, Bozic C, Milic-Emili J. – Noninvasive determination of respiratory system mechanics during mechanical ventilation for acute respiratory failure. *Am Rev Respir Dis*, 1985; 131: 414–420.
5. Bernasconi M, Ploysongsang Y, Gottfried SB, Milic-Emili J, Rossi A. – Respiratory compliance and resistance in mechanically-ventilated patients with acute respiratory failure. *Intensive Care Med*, 1988; 14: 547–553.
6. Benhamou D, Lorino AM, Lorino H, Zerah F, Harf A. – Automated measurement of respiratory mechanics in anaesthetized ventilated patients. *Bull Eur Physiopathol Respir*, 1987; 23: 423–428.
7. Nicolai T, Lanteri C, Freezer N, Sly PD. – Non-invasive determination of alveolar pressure during mechanical ventilation. *Eur Respir J*, 1991; 4: 1275–1283.
8. Bates JHT, Shardonofsky F, Stewart DE. – The low-frequency dependence of respiratory system resistance and elastance in normal dogs. *Respir Physiol*, 1989; 78: 369–382.
9. Chang HK, Mortola JP. – Fluid dynamic factors in tracheal pressure measurement. *J Appl Physiol: Respirat Environ Exercise Physiol*, 1981; 51: 218–225.
10. Behrakis PK, Higgs BD, Baydur A, Zin WA, Milic-Emili J. – Respiratory mechanics during halothane anesthesia and anesthesia-paralysis in humans. *J Appl Physiol: Respirat Environ Exercise Physiol*, 1983; 55: 1085–1092.
11. Rohrer R. – Der Strömungswiderstand in den menschlichen Atemwegen und der Einfluss der unregelmassigen Verzweigung des bronchial Systems auf den Atmungsverlauf in verschiedenen Lungenbezirken. *Pfluegers Arch Gesamte Physiol Menschen Tiere*, 1915; 162: 225–299.
12. Pepe PE, Marini JJ. – Occult positive end-expiratory pressure in mechanically-ventilated patients with airflow obstruction. *Am Rev Respir Dis*, 1982; 126: 166–170.
13. Otis AB, McKerrow CB, Bartlett RA, Mead J, McIlroy MB, Selverstone NJ, Radford EP Jr. – Mechanical factors in distribution of pulmonary ventilation. *J Appl Physiol*, 1956; 8: 427–443.
14. Similowski T, Bates JHT. – Two-compartment modelling of respiratory system mechanics at low frequencies: gas redistribution or tissue rheology. *Eur Respir J*, 1991; 4: 353–358.
15. Eyles JG, Pimmel RL, Fullton JM, Bromberg PA. – Parameter estimates in a five-element respiratory mechanical model. *IEEE Trans Biomed Engin*, 1982; BME-39: 460–463.
16. Lorino AM, Benhamou D, Lorino H, Harf A. – A computerized method for measuring respiratory mechanics during mechanical ventilation. *Bull Eur Physiopathol Respir*, 1986; 22: 81–84.
17. Gay PC, Rodarte JR, Tayyab M, Hubmayr RD. – Evaluation of bronchodilator responsiveness in mechanically-ventilated patients. *Am Rev Respir Dis*, 1987; 136: 880–885.
18. Gay PC, Rodarte JR, Hubmayr RD. – The effects of positive expiratory pressure on isovolume flow and dynamic hyperinflation in patients receiving mechanical ventilation. *Am Rev Respir Dis*, 1989; 139: 621–626.
19. Van den Berg B, Stam H, Bogaard JM. – Effects of PEEP on respiratory mechanics in patients with COPD on mechanical ventilation. *Eur Respir J*, 1991; 4: 561–567.