

# Effect of salbutamol on histamine induced bronchoconstriction in healthy infants

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## Abstract

**Background**—The effect of inhaled  $\beta_2$  adrenergic drugs on infants with wheezing disorders remains controversial. Salbutamol inhibits the bronchial responsiveness of infants to histamine and nebulised water but whether or not it acts as a bronchodilator in this age group is unclear. The aim of the present study was to determine whether salbutamol can hasten the reversal of histamine induced bronchoconstriction in infants.

**Methods**—Bronchial challenge with histamine was performed in 40 infants aged 12 months or less with no previous history of respiratory symptoms. Response to histamine was assessed by forced partial expiratory flow/volume curves to measure maximal flow at functional residual capacity ( $\dot{V}_{maxFRC}$ ). After a fall of 40% or more from baseline  $\dot{V}_{maxFRC}$ , each infant was randomly assigned to receive either salbutamol 0.5% or saline 0.9% solution by nebuliser. The rate of recovery of  $\dot{V}_{maxFRC}$  and the time to reach baseline  $\dot{V}_{maxFRC}$  were derived by linear regression.

**Results**—Infants who received salbutamol had a significantly faster rate of recovery (geometric mean 8.5 ml/s/min) than those who received saline (4.1 ml/s/min). Considerable interindividual variation was observed in the time from maximum bronchoconstriction to recovery of baseline  $\dot{V}_{maxFRC}$  in both groups of subjects. **Conclusions**—Salbutamol significantly speeds the reversal of histamine induced bronchoconstriction in infants during the first 12 months of life. This observation provides further evidence to support the presence of functional  $\beta$  adrenergic receptors in the airways of infants.

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The effect of inhaled  $\beta_2$  adrenergic drugs on infants with wheezing disorders remains controversial with many studies showing no improvement in lung function,<sup>1-4</sup> and others showing a decline in function.<sup>5-7</sup> The observed absence of a clear beneficial effect of  $\beta_2$  agonists in wheezy infants is not explained by an absence of  $\beta_2$  adrenergic receptors in the

infant lung, as studies have shown a protective effect of inhaled salbutamol on histamine challenge<sup>8</sup> and nebulised water challenge<sup>9</sup> in recurrently wheezy infants. A study by Tepper<sup>10</sup> suggested a therapeutic effect of isoprenaline after methacholine challenge in healthy infants, but this evaluation was neither controlled nor randomised. Histamine and methacholine have different pharmacological effects on the airways<sup>11</sup> and methacholine has been shown to provoke more central bronchoconstriction than the more peripheral action of histamine.<sup>12</sup> Histamine and methacholine also induce different time courses of bronchoconstriction in adult subjects with more rapid recovery following histamine challenge.<sup>13</sup> Recovery after histamine challenge in infants is also rapid but there is considerable intersubject variation.<sup>14</sup> There is no clear information on the effect of inhaled salbutamol on histamine induced bronchoconstriction. This study was designed to test the hypothesis that, in infants during the first 12 months of life, inhaled salbutamol would lead to a more rapid recovery of baseline lung function after histamine induced bronchoconstriction.

## Methods

Forty nine healthy infants taking part in a community based longitudinal survey of bronchial hyperresponsiveness were assessed. Forty (22 boys; age range 3-55 weeks) were identified who had a greater than 40% fall in  $\dot{V}_{maxFRC}$  after histamine inhalation, and they were studied. The infants were all randomly recruited from a general antenatal clinic and none was symptomatic at the time of study or had a history of recurrent wheeze. Approval for the study was obtained from the Research and Ethics Committee of Princess Margaret Hospital for Children. Informed consent was obtained from the parents of each infant studied.

Respiratory function was assessed by forced partial expiratory flow/volume curves.<sup>15</sup> The infants were given 80 mg/kg chloral hydrate and, once asleep, an inflatable jacket was wrapped around the chest and abdomen. The jacket was rapidly inflated at end inspiration and flow was measured at functional residual capacity (FRC). Inflation pressures of the jacket were gradually increased over a series of

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forced expirations until maximal flow at FRC ( $\dot{V}_{\text{maxFRC}}$ ) was obtained. Once this pressure had been established it was used for all forced expirations throughout that study. The infant breathed through a therapeutic putty face mask and flow was measured at the mouth with a Fleisch No. 1 pneumotachograph (P K Morgan Ltd, Chatham, UK) attached to a pressure transducer (Validyne DP45) and carrier amplifier (Validyne CD19; Validyne Co, California, USA). Volume was calculated by electronic integration of the flow signal. All data were recorded on a chart recorder (Polygraph WT-685G; Nihon Kohden Corporation, Tokyo, Japan). Flow and volume were displayed during the study on a digitising oscilloscope (Teknotronix 5223; Beaverton, Oregon, USA) and stored on magnetic tape (TEAC SR-50; TEAC Corporation, Tokyo, Japan). Taped data were transcribed to paper on an XY plotter (Hewlett Packard, Waltham, Massachusetts, USA). Arterial oxygen saturation ( $\text{SaO}_2$ ) and pulse rate were monitored throughout the study with a pulse oximeter (Nellcor N-200E; Nellcor, Hayward, California, USA).

