Research

Tidal breathing flow-volume loops in bronchiolitis in infancy: the effect of albuterol [ISRCTN47364493]

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Received: 14 August 2001
Revisions requested: 17 October 2001
Revisions received: 10 December 2001
Accepted: 4 January 2002
Published: 7 February 2002

Critical Care 2002, **6**:160-165

(Print ISSN 1364-8535; Online ISSN 1466-609X)

Abstract

Objectives To evaluate the effect of nebulized albuterol on tidal breathing flow-volume loops in infants with bronchiolitis due to respiratory syncytial virus.
Design A randomized, double-blind, control study.
Setting Pediatric unit in a community teaching hospital.
Participants Twenty infants younger than 1 year of age (mean age, 5.8 ± 2.8 months) with a first episode of wheezing due to respiratory syncytial virus bronchiolitis.
Interventions Chloral hydrate (50 mg/kg) was administered orally for sedation. One dose each of nebulized albuterol (0.15 mg/kg in 3 ml saline) and saline (3 ml) were given at 6 hour intervals in a random order.
Measurements Tidal breathing flow-volume loops were obtained before and after each aerosol treatment with a Neonatal/Pediatric Pulmonary Testing System (Model 2600; Sensor Medics, Anaheim, CA, USA). At the same time, the fraction of tidal volume exhaled at peak tidal expiratory flow (PTEF) to total tidal volume (V_{PTEF}/V_E), and the fraction of exhaled time at PTEF to total expiratory time (t_{PTEF}/t_E) were measured. The PTEF, the tidal expiratory flows at 10%, 25%, and 50% of the remaining tidal volume (TEF10, TEF25, and TEF50), and the wheeze score were also determined.
Results There were no significant changes in V_{PTEF}/V_E and t_{PTEF}/t_E after albuterol or saline treatment. PTEF increased significantly both after albuterol and saline treatments but the difference between the two treatments was not significant ($P = 0.6$). Both TEF10 and the ratio of the tidal expiratory flow at 25% of the remaining tidal volume to PTEF (25/PT) decreased significantly ($P < 0.05$) after administration of albuterol. All other investigated variables were not significantly affected by aerosol administration.
Conclusions Nebulized albuterol in infants with mild bronchiolitis due to respiratory syncytial virus did not improve V_{PTEF}/V_E and t_{PTEF}/t_E but did decrease TEF10 and 25/PT.

Keywords albuterol, bronchiolitis, pulmonary function tests, respiratory syncytial virus, tidal breathing flow-volume loops

Introduction

The use of inhaled bronchodilators to treat children with bronchiolitis remains controversial [1–4]. The controversy may be the result of differences in study populations, in choice of bronchodilators, or in measured outcome variables between trials. One common confounding variable of past studies has

25/PT = the ratio of tidal expiratory flow at 25% of the remaining tidal volume to peak tidal expiratory flow; PTEF = peak tidal expiratory flow; RSV = respiratory syncytial virus; TBFV = tidal breathing flow volume; TEF10 = tidal expiratory flow at 10% of the remaining tidal volume; TEF25 = tidal expiratory flow at 25% of the remaining tidal volume; TEF50 = tidal expiratory flow at 50% of the remaining tidal volume; t_{PTEF}/t_E = the fraction of exhaled time to achieve peak tidal expiratory flow to total expiratory time; V_{PTEF}/V_E = the fraction of exhaled volume to achieve peak tidal expiratory flow to total expiratory tidal volume.

been the inclusion of children with a history of recurrent wheezing.

The measurement of pulmonary function during infancy is difficult because of the lack of subject cooperation. It has been shown that analysis of flow-volume loops at tidal breathing is useful in evaluating lung function in infancy [5–7]. Morris and Lane [8] described a rapid rise of tidal expiratory flow to a maximum value in adult patients with airflow obstruction. In their study, the ratio of the time to PTEF to total expiratory time (t_{PTEF}/t_E) and the ratio of the tidal volume at PTEF to total exhaled volume (V_{PTEF}/V_E) were correlated with conventional measurements of airway obstruction [8].

