The response to $\beta$-agonists in wheezy infants: three methods compared

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Summary

Background: Studies into the effects of salbutamol in the treatment of wheeze in infancy have been conflicting, possibly due to differences in outcome variables. We aimed to assess the response to salbutamol using indices derived from passive and forced expiration.

Methods: We recruited 39 infants who had a history of wheezing (mean age 43 weeks) and measured maximum flow at functional residual capacity ($V_{\text{max FRC}}$) by rapid thoracoabdominal compression (RTC), and forced expired volume at 0.4 s (FEV$_{0.4}$) using the raised-volume RTC technique (RV-RTC). We calculated passive compliance ($C_p$), resistance ($R_p$) and time constant ($\tau$) from relaxed expirations that followed the augmented inspirations delivered during RV-RTC. Measurements were repeated after aerosol salbutamol (800 mcg).

Results: Data were obtained in 32 infants for $V_{\text{max FRC}}$; 22 for FEV$_{0.4}$ and 19 for passive mechanics. There were no mean changes in any index of forced expiration after salbutamol. Some individuals showed significant changes (improvement or worsening) in one or other index. Overall, there was a small increase in $C_p$ after salbutamol but no change in $R_p$ or $\tau$.

Conclusions: We found no consistent pattern of response in either index of forced expiration. Validated clinical scores or alternative physiological techniques may be preferable to respiratory mechanics in assessing bronchodilator response.

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Introduction

Up to 40% of infants experience wheeze in the first year of life.$^1$ Many are treated with $\beta$-2 agonists, although studies examining their effectiveness in wheezing infants in hospital$^{2-7}$ and in domiciliary settings$^8$ are conflicting. The reasons for these conflicting findings may relate to differences in study populations, the underlying pathology, the severity of airflow obstruction, the dose administered, methodology employed and the outcome techniques used to measure a response.

One of the most commonly employed experimental methods for assessing changes in respiratory function is the rapid thoracoabdominal compression (RTC) technique, from which maximum flow at functional residual capacity ($V_{\text{max FRC}}$) is measured.$^2-7$ This measurement has considerable inter-subject variability and is influenced by changes in FRC that may accompany effective bronchodilatation,$^9$ potentially reducing its sensitivity to detect any response. Its reproducibility...
has, however, been shown to be similar to spirometry in adults. The technique of raised-volume RTC (RV-RTC) permits recording of timed expired volumes, avoiding the need for a fixed volume landmark and mimicking spirometric measurements in older subjects. RV-RTC has been shown to be more reproducible than $V_{\text{max FRC}}$. Despite the application of these and other techniques, controversy still surrounds the effectiveness of $\beta$-2 agonists in improving lung function. Some studies have shown an improvement in lung function in response to salbutamol, others suggested that there was a worsening, while some failed to demonstrate a significant change, or showed changes in some subjects. Methodological issues could underlie these discrepant findings, and so the aim of this study was to compare different methods of assessing airway function in wheezy infants given a standard dose of salbutamol in a laboratory setting.

**Methods**

**Subjects**

Power calculations performed at the outset indicated that a difference of 1 standard deviation in the measurement of $V_{\text{max FRC}}$, significant at the 5% level, could be detected with a power of 81% if the study group comprised 32 infants. We recruited 39 infants to allow for occasions when the infant did not sleep well enough for us to collect sufficient data. They were aged 3–15 months, with a history of wheezing requiring either hospital admission or a period of medication lasting at least 6 weeks. Infants with other specific disorders of the respiratory or cardiovascular systems were excluded. Approval from the local Research Ethics Committee and written parental consent were obtained. At the time of the investigation, three of the infants were noted to be slightly wheezy. Sixteen of the infants were not on any medications and four were on ipratropium bromide alone. The remainder were taking inhaled steroids alone (five infants), $\beta$-2 agonists alone (six infants) or a combination of both (eight infants).

**Protocol**

Infants attended the laboratory as outpatients. A brief questionnaire was administered, an explanation of the procedure was given to the parents and the infant was examined. Baseline oxygen saturation was recorded and the infant was sedated with chloral hydrate (100 mg kg$^{-1}$ body weight, up to a maximum dose of 1 g). A pulse oximeter (Nellcor) was attached to the foot for safety and pulse rate monitoring.

