

## Non-invasive determination of alveolar pressure during mechanical ventilation

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**ABSTRACT:** The development of inadvertent positive end-expiratory pressure (PEEP) in ventilated infants is of clinical relevance and difficult to measure non-invasively. A method for estimating end-expiratory alveolar pressure by applying a multiple regression analysis to airway opening pressure, flow and volume recordings during mechanical ventilation was evaluated.

In eight open-chested, paralysed and mechanically ventilated mongrel dogs, alveolar pressure was measured directly with "alveolar capsules". Alteration of ventilation patterns and addition of a resistive element were used in three dogs to induce different levels of PEEP<sub>i</sub>. End-expiratory alveolar pressure measured directly and determined from multilinear regression of airway opening pressure correlated well (mean error  $0.06 \pm 0.53$  ( $\pm$ SD) hPa, limits of agreement -1.16 to +1.04 hPa). The other five dogs received inhalation challenges, two with histamine, two with hypertonic saline and one with methacholine resulting in a mean increase of respiratory system resistance of 230% (range 141-489%) of the baseline values. The mean error in determining PEEP<sub>i</sub> was  $0.54 \pm 0.37$  hPa, the limits of agreement were -0.20 to 1.28 hPa.

The method was then applied to seven mechanically-ventilated children (aged 2 months to 8 yrs, weight 4.9-23.5 kg) and the results were compared to the pressure at which inspiration began (equalling PEEP<sub>i</sub>). Seventy eight measurements were performed during open heart surgery, while compliance changed by between 3 and 186% of baseline values due to the surgical procedures. PEEP<sub>i</sub> estimated by multiple regression agreed well with the pressure at which inspiration began (mean difference  $0.25 \pm 0.68$  hPa, limits of agreement -1.12 to 1.62 hPa).

A computer model was used to determine the stability of the multiple regression method under conditions likely to stress the assumptions underlying this technique, *i.e.* in the presence of a high flow dependent endotracheal tube resistance and after introduction of noise in the simulated signals. Values usually encountered in clinical practice did not result in unacceptable errors in determining PEEP<sub>i</sub> from multiple regression analysis of airway pressure.

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The use of rapid rate ventilation in patients with lung disease may result in an alveolar pressure above airway opening pressure at end-expiration if the expiratory time is too short in relation to the expiratory time constant of the respiratory system. This pressure is known as intrinsic positive end-expiratory pressure (PEEP<sub>i</sub>) [1-4]. This pressure is not detected from pressure settings of the ventilator and may exceed the PEEP value applied externally. PEEP<sub>i</sub> is more likely to occur in patients with increased airway resistance, *e.g.* in infants with bronchopulmonary dysplasia (BPD) or bronchiolitis, or when small endotracheal tubes (ETT) are used. High PEEP<sub>i</sub> may increase the risk of pulmonary over-distension and pneumothorax. It may also influence gas exchange

and cardiac output [4, 5] and make the evaluation of the efficiency of specific ventilator settings or therapies more difficult. Measurements of dynamic compliance will be difficult to interpret in the presence of an unknown PEEP<sub>i</sub> [6].

Efforts to detect such pressures without interfering with the ventilation pattern have included measurements of pressures at the tip of the ETT [7]. However, this requires special tubes and will be very difficult to achieve in premature infants with the usual 2.5-3.5 mm internal diameter (I.D.) ETT. Furthermore, PEEP<sub>i</sub> due to high airway resistance will not be detected by this technique as all that is achieved is removal of the effect of the endotracheal tube.

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The technique proposed for measuring  $PEEP_i$  in adults involves making an end-expiratory airway occlusion and measuring the steady-state pressure at the airway opening shortly afterwards [1]. Some adult ventilators have an "end-expiratory-hold" button for this purpose. Commonly used infant ventilators do not have this facility, therefore end-expiratory occlusions must be made manually. Timing is crucial. If the occlusion is made before expiratory flow has stopped, the estimate of  $PEEP_i$  obtained will be artificially high. End-expiratory occlusions also interrupt the infant's pattern of ventilation.

This study was performed to evaluate a non-invasive technique for calculating  $PEEP_i$  without interfering with the infant's ventilation pattern. This technique consists of applying a multilinear regression analysis to measurements of flow and pressure at the airway opening. The technique was validated in open-chested puppies where the estimates of  $PEEP_i$  could be verified by direct measurements of end-expiratory alveolar pressure, and applied to children under anaesthesia. A computer model was also used to simulate the pulmonary mechanics of neonates and to investigate the effects of a flow-dependent ETT resistance and measurement "noise" on the stability of the estimates of  $PEEP_i$ .

## Methods

### Theory

In mechanically-ventilated subjects without respiratory muscle activity, and assuming that inertia plays a negligible role during tidal ventilation [8], the equation of motion describing a linear, single compartment model of respiration can be written:

$$P_{ao}(t) = R_{rs} \cdot \dot{V}(t) + 1/C_{rs} \cdot V(t) \quad (1)$$

where  $P_{ao}$  = pressure at airway opening,  $R_{rs}$  = resistance of the respiratory system,  $C_{rs}$  = compliance of the respiratory system,  $V$  = lung volume above the resting position of the respiratory system (elastic equilibrium volume),  $\dot{V}$  = flow at airway opening,  $t$  = time.

