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ORIGINAL ARTICLE

Bronchodilation in infants with malacia or recurrent wheeze

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Background: Controversy remains regarding the effectiveness of bronchodilators in wheezy infants.

Aims: To assess the effect of inhaled β_2 agonists on lung function in infants with malacia or recurrent wheeze, and to determine whether a negative effect of β_2 agonists on forced expiratory flow ($V'_{\max\text{FRC}}$) is more pronounced in infants with airway malacia, compared to infants with wheeze.

Methods: We retrospectively analysed lung function data of 27 infants: eight with malacia, 19 with recurrent wheeze. Mean (SD) age was 51 (18) weeks. Mean $V'_{\max\text{FRC}}$ (in Z score) was assessed before and after inhalation of β_2 agonists.

Results: Baseline $V'_{\max\text{FRC}}$ was below reference values for both groups. Following inhalation of β_2 agonists the mean (95% CI) change in mean $V'_{\max\text{FRC}}$ in Z scores was -0.10 (-0.26 to 0.05) and -0.33 (-0.55 to -0.11) for the malacia and wheeze group, respectively.

Conclusions: In infants with wheeze, inhaled β_2 agonists caused a significant reduction in mean $V'_{\max\text{FRC}}$. Infants with malacia were not more likely to worsen after β_2 agonists than were infants with recurrent wheeze.

Bronchodilators are widely used for wheezy infants, despite conflicting data on their effectiveness. There are studies showing a beneficial effect of β_2 agonist treatment in wheezy infants,^{1–3} studies showing no effect,^{4–7} and studies showing an adverse effect.^{8–10} It seems plausible that contradicting findings are a result of differences in lung function methodology, mode of aerosol administration, or aetiology of airway obstruction.

Airway malacia is a condition in which the airway is unusually collapsible, as a result of a weakness or deficiency of the cartilaginous elements of the airway wall, or from decreased tone of the myoelastic elements.¹¹ It has been shown that reduction of smooth muscle tone makes the airway more compliant,¹² and therefore more collapsible.¹³ In infants with intrathoracic tracheomalacia there is limited evidence to suggest that β_2 agonists cause deterioration in airway patency.¹⁰ Therefore, we hypothesised that a negative effect of β_2 agonists on airway calibre would be more likely and more severe in infants with airway malacia. The study aims were to assess the nature and magnitude of the bronchodilator response in infants with malacia or wheeze, and to determine whether a negative effect of β_2 agonists on forced expiratory flows is more pronounced in the infants with airway malacia.

MATERIALS AND METHODS

Subjects

We retrospectively analysed lung function data of infants with malacia or recurrent wheeze, who underwent infant lung function testing (ILFT) before and after the administration of a β_2 agonist. Measurements were performed as part of our clinical routine between 1998 and 2000 at the outpatient clinic for paediatric respiratory medicine of the Sophia Children's Hospital. The study population consisted of 27 infants (19 boys); eight infants had airway malacia, and 19 infants had aspecific recurrent wheeze. Aspecific recurrent wheeze was defined as dyspnoea with wheeze and/or coughing for at least three episodes of at least seven days, or chronic dyspnoea with wheeze and/or coughing for at least two months. Infants were suspected to have airway malacia if they had chronic lower

airway symptoms since the first weeks of life, not responding to any antiasthma therapy. In all infants with suspected airway malacia, the diagnosis was confirmed by bronchoscopy after ILFT. Bronchoscopy was performed by a paediatric pulmonologist who was unaware of the ILFT data. Airway malacia was defined as a general or localised weakness of the trachea or bronchi, resulting in excessive narrowing of the tracheal or bronchial lumen during expiration or whenever intrathoracic pressure increases.¹⁴ Exclusion criteria were other illnesses possibly accounting for the dyspnoea, such as preterm birth, cystic fibrosis, or hernia diaphragmatica. For ethical reasons bronchoscopy was not performed in the wheeze group. None of the infants had received bronchodilator treatment 12 hours prior to the test.

