

# Nebulised salbutamol does have a protective effect on airways in children under 1 year old

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**SUMMARY** Ten infants under the age of 1 year each of whom gave a history of recurrent wheezing attacks were studied with a total body plethysmograph. All the infants were free of wheeze when studied and were sedated with chloral hydrate. All 10 showed a significant deterioration in lung function when given nebulised water for two minutes with an increase in airways resistance and a decrease in specific conductance at one and five minutes after nebulisation compared with baseline readings. Measurements returned to baseline values within 15 minutes. When the same amount of nebulised water was given 20 minutes after nebulised salbutamol, however, there was no significant deterioration in lung function at one and five minutes after administration of nebulised water.

We conclude that the airways were protected against the bronchoconstricting effect of nebulised water by the  $\beta_2$  adrenoreceptor stimulant salbutamol.

Many doctors believe that  $\beta_2$  adrenoreceptor stimulants have little or no effect on the airways of infants under the age of 1 year. These children do, however, have  $\beta_2$  adrenoreceptors<sup>1</sup> and smooth muscle<sup>2</sup> in their airways and theoretically should respond to  $\beta_2$  adrenergic stimulants. Nebulised water has a bronchoconstricting effect on asthmatic children and adults,<sup>3-7</sup> and we have found that it also causes bronchoconstriction in wheezy infants (unpublished data).

The present study was designed to find out if nebulised salbutamol protects the airways of wheezy infants. Nebulised water was used as a bronchoconstricting challenge.

resistance were measured with total body plethysmography.<sup>8-11</sup> The total body plethysmograph had a capacity of 260 litres, and a servo controlled heating system maintained the face mask, shutter system, and rebreathing bag at 36°C. Thoracic gas volume was measured at the end of inspiration, and the tidal volume was subtracted before calculation. The children were nursed supine and firm latex masks applied to their faces. The dead space of each mask was 88 ml. There was a bias flow of air at 5 l/minute to the face mask. Signals were relayed to the axis of a cathode ray oscilloscope, all readings were made by the same observer,

## Patients and methods

Patients studied were under 1 year old and attending this hospital for routine assessment. All had had more than two wheezy episodes in the preceding months. Table 1 shows their age, sex, and history of bronchiolitis. At the time of the study all were clinically well and at least four months had elapsed since their bronchiolitic illnesses. Each study was done in the outpatient clinic, all patients were awake, and allowed home within three hours of arrival.

The infants were sedated with chloral hydrate (120 mg/kg), and thoracic gas volume and airways

Table 1 Details of 10 infants studied

Patient No	Age (months)	Weight (kg)	Sex	History of bronchiolitis
1	11	10.5	Male	Yes
2	10	9.1	Male	No
3	9	8.3	Female	Yes
4	9	8.0	Male	No
5	9	10.2	Male	Yes
6	10	8.9	Female	Yes
7	6	8.3	Male	Yes
8	9	8.2	Male	Yes
9	10	11.0	Male	Yes
10	11	11.2	Female	No

and calculations were made by standard techniques. Multiple breaths were analysed in each case. Baseline measurements of thoracic gas volume and airways resistance were calculated.

The infants were then given water nebulised ultrasonically at a temperature of 21°C from an Intersurgical Variosonic II nebuliser at setting number 3 through the face mask for two minutes with a flow rate of 5 l/minute. Thoracic gas volume and airways resistance were measured at regular intervals until they were stable (which was defined as no change in readings over a five minute period). The

dense mist occasionally escaped from the space between mask and face owing to an inadequate seal during the first few seconds of nebulisation. The mask was adjusted accordingly and the study restarted with an adequate seal. The infant was then given salbutamol (0.5 ml salbutamol respirator solution in 1.5 ml normal saline) through a Cirrus nebuliser chamber at a flow rate of 6 l/minute for five minutes. Thoracic gas volume and airways resistance were measured at regular intervals until they had returned to baseline measurements. Nebulised water was then given through the ultrasonic

Table 2 *Baseline readings in airways resistance and specific conductance, and changes after two minute challenge with nebulised water in 10 infants*

Patient No	Baseline readings			Time after challenge (minutes)					
	Thoracic gas volume ml/kg	Airways resistance	Specific conductance	1		5		10	
				Airways resistance	Specific conductance	Airway resistance	Specific conductance	Airway resistance	Specific conductance
1	17	17.2	0.31	25.8	0.21	33.1	0.16	17.2	0.31
2	31	23	0.15	27.6	0.14	32.2	0.12	23.7	0.16
3	25	21	0.22	21.3	0.23	30.9	0.17	25.6	0.20
4	28	21	0.21	22.0	0.20	27.4	0.17	21.0	0.21
5	32	22	0.15	27.3	0.10	28.8	0.10	21.8	0.14
6	33	21.5	0.15	27.6	0.12	33.7	0.10	25.0	0.13
7	39	15.5	0.22	20.3	0.17	25.3	0.14	20.0	0.17
8	65	17	0.12	20.3	0.10	21.4	0.10	17.3	0.12
9	38	21	0.11	24.8	0.09	27.4	0.08	20.9	0.11
10	17	21.0	0.25	32.0	0.15	40.7	0.12	21.0	0.25
Mean (SD)	32.5 (12)	20.1 (2.5)	0.19 (0.05)	25.0 (3.8)	0.15 (0.05)	30.1 (5.0)	0.12 (0.03)	21.3 (26.0)	0.18 (0.05)

Airways resistance is reported as cm H<sub>2</sub>O/l/second.