Histamine challenge tests were performed using methods described previously.<sup>14,16</sup> Nebulised normal saline was delivered from an Airlife Misty nebuliser (American Pharmaseal Co., Valencia, California, USA) with a flow rate of 6 l/min and inhaled by the infant by tidal breathing for one minute. The mean  $\dot{V}_{\text{maxFRC}}$  of five forced partial expiratory flow/volume curves was measured after saline and taken as baseline  $\dot{V}_{\text{maxFRC}}$ . Nebulised histamine was then administered in doubling concentrations from 0.125 g/l to 8.0 g/l at five minute intervals by the tidal breathing method. Five forced partial expiratory flow/volume curves were obtained after each concentration of histamine. The challenge was concluded when either a 40% fall occurred in  $\dot{V}_{\text{maxFRC}}$  (greater than two standard deviations from the mean for this measurement) or when the maximum concentration of histamine was reached. The provoking concentration of histamine causing a 40% fall in  $\dot{V}_{\text{maxFRC}}$  ( $\text{PC}_{40}$ ) was determined by linear extrapolation of a log dose-response curve of histamine concentration against percentage fall from baseline  $\dot{V}_{\text{maxFRC}}$ .

Note that the  $\text{PC}_{40}$  in the present study refers to the histamine concentration of the nebuliser solution rather than the inspired gas. It has recently been shown that, for comparison between infants, the concentration of histamine in the inhaled gas should be used to calculate  $\text{PC}_{40}$  to correct for air entrainment diluting histamine in the nebuliser output.<sup>17</sup> We did not correct for air entrainment in the present study as the protocol did not involve intersubject comparison of  $\text{PC}_{40}$ .

Infants who showed a response to histamine by a 40% or greater fall in  $\dot{V}_{\text{maxFRC}}$  before the maximum concentration of histamine was reached were eligible for the study. Measurement of  $\dot{V}_{\text{maxFRC}}$  was repeated five minutes after the concentration of histamine which had provoked a 40% fall. If  $\dot{V}_{\text{maxFRC}}$

was still 40% or more below baseline, the infant was randomised to receive either nebulised salbutamol or normal saline control. Randomisation was carried out before the study so that 20 infants each received salbutamol or saline. Treatment slips were sealed in opaque envelopes which were arranged in random order. A third party drew the top envelope at the start of the histamine challenge test and prepared either 2 ml 0.9% saline or 2 ml 0.5% salbutamol solution. The envelope was resealed and labelled with the infant's name and study number. The contents of the envelopes remained unknown to the principal investigators until all the studies were completed and their results calculated. Infants were given the nebulised therapy for one minute of tidal breathing during which the nebuliser delivers 0.3 ml as determined by weight loss of the nebuliser. The mass of salbutamol nebulised was therefore 1.5 mg for all infants. The concentration of salbutamol solution was chosen so that this mass could be delivered over a short time. If the nebulisation time was longer, recovery of  $\dot{V}_{\text{maxFRC}}$  may have occurred during the administration of the inhaled therapy when lung function measurements could not be made.

Measurements of  $\dot{V}_{\text{maxFRC}}$  were repeated one minute after completion of the nebulised salbutamol or saline and then at five minute intervals until the infant woke or the measurement returned to its baseline value. Pulse rate and  $\text{SaO}_2$  were measured continuously and their values were recorded at the time of measuring  $\dot{V}_{\text{maxFRC}}$ .

#### DATA ANALYSIS

The indices of recovery analysed after histamine challenge were the rate of recovery and the time taken to reach baseline  $\dot{V}_{\text{maxFRC}}$ . Methods of analysing serial data described by Matthews and colleagues<sup>18</sup> were used to derive these variables. A linear regression was fitted to a plot of  $\dot{V}_{\text{maxFRC}}$  against time for each subject. The slope of the regression line was taken as the rate of recovery and its intercept with baseline  $\dot{V}_{\text{maxFRC}}$  was taken as the time to recovery ( $T_r$ ). As the majority of infants woke before reaching baseline  $\dot{V}_{\text{maxFRC}}$  it was necessary to extrapolate the regression line so that a value for  $T_r$  was available for all infants studied.