Methods

Lung function measurements were performed when the infants were free from acute respiratory symptoms. To prevent the infants from waking up during the measurements, they were sedated with chloral hydrate (50–75 mg/kg). Functional residual capacity (FRC_p) was measured by means of a modified whole body plethysmograph (Jaeger, Würzburg, Germany). Equipment and procedures were in accordance with guidelines, in which the FRC_p measurement is described in detail.¹⁵ Mean FRC_p of 3–5 technically acceptable measurements was expressed as Z score.¹⁵ Forced expiratory flow at FRC ($V'_{\max\text{FRC}}$), used as a measure of airway patency, was assessed using the end tidal rapid thoracoabdominal compression (RTC) technique (custom made equipment, Department for Experimental Medical Instrumentation, Erasmus University Medical Centre, Rotterdam, Netherlands). In short, an inflatable jacket was wrapped around the infant's chest and

Abbreviations: CV, coefficient of variation; FRC, functional residual capacity; HR, heart rate; ILFT, infant lung function testing; MDI, metered dose inhaler; RTC, rapid thoracoabdominal compression; RVRTC, raised volume rapid thoracoabdominal compression; SaO_2 , transcutaneous oxygen saturation

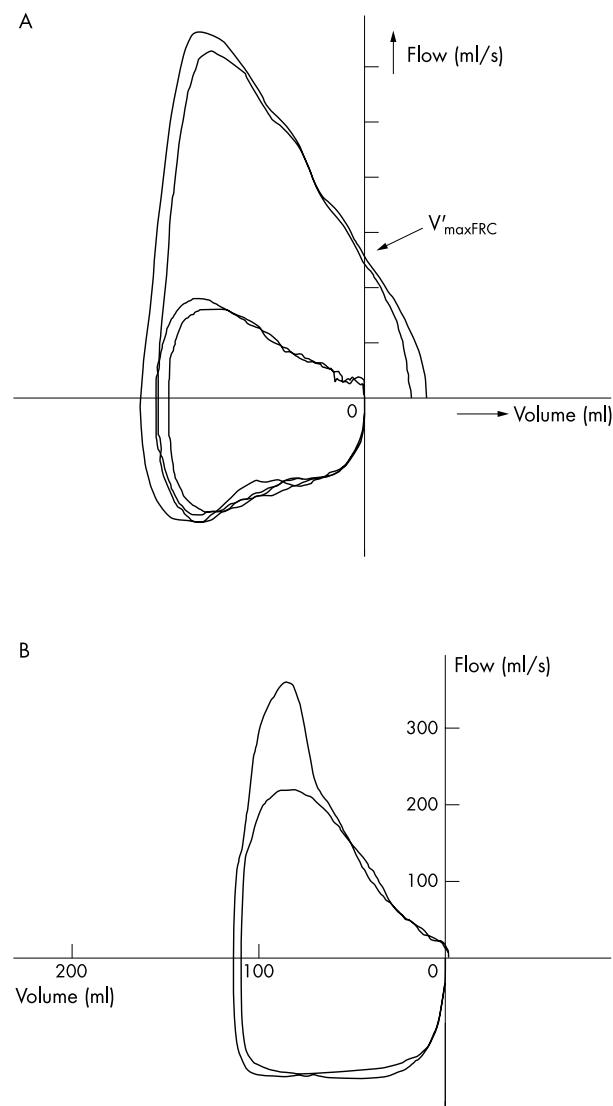


Figure 1 (A) An example of a flow-volume loop from an infant with recurrent wheeze. (B) An example of a flow-volume loop from an infant with airway malacia. Note that flow during forced expiration is similar to flow during tidal expiration.

abdomen with the arms outside the jacket. At end tidal inspiration the jacket was inflated rapidly, resulting in a forced partial expiratory flow-volume curve. The flow at FRC was measured (fig 1). Equipment and procedures were in accordance with guidelines, in which the RTC technique is described in detail.¹⁶ Mean $V'_{\max FRC}$ of 3–5 technically acceptable measurements was expressed as Z score.¹⁶

