The Effect of Inhaled Adrenaline on Lung Function of Recurrently Wheezy Infants Less Than 18 Months Old

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Summary. Inhaled bronchodilators have been shown not to improve lung function in infants with wheeze. This observation has led to the suggestion that airway wall edema may be more important than bronchoconstriction in infants with airway narrowing. Inhaled adrenaline is used to relieve upper airway edema in children with croup and has been demonstrated to improve clinical scores and lower pulmonary resistance in some infants with wheeze associated with bronchiolitis. The aim of the present study was to examine the effect of inhaled adrenaline on lung function in a group of infants with recurrent wheeze. Eleven infants aged 10 to 18 months with a history of recurrent wheeze were studied during an asymptomatic interval. Respiratory function was assessed (1) by measuring maximal expiratory flow at functional residual capacity (Vmax,FRC) during a forced partial expiratory maneuver and (2) by measuring conductance of the respiratory system (Grs) using a single expiratory occlusion technique. Following baseline measurements, the infants received 0.5 mg/kg adrenaline by nebulizer and serial lung function tests were repeated at 5 min intervals. Ten infants had abnormal baseline lung function (median Vmax,FRC 44.2% predicted; median Grs 34% predicted). Using a random effects model, Vmax,FRC and Grs declined significantly at 10 and 5 min after adrenaline, respectively. No significant improvements from baseline were observed in either measurement for up to 30 min following adrenaline delivery. It is concluded that inhaled adrenaline did not relieve airways obstruction in this group of asymptomatic infants with recurrent wheeze. Pediatr Pulmonol. 1995; 20:9–15.

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Key words: Adrenaline, wheezing infants, bronchodilators, pulmonary function tests.

INTRODUCTION

Recurrent wheeze is common in infants, but the effect of bronchodilators in this age group remains controversial. Several studies have demonstrated no improvement in lung function following inhalation of β2-adrenergic agonists1–4 and others have demonstrated paradoxical worsening of lung function.5–7 These observations have led to the suggestion that airway narrowing in infants could be due to airway wall edema rather than smooth muscle constriction. Inhaled adrenaline can be used to relieve upper airway edema in croup and, in an animal model, adrenaline has been demonstrated to reduce airway wall edema due to microvascular leakage.8 The effect of adrenaline in this situation is likely to be mediated by the α-adrenergic vasoconstrictor response of precapillary arterioles.9 The role of adrenaline has been studied in acute bronchiolitis in infants. Lenney and Milner demonstrated no change in pulmonary resistance following adrenaline in infants less than 18 months old with bronchiolitis.10 However, an earlier study by Holland and colleagues suggested a decrease in total respiratory effort following inhaled adrenaline in a small group of infants with lower respiratory infections.11 Sanchez and colleagues have recently demonstrated improvement in clinical severity and pulmonary resistance following inhaled adrenaline in infants with their first episode of bronchiolitis, but no significant effect of salbutamol on either measurement was observed.12 Recent work from our laboratory has demonstrated that infants with recurrent wheeze have abnormal lung function even when they are clinically asymptomatic.13 The aim of the present study was to examine the effect of the α- and β-adrenergic agonist adrenaline on lung function of a group of infants less than 18 months old and with a history of recurrent wheeze.

SUBJECTS AND METHODS

Eleven infants (9 males, 2 females) aged less than 18 months (median age 15 months; range 10–18 months)

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and with a history of two or more episodes of wheeze were studied. All of the infants were clinically wheeze-free at the time of study and had not had an acute wheezing illness in the previous 2 weeks. Approval for the study was obtained from the Research and Ethics Sub-Committee of Princess Margaret Hospital for Children and written parental consent was obtained for each infant studied.

