Lung Function Response to Bronchodilator Nebulization via Hood in Wheezy Infants: A Pilot Study

Ephraim Bar-Yishay PhD[1]*, Avraham Avital MD[1], Chaim Springer MD[1] and Israel Amirav MD[2]

[1]Institute of Pulmonology, Hadassah University Hospital and Hebrew University-Hadassah Medical School, Jerusalem, Israel
[2]Department of Pediatrics, Ziv Medical Center, Safed, Israel

ABSTRACT: **Background:** In infants, small volume nebulizers with a face mask are commonly used to facilitate aerosol therapy. However, infants may be disturbed by mask application, causing poor mask-to-face seal and thus reducing the dose delivered.

Objectives: To compare lung function response to bronchodilator nebulization via two delivery devices: hood versus mask.

Methods: We studied 26 recurrently wheezy infants aged 45.8 weeks (95% confidence interval 39.6–52.0). Inhalations of 0.30 mg/kg salbutamol were administered in two alliqots 30 minutes apart using mask and hood in alternating order (M+H or H+M). Response to inhalations was measured by maximal expiratory flows at functional residual capacity (V'maxFRC) at 5 minute intervals after each dose, and area under the V'maxFRC curve (AUC) was documented.

Results: A small but significant response to salbutamol was observed following the second inhalation with V'maxFRC, improving by 31.7% (7.2–56.2, $P < 0.02$) and AUC by 425 %•min (-154, 1004; $P < 0.02$). The improvement following salbutamol was similar by both delivery modalities but with a small but significantly better response when H was used after M ($P < 0.01$).

Conclusions: Nebulized salbutamol induced a variable but positive response in wheezy infants. Salbutamol via hood was as effective as conventional face mask delivery. Since it is simple and patient-friendly, it could replace the face mask method particularly with uncooperative infants.

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KEY WORDS: wheezy infants, partial forced expiratory flow-volume maneuver, maximal expiratory flow at functional residual capacity, salbutamol inhalation

Aerosol medications have long been used in infants for the treatment of various respiratory disorders [1-3]. Most devices used for administering aerosol medications to infants (e.g., nebulizers) are derived from those developed initially for adults and older children, and most were modified for use in infants simply by adding a small face mask covering the mouth and nose. For optimal therapy the edge of the mask must fit tightly on the infant's face. However, achieving a good mask-to-face seal may be difficult in many infants due to squirming and crying [4]. It has been shown that even a 1 cm gap between the mask and the face reduces the dose delivered by 50% [5]. Since nebulizer treatments can take up to 15 minutes, infants may become impatient and agitated, thus reducing the efficiency of drug delivery to their lungs [6,7].

There is clearly a need to develop more acceptable and patient-friendly interfaces for improving aerosol delivery to infants [3]. We previously demonstrated scintigraphically that inhalation via hood achieved a comparable lung deposition of salbutamol to that of conventional face mask [8]. With this mode of delivery, the hood consisting of a plexyglass cylinder 30 cm in diameter and 25 cm high is placed over the supine infant's head [Figure 1]. The opening around the neck is fitted loosely to allow fresh air to move freely in and out. This type of delivery arrangement had been used in the past for cold-mist delivery; however, it fell out of favor following reports of hypothermia. In the study of Amirav et al. [8] infants were found to tolerate the hood better than the mask, and there was a significant positive

Figure 1. Bronchodilator nebulization via the transparent hood

*** Present address: Head, Pulmonary Function Laboratory, Schneider Children's Medical Center of Israel, Petah Tikva**

V'maxFRC = maximal expiratory flow at functional residual capacity
AUC = area under the V'maxFRC curve

correlation between poor acceptance and upper airways and stomach deposition for both treatment modalities. In addition, parents unequivocally preferred the hood treatment.

The present study was designed to compare bronchodilator response to nebulized salbutamol between the two modalities of administration by objective infant lung function tests. We hypothesized that the hood mode of delivery would result in a more favorable bronchodilator response.

PATIENTS AND METHODS

Forty-one recurrently wheezy infants were recruited to the study using a convenience sample of patients attending outpatient pediatric pulmonology clinics. Inclusion criteria were: asthma clinically diagnosed by pediatric pulmonologists based on commonly used guidelines from the Global Initiative for Asthma; age 0–1 year, and failure to achieve control despite regular anti-asthma therapy (which included regular inhaled corticosteroids and salbutamol inhalations during exacerbations in all cases). Exclusion criteria were any respiratory exacerbation in the 2 weeks prior to testing, and any other concomitant cardiopulmonary disease.