By definition, lung volume at end-expiration is the functional residual capacity (FRC). Equation (1) can be rewritten to describe ventilatory excursions from FRC:

$$P_{ao}(t) = R_{rs} \cdot \dot{V}(t) + 1/C_{rs} \cdot V(t) + EEP \quad (2)$$

where  $V$  is the lung volume above FRC, and  $EEP$  is the alveolar pressure at end-expiration.  $EEP$  will be zero and equations (1) and (2) will be identical only if the lung is allowed to expire fully to its resting position after each inspiration. Equation (2) can be solved by fitting a multilinear regression (MLR) to measurements of  $P_{ao}$ , flow ( $\dot{V}$ ) and volume [9, 10]. The MLR then yields values for  $R_{rs}$ ,  $C_{rs}$  and  $EEP$ . For the purpose of this study,  $EEP$  will be used to denote the constant derived from multilinear regression of equation (2).

We derived  $EEP$  by MLR from airway opening pressure, flow and volume in three mechanically-ventilated, open-chested mongrel dogs, after different levels of  $PEEP_i$  had been induced by alteration of ventilation patterns and addition of a resistive element. This value of  $EEP$  was then compared to the end-expiratory alveolar pressure measured directly using alveolar capsules (see below).

In order to evaluate the effect of a more physiological model of increased airway resistance, we then studied a further five dogs during and after inhalation provocation with histamine (two dogs), methacholine (1 dog) and hypertonic saline (2 dogs). In dogs, the inhalation of histamine results mainly in an increase of tissue resistance [11], and hypertonic saline increases only airway resistance [12]. Methacholine was found to result in an increase of both tissue and airway resistive properties [13].

To investigate the effects of the chest wall properties (which were not present in the open-chested dogs), seven patients were studied during cardiac surgery which involved a median sternotomy and placement of chest retractors. Because the "alveolar capsule" technique cannot be used in humans, we manually determined airway pressure at the beginning of inspiratory flow as a method of estimating  $PEEP_i$ , and compared this with  $EEP$  from multilinear regression. This assumes that the ventilator must first overcome the positive alveolar pressure before inspiratory flow can be initiated.

The multiple linear regression technique of fitting ventilation data to equation [2] assumes that the respiratory system can be represented by a single compartment with a single value for resistance and compliance. These values represent "weighted average" values and do not necessarily assume that resistance and compliance are constant, either between inspiration and expiration or throughout the tidal volume range. Nonlinearities, such as those introduced by a flow dependent resistance (e.g. the small endotracheal tubes used for small infants) and by ventilating the respiratory system beyond its "linear range" may introduce errors into the values of  $C_{rs}$ ,  $R_{rs}$  and  $EEP$  obtained from MLR of equation (2). Therefore, a computer simulation of various ventilator settings, lung compliances and resistances and tube characteristics typical for neonates and prematures was used to determine the influence of these factors on the  $EEP$  value derived by MLR using equation (2).

### Animal studies

**Animal preparation.** Three mongrel puppies, 8–10 wks old, weight 7.0, 7.7 and 8.1 kg, were studied. The puppies were anaesthetized (sodium pentobarbital, 30 mg·kg<sup>-1</sup> i.v.), intubated with an uncut cuffed Portex ETT (size 6.0 mm I.D., the cuff inflated until no leak was detectable), paralysed with tubocurarine (1–3 mg) and mechanically ventilated using a piston pump (volume cycled) ventilator (tidal volume range 38–178 ml, frequency 0.4 Hz). The chest was widely opened by

midline sternotomy for placement of alveolar capsules (see below). An end-expiratory pressure of 5 hPa was applied to maintain lung volume. Anaesthesia and muscle relaxation were maintained with supplemental doses of pentobarbitone and tubocurarine approximately each hour. Heart rate and blood pressure were monitored continuously and used to judge the adequacy of anaesthesia.

Five other puppies (weight 5.0–7.0 kg), which were part of another study to determine the effects of different provocation methods on lung mechanics, were prepared in an identical fashion. Two dogs underwent inhalation provocations with increasing concentrations (3, 10, 30, 100 mg·ml<sup>-1</sup>) of histamine, one dog with methacholine (0.1, 0.3, 1, 3, 10, 30 mg·ml<sup>-1</sup>) and two dogs with 10% saline for increasing inhalation periods (0.5, 1, 2, 4, 8, 16 min). The aerosols were delivered by a Hudson updraft nebulizer driven by a flow of 10 l·min<sup>-1</sup> of compressed air, and the provocation steps with histamine and methacholine consisted of 2 min inhalations of each concentration during tidal ventilation.

**Alveolar capsule technique.** Alveolar pressure was measured in the open-chested puppies using the alveolar capsule technique of FREDBERG *et al.* [14]. Small plastic capsules were glued to the pleural surface with cyanoacetate glue (Loktite 416). The underlying alveoli were brought into communication with the capsule chamber by puncturing the pleura several times to a depth of approximately 0.5 mm with a 19 gauge needle. A piezoresistive pressure transducer (Endevco 8507B-2) identical to that used to measure airway opening pressure was introduced into the capsule to measure alveolar pressure. Two capsules were glued to the right upper and cardiac lobes.

**Data processing.** Data were collected over a 15 s period at 200 Hz through a 12 bit AD converter, filtered through 8 pole Bessel filter with a corner frequency of 100 Hz and recorded on a computer, using the "Labdat/Anadat" data collection and analysis package (RHT Data Systems, Montreal, Quebec, Canada). Any offset in the flow signal was removed by integrating flow to calculate volume, setting  $V = 0$  for the volume troughs and correcting the flow and volume signal accordingly. Rrs, Crs and EEP were then calculated by multilinear regression from Pao,  $\dot{V}$  and V tracings using equation (2). Studies were used for analysis if the coefficient of determination achieved by the fitting procedure was >0.9. The two alveolar pressure tracings were inspected for possible ventilation inhomogeneities and the mean signal was used for direct determination of end-expiratory pressures.