Respiratory function was assessed by the forced partial expiratory flow–volume technique. The infants were given 80 mg/kg of chloral hydrate and, once asleep, an inflatable plastic jacket was wrapped around the rib cage and upper abdomen with the arms outside the jacket. The jacket was rapidly inflated at end-inspiration and flow was measured at FRC of the preceding tidal breath. Jacket inflation pressure was gradually increased over a series of forced expirations until maximal flow (VmaxFRC) was reached. The same inflation pressure was used for all subsequent forced expirations during the study. The infant breathed through a putty face mask sealed around the nose and mouth with a fresh gas flow of 5 L/min between measurements. Flow was measured at the mouth with a Fleisch #1 pneumotachograph (P.K. Morgan, Chatham, U.K.) attached to a Validyne DP-45 pressure transducer and a Validyne CD-19 carrier amplifier (Validyne Corp., Northbridge, CA). Volume measurements were calculated by electronic integration of the flow signal with respect to time. Pressure at airway opening (Pao) and jacket inflation pressure were measured with a Gould 23p pressure transducer (Gould Inc., Dayton, OH) and Nihon-Kohden AP-621G carrier amplifiers (Nihon-Kohden Corp., Tokyo, Japan). Flow and volume signals were displayed on a Tektronix 5223 digitising oscilloscope (Tektronix, Beaverton, OR) and stored on magnetic tape (Teac SR-50, Teac Corp., Tokyo, Japan). Taped data were transcribed to paper on a Hewlett Packard XY Plotter (Hewlett Packard, Waltham, MA). Arterial oxygen saturation (SaO₂) and heart rate were measured continuously during the study with a Nellcor N200E pulse oximeter (Nellcor Inc., Hayward, CA). A single occlusion technique was used to measure the passive mechanics of the total respiratory system. Using a slide valve positioned between the face mask and the pneumotachograph, the airway was transiently occluded at end-inspiration during tidal breathing to induce the Hering-Breuer reflex. The occlusion was maintained for sufficient time to allow Pao to plateau. The subsequent passive expiration was used to calculate compliance (Crs) and conductance (Grs) of the total respiratory system. The total passive expiratory volume (Ve) after releasing the occlusion was calculated by extrapolating the linear portion of the flow–volume curve to zero flow. Compliance was calculated from Ve/Pao. The slope of the linear portion of the expiratory flow–volume curve represents the inverse of the expiratory time constant (Trs) from which Grs is calculated (Trs = Rs × Crs). Thoracic gas volume was measured in a whole body plethysmograph and specific compliance (sCrs) and conductance (sGrs) were calculated.

Following measurement of baseline lung function, the infants were given nebulized adrenaline 0.5 mg/kg of a 1% solution, diluted to 2 mL with 0.9% saline and delivered by a Turret nebulizer (Medic-Aid, Sussex, U.K.) with a gas flow of 8 L/min (mass median aerosol diameter 1.8 µm; geometric standard deviation 2.3 µm). The nebulized solution was inhaled by tidal breathing through a face mask until the nebulizer chamber was dry. Within 1 min of completing the nebulization of adrenaline, the forced partial flow–volume curves and passive respiratory system mechanics were repeated. Repeated measurements were made at 5 min intervals until the infant woke or no further changes in the measurements were observed.

ANALYSIS

To allow for serial correlation of repeated measurements in each subject, a random effects model was used. A single random effect was assumed to be normally distributed across subjects. To model the effect of time, seven dummy variables were used to represent differences from baseline at each measurement up to 30 min after adrenaline. These were dropped from the model and the change in -2 log likelihood was calculated. This followed approximately a χ² distribution with 7 degrees of freedom. Differences at individual time points were assessed using approximate t tests. The data for VmaxFRC were logarithmically transformed (log10) before applying the model as they were not normally distributed.

