

Monitoring of nonlinear respiratory elastance using a multiple linear regression analysis

K. Muramatsu*, K. Yukiwake[#], M. Nakamura[#], I. Matsumoto[#], Y. Motohiro[#]

Monitoring of nonlinear respiratory elastance using a multiple linear regression analysis. K. Muramatsu, K. Yukiwake, M. Nakamura, I. Matsumoto, Y. Motohiro. ©ERS Journals Ltd 2001.

ABSTRACT: The elastic pressure/volume (*P/V*) curve obtained by the multiple linear regression (MLR) technique using a new model, was compared with the quasi-static *P/V* points obtained by the rapid airway occlusion technique.

Seven infants were studied during mechanical ventilation using a pressure controlled mode. The resistive pressure was subtracted from airway opening pressure, thus determining the elastance related pressure, which was then plotted against the volume to make an MLR-elastance curve. Quasi-static *P/V* curves of the rapid occlusion technique were constructed by plotting the different inspiratory and expiratory volumes against the corresponding values of the quasi-static airway pressure.

The calculated MLR-elastance curves closely fit the experimental quasi-static *P/V* points obtained by the occlusion technique. There were, however, some discrepancies due to the viscoelastic behaviour of the respiratory system.

Although slightly altered by these discrepancies, the multiple linear regression-elastance curves did fit the observed quasi-static pressure/volume characteristics for use in clinical practice. The multiple linear regression technique may prove to be clinically useful by continuous monitoring of respiratory system mechanics during mechanical ventilation.

Eur Respir J 2001; 17: 1158–1166.

*Dept of Pediatrics, Fukuoka Tokushukai Medical Center, Kasuga City,
[#]Dept of Pediatrics, Fukuoka University, Nanakuma, Jonan-ku, Fukuoka, Japan.

Correspondence: K. Muramatsu, Dept of Pediatrics, Fukuoka Tokushukai Medical Center, 4-5 Suku-kita, Kasuga City, Fukuoka, 816-0864, Japan.
Fax: 81 925731733

Keywords: Elastance curve
multiple regression analysis
pressure/volume curve
respiratory mechanics
respiratory physiology

Received: February 28 2000
Accepted after revision December 12 2000

Respiratory system elastance has been shown to exhibit a negative lung volume dependence due to the curvilinear character of static pressure/volume [*P/V*] curves. During mechanical ventilation, the lungs are frequently inflated to the nonlinear level on the *P/V* curve. It is generally accepted that a graphic presentation of the *P/V* relationship at a given respirator setting can provide great insight regarding whether or not lung overdistension occurs.

The static *P/V* relationship, as a parameter for the elasticity of the respiratory system, can be determined by various methods. The super syringe technique is a continuous procedure of step-by-step inflation and deflation using a large syringe while the patient is disconnected from the ventilator [4]. The interrupter technique consists of rapid occlusions within a single breath cycle [5, 6] or of interrupting airways at different inflation and deflation volumes [7–9]. All occlusion data can then be plotted on a *P/V* diagram. The constant flow technique is performed during volume controlled mechanical ventilation using a very slow constant inflation flow of 3 L·min⁻¹ or 9 L·min⁻¹, and thus pressure consumed by the flow resistance in the airway is not considered to be of any clinical relevance [10, 11]. These techniques are sometimes not practical to perform or require the presence of a trained investigator and the respirator settings may

need to be changed. With the increasing availability of computer-based data acquisition systems, high speed data collection and analyses are now possible using the computerized least-squares multiple regression analysis technique [12]. Using a multiple linear regression (MLR) analysis to analyse the flow and pressure changes at the airway opening during mechanical ventilation, permits dynamic mechanics to be measured noninvasively without interfering with the ventilation pattern being employed. An MLR analysis also allows for the use of various respiratory system models [13]. Several investigators have examined the influence of the volume and flow on expiratory mechanics by including a volume-dependent term for elastance and a flow-dependent term for resistance in a model [3, 13, 14]. Thus, a model including a fourth-polynomial elastance term and a second-polynomial resistance term was investigated in the present study.

The elastic *P/V* curve obtained by an MLR analysis employing the new model, was compared with a plot of the quasi-static *P/V* points obtained by the rapid airway occlusion technique. The objective of this study was to utilize the MLR analysis for the new model to obtain additional data related to the *P/V* characteristics of mechanically ventilated subjects.

Methods

Subjects

The study was performed on seven neonates admitted to a neonatal intensive care unit (Tokushukai Medical Center, Fukuoka, Japan) and who were mechanically ventilated for respiratory disorders as a result of various diseases. Mechanical ventilation was started on the first day of life and lasted throughout the study and thereafter. All patients, except for case 7, were administered artificial surfactant because of the diagnosis of respiratory distress syndrome at admission. The patients were intubated transorally with endotracheal tubes with an internal diameter of 2–3.5 mm. Detailed information regarding the seven newborns is presented in table 1. The level of peak inspiratory pressure (PIP) and positive end-expiratory pressure (PEEP) was determined according to clinical requirements to improve oxygenation without causing any haemodynamic compromise. The study was performed with the subjects in the supine position while being regularly ventilated without any spontaneous respiratory movement or rapid eye movement. No sedative was administered before the study. The baseline shift in the volume curve during each breath was ensured to be within 5% to eliminate any breaths with air leakage around the endotracheal tube. Routine care, such as aspiration, had been performed in all patients before the study. The nature and aims of the investigation were explained to the next of kin, and their informed consent was obtained.

Equipment

The flow (V') was measured with a pneumotachograph made in the authors' laboratory, connected to a differential pressure transducer (Nihonkoden, Tokyo, Japan). This device was inserted between the Y-piece of the ventilator circuit and the endotracheal tube (ETT). The pneumotachograph was linear over the experimental range of flow. The volume was determined by electronically integrating the flow signal. Airway opening pressure (P_{ao}) was measured proximal to the ETT using a pressure transducer

(Nihonkoden, Tokyo, Japan). The transducers produced no appreciable shift or alteration in the amplitude at frequencies as great as 20 Hz. The signals were sampled at a frequency of 200 Hz, and then were digitally stored into a personal computer using a 12-bit analogue-to-digital converter (MacLab, NSW, Australia) for the subsequent data analysis. The elastance curves produced by a computerized MLR analysis (MLR-elastance curve) were then correlated against those obtained using the rapid airway occlusion technique.