Studies have also used tidal breathing flow-volume (TBFV) loops to evaluate airway function in healthy newborns and infants with and without wheezing [5–7,9–13]. Cutrera *et al*. [14] reported a good correlation between tidal expiratory flow patterns and conventional spirometric measurements in school-age children. Analysis of tidal breathing was used to predict wheezing illness during infancy [9,10,13]. Respiratory function in infants after respiratory syncytial virus (RSV)-proven bronchiolitis showed a lower t_{PTEF}/t_E ratio compared with that of age-matched healthy infants [15].

Several groups have studied pulmonary function in infants with bronchiolitis, with varying results [1–3]. The recent literature also suggests either a lack of efficacy or a very small efficacy for albuterol administration in the management of bronchiolitis [16,17]. The purpose of the present study is to evaluate the effect of nebulized albuterol administration on TBFV loops and wheeze scores in infants with bronchiolitis due to RSV.

Materials and methods

Selection of patients

The study was conducted in the pediatric unit of a community teaching hospital. Patients admitted to the pediatric unit were eligible for the study if they met the following criteria: age younger than 1 year; first episode of wheezing; clinical features of bronchiolitis (rhinorrhea, tachypnea, and wheezing and/or rales); and nasopharyngeal secretions positive for RSV as determined by enzyme immunoassay. Preterm infants and infants with underlying cardiopulmonary disease, bronchopulmonary dysplasia, previous history of wheezing, or those needing admission to the pediatric intensive care unit were excluded from the study. The study was approved by the hospital's Institutional Review Board. Informed, written consent was obtained from all parents before enrollment of patients.

Study design

Eligible patients were randomly assigned to receive either 0.15 mg/kg albuterol in 3 ml saline (group A) or 3 ml saline without albuterol (group B) via a nebulizer with an air flow of 6–8 l/min. The same patients were crossed-over to receive the alternate saline or albuterol treatment 6 hours after the first aerosol administration. The 6 hour interval before crossover measurements was used to exclude any carryover effect of nebulized albuterol or saline. The timing of postaerosol measurements was based on several previously published reports [2,4,18,19]. Observers were unable to distinguish between the two nebulizer solutions by any characteristics, and both nebulized solutions were dispensed by the pharmacy in identical syringes. Block randomization was also performed by the pharmacy department and the records were concealed until the end of the study.

Chloral hydrate (50 mg/kg, orally) was administered 30 min before the measurements were taken. An aerosol (either albuterol or saline) treatment was given following baseline measurements of heart rate, respiratory rate, wheeze score, arterial oxygen saturation by pulse oximetry, and pulmonary function. The same measurements were also repeated 15 min after the aerosol treatment. The entire procedure was repeated in 6 hours, with the second aerosol (either saline or albuterol) treatment. None of the patients received any other bronchodilators within 6 hours of the first aerosol treatment or between the first and second aerosol administration. In those infants who were on supplemental oxygen, the amount of supplemental oxygen was kept constant during the study period. Corticosteroids were not administered to any patients in the study.

Pulmonary function tests

All pulmonary function tests were performed by two experienced respiratory therapists. A SensorMedics 2600 Pediatric Pulmonary cart (SensorMedics Corp., Anaheim, CA, USA) was used to obtain TBFV loops. The TBFV loops were obtained and analyzed by a standard method described previously [5]. A close-fitting face mask (Model VR-3100; Ventlab Corporation, Mocksville, NC, USA) with an air-inflated cuff was used to ensure that no air leaks occurred. Four representative tidal flow-volume loops were stored for analysis. Each loop was chosen from a series of breaths during established tidal breathing. A minimum of 16 loops was collected to select the four stored loops. The loops were selected from tidal breaths, with as stable a volume and shape as possible. The means from these four loops were used as the results for each child.