Study design

After baseline lung function measurements, a β_2 agonist was administered by metered dose inhaler (MDI) per spacer (Nebuhaler using terbutaline, and Babyhaler using salbutamol). Spacer and canister were shaken for at least five seconds. One actuation from a salbutamol or terbutaline MDI was given at a time, while holding the spacer in a horizontal position. Next, the spacer was attached vertically to the optimal fitting facemask used for ILFT. After 10 breaths (counted by 10 opening movements of the inspiration valve of the spacer) the spacer was removed. Lung function measurements were repeated after 10 minutes, using the same jacket pressure as used before bronchodilation. Measurements of FRC_p after bronchodilation could not always be repeated as some children awoke after the post-bronchodilation $V'_{\max FRC}$ measurements. Heart rate (HR) and transcutaneous oxygen saturation (SaO_2) were monitored continuously by a pulse oximeter (Nellcor, Hayward, CA, USA).

Analysis

The effect of bronchodilation on ILFT for each infant was evaluated using a two tailed paired Student's *t* test. Subgroups were compared using the unpaired *t* test. Correlation coefficients between baseline and β_2 agonist responses were obtained from linear regression analyses. The significance level was set at $p < 0.05$.

RESULTS

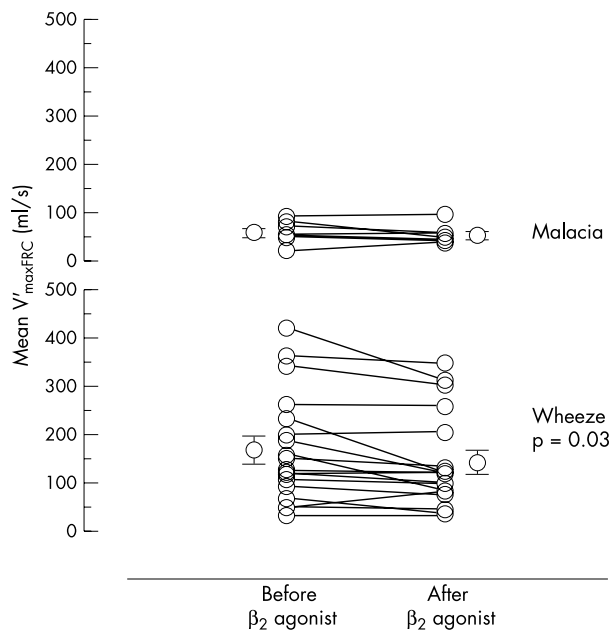
Table 1 shows anthropometric data of the 27 infants. Table 2 shows the results of β_2 agonist administration on $V'_{\max FRC}$ of the different groups. Baseline $V'_{\max FRC}$ was below reference values both groups (table 2). Baseline $V'_{\max FRC}$ in the malacia group was lower than in wheeze ($p = 0.01$). Administration of β_2 agonist resulted in a reduction of the mean $V'_{\max FRC}$ in both groups, but this reduction was only significant in the wheeze group (fig 2). Expressed in Z scores, the mean (95% CI) change was -0.10 (-0.26 to 0.05) for the malacia group, and -0.33 (-0.55 to -0.11) for the wheeze group ($p = 0.006$). When the reduction of $V'_{\max FRC}$ was expressed as percentage of baseline, a similar pattern was observed. For the entire group, mean (SD) coefficient of variation (CV) was 13.1% (7.25%). When a significant change in $V'_{\max FRC}$ was defined as being greater than twice the CV of the baseline measurement,⁴ only six of 19 infants in the wheeze group had a significant change in $V'_{\max FRC}$. Mean $V'_{\max FRC}$ increased in six of 27 infants after β_2 agonist administration (three with malacia, and three with wheeze). The mean (range) FRC_p in Z score at baseline for the total group ($n = 27$) was -0.20 (-1.66 to 0.54). As a result of waking up after the post-bronchodilator $V'_{\max FRC}$ measurements, FRC_p measurements before and after bronchodilation could only be obtained in 12 infants (four malacia, eight wheeze). For these 12 infants the mean (95% CI) change in FRC_p in Z score after bronchodilation was -0.12 (-0.15 to 0.39) ($p = 0.35$).