Multiple linear regression technique

The equation of motion for a single-compartment lung model (SCM) was solved using MLR [15, 16], and respiratory system elastance (E_{rs}) and resistance (R_{rs}) were computed during a complete respiratory cycle:

$$P_{ao} = E_{rs} \times V + R_{rs} \times V' + EEAP \quad (1)$$

where V is the volume obtained through the electrical integration of flow and EEAP (end-expiratory alveolar pressure) is the elastic recoil pressure when the volume equals zero.

This equation is a simple first-order linear model that encompasses the total R_{rs} and E_{rs} . E_{rs} , R_{rs} and EEAP were obtained by a linear regression of P_{ao} against V and V' . Due to the curvilinear character of the respiratory static P/V curves, the lung and chest wall elastances vary with lung volume. The pressure necessary to overcome lung elastance (P_{el}) can be expressed as a polynomial function of V [2, 17, 18]. A biquadratic polynomial equation was employed in the present study:

$$P_{el} = (k_1 + k_2 \times V + k_3 \times V^2 + k_4 \times V^3) \times V \quad (2)$$

where k_n is a constant. In general, the resistive pressure is not linearly related to the flow [19]. It should be noted that the ETT represents a substantial impedance to the ventilating flow [19–21]. Calculations of respiratory mechanics were performed after subtracting the resistance pressure due to the ETT from P_{ao} . Inspiratory and expiratory resistance pressures due to the ETT were calculated as

Table 1. – Characteristics of infants

Case	Sex	Gestational age week	Age at study days	Birth weight g	Study weight g	Diagnosis and indications for intubation	Ventilator settings at study			ET tube innerdiameter mm	Ventilator	
							F_{I,O_2}	PIP cmH ₂ O	PEEP cmH ₂ O			f min ⁻¹
1	M	25	0	832	832	RDS	0.45	14	1.5	60	2.5	S
2	F	24	4	670	545	RDS	0.35	12	2.0	35	2.0	IS
3	F	25	15	760	620	RDS, BPD	0.3	12	2.5	45	2.5	S
4	M	25	20	794	750	RDS, BPD	0.3	14	2.0	40	2.5	BC
5	M	27	36	920	1010	BPD	0.3	16	1.0	40	2.5	S
6	M	24	269	730	5556	BPD	0.35	19	2.5	35	3.5	S
7a	M	41	20	3590	3228	Asphyxia	0.21	19	3.5	35	3.5	S
7b			32		3456		0.21	15	0.0	35	3.5	S

F_{I,O_2} : inspiratory oxygen fraction; PIP: peak inspiratory pressure; PEEP: positive end-expiratory pressure; F: frequency; ET: endotracheal; RDS: respiratory distress syndrome; BPD: bronchopulmonary dysplasia; S: Sechrist (Sechrist Industries, Inc., CA, USA); BC: Bear Cub (Bear Medical Systems Inc., CA, USA); IS: Infant Star (Mallinckrodt, Inc., CA, USA).

flow-dependent resistance characterized by Rohrer's equation

$$(k_1 + k_2 \times V') \times V' \quad (3)$$

and were measured separately for inspiratory and expiratory flows *in vitro*. The resistance related pressure (P_{res}) due to respiratory system can also be described by the Rohrer's equation:

$$P_{res} = (k'_1 + k'_2 \times |V'|) \times V' \quad (4)$$

The absolute values of flow were used for the second order resistance term because the calculations were performed using the data derived from the whole respiratory cycle. The nonlinear characteristics of respiratory elastance were combined with resistance by modelling the elastance and resistance as a polynomial function of lung volume for elastance and flow for resistance, respectively, as shown in the following equation:

$$P_{ao} = (k_1 + k_2 \times V + k_3 \times V^2 + k_4 \times V^3) V + (k'_1 + k'_2 \times |V'|) \times V' + EEAP \quad (5)$$

The coefficients were obtained based on the linear regression of P_{ao} versus V , V^2 , V^3 , V^4 , V' and $|V'| \times V'$.

Subtracting the pressure required to overcome viscous resistance

$$P_{res} = (k'_1 + k'_2 \times |V'|) \times V' \quad (6)$$

from P_{ao} gives the elastance related pressure (P_{el-MLR}):

$$P_{el-MLR} = (k_1 + k_2 \times V + k_3 \times V^2 + k_4 \times V^3) \times V + EEAP \quad (7)$$

P_{el-MLR} was then plotted against the volume to yield an MLR-elastance curve. In order to make a well-matched comparison, eight complete breaths were selected for the MLR calculation (MLR-breath) between the test breaths examined by the occlusion technique. The data on MLR-breath were sampled during the period beginning 25 ms prior to the airway pressure rise of a breath and ending 25 ms after the rise of the next breath. The actual data of the eight MLR-breaths were averaged and analysed to yield the MLR-elastance curve at the given ventilator setting.

Four additional models were also evaluated to determine whether or not the respiratory mechanics can be estimated as well as the model (Equation 4) mentioned earlier.

$$P_{ao} = (k_1 + k_2 \times V + k_3 \times V^2 + k_4 \times V^3) \times V + k'_1 \times V' + EEAP \quad (8)$$

$$P_{ao} = (k_1 + k_2 \times V + k_3 \times V^2) \times V + (k'_1 + k'_2 \times |V'|) \times V' + EEAP \quad (9)$$

$$P_{ao} = (k_1 + k_2 \times V) \times V + (k'_1 + k'_2 \times |V'|) \times V' + EEAP \quad (10)$$

$$P_{ao} = k_1 \times V + (k'_1 + k'_2 \times |V'|) \times V' + EEAP \quad (11)$$

Equation 8 consists of a biquadratic elastance term and a single resistance term, which were used instead

of a second order resistance term in Equation 4. Equations 9, 10 and 11 consist of a third order, a second order and a first order elastance term respectively, in place of the biquadratic elastance term in Equation 4. The fit of the models to the data was judged based on the coefficient of determination (R^2) with the paired t-test.