The suitability of a linear model to explain the recovery of  $\dot{V}_{\text{maxFRC}}$  was tested by calculating the coefficient of linear regression ( $r$ ) and the analysis of variance (ANOVA) of observed measurements from the fitted linear model for each subject. The mean (95% CI) coefficient of linear regression for subjects who received salbutamol and whose results were based on three or more observations (15 subjects) was  $r = 0.87$  (0.78–0.96) and the goodness of fit was significant in every case (ANOVA,  $p < 0.01$ ). Infants who received saline and whose results were based on three or more observations (17 subjects) had a mean (95% CI) coefficient of linear regression of  $r = 0.93$  (0.88–0.98) and the goodness of fit was significant in every case (ANOVA,

Age, sex, baseline lung function, and PC<sub>40</sub> of 20 infants who received saline and 20 who received salbutamol after histamine challenge.

Subject	Saline				Salbutamol			
	Age (wks)	Sex	$\dot{V}_{max}FRC$ (%)	PC <sub>40</sub> (g/l)	Age (wks)	Sex	$\dot{V}_{max}FRC$ (%)	PC <sub>40</sub> (g/l)
1	4	M	35.4	0.50	3	M	92.9	1.54
2	4	M	124.0	0.80	3	M	88.1	7.10
3	4	M	112.2	1.00	4	M	*	2.24
4	4	F	97.7	1.12	4	M	107.5	0.35
5	4	F	133.7	0.62	4	M	179.4	2.40
6	5	M	83.2	7.10	4	M	153.9	4.95
7	5	M	90.3	0.50	5	M	96.7	7.80
8	5	F	75.9	3.10	6	M	78.3	0.20
9	5	F	75.1	0.50	6	F	162.5	0.88
10	5	F	56.0	1.50	8	F	62.8	1.50
11	6	M	81.9	2.80	9	M	68.8	1.05
12	7	M	88.3	3.20	20	F	94.1	6.22
13	7	M	46.5	1.63	25	F	29.9	0.31
14	7	F	65.2	0.13	27	M	72.9	3.25
15	24	F	72.3	1.54	28	M	80.9	1.48
16	25	M	133.9	0.20	30	M	49.3	1.05
17	26	F	65.6	1.87	51	F	144.7	1.75
18	54	M	92.9	0.64	51	F	100.0	0.46
19	54	F	184.4	0.78	53	F	59.7	7.25
20	54	F	114.1	2.00	55	F	61.8	0.49
Median	5.5				8.5			
Mean			91.4				93.9	
Geometric mean				1.04				1.54

\*Length not available (infant in splint).

$\dot{V}_{max}FRC$ —maximum flow at functional residual capacity; PC<sub>40</sub>—provoking concentration of histamine causing a 40% fall in  $\dot{V}_{max}FRC$ .

$p < 0.01$ ). A linear model therefore was accepted as an appropriate approximation to the pattern of recovery of  $\dot{V}_{max}FRC$  after histamine induced bronchoconstriction in the majority of infants studied.

The slopes of the fitted linear regressions were normally distributed after logarithmic transformation and the geometric means were compared using Student's *t* test. The values for  $T_r$  were compared using the Mann-Whitney test. Differences in pulse rate and SaO<sub>2</sub> from prenebulisation baseline values were normally distributed without transformation. Within group comparisons were made with paired *t* tests. Other comparisons between groups of data were made with non-parametric tests. A probability of less than 5% was used to reject the null hypothesis that there was no difference between the groups in all analyses.

## Results

Twenty infants received salbutamol after histamine challenge and 20 received normal saline. Their age, sex, baseline  $\dot{V}_{max}FRC$  (as percentage predicted)<sup>19</sup> and PC<sub>40</sub> (g/l) did not differ significantly (table). Mean (SD) baseline SaO<sub>2</sub> (before histamine challenge) was 99.2 (1.1)% in the saline treated infants and 99.1 (0.9)% in the salbutamol treated infants. After histamine challenge and before nebulised salbutamol or saline, measurements of SaO<sub>2</sub> were not significantly different from baseline in either group, 98.6 (2.0)% and 98.9 (1.2)% respectively.

After receiving nebulised salbutamol or saline  $\dot{V}_{max}FRC$  fell further by more than 10% (intrasubject coefficient of variation 9.5%)<sup>15</sup> in 11 of the 40 subjects; eight after

saline and three after salbutamol. The proportion of subjects experiencing a further decline in  $\dot{V}_{max}FRC$  after the nebulisation was significantly higher in the saline treated infants, ( $p < 0.05$ ,  $\chi^2$  test).