#### Measurements during cardiac surgery

Seven patients undergoing elective cardiac surgery at the Royal Childrens Hospital were included in the study. The study protocol was approved by the Ethics Committee of the hospital, and informed consent was obtained from the patients parents. Details of the patients are given in table 1.

The patients were prepared as usual for cardiac surgery, including extensive monitoring equipment for circulatory and blood gas parameters. The patients were anaesthetized, paralysed and mechanically ventilated using a constant-flow, pressure-limited, time-cycled paediatric ventilator (built by the RCH anaesthetic department). Flow and pressure at the airway opening (*i.e.* between the ETT adaptor and the ventilator head) were measured using equipment

Table 1. — Clinical details of the seven patients studied during cardiac surgery

Pat. no.	Age	Weight kg	Diagnosis	Crs·kg <sup>-1</sup> ml·hPa <sup>-1</sup> ·kg <sup>-1</sup>	Rrs hPa·s <sup>-1</sup> ·ml	Vt·kg <sup>-1</sup> ml·kg <sup>-1</sup>
1	2 mths	4.8	VSD	0.781	0.062	12.3
2	18 mths	9.1	ASD	0.525	0.103	23.6
3	4 yrs	16.7	TGA, PA	3.33	0.018	32.8
4	8 yrs	23.5	VSD	1.11	0.013	20.5
5	4 yrs	13.8	VSD	0.905	0.040	13.7
6	9 mths	7.5	VSD	1.32	0.051	22.7
7	7 mths	7.8	Fallot	1.50	0.060	20.5

VSD: ventricular septal defect; ASD: atrial septal defect; TGA: transposition of great arteries; PA: pulmonary atresia with multiple arterial-pulmonary communicating arteries; Crs: compliance of the respiratory system; Rrs: resistance of the respiratory system; Vt: tidal volume.

In order to induce high values of PEEP<sub>i</sub> a 2.5 mm I.D. (Vygon) ETT was connected in series between the ventilator and the dogs endotracheal tube by two standard tube connectors as an additional resistive element. This acted to increase the expiratory time constant of the respiratory system. Tidal volume was changed without altering ventilation rate to vary the level of PEEP<sub>i</sub>.

Airway opening pressure was measured proximally to the resistive element with a lateral pressure port and a pressure transducer as described above.

identical to the devices described in the section on animal studies. Measurements were performed over 20 s each, at a frequency of 200 Hz, and a low pass filter corner frequency of 10 Hz.

The ventilation pattern was set and varied by the anaesthetist according to the clinical situation, and the measurements of lung mechanics were performed without interfering with the surgical procedures. A slight external pressure to the larynx was applied as necessary to abolish any leak around the tube. Measurements were repeated before the chest had been

opened, and after sternotomy. Further measurements were performed after the chest wall had been closed at the end of the procedure.

Data analysis was performed in an identical way using the multilinear regression analysis as in the animal experiments. Studies were included in the analysis if the coefficient of determination from the MLR analysis was  $>0.95$ . Where practical, end-expiratory airway occlusions were made by manually triggering a solenoid driven valve at end-expiration.  $PEEP_i$  was estimated from the resulting plateau in airway opening pressure.

#### Computer model studies

The respiratory system was modelled as a one compartment lumped parameter system (see appendix), including an endotracheal tube which was represented as a flow dependent resistance ( $R_{ETT}$ ), characterized by Röhlers constants K1 and K2 [15, 16]:

$$R_{ETT} = K1 + K2 \cdot \dot{V} \quad (3)$$

This model was implemented on a computer as a differential equation [17, 18] and calculated at 1,000 Hz. The simulated ventilation pattern consisted of a constant-flow inspiration followed by a passive expiration until the inspired volume had been expired (see appendix). This ventilation pattern is similar to the one used in the children studied during cardiac surgery, and is commonly used to ventilate neonates. The ventilation pattern used in the dog experiments differs from this, with a more sinusoidal pattern of inspiratory flow.

**Ventilation patterns.** Different levels of inspiratory flow (50–150 ml·s<sup>-1</sup>) and  $PEEP_i$  (5–15 cmH<sub>2</sub>O) were used for the simulations. Inspiratory time was varied from 0.1 to 0.6 s. Tidal volume was kept within the 5–20 ml range for “small premature infants” with 2.5 mm I.D. tubes, 5–50 ml for “term babies”.

**Endotracheal tubes.** The ETT characteristics were varied according to values published for neonatal tube sizes: 2.5 mm I.D. (as used in premature infants of 25–30 wks gestation), 3.0 and 3.5 mm I.D. The exact values for K1 and K2 characterizing the ETTs vary with bending or secretions in the tubes. In practice they will be unknown at the moment of measurement. However, values typical for these instances (secretions, bending) have been published, and were included here [17, 18].

**Respiratory system characteristics.** To simulate “neonates” (with 3.0 or 3.5 mm I.D. ETTs), compliance values from 2–6 ml·hPa<sup>-1</sup> and resistance values of 0.02–0.04 hPa·s<sup>-1</sup>·ml [19] were used. In “prematures” (with 2.5 mm I.D. ETTs) compliance was varied between 0.5 and 2 ml·hPa<sup>-1</sup>, and resistance between 0.07 and 0.106 hPa·s<sup>-1</sup>·ml, thereby encompassing values found in neonatal respiratory distress syndrome (RDS) and bronchopulmonary dysplasia [20, 21].

