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The effect of positive endexpiratory pressure, peak inspiratory pressure, and inspiratory time on functional residual capacity in mechanically ventilated preterm infants

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Abstract In mechanical ventilation of preterm infants, positive endexpiratory pressure (PEEP) is widely used to prevent alveolar collapse, maintain functional residual capacity (FRC) and improve oxygenation. Prolongation of inspiratory time (t_i) and increase of peak inspiratory pressure (PIP) are also used for this purpose. We investigated the effect of variations of PEEP, PIP and t_i on FRC in ten infants with hyaline membrane disease and onset of bronchopulmonary dysplasia (BPD, $n = 7$), pulmonary hypertension ($n = 1$), pulmonary hypoplasia ($n = 1$) or severe BPD ($n = 1$) (gestational age 24–39 weeks, median 26 weeks; birth weight 590–2960 g, 785 g; chronological age 7–84 days, 19 days; weight 689–4650 g, 1185 g). FRC, measured using the sulphur hexafluoride washout technique, was between 6.2 and 48.3 ml/kg (median 21.5 ml/kg). PEEP was changed stepwise 2–5 times in each patient (median 3) and mean airway pressure (MAP) was modified independently of PEEP by changing PIP 0–2 times (median 1) and t_i 0–2 times (median 2). Changes of FRC correlated well with modifications of PEEP in each patient ($r = 0.90$, range 0.71–0.99). The slope factors of linear correlations had a median value of 2.94 ml/cm H_2O per kg, which was significantly different from zero ($P < 0.01$) and significantly higher than the slope factors of linear correlations between FRC and MAP after modifications of PIP or t_i ($P < 0.01$). The latter two were statistically not different from zero. The quotients ΔFRC/ΔMAP were significantly higher after adjustments of PEEP than after adjustments of PIP or t_i ($P < 0.01$). The time lag between the change of PEEP and the stabilization of FRC on a new level ranged from 2 to 14 min (median 5).

Conclusion FRC is mainly determined by PEEP but not by PIP or t_i. Stabilization of FRC after a change of PEEP can last up to 14 min. Its duration is unpredictable and has to be waited for when testing pulmonary function in ventilated preterm infants.

Key words Infant · Positive endexpiratory pressure · Mean airway pressure · Functional residual capacity · Sulphur hexafluoride washout technique

Abbreviations *FRC* Functional residual capacity · *PIP* Peak inspiratory pressure · *PEEP* Positive end-expiratory pressure · *MAP* Mean airway pressure · ΔFRC Magnitude of change of FRC after modification of ventilator setting · ΔMAP Magnitude of change of MAP after modification of ventilator setting · *P-V loop* Pressure-volume loop · t_i Inspiratory time · t_e Expiratory time · SF_6 Sulphur hexafluoride

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Introduction

In surfactant deficiency, pneumonia and other pulmonary diseases, mechanical ventilation with positive endexpiratory pressure (PEEP) has been shown to improve oxygenation [9, 12]. PEEP prevents endexpiratory collapse of alveoli and preserves the functional residual capacity (FRC) necessary for adequate gas exchange. Other means that increase mean airway pressure (MAP), such as prolongation of inspiratory time (t_i) and increase of peak inspiratory pressure (PIP) have also been shown to improve oxygenation [15, 22], but it has not been studied whether this effect is also mediated by an increase of FRC.

Inter-individual variations of pulmonary compliance and resistance require ventilator settings to be adjusted individually. The adjustment of PEEP may be particularly critical. If PEEP is too low, gas exchange may be impaired by collapse of alveoli, and lung damage may be increased [23]. Higher PEEP levels appear to reduce lung damage in a rabbit model of neonatal respiratory distress syndrome [23]. Inappropriately high PEEP, however, may impair expiration, decrease tidal volume, minute ventilation [1] and cardiac output [20] and may lead to over-distension of the lung, interstitial emphysema, pneumothorax and pneumopericardium [8]. The best pulmonary compliance is achieved with a PEEP that normalizes FRC [28].

