

Decrease of Functional Residual Capacity and Ventilation Homogeneity after Neuromuscular Blockade in Anesthetized Young Infants and Preschool Children

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Background: **Based on age-dependent differences in pulmonary mechanics, the effect of neuromuscular blockade may differ in infants compared with older children. The aim of this study was to determine the impact of neuromuscular blockade and its reversal by positive end-expiratory pressure (PEEP) on functional residual capacity (FRC) and ventilation distribution in young infants and preschool children.**

Methods: **The authors studied 14 infants (aged 0–6 months) and 25 preschool children (aged 2–6 yr). FRC and lung clearance index were calculated. Measurements were taken (1) after intubation, (2) during neuromuscular blockade, and (3) during neuromuscular blockade plus application of PEEP (3 cm H_2O).**

Results: **Functional residual capacity (mean ± SD) decreased from 21.3 ± 4.7 ml/kg to 12.2 ± 4.8 ml/kg ($P < 0.001$) during neuromuscular blockade in infants and from 25.6 ± 5.9 ml/kg to 23.0 ± 5.3 ml/kg ($P < 0.001$) in preschool children. With the application of PEEP, FRC increased to 22.3 ± 5.9 ml/kg (P = 0.4829, compared with baseline) in infants and 28.2 ± 5.8 ml/kg ($P < 0.001$) in children. The lung clearance index increased after neuromuscular blockade, whereas baseline values were regained after the application of PEEP. The changes induced by neuromuscular blockade were significantly greater in infants compared with preschool children ($P < 0.001$).**

Conclusions: **Although the use of neuromuscular blockade decreased FRC and ventilation distribution substantially in both groups, the changes were more pronounced in young infants. With PEEP, FRC increased and ventilation homogeneity was restored. These results provide a rationale to use PEEP in anesthetized, paralyzed infants and children.**

VARIOUS anesthetic agents, airway instrumentation, and ventilation strategies are used in infants and children undergoing anesthesia. Each of these factors can have a significant effect on various lung volumes. In this context, functional residual capacity (FRC), which is the most important volume parameter of gas exchange, is of special interest. Among the many factors that make children, particularly newborns and infants, vulnerable to hypoxemia when undergoing sedation or anesthesia are alterations in lung mechanics. Although there is general agreement that patients under general anesthesia have a reduced FRC, most studies assessed the overall effect of anesthesia induction, relaxation, intubation, and mechanical ventilation in comparison with the preanesthetic status. However, there is minimal information regarding the magnitude that each of these components contributes.[1–4]

In children undergoing anesthesia or sedation, optimizing FRC is of special importance, because they have smaller elastic retraction forces and a lower relaxation volume that makes them more prone to airway collapse.[5,6] Neuromuscular blockade inhibits this dynamic increase of the end-expiratory lung volume and thus might jeopardize oxygenation.

The purpose of the current study was to increase the understanding of the impact of neuromuscular blockade on FRC in anesthetized infants and children who have healthy lungs, and to assess the impact of positive end-expiratory pressure (PEEP) to reverse the changes induced by neuromuscular blockade. We hypothesized that neuromuscular blockade would reduce FRC and decrease ventilation homogeneity, while the additional application of PEEP (3 cm H_2O) would restore both FRC and ventilation homogeneity.

Materials and Methods

After approval by the local ethics committee (Basel, Switzerland) and obtaining parental written informed consent, two groups of patients were studied: 14 healthy infants aged 0–6 months (corrected to gestational age) and 25 healthy children, aged 2–6 yr. Patients with known cardiopulmonary diseases (including respiratory tract infection during the 2 weeks before surgery) or thoracic deformities were excluded from participation in the study.

Anesthesia

Infant Group. None of the infants received premedication. Inhalational induction was started with 8% sevoflurane and 50% nitrous oxide in oxygen. As soon as intravenous access was established (duration 2–4 min), sevoflurane and nitrous oxide were discontinued immediately, and 2–4 mg/kg intravenous propofol and 2 μg/kg intravenous remifentanil were administered. Then, the trachea was intubated with a cuffed endotracheal tube (3.0- or 3.5-mm ID; Microcuff-Heidelberg, Weinheim, Germany).