The testing procedure was explained in detail to the parent/s, oral consent was obtained in every case and the parents were encouraged to be present during the study if they so wished. Based on the infants' clinical history of uncontrolled wheezing, their routine clinical investigation included ILFTs which in our institution does not require (formal) institutional review board approval as they are considered clinical diagnostic tests. Both mask and hood modalities are regularly used in our institution to deliver bronchodilators.

The infants were studied while sleeping in the supine position, 15–45 minutes after 70–100 mg/kg of chloral hydrate sedation. Each infant inhaled 0.15 mg/kg nebulized salbutamol in 1.5 ml normal saline twice for a total of 0.3 mg/kg. The second inhalation was always given 30 minutes after the first one. Response to inhalations was measured by sequentially recording maximal flows at FRC (V'maxFRC) at 5 minute intervals up to 30 minutes post-inhalation. The protocol is depicted in Figure 2A. Infants were divided into two groups, in randomized fashion. In one, salbutamol was first delivered by a hand-held transparent face mask (Rendell-Baker, Soucek mask #2, UK) and then by hood (H): M+H arm. In the second group, the order was reversed: H+M arm.

The thoraco-abdominal squeeze technique was used to obtain partial forced expiratory flow volume curves, from which V'maxFRC had been measured. The method has been fully described elsewhere [9-11] and a detailed description is given in the online supplement. Only a brief summary is provided here. Briefly, the infant lies within a double walled squeeze jacket that covers his thorax and abdomen. At the end of inspiration, the jacket is rapidly inflated to produce forced expiration. During baseline (bl) determination, jacket compression pressure is increased until no further increase in V'maxFRC is observed. The maneuver is repeated at the optimal Pj and the highest V'maxFRC value is determined and subsequently used during follow-up [V'maxFRC(bl)]. The procedure to determine V'maxFRC(bl) lasts 10–15 minutes after which the first salbutamol inhalation begins. Inflated pressures are kept constant at a mean value of 33–35 cmH_2O (range 27–40), and transmitted pressure to the chest wall, pleural pressure/Pj, measures 43–52%. Ten minutes after the end of each inhalation, PEFV maneuvers are obtained and thereafter at 5 minute intervals up to 30 minutes after each inhalation [Figure 2A]. At each time interval, the best V'maxFRC of two or three attempts is recorded [10] and ΔV'maxFRC is calculated as:

$$\Delta V'maxFRC\ (\%) = \frac{V'maxFRC - V'maxFRC\ (bl)}{V'maxFRC\ (bl)} \times 100$$

The maximal response to each inhalation was represented by the highest ΔV'maxFRC value obtained. In order to determine the effective time course of response, and to sidestep artificially high values thought to be clinically meaningless,

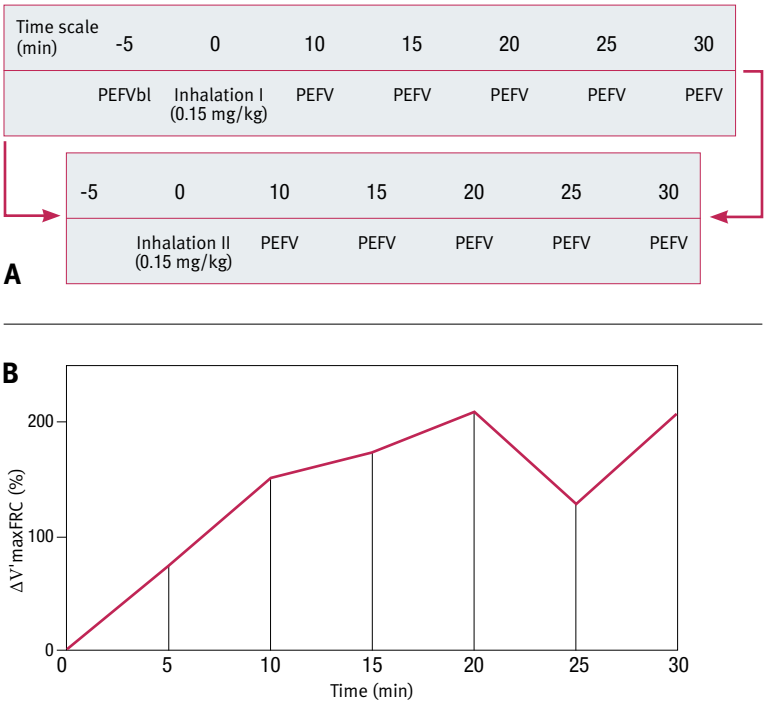


Figure 2. [A] Schematic representation of the protocol. Lung function tests (partial expiratory flow-volume maneuvers, PEFV) were performed at these times: **[B]** An example (infant # 15) of the algorithm used to calculate the area under the curve of ΔV'maxFRC (AUC)

ILFT = infant lung function test
Pj = jacket compression pressure
PEFV = partial forced expiratory flow-volume maneuver

the area under the curve of ΔV'maxFRC response was also calculated, as depicted in Figure 2B and fully described in the online supplement.