The power of the study to detect a clinically significant effect of adrenaline was calculated. Clinical significance was arbitrarily defined as a return to ≥70% of predicted respiratory function as all the infants in the study were asymptomatic by definition. The greatest effect of adrenaline on VmaxFRC was observed at 10 min. Therefore, the standard deviation of changes in VmaxFRC at 10 min was used for the power calculation, which was performed using the standardized difference (expected change/standard deviation) in the nomogram devised by Altman.18

RESULTS

All but one infant studied had abnormal lung function at baseline (Table 1). The median (range) VmaxFRC for the group was 0.5 TGV/sec (0.09–2.06 TGV/sec); the median percent predicted for height according to the data of Tepper et al.19 was 44.2% (11.2–199.6%). Passive respiratory mechanics were also abnormal for the group.
Median (range) sCrs was 0.046 mL cm H2O⁻¹ TGV⁻¹ (0.029–0.085 mL cm H2O⁻¹ TGV⁻¹) equating to 78% predicted normal (51–144%)²⁰ and median (range) sGrs was 0.098 sec⁻¹ cm H2O⁻¹ (0.048–0.207 sec⁻¹ cm H2O⁻¹) equating to 34% predicted normal (17–72%).²⁰ One infant (subject 9, Table 1) had a high Vmax,FRC (2.66 TGV/sec; 199% predicted) but sGrs was only 50% predicted.

Four infants woke after the first measurement of Vmax,FRC following the inhalation of adrenaline. In two of these subjects, Vmax,FRC fell by more than twice the intrasubject coefficient of variation of the measurement in recurrently wheezy infants.²¹ The infants who woke within 1 min after inhaling adrenaline did not have significantly greater changes in SaO₂ or heart rate than the remaining infants. Median changes in SaO₂ were −3.5% in the infants who woke and −0.5% in those who did not (P = 0.1, Mann Whitney U test) and median changes in heart rate were −7 and +12 bpm, respectively (P = 0.4, Mann Whitney U test). No significant changes in Vmax,FRC from baseline measurements were observed at any time up to 30 min after adrenaline (Fig. 1). Using the random effects model (Fig. 2), a significant decrease in mean Vmax,FRC was demonstrated at 10 min (P < 0.05, approximate t test), but no other significant changes from baseline were demonstrated. The effect of time on the model was investigated by dropping the 7 dummy variables which resulted in a nonsignificant change in −2 log likelihood (χ² = 3.11, P > 0.05).

Similarly, there were no significant changes in Grs from baseline measurements observed in the 7 infants in whom serial measurements were possible. Using a random effects model (Fig. 3) we observed a significant fall in Grs at 5 min (P < 0.02, approximate t test). No other significant changes were demonstrated and the effect of time on the model was not significant (χ² = 11.42, P > 0.05).

All infants had an increase in heart rate following adrenaline inhalation. At 1 min following completion of nebulized adrenaline the median increase was 9 bpm (4–23 bpm) which was significantly different from baseline heart rate (Wilcoxon signed rank test, P = 0.006). By 5 min, the median increase from baseline was 11 bpm, which was not statistically significant (P = 0.06). Median baseline SaO₂ was 98% (93–100%). There was a small, nonsignificant fall in SaO₂ (median decrease −1%, range −6% to +1%) at 1 min postadrenaline.

The power of our study to detect a clinically significant effect of adrenaline on Vmax,FRC (to ≥70% predicted) was 0.40. To increase the power to 0.90, it would be necessary to study 40 infants. The actual magnitude of change in Vmax,FRC in this study was a mean decrease of 7.1 mL/sec at 10 min. To demonstrate that a change of this magnitude was significant with α = 0.05 and a power of 0.90 would require a study of 1500 subjects.

