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Respiratory System Mechanics in Patients Receiving Aerosolized Ribavirin During Mechanical Ventilation for Suspected Respiratory Syncytial Viral Infection

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Summary. Respiratory syncytial virus (RSV) is an important respiratory pathogen for infants. Aerosolized ribavirin (AR) has been used in mechanically ventilated (MV) patients with RSV bronchiolitis. The purpose of this study was to measure respiratory system mechanics (RSM) in pediatric patients requiring MV and receiving AR for suspected RSV. Patients were prospectively randomized to receive AR, either at a regular dose (RD) (6 g/300 mL over 18 hr/day) or a high dose (HD) (6 g/100 mL over 2 hr, three times a day). To measure changes in RSM, a passive exhalation technique was used before and after each dose of AR; time constant (*tc*) in s, resistance (*Rrs*) in $cmH_2O/mL/kg/s$, and quasistatic compliance (*Crs*) in $mL/cmH_2O/kg$ were measured. Airway pressure and flow signals were obtained and analyzed using a pneumotachograph, a differential pressure transducer, and a computer interface. Statistical analysis was done by Mann-Whitney and Wilcoxon rank tests.

Thirteen patients were enrolled: 5 patients in the HD group (mean age of 52 months), and 8 patients in the RD group (mean age of 10 months). Four and 5 patients were positive for RSV by ELISA in the HD and RD groups, respectively. The RSM in the HD group were: *tc,* 0.58 ± 0.15 s and 0.55 ± 0.20 s before and after AR, respectively; *Rrs,* 0.03 ± 0.03 $cmH_20/mL/kg/s$ and 0.02 ± 0.02 $cmH_20/mL/kg/s$, respectively; and *Crs,* 0.63 ± 0.21 $mL/cmH_2O/kg$ and 0.70 ± 0.13 $mL/cmH_2O/kg$, respectively. In the RD group, the RSM were: *tc,* 0.37 ± 0.12 s and 0.31 ± 0.10 s before and after AR, respectively; *Rrs,* 0.03 ± 0.02 $cmH_20/mL/kg/s$ and 0.02 ± 0.01 $cmH_20/mL/kg/s$, respectively ($P < 0.05$); and *Crs,* 0.46 ± 0.20 $mL/cmH_2O/kg$ and 0.46 ± 0.19 $mL/cmH_2O/kg$, respectively.

We conclude that the use of AR for bronchiolitis in infants and young children during mechanical ventilation does not worsen RSM. **Pediatr Pulmonol. 1999; 28:117–124.**

Key words: ribavirin; bronchiolitis; mechanical ventilation; pulmonary function test; pediatrics; intensive care.

INTRODUCTION

Respiratory syncytial virus (RSV) is a common pathogen in infants, estimated to be responsible for 40–70% of all cases of bronchiolitis,[1,2] and in some a cause of serious lower respiratory tract infection.[3] It also been shown that infants with bronchiolitis have an increase in respiratory airway resistance.[4,5] Ribavirin, a synthetic nucleoside with inhibitory activity in vitro and in vivo against RSV,[6,7] has been reported to alter pulmonary functions in adult patients with chronic obstructive airway disease[21,22] or asthma.[21] The purpose of this study was to determine whether AR administered by two different regimens in pediatric patients requiring mechanical ventilation (MV) for bronchiolitis would alter respiratory system mechanics.

The American Academy of Pediatrics (AAP) Infectious Disease Committee has recommended the use of AR in patients with complicated congenital heart disease or bronchopulmonary dysplasia, the severely ill, and all patients mechanically ventilated for RSV infection.[8,9] Its efficacy has been demonstrated in several studies in non-intubated patients,[10–12] and in patients receiving mechanical ventilation.[13–15] A recent placebo-controlled trial failed to show improved clinical outcome in mechanically ventilated children with respiratory syncytial virus lower respiratory tract disease treated with aerosolized ribavirin.[16] The most recent report from the AAP

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concluded that ribavirin aerosol therapy "may be considered" in selected infants and young children at high risk for serious RSV disease.[17]

One controversial issue is the safety of aerosolized ribavirin administration during mechanical ventilation. Three studies reported no technical difficulties with its use in critically ill children.[18–20] Another issue is the possibility of an increase in airway resistance in patients receiving AR. Two studies reported changes in pulmonary function test by spirometry in nonintubated adults with chronic obstructive pulmonary disease,[21,22] or asthma.[21] These changes in pulmonary function associated with the use of AR would appear unfavorable in infants with RSV infection, who already have alterations in respiratory mechanics (i.e., increased respiratory resistance). Two studies have reported pulmonary function testing (PFT) in infants with RSV bronchiolitis receiving AR: one measured PFT in nonintubated patients,[23] and the second reported results in mechanically ventilated patients.[24] In this study, we used the technique of passive exhalation to measure changes in the time constant, resistance, and quasistatic compliance of the respiratory system.