Airway occlusion technique

There is considerable evidence in the literature to suggest that quasi-static characteristics can be estimated by the occlusion method [5–9]. A pneumatic occlusion valve that was produced in the laboratory was inserted between the pneumotachograph and the ETT (fig. 1). The equipment has 0.4 mL of dead space and the closing time is <20 ms. With the ventilator maintained at constant settings, a series of airway interruptions of 3-s durations were performed randomly at different volumes of the breathing cycle. Between occlusions, baseline ventilation was resumed for 2–4 breaths to restore a fixed previous pressure and volume history. Over a period of 30 min, 15–30 airway interruptions were performed at each ventilator setting. P_{ao} exhibited two distinct changes after rapid airway occlusions (fig. 2) [22, 23]. One was an immediate change of P_{ao} (ΔP_{init}) to a certain pressure level, dynamic elastance pressure ($P_{el,dyn}$), that was followed by a slower pressure change (ΔP_{diff}). The upward direction of the second slower pressure change was defined as positive ΔP_{diff} . ΔP_{init} represents the pressure change across the resistance of the airways and chest wall. The slower, secondary change in the pressure that eventually reaches a plateau represents the stress recovery or adaptation of the tissues and chest wall as well as the redistribution of gas among the different lung units observed with an uneven time constant distribution. The plateau pressure reflects the

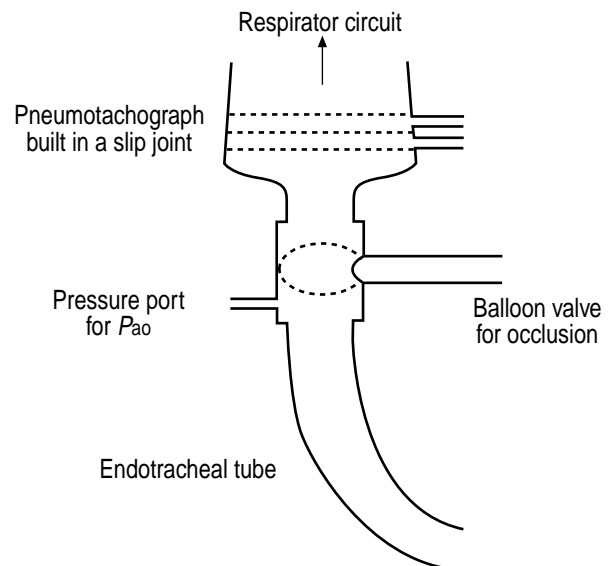


Fig. 1. – Schematic diagram of the pneumotachograph and occlusion valve demonstrating each position and pressure port. P_{ao} : airway opening pressure.

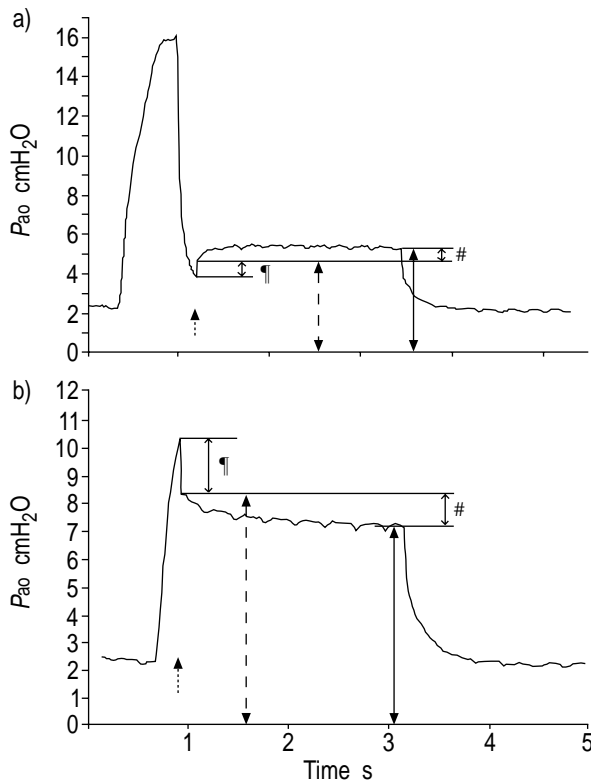


Fig. 2. – Recording of: a) the airway opening pressure (P_{ao})-time profile following midexpiratory occlusion; and b) an inspiratory study breath from the same infant. ΔP_{diff} is defined as negative in this case. The initial rapid pressure change (ΔP_{init} ; ¶), the secondary slower pressure change (ΔP_{diff} ; #), the dynamic elastic recoil pressure ($P_{el,dyn}$; - - -) and the static elastic recoil pressure ($P_{el,st}$; —) are shown. The dotted arrow indicates the time of airway occlusion.

static elastic recoil pressure of the respiratory system ($P_{el,st}$). P_{ao} showed oscillations after interruptions due to cardiac artifacts. The values for $P_{el,dyn}$ and $P_{el,st}$ were obtained from computer generated polynomial curves fit to the post-occluded P_{ao} signals, and then extrapolating the curve to the point in time when the valve was totally closed and to the plateau point. The quasi-static P/V curves resulting from the rapid occlusion technique were constructed by plotting the different inspiratory and expiratory volumes against the corresponding values of $P_{el,st}$. The profiles of the dynamic P/V relationship associated with the rapid occlusion technique were plotted in the same manner using $P_{el,dyn}$.

Comparisons and statistical analysis

The $P_{el,st}$ values and the corresponding P_{el} -MLR values at the same lung volume were subdivided into four groups at every 4 cmH₂O of the $P_{el,st}$ values (group 1: 0 cmH₂O $\leq P_{el,st} < 4$ cmH₂O; group 2: 4 cmH₂O $\leq P_{el,st} < 8$ cmH₂O; group 3: 8 cmH₂O $\leq P_{el,st} < 12$ cmH₂O; group 4: 12 cmH₂O $\leq P_{el,st} < 16$ cmH₂O). The differences between the two were evaluated at each $P_{el,st}$ step using the paired t-test. A p-value of < 0.05 was considered significant. All values are expressed as mean \pm SD.