Table 1 Anthropometric data

| Diagnosis | Gender (M/F) | Age (weeks) | Weight (kg) | Length (cm) |
|--------------|--------------|-------------|----------------|------------------|
| Malacia | 5/3 | | | |
| Mean (range) | | 48 (25–77) | 8.2 (6.0–11.1) | 72.0 (64.0–82.0) |
| SD | | 21 | 1.6 | 6.7 |
| Wheeze | 14/5 | | | |
| Mean (range) | | 52 (23–93) | 9.5 (7.7–11.3) | 75.7 (66.0–82.0) |
| SD | | 17 | 1.1 | 4.9 |
| Total | 19/8 | | | |
| Mean (range) | | 51 (23–93) | 9.1 (6.0–11.3) | 74.6 (63.5–82.0) |
| SD | | 18 | 1.4 | 5.6 |

Table 2 Effect of β_2 agonist administration on $V'_{\max\text{FRC}}$ expressed in ml/s and Z scores

| | Mean $V'_{\max\text{FRC}}$ ml/s (range) | | Mean $\Delta V'_{\max\text{FRC}}$ % from baseline (95% CI) | Mean $V'_{\max\text{FRC}}$ Z score (range) | | Mean $\Delta V'_{\max\text{FRC}}$ Z score (95% CI) |
|---------------|---|------------------------|--|--|------------------------|--|
| | Pre β_2 agonist | Post β_2 agonist | Post β_2 agonist | Pre β_2 agonist | Post β_2 agonist | Post β_2 agonist |
| Malacia (n=8) | 56.2 (17 to 89) | 47.5 (32 to 91) | -6.3 (-40.7 to 28.0) | -2.64 (-3.58 to -1.41) | -2.75 (-3.74 to -1.38) | -0.10 (-0.26 to 0.05) |
| Wheeze (n=19) | 167.1 (32 to 420) | 139.8 (32 to 344) | -13.1 (-25.1 to -1.1) | -1.50 (-3.94 to 1.72) | -1.83 (-4.02 to 0.44) | -0.33 (-0.55 to -0.11) |

**Figure 2** Individual responses of $V'_{\max\text{FRC}}$ before and after β_2 agonist administration. Output organised by groups. Separate dots are mean group values with SEM.

Because of the retrospective nature of this study, β_2 agonist dosage was not standardised. Mean dosage of terbutaline (n = 24) was 333 μg (range 250–750 μg); mean dosage of salbutamol (n = 3: malacia = 1, wheeze = 2) was 666 μg (range 600–800 μg). There was no correlation between β_2 agonist dosage and the difference in $V'_{\max\text{FRC}}$ as a percentage from baseline. Heart rate increased significantly after bronchodilation (mean increase (95% CI): 10 (6 to 14) beats/min), used as an indicator that an adequate dose was delivered into the lungs. Oxygen saturation did not change significantly after bronchodilation.

DISCUSSION

We observed a reduction in mean $V'_{\max\text{FRC}}$ after β_2 agonist administration in infants with wheeze and malacia. In the wheeze group this reduction was significant. Worsening of $V'_{\max\text{FRC}}$ following β_2 agonists was not more likely to occur in infants with malacia than in infants with wheeze. Therefore, we reject the hypothesis that a negative effect of β_2 agonist administration on $V'_{\max\text{FRC}}$ is more pronounced in infants with airway malacia, compared to infants with wheeze.