METHODS

We enrolled 13 patients admitted to the pediatric intensive care unit (PICU) with suspected or proven RSV bronchiolitis and requiring mechanical ventilation. This protocol was approved by the Institutional Review Board for studies involving human subjects, and informed parental consent was obtained before the study. Patients were receiving AR according to two different regimens, either regular dose (RD: 6 g/300 mL over 18 hr/day) or high dose (HD: 6 g/100 mL over 2 hr TID) as part of an ongoing ribavirin efficacy study.

Abbreviations

AAP	American Academy of Pediatrics
AR	Aerosolized ribavirin
Crs	Quasistatic compliance
CV	Coefficient of variation
ELISA	Enzyme-linked immunosorbent assay
HD	High dose
ICU	Intensive Care Unit
MV	Mechanical ventilation
PEEP	Positive end expiratory pressure
PFT	Pulmonary function testing
RD	Regular dose
Rrs	Resistance
RSM	Respiratory system mechanics
RSV	Respiratory syncytial virus
SD	Standard deviation
SEM	Standard error of the mean
tc	Time constant
TID	Three times a day

Experimental Protocol

While the patient was on mechanical ventilation and receiving aerosolized ribavirin, three sets of respiratory system mechanics (RSM) tests were performed within 20 min before and 20 min after each dose. Measurements taken were: 1) time constant (*tc*) in s, 2) resistance (*Rrs*) in cmH_20/mL/kg/s, and 3) quasistatic compliance (*Crs*) in mL/cmH_20/kg. Passive exhalation RSM were measured by obstructing gas flow near the end of inhalation with the use of a forceps. Two to three seconds were allowed before release of the clamp for the pressures within the lung to reach equilibrium, then allowing the patient to exhale to the atmosphere. Passive exhalation flow-volume curves and relaxation airway pressure were measured, allowing the calculation of *tc*, *Rrs*, and *Crs*, according to methods patterned after LeSouef et al.[25] The measurements were performed with the patient sedated and paralyzed to minimize chest wall interference. Although the best parameter to be used when comparing measurements of lung mechanics between patients is the lung volume at which they were obtained, respiratory mechanics parameters in infants have been shown to have correlation with the third power of the patient's height[26,27] and weight.[28,29] In this study, we utilized the patient's weight for purposes of comparison.

Measurement System

The setup used for measuring *tc*, *Rrs*, and *Crs* has been described elsewhere.[30] The equipment consisted of a Fleisch pneumotachograph #0 (±1 cmH_2O) or #00 (±2 cmH_2O) (OEM Medical, Inc., Richmond, VA) placed between the ventilator tubing and the endotracheal tube, and a variable reluctance pressure transducer-carrier demodulator system (MP45-32-871, CD 257, Validyne, Inc., Northridge, CA) used for airway pressure monitoring (± 100 cmH_2O). Pressure signals were conditioned and sampled by a 12 bit analog to digital converter (model 570, Keithley, Cleveland, OH) at 10 ms intervals. Analysis was performed on-line using an IBM PC/XT 16-bit computer (IBM, Inc., Boca Raton, FL).

For statistical analysis, the average values of three sets of RSM measurements were used. We utilized the Mann-Whitney U-test for comparison between groups, and Wilcoxon's signed rank test for paired measurements in the same group. The coefficients of variation (CV) were calculated on the measurements obtained (SD/mean × 100) and expressed as a percentage. Statistical significance was assumed when $P < 0.05$. Values are means ± SD.

RESULTS

A total of 13 patients participated in the study: 5 patients in the HD group, of whom 3 patients had a diag-

TABLE 1—Mechanical Ventilation Parameters[1]

	High-dose AR (n = 5)[2]	Regular-dose AR (n = 8)[2]
Inspired O_2 fraction	0.49 ± 0.09	0.46 ± 0.10
Tidal volume (mL/kg)	12 ± 3	9 ± 2
Frequency (breaths/min)	19 ± 5	20 ± 5
PEEP (cm H_2O)[3]	6 ± 3	6 ± 2
Inspiratory time (sec)	0.48 ± 0.11	0.46 ± 0.03

[1]All values are mean ± SD. There were no statistically significant differences between the two groups for any of the variables by Mann-Whitney U-test.
[2]Aerosolized ribavirin.
[3]Positive end expiratory pressure.

