Tidal breathing analysis and response to salbutamol in awake young children with and without asthma

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Tidal breathing analysis and response to salbutamol in awake young children with and without asthma. K-H. Carlsen, K.C. Lødrup Carlsen. ©ERS Journals Ltd 1994.
ABSTRACT: The purpose of the present study was to investigate: 1) whether tidal flow patterns can be used to discriminate between children with asthma and those without respiratory illness; and 2) whether reversibility to salbutamol in young children can be detected by tidal breathing analysis?

Lung function was measured by tidal flow-volume loops (SensorMedics 2600) in 26 awake young children (13 males) with asthma (aged 7–85 months; mean age 33 months), and 26 (13 males) (aged 3–72 months; mean age 34 months) without respiratory illness, before and 15 min after inhalation of nebulized salbutamol, 0.05 mg·kg⁻¹.

The ratios of the time and volume until peak expiratory flow to the total expiratory time and volume, respectively, (T_{PEF}/T_E and V_{PEF}/V_E), and the ratio of tidal expiratory flow at 25% remaining expiration to peak expiratory flow, $T_{EF_{25}}/P_{EF}$, were significantly lower in asthmatic children than in controls, and increased significantly after salbutamol inhalation in the former. Conversely, T_{PEF}/T_E and V_{PEF}/V_E, but not $T_{EF_{25}}/P_{EF}$ decreased significantly in the controls after salbutamol inhalation. Respiratory rate and expiratory volume·kg⁻¹ body weight did not differ significantly between the two groups before and after salbutamol inhalation.

We conclude that tidal breathing analysis can discriminate young children with asthma from children without respiratory illness, both regarding baseline lung function and reversibility to salbutamol.
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Bronchial asthma often starts early in life. It is important to monitor the activity of the disease and the results of the therapy. This may be done in older children, using maximum expiratory flow-volume curves. In infants and young children, lung function is more difficult to measure due to lack of co-operation. Partial forced expiratory flow-volume curves are often used for assessing airway obstruction and the effect of bronchodilator treatment in infants, but require sedation of the child [1]. In the clinical routine, it is not feasible to employ techniques that require sedation of the child. In our search for suitable techniques, we have found that it is possible to record tidal breathing flow volume (TBFV) loops in awake infants [2–4] and young children, and that they may give valuable information. In 1967, TAKISHIMA *et al.* [5] described flow-volume curves during quiet breathing in adult patients with chronic obstructive lung disease. Later reports have described the shape of TBFV loops in adults with and without airway obstruction [6], and the response to inhaled isoproterenol in airways obstruction [7]. TBFV loops have also been shown to correlate with forced expiratory volume in one second (FEV_1) in histamine bronchial provocation in school children [8].

The aims of the present study were to examine whether TBFV loops, measured in awake infants and young children, can discriminate between children with and without obstructive airways disease, and to evaluate whether tidal flow pattern analysis can be used to detect possible airway reversibility to salbutamol in young children.

Subjects and methods

Study design

The study consisted of measurements of TBFV loops: 1) in baseline conditions; 2) immediately after inhalation of nebulized salbutamol; and 3) 15 min after inhalation.

The study procedure was performed in the morning, prior to administration of any regular medication. The children did not receive inhaled β_2-agonists, ipratropium bromide or any other bronchodilating drug, inhaled corticosteroids or disodium cromoglycate during the last 12 h before measurements. None of the children used systemic β_2-agonists or theophylline.

The nebulized solution consisted of salbutamol (Ventoline®, Glaxo, UK), 5 mg·ml^{-1} diluted in 2 ml of isotonic saline, at a dose of 0.05 mg salbutamol·kg^{-1} body weight. It was nebulized by a Sidestream nebulizer connected to a CR60 compressor (Meditech, UK) with a flow of 8 l·min^{-1} using a facemask of the type used during lung function measurements (Vital Signs inc.). The output of the nebulizer was 0.46 ml·min^{-1} with 85% of particles having a diameter below 5 μm. The measurements were performed between 0800 and 1000 h. The average duration of each measurement of lung function was 15 min, and the entire sequence of lung function measurements before and after nebulization of salbutamol, including nebulization time and waiting time after nebulizaton lasted for approximately 50 min.