Despite the widespread use of mechanical ventilation with PEEP in neonatal care, few objective criteria have been available to the clinician for making decisions on ventilator settings such as the PEEP level. Blood gas values and chest X-rays only indirectly reflect alveolar distension. Direct measurement of FRC is not readily available. The influence of ventilator settings on FRC has not been clearly established. We have developed an easy-to-use FRC measurement device based on the sulphur hexafluoride (SF_6) washout technique [27] and used it to optimize ventilator settings in infants requiring prolonged mechanical ventilation. We studied the influence of variations of MAP achieved by three different interventions, i.e. by changing PEEP, PIP and t_i, on FRC and tested the hypothesis that variations of PEEP, but not PIP or t_i, would influence FRC in these infants. Furthermore, we determined the time needed to reach a new steady FRC after a modification of ventilator settings.

Methods

Patients

FRC was measured, in order to optimize ventilator settings, in 17 infants who failed to wean from mechanical ventilation, and who were considered by the clinicians to be difficult to manage. Of these, 7 infants were excluded from this analysis because FRC measurements after modifications of PIP or t_i were not done ($n = 6$) or because of a significant endotracheal tube leak ($n = 1$), distorting the results. Ten infants remained, who were ventilated because of hyaline membrane disease and beginning bronchopulmonary dysplasia (BPD, $n = 7$), pulmonary hypertension ($n = 1$), pulmonary hypoplasia ($n = 1$) or severe BPD ($n = 1$). All infants except numbers 2, 4 and 5 had received surfactant during their initial treatment. Each infant was monitored with a heart rate monitor, a transcutaneous $PaCO_2$ sensor and a pulse oximeter. SF_6 was supplied by Linde, Munich, Germany as a 1:1 mixture with nitrogen. This mixture has been approved by the Bavarian Government Health Authority for diagnostic use in humans. Informed consent was obtained from the parents of each infant.

FRC-measurement

FRC was measured by washout of SF_6, an insoluble, non-toxic tracer gas [2, 16]. The setup of the measurement apparatus, the measurement process and the algorithms for calculation of FRC have been described previously in detail [27]. In brief, a pneumotachograph and a fast mainstream infra-red SF_6 analyser (Siemens-Elema, Solna, Sweden) were inserted between the Y-piece of the ventilator circuit and the endotracheal tube. The pneumotachograph [24] had a dead space of 0.9 ml and a resistance of 1.1 kPa*s/l at 5 l/min. The cuvette of the SF_6 analyser had a dead-space of 1 ml and a resistance of 0.26 kPa*s/l at 5 l/min. The concentration of SF_6 during wash-in was 0.7–1.1%. Repetition of measurements was possible every 2 min. Dynamic compliance was measured by recording a pressure-volume (P-V) loop of a mechanically controlled breath and setting a cursor on each end point of the loop (two-point method). Mean values of three loops were determined and recorded. This software was only available for the last eight infants in our study.

Accuracy and reproducibility of the FRC measurement apparatus have been tested. A comparison of measured FRC of a dummy lung with its known, adjustable FRC resulted in a difference of $0.7 \pm 3.2\%$ (mean $\pm$ SD). The coefficient of variation across 20 FRC determinations in five adult rabbits was 1.7% during continuous positive airway pressure and 1.98% during controlled mechanical ventilation [27]. Measurement of dynamic compliance was tested with copper-wool filled bottles and found to have an error of $+3\%$ [29].

Mechanical ventilation

For mechanical ventilation, the time-cycled, pressure-limited infant ventilators Sechrist IV 100B (Sechrist, Anaheim, Calif.) and Stephan HF 300 (Stephan, Gackenbach, Germany), were used. PEEP was routinely adjusted to result in a diaphragm projection onto the posterior part of the ninth rib on chest X-rays taken at end-expiration. The ventilatory rate was set between 30 and 60/min. Special attention was given to the avoidance of inadvertent PEEP by allowing sufficient expiratory time for expiratory flow to cease before the next inspiration. Muscle paralysis was not used, spontaneous respiratory efforts were prevented by providing sufficient mechanical ventilatory support.