nosis of pneumonia and 2 had a diagnosis of bronchiolitis. The mean age was 52 ± 60 months, mean weight was 12 ± 8 kg, and the mean stay at the time of the evaluation in the intensive care unit and on mechanical ventilation was 20 ± 16 days and 16 ± 15 days, respectively. Four patients were positive for RSV by enzyme-linked immunoadsorbent assay (ELISA) or viral culture. Eight patients were in the RD group, of whom 2 had a diagnosis of pneumonia and 6 had a diagnosis of bronchiolitis, with a mean age of 10 ± 13 months, mean weight of 7 ± 4 kg, and a mean stay at the time of the evaluation in the intensive care unit and on mechanical ventilation for 22 ± 14 days and 16 ± 12 days, respectively. Five patients were positive for RSV by ELISA or viral culture. Age, weight, time in the ICU and on mechanical ventilation, and incidence of RSV disease were not statistically different between the two groups. The ventilator settings for both groups at the time of the measurements are shown in Table 1.

The RSM in the HD group (26 paired measurements; group mean was 5 paired measurements per patient, with a range of 2–13) were: *tc,* 0.58 ± 0.15 s (CV 18 ± 10%) and 0.55 ± 0.20 s (CV 16 ± 8%) before and after AR, respectively ($P = 0.68$) (Fig. 1); *Rrs,* 0.03 ± 0.03 cmH_20/mL/kg/s (CV 18 ± 17%) and 0.02 ± 0.02 cmH_20/mL/kg/s (CV 24 ± 6%), respectively ($P = 0.34$) (Fig. 2); and *Crs,* 0.63 ± 0.21 mL/cmH_2O/kg (CV 20 ± 6%) and 0.70 ± 0.13 mL/cmH_2O/kg (CV 27 ± 6%), respectively ($P = 0.22$) (Fig. 3). The differences from before to after the use of AR expressed in percentages for all the three RSM parameters were: *tc,* −3.8 ± 18%; *Rrs,* −8.6 ± 27%; and *Crs,* 21 ± 28%.

In the RD group (26 paired measurements; group mean was 3 paired measurements per patient, with a range of 2–4), the RSM were: *tc,* 0.37 ± 0.12 s (CV 29 ± 16%) and 0.31 ± 0.10 s (CV 24 ± 10%) before and after AR, respectively ($P = 0.23$) (Fig. 1); *Rrs,* 0.03 ± 0.02 cmH_20/mL/kg/s (CV 30 ± 18%) and 0.02 ± 0.01 cmH_20/mL/kg/s (CV 21 ± 10%), respectively ($P < 0.05$) (Fig. 2);