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Preschool Children Group. One hour before the induction of anesthesia, patches with a eutectic mixture of local anesthetics were applied to the dorsal side of each child's hands. Premedication consisted of 0.3 mg/kg midazolam administered orally or rectally 15 min before induction of general anesthesia. In uncooperative patients, 70% nitrous oxide in oxygen was administered for the insertion of an intravenous cannula. Nitrous oxide was immediately stopped when venous access was achieved. General anesthesia was induced with 3–4 mg/kg intravenous propofol and 3 μg/kg fentanyl, and the trachea was intubated with a cuffed endotracheal tube (Microcuff, Heidelberg, Germany).

Before tracheal intubation, sufficient depth of anesthesia was tested by applying a jaw-thrust maneuver. If there was no reaction to the maneuver, tracheal intubation was gently performed. In all participants, anesthesia was maintained with an intravenous propofol infusion (12 mg $\cdot$ kg^{-1} $\cdot$ h^{-1} for the first 10 min of general anesthesia, 9 mg $\cdot$ kg^{-1} $\cdot$ h^{-1} for another 10 min, and then 6 mg $\cdot$ kg^{-1} $\cdot$ h^{-1}).[7] Neuromuscular blockade was achieved with 0.6 mg/kg intravenous rocuronium and was monitored with a nerve stimulator. Total neuromuscular blockade was defined as no tactile twitch on a train-of-four stimulation. The degree of muscle relaxation was tested throughout the study period by train-of-four stimulation every 12 s. In case of reappearance of twitching, additional doses of rocuronium were given.

Ventilator Settings

All patients received 100% oxygen until correct tracheal intubation was confirmed. During anesthesia, a Centiva/5 critical care ventilator (Datex Ohmeda, Helsinki, Finland) was used. Settings were as follows: inspired oxygen fraction of 0.5 and tidal volume of approximately 8 ml/kg body weight for the remainder of the study period. Respiratory rate was adapted to achieve an end-tidal carbon dioxide of 35–40 mmHg. The ventilator delivered a continuous bypass flow that was needed to ensure an exact delivery of the tracer gas at all times. This bypass flow in the breathing system created a PEEP of 3 cm H_2O in the system. Therefore, the addition of PEEP (3 cm H_2O) created a total PEEP of 6 cm H_2O in our clinical setting.

Assessment Times

Before the first FRC assessment in the infant group, it was assured that there was no further end-expiratory sevoflurane for at least 2 min as measured by the anesthetic workstation (Avance S/5; Datex Ohmeda). The first set of measurements was performed 5 min after intubation, and the second set was performed 5 min after complete neuromuscular blockade had been confirmed. The last set of measurements was taken 5 min after the application of an additional 3 cm H_2O PEEP on top of the PEEP that was constantly delivered by the ventilator because of the continuous bypass flow.[8] For each study condition, two measurements were performed, and the average was used for all calculations.

Measurement Techniques

An ultrasonic transit-time airflow meter (Exhalyzer D with ICU insert; Eco Medics, Duernten, Switzerland) that simultaneously measures flow and molar mass of the breathing gas in the mainstream was placed between the ventilator circuit and the endotracheal tube. The technical setup of the measurement equipment has been described previously.[9] Briefly, a multibreath washout technique with sulfur hexafluoride as tracer gas was used to measure FRC, physiologic dead space volume, lung clearance index, and mean dilution number. Lung clearance index and mean dilution number are commonly used to measure the degree of ventilation homogeneity.[10–15] The lung clearance index is calculated as the cumulative expired volume needed to decrease the end-tidal tracer gas (sulfur hexafluoride) concentration to 1/40 of the starting concentration divided by the FRC, *i.e.*, the number of lung volume turnovers needed to clear the lungs of the marker gas.[16,17] The mean dilution number is the ratio between the first and the zeroth moments of the washout curve. The number of volume turnovers was calculated using the cumulative expired alveolar volume.[13,15] An increase in lung clearance index or mean dilution number reflects a decrease in ventilation homogeneity. FRC, dead space, mean dilution number, and lung clearance index calculations were performed using Spiroware software (version 1.5.2; ndd Medizintechnik AG, Zürich, Switzerland).