Results

The R^2 values were 0.985–0.994 (table 2). The differences were small but statistically significant. The data obtained during mechanical ventilation were best fitted by the biquadratic equation.

The calculated MLR-elasticity curves were compared to the quasi-static P/V points obtained using the occlusion technique. For each infant, the calculated MLR-elasticity curve closely fit the observed data points of the $P_{el,st}/V$ relation obtained by occlusion techniques, whether the relationship was linear (fig. 3, cases 3, 4, 6) or curvilinear (fig. 3, cases 1, 2, 5, 7a, 7b). The mean difference between the $P_{el,st}$ value and P_{el} -MLR value at the same lung volume was 0.06 cmH₂O and the SD was 0.49 cmH₂O. The highest value for the difference between the two was 1.3 cmH₂O at end-inspiration for case 6.

Although most results were quite similar, some differences were observed between the two (fig. 3, cases 5–7a, b). In these cases, the pressure values for the $P_{el,st}/V$ points at higher lung volume levels (at higher airway pressure levels) were lower than those indicated by the MLR-elasticity curve and higher at lower lung volume levels (at lower airway pressure levels). The MLR-elasticity curves intersected the $P_{el,st}/V$ curves in the middle range of the lung volumes (in the middle range of the airway pressure levels). Table 3 shows the differences between the two in the $P_{el,st}$ subdivided groups. When compared using all data together, no significant difference between the $P_{el,st}$ values and the corresponding P_{el} -MLR values was found. However, when calculated separately there were significant differences between the two at higher (12 cmH₂O $\leq P_{el,st} < 16$ cmH₂O) and lower (0 cmH₂O $\leq P_{el,st} < 4$ cmH₂O) airway pressure levels. The mean P_{el} -MLR value was 0.51 cmH₂O higher than the $P_{el,st}$ value at a higher airway pressure level. In contrast, the mean P_{el} -MLR value was 0.19 cmH₂O lower than the $P_{el,st}$ value at a lower airway pressure level. No significant difference was found in the midrange of $P_{el,st}$.

$P_{el,dyn}/V$ points and corresponding $P_{el,st}/V$ points in a representative case (case 7a) are shown in figure 4. The difference between the two corresponding points shows ΔP_{diff} at each interrupted lung volume. During the inspiratory phase and initial one-third of the

Table 2. – Coefficient of determination (R^2) in each equation using a different degree of polynomial expression in elastance and resistance terms

Equation	R^2	p-value
6 (E-4th, R-1st)	0.992 ± 0.003] < 0.02] < 0.001
4 (E-4th, R-2nd)	0.994 ± 0.003	
7 (E-3rd, R-2nd)	0.993 ± 0.003	
8 (E-2nd, R-2nd)	0.992 ± 0.003	
9 (E-1st, R-2nd)	0.985 ± 0.003	

Data are presented as mean \pm SD. R-1st: 1st order resistance term; R-2nd: 2nd order resistance term; E-1st: 1st order elastance term; E-2nd: 2nd order elastance term; E-3rd: 3rd order elastance term; E-4th: biquadratic elastance term