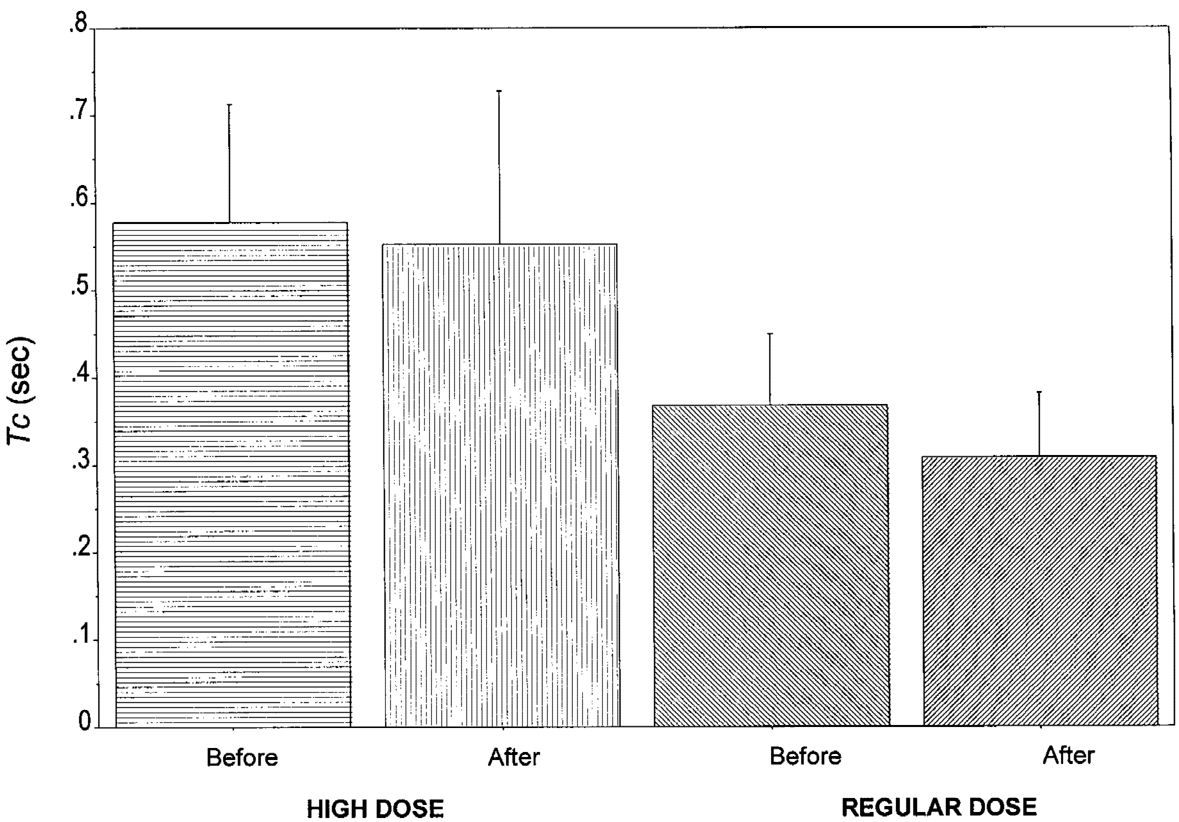

Fig. 1. Time constant (*tc*, in s) in both groups before and after ribavirin. Error bars are ±2 SEM.

and *Crs*, 0.46 ± 0.20 mL/cmH_2O/kg (CV 23 ± 14%) and 0.46 ± 0.19 mL/cmH_2O/kg (CV 15 ± 14%), respectively ($P = 0.32$) (Fig. 3). The differences before and after the use of AR expressed in percentage for all the three RSM parameters were: *tc*, –8.6 ± 18%; *Rrs*, –12 ± 17%; and *Crs*, 12 ± 26%.

Comparison of individual patient mean changes in *tc*, *Rrs*, and *Crs* before and after AR are shown in Figures 4–6, respectively.

DISCUSSION

The purpose of this study was to assess changes in RSM after treatment with AR in patients with suspected RSV infection receiving mechanical ventilation. Acute viral bronchiolitis represents the most common serious respiratory infection in patients during the first 12 months of life. Small airway obstruction and gas trapping (i.e., bronchiolitis) and/or pneumonia characterize the clinical presentation.

In an initial study by LeSouef et al.,[25] the authors reported respiratory mechanics values in 6 mechanically ventilated children for cerebral conditions using the passive exhalation technique; the mean *tc* was 0.60 ± 0.26 s, *Rrs* was 0.034 ± 0.026 mL/cmH_20/s, and Crs was 22.5 ± 11.2 mL/cmH_20. The authors concluded that the passive expiratory technique is simple, and appears to provide accurate measurements of respiratory mechanics in children.

In order to assess changes in respiratory mechanics in patients with acute respiratory syncytial virus bronchiolitis, Seidenberg et al.[4] measured RSM in 14 spontaneously breathing infants (mean age, 5 months) at day 8 of the illness by using passive expiratory flow-volume curve analysis. Subsequently, the results were compared to values obtained in normal infants (mean age, 4.8 months). The results showed no significant differences for *Crs* and *tc* between the two groups, but *Rrs* (mL/cmH_2O/s) was increased on average by 26% (0.049 vs. 0.039, $P < 0.05$) in the RSV bronchiolitis group. In a study by Hammer et al.,[5] the authors reported passive flow-volume curve analysis in 27 mechanically ventilated infants (mean age, 5.2 months) with RSV bronchiolitis, but to whom AR was not given. All patients were sedated and paralyzed during the measurements. The results showed a significant increase in *Rrs* in the RSV bronchiolitis group when compared to normal values: 0.37 mL/cmH_20/s vs. 0.06 mL/cmH_20/s, respectively ($P < 0.05$).

The present study examined changes in RSM in mechanically ventilated infants with suspected RSV infection immediately after receiving a dose of AR. In a ran-