Protocol of measurement

Each change of ventilator settings was followed by serial FRC measurements until no further trend was detectable on three consecutive measurements. This was assumed if FRC readings varied by less than 5% between measurements and in both directions, i.e. upward and downward. The means of the last three consecutive measurements of each series were calculated and subsequently referred to as 'steady state FRC values' (Fig. 2).

First, FRC was measured at least three times while ventilating the infants with the parameters chosen by the clinician. Next, PEEP was changed in steps of 2 cmH_2O. If FRC was less than 35 ml/kg, PEEP was first increased stepwise until the resulting increase of

FRC was less than 20% of the previous measurement or FRC was above 42.8 ml/kg (95th percentile in a meta-analysis of FRC values in healthy preterm and term infants [25]) or PEEP was above 6 cmH_2O. After PEEP had been returned to the initial value and FRC had stabilized, or if initial FRC was greater than 35 ml/kg, PEEP was decreased until the resulting decrease of FRC was less than 20% of the previous measurement or FRC was less than 65% of the initial value or less than 18.3 ml/kg (5th percentile [25]). Thereafter, the MAP was increased by doubling t_i without changing t_e and PEEP, followed by an increase of PIP by 2–4 cmH_2O with the initial t_i. Finally, PIP and t_i were returned to the initial settings and PEEP was set to result in a FRC of 20–30 ml/kg according to the results obtained during the previous measurements. When FRC had stabilized, the measurement apparatus was removed. Any manipulation detrimental to the infant, e.g. resulting in a proportionately large rise in $PaCO_2$ or O_2 requirement, was abandoned. As this protocol was time-consuming, it could not be continued to the end with each infant because of interference with standard patient care. Endotracheal tube leaks were excluded by continuous comparison between inspiratory and expiratory tidal volume. No suctioning or bagging was done during the study. Dynamic compliance was measured with each ventilator setting in the last eight patients.

Data analysis

For standardization, all FRC values were related to body weight. Values between 18.3 ml/kg and 42.8 ml/kg were considered normal (5th and 95th percentile in a meta-analysis of FRC values in healthy preterm and term infants measured with either the helium dilution or the nitrogen washout technique [25]).

Linear regressions of FRC versus PEEP (FRC = slope factor * PEEP + offset) of each patient were calculated separately from measurements before and after modifications of PEEP. Likewise, linear regressions of FRC versus MAP were calculated from measurements before and after modifications of PIP and from measurements before and after modifications of t_i. From the resulting values for slope factor and offset, median values across all patients were obtained. The Wilcoxon rank sum test was used to test whether the median slope factors were significantly different from zero.

To test the hypothesis that FRC is mainly influenced by PEEP, the magnitude of each change of FRC (ΔFRC) was divided by the respective change of MAP (ΔMAP). From these quotients, three median values were obtained separately for each patient, one for all modifications of PEEP, one for all modifications of PIP and one for all modifications of t_i. The latter two median values were compared with the median values obtained from modifications of PEEP by the Wilcoxon signed rank test for paired samples.

As five tests were performed altogether, a P-value less than 0.01 instead of 0.05 was considered significant, according to the Bonferroni correction for multiple testing.