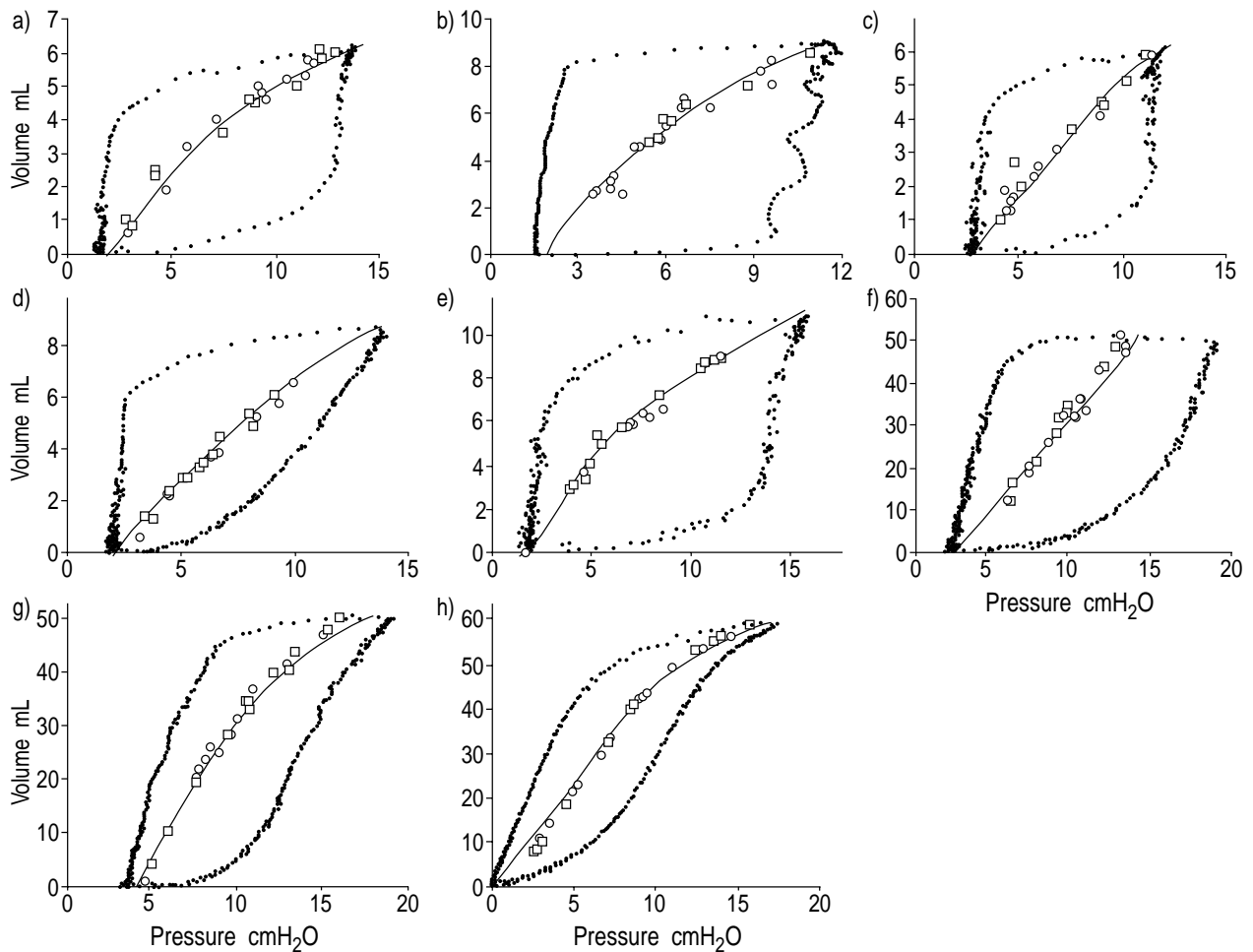


Fig. 3. – Representation of multiple linear regression-elasticity curves (lines) compared to experimental static elastic recoil pressure/volume ($P_{el,st}/V$) points during inspiration (\square) and expiration (\circ). a): case 1; b): case 2; c): case 3; d): case 4; e): case 5; f): case 6; g): case 7a; h): case 7b. No hysteresis in the $P_{el,st}/V$ relationship was observed. Dotted lines represent the airway opening pressure/volume curves.

expiratory phase, ΔP_{diff} remained negative, thus implying that $P_{el,dyn}$ was higher than $P_{el,st}$. The negative ΔP_{diff} values were the greatest at end-inspiration and the least at midexpiration. Through the next two-thirds of expiration, the ΔP_{diff} values became positive and gradually increased with the resulting $P_{el,st}$ points becoming higher than the $P_{el,dyn}$ points. The $P_{el,dyn}$ points indicate the presence of hysteresis, but no apparent quasi-static hysteresis was observed. The same behaviour for the viscoelastic characteristics were observed in every infant, a finding

which is consistent with a similar conclusion for the viscoelastic characteristics by JOHNSON *et al.* [8].

Discussion

BHUTANI *et al.* [15] used the SCM to calculate lung mechanics in neonates and obtained a strong coefficient of determination ($R^2 > 0.98$) to validate the linear assumption. SEEAR and WERNER [16] obtained MLR measurements using the SCM from 22 subjects.

Table 3. – The static elastic recoil pressure ($P_{el,st}$) values, the corresponding elastance related pressure-multiple linear regression (P_{el-MLR}) values at the same lung volumes and the difference between the two

$P_{el,st}$ subgroup cmH ₂ O	n	P_{el-MLR} cmH ₂ O	$P_{el,st}$ cmH ₂ O	Difference ($P_{el-MLR}-P_{el,st}$)	p-value
$0 \leq P_{el,st} < 4$	13	3.06 ± 0.57	3.25 ± 0.58	-0.19 ± 0.31	$p < 0.05$
$4 \leq P_{el,st} < 8$	74	5.77 ± 1.12	5.76 ± 1.15	0.01 ± 0.39	NS
$8 \leq P_{el,st} < 12$	72	9.94 ± 1.26	9.84 ± 1.08	0.10 ± 0.49	NS
$12 \leq P_{el,st} < 16$	18	13.4 ± 1.19	12.96 ± 0.93	0.51 ± 0.53	$p < 0.001$
Total	177	8.03 ± 3.20	7.94 ± 2.99	0.06 ± 0.49	NS

Data are presented as mean \pm SD. NS: nonsignificant.

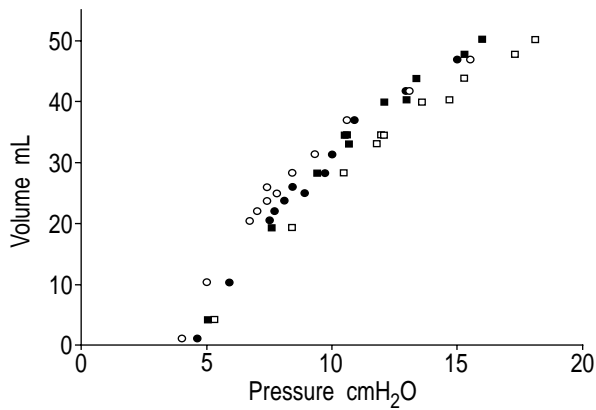


Fig. 4. – Inspiratory static elastic recoil pressure ($P_{el,st}$; ■), inspiratory dynamic elastic recoil pressure ($P_{el,dyn}$; ●), expiratory $P_{el,st}$ (○) and expiratory $P_{el,dyn}$ (○) versus volume for case 7a are shown. The difference between a pair of $P_{el,st}$ and $P_{el,dyn}$ values at the same lung volume is explained as viscoelasticity of the lung, secondary slower pressure change (ΔP_{diff}). During inspiration and early expiration, $P_{el,st}$ is lower than $P_{el,dyn}$ implying that ΔP_{diff} is negative. During the last half of expiration, $P_{el,st}$ is higher than $P_{el,dyn}$ indicating that ΔP_{diff} is positive. The $P_{el,st}$ /volume relationship shows no hysteresis. However, the $P_{el,dyn}$ /volume relationship demonstrates the presence of hysteresis.

Their results compared well with other measurements of mechanics over a wide clinical range. These findings suggest that the SCM is a very good approximation of the behaviour of the respiratory system. A fundamental assumption of the SCM is that elastance and resistance of the respiratory system is constant throughout the respiratory cycle. However, the respiratory system resistance depends on flow and sometimes on lung volume. In intubated subjects, mechanics measurements will include ETT resistance which is also dependent on flow. KANO *et al.* [24] evaluated a flow-dependent SCM to estimate the respiratory mechanics. Their results indicated that the data were not well described by a flow-dependent SCM. Their flow-dependent SCM consisted of a second order resistance term, but the elastance term was first order. Therefore, in the present study a second order flow-dependent expression for resistance was applied, as was a biquadratic elastance term in the same equation. This study indicates that although the effect of ETT was subtracted, the fit was better in the model with a second order resistance term (table 2). Figure 5 shows an MLR-elastance curve obtained by a calculation using Equation 6 (consisting of a first order resistance term) in case 7a. The variances of the curve from $P_{el,st}$ points were large and the shape of the curve (inflection point of the curve) was also different.