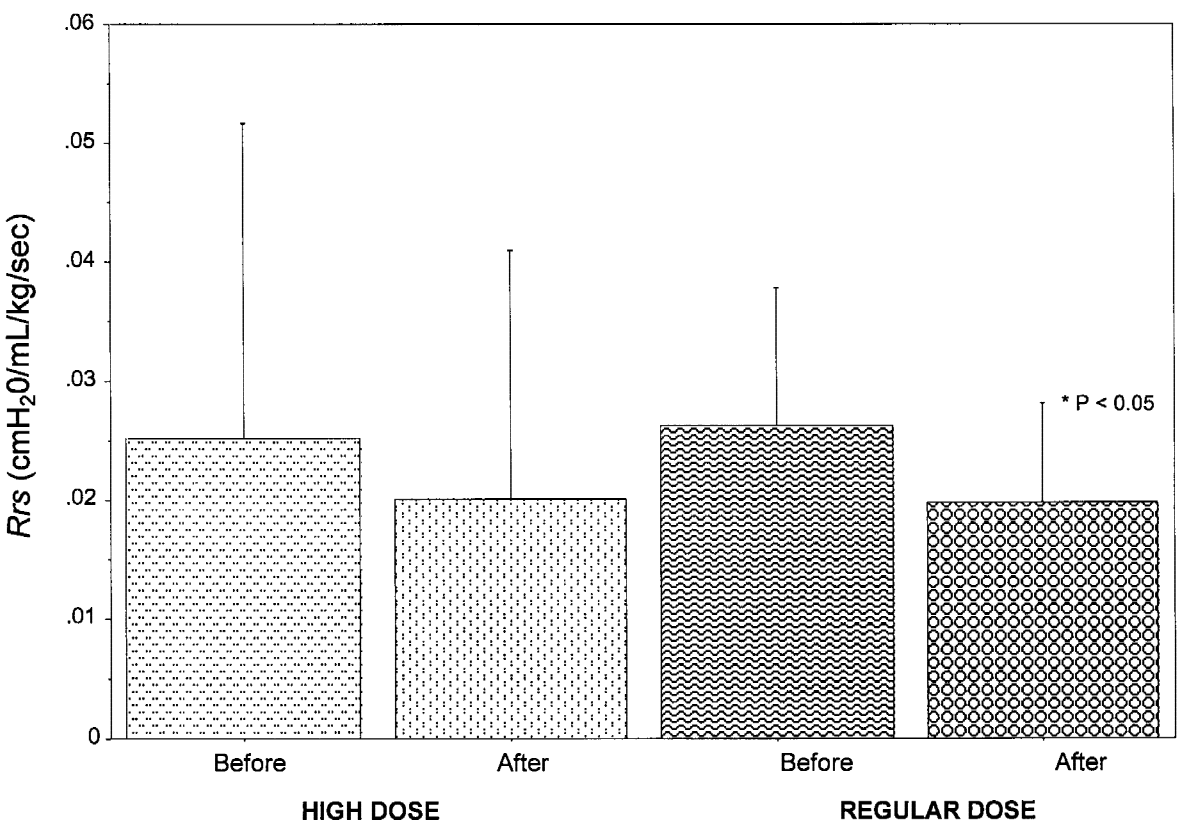

Fig. 2. Resistance (*Rrs*, in cmH_20/mL/kg/s) in both groups before and after ribavirin. Error bars are ±2 SEM.