STATISTICAL ANALYSIS

A priori calculation of sample size was performed and n=25 was judged sufficient to detect a 25% change in V'maxFRC with a probability of 5% and power of 80% to detect a significant difference between treatments, assuming a standard deviation of the population of 20% in V'maxFRC (see also online supplement). A single-factor ANOVA was performed when comparing baseline values to values following the two inhalations. In addition, linear regression, Pearson correlation coefficient, and paired and unpaired *t*-tests were used to compare responses (ΔV'maxFRC) to the different inhalations and the order in which they were administered. *P* values < 0.05 were considered significant.

RESULTS

Of the 41 infants who were recruited to the study, response to the first inhalation was obtained in 36 infants, and the complete protocol was accomplished in 26. Mean (95% confidence inerval) age of these 26 infants was 46 weeks (40, 52), weight 9.3 kg (8.6, 10.0), and length 74 cm (72, 76). Age, weight and length of the starting group were not different to that of the 26 who completed the study.

Results (mean ± 95% CI values) at baseline and after each inhalation are summarized in Table 1. Baseline V'maxFRC(bl) values were similar in the two groups, and the response to either the first or second inhalation did not depend on age or baseline V'maxFRC(bl). Maximal responses were reached 22–24 minutes post-inhalations. No changes were seen following either inhalation in terms of quiet breathing variables or O_2 saturation. As expected, heart rate increased significantly from baseline values.

The first inhalation of half the total dose (0.15 mg/kg salbutamol) did not result in a significant improvement in V'maxFRC or AUC(1) [Figure 3]. The second inhalation, which brought the total delivered dose to 0.3 mg/ml salbutamol, produced a significant improvement in ΔV'maxFRC over baseline ($P = 0.01$), but not over the first inhalation. This improvement was also noted when represented by AUC ($P < 0.02$), and was similar whether AUC was presented in absolute values (liters) or normalized to percent change from baseline values (%•min).

The mode of delivery seemed not to affect the outcome of the first inhalation, with ΔV'maxFRC being greater (22.9%; -13.6, 59.4) over baseline following mask inhalation (n=16), but due to the large variability in response it was not significantly different to ΔV'maxFRC after hood inhalation (2.4%; -7.4, 12.2; $P = 0.4$). After the second inhalation, however, the order in which nebulized salbutamol was given seemed to

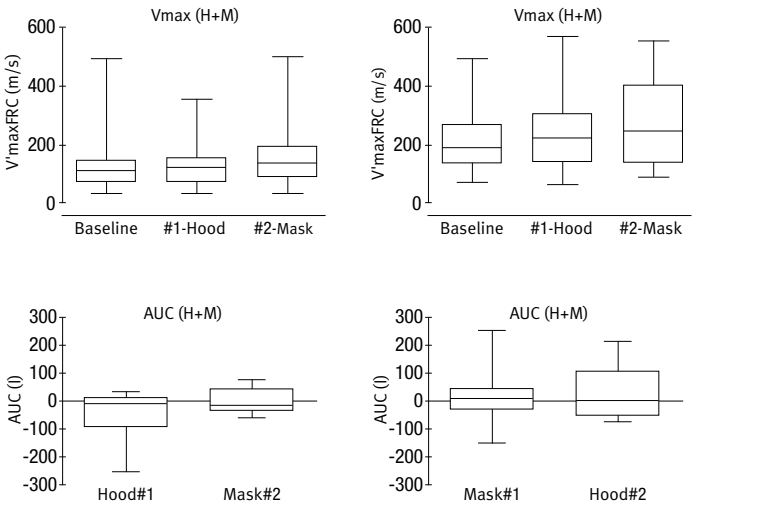
Table 1. Mean ± 95% CI values in 26 infants who completed both inhalation protocols