Specific conductance is reported as cm H<sub>2</sub>O<sup>-1</sup>s<sup>-1</sup>.

Table 3 *Baseline readings in airways resistance and specific conductance, and changes after two minute rechallenge given 20 minutes after nebulised salbutamol in 10 infants*

Patient No	Baseline readings			Time after rechallenge (minutes)			
	Thoracic gas volume ml/kg	Airways resistance	Specific conductance	1		5	
				Airways resistance	Specific conductance	Airways resistance	Specific conductance
1	17	17.2	0.31	17.2	0.37	17.1	0.37
2	29	23.7	0.16	23.0	0.16	23.0	0.16
3	23	21.3	0.23	23.8	0.22	23.8	0.22
4	28	21.0	0.21	20.5	0.28	20.4	0.22
5	32	21.8	0.14	14.2	0.22	14.1	0.22
6	32	25.0	0.13	21.0	0.16	21.0	0.16
7	39	15.4	0.22	15.5	0.23	15.4	0.22
8	61	17.3	0.12	16.8	0.12	16.5	0.12
9	38	20.9	0.11	20.1	0.11	20.2	0.13
10	17	21.0	0.25	20.5	0.26	20.5	0.26
Mean (SD)	31.5 (12)	20.4 (2.5)	0.18 (0.05)	19.0 (3.4)	0.2 (0.05)	19.2 (3.3)	0.19 (0.04)

Airways resistance is reported as cm H<sub>2</sub>O/l/second.

Specific conductance is reported as cm H<sub>2</sub>O<sup>-1</sup>s<sup>-1</sup>.

nebuliser for two minutes as described previously. Thoracic gas volume and airways resistance were measured until they were stable. Each infant was monitored continuously with an oxygen saturation machine and an electrocardiogram. Specific conductance was calculated from the readings taken. A paired *t* test was used to analyse the results.

The study was approved by the Nottingham University ethics committee. Informed parental consent was obtained for each of the studies.

**Results**

Baseline measurements of thoracic gas volume,

airways resistance, and specific conductance are shown in table 2 together with the changes in airways resistance and specific conductance after the administration of nebulised water. All infants showed significant increases in airways resistance one minute after the water had been given ( $p < 0.01$ ) and five minutes after it had been given ( $p < 0.001$ ); these had returned to baseline values after 10 minutes (fig 1). There were also significant decreases in specific conductance one minute after the water had been given ( $p < 0.01$ ); and five minutes after it had been given ( $p < 0.001$ ); these had returned to baseline values after 10 minutes (fig 2).

When rechallenged with a similar amount of

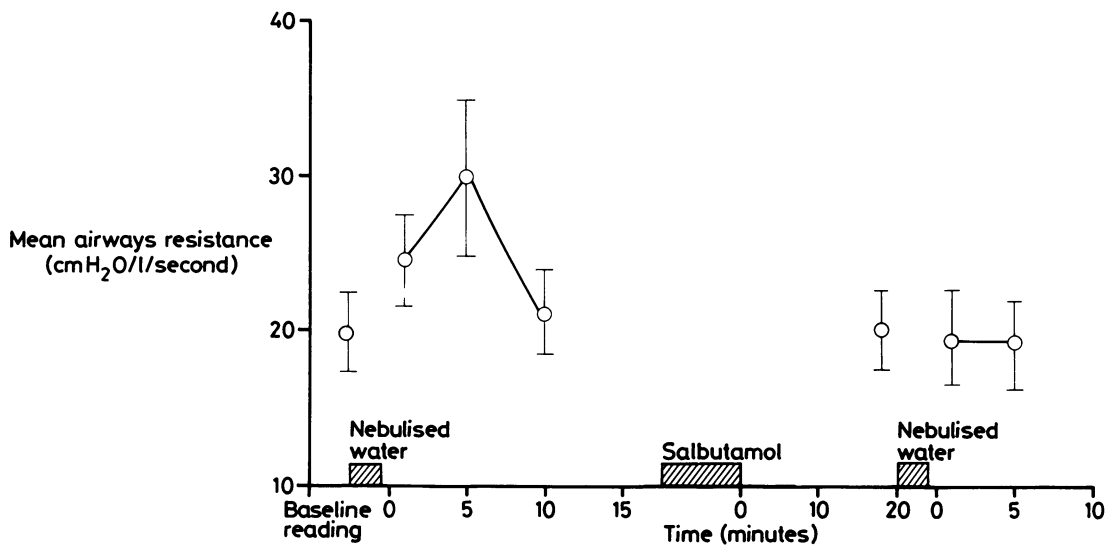


Fig 1 Mean (SD) airways resistance of 10 infants with history of wheezing showing changes after the administration of nebulised water and salbutamol.