Subjects

Fifty two young children, 26 with asthma and 26 without respiratory illness, were consecutively included in the study, controlling only for gender. There were 13 boys and 13 girls in both groups. Mean (±SD) age in the asthma group was 33±21 months, and in the control group 34±19 months. No significant differences were found between the two groups regarding age, weight, height or the frequency of atopy. Demographic data are shown in table 1.

All children were measured awake, sitting in their mother's or fathers lap. To be included in the asthma group, the child had to have suffered at least three episodes of bronchopulmonary obstruction [9], and the severity of asthma was graded according to AAS [10], with grade 1 denoting mild and few symptoms and grade 5 severe debilitating asthma. One child was graded 1, four graded 2, eight graded 3, nine graded 4, and four graded 5. However, all children were without clinical symptoms of bronchopulmonary obstruction at the time of testing. Eight children in the asthma group did not receive any regular treatment for asthma, whereas three used inhaled β$_2$-agonists regularly, three disodium cromoglycate, and 12 asthmatic children used inhaled steroids.

Of the 26 control children without respiratory illness, 14 children were healthy with no recognized disorder, 10 suffered from atopic eczema, one from urticaria, and one child suffered from gastrointesinal intolerance.

Atopy was defined as positive skin-prick test (a wheel of at least half the size of reaction to histamine 10 mg·ml^{-1}) or specific serum immunoglobulin E (IgE) (Pharmacia CAP System RAST® FEIA; class 2 or more) to prevalent food or aeroallergens in our area. Atopy was found in six of the 26 asthma children and in nine of 26 control children, not significantly different.

Methods

Measurements of TBFV loops were performed with the SensorMedics 2600 system, as described previously [3]. Flow was measured using a pneumotachograph (4500 series, Hans Rudolph, Missouri, USA) with a flow range

Table 1. – Demographic characteristics

	Asthma n=26	Control n=26
Gender M/F	13/13	13/13
Age yrs	33±21	34±19
	(7–85)	(3–72)
Weight kg	13.9±4.1	13.9±4.2
	(7.7–27.0)	(6.8–21.0)
Height cm	91.0±14.1	91.2±14.9
	(68–116)	(63–113)
Atopy/nonatopy n	6/20	9/17

Data are presented as mean±SD, and range in parenthesis. No significant differences were detected between the two groups. M: male, F: female.

of 0–30 l·min^{-1}. In the three oldest children, the peak tidal flow exceeded this flow range, and a pneumotachograph with a flow range 0–100 l·min^{-1} (4700 series, Hans Rudolph, Missouri, USA) was used in these three children. Volume was derived by the digital integration of the flow signal at a sampling frequency of 256 samples·s^{-1}.

The pneumotachograph was fitted to a close fitting facemask (infant or toddler size) with an air inflated cuff to ensure that no leaks occurred (Vital Signs inc.). Calibration of the flow and volume signals was performed daily, prior to measurements, with a known volume delivered by a precision syringe (Hans Rudolph). Further technical details of the equipment and of the measurement procedure have been given previously [3].

Signal processing

The ratio of time until peak tidal expiratory flow to total expiratory time (TPEF/TE) was calculated by separate measurements of the time to peak expiratory flow and total expiratory time by the computer. The volume until peak expiratory flow to total expiratory volume (VPEF/VE) was calculated by the computer, sorting through the flow and volume pairs to find the highest flow. The volume exhaled to the point of peak flow was calculated as a percentage of the total exhaled volume.

Sampling procedure

Four representative TBFV loops were stored for analysis, each chosen from a series of breaths during established tidal breathing. These curves were chosen from eight loops; four stored in the computer and the last four breaths. Selection of curves was based upon identifying loops with as stable volume and shape as possible, with the respiratory rate as low as possible. The results given for each child are the mean of these four curves.

Statistical methods

Real time analysis of the recorded data was performed by the SensorMedics 2600 system. Results are given as mean values with 95% confidence intervals (CI) calculated by the Student procedure [11], unless otherwise stated.

Demographic data are given as mean values±standard deviation (SD). All tests used in the analysis were two-tailed with a significance level of 5%. Comparison between groups was carried out using the nonparametric Mann-Whitney test for group comparison. Differences within groups were tested by Wilcoxon signed rank test for matched pairs. Correlation analysis was performed by use of Pearson's correlation coefficient.