These extremes of values and one point in the middle for each variable were evaluated,  $PEEP_i$  was varied in 10 steps between minimum and maximum value. Using these combinations of values, a full respiratory cycle was calculated, using the model of the respiratory system as described in the appendix. Random noise between  $\pm 0.5$  ml·s<sup>-1</sup> and  $\pm 0.1$  hPa, respectively, was added to the flow and airway opening signals.

A multiple regression analysis of equation (2) was then performed, using the airway opening pressure and flow “tracings” produced by the simulated ventilator cycle.  $Crs$ ,  $Rrs$  and  $EEP$  were thereby derived.

**Statistical analysis.** The results of the various estimates of  $PEEP_i$  were calculated using the method of BLAND and ALTMANN [22], where the limits of agreement are expressed as being 2 SD of the difference above and below the mean difference of two estimates.

## Results

#### Animal studies

The values for  $EEP$  derived from MLR in the first three dogs agreed well with the direct measurements of alveolar pressures at end-expiration ( $PEEP_i$ ), regardless of the fixed level of external  $PEEP$  set by the  $PEEP$  valve (fig. 1). The range of differences was -1.09 to +0.935 hPa, (-16.3 to 13.6% of end-expiratory alveolar pressure) and the limits of agreement were -1.16 to +1.04 hPa. This agreement was valid over a wide range of  $PEEP_i$  values (2–14 hPa).

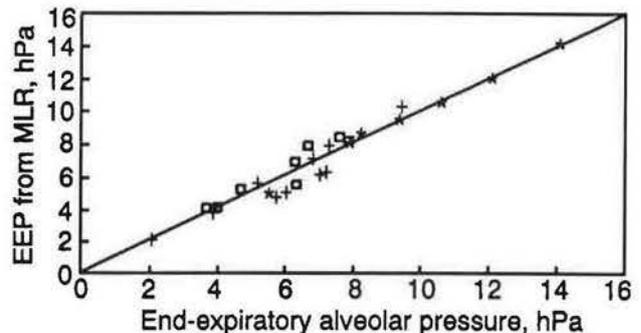


Fig. 1 - Correlation between end-expiratory alveolar pressure measured directly by alveolar capsules ( $PEEP_i$ ) and as determined from multiple linear regression of  $Pao$ , flow and volume ( $EEP$ ). The solid line is the line of identity.  $PEEP_i$ : intrinsic positive end-expiratory pressure;  $Pao$ : pressure at airway opening. □: Dog 1; \*: Dog 3.

The minimal pressure measured at the airway opening, i.e. determined by the  $PEEP$  valve, underestimated the end-expiratory alveolar pressure ( $PEEP_i$ ) measured directly (range of differences = 0.3–6.88 hPa, limits of agreement +6.83 to -2.1 hPa) (fig. 2). We then manually determined the pressure at the airway opening at the moment when inspiratory flow commenced by inspecting pressure and flow tracings. We found that this value corresponded well to the  $PEEP_i$

measured from alveolar pressure: mean difference  $0.46 \pm 0.26$  hPa, limits of agreement  $-0.06$  to  $0.98$  hPa. No significant ventilation inhomogeneities were observed when the two alveolar pressure tracings were compared.

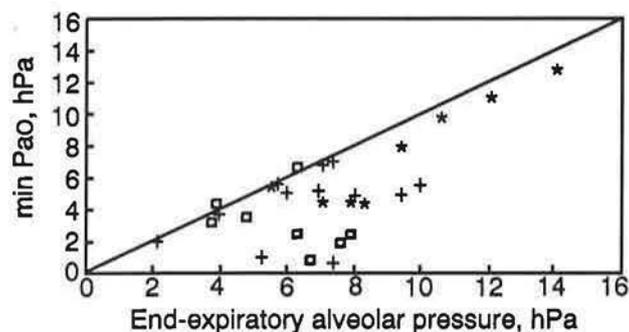


Fig. 2 - End-expiratory alveolar pressure measured directly by alveolar capsules and minimal airway opening pressure (min Pao). The wide differences indicate that intrinsic positive end-expiratory pressure (PEEP) was present. The solid line is the line of identity. □: Dog 1; +: Dog 2; \*: Dog 3.

During the inhalation provocations, Rrs increased to a mean of 230% (range 141 - 498%) of baseline, and the coefficient of determination achieved by fitting a one compartment, linear model of the respiratory system to the data decreased to 0.90 in some cases. However, the agreement between EEP from MLR analysis of the pressure, flow and volume measured at the airway opening, and PEEP<sub>i</sub> as determined from alveolar pressure deteriorated only slightly (mean difference =  $0.54 \pm 0.37$  hPa, limits of agreement  $-0.20$  to  $1.28$  hPa), (fig. 3).

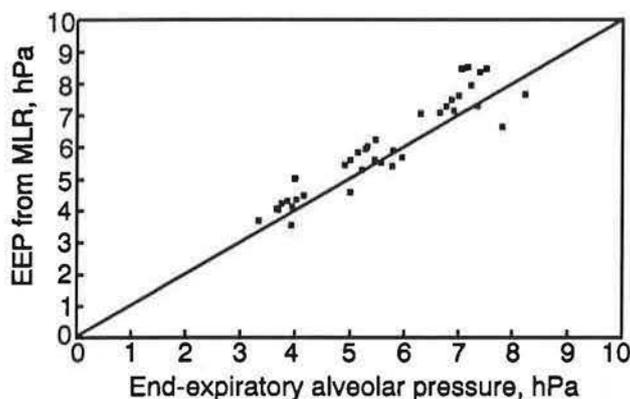


Fig. 3 - Correlation between end-expiratory alveolar pressure measured directly by alveolar capsules (PEEP<sub>i</sub>) and as determined from multiple linear regression of Pao, flow and volume (EEP) during inhalation provocation with histamine (two dogs), hypertonic saline (two dogs) and methacholine (one dog). The solid line is the line of identity. For definitions see legend to figure 1. Pooled data; ■: one measurement.