Changes in SaO<sub>2</sub> from prenebulisation values after salbutamol and saline are shown in fig 1 and changes in pulse rate are shown in fig 2. Both substances provoked a significant fall in SaO<sub>2</sub> with the reduction tending to be more prolonged in those infants treated with salbutamol although no significant differences were found between the groups. The pulse rate rose significantly after nebulised saline and salbutamol but in the saline treated subjects the rise was transient and the pulse rate

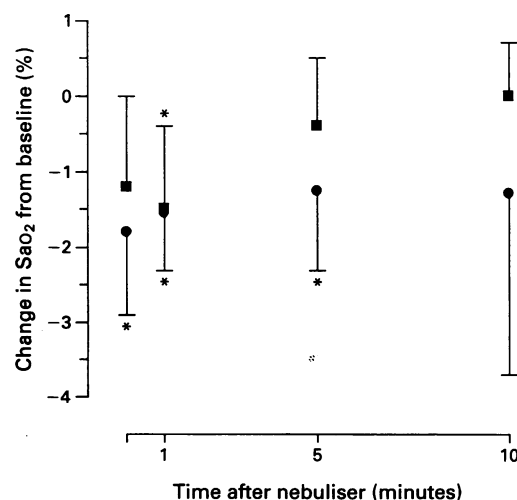


Figure 1 Mean (95% CI) changes in SaO<sub>2</sub> from prenebulisation baseline values for infants given saline (■) and salbutamol (●) following histamine challenge. \*Significant within group difference from baseline,  $p < 0.05$ .

Figure 2 Mean (95% CI) changes in pulse rate from prenebulisation baseline values for infants given saline (■) and salbutamol (●) following histamine challenge. \*Significant within group difference from baseline,  $p < 0.05$ ; †significant between group difference,  $p < 0.05$ .

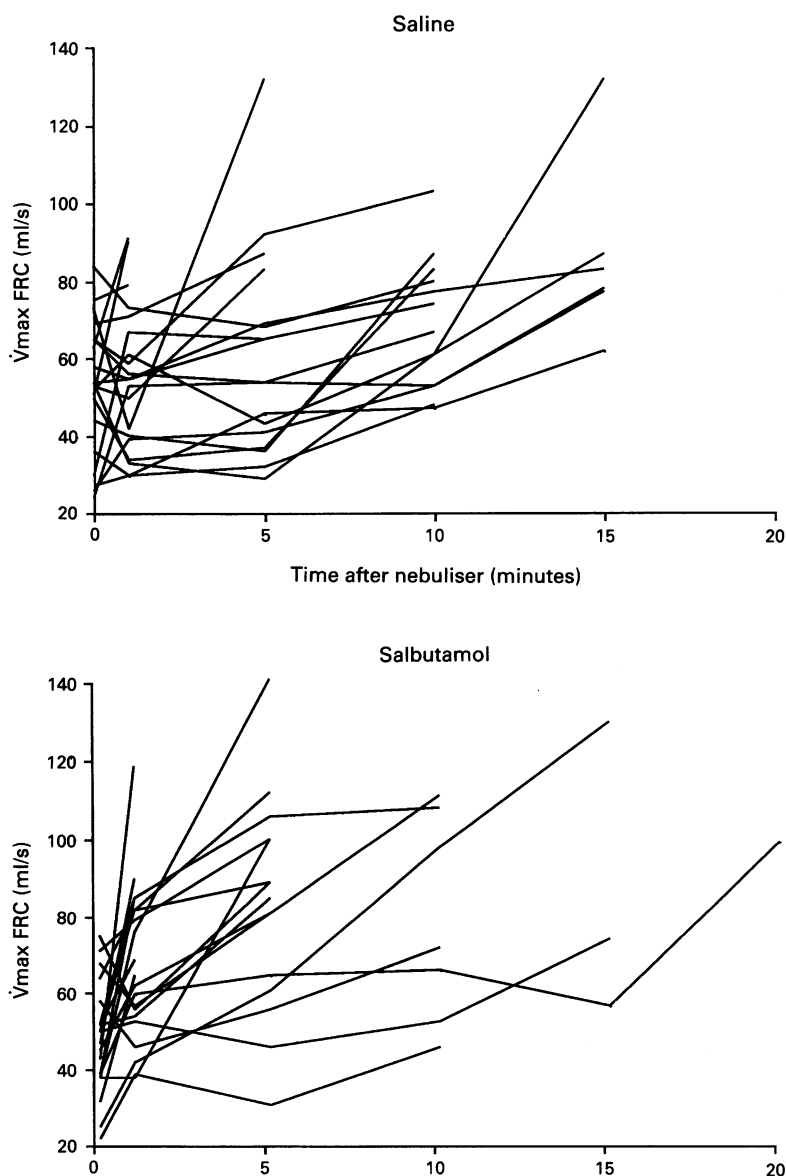
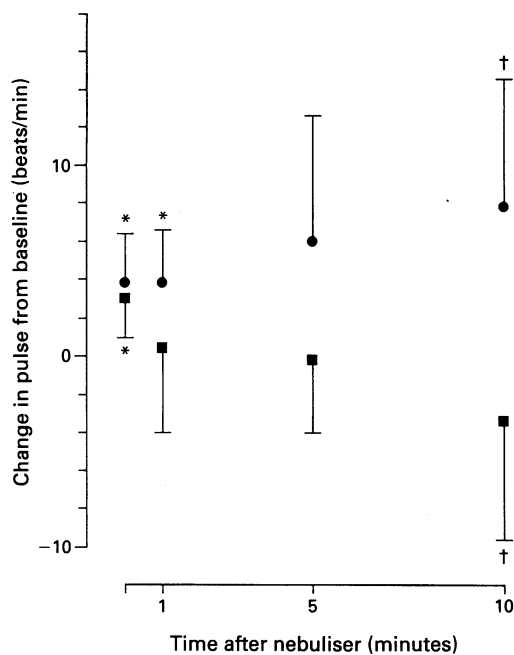