Results

The ten patients were born after 24–39 weeks gestation (median 26 weeks) and had a birth weight of 590–1690 g (785 g). They were studied at an age of 7–84 days (19 days) and weighed 689–2600 g (1185 g) at study time. The diagnoses were hyaline membrane disease and beginning BPD ($n = 7$), pulmonary hypertension ($n = 1$), pulmonary hypoplasia ($n = 1$) or severe BPD ($n = 1$). FRC was measured 21 times per patient (median, range 13–33) varying PEEP, PIP and t_i. The median variation coefficient of repeated measurements with unchanged ventilator settings was 4% (range 0–15%). PEEP was changed 2–5 times in each patient (median 3 times), and the MAP was modified independently of PEEP by changing PIP 0–2 times per patient (median 1) or by changing t_i 0–2 times per patient (median 2). Initial FRC values measured at the clinically selected ventilator settings were between 7.3 and 38.2 ml/kg (median 23.3). Initial FRC was below the 5th percentile (18.3 ml/kg) [25] in two patients and between the 5th and 95th percentile in eight. No patient had an initial value above the 95th percentile (42.8 ml/kg). When PEEP was reduced, FRC remained above the 5th percentile in only two patients (Table 1).

A measurement series is shown in Figure 1. The FRC of patient 3 declined markedly after lowering PEEP in two steps from 5 cmH_2O to 1 cmH_2O. Increasing t_i from 0.3 s to 0.6 s and thereby increasing MAP above the initial value and later increasing PIP did not change the FRC, but returning PEEP to 5 cmH_2O led to a rapid restoration of the previous FRC.

While overall correlation between FRC and PEEP or MAP was poor because of the wide variety of pulmonary pathology in the study patients, good correlations with correlation coefficients between 0.71 and 0.99 (median 0.90) were found when regressions between PEEP and FRC were calculated individually for each infant. The slope factors of linear correlations were between 0.62 and 4.68 ml/cmH_2O per kg (median 2.94) and the offset values between 2.42 and 16.6 ml/kg (median 9.95). Both were significantly different from zero ($P < 0.01$, Table 1 and Fig. 2).

In contrast, calculation of linear regressions for the relationship of FRC and MAP from measurements in which MAP had changed secondary to modifications of PIP or t_i, resulted in median slope factors of 0.44 and −0.08 ml/cmH_2O per kg, respectively, which were statistically not different from zero (Table 1).

The quotient ΔFRC/ΔMAP obtained after modifications of PEEP was between 0.76 and 8.11 ml/cmH_2O per kg (median 3.12) and significantly higher ($P < 0.01$) than that obtained after modifications of PIP (median 0.44, range −8.13–2.75) or t_i (median 0.06, range −6.41–2.17, Table 1).

Dynamic compliance could be measured in eight infants. Maximum values for each patient were between 0.34 and 0.68 ml/cmH_2O per kg (median 0.43). Dynamic compliance values did not correlate with absolute FRC values or the slope factors of linear correlations between PEEP and FRC.

The time lag from modification of PEEP until stabilization of FRC on a new level was 2–5 min after 52% of the 31 modifications, 6–10 min after 35% and 11–15 min after 13%. The minimum time was 2 min, owing to the duration of the measurement process. In three patients, a maximum time lag of 14 min was found. The time lag did not correlate with FRC or any ventilation parameter.

Table 1 Range and regressions of pulmonary functional residual capacity

Patients	Initial	Min.	Max.	Initial	Min.	Max.	Regression FRC-PEEP[a]	
	PEEP (cmH_2O)	PEEP (cmH_2O)	PEEP (cmH_2O)	FRC (ml/kg)	FRC (ml/kg)	FRC (ml/kg)	Slope ($ml/cmH_2O/kg$)	Offset (ml/kg)
1	6	3	6	23.9	11.3	23.9	3.88	2.42
2	6	2	6	12.0	9.4	14.3	0.62	9.58
3	5	1	5	38.2	15.1	39.2	3.76	15.8
4	6	2	8	21.9	17.6	31.9	2.23	11.9
5	3	1	6	7.3	6.1	10.2	0.62	5.77
6	5	0	7	20.0	10.0	24.2	1.84	10.3
7	2	2	5	22.6	19.6	29.4	0.75	24.0
8	3	3	7	30.2	26.1	48.7	4.68	16.6
9	5	3	5	25.5	16.2	26.5	4.40	2.67
10	6	3	7	27.9	12.1	29.6	3.64	4.48
Median							2.94*	9.95*