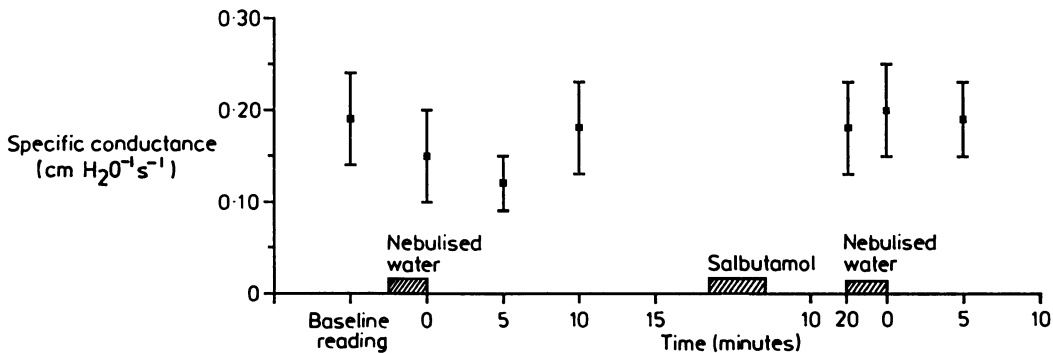


Fig 2 Mean (SD) specific conductance of 10 infants with history of wheezing showing changes after the administration of nebulised water and salbutamol.

nebulised water 20 minutes after nebulised salbutamol had been given however, there were no significant changes in airways resistance ( $p > 0.5$ ) or specific conductance ( $p > 0.5$ ) (fig 1). There were no significant changes in thoracic gas volume after any of the challenges.

There were no abnormalities in the electrocardiographic traces, and oxygen saturation did not fall below 84% in any of the patients during the study.

## Discussion

Subjective clinical observations have suggested that nebulised bronchodilators are helpful in treating some wheezy infants. There is little evidence from clinical trials, however, to recommend treatment of such infants with bronchodilators.<sup>12-23</sup>

Nebulised water produces bronchoconstriction in asthmatic subjects.<sup>3-7</sup> In the 10 infants we studied all of whom had history of wheezing, we confirmed that nebulised water in the regimen we gave caused bronchoconstriction. The measurements showing deterioration in lung function correlated well with the patients' clinical signs during the study. When rechallenged with the same amount of nebulised water 20 minutes after receiving nebulised salbutamol, however, there was no evidence of bronchoconstriction; the salbutamol had protected the airways.

Prendiville *et al* studied five infants and found that salbutamol had a similar protective effect when histamine was used as the challenge.<sup>1</sup> The results of this and the present study show that  $\beta_2$  adrenoreceptors do exist in infants.

The amount of nebulised water given is derived from the results of 20 studies we performed before this trial (unpublished data). We found that repeated stimuli with nebulised water also produced bronchoconstriction. This suggested that the lack of response to the administration of nebulised water after being given salbutamol was not because there was a refractory period after the original bronchoconstricting challenge. Hypo-osmolar solutions cause the release of histamine from mast cells<sup>24</sup> and we presume that this may be the cause of the bronchoconstriction seen in our infants, the histamine acting either directly on the smooth muscle or by reflex action on the vagus nerve.

During the studies some of the infants seemed clinically worse immediately after the administration of salbutamol. After completing the study we looked at a further 17 infants all of whom gave a history of wheezing.<sup>25</sup> In 13 of the 17 infants there was a rise in airways resistance and a fall in specific conductance when they were challenged with nebulised water. They also showed significant increases in airways resistance and decreases in specific

conductance after nebulised salbutamol had been given. We feel this may have been partly caused by the acid and preservatives in the solution. Until we have found out the specific cause of the paradoxical deterioration and how to eliminate it we cannot recommend the use of nebulised salbutamol at home for infants under 1 year old.

The validity of thoracic gas volume measurements in wheezy infants has recently been questioned by Godfrey *et al*.<sup>26</sup> They found low thoracic gas volume measurements in wheezy infants who had had bronchiolitis that were difficult to explain. In some of our patients the measurements were surprisingly low, and they changed remarkably little during the challenge procedures.

We used the plethysmograph to look for changes in the airway function of our infants and we feel that this is a valid use of it.

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