**Rapid thoracoabdominal compression**

The infant was wrapped in an inflatable ‘squeeze’ jacket and breathed through a facemask (Rendell Baker size 2) and pneumotachograph (Jaeger infant model). Three signals (mask pressure, flow and jacket pressure) were recorded onto a personal computer (Elonex) with specialist software (RASP, Physiologic, Newbury, Berks). A period of regular breathing of approximately 20 s was observed prior to inflating the jacket at the end of a tidal inspiration. Measurements of $V_{\text{max FRC}}$ were repeated over a range of jacket pressures up to a maximum of 6.5 kPa to obtain the highest values of $V_{\text{max FRC}}$ and the pressure at which this was achieved (the optimal pressure) was noted for each infant. Several measurements were obtained at optimal pressure.

**Raised-volume rapid thoracoabdominal compression**

A bias flow of air was attached to the pneumotachograph using a T-piece attached to an adjustable blow-off valve set at 2.0 kPa. Augmented breaths were delivered through the facemask by manually occluding the bias flow at the onset of inspiration so that air was directed into the lungs. At the end of inspiration (when the applied pressure and volume reached plateaux) the occlusion was removed and the infant breathed out passively. A series of four successive augmented inspirations were delivered with passive exhalations, followed by a fifth augmented inspiration, which was accompanied by jacket inflation at the end of inspiration using the previously determined optimal jacket pressure. Up to six measurements of RV-RTC were made in each infant.

The infant was then given salbutamol (Ventolin, Glaxo Smith Kline) 800 mcg by metered dose
inhaler, spacer (Babyhaler, Glaxo Smith Kline), and facemask (Laerdal size 2, Laerdal, Norway). All measurements were repeated 15 min after the salbutamol administration. Pulse rate was recorded every minute from the pulse oximeter, starting immediately before administration of salbutamol and continuing for 15 min afterwards.

Analysis

Measurements of $V'_{\text{max FRC}}$ were classed as technically satisfactory if a clearly defined peak flow was seen early in the breath (before 33% of the previous tidal volume had been exhaled) and if expiration proceeded smoothly beyond resting end-expiratory volume. $V'_{\text{max FRC}}$ was recorded as the highest value from a technically satisfactory manoeuvre, provided that a second measurement was within 10% of the best value, and also as the mean of the highest four values.

Measurements of RV-RTC (Fig. 1) were analysed using specialist software (‘Squeeze’ version 2.04, Dixon and Stocks, Imperial College, London, 1999), using a published technique. The first augmented breath was excluded from analysis, then remaining augmented breaths were inspected and the passive flow–volume relationship characterised by linear regression analysis to determine the elastic equilibrium volume (EEV), by extrapolation of the regression to the volume axis.

The slope of the regression line through the linear portion of the passive expiration was the time constant of the respiratory system, $\tau$. Compliance of the respiratory system ($C_{rs}$) was derived from the measured applied inflation pressure and the difference between inflation volume and EEV, and resistance of the respiratory system ($R_{rs}$) from $\tau = C_{rs}R_{rs}$. The mean values of $\tau$, $C_{rs}$ and $R_{rs}$ for each infant were based on all acceptable passive expirations.

The forced expired volume in the first 0.4 s of expiration (FEV$_{0.4}$) was measured from the RV-RTC and the highest individual value reported.

Statistical analysis

For each index ($V'_{\text{max FRC}}$, $\tau$, $C_{rs}$, $R_{rs}$ and FEV$_{0.4}$) the values obtained before and after salbutamol were compared by paired $t$-test. In order to see whether any changes in FEV$_{0.4}$ related to the baseline measurement, we performed a regression analysis of the absolute change against the baseline value.

For every infant, the standard deviation of each index was calculated from baseline measurements. A change in the measurement of 2 SD or more following salbutamol was taken as a significant difference for that infant.

Paired $t$-tests were used to establish whether there were any significant associations between indices of forced expiration and $C_{rs}$.

Results

Infants attended at a mean (SD) age of 43(18.8) weeks, weight of 9.5(1.8) kg, and length of 73.2(6.4) cm. The median (range) number of hospital admissions was 1 (0–10). Only one infant never had a hospital admission. Three infants had mild wheeze at the time of the appointment but were otherwise well. Sixteen received regular inhaled medications (10 inhaled corticosteroids (ICS) alone, one $\beta_2$ agonist alone, three a combination of ICS and $\beta_2$ agonist, and two ipratropium bromide). Eighteen of the infants had a family history of asthma in a first-degree relative.

Mean baseline oxygen saturation was 96.9% and the minimum saturation after salbutamol was 92.4 (SD 2.7)%.

Satisfactory paired measurements before and after salbutamol were obtained in 32 infants for $V'_{\text{max FRC}}$, 22 for FEV$_{0.4}$, and 19 for $\tau$, $C_{rs}$, and $R_{rs}$. Sometimes the infant woke before completion of measurements and on some occasions technically satisfactory measurements were not obtained. In 16 infants the response could be determined for all three indices of responsiveness.