Statistics

Sample size calculations were performed using nQuery Advisor 4.0 software (Statistical Solutions Ltd., Boston, MA). Sample sizes of 14 infants and 25 preschool children were calculated to detect an FRC difference of 2 ml/kg (infants) and 1.25 ml/kg (preschool children) after neuromuscular blockade, assuming an SD of differences (based on separate pilot data) of 2.1 ml/kg and 1.8 ml/kg, respectively, using a paired two-sided t test in each group with an α error of 0.05 and a β error of 0.1.

Demographic and procedural data were analyzed for normal distribution by the Shapiro-Wilk test, and data are reported as mean $\pm$ SD or median (interquartile range). Repeated measurements of continuous variables were analyzed with regression techniques using PROC MIXED procedures in SAS software version 9.1 (SAS Institute, Cary, NC). However, the regression model using the patient groups, the repeated-measures factors, and the interactions between the two as independent variables revealed highly significant interactions of all factors of interest. Therefore, for intragroup comparisons, a repeated-measures analysis of variance (with Bonferroni adjustment for multiple comparisons) was used to com-

Table 1. Patient Characteristics

	Infant (n = 14)	Preschool (n = 25)
Sex, M/F	11/3	14/11
Age, months	1 (0–6)	61 (26–77)
Height, cm	55.8 (44.2–64)	112 (87–122)
Weight, kg	4.55 (2.76–7.5)	19 (10.8–35.5)
Smoke exposure, n	4	3
Family history of asthma, n	4	2
Family history of severe allergic reactions, n	2	0

Values are median (range) or number.

pare data between the different study conditions, and intergroup comparisons were performed using the Wilcoxon signed rank test. $P < 0.05$ was considered significant.

Results

All 14 infants and 25 children were successfully studied. Intubation was preformed on the first attempt in all patients, and episodes of laryngospasm or bronchospasm were not observed. Patient characteristics are shown in table 1. Additional doses of rocuronium were needed in 4 infants and 8 preschool children. Neuromuscular blockade significantly decreased FRC and simultaneously increased lung clearance index, mean dilution number, and tidal volume–to–FRC ratio (table 2 and fig. 1). The changes between the FRC and lung clearance index values before and after neuromuscular blockade were significantly greater in infants compared with preschool children ($P < 0.0001$ for both parameters). The additional application of PEEP (3 cm H_2O) led to an increase of FRC and a decrease of lung clearance index, mean dilution number, and tidal volume–to–FRC ratio (table 2 and fig. 1). These changes of FRC and lung clearance index with the application of PEEP were significantly greater in infants compared with preschool children (FRC: $P = 0.0157$; lung clearance index: $P < 0.0001$; mean dilution number: $P < 0.0001$). Dead space volume did not change throughout the study period.

Discussion

This study examined the effects of complete neuromuscular blockade and PEEP (3 cm H_2O) on FRC and ventilation homogeneity in infants and preschool-aged children with healthy lungs. While FRC at baseline was lower in young infants compared with preschool children, the impact of neuromuscular blockade was also significantly larger in infants compared with preschool children (FRC decrease of 45% *vs.* 10%, respectively). Neuromuscular blockade also significantly impaired ventilation distribution. Both effects were completely reversed with the use of PEEP (3 cm H_2O).

Chest wall compliance decreases rapidly during child-

Table 2. Measured Parameters at the Three Assessment Times

	After Induction (Baseline)	After Neuromuscular Blockade	*P* Value	After PEEP	*P* Value
FRC, ml/kg					
Infants	21.3 (4.7)	12.2 (4.8)	< 0.0001	22.3 (5.9)	0.4829
Preschool	25.6 (5.9)	23.0 (5.3)	< 0.0001	28.2 (5.8)	< 0.0001
V_D, ml/kg					
Infants	2.41 (0.7)	2.28 (0.6)	0.1323	2.48 (0.8)	0.411
Preschool	1.11 (0.2)	1.14 (0.2)	0.234	1.13 (0.3)	0.3892
LCI					
Infants	8.92 [5.5–12]	15.3 [8.7–22]	0.0011	8.86 [6.8–11]	0.9775
Preschool	6.55 (0.7)	7.46 (1.3)	< 0.0001	6.47 (0.5)	0.709
MDN					
Infants	2.33 [1.5–3.2]	4.12 [3.0–5.2]	0.0067	2.51 [1.9–3.1]	0.9961
Preschool	1.89 (0.3)	2.11 (0.4)	0.0042	1.79 (0.2)	0.1778
V_T/FRC					
Infants	0.39 (0.1)	0.77 (0.3)	< 0.0001	0.38 (0.1)	0.8408
Preschool	0.33 (0.1)	0.37 (0.1)	< 0.0001	0.30 (0.1)	< 0.0001
Absolute PEEP, cm H_2O					
Infants	3	3		6	
Preschool	3	3		6	

Values are mean (SD) or median [interquartile range]. Significances as determined by a repeated-measures analysis of variance compared with baseline.

