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# Bronchodilator response in wheezing infants assessed by the raised volume rapid thoracic compression technique

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ABSTRACT

*Background:* Bronchodilator response (BDR) analyzed by the raised volume rapid thoracic compression (RVRTC) in wheezing infants is not yet well described, although bronchodilators (BD) are routine in the treatment of this population.

*Objective:* To evaluate BDR by RVRTC technique in infants with recurrent wheezing and compare to control group.

*Method:* Cross sectional study, 45 infants, age 56 weeks (38–67 weeks). Two groups: wheezing group (WG: history of recurrent wheezing) and control group (CG). RVRTC was evaluated, FVC, $FEV_{0.5}$, $FEF_{50}$, $FEF_{75}$, $FEF_{85}$, $FEF_{25-75}$ were measured. Salbutamol was delivered to infants and RVRTC evaluated again. BDR was determined by the increase greater than two standard deviation from the mean change in the CG.

*Results:* In WG (n = 32) lung function was worse than in CG (n = 13): $FEV_{0.5}$: 0.0(−0.9–0.9z score) *vs* 0.8(0.2–1.4z score); $FEF_{50}$: 0.2(−0.3–1.1z score) *vs* 0.9(0.5–1.4z score); and $FEF_{25-75}$: 0.2(−0.5–1.1z score) *vs* 1.1(0.6–1.6z score), respectively, $p < 0.05$. Both groups had similar increase after BD. In WG 11 patients (34%) were responder and these had worse lung function compared to nonresponder (n = 21) ($p < 0.05$). The increase in lung function after BD in responder was higher than in nonresponder: $FEV_{0.5}$: 6.5(2.1–7.1%) *vs* −0.5(−2.5–0.7%), $FEF_{50}$: 5.1(2.7–11.7%) *vs* 0.4(−1.1–2.8%), $FEF_{75}$: 20.7(4.7–23.6%) *vs* −1.3(−6.4–3.9%), $FEF_{25-75}$: 9.9(3.8–16.4%) *vs* 0.0(−1.5–1.0%), respectively, $p < 0.05$.

*Conclusion:* 34% WG showed BDR measured by the RVRTC. The best variables to detect BDR were $FEF_{75}$, $FEF_{25-75}$ and $FEV_{0.5}$. Patients with worse lung function showed better response to BD.



## 1. Introduction

Short-Acting Beta-Agonists (SABA) are indicated for treatment of wheezing infants to relieve symptoms [1,2]. However, there is controversy regarding the response to this medication and how this should be assessed.

In addition to symptom relief, bronchodilator response (BDR) in wheezing infants may be an alternative to predict childhood asthma. In a case-control study [3] the BDR assessed by lung function in infants has been associated with bronchial obstruction and airway disease in childhood for those using corticosteroid. This information was not confirmed by Hyvärinen et al. [4] and Debley et al. [5], who found no relation between BDR and the risk of childhood asthma. However, in one study the assessment was clinical [4] and, in the other one, a cross-sectional study was carried out [5].

The BDR can be detected clinically by reduced wheezing and respiratory distress [6]- a simple and quick way though subjective or, more precisely, by the lung function tests [7–11].

The assessment of lung function by raised volume rapid thoracic compression technique (RVRTC) is an objective way to assess BDR in infants. Goldstein et al. [10] studied the response to albuterol

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employing the RVRTC technique. The positive response was considered by the 24% increase in forced expiratory flow $(FEF)_{75}$ and $FEF_{25-75}$. The authors identified BDR in 22% of infants; however, only healthy infants were assessed as limiting to transpose these results for patients with lung disease. Saito et al. [9] using the same technique, observed BDR in 3 (18%) of the wheezing infants, but only 17 patients were studied. Recently, Debley et al. [5] described in a multicenter study that 25% of wheezing infants showed BDR, noted by the increase in $FEF_{25-75}$ and/or forced expiratory volume $(FEV)_{0.5,}$ but a control group was not included in this study to compare BDR.

Unlike those authors, other studies have found no BDR by the RVRTC technique in wheezing infants [7,8]. The reason for these results is based on the different severities of disease, difficulty in defining cutoffs for BDR in infants, the amount of bronchodilator used, and the different variables assessed in lung function between the studies.

Given the above, BDR by analysis of lung function in wheezing infants is not yet well determined, although bronchodilators (BD) are routinely used in the treatment of this population. The objective of this study was to evaluate bronchodilator response by the RVRTC technique in infants with recurrent wheezing in the absence of exacerbation, and to compare to the control group.

## 2. Methods

This is a cross sectional study. It was approved by the Ethics Committee of Federal University of Sao Paulo, Sao Paulo, Brazil, (#1958/2011). The protocol was performed in the Lung Function Laboratory of the Department of Pediatrics and all patients' parents gave written informed consent.