Several investigators have examined the influence of volume on respiratory mechanics by including volume-dependent terms for elastance in a model [3, 13, 24, 25]. Using a volume-dependent elastance model KANO *et al.* [24] found a considerable improvement in fit. They used a second order polynomial equation to analyse volume dependency. However, it is possible to apply a higher degree of polynomial expression in the method. YUKITAKE *et al.* [26] applied a biquadratic equation for MLR analysis and

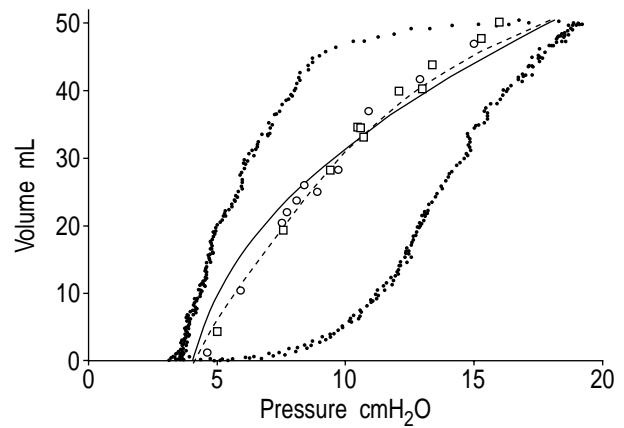


Fig. 5. – A multiple linear regression-elastance curve obtained by a calculation using Equation 6 (first order resistance term, —) in case 7a. Variances from static elastic recoil pressure ($P_{el,st}$) points are a little larger than those obtained using Equation 4 (second order resistance term, - - -). □: inspiration; ○: expiration.

reported that the MLR data for airway pressure computed using this kind of equation were closely correlated with the observed P_{ao} . They also tried a lower or a higher degree of polynomial expression to see whether or not the fit of the models to the data was good. The higher the degree, the better the fit, and they concluded that the biquadratic polynomial equation is sufficient for practical use. Figure 6 demonstrates that the MLR-elastance curves obtained from the equations, using the first-, second- and third-polynomial elastance terms, are not as accurate as those obtained using a biquadratic equation. Not only were the variances from the $P_{el,st}$ points large, but also the shapes of the curves (the inflection points) were substantially different. Figures 5 and 6 show that the higher the polynomial equation, the more closely the shape and the position of the P/V curve resembled those of the experimental P/V points regarding both the resistance terms and the elastance terms. This same phenomenon was observed in every case (data

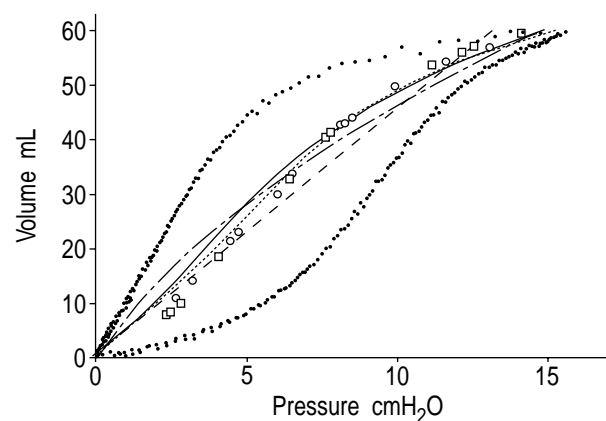


Fig. 6. – Multiple linear regression-elastance curves obtained by a calculation using Equation 9 (first order elastance term, - - -), Equation 8 (second order, — · —), Equation 7 (third order, —) and Equation 4 (biquadratic, - - -) in case 7b. □: inspiration; ○: expiration.

not shown). Finally, the equation with the fourth-polynomial elastance term and the second-polynomial resistance term was chosen. However, in the case of linear elastance, for example in cases 3, 4 and 6, the data closely correlated with all different distress models (data not shown). In acute respiratory distress syndrome, the inflation limb of the P/V curve has a sigmoid curve [27], with a low and upper inflection point. This kind of sigmoidal curve can only be described by a third order polynomial or a higher polynomial equation. The findings also suggest that the MLR analysis using a fourth order equation can provide a good approximation of the behaviour of the respiratory system (table 2).

The MLR-elastance curve was constructed by plotting P_{el} -MLR against the corresponding volume. P_{el} -MLR was obtained by subtracting the flow resistive pressure from P_{ao} in the dynamic state, thus implying that the MLR-elastance curve exhibited a dynamic elastance profile throughout the respiratory cycle. The value for $P_{el,dyn}$ also excluded ΔP_{init} from P_{ao} at the moment of interruption, as illustrated in figure 2. An interruption of the flow at a low airway pressure during expiration tends to result in stress recovery in alveolar pressure. Conversely, an interruption at a high airway pressure either during inspiration or expiration, tends to result in stress relaxation. The slow dynamics due to the viscoelasticity of the lung or pendelluft do not reach a steady state at any moment during usual ventilation, and therefore, the alveolar pressure dynamics should be expressed by the $P_{el,dyn}$ points. The alveolar pressures during inspiration and expiration at the same lung volume, in a dynamic state, should not be equal, even if the quasi-static alveolar pressures are the same, as shown in figure 4. During ventilation, the alveolar pressure has to move on a hysteresis curve consisting of the $P_{el,dyn}$ points, not on the quasi-static P/V curve. Both the P_{el} -MLR and $P_{el,dyn}$ indicate the mean alveolar pressure overcoming lung elastance in the dynamic state. Theoretically, P_{el} -MLR should be compared to the $P_{el,dyn}$ which is measured using the flow interruption technique. In the present study, the MLR calculations were performed using data from the entire respiratory cycle; there was no phase separation between expiration and inspiration. The $P_{el,dyn}/V$ points and MLR-elastance curve for case 7a are shown in figure 7. The MLR-elastance curve is positioned in the middle of the range of inspiratory and expiratory $P_{el,dyn}/V$ points. The same findings were observed for every case, regardless of the ventilator settings (data not shown). Consequently, it appears that P_{el} -MLR indicates the approximate mean values for the expiratory and inspiratory dynamic alveolar pressure changes throughout the respiratory cycle. At the same time, the quasi-static P/V points were also positioned near the centre, between the inspiratory and expiratory $P_{el,dyn}$ points in the middle and lower range of the airway pressure. As a result, the MLR-elastance curves were positioned very close to the quasi-static P/V curves.

