ABSTRACT: Paralysis with pancuronium bromide is used in newborn infants to facilitate ventilatory support during respiratory failure. Changes in lung mechanics have been attributed to paralysis. The aim of this study was to examine whether or not paralysis per se has an influence on the passive respiratory mechanics, resistance (Rs) and compliance (Cs) of the respiratory system in newborn infants.

In 30 infants with acute respiratory failure, Rs was measured during paralysis with pancuronium bromide and after stopping pancuronium bromide (group A). Rs was also measured in an additional 10 ventilated infants in a reversed fashion (group B): Rs was measured first in nonparalysed infants and then they were paralysed, mainly for diagnostic procedures, and the Rs measurement repeated. As Rs is highly dependent on lung volume, several parameters, that depend directly on lung volume were recorded: inspiratory oxygen fraction (F\textsubscript{I,O2}), arterial oxygen tension/alveolar oxygen tension (a/A) ratio and volume above functional residual capacity (FRC).

In group A, the Rs was not different during (0.236±0.09 cmH\textsubscript{2}O·s·mL\textsuperscript{-1}) and after (0.237±0.07 cmH\textsubscript{2}O·s·mL\textsuperscript{-1}) paralysis. Also, in group B, Rs did not change (0.207±0.046 versus 0.221±0.046 cmH\textsubscript{2}O·s·mL\textsuperscript{-1} without versus with pancuronium bromide). F\textsubscript{I,O2}, a/A ratio and volume above FRC remained constant during paralysis.

These data demonstrate that paralysis does not influence the resistance of the total respiratory system in ventilated term and preterm infants when measured at comparable lung volumes.


Paralysis of ventilated newborn babies does not influence resistance of the total respiratory system

R. Burger, S. Fanconi, B. Simma

In neonates with acute respiratory failure, muscle paralysis is sometimes used temporarily to facilitate controlled ventilation. Paralysis is believed to decrease changes in intracranial pressure [1] and incidence of intraventricular haemorrhage [2], and chronic lung disease [3], to improve ventilation/perfusion mismatch [4], and arterial oxygen tension [5], and to reduce pulmonary barotrauma [6, 7]. Pancuronium bromide may also have a beneficial effect on the circulation of preterm infants with hyaline membrane diseases [3, 8, 9]. However, neurological assessment is impossible in paralysed infants and development of atelectasis may be facilitated [4]. A former study in newborns [10] demonstrated an increase in the resistance of the total respiratory system (Rs) during muscle paralysis and a drop in Rs after discontinuation of paralysis. In the same study, a progressive reduction in dynamic compliance of the total respiratory system (Cs) during muscle paralysis and a significant improvement in lung mechanics after paralysis were reported. It is well known, that newborn infants try to maintain their lung volume by early activation of inspiratory muscles at end expiration and by laryngeal braking [11]. Endotracheal intubation and paralysis impedes this process and lung volume decreases [12] and Rs increases. As Rs is highly dependent on and increases at lower lung volumes, measurement of Rs should only be made at comparable lung volumes. Direct measurement of lung volumes as a routine procedure in the intensive care unit is difficult and cumbersome to perform. Thus, to answer the question as to whether or not paralysis per se increases Rs parameters that directly depend on lung volume such as inspiratory oxygen fraction (F\textsubscript{I,O2}), arterial oxygen tension/alveolar oxygen tension (a/A) ratio and Cs should be monitored carefully and kept constant.

The aim of this study was to examine whether or not paralysis per se has an influence on Rs in newborn infants. Observations on the changes in Rs measured in 30 term and preterm infants during and after paralysis are reported here. In 10 additional newborn infants, Rs was measured without paralysis and again after pancuronium bromide was given for invasive diagnostic or therapeutic procedures.