The patients were classified as responders to salbutamol when the increase in mean T_{PEF}/T_E (V_{PEF}/V_E, respectively) after inhalation of salbutamol exceeded 2 SD of the intrasubject variation. A paradoxical response were defined as a decrease in T_{PEF}/T_E (V_{PEF}/V_E, respectively) of at least 2 SD after salbutamol inhalation. Nonresponder FFrs had a difference in T_{PEF}/T_E (V_{PEF}/V_E, respectively)before to after salbutamol inhalation of less than 2 SD of the initial intrasubject variation. Possible differences between the asthma and control groups in the response to salbutamol were analysed by the Kruskal Wallis one-way analysis of variance (ANOVA) test.

The study was approved by the Regional Medical Ethics Committee, and informed consent from the parents were obtained prior to inclusion in the study.

Results

Baseline measurements

The baseline flow ratios (T_{PEF}/T_E, V_{PEF}/V_E and ratio of tidal expiratory flow at 25% remaining expiration to peak expiratory flow ($T_{EF_{25}}/P_{EF}$)) were significantly lower in the asthma group than in the control group (p<0.0001) (table 2), shown for T_{PEF}/T_E in figure 1. There were no significant differences between the two groups of children for respiratory rate or tidal volume·kg^{-1} body weight (table 2).

No significant differences related to gender were observed for T_{PEF}/T_E, V_{PEF}/V_E, $T_{EF_{25}}/P_{EF}$, tidal volume·kg^{-1} body weight, or respiratory rate in any group. Nor did we find any significant relationship between age and the ratios T_{PEF}/T_E, V_{PEF}/V_E and $T_{EF_{25}}/P_{EF}$ in any group.
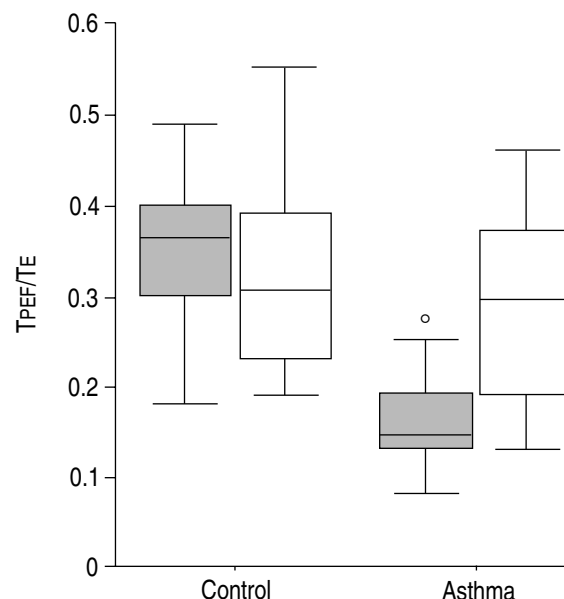

Fig. 1. – Box-whiskers plot of T_{PEF}/T_E before and after salbutamol inhalation in the asthmatic group and in the control group. Boxes represent the 25 and 75 percentiles, with median value (50 percentile) in the centre. The whiskers represent the range, except for one outlier (open circle) in the baseline asthma group located more than 1.5 times the box size from the box. ▨ : before salbutamol; ▢: after salbutamol. T_{PEF}/T_E: ratio of time until peak expiratory flow to total expiratory

However, there was a significant negative correlation between respiratory rate and age (in months) both in the asthma children (r=-0.49; p=0.01) and in the controls (r=-0.69; p<0.001). Also there was a significant positive correlation between tidal volume·kg^{-1} body weight and age both in the asthma group (r=0.44; p=0.02) and in the controls (r=0.54; p<0.01).

There was no significant correlation between tidal flow ratios and asthma severity (Aas score) in the asthma group, nor no significant differences in tidal flow ratios between asthmatic children with and without regular use of inhaled steroids.

No significant effects upon baseline T_{PEF}/T_E were detected by linear regression analysis for respiratory rate,

Table 2. – Tidal flow parameters in the asthmatic and control children

	Asthma (n=26)		Control (n=26)	
	Before salbutamol	After salbutamol	Before salbutamol	After salbutamol
T_{PEF}/T_E	0.16 (0.14–0.18)	0.29 (0.25–0.33)##	0.36 (0.33–0.39)*	0.32 (0.28–0.36)+
CV %	18.2	16.6	13.5	17.5
V_{PEF}/V_E	0.22 (0.19–0.24)	0.35 (0.32–0.39)##	0.43 (0.39–0.46)*	0.38 (0.34–0.41)++
CV %	15.4	16.8	14.9	18.1
$T_{EF_{25}}/P_{EF}$	0.62 (0.58–0.67)	0.71 (0.66–0.75)#	0.77 (0.74–0.80)*	0.75 (0.71–0.79)
CV %	10.4	10.0	10.5	10.0
V_T·kg^{-1} ml·kg^{-1}	11.2 (9.9–11.7)	10.8 (10.0–11.6)	10.9 (9.8–11.9)	10.9 (10.1–11.7)
CV %	11.6	9.3	10.8	10.5
f_R breaths·min^{-1}	33.2 (29.6–36.8)	38.3 (34.0–42.5)#	34.2 (28.2–40.3)	34.5 (28.3–40.8)