Patients	Regression slope FRC-MAP		Quotient ΔFRC/ΔMAP		
	Mod. PIP[b] ($ml/cmH_2O/kg$)	Mod.t_i[c] ($ml/cmH_2O/kg$)	Mod. PEEP[d] ($ml/cmH_2O/kg$)	Mod. PIP[e] ($ml/cmH_2O/kg$)	Mod.t_i[f] ($ml/cmH_2O/kg$)
1	1.98	–	5.72	2.75	–
2	–	−1.52	1.16	–	−0.59
3	0.46	−0.25	8.11	0.46	0.04
4	1.92	1.92	4.13	1.92	2.17
5	−0.14	0.087	0.76	−0.14	0.09
6	0.45	1.44	2.32	0.45	1.44
7	−0.12	−0.35	1.24	0.30	−0.08
8	−8.13	−5.52	3.75	−8.13	−6.41
9	0.44	1.14	2.49	0.44	1.01
10	−6.50	–	5.43	−6.50	–
Median	0.44**	−0.08**	3.12	0.44***	0.06***

[a] Linear regression of FRC and PEEP – slope factor and offset of regression line
* Significantly different from zero ($P < 0.01$)
[b] linear regression of FRC and MAP – slope factor of regression line, calculated only from measurements, in which MAP had changed secondary to modifications of PIP
[c] linear regression of FRC and MAP – slope factor of regression line, calculated only from measurements, in which MAP had changed secondary to modifications of t_i
[d] obtained after modifications of PEEP
[e] obtained after modifications of PIP
[f] obtained after modifications of t_i
** statistically not different from zero
*** significantly different from quotient ΔFRC/ΔMAP after modification of PEEP ($P < 0.01$)

Discussion

Using our FRC measurement device required only two modifications of the ventilator circuit to prepare it for measuring: insertion of the SF_6 injector into the ventilator tubing system and insertion of the flow- and SF_6 sensor unit between the Y-piece and the endotracheal tube. Additional sensor dead space was small (≈2 ml). After connection, all measurements were obtained without any further disturbance of the infant. Using SF_6 as tracer gas enabled us, in contrast to other methods, to perform rapid serial FRC measurements regardless of inspired O_2 concentration, because a SF_6 concentration of about 1% is sufficient. However, this method may be, like the others, susceptible to endotracheal tube leaks. If tracer gas gets lost, FRC would be underestimated. In several publications, data obtained by SF_6 washout did not show a systematic difference compared to those obtained by body plethysmography [6, 17], nitrogen washout [17] and helium dilution in healthy adult humans [6] as well as in adult rabbits [31]. The accuracy of our measurement setup and the reproducibility of the results have been established in animals [27]. In our non-sedated patients, a slightly higher variation coefficient was observed (median 4%, range 0–15%).

This study was done in somewhat older infants who failed to wean from mechanical ventilation and challenged the ability of the nursery staff to determine the most appropriate ventilator settings. We chose not to include preterm infants younger than 5 days, because their risk of intracranial bleeding when subjected to long inspiratory times or high peak pressures, with the possible changes in venous return and arterial pCO_2, may be increased. Therefore, our results may not apply to premature infants suffering from acute surfactant deficiency