Materials and methods

Patients

Two groups of infants were studied, group A and group B. The inclusion criteria for group A (30 patients) were:
patients had to be paralysed with the attending physician intending to cease paralysis. The inclusion criteria for group B (10 patients) were: patients had to be mechanically ventilated without paralysis. A therapeutic procedure requiring paralysis (mainly insertion of central venous lines) was planned. All patients were mechanically ventilated using a pressure-controlled time-cycled ventilation mode (Babylog 1, Draeger Inc., Lübeck, Germany). Ventilator parameters were set to achieve and maintain arterial oxygen tension \( (P_{aO_2}) \) at 6–8 kPa and an arterial carbon dioxide tension \( (P_{aCO_2}) \) of 4.8–6.7 kPa. Blood for arterial blood gas measurements was drawn from an umbilical arterial catheter. Determination of arterial blood gas levels (AVL 995; List Medizintechnik Inc., Graz, Austria) were made at every measurement of lung mechanics. The noncuffed endotracheal tubes had an inner diameter of 2.0–3.0 mm, according to the weight of the infant. Ventilatory strategy and the decision to induce and discontinue paralysis were made by the neonatologist attending the patient and not by the investigators. Lung function measurements were performed within the setting of routine care.

### Design and methods

Lung function measurements, by means of the single-breath passive flow technique, were usually performed on the second or third day of life. In group A, the first measurements were performed 20 min after the last dose of pancuronium bromide was given. The measurements were then repeated after 2–4 h, when spontaneous movements and breathing had returned. The pressure settings on the ventilator remained unchanged and the frequency was set according to the change in transcutaneous \( P_{aCO_2} \). In group B, the infants were not paralysed when the first measurements were performed. Muscle paralysis was then induced, and the measurements were repeated after 20 min. In all patients, the initial dosage of pancuronium bromide was 0.2 mg·kg·body weight\(^{-1}\) (BW) followed by 0.1 mg·kg·body weight\(^{-1}\) as needed.

All measurements of pulmonary mechanics were made using a single-breath passive flow volume technique previously described by Le SOUEF et al. [13, 14]. All patients were examined in the supine position to standardize study conditions. A manually operated sliding valve was inserted into the ventilatory circuit at the proximal end of the endotracheal tube. Airway pressures were measured using a Validyne MP 90 transducer (Validyne Engineering, Northbridge, CA, USA) which was calibrated using a water manometer. Expiratory flow was determined using a pneumotachograph (Fleisch 00; Fleisch Inc., Nyon UD, Switzerland) connected to a Validyne MP 45 pressure transducer. Calibration of the pneumotachograph was performed using constant gas flow from two flow meters (Wisag 110; Wisag Zurich, Switzerland), one for oxygen and one for air, with a linear output of 0.05–12 L·min\(^{-1}\). By mixing air with pure oxygen, the same \( FIO_2 \) as applied to the patient was used for calibration. The dead space of the system was 1.7 mL.

The single-breath passive flow volume technique requires totally passive expiration from the patient, as seen in paralysed infants [13, 14]. In nonparalysed infants, passive expiration is achieved by airway occlusion at end inspiration. This evokes the Hering-Breuer reflex, which results in relaxation of the respiratory muscles leading to total passive expiration after opening the occluded airway. The airway was occluded for \( \sim \)400–500 ms in paralysed and nonparalysed infants [15]. A constant pressure on the resulting pressure/time trace allowed the exclusion of any air leaks. Occlusion pressure and expiratory flow were recorded on a personal computer. A flow/volume curve was constructed by integration of flow to volume (fig. 1).

**Fig. 1.** – Expiratory flow/volume curve. The straight line represents the time constant and is extrapolated to zero volume and zero flow. Extrapolation to the point of zero flow gives the elastic equilibrium volume (EEV) or “relaxed functional residual capacity (FRC)”. The volume exhaled in incomplete expirations gives the end-expiratory level (EEL). The difference between EEV and EEL represents ΔEEL. Extrapolation to the point of zero volume gives the flow corresponding to the occlusion pressure (\( V_0' \)) at the airway opening at end inspiration (\( PAo \)).

Five measurements were made on each occasion and mean resistance and compliance and standard deviation were calculated for each set of measurements. \( FIO_2 \) was recorded and blood gas levels and \( pH \) measured to calculate the a/A ratio according to standard formulae. The endotracheal tube was aspirated immediately prior to the measurements in order to remove secretions which might interfere with measurement.
Analysis of the pre- and post-paralysis data was performed using a two-tailed paired t-test with the patient as his own control. If not stated otherwise, results are shown as mean±SD. A p-value <0.05 was considered significant.