Figure 3 Actual recovery of  $\dot{V}_{max}FRC$  following histamine induced bronchoconstriction in 20 infants who received nebulised saline and 20 who received nebulised salbutamol.

at one minute was not significantly higher than prenebulisation values. In the salbutamol treated infants the rise in pulse rate was sustained and the mean change at 10 minutes after nebulisation was significantly greater than that in the saline treated group (unpaired Student's  $t$  test,  $p < 0.05$ ).

The recovery of  $\dot{V}_{max}FRC$  with time for individual subjects is shown in fig 3 and the slopes of recovery derived from linear regression of  $\dot{V}_{max}FRC$  against time and the intercepts with mean baseline  $\dot{V}_{max}FRC$  are shown in fig 4. The geometric mean (95% CI) slope in the saline treated subjects was 4.1 ml/s/min (2.7–6.2 ml/s/min) which was significantly less than the slope of 8.5 ml/s/min (5.0–14.7 ml/s/min) for the salbutamol treated subjects (Student's  $t$  test,  $p < 0.05$ ). There was a trend for median  $T_r$  to be longer in the saline treated infants (14.0 minutes) than in those who received salbutamol (7.6 minutes) but the difference did not reach significance (Mann-Whitney U test). Fifteen subjects (six saline treated, nine salbutamol treated) reached their baseline  $\dot{V}_{max}FRC$  before waking. The median  $T_r$  in this subgroup was 12.5 minutes for those treated with saline and 5.0 minutes for those treated with salbutamol but the difference was not significant (Mann-Whitney U test).

There were no significant correlations between the minimum  $\dot{V}_{max}FRC$  (percentage baseline) after histamine challenge and slope of recovery in either the saline treated (Spearman's rank correlation test,  $r_s = 0.27$ ) or salbutamol treated ( $r_s = 0.09$ ) groups. Minimum  $\dot{V}_{max}FRC$  correlated with  $T_r$  in the saline treated subjects ( $r_s = 0.51$ ,  $p < 0.05$ ) but not in those treated with salbutamol ( $r_s = 0.13$ ).

There was a higher proportion of younger infants in the saline treated group than in the salbutamol group but no significant differences were observed in the slope of recovery or  $T_r$  between infants younger than six months and those older than six months in either the saline or salbutamol treated group. The geometric mean (95% CI) slope of recovery was 5.2 ml/s/min (3.0–9.2 ml/s/min) in infants under 6 months who received saline and 12.8 ml/s/min (5.7–28.8 ml/s/min) in those who received salbutamol (Student's  $t$  test,  $p > 0.05$ ). For infants of six to 12 months the geometric mean (95% CI) slope of recovery was 4.7 ml/s/min (3.5–6.1 ml/s/min) in those receiving saline and 8.2 ml/s/min (5.3–12.6 ml/s/min) in those receiving salbutamol (Student's  $t$  test,  $p = 0.05$ ).