Outcome measures

Several aspects of pulmonary function were chosen as outcome measures. These included the ratio of expiratory time to reach PTEF to the total expiratory time as a primary outcome measure, the tidal volume (V_T), PTEF, TEF10, TEF25 and TEF50, and 25/PT as other pulmonary function tests of interest. Heart rate, respiratory rate, oxygen saturation, and wheeze score (0 = no wheezing; 1 = end-expiratory wheezing only; 2 = wheezing during entire expiration ± inspiratory phase, audible with stethoscope only; 3 = expiratory and inspiratory wheezing audible without stethoscope) [20] were also measured.

Statistical analysis

To estimate the sample size, we analyzed pulmonary function studies of 14 infants with a recent history of wheezing illness that were performed in our pulmonary function laboratory. We calculated the intrasubject coefficient of variation for t_{PTEF}/t_E as 20–25%. A 40% difference (twice the coefficient of variation) was considered a clinically important improvement. Assuming an α level of 0.05 (two-tailed) and 90% power, a sample size of 17–20 patients per group was predicted. All values are presented as mean ± standard deviation.

Nineteen measurements were made all together in each of the two categories (saline treatment and albuterol treatment). The values for each investigated variable were compared with baseline measurements (19 measurements before nebulization with saline and 19 measurements before nebulization with albuterol) by repeated-measures analysis of variance followed by Bonferroni correction for multiple comparisons. These comparisons included: baseline before saline treatment versus baseline before albuterol treatment; saline treatment versus albuterol treatment; baseline before saline treatment versus saline treatment; and baseline before albuterol treatment versus albuterol treatment. The wheeze scores in various categories were compared with a non-parametric Friedman test followed by Dunn's test. Improvement after saline treatment and albuterol treatment from their respective baseline values were compared with a paired *t*-test. $P < 0.05$ was considered significant.

Results

Patient characteristics

Twenty patients were enrolled in the study during the study period. Analysis of one patient's flow-volume loops was consistent with grunting and the subject was excluded from the study. All 19 infants in our study had a cough (3.6 ± 2.8 days). Eighteen infants had symptoms of upper respiratory infection (2.94 ± 0.9 days), wheezing (2.3 ± 1.7 days), and breathing difficulties (1.7 ± 0.9 days). Sixteen infants had difficulties in feeding (1.6 ± 0.8 days), and nine of the 19 infants had fever (1.5 ± 0.7 days). A family history of wheezing or atopy was present in nine infants.

Table 1

Gender, age, and body weight distribution of infants in two groups

Variable	Group A	Group B	Total
Number of infants	10	9	19
Male	7	2	9
Female	3	7	10
Mean age (months)	5.1	5.8	5.4
Mean weight (kg)	6.81	7.1	6.96

Infants in group A received nebulized albuterol first followed by saline, and those in group B received saline first followed by nebulized albuterol.

Exposure to passive smoking and household pets were present in 12 and eight infants, respectively. One child presented with apnea, and four infants had otitis media at the time of admission. The duration of hospital stay in our study group was 3.9 ± 1.1 days. Five infants received oxygen supplementation and eight infants needed intravenous fluids for more than 1 day. All infants were positive for RSV and none were premature or had bronchopulmonary dysplasia.

All baseline demographic and clinical variables were evenly distributed between the two groups except for gender distribution (Table 1). No significant changes were observed in heart rate, respiratory rate, oxygen saturation, and wheeze score after aerosol treatments (Table 2). The PTEF increased both after albuterol and saline treatments but the difference between the two treatments was not significant. Both TEF10 and 25/PT significantly decreased after albuterol administration ($P < 0.05$). There were no significant changes in V_{PTEF}/V_E and t_{PTEF}/t_E either with albuterol or with saline (Table 3).