Confirmation that a physiologically active dose of salbutamol had been given was noted from the

![Figure 1](https://example.com/image1.png)  
**Figure 1** Example of flow volume loops from one infant showing three manoeuvres, each with an augmented inspiration with passive expiration and the subsequent augmented inspiration with forced expiration. The three manoeuvres have been overlaid and aligned at the EEV.
mean increase in heart rate of 21%. The increase was at least 10% in all but two infants.

There were no differences in the mean jacket inflation pressures and pressure applied at the airway opening during RV-RTC before and after salbutamol (Table 1).

### Indices of forced expiration

Baseline $V_{\text{max FRC}}$ was below the predicted value in most infants (mean (sd) score = $-2.17 (1.05)$). There was no response to salbutamol in terms of mean changes in $V_{\text{max FRC}}$ or $\text{FEV}_{0.4}$ (Table 2). However, some infants showed considerable change in one or more of these measurements (Fig. 2). Of 16 infants in whom the response could be determined for all three indices of responsiveness, one showed no response in any index, six showed an improvement in at least one index and another six demonstrated a worsening of function, and the remaining three infants had a mixed pattern with apparent worsening of one index and improvement in another. Patterns of response were unrelated to family history of asthma. The overall pattern of response showed that changes were most likely to be seen in $\text{FEV}_{0.4}$ and least likely to be seen in $V_{\text{max FRC}}$ (Fig. 3). Changes in $\text{FEV}_{0.4}$ were unrelated to the baseline value (data not shown).

The baseline coefficient of variation (the sd expressed as a percentage of the mean baseline values) was smaller for $\text{FEV}_{0.4}$, (mean (sd) 4.0(1.90)%) than for $V_{\text{max FRC}}$ (10.4(4.9)%).

### Indices of passive mechanics

The mean (sd) number of passive expirations on which passive mechanics was based was 5.2 (1.7).

Overall, there was a small but statistically significant increase in respiratory system compliance after salbutamol without any evidence of change in $\tau$ or $R_{\text{rs}}$ (Table 3). When statistically significant individual changes (based on 2 sd) were examined, four infants showed an increase in compliance and the remainder showed no change. $R_{\text{rs}}$ increased in three infants and decreased in four, and $\tau$ increased in five and decreased in one infant. There was no consistency between change in any index of passive mechanics and any index of forced expiration. The changes in passive mechanics were unrelated to family history of

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### Table 1  Applied pressures.

<table>
<thead>
<tr>
<th></th>
<th>RTC baseline</th>
<th>RTC post-salbutamol</th>
<th>RV-RTC baseline</th>
<th>RV-RTC post-salbutamol</th>
</tr>
</thead>
<tbody>
<tr>
<td>$P_j$ (kPa)</td>
<td>3.51 (0.16)</td>
<td>3.62 (0.21)</td>
<td>3.53 (0.18)</td>
<td>3.82 (0.24)</td>
</tr>
<tr>
<td>$P_{\text{inf}}$ (kPa)</td>
<td>1.79 (0.128)</td>
<td>1.82 (0.125)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

$P_j$ — lowest pressure used to inflate jacket to achieve one of the four best values of $V_{\text{max FRC}}$.

$P_{\text{inf}}$ — pressure applied to the airway opening during RV-RTC. Values are mean and standard deviation.

### Table 2  Forced expiratory indices.

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Baseline mean (sd)</th>
<th>Post-salbutamol mean (sd)</th>
<th>Mean difference</th>
<th>95% CI of difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximal $V_{\text{max FRC}}$ (ml s$^{-1}$)</td>
<td>32</td>
<td>133 (76.3)</td>
<td>135.7 (77.3)</td>
<td>2.3</td>
<td>-8.9, 13.5</td>
</tr>
<tr>
<td>Mean $V_{\text{max FRC}}$ (ml s$^{-1}$)</td>
<td>28</td>
<td>117.3 (74.9)</td>
<td>125.4 (78.0)</td>
<td>8.1</td>
<td>-1.9, 18.1</td>
</tr>
<tr>
<td>$\text{FEV}_{0.4}$ (ml)</td>
<td>22</td>
<td>139 (31.7)</td>
<td>142.1 (37.2)</td>
<td>3.1</td>
<td>-5.7, 11.9</td>
</tr>
</tbody>
</table>

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**Figure 2**  Individual changes in $V_{\text{max FRC}}$ and $\text{FEV}_{0.4}$.
Our finding that there was a significant increase in $C_{rs}$ led us to speculate that the infants with the greatest changes in $C_{rs}$ might be those who demonstrated significant changes in forced expiration, but there was no evidence of any significant association between $V'_{maxFRC}$ or FEV$_{0.4}$ and $C_{rs}$ (data not shown) ($P = 0.54$ and 0.10, respectively).