	Baseline	1st inhalation	2nd inhalation	*P*
ΔV'maxFRC (% predicted)	57.6 44.3, 70.8	62.1 47.4, 76.8	73.1 54.4, 91..8	NS
ΔV'maxFRC (%)	___	15.0 -9.0, 39.0	31.7 7.2, 56.2	‹ 0.02
ΔV'maxFRC (AUC-%•min)	___	24.3 -630.7, 679.3	425.0 -153.9, 1004.0	‹ 0.02
Tidal volume (ml/kg)	9.3 8.6, 10.0	9.5 8.8, 10.2	9.3 8.6, 10.1	NS
Respiratory rate (1/min)	34.5 31.7, 37.3	33.7 30.6, 36.8	34.6 31.7, 37.6	NS
Minute ventilation (ml/min/kg)	309.1 288.1, 330.2	315.0 280.3 349.6	328.3 287.3, 369.4	NS
SaO_2 (%)	95.0 94., 95.9	95.0 93.8, 96.2	95.3 94.0, 96.6	NS
Heart rate (1/min)	120.0 116.4, 123.5	127.5 123.2, 131.9	133.6 128.4, 138.7	‹ 0.005
Optimal inflation pressure, Pj (cmH_2O)	34.0 28.7, 39.3	34.7 29.2, 40.1	32.6 27.3, 37.9	NS
Time to maximal response (min)	___	22.3 19.5, 25.1	24.0 21.7, 26.4	NS
Ppl/Pj (%)	43.2 37.8, 39.3	49.4 40.6, 58.1	51.6 45.5, 57.7	NS

$$\Delta V'maxFRC\ (\%) = \frac{V'maxFRC\text{-}V'maxFRC\ (bl)}{V'maxFRC\ (bl)} \times 100$$

AUC (%·min) = area under the ΔV'maxFRC (%) curve over 30 minutes following inhalation
95%CI = 95% confidence interval
P value by single factor ANOVA
Ppl = pleural pressure

Figure 3. Median (95%CI) values of responses are presented both in terms of maximal change in V'maxFRC [ΔV'maxFRC (%), top panel], and as the area under the curve of V'maxFRC [AUC (%•min), bottom panel]. The left hand panels show the results of 16 infants in the M+H arm where inhalation via a facemask preceded that with the hood. The right hand panels show the results of the 10 infants in the H+M arm.



have produced a small but consistent difference. A significant improvement in ΔV'maxFRC over baseline was seen with the M+H protocol (37.7%; -2.9, 75.2; $P = 0.01$), while changes seen with the H+M protocol did not reach significance (18.8%; -3.5, 41.1; $P = 0.2$). Due to large inter-subject variability, ANOVA was not able to show if one of the regimens (M+H or H+M) was superior to the other when measured by ΔV'maxFRC. However, AUC(2) for the M+H protocol (711.7 %•min; -803.2, 933.6) tended to be slightly greater than with the H+M protocol (-336.7 %•min; -728.2, 54.9; $P < 0.05$).

In the 36 infants, in whom only a response to the first inhalation was obtained, neither baseline V'maxFRC(bl) value (70.0% predicted; 57.9, 82.0) nor the response to this inhalation (ΔV'maxFRC = 11.8%; -5.1, 28.7, AUC(1) = –55.1%•min; -476.5, 366.3) was significantly different from that found for the 26 infants who completed both parts of the study.

DISCUSSION

The results of this pilot study suggest that delivery of nebulized salbutamol in wheezy infants via hood (H) may be as effective as the conventional mode of treatment using a nebulizer with a face mask (M). The use of ILFT in this study complements previous studies that compared the hood to face mask according to clinical parameters [8,13,14].

Nebulizers with face masks are commonly used to administer aerosol medications to infants [14,15]. However, their use is associated with many difficulties, mostly related to poor acceptance by the infants which greatly decreases the efficiency and clinical efficacy of the treatment [2,3]. It is a common complaint of the parents, who find it very difficult to keep a mask tightly fitted to their infant's face for more than a few seconds at a time. We and others have reported the likelihood of poor aerosol delivery to infants using face masks, primarily due to an inadequate seal [4,17]. Another problem of the resisting child is that of persistent crying and screaming during treatment. In this situation, it has been shown that only a small amount of aerosol medication is deposited in the lungs [6,7]. Applying the mask by force, as some parents do, may make subsequent aerosol treatments even more difficult. It is noted that we were expecting a very high attrition rate because of the demanding protocol and the expectation that many infants will not remain asleep throughout the study. Indeed, of the 41 infants who were recruited to the study, 36 completed the follow-up of the first inhalation but only 26 completed the full protocol. Of these 10 fallouts, 8 were given the mask inhalation after the hood whereas in only 2 of the 10 was the mask applied first ($P = 0.025$ by 2 x 2 contingency table).