Discussion

Pulmonary function has been assessed in infants with bronchiolitis in several published reports. In these reports, the effects of bronchodilators on pulmonary function tests in children with bronchiolitis have been contradictory. Several other studies have demonstrated either no change in pulmonary

Table 2

Respiratory rate, heart rate, oxygen saturation, and wheeze score in all infants before and after albuterol and saline

	Albuterol		Saline	
	Pre	Post	Pre	Post
Respiratory rate (bpm)	42 ± 9.4	42 ± 10.7	41 ± 9.8	41 ± 10.8
Heart rate (bpm)	138 ± 16.4	136 ± 13.6	136 ± 16.3	135 ± 14.0
Oxygen saturation (%)	95 ± 3.3	95 ± 3.1	95 ± 2.7	94 ± 2.4
Wheeze score	0.79 ± 0.71	0.95 ± 0.71	0.53 ± 0.70	0.58 ± 0.77

Data presented as mean ± standard deviation.

Table 3

Pulmonary function tests before and after albuterol and saline

	Albuterol		Saline	
	Pre	Post	Pre	Post
PTEF (ml/s)	93.8 ± 28.4*	101.3 ± 28.5*	95.3 ± 25.1*	105.0 ± 30.5*
V_T (ml/kg)	6.4 ± 1.5	6.8 ± 1.3	6.9 ± 2.3	7.4 ± 3.5
t_{PTEF}/t_E	0.16 ± 0.09	0.13 ± 0.05	0.16 ± 0.08	0.14 ± 0.08
V_{PTEF}/V_E	0.22 ± 0.11	0.20 ± 0.06	0.22 ± 0.08	0.21 ± 0.07
TEF10 (ml/s)	39 ± 13.0*	33 ± 13.2*	43 ± 17.7	39 ± 18.2
TEF25 (ml/s)	55 ± 16.0	48 ± 16.9	57 ± 21.7	56 ± 19.4
TEF50 (ml/s)	77 ± 22	78 ± 25	77 ± 24*	83 ± 23*
25/PT	0.59 ± 0.15*	0.48 ± 0.13*	0.60 ± 0.19	0.53 ± 0.15

Data presented as mean ± standard deviation. PTEF, peak tidal expiratory flow; V_T, tidal volume per kilogram of body weight; t_{PTEF}/t_E, ratio of time to peak expiratory flow to total expiratory time; V_{PTEF}/V_E, ratio of exhaled volume to peak expiratory flow to tidal volume; TEF10, TEF25, and TEF50, tidal expiratory flow rates at 10%, 25%, and 50% of the remaining tidal volume; 25/PT, ratio of TEF25 to the PTEF. *$P < 0.05$ between pre and post values.

function [3,21] or worsening of pulmonary function following bronchodilator administration [22,23]. The low t_{PTEF}/t_E value found in our study may be indicative of bronchial narrowing, but it failed to improve after albuterol administration. Several of the previous studies were not randomized and included infants with recurrent wheezing. We used a randomized, double-blind study, including only infants with bronchiolitis due to RSV and excluding infants with recurrent wheezing, bronchopulmonary dysplasia, and prematurity.

Relationship between tidal flow indices and airflow obstruction

Morris and Lane [8] demonstrated that, in older children and adults, V_{PTEF}/V_E and t_{PTEF}/t_E values from TBFV loops correlate well with specific airway conductance, with forced expiratory volume in the first second, and with the ratio of forced expiratory volume in the first second to the forced vital capacity. They also showed that the values of V_{PTEF}/V_E and t_{PTEF}/t_E were significantly lower in subjects with obstructive airway disease.

In children younger than 2 years of age with bronchopulmonary obstruction, t_{PTEF}/t_E and V_{PTEF}/V_E values were lower than in the controls and improved after salbutamol administration [7]. The magnitude of change in t_{PTEF}/t_E was significantly correlated with the concentration of serum eosinophilic cationic protein (an inflammatory marker) [7]. The same investigators showed, in a different study, that V_{PTEF}/V_E, t_{PTEF}/t_E and 25/PT ratios were significantly lower in asthmatic children and improved significantly after salbutamol when compared with controls [24]. In another study in school-age children, however, the V_{PTEF}/V_E value was not significantly different in asymptomatic asthmatics when compared with age-matched healthy controls [14]. In addition, forced vital capacity, peak expiratory flow (by spirometry), and forced expiratory flow at 75% of forced vital capacity ($FEF_{75\%}$) were similar in both groups. Only $FEF_{50\%}$ and $FEF_{25\%}$ discriminated asymptomatic asthmatics from the healthy controls.