**DISCUSSION**

We have demonstrated no clinically significant effects of inhaled adrenaline on Vmax,FRC during an asymptomatic interval in this small population of infants with a history of recurrent wheeze. Previous studies of the effects of adrenaline in wheezing infants have focused on acute respiratory infections associated with wheezing. Holland and colleagues demonstrated a decrease in respiratory effort in some infants with lower respiratory infections.¹¹ Wennegren and co-workers observed significant clinical improvement and a small, significant increase in transcutaneous PO₂ (TcPO₂), but no lung function changes in an open study of children with wheezy bronchitis.²² Lowell and colleagues demonstrated improvements in clinical scores in a proportion of infants treated with subcutaneous adrenaline in a placebo-controlled study.²³ Sanchez and colleagues have recently demonstrated clinical improvement and decreased pulmonary resistance in infants with bronchiolitis who were treated with adrenaline in a double-blind comparison with salbutamol.¹² The discordance between our results and those

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**TABLE 1—Baseline Lung Function Measurements of 11 Infants With Recurrent Wheeze**¹

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age (months)</th>
<th>Vmax,FRC (TGV/sec)</th>
<th>% predicted</th>
<th>sGrs (mL sec⁻¹ cm H₂O⁻¹ TGV⁻¹)</th>
<th>sCrs (mL cm H₂O⁻¹ TGV⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>9</td>
<td>0.09</td>
<td>11.7</td>
<td>0.087</td>
<td>0.033</td>
</tr>
<tr>
<td>2</td>
<td>12</td>
<td>0.40</td>
<td>49.3</td>
<td>0.111</td>
<td>0.053</td>
</tr>
<tr>
<td>3</td>
<td>13</td>
<td>0.19</td>
<td>35.7</td>
<td>0.054</td>
<td>0.030</td>
</tr>
<tr>
<td>4</td>
<td>13</td>
<td>0.27</td>
<td>42.6</td>
<td>0.098</td>
<td>0.037</td>
</tr>
<tr>
<td>5</td>
<td>15</td>
<td>0.20</td>
<td>35.2</td>
<td>0.061</td>
<td>0.040</td>
</tr>
<tr>
<td>6</td>
<td>15</td>
<td>0.33</td>
<td>92.8</td>
<td>0.048</td>
<td>0.046</td>
</tr>
<tr>
<td>7</td>
<td>15</td>
<td>0.61</td>
<td>44.2</td>
<td>0.207</td>
<td>0.085</td>
</tr>
<tr>
<td>8</td>
<td>15</td>
<td>0.29</td>
<td>47.0</td>
<td>0.101</td>
<td>0.037</td>
</tr>
<tr>
<td>9</td>
<td>15</td>
<td>2.06</td>
<td>199.6</td>
<td>0.147</td>
<td>0.072</td>
</tr>
<tr>
<td>10</td>
<td>18</td>
<td>0.11</td>
<td>14.0</td>
<td>0.095</td>
<td>0.049</td>
</tr>
<tr>
<td>11</td>
<td>18</td>
<td>0.75</td>
<td>82.9</td>
<td>0.122</td>
<td>0.071</td>
</tr>
</tbody>
</table>

¹sGrs, specific respiratory system conductance (Grs/TGV); sCrs, specific respiratory system compliance (Crs/TGV).
of previous studies may be due to a number of factors, including the efficacy of delivery of adrenaline, the adrenaline preparation used, the method of assessing outcome, and the clinical status of the infants studied. The dose of adrenaline we used was 0.5 mg/kg. Wennergren et al. compared an equivalent dose to ours (0.45 mg/kg) with a higher dose (0.9 mg/kg) and found that both produced a significant increase in TcPO₂ but only the higher dose resulted in a significant clinical improvement. However, it appears that a pharmacologically active mass of adrenaline was delivered to the infants in our study as all had a rise in heart rate. Our results are unlikely to be due to our use of /-adrenaline rather than racemic adrenaline as there is no pharmacological evidence to favor one preparation over the other. A recent study comparing the efficacy of the two preparations in croup showed no difference in clinical outcome. It is possible that irritants in the inhaled solution could have altered lung function in some of the subjects in our study. The adrenaline solution which we used contained 1 g/L of sodium metabisulfite (MBS). MBS is a potent bronchoconstrictor in adults either through conversion to sulfur dioxide or through intrinsic properties. Although most inhaled sulfur dioxide is absorbed by the nasal mucosa, Kirkpatrick and others have demonstrated that concentrations of 0.5 ppm inhaled nasally for 5 min can induce bronchoconstriction in adults. When we tested our adrenaline solution for a 10 kg infant, a gas with a SO₂ concentration of 1.3 ppm was formed. While recent studies have shown a protective effect of salbutamol in both SO₂ and MBS induced bronchoconstriction, the interaction of adrenaline with these agents is unknown. Similarly, although the pH of the solution was 3.16 and, as such, may have had bronchoconstrictive properties, the β₂-agonist effects of adrenaline would be expected to negate this effect.