Despite variations in the values for viscoelasticity of the lung with the lung volume, the position of the static elastance curve can be estimated from the

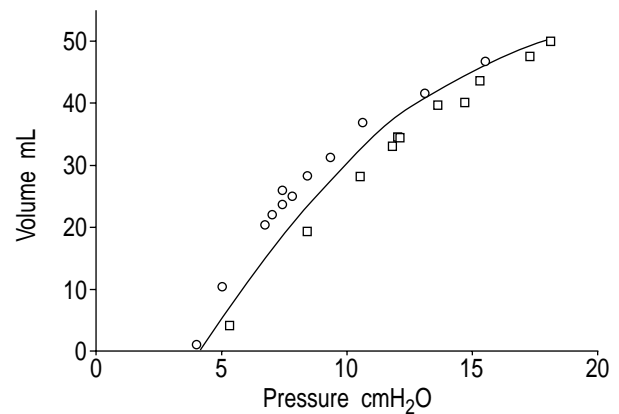


Fig. 7. – Multiple linear regression-(MLR) elastance curve (—) compared to experimental dynamic elastic recoil pressure/volume ($P_{el,dyn}/V$) points during inspiration (\square) and expiration (\circ) for case 7a. The MLR-elastance curve is closely positioned along the centre of the inspiratory and expiratory $P_{el,dyn}/V$ points.

MLR-elastance curve. For the purpose of clinical practice, the MLR-elastance curves correlated closely enough with the experimentally measured quasi-static P/V characteristics, especially when the lung was ventilated beyond the linear portion of the P/V relationship. The conventional methods for measuring static elastance are cumbersome and are, therefore, not routinely used in clinical practice. The elastance curve obtained by the MLR technique described in this report thus avoids a number of these handicaps.

The PEEP is known to increase the end-expiratory lung volume along a fixed static P/V curve of the respiratory system in patients demonstrating minimal concomitant alveolar recruitment [9]. Conversely, an upward shift along the volume axis of the P/V curve is observed in patients with alveolar recruitment [2]. When ventilation is performed with a low end-expiratory lung volume in patients with acute lung injury, thus resulting in repeated end-expiratory collapse and tidal reinflation, a lower inflection point is then exhibited in the inspiratory P/V relationship [11]. This kind of successive alveolar recruitment and derecruitment during inflation and deflation results in a wide hysteresis regarding the static P/V characteristics. The present study was performed at the preset PEEP level, and no hysteresis in the quasi-static P/V curve was observed in any patient. As a result, these findings indicate that only a minimal degree of recruitment or none at all occurred at the various respirator settings in the patients. Thus, it is possible to estimate the static P/V data from zero end-expiratory pressure by extrapolating the MLR-elastance line to 0 cmH_2O level in the P/V diagram. The MLR technique as originally described [12], used the entire respiratory cycle to calculate the mechanics. However, the respiratory system mechanics can be calculated for any portion of the respiratory cycle, by appropriate definitions of the data to be analysed. It is possible to obtain inspiratory and expiratory MLR-elastance curves separately. In the present study, the differences between inspiratory and expiratory elastance were minimal. However, in cases with a

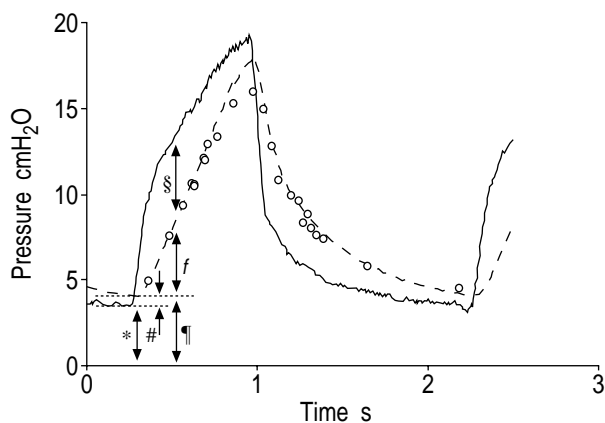


Fig. 8. – Time courses of airway opening pressure (P_{ao} ; —), elastance related pressure (P_{el-MLR} ; - - -) and static elastic recoil pressure ($P_{el,st}$; ○) for case 7a. *: positive end-expiratory pressure (PEEP); #: intrinsic positive end-expiratory pressure (PEEPi); †: end-expiratory alveolar pressure (EEAP) calculated by multiple linear regression (MLR) technique; ‡: elastic recoil pressure (P_{el}) = $(k_1 + k_2 \times V + k_3 \times V^2 + k_4 \times V^3) \times V$; §: resistive pressure = $(k'_1 + k'_2 \times |V'|) \times V'$; †† f = alveolar pressure = P_{el-MLR} .

wide hysteresis, the MLR-elastance curve should be separately obtained in each inspiratory and expiratory phase.

The time courses of P_{ao} , P_{el-MLR} and $P_{el,st}$ in case 7a are shown in figure 8. P_{ao} is equal to the sum of the pressure required to overcome the resistive force, the elastic force and the EEAP. P_{el-MLR} represents the mean alveolar pressure at a given moment. The relationship between EEAP, PEEP and intrinsic positive end-expiratory pressure is illustrated in figure 8. Some variances between $P_{el,st}$ and P_{el-MLR} are also seen due to the viscoelastic properties of the lung, especially at higher airway pressure range.

The multiple linear regression-elastance curve shown in the present study revealed a very good agreement with that obtained by the occlusion technique. Reliable information about the elastic properties of the respiratory system at the given respirator settings could be obtained by the multiple linear regression technique without disconnecting the subject from the ventilator. This enabled the respiratory system mechanics to be monitored continuously in the intensive care unit. The graphic presentation and continuous monitoring of how the lung expands can thus provide a better understanding of the physiological state of the respiratory system as well as help in establishing improved guidelines for determining an optimal therapeutic approach. However, the present study was performed using a limited group of patients, and therefore, further investigations based on individual analyses for each respiratory phase are necessary.