## Discussion

The results of the study show that salbutamol increases the rate of recovery of maximal expiratory flow rates after histamine induced bronchoconstriction in normal infants during the first year of life. This provides further evidence that infants in this age group have functional  $\beta_2$  receptors in their airways.

Salbutamol was administered by nebulising 0.5% solution directly into a face mask which

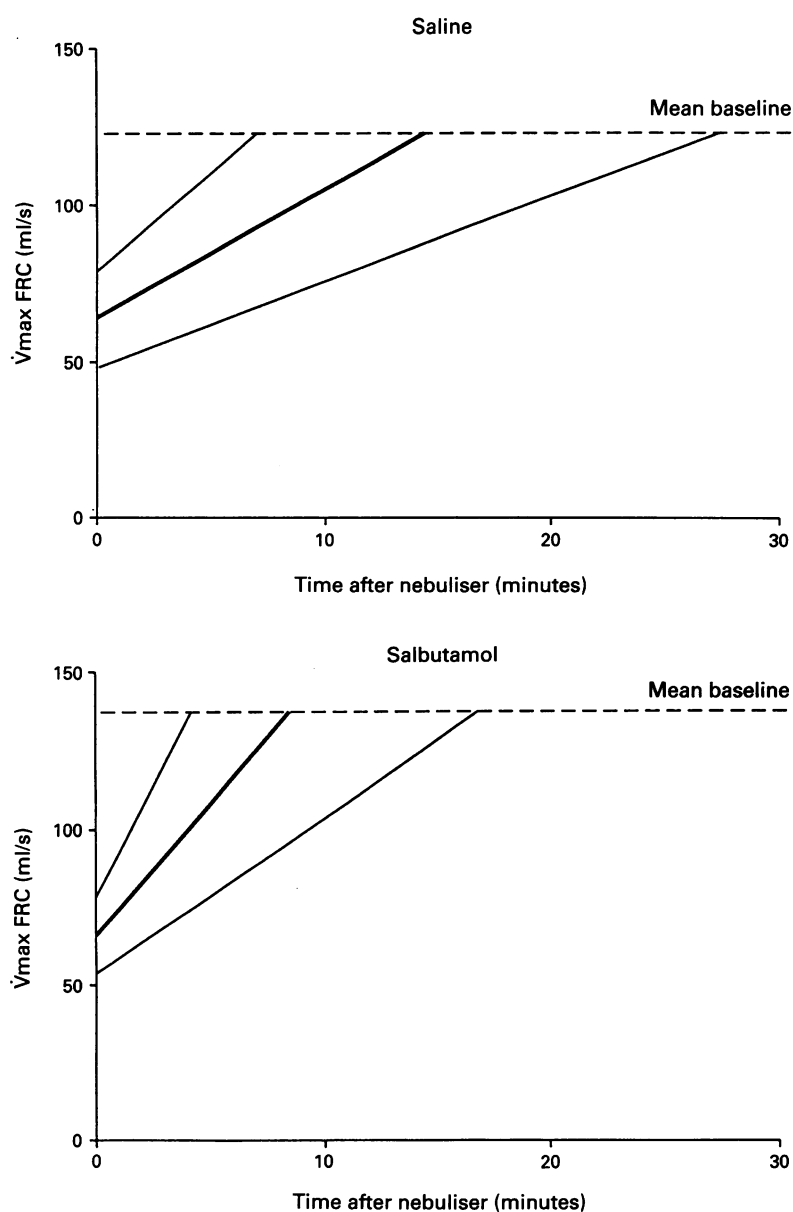


Figure 4 Recovery following histamine induced bronchoconstriction in infants who received saline or salbutamol. The mean (95% CI) for  $\dot{V}_{\max}\text{FRC}$  at time zero (immediately after saline/salbutamol) and the geometric mean (95% CI) slope are shown for each group.

was sealed around the infant's nose and mouth. The drug was inhaled by tidal breathing for one minute during which we calculated that 0.15 mg of salbutamol would be nebulised. This dose was considered to be appropriate for all the infants studied as we have shown that infants under one year of age inhale at a flow rate below that of nebuliser output and therefore tend to "size correct" their dose.<sup>17</sup> Pulse rate increased significantly after inhalation of salbutamol; the increase was maintained for 10 minutes and was significantly greater than the change in pulse rate after saline, which suggested that the infants had inhaled a pharmacologically active amount of the drug.