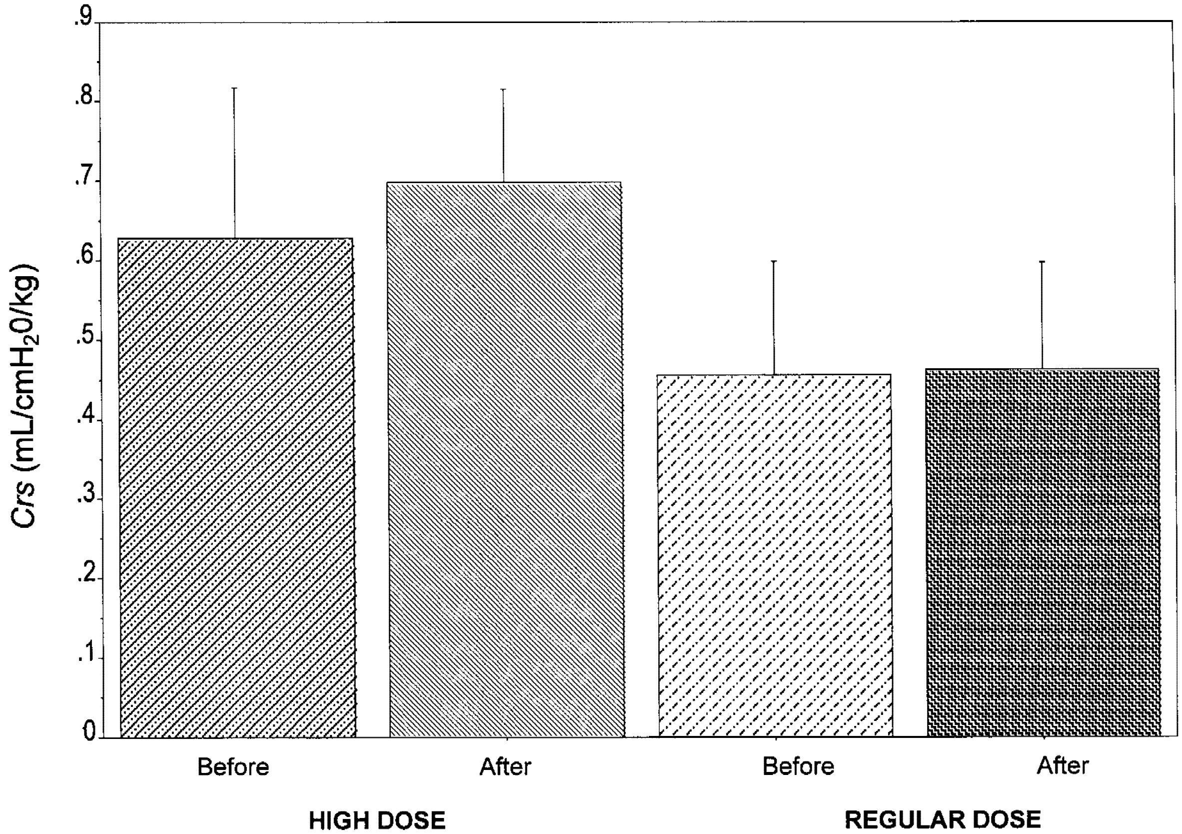

Fig. 3. Compliance (*Crs*, in mL/cm$H_2$0/kg) in both groups before and after ribavirin. Error bars are ±2 SEM.

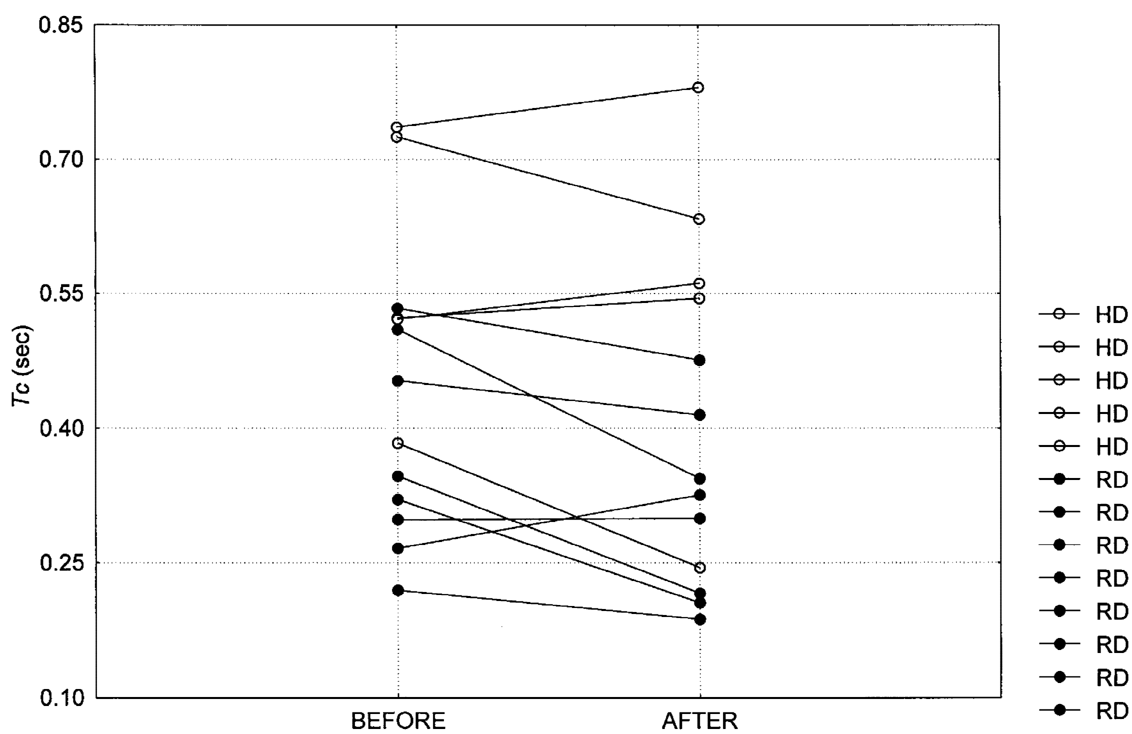

Fig. 4. Line plot of mean changes in time constant (*tc*, in s) in both groups before and after ribavirin.