The tidal flow index, t_{PTEF}/t_E, measured during the first 3 months of life, has been shown to be predictive of subsequent wheezing in boys during the first 3 years [9,10]. Alder *et al*. [13], however, concluded in their study that t_{PTEF}/t_E is only weakly associated with the development of lower respiratory tract illness during the first year of life, and the ratio is less precise and an epidemiologically less useful measure than maximum expiratory flow at functional residual capacity. Clarke *et al*. [25] were also not able to detect any difference in t_{PTEF}/t_E between healthy infants who did and did not develop lower respiratory illness.

In older infants (aged 6–14 months) who suffered from obstructive airway disease, Banovcin *et al*. [6] reported significant correlation between maximum expiratory flow at functional residual capacity corrected for lung volume and V_{PTEF}/V_E and t_{PTEF}/t_E. They also showed a weak correlation between V_{PTEF}/V_E and airway resistance, reported as percentage predicted [6]. Banovcin *et al*. concluded that V_{PTEF}/V_E and t_{PTEF}/t_E correlate better with measures of peripheral airway obstruction than with airway resistance reflecting mainly central airway patency. Dezateaux *et al*. [12] compared t_{PTEF}/t_E with airway function measured by plethysmography. They found a weak but significant association between t_{PTEF}/t_E and specific airway conductance in infants aged older than 3 months, irrespective of their previous wheezing status.

What determines the t_{PTEF}/t_E value? There is controversy in infants about the validity of tests to measure airway obstruction [26]. Little is known about the determinants of t_{PTEF}/t_E in

infancy. The relationship of t_{PTEF}/t_E to lung function may exist because t_{PTEF}/t_E quantifies the degree of active tidal slowing that occurs in response to respiratory system mechanics. In normal subjects, during expiration, the peak flow is reached approximately one-third of the way through the expiration. This is because of the slow cessation of inspiratory muscle activity at the end of inspiration. If the inspiratory muscle activity ceases abruptly at the end of inspiration, completely passive expiration results in early peaking of the flow due to unopposed recoil of the lung and the chest wall.

Both t_{PTEF} and t_E will influence the final value of the ratio t_{PTEF}/t_E. In a patient with airway obstruction, slow exhalation secondary to an increased expiration time constant will increase t_E. In addition, active breaking is diminished, leading to decreased t_{PTEF}. Both these mechanisms result in a low t_{PTEF}/t_E value in a patient with airway obstruction. This effect could be further increased in severe obstruction with active exhalation and no active breaking. In other words, t_{PTEF}/t_E may not be a direct indicator of airway caliber, but may reflect a neuromuscular response to respiratory mechanics in airway obstruction.

The behavior of V_{PTEF}/V_E mainly parallels that of t_{PTEF}/t_E. The same mechanisms responsible for determining t_{PTEF}/t_E may be operative in determining V_{PTEF}/V_E. The role of several measured tidal flows (TEF50, TEF25, TEF10) and ratios (25/PT) in the evaluation of pulmonary function is mostly unknown. In airway obstruction, tidal flows may become flow limited, especially towards the end of the tidal volume, because of dynamic compression [8]. The rate of airflow is highly dependent on the lung volume at which the flow is measured. Without knowing the lung volumes at which the tidal flows are measured, the tidal flows have limited value in the evaluation of lung function.

Tidal breathing parameters and bronchiolitis

Low t_{PTEF}/t_E values in infants with bronchiolitis may result from an increased time constant (i.e. increased t_E) and/or decreased active braking (i.e. reduced t_{PTEF}). Both of these changes can happen because of airway obstruction. Theoretically, sedation may reduce t_{PTEF}/t_E by diminishing active braking. In fact, t_{PTEF}/t_E was found to be lower in awake compared with sleeping newborn infants [11]. The mean value for t_{PTEF}/t_E (0.16 ± 0.09) in our study is lower than that previously reported values for healthy infants [10,15,27]. The probable explanation for the low values of t_{PTEF}/t_E in our study population is airway obstruction.