Many studies evaluating the effects of α- and β-adrenergic agonists on pulmonary function have demonstrated no beneficial effects; occasionally paradoxical deterioration has been observed. It has been suggested that such observations may be attributable to technical aspects of lung function measurements. Reversal of airways obstruction could lead to a reduction in gas trapping and a fall in FRC. As Vmax,FRC is volume dependent, a decrease in FRC could lead to an apparent reduction in Vmax,FRC despite actual improvement. However, this phenomenon has not been observed in previous studies in which Vmax,FRC has been measured before and after resolution of induced bronchospasm. Prendiville et al. have speculated that a paradoxical decrease in Vmax,FRC in healthy infants treated with salbutamol could be due to a reduction in airway tone without changes in airway caliber. This could result in increased dynamic airways compression at low lung volumes causing a fall in Vmax,FRC. In our study, serial measurements of conductance demonstrated similar changes to mea-

![Graph](image-url)
Fig. 2. Random effects model of changes in mean $\dot{V}_{\text{max},FRC}$ ($\pm 95\%$ confidence intervals) following inhaled adrenaline at time zero (**Significant difference, $P < 0.05$; approximate t-test). Note nonlinear time scale.

Fig. 3. Random effects model of changes in specific conductance of the respiratory system ($G_{rs}$) ($\pm 95\%$ confidence intervals following inhaled adrenaline at time zero (**Significant difference, $P < 0.02$; approximate t-test). Note nonlinear time scale.

measurements of $\dot{V}_{\text{max},FRC}$, suggesting that observed changes in the latter resulted from changes in airway caliber.

The observations in our study could have resulted from our decision not to evaluate infants during an acute exacerbation of their wheezing illness. However, all the in-
fants in our study had some evidence of airway obstruction despite being clinically asymptomatic. Stick and colleagues have recently shown that recurrently wheezing infants have significantly reduced $V_{max}$FRC compared with healthy controls, but no differences in their responsiveness to inhaled histamine. They have suggested that infants with recurrent wheeze may have abnormal airways with either reduced airway caliber or abnormal airway tone. Such infants are more likely to wheeze with intercurrent infections and may have constituted the majority of the group which we studied. However, we have no data to explain whether the abnormalities which we observed in baseline lung function in this group were due to abnormal airways, bronchoconstriction or airway wall edema.

Although our study population was small, we observed no changes in either measurement of lung function which exceeded 2 standard deviations of the measurement in a comparable population of infants. As the infants were clinically asymptomatic despite abnormalities of lung function, it is difficult to define a clinically significant effect of an intervention in this group. Our study had a power of 40% to detect an increase in $V_{max}$FRC to 70% predicted or greater; however, a much larger study would be required to demonstrate that the changes which we observed were statistically significant with an adequate power. It appears from our results in this population of infants with recurrent wheeze that adrenaline does not have a clinically beneficial effect on lung function. Further studies will be required in infants with abnormalities of lung function and in infants with acute wheezing illnesses to evaluate the therapeutic role of adrenaline in these populations.

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REFERENCES

28. Iredale MJ, Dixon CM, Ind PW. Salbutamol inhibits metabisul-