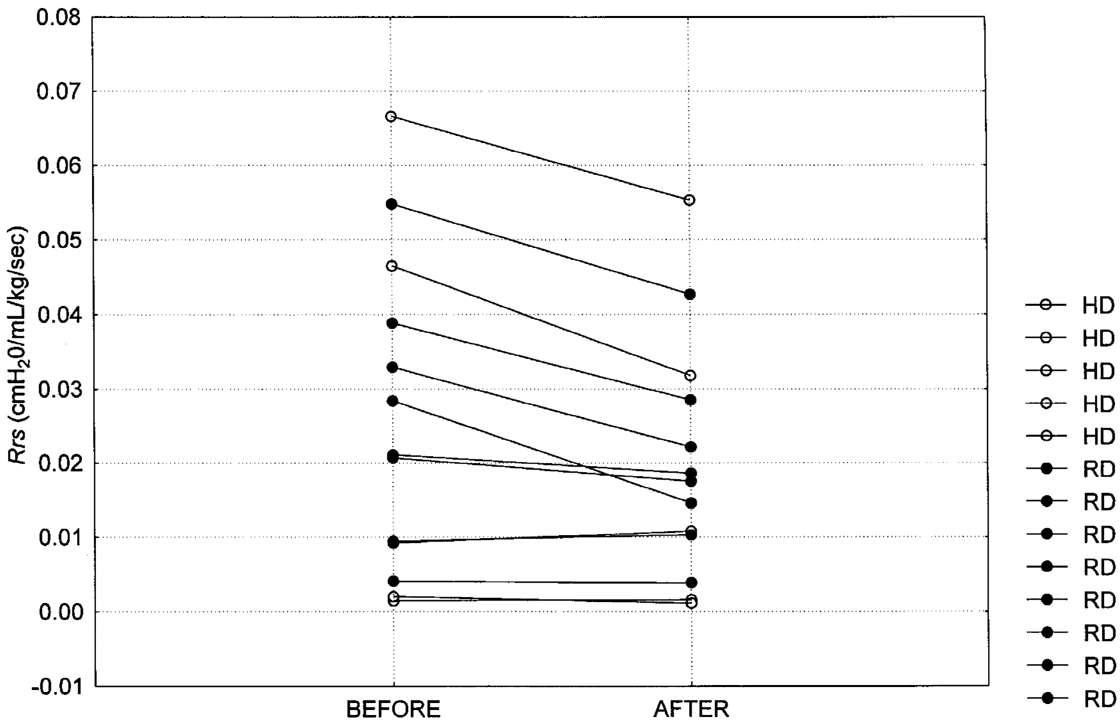

Fig. 5. **Line plot of mean changes in resistance (*Rrs*, in $cmH_20/mL/kg/s$) in both groups before and after ribavirin.**

domized, double blind, placebo-controlled study that included 19 nonintubated infants (mean age, 3.2 months) with RSV bronchiolitis, Janai et al.[23] assessed PFT by esophageal balloon method prior to the administration of the first aerosol treatment (Day 1) and on Day 2 and Day 7. The authors found no significant changes between the placebo and the ribavirin group regarding dynamic compliance and total lung resistance between Day 1 and Day