In contrast to the face mask, the hood facilitates efficient aerosol delivery without facial contact. Little cooperation on the part of the infant is required, aerosol delivery is entirely passive, parents are relaxed, and the baby comfortably inhales the medication while breathing tidally. Since the hood is not in direct contact with the baby's face and the clear plastic allows the infant to see the caregiver at all times, (s)he is much less likely to become afraid and even prolonged aerosol therapy can be readily administered. A study that compared the behavior of infants who underwent these two aerosol therapy interfaces clearly demonstrated the advantages of the hood [8]. Better overall adherence with the hood was achieved in all the infants and caregivers indicated a significant preference for the hood treatments, and lung deposition of the two methods was comparable. The present study supports the earlier finding by measuring a physiological endpoint to evaluate the response to either modality. While eye deposition from the hood may be of concern, a recent study found no difference in eye deposition between hood and face-mask delivery [18].

It is possible that the difference between delivery modalities is even greater under "real-life" conditions in awake infants. It is reasonable to assume that in real-life situations, when aerosol therapy is given to awake infants it is not easy to ensure a good seal around the mask [5]. Under such circumstances lung function response to the mask may be diminished [2]. In the present study, the infants lay supine and were sedated in both modalities. Another practical problem in applying the mask is that of choosing the right mask size since size does affect the delivered dose [18].

When designing the study we were considering the various options for best protocol. We chose not to study two groups of subjects with each group receiving a full dose of salbutamol by either mode of delivery, M or H. This approach would have required a much larger group size because of the known considerable intra-subject variability in response to bronchodilator therapy in wheezy infants. Alternatively, we could have studied the same number of infants but sedate each infant on two different occasions, once for each inhalation modality. We thought that neither of these options was justified ethically. Instead, we chose the stepwise approach that enabled us to perform a paired *t*-test comparison, which is the more sensitive test. We also employed the unpaired comparison between the groups to test for order effect.

The efficacy of bronchodilator therapy in this age group is controversial [20,21]. Our findings that the bronchodilator responses were significant, albeit small and variable, are within expectations. Yet, the purpose of the study was to compare two delivery methods, not to address the question of efficacy of bronchodilators. Hence, the clinical homogeneity of the study group is also less critical for two reasons: a) in clinical practice many wheezy infants (particularly those labeled as "asthmatic" during exacerbations) are treated with bronchodilators without objective evaluations, and b) each infant in the present study served as its own control.

Given the known large inter- and intra-subject variability in V'maxFRC, it may be argued that the reported broncho-

dilator response in the present study, as represented by the highest response of V'maxFRC, is pure chance. However, by calculating the area under the V'maxFRC response curve (AUC) we documented a consistent and significant improvement in V'maxFRC over 30 minute periods, presumably a better reflection of the clinical status of the infants.

Limitations of our crossover study should be acknowledged: It is possible that the maximum response to nebulized salbutamol was never reached as we followed the infants for only 30 minutes post-inhalation. In controlled clinical trials in adults and children it has been shown that while the onset of action by means of the forced expiratory volume in 1 second can be demonstrated at 5–15 minutes, the maximal response to nebulized bronchodilators may occur only 30–60 minutes post-inhalation [22,23]. We found that the maximal bronchodilator response was reached on average 22–25 minutes after inhalation [Table 1] and that in 95% of the cases it occurred in less than 30 minutes. A longer follow-up protocol may have been preferable, but we felt it might reduce the number of infants completing the study. Similarly, carryover effects were not believed to play a role for the reasons mentioned above. Moreover, they would have equally affected both protocols.

There seems to be no agreement on optimal dose schedules of nebulized bronchodilators. Since the guidelines advocate that the dose be based on weight, we chose to utilize this scheme. Specifically, we would like to cite the work of Collis and colleagues [24], who focused attention on the total amount of nebulized drug inhaled by young children. They showed that the quantity of nebulized aerosol that is inspired may be independent of the size of the patient after 6 months of age. In our study, 24 of the 26 infants were more than 6 months old. It is also possible that the bronchodilation observed was not so evident as we did not study the infants during respiratory exacerbation. In a recent study of slightly older toddlers and preschool children, we showed that the majority of such patients do not respond to bronchodilators [25]. Future larger studies comparing a full single-dose treatment by either hood or mask delivery is warranted.