**Results**

In group A (table 1), the mean gestational age was 32.6±4.8 weeks and the mean body weight 1,885±993 g. Twenty-two patients had hyaline membrane disease, two had sepsis with respiratory insufficiency and two primary pulmonary hypertension. In group B, the mean gestational age was 35.7±3.4 weeks and the mean body weight 2,179±788 g. Group B patients had a higher gestational age and birth weight but a similar male to female ratio and diagnosis compared to the patients of group A (table 1).

In all patients (groups A and B) ventilator settings during paralysis were as follows: peak inspiratory pressure 22±3.3 cmH2O, positive end-expiratory pressure (PEEP) 5.1±0.98 cmH2O, ventilator frequency 33±13.4 (range 15–71) breaths.min⁻¹, and FIO₂ 0.315±0.1. These settings were not significantly different from those without paralysis. The tidal volume or EEL achieved by these ventilator settings was 9.5±3.4 mL.kg⁻¹.body weight⁻¹ during paralysis and 9.0±2.1 mL.kg⁻¹.body weight⁻¹ after pancuronium bromide was stopped. The volume above the EEV, as shown in figure 2, was 9.8±3.4 mL.kg⁻¹.body weight⁻¹ in paralyzed infants and 10.6±3.6 mL.kg⁻¹.body weight⁻¹ without muscle paralysis, the difference not being statistically significant. This led to dynamic elevation of the EEL (ΔEEL=EEV-EEL) only being very small and showing no significant difference between those with and without pancuronium bromide.

In group A (fig. 3a) Rs, did not change significantly after pancuronium bromide was stopped (0.236±0.09 versus 0.237±0.07 cmH₂O.s.mL⁻¹). In group B (fig. 3b), Rs remained the same after pancuronium bromide was given (0.207±0.05 versus 0.221±0.05 cmH₂O.s.mL⁻¹). In group A patients, Cs (fig. 4) was not significantly different with or without muscle paralysis (0.49±0.21 versus 0.56±0.24 mL.cmH₂O⁻¹.kg body weight⁻¹). The a/A ratio (fig. 5) was the same with and without paralysis (0.37±0.15 versus 0.39±0.17) and FIO₂ was also essentially unchanged (0.32±0.08 versus 0.31±0.09).

The intrasubject variability of lung function measurements expressed as the coefficient of variation (CV) was (median and range): 4.5% (1.6–16%) and 5% (0.5–24.6%) in Rs with and without pancuronium bromide and 2.5% (0.6–12.1%) and 5.9 (1.3–43.5%) in Cs with and without pancuronium bromide. In accordance with Stey et al. [16], a significant change in repeated measurements can be defined as one that differs from the mean of the baseline

### Table 1. Patients characteristics

<table>
<thead>
<tr>
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<th>Group A</th>
<th>Group B</th>
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<tbody>
<tr>
<td>Patients</td>
<td>30</td>
<td>10</td>
</tr>
<tr>
<td>Gestational age weeks</td>
<td>32.6±4.8</td>
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<td>Birth weight</td>
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<td>Male/female</td>
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<tr>
<td>Age at investigation days</td>
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<td>3.4±1.7</td>
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<tr>
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<td>2</td>
</tr>
<tr>
<td>Other</td>
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<td>3</td>
</tr>
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</table>

Data are presented as n or mean±SD.
measurements by more than twice the CV (%). Using this definition, only six of 30 patients showed a significant change in $R_s$ after paralysis was stopped.

**Discussion**

In this study, it was demonstrated that the use of pancuronium bromide to achieve paralysis in ventilated infants does not change $R_s$. This is true when paralysis is stopped in infants with respiratory distress syndrome (RDS) or when pancuronium bromide is used in initially nonparalysed infants for elective procedures. Only in 1/30 infants could a substantial decline in $R_s$ be observed after paralysis was stopped. Additionally, introduction or discontinuation of paralysis led to neither an improvement in gas exchange nor a change in $R_s$. This was a consistent finding in all patients studied. The similar values obtained for $R_s$ during and after paralysis reflect the absence of errors made in measuring $R_s$ by the technique used.