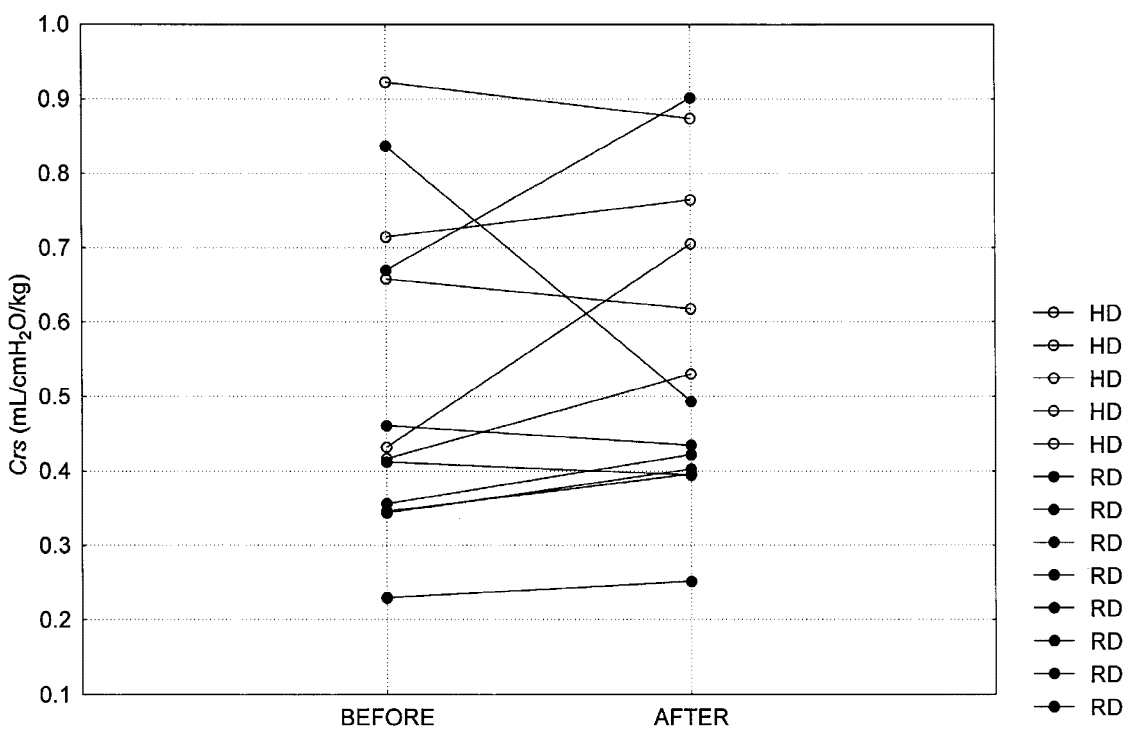

Fig. 6. **Line plot of mean changes in compliance (*Crs*, in $mL/cmH_20/kg$) in both groups before and after ribavirin.**

2. However, by Day 7, compliance had increased 30% in the placebo group and 210% in the ribavirin-treated group ($P = 0.05$). Significant differences in the rate of change of lung resistance were not seen at that time. In the present study, *Crs*, measured before and after AR, did not change significantly in either ribavirin group. However, the *Rrs* decreased in both AR groups, reaching statistical significance in the RD ribavirin group, but not in the HD ribavirin group.

In a study by Smith et al.,[24] the authors performed PFT in 12 infants (mean age, 2 months) with RSV bronchiolitis enrolled in a controlled randomized trial of ribavirin therapy and requiring mechanical ventilation. Using the passive exhalation technique, PFT was obtained before and after bronchodilators, 1 hr after the ribavirin aerosol generator was turned off. The results of the study demonstrated that on Day 1, there was an increased *Rrs* (100 ± 69 $cmH_20/L/s$; $P < 0.05$) and a significantly decreased *Crs* (0.76 ± 0.21 $mL/cmH_20/kg$; $P < 0.05$) in patients with RSV infection compared to normal controls. In patients with RSV infection, there was a significant decrease in *Rrs* after bronchodilator therapy on Day 1 and Day 4, but not on Day 7. It is important to mention that in the study by Smith et al.,[24] as well as in our study, there was considerable variability in individual responses, with some patients reported to have an improved response, and others a worse result. The situation of variability in PFT parameters was addressed by several authors,[23,31,32] reporting coefficient of variation values from 10–13% for *Crs*,[33–35] 28% for dynamic lung compliance,[36] 11–15% for *Rrs*,[33–35] and 56% for lung resistance.[36] Some of the factors accounting for this variability include: age of the patient, status of hydration, extent of viral infection, and concurrent drug therapy. It is important to mention that the same investigator performed all measurements in our study in order to minimize differences attributed to the technique itself.

Several studies have reported results regarding duration of mechanical ventilation in patients receiving ribavirin. Smith et al.[20] found that the use of ribavirin decreased the duration of mechanical ventilation. Frankel et al.[14] found no differences in length of ventilatory support between the ribavirin recipients compared to historical controls. Two recent studies found longer duration of mechanical ventilation associated with the use of ribavirin.[5,37] Although the duration of mechanical ventilation at the time of the study was on average 16 days for both groups, the primary goal of this study was to assess changes in lung mechanics before and after a dose of AR. Whether or not the use of ribavirin played a role in the duration of ventilator support in this population of patients is difficult to ascertain.

When analyzing the data on all 13 patients before and after AR, there was no worsening of RSM as evidenced by a mean reduction of 6.8% in *tc*, a mean reduction of 10.5% in *Rrs*, and an average increase of 15% in *Crs*. The analysis of the two groups showed that the HD group (5 patients) had an average decrease of 3.8% in *tc*, an average decrease of 8.6% in *Rrs*, and a 20% mean increase in *Crs*. The RD group (8 patients) had an average positive decrease of 8.6% in *tc*, an average decrease of 11.7% in *Rrs* ($P < 0.05$), and a mean increase of 11.5% in *Crs*. The same analysis was done for patients who had evidence of RSV infection. The differences were not significant compared to patients without evidence of RSV infection.

The results of this study suggest that the use of aerosolized ribavirin in infants with suspected RSV infection receiving mechanical ventilation does not have a detrimental effect on respiratory system mechanics.

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