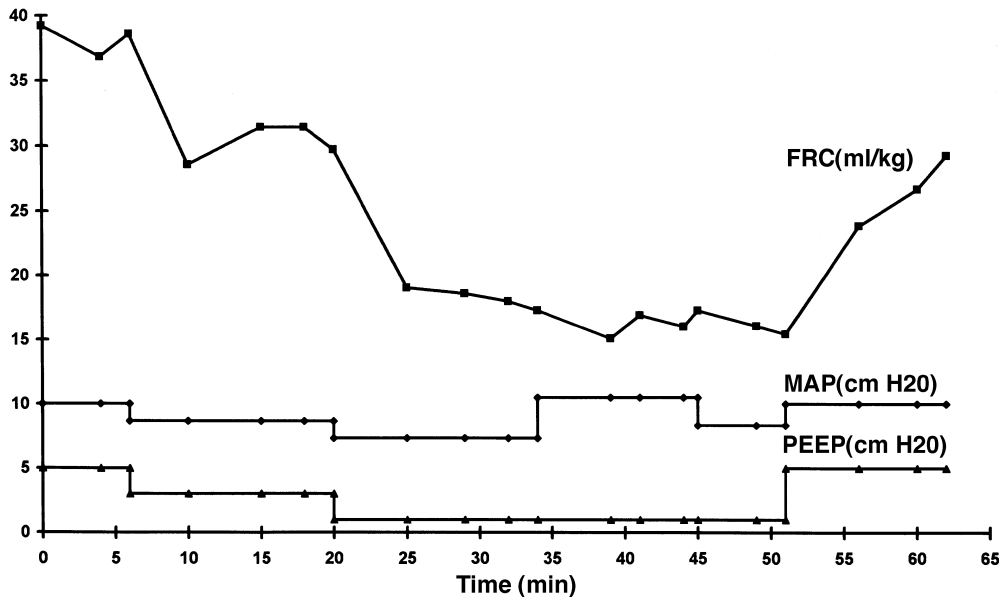

Fig. 1 FRC of patient 3 (initial ventilation pattern: PIP 20 cmH_2O, PEEP 5 cmH_2O, t_i 0.3 s, t_e 0.6 s): stepwise reductions of PEEP resulted in a rapidly decreasing FRC. Increasing MAP by prolonging t_i to 0.6 s from the 34th until the 45th min did not have any influence on FRC. Likewise, FRC remained constant after PIP was increased to 23 cmH_2O from the 45th until the 51st min (with $t_i = 0.3$ s). In contrast, FRC increased rapidly after PEEP was returned to the initial value (52nd minute)

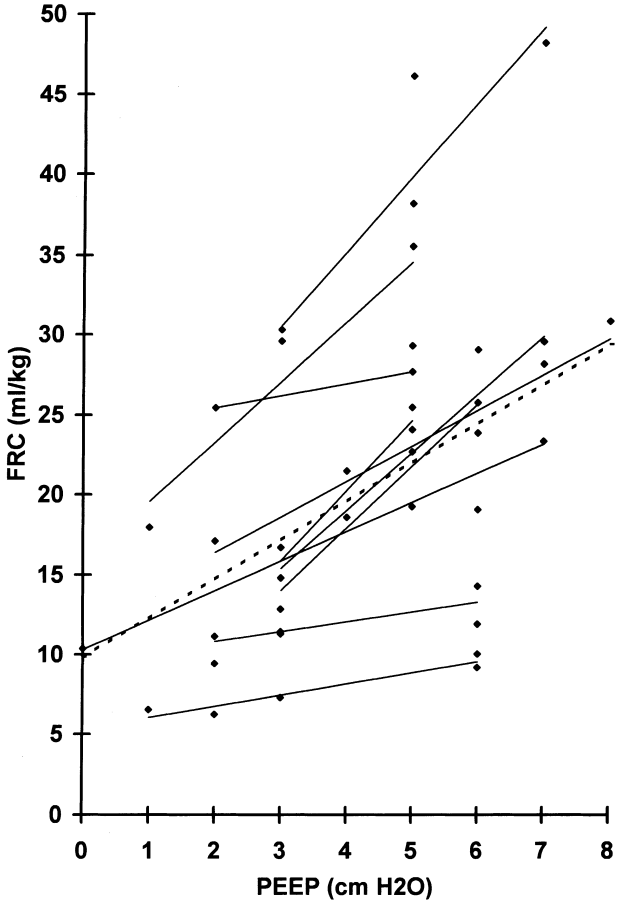

Fig. 2 Steady state FRC in relation to PEEP of all ten patients. Individual linear regressions were calculated for each infant and included in the figure (thin lines). Median values were obtained from the slope and offset values of all infants. The dashed bold line corresponds to the median values for slope and offset (FRC = 2.94 * PEEP + 9.95)