In our study, PTEFs have increased with the concomitant decrease in tidal flows near the end of exhalation (TEF10) and with the decrease in the 25/PT ratio. Peak flow during tidal breathing is submaximal; it can be increased with increased effort. Theoretically, it can also increase due to bronchodilation. We cannot determine whether bronchodilation or increased force of contraction of respiratory muscles resulting from aerosol administration is the cause of the increased PTEF in the present patients.

The later in expiration that the flow is measured, the more the measurement reflects the resistance of the very small airways [28]. A significant decrease in tidal expiratory flows at the remaining 10% of tidal volume in the present study may suggest narrowing of the small airways after albuterol administration. The ratio 25/PT will be influenced by the values of TEF25 as well as PTEF. In the present study, PTEF significantly increased and TEF25 decreased (although not statistically significant) after albuterol administration. Both these changes have lead to significant decrease in the ratio of 25/PT. Increased effort during exhalation can theoretically lead to an increase in PTEF and, by dynamic compression of smaller airways, to a decrease in TEF25; this leads to a decrease in 25/PT. The resistance of small airways is believed to have a greater effect on flow at lower lung volumes [28]. Although tidal volumes remained constant in the present study, we do not know whether the expiratory flows at the remaining 10% of tidal volume were measured at identical lung volumes before and after aerosol treatment.

The lack of improvement of tidal flow indices of airflow obstruction in the present study may be because of a true absence of bronchodilation in these patients, or because these indices are not sensitive enough to detect bronchodilation if one existed. As the index t_{PTEF}/t_E reflects the neuromuscular response of pulmonary mechanics, it may not be sensitive enough to detect small changes in the airway caliber. As we have not compared TBFV indices with conventional measures of airway obstruction, we cannot be certain whether we have missed bronchodilation, if one existed.

The small sample size and variability of the tidal flow indices might have also contributed to the negative results of the present study. The power of the study was to detect 40% improvement in t_{PTEF}/t_E. We could have easily missed a much smaller response because of the sample size, although the clinical significance of such a response is unknown. We have only used a single dose of aerosol and measured the pulmonary function once after the aerosol administration. Theoretically, we may have missed a peak effect of bronchodilation. Although we have used a standard method of aerosol delivery and a standard dose, altered respiratory mechanics and small-airway disease in these infants with bronchiolitis may have lead to a decrease in the delivered dose of bronchodilator, resulting in a lack of response.

Clinical scores in bronchiolitis

In recent years there have been several reports of improvement of clinical scores such as oxygen saturation and respiratory distress scores, etc., after bronchodilator administration in infants with bronchiolitis [19,20]. The failure of clinical scores to improve in the present study may be because of the small sample size and the inclusion of patients with mild

disease. However, the observed improvement in clinical scores in several previous studies may be due to mechanisms other than bronchodilation. Transient improvement in oxygenation may have occurred because of increased minute ventilation secondary to alteration in tidal breathing pattern following aerosol administration without bronchodilation. An improvement in respiratory distress scores may be explained by an increase in nasal and upper airway caliber, especially in the studies with epinephrine. In the present study group, there was no clinical improvement with a bronchodilator. The bronchodilators may increase oxygen consumption, precipitate paradoxical hypoxemia, and increase the cost of hospitalization.

Conclusions

This present study in infants with mild bronchiolitis due to RSV demonstrates that nebulized albuterol does not improve V_{PTEF}/V_E and t_{PTEF}/t_E, but can decrease TEF10 and 25/PT.

Competing interests

None declared.

Acknowledgments

The authors gratefully acknowledge the assistance of Mark McMurty and Mary Ellen in data collection, and Dr Dan Torbati for statistical analysis.

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