**Discussion**

For the group of wheezy infants as a whole, we failed to demonstrate a consistent physiological response to salbutamol using any index of forced expiration derived from the standard or raised-volume RTC. This was in spite of the fact that all except three infants had a negative SD score for $V'_{maxFRC}$, implying that they had the likely potential to improve their lung function from baseline. A minority of infants showed individual significant changes in lung function that usually consisted of an increase but occasionally a worsening of flow, during a single study.

Individual responses in $V'_{maxFRC}$ were defined as a change of $\pm 2SD$ from baseline. An alternative approach for assigning a significant change has been proposed, based on the 95% confidence interval of repeated measurements. In this approach a change of 27% from baseline would be significant. Had we adopted this method there would have been no substantive change in our findings; four infants who we considered to have a worsening of $V'_{maxFRC}$ after salbutamol would have been reclassified as non-responders.

The lack of consistent findings in previous reports may result from (i) differences in the age or underlying pathology of the infants, which could affect the nature of response to bronchodilator, (ii) differences in the dose and delivery system for administering $\beta$-2 agonists, and (iii) differences in the physiological outcome variables examined. Although the dose and delivery system has varied between studies, an increase in heart rate has usually indicated that a physiologically active dose has been absorbed, so it seems unlikely that this could have made a major contribution to differences in lung mechanics.

**Differences in the populations of infants tested**

Most investigations have included infants with an age range spanning many months. Some have included predominantly younger infants (under 6 months) with bronchiolitis, studied before hospital discharge, whereas others have looked at older infants in a symptom-free interval. Variation in the clinical status will affect the outcome as the degree of airway obstruction may influence both the effective dose delivered to the airway and the likelihood of detecting a response. Furthermore, the predominant causes of obstruction (contraction of airway smooth muscle, inflammation or mucus secretion) will affect the response to bronchodilator. There does not appear to be a consistent finding related to age, apart from one report in which infants aged below 3 years were studied and those

<table>
<thead>
<tr>
<th>Table 3 Passive mechanics ($n = 19$).*</th>
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<tbody>
<tr>
<td></td>
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<tr>
<td><strong>Baseline mean</strong></td>
</tr>
<tr>
<td>$C_{rs}$ (ml cm H$_2$O$^{-1}$)</td>
</tr>
<tr>
<td>$R_{rs}$ (cm H$_2$O$^{-1}$ s$^{-1}$)</td>
</tr>
<tr>
<td>$\tau$</td>
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</table>

*represents significant change after salbutamol.
found to respond were all under 1 year. Similarly, some reports have included infants with a diagnosis of RSV-positive bronchiolitis whereas others have involved infants with documented wheeze and tendency to atopy, and others have included all infants with wheezing. There is no clear pattern of measurable improvement in response to bronchodilator relating to the population of infants under study. In the current report there was no evidence of any relationship between a family history of asthma and responsiveness to bronchodilator. A recent consensus review concluded that there was no compelling evidence for use of bronchodilators in the management of bronchiolitis, although they may produce modest short-term improvements in clinical scores. Similarly, it would appear that there is no clear benefit of using agonists to treat recurrent wheeze in the first 2 years of life.

**Differences in outcome variables**

The issue of how to measure and interpret possible changes in respiratory function in response to salbutamol has been longstanding. Historically, changes in measurements of lung volume and airway resistance were used. The introduction of RTC enabled investigators to measure $V'_{\text{max FRC}}$, which is thought to be pressure-independent and therefore to reflect changes in intrathoracic airway function and more closely resemble the spirometric indices used in older subjects. Given apparent clinical improvements in wheezy infants following administration of salbutamol, it was surprising that early studies showed a fall in forced flows after salbutamol. Nevertheless, using $V'_{\text{max FRC}}$ this group showed that pre-treatment with salbutamol protected against histamine-induced bronchoconstriction, indicating the presence of functional $\beta$-2 receptors. Subsequently four studies have sought statistically significant changes in $V'_{\text{max FRC}}$ in individual wheezy infants, three of which showed variable responses whereas the other failed to identify any infant in whom $V'_{\text{max FRC}}$ improved. The limitations of the RTC technique relate mainly to the variability of end-exhalatory level (EEL). Interventions that change EEL, such as spontaneous changes in respiratory rate, can alter $V'_{\text{max FRC}}$. Hence RV-RTC was developed so that indices independent of EEL could be explored. The variability of measurements derived from RV-RTC has been reported to be less than $V'_{\text{max FRC}}$ in some studies but greater in others. They were found to be better able to detect early changes in lung function in infants with cystic fibrosis. Despite this, in a group of wheezing infants who were asymptomatic at testing there were no significant changes in response to salbutamol and this observation led us to restrict our analysis of RV-RTC parameters to the timed volume $FEV_{0.4}$.