#### Studies during cardiac surgery

A total of 78 measurements was performed in seven patients. Ventilation frequencies varied from 0.202-0.648 Hz, and further characteristics are given in table 1. One patient was detected to have developed significant PEEP<sub>i</sub> initially, which was corrected by

changes in the ventilatory pattern. Due to the surgical opening and closing of the thorax, Crs changed by a mean of  $70 \pm 66\%$  (range 3-186%) of baseline, Rrs changed by  $40 \pm 33\%$  (range 7-114%).

The mean coefficient of determination achieved by MLR-analysis was 0.977, only about 10% of the measurements had to be rejected due to poor signal quality or artifacts. Results are shown in figure 4. The regression between the manually determined pressure at which inspiratory flow began (as an estimate of PEEP<sub>i</sub>), and EEP as determined from multilinear regression analysis resulted in good agreement between the measurements. The mean difference between both values were  $0.25 \pm 0.68$  hPa, the limits of agreement  $-1.12$  to  $+1.62$  hPa.

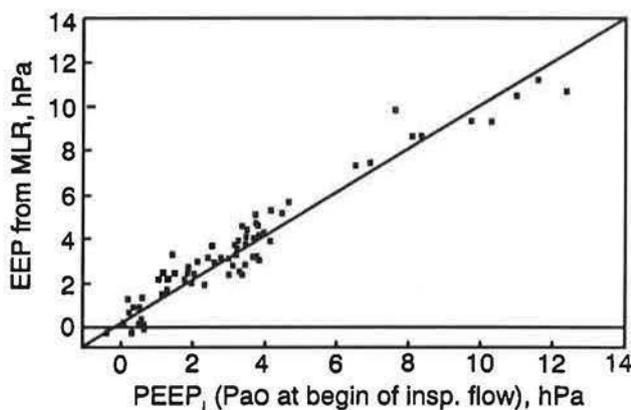


Fig. 4 - Correlation between the manually determined airway pressure at the moment when inspiratory flow commences (as estimate of PEEP<sub>i</sub>) and EEP determined from multiple linear regression of Pao, flow and volume from 78 measurements of seven children during cardiac surgery. The solid line is the line of identity. Pooled data; ■: one measurement.

End-expiratory occlusions were possible in each child at least once, and 27 satisfactory occlusions were performed. Occlusions were only accepted as satisfactory if close inspection of preceding mechanical breaths indicated that the occlusion had indeed been made immediately before the next inspiration would have commenced. The plateau in Pao reached after occlusion tended to overestimate PEEP<sub>i</sub> (determined from the airway opening pressure at which inspiration began in preceding ventilator breaths, as described above) to a variable degree. Mean overestimation was  $1.51 \pm 0.68$  hPa, limits of agreement 0.015 to 2.80 hPa, maximal error 3.21 hPa. If occlusions which appeared only slightly premature were used, the maximal error increased to 5.4 hPa.

#### Computer model studies

Results for three typical combinations of ventilator settings, ETT and patient characteristics are shown in figure 5. In all instances, the difference between EEP, determined by multiple regression analysis (equation (2)) and the preset PEEP<sub>i</sub> value (as used in the calculation of the simulated ventilator cycle) was small (fig. 5).