A proportion of infants whom we studied had low baseline  $\dot{V}_{\max}\text{FRC}$  (below 70% predicted for length). This may reflect the methodology of the study from which the predicted values were derived in which the maximum  $\dot{V}_{\max}\text{FRC}$  was used.<sup>19</sup> We calculated the mean  $\dot{V}_{\max}\text{FRC}$  from five curves which might

be expected to produce lower percentage predicted values. The distribution of baseline  $\dot{V}_{\max}\text{FRC}$  may, however, simply reflect the heterogeneity of the measurement in an unselected population of asymptomatic infants. A similar wide distribution of percentage predicted  $\dot{V}_{\max}\text{FRC}$ , independent of family history of asthma and parental smoking habit, has been shown previously in a large, randomly selected population of infants.<sup>20</sup> In the present study the proportions of infants with low baseline  $\dot{V}_{\max}\text{FRC}$  were similar in the two study groups and low baseline  $\dot{V}_{\max}\text{FRC}$ , although associated with low  $\text{PC}_{40}$ , was not related to the response to salbutamol. Low  $\dot{V}_{\max}\text{FRC}$  in infancy may be associated with a greater risk of subsequent wheezing illness in children<sup>21</sup> and may indicate those infants who will develop asthma. It seems unlikely, however, that our study was biased towards selecting infants at high risk of asthma or that the large number who appeared to respond to salbutamol after histamine induced bronchoconstriction were all at risk.

We used a linear model to calculate two indices of recovery after bronchoconstriction. Although the data do not necessarily recover in a true linear fashion (fig 3), the model explains a significant proportion of the variance of  $\dot{V}_{\max}\text{FRC}$  with time in every case and has the advantage of providing comparable results for all subjects. In our view the data are acceptably linear for this purpose and other methods such as extrapolation of the final two measurements of  $\dot{V}_{\max}\text{FRC}$  before recovery are likely to be no more accurate. The times to recovery of infants who recovered baseline  $\dot{V}_{\max}\text{FRC}$  before waking were similar to those predicted from the model, although there was no significant difference between the two groups.

A higher proportion of infants experienced a further fall in  $\dot{V}_{\max}\text{FRC}$  after nebulisation of saline. If the regressions were to include baseline  $\dot{V}_{\max}\text{FRC}$  in these cases, it is likely that the slopes of recovery would be lower and  $T_r$  longer, thus exaggerating differences from the salbutamol treated group. Regressions were therefore made from minimum  $\dot{V}_{\max}\text{FRC}$  after nebulisation, following which the linear model of recovery appeared to hold true.

We observed a small decrease in  $\text{SaO}_2$  after nebulisation of both saline and salbutamol. Prendiville and colleagues<sup>6</sup> reported a decrease in transcutaneous  $\text{PaO}_2$  associated with decreased  $\dot{V}_{\max}\text{FRC}$  following salbutamol in recurrently wheezy infants and suggested that this represented increased ventilation perfusion mismatch in these infants. Although no significant differences in  $\text{SaO}_2$  reduction were found between groups receiving salbutamol or saline in the present study of healthy infants, those given salbutamol tended to have a greater and more prolonged fall in  $\text{SaO}_2$ .

It seems likely that the mechanism of airways obstruction after histamine challenge differs from that which occurs in the natural disease state in infants with recurrent wheeze. Prendiville and colleagues did not find a

significant improvement in  $\dot{V}_{\text{maxFRC}}$  after nebulised salbutamol in recurrently wheezy infants.<sup>6</sup> This may be explained partly by differences in  $\beta$  receptor density which has been shown in animal experiments to be reduced in bronchial smooth muscle in recurrently wheezy animals.<sup>22,23</sup> The relatively fixed obstruction observed in recurrently wheezy infants<sup>6</sup> may also lead to mechanical differences in the airways compared with those which follow histamine challenge. Airway inflammation with widespread peripheral narrowing may contribute to increased dynamic compression during forced expiration<sup>24</sup> and reduced maximal expiratory flow. Stimulation of  $\beta$  adrenergic receptors may lead to a reduction in airway tone which could result in greater flow limitation than any increase in airway calibre resulting from smooth muscle relaxation. The more rapid improvement in maximal expiratory flow in normal infants receiving salbutamol than in those receiving saline could be explained by the advantages of smooth muscle relaxation and reduced mucosal oedema. Any reduction in airway tone would be less disadvantageous in this population with little or no fixed peripheral airway narrowing and therefore less likely to have widespread dynamic compression.