FRC = functional residual capacity; LCI = lung clearance index; MDN = mean dilution number; PEEP = positive end-expiratory pressure; V_D = dead space volume; V_T = tidal volume.

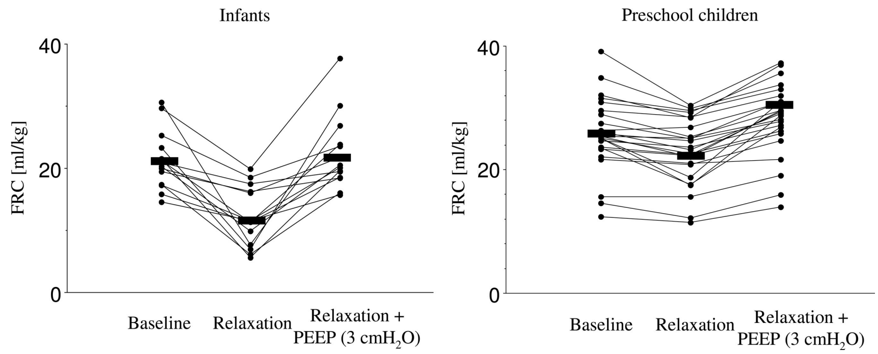

Fig. 1. Functional residual capacity (FRC, ml/kg) after induction of anesthesia (baseline), during neuromuscular blockade, and during neuromuscular blockade plus additional application of 3 cm H_2O positive end-expiratory pressure (PEEP) in young infants and preschool children. *Bars* indicate the mean values.

hood.[18] The balance between the chest and lung recoil pressure that determines the static resting volume of the lung is set at lower lung volumes in infants compared with older children.[18,19] During neuromuscular blockade, the highly sensitive mechanical interaction between chest wall compliance, elastic recoil, and tension of the diaphragm is reset at a new pressure–volume relation.[20] The highly compliant chest wall of infants results in relatively low transpulmonary pressures at end-expiration that leads to an increased tendency for collapse of the small peripheral airways even during normal tidal breathing.[21] Several mechanisms in infants increase the end-expiratory lung volume above the elastic equilibrium volume, including postinspiratory diaphragmatic muscle activity.[5,6,22] These mechanisms are generally assumed to be mainly active during the first year of life, and the major differences in pulmonary mechanics are most probably the underlying factor of the FRC differences observed in the current study.

Muscular activity is required to maintain FRC to counteract the gravitational forces that act on the chest and abdominal wall.[5,6,22] Because of their highly compliant chest wall, infants are more susceptible to changes in muscle tone.[18,19,23] Hence, neuromuscular blockade abolishes the infant's possibilities to increase the resting volume above this equilibrium[5,6,22] and a larger decrease in FRC after neuromuscular blockade might be expected in infants compared with preschool-aged children.

Positive end-expiratory pressure increases FRC and dynamic lung compliance, decreases total airway resistance,[24,25] and can be used to prevent alveolar collapse.[26] An additional PEEP of 3 cm H_2O led to an increase of FRC by 10% above baseline values in preschool children, whereas PEEP only restored FRC close to baseline in young infants.

By analyzing the washout curve of an insoluble tracer gas (sulfur hexafluoride), ventilation distribution can be assessed and expressed by a variety of indexes, among which lung clearance index and mean dilution number are the most commonly used, because they are very sensitive in detecting peripheral airway collapse.[10,17] The regions of the lung that obtain less of the tidal volume than others have a slower clearance compared with those receiving a higher percentage of the tidal volume. Obstructive airway disorders result in asymmetrical narrowing of the intrapulmonary airways and lead to an increased ventilation inhomogeneity as reflected by an increased lung clearance index.