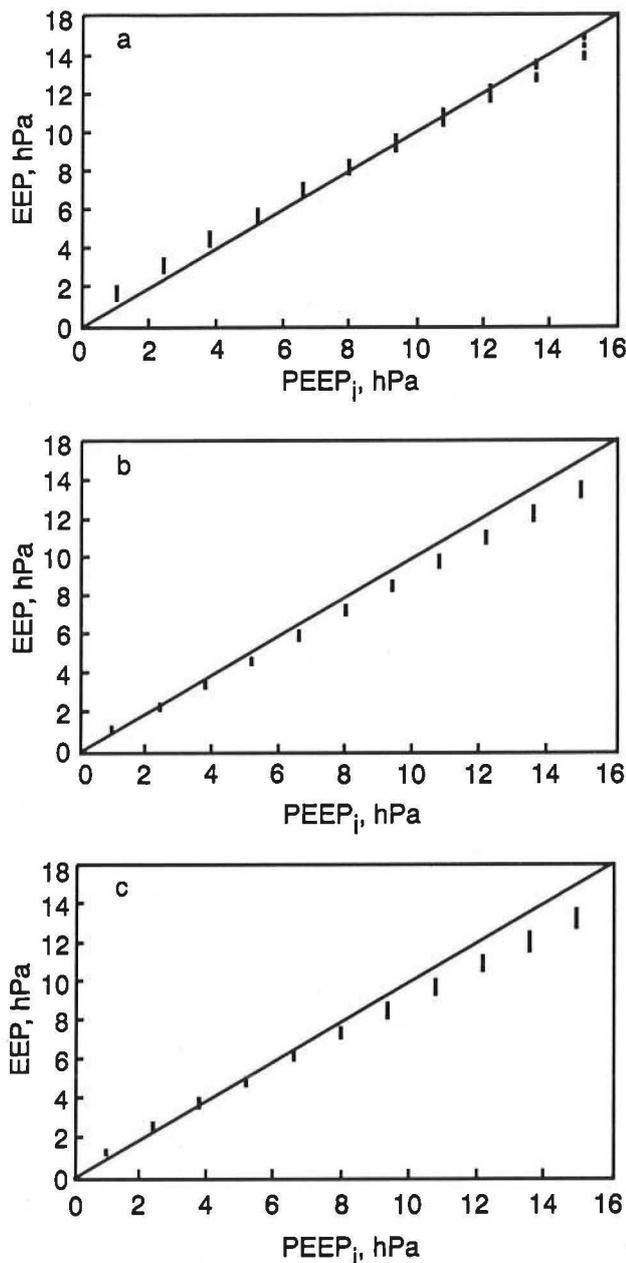


Fig. 5 - Computer simulation of various ventilator settings and different flow-dependent endotracheal tube resistances. The results are shown as identity plots between EEP (from multiple linear regression of simulated ventilation recordings) and the actual value of  $PEEP_i$  as preset in the model. The vertical bars represent the overlapping range of results. a) Simulation of premature babies with ETTs ranging from a cut, clean 2.5 to an uncut 3.0 I.D. tube. Ventilation parameters: peak pressures up to 40 hPa, inspiratory time 0.1–0.5 s, inspiratory flow 50–100 ml·s<sup>-1</sup>. ETT characteristics:  $K_1=0.02\text{--}0.04$  hPa·s·ml<sup>-1</sup>,  $K_2=0.0003\text{--}0.0007$  hPa·s<sup>2</sup>·ml<sup>2</sup>. Respiratory system parameters:  $Cr_s=0.5\text{--}2$  ml·hPa<sup>-1</sup>,  $Rr_s=0.07\text{--}0.1$  hPa·s<sup>-1</sup>·ml (typical for neonatal respiratory distress syndrome or bronchopulmonary dysplasia, see text). b) Simulation of term babies with a secretion filled 3.5 ETT after suctioning: ventilation parameters as in figure 5a. ETT characteristics:  $K_1=0.013\text{--}0.017$  hPa·s·ml<sup>-1</sup>,  $K_2=0.00012\text{--}0.00017$  hPa·s<sup>2</sup>·ml<sup>2</sup>. Respiratory system:  $Cr_s=2\text{--}6$  ml·hPa<sup>-1</sup>,  $Rr_s=0.01\text{--}0.02$  hPa·s<sup>-1</sup>·ml. c) The situation in a healthy neonate, with a 3.5 ETT with secretions after suctioning, other ventilatory values as in figure 5b, except inspiratory flows up to 150 ml·s<sup>-1</sup> were used. ETT: endotracheal tube. For further definitions see legend to figure 1.

In the lower ranges of  $PEEP_i$ , a slight overestimation was seen (up to 1 hPa), while higher  $PEEP_i$  values led to a tendency toward underestimating the real  $PEEP_i$  (up to 1.5 hPa at a  $PEEP_i$  of 15 hPa for the 3.5 mm I.D. ETT with secretions). This was somewhat more marked with a maximal error of 2.1 hPa at a  $PEEP_i$  level of 15 hPa in the simulations where very high inspiratory flows were used (fig. 5c).

### Discussion

The determination of  $PEEP_i$  is of particular interest in infants with small ETTs, rapid respiratory rates and high ventilatory pressures. Equipment using the multilinear regression approach to determine compliance and resistance of the lung from transpulmonary pressure is widely used [8] and even commercially available. If this method is applied to airway opening pressure,  $PEEP_i$  can be determined as part of the analysis. This simple method of determining end-expiratory alveolar pressure by multiple regression is only possible in mechanically-ventilated subjects with no spontaneous respiratory efforts. However, these are the situations most likely to result in  $PEEP_i$ .

Validation of the non-invasive estimation of end-expiratory pressure requires the direct measurement of alveolar pressure, which is not possible in patients. Therefore, the alveolar capsule technique in open-chested dogs was used to confirm the physiological validity of the MLR method for this purpose. The results of the present study show that the individual error in determining  $PEEP_i$  by MLR was small.

In closed-chested subjects, the influence of the chest wall may result in an additional error. However, the contribution of the chest wall to the behaviour of the respiratory system seems to be small, particularly in small infants [20], and will be reflected in altered values for compliance and resistance. The validity of equation (2) does not depend on the actual values of  $Cr_s$  and  $Rr_s$ , but only on the behaviour of the lung and chest wall combined as a single compartment. The results obtained from measurements during cardiac surgery show indeed that, despite the relatively high tidal volumes used during anaesthesia which might be expected to cause nonlinear behaviour of the pressure-volume characteristics of the chest wall, and despite the changes in chest wall compliance induced by sternotomy, EEP still remained a good estimate of  $PEEP_i$ .

We further stressed the MLR method by inducing marked increases in airway and/or tissue resistance in the second group of dogs. This represents a more realistic model of increased respiratory system resistance than the added external resistance which was used in the first three dogs to achieve very high values of  $PEEP_i$ . The fact that nonlinearities were thereby introduced into the system was reflected in the lower values for the coefficients of determination achieved by fitting a linear one compartment model to the pressure, flow and volume signals. The resulting small errors in the determination of  $PEEP_i$  show the

extent to which the respiratory system can be usefully modelled as a one compartment model at a given frequency. This is emphasized by the good fits achieved even in the cardiac surgery patients, most of whom did not have normal lungs, but various degrees of pulmonary vascular overload.