Data are presented as mean values with 95 percent confidence intervals in parenthesis. T_{PEF}/T_E: ratio of time until peak expiratory flow to total expiratory time; V_{PEF}/V_E: ratio of volume until peak expiratory flow volume to total expiratory volume; $T_{EF_{25}}/P_{EF}$: ratio of tidal expiratory flow at 25% remaining expiration to peak expiratory flow; V_T·kg^{-1}: tidal expiratory volume·kg^{-1} body weight; CV: mean intrasubject coefficient of variation; f_R: respiratory rate *:p<0.0001, significant difference between asthma and control children; #: p<0.01; ##: p<0.0001, significant increase after salbutamol inhalation in the asthma children; +: p=0.04; ++: p=0.03, significant decrease after salbutamol inhalation in the control group.

weight or tidal volume (V_T), nor did asthma severity score [10], sex or age significantly influence baseline TPEF/TE in the asthmatic children.

Response to salbutamol

In the children with asthma, tidal flow ratios increased significantly after salbutamol inhalation (tidal flow ratios after minus tidal flow ratios before salbutamol inhalation=δ): δTPEF/TE ($p<0.0001$); δVPEF/VE ($p<0.0001$); and δTEF$_{25}$/PEF ($p<0.01$) (table 2). Tidal volume·kg^{-1} body weight did not change significantly after inhalation in these children (table 2).

In the controls, a significant decrease in tidal flow ratios TPEF/TE (δTPEF/TE) ($p=0.04$) and VPEF/VE (δVPEF/VE) ($p=0.03$) was observed after salbutamol inhalation; whereas, TEF$_{25}$/PEF (δTEF$_{25}$/PEF) and tidal volume·kg^{-1} body weight did not change significantly (table 2). The overall decrease in flow ratios in the control group was caused by a paradoxical response to salbutamol in five subjects, whereas most control children did not have a significant change in TPEF/TE.

When comparing the response to salbutamol in the two groups, a significantly greater change, δTPEF/TE, δVPEF/VE and δTEF$_{25}$/PEF, was found in the asthma children ($p<0.05$) than in the control group. In the asthma group, 23 children were classified as responders to salbutamol by response in TPEF/TE (increase of ≥2SD of intra-individual variation of baseline measurement, and three children as non-responders (table 3). None of the asthma children had a paradoxical response (decrease of ≥2SD of intraindividual variation of baseline measurement). In the control group, only one child was classified as a responder to salbutamol, and 20 children as nonresponders, whereas five children had a paradoxical response. The classification of children into responders, nonresponders and paradoxical responders differed significantly between the asthma group and the control group ($p<0.0001$). The classification into responders, nonresponders and paradoxical responders for either group of children did not differ significantly whether employing TPEF/TE or VPEF/VE as parameter of lung function (table 3).

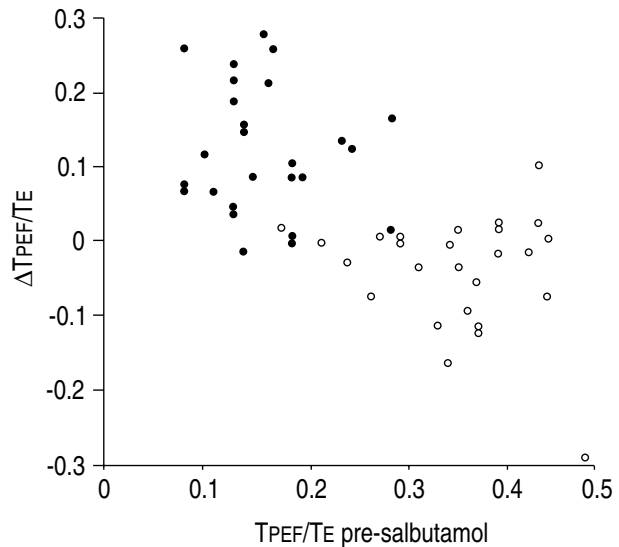A plot of the change in TPEF/TE with salbutamol inhalation against baseline TPEF/TE, demonstrates the