In conclusion, using the ILFT, this study suggests that in wheezy infants the hood mode of nebulization may be as effective as the conventional nebulizer with a face mask. It is likely, given the difficulty in keeping a mask sealed to an infant's or toddler's face, that the benefits of the hood may be even greater under real-life conditions where the medication is delivered by face mask to an awake and often agitated infant.

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Corresponding author:
Dr. E. Bar-Yishay
Head, Pulmonary Function Laboratory, Schneider Children's Medical Center of Israel, P.O. Box 47, Petah Tikva 49202, Israel
Phone: (972-77) 534-4934
Fax: (972-77) 534-4935
email: ephraimby@gmail.com, ephraimb@cc.huji.ac.il

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ONLINE SUPPLEMENT

Sample size:

n=25 was judged sufficient to detect a 25% change in V'maxFRC with a probability of 5% and power of 80% to detect a significant difference between treatments, assuming of a standard deviation of the population of 20% in V'maxFRC. Starting group size of 40 allowed for a 33% attrition. Forty-one infants were recruited to the study but the data of 36 who completed the first part were analyzed. Three infants did not fall asleep despite a full dose of sedataion, and another two infants were excluded from analysis: one infant only slept intermitently and his results were judged unreliable, and another infant woke up before the end of the first inhalation. Another 10 infants woke up during the second part, leaving 26 infants (22 males) who completed the full protocol. Their mean (95% confidence inerval, CI) age was 46 weeks (40, 52), weight 9.3 kg (8.6,10.0), and length 74 cm (72, 76). Age, weight, and length of the starting group were not different than that of the 26 who completed the study.

The hood:

This is a plexyglass cylinder 30 cm in diameter and 25 cm high with a 22 mm inlet for nebulized gas, as previously described [8] and shown in Figure 1. The opening around the neck fitted only loosely to allow fresh air to move freely in and out. The salbutamol was nebulized using a Respigard-II system driven by pressurized airflow of 5 L/min with an output of 0.34 ml/min. The same nebulizer and tubing were used for each subject, and output dose, particle size and time for nebulization were similar.

The thoraco-abdominal squeeze technique used to obtain partial forced expiratory flow volume (PEFV):

The technique was used to obtain partial forced expiratory flow-volume curves from which V'maxFRC was determined. The method was described previously [9,11]. The infant lay within a double walled squeeze jacket that covered his thorax and abdomen. At the end of inspiration, the jacket was rapidly inflated to produce forced expiration. Flow was recorded by a heated pneumotachograph linear up to 160 L/min (#3700, Hans Rudolph Inc., Kansas City, USA) and was sampled by the computer at 100 Hz. The flow signal was digitally integrated and the resultant PEFV curve was presented to the operator for possible exclusion. End-expiratory level was determined from the three tidal breaths just prior to jacket inflation and was used as a reference point for the determination of V'maxFRC for each PEFV. During baseline (bl) determination, jacket compression pressure (Pj) was increased from 15 cmH_2O until no further increase in V'maxFRC was observed. The maneuver was repeated at the optimal Pj and the highest V'maxFRC value was determined and subsequently used during follow-ups, V'maxFRC(bl). Pressure transmitted from the jacket to the respiratory system was determined in each infant by a brief occlusion of the airway opening, as was suggested by Turner et al. [12], and estimating pleural pressure, Ppl, from airway opening pressure during this brief occlusion. The procedure to determine V'maxFRC(bl) lasted 10–15 min after which the first salbutomol inhalation began. We chose not to utilize the newer maximal forced expiratory flow volume (MEFV) maneuver [12], as the raised lung volume maneuver requires repeated inflations to total lung capacity, which would have undoubtedly increased our failure rate even further.

Calculating the area under the curve (AUC) of ΔV'maxFRC response:

In order to determine the effective time course of response, the area under the curve (AUC) from the set of ΔV'maxFRC values was calculated by employing the usual trapezoid method as depicted in Figure 1b. For example, a rise of 10% in V'maxFRC over 5 minutes yields an AUC value of 50%•min. In our case, a constant rise of 10% in ΔV'maxFRC over the 30 minute recording period yields an AUC value of 275%•min. That is, a 10% rise in ΔV'maxFRC over a 5 minute interval times five intervals equals 250%•min plus the area of the triangle from time zero (end of inhalation) to the first measurement at 5 minutes.