The results obtained using the computer model demonstrate that the nonlinearities introduced by the highly flow dependent ETT resistances did not result in large errors in the determination of  $PEEP_i$  over the range of flows usually encountered in neonatal intensive care. Furthermore, the simulation shows that this process is relatively robust in the presence of random noise. However, caution must be exercised in the interpretation of results in the presence of a large leak around the ETT, as this is likely to result in a poor fit to the data by MLR and erroneous values for Rrs, Crs and EEP. In practice, a leak around the ETT can usually be abolished by slight external pressure applied to the larynx [20] as was done in the measurements during cardiac surgery.

If the flow dependence of the tube resistance is more marked than the values used above (e.g. the tube is severely blocked or kinked) or if Crs, Rrs, tidal volume or pressures are markedly different from the clinically relevant values given above, then larger errors than those described here could occur. Furthermore, any significant respiratory efforts will render the application of equation (2) invalid. The use of transpulmonary pressure instead of airway opening pressure for multiple regression avoids this problem. However, the multiple linear regression applied to equation (2) will then give a constant which does represent the difference between elastic recoil pressure of the lung and alveolar pressure at end-expiration. This value is not relevant for clinical purposes.

In adults, the standard method to measure alveolar end-expiratory pressure is to perform an end-expiratory airway occlusion and read airway opening pressure after pressure equilibration from the ventilator pressure transducer [1]. However, stress recovery of the lung tissue [23] can be expected to cause some degree of overestimation of dynamic end-expiratory alveolar pressures, particularly if the occlusion valve closes relatively slowly [24]. In addition, this method requires the use of a ventilator which provides an expiratory-hold button. Ventilators commonly used in infants and small children do not have this option. If the airway opening is occluded before expiration has finished, lung volume will be above its elastic equilibrium volume and alveolar pressure will be positive. This will result in a biphasic pressure increase measured at the airway opening; an initial rapid increase to a value equal to alveolar pressure followed by a second slower increase to the static elastic recoil pressure for that lung volume. Unless the valve closes in less than 20 ms it is not possible to easily distinguish these two pressure changes [24]. Furthermore, if the exact point of end-expiration is slightly missed due to manual triggering, artificially high estimates for

$PEEP_i$  will be obtained. This was observed in the children during cardiac surgery. The end-expiratory occlusion itself interferes with ventilation and has been reported to induce respiratory efforts in non-paralysed infants [25]. Therefore, particularly in small children ventilated with relatively high frequencies, a method to determine  $PEEP_i$  not interfering with the ventilation pattern and not requiring an expiration-hold device in the ventilator appears desirable.

Estimation of  $PEEP_i$  from pressure at the airway opening and flow during tidal breathing has been described [1], and a similar method was used here to validate the EEP measurements in the children during cardiac surgery. When the results of this method of determining  $PEEP_i$  from direct inspection of Pao and flow curves were compared with alveolar pressure measurements in the animal experiments, a similar degree of accuracy was found as for the MLR method. The direct determination of Pao at the beginning of inspiratory flow has the advantage that it requires no assumptions about the behaviour of the respiratory system. However, the manual inspection of the curves is much more cumbersome and not suitable for routine clinical measurements. The multiple linear regression analysis takes about 20 s to perform on a standard AT computer, and gives results for Crs, Rrs and EEP, averaged over a number of breaths.

The use of a simplified "static" version of equation (2), using tidal volume, mean inflation pressure and mean flow in order to estimate the work of breathing has recently been proposed [26]. However, fitting the equation to the actual pressure, flow and volume recordings can be expected to yield much more realistic estimates of respiratory parameters than the use of mean values.

In mechanically-ventilated adults, the presence of an end-expiratory pressure, measured with an oesophageal balloon, above the level of the externally applied PEEP has been used as an indication of  $PEEP_i$  [4]. However, placement of an oesophageal balloon is an invasive procedure in infants, the measurements may not represent mean intrapleural pressure due to chest wall distortion in small children [27] and it is more difficult to verify the correct position of the balloon in mechanically-ventilated subjects than in those breathing spontaneously. Also, the end-expiratory oesophageal pressure will equal the difference between  $PEEP_i$  and the elastic recoil pressure of the lung at that volume and will, therefore, not be a measure of  $PEEP_i$  itself.

### Conclusion

We have evaluated the accuracy of measuring end-expiratory alveolar pressure from multiple regression using measurements of airway opening pressure and flow in fully ventilated paralysed dogs, both during baseline conditions and after induction of increased airway and tissue resistance. Furthermore, we have evaluated the method in children during cardiac surgery, where significant changes in the compliance of

the thoracic wall and respiratory system occurred. The results indicate that this method is relatively robust and yields useful results over a wide range of combinations of respiratory mechanics and ventilator settings. The presence of flow-dependent endotracheal tube resistances and added noise did not introduce clinically relevant errors into the values of EEP obtained. This non-invasive method of estimating end-expiratory alveolar pressure should prove useful in detecting the presence of  $PEEP_i$  in mechanically-ventilated infants and children.

### Appendix

Ventilation of the respiratory system with a constant inspiratory flow ventilator (such as commonly used in neonatal intensive care) was simulated using the following model: The equation of motion for the single compartment model of the respiratory system can be written:

$$P_{ao} = R_{rs} \cdot \dot{V} + V/C_{rs} + EEP$$

A flow dependent ETT resistance represented by:

$$R_{ETT} = K1 + K2 \cdot \dot{V}$$

was added to the model. The alveolar pressure at the beginning of inspiration was set above airway opening pressure. This pressure represented  $PEEP_i$  (by definition).