during their first postnatal days. In fact, the infants studied were 7–84 (median 19) days old, and differed further in maturity and underlying diseases, which may be one reason for the fact that the slope factors of linear correlations between PEEP and FRC covered a wide range, between 0.62 and 4.68 ml/cmH_2O per kg (median 2.94). Only modifications of PEEP, however, had a consistent effect on FRC, as opposed to modifications of PIP and t_i.

To guide our ventilator setting modifications, we needed to compare the measured FRC with the normal range. Unfortunately, no determination of reference values in a large sample of healthy preterm and term infants was available. The only paper with a large database was a German meta-analysis, which also included the calculation of percentiles [25]. In this meta-analysis, eight papers with FRC measurements by the helium dilution or nitrogen washout techniques in 123 healthy preterm and term infants were included; three further articles were not included in the analysis because they yielded results significantly different from the rest. The FRC values were not normally distributed, and resulted in the following percentiles: 5%, 18.3 ml/kg; 10%, 20.9 ml/kg; 25%, 23.7 ml/kg; 50% (median), 27.5 ml/kg; 75%, 32.9 ml/kg; 90%, 39.4 ml/kg; 95%, 42.8 ml/kg. Therefore, we used 18.3 ml/kg as lower and 42.8 ml/kg as upper FRC limits.

The interrelation of FRC and PEEP has been investigated in animal models as well as in premature infants. An increase of FRC by 3 ml/cmH_2O PEEP (i.e. 1.2 ml/cmH_2O/kg) has been described in healthy adult rabbits (mean weight 2.53 kg, range 2.45–2.6 kg) [26, 27]. The FRC of healthy mongrel dogs (weight 20–25 kg) increased by about 100 ml/cmH_2O (4–5 ml/cmH_2O/kg) [5]. In mechanically ventilated preterm infants, a decrease from a PEEP of 3 cmH_2O (mean, range 2–4) to zero endexpiratory pressure reduced FRC by 29% to a median of 13.4 ml/kg [31], similar to our findings (me-

dian offset of linear regressions 9.95 ml/kg). The most extensive analysis, carried out in surfactant treated, preterm infants (age 3–7 days) using the helium dilution technique, found a non-linear but significant increase of FRC as PEEP was raised from 2 to 5 cmH_2O [3]. The increase of FRC was between 1.3 ml/kg (when PEEP increased from 2 to 3 cmH_2O) and 3.6 ml/kg (when PEEP increased from 4 to 5 cmH_2O), and thus similar in magnitude to the increase observed in our study on much older infants. Lung recruitment by increasing PEEP has also been demonstrated in human adults after open heart surgery [30] and with adult respiratory distress syndrome [21].

In our study, FRC was highly correlated to PEEP with a median linear slope factor of 2.94 ml/cmH_2O per kg, which is in the range of the published values cited above, but about seven times higher than expected from the measured dynamic compliance (median 0.43 ml/cmH_2O/kg). It is unlikely that this discrepancy was caused by measurement errors of dynamic compliance or FRC. The measurement of dynamic compliance may underestimate true compliance [14] if the lung is over-inflated during measurement, but we tried to minimize such errors by checking the P-V loops and chest X-rays for signs of over-inflation and by measuring compliance with different ventilator settings. Further, the employed ventilator settings make a seven-fold underestimation of true compliance owing to over-inflation of the lung very unlikely. The measurement of FRC may be influenced by endotracheal tube leaks, but undetected leaks cannot explain the large changes of FRC after modifications of PEEP observed here. Gas transport and tracer gas loss through a leak is larger when the pressure gradient is higher, and therefore, in the presence of a leak, FRC would be more underestimated with higher PEEP settings, thus diminishing, not increasing FRC differences between high and low PEEP. Further, we could exclude leaks by comparison of inspiratory and expiratory tidal volumes during measurement.