Table 3. – Characterization of response to salbutamol by tidal flow ratios in asthmatic and control children

| | TPEF/TE | | VPEF/VE | |
	Asthma	Control	Asthma	Control
Responders	23	1	21	2
Nonresponders	3	20	5	20
Paradoxical response	0	5	0	4

Responders had an increase in TPEF/TE or VPEF/VE, respectively, of at least 2 SD of their intra-individual variation of the baseline measurement. Nonresponders changed less than 2 SD, whereas paradoxical responders had a decrease in TPEF/TE or VPEF/VE, respectively, of at least 2 SD of the intra-individual variation of baseline measurements. For abbreviations see legend to table 2.

Fig. 2. – Δ TPEF/TE with salbutamol inhalation plotted against TPEF/TE pre-salbutamol. A significant negative correlation was found ($r=-0.65$; $p<0.001$). ●: asthma; ○: control. TPEF/TE: ratio of time until peak expiratory flow to total expiratory flow.

different distribution of asthma children *versus* control children, as shown in figure 2. There was a significant negative correlation between change in TPEF/TE (δTPEF/TE) and baseline TPEF/TE ($r=-0.65$; $p<0.001$).

Mean intrasubject coefficients of variation (CV) for TPEF/TE, VPEF/VE, TEF$_{25}$/PEF and tidal volume·kg^{-1} body-weight did not differ significantly between baseline measurements for the asthma and control children or between measurements before and after salbutamol inhalation (table 2).

Discussion

Tidal breathing flow-volume analysis demonstrated significant differences in flow ratios between infants and young children with asthma and subjects without obstructive airways disease. Furthermore, tidal flow ratios improved significantly in the asthma group after salbutamol inhalation; whereas, an overall decline in flow ratios was found after salbutamol inhalation in children without lower respiratory disease.

In the present study, significantly lower flow ratios were found in awake infants and young children with asthma, but without clinically detectable bronchopulmonary obstruction at the time of testing, compared to children without lower respiratory disease. This is supported by the findings of MORRIS and LANE [6], who described oval TBFV loops in normal adults and triangular-shaped curves in adults with airway obstruction. Furthermore, MARTINEZ *et al.* demonstrated that TME/TE (the equivalent of TPEF/TE) was lower in infants who subsequently wheezed during their first three years of life compared to those who did not [12]. The TPEF/TE values in the present study differed in the asthma group (mean 0.16) from those reported by MARTINEZ *et al.*

[12] in the group who subsequently developed wheezing (mean 0.24). However, TPEF/TE may be lower among infants and small children after acquiring bronchial asthma than before any symptoms have occurred. Furthermore, several of the infants who wheezed in the study of MARTINEZ *et al.* [12], did not develop asthma. Also, age has been found to influence this parameter in awake newborn infants [3, 4], and it is possible that the flow ratios may change from the newborn period to awake older infants and young children. Differences in tidal lung function measurements related to age were demonstrated in early infancy by HANRAHAN *et al.* [13]. MARTINEZ *et al.* [12] adjusted the TME/TE for age as they compared infants with and without wheezy respiratory illness. In both these studies [12, 13], lung function measurements were performed in infants younger than those in the present study.

The response to β₂-agonist in tidal flow pattern among the asthmatic children is in agreement with the findings of LONKY and TISI [7], who described reversibility of airways obstruction after inhaled isoproterenol in adults by TBFV loops. CUTRERA *et al*, [8] using a broncho-constrictor, found a correlation between changes in TBFV loops and FEV₁ in histamine bronchial provocation in school children. Although the effect of β₂-agonist in very young infants is still debated, reversibility to bronchodilators has been demonstrated in infants and young children with asthma or in reconvalescence after bronchiolitis by other lung function methods, such as body plethysmography [14]. YUKSEL and GREENOUGH [15] reported a response to inhaled nebulized salbutamol in preterm infants with a history of cough or wheeze, but not in preterm infants without a cough or wheeze history; and clinical improvement has been reported in children less than 2 yrs of age with acute bronchopulmonary obstruction [16, 17]. In the present study, we found a different distribution of asthmatic children and healthy children in the change in TPEF/TE with salbutamol inhalation, plotted against baseline TPEF/TE, and a significant negative correlation (r=-0.65; p<0.001) between these two parameters. This demonstrates a greater response to salbutamol in those children with the lowest baseline TPEF/TE.