#### Inspiration

Airway opening pressure  $P_{ao}(t)$  and volume  $V(t)$ , integrated from constant flow  $\dot{V}$  at the time  $t$  are then given by the following differential equations:

$$P_{ao}(t) = PEEP_i + V(t)/C_{rs} + (R_{rs} + K1) \cdot \dot{V} + K2 \cdot \dot{V}^2$$

$$V(t) = t \cdot \dot{V}$$

#### Expiration

Expiration immediately followed inspiration, without inspiratory pressure plateau, and was assumed to be passive without respiratory muscle activity. The corresponding differential equations are:

$$P_{ao}(t) = 0$$

$$\dot{V}(t+dt) = (PEEP_i + V(t)/C_{rs}) / (R_{rs} + K1 + K2 \cdot \dot{V}(t))$$

$$V(t+dt) = \dot{V}(t) + dt \cdot \dot{V}(t)$$

with incremental time intervals  $dt$ .

These equations were iterated numerically with a frequency of 1,000 Hz (*i.e.*  $dt = 1$  ms) over one full respiratory cycle (*i.e.* inspiration followed by expiration). Expiration was ended when the inspired volume had been expired. To determine the stability of parameter estimates from multiple linear regression in

the presence of measurement noise, a random fluctuation between  $\pm 0.5$  ml·s<sup>-1</sup> was added to the flow signal. A similar random noise of  $\pm 0.1$  hPa was added to the airway opening pressure signal. Various values of  $C_{rs}$ ,  $R_{rs}$ ,  $K1$ ,  $K2$ , inspiratory flow and time as well as  $PEEP_i$  were used to simulate conditions encountered clinically, *e.g.* in premature infants, sick neonates.

#### Calculation of respiratory system parameters from simulated ventilator cycles

For each set of ventilation parameters, ETT characteristics and respiratory system values, the resulting  $P_{ao}$ ,  $\dot{V}$  and  $V$  "tracings" generated from the above described simulation of a full ventilator cycle (including a flow-dependent resistance and measurement noise) were then used as input for multiple regression analysis of equation (2) (which assumes a flow-independent constant resistance). By fitting the simulated data to this equation, values for  $C_{rs}$ ,  $R_{rs}$  and EEP were obtained. The resulting EEP value was compared with the  $PEEP_i$  used in the simulation of the ventilator cycle.

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*Détermination non invasive de la pression alvéolaire au cours de la ventilation mécanique. T. Nicolai, C. Lanteri, N. Freezer, P. Sly.*

Le développement d'une PEEP involontaire (PEEP<sub>i</sub>) chez les petits enfants ventilés a une signification clinique, mais est difficile à mesurer de façon non invasive. Une méthode d'estimation de la pression alvéolaire à la fin de l'expiration, au moyen d'une analyse à régression multiple appliquée à la pression d'ouverture des voies aériennes, au débit et au volume, au cours de la ventilation mécanique, a fait l'objet d'une évaluation.

Chez huit chiens bâtards, thoracotomisés, paralysés et ventilés mécaniquement, la pression alvéolaire a été mesurée directement au moyen de "capsules alvéolaires". La modification des types ventilatoires et l'addition d'un élément résistif ont été utilisés chez trois chiens pour provoquer différents niveaux de PEEP<sub>i</sub>. La pression alvéolaire en fin d'expiration mesurée directement, et celle déterminée, à partir d'une régression multilinéaire de la pression d'ouverture des voies aériennes, sont en bonne corrélation (erreur moyenne 0.06±0.53 (±SD) hPa, limites de concordance -1.16 à +1.04 hPa). Les cinq autres chiens ont subi des provocations par inhalation, deux au moyen d'histamine, deux au moyen de solution saline hypertonique, et un au moyen de methacholine avec, pour résultat, une augmentation moyenne de la résistance du système respiratoire de 230% (extrêmes 141-489%) par rapport aux valeurs de base. L'erreur moyenne dans la détermination de PEEP<sub>i</sub> a été de 0.54±0.37 hPa, les limites de concordance étant de -0.20 à 1.28 hPa.

La méthode a été appliquée ensuite à 7 enfants ventilés mécaniquement (âge: 2 mois à 8 ans, poids: 4.9 à 23.5 kg) et les résultats ont été comparés à la pression à laquelle l'inspiration commençait (ce qui est égal à la PEEP<sub>i</sub>). Au cours de la chirurgie à coeur ouvert, 78 mesures ont été réalisées, avec des modifications de compliance entre 3 et 186% des valeurs de base par suite des interventions chirurgicales. La PEEP<sub>i</sub> estimée au moyen de la régression multiple est en bon accord avec la pression à laquelle l'inspiration commence (différence moyenne 0.25±0.68 hPa, limites de concordance -1.12 à 1.62 hPa).

Un modèle informatique a été utilisé pour déterminer la stabilité de la méthode à régression multiple dans des conditions susceptibles de renforcer des suppositions à la base de cette technique, c'est-à-dire en présence d'une résistance du tube endo-trachéal dépendant des hauts débits, et après l'introduction de bruit dans les signaux simulés. Les valeurs habituellement rencontrées en pratique clinique n'ont pas entraîné d'erreurs inacceptables dans la détermination de la PEEP<sub>i</sub> à partir de l'analyse à régression multiple des pressions des voies aériennes.

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