The large discrepancy between dynamic compliance readings and FRC changes, which has been found after surfactant treatment as well [7, 10, 14] may be explained by two different underlying mechanisms of air uptake: distension and recruitment [10, 11]. During inspiration, most of the air flows into alveoli which are already open and are then distended. Some collapsed alveoli may become recruited, but their number is limited because of the short duration of the inspiration, and they may collapse again during the next expiration. This is consistent with the demonstration of progressive recruitment after several inflations in adult heart surgery patients [30]. Thus, recording a P-V loop and determining compliance mainly measures compliance of those alveoli which are open and filled with air [10]. If PEEP is increased, some of the alveoli recruited during inspiration may now remain open. Others are added during the next inspiration and so on, leading to a markedly increased number of open alveoli and to an increased FRC after multiple cycles and sufficient time. Dynamic compliance measurements, which are limited to the duration of one respiratory cycle, cannot detect the stepwise recruitment occurring in consecutive respiratory cycles. After recruitment, compliance may be increased as well, because more alveoli are now being ventilated, but the increased distension of alveoli during expiration at higher PEEP settings limits the improvement of compliance. If alveoli are over-distended, compliance will fall again [7, 10, 14]. Decreasing PEEP allows alveoli to collapse in increasing numbers during the expirations, resulting in a progressive diminution of FRC. Both processes, recruitment and collapse, take much longer than one respiratory cycle. Stabilization of FRC was completed within 5 min in most cases, but lasted up to 14 min in three. The stabilization time should be taken into consideration when interpreting pulmonary function tests.

The quotient $\Delta FRC/\Delta MAP$ was significantly higher after modifications of PEEP than after modifications of PIP or t_i The slope factors of linear correlations between FRC and PEEP were significantly higher than zero, indicating correlation, but not those between FRC and MAP obtained by modifications of PIP or t_i. As the increase in PIP was limited in order to avoid additional barotrauma, the resulting increase of MAP was smaller than the increase of MAP by prolongation of t_i. We cannot exclude that a greater increase in PIP may increase alveolar recruitment and thus increase FRC in some patients. In our study, however, neither increase of PIP nor prolongation of t_i increased FRC and therefore did not prevent endexpiratory alveolar collapse. Likewise, ventilation with inverse I:E ratios did not reduce histological changes in a rabbit model of respiratory distress syndrome, in contrast to a higher PEEP [23]. It has been suggested that the improvement of oxygenation seen in inverse ratio ventilation could be the result of inadvertent PEEP because of inadequate expiratory time, and the use of a higher PEEP instead of an inverse I/E ratio was proposed [4]. Increasing PEEP, however, is limited because tidal volume and minute ventilation may be reduced. Higher PEEP settings can be used with higher ventilation frequencies, which allow for smaller tidal volumes. This approach has already been shown to reduce the complications of mechanical ventilation in clinical studies [13, 18, 19].

We have presented data on the influence of PEEP and, for the first time, PIP and t_i on FRC. It has been demonstrated that FRC was influenced by changes of PEEP, but not by changes of MAP achieved by variations of PIP and t_i at ventilatory rates of 30–60 breaths per minute in preterm and term infants requiring prolonged mechanical ventilation. We conclude that PEEP was the main determinant of FRC in our infants, and no further influence by PIP or t_i was detectable. However, this study was done in only ten patients, who differed from each other in maturity, age and underlying diseases. Therefore, the results presented here may not apply to other patient groups. The great variability of slope factors found among our patients hinders predic-

tions on the change of FRC after modification of PEEP. The change of FRC, therefore, should preferably be controlled by direct measurement.

Whether FRC-guided ventilator settings improve the outcome in critically ill infants was beyond the scope of this study and requires further investigation.

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