The present findings are to some extent in contrast to results published in the literature [10, 12, 17]. BHUTANI *et al.* [10] investigated 12 patients with respiratory failure in a noncontrolled study and found a substantial decrease in $R_s$ immediately after discontinuation of muscle paralysis. In that series, dynamic compliance and gas exchange also improved substantially. Measurement of $R_s$ is highly dependent on lung volume [12, 18]. It is therefore important to monitor all clinical variables that are dependent on lung volumes and ventilatory pattern may be the major factors influencing changes in respiratory mechanics. In the present study, patients’ $R_s$ did not change after stopping nor after giving pancuronium bromide. In summary, although $FRC$ was measured by means of the multiple occlusion test remains similar during spontaneous breathing and mechanical ventilation only if tidal volume remains constant. They concluded that absolute lung volumes and ventilatory pattern may be the major factors influencing changes in respiratory mechanics. In the present study, ventilatory parameters were not altered and $FRC$ did not change after stopping nor after giving pancuronium bromide. In summary, although $FRC$ was not measured, it can be confidently asserted that the lung volumes in the present patients with or without muscle paralysis did not change substantially, and that measurements of $R_s$ were made at comparable lung volumes.

Muscle paralysis is no longer used as a routine procedure in ventilated preterm and term infants. Although it has been shown that paralysis of ventilated infants may...
result in some beneficial effects on haemodynamics [5], cerebral blood flow [2] and intracranial pressure [1], other studies [24] have failed to show any positive effects of routine paralysis and its use has declined in recent years. Patients in the present study were recruited from newborns who were transferred to the intensive care unit and in whom paralysis was used to facilitate intubation and avoid complication during transport. In all of them, paralysis was stopped in the following days on the basis of clinical improvement and the discretion of the attending physician. The second group of patients recruited were newborns in whom paralysis was used for a short time, in conjunction with appropriate analgesia and sedation, in order to perform diagnostic or therapeutic procedures [28]. The patient population investigated was heterogeneous and reflected daily practice in neonatal intensive care medicine in that infants of a wide range of gestational age and weight were studied.

Passive respiratory lung mechanics have been measured in a broad range of healthy and sick infants [13, 14, 29]. The single-breath passive flow volume technique may be applied in infants who are spontaneously breathing or are mechanically ventilated. A necessary condition for obtaining valuable data by means of this technique is total relaxed expiration. This is achieved via the Hering-Breuer reflex, which results in a linear expiratory flow/volume curve. If paralysis, as judged by the Hering-Breuer reflex, is incomplete, these babies will make respiratory efforts during the brief period of occlusion and will start their next inspiratory breath before reaching their true FRC. Thus, their expiratory volume will be reduced and their FRC increased, leading to an underestimation of their lung compliance. These problems can be overcome by carrying out multiple brief occlusions during expiration. A second condition is that air leaks are not present during lung function measurements. This may be difficult to achieve because, in neonatal intensive care, endotracheal tubes without cuffs are commonly used. However, air leaks can easily be detected by means of any drop in airway pressure measured after occlusion and, in the authors’ experience, occurs in only ~10% of infants. In this study, only lung function measurements resulting in a linear flow/volume curve in the absence of air leaks were accepted.

Additionally, Rs is influenced by the inner diameter of the endotracheal tube in the sense that small tubes increase Rs. It is known that small changes in Rs may not be detected in infants intubated with small endotracheal tubes. However, as resistance is flow-dependent, the expiratory limb of the flow/volume curve becomes concave with respect to volume. This effect may be counteracted by the time constant inhomogeneities of the tube [30]. In the present study, data from lung function measurements were only accepted if the passive flow/volume curve was linear over ≥75% of the volume exhaled. The range of Rs seems to be greater than that reported in previous studies [14, 29, 31]. This is due to the significant number of infants in group A (14 of 30) with a birth weight of <1,500 g. They were usually intubated with an endotracheal tube with an inner diameter of 2.5 or even 2.0 mm in the smallest ones.

In conclusion, this study demonstrates that paralysis with pancuronium bromide does not change the resistance of the total respiratory system, when measured at comparable lung volumes.

References