The current study is the first to analyze the direct effect of neuromuscular blockade on ventilation homogeneity in infants and children. The increase in ventilation inhomogeneity after neuromuscular blockade, which was greater in infants compared with preschool children, is best explained by partial airway collapse in the dependent regions of the lungs in the supine position.[27] This age dependency can be explained by the less stable structures of the lung in young infants, which are more prone to airway collapse. Application of an additional PEEP (3 cm H_2O) restored lung clearance index and mean dilution number to the level before neuromuscular blockade. In our study, the tidal volume–to–FRC ratio increased after neuromuscular blockade. This potentially could have affected the degree of ventilation inhomogeneity, because lung clearance index and mean dilution number cannot be completely independent of the tidal volume–to–FRC ratio.[28] However, in spontaneously breathing healthy adults, lung clearance index and mean dilution number are not sensitive enough to measure ventilation maldistribution that occurs with a change of posture or a change of the tidal volume–to–FRC ratio.[29] This indicates that factors other than changes in the tidal volume–to–FRC ratio, such as partially collapsed alveoli and less well-distended distal bronchi, contribute to the observed ventilation maldistribution after neuromuscular blockade. Our results are consistent with previous results obtained in ventilated children with lung disease, where the application of PEEP increased FRC and improved ventilation homogeneity.[14]

Infants and young children are particularly prone to hypoxemic events while undergoing anesthesia.[23,30] Therefore, it is crucial to optimize respiratory function in anesthetized infants and children to ensure oxygenation. The risk for hypoxemic events is even more increased by the additional large decrease of FRC after neuromuscular blockade, especially in infants, with their small lung volumes and high oxygen demand. Based on the results of this study, we suggest avoiding neuromuscular blockade if possible or using PEEP if neuromuscular blockade is necessary in anesthetized infants and young children.

The fact that baseline measurements were not made at 0 PEEP is a limitation of this study. The continuous bypass flow necessary to enable a constant delivery of the tracer gas resulted in a PEEP of 3 cm H_2O. The impact of this effect cannot currently be quantified.

Comparison of lung volumes in children is difficult because the reported normal values have declined over the years in the pediatric population, which is most probably caused by changes in technology.[31] Furthermore, recent FRC reference data from a large study are not available for awake or anesthetized infants and/or preschool children. However, the FRC volumes obtained in this study are in a similar range as volumes measured with plethysmographic methods in spontaneously breathing infants sedated with chloral hydrate, which also exhibits muscle relaxant properties,[31,32] and FRC volumes measured in unsedated, spontaneously breathing, healthy infants with the same sulfur hexafluoride multibreath washout technique.[13]

The current study showed that the additional effect of neuromuscular blockade on FRC and lung clearance index could be reversed, in our setup, by the use of additional 3 cm H_2O PEEP. Therefore, it remains unclear from our study how much PEEP is necessary after neuromuscular blockade to restore FRC to the level of the awake state in the presence of spontaneous breathing.

For publication purposes, we combined the results of the two age groups into a single article, although the direct comparison of the results obtained in the two groups is potentially weakened by several factors. The data of the two age groups were collected independently, and the infants' data were only collected after the data of the preschool children had shown the described results. Because standard institutional induction techniques were used in the two age groups, different anesthetic agents (fentanyl *vs.* remifentanil) were used in the two study groups. Furthermore, a potential interaction between the brief exposure to sevoflurane at induction of anesthesia with the administered propofol and rocuronium in the infant group cannot be excluded. However, the duration of sevoflurane application was very short, and measurements only started when sevoflurane was no longer detected. Therefore, the potential impact of sevoflurane on the results is most probably negligible. But even if sevoflurane had an additional muscle relaxant effect in the infant group, the effect of rocuronium inducing a complete neuromuscular blockade in both groups resulted in greater FRC and lung clearance index changes in the infant group compared with the preschool children. On the other hand, only all preschool-aged children received a premedication with benzodiazepines, which might well decrease FRC by its myorelaxant effect[33,34] and therefore might have led to an underestimation of the observed difference between infants and preschool children.

In conclusion, neuromuscular blockade significantly reduces FRC and decreases ventilation homogeneity, and these changes are more pronounced in young infants compared with preschool children. The addition of PEEP (3 cm H_2O) was shown to be effective in restoring the effects of neuromuscular blockade on FRC, lung clearance index, and mean dilution number, and its use could prove to be beneficial in anesthetized, paralyzed infants and children.

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