### 2.1. Patients

Two groups of infants aged 4–20 months of age composed the protocol: wheezing group (WG) and control group (CG). For the WG we included infants born at full-term who had history of recurrent wheezing (RW - more than three wheezing episodes) but no acute respiratory symptoms in the previous 3 weeks. For the CG we invited infants born full-term without history of RW (maximal of one episode), with no use of inhaled or systemic corticosteroids, and no acute respiratory symptoms in the previous 3 weeks. We excluded infants with upper-airway obstruction, history of neuropathy, gastroesophageal reflux disease, or previous thoracic and/or abdominal surgery. The use of SABA was not allowed at least for six hours before the test.

### 2.2. Lung function

Before lung function test, infants were sedated with 50–80 mg/kg of chloral hydrate given orally. Measurements were obtained while the infants were sleeping in supine position with slight neck extension. Heart rate and oxygen saturation were monitored continuously during the test. Raised volume rapid thoracic compression (RVRTC) maneuvers from elevated lung volume were obtained according to ATS recommendations [12] employing the Infant Pulmonary Lab System (Collins Medical, CO), after daily calibration. The child laid with a mask sealed adapted to the face and connected to a pneumotachometer (Hans Rudolph 3700). The inflatable jacket was wrapped around the infant's chest and abdomen, keeping the arms out. Several sequential inflations with pressure set at $30cmH_2O$ were delivered prior to the thoracic compression in order to inhibit respiratory effort. The forced maneuvers were performed by the automatic jacket inflation at the end of the child inspiration. The chest compression was maintained until expiratory flow approaches to zero, or for a maximum of 4 s. The maneuvers were repeated with increasing jacket pressure until no further increase in flow ($FEF_{25-75}$) and volume (forced vital capacity) was observed (assumption of flow limitation) and at least two reproducible curves were performed at that jacket pressure ($\pm 5cmH_2O$). The measured variables were: forced vital capacity (FVC), forced expiratory volume in 0.5 s of FVC ($FEV_{0.5}$), and forced expiratory flows at 50, 75, 85 and between 25 and 75% of FVC ($FEF_{50}$, $FEF_{75}$, $FEF_{85,}$ $FEF_{25-75}$).

Four puffs of Salbutamol (100mcg each) were given using an inhaler with spacer (Babyhaler, GSK, UK) adapted to the equipment. Between each puff, the spacer was removed after 10 infant's breaths. The RVRTC technique was initiated 10 min after the BD. Maneuvers started at jacket pressure of $10cmH_2O$ lower than that necessary to reach flow limitation at pre BD phase and were increased as described in the pre BD maneuvers. The best curves, pre and post BD, were selected by the highest sum of FVC and $FEF_{25-75}$ and were used for the analysis.

To be considered responder the volunteers should increase at least one of the measured variables (FVC, $FEV_{0.5}$, $FEF_{50}$, $FEF_{75}$, $FEF_{85}$, or $FEF_{25-75}$).

We used the follow equation to calculate the percentage of increase, from the baseline values, after BD: $\frac{(post-pre)}{pre} \times 100$.

### 2.3. Statistical analysis

The BDR was defined as *Criterion 1*: infants with a percent increase greater than two standard deviation (SD) from the mean change in the control group for one or more of the variables: forced vital capacity (FVC) and/or $FEV_{0,5}$ and/or $FEF_{50}$ and/or $FEF_{75}$ and/or $FEF_{25-75}$; *Criterion 2* the increase, in at least, twice the variability of the lung function variables as previously described by our group [13].

Data normality was tested by the Shapiro-Wilk test. Variables presented a non-normal distribution and are presented in median and interquartile range (25–75% IQ). The Mann Whitney test was used to compare the Wheezing Group (WG) and the Control Group (CG) and to compare responders and nonresponders in WG. All comparisons were made with the values of lung function in z score. Spearman correlation was used between the variables of lung function and BDR. Chi square test or Fisher's exact test were used to compare data of family history between the WG and CG, and to compare family history between responders and nonresponders. Statistical significance was considered at $p < 0.05$. The statistical analyses were conducted using the SPSS for Win/v.17.0 (IBM SPSS Statistics, Somers, NY). The power of the sample studied was calculated based on the difference in lung function between groups (WG and CG). It presented effect size of 0.93 with $n = 32$ for WG and $n = 13$ for CG, achieving 81% of power.

## 3. Results

Fifty infants started the protocol, of which five were excluded, four for waking up before the assessment in the post BD and one for not having been determined the flow limitation in the post BD. Thus, the protocol remained with 45 infants with average age of 56 weeks (38–67 weeks), being 13 infants in CG (8 [61%] female), and 32 infants in WG (17 [53%] female). There were no significant differences in anthropometric characteristics between the groups (Table 1). The WG had lower lung function when compared to the CG (Table 1).

The mean number of wheezing in WG was six (IQ 25–75%: 4–9 attacks), with the first wheezing at three months (2–5 months), 13 (40%) of the infants of the WG were hospitalized due to wheezing. In the CG, seven infants had a single episode of wheezing and none