The present study demonstrated paradoxical responses to β₂-agonists in five children without bronchopulmonary disease. The number of such responses in healthy children was surprising, but the phenomenon of paradoxical responses has previously been documented in sick children [18]. A decline in oxygen saturation with prolonged hypoxaemia was reported after nebulized salbutamol [19]; and NICKLAS [20], by means of a literature search, recorded 126 reports of paradoxical bronchoconstriction in asthma patients after β₂-agonists using metered-dose inhalers and 58 reports using nebulized solution. Salbutamol and other β₂-agonists, in addition to their relaxing effect upon bronchial smooth muscle, have a vasodilating effect upon the bronchial vessels. One may speculate whether a possible swelling of the bronchial mucosa due to bronchial vasodilatation, may explain the paradoxical response observed in some children.

No significant age-related differences in the response to salbutamol were observed in this group of young asthmatic children. This is in contrast to the recent report of TURNER *et al.* [21] who found an age-related effect of nebulized salbutamol on maximum expiratory flow-volume curves (FEV₁, forced vital capacity (FVC) and forced mid-expiratory flow (FEF₂₅₋₇₅)) in 14 children aged 3–9 yrs, despite precautions to ensure that low co-operation among the youngest subjects should not influence the results. However, the only effort-independent lung function parameter in their study (arterial oxygen saturation measured by pulse oximetry), changed after salbutamol inhalation without age dependency [21].

In the present study, the control group consisted of infants and young children with no history of lower respiratory illness. As nine of the 26 control children were atopic, it may be argued that some control children may be predisposed to later occurrence of bronchial asthma. However, demographic variables, including the occurrence of atopy, did not differ significantly between the asthma and control group (table 1). Furthermore, if the occurrence of atopy among the control children had a possible influence upon the results of the present study, this would tend to reduce the differences between the two groups rather than the opposite.

Only four loops were stored for analysis in each test. This is probably not optimal, as investigator bias may influence the choice of curves stored. However, we aimed at storing curves selected from series of breaths during established tidal breathing, taking care that the curves must be representative as regards shape, tidal volume and respiratory rate. If doubt occurred, the curve with peak tidal expiratory flow nearest to mid-expiratory flow would be chosen. The intrasubject variation is given by coefficient of variation in the present study, as this variable has been used in other studies and permits direct comparison of variability. The CV of the tidal flow ratios in the present study did not differ significantly among the two groups, either before or after salbutamol inhalation. Furthermore, the CV in the controls were similar to that reported by STICK *et al.* [22] in sleeping infants using the Respitrace, and lower than the estimated CV in the three groups of infants in the study by MARTINEZ *et al.* [12].

No amount of change in tidal flow ratios has yet been defined to indicate the presence or absence of response or paradoxical response. We therefore chose the criteria of minimum 2 SD change in tidal flow ratios based upon the within child variation, to ensure that intrasubject measurement variability was accounted for during analysis of the data. Employing TPEF/TE or VPEF/VE to determine the response to salbutamol, did not affect the outcome.

Measurements of tidal breathing parameters in both sick and healthy infants and children of various ages has been encouraged [23]. To our knowledge, no study has been reported where the response to β₂-agonists has been assessed by tidal breathing lung function measurements in awake infants and young children, and comparing the results of asthmatic children with age-matched healthy controls. Most studies reported, have measured lung function by various methods in sedated infants and young children. In acutely ill patients with respiratory disease,

sedation may be hazardous, and during routine clinical work sedation is cumbersome and time-consuming. Additionally, in several countries (including Norway), sedation of healthy infants is not permitted for ethical reasons.

The present study demonstrates lung function values measured prior to salbutamol inhalation in 26 awake, healthy children. This study also demonstrated smaller flow ratios in the children with asthma compared to children without obstructive airways disease, as well as differences in the response to salbutamol between healthy children and children with asthma.

The method described may be used in clinical work, is not too time-consuming and sedation is not required. Furthermore, the method has been shown to be valuable, as it has been demonstrated that tidal flow-volume loops, as well as the response in tidal flow ratios to salbutamol, may help in discriminating healthy infants and young children from those with asthma.

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