References

- Bachofen H, Hildebrandt J, Bachofen M. Pressure-volume curves of air- and liquid-filled excised lungs: surface tension *in situ*. *J Appl Physiol* 1970; 29: 422–431.
- Valta P, Jukka T, Eissa NT, Milic-Emili J. Does alveolar recruitment occur with positive end-expiratory pressure in adult respiratory distress syndrome patients? *J Crit Care* 1993; 8: 34–42.
- Peslin R, Rotger M, Farre R, Navajas D. Assessment of respiratory pressure-volume nonlinearity in rabbits during mechanical ventilation. *J Appl Physiol* 1996; 80: 1637–1648.
- Matamis D, Lemaire F, Harf A, Brun-Buisson C, Ansquer JC, Atlan G. Total respiratory pressure-volume curves in the adult respiratory distress syndrome. *Chest* 1984; 86: 58–66.
- Gottfried SB, Rossi A, Calverley PMA, Zocchi L, Milic-Emili J. Interrupter technique for measurement of respiratory mechanics in anesthetized cats. *J Appl Physiol: Respir Environ Exercise Physiol* 1984; 56: 681–690.
- Björklund LJ, Vilstrup CT, Larsson A, Svenningsen NW, Werner O. Changes in lung volume and static expiratory pressure-volume diagram after surfactant rescue treatment of neonates with established respiratory distress syndrome. *Am J Respir Crit Care Med* 1996; 154: 918–923.
- Sydow M, Burchardi H, Zinserling J, Ische H, Crozier TA, Weyland W. Improved determination of static compliance by automated single volume steps in ventilated patients. *Intensive Care Med* 1991; 17: 108–114.
- Jonson B, Beydon L, Brauer K, Mansson C, Valind S, Grytzell H. Mechanics of respiratory system in healthy anesthetized humans with emphasis on viscoelastic properties. *J Appl Physiol* 1993; 75: 132–140.
- Ranieri VM, Giuliani R, Fiore T, Damhrosio M, Milic-Emili J. Volume-pressure curve of the respiratory system predicts effects of PEEP in ARDS: "occlusion" versus "constant flow" technique. *Am J Respir Crit Care Med* 1994; 149: 19–27.
- Lu Q, Vieira SRR, Richecoeur J, et al. A simple automated method for measuring pressure-volume curves during mechanical ventilation. *Am J Respir Crit Care Med* 1999; 159: 275–282.
- Servillo G, Svantesson C, Beydon L, et al. Pressure-volume curves in acute respiratory failure: automated low flow inflation versus occlusion. *Am J Respir Crit Care Med* 1997; 155: 1629–1636.
- Uhl RR, Lewis FJ. Digital computer calculation of human pulmonary mechanics using a least squares fit technique. *Comput Biomed Res* 1974; 7: 489–495.
- Rousselot JM, Peslin R, Duvivier C. Evaluation of the multiple linear regression method to monitor respiratory mechanics in ventilated neonates and young children. *Pediatr Pulmonol* 1992; 13: 161–168.
- Wensley DF, Noonan P, Seear MD, Werner H, Pirie GE. Pilot study for the development of a monitoring device for ventilated children. *Pediatr Pulmonol* 1991; 11: 272–279.
- Bhutani VKSE, Abbasi S, Shaffer TH. Evaluation of neonatal pulmonary mechanics and energetics: a two factor least mean square analysis. *Pediatr Pulmonol* 1988; 4: 150–158.
- Seear MWD, Werner H. Comparison of three methods for measuring respiratory mechanics in ventilated children. *Pediatr Pulmonol* 1991; 10: 291–295.
- Paiva M, Yernault JC, Erdeweghe PV, Englert M. A sigmoid model of the static volume-pressure curve of human lung. *Respir Physiol* 1975; 23: 317–323.

18. Peslin R, Saunier C, Duvivier C, Marchand M. Analysis of low-frequency lung impedance in rabbits with nonlinear models. *J Appl Physiol* 1995; 79: 771–780.
19. Gottfried SB, Rossi A, Higgs BD, *et al.* Noninvasive determination of respiratory system mechanics during mechanical ventilation for acute respiratory failure. *Am Rev Respir Dis* 1985; 131: 414–420.
20. Brown K, Sly PD, Milic-Emili J, Bates JHT. Evaluation of the flow-volume loop as an intra-operative monitor of respiratory mechanics in infants. *Pediatr Pulmonol* 1989; 6: 8–13.
21. Sly PD, Brown KA, Bates JHT, Spier S, Milic-Emili J. Noninvasive determination, of respiratory mechanics during mechanical ventilation of neonates: a review of current and future techniques. *Pediatr Pulmonol* 1988; 4: 39–47.
22. Bates JHT, Rossi A, Milic-Emili J. Analysis of the behaviour of the respiratory system with constant flow. *J Appl Physiol* 1985; 58: 1840–1848.
23. Bates JHT, Ludwig MS, Sly PD, Brown K, Martin JG, Fredberg JJ. Interrupter resistance elucidated by alveolar pressure measurement in open chested normal dogs. *J Appl Physiol* 1988; 65: 408–414.
24. Kano SLC, Duncan AW, Sly PD. Influence of nonlinearities on estimates of respiratory mechanics using multilinear regression analysis. *J Appl Physiol* 1994; 77: 1185–1197.
25. Lanteri CJKS, Duncan AW, Sly PD. Changes in respiratory mechanics in children undergoing cardiopulmonary bypass. *Am J Respir Crit Care Med* 1995; 152: 1893–1900.
26. Yuki take K, Muramatsu K, Nakamura M, Matsumoto I, Aida T. Evaluation of single compartment models (SCM) and elastance curve using multiple linear regression analysis (MLR). *Am J Respir Crit Care Med* 1998; 157: A121.
27. Venegas JG, Harris RS, Simon BA. A comprehensive equation for the pulmonary pressure-volume curve. *J Appl Physiol* 1998; 84: 389–395.