The effect of histamine on the airways is mediated by several different pathways; direct receptor mediated actions on airway smooth muscle, and stimulation of central and local neural reflexes.<sup>11</sup> The time course of bronchoconstriction after histamine has been studied in adults<sup>13</sup> in whom the mean rate of recovery was 2.43% of baseline lung resistance/minute with a mean recovery time of 25.5 minutes. This compares with a recovery rate of 3.3% baseline  $\dot{V}_{\text{maxFRC}}$ /minute and a median time to recovery of 19.0 minutes in the control population in the present study (14.0 minutes after saline nebulisation plus 5.0 minutes after previous concentration of histamine). The similarities in time courses are likely to correspond to similar pathophysiological changes in the lungs after histamine challenge in infants and adults. Salbutamol relieves airway obstruction in adults with asthma, however, but has little or no effect on lung function in infants with bronchiolitis or recurrent wheeze.<sup>1,4</sup> It seems likely, therefore, that airway obstruction in these conditions differs from that occurring in adult asthma or after histamine challenge. Attention has recently focused on the role of microvascular leakage leading to airway wall oedema in the aetiology of asthma.<sup>25</sup> The smaller airways of infants are likely to be more readily obstructed by airway wall oedema<sup>26</sup> and this may be a more important mechanism than smooth muscle constriction in causing airway obstruction in this age group. Although  $\beta$  adrenergic agonists may have an inhibitory effect on microvascular permeability,<sup>25</sup> salbutamol has been shown to have no effect on plasma leakage induced by platelet aggregating factor in animals.<sup>27</sup> The probable differences in the mechanisms of acute mucosal changes in the airways after histamine challenge and the

chronic mucosal changes associated with recurrent wheeze in infancy may therefore give rise to differences in pharmacological response even though the initial degree of airway obstruction is similar.

Our data suggest that functional  $\beta$  adrenergic receptors are present in the lungs of normal, healthy infants and that stimulation of these receptors with the  $\beta_2$  adrenergic agonist salbutamol leads to more rapid recovery from histamine induced bronchoconstriction than saline controls. The histamine challenge test is a useful tool for the study of bronchial responsiveness in adults and children, but the results of this study suggest that the pathophysiology of histamine induced airway obstruction in infants is likely to be different from the airway obstruction which occurs with acute bronchiolitis or recurrent wheeze in this age group.

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## Adventitia

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### Clinical chest radiology

Is the chest radiograph a special investigation or is it part of the clinical examination of the patient? It is my belief that it is the latter. As medical students we were taught that one should examine the patient first, make a provisional diagnosis, and then request the appropriate investigations, and for the most part, in the interest of financial and radiation economy, this must still be a guiding principle of diagnosis. In the practice of respiratory medicine, however, the plain chest radiograph is frequently the lynchpin of diagnosis, whether it be normal or abnormal. It was with some surprise that, as a thoracic house surgeon at Guy's Hospital, my "chief", Lord Brock, taught me to look at the chest radiograph first, then take the history and examine the patient, and finally go back to look at the radiograph. This fusion of the clinical approach and a basic investigation is an essential part of respiratory medicine. The place for the chest radiograph is in the ward at the bedside and not, as is the practice in many countries, including the USA, in the x ray department on the other side of the hospital.

There are pitfalls to this approach for we may be too greatly influenced by our preconceived ideas. As a house physician at the Brompton Hospital in the 1950s it was one of our duties to sit in a small cubicle in the outpatients department to take and record the clinical histories of the new patients attending the clinic. On one such day I had taken the histories of a Mr Brown, who was suffering from chronic bronchitis, and from a Mr Smith, who had for many years had

pulmonary tuberculosis treated by a right sided artificial pneumothorax which had become infected. Mr Brown's chest radiograph was normal but that of Mr Smith showed a shrunken right lung with thickened and heavily calcified overlying pleura. When I had completed all the history taking I joined the consultant to whom I was attached for teaching. This eminent physician was examining Mr Brown's chest but, unfortunately, the nurse had inadvertently put Mr Smith's radiograph on the viewing box. I entered the room just as the consultant was saying "Yes, there is definite dullness at the right base with diminished air entry, and I detect reduction in movement of the whole of the right side."

Interpretation of the radiograph can also be overinfluenced by the clinical findings. Dullness and loss of air entry is not always the result of fluid, and I recall several patients who, after several attempted aspirations, have been found to have large diaphragmatic hernias and not fluid. Immediate provision of the film on the ward or in the outpatient clinic can cause some logistic problems for radiologists in providing a reporting service. Perhaps we should have peripatetic radiologists reporting the films on the wards, a practice which would enable better contact with clinical colleagues. As an example of this, for the past two years a radiologist has visited the intensive care unit at the Royal Brompton Hospital daily to review with the clinicians all the radiographs which are taken immediately to the unit before reporting.

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