A range of different parameters can be analysed from RV-RTC. These include the volume expired, often referred to as forced vital capacity (although the manoeuvre neither begins at total lung capacity nor finishes at residual volume) and the timed volumes ($FEV_{0.75}$, $FEV_{0.4}$, etc.), all of which will be sensitive to inflation pressure. Moreover, since measurements of infant lung function are probably mainly made during nose breathing, flows at high lung volumes could be limited by nasal dimensions and nasal airway resistance rather than by the intrathoracic airways, as demonstrated in older children and adults. Flows that are early in the breath and therefore close to peak flow will be particularly affected. Similarly, the shorter-timed volumes will be disproportionally affected when compared with the longer-timed volumes such as $FEV_{0.75}$. Unless severe, nasal obstruction does not affect maximum flow at low volumes. Any fixed, nasal limitation to flow would be expected to reduce variability in timed volumes, and the least-variable index in the current study was indeed $FEV_{0.4}$. The small coefficient of variation may explain why this particular index was the one most likely to show significant changes in individuals.

The lack of group differences in indices of forced expiration after salbutamol (although individual infants appeared to respond), suggests that either these indices are not suitable for describing the effects of salbutamol or that the response is not consistent between infants. Passive mechanics ($C_{rs}$, $R_{rs}$) should not be influenced by inflation pressure in the same way as indices of forced expiration. We found a small but significant increase in compliance following salbutamol. This contrasts with the findings of Hughes et al. who found no differences in $C_{rs}$, $R_{rs}$ or $\tau$ in response to salbutamol, and Chavasse et al. who found an increase in $R_{rs}$ and a trend towards an increase in $C_{rs}$ and respiratory rate. However, the infants in these studies did not receive augmented inspirations and passive mechanics were measured by occluding the airway at the end of tidal inspiration. By augmenting inspiration, we were able to measure $\tau$ over an extended volume range. Our findings suggest that the respiratory system became less stiff in response to salbutamol, but we were unable to demonstrate any change in $R_{rs}$ that could indicate altered airway dimensions. Furthermore, individual changes in passive mechanics were unrelated to changes in any index of forced expiration. Changes in airway mechanics in response to bronchodilators or
bronchoconstrictors are complex, with changes in airway calibre and elastance influencing forced expiratory flow in opposing directions. This poses a problem for those interested in investigating the pathophysiology of wheezing disorders. Auscultation has been used in the investigation of bronchoconstriction in small children undergoing methacholine challenge, with the detection of wheeze being the endpoint of the challenge. The diminished airway potency observed in infants with transient wheeze has been assumed to support this as a practical method for detecting reduction in airway calibre. The response to bronchodilator involves an increase in airway compliance, which may diminish flow both by reduction in the speed of wave propagation and by an increase in dynamic compression. The point at which any increase in airway diameter overrides the alterations in compliance is not clear, but a combination of measurements of high-frequency input impedance with more classical techniques of lung function may gradually increase our understanding of underlying changes in airway physiology.

Conclusions

Although there are limited data testifying to the clinical effectiveness of salbutamol in the treatment of infants with wheezing, we have been unable to demonstrate a consistent pattern of response, despite looking at \(V_{\text{max,FRC}}\) derived from RTC, one timed volume (FEV\(_{0.4}\)) from RV-RTC, and passive lung mechanics (R\(_{CP}\) and C\(_{CP}\)). Even in infants with some evidence of response to salbutamol, there was inconsistency between physiological outcomes, raising doubts about the validity of the responses. Thus it seems probable that (i) our tests of lung function cannot detect subtle changes brought about by bronchodilators or (ii) individual infants respond in different ways and these are masked by studies of groups of infants with varying underlying pathology or (iii) there were no beneficial effects of bronchodilator in these patients. Investigation of individual patients and groups should perhaps revert to validated clinical scores, while groups of subjects should be placed in well-characterised phenotypes before study.

Acknowledgements

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References