A possible explanation for our finding could be that baseline $V'_{\max\text{FRC}}$ was significantly lower in the malacia group, with flows sometimes limited to (near) tidal levels (fig 1B), and thus leaving little room for further deteriorations. Conversely, at these levels a small deterioration in lung function may be clinically more significant than a larger deterioration at higher lung function, as was seen in the wheeze group. Another

explanation could be that, in malacia, forced expiration assessed with the RTC technique is affected by dynamic compression to such an extent that a further reduction of smooth muscle tone by bronchodilation does not result in further deterioration of airway patency. Furthermore, a decrease in FRC after bronchodilation could have masked a bronchodilator response, since airway resistance is higher at lower lung volumes.¹⁷ We think this is unlikely, as we could not show a change in mean FRC_p after bronchodilation.

The significant reduction in mean $V'_{\max\text{FRC}}$ in the wheeze group could be explained by the fact that the majority of infants (about 60%) with wheezing do not necessarily have reversible bronchoconstriction, but transient conditions associated with diminished airway patency.¹⁸ A reduction of smooth muscle tone by bronchodilation could make the airways more compliant, and therefore more collapsible, resulting in increased dynamic compression and reduced forced expiratory flows.^{12, 13} Another possible explanation for the significant reduction in mean $V'_{\max\text{FRC}}$ is that the wheeze group was studied while asymptomatic when scope for improvement may be limited and scope for deterioration greater. The significant reduction in mean $V'_{\max\text{FRC}}$ in the wheeze group cannot be explained by a difference in β_2 agonist dosage since the mean dose was not different between groups. One could argue whether the mean decrease in $V'_{\max\text{FRC}}$ in the wheeze group is clinically relevant, because when a significant change in $V'_{\max\text{FRC}}$ was defined as greater than twice the CV of the baseline measurement,⁴ no significant changes in $V'_{\max\text{FRC}}$ in either group were seen. The lack of a change in $V'_{\max\text{FRC}}$ after bronchodilators in wheezy infants has also been observed previously.^{4, 5} A possible explanation could be that, according to recommendations, $V'_{\max\text{FRC}}$ after bronchodilation is assessed with the same jacket pressure as used before the administration.¹⁶ Possibly, one should assess the lowest pressure at which the highest flows are obtained both before and after β_2 agonist administration.

Modl and co-workers¹⁷ showed a positive effect of β_2 agonist administration on mean $V'_{\max\text{FRC}}$ by means of the raised volume rapid thoracoabdominal compression (RVRTC) technique, suggesting that the RVRTC technique might be a better test for assessing forced expiratory flow. Assessing airway patency by means of the RVRTC technique is promising but has not yet proved to be beneficial over the RTC technique.¹⁹ Furthermore, RVRTC technique is not standardised since it lacks consensus.^{16, 20} Although the RTC technique is well accepted and standardised, several disadvantages have become apparent. First, measurement of $V'_{\max\text{FRC}}$ relies on FRC not changing between forced expirations. There is abundant evidence that FRC is not stable and shifts with dynamic events such as changes in airway calibre (bronchodilation) or sleep state.²¹ This explains the high variability of $V'_{\max\text{FRC}}$ for which coefficients of variation range from 11% to 36%.²¹ Second, flow limitation is difficult to ascertain, especially in healthy infants. Finally, RTC technique assesses airway function in the tidal volume range only, which reduces its sensitivity.^{20, 21}

This study suggests that, in clinically stable infants, mean forced expiratory flows by means of the RTC technique do not

improve following inhaled bronchodilators. On the contrary, β_2 agonist administration may produce an increase in mean work of breathing per minute,²² oxygen consumption, and minute ventilation, possibly as the result of an increase of metabolic rate.²³ Thus, β_2 agonists may not always be beneficial in infants with airway obstruction.

We conclude that mean V'_{maxFRC} is reduced and did not improve after inhalation of β_2 agonists in infants with malacia or wheeze. In infants with wheeze there was a significant reduction in mean V'_{maxFRC} after inhalation of β_2 agonists. Children with malacia were not more likely to worsen after β_2 agonists. We recommend that the response to inhaled β_2 agonists in infants with airway obstruction should always be critically evaluated.

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